The Evolution of Non-invasive Blood Glucose Monitoring System for Personal Application

Nurul Akmal Binti Abd Salam, Wira Hidayat bin Mohd Saad, Zahariah Binti Manap, Fauziyah bte Salehuddin,
Faculty of Electronic and Computer Engineering (FKEKK),
Universiti Teknikal Malaysia Melaka (UTeM), Malaysia.
nurulakmal1991@yahoo.com

Abstract— Glucose monitoring technology has been used by diabetic patients to monitor their blood glucose level for the past three decades. This technology is very useful for managing diet among diabetic patients. This paper reviews the fundamental technique of blood glucose detection method and the development of blood glucose monitoring systems that have been developed ever since. The most common and widely used technique is an invasive technique that requires users to prick their finger to draw the blood. However, recently a lot of new technologies have been developed for non-invasive technique to monitor blood glucose monitoring and studies in this area are growing rapidly. Among all, the optical and transdermal approach are the two most potential sensing modalities for non-invasive glucose monitoring that show a very good prospect.

Index Terms— Blood glucose, Personal-monitoring, Invasive technique, Non-invasive technique.

I. INTRODUCTION

Blood glucose monitoring device is used to monitor the blood glucose concentration level. Normally, such device is used by diabetic patients to monitor the blood glucose level throughout the day in order to help them to understand the behaviour of the blood concentration based on the food intake and activity [1, 2]. Commonly, blood glucose reading is taken by using a glucose meter as can be seen in Figure 1. In order to do this test, it requires user to draw their blood and apply it to the test-strip. This test strip needs to be inserted into the glucose meter to get the reading. Basically, this typical glucose meter is produced by several different manufacturers with a similar approach where in most systems, it measures the electrical characteristic of the voltage output from the biosensor or test-strip that goes through a filter mechanism in order to improve the signal for a better voltage to blood glucose concentration conversion.

Normally, the diabetes patients are advised to have an appropriate blood glucose monitoring regime in order to keep track on their glucose level. This information will be very helpful for their physician to recommend the right dosage of insulin intake. The diabetes patients are suggested to test their blood glucose level at approximately three to seven times a day in order to find out the behaviour of the glucose level reading [3].

Figure 1: Finger puncturing and blood test using a glucose meter.

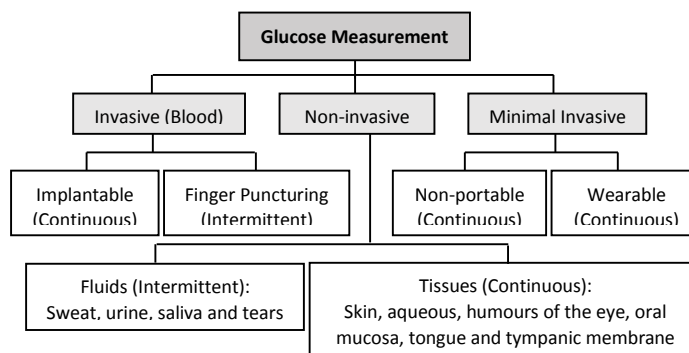## II. DEVELOPMENT OF A BLOOD GLUCOSE MONITORING SYSTEM

Figure 2: Overview of glucose measurement techniques.

Generally, the method of measuring blood glucose concentration can be divided into three major approaches which are invasive, non-invasive and minimally invasive or also known as interstitial. The invasive method will require a draw of blood sample by puncturing a finger using needles or syringes. This blood sample then will be transferred to the blood glucose measurement device to measure the glucose concentration. For partially invasive method, it requires an insertion of the sensor into the skin while taking a reading of glucose concentration. The invasive approach is the most commonly used by patients because the approach uses a device cheaper than the device used by the partially invasive and non-invasive approach. However, the invasive approach is not the best option for frequent blood glucose reading or continuous measurement since it causes discomfort to the patients every time when they take a reading. Therefore, minimally invasive and non-invasive methods are gaining their popularity for continuous monitoring of blood glucose concentration. These two methods offer many advantages over the invasive method: For instance, no blood sample is required for this test [4]. As

can be seen in Figure 2, for the non-invasive approach, the measurement is taken indirectly from the deposited of the excretory system such as urine, sweat, tears and etc.

Figure 3 shows the chronology of the blood glucose monitoring systems since its first generation when it was first introduced in the 70s [3, 4]. The developments undertake to improve the way of measuring the blood glucose depend on several parameters such as the reading accuracy, techniques and approach, size of the device, and technology of the embedded systems. Each of this generation will be briefly discussed in the next section.
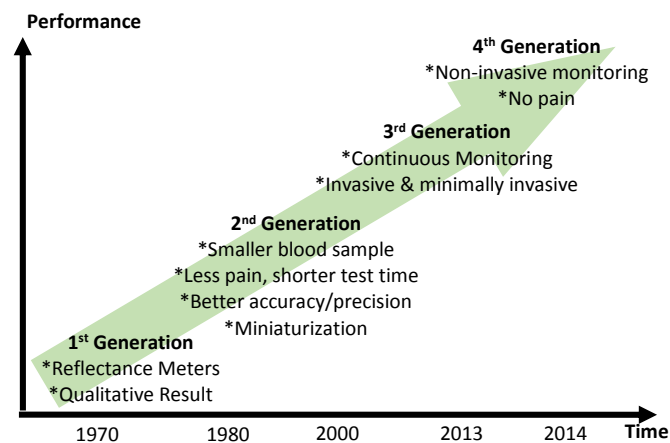

Figure 3: The graph of development of glucose monitoring.

A. First Generation (Invasive)

Anton Hubert (Tom) Clemens is an inventor of Ames Reflectance Meter (see Figure 4), the first blood glucose meter that had been patented in 1971 [4]. This glucose meter uses an enzyme test strip where the blood drop needs to be applied onto it and then washed away after the reading is taken. The blood glucose concentration will vary depending on the colour that will be read by the meter [5]. At the time when it was introduced, this instrument was expensive, relatively large in size and very heavy (approximately 1 kg). To use this device, it requires a relatively big amount of blood to be placed in the sensor area approximately 3/8 inch x 1/4 inch. The blood placement needs to be washed every time the blood glucose reading was taken, causing this device to be more suitable to be used in the hospital by the physicians rather than for personal home usage. This device became the reference design for subsequent reflectance colorimeters such as Eyetone (introduced in 1972) and the Ames Glucometer (introduced in 1971) [5, 6].

In 1975, Yellow Spring Instrument commercialised the YSI 23 model of glucose analyser based on the enzyme catalysed process glucose detection method developed by Clark and Lyons since 1962 [7]. This device utilized the oxidation of glucose, and subsequently the oxidation of the hydrogen peroxide that is formed during the initial response by glucose oxidase and enzyme horseradish peroxidase respectively [7]. In order to do the readings, this device requires only 25 µL of the whole blood sample, yet it was able to improve the detection accuracy in comparison to Ames reflectance meter [8]. Despite of being a stationary model linked to the doctor's office, this sensor technology had become the basis for the state-of-the-art

handheld devices of the second generation device, especially for home monitoring with an increasing amount of new products entering the market every year [5, 6].

Figure 4: Ames Reflectance Meter.

B. Second Generation (Invasive)

The ExacTech® strip is the first commercialised blood glucose meter for home application produced by MediSense (later it became part Abbott Laboratories) in 1987 [9]. This technology is based on the enzyme biosensor technology of Clark and Lyons as it utilizes an integrated electrochemical ferrocene-derivative mediator as an electron acceptor in contrast to the oxidation used in the earlier sensors [7, 10-12]. There is a lot of improvements that have been done to this device in terms of glucose reading accuracy, size and as well as its functionality for every version that has been released until now. This method of technology is still being used widely and it is run by several brands such as OneTouch by Lifescan and Nova Max Plus by NovaBiomedic. Examples of these glucose meters are presented in Figure 5 [13]. User needs to spend some money to buy the test strip because it is disposable and it comes with an expiration date [14].

Figure 5: The glucose meter in 21st century.

C. Third Generation (minimally invasive and continuous)

The third generation of the glucose monitoring system is more toward continuous monitoring. This monitoring technology is possible due to the development of a suitable sensor that can be inserted underneath a skin and can be left there for a week without requiring a draw of blood. The Medtronic MiniMed Company has been producing the first device of continuous glucose monitoring (CGM) system and this device has been approved by the American Food and Drug Administration (USFDA) in June 1991 [15]. Table 1 shows that there are only several types of commercially available CGM device approved by the USFDA or carry the European Commission (CE marking) for Europe market since the beginning of the twenty-first century. This personal CGM device is typically used by diabetes patients and pregnant mothers with gestational diabetes symptoms with the recommendation of their physician [16]. Some of personal CGM devices are available with alarms that indicate changes of glucose levels in blood using a marker or trend arrows, and some are equipped with predictive alarms, which can estimate whether the glucose threshold would be crossed based on the current value of glucose concentration and its rate of changes [17]. A personal CGM device is normally

owned by a patient. The patient can monitor their glucose level continuously every minute by using this system [18]. This CGM device can be used together with insulin pump where the whole systems are able to function like pancreases in the body. The insulin will be released into the blood circulation with the right dosage required by the body. This system is able to give a real-time glucose result that allows for immediate and continuous therapeutic adjustments on the insulin intake [13]. In this method, a nano-needle at the glucose sensor electrode is inserted under the skin to measure the glucose concentration levels in the tissue as shown in Figure 6.
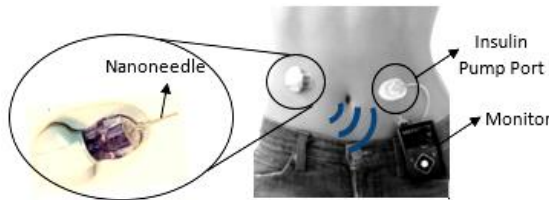

Figure 6: The minimal invasive CGM device

Table 1
Continuous Glucose Monitoring (CGM) Device [6, 19-23].

Device	Company
CGMS Gold® Guardian Telemetered Glucose Monitoring System and Guardian RT	Medtronic Diabetes (Northridge, CA)
GlucoWatch Biographer	Cygnus, Inc., (Redwood City, CA)
GlucoDay-S	A. Menarini Diagnostics, (Florence, Italy)
Dexcom Seven Plus	Dexcom (San Diego, CA)
FreeStyle Navigator	Abbott Diabetes Care (Alameda, CA)

D. Fourth generation (Non-invasive)

The recent development of the blood glucose monitoring device is more toward non-invasive method. This method is used to measure blood glucose levels in the human body by only placing the sensors directly to the human targeted area without drawing blood and insertion of needles or any types of biosensors as shown in Figure 7.

The study on the development of this technology has begun since 1957 and the works are still continuing up to the present. Since 2014, only a few numbers of devices that have been produced using this technology and they are only available in certain countries as can be seen in Table 2 [3]. Most of the non-invasive blood glucose monitoring device is registered under consumer product and not under a medical product because this device reads the value of the blood glucose without directly in contact with the blood. In the next section, the development of some of the available techniques of non-invasive glucose monitoring system are discussed.

Figure 7: The non-invasive method using ear lobe as a targeted area.

Table 2
Development of non-invasive device [24- 26].

Device	Description
C8 MediSensors - Optical Glucose Monitor System	• Technology used: Raman spectroscopy. • Target area: Skin • CE Mark approval (2011) • Available in certain countries • User characteristics: *pregnant *smokes *not exceeding 18 years old *skin tone (very light or dark)
GlucoTrack – Non-Invasive Glucose Monitors	• Technology used: Thermal, ultrasound, electromagnetic. • Target area: Ear lobe • CE Mark approved (2013) • Available in certain countries (2014)
OrSense NBM-200G (OrSense Ltd.)	• Technology used: Occlusion NIR spectroscopy • Target area: Fingertip • CE Mark approved
Echo Therapeutics – Continuous Glucose Monitor	• Technology used: Advanced skin permeation technology (three different permeation technology) • Target area: Skin

III. TECHNIQUES ON NON-INVASIVE BLOOD GLUCOSE MEASUREMENT

These are a few different approaches of non-invasive blood glucose monitoring technique. As can be seen in Figure 8, these techniques can be divided into two different methods, which are the use of transdermal or optical methods. By using a non-invasive method, it is an option for measuring the blood glucose level without any pain and no needle is involved [8]. This method uses an external sensor to indirectly track the blood glucose concentration, where the signal is recorded through the skin without imposing any damage [14, 27, 28]. The glucose measurement can be done on the fluids produced by the body other than blood, such as tears, sweat, saliva or urine [6-18, 27, 28]. However, continuous glucose monitoring using non-invasive approach can only be achieved by using direct measurement to the body tissues such as skin, tympanic membrane, cornea, tongue or oral mucosa. By using a suitable transducer of blood glucose sensor, it is able to detect a weak signal indirectly from the blood through intervening tissues, such as skin, bone and fat [28].
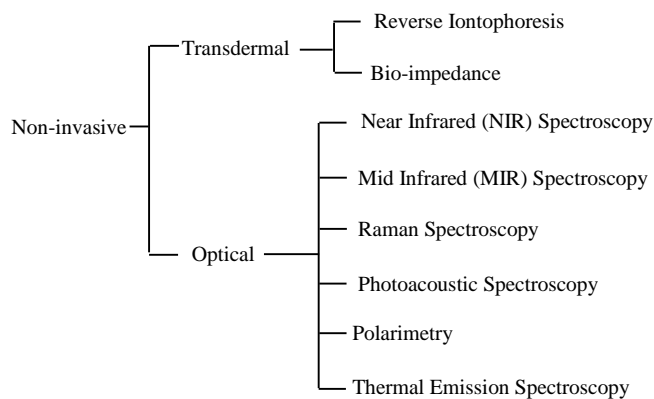
Figure 8: Non-invasive blood glucose measurement techniques.

A. Transdermal
i. Reverse Iontophoresis

The physical energy is used by reverse iontophoresis to access the interstitial fluid. In between the two electrodes across the skin, there is a low current applied as shown in Figure 9 [8, 27]. This will cause charged and uncharged molecules to pass across the dermis at a rate significantly greater than the passive permeability, the ions move in the skin to maintain the neutrality. At physiological pH (~5.0-6.0), skin is negatively charged [27]. Therefore, a positively charged ion will penetrate more easily across the skin than a comparably sized negative ion.
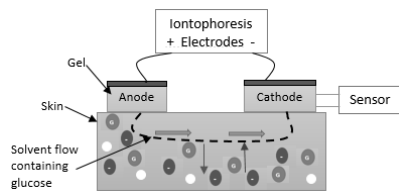

Figure 9: The basic concept of reverse Iontophoresis

This technique has several potential advantages over other enzyme-based electrode sensor systems. An oxygen supply is not a bound factor to glucose oxides that can cause an increase to the concentration of glucose. However, this technique requires a long time to get it ready for calibration and it is complicated [26]. The first commercial device that uses this technique is GlucoWatch biographer monitor developed by Cygnus Inc. [21, 28, 29]. However, GlucoWatch still has some problems, such as it is not reliable to detect hypoglycaemia [30].

ii. Bio-impedance spectroscopy

Bio-impedance spectroscopy method works by determining the dielectric properties of the skin tissue using two electrodes. As shown in Figure 10, the glucose concentration level in the body is determined by passing a small constant current at a fixed frequency between these electrodes and subsequently, determining the change of the voltage between these electrodes [6, 27].
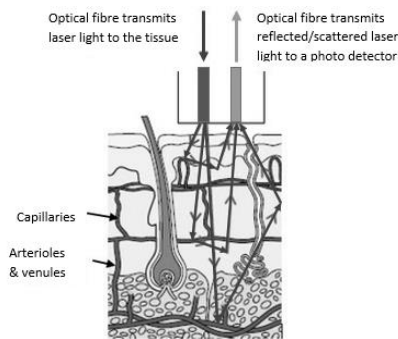

Figure 10: The basic concept of Transdermal.

The benefit of this method is the continuous nature of the measurement protocol (displayed the glucose level every minute), simple implementation and safety due to its non-invasive nature. However, this technology requires a high cost and a prolonged calibration period of about 1 hour [6]. This technology has been introduced in 2000. The first device in the market that uses this technique is Pendra Glucose Monitoring by Pendragon Medical in 2003, while Echo Therapeutics is the latest device that has been introduced to use this technique in 2011 [8, 26]. However, this device suffers serious inaccuracy limitations that could expose the user to potentially dangerous situations. The technique requires calibration and errors can occur due to variability, sweating and motion [27].

B. Optical

Spectroscopic technique is an optical method used to detect blood glucose by determining the quantity of light which is either absorbed, transmitted or emitted as a function of glucose concentration [6, 27]. A small variation of the light after the light is passing through the target tissue will be detected by the sensor [31]. Based on that concept, there are a few techniques that use an optical method for the glucose detection as can be seen in Figure 11 [32].
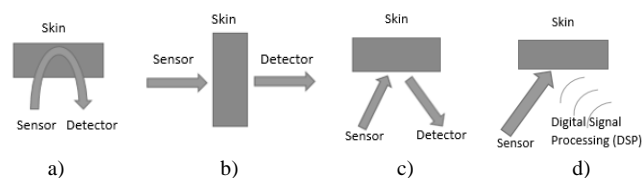

Figure 11: Diagram of different measurement configurations:
a) Transflectance b) Transmission c) Diffuse reflectance and
d) Photoacoustic.

i. Near-infrared spectroscopy (NIR)

NIR is based on the collection of tissue absorption or emission spectrum by diffused reflectance or transmission with a spectrometer as illustrated in Figure 12 [31]. This method utilizes light absorption or emission data with a wavelength between 700-2500 nm to detect the glucose in the blood glucose and Table 3 shows the characteristic of different wavelength region [33]. The absorption signature of water is less profound in this method, the signal related to glucose is weak compared to the MIR spectroscopy technology and powerful computer algorithms are required to interpret the sensor data [6, 14]. Burmeister and Arnold have done a study about NIR

transmission spectroscopy by using several different measurement sites, such as the cheeks, lip, tongue, nasal septum and tissue webbing and the results show that the tissue with less fat (tongue) provides spectrum with the highest signal to noise ratio [34].

Table 3
Characteristic of different wavelength region

Wavelength (nm)	Characteritics
700-1300	• Higher orders of glucose overtone regions • Little glucose absorption • Low light absorption of water
1500-2500	• Highest glucose absorption • Does not get effected by excessive water attenuation • Relative min. in water absorption spectrum

There are many researchers who had conducted a study in this area by using NIR and they had suggested that this technique is capable to detect the signal of glucose in the blood because NIR has a suitable wavelength ranging from 700 nm–1500 nm [35], and it has a high energy of measuring signal compared to MIR [36]. NIR has been used due to its cheaper cost, sensitivity, complexity, probability and selectivity [37]. Ilan Gabriely et al. and H. Michael have done a research based on NIR by using a transcutaneous NIR spectroscopy system to monitor blood glucose levels during glycaemia and hypoglycaemia [38, 39]. The results proved that NIR can be used to predict the glucose levels in the human body. Kamboh and Khan had done an experiment on non-invasive blood glucose monitoring by using NIR spectroscopy to compare the accuracy with a conventional invasive technique [40]. In that study, they used LED 1550E from ThorLab as a light source and Indium Gallium Arsenide (InGaAs) photodiode as a light detector. This experiment was tested on 80 people and the result shows that there is a correlation between these two measurements with high signal-noise-ratio (SNR) for glucose signals [36, 41].

The NIR technology for blood glucose monitoring has been used by Sensys Medical (USA), NIR diagnostics (Canada), Medicontract with Diabetic Trust (Germany) and Biocontrol Technology (USA) [42].
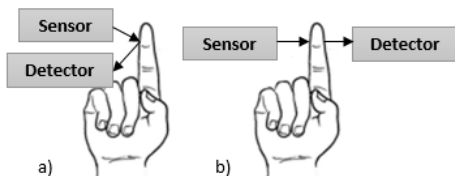

Figure 12: The basic concept of NIR and MIR: a) Diffuse reflectance b) Transmission

ii. Mid-infrared spectroscopy (MIR)
Similar to NIR, MIR is also based on light transmitting from the MIR transmitter through a skin tissue as can be seen in Figure 12. The glucose concentration light can be measured from the signal that is not being absorbed and can be detected by detectors. This method utilizes light with wavelength in the range between 2.5 to 10 µm [43, 44]. However, this method has the main disadvantage, which is a limitation of the light path to penetrate into the tissue [27]. Moreover, the result signal has the presence of noise that affects other molecules such as water and other non-glucose metabolites which modulates the magnitude of the absorption peak of glucose light [6]. Technology MIR has been used in the European Union (EU) project called "Clinicip" to monitor the glucose concentration in intensive care units [6].

iii. Raman spectroscopy
Raman spectroscopy applies a laser light of one wavelength, where the quantification and identification of blood glucose is judged by the changes in the frequency of the light that result from inelastic scattering of the oscillation and rotation motions in the glucose molecule [45, 46]. Figure 13 shows the basic concept on how Raman spectroscopy works for glucose detection. The advantage of Raman spectroscopy is that it has a high molecular specificity. It can reduce the interference of water compared to MIR or NIR spectroscopy due to weak diffusion index of water [28, 41]. However, the disadvantage of this technology is that it requires a laser radiation source. This can be dangerous to the cells because it may impend triggering photo thermal damage to the skin cells [28, 44]. Moreover, this technology requires a powerful detector and complicated instrumentation because of the detected signal is extremely weak causing the noise to be very visible after an interaction with different tissue component [44, 47].
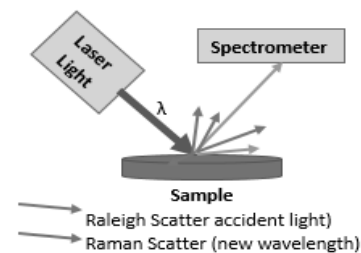

Figure 13: The basic concept of Raman spectroscopy.

iv. Photoacoustic spectroscopy
Photoacoustic spectroscopy utilizes waves of ultrasonic caused by the absorption of infrared light to measure the glucose concentration. The illustration of the Photoacoustic spectroscopy is shown in Figure 14. This method has the advantage of using optical radiation levels at several orders of magnitude below the threshold of pain or tissue damage as well as utilizing components that permit a compact portable sensor design to be made [48]. However, this technology suffers from the noise created from non-glucose blood components which needs to be excluded from the measurements [6].
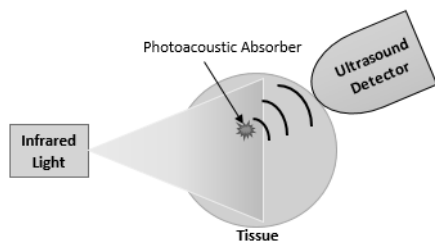
Figure 14: The basic concept of Photoacoustic spectroscopy.

v. Polarimetry

Polarimetry depends on the optical rotary dispersion of polarized light which means that all waves of light vibrate on the same plane [29, 49]. The rotation of the linear polarized light depends on some factors such as temperature, thickness and concentrations of the crossed sample [49, 50]. In the field of pharmaceutical and nutritional industries, this technology has been used since a long time ago to find out the level of the compounds in every mixture. However, the main target is not the skin tissues because high dispersion coefficient generates full beam depolarization [42]. This technology can be used to observe glucose from the aqueous humour of the eye which shows a minimal scattering and absorption effect and it interacts with the degree of rotation of the polarization vector that is proportional to the concentration of glucose. The use of complex multivariate calibrations can be bypassed using a single laser wavelength. This method has a weakness because it requires an external laser scanner which has to be accurately positioned in front of the eye and it is also sensitive towards variations of temperature and pH [50]. Additionally, this method also has a time lag for a few minutes before a change in the blood glucose concentration can be observed in the eye. This method has not yet undergone human trials due to safety limitation [28].

vi. Thermal emission spectroscopy

Thermal emission spectroscopy is based on the temperature variation measurement. By passing infrared (IR) signals through the human cell, the changes of the output signal generated from the IR is presented as changes in glucose concentration [27]. The light of IR radiation can be emitted by the human body and only specific wavelength can be permitted using a special filter for glucose measurement to pass to a detector [42]. The glucose concentration in blood depends on the intensity of the wavelength specific to the radiation. However, this technology is also affected by a variation of body temperature and sensitive to the motion [27, 28]. The technology for glucose fingerprint uses the same concept as standard clinical tympanic membrane thermometers and it requires an additional specific wavelength of 9.8 µm and 10.9 µm [27]. This technology has been applied by Infratec (Germany).

IV. CONCLUSION

Non-invasive glucose monitoring devices have many advantages for diabetic patients. Since 1970, a lot of work have been done to improve the overall method of non-invasive glucose meter and monitoring systems. It is designed to be compact, wearable, lightweight and water resistant with advanced microelectronics chips that can be monitored by smartphones. Most of these devices are very expensive and categorised under consumer device.

In general, all non-invasive optical glucose sensor technology suffers from human environmental factors such as body temperature, skin moisture, skin thickness and motion, which makes it difficult to be used due to the optical path of the excitation light. This technology also requires certain specifications of the user, given that the tissue composition and optical path length varies from one user to another. Because of that, glucose meter using strip is still very popular until now.

The most common technology that has been widely studied is the NIR spectroscopy and MIR spectroscopy approaches. This is due to the reason that this method has a spectrum range with the ability to penetrate the light from 1-100 mm deep into the tissue as can be seen by the characteristics map in Table 3. Between these two technologies, NIR is claimed to be a better technique due to its cheaper cost, better sensitivity, complexity, selectivity, and better SNR.

However, there are a few parameters such as temperature, skin thickness and skin colour that need to be focused and considered when using NIR spectroscopy technique since this will affect the measurement result. Therefore, improvements can be done by using a combination of various sensors to measure other parameters such as temperature and pulse sensors. Thus, the results will be considered in the algorithm development.

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