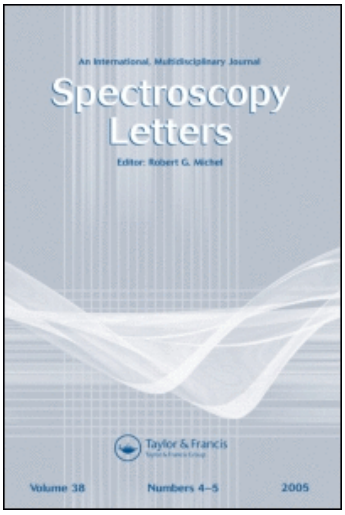

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

Application of Artificial Neural Network Multivariate Calibration to Near-Infrared Spectrophotometry Determination of Powdered Pharmaceutical Metronidazole

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To cite this Article Ren, Yulin , Gou, Yuhui , Ren, Ruixue , Liu, Peiyi and Guo, Yie(1999) 'Application of Artificial Neural Network Multivariate Calibration to Near-Infrared Spectrophotometry Determination of Powdered Pharmaceutical Metronidazole', Spectroscopy Letters, 32: 3, 431 — 442
To link to this Article: DOI: 10.1080/00387019909349996
URL: http://dx.doi.org/10.1080/00387019909349996

SPECTROSCOPY LETTERS, 32(3), 431-442 (1999)

APPLICATION OF ARTIFICIAL NEURAL NETWORK MULTIVARIATE CALIBRATION TO NEAR-INFRARED SPECTROPHOTOMETRIC DETERMINATION OF POWDERED PHARMACEUTICAL METRONIDAZOLE

Key words: artificial neural network(ANN), Near infrared spectrophotometry, diffuse reflectance, the degree of approximation, overfitting, nondestructive, metronidazole powder

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ABSTRACT

The application of artificial neural networks for pharmaceutical quantitative analysis is described. Real data sets from near-infrared reflectance spectra of Metronidazole powdered pharmaceuticals were used to build an artificial neural network to predict unknown samples. A new network evaluation criterion, termed the degree of approximation, was employed. The overfitting was discussed. Owing to the beneficial nonlinear multivariate calibration nature of ANN, the predicted results were reliable and precise.

INTRODUCTION

In the pharmaceutical industry, the quality of pharmaceuticals is becoming more rigid due to government regulations and clinical standards. The qualitative classification and quantitative analysis of pharmaceuticals in production and sale procedures are required especially for nondestructive identification and analysis[1]. The application of near-infrared (NIR) spectrophotometry in analysis of pharmaceuticals of various solid dosage forms is a significant advance, because it requires little or no sample treatment. The practical application of NIR is based on computer techniques and chemometric methods to a large extent. In most cases, the use of chemometric methods is necessary because of numerous overlapped absorption bands exiting within the NIR spectral region[2-6].

Due to strong interfering effects between pharmaceutical components, the concentrations are not proportional to their relative signals. Therefore a non-linear mode is required. It is well known that linear calibration techniques like PAR and PLS have the capability to model nonlinear response by including extra principal components or latent variables in the calibration model, however, high levels of noise in residual principal components or latent variables can render this approach ineffective[7]. Artificial neural networks exhibit good non-linear calibration nature, and they also are robust in respect to small variances in the data, such as noise. A neural network can speed up the calibration process due to its parallel structure[8]. In recent years, artificial neural networks have been applied to analytical chemistry by many chemists[9-13]. Back propagation (BP) is an ANN algorithm most widely used in chemometric practice[14-16].

In this paper, a back propagation network was used. A sigmoid function was chosen as the nonlinear transfer function. A new evaluation criterion was employed[1].

The definition of this criterion is given by Equations 1 and 2.

$$e_a=(n_1/n)e_1+(n_c/n)e_c+|e_1-e_c| \quad (1)$$

where e_a is the error of the approximation: e_1 e_c are the mean relative errors of

training set and control set; n_t, n_c are the numbers of training set and control set; n is the whole number of known samples; n_t/n, n_c/n are the weights contributed to the error of approximation (e_a) by training set and control set. Note that

$$D_a=c/e_a \qquad (2)$$

where D_a is the degree of approximation, and c is a constant number through which D_a is adjusted for optimization. It is very obvious that if the smaller e_a is or the bigger D_a is, the more the models of ANN approach the real nature of the data. Therefore, the effects of both training set and control set are considered in this evaluation criterion.

EXPERIMENTAL

A Shimadzu® UV-3100 spectrophotometer with an ISR-3100 integrating sphere was used for the near-IR diffuse reflectance spectra measurement. Data were transferred to a microcomputer through a RS-232C interface. A Pentinium-based microcomputer was used for data processing and computation.

Thirty-six Metronidazole powder samples were prepared according to the prescription. The Metronidazolum, starch, and Mg stearate (steras) powder were conformable to the pharmacopoeia. The entrance slit of the near-IR spectrophotometer used was 12 nm and the scan wavelength range was from 1100 to 2500 nm. Two repeated spectral scans were made for each sample and all the spectra used were the average of the two repeats. The extended delta-bar delta back-propagation training routines contained in Neural Works Explorer software package were used.

RESULTS AND DISCUSSION

The conventional near-IR reflectance spectra of pure Metronidazidum, Mg stearate and starch are shown in FIG. 1. Serious overlaps of the absorption bands can be seen from the FIG.1.

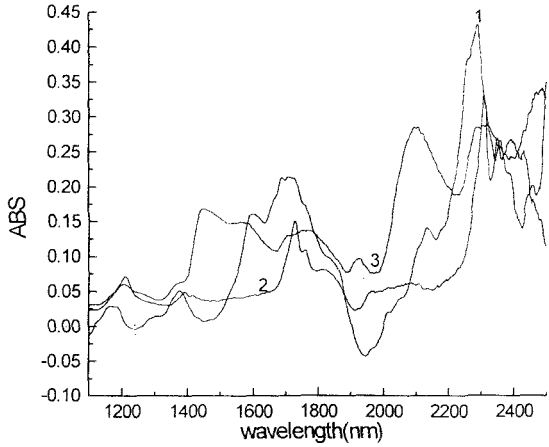

FIG 1. NIR reflectance spectra
1.pure metronidazolum 2.pure starch 3. pure Mg stearas

The Choice of Control Set

The thirty-six known samples were divided into two groups: the training set and the control set. It is very import to choose the control set samples properly. First, the number of samples in the control set should be sufficient to ensure its supervisory duties. Second, the samples of control set should be distributed evenly among the training set in order to control the whole training set[17]. TABLE 1 shows the statistical data of components and the contents of the control set and training set.

The Network Design

1. Input and output data

The input layer can be considered as an interface between the external world and the network. It contains all the information entered into the network. The output layer produces the output result of the neural network.

The spectral data were directly entered into the network. The wavelength interval was changed in order to sieve the data. FIG. 2 shows the effect of the

TABLE 1. Component Contents of Metronidazole (%,g/g)

	Metromidazolum			Starch			Mg Stearate		
	max.	min.	mean	max.	min.	mean	max.	min.	mean
Training set(27)	78.97	60.49	69.63	32.71	19.29	29.22	1.74	0.74	1.14
Control set (9)	78.26	62.43	69.34	32.01	27.14	29.62	1.41	0.92	1.04

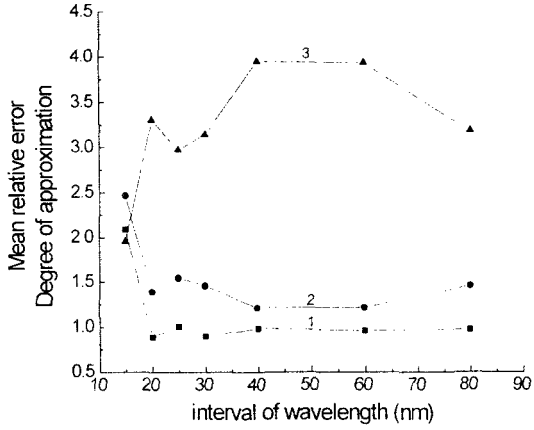

FIG 2. The effect of interval of wavelength on network
1. Mean relative error of training set;
2. Mean relative error of control set;
3. The degree of approximation.

different number of input neurons. The wavelength interval was changed as 15, 20, 25, 30, 40, 60, 80 nm, correspondingly, the numbers of input neuron were 81, 61, 49, 41, 31, 21, 16, respectively. When the interval of wavelength was 40 nm, the input layer contains thirty-one neurons, and the network has the highest D_a. When the input neurons used are reduced, some information will be lost. When the input neurons are increased, the result is not acceptable because of the limited operational ability of network and the computations required.

Because there is only one kind of active component in the samples, the output layer contains one neuron to predict the concentration of metronidazolum.

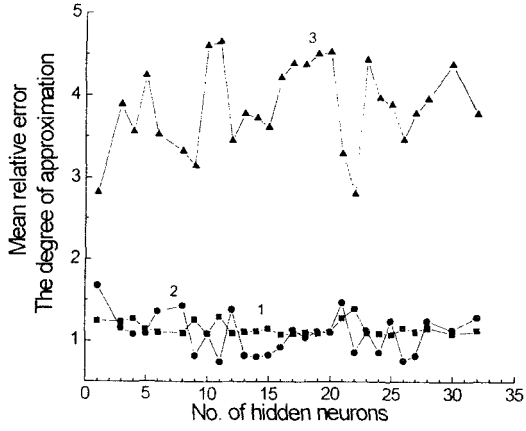

FIG 3. The effect of hidden neurons on network
1. Mean relative error of training set
2. Mean relative error of control set
3. The degree of approximation

2. The hidden layer neurons

The number of hidden layer neurons has great effect to the predicted result. The more the number of hidden layer neuron used, the more non-linear degree of fitting the network has. However, the prediction ability will decline due to overfitting, as the because the complexity of the network exceeds that of the samples[18]. The effect of hidden neurons is shown in FIG. 3.

The Effect of Momentum and Learning Rate

Momentum α and learning rate η affect the convergence and the result of the network. Too high η and α lead to network instablility[19]. FIG. 4(a) and (b) show the optimization of the learning rate and the momentum. In FIG.4(b) the convergence and stability of the training set were measured as the root-mean-square(RMS) error at the output layer as follows:

$$\mathrm{RMS}=\sqrt{\frac{1}{N}\sum_{i=1}^{N}(Y_i^t - Y_i^p)^2}$$

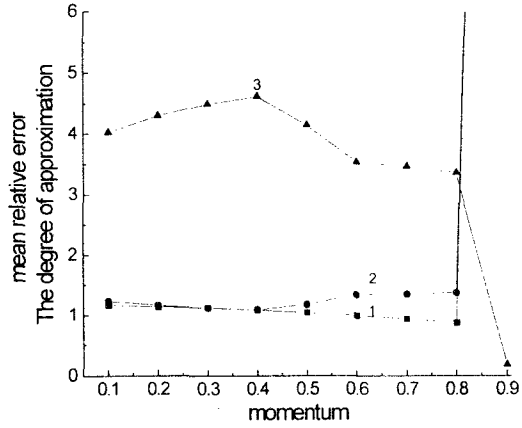

FIG 4.(a) The effect of momument on network

1.Mean realtive error of training set
2.Mean relative error of control set
3.The degree of approximation

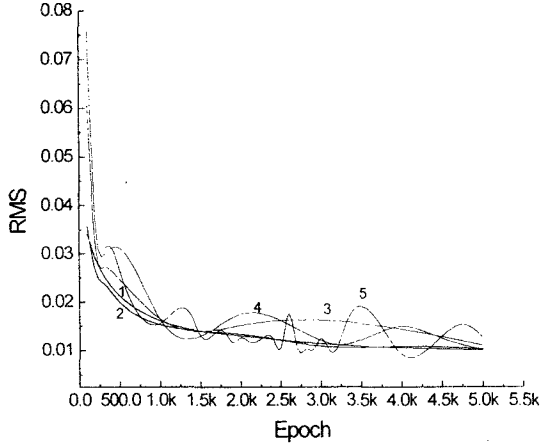

FIG 4.(b) The convergence situations under different learning rates

Leaning rate: 1. 0.1; 2. 0.3; 3. 0.5; 4. 0.7; 5. 0.9

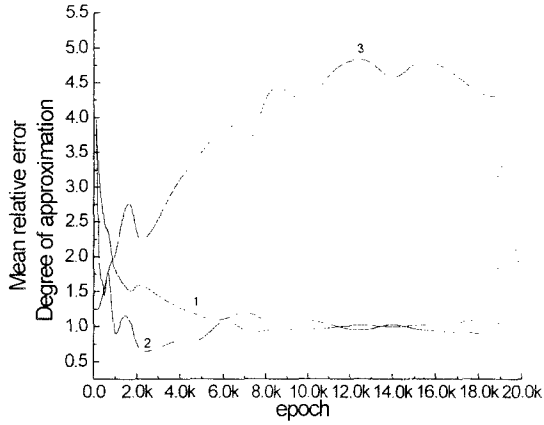

FIG 5. The effect of epoch on network
1. Mean relative error of training set;
2. Mean relative error of control set;
3. The degree of approximation

where Y_i is the actual output at neuron i; and YP_i is desired output at neuron i. When the learning rate was more than 0.3, the unstability of the network increased.

Epoch and Overfitting

The training time is also called the epoch. It is very clear in FIG. 5 that the error of the training set declines with epoch, while the error of the control set is increased after a certain epoch, which indicates the existence of overfitting. The curve of the degree of approximation displays this rule very well.

Evaluation of the Analytical Accuracy of the Calibration Model

An optimized network model was built through which the concentrations of metronidazolum in the samples was predicted. The relationship of the predicted and real concentrations of the training set and control set is shown in FIG. 6. All samples are close to the diagonal line. The statistical data are displayed in TABLE 2.

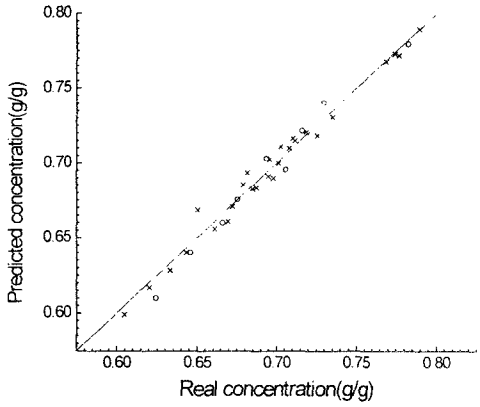

FIG 6. Relation of concentration
× training set ○ control set

TABLE 2. The Statistical Result of Predicted Metronidazolum in Metronidazole Powder Samples

	The relationship curve of real concentration to predicted concentration			RMS (%)
	Intercept	Slope	Correlation Coefficient	
training set	-0.0005	1.0004	0.9907	0.652
control set	0.0061	1.0860	0.9896	0.801

TABLE 3. Results of unknown samples obtained by ANN

NO	real value of samples (%,g/g)	value obtained by ANN (%,g/g)	relative error (%)	NO	real value of samples (%,g/g)	value obtained by ANN (%,g/g)	relative error (%)
1.	71.34	70.79	-0.76	5.	72.45	71.98	-0.65
2.	70.43	69.55	-1.23	6.	68.67	69.45	1.14
3.	69.15	70.06	1.31	7.	66.37	66.79	0.63
4.	67.64	67.00	0.95	8.	64.58	65.32	1.15

To verify the reliably of the network model further, eight more metronidazole powder drugs were prepared. The concentrations of metronidazolum in the samples are predicted by this BP model. The result is displayed in TABLE 3.

CONCLUSION

ANN is a valuable technique for non-linear calibration modeling. This technique is very good for use with near-infrared diffuse reflectance spectra of powders. NIR combined with ANN can be used to nondestructively analyze pharmaceuticals fast and reliably.

ACKNOWLEDGMENT

The authors are grateful to Li Mei, Sun Ying, Hui Chun (Senior Medical Training School ,Changchun, China) for their generous donation of samples.

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Date Received: August 17, 1998
Date Accepted: March 1, 1999