Fractal Fingerprinting of Chromatographic Profiles Based on Wavelet Analysis and Its Application To Characterize the Quality Grade of Medicinal Herbs

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Extracting chemical fingerprints is an important step for representing and interpreting chromatographic data. In this paper, the chromatographic profile is decomposed into components at different resolution levels using wavelet analysis, then the fractal dimensions of these components are computed as the chemical fingerprints. The chromatographic fingerprint is characterized by the vector composed of these chemical fingerprints, which can represent the chemical patterns of different categories of complex samples. Computer simulations reveal that the fractal fingerprints are more stable than the original chromatographic profile data with respect to variations of peak retention time. To demonstrate the validity of this method, the evaluation of the quality of the medicinal herb *Angelica sinensis* (Oliv.) *diels* is investigated. Principal component analysis of the fractal fingerprints indicates that samples belonging to the same quality grade are clustered together, while those belonging to different quality grades are separated. Using these fractal fingerprints taken from the chromatographic scans as inputs for an artificial neural network (ANN). The quality grades of two sets of the herbs were verified by cross-validation, indicating that 96.7% of the herbs are correctly identified with respect to their quality grades evaluated by experienced experts, and 100.0% of the herbs are correctly identified with respect to their quality grades determined by pharmacodynamical evaluation.

INTRODUCTION

It is well-known that modern chromatographic instruments like gas chromatograph, high-performance liquid chromatograph, and CE (Capillary Electrophoresis) can produce fingerprints of compounds that are found in samples of highly complex compositions.[1] These chromatographic fingerprints represent powerful tools useful for comparison, classification, identification, and evaluation of samples. As such, they have been used in a wide range of applications, including the identification of pharmaceutical manufacturer,[2] forensic investigations,[3] pollutant recognition,[4] and the evaluation of food quality.[5]

Extracting chemical fingerprints is an important step for representing and interpreting chromatographic data. Currently, perhaps the most commonly adopted method is to collect particular chemical fingerprints (e.g., retention time, amount and character of the eluting components, the ratio of the eluting components) from specific peaks of interest in the chromatograms. However, these chemical fingerprints rely heavily on experimental variables such as the method of peak detection. They also depend on many human variables since the analyst must decide which peaks to select from the chromatograms for effective classification or identification. The peak retention time of chromatographic profiles always varies due to many interfering factors. These limitations impede fast, automated, and impartial analysis of the chromatographic fingerprints.

The second method, which avoids the shortcomings of the first method, is to extract chemical fingerprints that encode information about the entire chromatographic profile. In the present study, we adopt this approach by introducing fractal dimension to quantify the complexity of the detailed features present in a chromatogram. Since the complexity of a chromatogram is related to the number of its peaks, the fractal dimension is useful as an effective global fingerprint feature for the chromatographic profile. Information about the global features of a chromatographic profile is often not sufficient for the classification of medicinal herbs; therefore, wavelet analysis has been employed to extract more information from the chromatographic profile. With the use of wavelet analysis to resolve the chromatographic profile into many components, the fractal dimensions are readily computed from the components at different resolutions of the chromatographic profile. These fractal dimensions extract information from each of the various resolution scales of the wavelet and, therefore, constitute a new vector for representing the chromatographic fingerprint. In this way, a method of extracting chemical fingerprints from a chromatographic profile can be developed. Computer simulations reveal that the fractal fingerprints extracted by the proposed method are much more stable than the chromatographic profile data with respect to variations of peak retention time.

Medicinal herbs have attracted interest for their beneficial role especially in the treatment of mild, chronic diseases.[6] However, quality control remains a serious problem with respect to medicinal herbs. The quality of medicinal herbs is often evaluated by experienced experts or by pharmacodynamical determination. With the development of modern

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analytical instruments, instrumental analysis has become more prevalent as a means to evaluate the quality of medicinal herbs. The medicinal herbs typically are complex formulations composed of many individual chemical compounds whose identity is only partially known. Many factors will influence the quality grades of herbs, including species variation and environmental conditions, as well as the precise time of harvesting, storage, and processing. The chromatographic profile of a medicinal herb is often unique for a given quality grade; hence, chromatographic fingerprints represent a powerful tool for the evaluation of the quality of herbs. In this work, with use of two sets of samples of *Angelica sinensis* (Oliv.) *diels* (*A. sinensis*) of different quality grades which are respectively evaluated by experienced experts and pharmacodynamical determination, wavelet analysis and fractal dimension have been used to extract the chemical fingerprints from their chromatographic profiles. Results show that these chemical fingerprints are useful for the evaluation of the quality of *A. sinensis*.

METHODS

Computing the Fractal Dimension of a Chromatographic Profile. In general, fractal analysis is applied to problems of shape characterization as a means of measuring the complexity of spatial coverage. Fractal dimension is a useful index to quantify the complexity of feature details presented in a one-dimensional curve. The larger the fractal dimension, the more complex is the curve. A chromatographic profile is also a one-dimensional curve. The fractal dimension of a chromatographic profile would be small for a chromatogram with few peaks but larger for a chromatographic profile with greater complexity. Therefore, fractal dimension can be used as a quantitative index that reflects the amount of chemical information contained in the chromatographic fingerprint.

There are many methods for computing the fractal dimension, such as the Hausdorff dimension, information dimension, and box-counting dimension. Here, the widely used box-counting dimension[7] has been adopted.

Assume that $F = \{f_n\}$ is the data array of a one-dimensional curve, where $n \in Z$ and $f_n \in R$. Consider a square net that is composed of k grids, such as

$$[m_1k,(m_1 + 1)k] \times ... \times [m_nk, (m_n + 1)k] \qquad (1)$$

where $k \in N$, m_1, m_2, ..., $m_n \in Z$. Assume that N_k is the number of grids that the curve crosses in the square net. A series of data pairs (k, N_k), obtained by assigning different k values, could be used for regression in the following manner:

$$\log_2 N_k = d \log_2 k + b \qquad (2)$$

where d is the box-counting dimension.

Multiresolution Analysis of the Wavelet. In the preceding section, it was shown how to compute the fractal dimension of a one-dimensional curve. However, the fractal dimension of a chromatographic profile alone is often not sufficient for characterizing medicinal herbs. The extracted fractal fingerprints could represent the chromatographic profile more completely by combining fractal dimensions with multiresolution analysis of wavelets.

A multiresolution analysis provides a simple hierarchical framework for interpreting the chromatographic profile. At each resolution, the details of a chromatographic profile generally characterize different structures of the profile. At a coarse resolution, these details correspond to the larger structures that provide the profile "outline". It is therefore natural to analyze first the profile details at a coarse resolution and then gradually increase the resolution. Such a "coarse to fine" strategy is very similar to the process by which experts recognized objects; thus, it also proves useful for extracting the fingerprints from a chromatographic profile.

Wavelet analysis, sometimes called the "mathematical microscope", is a powerful tool for the multiresolution analysis. Mallat[8] has proposed a pyramidal algorithm that could be used for multiresolution decomposition of one-dimensional curves with wavelet bases. Assuming $F = \{f_n\}$ is the data array of a one-dimensional curve, we could select the current resolution level as 2^0 and the curve could be represented as $A_{2^0}f$ since the interval between data points is small. After one transformation, $A_{2^0}f$ can be decomposed into the detail component $D_{2^{-1}}f$ and approximation component $A_{2^{-1}}f$ in wavelet space. Then, both $D_{2^{-1}}f$ and $A_{2^{-1}}f$ can be reconstructed to the original spatial dimension by applying Mallat's algorithm. For example, the curve F at a resolution 2^0 could be decomposed as follows:

$$F = D_{2^{-1}} + A_{2^{-1}} \qquad (3)$$

where $D_{2^{-1}}$ and $A_{2^{-1}}$ are, respectively, the detailed and approximation components of the original curve at a resolution 2^{-1}. Similarly, the approximation component $A_{2^{-1}}$ can be decomposed and thereafter reconstructed from the decomposed results. After n times of processing, the original curve would be decomposed into a series of components at discrete resolutions that vary from coarse to fine. The decomposition of the original curve could be expressed as follows:

$$F = A_{2^{-n}} + D_{2^{-n}} + D_{2^{-n+1}} + ... + D_{2^{-1}} \qquad (4)$$

where $D_{2^{-i}}$ ($i = 1, 2, ..., n$) is the detailed component of the original curve at a resolution 2^{-i}, and $A_{2^{-n}}$ is the approximation component at a resolution 2^{-n}.

The fractal fingerprints can be extracted from the components at different resolutions of the chromatographic profile using wavelet analysis and fractal dimension, thus forming a vector to represent the one-dimensional curve. The process for extracting the fractal fingerprints from the chromatographic profiles of a superior quality sample and a qualified sample is illustrated in Figures 1−3. Starting from the original chromatographic profile (Figure 1a), the profile is decomposed five times with Daubechies wavelet ($N = 3$). The components in wavelet space are reconstructed, and five detailed components at different resolutions together with an approximation component at the coarsest resolution are obtained. Finally, the fractal dimensions of all six components of the profile are computed. The approximation component at the coarsest resolution 2^{-5} (Figure 1b) depicts a coarse outline of the chromatographic profile. Figure 1c shows the detail component at a resolution of 2^{-5}. The detail component at the lowest resolution provides more information about the larger peaks. Figure 1d shows the detail component at a resolution of 2^{-1}. Information about smaller peaks can be extracted from the components at the relatively

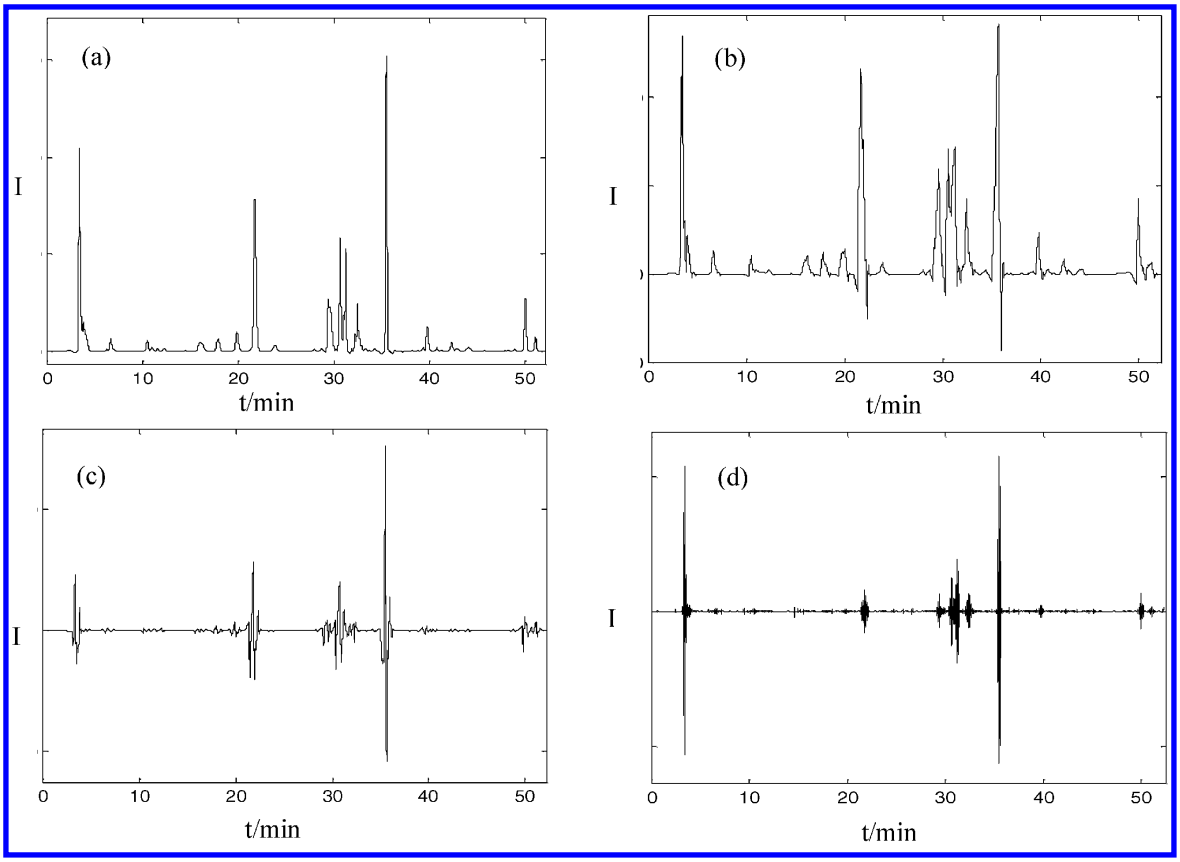

Figure 1. Plots of components of the chromatographic profile of a superior quality sample obtained by multiresolution analysis of wavelet: (a) original chromatographic profile; (b) the approximation component at the coarsest resolution 2^{-5}; (c) the detail component at a resolution 2^{-5}; (d) the detail component at a resolution 2^{-1}.

higher resolution levels. According to eq 2, the fractal dimensions are then calculated from the components of different resolutions of the chromatographic profile. The fractal dimensions at various resolutions can be used as fingerprints since they describe the chromatographic profile at different levels of detail. The vector of these fractal fingerprints can be used to represent the chromatographic profile. The vector is a six-dimensional vector, in which variable 1 represents the fractal dimension of the approximation component of the coarsest resolution 2^{-5}, and variables 2−6 represent the fractal dimensions of the detailed components of the resolutions from 2^{-5} to 2^{-1}, respectively. The vectors of fractal dimensions of a superior quality sample and a qualified sample are shown by the radar graph in Figure 3.

EXPERIMENTAL SECTION

Solvents and Materials. All the organic solvents used are of HPLC grade. Pure water is prepared with ultrapure water (Milli-Q, Millipore, Bedford, MA).

In this experiment, the root of *A. sinensis* was selected as the medicinal herbal materials. These medicinal herbal materials were collected from their native habitats. The quality of medicinal herbs is usually evaluated by experienced experts or by pharmacodynamical determination. The former relies on the experience of the herbal practitioner, who classifies the herbs into superior quality or qualified ones according to their habitats, morphological characters, anatomical observation, and so on. The latter usually classifies the grades of herbs according to the pharmacological effects related to their therapeutic function. One set of 32 samples was separated into the superior class (16 samples) and the qualified class (16 samples) according to the evaluation of experienced experts. Another set of 34 samples was separated into the superior class (19 samples) and the qualified class (15 samples) according to their inhibitory effect on platelet aggregation in rat models. Hereafter these sets are respectively called the "experienced set" and the "pharmacodynamical" set.

Apparatus. The chromatograms were obtained using an Agilent 1100 series modulus, and the system for liquid chromatography consisted of a quatpump, an autosampler, a degasser, a column oven, and a model HP 1100 photodiode-array detector (Agilent USA). The column was C_{18} VP-ODS (150 mm × 4.6 mm i.d.; Shimadzu, Japan) with 5 μm spherical particles. The eluents were as follows: eluent A was water; eluent B was methanol using a gradient as shown in Table 1. The sample injection volume was 20 μL, and the flow rate was 0.5 mL/min. Chromatographic runs were conducted at ambient temperature. The HP1100 photodiode array detector is set at 254 nm.

Sample Preparation. A 1 g sample of dried and pulverized plant material was refluxed with 30 mL of water for 30 min twice. After cooling, the solution was filtered through a glass filter covered with filter paper. The supernatant liquid was washed with 50 mL of water. The solution was evaporated under vacuum to about 40 mL and then diluted to 50 mL with water in a volumetric flask. The solution was filtered through a 0.45 μm membrane filter. A 20 μL sample of this solution was injected into the HPLC system.

Data Analysis. The chromatographic profile was digitized and stored in data files using the Hewlett-Packard Chem-

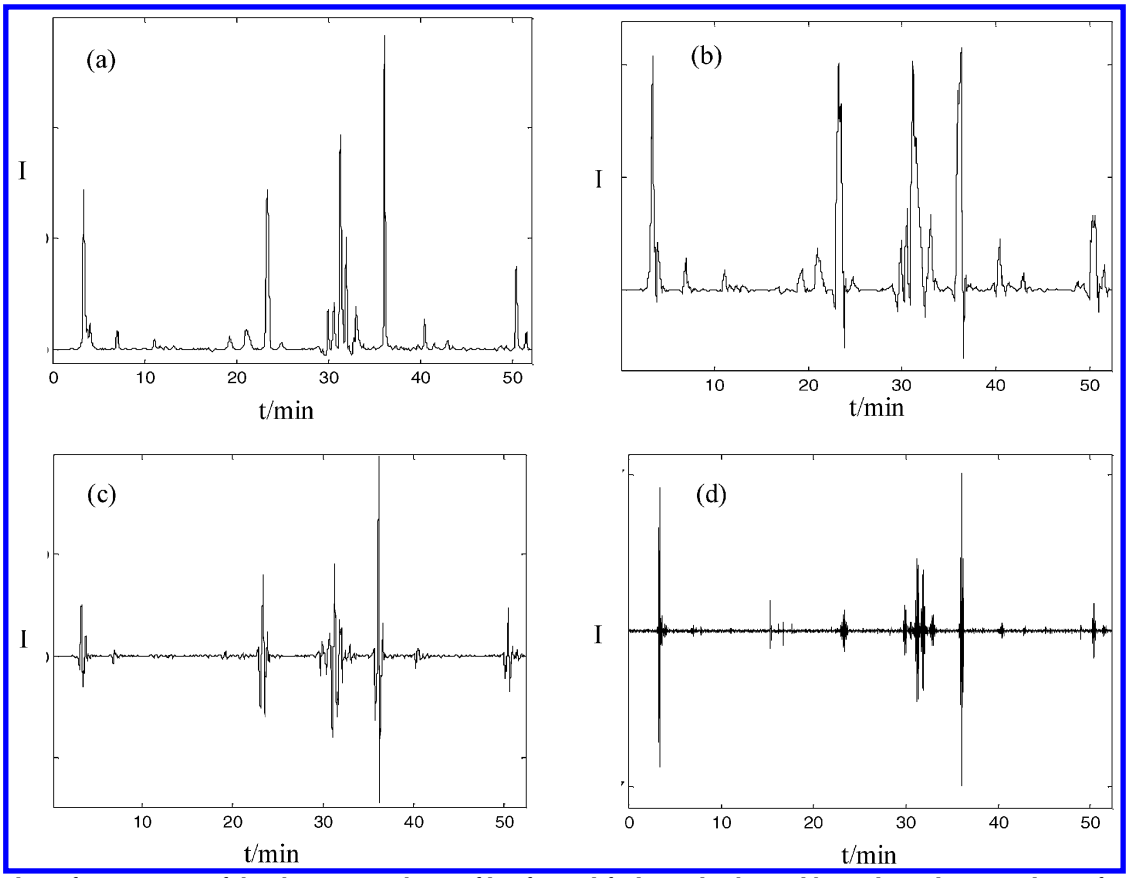

Figure 2. Plots of components of the chromatographic profile of a qualified sample obtained by multiresolution analysis of wavelet. The components are the same as those in Figure 1.

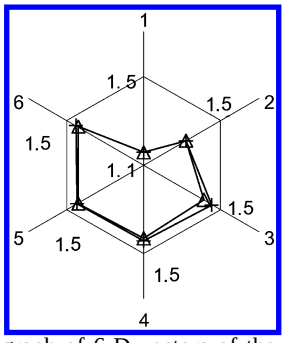

Figure 3. Radar graph of 6-D vectors of the fractal dimensions calculated from the components of Figures 1 and 2 for a superior quality sample and a qualified sample (△, superior quality sample; +, qualified sample).

Table 1. Summary of the Mobile-Phase Gradient

time (min)	solvent A (%)	solvent B (%)
0	100	0
20	94	6
60	10	90
70	0	100

station software. The data were then translated into the Matlab workspace using a computer program written by us.

First, the data were normalized; i.e., each data entry of a sample was divided by the maximum peak height in the chromatographic profile. Then, the fractal fingerprints were extracted from the data by wavelet analysis and fractal dimension. If, for example, it is assumed that 6 fractal fingerprints are extracted, each chromatographic profile would be represented as a six-dimensional data vector $\mathbf{x} = [x_1,x_2,x_3,x_4,x_5,x_6]$. Here, two data matrices composed of 6 columns/7 columns (fractal fingerprints) and 32 rows/34 rows (chromatograms) were collected for evaluation of the medicinal herbs. Principal component analysis (PCA) was used as a visualization technique to observe the clustering of the samples belonging to different quality grades. Two supervised pattern recognition methods, specifically linear discriminant analysis (LDA) and an artificial neural network (ANN), were used to classify the quality grades of the medicinal herbs. LDA was performed using the SPSS computer package (SPSS Inc.), and the others were programmed by us in Matlab code (V5.3) (Mathworks, Natick, MA).

RESULTS AND DISCUSSION

Investigation of the Influence of Variations in Peak Retention Time on the Fractal Fingerprints. While HPLC is extremely useful for fingerprinting medicinal herbs, it is not a panacea. HPLC profiles are always subject to concerns about reproducibility due to many interfering factors, in particular the variation in peak retention time. Obviously, the variation will make a great impact on the method that compares the chromatographic fingerprints with the chromatographic profile data, while its impact on the fractal fingerprints is questionable. Here, an index has been proposed as follows:

$$\sigma = \frac{\sqrt{\sum_{i=1}^{n}(x'_i - x_i)^2}}{\sqrt{\sum_{i=1}^{n}x_i^2}} \qquad (5)$$

Table 2. Influence of the Variation in Peak Retention Time on the Results Obtained with Different Features

	for given feature	
	extracted fractal fingerprints	chromatographic profile data
no. of shifting data points		
0	0	0
10	0.0146	0.4262
20	0.0123	0.7733
40	0.0130	1.1519
60	0.0120	1.2798
80	0.0097	1.3223
100	0.0096	1.3511

where $\mathbf{x} = [x_1,x_2,...,x_n]$ is the data vector which is composed of the chromatographic profile data or the extracted fractal fingerprints and $\mathbf{x} = [x'_1,x'_2,...,x'_n]$ is a similar data vector in which the chromatographic profile is distorted by variations in peak retention time. The index σ can be used to measure the impact of the variations in peak retention time on the method using the chromatographic profile data or the fractal fingerprints. A small σ value indicates that the method is robust.

As an example, one of the chromatograms was chosen to simulate the variation of peak retention by shifting 0, 10, 20, 40, 60, 80, and 100 data points, respectively. Its impact on the method using the chromatographic profile data or the fractal fingerprints was measured with eq 5, and the results are shown in Table 2. Obviously, the variation of peak retention has little impact on the method using the fractal fingerprints extracted by the wavelet and fractal dimension. Although the degree of variation of peak retention rises with each increment in the number of shifting data points, the index σ increases only slightly. However, the variation of peak retention makes a much greater impact on the method using the chromatographic profile data. When only 10 data points shift, the index $\sigma = 0.4264$ and continues to increase dramatically with each increment in the number of shifting data points. When the number of shifting data points is 100, $\sigma = 1.3511$ for the method using chromatographic profile data but only $\sigma = 0.0096$ for the method using the fractal fingerprints. It can be concluded that the fractal fingerprints are more robust with respect to variations of peak retention time and, therefore, more suitable for representing the chromatographic fingerprints.

Optimization of the Wavelet Basis and Resolution Level. For the multiresolution analysis of wavelet, the information obtained from the decomposed chromatogram varies with the choice of wavelet basis and resolution level. It is necessary to select the appropriate wavelet basis and resolution to optimize the performance of the fingerprints. Assume that the original sample set consists of N patterns, the number of pattern classes is C, and the number of patterns belonging to the ith class is n_i. Then the discriminating performance of the fingerprints vector $\mathbf{d}$ can be measured by

$$\xi = \frac{1}{N}\sum_{j=1}^{C}\sum_{k=1}^{n_j} NN(\mathbf{d}_k^j)/n_j \qquad (6)$$

where $\mathbf{d}_k^j$ is the kth samples in class j. $NN(\mathbf{d}_k^j)$ denotes the number of the nearest neighbors with the same class label as the sample point $\mathbf{d}_k^j$ in question. In other words, among the n_j samples having the nearest distance calculated with the vector $\mathbf{d}_k^j$, $NN(\mathbf{d}_k^j)/n_j$ is defined as the percent belonging to class j. The performance of the fingerprints vector is regarded as optimal when $\xi = 1$ and poor when $\xi = 0$.

Table 3. Optimization of Wavelet Basis and Resolution Level

wavelet basis	for given resolution level						
	2^{-1}	2^{-2}	2^{-3}	2^{-4}	2^{-5}	2^{-6}	2^{-7}
Db2	0.1120	0.1209	0.1232	0.1314	0.1366	0.1440	0.1405
Db3	0.1122	0.1203	0.1261	0.1410	0.1478	0.1434	0.1440
Db4	0.1139	0.1266	0.1359	0.1427	0.1383	0.1295	0.1319
Db5	0.1035	0.1145	0.1209	0.1332	0.1376	0.1434	0.1354
Db6	0.1064	0.1128	0.1197	0.1291	0.1355	0.1390	0.1407
Db7	0.1075	0.1139	0.1209	0.1249	0.1413	0.1395	0.1364
Db8	0.1087	0.1185	0.1151	0.1255	0.1344	0.1395	0.1353
Db9	0.1058	0.1122	0.1180	0.1214	0.1332	0.1407	0.1336
Db10	0.1052	0.1181	0.1268	0.1319	0.1347	0.1385	0.1359

The Daubechies wavelet basis and the resolution level are optimized for the data matrix of the experience set using eq 6. The optimization results, shown in Table 3, reveal that the discriminating performance of the fractal fingerprints improves up to a certain resolution level and then recedes monotonically. At the same time, the wavelet basis at lower rank seems to give better performance. According to the results shown in Table 3, Daubechies ($N = 3$) wavelet basis and resolution level 2^{-5} were selected as optimal for wavelet decomposition and extraction of fractal fingerprints. Daubechies ($N = 2$) wavelet basis and resolution level 2^{-6} were also selected for the data matrix of the pharmacodynamical set in the same way.

Principal Component Analysis. Principal component analysis was carried out to study the structure of the data set of fractal fingerprints and the distribution of samples belonging to different quality grades. The score plots of PC1 versus PC2 (Figure 4) of the two samples sets reveal that together these two principal components explain over 95% of the total variance of the data matrix. Each chromatogram is represented as a point in the score plots. In the two score plots, all chromatograms belonging to the same quality grade gather into a distinct cluster, while those belonging to different quality grades are separated. This result is significant in that it indicates that the medicinal herbs can be differentiated as to their quality grade on the basis of the fractal fingerprints. Inspection of the score plots revealed that the samples of the pharmacodynamical set give a slightly better separation than those of the experience set.

Evaluation of the Quality Grade of the Medicinal Herbs Using the Fractal Fingerprints. The performance of chromatographic fingerprinting was measured by its ability to evaluate the quality of the medicinal herbs. After extracting the fractal fingerprints, a pattern recognition method is used for classifying the quality grades of the medicinal herbs. LDA and ANN were employed for this purpose. Since the four samples marked by arrows are located far from their corresponding main clusters in the PCA plot (one in Figure 4a and three in Figure 4b), they are considered outliers and will not be used in the training or test sets. To reduce the effect of collinearity and to improve classification performance, PCA is used for preprocessing, and two principal components are used as the input variables for the LDA and ANN. The architectures of the ANN were 2−1−2 for the

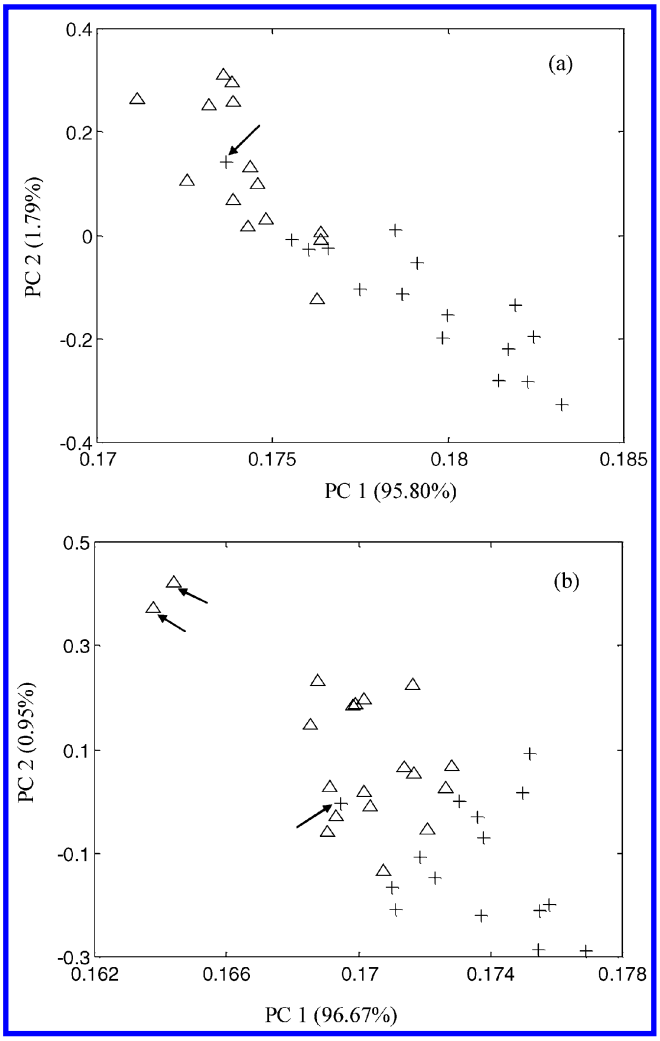

Figure 4. Plots of principal components (PCs) of the extracted fractal fingerprints. Each chromatogram is represented as a point in the map: (a) the experience set; (b) the pharmacodynamical set (△, superior quality sample; +, qualified sample). The values in parentheses represent the percent of the total variance. The samples marked by arrows are considered outliers here.

experienced set and the pharmacodynamical set. The Levenberg−Marquardt method taken from the neural network toolbox in Matlab has been used to train the neural networks.

The data matrix of fractal fingerprints obtained from 31 chromatograms of the experienced set was partitioned into 16 groups, and 15 groups are composed of the data obtained from two chromatograms for different classes. To simulate a realistic identification process, one group of data was selected as the test set. The other 15 groups of data were used to train the pattern recognition methods. The quality grade of the medicinal herbs in the test set was then predicted by the trained pattern recognition method and compared with the actual (true) quality grade. All 16 groups of data were tested in sequence using the same procedure. The data matrix of the pharmacodynamical set was also processed in a similar way.

The percent correct identification of the quality grades of these medicinal herbs using LDA and ANN with fractal fingerprints was >90% in all cases, meaning that the fractal fingerprints perform well in characterizing these chromatographic fingerprints (Table 4). More of the samples of the pharmacodynamical set were correctly identified than those

Table 4. Summary of Results Using Different Classifiers and Two Principal Components Obtained from the Extracted Fractal Fingerprints

		quality grade			
	classifier	superior	qualified	total	% correct
experienced set	LDA	14/16	14/15	28/31	90.3
	ANN	15/16	15/15	30/31	96.7
pharmacodynamical set	LDA	15/17	14/14	29/31	93.6
	ANN	17/17	14/14	31/31	100.0

of the experienced set, indicating that the fractal fingerprints extracted by wavelet and fractal dimension may be better in characterizing the quality grades of the medicinal herbs determined by pharmacodynamical evaluation.

A comparison of ANN and LDA results reveals that the two classifiers provide highly accurate classifications. The total number of misclassifications of the experienced set was one for ANN compared with three for LDA, and that of the pharmacodynamical set was zero for ANN compared with two for LDA.

CONCLUDING REMARKS

In this investigation, we have demonstrated that wavelet analysis and fractal dimension provide a fast and efficient method for extracting the chemical fingerprints from chromatographic profiles suitable for the classification of the quality grade of the medicinal herbs. Simulated experiments indicate that the extracted fractal fingerprints are much more stable than the chromatographic profile data with variation in the peak retention time. The proper selection of wavelet basis and decomposition resolution is an important consideration in this method, and in this report an index (σ) has been proposed for the optimal selection. Two classifiers, LDA and ANN, were used to classify the quality grades of the medicinal herbs. Cross-validation indicates that both classifiers show satisfactory classification performance (samples of correct identifications > 90%).

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