CLASSIFICATION OF MASS SPECTROMETRY DATA
Using Manifold and Supervised Distance Metric Learning

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Abstract: Mass spectrometry becomes the most widely used measurement in proteomics research. The quality of the feature set and applied learning classifier determine the reliability of the prediction of disease status. A well-known approach is to combine peak detection and support vector machine recursive feature elimination (SVMRFE). To compare the feature selection and to search for alternative learning classifier, in this paper, we employ a distance metric learning to classification of proteomics mass spectrometry (MS) data. Experimental results show that distance metric learning is promising for the classification of proteomics data; the results are comparable to the best results by applying SVM to the SVMRFE feature sets. Results also indicate that the good potential of manifold learning for feature reduction in MS data analysis.

1 INTRODUCTION

Mass spectrometry (MS), which includes a sequence of the ratios of mass/charge (m/z), is currently used for biomedical diagnosis and protein identification (Petricoin and Liotta, 2003). The data mining usually contains four steps, or pre-processing, feature extraction, feature selection and classification.

The objective of pre-processing is to purify the data, and systematically represent the data for the following steps. Generally speaking, MS data contain two kinds of noise, electric noise and chemical noise, which damage the classification result. The chemical noise, usually shows as a baseline along the spectrum, is generated by matrix or ion overloading. Baseline correction computes the local minimum value and draws a baseline representing as the background noise and subtracts the baseline from the spectrum. Williams *et al* proposed a robust algorithm for computing the baseline correction of MALDI-MS spectra (Williams et al., 2005). The electronic noise, usually randomly distributed in the spectra, is produced from the electronic instrument. To remove the noise, Chen *et al* designed a wavelet-based denoising (Chen et al., 2007). The denoised data are normalized to provide a systematic representation of the spectra.

The next steps include extracting features from the spectra, and forming the initial complete feature set. The simplest way is to obtain every data point as a discriminative feature, and finally have a huge feature set including more than 15000 features (Li et al., 2007), (Li et al., 2002), that is stupid for classification. Recently, some researchers employed an elaborated algorithm for peak detection and performed a more aggressive feature extraction (Coombes et al., 2007), (Hilario et al., 2006), (Shin and Markey, 2006). A popular method to deal with the feature selection in MS data classification is to apply support vector machine recursive feature elimination (SVMRFE) for getting a small subset of peaks as input variables for the classification (Guyon et al., 2002), (Vapnik, 1998), (Liu et al., 2008), followed by SVM for the final testing.

To search for promising alternative classifiers and to feature dimensionality reduction, in this paper, we apply a distance metric learning, called large margin nearest neighbor classifier (LMNN) that is proposed by Weinberger (Weinberger et al., 2006), to the classification of MS data. We also compare the testing results on the reduced feature sets with the use of a manifold learning. Experimental results show that distance metric learning is promising for the classification of proteomics data; the results are comparable to the best results by applying SVM to the SVMRFE

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The remainder is organized as follows. Preprocessing algorithms are briefly discussed in section two, LMNN is introduced in section three and experimental results are given in section four, followed by our conclusions in section five.

2 PREPROCESSING DATA

MS data have high dimensionality and small number of samples. Both chemical and electrical noises are involved in the signal. The redundancy of the spectra, different reference points, and unaligned feature points increase the computational intensity and decrease the classification accuracy. To deal with these issues, the proposed processing procedures include spectra re-sampling, wavelet de-noising, baseline correction, normalization, peak detection and alignment.

2.1 Spectra Re-sampling and Wavelet De-noising

The mass spectrum data is in a discrete format and the intervals are not equal in the whole spectrum. For high-resolution data, the high-frequent noise and redundant data points harm the quality of the dataset. So, we have to set the common low-frequent mass value to every sample spectrum in order to give a unified representation. By using spline interpolation, we resample the data and confine the interval to a unified size. Before re-sampling, the sample spectrum has a little variation from the true spectrum. The data is re-sampled to a standard discrete data which could be analyzed in frequency domain. The electrical noise is generated during the mass spectrum acquisition by the instrument and it is almost random distributed noise. The next step is to employ discrete wavelet transform for eliminating the electrical noise. By applying a wavelet transform, the original signal is decomposed into multi-level wavelet coefficients. By setting up a threshold value, given percentiles of lower value coefficients are removed. Then, we apply polynomial filter of second order to smooth the signal and get better data quality.

2.2 Baseline Correction and Normalization

To minimize the chemical noise, the baseline should be subtracted from the spectrum. In order to obtain the baseline, the local minima should be computed by assigning an appropriate window size. Then, we use spline interpolation to fit the baseline. In order to compare sample spectra, we need to normalize the data to represent the data in a systematic scale.

2.3 Peak Detection and Qualification

The final feature acquisition of MS data is to obtain the peak position and its magnitude. In our mass spectrum experiment, the peak detection method proposed by Coombes et al (Coombes et al, 2005) is performed on mean spectrum rather than individual spectra, and we used the ad hoc method based on signal to noise ratio to select the large peaks (Coombes et al., 2007).

3 DISTANCE METRIC LEARNING

Distance metric learning includes supervised learning and unsupervised learning.

For unsupervised distance metric learning or called manifold learning, the main idea is to learn an underlying low-dimensional manifold where geometric relationship between most of the observed data are preserved. Every dimension reduction approach is essentially to learn a distance metric without label information. Manifold learning algorithms can be divided into global linear dimension reduction approaches, including Principle Component Analysis (PCA) and Multiple Dimension Scaling (MDS), global nonlinear approaches, for instance, ISOMAP (Tenenbaum et al., 2000), local linear approaches, including Locally Linear Embedding (LLE) (Saul and Roweis, 2003) and the Laplacian Eigenmap (Belkin and Niyogi, 2003). Here we introduce a locally linear embedding proposed in Roweis and Lawrance, 2000) that is a local method to establish the mapping relationship between the observed data and the corresponding low-dimensional data and to preserve local order relation of data in both the embedding space and the intrinsic space, described as follows:

1. Find the n nearest neighbor for each x_i in the dataset. By assuming that each data point and its neighbors lie on a locally linear patch of the manifold, the local geometry of these patches can be characterized by linear coefficients that reconstruct each data point from its neighbors. The reconstruction error can be measured by

$$\varphi(\mathrm{W}) = \| x_i - \sum_j \mathrm{W}_{ij} x_{ij} \|^2 \qquad (1)$$

2. Construct the approximation matrix by minimizing

$$\sum_{i=1}^{n} \| x_i - \sum_{j}^{n} \mathrm{W}_{ij} x_{ij} \| \qquad (2)$$

$$\text{s.b.} \sum_j \mathrm{W}_{ij} = 1 \cdot$$

3. Construct a neighbor-preserving mapping. The idea is that the reconstruction weights reflect intrinsic geometric properties of the data and are invariant to the linear transform from a high dimensional coordinates of each neighborhood to global internal coordinates on a low dimensional manifold. The details are given in Roweis and Lawrance, 2000).

Supervised distance metric learning can be divided into global distance metric learning and local distance metric learning. The global learns the distance metric in a global sense, i.e., to satisfy all the pairwise constraints. The local approach seeks only to meet local pairwise constraints.

In supervised global distance metric learning, the representative work is to formulate distance metric learning as a constrained convex programming problem (Xing et al., 2003). It learns a global metric distance that minimizes the distance between the data pairs in the equivalence constraints subject to the constraint that the data pairs in the inequivalence constraints are well separated. In local adaptive distance metric learning, many researchers presented approaches to learn appropriate distance metric to improve KNN classifier (Domeniconi and Gunopulos, 2002), (Peng et al., 2002), (Goldberger et al., 2005), (Zhang et al., 2003), (Zhang et al., 2005).

Inspired by the work on neighborhood component analysis (Goldberger et al., 2005) and metric learning by energy-based models (Chopra et al., 2005), Weinberger et al. proposed a distance metric learning for Large Margin Nearest Neighbor classification (LMNN). Specifically, the Mahanalobis distance is optimized with the goal that k-nearest neighbors always belong to the same class while examples from different classes are separated by a large margin (Weinberger et al., 2006). LMNN has several parallels to learning in support vector machines (SVMs), for example, the goal of margin maximization and a convex objective function based on the hinge loss. In multi-classification, the training time of SVMs scales at least linearly in the number of classes, by contrast, LMNN has no explicit dependence on the number of classes (Weinberger et al., 2006). We introduce the idea of LMNN as follows:

Given a training set of n labeled samples and the corresponding class labels $\{x_i, y_i\}_{i=1}^{n}$, the binary matrix $y_{ij} \in \{0,1\}$ indicates whether or not the labels y_i and y_j match. And $\eta_{ij} \in \{0,1\}$ indicates whether x_j is a target neighbor of x_i. Both matrices y_{ij} and η_{ij} are fixed during training. The goal is to learn a linear transformation $\mathrm{L}: \mathrm{R}^d \to \mathrm{R}$ that optimizes KNN classification. The transform is used to compute squared distance as

$$\mathrm{D}(x_i, x_j) = \| \mathrm{L}(x_i, x_j) \|^2 \qquad (3)$$

The cost function is given as follows:

$$\begin{aligned} \varepsilon(\mathrm{L}) &= \sum_{ij} \eta_{ij} \left\| \mathrm{L}(x_i - x_j) \right\|^2 \\ &+ C \sum_{ijl} \eta_{ij} (1 - y_{jl}) \left[1 + \left\| \mathrm{L}(x_i - x_j) \right\|^2 - \left\| \mathrm{L}(x_i - x_l) \right\|^2 \right]_+ \end{aligned} \qquad (4)$$

Where $[z]_+ = \max(z,0)$ denotes the standard hinge loss and the constant C > 0. The first term penalizes large distances between each input and its target neighbors and the second term penalizes small distances between each input and all other inputs that do not share the same label.

The optimization of eq. (2) can be reformulated as an instance of semidefinite programming (SDP) Vandenberghe and Boyd, 1996) and the global minimum of eq. (2) can be efficiently computed. Mahalanobis distance metric $\mathrm{M} = \mathrm{L}^T \mathrm{L}$, then eq. (1) is

$$\mathrm{D}(x_i, x_j) = (x_i - x_j)^T \mathrm{M} (x_i - x_j) \qquad (5)$$

Slack variables ξ_{ij} for all pairs of differently labeled inputs are introduced so that the hinge loss can be mimicked. The resulting SDP is given by:
Minimize

$$\varepsilon(\mathrm{L}) = \sum_{ij} \eta_{ij} (x_i - x_j)^T M (x_i - x_j) + C \sum_{ijl} \eta_{ij} (1 - y_{jl}) \xi_{ijl}$$

Subject to

(1) $(x_i - x_l)\mathrm{M}(x_i - x_l) - (x_i - x_j)\mathrm{M}(x_i - x_j) \geq 1 - \xi_{ijl}$

(2) $\xi_{ijl} \geq 0$

(3) $\mathrm{M} \geq 0$

4 MATERIALS AND EXPERIMENTS

4.1 Dataset

The following two mass spectrometry datasets have been tested in our experiment.

1. High resolution time-of-flight (TOF) mass spectrometry (MS) proteomics data set from surface-enhanced laser/desorption ionization (SELDI) ProteinChip arrays on 121 ovarian cancer cases and 95 controls. The data sources can be accessed by FDA-NCI Clinical Proteomics at

http://home.ccr.cancer.gov/ncifdaproteomics/ppatterns.asp

2. The breast cancer QC SELDI spectra data set was studied by Pusztai et al. (Pusztai et al., 2004). Here we utilized data of 57 controls and 51 cases. The data set may be downloaded at:

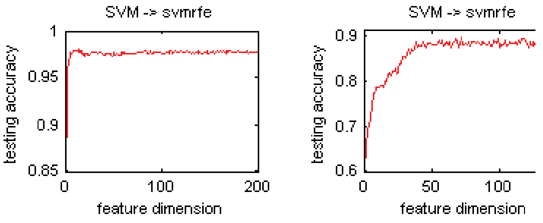
http://bioinformatics.mdanderson.org/Supplements/Datasets

We process the dataset according to the methods described in section 2 for peak detection. And then apply LMNN to the detected peak spectra data. Since SVMRFE is a classical feature selection based on the weights of the support vectors (Guyon et al., 2002) and is widely used in the classification of proteomics data with the use of SVM, we also compare the results by using LMNN with Euclidean distance, Mahalanobis distance, and energy-based classification (Weinberger et al., 2006) and SVM combining with SVMRFE on the detected peak data. In each experiment, 80% samples are randomly chosen for training and the remaining 20% samples are tested. We repeated the experiments 10 - 100 times and compared the average testing results.

Besides applying SVMRFE to the features chosen by peak-detection algorithm, we also apply the manifold learning to the features chosen by peak-detection and the features filtered by rank-sum test without peak-detection, and obtain the reduced features that are mapped from high-dimension to low-dimension, then we apply a support vector machine and KNN to the reduced feature sets and compare the testing results.

4.2 Experiments on Peak Detection with SVMRFE

Figure 1 list the average testing accuracy values by applying SVM to SVMRFE on ovarian cancer data set and breast cancer data set, respectively. These data sets were preprocessed with the use of peak-detection algorithms before the use of SVMRFE.



(a) Ovarian cancer (b) Breast cancer

Figure 1: The testing accuracy by applying SVM to the feature sets with the use of SVMRFE on ovarian cancer data set (a) and breast cancer data set (b).

Table 1 lists the average testing accuracy by applying LMNN classifiers to the peak data sets. Table 2 lists the best averaging testing accuracy by applying SVM to the feature sets chosen by SVMRFE from the peak data sets.

Table 1: Average testing accuracy with LMNN classifiers.

Data set	Classifier	Testing accuracy
Ovarian cancer	LMNN_energy	**99.3%**
	LMNN_Euclidean	84.6%
	LMNN_Mahalanobis	99.0%
Breast cancer	LMNN_energy	81.8%
	LMNN_Euclidean	84.6%
	LMNN_Mahalanobis	81.7%

Table 2: The best average testing accuracy by applying SVM to feature sets ranked by SVMRFE.

Data set	Testing accuracy
Ovarian cancer	98.0%
Breast cancer	**89.5%**

Comparing the results listed in tables 1 and 2, we can see that, although the testing results in table 1 are not as good as the best result by applying SVM to SVMRFE feature sets for breast cancer data set, the results by applying LMNN classifiers based on energy classification and Mahalanobis distance are both better than the best result obtained by applying SVM to SVMRFE feature sets. It indicates that LMNN classifiers with energy classification and Mahalanobis metric are competitive for the classification of proteomics data, especially considering that the best testing accuracy by applying SVM to SVMRFE feature sets after we tested each dimensionality from 1 to 200 for ovarian cancer data set and tested each dimensionality from 1 to 150 for breast cancer data set. Furthermore, normally we cannot accurately predict the best testing results that correspond to which dimensionality.

We also test the classification results by applying LMNN to the feature sets chosen by SVMRFE, and compare the best testing result and the least number of the features corresponding to the best result in each experiment against the results with the use of SVM, shown in table 3. Experimental results indicate comparable results by applying LMNN and support vector machines.

Table 3: The highest testing accuracy and the least number of the features corresponding to the highest testing results.

Data set	Classifier	Testing accuracy	Feature number
Ovarian cancer	LMNN_energy	**99.5%**	14
	LMNN_Euclidean	98.4%	10
	LMNN_Mahalanobis	**99.5%**	15
	SVM	99.3%	11
Breast cancer	LMNN_energy	92.6%	27
	LMNN_Euclidean	90%	28
	LMNN_Mahalanobis	92.5%	25
	SVM	**94%**	68

4.3 Manifold for Feature Reduction

We also preprocess the data sets by using peak-detection algorithms (method one) and filtered the data sets by using rank sum test without peak-detection (method two), then we apply the manifold learning Roweis and Lawrance, 2000) to reduce the features, finally we employ a SVM and a KNN to classify the data sets. Figure 2 gives the comparison of the testing accuracy of these two methods, with and without peak-detection on the ovarian cancer data. Figure 3 plots the testing results on breast cancer data.

Figures 2 and 3 indicate that the testing results on the reduced feature sets preprocessed from rank sum test are better than the results on the reduced feature sets preprocessed by peak detection. It seems to imply that peak detection cannot include all useful features. This is worthy of further study.

We also note that the testing results on ovarian data set are not better than the results obtained by using SVMRFE, shown in 4.2. However, the results on breast cancer are comparable to the results with the use of SVMRFE, given in section 4.2. It indicates that unsupervised metric learning or manifold learning holds good promise in dealing with high-feature dimension data for dimension reduction and this makes interesting future study.

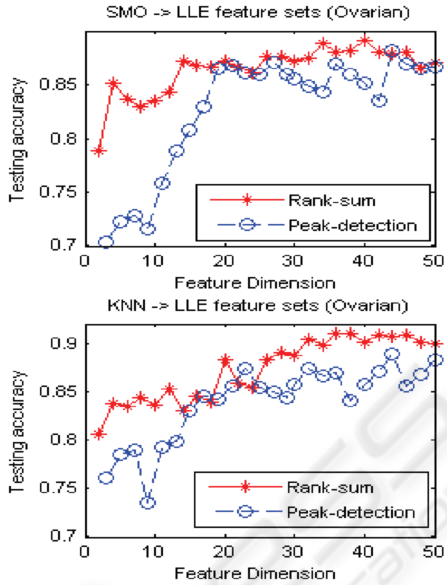


Figure 2: The testing results of the LLE reduce feature sets on peak-detection and rank sum test, ovarian cancer data.

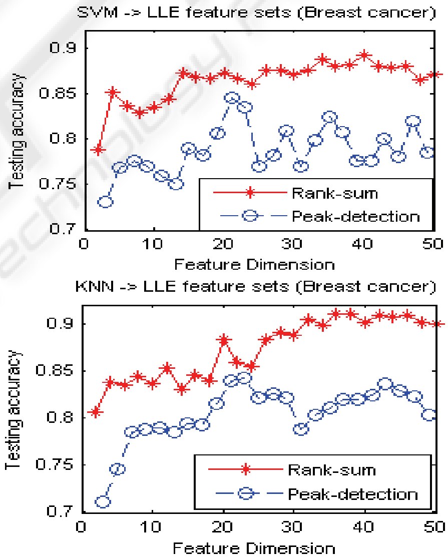


Figure 3: The testing results of the LLE reduce feature sets on peak-detection and rank sum test, breast cancer data.

5 CONCLUSIONS

In this paper, we compared a supervised distance metric learning, large margin nearest neighbor classifier and SVM for classification of mass spectrometry proteomics data. Experiments produced good results of applying distance metric learning to proteomics data, comparable to the results by applying SVM. Our results also indicate the potential of manifold learning in feature reduction. Further, our results also indicate that, peak detection may not be the optimal choice for pre-processing proteomics data.

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REFERENCES

Petricoin, E. and Liotta, L. (2003), Mass spectrometry-based diagnostic: the upcoming revolution in disease detection. *Clin. Chem*., 49, pp.533-534.

Williams, B., Cornett, S., Dawant, B., Crecelius, A., Bodenheimer, B. and Caprioli, R. (2005), An algorithm for baseline correction of MALDI mass spectra, *Proceedings of the 43rd annual Southeast regional conference*, March 18-20, 2005, Kennesaw, Georgia.

Chen, S., Hong, D. and Shyr, Y. (2007), Wavelet-based procedures for proteomic mass spectrometry data processing, *Computational Statistics & Data Analysis*, 2007, Vol. 52, issue 1, pp.211-220.

Li, L. *et al*. (2004), Applications of the GA/KNN method to SELDI proteomics data. *Bioinformatics*, 20, pp.1638-1640.

Petricoin, E. *et al*. (2002), Use of proteomics patterns in serum to identify ovarian cancer. *The Lancet*, 359, pp.572-577.

Coombes, K. *et al*. (2007), Pre-processing mass spectrometry data. In Dubitzky, M., et al. (eds.), *Fundamentals of Data Mining in Genomics and Proteomics*. Kluwer, Boston, pp.79-99.

Hilario, M. *et al*. (2006), Processing and classification of protein mass spectra. Mass Spectrom. *Rev*., 25:409-449.

Shin, H. and Markey, M. (2006), A machine learning perspective on the development of clinical decision support systems utilizing mass spectra of blood samples. *J. Biomed. Inform*. 39, pp.227-248.

Furey, T. *et al*. (2000), Support vector machine classification and validation of cancer tissue samples using microarray expression data. *Bioinformatics*, 16: 906-914.

Coombes, K. *et al.* (2005), Improved peak detection and quantification of mass spectrometry data acquired from surface-enhanced laser desorption and ionization by denoising spectra with the undecimated discrete wavelet transform, *Proteomics*, Volume 5, Issue 16.

Duan, K. and Rajapakse, J.C. (2004), SVM-RFE peak selection for cancer classification with mass spectrometry data. *APBC 2005*: pp.191-200.

Guyon, I., Weston, J., Barnhill, S. and Vapnik, V.N. (2002), Gene Selection for Cancer Classification using Support Vector Machines. *Machine Learning*. 2002 **46**(1-3): pp.389-422.

Vapnik,V.N. (1998), *Statistical Learning Theory*. John Wiley and Sons, New York.

Brown, M.P.S. et al. (2000), Knowledge-based analysis of microarray gene expression data by using support vector machines. *Pro. Nat Acad. Sci*., 97, pp.262-267.

Liu, Q., Sung, A.H., Chen, Z. and Xu, J. (2008), Feature Mining and Pattern Classification for Steganalysis of LSB Matching Steganography in Grayscale Images, *Pattern Recognition,* 41(1): pp.56-66.

Tenenbaum, J., Silva, V. de and Langford, J. C. (2000), A global geometric framework for nonlinear dimensionality reduction, *Science*, vol. 290, pp.2319-2323.

Saul, L. K. and Roweis, S. T. (2003), Think globally, fit locally: Unsupervised learning of low dimensional manifolds, *Journal of Machine Learning Research*, vol. 4, pp.119-155.

Belkin, M. and Niyogi, P. (2003), Laplacian eigenmaps for dimensionality reduction and data representation, *Neural Computation*, 15(6):1373-1396.

Xing, E., Ng, A., Jordan, M., and Russell, S. (2003), Distance metric learning with application to clustering with side-information, in *Proc. NIPS*, 2003.

Domeniconi, C. and Gunopulos, D. (2002), Adaptive nearest neighbor classification using support vector machines, *Proc. NIPS*, 2002.

Peng, J., Heisterkamp, D. and Dai, H. (2002), Adaptive kernel metric nearest neighbor classification, *Proc. International Conference on Pattern Recognition*, 2002.

Goldberger, J., Roweis, S., Hinton, G. and Salakhutdinov, R. (2005), Neighbourhood components analysis, in *Proc. NIPS*, 2005.

Zhang, Z., Kwok, J. and Yeung, D. (2003), Parametric distance metric learning with label information, in *Proc. International Joint Conference on Artificial Intelligence*, 2003.

Zhang, K., Tang, M. and Kwok, J. T. (2005), Applying neighborhood consistency for fast clustering and kernel density estimation. in *Proc. Computer Vision and Pattern Recognition*, 2005, pp. 1001-1007

Chopra, S., Hadsell, R. and. LeCun Y. (2005), Learning a Similarity Metric Discriminatively, with Application to Face Verification, *Proc. Computer Vision and Pattern Recognition,* 2005, Vol. 1, pp.539-546.

Weinberger, K., Blitzer, J. and Saul, L. (2006), Distance metric learning for large margin nearest neighbor classification, in *Proc. NIPS*, 2006, pp.1475-1482.

Pusztai et al. (2004), Pharmacoproteomic Analysis of Prechemotherapy and Postchemotherapy Plasma Samples from Patients Receiving Neoadjuvant or Adjuvant Chemotherapy for Breast Carcinoma, *Cancer* 100: pp.1814-1822.

Vandenberghe, L. and Boyd, S.P. (1996), Semidefinite programming, *SIAM Review*, 38(1): 49-95.

Roweis, S. T. and Lawrance, K. S. (2000), Nonlinear dimensionality reduction by locally linear embedding, in *Science*, vol. 290, 2000, pp.2323-2326.