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Noninvasive Blood Glucose Analysis using Near Infrared Absorption Spectroscopy[1]

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Abstract

This project aims to develop a noninvasive glucose sensor based on near infrared absorption spectroscopic technique. Two main issues need to be addressed before realization is possible. First, the extremely weak glucose absorption signal prompts a remarkably sensitive measuring instrument. Second, noise due to skin and tissue physiological variations need to be eliminated or compensated. Sensitivity analysis on two glucose absorption bands in the near infrared region, namely the first-overtone and the combination band region were done. The results suggested that glucose absorption peak at 4430cm^{-1} was of great importance for glucose prediction. A resolution of ± 0.5mmol/L was achieved for aqueous glucose solutions in quartz cuvette with 2-mm optical path-length. The effects of sample temperature variations on the absorption spectra were studied. Using Fourier filter post-processing algorithm, temperature effects were efficiently eliminated. Glucose absorption spectra in water and in human blood serum were compared. Extreme similarity between them justified the use of water as buffer in our experiments. Experiments were done to study the effects of a presence of scattering media, such as tissue, to simulate noninvasive, *in vivo* application. With such media, signal-to-noise ratio decreased due to higher radiation loss. Methods to increase the signal-to-noise ratio to compensate for the loss are discussed in this report.

1. Introduction

The purpose of this project is to develop a noninvasive blood glucose sensor for home and hospital use. Noninvasive blood glucose monitoring is a long pursued goal in clinical therapy as an invaluable tool that would aid in the treatment of diabetes. The importance of such device is marked by the market value of glucose testing devices, which was estimated to be more than $2.5 billion worldwide in 1997, and growing at 10-15% a year. A noninvasive glucose monitoring device would provide a safer and a more convenient method to treat and control diabetes. The goal of diabetes therapy, within and outside hospital, is to approximate the 24-hour blood glucose profile of a normal individual, which necessitates continuous monitoring.

Among various techniques, which have been discussed in the previous reports, near infrared absorption spectroscopic technique was chosen for our work. Its relatively higher signal-to-noise ratio makes it more suitable for noninvasive blood glucose measurement among other methods. The underlying principle of an absorption spectroscopic technique is that when a molecule is radiated with a range of frequencies (or wavelengths), it absorbs the radiation only at certain wavelengths. The absorption frequency location(s) in the spectrum reveals the molecular composition of the sample being investigated. The concentration of a particular molecule can be deduced from the intensity of its absorption peak. Realization of the method will depend on the signal-to-noise ratio achievable.

2. Overview of Accomplishments

1. Investigation of various potentially viable optical methods for noninvasive glucose measurement
2. Design and fabrication of a custom, modular Fourier transform spectrometer
3. Instrumental and experimental optimization through analysis of error sources
4. Sensitivity analysis on two NIR glucose absorption bands
5. Improving sensitivity with the use of Fourier filter post-processing algorithm
6. Comparison between glucose absorption spectra in water and in blood
7. Study of temperature effects on absorption spectra
8. Study of tissue scattering effects
9. Investigation of a new approach to increase sensitivity

Items 1 through 5 have been reported in the previous progress reports. In this report, we review and summarize the results on the sensitivity analysis of glucose in the combination band region and discuss the last four items.

3. Sensitivity Analysis of Glucose Absorption in the Combination Band Region (4000-5500 cm^{-1})

Our sensitivity analysis (details included in Progress Report 2-4) showed that the combination band region gave an order of magnitude improvement in sensitivity over the first-overtone region. Using digital Fourier-filtering technique and simple peak-to-peak absorbance measurement in the combination band region, we achieved a repeatability of less than +/- 0.5mmol/L in 2-mm optical path-length of aqueous glucose solutions. Figure 1 shows the typical Fourier-filtered aqueous glucose absorption spectra in the combination band region. Figure 2 shows the plot of absorption intensity as a function of glucose concentration.

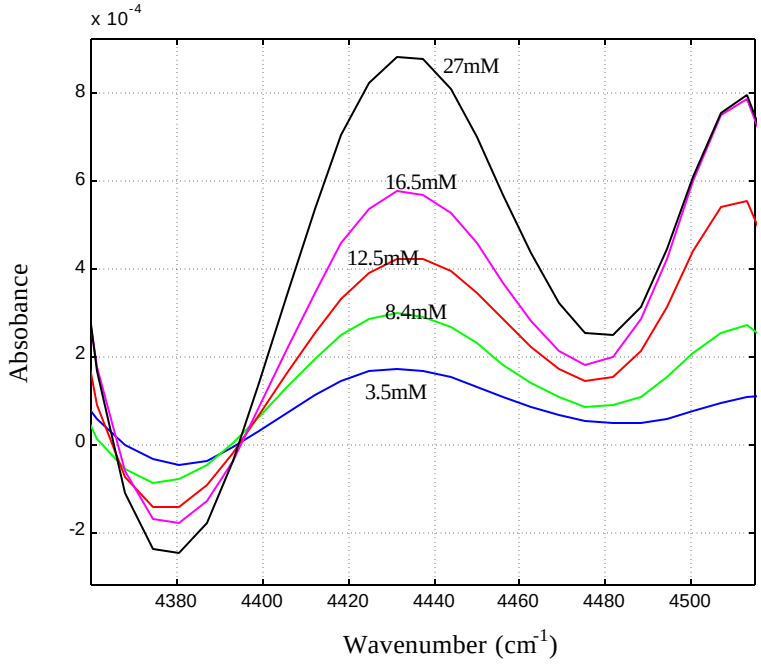

FIGURE 1. Fourier filtered absorbance spectra of aqueous glucose solutions

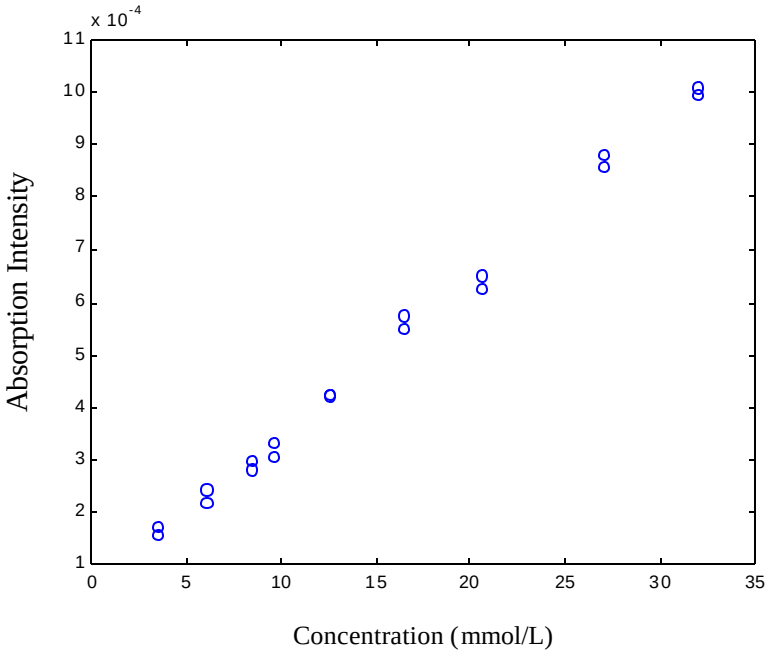

FIGURE 2. Peak-to-peak absorption vs. aqueous glucose concentration values

4. Comparison of Glucose Spectra in Water and in Blood Serum

In our previous experiments, we have always used water as buffers. This is because water is the main component of the blood, it is readily available and it provides a "pure" buffer with no interference of other substances, which is advantageous for careful study of glucose. The assumption is that spectral features of glucose in water are similar to those in the blood. Here, we show this assumption is valid. Figure 3 shows the absorption spectra of glucose in human blood serum referenced to serum at normal glucose level (~5mmol/L) with the same Fourier filter algorithm used for water. It is clearly seen that the spectral features are indeed similar to the aqueous glucose spectral features shown in figure 1. Glucose peak absorption occurs at 4430cm^{-1} as it does in water.

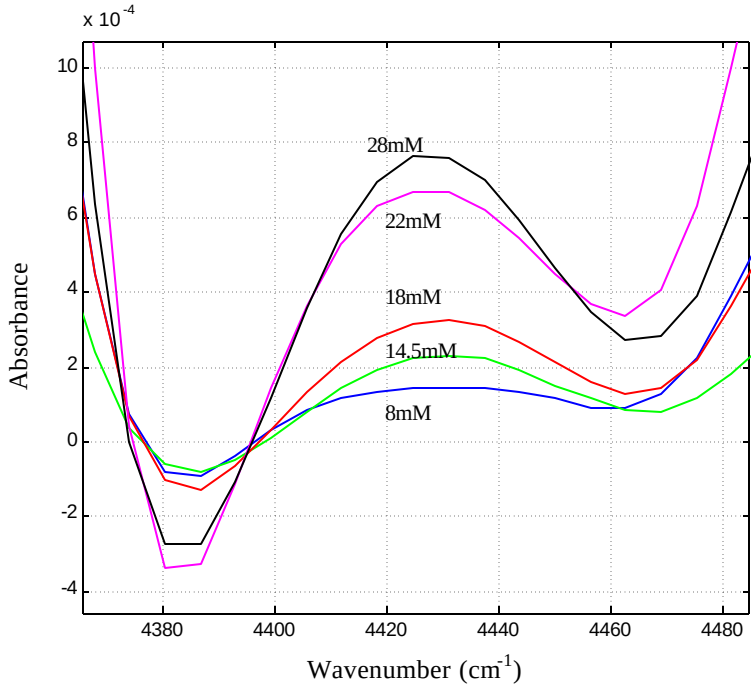

FIGURE 3. Spectra of glucose in blood serum

5. Study of Sample Temperature Effects

Many investigators in this research area have pointed out that sample temperature change is one of the main contributors to noise, and hence to readings irreproducibility. However, we will show that any sample temperature changes can be compensated or eliminated efficiently through the use of Fourier filter algorithm. The principle behind this is that the resolution of spectral changes due to temperature variation is different than the resolution of the spectral changes due to glucose variation. In the absorption spectrum, changes in temperature usually result in baseline variations, with a much lower resolution than the glucose absorption spectral peaks. The Fourier filter can be designed to only pass the spectral resolution of interest (similar to a band-pass filter in time-domain). Figure 4 shows the results.

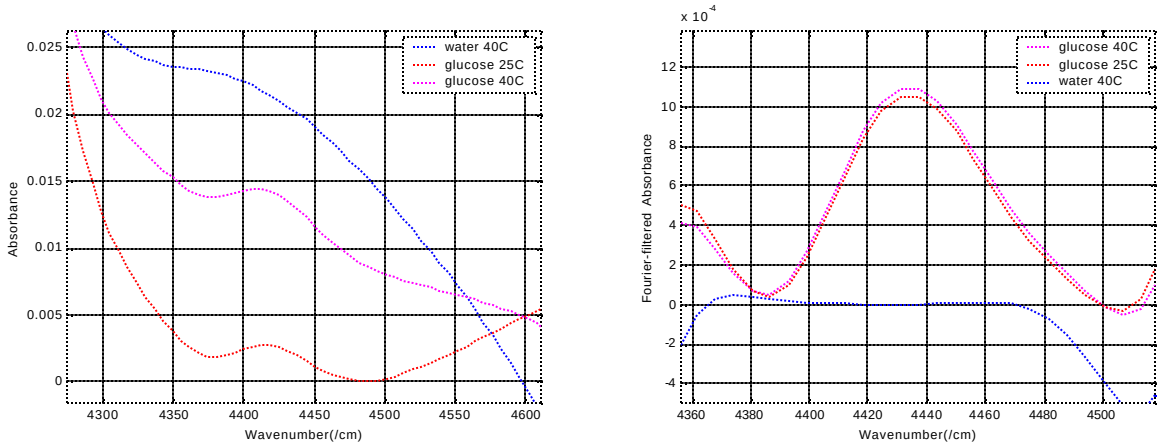

FIGURE 4. Left: Raw absorbance spectra referenced to water at 25^0C. Right: Fourier-filtered absorbance spectra of spectra on the left.

The figure on the left shows that the rise in sample temperature causes higher overall absorption values and varies with wavelength. However, it also shows that the variation is of low resolution. The figure on the right shows the Fourier-filtered spectra of glucose at two different temperatures. It can be seen that they become very close to each other albeit the large temperature differences between them. This shows that the temperature effect is efficiently eliminated.

6. Study of tissue scattering effects

So far, most of the experiments that have been done are in simple matrices such as in water and in serum. Here, we would like to extend our findings to studying the effect of scattering media such as tissue. For noninvasive application, the presence of such media is certain. To begin, a multi-layer tissue model can be useful in qualitatively explaining the effects of additional absorption and scattering due to the presence of tissue to the signal-to-noise ratio. Figure 5 shows the schematic of multi-layer tissue model.

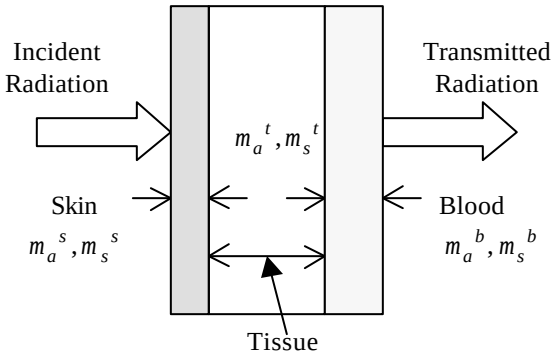

Figure 5. Multi-layer model of tissue

In noninvasive, *in vivo* applications, the radiation needs to be able to pass through the skin and tissue before it reaches the blood. Each of the layers as shown in the model has its own characteristic absorption and scattering, which can be described by the absorption and the scattering coefficients, m_a and m_s respectively. Assuming that the skin, tissue and blood coefficients are constant with respect to time (the only one varying is due to glucose), their presence reduces the signal-to-noise ratio due to the decreased transmitted radiation. When the system is detector noise limited, as is usually the case, the signal-to-noise ratio will decrease proportionally with the decrease of the detected radiation. In order for noninvasive glucose measurement to succeed, one needs to produce a system where the glucose absorption signal is significantly greater than the noise.

The higher the absorption and scattering due to other substances, the lower the radiation that reaches the detector (higher radiation loss). Thus, signal-to-noise ratio achievable is related to the absorption and the scattering coefficients of tissue, skin and blood, and can be qualitatively described with the following:

$$SNR \propto \frac{I^{glucose}}{(m_a + m_s)^{skin} + (m_a + m_s)^{tissue} + (m_a + m_s)^{blood}}$$

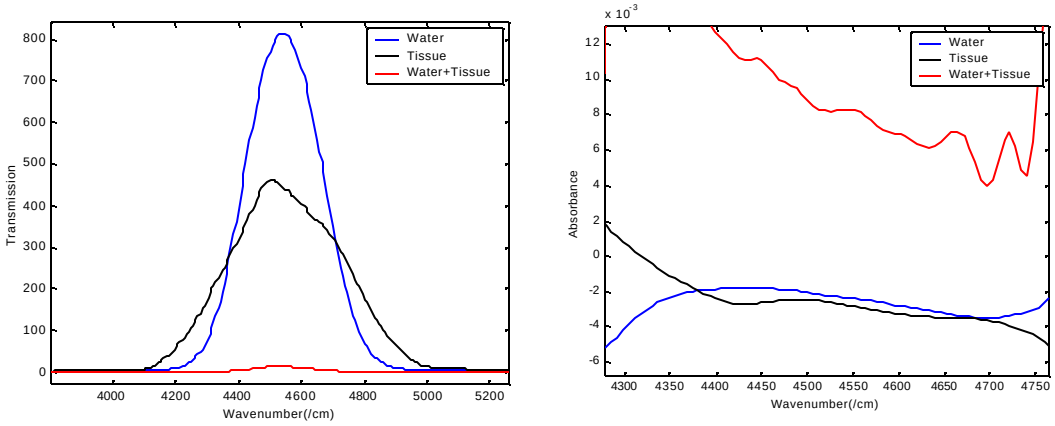

FIGURE 6. Left: Transmission spectra of water, tissue and water with tissue. Right: Absorption spectra of water, tissue and water with tissue referenced to water.

Figure 6 shows the radiation loss due to a presence of a scattering media and how it affects the spectral noise. It can be seen from the figure on the left that the presence of tissue significantly reduces the radiation arriving at the detector. The figure on the right shows that as a result, the spectral noise is increased. This has detrimental effect on the glucose prediction capability. Because the noise is increased by about an order of magnitude, the signal-to-noise ratio will be decreased by an order of magnitude. A resolution of 0.5mmol/L previously achievable with water-glucose solutions can no longer be attained. It has also been verified that Fourier filtering would not eliminate this type of noise. This is because the noise occurs at a range of resolutions, including the range where glucose signal is present.

7. Discussions on Errors and Signal-to-Noise Ratio

We have shown that using the near infrared combination band region, sensitivity for the in vitro aqueous glucose experiments were high. The achievable resolution was ±0.5 mmol/L, which was sufficient for glucose concentration prediction in the clinically relevant range. In the noninvasive application where scattering media such as skin and tissue are presence, however, the signal-to-noise ratio can be expected to decrease by an order of magnitude or more, depending on the thickness and the optical properties of the media. Furthermore, unlike the noise due to sample temperature changes, the noise due to the presence of tissue cannot be reduced or eliminated by post-processing algorithms. It is important to note that the noise does not come directly from the scattering media, but is due to the decreased radiation detected by the optical detector, and hence amplifying the effect of detector noise. Thus, the noise can be thought of as random errors.

There are a few possible ways to get solve this problem. The simplest way is to increase the source radiation power to compensate for the radiation loss through tissue. The limitation to this would be power consumption and sample damage. However, due to the diffuse nature of light (unless a laser is used), sample degradation is unlikely. Another solution is to increase the integration time, or the measurement time. Since detector noise is of random nature, it decreases with the square root of the integration time. However, too long of a measurement time will cause the system to be susceptible to slow-varying errors, such as instrument drifts. Thus, the speed of the instrument may need to be increased. First-order analysis suggests that using these approaches, we can improve the signal-to-noise ratio by ~5.

We have been investigating a new hardware and procedural approach to the spectral decomposition and recording. Our preliminary analysis suggests that using this method, the signal-to-noise ratio can be increased by more than an order of magnitude. We are currently doing preliminary testing.

We think that the main challenge for realization of noninvasive glucose sensing device is increasing the sensitivity of the measuring system to compensate for the extremely small signal-to-noise ratio of the near infrared, *in vivo* blood glucose signal. If the measuring system noise, which is of random nature, such as that of the optical detector's can be suppressed to an acceptable level, we believe that the physiological variations can be compensated through the use of an appropriate post-processing algorithm. An example of this was the compensation of sample temperature variation using Fourier filtering algorithm we discussed earlier.