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A Comparison of CNN and PLSR for Glucose Monitoring Using Mid-Infrared Absorption Spectroscopy

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Abstract

With the development of mid-infrared (MIR) photoelectric devices, mid-infrared spectroscopy has become one of the important methods for non-invasive detection of blood glucose. The mid-infrared region (4000 - 400 cm^{-1}) has the well-known fingerprint region (1200 - 800 cm^{-1}) of glucose, which has clearer characteristic absorption peaks and better specificity. There is a lot of molecular information about glucose in the MIR. The non-invasive detection of blood glucose by mid-infrared spectroscopy needs to achieve certain accuracy, and the quantitative model is an important factor affecting the accuracy of glucose detection. In this paper, the samples of imitation solution containing only glucose and the samples of imitation mixed solution are taken as the research objects, and the mid-infrared spectral data of the samples are collected. The full spectrum partial least squares Regression (PLSR) model, SNV + Ctr-PLSR model, MSC + Ctr-PLSR model, and convolutional neural networks (CNN) model of 3000 - 900 cm^{-1} band were constructed. Full spectrum PLS model and CNN model of 1200 - 900 cm^{-1} band were constructed. The experimental results show that the optimal model of the two bands is CNN, then the correlation coefficient of prediction set (Rp) of 3000 - 900 cm^{-1} band is 0.95, and the root mean square error of pre-diction set (RMSEP) value is 22.10. The Rp of 1200 - 900 cm^{-1} band is 0.95, and the RMSEP value is 22.54. The research results show that CNN is a promising method, which has higher accuracy than PLSR, and is especially suitable for modeling human complex environment. In addition, the study provides a theoretical and practical basis for CNN in feature selection and model interpretation.

Keywords

Mid-Infrared, Convolutional Neural Networks (CNN), Partial Least Square Regression (PLSR), Glucose

1. Introduction

Normal people's blood glucose concentration ranges from 70 to 110 mg/dL. Under normal condition, human blood glucose concentration is relatively stable, only slightly increasing after eating, and then returning to normal. Sugar metabolism disorders can cause hypoglycemia or hyperglycemia, and severe cases can lead to diabetes. Diabetes can bring a variety of complications. At present, there is no complete cure for diabetes [1]. It can only be controlled by constantly monitoring the blood sugar levels of diabetics and adjusting their diet and intake of related drugs. Accordingly, the detection of blood glucose has important guiding significance for the prevention and diagnosis of diseases [2].

Traditional blood glucose measurement is done by dripping blood, which increases the risk of infection and the pain of patient. Recently, continuous glucose monitoring (CGM) devices appeared in the market, although it provides a continuous detection method. It uses an enzyme sugar sensor that needs to be replaced regularly, and it needs to detect glucose in the interstitial fluid [3] [4]. Both of these measurements are intrusive. Optical methods provided a great solution, because it has the advantages of high sensitivity, noninvasive, etc. At present, the Non-invasive measure of glucose is generally studied in the near-infrared (NIR) region, but the absorption of glucose in the near-infrared region is weak and the scattering is high, so the prediction accuracy is always low [5]. The mid-infrared (MIR) region (4000 - 400 cm^{-1}) has the well-known fingerprint region (1200 - 800 cm^{-1}) of glucose [6], which has clearer characteristic absorption peaks and better specificity than NIR, and its basic molecular vibration is the most useful. There is a lot of molecular information about glucose in the MIR.

In recent years, some progress has been made in the study of glucose based on the MIR spectroscopy. The measurement of blood glucose based on three wavenumbers using multiple linear regression (MLR) model was developed by Kasahara R *et al.* in 2018 [7]. In order to compare the prediction accuracy of glucose in two fiber-coupled measurement setups based on attenuated total reflection spectroscopy and direct transmission spectroscopy, partial least squares regression (PLSR) model was used for glucose prediction by Jernelv I L *et al.*, and both of the root-mean-square error of cross-validation (RMSECV) of less than 20 mg/dL [8]. Traditionally, chemometrics has been used to process spectral data, such as MLR, principal component analysis (PCA), PLSR, and so on. However, In the MLR model, the variables participating in the regression cannot exceed the number of samples in the training set, and there is a problem of collinearity in the spectral matrix, which makes it impossible to solve the inverse matrix. Although both the PCA and the PLSR models solve the problem of collinearity, the absorption band of the interfering substance overlaps the absorption band of glucose in the mixed solution, which makes it more difficult to predict grapes and cannot solve the nonlinear problem. These difficulties can be sloved by Artificial Neural Networks (ANN). For example, Miguel Sanchez-Brito *et al.* used ANN to estimate the glucose value in saliva correctly [9]. However, the tradi-

tional ANN is a fully connected neural network, which makes the network learn too many weight parameters, resulting in slow training and over-fitting. Therefore, it is necessary to establish a new quantitative analysis model. Convolutional neural network (CNN) provides a better solution, and it has the characteristics of local conjunctions, shared weights, and translation invariance, etc [10]. It has been widely used in processing image recognition [11], speech detection, etc [12]. At the same time, it was reviewed that advances in one-dimensional spectral data analysis, for example, Qianqian Li *et al.* used the CNN model combined with MIR spectrum to analyze the corn syrup adulteration in acacia honey, and proposed that the convolution kernel could amplify signals in important spectral interval [13]. Xu Yan *et al.* used CNN combined with online Raman spectroscopy to monitoring of Cornu Caprae Hircus (GH) hydrolysis, and proposed that the convolutional kernel has a function similar to spectral pretreatment [14]. These examples provide a good direction. But how to make the combination of CNN and MIR predict glucose in mixed solution requires further study.

In views of the above, this paper reports the quantitative analysis of glucose in pure solution and mixed solution in the MIR. The accuracy of their predictions for glucose of CNN was compared to PLSR model. The selecting features automatically of CNN become an example of modeling under nonlinear factors.

2. Materials and Methods

2.1. Experimental Setup

The study was conducted at Wuhan (China) using FTIR spectrometer (Brucker IN-VENIO-R, Germany) with liquid nitrogen cooled-mercury cadmium telluride (LN-MCT) detector and attenuated total reflection (ATR) equipment. Data acquisition was done with an dual channel 24-bit dynamic range analog-to-digital converter card (ADC), Each sample is detected in the range of 4000 cm^{-1} to 800 cm^{-1} with a resolution of 4 cm^{-1} by 16 scans, After each measurement, the ATR is cleaned with distilled water and dried with mirror paper, the output of spectrometer is obtained by calculating the absorbance (A = –lgT(v)), Where T(v) is the light transmittance at wavenumber (v) after absorption by the sample. Finally, OPUS software (Brucker, Germany) was used for exporting spectral data.

2.2. Sample Overview

20% Fat Emulsion Injection diluted (C14-24, FRESENIUS KABI SSPC, Jiang su, China) to 10% was used as the background solution, which was used to simulate the human environment and maintain a constant pH. 32 samples with only glucose in 10% Fat Emulsion Injection were prepared with a concentration range of 40 - 280 mg/dL and interval of 10 mg/dL, which was used to test the stability of system.

The mixed solution consists of different concentrations of glucose, albumin, lactate, urea, cholesterol and fructose, the concentration ranges of which are shown in Table 1. We aim at exploring whether the presence of interferers affects glucose prediction, the 64 mixed solution samples were prepared using DOE algorithm, in order to maintain the robustness of the experiment when using fewer experimental samples.

2.3. Data Analysis Methods

2.3.1. PLSR and CNN

PLSR is a common multiple linear regression model. Preprocessing is needed before PLSR modeling to reduce the impact of noise on the model, and the preprocessing used in this paper includes multiplicative signal correction (MSC), standard normal variate (SNV), scaling (SCA), normalization, centering (Ctr), first derivative, second derivative, moving window average smoothing (MWA) and Savitzky-Golay smoothing (SG).

The CNN model is a feed forward neural network. The structure of CNN used in the article is shown in Figure 1 and the algorithm can be divided into the following three steps: Initialize parameters, Forward propagation and Loss function and back propagation. Forward propagation means that information spreads in a single direction in CNN without any feedback. This paper uses 8 layers of network structure, including the input layer, convolution layer, nonlinear layer, BN layer, pooling layer, dropout layer, FC layer and output layer. The input layer and the output layer respectively refer to the input of 1D spectral data and the output of predicted concentration. In order to speed up the training speed of the network, the spectral data and the corresponding concentration are respectively standardized before inputting them. This paper sets the number of convolution kernels number, the size of convolution kernels, the step size and the filling method to 20, 15, 1, and same Padding, respectively. But putting the BN layer behind the ReLU layer has a better effect [15], so this paper uses the same method. This paper sets the pooling size, the step size and the Filling method to 2, 1, and Same Padding, respectively. Loss function is used to measure the accuracy of the network. The back propagation algorithm calculates the gradient of each weight by taking the chain derivative of the loss function, and then updates the weight. The number of training is set as 1200 in this paper. This function is realized by creating an Adam optimize. The learning rate is an important hyper parameter, and it is 0.001 in this paper.

2.3.2. Evaluation Method

In the paper, the leave one out cross validation (LOOCV), the correlation coefficient of training set (Rc), the correlation coefficient of prediction set (Rp), the root mean square error of training set (RMSEC), the root mean square error of prediction set (RMSEP), and the Root Mean Square Error of cross validation (RMSECV) were used to evaluate the results. The CNN model was built in python 3.7, Tensor Flow 2.1.0 and keras 2.3.1.

Table 1. The concentration ranges of the mixed solution.

Composition of the mixed solution	Concentration range
Glucose	40 - 280 mg/dL
Albumin	2000 - 4000 mg/dL
Urea	10 - 75 mg/dL
Lactate	10 - 75 mg/dL
Fructose	10 - 75 mg/dL
cholesterol	40 - 280 mg/dL

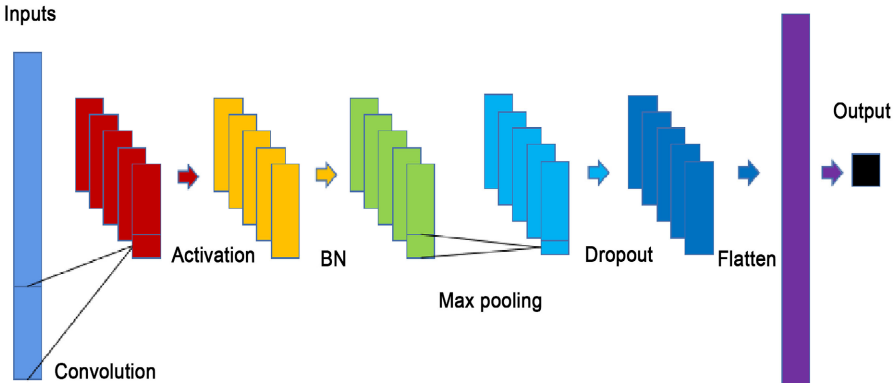

Figure 1. The structure of CNN model.

3. Results and Discussion

3.1. Spectrum of Pure Solution

After the two samples with concentrations of 100 mg/dL and 320 mg/dL were lost duing to technical errors, the spectra of 30 glucose samples were shown in Figure 2. There is a lot of machine noise below 900 wave number and too much water noise above 3000 wave number. These noises are needed to be manually removed. Figure 3 shows four examples of noise removal, and other than that without any spectral pretreatment. The main chemical bond absorption is as follows: the stretching vibration of C-O is about in the range of 1200 - 900 cm^{-1}, the stretching vibration of C-H is about in the range of 3000 - 2800 cm^{-1}.

Figure 4 shows the prediction results of glucose in the pure solution using PLSR and LOOCV. The PLSR model uses 14 LVs with RMSECV and R values of 24.70 and 0.94, respectively. From the results, it can be concluded that there is a strong correlation between glucose concentration and absorbance, and it is easy to predict glucose in the pure solution.

3.2. Spectrum of the Mixed Solution

The absorbance spectra of the 64 samples in the mixed solution are shown in Figure 5, which have a large amount of machine noise and water noise just like

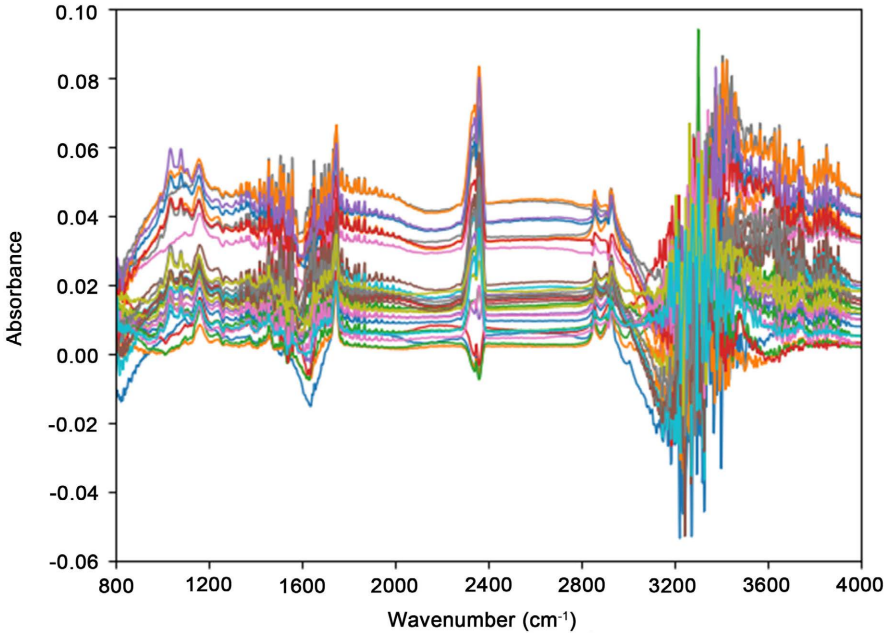

Figure 2. Absorbance spectra of different glucose concentrations.

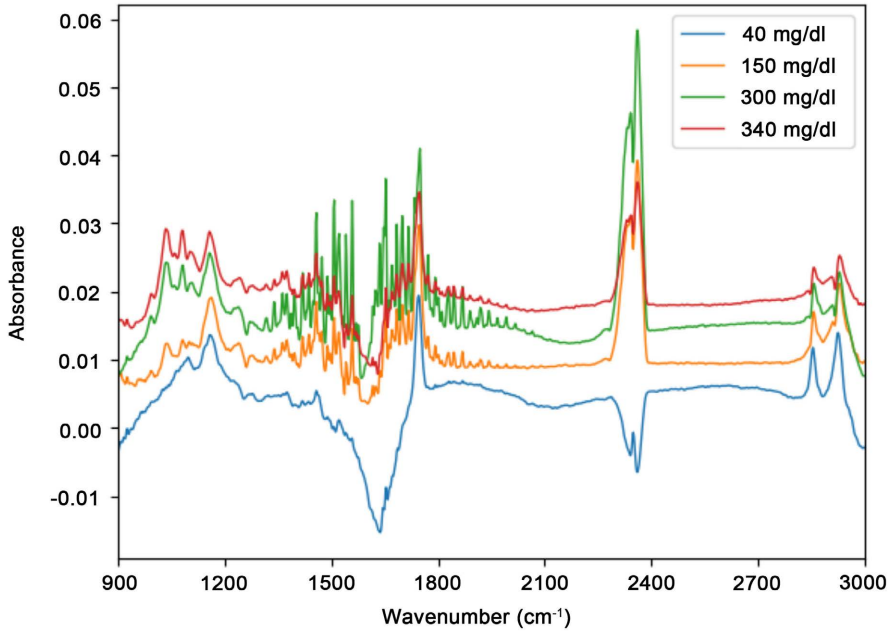

Figure 3. Absorbance spectra of four pure glucose solutions after removing machine noise and water noise.

pure glucose. The same treatment is applied to these samples, and the remaining spectra after removing the noise are shown in **Figure 6**.

During the configuration of the mixed solution, duing to the addition of too many substances, personal operationl or machine errors can interfere with the actual concentration of glucose. In the analysis of infrared Spectroscopy, there is a certain correlation between the absorbance spectra and the chemical value of the measured object. The existence of abnormal samples weakens the correlation

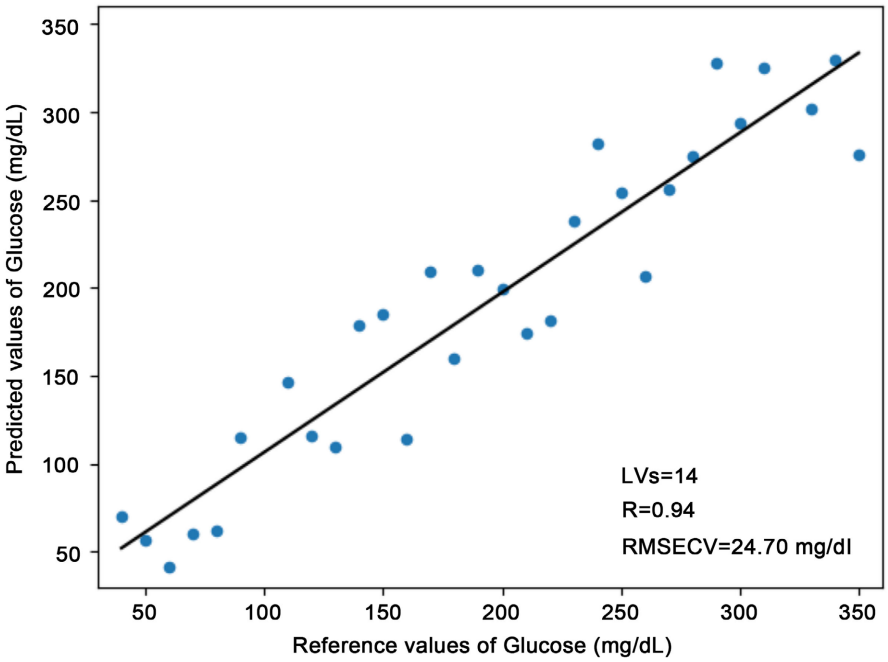

Figure 4. Glucose in the pure solutions was predicted using PLSR model and LOOCV.

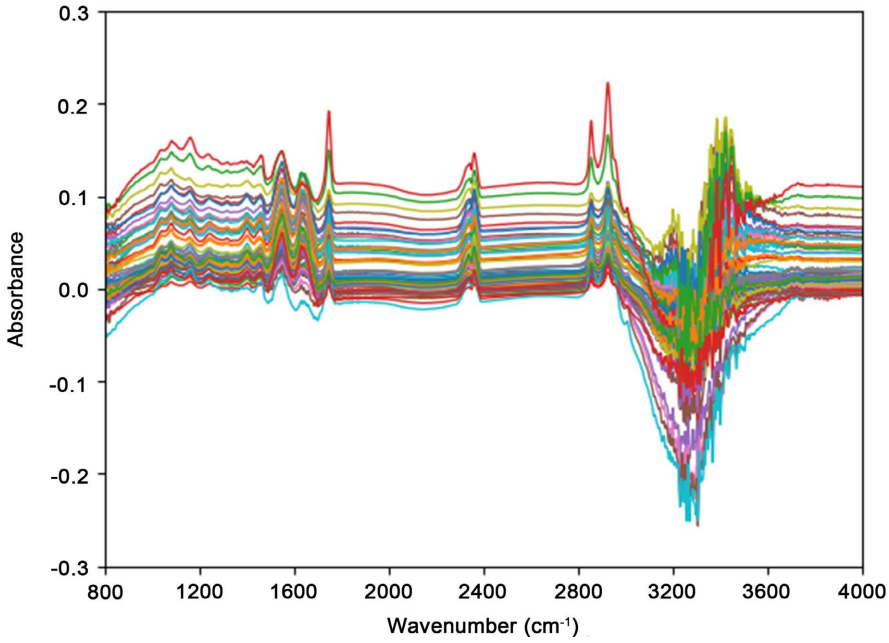

Figure 5. Absorbance spectra of mixed solutions with different concentrations.

between the two, thus affecting the performance of the algorithm. Therefore, Principal Component Analysis-Mahalanobis Distance (PCA-MD) was used to eliminate abnormal samples, in which PCA extracted 1 principal component number and played a role in dimensionality reduction of data. The result is shown in Figure 7, where the red circle represents abnormal samples 49, 53 and 54 were eliminated; the corresponding glucose concentrations were 260 mg/dL, 260 mg/dL and 280 mg/dL, respectively.

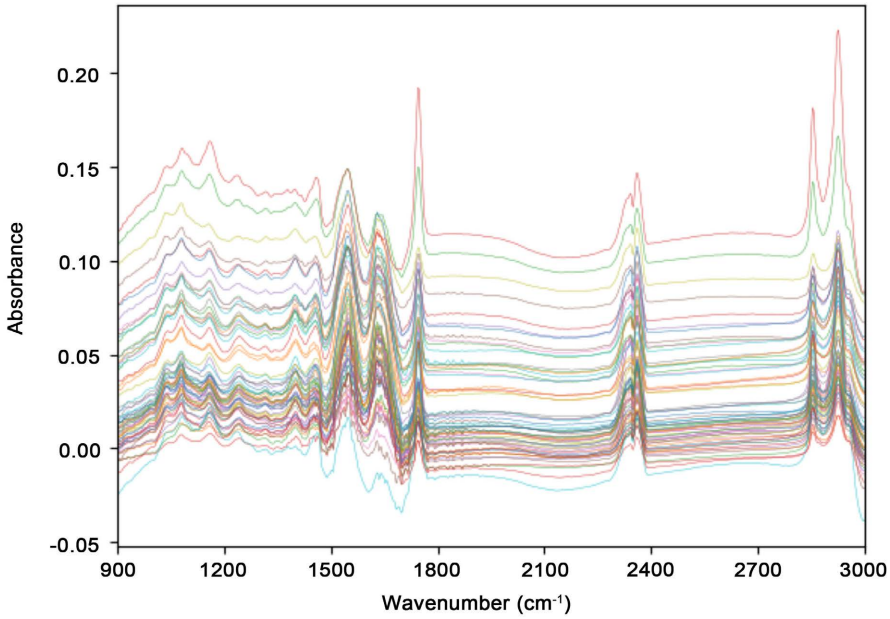

Figure 6. Absorbance spectrum of mixed solution after removing machine noise and water noise.

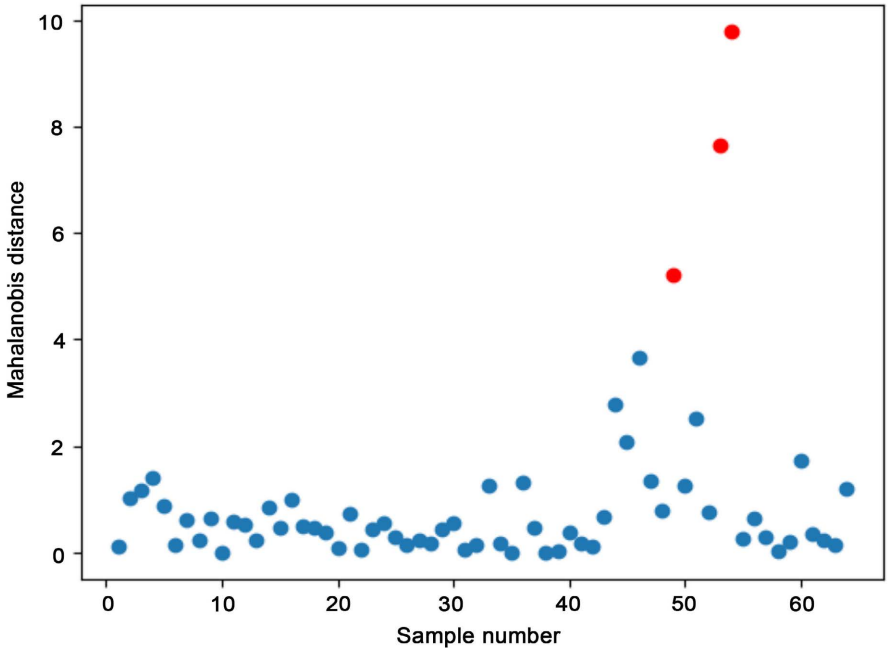

Figure 7. Abnormal samples were removed by PCA-MD.

Figure 8 shows the prediction results of glucose in mixed solution using PLSR and LOOCV. The PLSR model uses 14 LVs with RMSECV and R values of 27.82 and 0.89, respectively. Compared with the results in Figure 4, it is much more difficult to predict glucose in mixed solutions.

Then the Kennard-Stone (KS) algorithm was used to divide the remaining 61 samples, of which 40 were used for the training set and 21 were used for the prediction set.

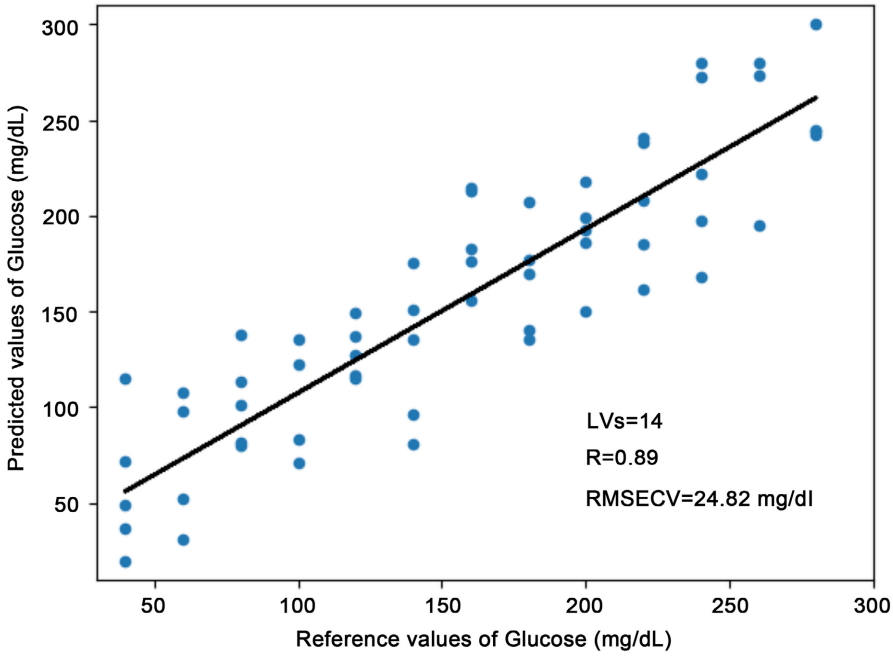

Figure 8. Glucose in the mixed solution was predicted using PLSR model and LOOCV.

The prediction results of mixed solution using PLSR and the CNN models in the wavenumber range 3000 to 900 cm^{-1} are illustrated in Table 2. Among them, the pretreatments used in this paper include single pretreatments or the combination of two different pretreatments. And only the better predicted results after preprocessing were listed in the table. The best result was the combination of MSC + Center, then the PLSR model extracted 11 LVs, and the RMSEP and R of the prediction set are 27.17 mg/dL and 0.92, respectively. For CNN, the model parameters of CNN are model1 in Table 4, the RMSEP and R of the prediction set are 22.10 mg/dL and 0.95, respectively. The result shows that in this wave-number region, PLS needs to be combined with many pretreatments to achieve a better modeling effect. Compared with PLS, the nonlinear nature of CNN makes it have better prediction ability.

Many studies have found that there is a fingerprint region of glucose in the mid-infrared [16] [17], and there are obvious characteristic absorption peaks in the wave-number range from 1200 to 900 cm^{-1}. In order to explore their correlation, this wave number range is used as a way of wavelength selection to build the model.

The results are shown in Table 3. For the PLSR model, the results of PLSR model without pretreatment were the best, then PLSR model extracted 6 LVs, and the RMSEP and R of the prediction set were 30.94 mg/dL and 0.90, respectively. For the CNN model, the model parameters of CNN are model 2 in Table 4, the RMSEP and R of prediction set are 22.54 mg/dL and 0.95, respectively. The result shows that, compared with the previous selected wavenumber range, the prediction result of the PLSR model without pretreatment is better, indicating that the region is highly correlated with glucose absorption, and excessive

Table 2. In the 3000 to 900 wavenumber range, PLSR and CNN were used to predict the glucose in the mixed solution.

Methods	Wavenumber range	Pretreatment	Rc	RMSEC	RMSEP	Rp	LVs
PLSR	3000 - 900	None	0.92	28.78	38.47	0.84	10
PLSR	3000 - 900	SNV + Ctr	0.95	23.20	32.00	0.89	11
PLSR	3000 - 900	MSC + Ctr	0.95	23.17	27.17	0.92	11
CNN	3000 - 900	standardization	0.98	14.10	22.10	0.95	-

Table 3. In the 1200 to 900 wavenumber range, PLSR and CNN were used to predict the glucose in the mixed solution.

Methods	Wavenumber range	Pretreatment	Rc	RMSEC	RMSEP	Rp	LVs
PLSR	1200 - 900	None	0.92	30.05	30.94	0.90	6
CNN	1200 - 900	standardization	0.97	17.28	22.54	0.95	-

Table 4. Optimized hyperparameters for each CNN model.

CNN model	Wavenumber range	Regularizer	Rate
Model1	3000 - 900	L1 (a = 0.4)	P = 0.5
Model2	1200 - 900	L1 (a = 0.01)	P = 0.1

pretreatments may cause the loss of important spectral information. At the same time, it can be found that CNN only changes the regularizer and rate hyperparameters, which can get the prediction result similar to the wavenumber range from 3000 to 900 cm^{-1}. It indicates that increasing regularization and discarding rate can automatically reduce the interference of noise, and reducing regularization and discarding rate can reduce the loss of spectral information.

The Clarke error grid Analysis was used to evaluate the accuracy of glucose prediction, where regions A and B are clinically accepted [18] [19]. **Figure 9** shows the results of different models of Clarke error grid. In the two selected wavenumber region, the PLSR and CNN models both reported that the prediction result of a sample with a concentration of 60 mg/dL was in region D, indicating that the sample deviated greatly from the fitting model and was regarded as an abnormal sample. Although the predictions of the PLSR and the CNN models are in regions A, B and D, the number of the CNN predictions in region A is significantly more than in the PLSR model.

4. Conclusion

This article uses PLSR and CNN to quantitatively analyze glucose in imitation solution. The Rp of the PLSR model is lower than that of the CNN model, and the RMSEP value of the PLSR model is higher than that of the CNN model, no matter which band and what pretreatment methods were used. In addition, the PLSR model of two bands without any pretreatment, the Rp of 1200 - 900 cm^{-1}

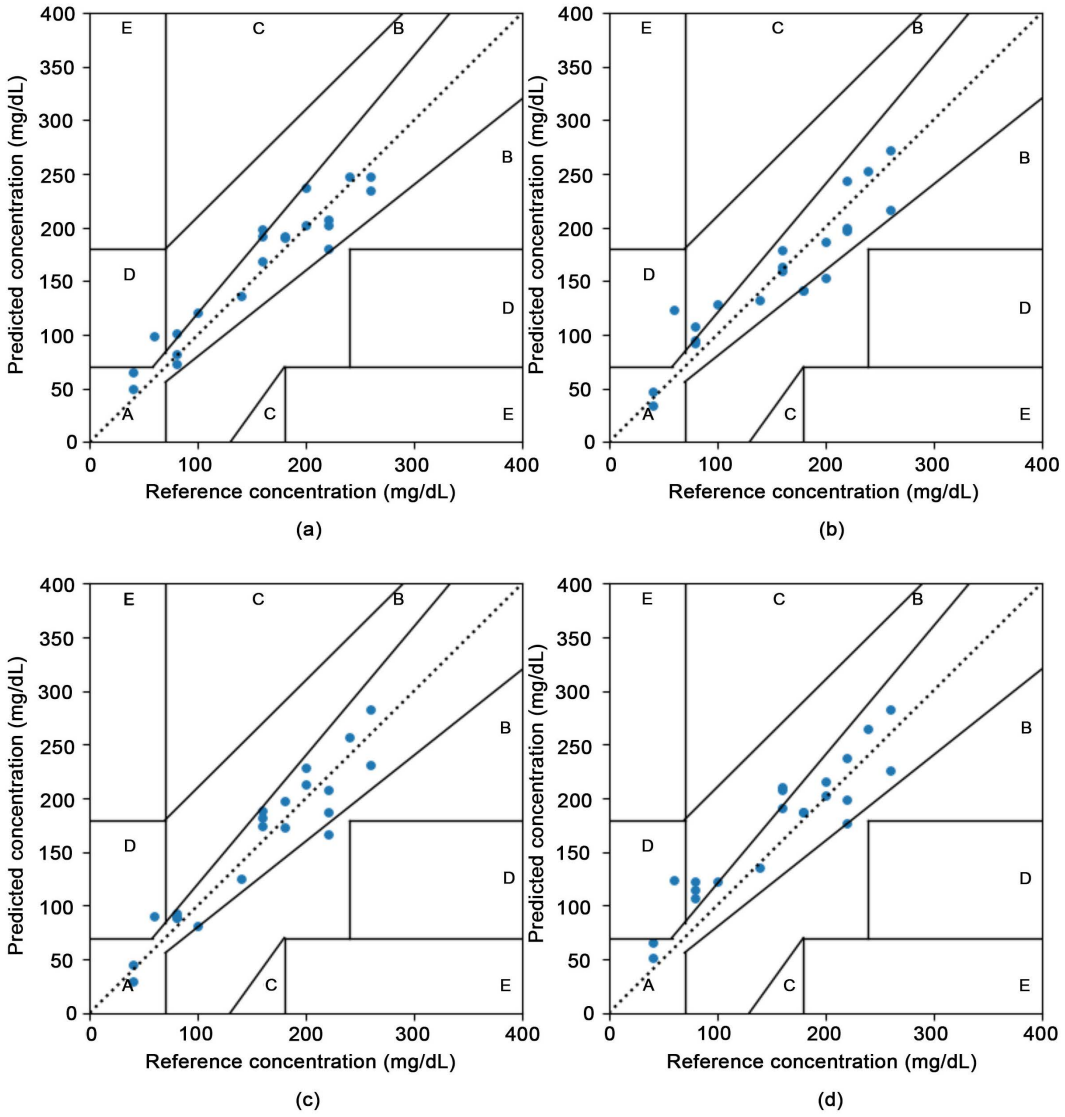

Figure 9. The Clarke error grid analysis plots for PLS model and CNN model was used in different wave-length ranges: In the 3000 to 900 wavenumber range: (a) CNN (Model 1); (b) PLSR (MSC + Ctr), In the 1200 to 900 wavenumber range: (c) CNN (Model 2); (d) PLSR (none).

band is 0.9 which is higher than 0.84 of 3000 - 900 cm^{-1} band. The RMSEP value of 1200 - 900 cm^{-1} band is 30.94 which is less than 38.47 of 3000 - 900 cm^{-1} band. It indicates that 3000 - 900 cm^{-1} band will introduce more noise, and more bands and spectral data will not help improve accuracy. However, the detection accuracy of CNN model in two bands is almost the same, indicating that CNN model has better adaptability. With the nonlinearity and generalization capabilities of CNN, it is suitable for processing spectral data under multiple interferences. In the future, our goal is to study how interferences affect glucose prediction and obtain more spectral data to validate our model.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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