

Low glucose concentration estimation based on reaction with 4,4'-biphenyl boronic acid using deep learning

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Abstract. Minimally invasive blood glucose level estimation with Raman spectroscopy is an important research field and attracts great attention. However, glucose concentration in blood is low and is difficult to be accurately measured. In this paper, we creatively proposed applying the 4,4'-biphenyl boronic acid to react with different concentrations of glucose to obtain the complex—(C₃₆H₄₀O₁₈B₄)_n. We performed a regression of the Raman spectral data of (C₃₆H₄₀O₁₈B₄)_n and the glucose solution separately to compare their estimation results. We applied a deep learning network, ResNet, and compared it with regression models of conventional machine learning, uniformly using ten-fold cross-validation. The experimental results show that the generated (C₃₆H₄₀O₁₈B₄)_n can effectively improve the estimation performance of glucose. The results showed, the ResNet model does not require explicit feature extraction and can achieve fast and accurate estimation. Its performance is significantly better than the traditional linear analysis method, and the R square can reach 0.93. The method in the article can effectively improve the estimation effect of low-concentration glucose.

keyword: Raman; ResNet; Specific binding; Glucose estimation.

1. Introduction

With the improvement of living standards and economic conditions, health issues have become the focus of increasing attention. As an indispensable medical index for clinical diagnosis, the human blood glucose level reflected the health of the body in a certain period. Therefore, blood glucose detection have crucial guiding significance in daily life for improving the regularity of life, exercise and eating habits, and drug rationalization. Taking the high-incidence chronic disease diabetes in clinical diseases as an example, blood glucose estimation was the essential part of its prevention, diagnosis, and treatment. The results can help assess the degree of glucose metabolism disorders in the living organism to further formulate a reasonable treatment plan, maintain the stability of blood sugar levels and the health of the subject.

Traditional blood glucose measurement methods required daily collection of patients' blood, which can easily cause inconvenience such as patient discomfort, infection, environmental pollution, and resistance in achieving continuous multiple measurements. Therefore, the development of non-invasive blood glucose measurement technology have great research significance and practical value, and most scholars have carried out extensive research many times.

As a result of the energy change of incident photons in Raman scattering come from the inelastic collision between photons and internal molecules of the substance, the scattered light contains rich molecular vibration information. The Raman spectrum characteristics of different molecules were distinct to be used as a "fingerprint" spectrum for molecular recognition [1,2]. Raman spectroscopy have the advantage of high resolution, good reproducibility, simplicity, and high sensitivity. The Raman scattering method was particularly suitable for the study of solution systems, especially the

study of biological samples and inorganic substances. Furthermore, quantitative detection of specific components of the organism can be accomplished using the Raman spectrum, which have clear, sharp, and non-overlapping peaks, and the peak intensity was positively correlated with the concentration of the active ingredient of the measured material, especially when the tested substance was a single component. Based on the characteristics and advantages of the above technology, the use of Raman spectroscopy for non-invasive blood glucose detection have become a research hotspot in recent years.

However, the use of Raman spectroscopy technology for blood glucose measurement also have difficulties: the Raman scattered light signal of the measured substance is weak and easily affected by fluorescence and stray light, resulting in the collected Raman spectroscopy signal may contain a lot of noise Information, which will adversely affect the further analysis of Raman spectroscopy data. Especially when the glucose concentration is low, the Raman signal of glucose will be overwhelmed by other signals from unrelated substances or noise signals from dark current, read noise, and random noise. In addition, since the blood glucose concentration of the human body is constantly changing, it was difficult for most existing equipment to measure glucose level accurately. Although the Raman signal of blood sugar is weak, it was worth noting that the glucose molecules in blood sugar will react specifically with other substance components. As a product of the body's automatic binding, Glycated hemoglobin is already the standard for monitoring patients' blood glucose status [3]. Under suitable conditions, the Raman spectroscopy signal of a specific substance can be measured indirectly (usually in this case, it is many times stronger than the blood glucose signal), and by further establishing an accurate chemometric model, it was possible to accurately measure the blood glucose concentration. It provided an alternative way for non-invasive blood glucose detection, for which many scholars have launched related research. Researchers developed a glucose molecular sensor for continuous glucose monitoring (CGM) based on the reaction of glucose and boric acid [4], A glucose-responsive fluorescent monomer (GF-monomer) with boric acid and anthracene moiety that served as the particular glucose-recognition and fluorogenic sites, respectively. Anthracene's fluorescence was muted by a photo-induced electron transfer (PET) in the absence of glucose molecules. PET was inhibited when glucose molecules were bound to boric acid, and the fluorescence of anthracene increased as a result of a strong interaction between nitrogen and boron atoms. Furthermore, the boric acid molecule have a higher glucose selectivity than other sugars. To generate glucose-responsive fluorescent microbeads, GF-monomer was immobilized in polyacrylamide hydrogel (GF-beads). The investigation discovered that the fluorescence intensity of GF-beads implanted under the skin of mice ears might detect changes in blood glucose content throughout the body. Heo Y J et al. [5] developed a long-term in vivo glucose monitoring approach based on fluorescence hydrogel fibres, in which glucose-responsive fluorescence hydrogels were created in the fibrous structure, allowing the sensor to remain at the implantation site for an extended period of time. What's more, when compared to polyacrylamide (PAM) hydrogel fibres, the PEG-bonded (PAM) hydrogel fibres reduced inflammation transdermal luminescence, and continued to transmit in response to the concentration for up to 140 days. Wu X et al. [6] discovered that the direction and relative position of the hydroxyl group determine the binding strength of boric acid and sugar, allowing boric acid to distinguish sugar molecules with similar structures. Selectivity for specific sugar targets can be improved by incorporating several boronic acid groups into a covalent framework or non-covalent assembly of boronic acid, particularly for glucose. Many studies have improved the structure of boric acid on this basis in order to improve the anti-interference capacity against other biological molecules and the sensitivity of the reaction [7, 8, 9].

Researchers also have conducted numerous studies on how to quantify blood glucose concentrations from Raman spectra. Lin Man-Man [10] et al. performed a linear analysis of blood glucose levels by Raman spectroscopy of mice at 1125 cm^{-1} and 1549 cm^{-1} by the intensity of the characteristic peaks, the scientific validity of which is debatable. Zheng Yi et al. [11] used the spectral characteristic peak area as the main calculation reference and peak intensity as a secondary reference for spectral quantification. Nonlinear multivariate partial least squares models based on dominant factors were developed for different samples separately to calculate glucose levels. Enejder [12] et al.

tested 17 healthy individuals in 2005 and collected 461 Raman spectra along with true blood glucose values. The R square value for each subject was 0.83 ± 0.10 by least squares calibration. In 2015, Shih [13] et al. conducted an in-depth study on the quantitative analysis of blood glucose concentration, which made statistical methods such as Partial Least Square (PLS) widely accepted by domestic and international colleagues in the quantitative analysis of blood glucose in vivo.

Based on our investigation, in view of the problems in the detection of blood glucose concentration by Raman spectroscopy, this paper proposed a new glucose concentration estimation strategy, that is, by applying the characteristics of the reaction between glucose and boric acid to construct a new complex, and obtained the Raman spectrum signal of the complex after the reaction. Through the corresponding spectral characteristic information, the current advanced deep learning method was used to construct a blood glucose quantitative calculation model, which effectively improved the accuracy of blood glucose concentration detection without increasing the detection cost, and provided a more accurate and reliable method for blood glucose concentration detection.

2. Experiment and Materials

2.1 Materials.

In our research, 4,4'-Biphenylboronic acid (97%, Macklin), glucose (99.0%, Energy Chemical), and NaOH (99.0%, Energy Chemical) were used without further purification. Ultrapure distilled and deionized water were used for all solution preparations.

2.2 Preparation of glucose detection solution based on 4,4'-Biphenylboronic acid mediums.

A certain amount of glucose was dissolved in 20 mL deionized water (Solution A, the amount of glucose is 0.1-0.24 mmol), 0.24 mmol 4,4'-Biphenylboronic acid was dissolved in 20 mL deionized water (Solution B). 4,4'-Biphenylboronic acid was a weak Lewis acid. In acidic environment, 4,4'-Biphenylboronic acid existed in a non-ionized hydrophobic situation. At pH above 8, 4,4'-Biphenylboronic acid can combine with OH^- to improve its hydrophilicity, so it was easier to covalently bind with organics compounds containing vicinal diol such as glucose. The pH of the solution was adjusted to 8-9. After mixing solution A and solution B and stirring at 40°C for 12 h, 4,4'-Biphenylboronic acid reacted with glucose and formed a hydrophilic complex (a borate ester derivative-- $\text{C}_{18}\text{H}_{22}\text{O}_{10}\text{B}_2$), and the $\text{C}_{18}\text{H}_{22}\text{O}_{10}\text{B}_2$ has a further condensation reaction to form $(\text{C}_{36}\text{H}_{40}\text{O}_{18}\text{B}_4)_n$ (Figure 1). The obtained product was transferred to the cuvette for testing. Then, the groups with different concentrations (different levels of glucose; 12 mmol/mL 4,4'-Biphenylboronic acid) were prepared according to the above steps for testing.

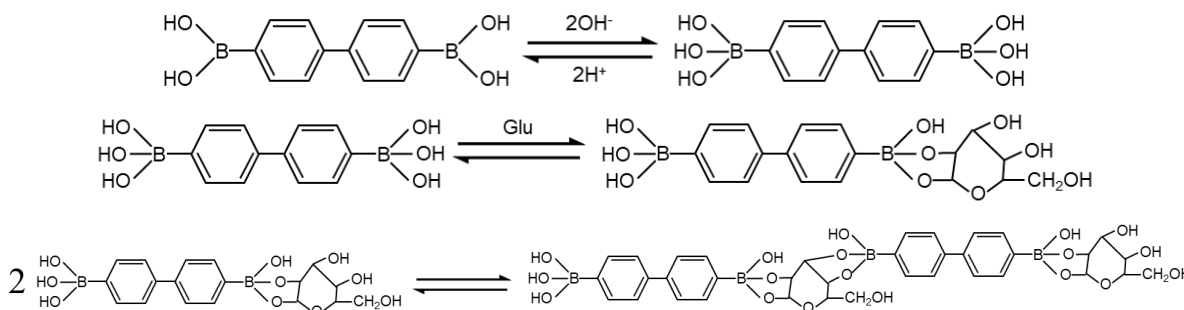


Figure 1. The reaction process for 4, 4'- Biphenylboronic acid and glucose.

2.3 Spatial heterodyne Raman spectrometer

In our research, the dataset was collected by the Spatial Heterodyne Raman Spectrometer (SHRS) that we developed in the lab specifically for this project, for details see [Research on a Near-infrared Spatial Heterodyne Raman Spectrometer, in preparation] The SHRS was a new type of Fourier transform Raman spectrometer. It replaced the mirrors of the two arms of the Michelson

interferometer with gratings, and no moving parts existed in the spectrometer. It possessed high throughput, spectrum resolution, and sensitivity, as well as good stability. The spectral resolution of our self-developed spatial heterodyne Raman spectrometer can reach 3.5cm^{-1} , and the detected Raman spectrum range was $170\text{cm}^{-1}\sim 3050\text{cm}^{-1}$. The wavelength of the laser light source was 830nm , and the maximum power was 500mw .

2.4 Data acquisition

We prepared glucose detection solution and 4,4'-Biphenylboronic acid -glucose conjugate solution, respectively. The concentration gradient was 1mmol/L . The samples were put into quartz cuvettes, and the optical probe was used to irradiate the cuvette vertically, keep the distance at the focal length of the probe-7 mm. Each integration time lasted 10 s, and each sample was continuously sampled in 60 groups, keeping the illumination and room temperature constant. The Schematic diagram of data acquisition by SHRS was shown in Figure 2.

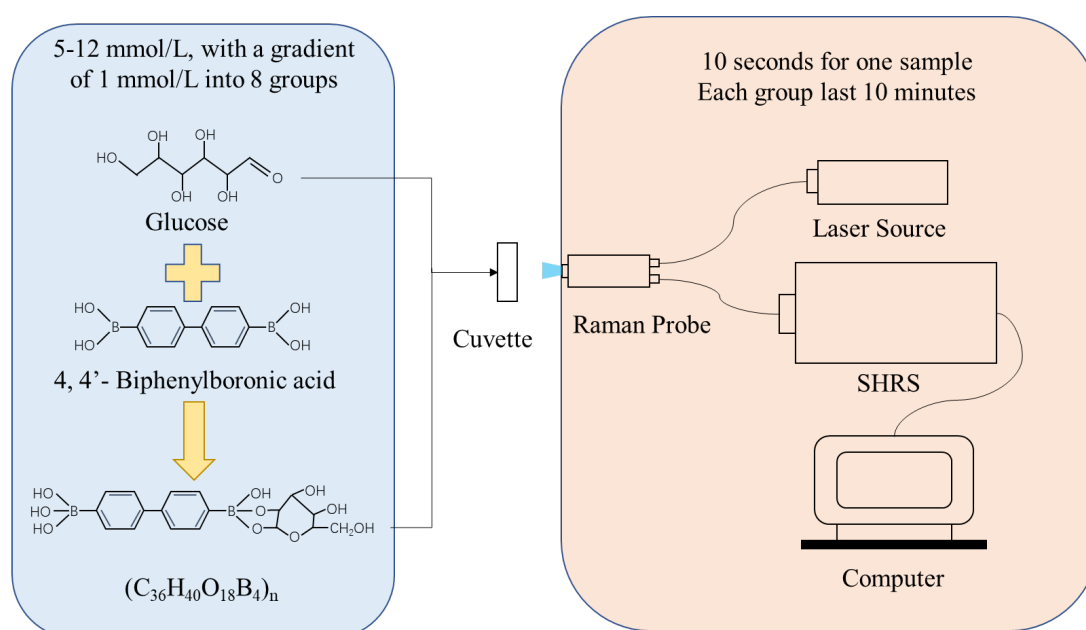


Figure 2. The Schematic diagram of data acquisition by SHRS.

3. Related work and Method

3.1 Interferogram pre-processing.

The interferogram on the detector was finally obtained from SHRS and needed to be Fourier transformed to obtain the information of the Raman spectrum, but the direct inversion of the interferogram cannot be clear. For high-quality Raman spectroscopy, the interferogram data needed to be preprocessed.

The practical situation for SHRS was not ideal. There were many interference factors: the non-uniform illumination of the front collimator, and the non-uniform illumination of the beam splitting prism, grating surface contamination, and existing scratches, system installation errors, etc. These factors affected the interferogram and caused the decreased quality of the spectrum. Therefore, a corresponding interferogram data pre-processing method was required to remove the interference factors to obtain a clear and high-quality Raman spectrum. Figure 3. is a flow chart of the pre-processing method of interferogram data?

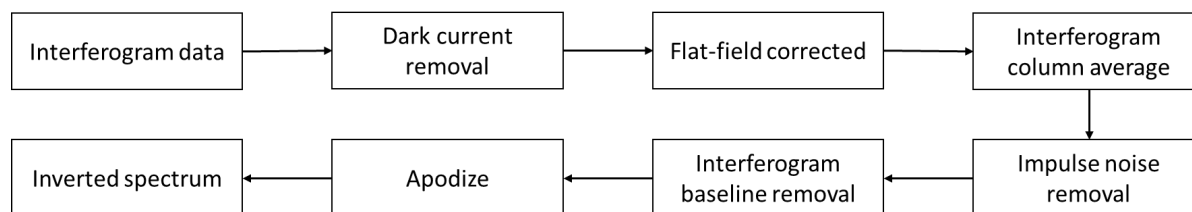


Figure 3. The flow chart of the pre-processing method of interferogram data.

3.2 Raman Signal pre-processing

The Raman spectral signal was the foundation for constructing a quantitative analysis model. However, the interference noise will be formed throughout the acquisition process due to factors such as detector noise and the fluorescence background generated by the sample itself. As a result, pre-processing the spectral data was required to highlight the sample signal's properties.

3.2.1 Denoising.

Zhao Xiaoyu et al. [14] proposed a Raman spectroscopy denoising method based on the overall average empirical mode decomposition (EEMD), which overcame the problem of EMD decomposition modal aliasing. Compared with wavelet transform, EEMD was simpler and more adaptable. However, the intrinsic mode component (IMF) noise after EEMD decomposition have residuals, and white noise of different amplitude needed to be added each time.

In the complete empirical mode decomposition (CEEMDAN) process based on adaptive noise, the IMF component was obtained by EMD decomposition of the added Gaussian white noise instead of the Gaussian white noise added each time in the EEMD decomposition process [15].

In this paper, the Raman spectral signal was denoised by CEEMDAN. In order to ensure that the high-frequency noise was effectively removed without losing useful information, and after comparison, we removed IMF1 and then recombined the rest of the signal to achieve the effect of denoising.

3.2.2 Baseline removal.

Improved Modified Multi-Polynomial Fitting (I-ModPoly) was proposed for baseline removal [16]. An iterative process was applied to adjust the polynomial function, and the fluorescence was modeled as a Raman spectrum. The non-fluorescent Raman spectrum was calculated by subtracting the adjusted polynomial from the original Raman spectrum.

3.3 ResNet

Due to the backpropagation algorithm and the growth of the number of parameters, deep convolutional neural networks outperformed traditional neural networks in many tasks and even surpassed human performance [17]. However, as the number of layers increased further, the performance of deep convolutional networks was likely to degrade. Residual learning was introduced in [18] to overcome the degradation problem in deep convolutional neural networks. By introducing a shortcut to the modulated features, ResNet was easier to optimize, making it possible to build very deep neural networks. A modulation block of the network was denoted by $y=H(x)$, and a residual block by $H(x)=F(x)+x$, where $F(x)$ denoted the residual, which was typically composed of two convolutional layers, and x denoted the shortcut that was directly summed to the residual.

Resnet-18 was used as the backbone network in this work. We simply modified the input convolutional layer channel of the ResNet-18 to 1 to fit the Raman spectral data. The final component of the network was a 512×1 fully connected (FC) layer that functioned as a regressor.

There were eight sets of data based on labels with different concentration values for glucose solutions and $(C_{36}H_{40}O_{18}B_4)_n$, respectively. Each set of data was randomly divided into ten splits of equal size, of which eight splits were the training set, one split was the validation set, and one copy was the test set. In this process, one subset was randomly selected for testing, another for validation, and the rest for training, and repeated ten times until all subsets were used for testing and ten-fold

cross-validation was completed. The number of rounds per training was, 200 and the learning rate was 0.0001.

The ResNet model was implemented on Pytorch and built in python language. Experimental environment: Intel(R) Core (TM) i7-10700 CPU; GTX 1660 SUPER GPU; 16GB RAM.

3.4 Metrics

In this paper, we used R-squared (R²), and root mean square error (RMSE) to quantitatively evaluate the final data regression results.

3.4.1 R-squared

R-squared (R²) is a statistical indicator that indicates the proportion of all changes in the dependent variable that can be explained by the independent variable through the regression relationship.

$$R^2 = \frac{S_1}{S_2} = 1 - \frac{S_3}{S_2} = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y})^2} \quad (1)$$

In formula (1), S_1 is the regression sum of squares, S_2 denotes the total sum of squares, S_3 is the residual sum of squares, y_i denotes the observed value, $\hat{y}_i$ is the fitted value, and $\bar{y}$ is the average value.

3.4.2 Root mean square error

The value of the root means square error (RMSE) is the quantity predicted by the model or the estimated quantity observed [19]. The RMSE represents the sample standard deviation of the difference between the predicted value and the observed value.

$$RMSE = \sqrt{\frac{1}{N} \sum_{i=1}^n (Y_i - f(x_i))^2} \quad (2)$$

In formula (2), Y_i is the true value and $f(x_i)$ is the predicted value.

4. Results and Discussion

4.1 Raman Spectroscopic Characteristics of Glucose

The scanning band range of the Raman spectrum of the solution sample was 170cm⁻¹~3050cm⁻¹. The chemical formula of glucose is C₆H₁₂O₆.

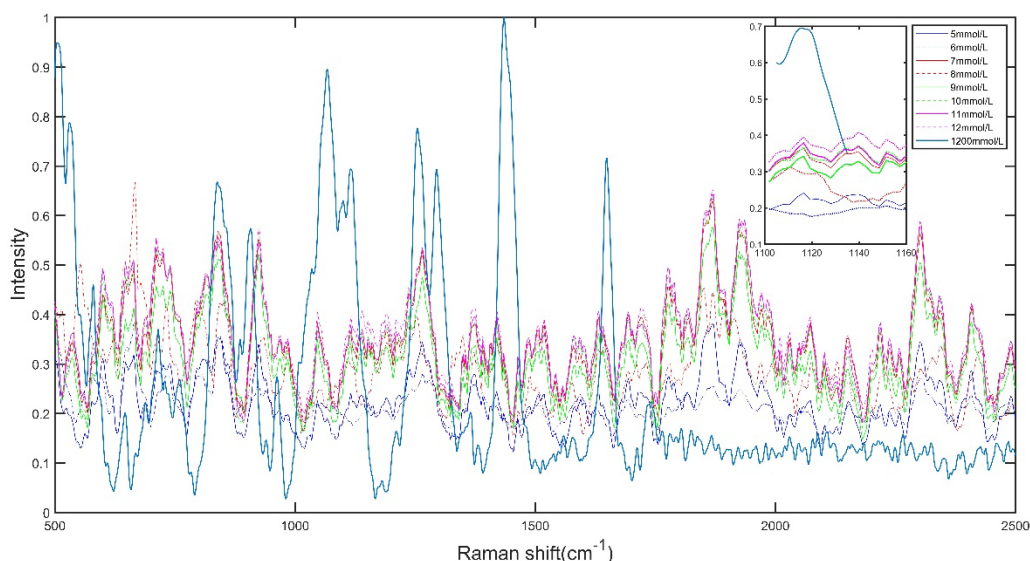


Figure 4. Pre-processed Raman spectrum of 5-12mmol/L glucose solution.

The Raman effect vibration band changed according to the changes in the chemical bonds of the main functional groups contained in different structures. Among them, the main vibration band

regions were summarized as follows: the C-C single bond skeleton vibration produces a series of characteristic bands in the range of 800 to 1100 cm^{-1} ; The bending vibration of -OH is near 818 cm^{-1} ; the C-O single bond vibration produces a characteristic waveband in the range of 1000 to 1300 cm^{-1} ; the vibration of the C-H bond of the aldehyde group (-CHO) appears near 1390 cm^{-1} , and its characteristic waveband is in the range of 1300 to 1500 cm^{-1} , and the characteristic band of the carbonyl C = O double bond is about 1550 ~ 1800 cm^{-1} . [20] The Raman spectra of different concentrations of glucose solutions obtained in this experiment are shown in Figure 4 (1200 mmol/L as reference):

In general, the characteristic peak of glucose was around 1115-1130 cm^{-1} . Compared with the high concentration (1200 mmol/L), the Raman characteristic peak of the low concentration glucose solution, although obvious, have a significantly lower intensity. The intensity of the characteristic peaks increased with increasing concentration but clearly did not follow a linear relationship. This indicated that at low concentrations, direct use of the characteristic peaks of the Raman spectrogram to estimate the concentrations could be biased.

As designed, we applied the 4,4'-Biphenylboronic acid mediated method to amplify the weak Raman signal of glucose by testing the strong Raman signal of the reaction product (($\text{C}_{36}\text{H}_{40}\text{O}_{18}\text{B}_4$)_n) of boric acid and glucose. Furthermore, compared to the traditional linear method, the deep learning method did not focus on the local Raman characteristic peaks but the information of the whole spectrum. This can effectively save the cost of feature extraction and keep the implicit feature in the data. The final choice of the deep learning method was to calculate the concentration based on the Raman data of the whole spectrum.

4.2 Evaluation of the ($\text{C}_{36}\text{H}_{40}\text{O}_{18}\text{B}_4$)_n

To verify that the ($\text{C}_{36}\text{H}_{40}\text{O}_{18}\text{B}_4$)_n can effectively enhance the estimation performance of low concentrations of glucose, we used ResNet to estimate the regression of the two types of data separately. In this study, the glucose concentration was 5-12 mmol/L; the concentration range is in line with human blood glucose concentration. In order to compare the accuracy of clinical blood glucose estimation value and reference value more professionally, Clarke error network analysis was used to quantify the relationship between the glucose concentration and the estimation glucose concentration [21]. The Clark error network under the ResNet model was shown in Figure 5.

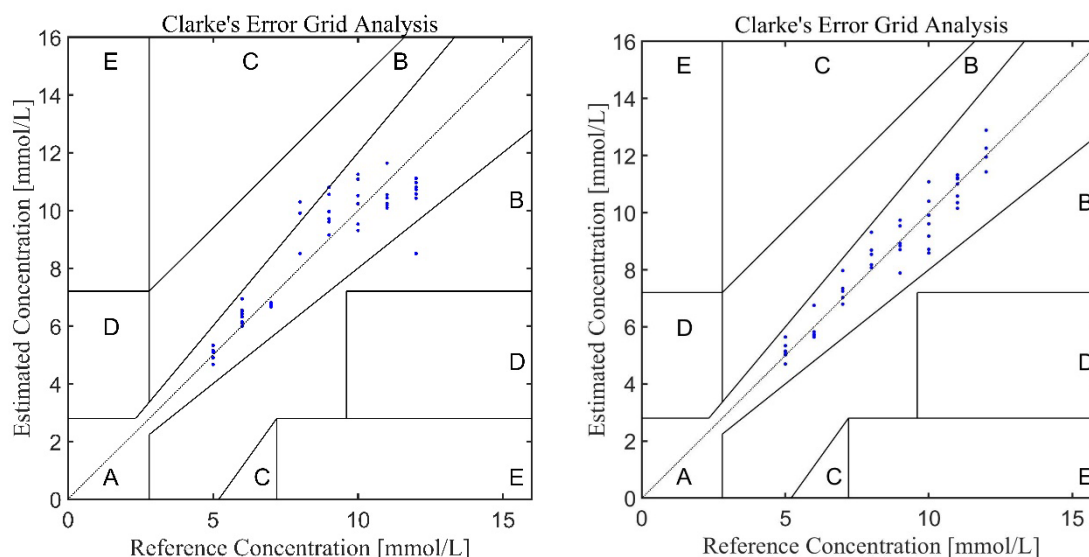


Figure 5. The Clark error network of glucose solution and ($\text{C}_{36}\text{H}_{40}\text{O}_{18}\text{B}_4$)_n under the ResNet model.

Clarke error grid analysis results showed that all measuring points of ($\text{C}_{36}\text{H}_{40}\text{O}_{18}\text{B}_4$)_n were within the range of area A, and there were no values in areas B, C, D, and E. The results showed that there was no different risk category between Raman spectroscopy quantitative analysis and clinical analysis. However, for the glucose solution, there were still some points that fell in the B area. If the

concentration of glucose was directly detected, it would affect the medical diagnosis to a certain extent.

4.3 Comparison of estimation accuracy of different regression models

To verify that $(C_{36}H_{40}O_{18}B_4)_n$ better reflected low concentration compared to glucose solution under any model and the advantage of deep learning for low concentration detection, some machine learning regression algorithms were used in this paper to estimate the concentration based on the Raman spectral data of the solution. Partial Least Squares Regression (PLSR) and Support Vector Regression (SVR), were compared with ResNet18. RMSE and R^2 were calculated by doing ten-fold cross-validation on these regression algorithms [22].

Table 1. The estimation results of concentration under different regression methods.

Regression algorithm	$(C_{36}H_{40}O_{18}B_4)_n$		Glucose	
	R^2	RMSE	R^2	RMSE
ResNet	0.9345	0.568	0.7910	1.040
PLSR	0.7944	1.1013	0.7419	1.1669
SVR	0.8442	0.6958	0.7441	1.0679

It can be seen from Table 1 that the regression effect of the $(C_{36}H_{40}O_{18}B_4)_n$ was better than that of the glucose solution. Each method calculated that the R^2 of the $(C_{36}H_{40}O_{18}B_4)_n$ was greater than the R^2 of the glucose solution, and the RMSE of the $(C_{36}H_{40}O_{18}B_4)_n$ was smaller than the RMSE of the glucose solution. In the comparison of regression methods, we can see that ResNet's regression results was better than two machine learning algorithms. When ResNet was used to process $(C_{36}H_{40}O_{18}B_4)_n$, the largest R^2 and the smallest RMSE were obtained. This showed that the new glucose detection method combining deep learning could effectively improve the effect of low-concentration blood glucose detection.

The loss function in the network training process was shown in Figure 6. It can be seen that as the number of iterations increases, the network gradually converges. From a macro point of view, the curve showed a downward trend, indicating that the learning state was considerable and there was no over-fitting phenomenon.

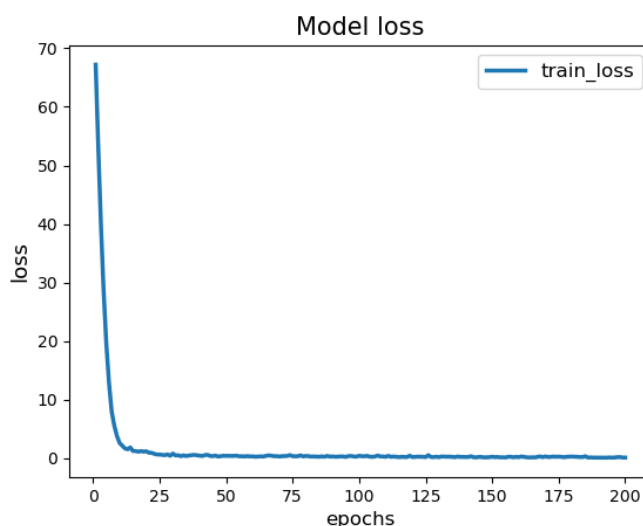


Figure 6. The loss function in the network training process.

5. Conclusion

In this paper, a new strategy for blood glucose concentration detection was proposed, by combining the characteristics of the reaction between glucose and 4,4'-biphenyl boronic acid to construct $(C_{36}H_{40}O_{18}B_4)_n$; spatial heterodyne Raman spectrometer was used for the signal acquisition. The Raman spectral signals of the glucose solution and $(C_{36}H_{40}O_{18}B_4)_n$ were obtained after multi-

step pre-processing, respectively. Regression was performed using ResNet18 network, PLSR, and SVR for both data sets, respectively. The experimental results demonstrated that $(C_{36}H_{40}O_{18}B_4)_n$ can effectively improve the low concentration glucose detection accuracy with significant improvement in R2 and RMSE, regardless of which model was used. Meanwhile, deep learning method, ResNet also have better performance compared with other machine learning models. This article illustrated that the combination of glucose specific binding and deep learning could facilitate the detection of low glucose concentrations. Although the current work is still in the in vitro verification phase, we believe that this method will also have the potential to play a key role in minimally invasive human blood glucose detection.

Acknowledgments

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