Comparison of Gene Selection and Machine Learning for Tumor Classification

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Abstract. Class prediction and feature selection are two learning tasks that are strictly paired in the search of molecular profiles from microarray data. In this paper, we apply the recursive gene selection proposed in our previous paper to six types of micaroarray gene expression data for tumor classification. In comparison with other two well-known gene selections, SVM-RFE (Support Vector Machine Recursive Feature Elimination) and T-test, our method outperforms best. The kernel type and kernel parameters are critical to the classification performances for the kernel classifiers. Our experiments indicate that RBF kernel classifiers are pretty good under low feature dimensions; their performances increase initially and then decrease as the feature dimension increases.

1 Introduction

Microarrays are capable of profiling the gene expression patterns of tens of thousands of genes in a single experiment. DNA targets are arrayed onto glass slides (or membranes) and explored with fluorescent or radioactively labeled probes [1]. Obtaining gene expression data from cancerous tissues gives insight into the gene expression variation of various tumor types, thus providing clues for cancer classification of individual samples. One of the key challenges of microarray studies is to derive biological insights from the unprecedented quantities of data on gene expression patterns. Partitioning genes into closely related groups has become an element of practically all analyses of microarray data [2]. However, identification of genes is faced with many challenges. The main challenge is the overwhelming number of genes compared to the smaller number of available training samples. In machine learning terminology, these data sets have high dimension and small sample size. Many of these genes are irrelevant to the distinction of samples. These irrelevant genes have a negative effect on the accuracies of the classifier. Another challenge is that DNA array data contain technical and biological noises. Thus, it is critical to identify a subset of informative genes from a large data pool that will give higher classification

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accuracy.

Because DNA microarray data has high dimension and small samples, the gene selection is very important to the classification accuracy. T-TEST [3] is one well-known gene selection in DNA microarray analysis. It ranks the significant genes according to the p-values. Unfortunately, it just considers the individual gene, not the interaction of genes. And the problem probably is that we might end up with many highly correlated genes. If there is a limit on the number of genes to choose we might not be able to include all informative genes. The method in [4] is to retrieve groups of similar genes, and apply a test-statistic to select genes of interest. SVM-RFE (Support Vector Machine Recursive Feature Elimination) is another well-known gene selection which refines the optimum feature set by using SVM in a wrapper approach [5]. Peng, Long and Ding [6] presents a feature selection to achieve the max-dependency, max-relevance, and min-redundancy based on mutual information. Recently, a scheme of gene selection based on recursive feature addition and similarity measures between the chosen genes and the candidates [7]. In comparison with the well-known gene selections, T-TEST and SVM-RFE using different classifiers, on the average, the method of recursive gene selection is the best regarding the classification accuracy under different feature dimensions.

In this paper, we apply the three gene selections of recursive feature addition [7], SVM-RFE [5] and T-test. We compare the mean test accuracy and the highest test accuracy under the highest train accuracy, and the highest test accuracy in the experiments. Additionally, we apply several learning classifiers to the experiments, and compare the classification performances on the gene selections. Generally, in the three gene selection, recursive gene addition performs the best; in the learning classifiers, on the average, Nearest Mean Scale Classifier (NMSC) and kernel classifiers with polynomial kernels have better classification accuracy than others. Under the high feature dimensions, the classification performances of RBF kernel classifiers decrease along with the increase of the feature dimension.

2 Recursive Feature Additions for Gene Selection

Liu and Sung [7] proposed a scheme of gene selection based on supervised learning and similarity measure between chosen genes and candidates. We described it in brief as follows:

1. Insignificant or noise microarray gene data is filtered out according to test-statistical selection.

2. Each individual gene is ranked in the order from the highest classification accuracy to the lowest classification accuracy with some classifier.

3. The gene with the highest classification accuracy is chosen as the most important feature, or the first feature. If there are many genes with the same highest classification, the most important feature is set to the gene with the lowest p-value measured by test-statistic. At this point the chosen feature set, G_1, consists of the first feature, g_1, which corresponds to feature dimension one.

4. The $N + 1$ – dimension feature set, $G_{N+1} = \{ g_{1,} g_2 ,\ldots, g_N , g_{N+1}\}$ is produced by

adding g_{N+1} into the chosen N-dimension feature set, $G_N = \{ g_1, g_2, \ldots, g_N\}$. The choosing of the $N+1^{\text{th}}$ feature g_{N+1} is described as follows.

Each gene g_i $(i \neq 1, 2, \ldots, N)$ outside of G_N is added into G_N; the classification accuracy of each feature set $G_N + \{g_i\}$ is compared, the g_c with the highest classification accuracy is marked and put into the set of candidates, C. Generally, the set of candidates consists of many genes, but only one gene in the set of candidates will be the chosen. Three strategies are designed for choosing the g_{N+1}:

The first strategy is to compare the individual classification accuracy of the candidates. The candidates with the highest accuracy will be put into the final stunt; the gene with the lowest p-value in the final stunt is chosen as the $N+1^{\text{th}}$ feature g_{N+1}.

The second strategy is to measure the similarity of chosen genes and candidate genes. Pearson's correlation [19] between the chosen gene g_n ($g_n \in G_N$, $n = 1, 2 \ldots N$) and the candidate g_c ($g_c \in C$, $c= 1,2 \ldots m$; *m is the number of the elements in C.)* is calculated. The sum of the square of the correlation (SC) is calculated to measure the relation, defined as follows:

$$\mathrm{SC}(g_c) = \sum_{n=1}^{N} \mathrm{cor}^2(g_c, g_n) \tag{1}$$

Where, $g_c \in C$, $g_n \in G_N$, $n = 1, 2 \ldots N$. The g_c with the minimal value of SC(g_c) is chosen as g_{N+1}.

The third strategy is to calculate the maximum value of the square of the correlation (MC),

$$\mathrm{MC}(g_c) = \max(\mathrm{cor}^2(g_c, g_n)),\ n = 1, 2 \ldots N. \tag{2}$$

Where, $g_c \in C$, $g_n \in G_N$. The g_c with the minimum value of MC(g_c) is chosen as g_{N+1}.

In the methods mentioned above, a feature is recursively added into the feature set under the supervised learning. Similar to the name of SVM-RFE, we call the strategies Classifier-Recursive Feature Addition (C-RFA), Classifier Minimal Sum of the square of Correlation-Recursive Feature Addition (CMSC-RFA), Classifier Minimal Maximal value of the square of Correlation-Recursive Feature Addition (CMMC-RFA), respectively. For example, if the classifier is Naïve Bayes Classifier (NBC), we record them NBC-RFA, NBCMSC-RFA, and NBCMMC-RFA, respectively.

3 Experiments

3.1 Data Sets

The following benchmark datasets are tested in our experiments. If the data source is not mentioned, it is available at:
http://www.broad.mit.edu/cgi-bin/cancer/datasets.cgi.

1) The LEUKEMIA data set consists of two types of acute leukemia: 48 acute lymphoblastic leukemia (ALL) samples and 25 acute myeloblastic leukemia (AML) samples, over 7129 probes from 6817 human genes. It was originally studied in the

paper [8].

2) The LYMPHOMA data set consists of 58 diffuse large B-cell lymphoma (DLBCL) samples and 19 follicular lymphoma (FL) samples. It was studied in the paper [9]. The data file, lymphoma_8_lbc_fscc2_rn.res, and the class label file, lymphoma_8_lbc_fscc2.cls are used in our experiments for identifying DLBCL and FL.
3) The PROSTATE data set in the paper [10] contains 52 prostate tumor samples and 50 non-tumor prostate samples.
4) The COLON data set in the paper [11] contains 62 samples collected from colon-cancer patients. Among them, 40 tumor biopsies are from tumors and 22 normal biopsies are from healthy parts of the colons of the same patients. 2000 genes were selected based on the confidence in the measured expression levels. The data source is available at:
http://microarray.princeton.edu/oncology/affydata/index.html.
5) Only dataset C in the dataset of Central Nervous System (CNS) embryonal tumor [12] that is used to analyze the outcome of the treatment contains 60 patient samples, 21 are survivors who are alive after treatment and 39 are failures who succumbed to their diseases. There are 7129 genes.
6) Breast cancer dataset associated with the paper [13] contains 97 patient samples, 46 patients are relapse who had developed distance metastases within 5 years, and 51 patients are non-relapse who remained healthy from the distance after their initial diagnosis for interval of at least 5 years. The data source is available at: http://www.rii.com/publications/2002/vantveer.htm.

3.2 Experimental Setup

Our experiments are described as follows:

1. The training samples are chosen from the datasets at random. The rest samples are used for test. The ratio of training sample to test sample is 3:2 in the same class.
2. The gene selections, T-TEST, SVM-RFE, and the Recursive Feature Additions are applied for gene selection based on the training samples. Different feature sets of the gene expression data are produced under the feature dimension 1 to 50.
3. Several classifiers are applied to the feature sets extracted from test samples.
4. Repeat steps 1-3 30 times.

Although the results in [7] show that, regarding the average test accuracy in each feature dimension, overall, the recursive gene addition performs best, the statistic for evaluation is not enough. In our new experiments, the following statistics are measured to evaluate the performances of the gene selections.

(1) The average test accuracy under the condition that the associated train accuracy is the highest in the experiments.
(2) The highest test accuracy under the condition that the associated train accuracy is the highest in the experiments.
(3) The highest test accuracy in the experiments.

In our experiments, Naive Bayes Classifier (NBC) is applied for recursive gene addition. The test classifiers are Nearest Mean Scale Classifier (NMSC), Kernel Fisher Discriminant (KFD), Support Vector Machine (SVM), NBC, and uncorrelated normal based quadratic Bayes Classifier that is recorded as UDC [14, 15, 16, 17, 18].

3.3 Comparison of Gene Selections

3.3.1 Comparison of the Average Test Accuracy and the Highest Test Accuracy Under the Condition that the Associated Train Accuracy is the Highest

Generally, the feature set that is associated with the highest train accuracy is prone to be treated as the final feature set. We compare the mean test accuracy and the highest test accuracy under the condition that the associated train accuracy is the highest.

Fig. 1 lists the average test accuracy associated with the highest train accuracy. Fig. 1 indicates that, NBCMSC-RFA is the best, followed by NBCMMC-RFA, SVM-RFE and NBC-RFA. On the average, T-TEST is not better than others. Fig. 2 lists the highest test accuracy associated with the highest train accuracy in the experiments. Fig. 2 also indicates that NBCMSC-RFA is the best, followed by NBCMMC-RFA, SVM-RFE, and NBC-RFA. T-TEST is the least one. Because of the space limit, the classification with the use of KFD is not shown in the figures.

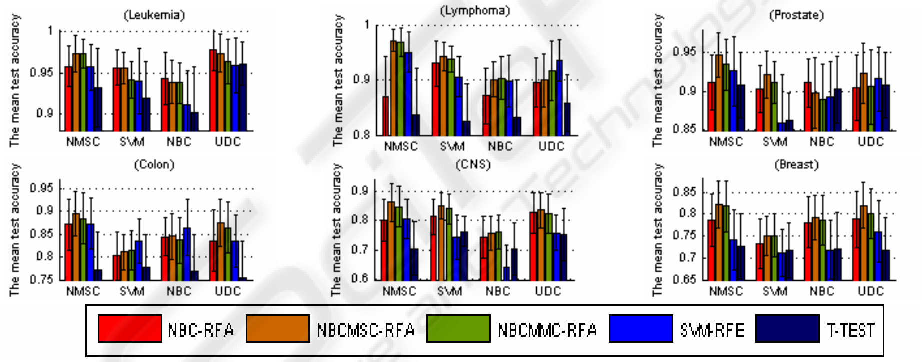


Fig. 1. The mean test accuracy associated with the highest train accuracy. In the 24 groups, NBCMSC-RFA is the best in 16 groups; NBCMMC-RFA is the best in the 4 groups (applying NMSC to Leukemia, NBC to Lymphoma and CNS, and SVM to Breast); SVM-RFE is the best in the 3 groups (applying UDC to Lymphoma, SVM to Colon, and NBC to Colon); and NBC-RFA is the best in 3 groups (applying NBC and UDC to Leukemia, NBC to prostate). The highest test accuracy is obtained by recursive gene selection based on the correlation measures in the five types of cancer data (Lymphoma, Prostate, Colon, CNS, and Breast) and NBC-RFA gains the highest test accuracy for Leukemia data classification.

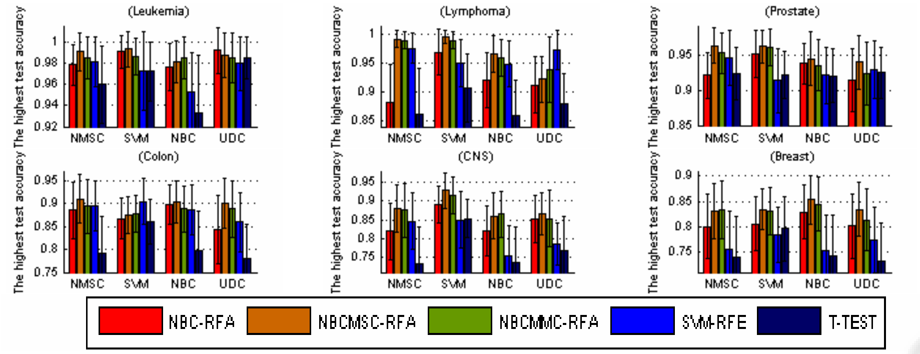


Fig. 2. The highest test accuracy associated with the highest train accuracy. In the 24 groups, NBCMSC-RFA is the best in the 18 groups; NBCMMC-RFA is the best in the 3 groups (applying NBC to Leukemia and CNS, NMSC to Breast); SVM-RFE outperforms others in 2 groups (applying UDC to Lymphoma, and SVM to Colon). NBC-RFA and T-TEST gain no championship. For the six types of cancer data, all the highest test accuracy is obtained by recursive gene selection based on the correlation measures.

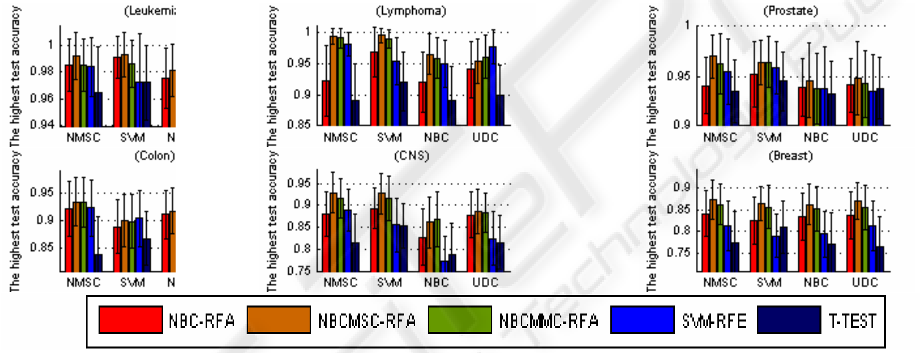


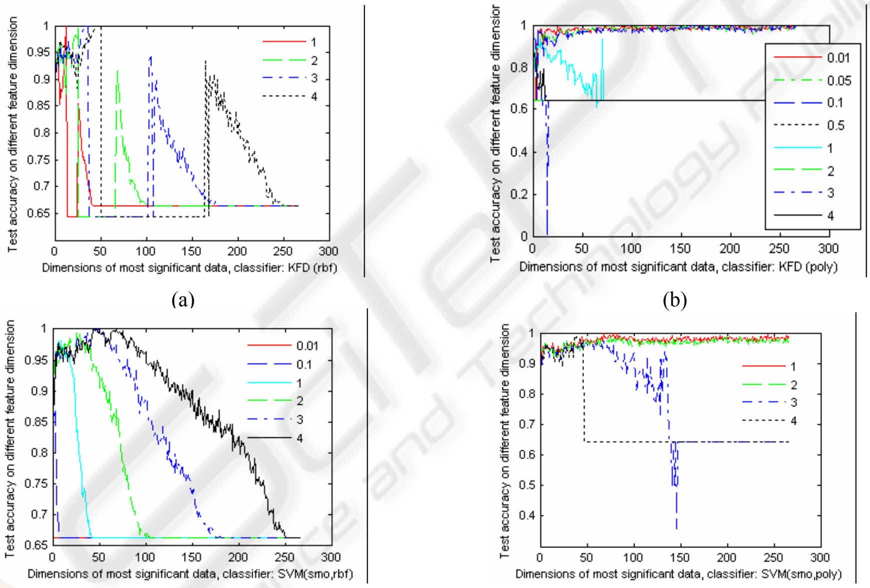
Fig. 3. The highest test accuracy under the feature dimension 1 to 5. In the 24 groups, NBCMSC-RFA is the best in 19 groups; NBCMMC-RFA is the best in 3 groups; SVM-RFE is the best in 2 groups (applying UDC to Lymphoma, SVM to Colon); NBC-RFA is the best in 1 group; and T-TEST gains no championship. In the test for each type of cancer data, all the highest test accuracy is obtained by recursive gene selection based on the correlation measures.

3.3.2 Comparison of the Highest Test Accuracy

Fig. 3 lists the highest test accuracy, regardless of the train accuracy. In the 24 groups, NBCMSC-RFA is the best in 19 groups; NBCMMC-RFA is the best in 3 groups; SVM-RFE is the best in 2 groups (applying UDC to Lymphoma, SVM to Colon); NBC-RFA is the best in 1 group; and T-TEST gains no championship. In the test for each type of cancer data, all the highest test accuracy is obtained by recursive gene selection based on the correlation measures. It also indicates that NBCMSC-RFA is the best, followed by NBCMMC-RFA, SVM-RFE, and NBC-RFA. T-TEST is the worst in comparison with other gene selections. On the average, regarding different classifiers, Figures 1 to 3 indicate that NMSC and SVM outperform others.

3.4 Comparison of Kernel Classifiers

Fig.4 - Fig. 6 compares the performances of the kernel classifiers, KFD and SVM with different RBF kernel and POLY kernel for the gene selection of T-TEST under different feature dimensions. Where, SMO (Sequential Minimal Optimization for binary SVM with L1-soft margin) is applied to train model. The legends marked in the Figures are the kernel arguments. The regularization of SVM is 10, and regularization of KFD criterion is 0.0001. Fig.4 - Fig. 6 indicates that the kernel type and the kernel parameters are very important to the classification accuracy. They show that the performances of the kernel classifiers, KFD and SVM with a RBF kernel will increase initially as the feature dimension increases, and then decrease when the feature dimension increases continually. While the recognition performances of the POLY kernel classifiers improve as feature dimension increases. The exception shown in Fig. 4 (a) are resulted from the bad train models.



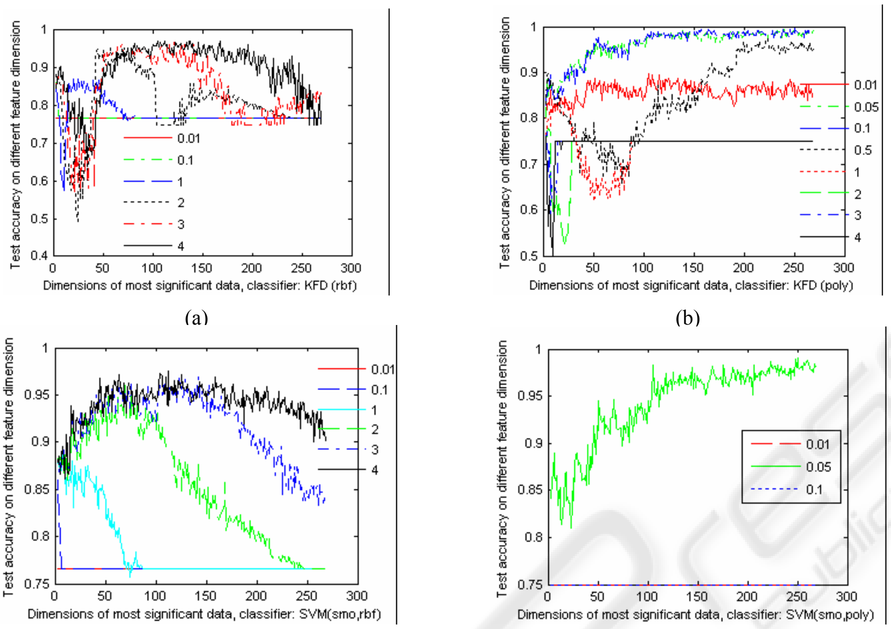
(a)

(b)

(c)

(d)

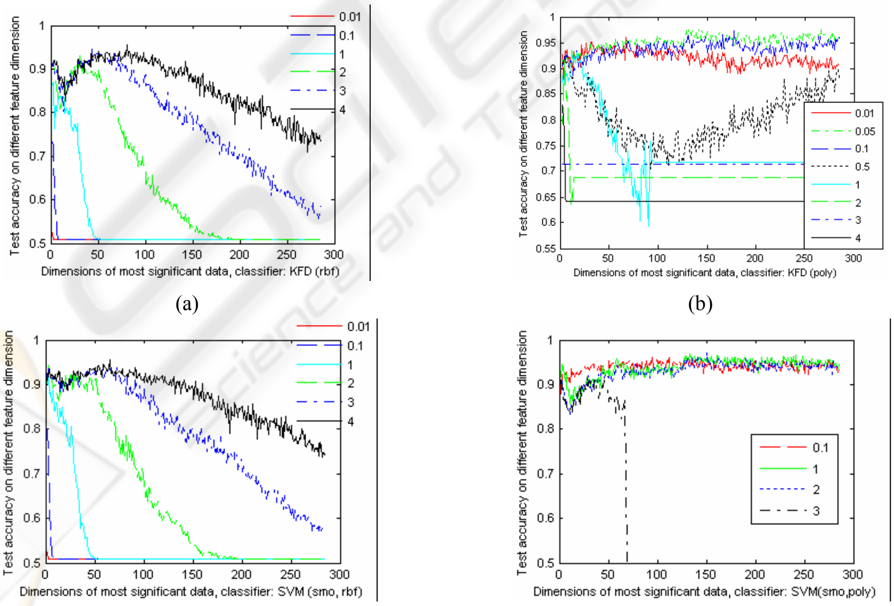
Fig. 4. The test classification of KFD with different RBF kernels (a) and POLY kernels (b) and SVM with different RBF (c) and POLY (d) kernels for LEUKEMIA.



(a) (b)

(c) (d)

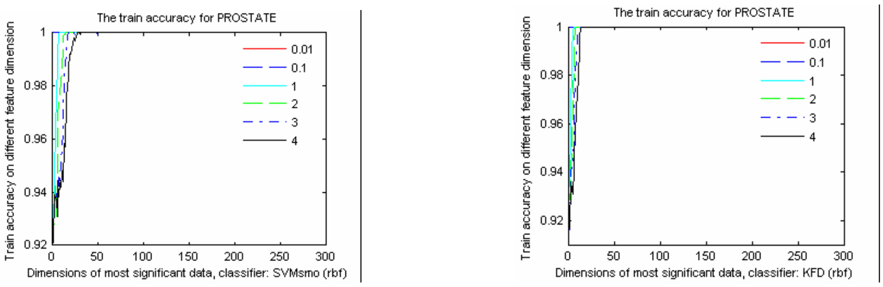
Fig. 5. The test classification of KFD with different RBF kernels (a) and POLY kernels (b) and SVM with different RBF (c) and POLY (d) kernels for LYMPHOMA.



(a) (b)

(c) (d)

Fig. 6. The test classification of KFD with different RBF kernels (a) and POLY kernels (b) and SVM with different RBF (c) and POLY (d) kernels for PROSTATE.



(a) (b)

Fig. 7. The train accuracy of SVM with RBF kernels (a) and KFD with RBF kernels (b) for PROSTATE.

Fig. 7 shows the train classification accuracy of the KFD and SVM with RBF kernels. It show that the train accuracy values of the RBF kernels are pretty high, almost 100%. We infer that, from the difference between the train accuracy (Fig. 7) and the test accuracy (Fig. 6 (a), Fig. 6(c)), in a high feature dimension, even the training error (or empirical risk) is very low, does not imply a small expected value of the test error (called risk) [14, 20].

4 Conclusions

On the average, the recursive feature addition based on supervised learning and correlation measures is better than the well-known gene selection methods of SVM-RFE and T-TEST regarding the mean test accuracy and the highest test accuracy under the highest train accuracy, and the highest test accuracy in the experiments.

Regarding the classifiers in our experiments, on the average, NMSC and SVM outperform others in the majority tests. And the kernel type and kernel parameters are important to the classification performances of the kernel classifiers. The RBF kernel classifiers are pretty good under low feature dimensions; their performances increase initially and then decrease as the feature dimension increases. The classification performances of the POLY kernel classifiers improve as the feature dimension increase.

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