Applying the reference-wavelength method to improve the precision of glucose measurement by near infrared spectroscopy

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The reference-wavelength method is proposed to diminish the influence of noises on glucose measurement by differentially processing two signals at the reference and measuring wavelengths. At the reference wavelength, the radiation intensity is insensitive to the changes of glucose concentration. Therefore, it can be used as the internal reference to estimate the noise and then to extract the effective glucose signal at the other wavelengths. The validation experiments are constructed in the non-scattering samples with the reference wavelength of glucose at 1525 nm. The results show that the reference-wavelength-based glucose-specific signal extracting method can largely improve the glucose prediction precision from 17.56 to 8.87 mg/dL in the two-component experiment and from 26.82 to 9.94 mg/dL in the three-component experiment.

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Over the past few decades, non-invasive blood glucose monitoring has become an increasingly interesting and challenging field in the area of biomedical engineering, particularly after optical approaches having stepped into this endeavor[1−3]. However, there is still not a clinically feasible instrumentation available for continuous monitoring of human blood glucose concentration *in-vivo*. This is largely due to the sensitivity of instrument response to the glucose specific signals that are unfortunately swamped within a complex physiological system. Those undesired noises from the instrumental drift, environmental condition variations, absorption from other physiological components and differences between individual people all make it difficult to extract the glucose specific signal, and thus lead to the relatively poor prediction precision. Therefore, an effective solution to this problem will be not only meaningful but also inspiring for shedding a new light into the field of non-invasive blood glucose detection.

Generally, in the quantitative near infrared (NIR) measurement, background deduction method is widely used to eliminate the undesired noises. In the traditional data processing procedure, the sample and background spectra are simply deducted. This is practically deficient, since it assumes that the sample and background spectra share the same noises, which requires that the two spectra must be obtained under the same optical path simultaneously. This is obviously impossible. Therefore, the efficiency of the traditional background deduction method is rather limited. Especially when it is adopted in the complicated sample, the root mean square error of prediction (RMSEP) increases along with the complexity[4].

In this paper, the reference-wavelength method, an effective way to extract the glucose-specific signal in complicated samples, is proposed. The corresponding validation experiments are constructed in the non-scattering glucose solutions. Two different data processing methods, the traditional background deduction method and the proposed method, are used to extract glucose signal. And the comparison on efficiency of these two methods is perfored to evaluate the novel method's feasibility and practicability.

For glucose measurement, the radiation information from human body at wavelength λ can be divided into two sections: the information related to the glucose concentration I_{G} and the information related to the noise I_{N} which results from the instrumental drift, human body physiological background and other factors. This can be represented as

$$I\left(\lambda, c_{\mathrm{g}}, N\right) = I_{\mathrm{G}}\left(\lambda, c_{\mathrm{g}}\right) + I_{\mathrm{N}}\left(\lambda, N\right), \qquad (1)$$

where c_{g} is the blood glucose concentration, N is the noise.

By differential measurement method, the glucose concentration variation information is obtained as

$$\Delta I_{\mathrm{G}}\left(\lambda, \Delta c_{\mathrm{g}}\right) = \Delta I\left(\lambda, \Delta c_{\mathrm{g}}, \Delta N\right) - \Delta I_{\mathrm{N}}\left(\lambda, \Delta N\right). \qquad (2)$$

However, the interference noise $\Delta I_{\mathrm{N}}\left(\lambda, \Delta N\right)$ changes with time, which makes it difficult to extract directly the glucose information from $\Delta I\left(\lambda, \Delta c_{\mathrm{g}}, \Delta N\right)$.

The reference-wavelength method is used to eliminate the influence of various noises. At the reference wavelength of glucose λ_{r}, the radiation intensity is insensitive to the variation of glucose concentration. Consequently, the variations of radiation intensity at the reference wavelength are completely induced by noises. Thus, the reference wavelength can be used as the internal reference to estimate the noise and then to extract the effective glucose signal at the other wavelengths. By the simplest way, the internal relation between the noise $\Delta I_{\mathrm{N}}\left(\lambda_{\mathrm{r}}, \Delta N\right)$ at the reference wavelength λ_{r} and $\Delta I_{\mathrm{N}}\left(\lambda_{\mathrm{m}}, \Delta N\right)$ at the measuring wavelength λ_{m} is assumed as constant. Thus, the effective glucose signal can be expressed as

$$\Delta I_{\mathrm{G}}\left(\lambda_{\mathrm{m}}, \Delta c_{\mathrm{g}}\right) = \Delta I\left(\lambda_{\mathrm{m}}, \Delta c_{\mathrm{g}}, \Delta N\right) - \eta \cdot \Delta I\left(\lambda_{\mathrm{r}}, \Delta c_{\mathrm{g}}, \Delta N\right), \qquad (3)$$

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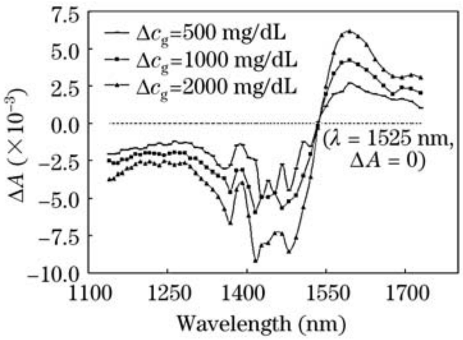

Fig. 1. Absorbance values with different glucose concentrations.

where η is the proportional factor which can be obtained by repeating measurements under the condition of relatively constant glucose concentration. $\Delta I\,(\lambda_{\rm m}, \Delta c_{\rm g}, \Delta N)$ and $\Delta I\,(\lambda_{\rm r}, \Delta c_{\rm g}, \Delta N)$ can be acquired by practical measurement.

According to Eq. (3), the existence of reference wavelength is the basis and precondition of the floating-reference method. By the experiment of aqueous glucose solutions, the relative absorbance values, ΔA derived from different glucose concentrations are shown in Fig. 1. Obviously, the curves intersect with relative absorbance values of zero at the wavelength of 1525 nm, where the absorbance as well as the radiation intensity is insensitive to the variation of glucose concentration. Therefore, the reference wavelength for pure absorption samples exists at 1525 nm.

In this system, a tungsten-halogen lamp (Model PG64623, OSRAM, German) is used as the light source, and a non-collinear TeO_2 acousto-optic tunable filter (AOTF) (Model TEAF10-1.0-1.8-S, with Model VFI-80-50-DDS-B1-C2-E driver, Brimrose Company, USA) is used to perform the wavelength scan. Thus, monochromatic radiation ranging from 1100 to 1750 nm can be obtained by time-sharing. When the monochromatic radiation diffracted by AOTF enters the sample in the quartz sample cell, the transmitted intensity is converted into analog signal by the InGaAs positive-intrinsic-negative (PIN) photodiode (Model G5851-21, Hamamatsu Photonics, Japan). And then, the signal is inputted into the computer after being digitized by 16-bit data acquisition card (Model PCI-MIO-16XE-50, National Instrument Inc., USA). The computer controls the closed-loop process. The detailed description and layout of this system have been discussed in our previous study[5].

Two experiments with different samples were conducted to validate the effect of the reference-wavelength method. The first one was with two components as glucose dissolved into distilled water, and the second one with three components as glucose dissolved into distilled water and albumin. For each experiment, 30 samples with glucose concentrations ranging from 10 to 300 mg/dL were prepared. The glucose concentration interval was 10 mg/dL. In the three-component experiment, the albumin concentrations were changed from 10 to 155 mg/dL with interval of 5 mg/dL.

In order to diminish the impact of instrument drift, random sampling was adopted. Besides, before each sample was measured, the spectrum of distilled water was measured in advance as the background. Two different data processing methods were carried out to obtain the specific information related to the glucose concentration variation. For the traditional background deduction method, for each sample, the spectrum of distilled water which was recorded immediately before the sample measurement was used as the background to eliminate the noise[6]. For the reference-wavelength method, as mentioned above, the radiation intensity at the reference wavelength was used as the background for the rest of wavelengths to eliminate the noise.

Based on the original spectra data as well as the data processed respectively by these two methods, three calibration models for each experiment were built by the partial least squares (PLS) method[7]. The main component numbers of the models were set as 2 for the two-component experiment and 3 for the three-component experiment. And then, the full cross validation method[8] was applied to evaluate the prediction ability of the different models.

We used the correlation coefficient and RMSEP to evaluate the efficiency of the calibration models built on the original spectra data and the spectra data processed by the traditional background deduction method and reference-wavelength method. The results are shown in Table 1.

According to the experiment results shown in Table 1, the noise of the instrumental drift and environmental condition variations interfere the glucose prediction very much. In the traditional background deduction method, since we have strictly confined the time intervals between all the sample and background spectra, the influences of the system shift and environmental noises are to some extent under control in the two-component experiment, and thus the RMSEP is reduced from 17.56 to 9.46 mg/dL. But the situation is not so good in the three-component experiment, which is mainly because the traditional background deduction method cannot diminish the noises from the samples. Therefore, the prediction error increases as the complication degree of components raises, which results in a RMSEP of 18.25 mg/dL in the three-component experiment.

In the reference-wavelength method, the radiation intensity at the reference wavelength is used as the internal reference to estimate the noise and then to extract the effective glucose signal at the other wavelengths. The

Table 1. Results of the Two Different Validation Experiments

	Two-Component Experiment		Three-Component Experiment	
	Correlation Coefficient	RMSEP (mg/dL)	Correlation Coefficient	RMSEP (mg/dL)
Original Spectra	0.9832	17.56	0.9788	26.82
Traditional Method	0.9932	9.46	0.9863	18.25
Proposed Method	0.9946	8.87	0.9912	9.94

measurement at the reference wavelength and the other wavelengths can be regarded as almost at the same time for the same sample. So, it is better than the traditional background deduction method as to effectively eliminate the disturbance brought by the time asynchronies and the concentration variation of other components. The validation experiment results also indicate that the reference-wavelength method can largely eliminate the influence of various noises on the glucose-specific signal extraction. As shown in Table 1, we can obtain good prediction precision with the RMSEP of 8.87 mg/dL in the two-component experiment and 9.94 mg/dL in the three-component experiment.

However, the application of this novel method is confined into the non-scattering samples in this paper. The further investigation of its wider implementation in complicated scattering sample is to be held in order to gain our final aim as to apply this method in the *in-vivo* human blood glucose concentration detection.

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