Scattering-independent glucose absorption measurement using a spectrally resolved reflectance setup with specialized variable source-detector separations

JIN LIU,1,4 CAIGANG ZHU,2,4 JINGYING JIANG,3,5,6 AND KEXIN XU1,5,7

1State Key Laboratory of Precision Measuring Technology and Instruments, Tianjin University, Tianjin, China
2Department of Biomedical Engineering, Duke University, Durham, NC 27708, USA
3Paul C Lauterbur Research Center for Biomedical Imaging, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China
4These authors contributed equally to this work.
5These senior authors contributed equally to this work.
6jy.jiang@siat.ac.cn
7kexin@tju.edu.cn

Abstract: We report a novel approach for the accurate measurement of glucose absorption in turbid media using a spectrally resolved reflectance setup. Our proposed reflectance setup with specialized variable source-detector separations enables scattering-independent absorption measurement, which is critical to in vivo long-term glucose concentration monitoring. Starting from the first-order approximation of the radiative transfer equation (RTE), we developed a scattering-independent glucose absorption measurement method and then evaluated this approach by Monte Carlo simulations as well as tissue-mimicking phantom studies in which glucose concentration was accurately measured. Our study demonstrates the potential of our proposed scattering-independent absorption measurement technique as an effective tool to quantify glucose levels in turbid media, which is an important step towards future in vivo long-term glucose concentration monitoring in human subjects.

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1. Introduction

Near-infrared spectroscopy (NIRS) techniques have been explored extensively for biomedical applications in the past decade [1]. Particularly, NIRS has been considered as one of the most promising techniques for in vivo glucose monitoring as it can potentially provide simple, economical, non-invasive, and convenient real-time measurement on human subjects [2–4]. Truly non-invasive continuous glucose monitoring techniques would allow millions of diabetes patients to check their metabolic control at their best conveniences [5].

NIRS based glucose monitoring methods can be divided into two categories. The first category of NIRS methods applies the glucose scattering property to predict glucose concentrations. Bruulsema et al found that there was a strong correlation between blood glucose concentrations in diabetics and noninvasively measured tissue scattering coefficients [6]. Heinemann et al further demonstrated that an increase of glucose concentration leads to a decrease of scattering coefficient of turbid suspension in both phantom studies and Type I diabetic patients [7]. Later the same group used a portable NIRS system to monitor glucose levels by incorporating the glucose scattering information during an oral glucose tolerance test [2]. However, they found that it was challenging to achieve clinically acceptable accuracy for in vivo glucose measurement based on glucose scattering information. This is likely because: (1) glucose-induced scattering change is too small to be detected accurately [7]; and
body temperature perturbation may induce significant changes in tissue scattering [6] that could reduce accuracy in glucose scattering quantification.

The second category of NIRS methods uses the Beer’s law to estimate glucose concentrations by quantifying glucose absorption. The great potential of absorption-based approach for glucose monitoring is evidenced by the fact that there were over hundreds of relevant papers published over the past few years [8–10]. The key for absorption based NIRS approach for glucose quantification is to extract glucose absorption features from measured tissue spectral data. Tissue absorption in the NIR window is mainly contributed by water, fat, hemoglobin et al [11,12] in addition to glucose. Several analyzing methods [10] including principal component regression (PCR), partial least squares regression (PLSR), net analyte signal (NAS) have been explored extensively for extraction of meaningful glucose absorption features. It has been found that the most useful absorption peaks for glucose centration measurement are located at 960 nm, 1150 nm, 1400 nm, and 1600 nm [12]. It is worth mentioning that body temperature change may affect tissue absorption as well [13,14], however, this effect can be easily excluded by using special data processing techniques [10,14]. Basically, body temperature was treated as a component similar to the other absorbers in the spectral data processing [15,16]. Tissue background scattering is another major factor that could alter the glucose absorption features extraction [17,18]. Many analyzing techniques have been developed to reduce scattering effect and some of them achieved decent results as long as sufficient training data was used [19–22], while most of these techniques failed when they were used for in vivo long-term glucose monitoring [23,24]. This is likely because tissue scattering is sensitive to body temperature and motion artifact et al [25]. In order to adapt absorption based NIRS techniques to accurately monitor glucose levels in human subjects in vivo, it is vital to minimize tissue background scattering effect.

To minimize the scattering effect on tissue absorption measurement, many other groups have developed different isobaric-points based approaches to perform scattering-independent optical measurements. Kumar et al reported two opposite sensitivities of NIR reflectance to the reduced scattering coefficient and demonstrated that the sensitivity of the reflectance to the variations of the reduced scattering coefficient can be minimized for some source and detector separations [26]. Mourant et al found that for appropriate separations between source and detector fibers, the optical path length of the collected photons does not depend on scattering parameters for a range of biological tissue relevant optical properties [27]. Liu et al conducted a unified analysis on these findings to provide some theoretical support and meaningful guidelines for the use of isobaric-points based approaches [28]. Kanick et al later developed an empirical model to describe this phenomenon and utilized their model to explore the path length isobaric-points in both ultraviolet/visible and near-infrared regions [29]. Mehrabi et al have adapted this isobaric-points based approach in an oximeter design to reduce the influence of unconscious movement [30]. Duadi et al [31] has taken an angular-isobaric-points based approach to perform scattering insensitive reflectance measurements on cylindrical tissues like fingertip or earlobe with a goal of quantifying tissue blood content. Their angular-based source-detector design will potentially improve the accuracy of vascular endpoints quantification using a pulse oximeter [32].

In our study, we further developed the isobaric-points based approach by providing a strong theoretical support and demonstrating its use for glucose concentration monitoring. Starting from the first-order approximation of the radiative transfer equation (RTE) [33], we developed a novel equation to describe the relationship between the scattering independent source-detector separations and the tissue background optical properties. We then further evaluated our approach by using Monte Carlo simulations [34] as well as tissue mimicking phantom studies. By using a set of specialized source-detector separations, our method is only sensitive to glucose absorption changes but insensitive to medium background optical properties. To demonstrate the proof-of-concept, we reported a reflectance setup with
specialized variable source-detector separations to enable accurate glucose absorption measurement from a turbid medium. Our optical reflectance setup was tested by tissue-mimicking phantom studies from which scattering-independent glucose absorptions were accurately extracted. The foundation of our technique is that diffuse reflectance intensities are insensitive to medium background optical properties but sensitive to the absorption perturbations at certain special source-detector distances for a given turbid medium [27]. Our study demonstrates the great potential of our technique for scattering-independent glucose absorption measurement in turbid media, which is an important step towards future long-term in vivo glucose concentration monitoring in human subjects. It should be noted that the isobaric-points based techniques would generally be applicable to the characterization of other tissue components [35] in addition to glucose, other fields including milk purity characterization, juice purity characterization, and so on, as long as the specialized source-detector separations for a given turbid medium were found.

2. Materials and methods

2.1 Scattering-variation-insensitive source-detector separations (SVI-SDS)

The first-order approximation of steady-state diffuse light flux density \( \varphi(\rho) \) in an infinite media is:

\[
\varphi(\rho) = \frac{1}{4\pi D} \exp(-\mu_{\text{eff}} \cdot \rho)
\]

where \( \rho \) is source-detector separation (SDS); \( \mu_{\text{eff}} \) is the effective attenuation coefficient, defined as \( \mu_{\text{eff}} = \sqrt{3 \mu_a \cdot (\mu_a + \mu_s')} \) in which \( \mu_a \) is the absorption coefficient; \( \mu_s \) is the scattering coefficient, \( \mu_s' \) is the reduced scattering coefficient defined as \( \mu_s' = (1-g) \cdot \mu_s \) in which \( g \) is anisotropy factor, \( D \) is diffusion coefficient defined as \( D = (3 \cdot (\mu_a + \mu_s'))^{-1} \).

Partial differentiations of the flux density \( \varphi(\rho) \) over scattering and absorption are:

\[
S_{\varphi, s} = \frac{\partial \varphi}{\partial \mu_s} = \varphi \cdot (3D - 3 \cdot 2 \rho D \mu_{\text{eff}}) 
\]

\[
S_{\varphi, a} = \frac{\partial \varphi}{\partial \mu_a} = \varphi \cdot (3D - 2 \rho D \mu_{\text{eff}} - \frac{1}{2} \rho D^{-1} \mu_{\text{eff}}^{-1})
\]

Scattering-variation-insensitive SDS (SVI-SDS) denoted by \( \rho^* \) can be found from Eq. (2) by setting \( S_{\varphi, s} = 0 \). Similarly, absorption-variation-insensitive SDS, denoted as \( \rho^\prime \), can be found from Eq. (3) by setting \( S_{\varphi, a} = 0 \). In NIR band, skin tissue optical properties enable it commonly meets \( \rho^\prime \ll \rho^* \) & \( \rho^s \approx 0 \), then we have

\[
\rho^* \bigg|_{\rho^s \approx 0} = \frac{2}{\mu_{\text{eff}}} \quad \rho^\prime \bigg|_{\rho^s \approx 0} = \frac{2}{\mu_{\text{eff}} + \frac{1}{3} D^{-2} \mu_{\text{eff}}^{-1}}
\]

At SVI-SDS, scattering and absorption variation induced diffuse light energy flux density change \( \Delta \varphi(\rho) \) is:

\[
\Delta \varphi \big|_{\rho \rightarrow \rho^*} = S_{\varphi, a} \cdot \Delta \mu_a + S_{\varphi, s} \cdot \Delta \mu_s = -\frac{1}{\mu_s} \cdot \varphi \cdot \Delta \mu_s
\]
Diffuse reflectance intensity is expressed as \( I(\rho) = \varphi(\rho) \cdot A \cdot \Theta \), where \( A \) is the collection area and \( \Theta \) is the collection angle. According to Eq. (5), diffuse reflectance detected at SVI-SDS will be only sensitive to absorption variation. Further, scattering and absorption variation induced diffuse reflectance change for a medium with background absorption \( \mu_s \) is:

\[
\frac{\Delta I(\rho^*)}{I(\rho^*)} = \frac{\Delta \varphi(\rho^*)}{\varphi(\rho^*)} = \frac{\Delta \mu_s}{\mu_s}
\]  

(6)

If we define \( R_l(\rho) \) as \( R_l(\rho) = \frac{\Delta I(\rho)}{I(\rho)} \) and \( R_{r_s} \) as \( R_{r_s} = \frac{\Delta \mu_s}{\mu_s} \), we get:

\[
R_l(\rho^*) = R_{r_s}
\]  

(7)

where the reflectance intensity change measured at \( \rho^* \) is equivalent to the medium’s absorption change.

The SVI-SDS derivation from an infinite media from Eq. (1) to (7) will be generally applicable to a semi-infinite medium, in which the diffusion approximation is:

\[
I(\rho) = \frac{1}{4\pi} \left[ Z_0 (\mu_{\text{eff}} + \frac{1}{r_1}) \exp(-\mu_{\text{eff}} r_1) + (Z_0 + 2Z_0)(\mu_{\text{eff}} + \frac{1}{r_2}) \exp(-\mu_{\text{eff}} r_2) \right]
\]  

(8)

where \( r_1 = \sqrt{\rho^2 + Z_0^2} \), \( r_2 = \sqrt{(\rho^2 + Z_0^2)^2} \) and \( Z_0 = 1/\mu_s \), \( Z_0 = 2D \). SVI-SDS, i.e. \( \rho^* \), for a semi-infinite medium can be easily found by numerical simulations.

### 2.2 Monte Carlo simulations

Monte Carlo (MC) method was used to validate SVI-SDS in a homogenous skin tissue model. The public MC code \[34\] was modified to simulate light transport in a semi-infinite turbid media. Illumination and detection configurations were illustrated in Fig. 1. Point source was used for illumination and ring fibers were used for collection. Ring thickness of each collection fiber was set to be 0.01 cm and source-detector separations were varied from 0.01 cm to 1 cm. The numerical aperture (NA) for all collection fibers was set to 1.0 to ensure sufficient signal will be collected.

![Fig. 1. Illumination and collection configurations used in MC simulations. Point source was used for illumination while ring fibers were used for collection. Source-detector separations were varied from 0.01 cm to 1 cm by every 0.01 cm. The numerical aperture (NA) for all collection fibers was set to 1.0.](image)

Diffuse reflectance intensities at each of the 20 wavelengths (1000–1400 nm with 20 nm interval) for a range of source-detector separations were simulated. Generally, two groups of skin tissue-mimicking phantoms were simulated. The first group of phantoms was glucose-free media with a wide range of background absorption and scattering. This group of simulations was used to simulate SVI-SDS for given tissue background optical properties. The second group of turbid phantoms contained glucose with varying concentrations (180-900 mg/dL by every 180 mg/dL). Diffuse reflectance intensities from these phantoms were
simulated at their corresponding SVI-SDS acquired from the first group of phantoms. The second group of phantoms was used to validate the SVI-SDS based glucose prediction model. In total, one billion $10^9$ photons were launched in all MC simulations. The simulated diffuse reflectance intensities were used to find the SVI-SDS based on Eqs. (1)-(8) described above. Optical properties of the phantoms in the wavelength range of 1000–1400 nm [36–38] along with their corresponding theoretical SVI-SDS are summarized in Fig. 2. The theoretical SVI-SDS values (Figs. 2(D)-(E)) calculated by Eq. (4) showed that lower absorption levels lead to larger SVI-SDS values, higher reduced scattering level leads to a smaller SVI-SDS. The wavelength-dependent optical parameters of glucose solutions were estimated based on the equation reported by Kohl et al [39].

![Image](image_url)

**Fig. 2.** (A)-(C): Optical properties of turbid media used in MC simulations, (D) corresponding theoretical SVI-SDS for a range of absorption coefficients and reduced scattering coefficients, (E) contour plot of theoretical SVI-SDS. Note: $\mu_a$, absorption coefficient; $\mu_s$, scattering coefficient; $\mu_s^*$, reduced scattering coefficient; $g$, anisotropy. The g values for three different Intralipid levels are comparable to each other. The theoretical SVI-SDS values were calculated using Eq. (4).

### 2.3 Phantoms and optical measurements

Skin tissue mimicking phantom studies were performed to further evaluate the SVI-SDS based approach for glucose concentration prediction. Intralipid based turbid phantoms with glucose were prepared for optical experiments. Intralipid concentrations were set to be 5%, 10%, and 15%. For each set of intralipid phantoms, glucose concentration was varied from 0 to 6000 mg/dL by every 1000 mg/dL. Pure glucose-water solutions with the same concentrations were also prepared to serve as references.

A custom designed optical spectroscopy system was used to perform diffuse reflectance measurements on phantoms. The optical measurement system is briefly illustrated in Fig. 3. The system consists of a super-continuum laser source (SC46, 240-2000 nm, YSL photonics, China), an Acousto-Optic Tunable Filter (AOTF), a Glan-Taylor prism, a stepper motor, and an InGaAs photoelectric detector (Hamamatsu Photonics, G5851-21). Two optical fibers (NA = 0.27, Nanjing Chunhui Science and technology industrial Co. Ltd, China) were used for illumination (600 μm) and collection (200 μm) respectively. The stepper motor was used to change source-detector fiber distance. The source-detector distances can be varied from 0.6 mm to 50.6 mm by every 0.1 mm rapidly. The entire system was controlled by a Labview software.
2.4 Prediction model for glucose concentration estimation

According to Eq. (7), $R_i (\rho^*)$ is a function of tissue background absorption $\mu_b$ and its variation $\Delta \mu_a$. The prediction model based on $R_i (\rho^*)$ is illustrated in Fig. 4.

![Fig. 3. The schematic diagram of the system](image)

Glucose absorption spectra at SVI-SDS extracted from pure glucose solutions and turbid media are expected to be the same if the glucose concentrations in these media are identical, thus reference phantoms could be used as calibration models to predict glucose concentrations from in vivo measurement as long as the SVI-SDS for a tissue equivalent media have been found. These reference phantoms were used to build a PLS prediction model to predict glucose concentration for a new set of measurement. The mean relative error (MRE) based on Eq. (10) was used to evaluate prediction performance.

$$MRE = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{Y_{\text{pred},C_{gi}} - Y_{\text{true},C_{gi}}}{Y_{\text{true},C_{gi}}} \right) \times 100\%$$

(10)

where $Y_{\text{pred},C_{gi}}$ is predicted glucose concentration, $Y_{\text{true},C_{gi}}$ is true answer, $i$ is the number of samples.

To account potential offset caused by the difference among background absorption and scattering of different media, a linear calibration model based on Eq. (11) was used to improve prediction accuracy.

$$Y_{\text{pred},C_{gi}} = K \cdot Y_{\text{pred},C_{gi}} + b$$

(11)

where $Y_{\text{pred},C_{gi}}$ is predicted glucose concentration without offset calibration while $Y_{\text{pred},C_{gi}}$ is the final calibrated glucose concentration. The calibration coefficients $K$ and $b$ can be easily acquired based on phantom studies. If there was small variation in the background absorption and scattering among reference media and target media, we have $K = 1$, $b = 0$. 

![Fig. 4. Prediction model for glucose concentration estimation.](image)
3. Results

3.1 MC simulation of SVI-SDS in turbid media

Figure 5(A) shows MC simulated $R_i$ at different source-detector separations for turbid media with fixed background scattering levels (5% intralipid, $\mu_s = 52.96 \text{ cm}^{-1}$) but with perturbed background absorption levels ($\mu_a = 0.806 \text{ cm}^{-1}$, with 2%, 3%, and 5% perturbations) at 1000 nm. The data shows that the $R_i$ is sensitive to absorption perturbations at all non-zero source-detector distances. Figure 5(B) shows MC simulated $R_i$ at different source-detector distances for turbid media with fixed absorption levels ($\mu_a = 0.806 \text{ cm}^{-1}$) but with perturbed scattering levels (5% intralipid, $\mu_s = 52.96 \text{ cm}^{-1}$, with 2%, 5%, and 10% perturbations) at 1000 nm. The data shows that the $R_i$ is also sensitive to scattering perturbations for most of source-detector distances, however, the $R_i$ is insensitive at certain source-detector distance for a given wavelength. This special source-detector distance will be referred as a SVI-SDS as introduced previously. For example, a SVI-SDS for 1000 nm was found to be about 0.11 cm in Fig. 5(B).

Figure 5(C) shows the $R_i$ at different source-detector distances for turbid media with both perturbed absorption levels and perturbed scattering levels (same as that in (A) and (B)) at 1000 nm. The special source-detector distance for 1000 nm was found to be about 0.09 cm in Fig. 5(C). It should be noted that the special insensitive source-detector distance in Fig. 5(C) was shifted compared to that found in Fig. 5(B). This shift was likely due to the joint effect of absorption and scattering perturbations, thus the special joint point in Fig. 5(C) will be a background absorption and scattering insensitive source-detector distance. Figure 5(D) shows simulated SVI-SDS at all wavelengths (1000-1400 nm) for turbid media with different scattering levels.

![Fig. 5. MC simulation of SVI-SDS in turbid media. (A) $R_i$ at different source-detector distances for turbid media with perturbed absorption levels but fixed scattering levels at 1000 nm; (B) $R_i$ at different source-detector distances for turbid media with perturbed scattering levels but fixed absorption levels at 1000 nm; (C) $R_i$ at different source-detector distances for turbid media with perturbed scattering levels and perturbed absorption levels at 1000 nm; (D) MC simulated SVI-SDSs at 1000-1400 nm for 5%, 10% and 15% Intralipid phantoms.](image-url)
3.2 Glucose concentrations prediction using MC simulated spectra at SVI-SDS

MC simulated spectra from glucose phantom at SVI-SDSs over the band of 1000-1400 nm were used to evaluate the SVI-SDS based approach for the prediction of glucose concentrations. Figure 6(A) shows MC simulated $R_i(\rho')$ spectra for 5% intralipid turbid media with different glucose concentrations. As expected, it shows that $R_i(\rho')$ spectra at certain wavelength band decreased when the glucose concentrations were increased. Figure 6(B) shows MC simulated $R_i(\rho')$ spectra from scattering perturbed turbid media with 900 mg/dL glucose. The intralipid levels were varied from 10% to 16.5%. As expected, the $R_i(\rho')$ spectra did not change with the scattering variations as long as the glucose concentration was fixed. Figure 6(C) shows the PLS model predicted glucose concentrations compared to their true values using MC simulated spectral data. The comparison shows great agreement between the predicted glucose concentrations and their true values when the $R_i(\rho')$ spectra were used in the PLS model. The MRE for glucose concentrations predictions in the media of 5%, 10% and 15% intralipid solutions were 5.9%, 5.4%, and 5.4% respectively.

![Fig. 6. Glucose concentrations prediction using MC simulated spectra at SVI-SDS over 1000-1400. (A) $R_i(\rho')$ spectra for 5% intralipid media with glucose varied from 180mg/dL to 900 mg/dL; (B) $R_i(\rho')$ spectra for intralipid media with different scattering levels for the glucose concentration 900 mg/dL; (C) PLS predicted glucose concentrations against their true values using MC simulated data.](image)

3.3 Glucose concentrations prediction using optically measured spectra at SVI-SDS

Figure 7(A) shows optically measured SVI-SDS values for phantoms with three different intralipid levels using our proposed reflectance setup. Figure 7(B) shows optically measured $R_i = \Delta \mu_r / \mu_s$ spectra from pure glucose solutions which can serve as the standard. The glucose concentrations were varied from 2000 to 6000 mg/dL by every 1000 mg/dL for all data shown here. Figure 7(C) show optically measured $R_i(\rho')$ from 15% intralipid solutions with different concentrated glucose. Clearly, measured spectra show that $R_i(\rho')$ at certain wavelength bands decreased when the glucose concentrations were increased for both pure glucose solutions and intralipid media. Figure 7(D) shows PLS model predicted glucose concentrations compared to their true values using the glucose prediction model built from MC simulations. The comparison shows strong agreement between the PLS model predicted glucose concentrations and their true values when the $R_i(\rho')$ spectra were used in the PLS model. The MRE for all predictions was less than 3% on average.
4. Discussion

Absorption based NIRS techniques are believed to be the most promising approaches for non-invasive glucose quantification on human subjects. However, current existing NIRS techniques still do not meet clinical requirement due to the unsatisfied degree of measurement accuracy. This is likely due to the fact that it is difficult to remove skin tissue background scattering-induced distortions on the measured spectra which can significantly reduce the accuracy of glucose concentration determination. We proposed a reflectance setup with specialized variable source-detector separations to enable scattering-independent glucose absorption measurement. In both of our numerical simulations and phantoms studies, we confirmed that diffuse reflectance intensities for turbid medium were insensitive to tissue background optical properties but sensitive to glucose absorption changes at certain special source-detector distances. Building on this foundation, we developed a novel approach to successfully predict glucose concentration with high accuracy using both MC simulated spectra and optically measured reflectance data. Our reported method offers new opportunities for improving accuracy of glucose concentration measurement using NIRS techniques. Our current study demonstrated the capability of our SVI-SDS based approach for glucose concentration measurement in skin tissue-mimicking phantoms, while our technique will be generally applicable to a range of disciplines as long as the sample is turbid medium.

We used the diffusion equation development process to provide a strong theoretical support for our SVI-SDS based approach. For biomedical applications, MC modeling or calibration phantom studies will be necessary to find accurate SVI-SDS for complex layered tissue models. Our simulated data in Fig. 5(A) showed that there was a great linear relationship between \( R_{\text{rel}}(\rho) \) and \( \rho \) beyond a certain threshold, which suggested that our SVI-SDS approach would be valid as long as the \( \rho^* \) falls in this linear range. We did observe that there were mismatches between the theoretical SVI-SDS values and the SVI-SDS values achieved via MC simulated or phantom studies as shown in Fig. 2(D), Fig. 5(D), and Fig. 7(A). These mismatches further underscored the importance of MC modeling or baseline phantom measurement for SVI-SDS determination. Nevertheless, the RTE equation provided...
a strong theoretical support on our technique and a starting point for one to find accurate SVI-SDS values. In this study, we used simple homogenous tissue models in our MC simulations and phantom experiments that provided SVI-SDS values that have a range of 1-3 mm. We plan to develop a fiber-probe based setup for actual optical measurement in future. A source-detector separation at millimeter scale will be practical for a fiber-probe fabrication. The fiber-probe based approach will help avoid specular reflection by contacting probe on skin surface during an actual measurement. A SVI-SDS that close to 1-3 mm would yield a sensing depth of over 500 µm, which is sufficient enough for measuring vascular network on skin given that vessels are within and under dermis layer, which is about 150 µm deep from tissue surface [40].

In the current proof-of-concept study, we used a glucose concentration range that is much higher than that in human body. To move our technique forward towards human subject glucose quantification, an instrument with higher sensitivity is necessary. Also, more work needs to be done to improve the sensitivity of the SVI-SDS based technique, which can be achieved by increasing the number of most meaningful wavelengths or SVI-SDS. However, there will be a possibility that certain substance other than glucose might show absorption lines in similar wavelength region, thus careful selection of wavelengths is critical for achieving a clinical acceptable specificity. In one word, there will be always a trade-off between the sensitivity and specificity when picking the wavelengths for data processing. To show glucose relevant SVI-SDS for a wide range of wavelengths in the NIR band, more than 9 wavelengths from 1000 nm to 1400 nm were investigated for glucose concentration quantification. Our former study found that the most useful absorption peaks for glucose centration measurement are located at 960 nm, 1150 nm, 1400 nm, and 1600 nm [12]. By using these wavelengths might help improve the specificity for glucose quantification with a reasonable sensitivity. It should be noted that the use of multiple SVI-SDS would potentially increase the complexity of an actual optical system design. We intend to reduce the SVI-SDS number without sacrificing prediction accuracy and specificity. Our preliminary test showed that it is feasible to reduce the SVS-SDS number as long as the most meaningful wavelengths were picked. SVI-SDS can be easily estimated either through MC simulations or tissue-mimicking phantom studies for a given subject as long as its baseline optical properties (assuming it contains minimal glucose content) are given. However, it will not be practical to use MC simulations or phantom studies to find precise SVI-SDS for a particular human subject. To address this challenging, we are currently collecting optical data from volunteers to build a big human skin spectral database from which we intend to find the correlation between SVI-SDS values and human skin optical properties. We expect that the big database will enable us to look for SVI-SDS with a reasonable accuracy for a subject that has a set of skin tissue optical properties that fall within the database.

It has been noticed that it is challenging to adapt the glucose prediction model built from one subject to other different subjects using existing NIRS techniques. This is likely because different subjects might have significantly different background tissue optical properties, while the background tissue scattering properties have a strong effect on the performance of a glucose concentration prediction model. It is also not feasible to use existing NIRS techniques to perform long-term in vivo glucose monitoring since human skin tissue optical properties are sensitive to body temperature change. Our technique might be able to address these problems as the measured diffuse reflectance at SVI-SDS is insensitive to tissue background optical properties. Even if there are considerable differences of tissue background optical properties among different subjects or different time points for the same subject, a simple linear calibration can be easily utilized to reduce any offset of glucose concentrations as illustrated in Fig. 4. Because of the above reasons, our technique will have great potential for in vivo long-term glucose concentration measurement on human subjects.

To move our technique forwards towards clinical applications, we will continue to develop our technique for in vivo studies. Specifically, we are interested in performing long-
term diffuse reflectance measurements at different skin locations on volunteers to understand the key factors that might affect the performance of our method. Ultimately, we will optimize the SVI-SDS number, wavelengths, prediction model etc. with a goal of pushing our technique for human subject applications.

5. Conclusion

Our study demonstrates that our proposed SVI-SDS based technique is an effective approach for scattering-independent glucose absorption measurement, which is critical to in vivo long-term glucose concentration monitoring. Our scattering-independent glucose absorption quantification method provides new opportunities to improve the accuracy of in vivo glucose concentration measurement with an ultimate goal of providing clinical acceptable non-invasive NIR optical instrumentations for diabetes patients.

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Disclosures

The authors declare that there are no known conflicts of interest related to this article.

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