Internal floating reference method for noninvasive measurement of blood glucose with near-infrared spectroscopy

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Weak signal and great background variation have been the major challenges for noninvasive measurement of blood glucose. Two kinds of noise are analyzed, and it is found out that, when instruments achieve a high level of signal to noise ratio, physiological variation other than glucose concentration becomes the dominant over instrument noise. After analyzing the sensitivity of glucose concentration on diffuse reflectance spectroscopy at different source-detector separation, floating-reference method is proposed firstly. This method discusses how to extract signal relating to glucose and signal only relating to background variation respectively, by making use of two special points, reference point and measuring point. Experiments on phantom and Monte Carlo simulations have been performed to validate the feasibility of floating-reference method.

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1. Introduction

Noninvasive measurement of blood glucose concentration is a long pursed goal in clinical diagnostic [1]. Among several other optical methods, including mid-infrared spectroscopy [2], near infrared spectroscopy [3], photoacoustic spectroscopy [4], Raman spectroscopy [5], optical coherence tomography [6], scattering [7] and polarization [8] technique, near infrared spectroscopy is the most promising one for the noninvasive application to date. Despite of great efforts having been paid by optics scientists and engineers, products available in clinic have not been realized. Major obstacles lie among weak signal and great background variation, which result in low sensitivity and low signal-to-noise ratio pertinent to physiological blood glucose measurement using the near infrared spectroscopy technique. Sensitivity analysis of aqueous glucose absorption signals in the combination band region and the first-overtone region was studied by V.A. Saptari *et al* [9]. After sources of noise were analyzed, a method of Fourier filter was applied to compensate the noise due to temperature variation. Dependency between sensitivity of glucose concentration to diffused light intensity and different source-detector separations was investigated by Luo *et al*[10], in which it was pointed out that different source-detector separation can be adopted for different application purpose using scattering or absorption effect.

For a typical system schematic of a noninvasive optical-based glucose sensor, it includes two principal modules, software and hardware, as shown in figure 1[9]. Correspondingly, noise also comes from two sides: instrumental and physiological variation. Instrumental noise includes errors introduced by each of the hardware components, for example, detector noise, digitization noise and light source fluctuations. Physiological noise includes variations such as tissue temperature, skin humidity and blood hemoglobin level changes et al.

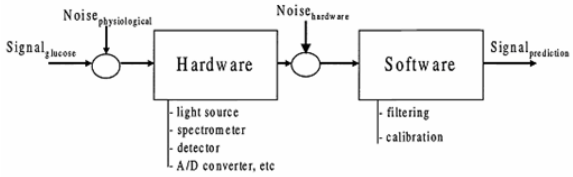


Fig. 1. System schematic of a noninvasive optical-based device.

Apparently, it's of most importance to reduce the noise level of instruments as low as possible. However, the improvement of signal to noise ratio (SNR) attributes little to measurement accuracy, which is usually denoted as root-mean-square-error of prediction (RMSEP) in near infrared spectroscopy measurement, when SNR achieves to a certain value. Fig. 2 is our experimental result on a FT-IR spectrophotometer (Spectrum GX, PerkinElmer, USA). As shown in Fig. 2, RMSEP decreases quickly as SNR increases until SNR achieves 10000, thereafter, RMSEP improves very slightly due to increase of SNR, which implies that how to eliminate the interference of the physiological noise on measurement signal is more practical.

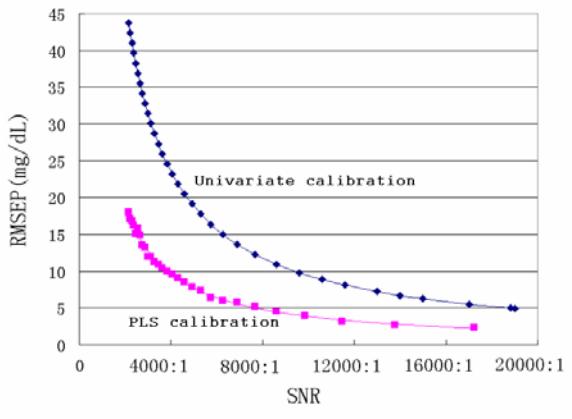


Fig. 2. Dependency of measurement accuracy on signal to noise ratio.

Most of the previous efforts in compensating noise have been focused on software [11-13], which is mainly focused on the development of mathematical algorithms in the form of "calibration" techniques to extract spectral information due to glucose variation and suppress spectral noise and other unwanted variation. They involve taking a sufficiently large amount of data from measurements of known glucose concentration values and building calibration algorithms to fit the data, and good results have been obtained in aqueous solution of glucose and other solutions. Although this is an important and necessary operation, the importance of understanding the origins and characteristics of both the noise and signal is often overlooked. Particularly, comprehension of effect of change in glucose concentration on light propagation and further effect on diffused light distribution on the surface of medium will help understand the mechanism of noninvasive measurement of blood glucose and design optical probes properly.

In this paper, we investigate the influence of glucose concentration variation on light propagation, and then propose a novel method, in which diffused lights are collected at two points, points possessing maximal sensitivity and zero sensitivity to variation of glucose concentration. Experiments on milk are performed to provide the dependency of glucose concentration variation and optical parameters of milk. And Monte Carlo results have demonstrated this method effective in suppressing the interference of background noise.

2. Theoretical formulation

2.1 Effects of glucose concentration on optical parameters

The effects of glucose on light propagation can be divided into three categories [14,15], change of absorption coefficient, scattering coefficient and anisotropic factor.

On one hand, increasing glucose concentration reduces the molarity of water and accordingly the contribution of water to the absorption coefficient of aqueous glucose solution is reduced. For a temperature of 20℃, the molarity of water for zero glucose concentration is 55.4M and decreases to 54.17M with increasing glucose concentration to 200 mM [14]. On the other hand, absorption of the solution increases due to the "intrinsic" glucose absorption. The overall change of the solution is the summary of the two terms analyzed above. In case of human body, however, molarity of water is assumed to keep constant while glucose concentration varies, so that absorption variation is dependent on only glucose concentration variation.

As the increase of glucose, the refractive index of background medium will increase [14], and then the relative refractive index between background medium and scattering particles decrease, which will result in a decrease of scattering coefficient according to the equation $\mu_s = k\left(\frac{n_1 - n_0}{n_0}\right)^2$, where k is a coefficient relating to wavelength and particle size. And also anisotropic factor g will vary when the relative refractive index changes. Usually, the two factors are combined in a reduced scattering coefficient with equation $\mu_s' = (1-g)\mu_s$.

2.2 Sensitivity to glucose concentration

Firstly, we can introduce a very universal theory, i.e. Lambert-Beer law, to describe the reflectance distribution as a function of source-detector separation and optical properties of media.

$$I(r) = I_0(r)\exp\left[-\varepsilon_g c_g l + \sum_{i=1}^{n} \varepsilon_i c_i l\right] \qquad (1)$$

where $I_0(r)$ is photon distribution when absorption is absent, ε_g and ε_i is absorption cross section of glucose and other components respectively. l is path length in experienced by photons and dependent on scattering coefficient and scattering function.

Here, we analyze the sensitivities of diffuse reflectance to changes in glucose concentration. So dependence of diffuse reflectance variation on glucose concentration variation will be,

$$\Delta I(r) = \frac{\partial I(r)}{\partial C_g}\cdot \Delta C_g = \left(\frac{\partial I(r)}{\partial \mu_a}\cdot\frac{\partial \mu_a}{\partial C_g} + \frac{\partial I(r)}{\partial \mu_s'}\cdot\frac{\partial \mu_s'}{\partial C_g}\right)\cdot \Delta C_g \qquad (2)$$

From equation (2), it's evident that glucose affects the diffuse reflectance through absorption and scattering. The former item in the bracket is sensitivity of diffuse reflectance to glucose concentration through absorption effect Sen_a, and the latter is absolute sensitivity to glucose concentration through scattering effect Sen_S. Inserting equation (1) into Sen_a, Sen_S for further calculation as follows,

$$\mathrm{Sen_a} = \frac{\partial \mathrm{I(r)}}{\partial \mu_a} \cdot \frac{\partial \mu_a}{\partial \mathrm{C_g}} = -\mathrm{I(r)l}\varepsilon_g \tag{3}$$

$$\mathrm{Sen_s} = \frac{\partial \mathrm{I(r)}}{\partial \mu_s'} \cdot \frac{\partial \mu_s'}{\partial \mathrm{C_g}} = \mathrm{I_0(r)}\left[\frac{\mathrm{dI_0(r)}}{\mathrm{I_0(r)d}\mu_s'} - \left(\varepsilon_g \mathrm{c_g} + \sum_{i=1}^{n} \varepsilon_i \mathrm{c_i}\right)\frac{\mathrm{dl}}{\mathrm{d}\mu_s'}\right] \cdot \frac{\partial \mu_s'}{\partial \mathrm{C_g}} \tag{4}$$
$$= \mathrm{I(r)(Sen_{s1} + Sen_{s2})}\delta\mu_s'$$

In equation (4), $\mathrm{Sen_{s1}}, \mathrm{Sen_{s2}}$ represents the variation fraction due to re-distribution of photons and due to additional absorption for changed path-length. Actually, it's more necessary to analyze the relative sensitivity of diffuse reflectance to glucose concentration instead of absolute sensitivity. Analyzing equation (3) and (4), we can find that Sen_a is always negative, and Sen_s may have positive or negative value at different separation from source *r*. When the summary of Sen_a and Sen_s equals zero, it means that diffuse reflectance at this point, denoted as reference point r_C, doesn't change according to glucose concentration variation. Meanwhile, the measuring point r_M where the summary of Sen_a and Sen_s achieve maximal absolute value, means possessing greatest sensitivity of diffuse reflectance to glucose concentration variation.

2.3 Floating-reference method

In practice, light intensity measured at reference point r_C, and measuring point r_M can be divided into two components, i.e. signal I_S due to glucose concentration variation and noise I_N due to the change of components other than glucose.

$$\mathrm{I}(\mathrm{r_C}, \mathrm{C_g}) = \mathrm{I_S}(\mathrm{r_C}, \mathrm{C_g}) + \mathrm{I_N}(\mathrm{r_C}) \tag{5}$$

$$\mathrm{I}(\mathrm{r_M}, \mathrm{C_g}) = \mathrm{I_S}(\mathrm{r_M}, \mathrm{C_g}) + \mathrm{I_N}(\mathrm{r_M}) \tag{6}$$

Therefore, when glucose concentration varies with amount of $\Delta \mathrm{C_g}$, light intensity at r_c and r_M can be express as,

$$\Delta\mathrm{I}(\mathrm{r_C}, \Delta\mathrm{C_g}) = \Delta\mathrm{I_S}(\mathrm{r_C}, \Delta\mathrm{C_g}) + \Delta\mathrm{I_N}(\mathrm{r_C}) = \Delta\mathrm{I_N}(\mathrm{r_C}) \tag{7}$$

$$\Delta\mathrm{I}(\mathrm{r_M}, \Delta\mathrm{C_g}) = \Delta\mathrm{I_S}(\mathrm{r_M}, \Delta\mathrm{C_g}) + \Delta\mathrm{I_N}(\mathrm{r_M}) \tag{8}$$

The second part of equation comes into existence with the precondition of $\Delta\mathrm{I_S}(\mathrm{r_C}, \Delta\mathrm{C_g})$ equaling to zero. Usually, noise at r_c and r_M is supposed to be proportional with a coefficient of η, and η can be determined by repeated measurements when glucose level is kept relatively constant.

$$\Delta\mathrm{I_N}(\mathrm{r_M}) = \eta \cdot \Delta\mathrm{I_N}(\mathrm{r_C}) \tag{9}$$

Combining equations (7), (8) and (9), change in light intensity at r_M completely due to change in glucose concentration will be,

$$\Delta\mathrm{I_S}(\mathrm{r_M}, \Delta\mathrm{C_g}) = \Delta\mathrm{I}(\mathrm{r_M}, \Delta\mathrm{C_g}) - \eta \cdot \Delta\mathrm{I}(\mathrm{r_C}, \Delta\mathrm{C_g}) \tag{10}$$

In equation (10), the items of $\Delta\mathrm{I}(\mathrm{r_M}, \Delta\mathrm{C_g})$, $\Delta\mathrm{I}(\mathrm{r_C}, \Delta\mathrm{C_g})$ corresponding to variation of light intensity measured at measuring point and reference point, can be determined directly by measurements. So the effective signal $\Delta\mathrm{I_S}(\mathrm{r_M}, \Delta\mathrm{C_g})$ due to glucose concentration variation can be determined. Superiority of the floating method over traditional single point measurement, as can be seen from equation (10), lies in elimination of noise of background.

3. Experiment and simulation

3.1 Measurement of absorption and scattering effect of glucose concentration variation

In this series of experiments, a double-integrating-spheres (IS-060-IG, LabSphere, USA) system is used to measure the optical properties of the samples as shown in Fig. 3. The FT-IR spectrophotometer (Spectrum GX, PerkinElmer, USA) is used as the light source, and four InGaAs PIN photodiodes (G5851-21, Hamamatsu Photonics K.K, Japan) are used to collect the reference light intensity (D1), reflectance diffused by the sample (D2), diffused transmittance (D3), and collimated transmittance (D4). Signal collected by the photodiodes is sent to computer after a 16-bit data acquisition card (PCI-MIO-16XE-50, National Instrument Inc, USA). Samples are pumped into a quartz sample cell with thickness of 1 mm. Pure milk and milk with additional glucose concentration of 1000mg/dl, 2000mg/dl, 3000mg/dl, 4000mg/dl respectively were measured with this system shown in Fig. 3.

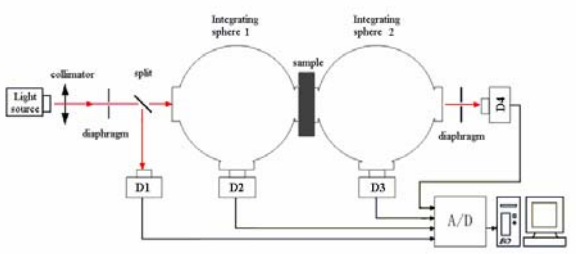


Fig. 3. Experimental system of double integrating spheres.

3.2 Monte Carlo simulation of light distribution

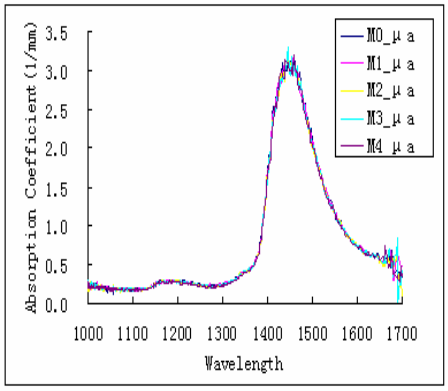
In order to calculate photon distribution, path-length and sensitivity referred above, Monte Carlo simulation has

been adopted, because it can deal with three-layered boundary conditions more easily than other methods [16-21]. Photons were launched normally into a semi-infinite medium perpendicularity, with certain initial values for each photon. And then their trajectories were traced until they were either re-emitted at the surface of medium .Every step size of photons was sampled according to a statistical distribution function, $P(s) = \mu_t e^{-\mu_t s}$, where μ_t representing total attenuation coefficient. During the propagation of each photon in tissue, path length of each photon l_j is the summary of *s* for each scattering step, and mean path length can be obtained by averaging the path length l_j of all photons collected the source-detector separation *r*.

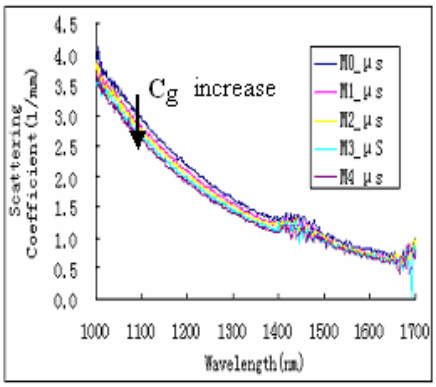
4. Results and discussions

Optical parameters of different samples were calculated from diffuse reflectance, total diffuse transmittance, collimated transmittance with inverse Monte Carlo simulations. In Fig. 4, (a), (b) and (c) show spectral absorption coefficient, scattering coefficient and anisotropic factor. It can be seen clearly that absorption coefficient and anisotropic factor change slightly while glucose concentration varies from 0 to 4000 mg/dl. Meanwhile, scattering coefficient, shown in (c) presents obvious descending while the concentration of glucose increases. Plot (d) is the relation between optical parameters and glucose concentration at the selected wavelength of 1600 nm, which is in the absorbing band of glucose.

For further validation of the influence of glucose concentration variation on diffused light along different source-detector separation, we performed Monte Carlo simulation with the optical properties and their dependence on glucose concentration. The results are plotted in Fig. 5, line with square, diamond, triangle corresponding to the change due to variation of absorption coefficient, scattering coefficient, and anisotropic factor respectively. And line with cross is the total effect of all these three parameters. From line with cross, points of zero sensitivity and maximal sensitivity approach to 1.5 mm and 2.0 mm. Further application of floating-reference method should involve mathematical methods such as partial least square (PLS), principal component analysis (PCA), or net signal analysis (NSA), which is beyond the covering of this presentation.



a



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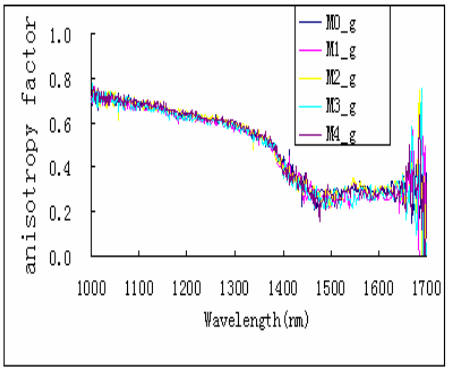

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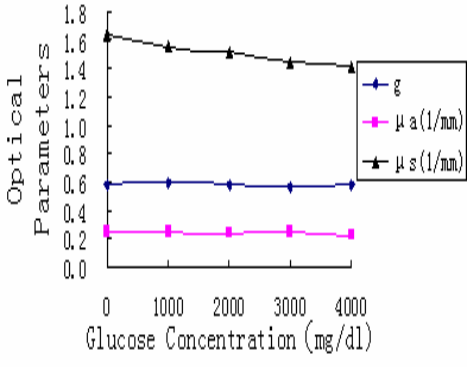

d

Fig. 4. Optical parameters of milk with different concentrations of glucose.

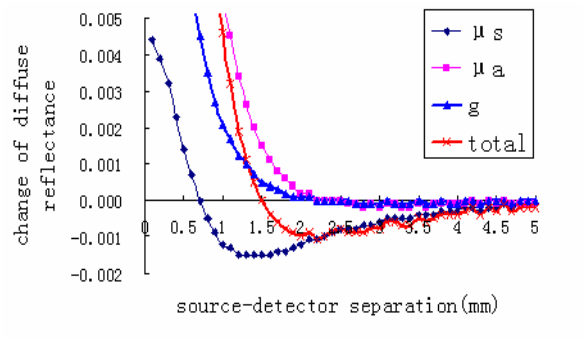

Fig. 5. Change of diffuse reflectance due to variation of optical parameters.

5. Conclusions

Weak signal and great background variation prohibit the realization of noninvasive measurement of blood glucose with NIR spectroscopy. When instruments achieve a high level of signal to noise ratio, physiological variation other than glucose concentration becomes the dominant noise. After analyzing the sensitivity of glucose concentration on diffuse reflectance at different source-detector separation, floating-reference method is put forward for the first time. As a novel method, much research work is needed before its successful application. However, it doesn't prevent floating-method being expected to attribute significance to improve precision of noninvasive measurement of blood glucose with NIR.

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