Reference point of floating-reference method for blood glucose sensing

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Received August 12, 2009

A problem in terms of the accuracy of noninvasive measurement of blood glucose with near-infrared (NIR) spectroscopy is mainly caused by the weak glucose signal and strong background variations. We report the existence of the radial reference point in a floating-reference method, which is supposed to solve this problem. Based on the analysis of the infinite diffusion theory, the local condition of the reference point is deduced theoretically. Then the experiments using the intralipid solutions are constructed to testify the existence of the reference point. In order to further validate our results, Monte Carlo simulations are performed to calculate the diffused light distribution according to the variation of the glucose concentration in the intralipid solutions. All the reference points existing in three-layer skin model are also listed at the wavelength of 1200 – 1700 nm.

OCIS codes: 300.0300, 070.4790.

doi: 10.3788/COL20100804.0421.

In the past few decades, various optical methods have been developed to achieve noninvasive and continuous monitoring of blood glucose concentration in human body, which is an urgent requirement for diabetic patients[1]. Among these methods, near-infrared (NIR) spectroscopy is one of the most promising methods for noninvasive applications[2−6]. Based on chemometrics, NIR spectroscopy has shown great potential in noninvasive measurement of physiological information, such as glucose and hemoglobin concentration in biological tissues[7,8]. Maruo *et al*. applied a new methodology that could build calibration models essentially from numerical simulation, while the conventional methodology required pre-experiments such as sugar tolerance tests[9]. Kramer *et al*. measured the reference spectrum repeatedly in the warming-up stage of their spectrometer, and based on the acquired spectra, corrected their predefined calibration model[10]. Despite of great efforts made by optical scientists and engineers, products available clinically have not been realized. The major obstacle is the low sensitivity of the diffuse reflectance to the blood glucose concentration because of the existence of the weak blood glucose signal in a great variety of human physical backgrounds, which results in difficulties to extract effective glucose information. This phenomenon also appears in *in vitro* experiments due to the variable background noise. A standard material that will diminish the noise disturbance to the componential signal can be easily found for calibration in *in vitro* experiments[11]. However, it is hard to find the reference material similar to the physiological characteristics. So clinical applications of this technology have been limited.

Previously, our group proposed the floating-reference method to eliminate the physiological noise[12]. The glucose concentration will change the absorption and scattering characteristics of human tissue, which synthetically results in the variation of diffuse reflectance. A special source-detector separation exists to be the internal reference point for blood glucose sensing, where the reflected light intensity is insensitive to the variation of glucose concentration in virtue of the counteractive effects of absorption and scattering. So the diffuse reflected light at this separation contains the information of human physiological changes, other than the blood glucose concentration. The spectrum measured in the reference point can be used as a reference signal to effectively diminish the influence of biological interference and enhance the sensitivity of glucose measurement.

The key technology of floating-reference method is to locate the reference point. We analyze the infinite solution of diffusion equation. Since the condition of the experiment that we construct is infinite, the distribution of the diffused light is expressed as[13]

$$\Phi(r) = \frac{1}{4\pi D}\frac{1}{r}\exp(-\mu_{\rm eff} r), \tag{1}$$

where $\Phi(r)$ denotes the fluence rate, r denotes the separation between the source and the detector, $D = \{3[\mu_{\rm a} + \mu'_{\rm s}]\}^{-1}$ is the diffusion coefficient and $\mu_{\rm eff} = \{3\mu_{\rm a}[\mu_{\rm a} + \mu'_{\rm s}]\}^{1/2}$ is the effective reduced coefficient; $\mu'_{\rm s} = (1-g)\mu_{\rm s}$; $\mu_{\rm a}, \mu_{\rm s}$, and g are the absorption coefficient, scattering coefficient, and anisotropic factor of the sample, respectively. The variation of the glucose concentration $c_{\rm g}$ will cause changes in those coefficients, and then cause the variation of the light intensity. So the sensitivity of light intensity to glucose concentration can be expressed as

$$S = \frac{{\rm d}\Phi(r)}{{\rm d}c_{\rm g}} = \frac{\partial\Phi(r)}{\partial\mu_{\rm a}}\frac{{\rm d}\mu_{\rm a}}{{\rm d}c_{\rm g}} + \frac{\partial\Phi(r)}{\partial\mu'_{\rm s}}\frac{{\rm d}\mu'_{\rm s}}{{\rm d}c_{\rm g}}, \tag{2}$$

where

$$\frac{\partial\Phi(r)}{\partial\mu_{\rm a}} = \frac{1}{4\pi r}\left[3 - \frac{r}{2}\left(\mu_{\rm a}^{-\frac{1}{2}}D^{-\frac{3}{2}} + 3\mu_{\rm a}^{\frac{1}{2}}D^{-\frac{1}{2}}\right)\right]\exp(-\mu_{\rm eff} r), \tag{3}$$

$$\frac{\partial\Phi(r)}{\partial\mu'_{\rm s}} = \frac{1}{4\pi r}\left(3 - \frac{3r}{2}\mu_{\rm eff}\right)\exp(-\mu_{\rm eff} r). \tag{4}$$

The existing condition of the reference point $r_{\rm r}$ is that S equals to zero due to the counteractive effects of absorp-

tion and scattering, which can be described as

$$\left[3-\frac{r_{\rm r}}{2}\left(\mu_{\rm a}^{-\frac{1}{2}}D^{-\frac{3}{2}}+3\mu_{\rm a}^{\frac{1}{2}}D^{-\frac{1}{2}}\right)\right]\times\delta\mu_{\rm a}+\left(3-\frac{3r_{\rm r}}{2}\mu_{\rm eff}\right)\delta\mu_{\rm s}'=0, \quad (5)$$

where $\delta\mu_{\rm a}=\mathrm{d}\mu_{\rm a}/\mathrm{d}C_{\rm g}$ denotes the change of $\mu_{\rm a}$ caused by the variation of glucose concentration; $\delta\mu_{\rm s}'=\mathrm{d}\mu_{\rm s}'/\mathrm{d}C_{\rm g}$ denotes the change of $\mu_{\rm s}'$ caused by the variation of glucose concentration.

According to Eq. (5), we can obtain

$$r_{\rm r}=\frac{6(\delta\mu_{\rm a}+\delta\mu_{\rm s}')}{\delta\mu_{\rm a}\left(\mu_{\rm a}^{-\frac{1}{2}}D^{-\frac{3}{2}}+3\mu_{\rm a}^{\frac{1}{2}}D^{-\frac{1}{2}}\right)+3\mu_{\rm eff}\delta\mu_{\rm s}'}=\frac{(\delta\mu_{\rm a}+\delta\mu_{\rm s}')}{\delta\mu_{\rm a}\left(\frac{\mu_{\rm t}'}{\mu_{\rm a}}+1\right)+\delta\mu_{\rm s}'}\times\frac{2}{\mu_{\rm eff}}, \quad (6)$$

where $\mu_{\rm t}'=\mu_{\rm a}+(1-{\rm g})\mu_{\rm s}$.

Obviously, $r_{\rm r}$ can be divided into two parts. The first part can be expressed as $\rho(\Delta c_{\rm g})$. It mainly represents the relation between the variations of optical properties and glucose concentration. The second part is determined by $\mu_{\rm a}$ and $\mu_{\rm s}'$ of the sample. Equation (6) can be expressed as

$$r_r=\rho(\Delta c_{\rm g})\times\frac{2}{\mu_{\rm eff}}. \quad (7)$$

For the same sample, the second part of Eq. (7) is fixed. Then the location of reference point is mainly affected by the coefficient $\rho(\Delta c_{\rm g})$.

We use 10% intralipid solution as the sample. The optical parameters are based on Ref. [14], and the influence of glucose concentration on the sample is based upon Ref. [15]. At the wavelength of 1300 nm, the reference point of 10% intralipid is calculated at the source-detector separation of 1.1 mm according to Eq. (6).

To experimentally validate the existence of reference point, the distributions of diffuse reflected light are detected in the 10% intralipid solutions with different glucose concentrations. As shown in Fig. 1, two optical fibers are immerged into the intralipid solution at the same level. The incident fiber is fixed, while the collecting fiber moves along the radial direction from 0 to 2 mm, at 0.08-mm interval. A laser diode (QDFBLD-1300-20, Qphotonics, LLS, USA), working at the wavelength of 1310 nm and the power of 20 mW, is used to provide the NIR light. The light is injected into the phantom through the incident fiber, and then the diffuse light is detected by the InGaAs photodiode (G5853-203, Hamamatsu Photonics K.K., Japan) through the collecting fiber, which is then input into the computer after being digitized by a 16-bit data acquisition card (PCI-MIO-16XE-50, National Instrument Inc., USA).

By processing the data, the difference of diffuse reflectance is obtained between the pure intralipid solution and intralipid solutions with different glucose concentrations. Figure 2 shows that the radial distribution of diffuse reflected light changes with the variation of glucose

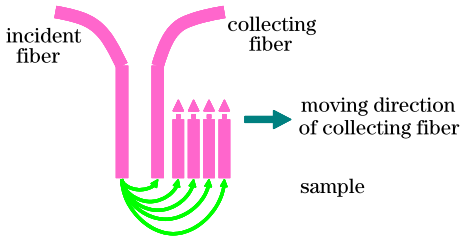

Fig. 1. Radial light distribution measurement system.

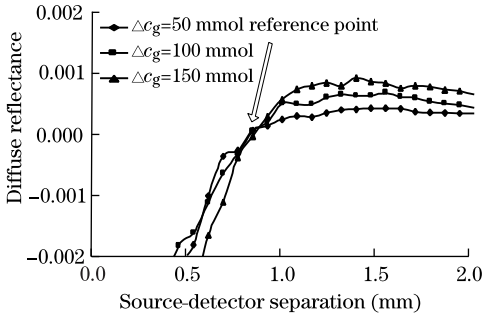

Fig. 2. Reference point of glucose in 10% intralipid solution by experiment.

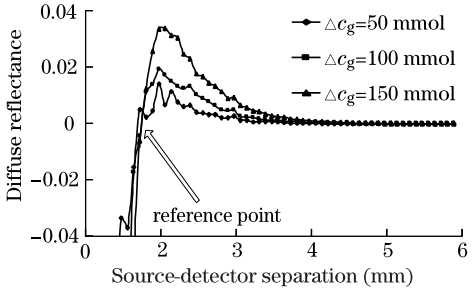

Fig. 3. Reference point of glucose in 10% intralipid solution by simulation.

concentration, and the reference point of 10% intralipid solution is apparently located at the source-detector separation of 0.8 mm at the wavelength of 1310 nm.

In order to further validate the existence of the reference point, Monte Carlo simulation[16] is then performed. In Monte Carlo code, the photons are injected into the medium and their trajectories are traced according to statistical rules until they are detected or exited. The ratio of reflective photons, which represents the diffuse reflected light intensity at different radial distances, can be calculated by the program. After deducting the light intensity of the background sample (pure intralipid solution), we can get the change of reflectance induced by glucose against with different source-detector separations. As shown in Fig. 3, at the wavelength of 1300 nm, a radial reference point where the diffuse reflectance is insensitive to the variation of glucose concentration exists at the source-detector separation of 1 mm in 10% intralipid solution, which is consistent with the results of experiment and analytical theory.

Because the skin can be regarded as a semi-infinite medium and multiple layers, it is much harder to be managed using the diffusion theory. In this case, Monte

Table 1. The Reference Points of Three-Layer Skin Model at 1200 – 1700 nm

Wavelength (nm)	Layer	μ_a (cm^{-1})	μ_s(cm^{-1})	g	Reference Point (mm)
1200	Epidermis	0.2869	152.7897	0.9	3.1
	Dermis	0.8607	152.7897	0.9	
	Subcutaneous	2.623	96.9951	0.9	
1250	Epidermis	0.2545	151.7857	0.9	2.2
	Dermis	0.6991	151.7857	0.9	
	Subcutaneous	0.8688	96.0714	0.9	
1300	Epidermis	0.2049	148.4979	0.9	2.8
	Dermis	0.7787	148.4979	0.9	
	Subcutaneous	0.2049	94.4206	0.9	
1350	Epidermis	0.8065	147.4194	0.9	1.8
	Dermis	2.1505	147.4194	0.9	
	Subcutaneous	0.4301	93.5484	0.9	
1400	Epidermis	3.6885	144.6352	0.8804	1.4
	Dermis	11.2295	144.6352	0.8804	
	Subcutaneous	1.8852	91.8455	0.8804	
1450	Epidermis	6.3441	143.5484	0.8587	0.9
	Dermis	19.4086	143.5484	0.8587	
	Subcutaneous	1.7742	90.9677	0.8587	
1500	Epidermis	4.4672	140.7725	0.8618	none
	Dermis	14.4672	140.7725	0.8618	
	Subcutaneous	1.8852	88.8412	0.8618	
1600	Epidermis	1.5574	137.7682	0.9	none
	Dermis	5.2869	137.7682	0.9	
	Subcutaneous	0.8197	86.6953	0.9	
1700	Epidermis	1.2295	134.7639	0.9	none
	Dermis	4.877	134.7639	0.9	
	Subcutaneous	9.3443	84.97885	0.9	

Carlo simulation is the optimal method to deal with three-layer boundary conditions. In this simulation, the structure of the human skin is regarded as three layers, namely epidermis, dermis, and subcutaneous tissue. The thicknesses of the first and second layers are 0.5 and 3.5 mm, respectively. The third layer is assumed to be infinite. The optical parameters are based on Ref. [17].

The changes of optical parameters in dermis are only considered according to the variations of glucose concentrations, whereas the parameters of epidermis and subcutaneous tissue are supposed to be constant. The reference points at the wavelength of 1200 – 1700 nm are shown in Table 1. The tissue optical parameters of different skin layers which we input in Monte Carlo program are also listed. We can see that the reference points exist at the wavelength of 1200 – 1450 nm and there is no reference point for the wavelength of 1500 – 1700 nm, which validate the characteristic of wavelength-dependence. The photons for Monte Carlo simulation are about 10^8.

The radial reference point is analyzed aiming at the application of floating-reference method. By the sample of 10% intralipid, we investigate the existence characteristics in three aspects: the analytical theory, the *in vitro* experiment, and Monte Carlo simulation. All these results validate the existence of the reference point. But in *in vivo* measurement, the variability of optical characteristics on living body is obvious and the diversification of races, ages, and appearances will lead to differences in skin tissue structure properties. They both affect the reference point in the actual *in vivo* measurement. These influences on the reference point have been discussed[18], and further investigations should be conducted for the application of this novel method.

In conclusion, a novel method called floating-reference method is proposed to solve the problem of weak glucose signal and strong background variations in noninvasive measurement of blood glucose with NIR spectroscopy. The key factor of this method is whether a reference point exists. Based on the diffusion equation, we analyze the sensitivity of the diffused light to the variation of the glucose concentration, and then derive the condition and distribution characteristics of the reference point. The 10% intralipid solution is constructed as the sample. At the wavelength of 1300 nm, the reference point is calculated at the source-detector separation of 1.1 mm. The *in vitro* experiment is performed by the double-fiber system, and the result shows that the diffused light is not sensitive to the variation of glucose concentration at the location of 0.8 mm. For further validation, Monte Carlo method is used to calculate the diffused light distribution. The result indicates that the reference point is located at about 1 mm. The simulation results of reference point in three-layer skin model are given at the wavelength of 1200 – 1700 nm. The results of the experiment and simulation show that the reference point could be found in a particular source-detector location in particular phantom, which provides guarantee for further research of floating-reference method.

This work was supported by the "111" Project of China (No. B07014), the National Natural Science Foundation of China (Nos. 30600126, 30700168, and 60938002), and the Research Fund for the Doctoral Program of Higher Education of China (No. 20070056069).

References

1. O. S. Khalil, Diabetes Technol. Ther. **6,** 660 (2004).
2. W. Chen, R. Liu, H. Cui, K. Xu, and L. Lü, Chin. Opt. Lett. **2,** 411 (2004).
3. J. T. Olesberg, L. Liu, V. V. Zee, and M. A. Arnold, Anal. Chem. **78,** 215 (2006).
4. S. Xie, H. Yang, Z. Guo, H. Li, and S. Liu, Chin. Opt Lett. **6,** 928 (2008).
5. Y. Liu, X. Chen, and A. Ouyang, Acta Opt. Sin. (in Chinese) **28,** 478 (2008).
6. H. Ao, D. Xing, H. Wei, G. Wu, and J. Lu, Chinese J. Lasers (in Chinese) **35,** 792 (2008).
7. K. Maruo, T. Oota, M. Tsurugi, T. Nakagawa, H. Arimoto, M. Tamura, Y. Ozaki, and Y. Yamada, Appl. Spectrosc. **60,** 441 (2006).
8. J. Lee, D. J. Saltzman, A. E. Cerussi, D. V. Gelfand, J. Milliken, T. Waddington, B. J. Tromberg, and M. Bren-

ner, Physiol. Meas. **27,** 757 (2006).
9. K. Maruo, T. Oota, M. Tsurugi, T. Nakagawa, H. Arimoto, M. Hayakawa, M. Tamura, Y. Ozaki, and Y. Yamada, Appl. Spectrosc. **60,** 1423 (2006).
10. K. E. Kramer and G. W. Small, Appl. Spectrosc. **61,** 497 (2007).
11. X. Gu, R. Liu, W. Chen, and K. Xu, Proc. SPIE **5696,** 222 (2005).
12. Y. Luo, L. An, Z. Ma, R. Liu, and K. Xu, Proc. SPIE **6094,** 60940K (2006).
13. T. J. Farrell, M. S. Patterson, and B. Wilson, Med. Phys. **19,** 879 (1992).
14. T. L. Troy and S. N. Thennadil, J. Biomed. Opt. **6,** 167 (2001).
15. M. Kohl, M. Essenpreis, and M. Cope, Phys. Med. Biol. **40,** 1267 (1995).
16. L. Wang, S. L. Jacques, and L. Zheng, Comput. Methods Programs Biomed. **47,** 131 (1995).
17. K. Maruo, M. Tsurugi, J. Chin, T. Ota, H. Arimoto, Y. Yamada, M. Tamura, M. Ishii, and Y. Ozaki, IEEE J. Sel. Top. Quantum Electron. **9,** 322 (2003).
18. Y. Yang, K. Xu, L. Ding, Z. Shi, and W. Chen, Proc. SPIE **7186,** 71860N (2009).