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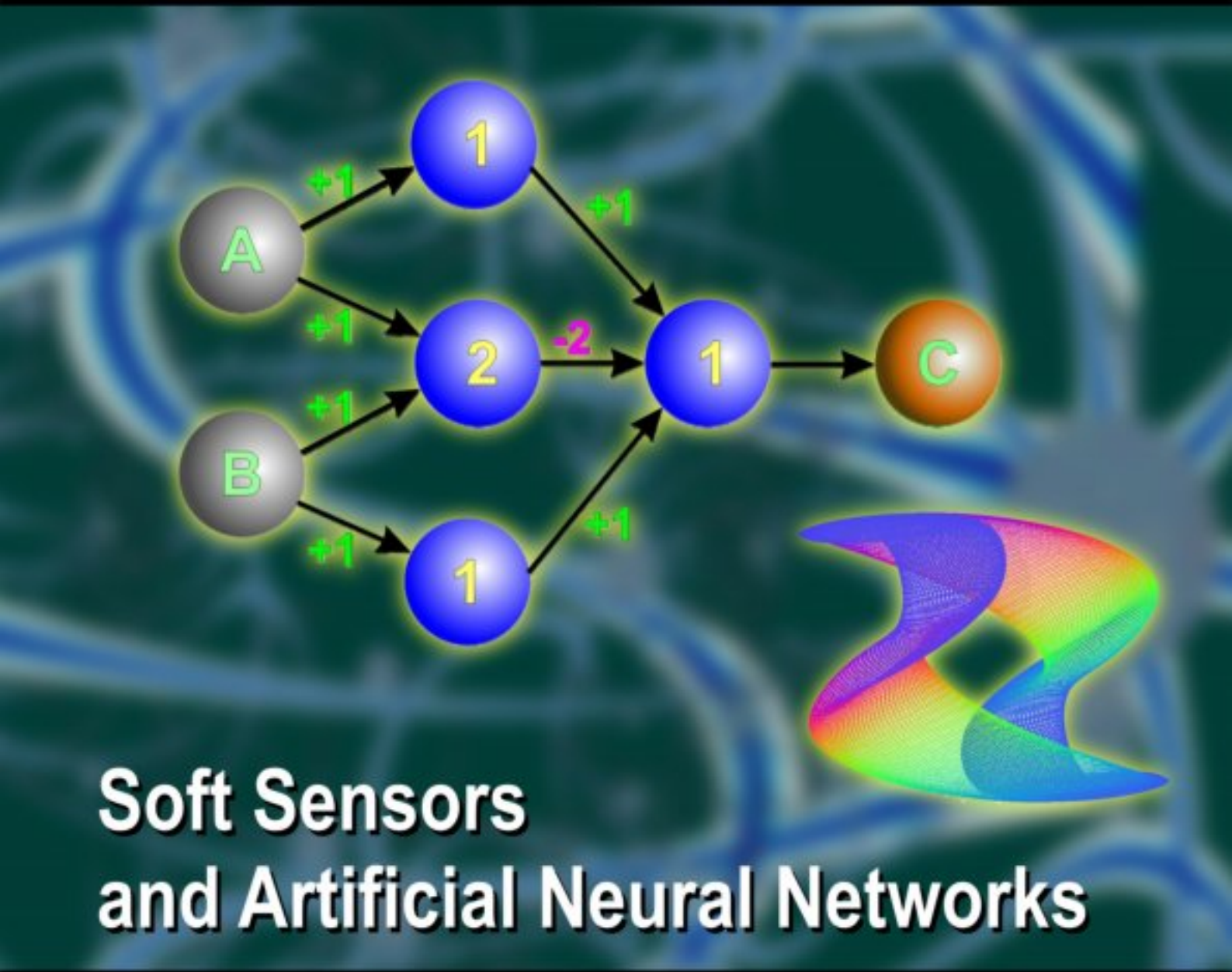

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Investigation of Glucose Non-Invasive Measurement Based on NIR Laser

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Abstract: Near-infrared (NIR) diffuse reflectance spectroscopy represents a feasible and promising approach to the noninvasive prediction of blood glucose concentration. This paper experimentally studied and proposed a novel method to develop a stand-alone measurement system, in which laser beams at several particular wavelengths are collimated and illuminated a sample with low-energy NIR by an optical fibre probe, and the diffused reflectance from the sample is collected by a detector. The experimental scheme of the measurement system has been demonstrated to be reasonable and suitable for detecting the change of diffuse reflected absorbance from phantoms and finger tissue. The experimental results have presented the good correlation between the diffuse reflected absorbance and glucose concentration at several particular wavelengths. The spectra lines are perfectly separate from each other at different glucose concentration in vitro. Obvious differences exist in the diffuse reflected absorbance for different glucose concentration. According to the testing standard of the Oral Glucose Tolerance Test (OGTT), the dynamic changes, which the diffuse reflected absorbance from tissue is accompanied with the change of the glucose concentration, have been explored by taking a certain amount oral glucose solution. The results have presented that the sensing system proposed is already able to sense the glucose change from fingertip tissue though the overlapping spectra are encountered. Also, the temperature effect of the sample on the diffuse reflected absorbance of the glucose has been taken into consideration.

Keywords: Blood glucose; Non-invasive measurement; Near-infrared laser sources; Diffused reflectance; Optical fibre probe

1. Introduction

Glucose is a form of sugar produced when the human body digests carbohydrates (sugars and starches). Glucose is the human body's major fuel for the energy it needs. When insulin is absent or ineffective, the blood glucose level increases. High blood glucose levels can lead to both short and long-term problems. Diabetes is a chronic disease in which the human body does not make, or does not properly use, insulin. There are roughly over 100 million people in the world currently diagnosed with diabetes. The majority of patients with diabetes, as well as diagnosed as pre-diabetic, need to frequently monitor their blood glucose levels, establishing an individual blood glucose profile in order to adjust diet, medication, exercise, or to lower the blood glucose while avoiding hypoglycemia. In well-regulated patients, two or three blood samples are tested for glucose daily and are usually sufficient. In new or difficult patients, or when monitoring for hypoglycemia is required, blood samples may be required in rapid (every few minutes) succession. As a result, an increasing need has developed for non-invasive techniques in predicting the concentration of blood glucose instead of the blood sample testing by puncture of fingertip. In this regard, a significant number of researchers have attempted over the past few decades to develop non-invasive glucose monitors using near-infrared spectrometers. These new technologies will reduce or eliminate the skin trauma, pain, and blood waste.

Studies have demonstrated that NIR diffuse reflectance spectroscopy represents a feasible and promising approach to the noninvasive prediction of blood glucose concentration. However, light attenuation is caused not only by the absorption of blood glucose but also by the absorption of other different chemical components within human tissue, such as, water, fat, protein, hemoglobin and melanin. The main problems in the NIR non-invasive diffused reflectance measurement are: (1) The absorption changes are so small that it is really difficult to estimate the glucose concentration from the measured changes in the absorption spectrum; (2) The absorption spectrum obtained is an overlapping of the spectral signatures of many tissue components, as mentioned above. As a result, the measurement is further complicated by the complex and varying background signals of other components presented in tissue; (3) Some limitations, included sensitivity, sampling, time lag, calibration bias, long-term reproducibility and instrument noise and so on, would affect the acceptance of such a method as a commercial product.

Surrounding these three main problems, numerous approaches have been explored. There has been remarkable progress in both optical technology for non-invasive glucose sensing and multivariate regression algorithms as well as calibration models for glucose concentration prediction. Maruo et al chose the first overtone and combination band regions in the near-infrared spectrum (from 1300nm to 1900 nm), and designed an optical fibre probe for monitoring the blood glucose level non-invasively from the forearm [1]. Amerov et al and Yoon et al have developed the method for non-invasive measurement of blood glucose concentration based on the diffuse reflectance. Their research presented that influence of water and some other components concentration variations to the estimation of the glucose concentration can be compensated using spectral analysis on several specially selected wavelengths and proposed algorithm. They believed that the 1575nm-1700nm spectral bands would be appropriate for this analysis because it incorporates all the glucose spectral information [2-3]. Emil et al has developed a dynamic model using non-invasive spectroscopy technique in order to accurately predict blood glucose levels. The dynamic modeling equation provides a way to recalculate the equation when the model no longer accurately reflects the patient’s glucose profile [4]. Arimoto et al

has given some instrumental requirements for non-invasive blood glucose measurement using NIR spectroscopy by Monte Carlo simulation and measurements of absorbance spectra of aqueous glucose solution [5]. Although many developments have been achieved in NIR diffuse reflectance spectroscopy area, there is unfortunately no reliable and accurate noninvasive blood glucose measurement device based on the technique approved by certifying agencies so far. So with regard to accurate and reliable glucose measurement there is a need to be urgently met.

2. Methodology

Potential use of near-infrared diffuse reflectance spectroscopy for non-invasive glucose measurements has attracted significant recent attention. According to a literature review, the main points of the proposing method are below: (1) It has been proven that there are abundant capillary vessels in the dermis layer of human skin and blood glucose is easily permeated to dermis tissue according to the structure of the human skin tissue [1,6]. These have provided the useful technology for extracting glucose information from the dermis layer of the human tissue. The spectra characteristics of the glucose are unique and distinguishable even though the NIR spectra of glucose and those of other components of human blood are overlapping. These are the necessary premise of the research; (2) Successful preliminary results using LED array as light sources at three or four wavelengths have been achieved to determine glucose concentration in water solutions with polystyrene beads [2,3]. Hence, it is possible to choose laser diode array as light sources at four wavelengths required, since laser source has remarkable features in homochromatism, convergency, dot pointing and output power in comparison with other light sources commonly used in glucose non-invasive measurement; (3) Unique design of optical fibre probe and compact assembling of personal monitoring device will be presented to carry out non-invasive measurement in vitro and vivo; (4) An efficient algorithm based on the ratio of absorption difference will be developed to determine glucose concentration at four particular wavelengths instead of the traditional multivariate analysis method.

The main aim of the proposed research is to develop a stand-alone measurement system, in which laser beams are collimated and illuminated the skin surface by a novel optical fibre probe, and the diffuse reflectance light from inner dermis tissue layer is collected by a detecting fibre and detector to yield the signal to noise ratio required for blood glucose concentration prediction. The personal device can be used for in vivo real-time determination of glucose level based on diffuse reflected absorbance measurements at four discrete wavelengths.

3. Experimental Configuration

The measurement system involves two main parts: experimental layout and source-sample-detector geometry.

3.1 Experimental layout

The compact measurement system consists of a laser source, optical fibre switch, optical fibre probe, detector and data acquisition unit as well as a computer system. The experimental layout is shown in Figure 1 and experimental conditions are demonstrated in Table 1.

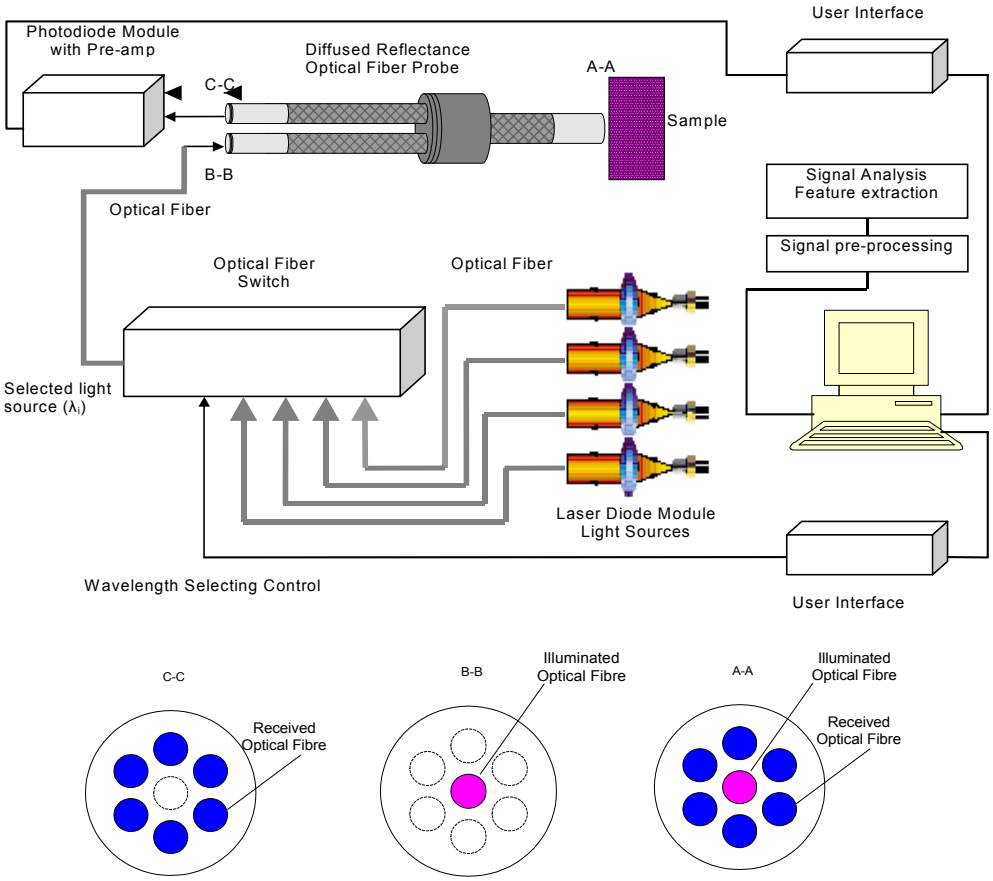


Fig. 1. Experimental layout.

Table 1. Experimental conditions.

Light source:	PRO8000 WDM with FC/APC connector
	Wavelength: 1553.69-1556.19nm adjustable
	Output power: 3.0-13.0dBm adjustable,
Optical probe:	P/N A74TFONIR tapered six-around-one diffused reflectance
Detector:	TIA-500I photodetector with amplifier gain ×10 and transimpedance 14K
Mediums:	Water; Fresh milk;
	D-MEM (1x) liquid (High Glucose, w L-Glutamine, w Sodium Pyruvate);
	D-MEM (1x) liquid (Low Glucose, w L-Glutamine, w Sodium Pyruvate);
	Finger skin tissue.

● Laser source

The laser sources contain a mainframe chassis, with 4 WDM laser modules emitting 12mW continuous wave output power, respectively at 1625 nm, 1225 nm, 1364nm and 1300 nm; all modules have SMA output connectors; the stability of optical output power < 0.002/0.005/0.01dB over 15 s/15 min/24 h; light source is controlled by the optical fibre switch and computer interface.

● Optical fibre switch

The optical fibre switch has four input fibres and one output fibre, to deliver different wavelength beam from different laser sources to one output fibre, which is coupled to source fibre of the fibre probe to illuminate the sample at different time. The optical fibre switch is switched in time by the computer via an interface.

● Optical fibre probe

Tapered 6+1 reflectance probe for NIR range with a core diameter of 400 μm (NA=0.22, multimode silica fibre) and a cladding diameter of 440 μm. The probe contained 6 collecting fibres around 1 center source fibre as shown Fig. 2. The distance between illuminating optical fibre end face and receiving optical fibre end face is 0.8mm .The most important feature of the six-around-one fibre probe is that the end face of the collection fibres is slanted at a slight angle (i.e. end face vector not parallel with the fibre optical axes). This technique helps to maximize the collection efficiency of the diffusely scattered light while minimizing the detection of specularly reflected radiation from the sample surface. The illuminating and detection active areas at the end of the optical fibre probe are considered to be these two areas, i.e., the illuminating active area for the centered 0.4 mm circle, and the detection active area for an annular area between circles of 1.2 mm and 0.4 mm.

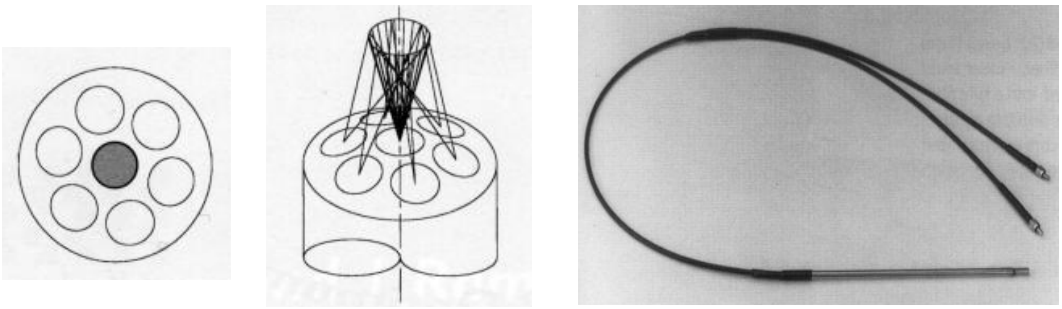


Fig. 2. End face of the optical fibre probe.

● Detector

The TIA-500I optical to electrical converter is a convenient battery-operated detector/amplifier combination that mounts directly on the input of the data acquisition unit. The TIA-500I contains an

Indium-Gallium-Arsenide detector and is well responsive in the 900 to 1700 nm spectral region. The sensitivity of the detector is 1×10^5V/W at 1300 nm and the active detection area is the center of 1 mm spot.

● Data acquisition unit

NI PCI-6071E multifunction DAQ is used to obtain data in time and control the optical fibre switch to output the appropriate wavelength laser to the source fibre of the probe. Sampling and controlling are based on the NI labVIEW 7.0 Professional package environment.

3.2 Source-sample-detector geometry

● Penetration depth

The actual penetration depth of radiation at a particular wavelength for a particular sample is dependent upon its physical, optical, and compositional characteristics including source-sample-detector route attribution. If the cuvette with water and scattering particles is presented as sample and it is assumed that scattering particles have no absorption, the μ_a, μ_s and g of the water at wavelength 1553.69 nm are, respectively, 0.11 mm, 17 mm and 0.25. Therefore, the actual penetration δ should be around 0.49mm in terms of the relation between δ, μ_a, μ_s and g [5, 7].

In the case of skin tissue, the structure of human skin tissue is given in Fig. 3. The skin is a complex organ with each square centimeter of skin, on average 3 mm thick, containing 10 hair follicles, 100 sweat glands, and up to 2,500 sensory cells as well as 3 metres of lymphatic and blood capillaries, 12 metres of nerve fibres [6]. There are sufficient capillary vessels in the dermis layer. So the dermis layer is the perfect detection source of human blood glucose by using an optical fibre probe. The rays from the optical fibre probe penetrate deep into the skin, 15% of them reaching the hypodermis layer as estimated. At the spectral range from 1580 to 1600 nm where the absorption peak of blood glucose exists, the average optical path lengths in the tissue-simulated phantom are between 2.2 and 2.4 mm. Considering that the distance between the illuminating fibre and receiving fibre in this work is 0.8 mm, so the average penetration depth in the tissue-simulated phantom is around 0.7-0.8 mm. It is just there that the dermis layer is located. So the arrangement of the illuminating fibre and receiving fibre is suitable for detecting.

● Sample volume

The penetration depth multiplied by the surface area illuminated by the light beam (commonly a circular spot) effectively defines the sample volume being interrogated of the sample [7]. The diameter of the illuminating fibre core located in the center is 0.4 mm in the work, so the sample volume being interrogated of the sample or skin tissue is going to be (0.7~0.8) mm × 3.14 × (0.4/2) mm^2 = 0.4396~0.5024 mm^3.

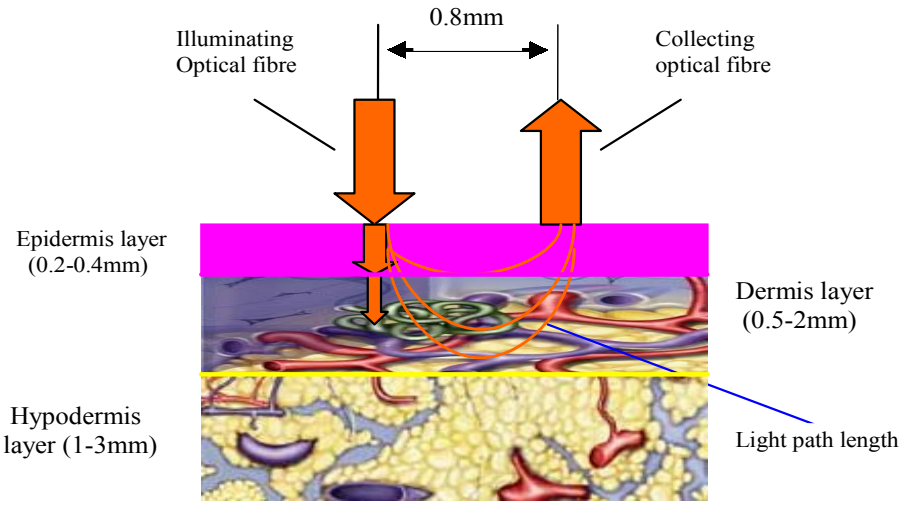


Fig. 3. Structure of human skin tissue.

An alternative to the arrangement of the optical fibre array is to use the source and collecting fibres inversely, i.e., 6 fibres located between an outer circle and the central fibre are used for illuminating, and the central fibre is used for collecting. In this way, in terms of calculating the sample volume being interrogated of the sample is going to be (0.7~0.8) mm × 6×3.14 × (0.4/2) mm^2 = 2.6376~3.0144 mm^3. It is very distinct that the sample volume being interrogated in inverse way is as 6 times as in forward way. It seems useful for enlarging the portion of the sample contributing to the measurement. The corresponding experimental research and discussion about sample volume will be given in the next section to validate further the active sample volume in a different arrangement of the optical fibre array.

4. Experiment Results and Discussions

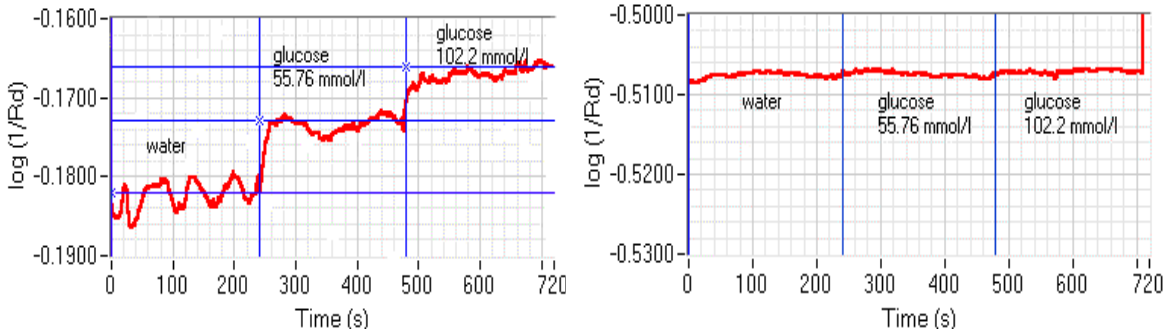
The preliminary experiments have been implemented to interrogate the characteristics of the laser source, the interrelation and coupling of the source-sample-detector geometry, the absorbance features of the different phantoms at the specified wavelength under corresponding experimental conditions, effect of probe-to-target distance on received signal, diffuse reflected absorbance from real skin tissue and temperature effect.

4.1 Arrangement of the fibre array

To find out the active sample volume in different arrangement of the optical fibre array, experiments of two groups were carried out with respectively water and fresh milk plus D-MEM (1x) liquid (cell culture liquid) by adding a certain amount of glucose solution under the same experimental conditions. The experiment results are, respectively, shown in Figure 4 and 5.

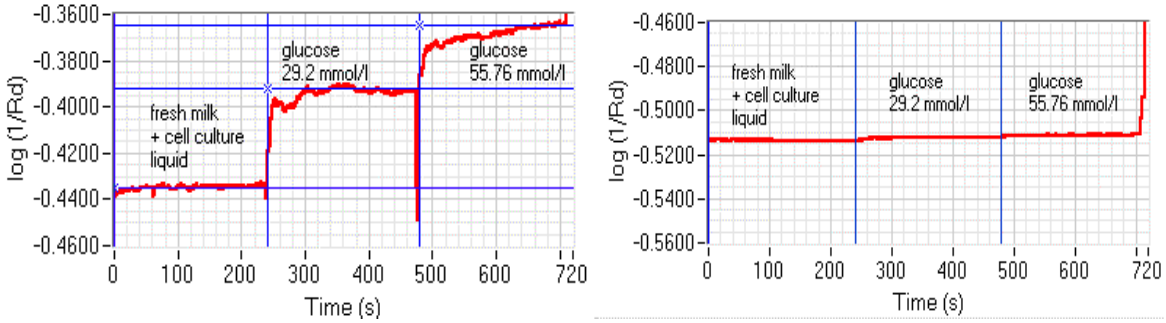
If 6 (collecting) +1 (central illuminating) fibre array is laid out, the experimental results given in Fig.4 (a) and 5 (a) have clearly presented that the quite large changes in diffuse reflected absorbance light intensity can be caught when varying the glucose concentration by adding a certain amount of glucose

solution at 240th second and 480th second. The absorption light intensity changes are, respectively, 0.01 (at 240th) and 0.006 (at 480th) for water medium, 0.04 (at 240th) and 0.03 (at 480th) for fresh milk plus cell culture liquid medium. The reason that the absorbance light intensity changes in water are distinctly less than the changes in fresh milk plus cell culture liquid is that water has higher absorption qualities.



(a) 6 (collecting) +1 (central illuminating) fibre array (b) 6 (illuminating) +1 (central collecting) fibre array

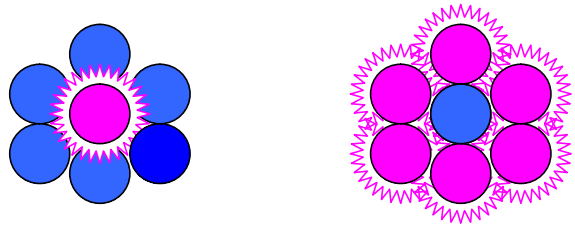
Fig. 4. Experiments of different fibre layout with water medium.



(a) 6 (collecting) +1 (central illuminating) fibre array (b) 6 (illuminating) +1 (central collecting) fibre array

Fig. 5. Experiments of different fibre layout with fresh milk plus cell culture liquid medium.

Inversely, If 6 (illuminating) +1 (central collecting) fibre array is laid out, the experimental results given in Figure 4 and Figure 5 (b) have shown that almost no obvious change can be seen when varying the glucose concentration by adding the same amount of glucose solution at the same time point. But it is just in this layout that the theory calculation value of the sample volume is far larger than the first layout mentioned above. In terms of the scheme of the fibre array shown in Fig. 6(b), although the areas illuminated by laser sources are larger than one of Fig. 6 (a), only the parts of the diffused reflectance from sample, which are close to the central collecting fibre, are luckily collected by the detector. On the other hand, the diffused reflectance from sample shown in Fig. 6 (a) is almost received by the surrounding collecting fibre. It can therefore be understood the active sample volume in 6 (illuminating) +1 (central collecting) fibre array layout is actually less than one in 6 (collecting) +1 (central illuminating) fibre array layout.



(a) 6 (collecting fibres) +1 (central illuminating fibre) fibre array

(b) 6 (illuminating fibres) +1 (central collecting fibre) fibre array

Fig. 6. Fibre array layout.

4.2 Diffuse reflected absorbance

The diffuse reflected absorbance of the different phantoms at the specified wavelength under corresponding experimental conditions have been observed to interrogate and examine the feasibility of the measurement system including laser source, experimental layout, optical path, sample characteristics and response ability.

Three different phantoms (water, fresh milk plus D-MEM (1x) liquid (cell culture liquid) and D-MEM (1x) liquid only) have been used. The surface of the cuvette with phantom was irradiated by the laser source at 1553.69 nm wavelength, and the diffuse reflectance light was received by collecting optical fibre and detector. The observation lasted for a length of time. Meanwhile, the certain amount of glucose solution was respectively injected to the cuvette at different time points. The relationship curves between the change of the diffuse reflected absorbance log (1/ R_d) and glucose concentration are represented in Figure 7.

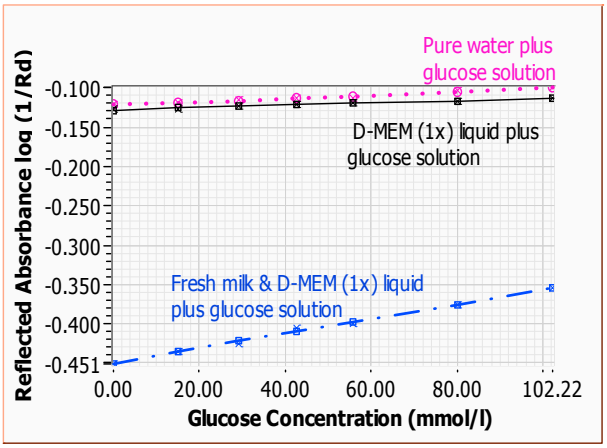


Fig. 7. Relationships between the diffuse reflected absorbance log (1/Rd) and glucose concentration.

When the glucose concentration in the medium changes, the absorption coefficient of the medium is changed by two main factors. The first one is the change of the glucose concentration. When the glucose concentration in the medium increases, the inner absorbance of glucose own increases depending on the glucose concentration. The second one is the change in the volume of water in the medium. When the glucose concentration in the medium increases, the absorbance by water decreases as water is displaced by increased glucose.

On the other hand, the scattering coefficient is related to the size and shape of scattering particles, refractive index of the particle material as well as the difference in the refractive indices between the particles and the surrounding fluid. For simplicity, the change in the scattering coefficient is assumed to be mainly caused only by the change in the difference of the refractive indices between the particles and the surrounding fluid. Since the glucose concentration in water increases, the refractive index of solvent increases too, because the refractive index of aqueous glucose is higher than that of pure water. Hence, the difference in refractive indices between the scattering particles and the surrounding solvent decreases. As a result, the intensity of light that is diffusely reflected from the medium reduces, and the absorbance of diffuse reflection increases.

As explained above, it is clear that the diffuse reflected absorbance increases with the raising of glucose concentration from Fig. 7. There are different baselines of the diffused reflection absorbance for the different phantoms. The pink curve is created using pure water by adding a certain amount of glucose solution at different time points, the black one using D-MEM (1x) liquid (cell culture liquid) only and the blue one using fresh milk plus D-MEM (1x) liquid by adding a certain amount of glucose solution. For the same change of the glucose concentration, the change in the diffused reflection absorbance of the blue curve looks bigger than others because, apart from the inner absorbance of glucose own increasing depending on the glucose concentration, the intensity of light that is diffusely reflected from the medium reduces relying on the scattering coefficient, thereby the absorbance of diffuse reflection obviously increases.

The experiments have proven that the smallest absorbance change, which can respond rapidly to the least change of glucose concentration, is affected mainly by several factors mentioned below. (1) The active sample volume formed by the source-sample-detector geometry. (2) The signal to noise ratio, drift level and sensitivity of the detector. The thermal noise level should be less than $1x10^{-5}$ for the estimation of the absorbance change ($5x10^{-5}$) glucose-induced, but drift level is so hard to front that it should be held down at least less than $5x10^{-6}$ to realize measurement of 0.556 mmol/l (10 mg/dL) resolution. (3) The absorbance of 10^{-5} means 0.001% normal fluctuation of signal power caused by the change of 0.556 mmol/l (10mg/dL) glucose concentration due to defined by the common logarithm at base 10. Therefore, simultaneous measurements of reference and sample signals as well as dark current signal are a possible approach to diminish noise and error and enhance the reliability of the measurement system.

4.3 Effect of probe-to-target distance on diffuse reflected absorbance

The experiments at different distances between the optical fibre probe and the cuvette were done to compare the change of the diffuse reflected absorbance and find out the optimum detection distance. The experimental results are shown in Figure 8.

In terms of the results shown in Figure 8, the changes of the diffuse reflected absorbance corresponding glucose concentration of 1 mmol/l are, respectively, 9.49×10^{-4} for 0mm distance and 2.64×10^{-4} for 0.4mm probe-to-sample distance with fresh milk plus D-MEM (1x) liquid. The experimental results have proven that larger change in diffuse reflected absorbance can be caught when the optical fibre probe touches the sample surface.

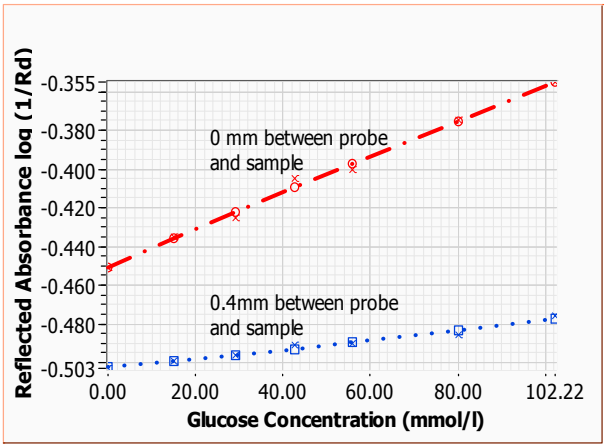


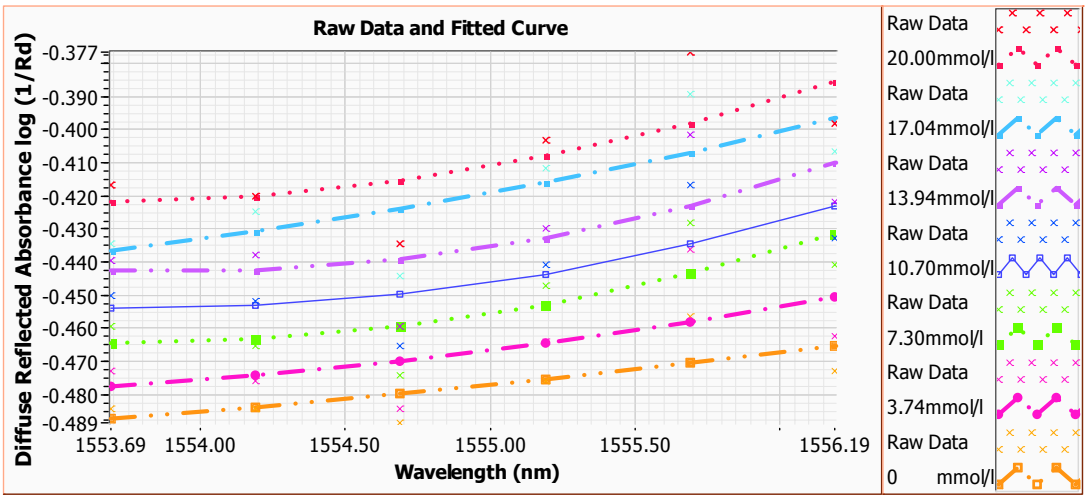
Fig. 8. Changes of the diffuse reflected absorbance with fresh milk + D-MEM (1x) liquid at different probe-to-sample distances.

4.4 Static testing in vitro

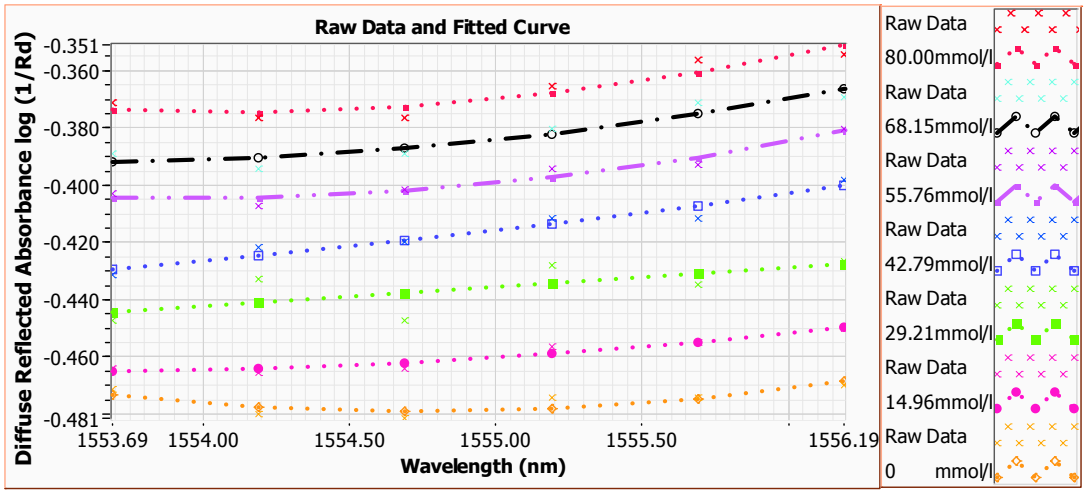
The static testing in vitro has been carried out under corresponding experimental conditions by adding glucose concentration in experimental mediums.

Three different phantoms (1ml pure water plus 1ml fresh milk, 1ml D-MEM (1x, low glucose) liquid plus 1ml fresh milk, 1ml D-MEM (1x, high glucose) liquid plus 1 ml fresh milk) have been used. The surface of the cuvette with mixed medium was irradiated by the laser source at wavelength range from 1553.69 to 1556.19 nm. And the diffused reflectance light was received by the collecting optical fibres and detector. The observation lasted for a length of time. Meanwhile, the certain amount of glucose solution was respectively injected to the cuvette at different time points to make the glucose concentration in the cuvette gradually increase. The relationships between the changes of the diffuse reflected absorbance log (1/ R_d) and the changes of the wavelengths for different glucose concentrations with three kinds of different phantoms are respectively represented in Figure 9 (a), (b) and (c).

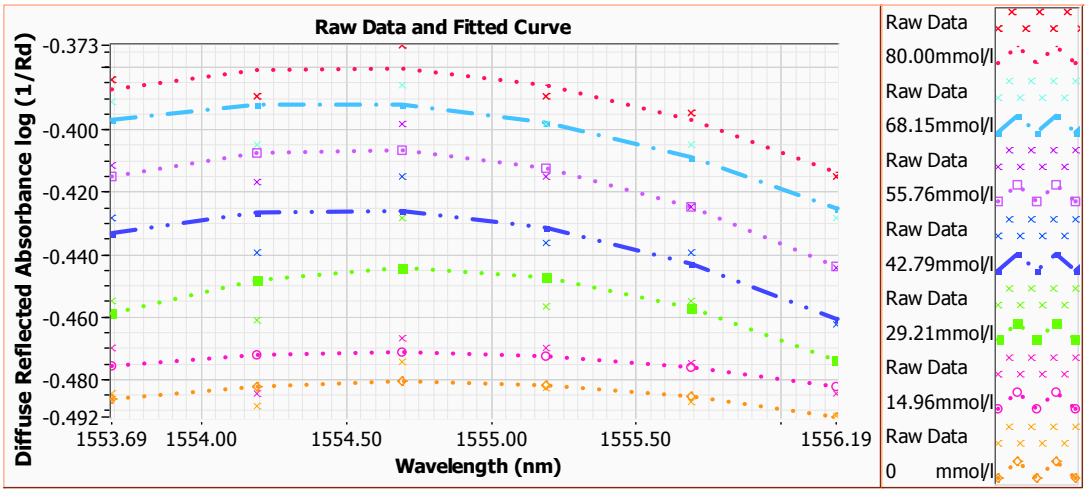
The experimental results have shown that there are different diffuse reflected absorbance spectra for different phantoms. The spectral lines obtained by using pure water plus fresh milk in Figure 9 (a) are similar to the spectra lines obtained by using D-MEM (1x, high glucose) liquid plus fresh milk.



(a) With pure water plus fresh milk



(b) With D-MEM (1x, high glucose) liquid plus fresh milk



(c) With D-MEM (1x, low glucose) liquid plus fresh milk

Fig. 9. Relationships between the diffuse reflected absorbance log (1/ R_d) and the wavelengths for different glucose concentrations.

As described by Lambert-Beer law, the diffuse reflected absorbance at a particular wavelength is basically proportional to the glucose concentration because only that concentration was changed after measurement of the diffuse reflected absorbance spectrum. The experimental results have presented a good correlation between the diffuse reflected absorbance and glucose concentration at a particular wavelength.

The relationships between the changes of the diffuse reflected absorbance log (1/ R_d) and the changes of the glucose concentrations at different wavelengths with three different phantoms are respectively shown in Figure 10. It is obvious that the diffuse reflected absorbance increases with the increment of the glucose concentration in the medium. In general, there is different diffuse reflected absorbance for different wavelengths at same glucose concentration level. However, in some cases, the same diffuse reflected absorbance for different wavelengths at same glucose concentration level are presented so that two curves are going to be overlapping, for instance, the green and pink curves in Figure 10.

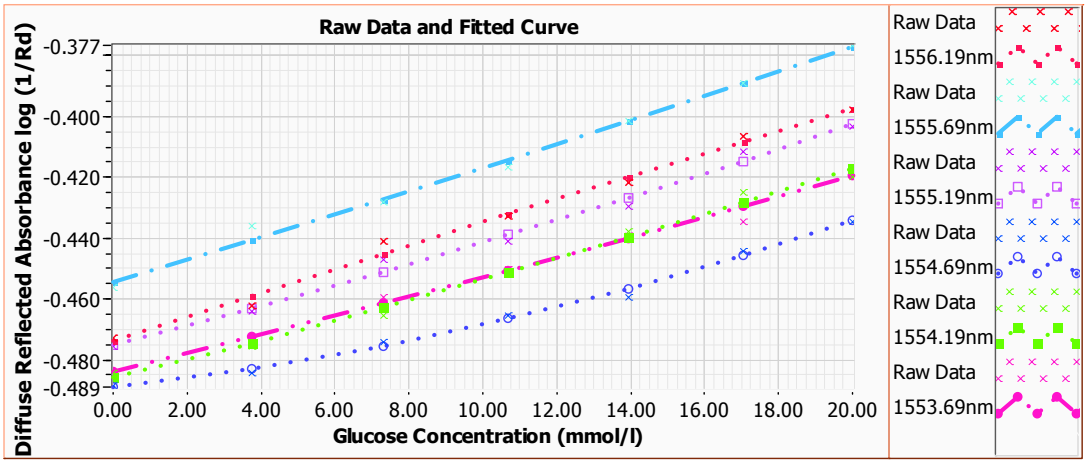


Fig. 10. Relationships between the diffuse reflected absorbance log (1/ R_d) and the glucose concentrations at different wavelengths with water mixed milk.

4.5 Preliminary testing in vivo

In order to interrogate the dynamic change process of glucose level in skin tissue (fingertip) testing when the glucose concentration level increases in human body, two oral glucose intake experiments have been performed for one subject to observe the dynamic interrelation between diffuse reflected absorbance and the glucose concentration change of the volunteer by taking a certain amount oral glucose, according to the testing standard of OGTT.

Experimental condition:

Laser source: Wavelength 1556.19 nm, output power 10.08 dBm.
Subject: female 38-48 year old non-diabetic volunteers. The diffused reflectance signal was obtained from the index fingertip of the volunteer. The capillary blood samples for the reference were taken by puncture of the fingertip and measured by "Medi Sense" self-monitoring blood glucose meter (Abbott Laboratories, US).

During the first test, the volunteers firstly took 112.5 ml pure water at 420-th second in preprandial, and six minutes later, took 18g oral glucose dissolved in 112.5 ml pure water at 840-th second. The dynamic change of diffused reflection absorbance from the fingertip tissue of the subject is given in Figure 11.

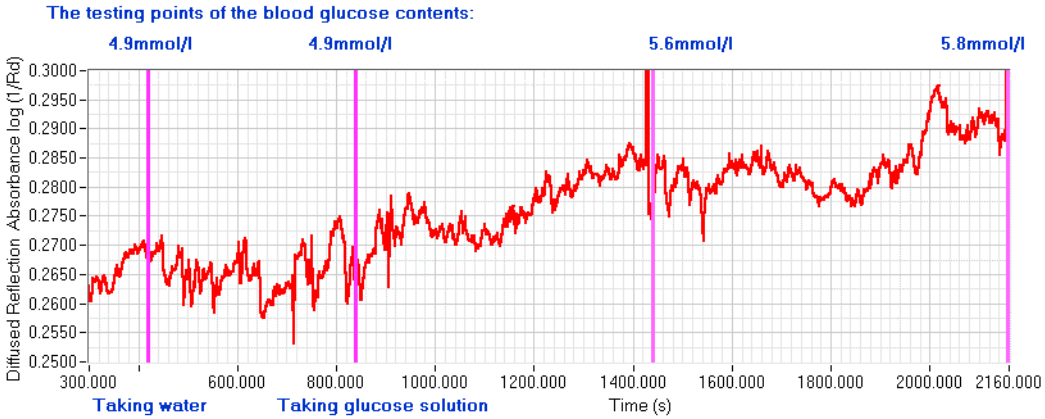


Fig. 11. Dynamic changes of diffuse reflected absorbance from the fingertip tissue of the subject for water intake and glucose intake tests.

In the second test, the amount of glucose drunk by the subject at 500-th second in preprandial was 36g (almost half amount of the oral glucose in OGTT) oral glucose dissolved in 250ml pure water. The dynamic change of diffused reflection absorbance from the fingertip tissue of the subject is given in Figure 12.

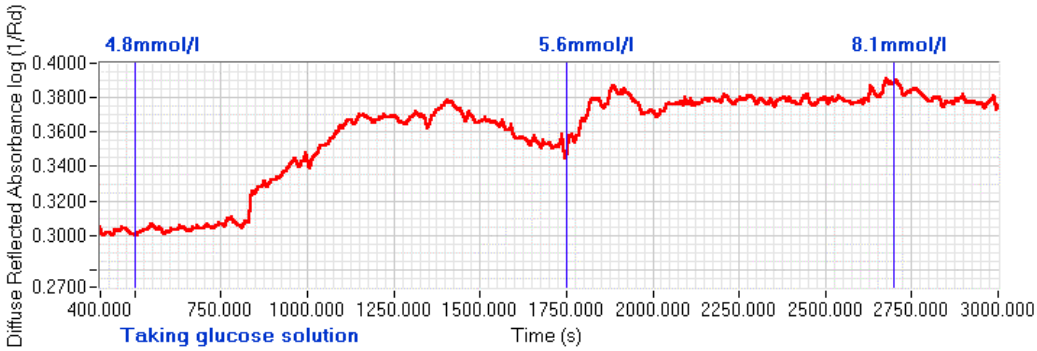


Fig. 12. Dynamic changes of diffused reflection absorbance from the fingertip tissue of the subject for glucose intake tests.

From the result shown in Figure 11, it is apparent that the diffuse reflected absorbance from the fingertip tissue shows a certain fluctuation around some mean value but no obvious change trend to have been formed before and after taking pure water. The results from capillary blood samples testing before and after taking pure water have also proved that there is no change of the glucose content in this case. Further, after taking the oral glucose solution at 840-th second the diffuse reflected

absorbance of the subject starts to increase gradually. The increasing blood glucose contents by blood samples testing have presented the trend. With the increment of the diffuse reflected absorbance from the fingertip tissue the glucose content is 5.6mmol/l at 1440-th second, then it reaches 5.8mmol/l at 2160-th second. Though the overlapping spectra are encountered in the case of tissue measurement, the explicit change of the diffuse reflected absorbance glucose-induced could be obtained by the proposed measurement system. Figure 12 gives a longer monitoring process, in which the volunteer subject takes (preprandial) 36 g oral glucose dissolved in 250 ml pure water at 500-th second, then the diffuse reflected absorbance starts to increase gradually. The increasing change tendency of the diffuse reflected absorbance shows a good agreement with the results of the blood samples testing by puncture of the fingertip. Even though this is only a qualitative testing, not the calibration result, the experiments truly reflect the dynamic change process of glucose level of the non-diabetic subject after taking oral glucose solution by the diffuse reflected absorbance. Therefore, this is of great benefit to future work. Furthermore, the experiments have also presented that it is necessary to keep constant contact pressure in skin tissue measurement to maintain the reproducibility of measurements by corresponding experimental rig.

4.6 Temperature effect on diffuse reflected absorbance of sample

In the NIR wavelength range, the temperature fluctuation of a sample will greatly influence the baselines of the sample absorption spectra [8]. To make sure the temperature effects on diffuse reflected absorbance of sample, the related experiments were performed using a phantom by quickly increasing the temperature of the sample to a certain value, meanwhile observing and recording the change of the diffuse reflected absorbance of the sample in the increased compulsively and decreased naturally processes of the sample temperature. A phantom (1.5 ml pure water plus 1.5 ml fresh milk with 0.2 ml glucose solution) has been used in the experiments. The surface of the cuvette with phantom was irradiated by the laser source at wavelength 1556.19 nm, and the diffused reflectance light was received by collecting optical fibre and detector. The observation lasted for a long while.

In the first place, the temperature of the sample was quickly increased from 26.0^{o}C to 37.0^{o}C at 240-th second in the surveying process. The original baseline is around -0.467. The diffuse reflected absorbance from sample decreases rapidly when the temperature of the sample rises, then it reduces quite slowly with the reduction of the sample temperature. The interesting phenomena can be seen from Figure 13 (left). In the second case, the experimental conditions are the same as the first case but only difference is without glucose in the sample. The diffuse reflected absorbance from samples shows some small fluctuation when the temperature of the sample rises but no obvious step change and returning process are seen with the change of the sample temperature in this case (see Figure 13 (right)). The comparison results of above two cases imply that the temperature change of the sample will greatly affect the diffuse reflected absorbance of the glucose in the phantom. It means that the effect of temperature cannot be ignored when the diffuse reflected absorbance is measured to predict glucose concentration.

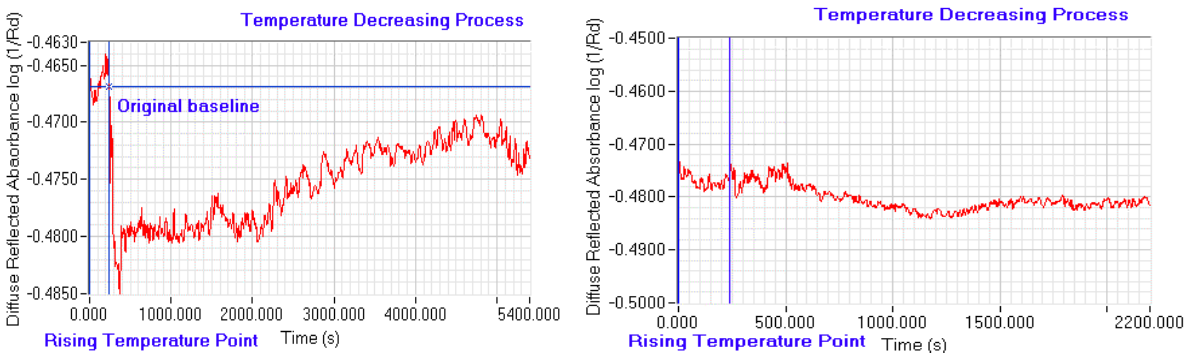


Fig. 13. Temperature effects on diffuse reflected absorbance of sample with water + fresh milk.

5. Conclusions

The main targets have been reached in this stage through carrying out the preliminary experiments. The results of this work can be used to conclude that the change of diffuse reflected absorbance glucose-induced has been presented in vitro and vivo. The experimental scheme of the measurement system has been demonstrated to be reasonable and suitable for detecting the change of the diffuse reflected absorbance from phantoms and finger tissue. With the measurement system, the changes of the diffuse reflected absorbance caused by physical glucose changes in the transparent and turbid medium as well as fingertip tissue have been obtained. The experimental results have presented a good correlation between the diffuse reflected absorbance and glucose concentration at several particular wavelengths. The spectra lines are perfectly separate from each other at different glucose concentrations. There are obvious differences in the diffuse reflected absorbance for different glucose concentrations. The experimental results of the arrangement of the optical fibre array have shown that the active sample volume is an important parameter that depends on the active illuminating area and the penetration depth of the incident laser beam. In addition, the probe-to-target distance has been validated and discussed so that the best measurement result can be gained when the probe touches the sample surface. Furthermore, it is necessary to keep constant contact pressure in tissue measurement to maintain the reproducibility of measurements. According to the testing standard of the OGTT, the dynamic change of the diffuse reflected absorbance from finger tissue with the change of glucose concentration of the subject has been explored by taking a certain amount oral glucose solution. The result presents that the sensing system proposed is already able to sense the glucose change from fingertip tissue though the overlapping spectra are encountered. Also, the temperature effects of the sample on the diffuse reflected absorbance of the glucose have been taken into consideration.

Future efforts will be directed towards several aspects. Firstly, the measurements of three real signals, i.e. the skin spectra signal, the dark noise signal and the reference signal, in sequence at four specified wavelengths, will be carried out together with the glucose concentration prediction by using a four-wavelength calibration model. Next, it is expected that a relatively constant optical sampling of the tissue is likely to be necessary to calibrate to blood constituents. But contact pressure variations have been found to lead to changes in the optical sampling of the tissue in the experiments. This kind of sampling effect could be enough to confound efforts at calibration by changing the signal strength for specific levels of analysis. As a result, the optical probe that physically touches the tissue sample of the

human skin must be designed to provide reproducible contact energy to eliminate the change effect caused by contact pressure variations in multi-measurements. Afterwards, a large number of diabetic and non-diabetic subjects at different age, gender and fitness levels will be involved in the experiments to calibrate the monitoring device and further analyze the error. Finally, of particular interest is the comparison of the measurement results by using the proposed system at several specific wavelengths with traditional partial least square regression analysis in a wide NIR spectra range with a common halogen light source.

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