Everything You Wanted to Know About Noninvasive Glucose Measurement and Control

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Abstract

Diabetes is a chronicle disease where the body of a human is irregular to dissolve the blood glucose properly. The diabetes is due to lack of insulin in human body. The continuous monitoring of blood glucose is main important aspect for health care. Most of the successful glucose monitoring devices is based on methodology of pricking of blood. However, such kind of approach may not be advisable for frequent measurement. The paper presents the extensive review of glucose measurement techniques. The paper covers various non-invasive glucose methods and its control with smart healthcare technology. To fulfill the imperatives for non-invasive blood glucose monitoring system, there is a need to configure an accurate measurement device. Noninvasive glucose-level monitoring device for clinical test overcomes the problem of frequent pricking for blood samples. There is requirement to develop the Internet-Medical-Things (IoMT) integrated Healthcare Cyber-Physical System (H-CPS) based Smart Healthcare framework for glucose measurement with purpose of continuous health monitoring. The paper also covers selective consumer products along with selected state of art glucose measurement approaches. The paper has also listed several challenges and open problems for glucose measurement.

Index Terms

Smart Healthcare, Internet-of-Medical-Things (IoMT), Healthcare Cyber-Physical System (H-CPS), Diabetes, Glucose measurement, Non invasive measurement, Spectroscopy and calibration

I. INTRODUCTION

The glucose is considered as important source of energy for the human body. The body requires blood glucose of normal range (80 to 150 mg/dl) in order to perform the daily activities [1]. However, the higher or lower value of glucose would lead to various complication inside the body. At the same time, insulin is also crucial hormone generated inside the body from the food intake. The glucose is produced from the food digestion which enters the blood cell to supply the energy and also helps in the growth. In case, the insulin is not properly generated then blood would accumulate the high glucose concentration. Fig. 1 illustrates the closed-loop of glucose generation and consumption in human body [2]. A consistently high blood glucose concentration is possible if the generation of α cells is larger as compared to that of the β cells. Because of this condition, enough insulin is not secreted in the body for glucose consumption. This condition refers to as the Diabetes Mellitus. Diabetes is termed as chronic disease which defines high blood glucose levels inside the human body. The unbalanced glycemic profile is main reason for the cause of diabetic condition. The rate of prevalence for Non Communicable Diseases (NCD)/Chronic Disease has increased with many fold from last several years. There are around 20 million death reported yearly through cardiovascular disease, for which high blood glucose is significant predisposing factors. Moreover, people with diabetes are more affected during the viral pandemic outbreaks [3], [4], [5].

There has been exponential growth of diabetes patients over past few years because of obesity, unhealthy diet plan, old-age population, and inactive lifestyle. Diabetes is considered as one of the fastest growing
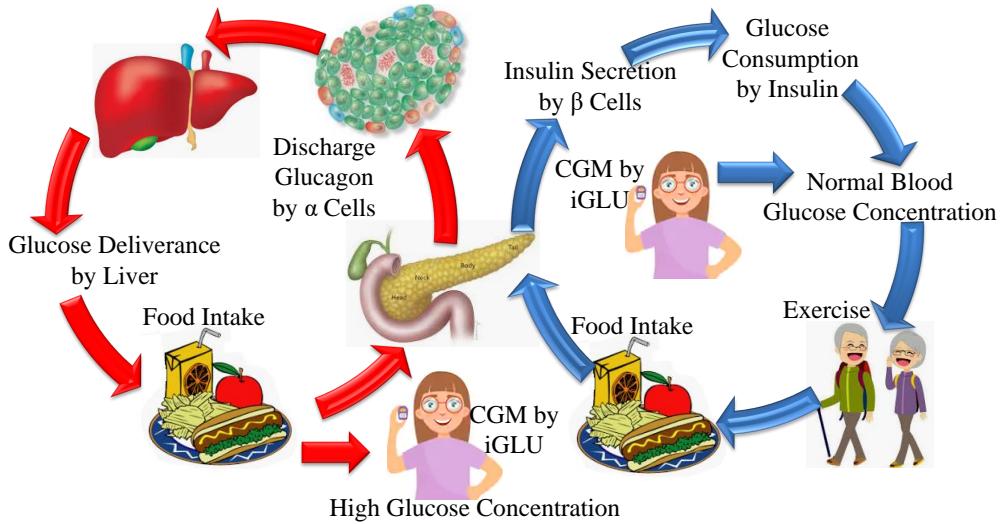
Fig. 1: Illustration of the closed loop form of glucose generation and consumption [2].

health challenges, with the number of adults living with diabetes having more than tripled over the past 2 decades (Refer Fig. 2) [6]. The prevalence of diabetes around the world was 9.3% during 2019 with approximate 463 million people. It is expected to rise to 578 million by 2030 with 10.2% prevalence rate and the same would be 10.9% with 700 million population by 2045. It has been observed that prevalence is quite higher in urban to 10.8% whereas 7.2% in rural region. Almost half of the diabetes patients unaware about their situation due to lack of knowledge. The diabetes has indeed global outbreak which has affected presently almost 1 in 10 people around the world. It is projected that more than 0.5 billion adults would suffer from the diabetes in the next decade [7]. As per the report from International Diabetes Federation (IDF), the death from diabetes has large number than combined death from Malaria (0.6mio), HIV/AIDS (1.5mio) and tuberculosis (1.5mio) [8]. There are around 8 million new patients are being added to diabetic community every year. This has grown the demands immensely for the effective diabetic management. It is important to monitor the blood glucose over time to time for avoiding late-stage complication from diabetes. This has necessitate the design of various reliable and robust solutions for efficient diabetes management. The market of diabetes devices has also grown rapidly with significant requisite for frequent glucose measurement for better glycemic profile control.

Diabetes is one of the major chronic disease which has long-term impact of the well-being life of a person. Diabetes Mellitus (DM) is considered as physiological dysfunctions with high blood glucose because of insufficient insulin, insulin resistance, or excess generation of glucagon [9]. It is the critical health issue of 21st century. Type 2 Diabetes (T2DM) has shown rapid growth around the world from past few years. Any form of diabetes may lead to complications in various body parts which increase the possibility of premature death. The higher value of blood glucose known as hyperglycemia, would lead to thickening of blood vessels which could resulted in kidneys damage and loss of sight and some times even to these organs failure. Diabetes is also associated with limb amputation, peripheral vascular diseases and myocardial. Contrary, the low blood glucose defined as hypoglycemia may occur in Type 1 Diabetes Patients (T1DM) for excessive insulin dosage [10]. The most common symptoms for hypoglycemia pateints are dizziness, sweating and fatigue and in the worst case it can lead to coma and death. The diabetic patients would have several common symptoms such as thirsty, tiredness, changes in vision, consistently hungriness, unexpected weight loss and the excretion of urine within short durations [11]. If the diabetes remain untreated over the period of time, it may cause blindness, heart stroke, kidney disease, lower limb amputation and blindness. It would lead to increase the probability of death almost
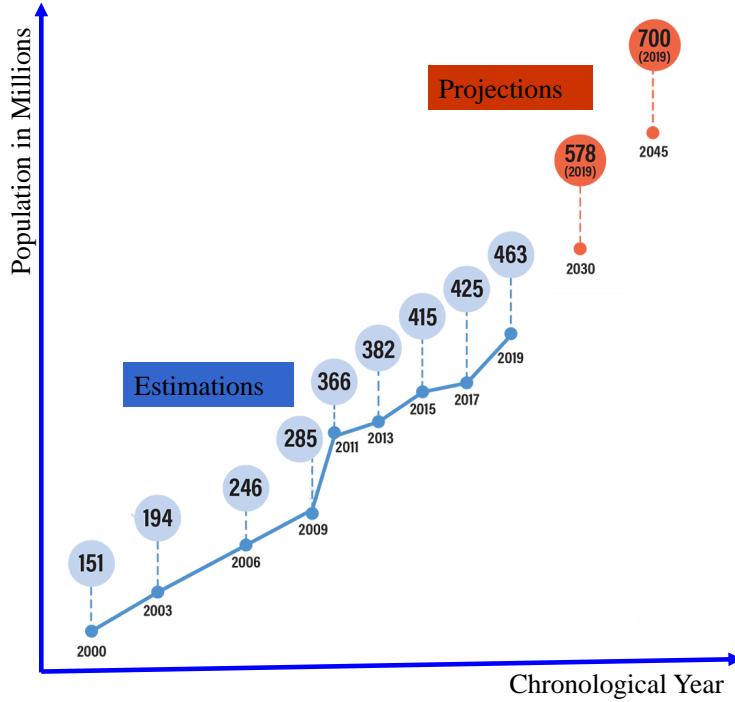
Fig. 2: Global trend of Diabetes, Adopted from [6].

50% higher in comparison of the patients without diabetes. The diabetes also brings the additional financial burden for the treatment and point of care. The diabetic patients could also result in loss of productivity at workplace and may lead to disability. There are several health issues which may also arise from diabetes like depression, digestive problem, anxiety disorders, mood disorder and eating habits change. The diabetes could be controlled with proper diet plan, through some physical exercise, insulin dosage and medicines. The early stage of diabetes is possible to control with oral medicines. The diabetes control also helps to reduce the associated risk of high blood pressure, cardiovascular and amputation.

The rest of the article is organized in the following manner: Section II briefly presents different types of diabetes while making case for the need of glucose level monitoring. Section III presents overview of various types of glucose-level measurement mechanisms. Section IV provides details of available approaches for noninvasive glucose-level monitoring. Section V has discussions on various post-processing and calibration techniques for noninvasive glucose-level monitoring. Section VI briefly discusses various consumer products for noninvasive glucose level measurement. Section VII presents the approaches for glucose-level control and corresponding consumer products. Section VIII provides the Internet-of-Medical-Things (IoMT) perspectives of glucose level measurements and control in healthcare Cyber-Physical Systems (H-CPS) that makes smart healthcare possible. Section IX outlines the shortcomings and open problems of glucose-level measurements and control. Section X summarizes the learning of this comprehensive review work.

II. THE HEALTH ISSUE OF DIABETES AND NEED FOR GLUCOSE-LEVEL MEASUREMENT

This Section presents details of different types of diabetes, the health issues arise due to diabetes, while making case for the need of glucose level monitoring.

A. Types of Diabetes

The diabetes occurs because of insufficient insulin with respect to glucose generated inside the body. The insulin from body is either insufficient or not any which is generated from beta cells of the pancreas. In case of diabetes, the cells of liver, muscles and fat unable to balance glucose insulin effectively. The diabetes are classified mainly in three categories: Type 1 diabetes, Type 2 diabetes and gestational diabetes (Refer Fig. 3) [12].
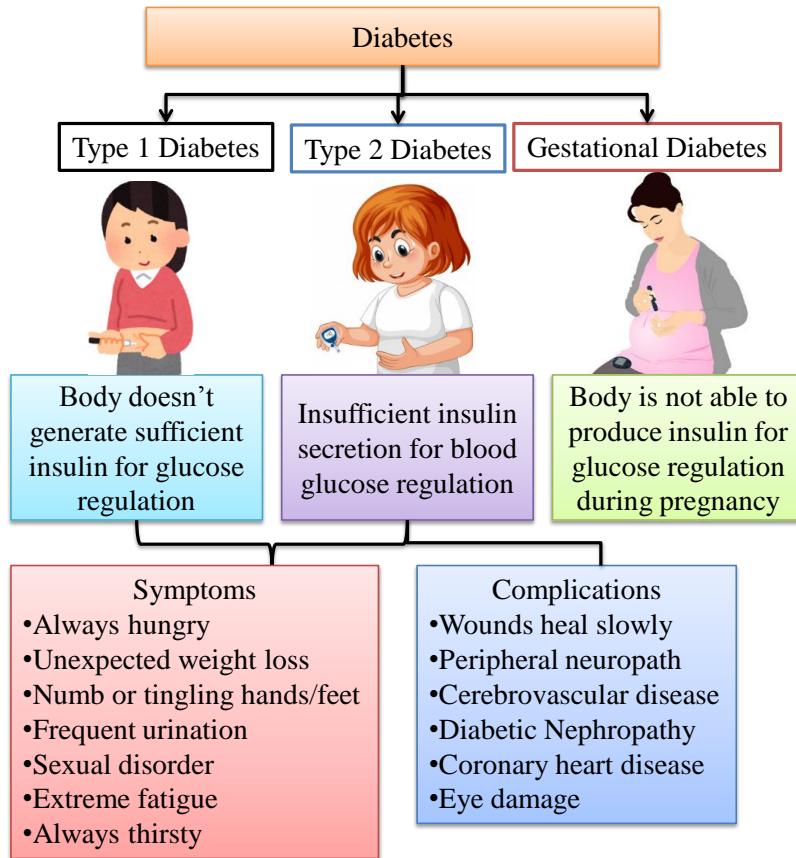

Fig. 3: Different types of diabetes and their symptoms.

For diabetes of type-1, the pancreas does not produce insulin inside the body which is resulted in a weak immune system. This results in a person who is unable to generate insulin naturally [2], [13]. In case of type 2 diabetes, the amount of insulin from pancreas is not sufficient to maintain glycemic profile of the body. Gestational diabetes usually occurs in a pregnant woman at later stage of the delivery. in the year 2020, total 2 billion adults around the globe suffers from overweight, and 300 million of them are obese. In addition, a minimum of 155 million children in the world is overweight or obese. It is projected that the prevalence of hyperglycemia is 8.0% and expected to increase to 10% by 2025 [7]. There has been concern for diabetic people specially in developing countries due to increase in Type 2 Diabetes cases rapidly at earlier age which have overweight children even before puberty. Whereas for developed countries, most of people have high blood glucose at age around 60 years. Most frequently affected are at middle aged between 35 and 64 in developed countries [6]. In 2019, 69.2 millions population in India had Type-2 diabetes. Approximately 2.35 million adults have Type-1 diabetes. In general, there are around 5% adults have been considered for Type-1 diabetic patients while the others 90-95% are of Type-2 diabetic patients. Type-1 diabetic patient must have insulin to control the blood glucose level.

Type-2 diabetic patients can control their glucose level by following an optimized diet with medication and a regular physical exercise schedule.

B. The Health Crisis due to Diabetes

The diabetes mainly occurs due to unbalanced glucose insulin level of the body where insulin is demolished and muscles and cells are not able to generate insulin properly [14], [13]. The probability of death would also increase upto 50% in comparison to non-diabetes case. The control action of the diabetes would be possible using proper precautionary measure after frequent glucose measurements. Therefore, there is a real need for smart healthcare solution which would provide instant self measurement of blood glucose with high accuracy.
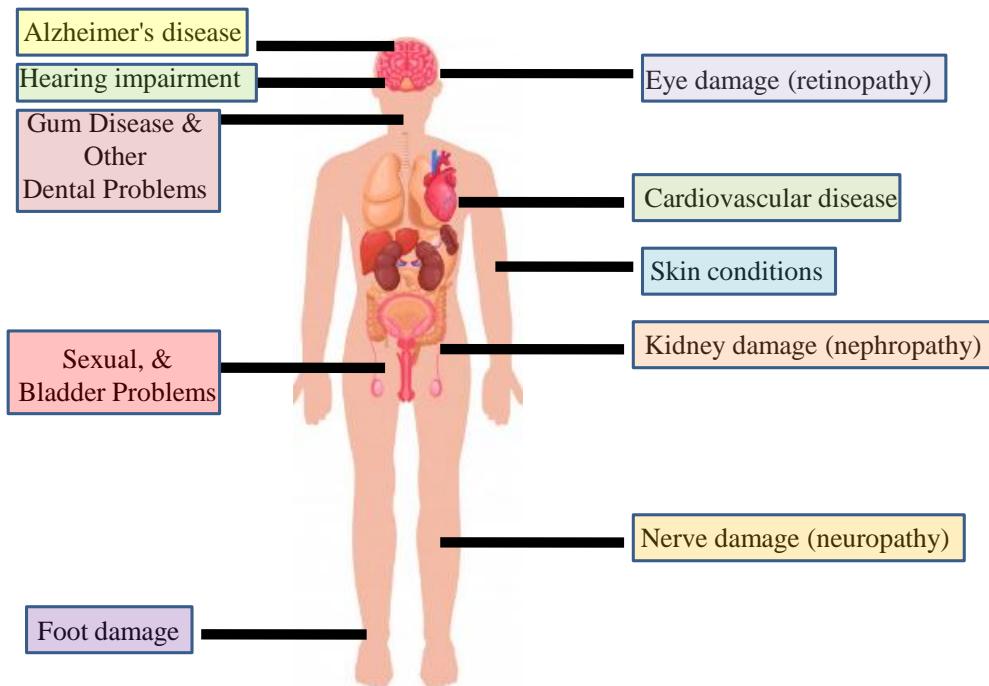

Fig. 4: Diseases in human body due to diabetes

Hyperglycemia is the major issue which has been considered by several health organizations at worldwide level [15], [16]. There are several attempts which have been used for glucose measurement [17]. There have been substitutional work using various techniques to make the device more familiar with clinicians and patients [18]. Diabetes is possible in the age group 18 to 80 years usually [19], [20]. The normal range of glucose is in the range of 70-150 mg/dL and pathophysiological would be from 40 mg/dL to 550 mg/dL [21]. One of the emerging issues is to design the glucose measurement device for continuous health care monitoring [22]. The devices for monitoring the glucose level are available for last two decades [23].

C. Glucose Measurement: A Brief History

The glucose meter (aka glucometer) is a portable medical device for predicting the glucose level concentration in the blood [24], [25]. It may also be a strip based dipped into any substance and determined the glucose profile. It is a prime device for blood glucose measurement by people with diabetes mellitus or hypoglycemia. With the objective of glucose monitoring device advancement, the concept of the biosensor has been proposed earlier in 1962 by Lyons and Clark from Cincinnati. Clark is

known as the "father of biosensors", and modern-day glucose sensor which is used daily by millions of diabetics. This glucose biosensor had been composed with an inner oxygen semipermeable membrane, a thin layer of GOx, an outer dialysis membrane and an oxygen electrode. Enzymes could be gravitated at an electrochemical detector to form an enzyme electrode [26]. However, the main disadvantage of first-generation glucose biosensors was that there was the requirement of high operation potential of hydrogen peroxide amperometric measurement for high selectivity. The first-generation glucose biosensors were replaced by mediated glucose biosensors (second-generation glucose sensors). The proposed biosensors till present scenario represent the advancements in terms of portability of device and precision in measurement. But, due to some environmental and measurement limitations; these biosensors were not taken for real-time diagnosis. The history of glucose measurement is shown in Fig. 5 [27].
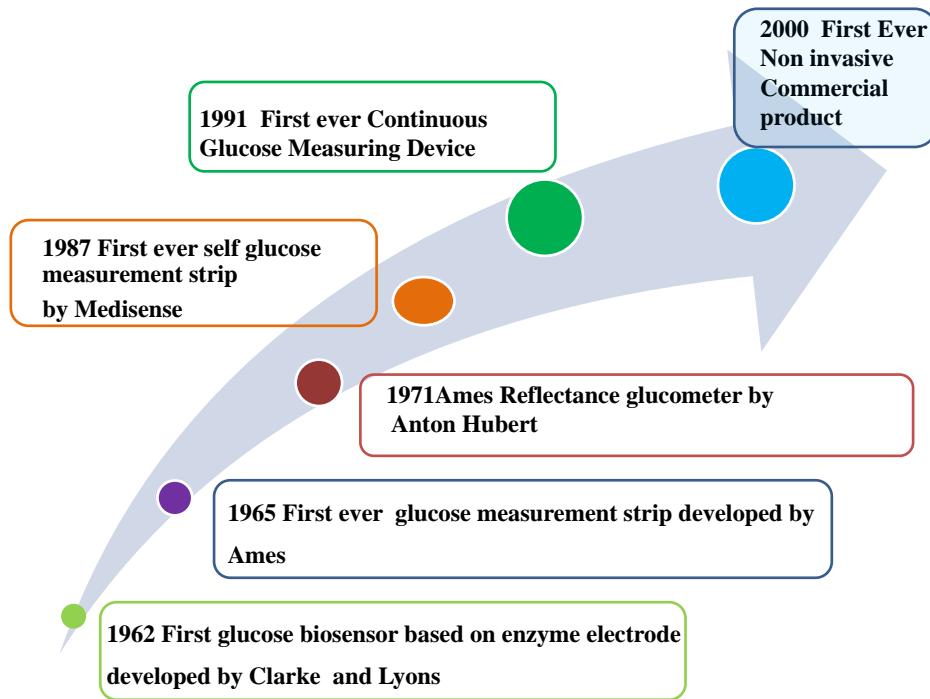
Fig. 5: History of Glucose Measurement.

D. Glucose Measurement Technique

Presently, the glucose monitoring is carried out either laboratory based technique or home based monitoring. These both approaches are invasive in nature which provides discomfort by blood pricking and it only helps to measure the glucose measurement at that point of time. It is also not very convenient for the user to take out blood samples multiple times in a day and many patients are reluctant to opt such type of solution. Therefore, significant changes of glycemic profile may go unnoticed because of unanticipated side effects and low compliance from the patients. This could impact on improper insulin dosage and unknown food ingredient. However, they are reliable solution due to their good sensitivity and higher accuracy for glucose measurement [28], [29].

The novel approach for glucose measurement has been explored from past several years which is based on the principle of physical detection than conventional chemical based principle. Such non-invasive based method does not require the blood sample but uses the interstitial fluid (ISF) for glucose molecule detection. There are several attempts in the same direction for glucose measurement through sweat, saliva, tears and skin surface [30]. However, the main challenge is to have precise measurement, good sensitivity and
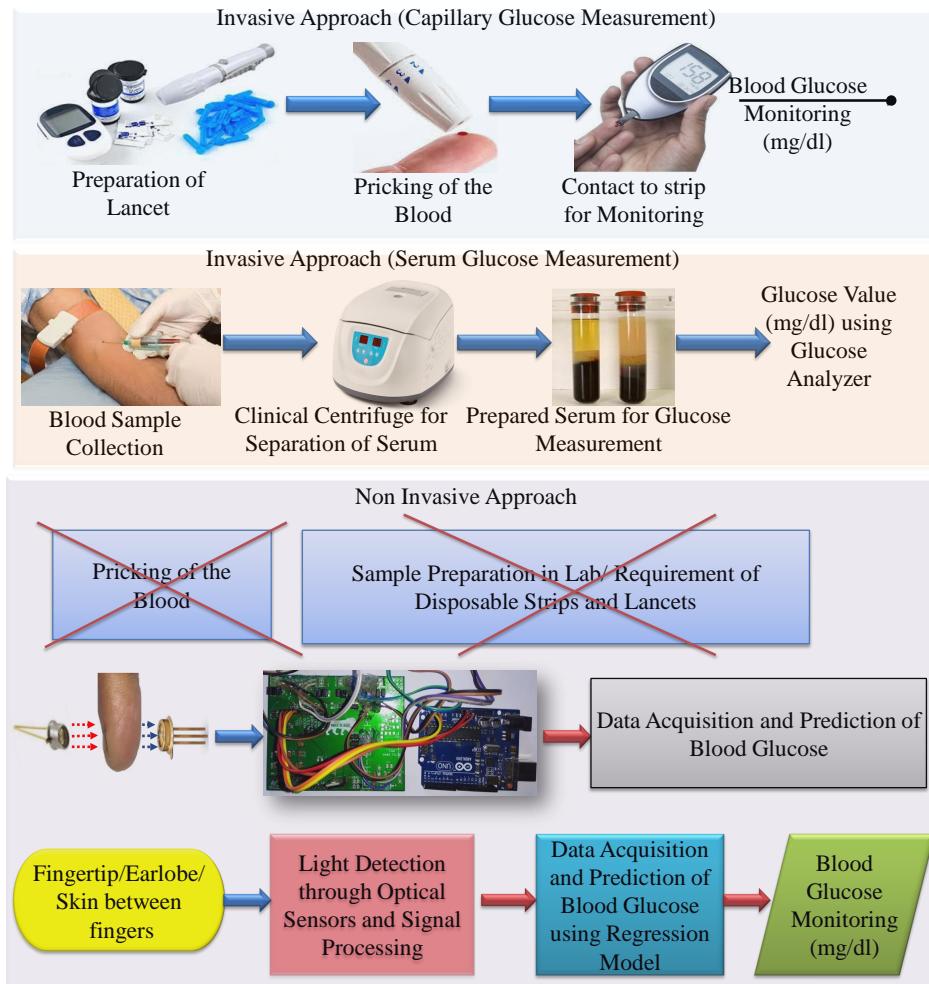
Fig. 6: Invasive versus Noninavsive Glucose Measurement.

reliability from such measurement. Such approach could be suitable for Continuous Glucose Measurement (CGM) and self monitoring purpose. Such CGM techniques would provide the frequent measurement in a day which would helpful for better glucose control and also for the necessary preventive actions for hyperglycemia and hypoglycemia patients. Such kind of techniques would also support for the dietician and healthcare provider to prepare proper diet plan according to glucose fluctuation for the patient.

E. The Need for Continuous Glucose Measurement (CGM)

The measurement of glucose could be done through non-invasive, semi (or minimal) invasive and invasive approach. The frequent measurement may not be possible using invasive method which can cause trauma. The semi-invasive and non-invasive could be useful for Continuous Glucose Measurement (CGM) without any pricking of the blood. However, the non-invasive glucose measurement is most suitable technique which helps to measure the blood glucose painlessly [31].

CGM assist to have proper blood glucose level analysis at each prandial mode. It helps to measure glucose insulin level after insulin secretion,hysical exercise or subsequent to medication. The frequent glucose reading also helpful to endocrinologist for providing the proper prescription. It mainly helps for type 1 diabetic patients to take care of their insulin dosage over the period of time. The proper diet management could be possible with help of recurrent glucose monitoring and flow diagram of CGM is

shown as Fig. 7 [28], [29]. The CGM is useful for the patients for frequent glucose measurement over the period of time. This would helpful to identify the average blood glucose value for the last 90 days, by which glycated haemoglobin (HbA1c) can be determined.
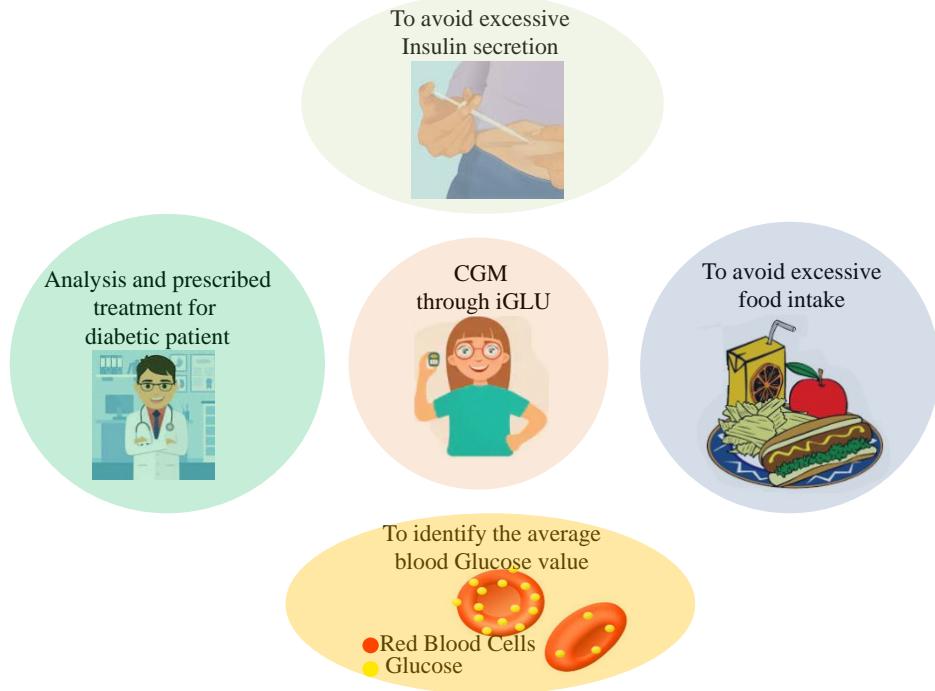

Fig. 7: The objectives of continuous glucose monitoring.

III. APPROACHES FOR GLUCOSE-LEVEL MEASUREMENT: A BROAD OVERVIEW

This Section discusses an overview of various types of glucose-level measurement mechanisms. In the past, many works has done for the glucose measurement. They can be invasive, non-invasive, or minimally invasive. A lot of works has been completed based on the non-invasive technique. They are technically based on optical and non-optical methods. Some of the optical techniques used methods based on Raman Spectroscopy, NIR spectroscopy, and PPG method. A taxonomy of the different methods is provided in Fig. 8 [25], [28], [29], [32].

A. Invasive Methods

Many commercial continuous blood glucose measurement devices use cost-effective electrochemical sensors [33]. They are available to respond quickly for glucose detection in blood [34]. Lancets (for pricking the blood) is used at the primary stage for blood glucose monitoring for various commercial devices available in the market [35]. The frequent measurement through the process is so much panic due to picking the blood sample from the fingertip more than 3-4 times in a day for frequent monitoring[36]. The low invasive biosensor for glucose monitoring has been developed with glucose oxidase that require around 1mm penetration inside the skin for measurement [37]. The technique of photometric was attempted to detect glucose with help of small blood volumes [38].

B. Minimally Invasive Methods

The minimally invasive method using prototype sensor was developed to have frequent monitoring of glucose tissue [39]. The sensor is wearable and is implanted on membrane which contains the immobilized
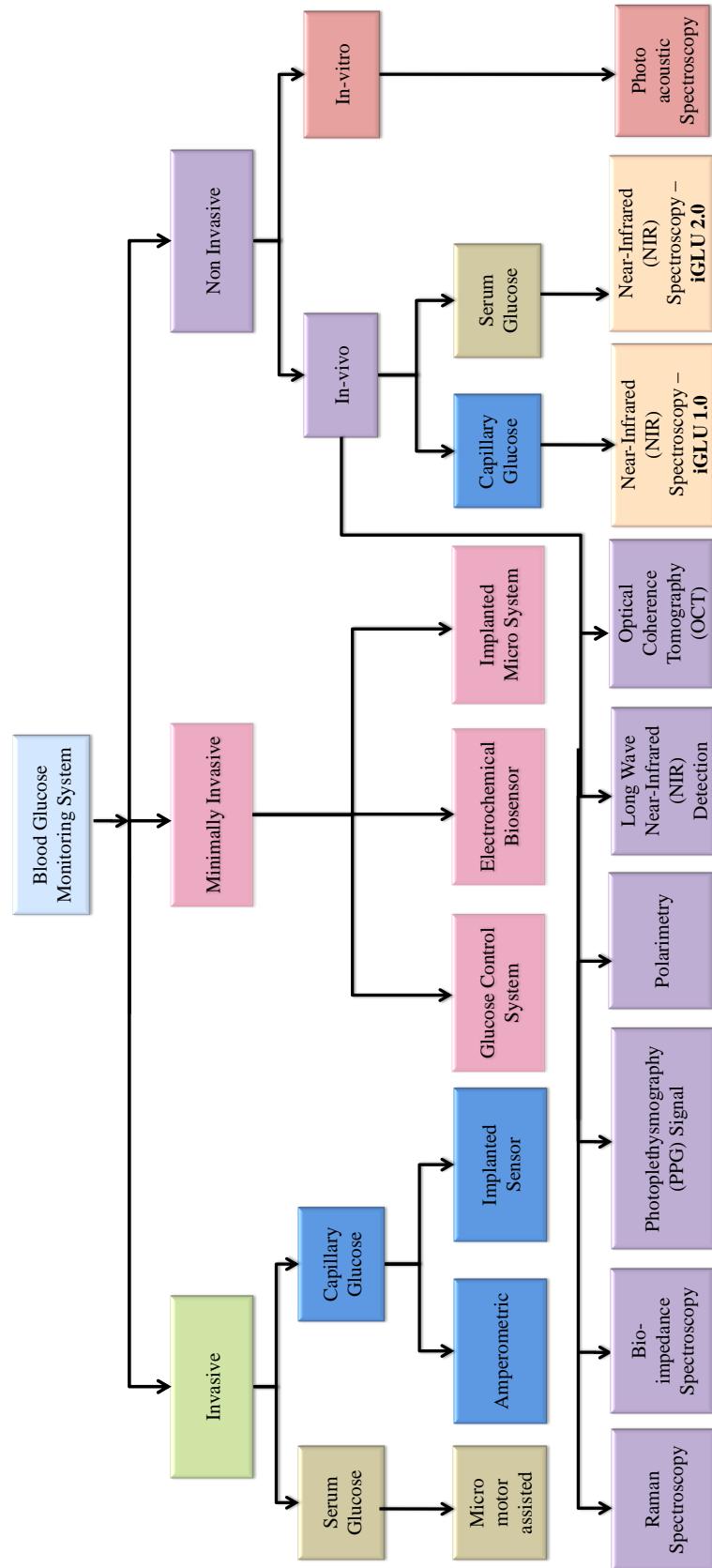
Fig. 8: An overview of the Glucose Measurement Options [32], [28], [29], [25].

glucose oxidase. The glucose monitoring through implantable devices were developed [40]. The semi or minimal invasive method using biosensors designed for diabetes patient [41]. The wearable micro system explored for frequent measurement of glucose [42]. Similarly, there was an attempt of continuous glucose monitoring with help of microfabricated biosensor through transponder chip [43]. The signal coming out of transponder chip was used for the calibration for semi invasive approach of Dexcom sensor [44]. The diabetes control explored by glucose sensor with artificial pancreas system [45]. The minimal invasive approaches have limitations mainly accuracy and may have shorter life span for monitoring.

This is a *wearable microsystem* for the continuous monitoring of the blood glucose. It's a minimally invasive method for the glucose monitoring. The main idea behind this is that it uses micro-actuator which consists the shape memory alloy (SMA) for the extraction of the blood sample from human skin [46]. An upgraded version of SMA is used for the implementation of PCB. Because of it's feasibility and performance, it can be considered as the first wearable device for the glucose monitoring but it is large in size which makes it inconvenient.

C. Non-invasive Methods

Non-invasive measurement would mitigate all the previous issues and would provide painless and accurate solutions [47], [48]. The non-invasive glucose measurement solution for smart healthcare had developed through portable measurement [31]. A lot of approaches have been introduced for glucose measurement [49]. The non-invasive measurement are more convenient for continuous glucose measurement in comparison to invasive method and semi invasive [47], [48]. The glucose measurement with help of optical method has observed more reliable and precise in the literature [50]. The popular optical methods include non-invasive measurement such as Raman spectroscopy, near infer-red spectroscopy,polarimetric,scattering spectroscopy [51], photoacoustic spectroscopy [52] etc. For the development of a non-invasive measurement device, it is considered by the researcher that the device would be much convenient for the user's perspective [53], [54]. Calibration of the blood glucose to interstitial glucose dynamics have been considered for the accuracy of continuous glucose monitoring system [55], [56]. Several calibration algorithms have been developed and implemented for portable setup [57]. There has been several concious efforts towards the development of the self-monitoring system [58].
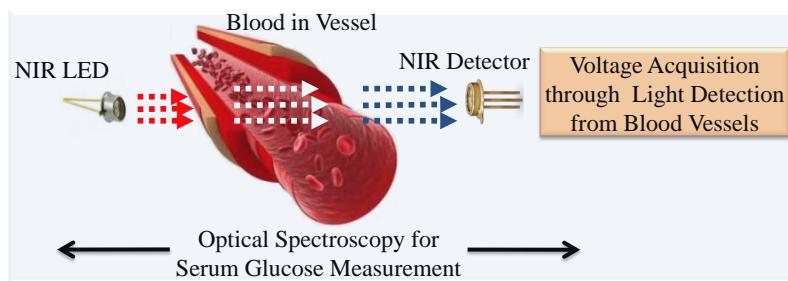

Fig. 9: NIR Spectroscopy Mechanism of Serum Glucose Measurement.

D. Invasive Versus Non-invasive Glucose Measurements: The Trade-Offs

Recent glucose measurement methods for the ever-increasing the diabetic patients over the world are invasive, time-consuming, painful and a bunch of the disposable items which constantly burden for the household budget. The non-invasive glucose measurement technique overcomes such limitations, for which this has become significantly researched era. Although, there is tradeoff between these two methods which is represented in Fig. 10.
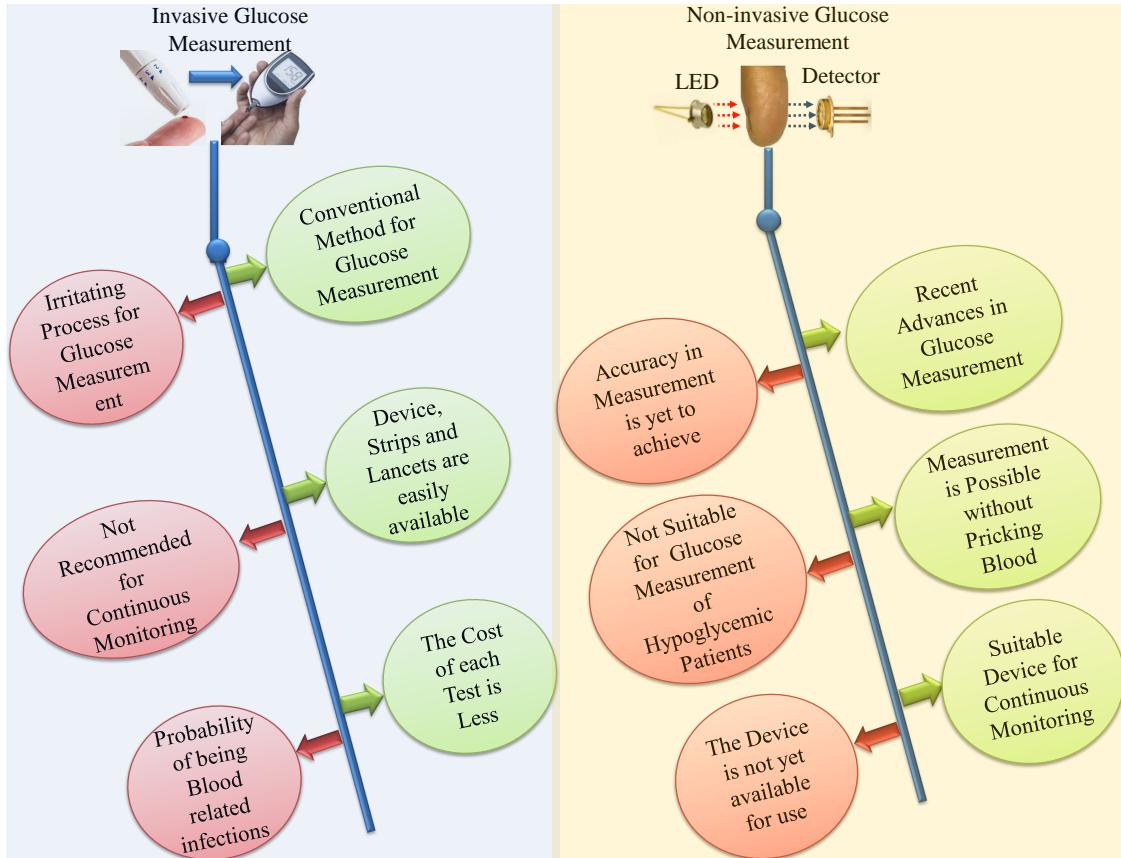
Fig. 10: Representation of Tradeoffs between Invasive and Non-invasive Glucose Measurement.

E. Capillary Glucose versus Serum Glucose for Noninvasive Measurement

The serum glucose value is precise which is always close to actual blood glucose measurement with compare to capillary glucose level. Traditional approaches able to measure capillary glucose instantly but the serum glucose measurement identification is difficult. It is observed that the glucose level of capillary is always higher than serum glucose. The accurate measurement of blood glucose would help for appropriate control actions. Therefore, it is really important to measure the serum glucose than the capillary glucose which is more reliable for medication. Capillary blood glucose measurement has been used widely than serum glucose estimation for medication purpose. The serum glucose is not possible for continuous glucose measurement or frequent measurement for diabetes. The blood glucose is controlled in much better way if one can measure serum glucose at regular interval. Laboratory analysis of glycosylated haemoglobin (HbA1c) which provides 6-8 weeks blood glucose measurement is also being done through the serum blood only. For the non-invasive measurement point of view, serum and capillary glucose are being measured through the optical spectroscopy. The mechanism of blood glucose measurement is based on received IR light after absorptions and scattering from glucose molecules which flow in blood vessels. The methodology is quite similar for both types of glucose measurement except the post-processing computation models which are necessary for blood glucose estimation.

F. Non-invasive Method for Glucose Level Estimation by Saliva

As the most convenient method to estimate glucose level is via saliva [59] and is used for children and adults. This saliva has specific type of parts which can be defined as: (1) gland-specific saliva and (2)

whole saliva. The collection of the Gland-specific saliva is done by individual glands like parotid, Sub mandibular, sublingual, and minor salivary glands. This diagnosis is done by the history of the patient in terms of associated risk factors, family history, age, sex, duration of diabetes,and any associated illness. Other Glucose measuring methods consist of measurement using photo-metric glucometers requiring very small sample volumes [60]. The basic approach is based on the reaction of the chemical test strip that reacts with sample. Measurement is done by capturing the reflections of the test area and then glucose level is estimated. It requires validation in large number of patients.

IV. APPROACHES FOR NONINVASIVE GLUCOSE-LEVEL MEASUREMENT

This Section presents detailed discussions of various available approaches for noninvasive glucose-level monitoring. There have been several efforts for noninvasive glucose measurement using optical techniques [27], [29], [61], [62]. These techniques are mainly based on various spectroscopy based methods. For the development of a non-invasive measurement device, it is considered by the researcher that the device would be much convenient for the users perspective. Fig. 11 presents summary of various types of noninvasive glucose measurement techniques, whereas their comparative perspectives are presented in Fig. 12. A qualitative comparative perspective of various noninvasive methods is summarized in Table I.
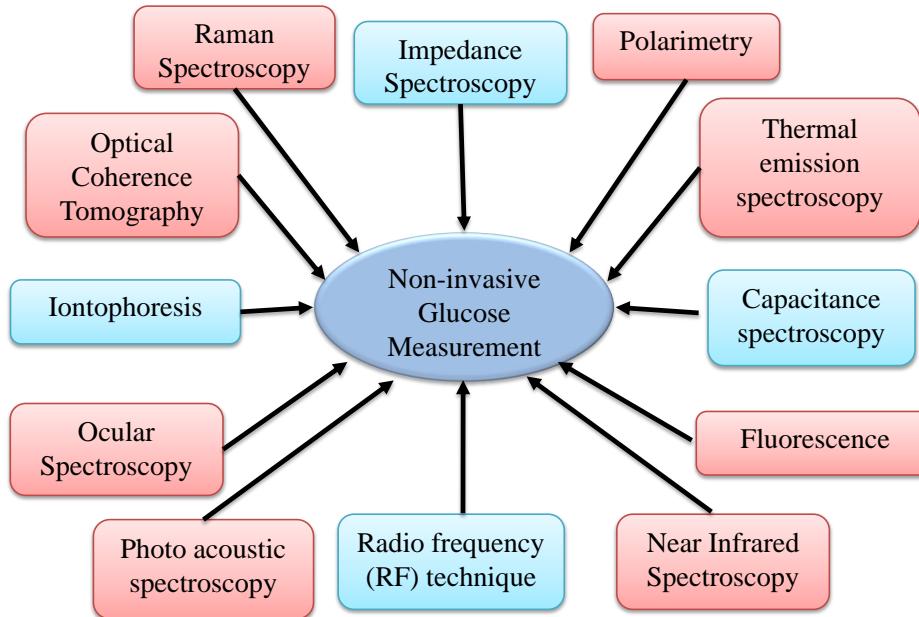

Fig. 11: Various spectroscopy techniques for noninvasive glucose measurement.

TABLE I: Qualitative comparison of various noninvasive glucose-level monitoring methods.

| Technique	Advantages	Disadvantages
Near Infra-Red (NIR)	• The signal intensity is directly proportional to glucose molecule • The glucose detection concept would work with other interfacing substance such as plastic or glass	• The glucose signal weak comparatively so complex machine learning model is required for interpretation • High scattering level
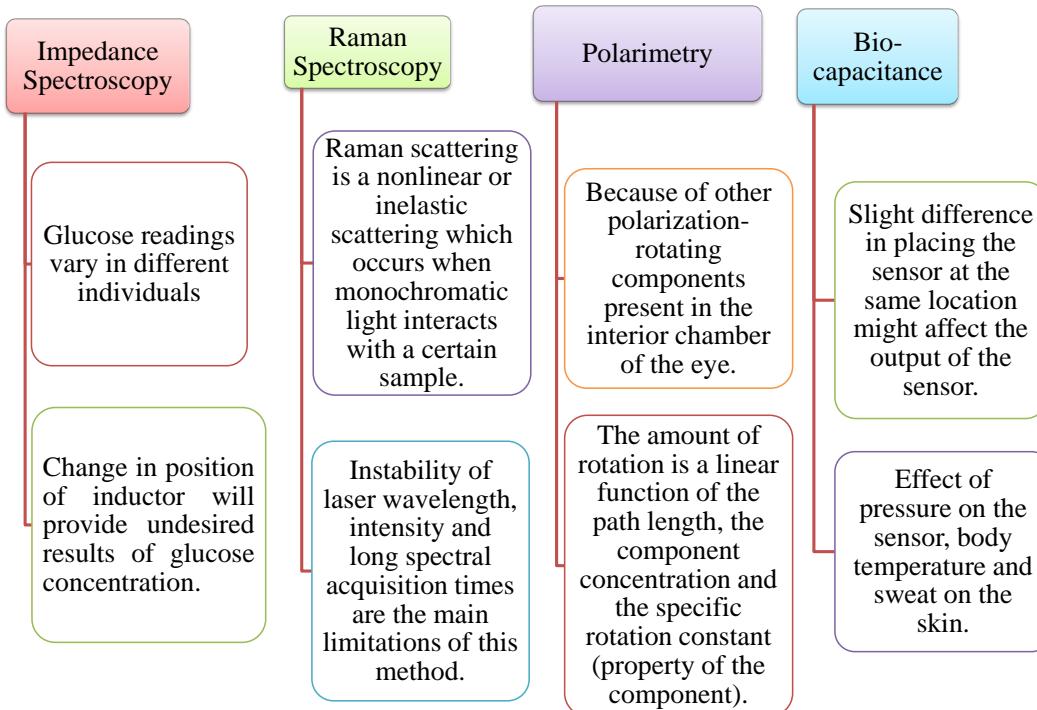
Fig. 12: Comparative Perspective of Various popular spectroscopy techniques for noninvasive glucose measurement.

Technique	Advantages	Disadvantages
Mid Infra-Red (MIR)	- The glucose molecule absorption stronger - Low scattering	- The light has limited penetration with tissue - Noise is present in the signal so water and other non-glucose metabolites would be detected.
Far Infra-Red (FIR)/Thermal emission spectroscopy	- Frequent Calibration is not required - Least sensitive towards scattering	- The radiation intensity depends on temprature and substance thickness - Strong absorption with water so it is difficult to have precise glucose measurement
Raman Spectroscopy	- Less sensitivity towards temperature and water - High specificity	- Requirement of the laser radiation source hence it can dangerous cell for CGM - Susceptible towards noise interference so low SNR

Technique	Advantages	Disadvantages
Photo acoustic	- Simple and compact sensor design - Optical radiation will not harmful for the tissue	- Signal is vulnerable towards acoustic noise, temperature,motion etc. - It carries some noise from some non-glucose blood components
Polarimetry	The laser intensity variation will not change much the glucose prediction	- Requirement external laser source and requires proper alignment with eye - sensitive for the change in PH and temperature
Reverse Iontophoresis	- Based on simple enzyme based electrode system - Highly accurate as it measure glucose from interstitial fluid	- Difficult to have proper calibration - Not so user-friendly approach due to passing of the current through skin
Fluorescence	- Highly sensitive for glucose molecule detection due to immune for light scattering - Good sensitivity because of distinctive optical properties	- Very much sensitive for local pH and/or oxygen, - Suffers from foreign body reaction
Bio impedance spectroscopy	- Comparatively less extensive - Easy for CGM	- Prone towards sweating, motion and temperature - Require large calibration period
Millimetre and Microwave sensing	- Deep penetration depth for precise glucose measurement - No risk for ionization	- Poor selectivity - Very much sensitive for physiological parameters such as sweating, breathing and cardiac activity
Optical Coherence Tomography	- High resolution and good SNR - Not vulnerable for blood pressure and cardiac activity	- Glucose value may change as per skin and motion - Suffers from tissue inhomogeneity
Surface Plasma Resonance	Small glucose molecule can be detected due to high sensitivity	- Long calibration process and size is bulky - Glucose value changes with variation in temperature,sweat and motion

Technique	Advantages	Disadvantages
Time of flight and THz Time domain Spectroscopy	• strong absorption and dispersion for glucose molecule	• Lesser depth resolution and longer time for measurement
Metabolic Heat Conformation	• Uses the concept of well-known various physiological parameters for glucose prediction	• Sensitive towards variation in temperature and sweat
Electromagnetic sensing	• low-cost and can be easily miniaturized • No risk of ionization	• Lack of selectivity due to dielectric constant is mainly affected with other blood components • More sensitive for the slight change of temperature
Ultrasound Technology	• Well established technology with not much harm to tissue cell • Long penetration below the skin or tissue	• Limited accuracy with ultrasound only hence mostly used with NIR as multi-model • costly technology for measurement and not useful for CGM
Sonophoresis	• Favourable technology as there is no side-effect to skin • Based on well known enzymatic method	• Error prone due to environmental parameters

A. Near-Infrared (NIR) Spectroscopy

It is well known as Infrared spectroscopy (IR spectroscopy) or vibration spectroscopy where radiation of infrared type are incident on the matter [63], [64]. Various types of IR spectroscopy is shown in Fig. 13. In general, IR spectroscopy includes reflection, scattering and absorption spectroscopy [65]. The wave from IR absorption cause the molecular vibration and generate the spectrum band with wavelength number in cm^{-1} [66].

In this case, the light in the wavelength range of 700nm to 2500nm for Near-infrared region is applied at the object (may be finger or ear lobe) [68]. The light may interact with blood components and it may scattered, absorbed and reflected [69], [70]. The intensity of received light varies as per glucose concentration as per Beer-Lambert law [71], [72] The receiver would help to measure the presence glucose molecule from the blood vessel [73].

1) Long-Wave versus Short-Wave NIR Spectroscopy: The optical detection is useful approach to have precise glucose measurement. FIR (Far infra-red) based optical technique help to get the resonance between OH and CH for first overtone. However, long wave NIR has good performance in vitro testing. In similar way, the fiber-optic sensor is used along with laser based mid-infrared spectroscopy for vitro based glucose measurement. The continuous glucose measurement has been achieved with multivariate calibration model for error analysis [74]. The FIR approach has limitation of shallow penetration in comparison with short wave NIR. The short NIR would help to detect the glucose molecule more
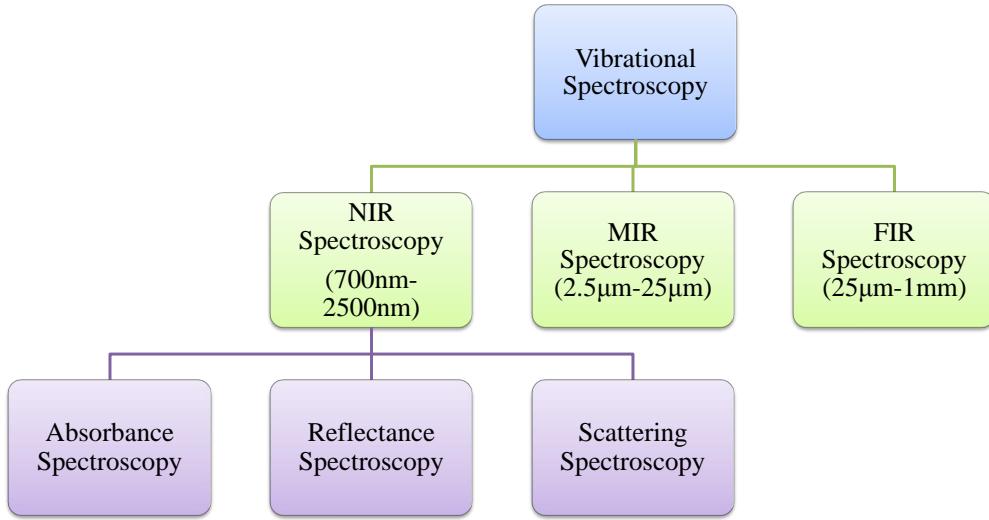
Fig. 13: Classification of vibrational spectroscopy [67].
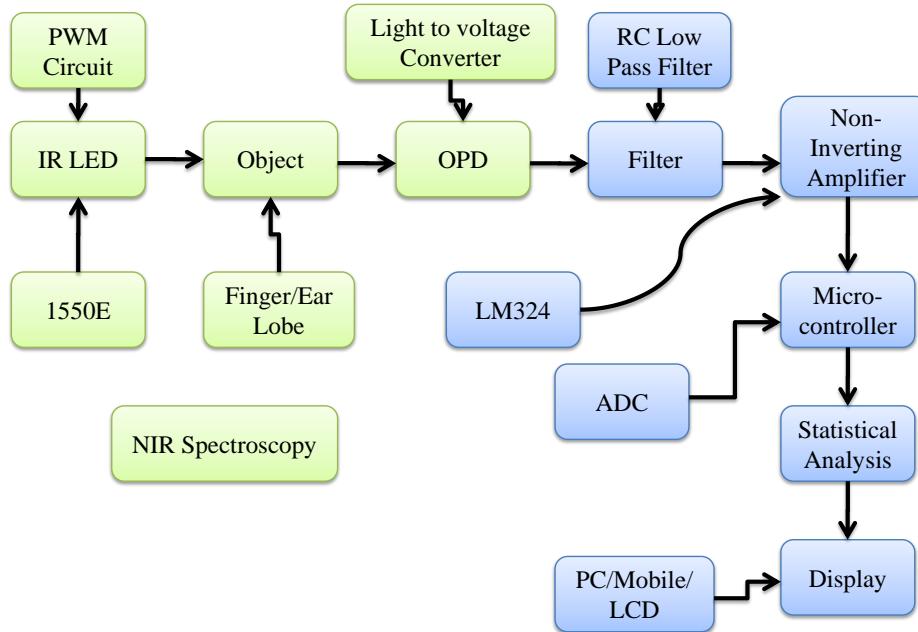
Fig. 14: Block diagram representation of IR spectroscopy.

accurately [75]. The concept of NIR spectroscopy for glucose detection is shown in Fig. 15. The specific wavelength of NIR spectroscopy has already been applied earlier for precise glucose measurement using non-invasive measurement [76]. Some specific wavelength such as 940 nm has been considered for the detection of glucose [77]. The vibration of CH molecule has been observed at 920 nm with NIR spectroscopy [76]. In some other works, the glucose absorption has been validated for the range 1300 to 1350 nm and stretching of glucose has been identified in NIR region [78], [79]. The presence of glucose component has been measured at 1300 nm in the work [80].
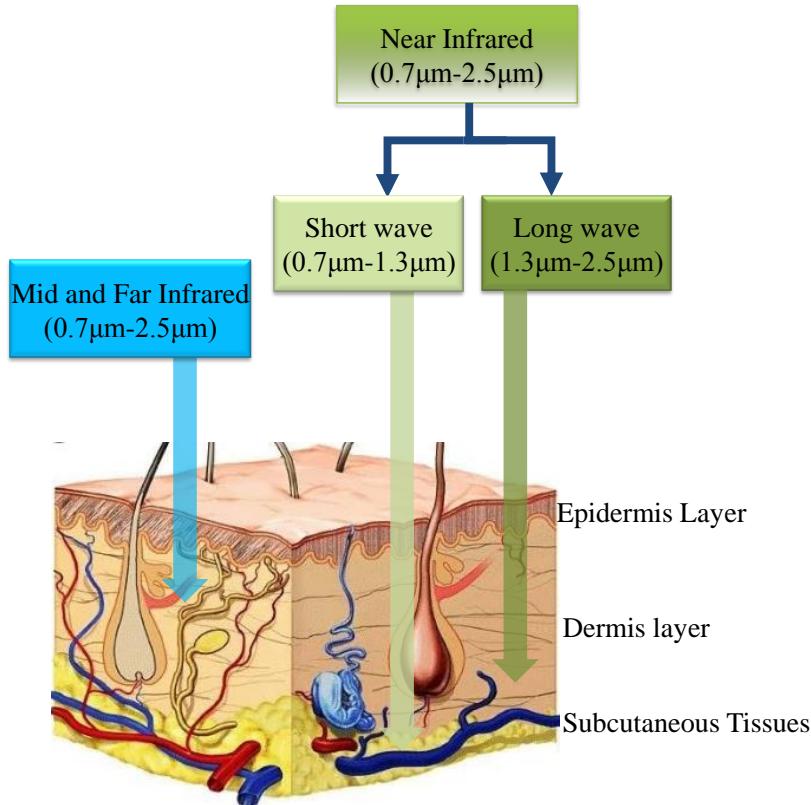
Fig. 15: Penetration depth various Infrared Signals in Human Skin [25], [32].

2) NIR Spectroscopy Based Methods: A method to estimate the non-invasive blood glucose with NIR spectroscopy using PPG has been proposed in literature [81]. This method is performed using NIR LED and photo detector with an optode pair. At NIR wavelengths(935nm, 950nm, 1070nm), PPG signal is obtained by implementation of analog front end system. The glucose levels has been estimated using Artificial Neural Network (ANN) running in FPGA. A microcontroller is used, for the painless and autonomous blood extraction [82]. The ideal system Blood Glucose Measurement (BGM) in which the microcontroller is used to display the blood glucose and for the transmission of blood glucose. A remote device is used for the tracking of the insulin pump which is needed for diabetes management. This type of measurement [83] method uses change in the pressure of the sensitive body part, because it generates the sound waves. The response of the photo acoustic signals will be stronger when glucose concentration is higher. In order to improve SNR and for the reduction of noise to transfer the signal to the computer for further processing,the signal is then amplified. Feature extraction and glucose estimation is estimated by photo acoustic amplitude. In order to gather the photo acoustic signals, two pulsed laser diodes and piezoelectric transducer is used. Utilization of the LASER makes the setup costly and bulky.

3) Non-invasive Blood Glucose Measurement Device (iGLU): In this approach, "Intelligent Glucose Meter (iGLU)" [84] has been utilized for the acquisition of data. This device works on a combination of NIR spectroscopy and machine learning. This device has been implemented using three channels. It uses an Internet-of-Medical-Things platform for storage and remote monitoring of data. In the proposed device, an NIR Spectroscopy is used with multiple short wavelengths [85]. It uses three channels for data collection. Each channel has its own emitter and detector for optical detection. Then the data collection processed by a 16 bit ADC with the sampling rate of 128 samples/second. Regression techniques is used to calibrate and validate the data and analyse the optimized model. The data that is stored on cloud can

be used and monitored by the patients and the doctors. Treatment can be given based on the stored data values. This is a low cost device with more than 90 % accuracy but it does not give real time results.

4) Why NIR is Preferred Over other Noninvasive Approaches?: Glucose measurement has been done using various non-invasive approaches such as impedance spectroscopy, NIR light spectroscopy, PPG signal analysis and so on. But, apart from optical detection, other techniques have not be able to provide the precise measurement. PPG is one of the promising alternative but the PPG signal varies according to blood concentration [86], [87]. It may not be useful to have precise prediction of the blood glucose. The saliva and sweat properties vary from one person to another person. Therefore, it could not be reliable glucose measurement method. The other spectroscopy have been also applied for glucose measurement. However, they are not able to provide portable, cost effective and accurate prediction of body glucose.The glucose measurement using optical detection using long NIR wave which is not capable to detect the glucose molecules beneath the skin as it has shallow penetration [75]. Therefore, small NIR wave has been considered as potential solution for real-time glucose detection [77], [88].

B. Mid Infrared (MIR) Spectroscopy

The bending and stretching of glucose molecules would be observed very well with Mid Infrared (MIR) spectroscopy [89]. The depth of skin penetration is very less because it tends to have larger absorption of water. This technique helps to have ISF glucose value in vivo measurement. There are some attempts for precise glucose measurement through saliva and palm samples.

C. Blood Glucose Level Measurement using PPG

The change of blood volume with absorption of the light from tissue has been detected with PPG signal [87]. The change of the blood volume has been measured using pressure pulse with help of light detector [86]. The change in volume of blood would result as the change of light intensity hence it may not be occur due to glucose molecule. This may result as inaccurate glucose measurement. The difference of NIR against PPG has been shown in Fig 16. The intelligent glucose measurement device iGLU is mainly based on principle of NIR spectroscopy which helps to have precise glucose measurement. There have been several work for glucose detection based on PPG signal [90]. The data from patient body has logged to estimate the presence of glucose using PPG. Subsequently, various machine leaning models have been used for prediction of body glucose value [91]. The different parameters from total 70 subjects of healthy and diabetes have been considered for the prediction using Auto-Regressive Moving Average (ARMA) models [92]. There have been also several other smart solutions for glucose estimation using PPG signal with intelligent algorithms [93], [94], [95].

One of the optical based techniques is Photo-plethysmography (PPG) which is used in advanced health care. It is non-invasive glucose measurement technique. In NIR spectrum a sensor similar to a pulse oximeter is used to record the PPG signal [87]. Photo transmitter and receiver is used to build the sensor which will operate in near infrared region at 920nm. At wavelength 920nm, by measuring changes in the absorption of light, a PPG signal can be obtained. The veins in the finger grow and contract with every heartbeat.

A method of measuring blood glucose using pulse oximeter and transmission of the PPG glucose monitoring system is available [90]. As the glucose concentration increases, there is decrease in the light absorbance in the blood. The obtained signal is in the form of photo current, and for the filtering of this signal is then changed into the measurable voltage values. For the processing of filtered signal, lab view is used to estimate the blood glucose level.

A system using machine learning techniques and PPG system for the measurement of blood glucose level non-invasively has been prototyped [86]. In this model, a PPG sensor, an activity detector, and a signal processing module is used to extract the features of PPG waveform. It finds the shape of the PPG

waveform and the blood pressure glucose levels, the functional relationship between these two can be obtained then.

In PPG, the change in light intensity will be varied according to changes in blood volume. PPG signal analysis is not based on the principle of glucose molecule detection. Hence, the system has limited accuracy [25], [32]. Fig. 16 illustrates the differences.
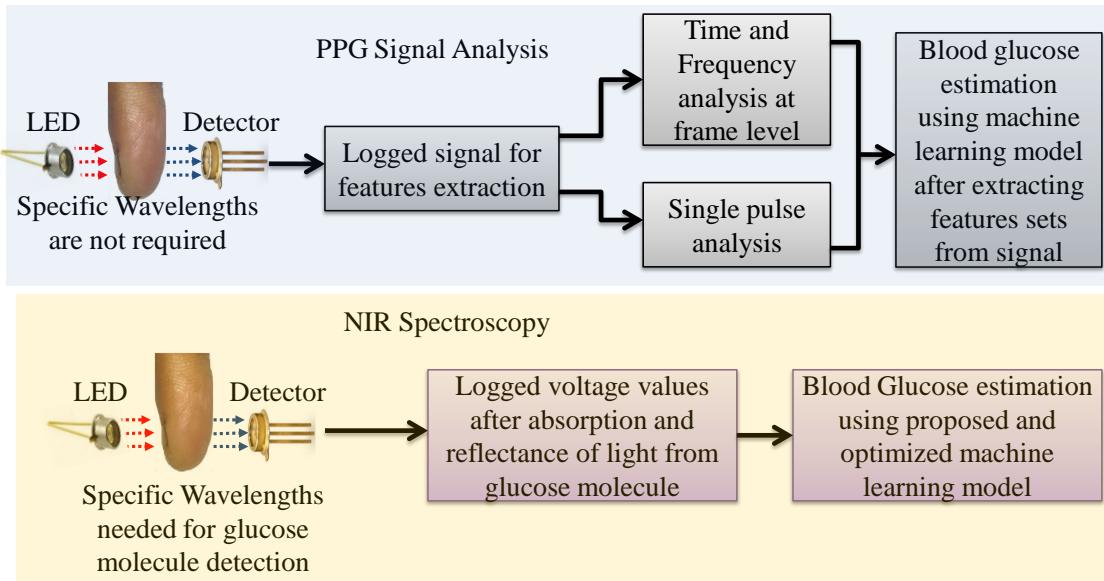

Fig. 16: PPG Versus NIR for Non-invasive Glucose Measurement [25], [32].

D. Impedance Spectroscopy

Impedance spectroscopy (IMPS) refers to the dielectric spectroscopy [96]. The steps of impedance spectroscopy (IMPS) is shown in Fig. 17. This technique finds the dielectric properties of skin [97]. The current is directed through the skin [98]. Due to directed small current at multiple wavelengths, the impedance range is obtained [99]. The range lies between 100 Hz to 100 MHz [100], [101]. Change in glucose concentration will reflect the change in sodium ions and potassium ions concentration [102]. So, the cell membrane potential difference will be changed [103]. Thus, the dielectric value will be changed which predicts the glucose value of human body [104].

An enzyme sensor in a flow cell has been explored for glucose measurement in saliva [105]. Polypyrrole (PPy) supported with copper (Cu) nanoparticles on alkali anodized steel (AS) electrode for glucose detection in human saliva is available in [106]. The high precision level cannot be possible through these methods as sweat and saliva properties vary according to person. Hence, this approach is not suitable for glucose measurement in smart healthcare.

E. Raman Spectroscopy

Due to the interaction of light with a glucose molecule, the polarization of the detected molecule will change [107]. In this technique, oscillation and rotation of molecules of the solution are possible through the incident of LASER light [108]. The vibration of the molecule affects the emission of scattered light [109]. Due to this principle, blood glucose concentration can be predicted as [110]. This technique provides more accuracy with compared to infra-red spectroscopy technique [111]. There has been several research based on Raman spectroscopy to have precise glucose measurement. The validation has been
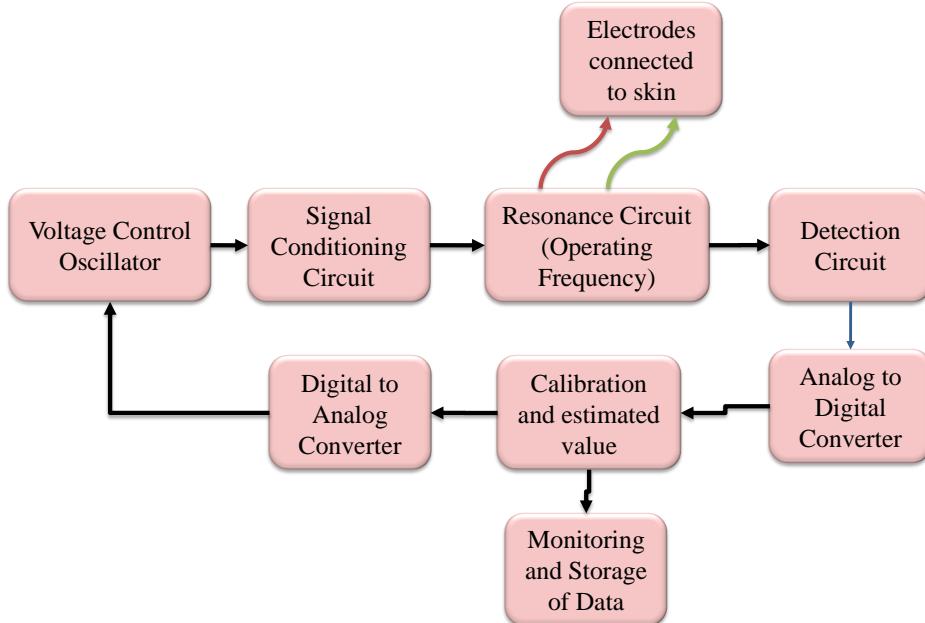
Fig. 17: The Steps of Impedance Spectroscopy (IMPS).

also carried out on using vivo testing. Fig. 18 presents basic framework of Raman spectroscopy, whereas Fig. 19 presents its usage for noninvasive glucose measurement.
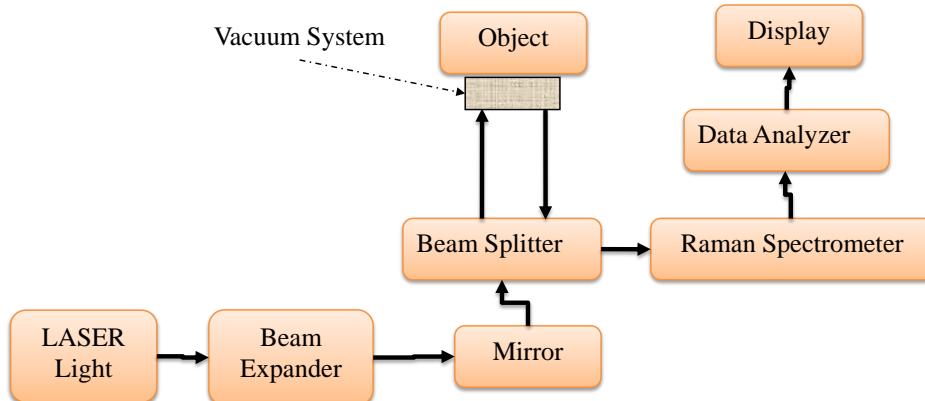
Fig. 18: Building blocks of Raman spectroscopy.

F. Time of Flight and THz Domain

The blood glucose estimation is adopted though Time of Flight (TOF) measurements for vitro testing [112]. The short pulse of laser light is inserted in the sample for photon migration measurement. This photon will experience scattering and absorption phenomenon while traveling from the sample. The optical analysis of the photons would be useful for precise glucose measurement.
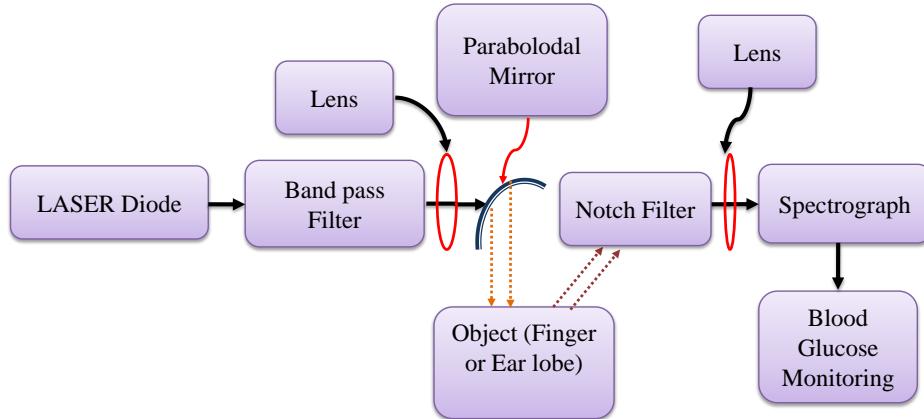
Fig. 19: Noninvasive glucose measurement using Raman spectroscopy.

G. Photo Acoustic Spectroscopy

Photoacoustic spectroscopy refers to the photoacoustic effect for the generation of the acoustic pressure wave from an object (refer Fig. 20) [113]. In this spectroscopy technique, the absorption of modulated optical input provides the estimation of blood glucose detection [114]. High intense optical light is absorbed by an object according to its optical conditions [115]. This process provided excitations of particular molecules according to its resonant frequency [116]. The absorbed light is considered as heat which provides rising in localized temperature and thermal expansion of the sample [117]. The expansion in volume generates pressure in acoustic form [118]. The generated photoacoustic wave can be used to predict the glucose concentration through specific excited wavelengths which are resonant for the vibration of glucose molecules [119]. At the specific resonance frequency, the glucose molecule changes own characteristic. This change is in the acoustic waveform [120]. In previous work, 905 nm wavelength optical light is used for excitation [121], [122].

H. Capacitance Spectroscopy

In the capacitance spectroscopy technique, inductor stray capacitance varies according to body capacitance (Fig. 21) [123]. The body capacitance is used to estimate body glucose concentration [124]. Flexible inductor based sensor follows the coupling capacitance principle for body glucose detection. In this technique, there is not any interaction between the inductive sensor and body skin through the current [125]. This is the advantage of the impedance spectroscopy technique. The stray capacitance of the inductive sensor will vary according to body glucose. In this technique, the effect of fat and muscles will be negligible with respect to body glucose [126].

I. Surface Plasmon Resonance (SPR)

The Surface Plasmon Resonance (SPR) utilizes electron oscillation approach at dielectric and metal interface for glucose sensing [127]. It detects mainly the change in refractive index before as well as after the analytes interaction. The optical fiber based SPR has been used for point of care measurement for glucose due to its portability.

J. Radio Frequency (RF) Technique and Microwave Sensing

In the RF technique, the variation in the s-parameters response reflects the change in blood glucose [128], [129]. Fig. 22 shows typical steps of this technique. The response is determined through the antenna
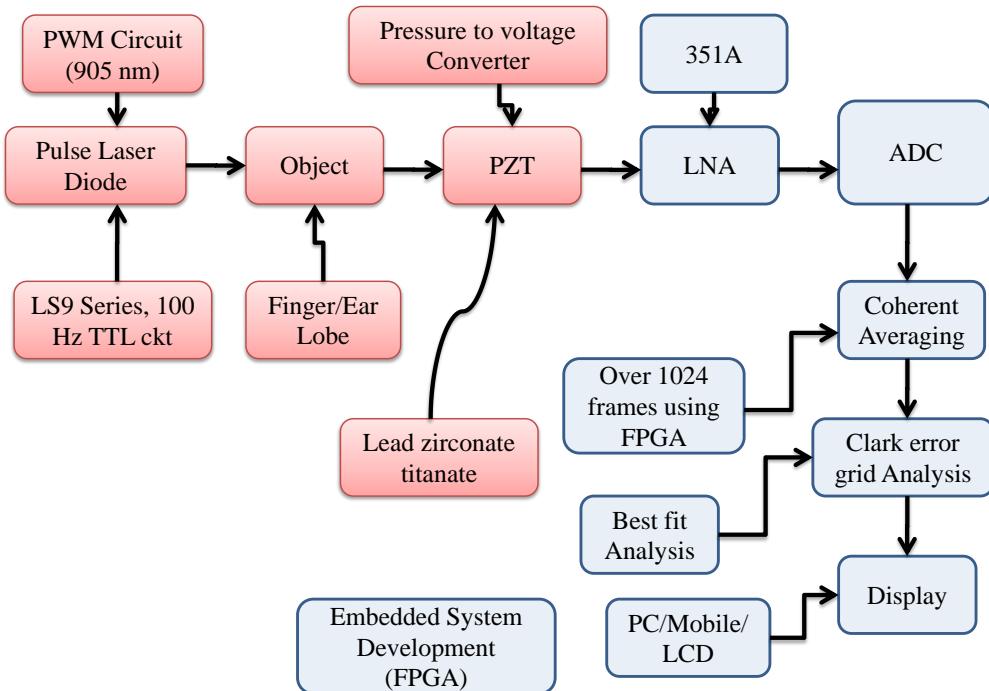
Fig. 20: Photo acoustic spectroscopy.
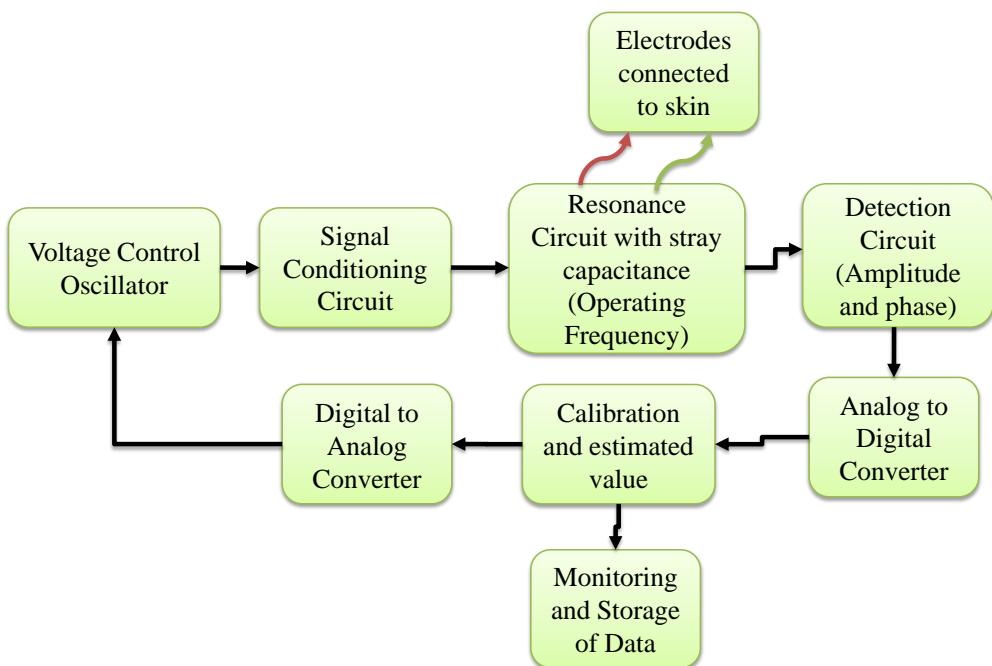
Fig. 21: The typical steps of capacitance spectroscopy.

or resonator [130], [131]. They follow the changes in dielectric constant value through the transmission [132]. The change in dielectric constant can be found as the change in resonance frequency spectrum through the antenna or resonator [133], [134]. The dielectric of blood varies according to blood glucose concentration. The human finger is an appropriate measurement object but there are many factors that play a cardinal and dominant role in the accuracy of measurement and repeatability. These are; the skin thickness, fingerprints, the applied pressure by the fingertip during measurement and positioning of a finger on the sensor [135].
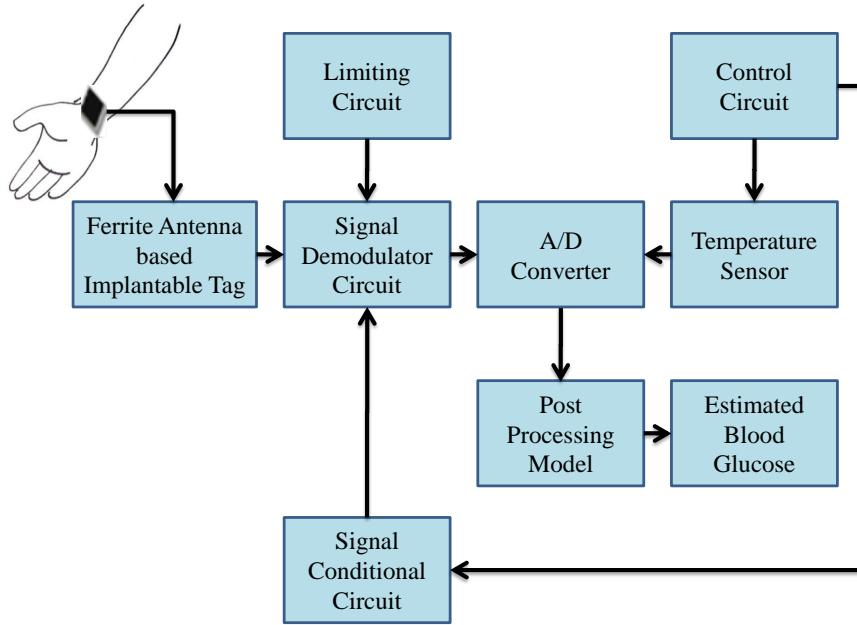
Fig. 22: Glucose measurement using RF sensing technique.

K. Ocular Spectroscopy

In the Ocular Spectroscopy technique, glucose concentration is measured through the tears. A specific lens is used to predict the body glucose concentration [136]. A hydrogel wafer is deposited to the lens. This wafer is prepared by boronic acid with 7 μm thickness. The wafer is deposited on lens and then optical rays are inserted on the lens. Then reflected light will change its wavelength. Change in wavelength will refer to a change in glucose concentration in tears.

L. Iontophoresis

In the Iontophoresis or Ionization technique, a small electric current passes through the skin diffusively. Three electrodes are used for the same [137]. A small potential is applied through the electrodes to the different behaviour electrodes. During this process, glucose is transferred towards the cathode. The working electrode can have the bio-sensing function by the generation of current during applied potential through electrodes. This biosensor determines passively body glucose. The measurement is possible through wrist frequently [138].

M. Optical Coherence Tomography

The Optical Coherence Tomography technique is based on the principle followed by reflectance spectroscopy. In this technique, low coherent light is excited through the sample (sample is placed in

an interferometer). In an interferometer, a moving mirror is placed in reference arc. A photodetector is placed on another side and it detects the interferometric signal. This signal contains backscattered and reflected light. Due to this process, we could get high-quality 2-D images. The glucose concentration increases with the increment of the refractive index in interstitial fluids. Change in the refractive index indicates the change in the scattering coefficient [107]. So, the scattering coefficient relates to glucose concentration indirectly.

N. Polarimetry

The Polarimetry technique is commonly used in a clinical laboratory with more accuracy. The optical linear polarization-based technique is used for glucose monitoring [139]. This technique is usually based on the rotation of vector due to thickness, temperature and concentration of blood glucose. Due to the process of prediction of glucose, the polarized light is transmitted through the medium containing glucose molecule. Due to high scattering through the skin, the depolarization of beam is possible. To overcome this drawback, a polarimetric test has been done through the eye. The light passes through the cornea. This technique is totally unaffected due to rotation of temperature and pH value of blood [140].
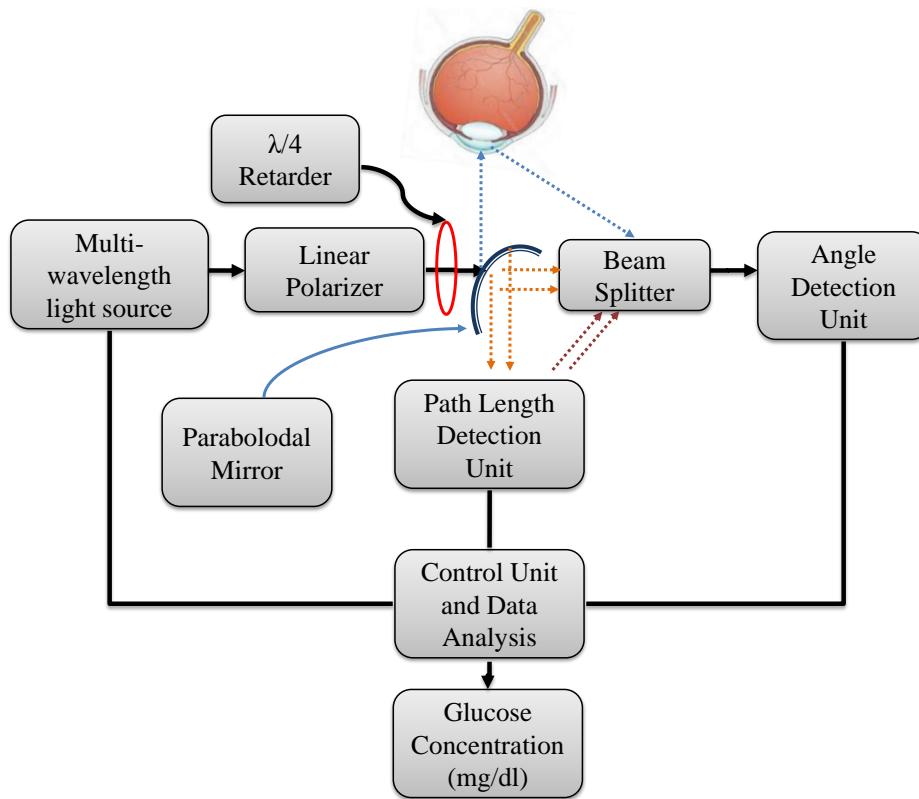
Fig. 23: Non-invasive glucose measurement using Polarimetry.

O. Thermal Emission Spectroscopy

The Thermal Emission Spectroscopy based technique is based on the naturally generated IR wave from the body. The emitted IR waves will vary according to body glucose concentration. The usual mid-IR emission from tympanic membrane of human body is modulated with tissue emitting. The selectivity of this technique is same as the absorption spectroscopy. Due to this technique, glucose

can be determined through the skin, fingers and earlobe. This technique is highly precise and accurate for glucose measurement [141]. It could provide the useful solution which is precise and acceptable at clinical with measurement of thermal emission from tympanic membrane.

P. Ultrasound

The Ultrasound method is based on low frequency components to extract the molecules from skin similar as reverse iontophoresis method [142]. It is also alike sonophoresis and has larger skin permeability than reverse iontophoresis. Few or several tens of minutes of ultrasound exposure are required to pull glucose outward through the skin. There are few attempts for such technology and there is not any commercial device with such type of technology.

Q. Metabolic Heat Conformation (MHC)

The Metabolic Heat Conformation (MHC) method helps to measure the glucose value with metabolic heat and oxygen level along various physiological parameters considerations [143]. The mathematical model for metabolic energy conservation has been modified by several physiological parameters consideration such as pulse rate, oxyhemoglobin saturation, heat metabolic rate and the blood flow volume. This method has shown good reproducibility and decent accuracy in humans.

R. Fluorescence

The Fluorescence technique is based on the excitation of blood vessels by UV rays at particular specified frequency ranges [144]. This is followed through the detection of fluorescence at a specified wavelength. The sensing of glucose using fluorescence through tear has been done by the diffraction of visible light. At 380 nm, an ultraviolet LASER was taken for excitation through the glucose solution medium. Fluorescence was estimated which is directly related to glucose concentration. In this technique, the signal is not affected by variation in light intensity through the environment.

S. Kromoscopy

The Kromoscopy technique uses the response from various spectroscopic of NIR light with four different detectors over different wavelength [145]. It employs the multi-channel approach with overlapped band-pass series filters to determine the glucose molecule. In this method, the radiation of IR are imparted on the sample and this will be divided among four detectors with band-pass filter. Each detector will detect the light of the similar structure of the tissue. Subsequently, the complex vector analysis has been utilised to measure the glucose concentration.

T. Electromagnetic Sensing

In the Electromagnetic Sensing method, the variations in blood sample conductivity is observed by change in blood glucose concentration [146]. The alternation of electric field would be measured by electromagnetic sensor whenever there will be change in blood glucose concentration. This method utilizes the dielectric parameter of the blood samples. The frequency range for electromagnetic sensing is in the range of 2.4 to 2.9 MHz. The glucose molecule has maximum sensitivity at particular optimal frequency for given temperature of the medium.

U. Bioimpedance Spectroscopy and Dielectric Spectroscopy

It is useful to measure the variation of the blood glucose with help of conductivity and permittivity from red blood cells membrane [147]. The spectrum of bioimpedance spectrum is measured from 0.1 to 100 MHz frequency range. It help to find the resistance with passing through electric current which is flowing from human biological tissue. The change of plasma glucose would allow the changes in potassium and sodium to have the change in conductivity of the membrane of the red blood cell. The multisensor approach is usually incorporated with this spectroscopy in order to measure sweat, moisture, movement and temperature for precise glucose measurement.

V. Reverse Ionospheresis

The small DC current is passed from anode to cathode on the skin surface to have small interstitial fluid (ISF). Iontophoresis is employed for ionized molecules penetration at skin surface by such low current [148]. The electric potential is passed from anode and cathode to electroosmotic flow across the skin. This would allow to extract the molecules through skin whereas the the molecules of glucose are moved towards the cathode. The enzyme method helps to sense the concentration of glucose molecules through oxidation process. the method has very widely accepted and has good potential to measure accurate glucose value.

W. Sonophoresis

The Sonophoresis technique is based on the cutaneous permittivity of the interstitial fluid (ISF) [149]. It also uses enzyme method for glucose measurement. The low frequency ultrasound wave has been applied in order to have glucose molcules at the skin surface. The cutaneous permittivity of the ISF is increased to enable glucose at the epidermis surface. The contraction and expansion occurs in stratum corneum that subsequently opens the ISF pathway. There has been some attempts with this method for glucose detection but it has been observed that it could be helpful in drug delivery in stead of glucose measurement.

X. Occlusion Spectroscopy

The Occlusion spectroscopy based methods depend on the concept of light scattering which is of inverse proportion of glucose concentration [150]. The flow is ceased for few seconds by applying pressure with pneumatic cuff. The volume of blood would change due to pulse generated from the pressure excursion. The light is transmitted through the sample and the variation of the intensity of in a received light defines the glucose concentration. The momentary blood flow cessation helps to get higher SNR value of the received signal. Hence, the sensitivity for glucose detection would be increases with good robustness for accurate glucose measurement.

Y. Skin Suction Bluster Technique

The Skin Suction Bluster technique uses the concept of blister generation through vacuum suction over limited skin area [151]. The glucose measurement is performed on fluid which is collected from the blister. It has lower glucose molecules than plasma but it is well enough to have the glucose measurement. This method has low risk of infection, painless and well-tolerated. It is actually useful to measure HbA1c value which represents three month average glucose value.

Z. Multimodal approach based measurement

A two modal spectroscopy combining IMPS and mNIR spectroscopy is explored for high-level re-producibility of non-invasive blood glucose measurement [152]. These two techniques are combined to overcome the limitation of individual employed technique [153]. Impedance spectroscopy based circuit measures the dielectric constant value of skin or tissue through RLC resonant frequency and impedance to predict glucose level [154]. To improve the accuracy of NIR spectroscopy, mNIR spectroscopy technique is used. In this technique, three wavelengths 850 nm, 950 nm and 1300 nm are used [155]. For precise and accurate measurement, IMPS and mNIR are joined by an ANN (Artificial Neural Network) through DSP processor [80]. Therefore multimodel approaches have been explored for precise glucose measurement in the literature [**?**], [**?**].
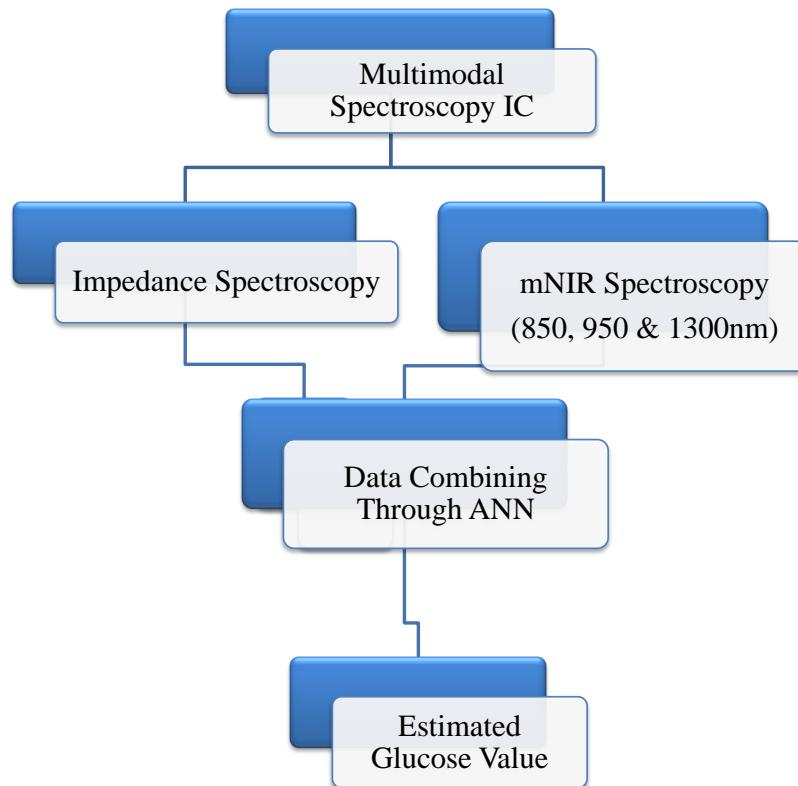
Fig. 24: Multimodal IC based non invasive glucose measurement.

V. POST-PROCESSING AND CALIBRATION TECHNIQUES FOR NON-INVASIVE GLUCOSE-LEVEL MEASUREMENT

This Section presents various post-processing and calibration techniques which are deployed in various systems or frameworks for noninvasive glucose-level monitoring.

A. Post processing and calibration techniques

Various calibration processes have been applied for a high level of accuracy and noise reduction from received signal. These post-processing techniques are used to design the model for errorless continuous monitoring [165], [166].

TABLE II: Approaches Comparison with Noninvasive Works [25], [32].

Works	Spectroscopy technique	Spectra	Specific wavelength	Measurement range	Linearity (%)
Singh, et al. [160]	Optical	-	-	32-516 mg/dl	80
Song, et al. [80]	Impedance and Reflectance	NIR	850-1300 nm	80-180 mg/dl	-
Pai, et al. [161]	Photoacoustic	NIR	905 nm	upto 500 mg/dl	-
Dai, et al. [162]	Bioimpedance	-	-	-	-
Beach, et al. [163]	Biosensing	-	-	-	-
Ali, et al. [88]	Transmittance and Refraction	NIR	650 nm	upto 450 mg/dl	-
Haxha, et al. [77]	Transmission	NIR	940 nm	70-120 mg/dl	96
Jain, et al. [164]	Absorption and Reflectance	NIR	940 nm	80-350 mg/dl	90
Jain, et al. (iGLU 1.0) [32], [28]	Absorption and Reflectance	NIR	940 and 1300 nm	80-420 mg/dl	95
Jain et al. (iGLU 2.0) [29], [25]	Absorption and Reflectance	NIR	940 and 1300 nm	80-420 mg/dl	97

TABLE III: Statistical and Parametrical Comparison with Noninvasive Works [25], [32].

Works	R value	MARD (%)	AvgE (%)	MAD (mg/dl)	RMSE (mg/dl)	Samples (100%)	Used model	Measurement sample	Device cost
Singh, et al. [160]	0.80	-	-	-	-	A&B	Human	Saliva	Cheaper
Song, et al. [80]	-	8.3	19	-	-	A&B	Human	Blood	Cheaper
Pai, et al. [161]	-	7.01	-	5.23	7.64	A&B	in-vitro	Blood	Costly
Dai, et al. [162]	-	5.99	5.58	-	-	-	in-vivo	Blood	Cheaper
Beach, et al. [163]	-	-	7.33	-	-	-	in-vitro	Solution	-
Ali, et al. [88]	-	8.0	-	-	-	A&B	Human	Blood	Cheaper
Haxha, et al. [77]	0.96	-	-	-	33.49	A&B	Human	Blood	Cheaper
Jain, et al. [164]	0.90	5.20	5.14	5.82	7.5	A&B	Human	Blood	Cheaper
Jain, et al. (iGLU 1.0) [32]	0.95	6.65	7.30	12.67	21.95	A&B	Human	Blood	Cheaper
Jain et al. (iGLU 2.0) [29]	0.97	4.86	4.88	9.42	13.57	Zone A	Human	Serum	Cheaper

1) Noise Minimization and Signal Conditioning: The coherent averaging technique has been adapted to minimize the variance of random noise [167]. The impact of noise is minimized with averaging of N number of individual samples coming from the continuous frames [168]. Frames in the maximum count have been chosen for averaging to have SNR improvement [169]. This proposed coherent averaging has been used frequently through MATLAB and coherent averaged signal acquired. Golay code has been proposed as calibration of measured data. The filtering or cancellation of unusual measured data has been achieved through the implementation of Golay code [170], [171], [172].

2) Computation Models for glucose Estimation: The regression model of regularized least square is proposed by several researchers for measurement [173]. The estimated value is computed from photoacoustic signals. These photoacoustic signals are used to calibrate for estimation of glucose concentration [174]. This can be possible through multi-variable linear regression model [175]. With the objective of high-level accuracy, a post-processing SVM technique is proposed [176]. Support vector machine is a better option of correct measurement in glucose monitoring system [177]. Artificial Neural Network (ANN) has also been proposed for data combining [178]. The measured data from multiple techniques are combined through the proposed neural network model [179]. This artificial neural network has been implemented in DSP processor [180], [?]. This proposed data interpretation model has been used for combining and calibrating of data for final estimated glucose concentration [181].

B. Metrics for Model Validation

The calibration method is used to have precise blood glucose estimation for measurements [182]. The obtained glucose concentration values are used to compare with conventionally measured glucose concentrations [183]. The Clarke error grid analysis has been considered maximum measurement for analysis which is used to check the performance of any device for accuracy measurement [184]. The process flow is represented in Fig. 25.
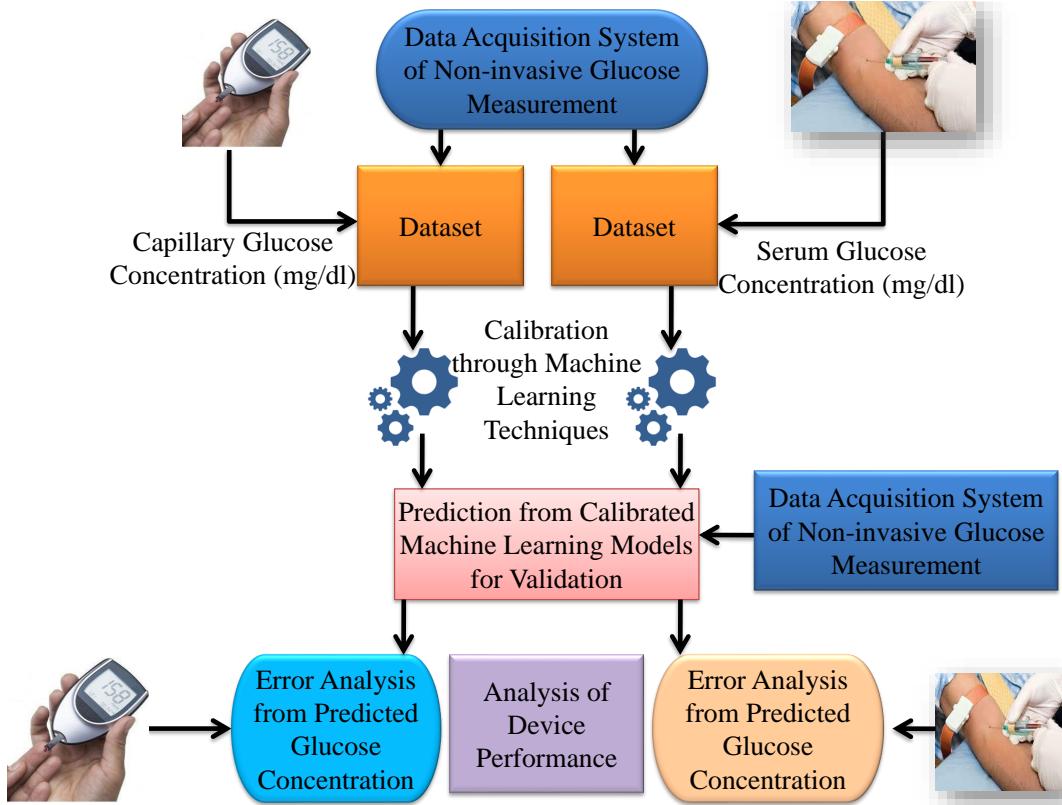

Fig. 25: Representation of Metrics for model Validation.

C. Clinical Accuracy Evaluations using Clarke error grid analysis

The Clarke Error Grid has been analysed as benchmark tool to examine the clinical precision for biomedical application. It has prediction of point as well as rate accuracy, and it amends for physiologic time lags inherent for measurement of body glucose. The exploitation of the Clarke error grid modelling will significantly make easy the development and refinement of a precise biomedical device. In 1970, this technique was developed by C.G. Clark to identify the accuracy of the clinical trials which helps to find the precision of estimated blood glucose with blood glucose value through the conventional method. A description of the Error Grid Analysis came into view in diabetes care in 1987. The grid is divided with five different zones mainly as zone A, zone B, zone C, zone D, and zone E. If the values residing in either zone A or zone B then it signifies satisfactory or accurate prediction of glucose results according to Beckman analyzer. The zone C values may prompt gratuitous corrections which may lead to a poor outcome. If the values are under zone D which actually defines a hazardous failure to sense. Zone E reflects the "erroneous treatment" [185].
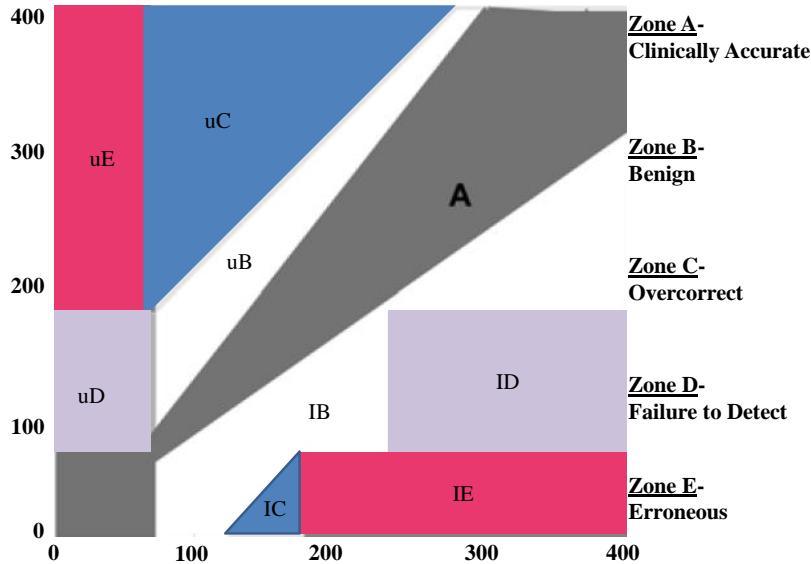
Fig. 26: Clarke error grid analysis.

VI. Consumer Products for Glucose-Level Measurement

There have been several non-invasive glucometer at market(such as Freestyle Libre sensor, SugarBEAT from Nemaura medical) which used for proper medication. They would be like skin-patch with daily disposable feature and adhesive to have the continuous glucose monitoring. Most of the consumer products fail to provide precise glucose measurement and hence they are much popular for diabetes management. There are some products as DiaMon Tech, glucowise, glucotrack, glutrac and CNOGA medical device. Glutrac is smart healthcare device but it has accuracy issues for the blood glucose measurement. It has higher cost while precision is still not acceptable. The non-invasive stripless device known as Omelon B-2 has been used for the CGM. The fluorescent technique based Glucosense has been made for contonuous monitoring of the glucose value. The flexible textile-based biosensor has developed from Texas University to measure the glucose level. All the available device have accuracy issues and considerable higher cost.

A. Wearable versus Non-wearable for Glucose Monitoring

The glucose monitoring have been attempted using non-wearable and wearable solutions in the literature. Most of the non-wearable approaches are based on various spectroscopy such as photoacoustic spectroscopy, Raman spectroscopy etc. The implantable devices are of semi-invasive type and are mainly of biosensors in nature. Sweat patches, Glucowatch and Smart contact lenses are of wearable devices category. LifePlus has developed non-invasive and wearable device for CGM purpose and it is under consideration for commercialization. Most of non-invasive device are wearable and helpful for frequent glucose measurement. The continuous glucose monitoring would be more acceptable if they could measure the blood glucose values in day to day life. Therefore, the wearable devices are more state of art solutions then non wearable devices.

B. Noninvasive Glucose Measurement Consumer Products

There are variety of products such as GlucoTrack®, glucometer from Labiotech [186], and similar available solutions have accuracy issues and cost is also high. The glucowise is another non-invasive device for continuous glucose measurement from Medical Training Initiative (MTI) ™. The Raman scattering spectroscopy based non-invasive solution is also developed by 2M Engineering [187]. These devices

are not much popular because of their cost and precision. Further for the high level of accuracy of glucose measurement, Glucotrack™ has been developed by integrity applications Ltd. [188]. This non-invasive glucose monitoring device employed three consecutive ultrasonic spectroscopy, thermal emission and electromagnetic techniques. This device is highly precise and accurate because of a combination of three techniques [189]. A comparative perspective of various consumer products for noninvasive glucose measurement has been summarized in Table IV.

TABLE IV: A Comparative perspective of a selected consumer products for noninvasive glucose measurement.

Company	Device	Technology	Object	Summary	Snapshot
Cygus Inc. (USA)	GlucoWatch G2 Biographer	Reverse iontophoresis	Wrist skin	It would be worn as watch is used with disposable component, autosensor which is to be attached at back of biographer that contact with the skin to provide frequent glucose monitoring	
CNOGA (Israel)	Combo glucometer	Tissue photography analysis	Finger	On basis of tissue photography analysis from fingertip capillaries, this device can analyze various bio parameters in very short time	
Pendragon Medical (Switzerland)	Pendra	Impedance Spectroscopy	Wrist Skin	It helps to measure the glucose with sodium transport of erythrocyte membrane, The change of fluxes of transmembraneous sodium occur due to impedance field which is detected by device to generate final glucose value	
OrSense Ltd. (Israel)	OrSense NBM-200G	Occlusion Spectroscopy	Fingertip skin	It is based on optical concept on finger which is attached to a ring-shaped sensor probe. The probe has red/near-infrared RNIR spectral region light source as well as detector. It has pneumatic cuffs which generates systolic pressure to produce optical signal for glucose monitoring	

Company	Device	Technology	Object	Summary	Snapshot
C8 Medis-ensors (USA)	C8 Medis-ensor Glu-cose detec-tor	Raman Spec-troscopy	Fingertip skin	This technique is based on monochromatic light source passes through skin where scattered light is detected. The generated colors from Raman spectra helps to exact chemical structure of glucose molecule	
Integrity Appli-cations (Israel)	Glucotrack	Combination of Electro-magnetic, ultrasonic and Thermal	Ear lobe tissue	In this device, three differ-ent techniques are used concur-rently to increase the accuracy and precision	
Tech4Life Enter-prises (USA)	Non invasive glucometer	Infra red Spectroscopy	Finger	It is helpful for Hyperglycemia or Pre-Diabetic patients which allow for regular monitoring of precise blood glucose measure-ment at every 30 seconds	
MediWise Ltd. (United King-dom)	Glucowise	Radio Wave Spectroscopy	Forefinger skin/Earlobe	This non invasive wireless de-vice can measure glucose con-centration in very short time. It is based on electromagnetic waves of specific frequencies for blood glucose detection. It uses a thin-film layer of meta-material which increases the penetration for precise glucose measurement	
Nemaura Medical (united King-dom)	SugarBeat	Reverse ion-tophoresis	Arm,Leg and adbomen	This has been proved accu-rate device, pain-free contin-uous blood glucose monitor-ing. SugarBEAT® provides real-time, needle-free glucose mea-surement. Generally, it needs one time finger-prick test for calibration. One time finger prick is used when new patch is required to insert	

Company	Device	Technology	Object	Summary	Snapshot
Abott Ltd. (USA)	Free Style Libre	Glucose oxidase method	Fore-arm skin	It uses enzyme glucose sensing technology for the detection of glucose levels through interstitial fluid Glucose oxidase method is applied through sensor where electrical current proportional to the glucose concentration and glucose can be measured.	
C8 Medisensor	Non invasive glucose monitor	Raman Spectroscopy	Fore arm skin	Raman spectroscopy technique based this device can detect glucose in blood through returning spectrum from the skin	

VII. GLUCOSE LEVEL CONTROLS APPROACHES AND CONSUMER PRODUCTS

Various models have been developed for diet control using various parameters for glucose-insulin balance. The parameters are mainly includes net hepatic glucose balance, renal excretion rate, glucose absorption rate and peripheral glucose utilization for the glucose consumption prediction for the diabetic patients. These are useful parameters to calculate the glucose level by proper insulin dosage along with scheduled diet plan. Therefore, the glucose-insulin control model was designed to balance glucose insulin level in the body for diabetes persons using proper medication.

A. Glucose Controls Approaches

The mathematical models for insulin delivery have been presented to determine the coefficients of blood regulation. The model has been proposed for insulin secretion with glycemic profile for type 2 diabetic person [190], [191]. The non-linear model is developed using differential equation with delay model with help of non-diabetic subjects [192]. Most poplar "Uva/Padova Simulator" was also explored which was approved from FDA to have the proper clinical trials. The parameter are extracted with type 1 diabetic virtual patients [193]. The intravenous test for glucose tolerance with Hovorka maximal model has explored for non-diabetic subjects [194]. The samples from type 1 diabetic persons were collected to explain the model with help of time monitoring. The model is proposed mathematically for blood glucose value prediction in the postprandial mode for type 1 diabetes patients [195], [196]. The mathematical model for glucose-insulin balance for longer period is explored using two days clinical information [197]. A algorithm was developed for T1DM patient meal detection for the purpose of frequent glucose measurement. The work has integrated bolus meal mathematical model for glucose-insulin delivery model [198]. Diabetic and healthy people were considered to acquire the values for the variable state dimension algorithm. The diet plan was examined in the absence of meal profile to have the glycemic profile balance, an intelligent PID controller (iPID) was developed to type 1 diabetic person [199], [200].

B. Glucose Controls Consumer Products

Type-1 diabetic patients aren't able to produce insulin. Insulin is a hormone that can balance body sugar (glucose) which is a prime source of energy that obtains from carbohydrates. If anybody has type 1 diabetes, it is necessary to be ready for insulin therapy. Insulin may be injected by self-injection, patients who take multiple injections daily of insulin may also think about use of an insulin pump. An insulin pump gives short-acting insulin all day long continuously. The insulin pump replaces the requirement of long-acting insulin. A pump also substitutes the requirement of multiple injections per day along with

continuous insulin infusion and also serves to improve the glucose levels. Various types of insulin pumps are already available in the market as consumable product mainly as Animas, Medtronic, Roche, Tandem and Omnipod insulin pump are consumables. These insulin pumps are advanced to each other in terms of their upgraded features. A comparative perspective of a selected state of art approach for glucose measurement to have better glyncenic profile control is presented in Table V.

TABLE V: A comparative perspective of a selected state of art approaches for glucose measurement

Work Technology	Object	Findings	Observation
[86] photoplethy--smography (PPG)	Finger	It helps to extract the features of PPG signal through machine learning models to estimate Systolic and diastolic blood pressure and blood glucose values	machine learning models applied where random forest technique has best prediction results as R^2_{SBP} = 0.91, R^2_{DBP} = 0.89 and R^2_{BGL} = 0.90. CEG has 87.7% observation in Zone A, 10.3 % in Zone B, and 1.9% in Zone D
[201] mid-infrared attenuated total reflection (ATR) spectroscopy and trapezoidal multi-reflection ATR prism	oral mucosa inner lips	Using a multi-reflection prism brought about higher sensitivity, and the flat and wide contact surface of the prism resulted in higher measurement reproducibility & spectra around 1155 cm−1 for different blood glucose levels for fasting and before fasting	the coefficient of determination R^2 is 0.75. The standard error is 12 mg/dl, and all the measured values are in Region A
[202] Optical Coherence Tomography	Fingertip	It measures the optical rotation angle and depolarization index of aqueous glucose solutions with low and high scattering, respectively. The value of angle increases while depolarization index decreases with glucose value increases	The correlation factor has a value of R^2 0.9101, the average deviation is found around 0.027.
[203] Contactlenses fluoresence	Tears	The fabrication of a soft, smart contact lens in which glucose sensors, wireless power transfer circuits, and display pixels to visualize sensing signals in real time are fully integrated using transparent and stretchable nanostructures	The usage of smart and soft lens would provide the wireless operation at real-time for glucose monitoring in tears

Work Technology	Object	Findings	Observation
[204] transmission spectroscopy	Sliva	After completely absorbing the sufficient amount of saliva on the strip, the sample would reach detection zone via paper microfluidic movement and enzymatic reaction between GOx and salivary glucose would initiate a pH change, resulting in a change in strip color that was recorded by using RGB detector on the handheld instrument which helps for glucose detection	The developed biosensor had a wide detection range of detection between 32- and 516- mg/dL glucose concentration while the sensitivity of detection was 1.0 mg/dL/count at a limit of detection (LOD) of 32 mg/dL within a response time of 15 s
[205] impedance spectroscopy (IMPS) and multi-wavelength near-infrared spectroscopy (mNIRS)	Left Handand wrist Hand	IMPS and mNIRS use the indirect dielectric characteristics of the surrounding tissue around blood and the optical scattering characteristics of glucose itself in blood, respectively, the proposed IC can remove various systemic noises to enhance the glucose level estimation accuracy	mean absolute relative differences (mARD) to 8.3% from 15.0% of the IMPS and 15.0–20.0% of the mNIRS in the blood glucose level range of 80–180 mg/dL. From the Clarke grid error (CGE) analysis, all of the measurement results are clinically acceptable and 90% of total samples can be used for clinical treatment
[84] NIR Spectroscopy	Fingertip	short NIR waves with absorption and reflectance of light using specific wavelengths (940 and 1,300 nm) has been introduced	The Pearson's correlation coefficient (R) is 0.953 and MAD is 09.89 which is RMSE 11.56
[206] Microwave Detection	earlobe	The absorption spectrum of microwave signal helps to measure using two antenna. The sine wave of 500 MHz is for blood glucose measurement.	It can measure blood glucose from 0 to 500 mg/dl with step size of 200 mg/dl used for the experiment for testing the resolution. It obtained 0.5226 mean standard deviation while the minimum value of standard deviation is 0.04119.

Work Technology	Object	Findings	Observation
[94] PPG	Finger	The prediction of blood glucose was with machine-learning using a smartphone camera. First the invalid data was separated and The system did not require any type of calibration	The device was able to measure glucose only 70-130 mg/dl range. The results show accuracy of 98.2% for invalid single-period classification and and the overall accuracy is 86.2%.
[46] MEMS	Finger	It is minimally invasive technique known as e-Mosquito which extracts blood sample with shape memory alloy (SMA)-based microactuator. It considered as first ever wearable device which performs the automatic situ blood extraction and performs the glucose analysis.	The method provided linear correlation (R^2 = 0.9733) between standard measurements and the e-Mosquito prototype.
[207] Visible NIR	Wrist	The paper developed biosensor which helps to exploit pulsation of arterial blood volume from the wrist tissue. The visible NIR spectroscopy was used for reflected optical signal to estimate blood glucose.	The correlation coefficient (Rp) value after averaging all observation is 0.86, whereas the standard prediction error is around 6.16 mg/dl.
[201] mid-infrared attenuated total reflection (ATR) spectroscopy	inner lip mucosa	Novel optical fiber probe was introduced using multireflection prism with ATR spectroscopy. The sensitivity increases with the number of reflections while measurement reproducibility was higher due to prism's wide and flat & wide contact surface.	The experimental results reveals the glucose signature at various spectra between fasting state and after the glucose injection. The plot for calibration defines peak for absorption at 1155 cm^{-1} which has glucose measurement error less than 20%

Work	Technology	Object	Findings	Observation
[?]	modulated ultrasound and infrared technique	Finger	the MATLAB toolbox is used with Fast Fourier Transform (FFT) for blood glucose extraction. The random blood glucose level test and oral glucose tolerance test was done for the human subjects for performance measurement	The RMSE value of noninvasive and invasive measurement from both tests 28.20 mg/dl and 23.76 mg/dl. The pearson correlation coefficient was 0.85 and 0.76, respectively. At the same time MSE was 17.76 mg/dl and 15.92 mg/dl.

VIII. GLUCOSE-LEVEL MEASUREMENT AND CONTROLS - IoMT PERSPECTIVES

The practical and sustainable mechanisms are the prime factors of smart and automated healthcare system. These are being optimized to support the population migration and quality of life in smart cities and smart villages [208], [209]. The features of smart healthcare system are continuous monitoring for critical care, ambient intelligence and quality of service for proper point of care mechanism [210], [211]. The non-invasive and precise glucose measurement is requirement for diabetic person and would also needed to store the information using IoMT for proper treatment [26]. The traditional method for glucose measurement has limited capability and is not able to assist the remotely located healthcare provider. The diabetic person would like to monitor their glycemic profile frequently in a day with support of storing at cloud server. The smart health care system would allow the point of care treatment for diabetes person with frequent monitoring.

The internet of Medical Things (IoMT) has allowed to connect the patients with doctors remotely for rapid treatment and special assistance using smart healthcare [208]. The continuous monitoring of vital parameters have provided to awareness about the diet plan and routine activity management with contemporary healthcare consumers devices. With the active support of remote healthcare solution, the smart healthcare has potential to ameliorate the quality of service at reduced cost. The smart sensors would capture the patient data continuously and help to store the data on cloud data centre. It is also useful for the analysing the data and easy exchange of the information through mobile applications to doctors as well as patients. The healthcare Cyber-Physical System (H-CPS) has been used successfully to address the various challenges of healthcare sector with intelligent algorithms.

The continuous glucose monitoring would certainly help the diabetic patients to plan their diet for the purpose of glucose control. The solution should be precise, low cost and easy to operate for rapid diagnosis [32], [28]. The serum glucose would always consider as accurate than capillary measurement. Therefore, the rapid serum glucose measurement solution with continuous monitoring is desired for the smart healthcare. The novel serum glucometer is portable device and is also integrated with IoMT to store the glucose values continuously at cloud. It would be useful for the healthcare provider to track the health records of remote located diabetes person. The smart healthcare management of continuous glucose measurement is defined in Fig. 27.

A detailed example of a closed-loop system that presents glucose-level monitoring and insulin release to control it is illustrated in Fig. 28 [2]. This IoMT framework can provide a better solution for evaluation of insulin doses through the closed-loop automated insulin secretion diabetes control. Such an integrated IoMT framework can be implemented to diagnose and for the treatment of diabetic patients in terms of controlling their blood glucose level in smart healthcare and be effective in smart village and smart cities for healthcare with limited medical personnel.

The security and privacy issues of the medical devices are paramount aspect in any IoT network. The hardware security of wearable device is very crucial because control actions mainly occur in wireless media. The security vulnerabilities are defined for glucose measurement device and its control are shown in
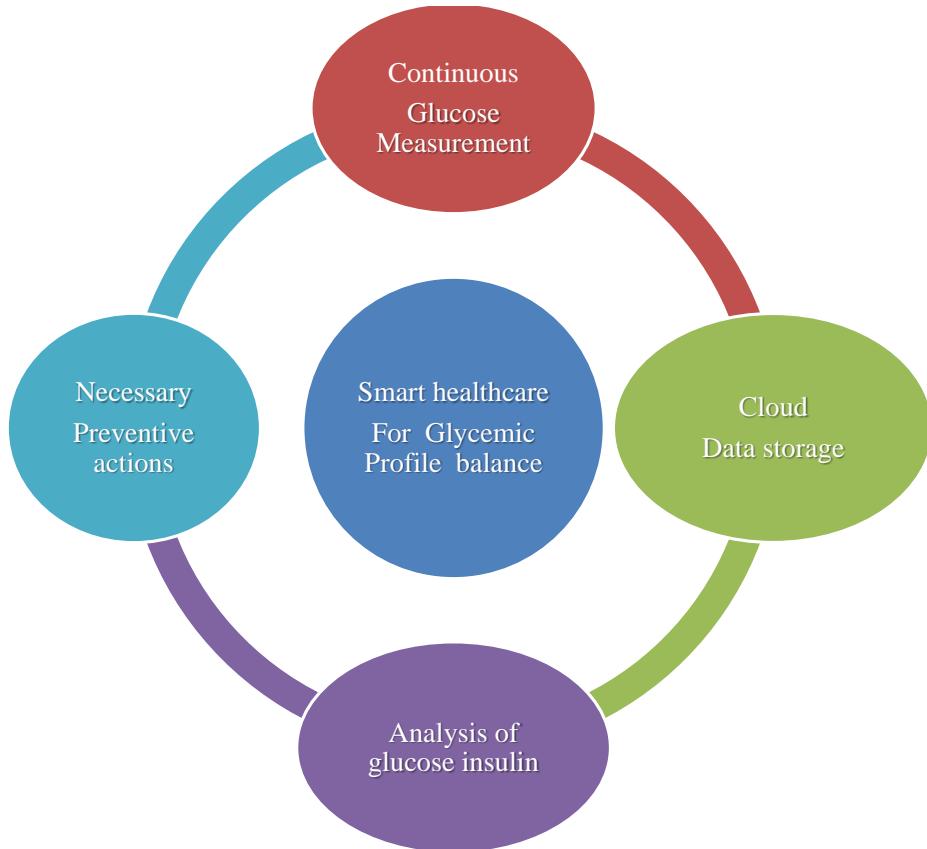
Fig. 27: Blood glucose diagnosis and Control in smart health care system.

Fig. 29. The devices security are important due to connected health system in an insecure and unreliable IoMT framework [212]. The integrity of useful medical information is also crucial security aspect of smart healthcare. All patients medical records are stored over the server therefore the security of such data are also really important. The controlled access with proper authentication is required to have secure monitoring with proper patient treatment.

IX. SHORT-COMINGS OF EXISTING WORKS AND OPEN PROBLEMS

This Section outlines the shortcomings and discusses some open problems of glucose level measurements and control.

A. Limitations of the Existing Approaches and Products

1) Photoacoustic spectroscopy has been implemented for glucose measurement. Real-time testing and validation have not been done from human blood. The artificial solution was prepared in the laboratory for glucose measurement. The prototype module with LASER and corresponding detector is costly and at the same time requires considerable bigger area and does not provide portable solution. Therefore, it is not much popular solution for continuous glucose monitoring.

2) Raman spectroscopy is a nonlinear scattering which occurs when monochromatic light interacts with a certain sample. Raman spectroscopy based solution is applicable for a laboratory test and also occupies the significant larger area. Hence, the system based on this approach will not be applicable for frequent glucose measurement.
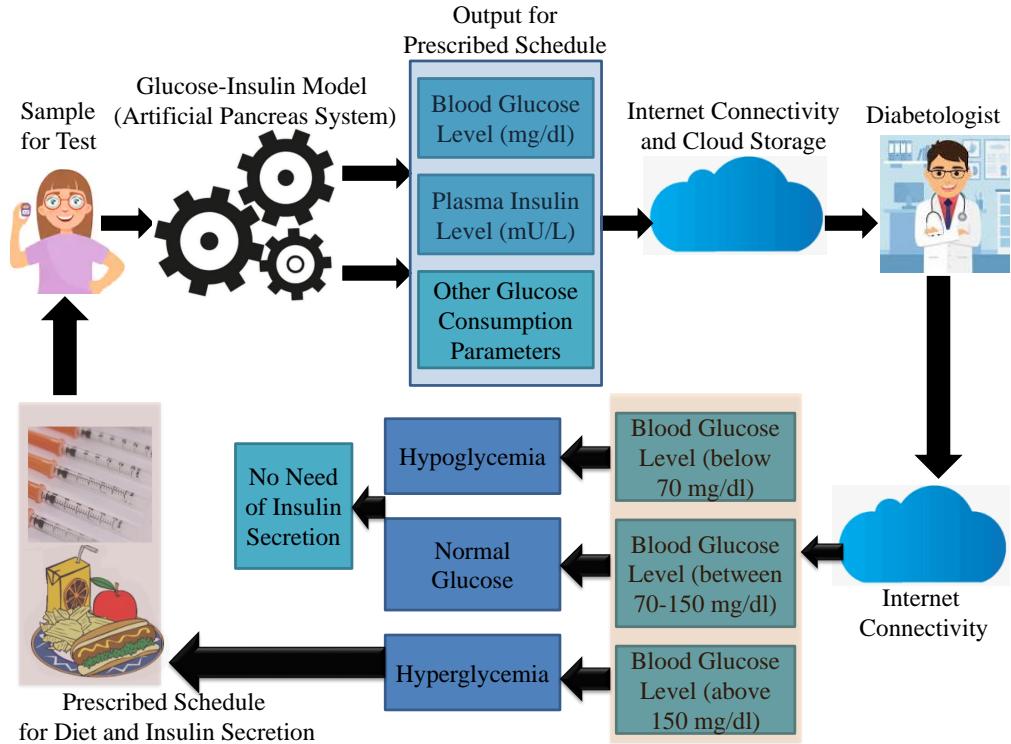
Fig. 28: A closed-loop automated insulin secretion diabetes control system in an IoMT framework [2].
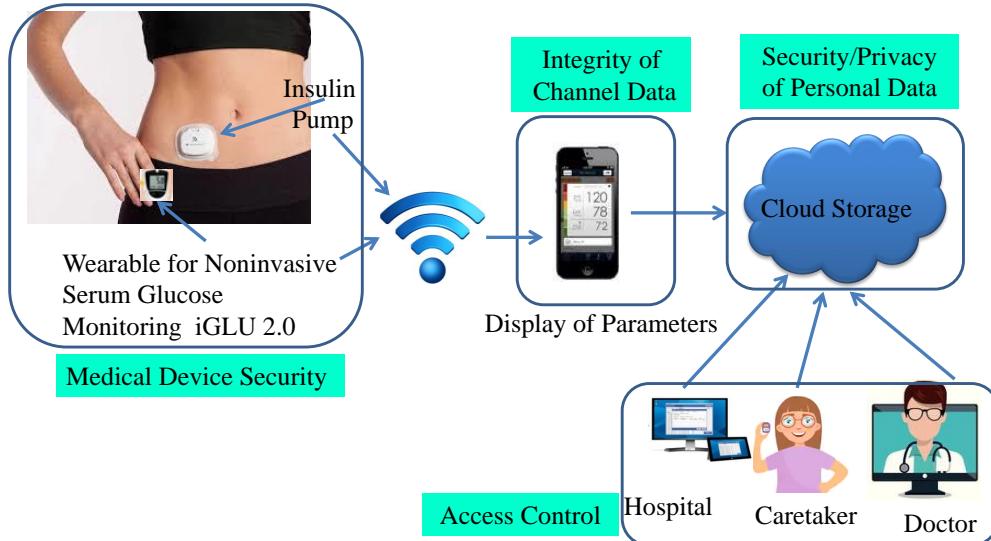
Fig. 29: Our Long-Term Vision of Security-Assured Non-invasive Glucose-Level Measurement and Control through our Proposed iGLU.

3) The retina based glucose measurement is also one of the alternate non-invasive glucose detection approach, data has also been collected through retina for glucose measurement. Such technique is not useful for the glucose measurement all the time.

4) In case of bio-capacitance spectroscopy, the slight difference in placing the sensor at the same

location might affect the output of the sensor. Effect of pressure on the sensor, body temperature and sweat on the skin may also affect the output of the sensor.

5) Glucose detection is performed with the impedance spectroscopy (IMPS) by electrodes connection to the skin which is affected with skin. The accuracy is always an issue as the saliva and sweat could change for each individual and that may reflect to the precision of glucose. Therefore, this technique is not best for reliable glucose measurement in smart healthcare.

6) PPG signal has been used to extract features for blood glucose level prediction. But the PPG may be precise blood glucose measurement technique where the output value would vary according the blood volume only. Therefore, the glucose molecule has not been detected precisely in the blood sample using this technique.

B. The Open Problems in Non-invasive Glucose Measurement

There are lots of challenges for commercialization of non-invasive glucose measurement device. But, some open problems have been discussed which are prime challenges for precise non-invasive glucose measurement. These challenges have been represented in Fig. 30. The precise glucose measurement of hypoglycemic patient and long-time continuous glucose measurement without instantaneous error are the open problems which are focussed by the researchers recently.
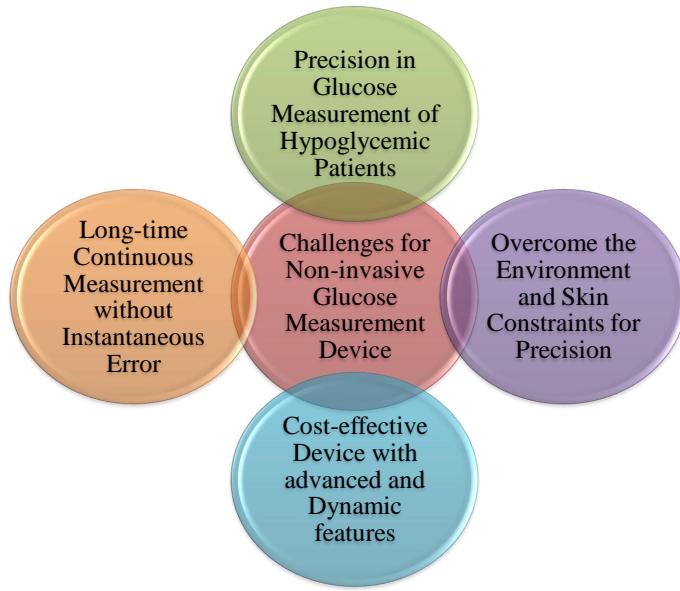
Fig. 30: Open Challenges in Noninvasive Glucose-Level Measurement.

- The effect of blood pressure, body temperature and humidity have not been considered in the literature which affect the values of glucose measurement.
- The cost effective and portable solution of continuous glucose measurement device has also not been addressed properly.
- The accurate glucose measurement has been also been open challenge for full rage from 40 mg/dl to 450 mg/dl.
- The effective integration of glucometer with internet of medical things for continuously data logging to the cloud has still not potentially resolved.
- The mathematical model for automatic insulin secretion according to measured glucose value has to be address in better manner with internet framework.

- The privacy and security issues of insulin and blood glucose measurement system is still not resolved yet.
- The efficient power management mechanism has to be developed for continuous glucose measurement with insulin delivery system.

X. Conclusions and Future Research

The paper presents survey of glucose measurement approaches along with overview of glucose control mechanism. Many techniques available in literature are only a proof of concept, showing good correlation between device estimated result and reference value of blood glucose. However, they are neither accurate nor cost effective solutions and not available for commercial purpose. The optical detection using short NIR has been potential solution to mitigate the drawbacks of all previous methods. In future, the multi-model approaches could be considered for precise glucose estimation. The device or prototype model should be more effective in different zones to support the continuous health monitoring. It should be implemented as a portable device for real time application with more frequently. This device should be developed as continuous health monitoring with minimum cost.

The future research for upcoming noninvasive glucose monitoring device is mentioned in Fig. 31. The device is required to be integrated with advanced IoMT framework. This advanced IoMT framework will alow to connect the device with all nearest diabetic centers to get best treatment. Unification of glucose-level measurement and automatic diet quantification can have strong impact on smart healthcare domain [213]. The durability, portability and user-friendly device is also the future vision in this era. The device should have the feature of border-line cross indication. Because of this feature, any person will be aware to take own blood glucose level. A secured device with end to end users control and authentication is also necessary for future advancement. Physical Unclonable Function (PUF) based security of IoMT-devices can be effective for IoMT-devices which are intrinsically resource and battery constrained [212], [214]. Unified healthcare Cyber-Physical System (H-CPS) with blockchain based data and device management can be effective and needs research [215], [216].
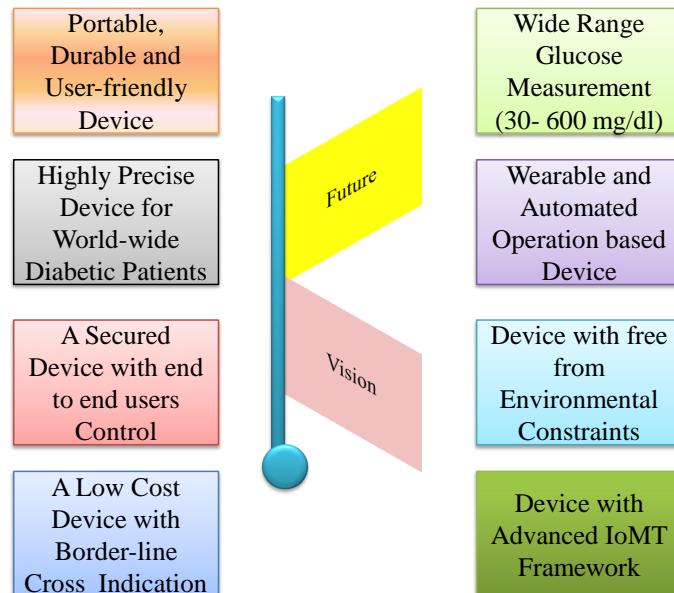

Fig. 31: Our Future Vision for Non-invasive Glucose-Level Measurement.

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