M@CBETH: Optimizing Clinical Microarray Classification

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Abstract

The M@CBETH (MicroArray Classification BEnchmarking Tool on Host server) web service, available at http://www.esat.kuleuven.be/MACBETH/, offers a simple tool for making optimal two-class predictions in a clinical setting [3]. This web service compares different classifiers and selects the best in terms of randomized test set performances. The M@CBETH website offers two services: benchmarking and prediction. Benchmarking involves selection and training of an optimal model based on a benchmarking dataset. This model is stored for immediate or later use on prospective data. The prediction service offers a way for later evaluation of prospective data by reusing an existing optimal prediction model, which is useful for classifying new unseen patients. Nine different classification methods are considered. Application of the M@CBETH benchmarking service on two binary classification problems in ovarian cancer confirms that it is important to select and train an optimal model for each microarray dataset.

1. Introduction

Microarray technology has shown to be useful in supporting clinical management decisions for individual patients in combination with classification methods. Finding the best classifier for each dataset can be a tedious and non-straightforward task for users not familiar with these classification techniques. Moreover, systematic benchmarking of microarray data classification revealed that either regularization or dimensionality reduction is required to obtain good test set performances [2]. Different combinations of nonlinearity and dimensionality reduction can be explored in order to obtain an optimal classifier for each dataset with fine-tuning of all hyperparameters.

Recently, the M@CBETH web service was presented that compares, for each microarray dataset introduced to this service, different classifiers and selects the best in terms of randomized independent test set performances [3]. As a test case, we applied our tool on a dataset we recently generated in the context of a clinical study. Differences between stage I and advanced-stage (stage III-IV) ovarian cancer, and between platin-sensitive and platin-resistant advanced-stage disease, reflected in the expression patterns, have been modelled by the M@CBETH web service.

2. Materials and Methods

2.1. Dataset

Tumor biopsies were taken from three groups of patients: 7 from patients with stage I without recurrence, 7 from patients with advanced-stage platin-sensitive (all with a platin-free interval of at least twelve months after first-line platin-based chemotherapy), and 6 from patients with advanced-stage platin-resistant (all with progression during or recurrence within six months after first-line platin-based chemotherapy) disease. Each tumor was hybridized twice (with dye-swap) against a common reference pool on a cDNA microarray containing 21372 probes. Background corrected intensities were log-transformed, and subsequently normalized using the intensity-dependent Lowess fit procedure. The mean of the replicate and normalized log-ratios (i.e., patient over reference) was used as a measure for expression. More detailed information can be found in [1].

2.2. Methods

The M@CBETH benchmarking service is used to compare 9 classification methods. The number of randomizations is set to 20 and normalization is switched on. Benchmarking results in a table showing summary statistics for

all selected classification methods, highlighting the best method.

3. Results

3.1. Discrimination between early-stage and advanced-stage ovarian tumor samples

As a first clinical problem, we wanted to investigate whether we can discriminate between early-stage and advanced-stage ovarian tumor samples. Figure 1 shows the results of submitting all 20 samples to the benchmarking service, considering the 7 early-stage as one class and the 13 advanced-stage samples as the other class. LS-SVM with an RBF kernel is selected as the best classification method for this classification problem with an average test set accuracy (ACC) of about 92% and an average test set Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) of about 99%.

	LOO-CV	training ACC	test ACC	training AUC	test AUC
1.	90.48 ± 5.22	100.00 ± 0.00	91.27 ± 8.53	100.00 ± 0.00	99.40 ± 2.73
2.	92.18 ± 3.85	98.30 ± 7.79	92.06 ± 10.03	100.00 ± 0.00	98.81 ± 5.46
3.	49.32 ± 14.62	50.68 ± 8.72	51.59 ± 19.65	50.05 ± 5.82	49.40 ± 23.54
4.	94.22 ± 5.35	99.32 ± 2.15	83.33 ± 14.91	99.89 ± 0.48	93.45 ± 9.37
5.	95.58 ± 4.78	99.66 ± 1.56	85.71 ± 16.90	100.00 ± 0.00	93.45 ± 12.88
6.	93.88 ± 5.19	98.64 ± 3.66	83.33 ± 14.91	99.68 ± 1.06	95.24 ± 8.36
7.	94.90 ± 5.12	99.66 ± 1.56	86.51 ± 17.17	100.00 ± 0.00	93.45 ± 12.88
8.	97.28 ± 4.21	99.66 ± 1.56	82.54 ± 16.22	99.89 ± 0.48	89.88 ± 14.04
9.	97.96 ± 3.31	99.66 ± 1.56	82.54 ± 14.41	100.00 ± 0.00	90.18 ± 15.13

Figure 1. Results of discriminating early-stage from advanced-stage ovarian tumor samples. Methods are: 1. Least Squares Support Vector Machines (LS-SVM) with linear kernel, 2. LS-SVM with Radial Basis Function (RBF) kernel, 3. Fisher Discriminant Analysis (FDA), 4. Principal Component Analysis (PCA) (unsupervised principal component (PC) selection) + FDA, 5. PCA (supervised PC selection) + FDA, 6. Kernel PCA with linear kernel (unsupervised PC selection) + FDA, 7. Kernel PCA with linear kernel (supervised PC selection) + FDA, 8. Kernel PCA with RBF kernel (unsupervised PC selection) + FDA, 9. Kernel PCA with RBF kernel (supervised PC selection) + FDA. The best classification method is highlighted.

3.2. Discrimination between platin-sensitive and platin-resistant advanced-stage ovarian tumor samples

Secondly, we wanted to investigate whether we could predict chemoresistance in advanced-stage ovarian cancer. Figure 2 shows the results of submitting 13 samples to the benchmarking service, taking the 7 platin-sensitive advanced-stage samples as one class and the 6 platin-resistant advanced-stage samples as the other class. LS-SVM with a linear kernel is selected as the best classification method for this classification problem with an average test set ACC of about 75% and an average test set AUC of about 82%.

	LOO-CV	training ACC	test ACC	training AUC	test AUC
1.	56.08 ± 8.22	100.00 ± 0.00	75.00 ± 17.68	100.00 ± 0.00	82.14 ± 22.56
2.	63.49 ± 7.97	85.71 ± 20.83	60.71 ± 16.90	100.00 ± 0.00	82.74 ± 22.53
3.	50.26 ± 5.69	51.32 ± 8.94	52.38 ± 24.88	53.33 ± 7.80	46.43 ± 38.96
4.	64.55 ± 14.32	91.53 ± 12.12	61.90 ± 15.04	96.43 ± 6.92	80.95 ± 23.59
5.	67.20 ± 10.23	100.00 ± 0.00	64.29 ± 20.27	100.00 ± 0.00	78.57 ± 19.82
6.	66.67 ± 14.49	92.06 ± 12.74	59.52 ± 14.74	97.14 ± 6.04	76.19 ± 23.02
7.	65.08 ± 13.28	97.88 ± 5.69	58.33 ± 21.41	97.86 ± 7.68	73.81 ± 21.62
8.	79.89 ± 9.04	96.30 ± 9.51	53.57 ± 8.96	97.62 ± 7.18	64.29 ± 26.89
9.	83.60 ± 10.32	100.00 ± 0.00	57.14 ± 11.57	100.00 ± 0.00	65.48 ± 20.12

Figure 2. Results of discriminating platin-sensitive from platin-resistant advanced-stage ovarian tumor samples. Methods: see Figure 1.

4. Conclusions

By applying the M@CBETH benchmarking service on two binary cancer classification problems in ovarian cancer, we showed that it is possible to optimally choose an optimal classification method for each microarray dataset.

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