

Investigation into various optical methods for Non-Invasive Blood Glucose Measurement

Chad M. Steel

Villanova University

ECE Department

December 15, 1998

Introduction

Diabetes currently affects 5.9% of the population in the United States. Costs attributed indirectly and directly to the disease are estimated to be \$92 billion annually in the United States alone. The side affects of Diabetes are dangerous as well. Diabetes is the major cause of blindness and kidney disease in the world. 56,000 amputations related to diabetes and 77,000 deaths from diabetes-related heart disease also occur annually. Diabetes affects the bodies ability to produce or utilize insulin, a hormone which is needed to properly process blood glucose. As a result, diabetics must regulate their own blood sugar levels through diet and insulin injections. The key point in the regulation of blood sugar is the accurate measurement of the blood sugar level.¹

Currently, Blood Glucose can only be monitored through the use of invasive techniques. Most of these involve drawing blood through a small pinprick and placing a drop on a test strip. The glucose level in the blood is then measured using one of several ways, which will be covered later. These measurements must be taken several times, generally around half a dozen, a day by those with diabetes. The risk of infection and measurement inaccuracy are present with all of the invasive techniques. In addition, due to the discomfort caused by the pinprick and the resultant bruising, many diabetics do not check their glucose levels as often as recommended and as a result increase their chance of having sugar shock or diabetic coma occur.

At the present time, though several companies are working on non-invasive measurement techniques, there are no FDA approved meters available. My research will test the feasibility of the measurement of blood glucose through various non-invasive techniques which involve light absorption and phase change in the visible and near-infrared wavelengths. The investigation involves both direct absorption and phase-change related properties of water-glucose solutions of the same concentration as naturally occurs in the blood.

Current Methods

Currently, there are three popular types of blood glucose tests available for home use. All three are invasive techniques and require small amounts of blood to be drawn. This is accomplished by using a lancet or laser (see Invasive Laser Methods section) to obtain a drop of blood, and then placing this drop on a slide to be measured. The measurements are performed in one of the following three ways:

Current Change

The first type of test strip causes a small current to be generated through the blood based on an enzyme reaction with the glucose in the blood. The amount of current present is measured, and this measurement is correlated to the amount of glucose present in the blood. The newer blood glucose meters using this technique conform to the American Diabetic Association's current guidelines of being within 5% of the equivalent lab measurement.

Visual Reading

A second type of test strip involves a chemical reaction with the blood glucose. This reaction causes the strip to change color, and this color is read against a chart to give a number corresponding to blood glucose ranges. The method does not rely on

actual electronic measurement - it is dependent on human vision to match the color to a given reference chart. Due to the subjectivity of the human visual system and the varying lighting conditions, this method is generally not very accurate.

Electronic Reading

The second type of test strip also causes a reaction with the blood glucose, but this reaction changes the molecular makeup of the blood glucose to give it certain reflective properties. The strip is then placed in a device which reads the reflectivity of the sample and outputs a number. This number is then checked against a reference chart either by the meter or by the user and a glucose level is obtained. These meters are within 5% of the lab measurement if they were designed after 1993, or within 10% if they were designed prior to 1993 (the ADA changed it's standards, but grandfathered in older designs.)

Invasive Laser Methods

In addition to the current standard methods for measuring blood glucose, the FDA has recently (December 8, 1998) approved a product from Cell Robotics designated the Lasette, for use by diabetics with a doctor's prescription. The Lasette utilizes a battery powered laser to drill a small hole in the skin, which causes a droplet of blood to form (the same as with the lancets.) The droplet is then used with one of the techniques detailed above to obtain a glucose level. The benefit is the laser is reported to be painless and does not cause bruising as the lancets do. The cost of the laser is approximately \$2,000 for the doctors' office version, but a home version with significantly lower cost is scheduled to be released early next year.²

Current Research into Non-invasive methods

There are several companies currently researching the area of non-invasive blood glucose absorption. The major companies are Cygnus, BioControl, Futrex, Integ, Boston Advanced Technology, VivaScan, and SpectRx.. None of these companies have fully functioning meters for home use. There have also been no FDA approvals on any non-invasive meters yet. Several patents have been filed, but no working devices have been successfully demonstrated. Only the first four companies mentioned above have claimed substantial progress, and their product research is summarized as follows:

Cygnus

Cygnus is working on the creation of a non-invasive blood glucose meter in the form of a watch which they have dubbed the “GlucoWatch.” The glucose watch uses disposable pads which collect glucose from skin cells. The glucose is extracted using from intact skin utilizing a proprietary process called electroosmosis, which uses low levels of electric current. An attached biosensor measures the electron emission from an electrochemical reaction triggered by the extracted glucose.³

Cygnus claims clinical results which show promise, but does not provided a complete data set to back up their claims. They also claim to have filed for FDA approval, but the their filing was for a 510k application. Current FDA regulations require all non-invasive blood glucose measurement devices to apply for a PMA (Pre-market Approval), which is more complex and requires more in-depth clinical trials before approval. Cygnus is investigating the possibility of filing for this in the near future.⁴

BioControl

The BioControl Diasensor product has been approved for use in the UK and Germany. It is not approved in the US at this time. The Diasensor uses the forearm and measures light reflectance to obtain blood glucose levels. The Diasensor is priced beyond the range for home use, costing approximately \$8,500.00 as it is currently marketed in

Europe. In addition, the unit needs to be calibrated to the at a specialized calibration center.⁵

Biocontrol is currently seeking FDA approval for their device. A previous application was rejected due to insufficient clinical trial results, but this appears to have the most promise of the current competitors for obtaining FDA approval in the near future.

Futrex

Futrex developed a product called the Dream Beam for non-invasive blood glucose measurement using infrared techniques. This product has ceased development due to Futrex being under investigation by the SEC for fraud. Research on the Dream Beam had also stopped, but has begun again recently.⁶ As with Cygnus, Futrex had filed under the auspices of the 510k and will most likely need to file again under the new PMA required guidelines.⁷

Integ

Integ's offering in the field is the LifeGuide meter. It functions by taking a sample of the interstitial fluid from the outer layer of skin and measures absorbance using far-infrared absorption. The meter is semi-invasive and uses a correlation technique to extrapolate blood glucose levels from interstitial fluid glucose levels.⁸ Recently, an 455-person internal study found the following:

- There is a correlation between interstitial fluid and venous plasma blood glucose concentrations
- The Lifeguide accurately collected the appropriate amount of interstitial fluid for the meter to measure the data properly
- The IR measurement performance was below that required to initiated clinical studies

As a result of the above study, Integ has stopped research on the current method outlined for glucose measurement and is focusing on different methods for the measurement of blood glucose.⁹

Problems with Prior Art

The main problem experienced with prior attempts at blood glucose measurement is calibration. Because of varying amounts of protein, fats, and water in different people, a single, universal measurement scheme has not been developed yet. Interference in the absorption of these with the absorption of blood glucose has caused the most problems with prior research.

The actual measurement of blood glucose through absorption in the visible to low near infrared region has the problems of interference through protein and fat absorption. Measurement in the near infrared region has the problems with interference from water. Work by Aristarchof and Balashowsky shows that there is a measurable difference even with the large water absorption with a change of .005 to .02 in absorption at 1410 and 1450 nm ranges, with little fat and protein interference. The actual blood glucose to water ratio is in the range of 1 to 10000.¹⁰

Due to the strong interference in the visible and near-infrared bands as mentioned above, none of the invasive techniques have currently shown much success when brought to clinical trials. There has been little in the way of base figures on the effectiveness of different techniques available from the product research mentioned above, and the academic research that is relevant has been focused on other areas, such as Aristarchof and Balashowsky and their measurement of the water properties with some subsidiary glucose findings.

Some recent work has also overlapped into the area of glucose concentration measurements. Lenferink, Schipper, and Kooyan demonstrated the effectiveness of a feedback setup utilizing Mach-Zehnder interferometric techniques¹¹ to accurately measure glucose concentrations substantially less than that contained in the human body and required for a glucose concentration reading from a non-invasive meter.

Difference in My Research

To my knowledge, no work has been done correlating the combination of visible and IR absorptions to each other, only to other absorptions in the same band. By combining the two bands I hope to factor out interference from two of the major sources, those being hemoglobin absorption and water absorption.

The hemoglobin absorption will be factored out by using a wavelength of 700nm, at which there is a low absorption for all forms of blood hemoglobin.¹² Water absorption will be factored out using a low wavelength for absorption in the infrared band. This will preferably be between 900 and 1100nm, and the actual wavelength used will depend on availability. The third wavelength, at 800nm, will be used as the varying wavelength for differing glucose absorptions. Differences in the .02 range for this wavelength have been found for varying concentrations of glucose.¹³

Experimental Setup and Method

Three distinct setups were used to measure the glucose concentrations in various water solutions - one absorption setup and two interferometric setups. Minor changes were used with each of the setups at different points to obtain more accurate results and minimize noise, but the intermediate results from these were not recorded. The three setups resulted in four distinct data sets being recorded, two for the initial absorption setup and one for each of the interferometric setups.

Absorption Setup 1

The initial absorption setup is shown pictured in Figure 1, Simple Absorption Measurement setup. The light source used was a broadband white light Tungsten Halogen source. The source provided adequate light level magnitudes for measurement across the desired wavelengths in both the visible and near-IR regions. The output of the

lamp is passed through a chopper to provide a signal which can be measured by the pyroelectric detector (PD1). The light then passes through a bandpass filter (BPF1).

The bandpass filters used were 700nm, 800nm, and 900nm. In addition, a 660nm bandpass filter was used for calibrations purposes due to the visible nature of the light it provided and the band proximity to the other filters used. The bandwidth of the filters was narrow, with less than a 20nm window centered on the appropriate wavelength of light passed.

A sample holder (SH1) was setup to use a 4.5ml cuvette held within a small sheet metal (Aluminum) shield. The holder was optically flat plastic and had a transmission percentage on the order of 90% in the tested ranges.

Within the holder various glucose concentrations were used. The samples had a varying degree of glucose-water concentrations in the range of 0 mg/dl to 400 mg/dl. Actual samples were created for the full range at increments of 10, 50, 100, 200, and 300mg/dl. This range represents the recommended testing range suggested by the FDA for any blood glucose meter.¹⁴

The method used to measure the glucose level was through a pyroelectric detector (PD1). The light was allowed to pass through the sample holder containing the glucose solution, then the actual output wattage of the remaining light was taken for all of the samples.

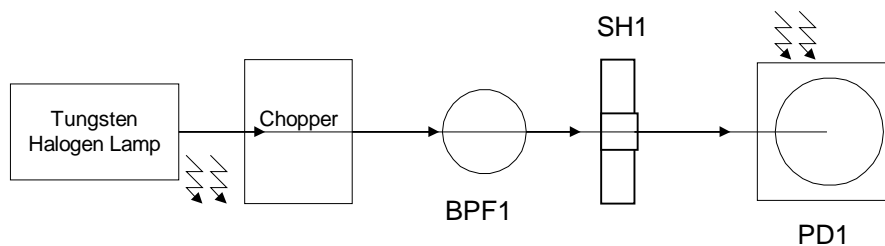


Figure 1. Simple Absorption Measurement Setup

Absorption Setup 1 - Method

Within the first absorption setup, glucose solutions were obtained by mixing pure glucose in weights of 10, 50, 100, 200, and 300 milligrams each with 1dl of water. The solutions were then each placed into a cuvette and labeled for their respective concentrations.

The cuvettes mentioned above were then placed in the sample holder, starting with pure water. Light from the Tungsten Halogen source was allowed to shine through a 700nm bandpass filter (BPF1) and then the sample and was measured with the pyroelectric detector (PD1). Each cuvette was replaced with the next highest concentration after a reading was taken.

Once a full set of measurements had been taken at a given wavelength, the filter (BPF1) was replaced with an 800nm bandpass filter and then a 900nm bandpass filter, with a full set of measurements read at each. The initial setup was slightly less stable than was desirable, and as a result a slightly modified setup was attempted.

Absorption Setup 2

After the initial absorption results were taken, a second setup was prepared. The absorption results from the initial setup showed a low Signal/Noise ratio and major fluctuations due to instability in the system. To remediate these problems, several changes were made to the initial setup. The changes made are as follows:

1. The sample holder (SH1) was better secured. Small fluctuations in the holder position caused large changes in the output signal strength and by securing the sample holder better the fluctuations were diminished.
2. The aluminum shield was extended in size. This was done to reduce the intensity of ambient and extraneous source light which struck the detector.
3. A lens was placed before the bandpass filter to provide a slightly stronger output signal.

The changes to the original setup used in Absorption Setup 2 are shown in Figure 2, Revised Absorption Measurement Setup.

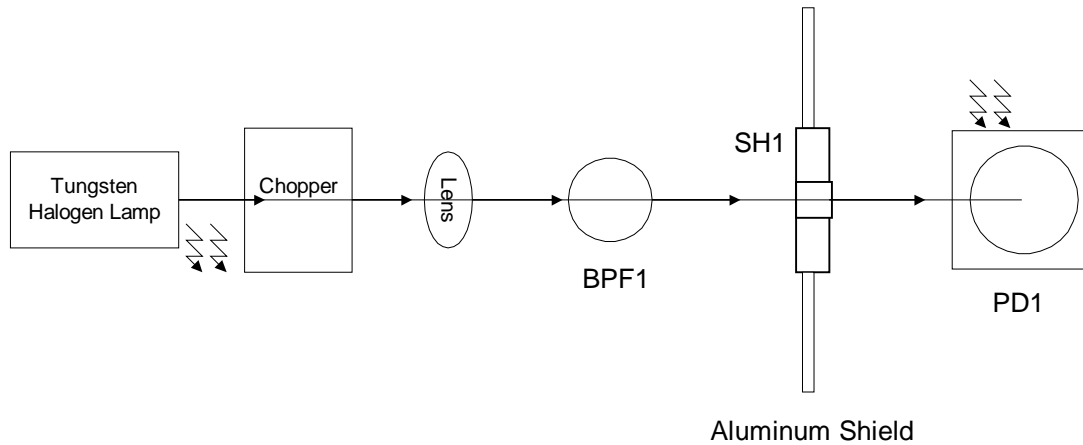


Figure 2. Revised Absorption Measurement Setup

Absorption Setup 2 - Method

In addition to the changes made to the experimental setup, several changes to the method in the Revised setup were used. The changes are as follows:

1. All glucose measurements were taken at twice the amount required. This was done to minimize the measurement error inherent in the graduated cylinder and electronic balance used.
2. All sample measurements were taken with and without the cuvette and the ratio of the two numbers was used. This allowed some of the temperature fluctuations due to the Tungsten Halogen lamp to be factored out.
3. The Tungsten Halogen lamp was shut off between measurements. As with the two measurement ratio, this was done to reduce the amount of temperature shift from the light source.
4. Six sample sets were taken and averaged. Instead of a single sample set, six were taken and the average ratio was used in the final comparisons.
5. Each sample set was taken at 50, 100, 150, 200, 250, 300, 350, and 400 mg/dl concentrations for greater accuracy across the required range.

Interferometric setup 1

The initial interferometric setup measured the intensity of the primary fringe of the result of a split-passthrough-recombine setup to generate interference. The actual setup used was a Mach-Zehnder interferometer and is shown pictured in Figure 3 - Interferometric Measurement Setup.

The light source, chopper, filter, and pyroelectric detector were the same as those used in the absorption setups above. There were some additional optics purchased for the setup and some specially manufactured components used as well.

The beam splitter (BS1) was a standard cube beamsplitter (Newport 25.4mm part # 10BC17MB.2) which covered the desired wavelength. The beam from the bandpass filter was split into two equal beams and each of these was passed through an appropriate mirror/sample combination. Both mirrors (M1 and M2) were silver coated high reflectance broadband mirrors (Newport 2inch part # 20D520ER.2) which reflected the wavelengths of light used. The first light beam was sent through a sample holder first and then reflected, the second was reflected and then sent through the sample holder.

Each of the two sample holders was identical and specifically constructed from a solid block of aluminum. The aluminum was chosen because of its stability, and due to the fact that it does not allow light transmittance at the wavelengths used. The holders were secured to the base as were the other components, and there was very little to no vibrations in the sample holders themselves. The holders were able to retain the cuvettes with little tolerance on the sides, and to provide an equal amount of blocked light for both the reference and variable samples.

Once both beams had passed through their respective sample holders and were reflected by their mirrors, they were combined using a second beamsplitter (BS2) identical to the first and the output intensity was measured directly with the pyroelectric detector (PD1).

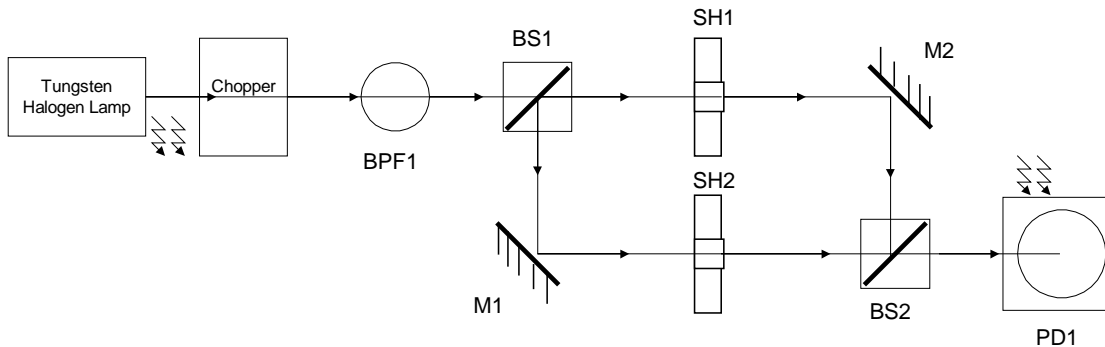


Figure 3. Interferometric Measurement Setup

Interferometric Setup 1 - Method

As with the absorption method, sample concentrations from 50mg/dl to 400mg/dl of glucose solution were made in 50 mg/dl increments. The various concentrations were then placed into holders and pipetted into the variable sample holder as needed. The reference sample holder contained water.

Each of the concentrations was pipetted into the variable sample holder and then a measurement of the intensity of the primary fringe was taken. This was repeated for each of the three wavelengths investigated. The reference sample contained the same water throughout. The choice to use the same cuvette and pipette in and out the various concentrations was made for two reasons:

1. Eliminate any changes in intensity due to the various makeups of mass produced cuvettes.
2. Eliminate any changes in intensity due to the positioning of the cuvette.

The samples were taken by turning on the Tungsten Halogen lamp for each measurement and turning it off immediately afterward, as with the Absorption Setup 2 mentioned above. Initially, the setup was calibrated to obtain the maximum strength with a 660nm bandpass filter by hand.

Interferometric Setup 2

The second interferometric setup was done with two Si photodiodes (PC1 and PC2, Hamamatsu Metal Package type # S1336-5BK) instead of the pyroelectric detector for their greater measurement range. In addition, a lock in amplifier was used to compare the reference and variable samples in place of the interference pattern generated by the second beamsplitter in the first setup. The basic setup is shown below in Figure 4 - Revised Interferometric Measurement Setup.

The majority of the components in the second interferometric setup are utilized the same as those in the first. The changes from the first in the actual experimental setup are as follows:

1. Two Si photodiodes were added to more accurately measure the reference and variable beams. The outputs of both photodiodes were fed into 741 operational amplifiers which setup to act as current->voltage converters.
2. A lock-in amplifier was added to accurately compare the output of the two photodiodes.
3. The output of the chopper was fed as a reference signal into the Lock-in amplifier (EG&G Model 128A) and the differential signal between the variable and the reference was produced. Use of the lock-in amplifier allowed phase sensitive readings and smoothing of the high frequency noise.

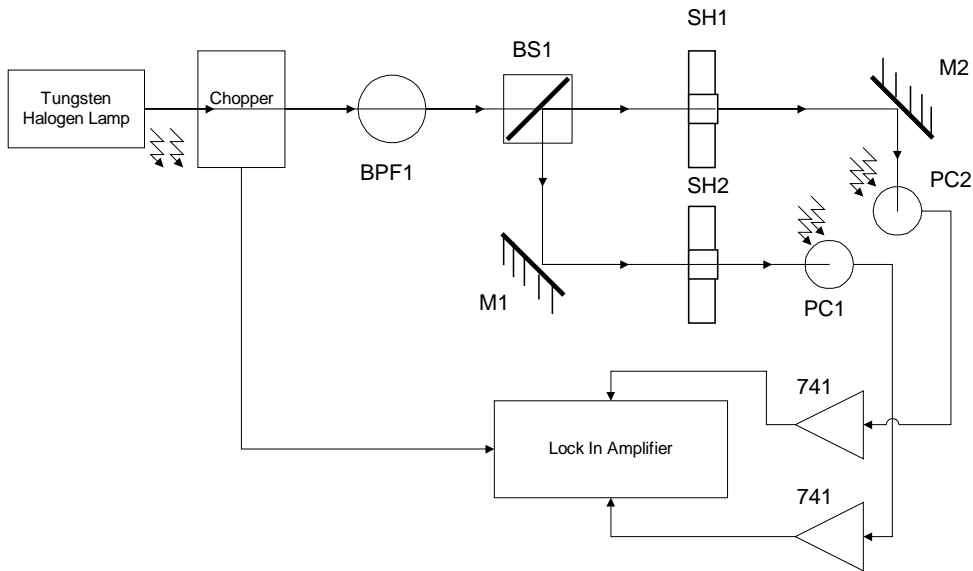


Figure 4. Revised Interferometric Measurement Setup

Interferometric Setup 2 - Method

The method used to measure the differences in the signals for the second interferometric setup was significantly different from that in the first setup. Initially, the setup needed to be accurately calibrated before any measurements were able to be properly taken.

The calibration was performed using a laser photodiode. The laser light was shone through the setup and the photodiodes placed properly to equalize their outputs. The laser diode was replaced by the Tungsten Halogen lamp and the photodiode outputs were once again equalized.

Once the setup was properly calibrated, the full complement of samples were pipetted in for all three wavelengths the same as in the initial interferometric setup. The light was then turned on and the lock-in amplifier allowed to stabilize. Once the amplifier output had stabilized, it was read using a digital multimeter.

Results

The results from the various setups were measured as per above. The actual summary results are displayed below, and the raw data is attached in Appendix A. A discussion of the results follows each data set.

Absorption Results 1

The results of the first absorption setup are shown below in Figure 5. The raw data is attached in Appendix A. As it is shown, all data is in the range of one microWatt, which is at the noise threshold of the measuring equipment. The expected results would be a decreasing intensity from 0 to 300mg/dl. The expected absorption of the glucose would result in a change similar to that at 800nm, but with a significantly steeper curve.

As the experiment was progressing, it was noted that the readings on the pyroelectric meter were linearly increasing with time. This appeared to be due to the heating caused by the Tungsten Halogen lamp being continuously turned on. This result is reflected in the highest intensity output at 700nm, which is actually increasing in value as the concentration of glucose (and the amount of light absorbed) are increasing.

Also evidenced was a large relation between the position of the cuvette in the sample holder and the results. Small movements in the sample holder caused large fluctuations in the measured intensity.

As a result of the above, the first set of absorption data was deemed to contain too much noise to extract any useful information from, and the second data set should be taken so that the following criteria are satisfied:

1. The order of magnitude is raised by at least one.
2. The sample holder is more stable and multiple samples are averaged to determine a closer approximation of the actual value.
3. Heating by the light source is factored out.

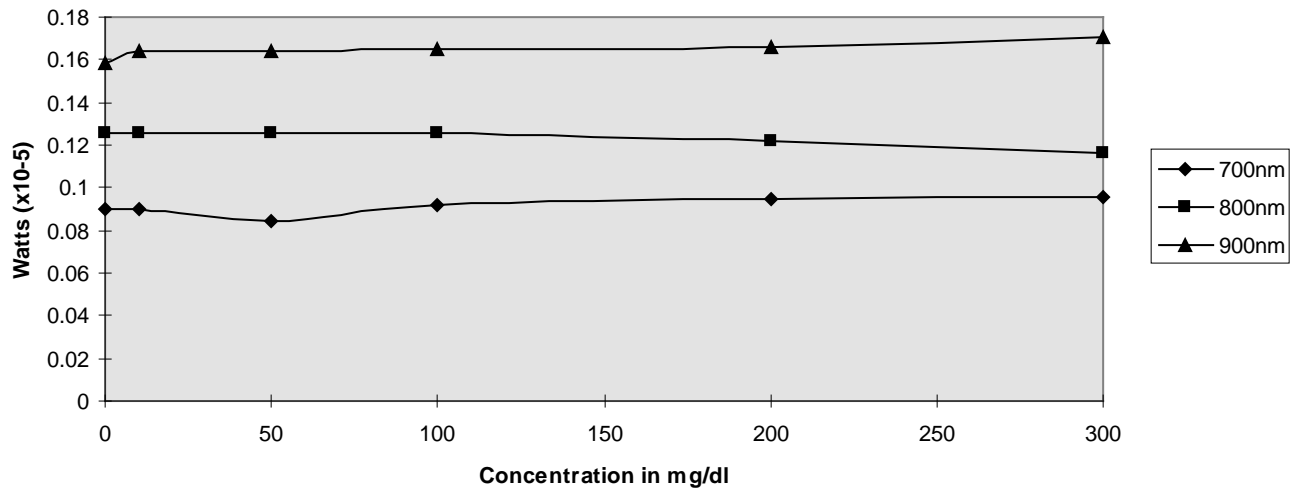


Figure 5. Intensity vs. Concentration

Absorption Results 2

The confidence in the results from the second absorption setup was significantly higher than that of the first absorption data set. The actual raw data is shown in Appendix A, but a summary of the data is shown in Figure 6. Six sample sets were taken in total and Figure 6 reflects the average of those sets.

An increase in intensity of about half an order of magnitude was obtained using the second setup over the first. The increasing readings due to heating effects were present in the raw data, but by taking the ratio of the sample to a baseline reading with no sample allowed those to be factored out fairly easily. The vibrations were also significantly cut down over the original setup.

The expected results would be all ratios being strictly decreasing. As the glucose concentration increases, so should the absorption. Therefore, the ratio of the measured value to the baseline should be decreasing as the concentration is increased. This is not evidenced in the results achieved.

There appears to be little correlation between glucose concentration and measured absorption. There does appear to be some correlation between the results at each of the three wavelengths measured, however. This tends to suggest that some outside factor was being measured, as opposed to the glucose concentration. One possibility is the measurement of changes in the refractive index between different cuvettes.

Overall, the results of the absorption testing were not consistent with expectations. Even with the more stable second experiment there was significant noise present, and the magnitudes being measured were less than that necessary to provide a good signal-noise ratio. Due to the very low intensities being measured, an interferometric technique was used in the next set of measurements.

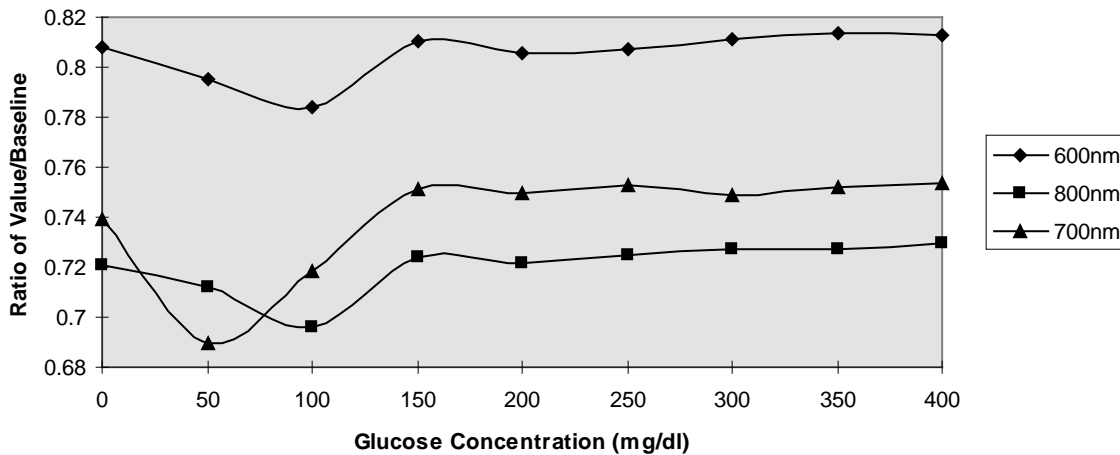


Figure 6. Ratio of Intensities vs. Concentration

Interferometric Results 1

The interferometric measurement was taken as an intensity of the primary fringe. The intensity was an order of magnitude ($\times 10^{-4}$ Watts) higher than that from the straight absorption experiments. The raw data is attached in Appendix A, and summary data can be seen below in Figure 7.

The results show no correlation between the interference pattern main fringe and the intensity measured. The relatively straight lines for each of the wavelengths measured indicate that the intensity is not measured as expected. It was expected that the intensity would drop over the course of the glucose additions due to a greater phase change caused by the higher concentrations. This was not apparent in the measurements below.

The possible reason for the lack of coherent data is a slight misalignment of the optics equipment. Further investigation after the original results were taken showed the optical alignment to be slightly off, but this was corrected for the final experimental setup.

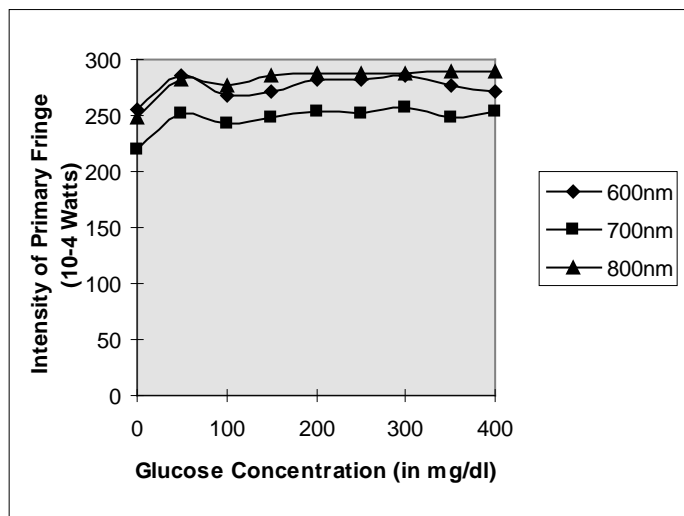


Figure 7. Primary Fringe Intensity vs. Glucose Concentration

Interferometric Results 2

The interferometric results from the second setup showed the most promise out of any of the setups. The results are consistent with expectations, and a summary of the results is shown in Figure 8.

The results indicate the presence of four fringes across all of the wavelengths measured. This is consistent with Lenferink, Schipper, and Kooyman¹⁵. The phase shift corresponds to $2\pi n_d / \lambda$. This results in the refractive index being equal to $(\text{phase shift})\lambda / 2\pi$. For the maximum phase shift evidenced in the 700nm filter, assuming a refractive index change on the order of $.5 \times 10^{-4}$ (the concentrations were

approximately an order of magnitude greater than the results from Lenderink et. al. mentioned above), the resultant measurement in phase shift is expected to be on the order of 18 (or slightly less than 3 fringe shifts), which is consistent with the measured shifts shown in the raw data for the first 100mg/dl glucose change. The total fringe shifts is 3 over the glucose concentrations measured below (plus one over the air->water transition.) This is consistent with the calculated results and the prior work.

The accuracy of the measurement cannot be adequately determined over the course of the three fringes. The actual change should be determined using a path length of approximately 1/3 the size currently used, corresponding to one fringe change for the concentrations shown.

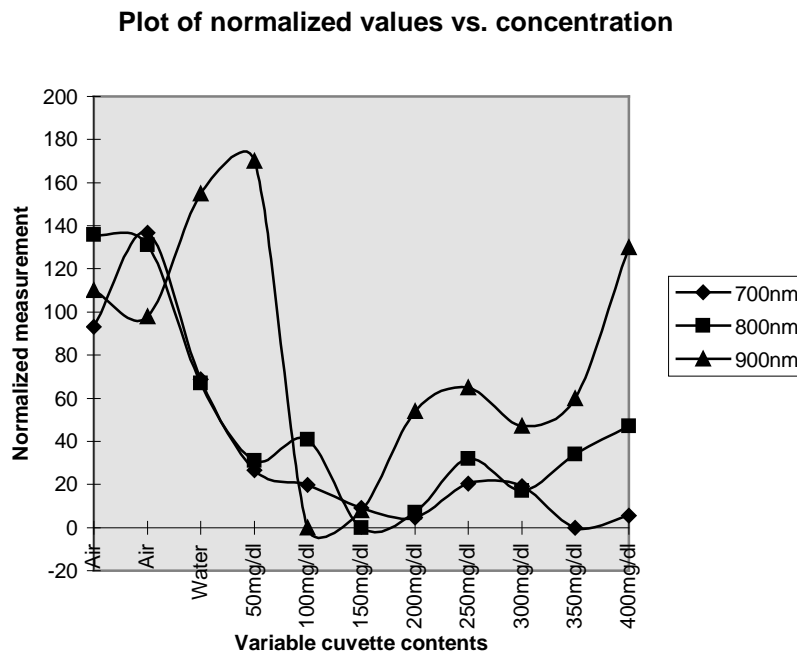


Figure 8. Plot of Phase Change vs. Concentration

Conclusions

The results of the above methods indicate that the direct measurement of blood glucose non-invasively through pure absorption techniques is not feasible. The signal to noise ratio is too low and the actual change in Watts due to glucose concentration change is below the noise threshold of readily available measurement equipment.

The interferometric techniques, specifically the second setup, showed great promise. The second setup should have several changes made to verify the results and conclusions drawn from them are valid for the concentrations used. Several things could be done to the setup to improve it. Several of these are as follows:

1. Use of a laser diode in place of the Tungsten Halogen lamp/filter setup. The choice of diodes in the precise absorption bands of glucose with a few nanometers (instead of 20nm) bandwidth and higher power output would provide more accurate results.
2. Better shielding of the light source. Although this would not be a problem if laser diodes were used, with the Tungsten Halogen lamp the optional shields should be attached to the sample holders.
3. The sample holders should be 1/3 the thickness they are currently. The cuvettes are too thick and are resulting in a multiple fringe change. The results between fringes show promise for performing as expected (decreasing in value), but to be completely verified this experiment should be performed using thinner samples.
4. The use of glass or quartz cuvettes. The optical properties of the plastic cuvettes used may have caused some of the noise in the initial absorption measurements.
5. Increased measurement resolution in 10mg/dl increments. This along with number 3 above would verify the results within a single fringe.

In addition to the above, once a signal within one fringe is obtained using the above, the ratio between the measures. The first measure would be the 400mg/dl measurement. The other solutions will then be measured with a proportional measure, using the Beer Lambert Law as follows:

$$T = \frac{I}{I_0}$$

Transmittance of the sample can be measured directly by taking the strength of the wavelength measured and dividing it by initial strength. The Absorbance can then be calculated as in the following:

$$A = -\log(T)$$

Absorbance is also equal to abc , which is the absorptivity coefficient (a) multiplied by the path length (b) multiplied by the concentration (c). The actual glucose level will be measured against a baseline wavelength which changes little with glucose levels, or λ_1 . The wavelength which varies with glucose levels will be λ_2 . The actual concentration will be

$$A(\lambda_1) - A(\lambda_2) = bc(a_1 - a_2)$$

With a known glucose level (in this case 400 mg/dl), $a_1 - a_2$ can be calculated from the above equation. Once this is known, all other concentrations measured can be calculated as a ratio of the initial concentration, where $a_1 - a_2$ and b are both constants. This gives the following equation:

$$\frac{A_1(\lambda_1) - A_1(\lambda_2)}{A_2(\lambda_1) - A_2(\lambda_2)} = \frac{(a_1 - a_2)bc_1}{(a_1 - a_2)bc_2} = \frac{c_1}{c_2}$$

This gives the concentration as a ratio to the initial concentration of 400 mg/dl (c_2). The concentration ratio would then be checked against the known concentrations of the glucose solutions and plotted to determine the characteristic equation of the ratio to the actual concentration.

The overall investigation into non-invasive measurement techniques for blood glucose, both experimentally and through the work of others, indicates that it is a non-trivial problem. It was proven that direct absorption measurement is extremely difficult if it is even possible, and the use of interferometric techniques would need to take into account factors such as finger thickness (i.e. require calibration for an individual.) Despite the problems, the interferometric results show that it is a viable technique for the measurement of glucose concentrations in the blood and warrants further investigation.

Appendix A

Raw Result Data

Absorption Setup 1 Raw Data

Glucose Concentration in mg/dl	Wavelength		
	<u>700nm</u>	<u>800nm</u>	<u>900nm</u>
<u>0</u>	0.09	0.126	0.158
<u>10</u>	0.09	0.126	0.164
<u>50</u>	0.084	0.126	0.164
<u>100</u>	0.092	0.126	0.165
<u>200</u>	0.095	0.122	0.166
<u>300</u>	0.096	0.116	0.171

Note: All numbers are Watts x 10⁻⁵

Absorption Setup 2 Raw Data

	<u>Concentration (in mg/dl)</u>	600nm			700nm			800nm		
		<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>
Trial 1	<u>0</u>	328	255	0.77744	392	312	0.79592	675	498	0.73778
	<u>50</u>	330	258	0.78182	405	325	0.80247	683	515	0.75403
	<u>100</u>	337	268	0.79525	411	319	0.77616	693	505	0.72872
	<u>150</u>	335	268	0.8	415	330	0.79518	695	524	0.75396
	<u>200</u>	341	269	0.78886	420	334	0.79524	701	528	0.75321
	<u>250</u>	338	268	0.7929	423	338	0.79905	704	531	0.75426
	<u>300</u>	333	267	0.8018	425	335	0.78824	710	528	0.74366
	<u>350</u>	335	272	0.81194	430	339	0.78837	712	533	0.7486
	<u>400</u>	338	273	0.80769	428	340	0.79439	706	536	0.75921
Trial 2	<u>0</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>
	<u>0</u>	317	260	0.82019	522	368	0.70498	712	519	0.72893
	<u>50</u>	327	268	0.81957	531	378	0.71186	724	534	0.73757
	<u>100</u>	332	268	0.80723	537	376	0.70019	731	528	0.7223
	<u>150</u>	337	276	0.81899	542	386	0.71218	736	546	0.74185
	<u>200</u>	340	274	0.80588	546	390	0.71429	739	547	0.74019
	<u>250</u>	339	274	0.80826	547	395	0.72212	740	553	0.7473
	<u>300</u>	340	277	0.81471	558	404	0.72401	748	555	0.74198
	<u>350</u>	344	280	0.81395	560	404	0.72143	751	562	0.74834
<u>400</u>	344	278	0.80814	567	412	0.72663	755	565	0.74834	

	600nm			700nm			800nm		
	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>
<u>0</u>	347	282	0.81268	606	426	0.70297	763	558	0.73132
<u>50</u>	355	282	0.79437	616	424	0.68831	761	563	0.73982
<u>100</u>	359	282	0.78552	622	430	0.69132	761	549	0.72142
<u>150</u>	360	290	0.80556	630	445	0.70635	766	566	0.7389
<u>200</u>	364	290	0.7967	639	444	0.69484	773	574	0.74256
<u>250</u>	364	293	0.80495	641	448	0.69891	774	578	0.74677
<u>300</u>	364	293	0.80495	638	450	0.70533	776	580	0.74742
<u>350</u>	366	294	0.80328	639	451	0.70579	783	585	0.74713
<u>400</u>	365	296	0.81096	643	454	0.70607	783	585	0.74713

Trial 3

	600nm			700nm			800nm		
	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>
<u>0</u>	390	314	0.80513	536	395	0.73694	730	552	0.75616
<u>50</u>	387	308	0.79587	538	392	0.72862	634	547	0.86278
<u>100</u>	384	304	0.79167	537	375	0.69832	730	531	0.7274
<u>150</u>	386	311	0.8057	535	398	0.74393	730	557	0.76301
<u>200</u>	383	309	0.80679	533	394	0.73921	730	552	0.75616
<u>250</u>	383	308	0.80418	534	397	0.74345	730	554	0.7589
<u>300</u>	380	307	0.80789	533	398	0.74672	725	550	0.75862
<u>350</u>	380	304	0.8	532	398	0.74812	718	549	0.76462
<u>400</u>	373	302	0.80965	528	395	0.74811	713	542	0.76017

Trial 4

	600nm			700nm			800nm		
	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>
<u>0</u>	363	296	0.81543	570	395	0.69298	745	562	0.75436
<u>50</u>	361	285	0.78947	560	378	0.675	744	554	0.74462
<u>100</u>	360	276	0.76667	554	362	0.65343	741	536	0.72335
<u>150</u>	361	293	0.81163	550	383	0.69636	744	569	0.76478
<u>200</u>	358	293	0.81844	541	378	0.69871	744	565	0.75941
<u>250</u>	357	293	0.82073	535	374	0.69907	738	569	0.771
<u>300</u>	355	290	0.8169	525	367	0.69905	737	561	0.76119
<u>350</u>	354	292	0.82486	512	359	0.70117	737	562	0.76255
<u>400</u>	354	290	0.81921	496	346	0.69758	734	564	0.76839

Trial 5

	600nm			700nm			800nm		
	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>
<u>0</u>	353	289	0.8187	609	421	0.6913	723	524	0.72476
<u>50</u>	352	278	0.78977	606	404	0.66667	724	217	0.29972
<u>100</u>	351	266	0.75783	605	396	0.65455	715	493	0.68951
<u>150</u>	348	285	0.81897	603	416	0.68988	710	528	0.74366
<u>200</u>	347	283	0.81556	607	416	0.68534	705	526	0.7461
<u>250</u>	345	281	0.81449	603	415	0.68823	703	520	0.73969
<u>300</u>	342	280	0.81871	585	409	0.69915	693	513	0.74026
<u>350</u>	335	277	0.82687	581	405	0.69707	688	511	0.74273
<u>400</u>	333	274	0.82282	573	403	0.70332	684	506	0.73977

Trial 6

	<u>Concentration (in mg/dl)</u>	600nm			700nm			800nm		
		<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>	<u>Base</u>	<u>Actual</u>	<u>Ratio</u>
	<u>0</u>	349.6667	282.6667	0.80826	539.1667	386.1667	0.72085	724.6667	535.5	0.73889
	<u>50</u>	352	279.8333	0.79514	542.6667	383.5	0.71216	711.6667	488.3333	0.68976
	<u>100</u>	353.8333	277.3333	0.78403	544.3333	376.3333	0.69566	728.5	523.6667	0.71878
	<u>150</u>	354.5	287.1667	0.81014	545.8333	393	0.72398	730.1667	548.3333	0.75103
Average	<u>200</u>	355.5	286.3333	0.80537	547.6667	392.6667	0.72127	732	548.6667	0.74961
	<u>250</u>	354.3333	286.1667	0.80758	547.1667	394.5	0.72514	731.5	550.8333	0.75299
	<u>300</u>	352.3333	285.6667	0.81083	544	393.8333	0.72708	731.5	547.8333	0.74886
	<u>350</u>	352.3333	286.5	0.81348	542.3333	392.6667	0.72699	731.5	550.3333	0.75233
	<u>400</u>	351.1667	285.5	0.81308	539.1667	391.6667	0.72935	729.1667	549.6667	0.75383

Note: All Base and Actual numbers are in units of Watts x 10⁻⁵

Interferometric Setup 1 Raw Data

		Wavelength		
<u>Concentration (in mg/dl)</u>		<u>700nm</u>	<u>800nm</u>	<u>900nm</u>
Trial 1	<u>0</u>	350	167	285
	<u>50</u>	376	185	357
	<u>100</u>	381	182	322
	<u>150</u>	373	171	324
	<u>200</u>	366	191	326
	<u>250</u>	362	179	326
	<u>300</u>	369	188	323
	<u>350</u>	385	174	325
	<u>400</u>	337	181	324
	Trial 2		<u>700nm</u>	<u>800nm</u>
<u>0</u>		332	184	280
<u>50</u>		366	216	314
<u>100</u>		295	191	318
<u>150</u>		298	190	313
<u>200</u>		310	183	326
<u>250</u>		330	193	328
<u>300</u>		329	190	323
<u>350</u>		275	185	324
<u>400</u>		291	188	313
Trial 3		<u>700nm</u>	<u>800nm</u>	<u>900nm</u>
	<u>0</u>	238	326	257
	<u>50</u>	273	364	271
	<u>100</u>	259	370	264
	<u>150</u>	273	382	292
	<u>200</u>	282	377	270
	<u>250</u>	276	383	253
	<u>300</u>	282	396	265
	<u>350</u>	281	393	260
	<u>400</u>	280	400	257
Trial 4		<u>700nm</u>	<u>800nm</u>	<u>900nm</u>
	<u>0</u>	203	219	211
	<u>50</u>	232	235	247
	<u>100</u>	214	244	250
	<u>150</u>	223	248	248
	<u>200</u>	244	239	238
	<u>250</u>	239	259	246
	<u>300</u>	245	256	256
	<u>350</u>	240	242	256
	<u>400</u>	240	247	257

	<u>700nm</u>	<u>800nm</u>	<u>900nm</u>	
Trial 5	<u>0</u>	205	220	226
	<u>50</u>	234	257	255
	<u>100</u>	224	231	249
	<u>150</u>	236	242	247
	<u>200</u>	242	270	252
	<u>250</u>	243	250	259
	<u>300</u>	243	256	249
	<u>350</u>	240	239	267
	<u>400</u>	225	247	263
	<u>700nm</u>	<u>800nm</u>	<u>900nm</u>	
Trial 6	<u>0</u>	209	204	226
	<u>50</u>	231	251	251
	<u>100</u>	239	240	253
	<u>150</u>	221	257	287
	<u>200</u>	245	262	309
	<u>250</u>	244	249	315
	<u>300</u>	245	253	305
	<u>350</u>	245	255	300
	<u>400</u>	252	260	324
	<u>700nm</u>	<u>800nm</u>	<u>900nm</u>	
Average	<u>0</u>	256.1667	220	247.5
	<u>50</u>	285.3333	251.3333	282.5
	<u>100</u>	268.6667	243	276
	<u>150</u>	270.6667	248.3333	285.1667
	<u>200</u>	281.5	253.6667	286.8333
	<u>250</u>	282.3333	252.1667	287.8333
	<u>300</u>	285.5	256.5	286.8333
	<u>350</u>	277.6667	248	288.6667
	<u>400</u>	270.8333	253.8333	289.6667

Note: All measurements are in 10⁻⁴ Watts

Interferometric Setup 2 Raw Data

Reference Cell	Variable Cell	700nm Filter				800nm Filter				900nm Filter			
		<u>0</u> <u>degrees</u>	<u>90</u> <u>degrees</u>	<u>0 - 90</u> <u>degrees</u>	<u>normalized</u>	<u>0</u> <u>degrees</u>	<u>90</u> <u>degrees</u>	<u>0 - 90</u> <u>degrees</u>	<u>normalized</u>	<u>0</u> <u>degrees</u>	<u>90</u> <u>degrees</u>	<u>0 - 90</u> <u>degrees</u>	<u>normalized</u>
Air	Air	-182.1	145.7	-327.8	93.2	-1201	837	-2038	136	-725	537	-1262	110
Water	Air	-158.3	125.9	-284.2	136.8	-1203	840	-2043	131	-730	544	-1274	98
Water	Water	-202.8	149.3	-352.1	68.9	-1246	861	-2107	67	-705	512	-1217	155
Water	50mg/dl	-224.2	170.1	-394.3	26.7	-1270	873	-2143	31	-694	508	-1202	170
Water	100mg/dl	-228.4	172.7	-401.1	19.9	-1259	874	-2133	41	-787	585	-1372	0
Water	150mg/dl	-236.3	175.7	-412	9	-1286	888	-2174	0	-781	583	-1364	8
Water	200mg/dl	-238.4	177.9	-416.3	4.7	-1281	886	-2167	7	-761	557	-1318	54
Water	250mg/dl	-226.5	174.2	-400.7	20.3	-1269	873	-2142	32	-754	553	-1307	65
Water	300mg/dl	-227.4	174.5	-401.9	19.1	-1277	880	-2157	17	-765	560	-1325	47
Water	350mg/dl	-242	179	-421	0	-1260	880	-2140	34	-757	555	-1312	60
Water	400mg/dl	-238	177.5	-415.5	5.5	-1263	864	-2127	47	-720	522	-1242	130

References

- ¹ American Diabetes Association, *Diabetes Info*, 1998; pp. **1-3**
- ² Neergaard, Laura, "Diabetes Laser Blood Test Approved", Associated Press, December 8, 1998.
- ³ Cygnus Promotional literature, Cygnus Corporation, 1997.
- ⁴ Cygnus website, www.cygn.com/gluowatch.html, 1998.
- ⁵ Children with Diabetes website, http://www.castleweb.com/diabetes/d_06_e10.htm, 1997.
- ⁶ Children with Diabetes website, http://www.castleweb.com/diabetes/d_06_e00.htm, 1998.
- ⁷ Futrex website, <http://www.futrex.com/futrex/cgi-bin/toc.cgi?896280569>, 1998.
- ⁸ IntegOnline website, <http://www.integonline.com>, 1997.
- ⁹ IntegOnline website, <http://www.integonline.com/new/htm/timeline.htm>, 1998.
- ¹⁰ Aristarchof, Balashowsky, *Influence of Glucose on Water Infrared Spectra*, Clinical, Laboratory Diagnostoc (rus), 1997; pp. **1-3**
- ¹¹ A.T.M. Lenferink, E.F. Schipper, and R.P.H. Kooyman, *Improved Detection Method for Evanescent Wave Interferometric Chemical Sensing*, Review of Scientific Instrumentation, American Institute of Physics, March 1997; pp. **1-5**.
- ¹² B. Manke, J. Schwider, S. Junger, J. Kranz, *Multiwavelength Pulse Oximetry in the Measurement of Hemoglobin Fractions*, FORMIKROSYS, 1996. p. **3**.
- ¹³ Fischbacher C, Jagemann KU, Danzer K, Müller UA, Papenkordt L, Schüler J., *Enhancing calibration models for non-invasive near-infrared spectroscopical blood glucose determination*, Fresenius J Anal Chem. 1997; **359**: **78-82**.
- ¹⁴ Hackett, Joseph, *Review Criteria Assessment of Portable Blood Glucose Monitoring In Vitro Diagnostic Devices Using Glucose Oxidase, Dehydrogenase, or Hexokinase Methodology*, Clinical Devices Branch, FDA, 1997; p. **6**.
- ¹⁵ A.T.M. Lenferink, E.F. Schipper, and R.P.H. Kooyman, *Improved Detection Method for Evanescent Wave Interferometric Chemical Sensing*, Review of Scientific Instrumentation, American Institute of Physics, March 1997; p. **4**.