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Trends and Development of Non-Invasive Glucose Measurement in Self health careApplication

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ABSTRACT

The proposed work is based on a non-invasive method for measuring glucose concentration in human blood usinga biosensor based on near-infrared optical technique. In recent medical practice, the concentration of glucose in the blood is measured using invasive techniques that usually involve puncturing the finger. In general, a few ml of blood is drawn, whereas in recent practice, less than a drop of blood is drawn and subjected to standard chemical tests to determine glucose concentration. These procedures are both costly and painful. Therefore, the advanced system used circuit diagram modeling of bio-sensor contains transmitter and receiver module in non-invasive measurement, based on the principle of photodetector.The variation in the intensity of the received signal obtained after reflection is used to determine the glucose concentration in the blood.

Keywords: - noninvasive glucose monitoring, self-monitoring of blood glucose,Biosensor, Photodetector,current to voltage converter.

I. INTRODUCTION

Diabetes is a type a metabolic disease in which the blood glucose (blood sugar) level in human body increases drastically from its normal level. The increase in sugar level is either due to inadequate production of insulin in blood cells or can be because of the improper response of body cells to the insulin or can be because of both the reasons. diabetes can lead to major complications like heart failure and blindness in the human body. Hence regular monitoring of glucose level is important[1] .The World Health Organization (WHO) estimated that the number of people with diabetes is more than 200 million. Diabetes is a state of a body where it not able to produce the quantity of insulin sufficiently required to maintain normal level of blood glucose. So, diabetic patients regulate their blood glucose levels through proper diet as well as by injecting insulin [2]. For the effective treatment of diabetes, patients have to measure the level of blood glucose periodically. At present, diabetic persons are using invasive figure pricking instrument knows as glucose meter to know the concentration of blood glucose.Table 1 shows the standard values of blood glucose level present in non-diabetic and diabetic patient.

TABLE-1: Blood glucose present in non-diabetic-diabetic and diabetic persons.

S.NO.	Glucose in milligrams per deciliter (mg/dL)
1.Non-diabetic	100
2.Pre-diabetic	100 to 125
3.Diabetic	126+

It depends on physiological condition.

1.1 DIFFERENT TYPES OF DIABETES:

There are two main types of diabetes: **type 1and type 2**.[1]

Type 1 Diabetes

Type 1 diabetes is thought to be caused by an autoimmune reaction (the body attacks itself by mistake) that stops our body from making insulin. Approximately 5-10% of the people who have diabetes have type 1.

Type 2 Diabetes

With type 2 diabetes, our body doesn't use insulin well and can't keep blood sugar at normal levels. About 90-95% of people with diabetes have type 2. It develops over many years and is usually diagnosed in adults (but more and more in children, teens, and young adults).

II. LITERATURE SURVEY

Diabetes is a widely spreading disease which causes several secondary complications and claims millions of lives every year [10,11]. According to the World Health Organization (WHO) estimation in2016, the number of people with diabetes has increased from 108 million in 1980 to 422 million in2014 worldwide [12].

The prevalence of diabetes among adults over 18 years has risen from 4.7% in 1980 to 8.5% in 2014 worldwide. WHO data indicated that about 1.6 million of deaths in 2015 were directly related to diabetes. The International Diabetic Federation (IDF) data approximated the global

number of people with diabetes between the age of 20-79 years to be 425 million in 2017 [13]. This number will rise to 629 million by 2045. It was indicated that about 49.7% of people with diabetes remain undiagnosed [14]. IDF data also stated that 79% of people with diabetes live in low-income and middle-income countries. IDF indicated that about 16.2% of births are affected by gestational diabetes. Four million global deaths were attributable to diabetes in 2017 and 12% of global healthcare expenditure worth USD727 billion was spent on diabetes.

Current available invasive blood glucose monitors require finger prick which causes pain, inconvenience, discomfort, distress, and prone to infections. The costs of disposable test strips in invasive techniques and unavailability of clinically dependable non-invasive blood glucose monitors are also the challenges of blood glucose monitoring. Recently introduced minimally invasive glucose monitors have limited lifespan, and unstable accuracy, and require invasive methods for regular calibration. Hence, the design of reliable non-invasive blood glucose monitor is needed. Several techniques have been attempted to develop non-invasive blood glucose monitors since last few decades. The optical methods which include; fluorescence spectroscopy [15,16], near-infrared spectroscopy [17], photoacoustic spectroscopy [18,19], optical coherence tomography [20,21], polarimetry [22], and Raman spectroscopy [23,24] techniques have been widely studied. Their limitations are; poor signal to noise ratio, lack of accuracy, poor linearity and sensitivity, susceptibility to environmental variations and tissue compositions. Other methods such as electromagnetic [25], reverse iontophoresis [25,26], bioimpedance spectroscopy [27,28] and ultrasound glucose sensing techniques are also studied extensively. These methods are sensitive to environmental changes, the composition of tissues, and affected by the physiological time lag of blood glucose. Recent blood glucose monitoring techniques are widely discussed in [29] with their merits and limitations.
Thus, a non-invasive blood glucose monitor is required which isbased on visible laser light (LAB-NIBGM). It was demonstrated that visible red laser light of 650nm wavelength has better penetration, signal to noise ratio and improved accuracy over near-infrared spectroscopy of 950nm [30]. But, high power laser of 1.5W was used which might cause potential hazards to skin and eye.

III. METHODS FOR MONITORING BLOOD GLUCOSE CONCENTRATION

According to whether the blood glucose test has caused injury to human skin, it can be simply divided into invasive and non-invasive blood glucose monitoring.

Invasive Blood Glucose Monitoring

At present, invasive blood glucose detection technology is mainstream, convenient and practical, so both hospitals and household glucometers adopt the method of blood sampling first and thenanalyzing it in vitro for blood glucose measurement. In hospitals, the blood drawn from the subjects on an empty stomach in the morning, and the blood glucose concentration is accurately measured byautomatic biochemical analyzer. Although the results of this method are precise and can be used as animportant basis for the diagnosis of diabetes, it is unfit for continuous monitoring of diabetics due toits tedious process, long detection time and large amount of venous blood extraction.

Non-Invasive Blood Glucose Monitoring

Non-Invasive Blood Glucose Monitoring, as its name implies, refers to the detection of human blood glucose without causing damage to human tissues. There are lots of methods for non-invasive blood glucose detection, which can be generally divided into optical methods, microwave methodsand electrochemical methods.

Recent glucose measurement methods for the ever-increasing the diabetic patients over the worldare invasive, time-consuming, painful and a bunch of the disposable items which constantly burden forthe household budget. The non-invasive glucose measurement technique overcomes such limitations, forwhich this has become significantly researched era. Although, there is tradeoff between thesetwomethods.

IV. PRINCIPLE OF BLOOD GLUCOSE MEASUREMENT IN NON-INVASIVETECHNIQUE

When an incident laser light is allowed to pass through a medium of aqueous glucose solution, it refracts or transmits. The degree of laser light refraction depends on the concentration of glucose. The variations in refractive angle and the refractive index of the light depend on glucose concentration. The glucose aqueous solution changes the speed of laser light that passes through it. This slows down its speed and changes the direction of laser light. When a light ray interacts with human body tissues, it is scattered as well as absorbed by the tissues, resulting in attenuation. Light scattering occurs in tissues due to a mismatch between the refraction index of extracellular fluid and the cell membrane. Extracellular fluid refraction index varies with glucose concentration, whereas cellular membrane refraction index is assumed to be relatively constant. In absorbance measurement, the Beer-Lambert Law states that the absorbance of light through any solution is proportional to the solution's concentration and the length of the light ray's path [5].The effect of glucose molecules on the light path is

depicted in Figure- 1a. Less glucose causes more scattering, longer path lengths, and thus less absorption, whereas more glucose tissues cause less scattering, shorter path lengths, and thus more tissue absorption.

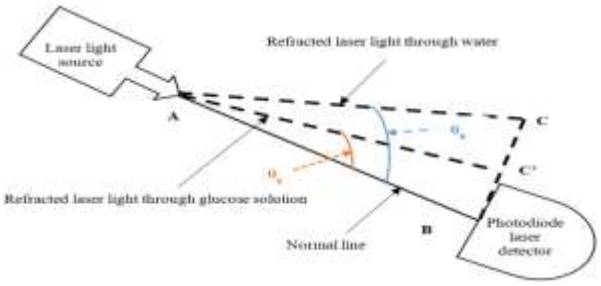

Figure 1. The correlation between glucose concentration and refractive parameters

Because high glucose tissue absorbs more light, reflected light has a lower intensity than tissue with a lower glucose content. Light transport theory describes light attenuation as shown in relation below:

$$I = Ioe^{-\mu_{eff}L} \quad (1)$$

where, I is the reflected light intensity, I_0 is the incident light intensity and L is the length of the optical path inside the tissue. The attenuation of light inside the tissue is illustrated in figure 1(b):

The attenuation of light inside the tissue depends on the coefficient knownthe as effective attenuation coefficient which is defined as

$$\mu_{eff} = \sqrt{3\mu_a(\mu_a+\mu'_s)} \quad (2)$$

The absorption coefficients described as the probability of absorption of photons inside tissue per unit path length and is given by

$$\mu_a = 2.303 \epsilon C \quad (3)$$

ϵ is the extinction coefficient and C is the tissue chromophore concentration and the reduced scattering coefficient is given by eq.4

$$\mu'_s = \mu_s(1-g) \quad (4)$$

where, g defines the average of the cosine of thescattering angles which has a representative value of0.9and μ_s is defines the scattering coefficient.

With increase the glucose concentration path length decreases. With the assumption that refractive index of blood cell remains constant (approximately 1.350-1.460) with increase in the glucose concentration scattering properties decreases. From the equations above (1-4) it can be concluded that also depends on the blood glucose concentration, the increase in the glucose concentration increases the value of absorption coefficient and hence the effective attenuation coefficient *eff m* also increases which in terms results in increase in the attenuation level. Hence from equation (1) it can be 4 concluded that increase in attenuation decreases the intensity of reflected light. Human finger skin tissue consists of epidermis, dermis and subcutaneous tissue layers. When optical signal is sent perpendicularly into the human body part the signal passes through epidermis layer and gets reflected in dermis layer and follows banana shaped path as shown in Figure 2.

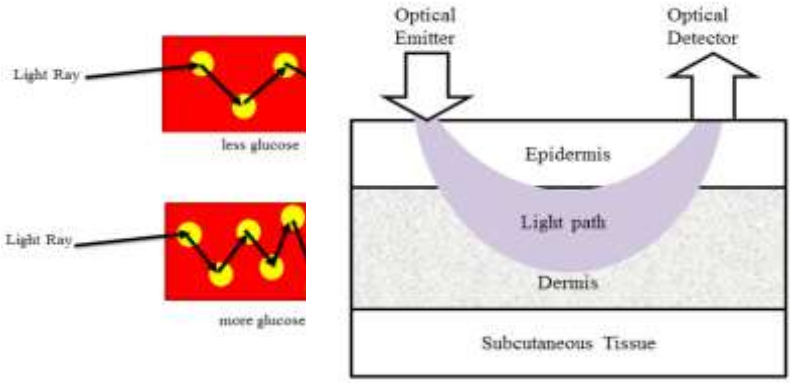

Figure 2(a)Effect of blood tissues in light path and (b)Effect of Glucose On light Path

Light absorption peaks for glucose are at wavelengths of 940 nm, 970 nm, 1197 nm, 1408 nm, 1536 nm, 1688 nm, 1925 nm, 2100 nm, 2261 nm, and 2326 nm1, respectively. However, because other constituents of the blood, such as water, platelets, and red blood cells, attenuate optical signals at 940 nm wavelength, a desired depth of penetration can be achieved and actual glucose concentration can be predicted [5]. Glucose has light absorption peaks at wavelengths of 940 nm, 970 nm, 1197 nm, 1408nm, 1536nm, 1688nm, 1925 nm, 2100nm, 2261nm and 2326nm, butat 940 nm wavelength the attenuation of optical signals by other constituents of the blood like water, platelets, red blood cells etc. is minimum, hence a desired depth of penetration can be achieved and actual glucose concentration can be predicted.

The mathematical expression to obtained glucose level is computed using a polynomial regression tool relating the analog voltage and the glucose level shown below:

$$y = (8*10\text{-}5)\ x2 + 0.1873x + 46.131$$

the relation is derived 24 diabetic individuals including both genders are considered. Glucose level of these individuals is measured in the laboratory by the invasive method and at the same time the analog voltage corresponding to their glucose level.[7][8][9].

where x and y are analog voltage (mV) and glucose level (mg/dl) respectively.

V. GENERAL BLOCK DIAGRAM OF BIOSENSOR BASED GLUCOMETER

The general model of biosensor-basedglucometer useda hardware prototype using VHDL/Verilog like a programming language. The model consists of infrared transmitter and receiver followed by a current-to-voltage converter. The designed system shows response from analog and mixed signals, as shown in figure below:

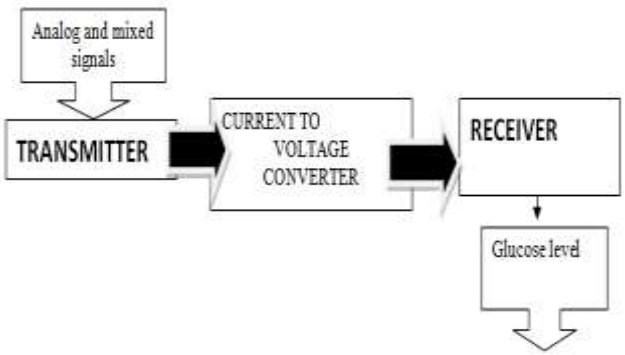

Figure 3: Block-level diagram of Biosensor based Glucometer

VI. LIST OF ADVANCED DEVICES USED IN GLUCOSE MEASUREMENTUSING NON-INVASIVE METHOD

DEVICE	TECHNIQUE	ADVANTAGE	DISADVANTAGE
1. Raman Spectroscopy	Raman scatteringis a nonlinear orinelastic scattering whichoccurs whenmonochromatic light interactswith a certainsample.	Less sensitivity towards temperatureand water. High specificity	Requirement of the laser radiationsource hence it can dangerous cellfor CGM. Susceptible towards noise interferenceso low SNR
2. Polarimetry	Because of other Polarizationrotating Components present in	The laser intensity variation will not Change much the	Requirement external laser sourceand requires proper alignment with Eyesensitive
	theinterior chamber of the eye.	glucose prediction	for the change in PH and Temperature.
3. BIO Impedance Spectroscopy	Glucose readings vary in different individuals	Comparatively less extensive. Easy for CGM.	Prone towards sweating, motion andtemperature. Require large calibration period.
4. Photo acoustic	Simple and compact sensor design	Optical radiation will not harmful forthe tissue.	Signal is vulnerable towards acoustic noise,temperature,motion etc. It carries some noise from some nonglucose blood components.
5. Electromagnetic sensing	low-cost and can be easily miniaturized	No risk of ionization	Lack of selectivity due to dielectricconstant is mainly affected with other blood components. More sensitive for the slight changeof temperature.
6. Ultrasound Technology	Long penetration below the skin or tissue	Well established technology with not much harm to tissue cell.	Limited accuracy with ultrasound only hence mostly used with NIR as multi-model. costly technology for measurementand not useful for CGM.
7. Sonophoresis	Based on well known enzymatic method	Favourable technology as there is noside-effect to skin.	Error prone due to environmental parameters.

TABLE 2: Qualitative comparison of various noninvasive glucose-level monitoring methods.[31]

VII. PERFORMANCE INDICES OF BIO-SENSOR

Repeatability

Repeatability is evaluated at five glucose concentrations spread across the measuring interval (30–50 mg/dL,51–110mg/dL, 111–150 mg/dL, 151–250 mg/dL, and 251–400 mg/dL) and should be measured over a short span of time, not to exceed one day per meter, with the same user, meter, and reagent lot.

Intermediate precision

Intermediate precision is defined as precision under "conditions where the test results are obtained with the same method on identical test items in the same location, but where other variables such as operators, equipment, calibration, environmental conditions, and/or time intervals differ."

Accuracy

System accuracy is evaluated with at least 100 different subjects and two different meters over at least 10 days with capillary blood samples. Samples are measured by two different meters and at least in duplicate. The evaluation should be conducted in actual conditions of use, so that the effects of systematic error and random error that would be experienced by individual users are included.

Linearity

Glucose biosensors should be evaluated for linearity across the reportable range. Therefore, data collection requires two to four replicates from 5 to 11 samples with varying concentrations that are known relative to one another by the dilution ratio or by the formulation. The correlation coefficient and linear regression equations are calculated from the obtained results *versus* glucose concentration

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