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Inference of Common Genetic Network Using Fuzzy Adaptive Resonance Theory Associated Matrix Method

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Inferring genetic networks from gene expression data is the most challenging work in the post-genomic era. However, most studies tend to show their genetic network inference ability by using artificial data. Here, we developed the fuzzy adaptive resonance theory associated matrix (F-ART matrix) method to infer genetic networks and applied it to experimental time series data, which are gene expression profiles of *Saccharomyces cerevisiae* responding under oxidative stresses such as diamide, heat shock and H_2O_2. We preprocessed them using the fuzzy adaptive resonance theory and successfully identified genetic interactions by drawing a 2-dimensional matrix. The identified interactions between diamide and heat shock stress were confirmed to be the common interactions for two stresses, compared with the KEGG metabolic map, BRITE protein interaction map, and gene interaction data of other papers. In the predicted common genetic network, the hit ratio was 60% for the KEGG map. Several gene interactions were also drawn, which have been reported to be important in oxidative stress. This result suggests that F-ART matrix has the potential to function as a new method to extract the common genetic networks of two different stresses using experimental time series microarray data.

[**Key words:** genetic network, fuzzy adaptive resonance theory, gene expression profile, clustering, oxidative stress]

Rapid advances in DNA microarray technologies over the last several years have made it possible to measure the expression levels of thousands of genes simultaneously under different conditions. The data obtained by microarray analysis are called expression profile data. Many researchers have tried to extract correlated genes from these data by just clustering and without a priori knowledge. If genetic networks could be drawn from these data, we would be able to prioritize target genes for the development of medicinal compounds such as metabolic inhibitors, anticancer drugs, and so on. Thus, the identification of genetic networks is significant and important. However, the candidates of gene interactions are too numerous to be identified by experimental methods. For the selection of gene interactions, computational methods are now being investigated. Several methods for identifying genetic networks have been proposed, including a qualitative model (1), statistic model (2), hybrid model (3), and Boolean model (2). A standard method for determining a genetic network has not yet been established. Most studies tend to show their genetic network inference ability by using artificial data, while only a few have used the raw data in their analyses. In the present paper, we report the inference of genetic interactions without a priori knowledge. We have applied a fuzzy adaptive resonance theory associated matrix (F-ART matrix) method to time series microarray data of oxidative stress in *Saccharomyces cerevisiae* to infer to the genetic network.

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MATERIALS AND METHODS

Data processing We used gene expression profile data from a yeast microarray (4), which includes 6152 genes. In the present paper, *S. cerevisiae* DBY7286 was grown at 25°C to early-log phase, and then the cells were exposed to different oxidative stresses such as diamide (0.3 mM), heat shock (37°C) and H_2O_2 (0.3 mM). Time series data were collected at arbitrary intervals as shown in Table 1. The expression ratio R_t of each gene is defined as follows.

$$R_t = \frac{\text{mRNA measured at time } t}{\text{mRNA measured just before culture was exposed to stresses}} \quad (1)$$

Fuzzy adaptive resonance theory (Fuzzy ART) model In the present paper, fuzzy adaptive resonance theory (Fuzzy ART) (5) was used as a modeling method that enables one to decrease the number of time course gene expression patterns for the simplicity

TABLE 1. List of sampling times for each stress

Stress	Sampling times (min)
Heat shock	0, 5, 15, 30, 60
H_2O_2	0, 10, 20, 30, 40, 50, 60, 80, 100, 120, 160
Diamide	0, 5, 10, 20, 30, 40, 50, 60, 90

Time series microarray data used here were reported by Gasch *et al.* (4). *S. cerevisiae* DBY7286 was grown at 25°C to early-log phase in YPD culture and then each culture was exposed to different stresses (oxidative stresses). Samples for time series microarray were collected at each stress.

of implementation. Fuzzy ART has superior robustness and correctness compared with other clustering methods. Briefly, the learning procedure for Fuzzy ART is described below.

Fuzzy ART includes an input vector I, a weight vector W_j of category j, a choice parameter α, a learning rate parameter β, a vigilance parameter ρ, a choice function T_j, and a match function M_j (5). Input vector I has a dimension corresponding to sampling points. First of all, an input vector itself is provided as a weight vector.

As a first step, a winner category for each input I is determined as follows. The choice function T_j of category j is defined as Eq. 2, which indicates the similarity between I and W_j based on W_j.

$$T_j = \frac{|I \wedge W_j|}{\alpha + |W_j|} \tag{2}$$

where the minimum operator Λ is "and" operator in fuzzy theory and the operator $|x|$ is the sum of its components. The category j that has the maximal T_j is defined as the "winner" category for input I.

As a next step, the category selected above is judged to follow the "resonance" procedure or "mismatch reset" procedure by the match function defined in the following equation.

$$Match\ function = \frac{|I \wedge W_j|}{|I|} \tag{3}$$

"Resonance" procedure is carried out if the match function of the winner category for input I is bigger than ρ; that is expressed as

$$\frac{|I \wedge W_j|}{|I|} \geq \rho \tag{4}$$

The match function indicates the similarity between I and W_j based on I. When the "resonance" procedure should be done, learning of the weight vector of the winner category is performed. Learning of the weight vector W_j is updated according to the following equation.

$$W_j^{new} = \beta(I \wedge W_j^{old}) + (1-\beta)W_j^{old} \tag{5}$$

Otherwise, if the match function of the winner category for input I is lower than ρ, the "resonance" procedure is not done and the "mismatch reset" procedure is carried out. A new category that has the next maximal T_j is chosen by Eq. 2 again. When any category cannot satisfy Eq. 4, a new category is generated according to input vector I.

These steps mentioned above are continued until every input vector I is assigned to a category.

Clustering gene expression data Gene expression data were clustered by Fuzzy ART (5). In this clustering step, we carried out the screening of the genes, which are related to oxidative stress and show strong expression, as well as clustering. First of all, in order to focus on genes relating to oxidative stress, 55 genes were selected as the candidate genes responding to oxidative stress, which appear on the five metabolic maps of the Kyoto Encyclopedia of Genes and Genomics (KEGG) (Table 2). Expression data of these genes were utilized in Fuzzy ART analysis. The ranges of $\log_2 R_i$ of the selected genes were from −3.88 to 5.06, and the genes were normalized from 0.0 to 1.0 to be used as the input data for the fuzzy operator.

Generally, the number of clusters is arbitrarily determined by the analyst. In the present paper, the optimal clustering index (OCI) was defined to objectively optimize the cluster number.

$$\mathrm{OCI} = \frac{\text{Number of clusters}}{\text{Maximum number of clusters (number of input patterns)}} + \frac{\text{Total gap index}}{\text{Maximum total gap index in the case that the number of clusters is one}} \tag{6}$$

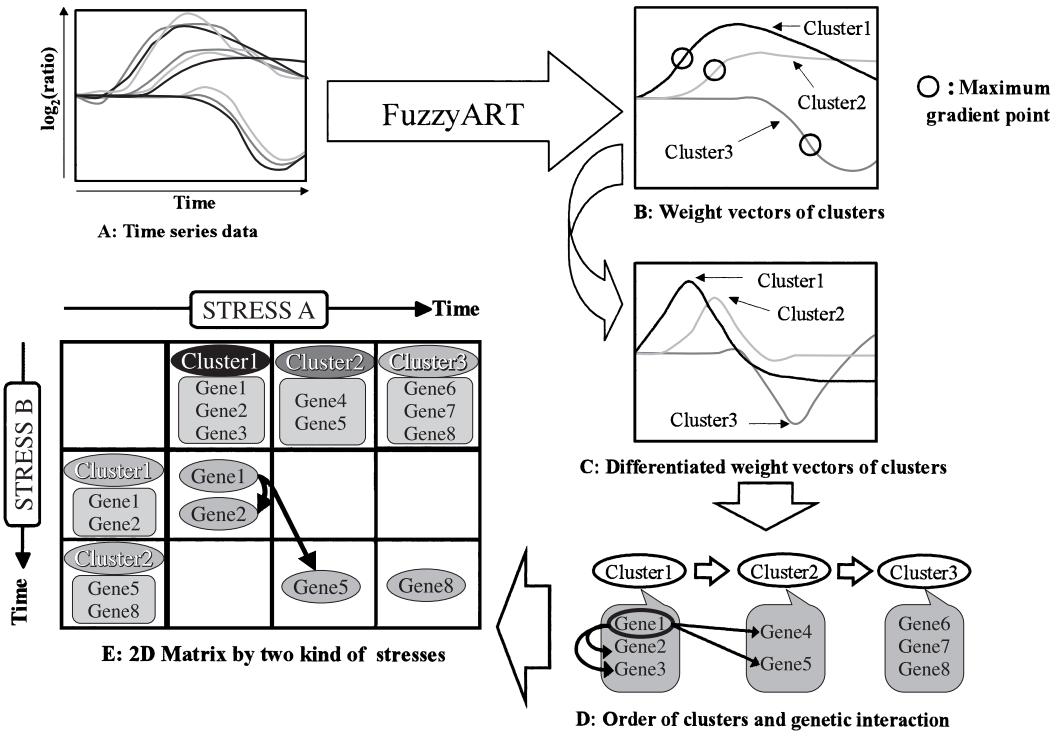

FIG. 1. Proposed genetic network inference scheme. Gene expression data were categorized by Fuzzy ART (Fig. 1A, B). To predict genetic interactions, we differentiated the weight vectors (Fig. 1C). We then arranged the clusters in order of the maximum gradient points of the differentiated patterns, and we assumed that genes in the earlier clusters influence ones in the same or later clusters (Fig. 1D). Next, we made a 2-dimensional matrix with two kinds of stresses to determine the common reacting gene interaction, and extracted the common gene network (Fig. 1E).

The gap index has been defined by us (5) and it corresponds to the distribution of profiles at each time. The total gap index is the sum of the gap indexes at each time for each cluster. The smaller OCI becomes, the better that clustering condition is. The numbers of clusters became 10 (diamide), 10 (heat shock) and 10 (H_2O_2), respectively. After clustering, we discarded some clusters with low expression, in which the weight vector was less than 2.0-fold in the expression level during the time course in the following analysis. Here, the weight vectors are the synthesized representative pattern in a cluster through the learning of time series gene expression data. Consequently, the numbers of clusters became 7 (diamide), 8 (heat shock) and 9 (H_2O_2), respectively (Fig. 1A, B).

To determine the expression order of the genes, the weight vectors were differentiated by time (Fig. 1C), and then the differentiated weight vectors are interpolated by the B-spline interpolation (6), and the maximum gradient points are determined. As preprocessing before genetic interaction analysis, we introduced the cut-off distance D and postulated that two clusters should be combined if the distance between two maximum gradient points of clusters is smaller than D, since it is highly possible that these two clusters are controlled by the same gene. In the present paper, we used 1.1 min for the cut-off distance D, and 5, 5, and 6 clusters were isolated for diamide, heat shock and H_2O_2, respectively, to be used in the following analysis.

Inference of gene interactions by F-ART matrix To infer the gene interaction, one hypothesis was made; a gene that has an earlier maximum gradient point in the gene expression pattern will influence a gene in the same cluster or a gene with a proximate maximum gradient point. Therefore, we arranged the clusters in order of the maximum gradient points of differentiated patterns (Fig. 1D).

To extract the common genetic interaction between two stresses, we constructed a 2-dimensional matrix in which the cluster genes for each stress are located in a time series on columns or lines (Fig. 1E). In the two stresses, the clusters constructed were different; cluster 2 of stress A consists of genes 4 and 5 and cluster 2 of stress B consists of genes 5 and 8 (Fig. 1E). We focused on the common genes in the two stresses. In the 2-dimensional matrix (Fig. 1E), the intersectional cell between the column containing the gene in stress A and the line containing the same gene in stress B was selected and the name of the gene was inserted in. This operation was applied to all of the genes, resulting in determination of the position of the common genes on two independent stresses. Next, an arbitrary cell containing any common gene was focused. The cell is adjacent to eight other cells. We assumed that the genes can interact with the other genes belonging to the same cell and the genes containing only adjacent three cells, which are located on the right side, down side and right-down side (Fig. 1E). Thus, all of the interactions were extracted from this matrix as inferred interactions. The inference results were evaluated as follows.

Evaluation method for inferred genetic interaction We used the KEGG metabolic map to evaluate the inference result from the F-ART matrix method. KEGG is a metabolic map drawing metabolite flow, not a genetic interaction map. Therefore, we defined the following criteria (Fig. 2) to evaluate the inference result by using the metabolic map. When a genetic interaction between gene A and gene B was estimated by the F-ART matrix method, we assumed that the estimated interaction was correct if the following biological or genetical findings on these two genes were present; (i) the adjacent rule; an enzyme from effector gene A can produce the substrate for acceptor gene B (gene A is adjacent to gene B in metabolic map), (ii) the broad adjacent rule; an enzyme from effector gene A can produce the substrate A for an enzyme from mediator gene C and an enzyme from gene C can produce the substrate C for acceptor gene B (gene A is adjacent to gene B, interposing gene C between genes A and B), and (iii) the homologous rule; two proteins from two genes can form a complex or are homologous.

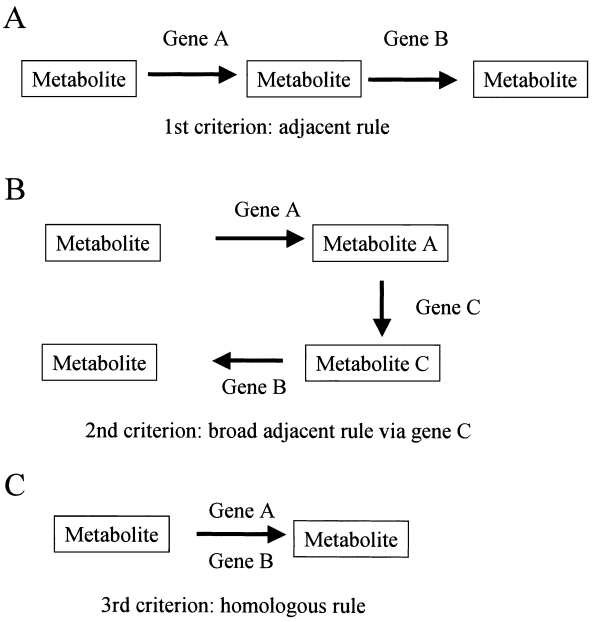

FIG. 2. Criteria for matching with metabolism map and genetic network. To compare the inferred genetic interaction and KEGG metabolic map, we defined three criteria, assuming that the estimated interaction was correct if the following biological or genetical findings on these two genes were present; (A) adjacent rule: an enzyme from an effector gene A can produce the substrate for acceptor gene B (gene A is adjacent to gene B in metabolic map); (B) broad adjacent rule: an enzyme from an effector gene A can produce the substrate A for an enzyme from mediator gene C and an enzyme from gene C can produce the substrate C for acceptor gene B (gene A is adjacent to gene B, interposing gene C between genes A and B); (C) homologous rule: two proteins from two genes can form a complex or are homologous. Gene A, Effector gene product; gene B, acceptor gene product; gene C, interposing gene.

To evaluate the inference result, we introduced two parameters; the hit and folding ratios.

$$\text{Hit ratio} = \frac{\text{The matching gene interactions in gene interaction map from KEGG}}{\text{All inferred gene interactions}} \quad (7)$$

This parameter corresponds to the ratio of correct interactions in inferred genetic interactions. The larger it becomes, the better that inferred result is.

$$\text{Folding ratio} = \frac{\text{All interactions on common gene of two stresses } ({}_nP_2\text{: n = the number of common genes})}{\text{Interaction selected by F-ART matrix}} \quad (8)$$

This parameter corresponds to the degree of screening. The higher it becomes, the better that inferred result is.

RESULTS AND DISCUSSION

Identification of vigilance parameter for Fuzzy ART We selected 55 genes (Table 2) from the database. Before clustering, the effect of a vigilance parameter on Fuzzy

TABLE 2. List of stress response genes selected in this study

Name	ORF	Stress[a]			Metabolic map[b]
		Diamide	Heat shock	H_2O_2	
NIT2	YJL126W				Cyanoamino acid
FOX2	YKR009C		+	+	Cyanoamino acid
ECM38	YLR299W	+	+	+	Cyanoamino acid, glutathione taurine and hypotaurine
ASP1	YDR321W	+	+		Cyanoamino acid
ASP3-1	YLR155C				Cyanoamino acid
ASP3-2	YLR157C				Cyanoamino acid
ASP3-3	YLR158C				Cyanoamino acid
ASP3-4	YLR160C				Cyanoamino acid
SHM1	YBR263W				Cyanoamino acid
SHM2	YLR058C	+		+	Cyanoamino acid
AMD2	YDR242W				Cyanoamino acid
CHA1	YCL064C				Cysteine
SED1	YIL167W	+		+	Cysteine
SDL1	YIL168W				Cysteine
AAT1	YKL106W				Cysteine, glutamate
AAT2	YLR027C				Cysteine, glutamate
YNL247W	YNL247W				Cysteine
YFR055W	YFR055W				Cysteine
YGR012W	YGR012W				Cysteine
MET17	YLR303W	+	+	+	Cysteine
STR2	YJR130C		+	+	Cysteine
YML082W	YML082W				Cysteine
CYS3	YAL012W				Cysteine
UGA1	YGR019W	+	+		Glutamate
GDH2	YDL215C				Glutamate
GDH3	YAL062W				Glutamate
GDH1	YOR375C				Glutamate
YDR111C	YDR111C	+		+	Glutamate
YLR089C	YLR089C				Glutamate
GLT1	YDL171C				Glutamate
GSH2	YOL049W				Glutamate, glutathione
GSH1	YJL101C				Glutamate, glutathione
YGL245W	YGL245W				Glutamate
MSE1	YOL033W				Glutamate
GAD1	YMR250W	+	+	+	Glutamate, taurine and hypotaurine
GLN1	YPR035W				Glutamate
GFA1	YKL104C				Glutamate
ADE4	YMR300C				Glutamate
QNS1	YHR074W				Glutamate
GUA1	YMR217W	+	+	+	Glutamate
GNA1	YFL017C				Glutamate
URA2	YJL130C				Glutamate
CPA2	YJR109C		+	+	Glutamate
CPA1	YOR303W		+	+	Glutamate
PUT2	YHR037W				Glutamate
UGA2	YBR006W	+	+	+	Glutamate
GLR1	YPL091W				Glutamate, glutathione
GLN4	YOR168W				Glutamate
GPX2	YBR244W	+		+	Glutathione
GPX3	YIR037W	+	+	+	Glutathione
GPX1	YKL026C		+	+	Glutathione
ZWF1	YNL241C	+	+	+	Glutathione
IDP1	YDL066W				Glutathione
IDP2	YLR174W				Glutathione
IDP3	YNL009W				Glutathione

[a] Selected genes in each stress are marked.
[b] Metabolic map in KEGG, in which each gene is described.

ART clustering was investigated. The number of generated clusters increased when a relatively higher vigilance parameter was used. Figure 3 shows the number of clusters generated under various vigilance parameters. Referring to heat shock, when the vigilance parameter was less than 0.95, the number of generated categories was only slightly affected by the vigilance parameter. With the range over 0.95, the sensitivity of the vigilance parameter increased sharply. The lower the number of clusters and the distribution of profiles clustered are, the better the clustering is. To extract the opti-

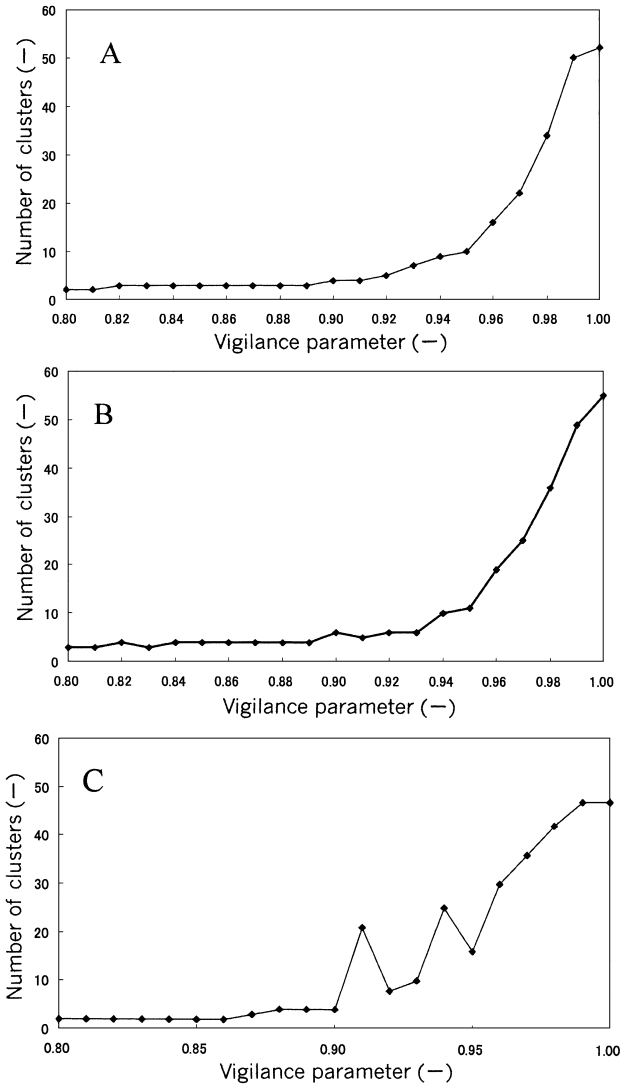

FIG. 3. Effect of vigilance parameter on the number of clusters generated by Fuzzy ART (choice parameter α: 0.1 and learning rate parameter β: 0.01). (A) Diamide stress, (B) heat shock stress, (C) H_2O_2 stress.

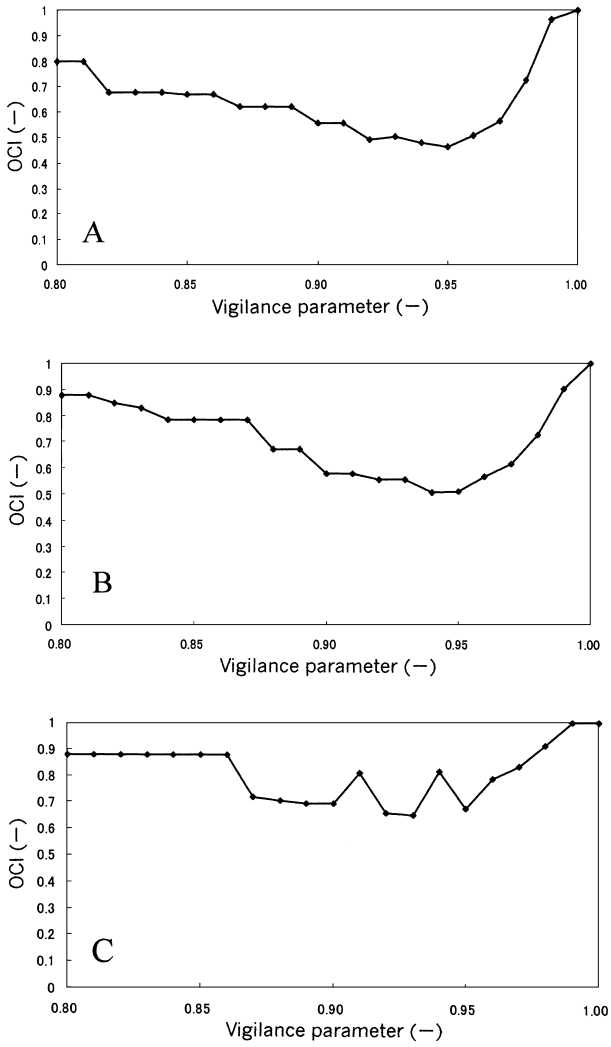

FIG. 4. Comparison of OCI on various vigilance parameters. (A) Diamide stress, (B) heat shock stress, (C) H_2O_2 stress.

mal vigilance parameter, we defined OCI (Eq. 6) and OCI values were calculated under various vigilance parameters (Fig. 4). As shown in Fig. 4, the optimal vigilance parameters were 0.95 (diamide), 0.94 (heat shock) and 0.93 (H_2O_2), respectively. In the same way, the curve of cluster number described in Fig. 3 was smoothed by B-spline interpolation. When the smoothing curve was utilized for determining the optimal vigilance parameter, very similar results were obtained, that is 0.943 (diamide), 0.944 (heat shock) and 0.924 (H_2O_2), respectively. Therefore, the optimal parameter from the former method was used.

By minimizing OCI, the numbers of clusters became 10 (diamide), 10 (heat shock) and 10 (H_2O_2), respectively. As shown in Fig. 4, the minimum OCI values were 0.47 (diamide), 0.51 (heat shock) and 0.65 (H_2O_2), respectively. This means that H_2O_2 stress consisted of time course data with a relatively high level of noise such as experimental error. Indeed, the total gap indexes of the clusters constructed were 9.3 (diamide), 6.0 (heat shock), and 14.5 (H_2O_2), and a cluster with a gap index of 9.0 existed in H_2O_2 stress. After clustering, the clusters with low expression, in which the weight vector was less than 2.0-fold in the expression level, were discarded.

Consolidation of clusters by cut-off distance D As a result of Fuzzy ART, 7, 8, and 9 clusters were isolated for diamide, heat shock and H_2O_2, respectively. The remaining genes are marked in Table 2. As shown in Table 2, 13 genes for diamide, 14 genes for heat shock, and 16 genes for H_2O_2 remained, and they were used for the F-ART matrix method. In the case of diamide and heat shock stress, 9 genes existed as the common genes as shown in Table 2.

Next, the maximum gradient points were determined by differentiation of the weight vectors (Fig. 5). Figure 5 shows the time at the maximum gradient point. It is noted that there were some clusters which must be consolidated since the time at the maximum gradient point is very close. In the case of heat shock stress, it is preferable to regard clusters no. 1 and 2, and clusters no. 3, 4, and 5 as the same cluster (Fig. 5). Even when the vigilance parameter was varied,

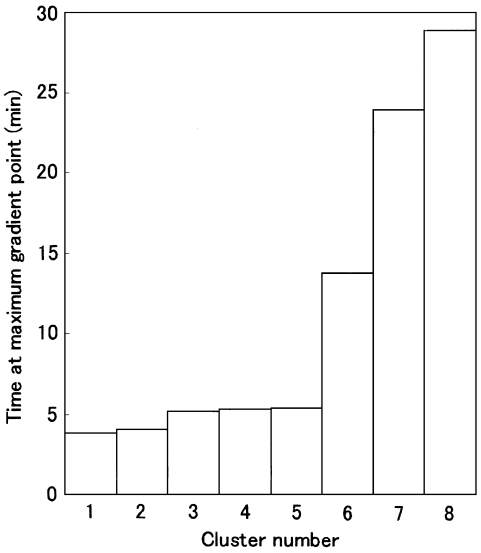

FIG. 5. Time at the maximum gradient point for each cluster (heat shock). Vigilance parameter for clustering: 0.94.

these clusters were never consolidated. Therefore, we defined the cut-off distance D as mentioned in the Materials and Methods. As a result, the cut-off distance D was defined to be 1.1 min. After consolidation, the number of clusters became 5 (clusters 1+2, 3+4+5, 6, 7, and 8) from 8 in the case of heat shock. At the step of inference by 2-dimensional matrix, each consolidated cluster was positioned in the independent column or line.

Inference of genetic networks By applying the F-ART matrix method to the time series microarray data with the oxidative stresses (diamide, heat shock and H_2O_2), 2-dimensional matrix was constructed. Here, the cluster genes for each stress are located in a time series on columns or lines and only the order of gene expression was considered for the simplified analysis. The time scale is not significantly different (Table 1). In the case that data with quite different time scale should be compared, the interpolation of time course pattern using spline function will be available and the matrix in which expression time is considered well should be constructed.

The case of diamide and heat shock stress is described in Fig. 6. Since 5 clusters were constructed from Fuzzy ART in these two stresses, the 2D matrix consisted of 5 columns and 5 lines. In this case, 9 common expression genes were inserted into the intersectional cell. The gene *gad1* was located in the hatched cell, and the interactions with *ecm38*, *uga1*, *uga2*, and *zwf1* were estimated.

The common genetic interactions were extracted from this procedure. The combination of diamide–heat shock (Fig. 7A), H_2O_2–diamide (Fig. 7B) and H_2O_2–heat shock (Fig. 7C) are shown. In Fig. 7, the characters with circle, m, p and g, indicate the databases referred to for evaluation; metabolic interactions of KEGG, protein interactions of Biomolecular Relations in Information Transmission and Expression (BRITE: http://www.genome.ad.jp/brite/), and genetic interactions reported by Coleman *et al*. (7). In particular, g with a circle indicates the interactions between *gad1* and *uga1* or *uga2* are important genetic networks for oxidative stress. The interaction has been proven to occur via γ-aminobutyric acid (GABA) as a second messenger, which is formed from L-glutamate by enzyme reaction of *gad1* product and can induce the gene expression of *uga1* and *uga2* (7). In H_2O_2 stress, microarray data of *uga1* was incomplete time course data and the data could not be applied to Fuzzy ART. Therefore, the absence of an interaction from *gad1* to *uga1* was obtained in Fig. 7B and 7C. As briefly summarized, similar interactions were described in three combinations. However, the following particular interac-

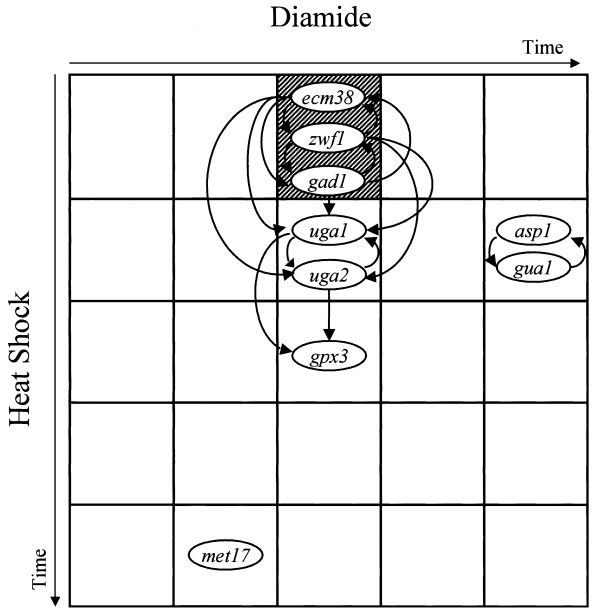

FIG. 6. Two-dimension matrix (diamide–heat shock).

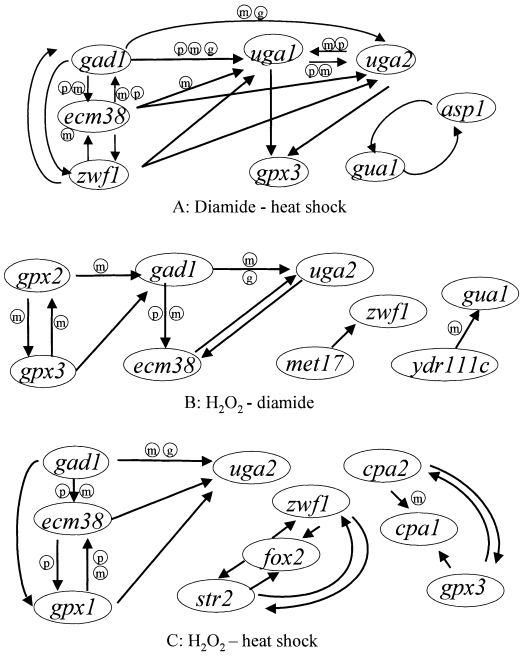

FIG. 7. Inferred genetic network. (A) Diamide–heat shock, (B) H_2O_2–diamide, (C) H_2O_2–heat shock.

TABLE 3. Hit and folding ratios

	Diamide–heat shock		H_2O_2–diamide		Heat shock–H_2O_2	
	Hit ratio	Folding ratio	Hit ratio	Folding ratio	Hit ratio	Folding ratio
Without F-ART matrix[a]	0.22	1.00 (72)	0.22	1.00 (110)	0.16	1.00 (132)
With F-ART matrix	0.44	4.00 (18)	0.60	11.00 (10)	0.24	7.76 (17)

[a] This value corresponds to all interactions ($_nP_2$: n = the number of common genes) concerning common genes of two stresses. Values in parentheses indicate the number of interactions.

tions were found; for example, the interaction from *gpx2* to *gad1* does not occur under heat shock stress, and the interaction from *ecm38* to *gad1* does not occur under H_2O_2 stress (*gad1* expression was significantly earlier than *ecm38*). Next, we calculated the hit ratio and folding ratio for the inferred genetic network (Table 3). As shown in Table 3, the hit ratio increased and the interactions decreased by using F-ART matrix. The folding ratios ranged from 4 to 11. The hit ratios of "diamide–heat shock" and "H_2O_2–diamide" were very high and were 0.44 and 0.60, respectively. On the other hand, the number of inferred interactions of "H_2O_2–diamide" was low and the hit ratio of "H_2O_2–heat shock" was also low. This may be because H_2O_2 stress included data with a large degree of noise. As described above, the gap index of clusters constructed for H_2O_2 stress was the highest among the three stresses and a cluster with a gap index of 9.0 was constructed.

As mentioned above, important stress responsible interactions in the two stresses were extracted. The F-ART matrix method proposed here is superior for this purpose. If the responsible interaction against three independent stresses would be extracted directly, a 3D matrix should be drawn. This expansion is easy to develop. In the present paper, we attempted a direct comparison of the three stresses. Only 2 interactions consisting of 3 genes, such as *gad1* to *uga2* and *gad1* to *ecm38*, remained after the analysis. This means that the three stresses are too different to extract any common responses.

In the present paper, we focused on the common genes in two stresses to extract important stress responsible interactions. This is due to the hypothesis that sequential gene expression will be conducted under any stress if a genetic interaction exists between genes A and B. On the other hand, other genes, except common genes, are specifically induced under the stress. For example, the interaction from *gpx2* to *gad1* was only obtained in the combination of H_2O_2–diamide, as mentioned above. Gene expression of *gpx2* was induced in the diamide and H_2O_2 stresses, but not the heat shock stress. Since Sugiyama *et al*. (8) reported that the *gpx2* gene was not induced in heat shock stress although the gene encodes a glutathione peroxidase 2 that is closely related to oxidative stress, it is reasonable that the relationship was not found as a common genetic interaction in Fig. 7.

Figure 7 shows the inferred genetic network, which consists of the common genetic interactions. In the inferred genetic network, several gene interactions were found to be important in oxidative stress. Several interactions coincided well with responsible networks already reported by other researchers or other databases. Our result suggests that F-ART matrix has the potential to function as a new method for primary screening of common genetic networks of two different stresses using experimental time series microarray data.

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