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Error Grid Analysis of Reference and Predicted Blood Glucose Level Values as Obtained from the Normal and Prediabetic Human Volunteers

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Abstract **Background:** In this research paper, we represent a new noninvasive blood glucose level determining technology based on Amplitude Modulated Ultrasound and Infrared techniques. The successful advent of a noninvasive blood glucose determining technology will be helpful for patients with abnormal episodes of elevated Blood Glucose Levels. Noninvasive device will increase patient's compliances along with firm control over elevated Blood Glucose Levels (BGL). Moreover, it will reduce diabetes related medical emergency and burden from the shoulders of healthcare professionals. **Research Design:** A total of 10 adult human volunteers (02 Normal and 08 Prediabetic) had been engaged in this experimental pilot study. Main objective of these experiments are to analyze and compare the blood glucose levels as obtained from the established invasive (Accu-chek Active invasive blood glucose monitoring system from Roche Diagnostics) and indigenously developed noninvasive BGL determining technology (Amplitude Modulated Ultrasound and infrared Unit) respectively. The blood glucose levels after overnight fasting and 02 hour after meal had been observed in Normal and Prediabetic volunteers. Again following the next day, blood glucose level at fasting stage and 02 hour after 75gm/100ml glucose solution consumption had been monitored in those Normal and Prediabetic volunteers. Moreover, the invasive (reference) and noninvasive (predicted) blood glucose levels as obtained had been plotted over Clarke and Parkes Error Grids for evaluating indigenously developed technique performances. **Results:** The experimental findings reveal that Normal volunteers fasting blood glucose level exists more or less between (80-110) mg/dl. Similarly in separate pilot studies, their Blood Glucose Level varies more or less between (130-140) mg/dl after 02 hour of meal consumption and 75gm/100ml of glucose solution consumption respectively. But in case of Prediabetic volunteers, their fasting blood glucose level exists more or less above 110 mg/dl. Likewise in separate experimental studies, their Blood Glucose Level ranges more or less between (140-199) mg/dl after 02 hour of meal consumption and 02 hour after 75gm/100ml glucose solution consumption respectively. Moreover, the invasive (reference) and noninvasive (predicted) blood glucose levels of all the volunteers (normal and prediabetics) occupies medically significant and acceptable A and B zones in Clarke and Parkes Error Grids Analysis respectively. **Conclusions:** Experimental observations indicates the potential and prospective capability of our indigenously developed noninvasive Blood Glucose Level determining technique (Amplitude Modulated Ultrasound and Infrared unit) as revealed from the pilot studies over Normal and Prediabetic volunteers.

Keywords Clarke and Parkes Error Grid Analysis, Invasive, Noninvasive, Blood Glucose, Amplitude Modulated Ultrasound, Infrared Techniques

1. Introduction

Individual with elevated blood glucose level but not as much high as compared with diabetic patients are generally suffering from the IGT (Impaired Glucose Tolerance) or IFG (Impaired Fasting Glucose) related symptoms [1-3]. IGT refers to the medical condition in which blood glucose level elevates within the range between (140-199) mg/dl even two hours after food consumption [1-3]. Similarly, the IFG refers to the medical situation where blood glucose level elevates above 110mg/dl even after overnight fasting time period [1-3]. The global populations resembling such typical symptoms are termed as prediabetics [1-3]. Consequently; the individuals with Prediabetic symptoms are severely prone to develop Type II Diabetes in near future [1-3]. Moreover, the IGT resembles Type II Diabetes symptoms adjunct with obesity, age progression, incapability of the human bodies to utilize insulin secreted form beta cells of the pancreas [1-3].

Complete change in lifestyle pattern, increased physical activity, controlled diet with low glycemic index food

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consumption checks the progression of IGT towards Type II Diabetes Mellitus [1-3]. Globally 31.6 crores of people suffer from IGT related symptoms [1]. These numbers globally shares 6.9% of the present total adult population [1]. Moreover, large proportion of these population resides in lower as well as middle income territories. Worldwide 15.3 crores of the adult population suffer from these IGT symptoms within 50 year span of their life [1]. They also possess increased possibility to extend it towards Type II Diabetes Mellitus in later part of their life [1]. The global dominance of IGT resembles diabetes pervasiveness, with enormous proportion in African and European countries as compared to South-East Asian countries [1]. As per future estimations during the year 2035 A.D, 47.1 crores of peoples from the world population will suffer from IGT related symptoms or nearly 8.0% from the then total adult world population [1].

The crucial points of care for robust supervision of elevated blood glucose level include its 3 to 4 times regular monitoring on a daily basis [1-5]. Invasive glucometers rigorously perform such measurements each and every time with respective tissue puncturing procedures. Consequently the diabetic patients generally experiences mental agony for regular tissue puncturing and patient incompliance occurs [3-5]. All this factors drives the urge for a nascent, novel noninvasive blood glucose determining technology with successful clinical applications [4, 5, 20-22]. In recent years, several optical techniques based noninvasive blood glucose level determining approaches had arrived with good potentiality and promising aspects [4-6, 20-22]. Such novel approaches mainly consists of Infrared Spectroscopy [7, 8, 20-22], Raman Spectroscopy [9, 20-22], Scattering Spectroscopy [10], Fluorescent Spectroscopy [11, 20-22], Polarimetry [12, 13, 20-22], Thermal Gradient Spectroscopy [14, 20-22], Photo-Acoustic Technology [15, 20-22], OCT (Optical Coherence Tomography) [16, 20-22], Occlusion Spectroscopy [17, 20-22], Photo-Thermal Technology [18], Ultrasound-Modulated Optical Techniques [19], etc.

The blood glucose exhibit weak signals and overlapped by numerous interferences from the surrounding optically active similar molecules [20-22]. To override such signal interferences we had applied Amplitude Modulated Ultrasound and Infrared Techniques altogether here. Moreover, this research paper focuses on the performance evaluation of indigenously developed noninvasive technique for determination of blood glucose levels in Normal and Prediabetic human volunteers.

Rest of Research Paper organizations are as follows: Section II describes the principle and working methodology. Section III illustrates the Instrumental block diagram, light wavelength and ultrasound band selection criteria. Section IV contains the experimental results and discussion portions. Section V provides the conclusive part of the research paper followed by acknowledgment and references.

2. Principle and Working Methodology

Noninvasive technique includes mainly amplitude modulated ultrasonic waves, infrared light beam and its respective IR (Infra Red) detector for determining blood glucose levels in Normal and Prediabetic Human Volunteers.

When standing ultrasonic waves propagates through the finger based blood tissue complex medium of human volunteers, it initiates the process of vibration throughout that respective medium. The molecules vibrate depending upon their respective mass, physical, chemical properties [23-25]. Moreover, the effect of radiation forces applied over the molecules had been derived from the gradient of molecular acoustic potential energy [23-32] and expressed as follows:

$$\mathbf{F_r} = -\left[\frac{\pi \mathbf{p_o^2 V_c \beta_w}}{(2\lambda)}\right].\phi(\boldsymbol{\beta}, \boldsymbol{\rho}).\sin(4\pi \mathbf{z}/\boldsymbol{\lambda}) \quad (1)$$

The symbols like **(F_r), (V_c), (z), (P_0),** and **(λ)** stands for radiation force characteristics, volume of the respective molecules, space form the node of pressure, ultrasonic wave peak amplitude and wavelength of ultrasound respectively [23-32].

When compressibility aspects ($\boldsymbol{\beta_w}$) of the suspending (blood tissue complex) segment present in human volunteers finger are considered, the mathematical expression had been represented as given below:

$$\phi(\boldsymbol{\beta}, \boldsymbol{\rho}) = \left[\frac{5\rho_c - 2\rho_w}{2\rho_c + \rho_w} - \left(\frac{\beta_c}{\beta_w}\right)\right] \quad (2)$$

The symbols like ($\boldsymbol{\beta_c}$) stands for compressibility of the molecules and ($\boldsymbol{\rho_c}$), ($\boldsymbol{\rho_w}$) signifies molecular density of the suspending molecules and suspending segment respectively [23-32].

When infrared light beam propagates through these ultrasound (amplitude modulated ultrasonic waves) excited (blood tissue complex) optical medium, the glucose molecule vibration specific signatures are captured by the respective IR sensitive detectors. This light interaction phenomenon had been represented by Beer-Lambert Law [23-32] as follows:

$$\mathbf{A(v)} = -\mathbf{log\, I(v)/I_0(v)} \quad (3)$$

The symbols like **(A), (v), (I_0)** and **(I)** signifies Absorption patterns, wave number, light intensity from the surrounding medium and light intensity after transmission through the path length of measurement sample respectively [23-32].

3. MUS-IR Experimental Setup and Its Functional Part Depictions

Main functional parts of the MUS-IR Experimental setup had been illustrated as follows:

Synchronous square wave generator:

This functional part produces square wave based pulses to the IR LED (Infra Red Light Emitting Diode) light source.

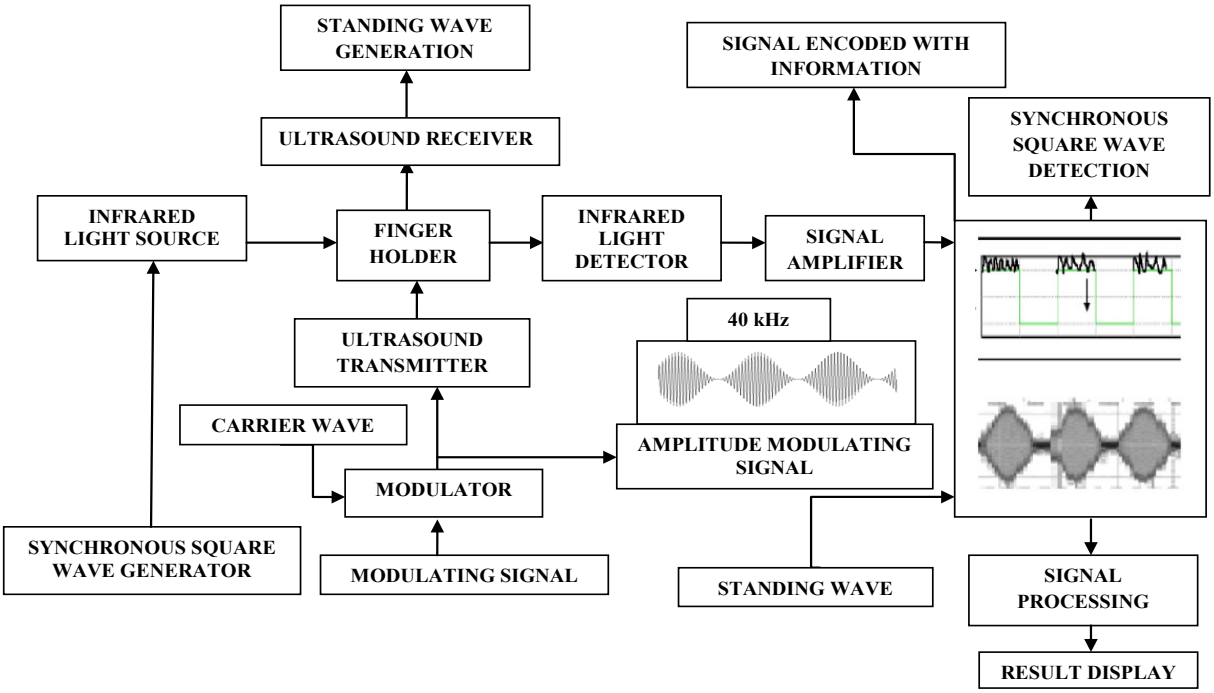


Figure 1. Block diagram of the MUS-IR (Modulated Ultra Sound-Infrared) Experimental Setup

Infrared light source:

IR LED of specific 940nm spectral wavelength had been selected and applied here. Actually 940nm occupies the position between "tissue optical window range" extending from 700nm to 1100nm [4, 33]. Within this zone the unwanted influence of other optically active molecules such as water, oxyhemoglobin, deoxyhemoglobin, etc. are reasonably negligible as depicted from Figure No.2, 4 respectively [4, 34-36]. Moreover, from Figure No.3 it can be revealed that glucose molecule exhibits absorption peaks near to 940nm wavelength [4, 34-36]

Modulating unit:

The modulating unit produces amplitude modulating standing wave pulses to UST (Ultra Sound Transmitter) unit. This functional component had been connected with two other primary parts such as carrier wave and modulating signal units.

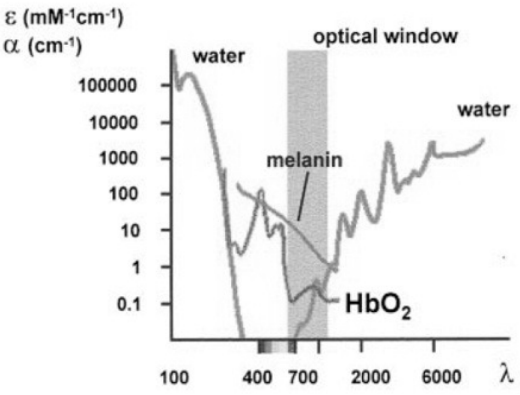


Figure 2. Absorption characteristics of chief intracellular components within the light spectral domain extending from 100nm to 6000nm [4, 33]

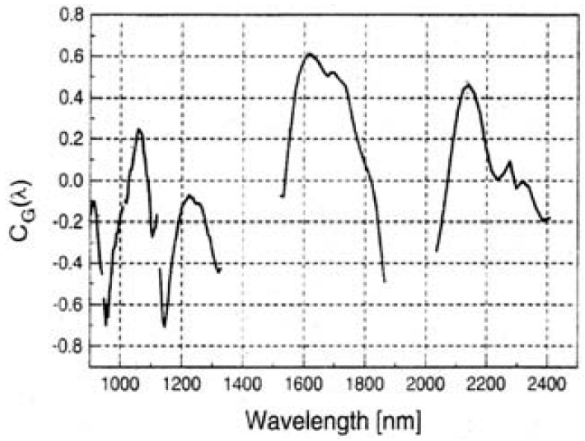


Figure 3. Absorption coefficient characteristics of Glucose within the light spectral domain extending from 900nm to 2400nm [4, 34-36]

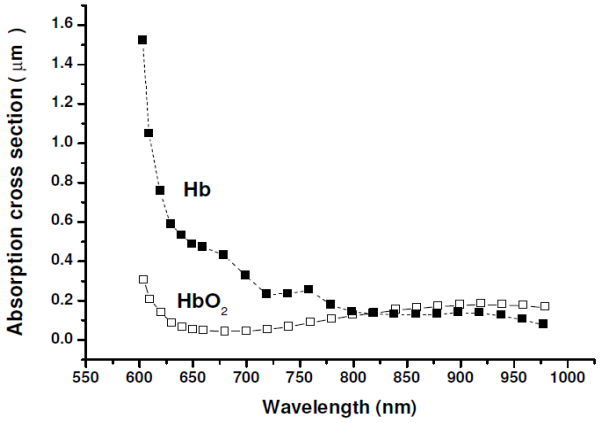


Figure 4. Absorption characteristics of Oxygenated Hemoglobin (HbO_2) and Deoxygenated Hemoglobin (Hb) within the light spectral domain extending from 550nm to 1000nm [4, 34-36]

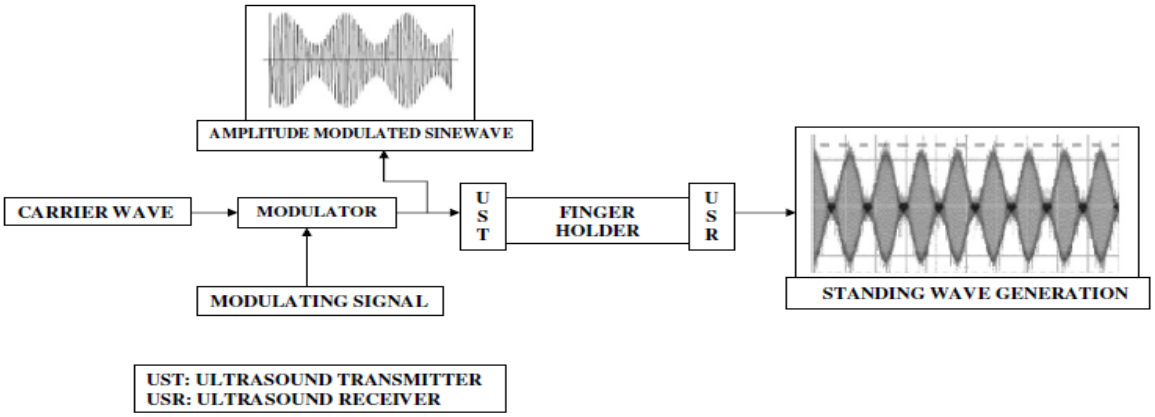


Figure 5. Shows the generation of amplitude modulated ultrasonic waves in MUS-IR Experimental unit

Ultra Sound Transmitter (UST):

Ultrasound Transmitter of 40 kHz central frequency had been selected and applied here. Actually the 40 kHz ultrasonic wavelength is medically safe for its use in human beings [24, 31, 32].

Moreover, amplitude modulated standing wave pulses as generated from the respective modulating unit serve as the signal input to UST unit. Consequently, the UST functional unit produces output signal in the form of ultrasonic amplitude modulated standing wave towards the finger holder unit. This phenomenon had been depicted here in the Figure No.5 as provided above.

Finger Holder Unit:

It upholds the human finger in precise geometrical position required for accurate IR light, ultrasonic wave transmission purposes. It helps in holding steady perpendicular orientation of IR light and ultrasonic unit with respect to finger positioning during signal acquisition periods. Moreover, it minimizes the unwanted errors such as motion related artifacts, wrong finger positioning, etc.

Ultra Sonic Receiver (USR):

Again, the Ultra Sonic Receiver of 40 kHz central frequency had been selected and applied here. Actually the 40 kHz ultrasonic wavelength is medically safe for its use in human beings [24, 31, 32]. USR unit checks the quality of ultrasonic waves generated from the UST unit. It is very important as it plays the key factor in blood glucose level determination purposes.

Infra Red (IR) detector:

It picks up the transmitted IR light signals and records the blood glucose specific vibrational patterns for its relevant concentration determinations.

Signal amplifier & processing unit:

This part performs the signal conditioning, amplifications and unwanted noise filtrations functions. Subsequently, the resultant signals were analyzed through the MATLAB toolbox to determine blood glucose concentration related embedded information. The peak to peak voltage amplitude spectrum variations in FFT (Fast Fourier Transform) domain with respect to BGL (Blood Glucose Level) concentration were observed here. Actually, those typical voltage amplitude pattern variations serve as a functional indicator for respective change in the BGL levels.

Result Display:

This part of MUS-IR unit displays the noninvasive BGL (Blood Glucose Level) in mg/dl.

Clinical status of the Volunteers:

A group of 10 (seven males, three females, aged 35±6.5 years, of height 173±5.5cm, weight 70±11.5 kg) adult volunteers were selected. From which 02 volunteers are normal and healthy adults. Other 08 adult volunteers are with history of Prediabetic symptoms like IGT and IFT. Written consent had been obtained from all the volunteers. Institutional Ethical Committee approved the pilot study.

Clarke and Parkes Error Grid Analysis:

Clarke Error Grid analysis had been utilized to evaluate medical importance of the differentiations between blood glucose level predicting technique under examination and the established invasive blood glucose reference method. Clarke et al in the year 1986 A.D presented this novel analytical approach [37-42] and represents a Cartesian plot based diagrammatic approaches to characterize values of the reference (invasive) technology versus the predicted (predicted) technology [37-42]. As for illustration, if a human volunteer's Blood Glucose Levels is predicted to be 121mg/dl for a particular moment where the reference BGL value is 113mg/dl, this fact will be produced by the particular point as (113,121) in the XY Cartesian domains [37-42]. In this fashion, the diagonal line such as Y=X symbolizes the ideal determinations, points under and over the diagonal line, designates over assessment and under assessment of the real BGL values. Interestingly, the Cartesian XY graph had been divided into several grid zones based on the degree of severity of miss judgments [37-42]. The Error Grid name also signifies these facts. Clarke et al divided the respective Cartesian graph into 05 different zones (A to E) [37-42] respectively, with the following interpretations as follows:

Zone A: signifies predicted blood glucose values which diverge as of the reference blood glucose values by 20% or less. It also include hypoglycemic ranges (<70mg/dl) of both the predicted and reference BGL values respectively [37-42]. These BGL values are medically accurate and suitable. For that, required medical supervision will be proper [37-42].

Zone B: signifies predicted BGL values which differ as of the reference BGL values by more than 20%. Within this zone we are nearer to medically erroneous BGL values but the medical supervision has an elevated likelihood of being accurate [37-42].

Zone C-E: the BGL values occupying those zones are extremely hazardous, as the determination or estimation is far away to be medically significant and the designated medical attention will differ from the accurate medical action required [37-42].

Parkes et al in the year 2000 A.D reentered the concept of respective zones and designed a new set of innovative error grids, based on the proficiency of big group of medical experts. These new Error Grids were designed differentiating for Type I and Type II diabetic subjects. Parkes Error Grids had been divided into 05 parts such as Zone A to Zone E respectively [43-45].

Zone A signifies medically correct determinations, with no consequence over medical supervision [43-45].

Zone B signifies changed medical action, minute or no consequences over medical treatment [43-45].

Zone C signifies changed medical action, probable to influence medical treatment [43-45].

Zone D signifies changed medical action, might comprise imperative medical jeopardy [43-45].

Zone E signifies changed medical action, might comprise unsafe effects [43-45].

Recently in the area of diabetes technology assessments, existence of the widely acceptable Consensus Error Grids (EGs) for checking errors between reference and predicted blood glucose level determinations is not available. For that reason, we had utilized both the available (Clarke and Parkes) Error Grids (EGs) for result analysis and evaluation purposes [37-45]

4. Experimental Results and Discussions

The experiments were conducted in two phases.

The Phase I includes determination of invasive (reference) and noninvasive (predicted) BGL values of both the Normal and Prediabetic volunteers after overnight fasting and after 02 hours of meal consumption.

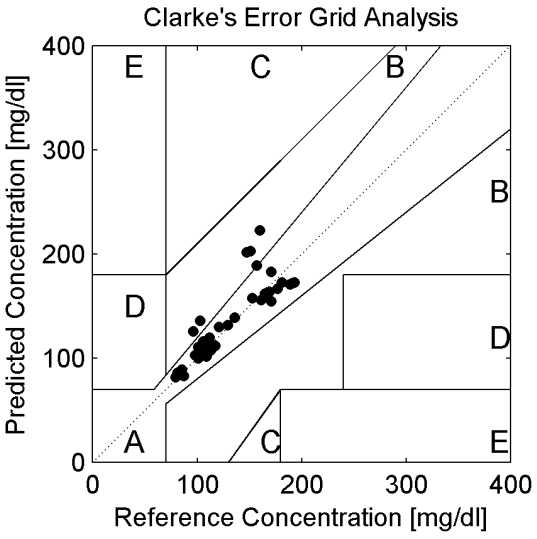
The Phase II includes determination of invasive (reference) and noninvasive (predicted) BGL values of both the Normal and Prediabetic volunteers next day after overnight fasting and 02 hours after 75gm/100ml of glucose solution consumption.

For invasive blood glucose level determinations the Accu-chek Active blood glucose monitoring system of Roche Diagnostics GmbH had been utilized here. Similarly, for noninvasive blood glucose level predictions we had utilized our indigenously designed and developed MUS-IR (Modulated Ultra Sound-Infra Red) unit.

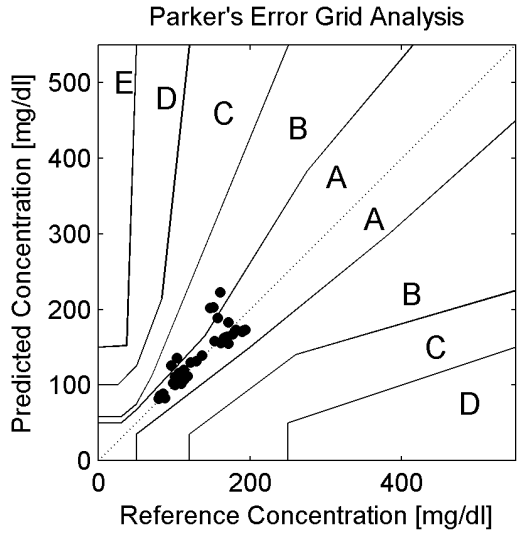
Table No.1 and 2 shows the comparison of invasive (reference) and noninvasive (predicted) Blood Glucose Levels (BGL) as obtained from the Normal and Prediabetic subjects during Phase I and II experimental pilot studies respectively.

Both the invasive (reference) and noninvasive (predicted) results were plotted over Clarke and Parkes Error Grids for critical analysis purposes.

Figure No. 6(a) and 6 (b) depicts the Clarke and Parkes Error Grid Analysis based graphical plotting of the Invasive (reference) and Noninvasive (predicted) BGL values of the Normal and Prediabetic volunteers as acquired during the experimental pilot study respectively.



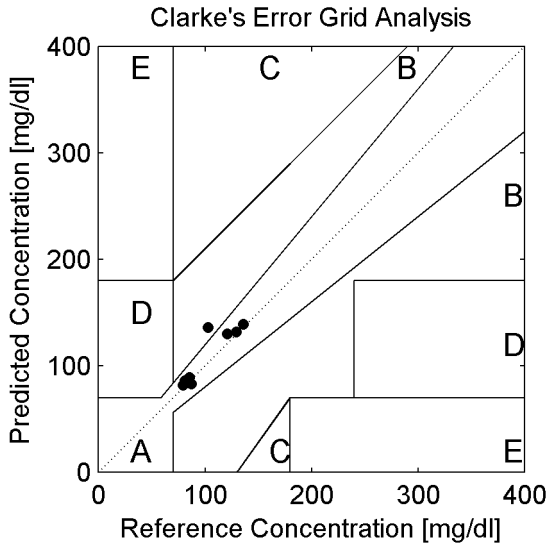
(a)



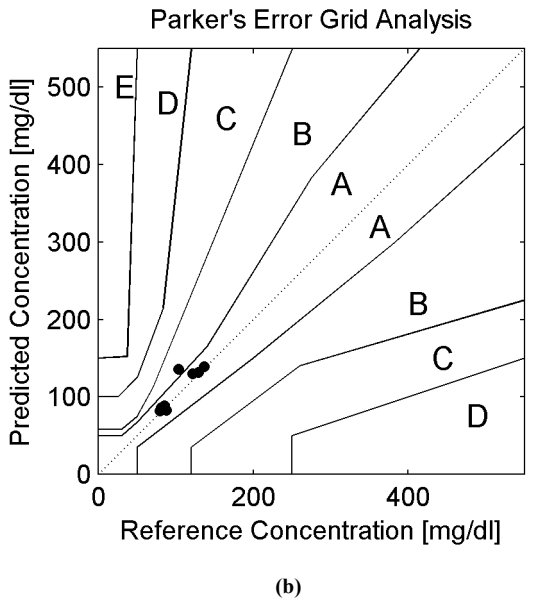
(b)

Figure 6. Represents Graphical depiction of Clarke and Parkes Error Grid Analysis of the invasive (reference) and noninvasive (predicted) BGL values as obtained from the Normal and Prediabetic subjects during the experimental pilot study respectively

Likewise, the Clarke Error Grid analysis based relevant BGL determining accurateness dependent proportional values as acquired from figure No.6 (a) are grouped as follows: A zone=85.00%, B zone=15.00%, C zone=00.00%, D zone=00.00% and E zone=00.00% respectively. Similarly, the Parkes Error Grid analysis based relevant BGL determining accurateness dependent proportional values as acquired from figure No.6 (b) are grouped as follows: A zone=85.00%, B zone=15.00%, C zone=00.00%, D zone=00.00% and E zone=00.00% respectively.



(a)

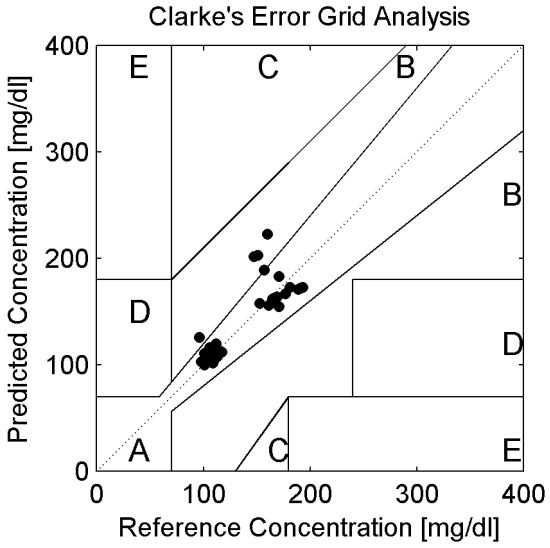


(b)

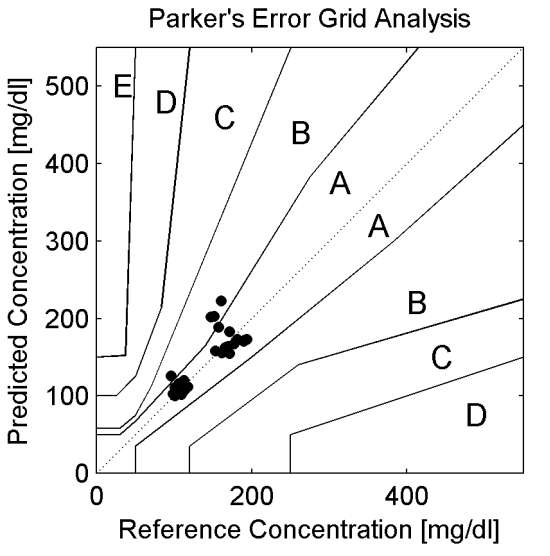
Figure 7. Represents Graphical depiction of Clarke and Parkes Error Grid Analysis of the invasive (reference) and noninvasive (predicted) BGL values as obtained from the Normal subjects during the experimental pilot study respectively

Clarke and Parkes Error Grid Analysis based graphical plotting for all the Normal volunteer's invasive (reference) and noninvasive (predicted) BGL values as obtained during this experimental pilot study had been depicted in Figure No.7 (a) and 7 (b) respectively.

The Clarke Error Grid analysis based respective BGL determining accuracy dependent percentage values from figure No.7 (a) are categorized as follows: A zone=87.50%, B zone=12.50%, C zone=00.00%, D zone=00.00% and E zone=00.00% respectively. Correspondingly, the Parkes Error Grid analysis based respective BGL determining accuracy dependent percentage values from figure No.7 (b) are categorized as follows: A zone=87.50%, B zone=12.50%, C zone=00.00%, D zone=00.00% and E zone=00.00% respectively.



(a)



(b)

Figure 8. Represents Graphical depiction of Clarke and Parkes Error Grid Analysis of the invasive (reference) and noninvasive (predicted) BGL values as obtained from the Prediabetic subjects during the experimental pilot study respectively

Graphical plots in Figure No.8 (a) and 8 (b) respectively depict the Clarke and Parkes Error Grid Analysis for the Prediabetic volunteer's invasive (reference) and noninvasive (predicted) BGL values.

Moreover, the Clarke Error Grid Analysis based accuracy dependent percentage values of the BGL invasive (reference) and noninvasive (predicted) readings are classified as follows: A zone=84.3750%, B zone=15.6250%, C zone=00.00%, D zone=00.00% and E zone=00.00% respectively. Similarly, the Parkes Error Grid Analysis based accuracy dependent percentage values of the BGL readings are classified as follows: A zone=84.3750%, B zone=15.6250%, C zone=00.00%, D zone=00.00% and E zone=00.00% respectively.

Results obtained from analysis depicts that Prediabetic subject's blood glucose levels were elevated than normal physiological ranges but not as high compared to diabetic subjects during both the Fasting stage and 02 hr after meal or glucose solution consumption respectively. Similarly, for Normal subjects the blood glucose levels during Fasting stage and 02 hr after meal or glucose solution consumption are always within normal physiological range extending between (80-140) mg/dl.

Moreover, all the invasive and noninvasive BGL values occupy the medically acceptable A and B zones respectively. This fact indicates dependable performance of our indigenously developed MUS-IR unit. All these results also correlate our previous blood glucose determination experimental values [24, 25, 31, 32]. The vital factor driving this technique comprises

(i) Amplitude Modulated Ultrasonic wave utilizations for exciting specific molecules (glucose) present within the blood tissue complex.

(ii) Specific and useful extraction of amplitude modulated ultrasound induced blood glucose concentration related information embedded signals from the transmitted infrared light.

The combined use of ultrasound and infrared light provides a new dimension for noninvasive detection of blood glucose levels. Few unwanted, erroneous signals had been obtained due to various types of factors like skin tissue related pigmentations, background light intensity, pulsatile flow of blood, machine related drifts, time dependent drifts, motion related artifacts, other physiological or pathological factors, etc. All these interfering sources modify the blood tissue complex induced bio signals and provide erroneous impact over blood glucose level determinations.

Table 1. Shows the comparison of invasive (reference) and noninvasive (predicted) Blood Glucose Levels (BGL) as obtained from the Normal subjects during Phase I and II experimental pilot studies respectively

NORMAL SUBJECTS	BLOOD GLUCOSE LEVEL (mg/dl)							
	Phase I				Phase II			
	BGL (mg/dl) After Overnight Fasting		BGL (mg/dl) 2hr After Meal Consumption		BGL (mg/dl) After Overnight Fasting		BGL (mg/dl) 2 hr after 75 gm/100ml Glucose Solution Consumption	
	Invasive method	Noninvasive method	Invasive method	Noninvasive method	Invasive method	Noninvasive method	Invasive method	Noninvasive method
SUBJECT1	81	86	103	136	79	82	121	130
SUBJECT2	85	89	136	139	87	83	129	132

Table 2. Shows the comparison of invasive (reference) and noninvasive (predicted) Blood Glucose Levels (BGL) as obtained from the Prediabetic subjects during Phase I and II experimental pilot studies respectively

PREDIABETIC SUBJECTS	BLOOD GLUCOSE LEVEL (mg/dl)							
	Phase I				Phase II			
	BGL (mg/dl) After Overnight Fasting		BGL (mg/dl) 2hr After Meal Consumption		BGL (mg/dl) After Overnight Fasting		BGL (mg/dl) 2 hr after 75 gm/100ml Glucose Solution Consumption	
	Invasive method	Noninvasive method	Invasive method	Noninvasive method	Invasive method	Noninvasive method	Invasive method	Noninvasive method
SUBJECT3	101	100	177	167	106	116	151	203
SUBJECT4	107	109	169	164	109	102	171	183
SUBJECT5	115	112	165	162	107	104	189	171
SUBJECT6	107	104	161	156	101	111	167	163
SUBJECT7	113	108	153	158	110	105	193	173
SUBJECT8	110	114	181	173	96	126	160	223
SUBJECT9	98	103	191	172	112	120	147	202
SUBJECT10	105	110	171	155	117	112	157	189

5. Conclusions

The hybridized potential aspect of utilizing amplitude modulated ultrasound and Infra Red technique for determining noninvasive blood glucose levels had been reported in this research paper. For cross validations of acquired noninvasive BGL values, the invasive glucometer of Roche diagnostics had been applied here. Furthermore, the 940nm LED and 40 kHz-generating central frequency based Ultrasound Transmitter forms the main instrumental base for this noninvasive technology. For validating the performance of noninvasive blood glucose detecting technology the Error Grid Analytical approaches had also been applied here. Error Grid Analysis shows that all the invasive (reference) and noninvasive (predicted) BGL values occupy within the medically significant A and B zones.

At present all new noninvasive BGL determining techniques requires invasive glucose sensors for calibration purposes. Hope our nascent noninvasive BGL determining technology will be successful in near future with all the aspects.

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