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Multisensor noninvasive blood glucose monitoring system

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MULTISENSOR NONINVASIVE BLOOD GLUCOSE MONITORING SYSTEM

A Thesis by

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Submitted to the Department of Electrical Engineering and Computer
Science and the faculty of the Graduate School of
Wichita State University
in partial fulfillment of
the requirements for the degree
of Master of Science

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MULTISENSOR NONINVASIVE BLOOD GLUCOSE MONITORING SYSTEM

The following faculty members have examined the final copy of this thesis for form and content, and recommend that it be accepted in partial fulfillment of the requirement for the degree of Master of Science with a major in Computer Networking.

Dr. Abu Asaduzzaman, Committee Chair

Dr. Deepak Gupta, Committee Member

Dr. Yi Song, Committee Member

DEDICATION

To the Almighty, my family for their ultimate encouragement throughout my education and for incomparable advice throughout my life and my gems Ishanee, Tisya, Adrisha, Swaraj, Swayum and Aayana who always find a way to cheer me up.

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ABSTRACT

Diabetes and related complications are responsible for early death – one person in every 7 seconds. Long term and short term complications due to diabetes can be reduced through proper diet, physical exercise, and medication. In order to assess the pattern of glucose changes of diabetic patients (for determining the appropriate drugs), concentration of glucose in blood needs to be monitored. The pain and inconvenience (due to pricking fingers) in the current invasive blood glucose monitoring technique has led to the emergence of noninvasive blood glucose monitoring (NIBGM) techniques. In this paper, we propose a multi-sensor NIBGM system using infrared (IR) sensor and ultrasonic micro-electro-micro mechanical (MEMS) technology. We simulate the proposed NIBGM system using COMSOL Multiphysics software and calibrate the system using Matlab code. Lead free piezoelectric materials are evaluated for ultrasonic sensors. Behavior of ultrasonic MEMS is simulated by varying the concentration of blood glucose. The simulation results are cross validated with actual glucose concentration to assess errors. According to simulation results and Clarke error grid analysis (EGA), the proposed NIBGM system has potential to enhance accuracy. By adding easiness and comfort (due to no pricking), the proposed multi-sensor NIBGM device should provide better assistance to manage diabetes.

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LIST OF ABBREVIATIONS

BNN	Barium Sodium Niobate
BT	Barium Titanate
CAPPLab	Computer Architecture and Parallel Programming Laboratory
LIN	Lithium Niobate
MIR	Mid Infrared
MEMS	Micro Electronic Mechanical System
NIBGM	Noninvasive Blood Glucose Monitoring
NIR	Near Infrared
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

According to World Health Organization (WHO), the pervasiveness of diabetes was estimated to be 9% among adults, 4.9 million deaths were caused by diabetes in 2014 and diabetes will be the 7th leading disease cause of death in 2030. Diabetes and its complications are responsible for early death, where 1 person dies in every 7 seconds [1]. With regards to economics, cost of diabetes covers 6 to 15% of the budget of National Health System in the European Union [2].

1.1 The Diabetes Mellitus

Diabetes Mellitus, commonly referred as diabetes, is a metabolic disease that occurs when person has uncontrollable blood glucose levels over a long period.

1.1.1 Regulation of Blood Glucose Levels in Human Body

Glucose is the main source of energy for the human body. Glucose levels are regulated to keep the body homeostasis so that blood glucose level remains stable and relatively constant. There are many hormones that are involved in this process but insulin is the most important one. Insulin is produced by the beta cells of the pancreas and it is provided to remove excess glucose from the blood. It also acts a controlling signal to breakdown glucose to glycogen for internal storage in blood [3]. As the blood glucose level increases, insulin stimulates the cell to utilize more glucose and acts a controlling signal by sending the signal to the liver to convert excess glucose to glycogen for the later use so that when there is a fall in blood glucose level, glucagon helps the breakdown of glycogen into glucose as shown in Figure 1.

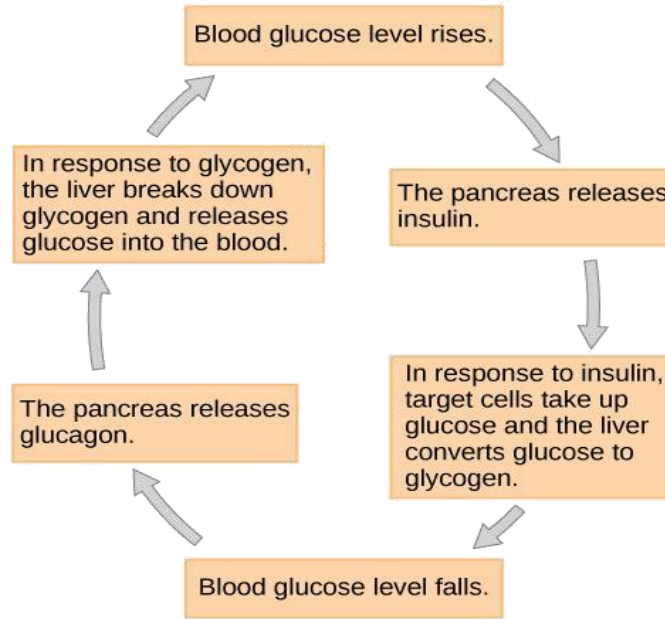


Figure 1. Regulation of Blood Glucose Levels by Insulin and Glucagon [3].

In this way, both insulin and glucagon work together to maintain the glucose level constant and stable.

1.1.2 Types of Diabetes

The three most common type of diabetes are Type 1 diabetes, Type 2 diabetes, and gestational diabetes. Although there are also other types of diabetes including congenital diabetes, cystic-fibrosis related diabetes, and steroid diabetes [4].

Type 1 or Insulin Dependent Diabetes Mellitus (IDDM) is an auto immune disease in which body cannot produce sufficient insulin leading to insulin deficiency due to loss of insulin-producing beta cells. Type 2 diabetes or Non-Insulin Dependent Diabetes Mellitus (NIDDM) is due to reduced insulin secretion. Gestational diabetes usually occurs to women during their pregnancy. It generally resolves after pregnancy or else it may lead to Type 2 diabetes. 90% cases of diabetes are of Type 2 diabetes which mostly affects the adult people.

1.1.3 Complications related to Diabetes

Blood glucose level is the amount of glucose present in blood .It is commonly measured in mg/dl. Diabetes patients have abnormally excessive glucose level or diminished glucose level. Symptoms of diabetes include Polydipsia, Polyphagia, etc. as shown in Figure 2. This condition can be classified as hypoglycemic, where blood glucose level is less than 72mg/dl or hyperglycemic, where blood glucose level is more than 200mg/dl [5].

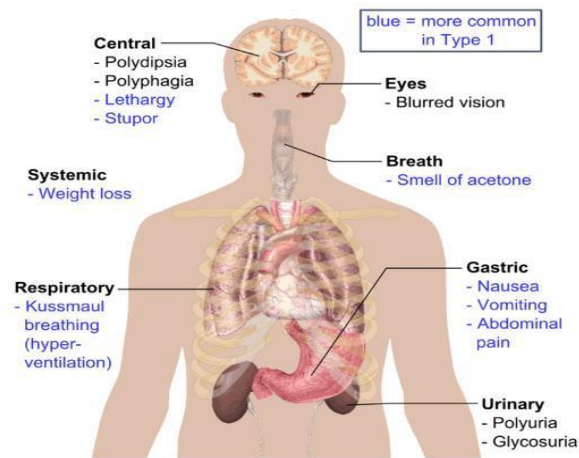


Figure 2. Symptoms of Diabetes [6]

Hyperglycemia has no immediate damaging effects for patients but it has long-term complications. The long term complications include nerves damage, renal failure, blindness, coronary heart disease, strokes and peripheral vascular disease. In order to prevent the above complications, patients should have a proper dietary management, physical activity and use of proper medications like insulin injections or tablets before meals.

Hypoglycemia has short term effects and it usually affects brain. It is classified on the basis of glucose level:

- Mild hypoglycemia: Blood glucose level is between 55 and 70 mg/dl. It is characterized by palpitations, extreme hunger, trembling, cold or excessive sweating and visual paleness due

to poor peripheral blood circulation. In this case, eating small amount of carbohydrate can restore normal glucose levels.

- Moderate hypoglycemia: Blood glucose level is between 40 and 55 mg/dl. It is characterized by mood changes, confusion, blurred vision, weakness and drowsiness since it affects the central nervous system.
- Severe hypoglycemia: Blood glucose level is less than 40 mg/dl. It is characterized by convulsions, loss of consciousness and coma. In this case glucagon injection is required [7].

A patient needs to monitor the blood glucose level on daily basis to control blood sugar levels.

1.2 Blood Glucose Level Monitoring

Long term and short term complications can be reduced through proper diet, physical exercise, and medication. But to know the pattern of glucose changes of a diabetic patient, concentration of glucose in blood (glycaemia) needs to be monitored. Blood glucose level can be monitored in minimal invasive way and noninvasive manner. Currently, glucose monitoring techniques that are minimal invasive are in practice.

Minimal invasive technique is done by piercing the skin, typically the finger tip, to draw blood and drop blood onto a reagent test strip and determine the glucose concentration by inserting the strip into the measurement device. This technique converts the glucose concentration into electrical signal. Mostly it works on glucose-oxidase principle. Other principles based on binding of glucose with other molecules or glucose spectral properties [8].



Figure 3. Invasive (Left) and Noninvasive (Right) Glucose Monitoring [9, 10]

Noninvasive technique measures glucose concentration through skin without extracting blood or interstitial fluid or without a needle penetrating through skin for reaching these fluids. It measures the physical properties of the fluid or underlying tissue like optical, acoustic, and electrical properties whose value changes with any change in blood glucose level. Various noninvasive technique in research are MIR/NIR Spectroscopy, Raman Spectroscopy, Occlusion Spectroscopy, Optical Coherence Tomography, Fluorescence, Polarimetry, Photo acoustic Spectroscopy, Impedance/Dielectric Spectroscopy, Electromagnetic as illustrated in Figure 4. These techniques are affected by external factors, making it more difficult to perform an accurate measurement [10].

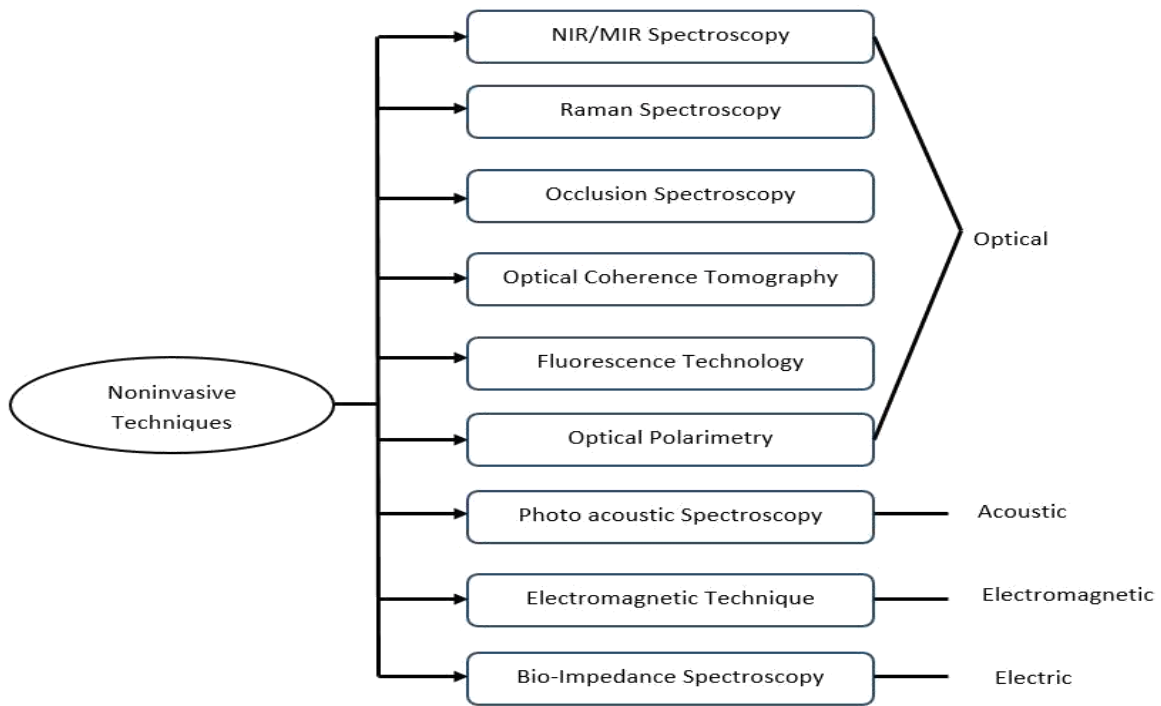


Figure 4. Noninvasive Techniques for Blood Glucose Monitoring

1.3 Micro-Electro-Mechanical Systems

Micro-Electro-Mechanical System (MEMS) is the method to combine electrical and mechanical components together on a chip, to make a system of miniature scale.

In the United States they are mainly called MEMS, whereas in some other parts of the world they are called “Microsystems Technology” or “micro machined devices”.

Now-a-days, MEMS are being preferred for sensors because of the following reasons:

- Size is smaller as compared to actual sensor.
- Power Consumption is low.
- Sensitivity to input variation is high.
- Cost is less.

1.4 Regression Analysis and Calibration

Noninvasive method of glucose monitoring is partial in the prediction of blood glucose.

There are two reasons responsible for this inaccuracy. It includes problem related to engineering and second, may be due to data analysis problem. Partial work of our proposed technique is to find out the best regression model and implementation it as calibration model. Calibration is essential to achieve the uniformity in the measurement. Every so often calibration comprises forming the relationship between a device response (response of sensors in this case) and one or more reference values (actual glucose value in this case).

1.5 Problem Statement

Invasive method of blood glucose monitor has many shortcomings such as pain, discomfort, and risk of infection. Therefore, cost-effective noninvasive glucose monitor is desirable. However, contemporary noninvasive glucose monitors are not capable to give the required accuracy because of engineering problems and statistical issues to analyze the data.

1.6 Contributions

In this work, an ultrasonic MEMS sensor and near infrared sensor transceivers assembly are introduced for blood glucose predictions by noninvasive approach. The goal of this project is to improve the accuracy of noninvasive technique to predict glucose level. The major contributions of this work include:

- Introduction of ultrasonic MEMS sensor along with near infrared sensor to overcome the disadvantage of near infrared noninvasive technique and photo acoustic spectroscopy.
- Improvement of the accuracy and sensitivity of the device.
- Implementation of the best regression model for calibrating the device.

1.7 Thesis Organization

The rest of the manuscript is organized as follow:

In Chapter 2, we discuss invasive and noninvasive techniques of glucose monitoring system and about regression analysis method and calibration that are explained in various conference and journal papers.

In Chapter 3, we introduce the proposed multisensor noninvasive blood glucose monitoring system.

In Chapter 4, we describe the system parameters, experimental setup and input parameters that are used for this experiment.

In Chapter 5, we present experimental results to evaluate the proposed technique.

In Chapter 6, we conclude this work and list of possible future extensions of this proposed technique.

CHAPTER 2

LITERATURE SURVEY

In this chapter, some related published articles are discussed to understand various invasive and noninvasive techniques of glucose monitoring and various regression analysis methods.

2.1 Invasive Blood Glucose Monitoring

In invasive glucose meter, patients monitor their blood glucose levels by keep small amount of their blood on test strip of glucose monitor device as shown in Figure 5.



Figure 5. Regulation of Blood Glucose Levels in Invasive Way [11]

Invasive glucose monitor device based on the principle of electrochemical cell and it contains two major parts. They are:

- Testing strips: These are single use. It is a small piece of paper which has certain chemicals, which allow it to react with glucose in the blood. It has a hard plastic base to give strength to the strip as shown in Figure 6. Several chemical layers are separated by spacers. One layer

contains enzyme glucose oxidase, another contains potassium ferricyanide. Another layer has two electrodes to measure current flow. In between these layers, one layer of chemical present which protect the above layers and helps to react all layers with blood.

- Monitor: Monitor measures the electrical current flow through the test strip and change the current conferring to the amount of glucose present in blood.

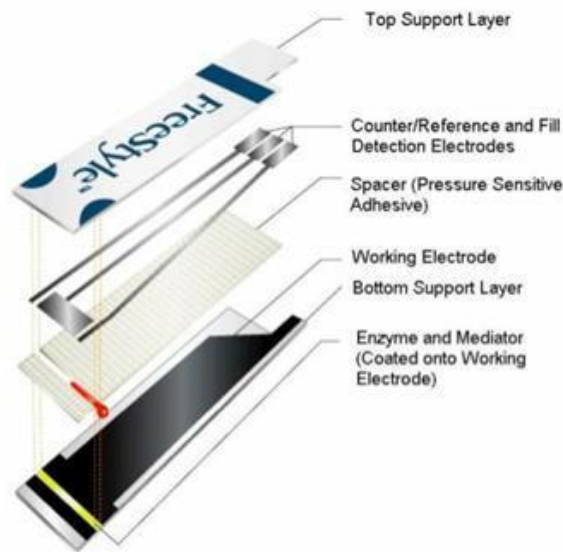
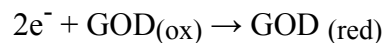


Figure 6. Electrochemical Blood-Glucose Monitoring Strip [12]

When patient puts small amount of blood on test strip, the blood is pulled up the sides of the test strip through capillary action. As the blood flows into the test strips, it comes in contact with glucose oxidase layer. Then Glucose oxidase enzyme (GOD) reacts with glucose in blood and produces gluconic acid.



Then the gluconic acid reacts to potassium ferricyanide layer to form potassium ferrocyanide. Then potassium ferrocyanide reacts with metals in the electrode and cause current to flow in electrode layer.

So the more glucose in blood, more gluconic acid will form. More gluconic acid will form, more ferrocyanide will form. And more ferrocyanide, more current will flow through electrodes [12].

Eventhough invasive type glucose monitoring provides accurate results and active management of glucose level, it has many disadvantages too, like:

- Cost of blood glucose test strips, tends to increase the recurring cost of diabetic device. As test strips are single use only.
- Discomfort for the patient as some patients are not comfortable with sharp device or seeing their blood.
- Inconvenience for patient for frequent testing as with every time testing, they are losing some amount of blood from their body.
- Patients need to carry required equipment and supplies. Starting from cotton, alcohol to glucose monitor, they need to carry for not getting infection later.

2.2 Non Invasive Blood Glucose Monitoring

Noninvasive Blood Glucose Monitoring are in research area for obvious reason related to comfort of patient. Even if they do not provide accurate results, there has been gradually a increase in the development of these noninvasive technologies. Before going to individual technology, the properties of skin and glucose are discussed which will be the base for measuring blood glucose level. Then the different noninvasive technologies are discussed with their respective working principles, advantages and disadvantages.

2.2.1 Properties of Skin and Glucose

To design a noninvasive glucose monitoring device, it is necessary to know about the properties of skin and glucose. Due to the noninvasive approach, properties of skin plays a vital role to determine the accuracy of the device.

2.2.1.1 Properties of Skin

To understand the characteristics of noninvasive glucose monitoring sensors, it is convenient to know the skin morphology and distribution of blood within the layers.

Skin is composed of several layers as exemplified in Figure 7. The uppermost layer is stratum corneum of epidermis, composed of dead keratinized. Second layer is epidermis and followed by dermis. Below to that is the subcutaneous tissue, which is composed of underlying fat and muscle. The dermis is again subdivided into three different layers: upper vascular plexus, reticular dermis, and deep vascular plexus. Epidermis does not contain its own vascular system. Fraction of blood vessels in the dermis is in the range of 1%-20%, mainly in upper and deep vascular plexus [13].

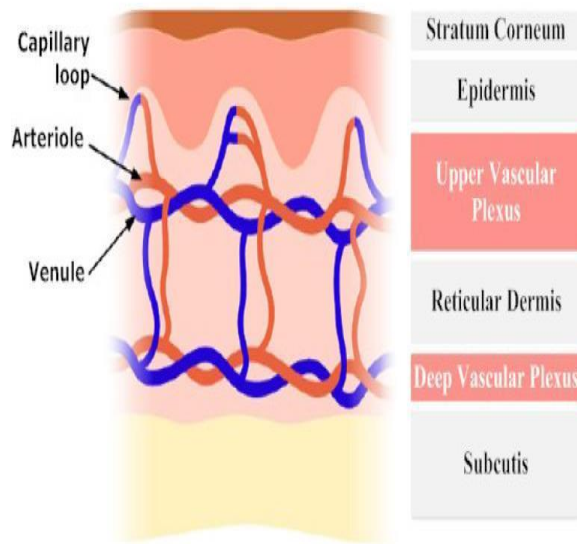


Figure 7 Skin Layered Structure and Distribution of Blood [13]

Most noninvasive glucose sensors exploit different properties to interact with skin which can measure blood glucose level. These properties include optical, acoustic, and electric.

2.2.1.2 Properties of Glucose

Blood has average density of 1060 kg/mm^3 with average glucose level of 70 mg/dl . But there will be a fluctuation of blood glucose level during the course of a day [14]. So density of blood will increase with increase in glucose level.

Both physical and chemical properties of glucose should be studied in order to design a noninvasive glucose sensor. Table 1 [15] shows the spectral characteristics for absorption band of glucose and Figure 8 shows the absorbance spectrum of glucose [16]. Absorption coefficient of glucose is also shown in Figure 9 with feasible region for the measurement of glucose [17].

Table 1. Glucose absorption band spectral characteristics

Wavelength (nm)	Possible Assign.	Description
939	3 ν O-H stretch	A second O-H overtone band
1126	3 ν C-H stretch	A second harmonic C-H overtone band
1408	2 ν O-H	A first O-H overtone band
1538	ν O-H + ν C-H	O-H and C-H combination band
1688	2 ν C-H	A C-H overtone band
2261	ν C-H + ν C-C-H + O-C-H	Combination of a CH stretch and a CCH, OCH deformation
2326	2 ν O-H	A first O-H overtone band

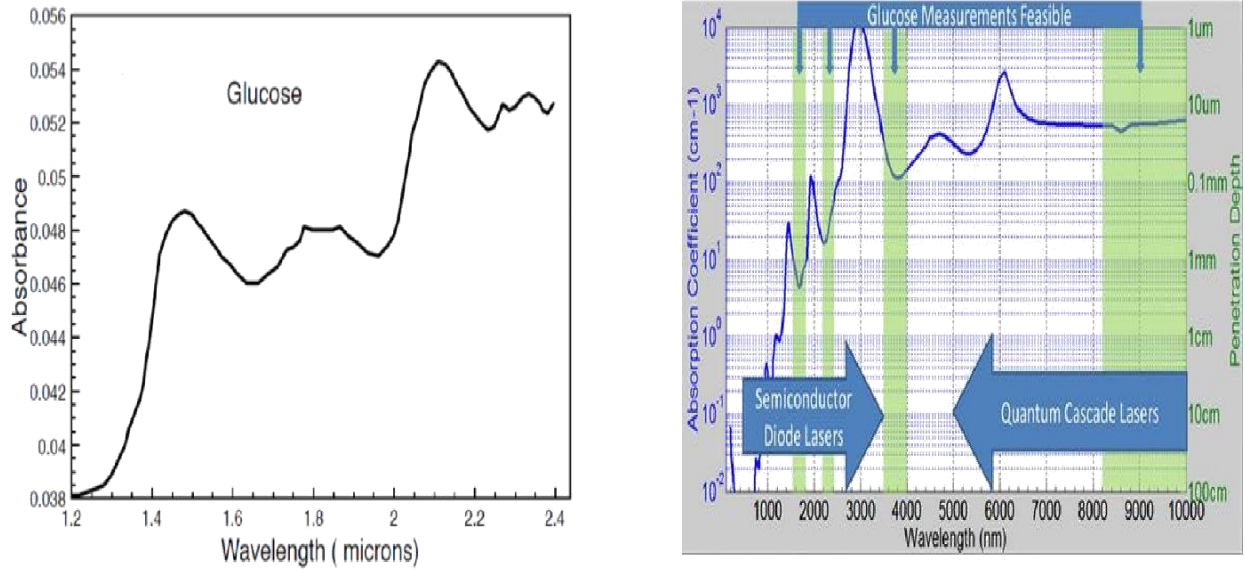


Figure 8. Absorption spectrum of glucose [16, 17]

It is observed from Figure 8 that the absorption of glucose which is measured as absorbance (unit A.U- Absorbance Unit which is unit less) has the highest peak at wavelength 1440 nm and 2270 nm. But at 1440 nm, absorption of infrared due to water is also high. So it will be difficult to distinguish the characteristics of glucose at 1440 nm. So wavelength of 2270 is preferred.

It is also observed that the absorption coefficient depends on wavelength for a specific material. Here the value of absorption coefficient is high in the range of 2000 to 3000 nm. Again feasible range to measure the blood glucose level lies in the green region. As the cost of the device is also a major concern, semiconductor diodes are of less cost when compared to Quantum Cascade Lasers. Due to which 1440 nm to nearly 4000 nm would be feasible for the measurement.

2.2.2 Optical Techniques for NIBGM

When light passes through skin, it undergoes various properties of light like Reflection, Scattering and Absorption. It is reflected by the stratum corneum, absorbed by the skin and

remaining part is scattered and diffused into multiple directions. Figure 9 shows the interaction of light with skin.

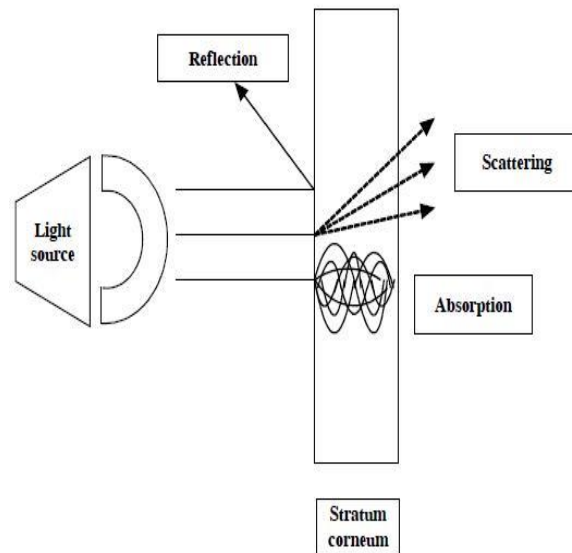


Figure 9. Interaction of Light with Skin [15]

These optical properties of light are useful for detecting glucose level in blood. Spectroscopy analyses the optical properties of light with various wavelength of radiation. Spectroscopy is also helpful for finding the constituent in the material along with their concentration since each constituent exhibit different spectral properties. Different sensors based on the spectroscopy principle can be classified according to the optical properties of light which is applied.

2.2.2.1 Near Infrared (NIR) Spectroscopy

Near infrared spectroscopy is based on Absorption-Transmittance Photometry as shown in Figure 10. Changes in glucose concentration in blood level can change in the amount of light absorbed by the skin.

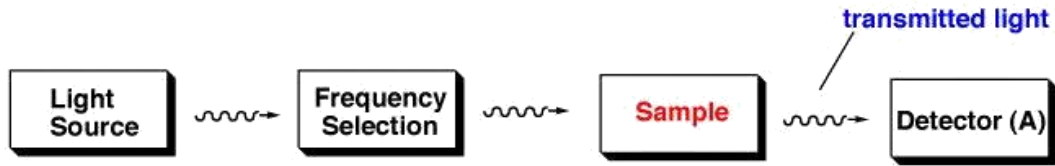


Figure 10. Infrared Spectroscopy Principle [16]

In near infrared spectroscopy, light in near infrared range (750-2000 nm) is used. Light of these wavelengths pass through the stratum corneum and measures the light absorbed in the deep tissue in the range of 1mm to 100 mm of depth due to the glucose in blood [16].

Benefits

- The photoconductive detectors which is used for NIR Spectroscopy is highly sensitive.
- Water absorbs less near infrared. So it's very useful for measuring blood glucose level.
- Strength of signal is high as compared to mid infrared spectroscopy.
- Materials which are used for infrared spectroscopy are low in cost and available in wide range.
- Tested for human successfully.
- Safe for human body.

Restrictions

- Multivariate analysis is required.
- Device needs to be in miniaturization scale.
- Factors like blood pressure, body temperature and skin hydration are tormenting effects the blood glucose measurement.
- External factors like temperature, humidity, carbon dioxide, and atmospheric pressure can also cause error.
- Hardware is less sensitive and stable for near infrared sensor [17].

NIR Spectroscopy Based Glucose Monitoring Device

Glove instrument and Cnoga medical developed glucose monitoring device based on near infrared principle as shown in Figure 11 and Figure 12 [18, 19].

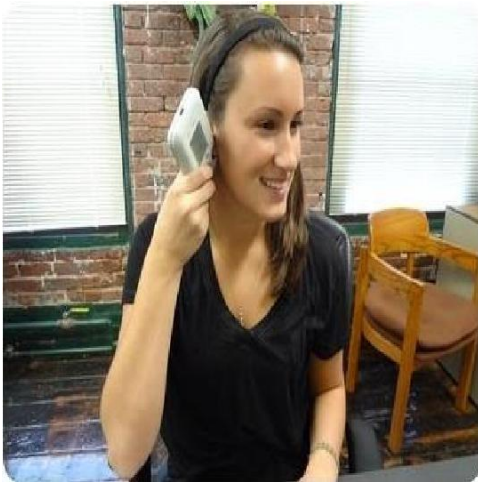


Figure 11. Glove Instrument [18]



Figure12. Cnoga Medical [19]

2.2.2.2 Mid Infrared (MIR) Spectroscopy

In mid infrared spectroscopy, light in mid infrared region (2500-10000 nm) is used. It employs same principle as near infrared spectroscopy. With change in concentration of glucose in blood, there is change in absorption of mid infrared.

Benefits

- Scattering effect is less and still increased absorption compare to NIR spectroscopy due to higher wavelength.
- Response peak of biological compounds are sharper with MIR than NIR [20].

Limitations

- Mid infrared penetration through skin is very poor.
- Absorption of mid infrared due to water is more compared to glucose in blood [21].

2.2.2.3 Raman Spectroscopy

Raman Spectroscopy is based on the principle of scattering effect of light. It uses laser light in the range of 200 cm^{-1} to $2,000\text{ cm}^{-1}$ to prompt oscillation in glucose contained fluid. Intensity of scattered light depends on the rotational and vibrational energy of glucose molecule, which is base for measuring the glucose concentration in human body [22]. This is illustrated in Figure 13 [23].

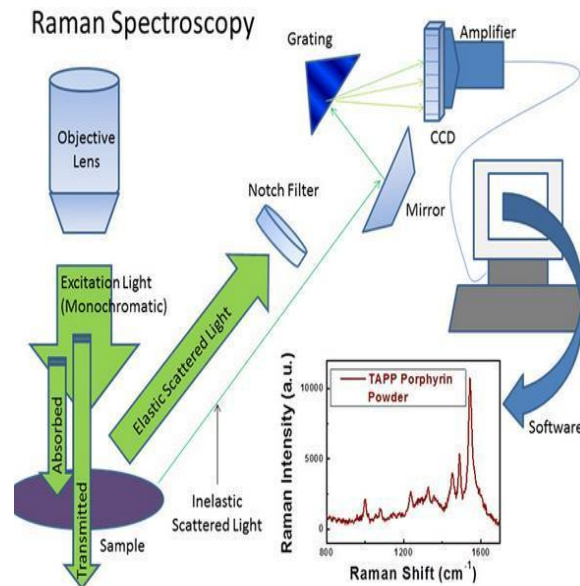


Figure 13. Raman Spectroscopy [23]

Benefits

- It provides sharper spectra compared to NIR and MIR spectroscopy.
- It is less sensitive towards temperature.
- It is very less sensitive to water.

Limitations

- Laser wavelength and intensity is very unstable.
- Light source is very harmful for human body.
- Interference from other biological compounds like hemoglobin is high.

- Collection time is long.
- Not tested in human.

Raman Spectroscopy Based Glucose Monitoring Device

C8 MediSensor is developed which is based on the principle of Raman Spectroscopy which is shown in Figure 14 [24].



Figure 14. C8 MediSensor using Raman Spectroscopy [24]

2.2.2.4 Occlusion Spectroscopy

Occlusion Spectroscopy is based on the scattering phenomenon of light. With increase in level of glucose, results into decreasing the diffusion coefficient of light and boosted the transmission of light as shown in Figure 15. This technique will happen after the erythrocyte (a red blood cell in humans that is typically a biconcave disc without a nucleus) aggregation which is done by applying pressure on the skin. First signal is collected without applying any pressure and it is combined with the occlusion signal (after applying pressure) in order to calculate glucose concentration [25].

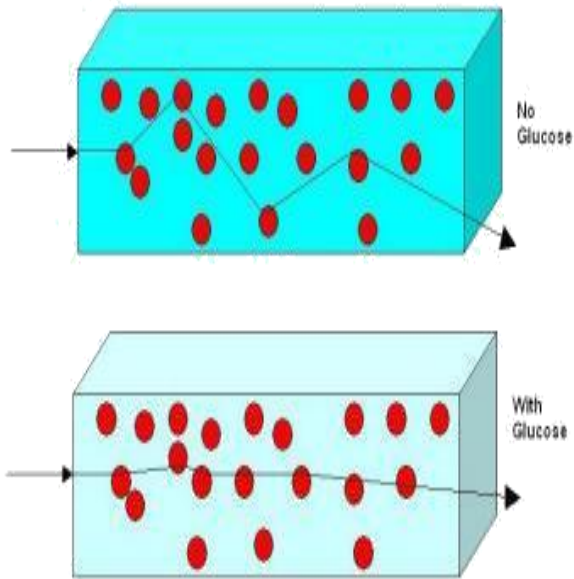


Figure 15. Occlusion Spectroscopy [25]

Benefits

- It measures glucose level of blood in artery.

Limitations

- Previous erythrocyte aggregation and fat deposition greatly interfere with the measurement of glucose.

Occlusion Spectroscopy Based Glucose Monitoring Device

OrSense NBM-200G is a glucose monitoring device which is based on the occlusion spectroscopy [26] is shown in Figure 16.



Figure 16. OrSense NBM-200G using Occlusion Spectroscopy [26]

2.2.2.5 Optical Coherence Tomography

Optical Coherence Tomography was originally developed for tomographic imaging of the eye. It uses a laser source with low power, an interferometer and a photodetector to measure the interferometric signal as shown in Figure 17.

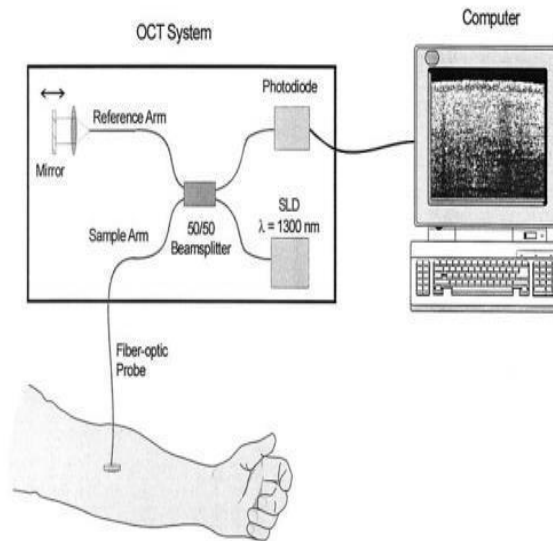


Figure 17. Optical Coherence Tomography [27]

It uses low coherence light where the emitted photons are synchronized in time and space. The skin is irradiated with a low coherence light. Radiations then scattered from the tissue and combine with the light returned from reference arm and results into interferometric signal which is then detected by photodetector.

With increase in concentration of glucose in the interstitial fluid, the refractive index of glucose also increases. This will create a mismatch between reference and sample indices and hence the concentration of glucose in human body can also be measured [27].

Benefits

- High signal to noise ratio as interferometric signal can be only formed within coherence source.

- High resolution and penetration is also high due to the coherence sources.

Limitations

- Effect of skin temperature is very high on the measurement for higher degrees and leads to inaccuracy.
- It is very sensitive to motion of individuals [28].

Optical Coherence Tomography Based Glucose Monitoring Device

Sentris-100 glucose monitoring device is based on optical coherence tomography technology as illustrated in Figure 18.



Figure 18. Sentris-100 using Optical Tomography [29]

2.2.2.6 Fluorescence Technology

Fluorescence Technology is based on the principle that human tissue will generate fluorescence when excited by lights at specific frequencies.

This technique uses fluorescence reagents which are shown in Figure 19 which helps to track the presence of glucose molecules in blood.

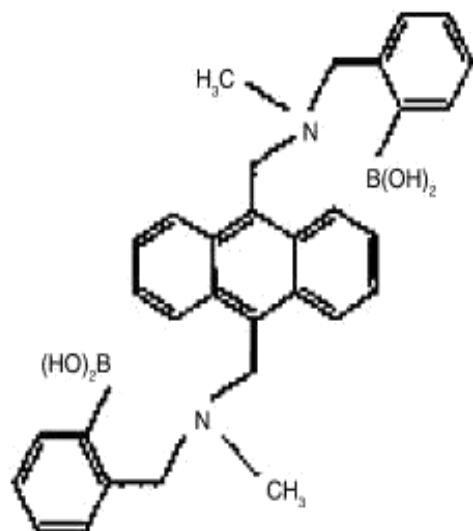


Figure 19. Diboronic Acid-fluorescence reagent used in Fluorescence Spectroscopy [30]

Based on the affinity principle, fluorescence resonance energy transfers between a fluorescent donor and an acceptor as seen in Figure 20. With increase in glucose level, glucose molecule will also increase leading to generation of more fluorescence energy [31].

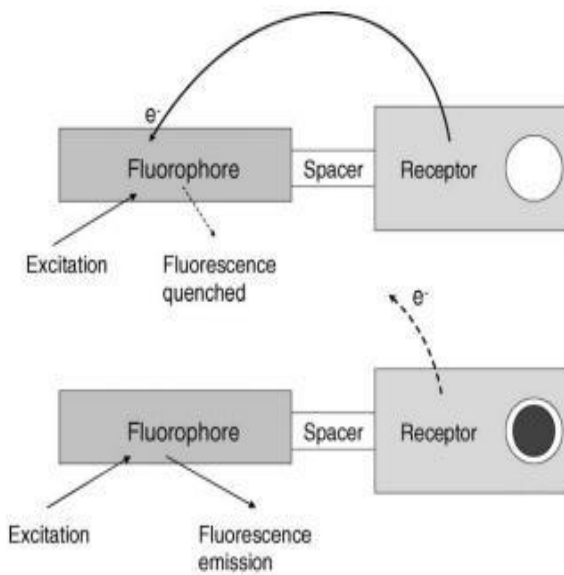


Figure 20. Fluorescence Spectroscopy Principle [31]

Benefits

- This technology is highly sensitive. It can detect single glucose molecule.

Limitations

- It is highly affected by scattering phenomenon of light.
- Life span is short and it is not bio compatible.

Fluorescence Technology based Glucose Monitoring Device

SCOUT DS is the device based on fluorescence technology as seen in Figure 21. It was invented in 2011 and has received approval from health Canada for commercial distribution [32].



Figure 21. Photo Induced Electron Transfer [32]

2.2.2.7 Optical Polarimetry

Chiral molecules are the ones which are asymmetric in such a way that the structure and its mirror image are not superimposable. Typically, chiral compounds are optically active. Glucose is an example of chiral compounds which is base of the working of optical polarimetry. When polarized light, all waves oscillating in the same plane, passes through the solution containing chiral molecules, its polarization plane is rotated by a certain angle, which depends on concentration of chiral molecule and chiral molecule is glucose in this case as seen in Figure 22.

Based on this, the glucose level can be measured by passing the polarized light into aqueous humor like tear. For this reason, the preferred site is the eye [33, 34].

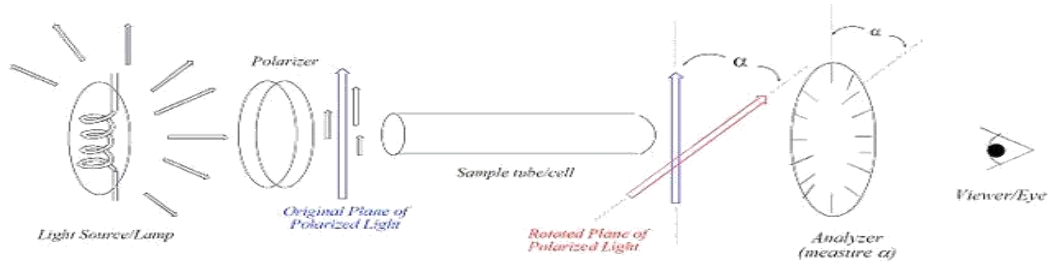


Figure 22. Optical Polarimetry [33]

Benefits

- Light absorption and scattering effects in eye is low as there are no large proteins in aqueous humor and main component is glucose.
- Visible light is used in this technique and parts can be easily scaled down.

Limitations

- Skin cannot be used for monitoring glucose level due to scattering effect.
- Eye movement is the major source of error.
- Presence of albumin and cholesterol makes the specificity of this technique poor.

Optical Polarimetry Based Glucose Monitoring Device

Efficient device based on this technology has not been developed yet. Researchers have done the experiments on rabbit's eyes using dual wavelength as shown in Figure 23 [35].

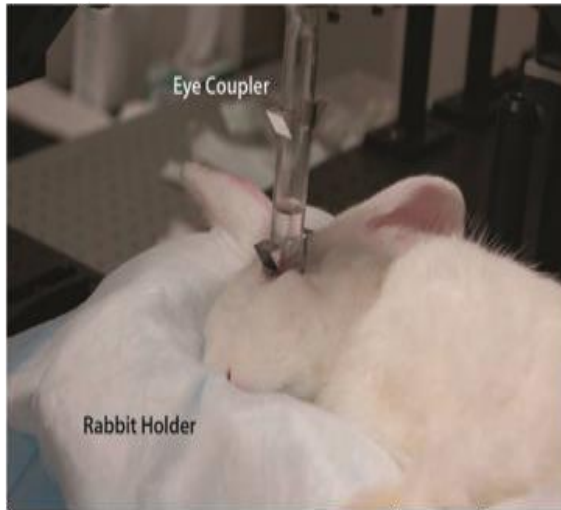


Figure 23. Experiment on Optical Polarimetry [35]

2.2.3 Photo Acoustic Spectroscopy for NIBGM

Photo acoustic spectroscopy for NIBGM is based on the principle that when an energy source exposes the skin, it causes thermal expansion. Due to the thermal expansion, acoustic waves are released. Usually acoustic wave is measured in terms of pressure. In other words, when the skin gets irradiated from energy source, it generate pressure as a wave which depends on the density.

With increase in glucose concentration in body, it increases the density of the medium (blood). With increase in density, pressure generated from energy source will also change, hence the glucose level in human body can be measured [36]. Overall mechanism is illustrated in below Figure 24.

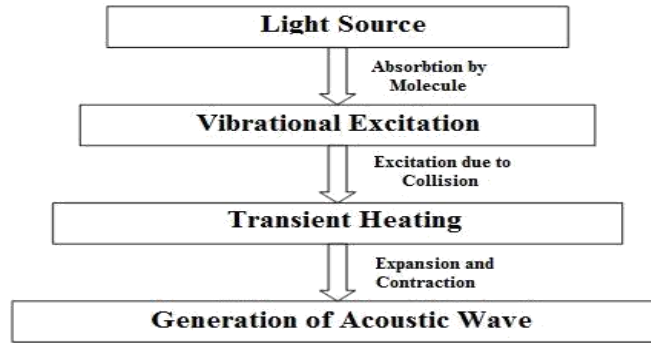


Figure 24. Photo Acoustic Spectroscopy

Benefits

- Sensitivity is higher than other spectroscopy in determination of glucose as photo acoustic response of blood is better than water.

Limitations

- Sensitive to fluctuation of temperature.
- Instrument is expensive.

Photo Acoustic Based Glucose Monitoring Device

Device named *Aprise* is developed which is based on the principle of photo acoustic spectroscopy principle as shown in Figure 25.



Figure 25. Aprise Glucose Monitoring Device [37]

2.2.4 Electromagnetic Technique for NIBGM

This technique accesses the dielectric properties of blood using electromagnetic coupling between inductors wrapped around the medium. Voltage at particular frequency is applied to one of the two inductors and signal due to electromagnetic coupling is produced in other inductor. Mechanism is shown in below Figure 26.

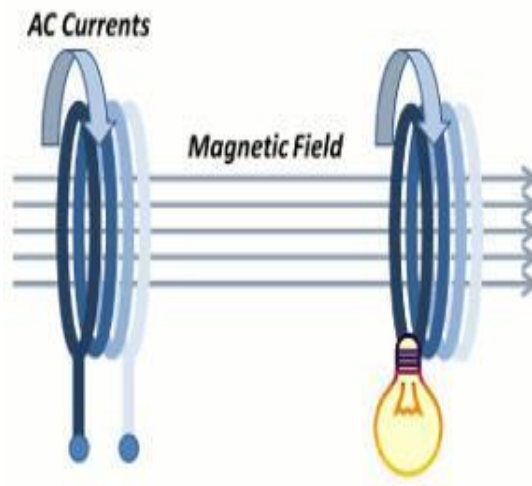


Figure 26. Electromagnetic Coupling between Two Inductors [38].

With change in glucose concentration, dielectric parameters will also change. This leads to change in electromagnetic coupling signals. Hence the value of glucose level can be measured [39].

Benefits

- It minimizes the effect of cholesterol.
- Safe for human body.

Limitations

- Effect of temperature on measurement is very high.
- Dielectric properties of blood depend on other components of blood, not just glucose. This leads to inaccuracy for the measurement.

Electromagnetic Technique Based Glucose Monitoring Device

Glucoband is the glucose measuring device based on electromagnetic coupling principle. It is shown in Figure 27 [40].



Figure 27. Glucoband using Electromagnetic Sensing [40]

2.2.5 Bio-Impedance Spectroscopy for NIBGM

Impedance spectroscopy is based on the method of measuring the resistance of the medium after applying electric current. Spectrum in impedance spectroscopy is measured in range of 0.1 to 100 MHz frequency [41]. This is shown in Figure 28.

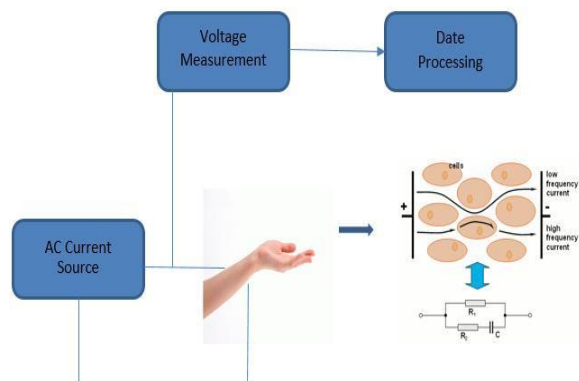


Figure 28. Bio- Impedance Spectroscopy [42]

With change in glucose level in blood, ion concentration of blood will also change. This will result in change of impedance of blood.

Benefits

- It doesn't need any statically derived calibration model.
- Easy to use
- Low cost

Limitations

- Effect of water content in body is high.
- It needs long time for equilibrium process.

Bio-Impedance Spectroscopy Based Glucose Monitoring Device

Biosensor Inc. developed a device based on the above principle and is under development. It is seen in Figure 29.



Figure 29. Biosensor Inc. using Bio - Impedance Spectroscopy [43]

2.3 Noninvasive Blood Glucose Monitoring Systems

Different types of NIBGM techniques are discussed with their advantages and disadvantages. In this section we will summarize the benefits and limitations of all NIBGM techniques and developed devices based on this technologies.

2.3.1 Benefits and Limitation of NIBGM Techniques

The advantages and disadvantages of NIBGM techniques are summarized and shown in Table 2.

Table 2. Benefits and Limitations of Various Noninvasive Glucose Monitoring Techniques

Noninvasive Glucose Monitoring techniques	Benefits	Limitations
Near Infrared (NIR) Spectroscopy	<ul style="list-style-type: none"> • Tested for human successfully • Not harmful for human body • Effect of interference is less • The photoconductive detectors which is used for NIR Spectroscopy is highly sensitive. • Water absorbs less near infrared. So it's very useful for measuring blood glucose level. • Strength of signal is high as compared to mid infrared spectroscopy. 	<ul style="list-style-type: none"> • Multivariate analysis is required • Device needs to be miniaturization scale • Scattering effect is more • Factors like blood pressure, body temperature and skin hydration are tormenting effects the blood glucose measurement. • External factors like temperature, humidity, carbon dioxide, and atmospheric pressure can also cause error.
Mid Infrared (MIR) Spectroscopy	<ul style="list-style-type: none"> • Scattering effect is less and still increased absorption compare to NIR spectroscopy due to higher wavelength. • Response peak of biological compounds are sharper with MIR than NIR 	<ul style="list-style-type: none"> • Mid infrared penetration through skin is very poor. • Absorption of mid infrared due to water is more compared to glucose in blood

Table 2. (continued)

Raman Spectroscopy	<ul style="list-style-type: none"> • It provides sharper spectra compared to NIR and MIR spectroscopy. • It is less sensitive towards temperature. • It is very less sensitive to water. 	<ul style="list-style-type: none"> • Laser wavelength and intensity is very unstable. • Light source is very harmful for human body. • Interference from other biological compounds like hemoglobin is high. • Collection time is long • Not tested in human
Occlusion Spectroscopy	<ul style="list-style-type: none"> • It measures glucose level of blood in artery. 	<ul style="list-style-type: none"> • Previous erythrocyte aggregation and fat deposition greatly interfere with the measurement of glucose.
Optical Coherence Tomography	<ul style="list-style-type: none"> • High signal to noise ratio as interferometric signal can be only formed within coherence source. • High resolution and penetration is also high due to the coherence sources. 	<ul style="list-style-type: none"> • Effect of skin temperature is very high on the measurement for higher degrees and leads to inaccuracy. • It is very sensitive to motion of individuals
Fluorescence Technology	<ul style="list-style-type: none"> • This technology is highly sensitive. It can detect single glucose molecule. 	<ul style="list-style-type: none"> • It is highly affected by scattering phenomenon of light • Life span is short and it is not bio compatible.
Optical Polarimetry	<ul style="list-style-type: none"> • Light absorption and scattering effects in eye is low as there are no large proteins in aqueous humor and main component is glucose. • Visible light is used in this technique and parts can be easily scaled down. 	<ul style="list-style-type: none"> • Skin cannot be used for monitoring glucose level due to scattering effect. • Eye movement is the major source of error. • Presence of albumin and cholesterol makes the specificity of this technique poor.
Photo acoustic Spectroscopy	<ul style="list-style-type: none"> • Sensitivity is higher. 	<ul style="list-style-type: none"> • Sensitive to fluctuation of temperature. • Instrument is expensive.
Electromagnetic Sensing	<ul style="list-style-type: none"> • Safe for human body. • It minimizes the effect of cholesterol. 	<ul style="list-style-type: none"> • Effect of temperature is high • Dielectric properties of blood depend on other components of blood, not just glucose. This leads to inaccuracy for the measurement.
Bio-Impedance Spectroscopy	<ul style="list-style-type: none"> • Instrument is low in cost • Effect of cholesterol is less. • It doesn't need any statically derived calibration model. 	<ul style="list-style-type: none"> • Calibration process is long • Effect of sweat, movement and temperature is high.

2.3.2 Devices Based on NIBGM

With the emerging field in research for NIBGM techniques, there are some devices based on various techniques. Devices along with technology and status are shown Table.3

Table 3. Various Noninvasive Glucose Monitoring Device

Device/company	Technology	Status	URL
Cnoga Medical	Near Infrared (NIR) Spectroscopy	Developed in 2010 and delivered to FDA for approval in 2011	http://www.cnoga.com/Medical/Products/Glucometer.aspx
Glove Instruments	Near Infrared (NIR) Spectroscopy	Developed in 2008	http://groveinstruments.com/
C8 MediSensors	Raman Spectroscopy	Developed in 2011 and is investigational status	http://www.c8medisensors.com/us/home.html
Sentris-100	Optical Coherence Tomography	Appeared in 2009 in Europe market	http://cloud-computing.tmcnet.com/news/2007/08/29/2895935.htm
SCOUT DS, VeraLight Inc	Fluorescence Technology	Appeared in 2011 and has received approval from health Canada for commercial distribution	http://www.veralight.com/products.html
Aprise	Photo acoustic Spectroscopy	Developed in 2005	http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=47288
Glucoband	Electromagnetic Sensing	Developed in 2005 and is under pilot construction	http://www.calistomedical.com/

2.4 Approach of Multisensor for NIBGM

In comparison to invasive glucose monitoring, noninvasive way of glucose monitoring always faces problem of inaccuracy. Various factors are responsible for these limitations of noninvasive glucose monitoring. To find a solution for this problem, multi-sensor approach is into consideration in last years. It consists of the combination of some of the above-mentioned noninvasive techniques of glucose monitoring for better performance in terms of sensitivity and specificity. There are some properties which may affect the measurement of glucose level, such as:

- Environmental factors like temperature or humidity.
- Effect of water or other biological compound.

According to earlier discussions it is evident that each technique has its own advantage and disadvantages. So combining into multi-sensor approach one might deal with above problem. Apart from above problem, one important factor which is responsible for accuracy is the calibration model using different regression analysis.

2.4.1 Existing Sensors Based on Multi-Sensor Approach

GlucoTrack is the noninvasive glucose monitoring device based on the Multisensor approach. It is developed by Integrity Applications. *GlucoTrack* is based on three technologies namely Photo acoustic spectroscopy, electromagnetic sensing and thermal emission technology. It is shown in Figure 30.



Figure 30. GlucoTrack Based on Multisensor Approach [45].

Clip like parts need to be hold the ear. Each of the technologies provide a signal that is calibrated into a glucose level with a suitable regression analysis model. This device price is estimated to be \$2000 with personal ear clip of \$100 which need to be replaced every six months. Cost factor is the disadvantage in this case [45].

Amaral and Coworkers Company developed a prototype which is based on near infrared and mid infrared spectroscopy [46].

Swiss medical company, Solianis Monitoring AG also developed a device based on near infrared spectroscopy along with several other sensor embedded in same substrate to know the effect of temperature, pressure and humidity [47].

2.4.2 Infrared and Ultrasound Technology – The Power of Two

Infrared is a type of electromagnetic radiation of wavelength between roughly 700 nm to 300 μm which is longer than the wavelength of visible light. It is emitted by all living beings and surrounding objects. It is frequently helpful to think of infrared in terms of radiated heat in terms of transmission and absorption.

Ultrasound is an oscillating pressure wave of sound of frequency greater than hearing capacity of human. Piezoelectric transducer is used for getting ultrasound which converts electrical energy into an ultrasonic wave.

Infrared Sensor and ultrasonic sensor are combined together for maximum accuracy. This technology will overcome the lack of sensitivity of infrared sensors and increase the specificity of both infrared and ultrasonic sensors [48, 49].

Factors which were already discussed as disadvantages for near infrared technology and photo acoustic technology are also to be considered. They are:

- Near infrared spectroscopy based glucose monitoring device needs to be scaled in miniaturization scale.
- Ultrasonic sensors used in photo acoustic are very costly.

To overcome the above disadvantages, it is preferred to accept the MEMS technology.

2.5 Micro-Electro-Mechanical System Technologies

Infrared Sensor and ultrasonic sensor are combined together for maximum accuracy. This technology will overcome the lack of sensitivity of infrared and increase the specificity of both infrared and ultrasonic sensors. Size of the system also becomes a shortcoming factor for any technology including NIBGM which not only affect the cost but also the portability. To overcome this it's needed to be scaled down in miniature form. Henceforth we concentrate on MEMS technology which exhibit substantial meaning for miniaturized system.

2.5.1 Introduction to MEMS

Micro-Electro-Mechanical System (MEMS) is the method to combine electrical and mechanical components together on a chip, to make a system of miniature scale.

There are type of sensors which can be used as MEMS. They are

- Mechanical Sensors
- Optical Sensors
- Thermal Sensors
- Chemical and Biological Sensors

2.5.2 Advantages of MEMS

Now-a-days MEMS are being preferred for sensors because of the following reasons:

- Size is smaller as compared to actual sensor.
- Flexible design.
- Power Consumption is low.
- Sensitivity to input variation is high.
- Collaboration phenomenon with different frequencies for integrating with other supportive system.
- Cost is less.

2.6 Regression Analysis Models for Calibration

Noninvasive method of glucose monitoring is partial in the prediction of blood glucose.

There are two reasons responsible for this inaccuracy. It includes problem related to engineering and second, may be due to data analysis problem. Partial work of our purpose technique is to find out the best regression model and implementing it as a calibration model. Calibration is essential to achieve the uniformity in the measurement. Every so often calibration comprises forming the relationship between a device response (response of sensors in this case) and one or more reference values (actual glucose value in this case). Linear regression is one of the most commonly used statistical methods in calibration. Once the relationship between the reference

value and the response value is established, the calibration model is used in converse to predict a value from a device response.

2.6.1 Clarke Error Grid Analysis

There are two factors which are responsible for the model’s performance. They are Average prediction error in percentage (PAPE) and percent of acceptable points by “± 20% rule” as shown in equation 1.

$$\text{Average prediction error (APE)} = \frac{1}{n} \sum_{i=1}^n (Y_i - Y_i') \dots\dots\dots (1)$$

Where,

Y_i = actual glucose value at i^{th} observation

Y_i' = predicted glucose value at i^{th} observation n = number of the observations

Equation 2 shows APE in percentage. APE will consider as PAPE in equation 2.

$$\text{Average prediction error in percentage (PAPE)} = \frac{100\%}{n} \sum_{i=1}^n \frac{(Y_i - Y_i')}{Y_i} \dots\dots\dots (2)$$

According to “± 20% rule”, data or point is accepted if the prediction error is less than or equal

to ± 20%: $\left| \frac{Y_i - Y_i'}{Y_i} \right| \times 100\% \leq 20\%$

For a better regression model, PAPE should be small and acceptable data should be more. In order to compare between regression models, these values need to be considered. A

Clarke Error grid analysis graph is used to exhibit the “± 20%” rule. Value within Region A are within 20% values, Region B contains points that are outside of 20% but not lead to unsuitable glucose monitoring value, Region C leads to unnecessary treatment, Region D indicates dangerous failure to detect hypoglycemia or hyperglycemia, and Region E gives the ambiguous

data for the treatment of hypoglycemia for hyperglycemia. This graph is usually used to exhibit the performance of the blood glucose monitor. This is shown in Figure 31 [51].

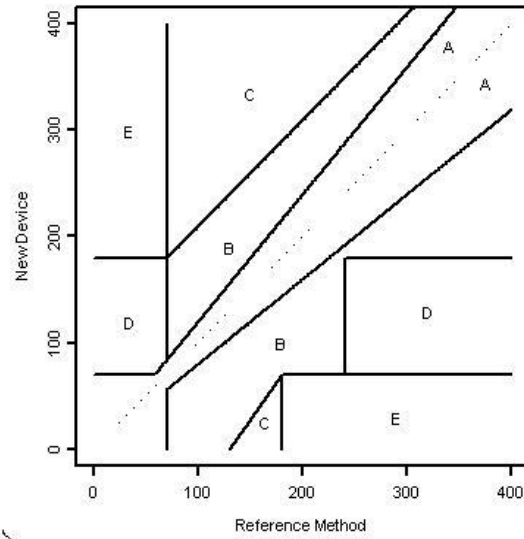


Figure 31. Clarke Error Grid [51]

2.6.2 Multiple Regression Analysis

In statistics, regression is used to describe a group of approaches that recapitulate the degree of association between the responses and references. Any regression have to begin with a proper aspect at the data. Like form where the data is coming, the way it is measured, the measurement is proper or with noise, number of available observations, units of the data, magnitudes and ranges of the values of data, and the most important is the way response is depending the reference. In simple linear regression, a desired variable is predicted from one response variable. In multiple regression, the desired value is predicted by two or more variables.

Common statistical method used to do this is least-squares regression.

CHAPTER 3

PROPOSED NONINVASIVE BLOOD GLUCOSE LEVEL MONITORING SYSTEM

In this chapter, the proposed method and its working principle to monitor the blood glucose level in noninvasive way are explained with a block diagram.

3.1 Overview

As per the advantages of multi-sensor approach discussed earlier, the following approach of using infrared sensor and ultrasonic MEMS for noninvasive blood glucose level monitoring is proposed. It is calibrated using multiple regression model. It is based on the principle of both near infrared spectroscopy and photo acoustic spectroscopy.

As both IR sensor and ultrasonic sensor are considered, it is very important to see the behavior of these sensors to human skin. As the properties of skin and glucose were discussed in chapter 2, the respective parameters are chosen for the proposed techniques. According to the absorption spectrum of glucose in blood, it was observed that there are two peaks of the spectrum: one at 1440 nm and other at 2270 nm. Presence of hemoglobin will not affect the absorption of IR for glucose or water [52]. At 1440 nm, the absorption of water is also high so 2270 nm is preferable to predict the glucose concentration. For ultrasonic sensor, the density of medium is considered to measure the concentration of glucose. For 70mg/dl of glucose, the density will be approximately 1060 kg/m^3 . As the concentration of glucose will increase, the density will also increase. Using these values the glucose concentration is calculated in the proposed method.

In this chapter we will discuss about the proposed method in detail using the block diagram and workflow of the proposed method.

3.2 Proposed Method

IR sensors and Ultrasonic MEMS sensors are used for monitoring the glucose concentration in a noninvasive approach. Two IR sensor as transmitter and receiver and two Ultrasonic MEMS as transmitter and receiver are considered here. Proposed method will work on the principle of NIR spectroscopy and Photo acoustic Spectroscopy. The output from two receivers will feed to a calibration model to predict the blood glucose concentration. Calibration model is built using multiple linear regression analysis.

For the measurement of blood glucose concentration in noninvasive approach, it is very important to choose the proper target location (such as finger webbing, earlobe, tongue, finger, nasal septum, cheek and lips) for the device on human body. In this work, earlobe is considered due to some advantages i.e., earlobe has a large supply of blood as it doesn't contain cartilage and earlobe makes it easy for NIR and ultrasonic to reach dermis region due to its low thickness. So two transmitters are placed on one side of the ear lobe and two receivers are placed on other side of the ear lobe. Block diagram of the proposed technique is explained in next section.

3.3 Block Diagram of the Proposed Method

IR (infrared) and ultrasonic transmitters and IR and ultrasonic receivers are used for the noninvasive monitoring of blood glucose. The proposed system with IR and ultrasonic MEMS sensors is illustrated in Figure 32.

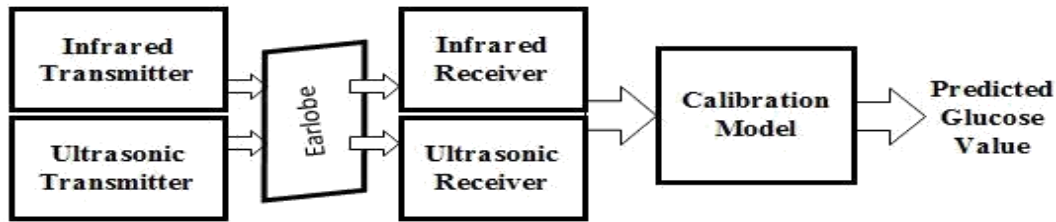


Figure 32. Block diagram of proposed NIBGM system

IR transmitter incidents light on skin (such as earlobe) in near infrared region of light and the light returned from the skin has been received by the IR receiver. Similarly, ultrasonic wave from ultrasonic MEMS sensor generates pressure wave in medium (such earlobe) and is collected by ultrasonic MEMS receiver. In order to generate ultrasonic wave, piezoelectric device is used. Results from both sensors are then calibrated to get blood glucose concentration using multiple linear regression analysis. All the individual parts in that block diagram are explained below as follows:

Infrared Transmitter: The functional wavelength of 2270 nm will be utilized here for the experimental purposes. This unit is connected to one side of earlobe.

Ultrasonic Transmitter: A piezoelectric based ultrasound transmitter with 2 MHz of operating frequency will be supplied for the generation of acoustic wave. This unit is also connected to the same side of earlobe as Infrared Transmitter.

Infrared Receiver: The blood glucose tends to have a precise vibrational pattern for its respective concentration measurements tend to change in absorption will be responded by this very sensitive IR receiver unit.

Ultrasonic Receiver: Again, the piezoelectric based ultrasound receiver with 2 MHz as operating frequency has been utilized here. The prime task of this unit is to plaid the pattern and orientations of the generated acoustic waves.

Calibration Model: The output values from two receivers will be fed to this model. Using multiple linear regression analysis, the values are processed in MATLAB to predict the blood glucose level concentration.

3.4 Working Principle of the Proposed Method

Ultrasonic wave is a sound wave transmitted at a frequency greater than 20 KHz or beyond the normal hearing range of human. When ultrasonic wave will pass through the biological tissue, it produces vibrational patterns into the medium. These wave can be generated from a piezoelectric transducer. Standing waves has maximum and minimum value namely: antinodal and nodal which are double over a length of a single wavelength. This leads to the generation of acoustic energy due to its existence in the ultrasonic field. When diameters of molecule are smaller as compared to the ultrasonic wavelength, radiation force (F) applied over the volume of molecule (V) having path length of (z) from the pressure node can be represented from the gradient of the acoustic potential energy of the molecule and is shown in equation 3.

$$F = - [\pi P_0^2 V \beta_w / (2\lambda)]. \Phi (\beta, \rho). \sin 4\pi z / \lambda \dots\dots\dots (3)$$

Where,

P_0 = amplitude of the ultrasonic waves

λ = wavelength of ultrasonic standing waves.

ρ = density of the material

When the concepts of compressibility factor come into picture, then following equation 4 comes into picture:

$$\Phi (\beta, \rho) = [- (\beta_c / \beta_w)] \dots\dots\dots (4)$$

Where,

β_w = factor of compressibility.

β_c = compressibility of molecule present in medium.

ρ_c = densities of molecules present in medium.

ρ_w = densities of suspending medium present.

In the air domain, the wave equation which is describe in equation 5 describes the pressure distribution:

$$\cdot (-1/\rho_0 (\Delta P)) - \omega^2 P / \rho_0 C^2 = 0 \dots\dots\dots (5)$$

Where,

ρ_0 = density of the medium.

P = pressure generated in the medium from ultrasonic radiation.

ω = angular velocity of the radiation.

C = speed of the radiation.

So increase in the glucose concentration in blood will increase the pressure generated from the transducer. Hence we will be able to monitor the glucose level using the pressure measurements.

When light from infrared sensor will be applied to the medium, then absorption depends on the number of molecules present. This is better can be explained by Beer-Lamberts law as shown in equation 6.

$$A(\nu) = -\log I(\nu) / I_0(\nu) \dots\dots\dots (6)$$

Where,

$A(\nu)$ = absorbance at wavelength of $1/\nu$.

ν = wave number.

I = light intensity of the adjacent medium.

I_0 = light intensity after penetrating through the medium.

Absorbance can also defined in terms of absorptivity coefficient, concentration of molecule and path length as shown in equation 7.

$$A(\nu) = a * b * c \dots\dots\dots (7)$$

Where,

a = absorptivity coefficient

b = path length

c = concentration.

Here, c is considered as the concentration of blood glucose. So, increase in level of glucose will increase the absorbance. In this way finding the value of glucose level is achieved by comparing absorbance value to a reference absorbance value.

After getting the value of pressure generated from ultrasonic MEMS and absorbance from infrared sensor, the system calibration is done using multiple regression model and hence the prediction of the glucose value is done more accurately.

CHAPTER 4

EXPERIMENTAL DETAILS

Proposed multisensor noninvasive blood glucose monitoring system is simulated using COMSOL and Matlab to evaluate its effectiveness. For ultrasonic sensor, COMSOL Multiphysics 4.3 software is used in order to measure the concentration of blood glucose level. For calibration of the system, Matlab multiple regression analysis is used.

4.1 COMSOL Multiphysics 4.3

COMSOL Multiphysics is a powerful cooperative environment for modeling and analyzing scientific and other problems. It provides an influential integrated desktop location with a Model Builder, where it is able to simulate complex problems by accessing functionalities.

In case of simulation, the blood is considered as a medium. Piezoelectric material is used as ultrasonic wave transceiver (transmitter and receiver). Figure 33 illustrates the geometry of the ultrasonic MEMS sensor for blood medium where quarter is represented as medium and rectangle portion is represented as piezoelectric material.

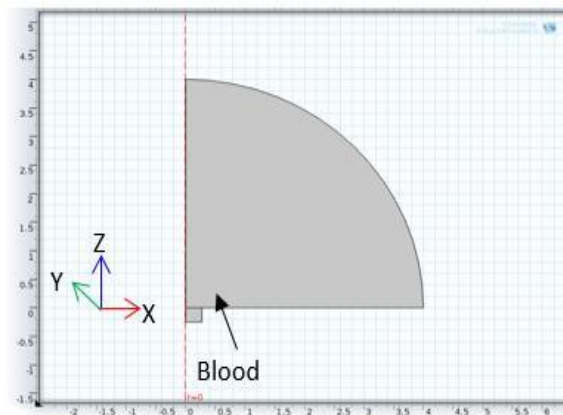


Figure 33. Geometry of ultrasonic MEMS sensor and blood

4.1.1 Boundary Conditions and Assumptions for Simulation

Some important assumptions that are made during the experiment include:

- Blood medium is represented as a quarter with radius of 4 mm.
- Lead free piezoelectric materials are considered for ultrasonic sensors. Size of piezoelectric device used is 0.25 mm x 0.225 mm.
- Alternating current (AC) electric potential of 1.5 V is applied over the upper surface of the transducer and the bottom part is grounded. Frequency is varied from 1 MHz to 4 MHz. It is observed that at 2 MHz, the generated pressure is high. Hence the frequency of 2 MHz is used as the exciting frequency in rest of our experiment.
- It is found that the piezoelectric device gives high pressure at 2MHz [54]. So, 2 MHz frequency is used as the frequency for simulation.
- The bottom surface of the piezo transducer is assigned to a roller boundary condition to prevent it to travel vertically, along the z-axis. The piezoelectric coefficient is dependent on size due to the strong orientation of axis. When the ultrasonic sensor reaches axis orientation, the piezoelectric coefficient increases rapidly [55].

4.2 Matlab

Matlab code is used to enhance the accuracy by performing calibration of the system. It takes pressure and absorbance as inputs and provides the blood glucose value as output.

4.2.1 Assumptions for Calibration System

The outputs of sensors are considered as inputs to the calibration model to fine tune the value of glucose. Multiple linear regression analysis are used for calibration. In multiple linear regression models, relation between glucose level and other parameters can be defined using equation 8.

$$Y_i = \beta_0 + \beta_1 X_{i1} + \dots + \beta_{p-1} X_{ip-1} + \epsilon_i \dots \dots \dots (8)$$

Where, Y_i is actual glucose value; $\beta_0, \beta_1, \beta_{p-1}$ are regression parameters; X_i, X_{ip-1} are variables measured from the sensors; here ϵ_i is a constant, and p is a regression parameter. The optimal regression parameter values can be determined by checking the appropriate calibrated value (Q) by using equation 9 [53].

$$Q = \sum (Y_i - \beta_0 - \beta_1 X_{i1} - \dots - \beta_{p-1} X_{ip-1})^2 \dots \dots \dots (9)$$

When the regression parameters are estimated, calibration model using multiple regression analysis can be used to predict the glucose level.

CHAPTER 5

RESULTS AND EVALUATION

In this chapter, we present the impact of piezoelectric materials on pressure followed by pressure generated in blood and predicted blood glucose concentration. Then we compare the predicted glucose values with those from NIR spectroscopy. Finally, we perform Clark EGA for the predicted glucose values.

5.1 Noninvasive Monitoring of Blood Glucose Level

For the measurement of blood glucose measurement in a noninvasive way, IR sensor and ultrasonic MEMS sensor are considered. The simulation for the ultrasonic MEMS sensor for different piezoelectric devices are done using COMSOL Multiphysics and the calibration model is done in Matlab. The data related to blood glucose level for IR sensor and Ultrasonic MEMS sensor are analyzed.

5.1.1 Simulation of Different Piezoelectric Materials

Lead free piezoelectric materials such as Lithium Niobate (LiNbO_3 ; LIN), Barium Sodium Niobate ($\text{Ba}_2\text{NaNb}_5\text{O}_{15}$; BNN), and Barium Titanate (BaTiO_3 ; BT) are only considered here. Pressures generated due to the piezoelectric materials for given blood glucose concentration is shown in Table 4. Here, the normal human blood glucose values (from 70 mg/dl to 449 mg/dl) and blood density (from 1060.00 kg/m³ to 1053.89 kg/m³) are considered.

Table 4. Pressure Generated in Blood by Different Piezoelectric Materials

Blood Glucose Concentration (mg/dl)	Density of Blood Medium (kg/m³)	Pressure Generated by LIN (Pa x 10⁻²)	Pressure Generated by BNN (Pa x 10⁻²)	Pressure Generated by BT (Pa x 10⁻²)
70	1060.00	-80521.5638	-156450.872	-212450.872
87	1060.17	-80524.9506	-156471.570	-212471.570
155	1060.85	-80541.4010	-156572.102	-212572.102
227	1051.57	-80559.0608	-156680.025	-212680.025
340	1052.70	-80586.6389	-156848.561	-212848.561
390	1053.20	-80598.0088	-156918.044	-212918.044
408	1053.38	-80602.3632	-156944.654	-212944.654
415	1053.45	-80604.2985	-156956.481	-212956.481
449	1053.89	-80613.9748	-157015.615	-213015.615

Experimental results show that the pressure generated due to BT is significantly higher than that are generated due to LIN and BNN. Therefore, BT is preferred for modelling the ultrasonic sensor. The waveform of acoustic pressure generated in blood sample with varying glucose concentration are observed by simulating using BT. Piezoelectric materials with high lead (such as Lead Zirconate Titanate with more than 60% lead by mass) are not considered due to possible health hazard.

5.1.2 Analysis of Data for Measuring Concentration of Glucose

As IR sensor and ultrasonic sensor are used, the data for both sensors for measuring the concentration of glucose should be analyzed. In this section first analysis is performed using ultrasonic MEMS sensor, then using IR sensor and then it is finally analyzed for the proposed technique.

5.1.2.2 Using Ultrasonic MEMS Sensor

As the glucose concentration of blood increases, it enhances the change in density of blood. As a result, acoustic pressure generated in blood due to the piezoelectric material varies.

As shown in Figure 3(a) and 3(b), the acoustic pressure generated by the piezoelectric device BT in blood having glucose concentration 54.05 mg/dl is -4325.3 Pa and for 180.18 mg/dL, pressure is -4330.9 Pa. It should be noted that the (-) sign is used to indicate the pressure gradient.

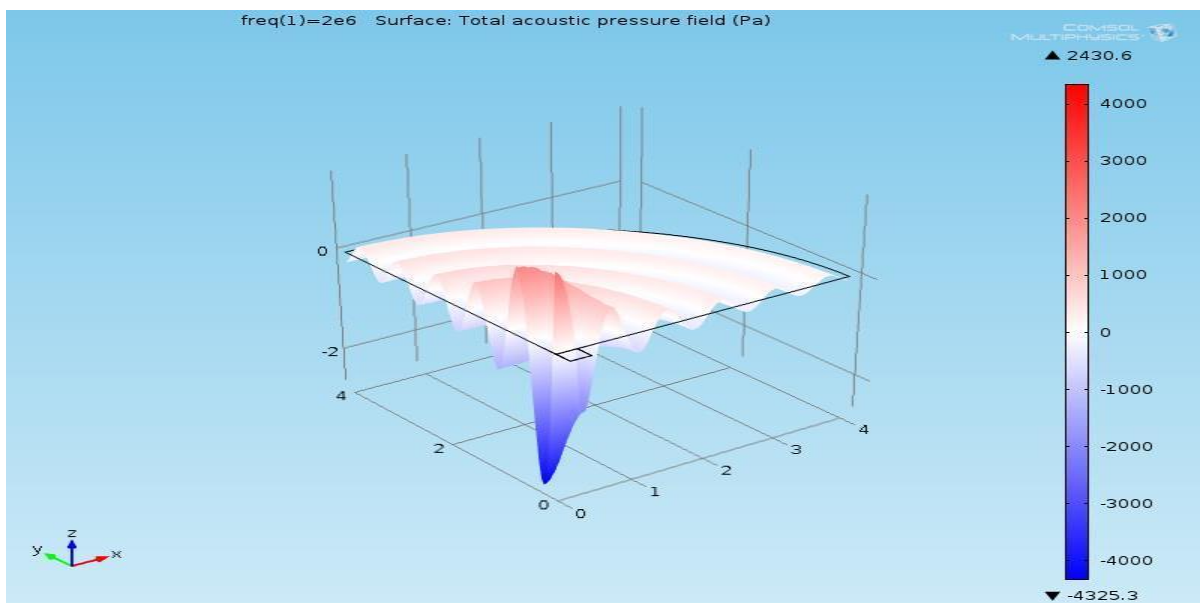


Figure 34 (a). Waveform of Acoustic Pressure Generated in Blood of Concentration 54.05mg/dL

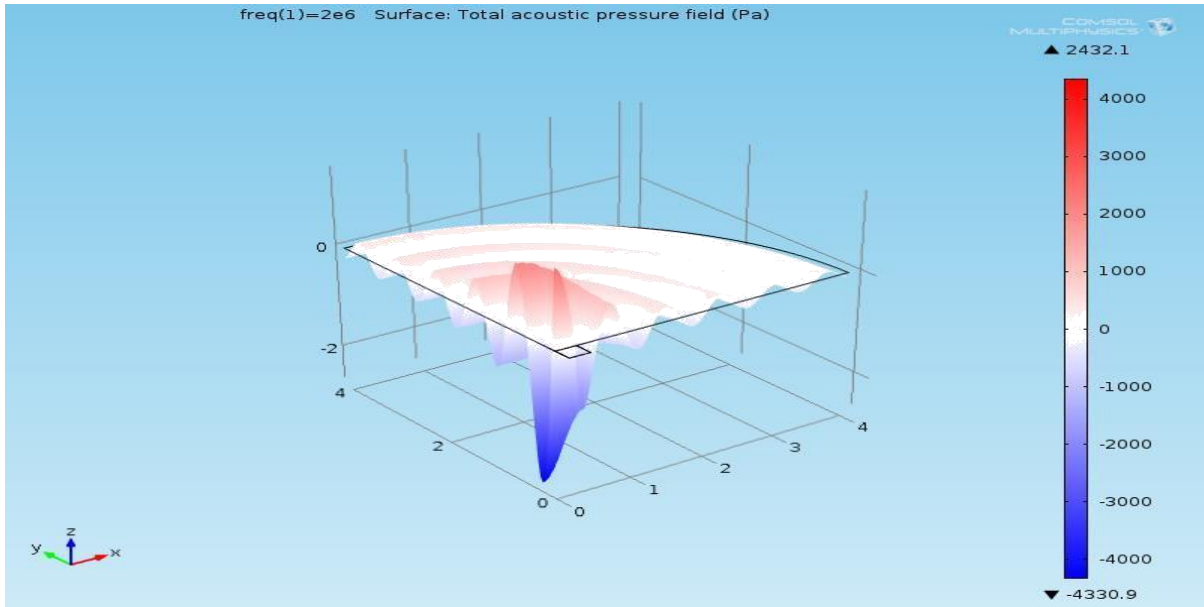


Figure 34 (b). Waveform of Acoustic Pressure Generated in Blood of Concentration 180.18mg/dL

Generated pressures and absorption values due to the piezoelectric device BT for various blood glucose concentrations are shown in Table 5.

It is observed from the Table 5 that with increase in concentration of blood glucose level, the density of the blood will also increase. Due to change in density, the pressure generated by the piezoelectric device also increases. This becomes a baseline for the measurement of blood glucose concentration using ultrasonic MEMS.

Table 5. Pressure Generated by BT in Blood for Various Glucose Concentration

Glucose Concentration(mg/dl)	Density(kg/m3)	Pressure generated by BT(Pa)
54.0546	1104.0546	-4325.3
63.0637	1113.0637	-4325.7
68.46916	1118.46916	-4325.9
72.0728	1122.0728	-4326.1
81.0819	1131.0819	-4326.5
86.48736	1136.48736	-4326.7
90.091	1140.091	-4326.9
99.1001	1149.1001	-4327.3
104.50556	1154.50556	-4327.5
108.1092	1158.1092	-4327.7
117.1183	1167.1183	-4328.1
122.52376	1172.52376	-4328.3
126.1274	1176.1274	-4328.5
135.1365	1185.1365	-4328.9
140.54196	1190.54196	-4329.1
144.1456	1194.1456	-4329.3
153.1547	1203.1547	-4329.7
162.1638	1212.1638	-4330.1
171.1729	1221.1729	-4330.5
180.182	1230.182	-4330.9

In the proposed NIBGM system, this pressure is collected by ultrasonic receiver. So, monitoring of blood glucose level can be done using the output from ultrasonic sensor.

5.1.2.1 Using Infrared Sensor

On the basis of NIR Spectroscopy, it is possible to measure the blood glucose level. For a certain wavelength, the absorptivity coefficient of glucose is constant. Here a wavelength of 2270 nm is considered, hence the absorptivity coefficient as 2.0×10^{-5} AU/mM mm and thickness of the medium as 1 mm. Absorption for various glucose concentration was observed [56] and shown in Table 6.

It is observed that at a particular wavelength, absorption of the infrared depends on concentration of glucose. So, by measuring the absorption spectrum for particular wavelength, it is possible to calculate the concentration of blood glucose level.

Table 6. Absorption of IR for Various Glucose Concentration

Glucose(mg/dl)	Absorption(AU)
54.0546	6.7776
63.0637	7.8902
68.46916	7.6038
72.0728	8.1826
81.0819	9.5008
86.48736	8.5716
90.091	9.4532
99.1001	10.667

Table 6. (continued)

104.50556	12.0944
108.1092	13.2992
117.1183	13.92
122.52376	14.538
126.1274	14.0454
135.1365	15.1562
140.54196	16.0012
144.1456	16.2904
153.1547	16.218
162.1638	17.7284
171.1729	18.9216
180.182	20.3608

5.1.2.3 Using Proposed Technique

In the proposed multi-sensor NIBGM system, both IR and ultrasonic sensors are considered. Output values from IR sensor and ultrasonic sensor are captured in terms of absorbance and pressure, respectively. By using the output values of both IR sensor and ultrasonic sensor, calibration is performed using multiple regression analysis. After calibration, the predicted blood glucose concentration is obtained due to the proposed multi-sensor NIBGM system. Table. 7 shows the output value of both sensors with change in glucose concentration.

Table 7. Absorption and Pressure Generated Value for Various Glucose Concentration

Glucose (mg/dl)	Absorption (AU)	Pressure Generated by BT (Pa)
54.0546	6.7776	-4325.3
63.0637	7.8902	-4325.7
68.4692	7.6038	-4325.9
72.0728	8.1826	-4326.1
81.0819	9.5008	-4326.5
86.4874	8.5716	-4326.7
90.0910	9.4532	-4326.9
99.1001	10.6670	-4327.3
104.5056	12.0944	-4327.5
108.1092	13.2992	-4327.7
117.1183	13.9200	-4328.1
122.5238	14.5380	-4328.3
126.1274	14.0454	-4328.5
135.1365	15.1562	-4328.9
140.5420	16.0012	-4329.1
144.1456	16.2904	-4329.3
153.1547	16.2180	-4329.7
162.1638	17.7284	-4330.1
171.1729	18.9216	-4330.5
180.1820	20.3608	-4330.9

The output values of the sensor are observed to be changing with change in concentration of glucose in blood. These values will be fed to the calibration model to predict the blood glucose level.

5.2 Calibration Model for Measuring Blood Glucose Concentration

As the values from both receivers are available, the device is modelled to get the actual glucose value. This can be done using the calibration model. During the practical application, a larger number is received. Hence, the regression analysis method is adapted to build the calibration model. Calibration model gives the value of glucose by sensing the values from two receivers. In this section, the glucose value for only IR sensor is predicted by implementing only NIR Spectroscopy and for proposed technique using regression analysis.

5.2.1 Calibration Model in NIR Spectroscopy using IR Sensor

Using regression analysis and output from IR sensor, the glucose level can be predicted as shown in Table 8.

From Table 8, we can get the following regression statistics:

- Coefficient of multiple correlation (Multiple R) is 0.989239681.
- Coefficient of determination (R Square) is 0.978595146.
- Adjusted R Square is 0.977405987.
- Standard Error is 5.620920783.

Table 8. Predicted Glucose Value for NIR Spectroscopy

Observation	Actual glucose Value(mg/dl)	Predicted Glucose Value for Infrared Spectroscopy(mg/dl)
1	54.0546	58.98367323
2	63.0637	69.03925908
3	68.46916	66.45079981
4	72.0728	71.68194586
5	81.0819	83.59572734
6	86.48736	75.19769536
7	90.091	83.16552252
8	99.1001	94.13574552
9	104.5056	107.0364675
10	108.1092	117.9253492
11	117.1183	123.5360878
12	122.5238	129.1215202
13	126.1274	124.6694425
14	135.1365	134.7087601
15	140.542	142.3457995
16	144.1456	144.959565
17	153.1547	144.3052198
18	162.1638	157.9560888
19	171.1729	168.7401308
20	180.182	181.7475001

5.2.2 Calibration Model in Proposed Technique

For the calibration model of proposed technique, the values from two sensors are considered. By applying the multiple linear regression analysis, the glucose level can be predicted as shown in Table 9.

Table 9. Predicted Glucose Value for proposed technique

Observation	Actual glucose Value	Predicted Glucose Value using Proposed technique
1	54.0546	54.38117445
2	63.0637	63.37451656
3	68.46916	67.87318322
4	72.0728	72.36980099
5	81.0819	81.36265622
6	86.48736	85.8628451
7	90.091	90.35874581
8	99.1001	99.35184827
9	104.5056	103.8464565
10	108.1092	108.3415918
11	117.1183	117.3360985
12	122.5238	121.8326235
13	126.1274	126.3317785
14	135.1365	135.3251248
15	140.542	139.8211122
16	144.1456	144.3184158
17	153.1547	153.3145641
18	162.1638	162.3069642
19	171.1729	171.3001154
20	180.182	180.2926841

The following regression statistics is obtained:

- Multiple R is 0.999944192.
- R Square is 0.999888388.
- Adjusted R Square is 0.999875257.
- Standard Error is 0.417655706.

It is observed from Table 8 and Table 9 that the statistical data are in favor of the proposed technique. In the proposed technique, minimum error is obtained when compared to NIR spectroscopy and the values of Multiple R and R Square are more when compared to NIR Spectroscopy.

5.3 Analysis of Error for the Prediction of Glucose Concentration

Although there are lots of advantaged of NIBGM over invasive methods, but still it is facing some disadvantages like accuracy, sensitivity, specificity, etc. In this section we will observe the accuracy for NIR Spectroscopy and Proposed technique by calculating the error related to predicted glucose value.

5.3.1 Error Analysis for Glucometer using NIR Spectroscopy and Proposed Technique

In the proposed multi-sensor NIBGM system, both IR and ultrasonic sensors are considered. Output values from IR sensor and ultrasonic sensor are captured in terms of absorbance and pressure, respectively. By using the output values of both IR sensor and ultrasonic sensor, calibration is performed using multiple regression analysis. After calibration, the predicted blood glucose concentration are obtained due to the proposed multi sensor NIBGM system.

In this section the accuracy of NIR Spectroscopy and Proposed technique are analyzed and as shown in Table 10.

Table 10. Predicted Glucose Value for IR spectroscopy and Proposed NIBGM system

Number of Experiments	Actual Glucose Value (mg/dl)	Predicted Glucose Value for only IR Spectroscopy (mg/dl) [22]	Residuals for Infrared Spectroscopy	Predicted Glucose Value Using Proposed NIBGM System (mg/dl)	Residuals for Proposed Technique
1	54.0546	58.98367	-4.92907	54.3811745	-0.32660
2	63.0637	69.03926	-5.97556	63.3745166	-0.31080
3	68.4692	66.45080	2.01836	67.8731832	0.59598
4	72.0728	71.68195	0.39085	72.3698010	-0.29700
5	81.0819	83.59573	-2.51383	81.3626562	-0.28080
6	86.4874	75.19770	11.28966	85.8628451	0.62451
7	90.0910	83.16552	6.92548	90.3587458	-0.26770
8	99.1001	94.13575	4.96435	99.3518483	-0.25170
9	104.5060	107.03650	-2.53091	103.8464570	0.65910
10	108.1090	117.92530	-9.81615	108.3415920	-0.23240
11	117.1180	123.53610	-6.41779	117.3360990	-0.21780
12	122.5240	129.12150	-6.59776	121.8326240	0.69114
13	126.1270	124.66940	1.45796	126.3317790	-0.20440
14	135.1370	134.70880	0.42774	135.3251250	-0.18860
15	140.5420	142.34580	-1.80384	139.8211120	0.72085
16	144.1460	144.95960	-0.81396	144.3184160	-0.17280
17	153.1550	144.30520	8.8495	153.3145640	-0.15990
18	162.1640	157.95610	4.20771	162.3069640	-0.14320
19	171.1730	168.74010	2.43277	171.3001150	-0.12720
20	180.1820	181.74750	-1.56550	180.2926840	-0.11070

It is observed that the proposed NIBGM technique provides better accuracy (as residuals are lower) when compared with that due to IR spectroscopy. Analysis of error is shown in Figure 35 by actual and predicted glucose level.

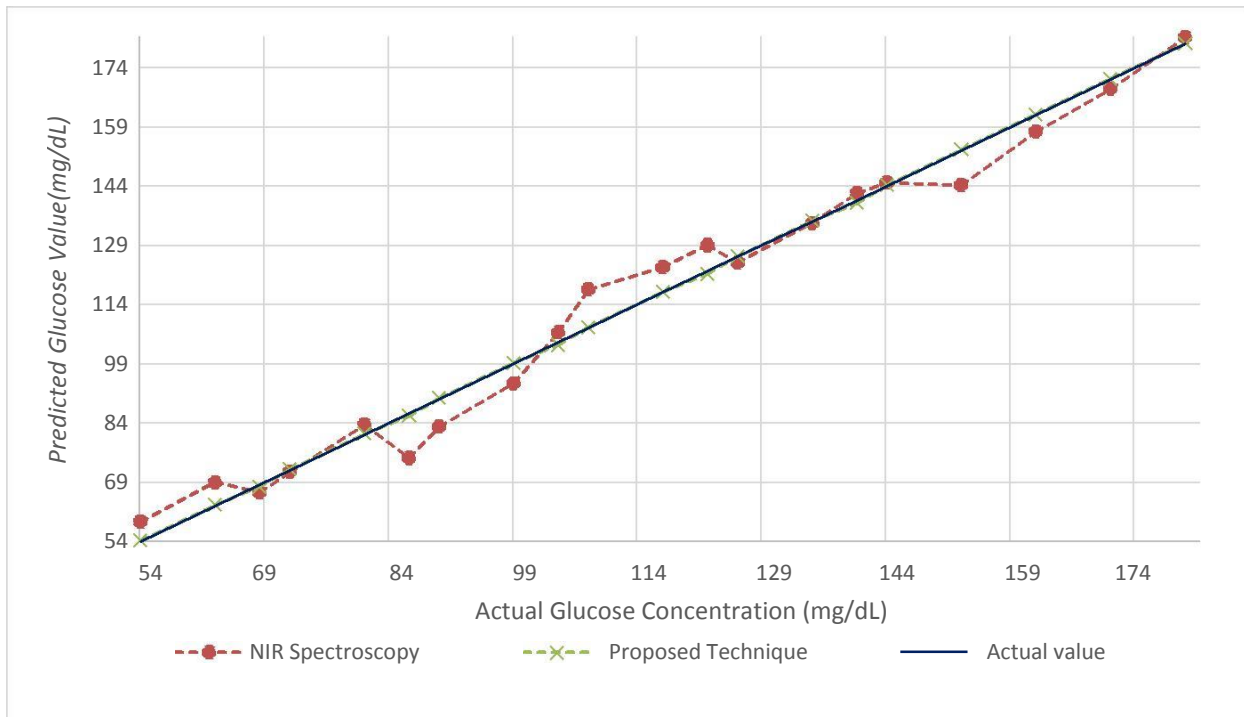


Figure 35. Predicted Glucose Value vs Actual Glucose Value for IR spectroscopy and Proposed NIBGM system.

It is observed from Figure 35 that the predicted value of glucose for NIR Spectroscopy is not linear to actual value of glucose but the predicted value of glucose for proposed technique is linear to actual value of glucose and hence leads to more accurate results.

5.3.2 Clarke Error Grid Analysis for the Proposed Technique

Finally, Clarke error grid analysis is performed to validate the proposed NIBGM system. The Clarke EGA is to quantify clinical accuracy of patient estimates of their current blood glucose as compared to the blood glucose value obtained in their meter. It can also be used to

quantify the clinical accuracy of blood glucose estimates generated by meters as compared to a reference value.

As illustrated in Figure 36, predicted glucose concentration due to the proposed NIBGM system is plotted for Clarke error grid analysis.

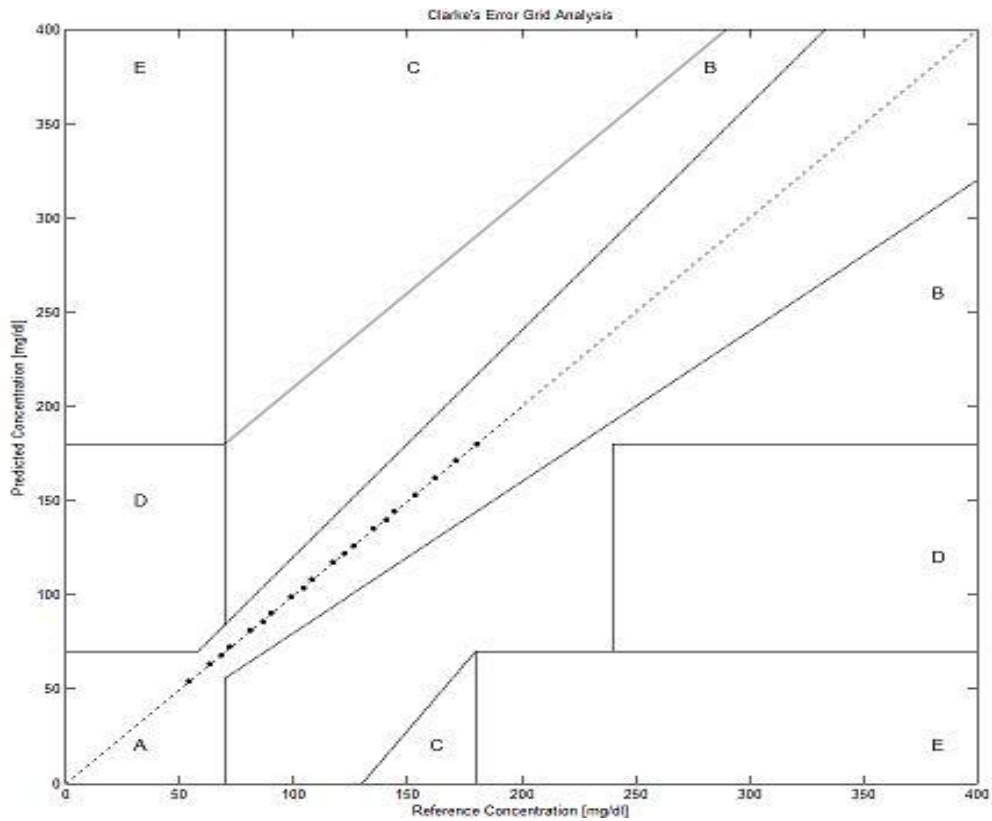


Figure 36. Clarke error grid analysis for the proposed NIBGM system

As shown in the Figure 36, the predicted glucose values due to the proposed system are in Region A which shows improved accuracy.

5.3.3 Important Hardware Considerations

While making decision to integrate infrared sensors and ultrasonic sensors into a single system, following are some important issues need to be considered.

- **Components Required:** Components required to integrate both sensors into single system varies from applications to applications. For most applications, to connect sensors, one will need a microcontroller to control the output of the integrated system.
- **Power Supply:** Power supply should be chosen based on the application with a maximum of 5 V is required for microcontroller. It is extremely important not to exceed the power limit of sensors.
- **Compatibility:** There are components that may not be compatible with a specific microcontroller. To keep the system low-cost and simple, one should address the compatibility first.

Mainly biocompatible hardware are preferred for measuring blood glucose level. Two infrared sensor, two ultrasonic sensors and microcontroller are used for the proposed technique. Overall estimated cost of proposed technique is shown in Table 11.

Table 11. Estimated overall cost of the device based on proposed technique

Components Required	Estimated Price (\$)
Infrared sensor (2)	50
Ultrasonic MEMS (2)	150
Microcontroller (1)	175
Total Estimated Cost	375

Blood glucose monitoring based on multi-sensor approach which is now available in market is GlucoTrack which costs of \$2000 with ear clip of \$100 which needs to be replaced every six months. After comparing the cost of the available device in market and with estimated cost of proposed technique, cost of the device based on proposed technique is less.

CHAPTER 6

CONCLUSIONS AND FUTURE EXTENSIONS

We hope the experimental results and discussion presented in this work motivates the interested scholars into considering research in the challenging but prosperous area of noninvasive blood glucose monitoring. Existing NIBGM systems can be upgraded with the proposed design for accuracy improvement at low cost. This chapter concludes the work and offers some possible future extensions.

6.1 Conclusions

Both long term and short term complications from diabetes can be reduced through suggest diet, physical exercise, and proper medication. In order to determine the appropriate drugs, blood glucose concentration is regularly monitored. However, traditional invasive blood glucose monitoring systems are expensive, inconvenience, and painful (due to pricking fingers). In this work, a promising multisensory noninvasive blood glucose monitoring system is proposed.

The proposed multi-sensor approach is based on the principle of infrared spectroscopy and photo acoustic spectroscopy. In addition to the IR sensors, ultrasonic MEMS technology is used. A simulation model is developed using COMSOL Multiphysics software. Calibration is done using Matlab multiple regression analysis method to improve accuracy. Behavior of ultrasonic MEMS is studied for different blood glucose concentration. The simulation results are compared with results from previous studies and cross validated with actual glucose concentration to justify the proposed NIBGM system. The Clarke EGA is completed to quantify the accuracy of the proposed system.

Experimental results show that the proposed NIBGM system generates lower residuals when compared with those from a recently introduced noninvasive IR sensor-based approach. The Clarke EGA suggests that the proposed NIBGM device should be medically acceptable. Thus, the proposed NIBGM device will help diabetic patients monitor blood glucose level better because this device is painless and easy to use.

6.2 Future Extensions

The proposed method can be extended to offer the following features:

- Wi-Fi or similar technology as an extension to the proposed multi-sensor NIBGM system so that the blood glucose values can be stored in a remote machine for further analysis.
- Monte Carlo simulation for the calibration model of the proposed technique to attend better accuracy.

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