APPLICATION OF SMARTPHONE-BASED BIOPHOTONIC INSTRUMENTATION FOR GLUCOSE SENSING USING PHOTOMETRIC METHOD

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by

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LIST OF SYMBOLS

$C_6H_{12}O_6$	Glucose
°C	Degree celcius
dL	Decilitre
g	Gram
g/cm^3	Gram per centimetre cube
g/dl	Gram per decilitre
g/mol	Gram per mol
GaAs	Gallium arsenide
Hz	Hertz
kB	Kilobyte
kΩ	Kiloohms
$LiNbO_3$	Lithium niobate
mA	Milliampere
MB	Megabyte
mg	Milligram
mg/dL	Milligram per decilitre
ml	Milimetre
mm	Milimetre
nm	Nanometre
V	Volt

LIST OF ABBREVIATIONS

AC	Arm Cortex
ADC	Analog-to-digital converter
ADC_VREF	Analog-to-digital converter reference voltage
AOM	Acousto-optic modulator
APD	Avalanche photodiode
ATP	Adenosine triphosphate
BAQS	Bioluminescent-based Analyte Quantitation by Smartphone
CCD	Charge-coupled device
CMOS	Complementary metal-oxide semiconductor
CPU	Central processing unit
DAC	Digital-to-analog converter
DM	Diabetes mellitus
DRS	Diffuse reflectance spectroscopy
e.g.	Exempli gratia
EOM	Electro-optic modulator
FTIR	Fourier Transform Infrared
GND	Ground
GP	General purpose
GPIO	General-purpose input/output
GPS	Global positioning system
HPLC	High-performance liquid chromatography
IBGDD	Integrated Blood Glucose Detection Device
IBM	International Business Machines
IoT	Internet-of-Things
ISO	International Organization for Standard
LED	Light emitting diode

MB	Microcontroller board
MyFCD	Malaysian Food Composition Database
NIR	Near-infrared
NREA	Noise reduction by ensemble averaging
OCT	Optical coherence tomography
OGTT	Oral glucose tolerance test
OS	Operating system
OTG	On-the-go adapter
PMT	Photomultiplier tube
PWM	Pulse width modulation
RAM	Random access memory
RGB	Red, green and blue
RI	Refractive index
SNR	Signal-to-Noise ratio
T2DM	Type 2 diabetes mellitus
TOM	Thermo-optic modulator
USB	Universal serial bus
USDA	United States Department of Agriculture
UV	Ultraviolet
Vpp	Voltage peak-to-peak
YSI	Yellow Springs Instrument

APLIKASI INSTRUMENTASI BIOFOTONIK BERASASKAN TELEFON PINTAR UNTUK PENGESANAN GLUKOSA MENGGUNAKAN KAEDAH FOTOMETRI

ABSTRAK

Pengesanan glukosa adalah penting dalam kesihatan seperti pemantauan tahap glukosa dalam darah dalam pengurusan penyakit diabetes, dan juga dalam penjagaan kualiti makanan, contohnya, pengesanan madu tiruan. Kaedah terkini melibatkan teknik invasif, peralatan yang mahal dan juga ahli kakitangan yang terlatih untuk menjalankan ujian. Hal ini boleh mengehadkan aplikasi pengesanan glukosa pada tempat kajian. Kajian ini bertujuan untuk mengaplikasikan instrumentasi biofotonik berasaskan telefon pintar untuk mengukur kepekatan glukosa menggunakan kaedah fotometrik. Peranti fotonik yang direka bentuk terdiri daripada diod pemancar cahaya inframerah dekat (NIR LED) 940 nm sebagai pemancar, fotodiod BPW34 sebagai alat pengesan, papan mikropengawal Raspberry Pi Pico yang bertindak sebagai perantara digital untuk menukarkan data yang diterima kepada voltan keluaran, dan beserta aplikasi Android iaitu Scoppy sebagai osiloskop digital untuk memaparkan nilai voltan yang dikesan. Instrumen yang direka bentuk dapat mengesan glukosa pada kepekatan berbeza. Julat kepekatan glukosa yang lebih rendah dan lebih tinggi telah diuji iaitu 50 – 300 mg/dL untuk tujuan pengesanan glukosa dalam badan manusia, manakala 10 – 100 g/dL untuk menunjukkan tahap glukosa dalam makanan tiruan seperti madu. Penemuan kajian menunjukkan bahawa kepekatan glukosa yang lebih tinggi menghasilkan nilai voltan keluaran yang lebih tinggi. Analisis regresi linear yang diperolehi ialah R^2 = 0.9389 dengan nilai kecerunan 0.0002 untuk julat glukosa yang lebih rendah, dan R^2 = 0.9641 dengan nilai kecerunan 0.0011 untuk julat glukosa yang lebih tinggi. Keputusan yang diperolehi untuk penyerapan foto dan kehantaran foto masing-masing ialah $A < 1$, dan $T > 1$ bagi kedua-dua julat kepekatan glukosa. Kajian ini menunjukkan hasil yang baik dari segi kebolehlaksanaan, kepekaan dan kebolehgunaan dalam mengintegrasikan instrumentasi biofotonik dengan telefon pintar.

APPLICATION OF SMARTPHONE-BASED BIOPHOTONIC INSTRUMENTATION FOR GLUCOSE SENSING USING PHOTOMETRIC METHOD

ABSTRACT

Glucose sensing is vital in health such as monitoring blood glucose levels in managing diabetes and food quality, for instance, adulterated honey detection. Current methods involve invasive, expensive equipment and highly trained personnel to carry out the test, which can limit the detection and application of glucose at on-site determination. This study aimed to apply smartphone-based biophotonic instrumentation for measuring glucose concentrations using the photometric method. The photonic device constructed consists of a 940 nm near-infrared light-emitting diode (NIR LED) as an emitter, a BPW34 photodiode as a detector, a Raspberry Pi Pico microcontroller board acts as a digital interface to convert the receiving data into output voltage, and an Android app; Scoppy as a digital oscilloscope to display the output voltage value on a smartphone. The instrument detected the glucose at different concentrations. A lower and higher range of glucose concentrations was tested which is 50 – 300 mg/dL for glucose in human body detection purposes, whereas 10 – 100 g/dL demonstrates the level of glucose in adulterated food such as honey. The findings indicated that higher glucose concentrations resulted in higher detector output voltages. The linear regression analysis obtained is $R^2 = 0.9389$ with slope value of 0.0002 for lower and $R^2 = 0.9641$ with slope value of 0.0011 for higher range of glucose concentration. Results obtained for photoabsorption and phototransmittance were $A < 0$, and $T > 1$, respectively, for both range of glucose concentrations. This study demonstrates a promising result in terms of feasibility,

sensitivity, and applicability in integrating biophotonic instrumentation with a smartphone.

CHAPTER 1

INTRODUCTION

1.1 Background of study

1.1.1 Glucose sensing

Glucose, a type of simple sugar, also known as a monosaccharide, is a combination of carbon, hydrogen, and oxygen with the molecular formula denoted by $C_6H_{12}O_6$. It is a vital energy source for living organisms and a key product of photosynthesis in plants. In humans, glucose is obtained through the breakdown of carbohydrates in food or meals such as bread, pasta, fruits, and vegetables. Once in the body, glucose is transported through the bloodstream and taken up by cells, where it undergoes cellular respiration to produce adenosine triphosphate (ATP), the key molecule driving cellular functions. Meanwhile, glucose is also a key monosaccharide abundant in many foods such as common starch-containing foods including corn, bread, rice, and potatoes, in plants and fruits, and sugary drinks, particularly abundant in honey. Foods that are broken down quickly, like simple sugars and refined grains, tend to be high in glucose and can cause rapid spikes in blood glucose levels.

Glucose sensing is vital across various domains, including health, food quality, and economy. In the context of health, glucose detection is essential for monitoring blood glucose levels in preventing and managing conditions like diabetes. Moreover, in the detection of adulterated food, honey adulteration is a common issue since glucose content is a key indicator of honey authenticity. Economically, the ability to accurately sense glucose levels will impact the food industry by ensuring the quality of products like honey as it helps ensure the quality and authenticity of honey products, which can impact consumer trust and ultimately the industry's profitability.

1.1.2 Optical methods in glucose sensing

Considering that optical methods have gained significant attention due to their non-invasive nature and rapid analysis capabilities, there are few approaches of optical methods accessible for glucose sensing. According to Ramachandran *et al*. (2023), the non-invasive blood glucose measurement system has been improved by using optical approaches such as near-infrared (NIR) spectroscopy, Raman spectroscopy, and optical coherence tomography (OCT). NIR spectroscopy employs light to determine glucose levels, by shining light at the specific NIR wavelengths on the sample/subject, and the amount of light that is transmitted or reflected is then measured. The glucose level can be determined by calculating the amount of light received. Raman spectroscopy, which operates on the same principle as NIR spectroscopy, measures glucose levels using laser light. The emitted laser will interact with the glucose molecules to measure and calculate glucose levels in the sample. This interaction will cause the molecules to vibrate in a unique way. Moreover, OCT is a technique that employs light waves to generate a three-dimensional image of the skin tissue. The changes in glucose concentration produce changes in the tissue, which may then be analysed to determine the glucose levels.

On the flip side, optical methods are also employed in adulterated food like honey authenticity detection. For example, fibre optic sensors, such as fibre optic displacement sensors, can also detect glucose adulteration by measuring changes in the refractive index of honey. Moreover, optical methods like the Fourier Transform Infrared (FTIR) spectroscopy technique identify unique spectral fingerprints of pure honey, distinguishing it from adulterated samples by analysing their molecular composition and light interaction properties (Mail *et al*., 2019). These optical offer advantages such as simplicity, low-cost, and non-contact sensing, making them promising tools for both glucose sensing in the human body and adulterated food detection.

1.1.3 Application of smartphone in biophotonics

In 1994, the leading smartphone namely Simon Personal Communicator was launched by International Business Machines Corporation (IBM) and smartphones began to be familiarised throughout the year (Nuhel, 2021). Over the years, smartphones have undergone significant evolution by various companies such as Samsung, Apple, and Nokia, transitioning from basic devices to powerful tools with advanced features and capabilities. The smartphone industry continues to innovate, with technical features evolving rapidly, elevating its usage potential in health. Equipped with advance sensors, cameras, and connectivity features, smartphones have become ubiquitous, making them an ideal platform for various health applications, including fitness tracking heart and activity monitors (Majumder & Deen, 2019), and glucose sensing (Bartolic *et al*., 2018). Health apps can analyse data from embedded sensors to offer personalized insights, reminders and alerts, empowering users to manage conditions like diabetes, hypertension and mental health more effectively.

In addition, smartphones can be integrated with photonic devices to enhance health monitoring and sensing through biophotonic applications. One approach is to use smartphones as platforms for optical fibre biosensors, which can be integrated with the phone's camera and flashlight as a light source to enable real-time monitoring and data analysis (Bowden & Hussain, 2021). Another approach is to leverage the smartphone's built-in sensors such as ambient light sensors and thermal sensors, to develop wearable optical sensors that can monitor physiological parameters like heart rate, blood oxygenation and skin temperature. Furthermore, smartphones can be used in spectroscopic applications, e.g., control external optical systems such as spectrometers, by capturing the wavelength spectrum using the phone camera.

1.2 Problem statement

The current condition in Malaysia is that most of the available glucose sensing devices' prices are relatively high, resulting only some people can afford to buy them for home or laboratory use. In health issues, current methods in determining glucose levels are still invasive, in which it require skin pricking. Moreover, people diagnosed with diabetes who do not have the proper equipment to check their glucose level must come to health services centres such as hospitals, public health centres, and private clinics, which often has many obstacles in utilizing the facilities either because of the distance, costs, or time. In this regard, there is an urgent need for an alternative solution, which is a cost-effective non-invasive glucose detection device that will allow individuals to monitor their glucose levels independently. Furthermore, in the food industry, food adulteration such as honey authenticity issue has come into question. Even though existing methods such as high-performance liquid chromatography (HPLC) tests are suitable for complex mixtures, however, it requires expensive equipment and highly qualified trained personnel to carry out the test. These requirements limit the detection and application of glucose at on-site determination.

Considering that health monitoring applications and devices are becoming more popular, such as heart rate and blood pressure monitoring, researchers have coupled optical methods for glucose sensing using smartphone-based technologies in order to overcome this issue. Sathiyanarayanan *et al*. (2019) have proposed a non-invasive near-infrared spectroscopy model with a smartphone application. Meanwhile, Wang *et al*. (2020) conceived developing an optical method for urine glucose detection using a smartphone ambient-light sensor. However, the details of the feasibility, sensitivity, and applicability of the designed system are not being properly highlighted in the mentioned study. This study will design and construct a suitable smartphone-based biophotonic instrumentation for glucose sensing that can verify the feasibility, sensitivity, and applicability of the designed instrumentation. Hence, it could be further consolidated into the form of a wearable, reliable and easy-to-perform glucose monitoring device, in terms of health monitoring and/or food adulteration detection.

1.3 Aim of study

The aim of this study is to apply smartphone-based biophotonic instrumentation for measuring glucose concentrations using the photometric method.

1.3.1 Specific objectives

1. To design and construct smartphone-based instrumentation using NIR light-emitting diode (LED), BPW34 photodiode, and Raspberry Pi Pico microcontroller board configured for photometric measurement.
2. To prepare glucose solution with different glucose concentrations.
3. To measure phototransmittance and photoabsorption of glucose solution using the Scoppy application.
4. To analyse the feasibility, sensitivity and applicability of the constructed instrumentation and method for glucose sensing.

1.4 Significance of study

The purpose of this study is to implement a suitable smartphone-based biophotonic instrumentation for glucose sensing purposes by utilizing photometric method. Then, the degree of feasibility, sensitivity, and applicability of the constructed instrumentation and method for glucose sensing purpose can be determined. This study aims to provide individuals with or without diabetes with accurate glucose level measurement values in managing their health condition. In addition, society may gain a better understanding of the importance of self-monitoring glucose levels in their body and consuming nutritionally rich foods; alternative sweeteners such as pure honey is crucial, thus able to control their dietary lifestyle, and aiding better glycaemic control. Besides, the detection of adulterated food raises society the awareness about the prevalence and risks of adulterated food such as honey, and diabetic individuals can make more informed choices by selecting certified pure honey, thereby avoiding the potential health risks associated with adulterated products. Furthermore, it may assist the researcher gain an in-depth understanding of the application of smartphones in health monitoring, and into more accurate and efficient detection methods contributing to the development of advanced analytical techniques. Moreover, practitioners such as doctors, nurses, or medical assistants may recommend preferable methods that can be used to accurately determine patients' glucose levels based on their knowledge and experiences, able to educate patients and help dietitians and nutritionists in providing more precise dietary advice. Finally, this study provides the government with a new perspective to suggest a new method for managing the prevalence of diabetes in the country, reducing the risk of mortality due to this chronic disease across the country and globally as well as leading to stricter regulations and standards in the food industry.

CHAPTER 2

LITERATURE REVIEW

2.1 Glucose

2.1.1 Physical properties of glucose

Glucose, also called dextrose or the compound D-(+)-glucose is a 6-carbon structure with an aldehyde group, a molecular weight of approximately 180.16 g/mol, and a density of 1.5620 g/cm^3 (at 18°C). Glucose can be found in different states, including dissolved in water, dispersed as a crystalline phase, immobilized in amorphous or glassy form, or in combinations of these states. The ability of glucose to dissolve in aqueous or water-based solution has become an important property of glucose, since the blood, the extracellular fluid, and the fluid inside cells are all water-based, for glucose to dissolve in the bloodstream and be able to pass into cells, it must dissolve well in water (Narkhede *et al*., 2016). All forms of glucose are colourless, taste sweet and easily soluble in water, acetic acid and several other solvents. In terms of thermal properties, glucose has a melting point of around 146°C and a boiling point of 294.8°C. Overall, the physical properties of glucose are critical in understanding its behaviour in various applications, from medicine, health, food processing to industrial use.

2.1.2 Glucose in the human body

Glucose serves as the primary source of energy for all human living cells. In humans, glucose is obtained through the breakdown of carbohydrates in meals such as bread, pasta, fruits, and vegetables. Once in the body, glucose is transported through the bloodstream and taken up by cells, where it undergoes cellular respiration to produce ATP, the key molecule driving cellular functions. The level of glucose in the blood is tightly regulated by various hormones, particularly insulin and glucagon, to ensure a constant and adequate energy supply to cells. In general, the pancreas plays a significant role in regulating blood glucose levels. In instances of high blood glucose, the pancreatic β-cell will secrete the insulin hormone, in which the release of insulin facilitates the conversion of glucose into glycogen for storage or utilization by insulin-dependent tissue, such as muscle cells (Rahman *et al*., 2021).

Conversely, when the blood glucose level drops too low, a peptide hormone known as glucagon will be produced in the α-cells of the pancreas, and released, in order to raise the blood glucose level. Glucagon prompts the liver for glycogen to breakdown into glucose, which is then released into the bloodstream. Glucose metabolism is critical for the proper functioning of the brain, muscles, and other vital organs. Disruptions in glucose homeostasis can lead to metabolic disorders such as diabetes mellitus (DM). In individuals with DM condition, there is an imbalance in insulin and glucagon secretion, often resulting in either absent and/or impaired insulin function, leading to a condition known as insulin resistance (Sapra & Bhandari, 2023). Insufficient of insulin leads to abnormal carbohydrate metabolism and elevated glucose levels in the bloodstream and, therefore, could lead to hyperglycaemia (Dhatariya *et al*., 2020).

The typical normal range blood glucose level (fasting) and after eating (postprandial) falls within the range of 70 – 100 mg/dL and <140 mg/dL, accordingly. When a person having blood sugar level exceeds these thresholds, is indicative of having diabetes. Specifically, for prediabetes or type 2 diabetes mellitus (T2DM), impaired fasting glucose range is defined as levels ranging from 100 – 125 mg/dL, while impaired oral glucose tolerance test (OGTT) range at two hours post-ingestion of 75-g oral glucose range from 140 – 199 mg/dL (Rao *et al*., 2004; Eyth *et al*., 2023). The 75-g OGTT is a glucose level determination conducted using a second blood sample that is collected two hours after consuming a sweet drink containing 75 grams of glucose. Besides, for diabetes people, the range of blood sugar level is ≥200 mg/dL for two hours post-OGTT, and at or above ≥126 mg/dL for fasting blood glucose (Mathew *et al*., 2023).

Table 2.1 Blood glucose level at different conditions (Saleh *et al*., 2018)

Condition	Fasting	Just ate	3 h after eating
Normal	80–100	170–200	120–140
Pre-diabetics	101–125	190–230	140–160
Diabetic	≥126	220–300	≥200

2.1.3 Glucose in food

Glucose is a fundamental component of various foods, often present either as a free monosaccharide, commonly bound to other simple sugars, forming disaccharides like sucrose and lactose, and polysaccharides such as starch and cellulose (Steyn & Temple, 2014). Glucose can be found naturally in fruits, honey, and some vegetables, which contributes to their sweet taste and nutritional value or is added to processed foods in the form of dextrose, which is extracted from cornstarch. In food applications, glucose serves numerous purposes such as sweetening agents e.g., glucose syrup and glucose-fructose syrup (Piekara *et al*., 2020), humectant to maintain moisture as it is highly interacted with water (Tas *et al*., 2022), fermentation substrate to produce alcoholic beverages e.g., ethanol fermentation (Maicas, 2020) ingredient in confectionery products like candies, toffee and fondant (Lungade *et al*., 2022).

In the context of honey, honey is a natural sweetener primarily composed of various sugars, with glucose and fructose being the most prevalent. It is a highly concentrated sugar solution, with sugars accounting for about 80 – 85% of the total solids in most honey (Islam *et al*., 2020), and can vary significantly as the exact composition can depend on factors such as the types of flowers used by the honeybees, as well as regional and climatic conditions. According to the Malaysian Food Composition Database (MyFCD) (2022), approximately 27.6g amount of glucose in 100g serving of honey. Meanwhile, according to the United States Department of Agriculture (USDA) (2019), 35.8g of glucose typically accounts in a 100g portion of honey. However, in adulterated honey, honey has been tampered with by adding substances such as sugar syrups, corn syrups, glucose, dextrose, molasses, inverted sugar, or other sweeteners (Kingsta *et al*., 2018). The presence of glucose in food is not only essential for providing energy but also influences metabolic health, appetite regulation and the risk of developing metabolic disorders.

2.2 Biophotonic

2.2.1 Definition

Biophotonics involves the use of optical or photonic technology or device to examine, track and perhaps to control a biological process at different levels ranging from molecules, cells, tissue and organismal levels (Yeh & Krishnan, 2018). In general, this field encompasses the ideas of optical devices such as light sources, detectors, and cameras, as well as special instruments such as microscopes to study biology. The field of biophotonics has developed rapidly since the emergence of optoelectronics half a century ago. (Månefjord *et al*., 2022). Over the last few years, researchers have applied biophotonic instrumentation for various purposes such as environmental monitoring

(Brydegaard & Svanberg, 2018), medicine; phototherapy in cancer treatment (Spyratou *et al.,* 2023) and imaging system for in vivo and in vitro studies (Alam *et al*., 2018).

2.2.2 Photonic devices

2.2.2(a) Emitter

In the realm of photonic devices, an emitter refers to a quantum source that generates photons with specific properties, consisting of a continuous stream of photons, or quantized, where individual photons are emitted. Emitters are crucial in photonic devices as they enable the manipulation and detection of light. In photonic devices, emitters are typically semiconductor-based and can be categorized into different types depending on their functionality. The process of converting electrical energy into light by emitter involves the movement of electrons within a semiconductor material. When a voltage is applied, an electric current flow through the material and electrons will recombine with electron holes in the device to release energy in the form of photons (Zarrintaj *et al*., 2018).

This phenomenon is known as electroluminescence in emitters like LED. This process is vastly different from photoluminescence. Photoluminescence, on the other hand, is the spontaneous emission of light from a material under optical excitation. The photoluminescence technique relies on the emission of energy from a specific range of electronic states that are occupied by thermalized electrons. This results in a narrower and more sensitive spectrum compared to the absorption spectrum, which is measured by different processes (Alshehawy *et al*., 2021).

2.2.2(b) Detectors

On the other hand, a detector in photonic devices is a component that is essentially used for detecting and capturing optical signals, and convert it into a signal of another form, commonly an electrical response. There are two types of detectors, which are photon detectors and thermal detectors. The fundamental working principle of photon detectors involves the photoelectric effect, where photons interact with the detector material to produce an electrical response, specifically, incident photons are absorbed by the detector material, which then generates electron-hole pairs. These charge carriers are then separated and collected to produce a measurable electrical current (Yang *et al*., 2021) or voltage proportional to the intensity of the incident light.

Meanwhile, thermal detectors operate by converting photon energy into heat. However, most thermal detectors are rather inefficient and relatively slow as a result of the time required to change its temperature. Consequently, for most applications in photonic, this type of detector is not suitable to be used. The response of photonic detectors is typically wavelength-dependent, whereas thermal detectors have a nearly constant response across a wide spectral range. Compared to thermal detector, the prior one are essential components in a wide range of applications, including optical communications systems where they convert light signals back into electrical signals for data processing (Nkemdilim & Chukwujekwu, 2021)., and imaging systems such as cameras and medical diagnostics equipment like X-ray (Ren *et al*., 2018). The detector's response is a function of the optical wavelength, with different types of detectors exhibiting varying levels of sensitivity and wavelength range. The main configurations of photonic detectors include PN photodiodes, PIN photodiodes, the avalanche photodiode (APD), and the Schottky photodiode (Damulira *et al*., 2019) each with specific characteristics tailored to different applications.

2.2.2(c) Manipulator/modulator

A manipulator or modulator in photonic devices refers to a mechanism that can manipulate or modulate the properties of light signals. This component is used to modify the amplitude, phase, or polarization of light, which is essential for applications such as data transmission, sensing, and imaging. There are several types of photonic modulators, each with distinct working principles. The electro-optic modulator (EOM) utilises the electro-optic effect, which provides the necessary change in the optical properties of certain materials when subjected to electric fields of a frequency substantially below the light wave (Sinatkas *et al*., 2021). A common material for EOM is lithium niobate ($LiNbO_3$) (Wooten *et al*., 2000, Li *et al*., 2020) which it has strong electro-optic properties. The modulator of the electro-refraction type is when the electro-optic effect modifies the refractive index, commonly employing an interferometer, for instance, Mach-Zehnder structure or a resonator such as a microring, meanwhile, the modulator of electro-absorption type is when the material losses are modified (Sinatkas *et al*., 2021b).

Next, thermo-optic modulator (TOM) rely on the thermo-optic effect, where the refractive index of a material changes strongly dependent on temperature in many cases (Pisal *et al*., 2016; Xie *et al*., 2023). The phase or amplitude of the light can be modulated by locally heating the device to change the temperature of a waveguide. A common material for TOM is usually silicon due to its high thermo-optic coefficient and demonstrates excellent performance, compatible with complementary metal-oxide semiconductor (CMOS) fabrication process (Wu *et al*., 2024). Then, in exploiting the acousto-optic effect, where the presence of strain from acoustic waves generates a periodic modulation in the refractive index of a medium, an acousto-optic modulator (AOM) is utilised. The frequency and amplitude of the radiofrequency mechanical waves manipulate and control the deflected light into different spatial modes, modulate the intensity, frequency shifting, and rotation of the polarization of light (Beller & Shao, 2022). This modulator is widely used in laser-based systems for beam shaping and frequency control (Grünewald *et al*., 2022). The AOM offers outstanding performance including high extinction ratios, large carrier suppression, broad optical bandwidths, and fast responses, which are challenging to achieve using other approaches like EOM and TOM (Beller & Shao, 2022b). Each type of modulator has its advantages and trade-offs in terms of speed, efficiency, integration capability and operational wavelength range.

2.2.3 Optical methods

2.2.3(a) Photometric

The photometric approach concerned with measuring, and analysis of the light intensity transmitted, absorbed, scattered or reflected by samples. In this context, the interaction between light and glucose molecules in the sample will produce signals in voltage value that can be detected and analysed, in which the method involves the usage of the emitter and a photodetector as a receiver. This setup allows for the precise measurement of light absorption, transmission or reflection in the samples. Various research papers provide insights into photometric techniques in biophotonic. Nosova *et al*. (2015) discussed the importance of photometric curves in coagulation tests, highlighting the significance of optical focus and reagent mixing methods. Additionally, Manurung *et al*. (2019) focused on an Internet-of-Things (IoT) using a machine learning model for a non-invasive blood glucose monitoring system, in which the study emphasized the near-infrared spectroscopy that consists of NIR LED as a transmitter and NIR photodiode as a receiver. These studies collectively showcase the diverse applications of photometric methods in biophotonics, ranging from coagulation tests to blood glucose monitoring.

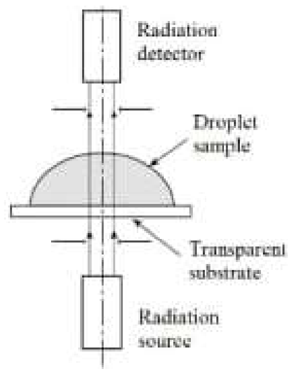

Figure 2.1 Proposed method of photometric study of droplet samples (Nosova *et al*., 2015)

2.2.3(b) Spectrometric

Spectrometric is the measurement of the interaction between electromagnetic radiation and matter, typically involving the analysis of the amount and wavelength distribution of light absorbed or emitted by a sample. The idea of spectrometric is that because different substances undergo different motions on the subatomic or molecular scale, the spectrum of each must have a unique pattern of peaks (Lewis & Kim, 2013). In reality, however, substances with very similar structures could behave in a very similar manner, with the result that instrumentation is not capable of discriminating them. In addition, the spectrometric technique uses either monochromator or polychromator to isolate specific wavelengths from a light source and measure absorption across the electromagnetic spectrum. For instance, a study by Campbell *et al*. (2020) developed the NIR reflectance glucometer using a spectrometric technique in the detection of a change in glucose concentration. In a study by Yuniati and Rifai

(2019), the researchers developed a spectrophotometer, which is a type of spectrometer that used a spectrometric technique, tested to measure the wavelength absorbed by the copper (II) sulphate samples with varying concentrations and two types of food dye solutions.

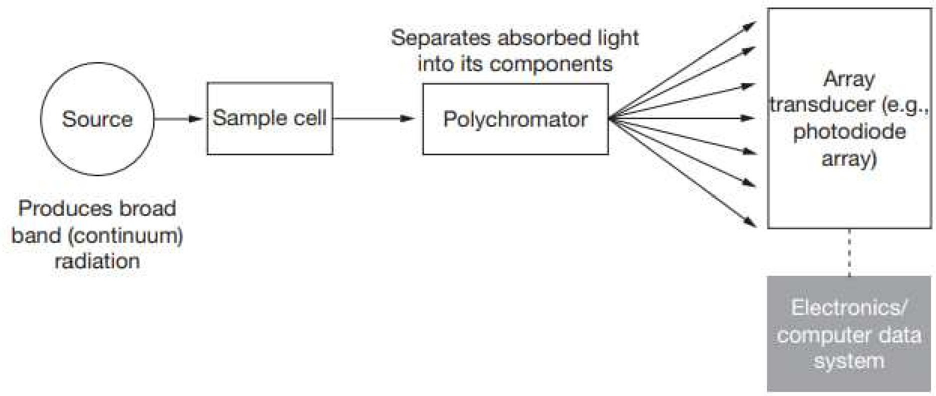

Figure 2.2 Schematic diagram of an array spectrometer (Lewis & Kim, 2013).

2.2.3(c) Colorimetric

The colorimetric method in biophotonics is a technique that involves measuring the concentration of a specific substance in a solution based on the colour changes that occur during the chemical reaction. The working principle of this technique also relies on the Beer-Lambert Law, which states that the absorbance is directly proportional to the concentration. In practice, a sample containing the analyte of interest is mixed with a reagent that reacts to produce a colour change. The intensity of the resulting colour is measured using a colourimeter (Choodum & NicDaeid, 2016). In biophotonic applications, colorimetric is often used to determine the concentration of analytes in solutions. For example, a colorimetric sensor for cholesterol assay was constructed by combining a molecular imprinting technique with photonic crystals, allowing for the detection of cholesterol levels in biological samples. Additionally, the colorimetric technique can be utilised to analyse the chemical composition of biological samples, such as glucose in the blood (Wang *et al.*, 2019), urine (Flaucher *et al.*, 2022), and proteins (Gee *et al*., 2017) to monitor health status, disease detection or to be used in laboratory settings.

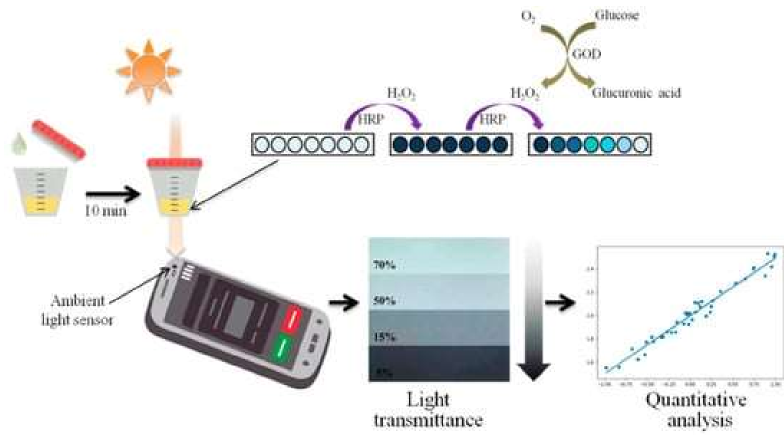

Figure 2.3 Illustration of colorimetric detection of urine glucose (Wang *et al*., 2020)

2.2.3(d) Fluorometric

Fluorometric are used to analyse and quantify chemical substances with molecules capable of presenting fluorescence. This technique depends on the production of a fluorescent compound because of enzyme activity between a substrate and an enzyme. When the fluorophore binds to the analyte, it frequently undergoes photophysical changes, resulting in variations in the fluorescence signal or the upper state lifetime, or a shift in emission wavelength. These changes can be detected with the aid of readout devices including fluorometers, microscopes or cytometers, that are equipped with a photomultiplier tube (PMT) or a charge-coupled device (CCD)/complementary metal-oxide semiconductor (CMOS) camera (Nath *et al*., 2023). Moreover, the fluorometric technique is applied in various biophotonic studies, such as the measurement of alcohol metabolites (Zhang *et al*., 2024), detection of bacterial infection (Sheini, 2021), and detection of chloride ions in sweat (Zhang *et al*., 2017). Due to their sensitivity, specificity, fast operation, and the availability of diverse types of fluorophores that absorb and emit light across a broad range of wavelengths from ultraviolet to infrared, thus, the use of fluorometric technique in fluorescence assays has become widespread (Nath *et al*., 2023b).

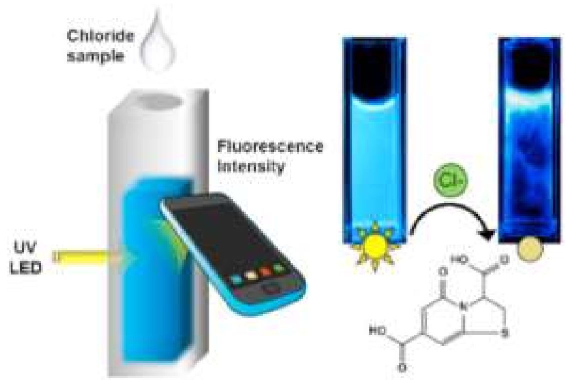

Figure 2.4 Design of smartphone-based chloridometer using the fluorometric method for chloride ions detection in sweat (Zhang et al., 2017).

2.3 Smartphone-based biophotonic instrumentation using photometric method

2.3.1 Near-infrared LED

Light-emitting diode (LED) serve as efficient light source due to its controllable emission spectrum, low power consumption, and can be tuned to emit specific wavelengths of light. Near-infrared (NIR) LED are increasingly utilised in biophotonic instrumentation due to their ability to penetrate biological tissues with minimal scattering absorption. The wavelength for near-infrared light region is generally 780 – 2500 mm (Jiao *et al*., 2023). In the near-infrared spectral range, light has a relatively strong ability to penetrate biofluids and soft tissues (>0.5 mm) (Tang *et al*., 2020), with lesser scattering compared with ultraviolet (UV) with a wavelength of 10 – 400 nm (Adzhani *et al*., 2022), and visible light with a wavelength of 400 – 700 nm (Gorman, 2023). Moreover, its sensing and measurement can be achieved by both reflection and transmission.

The general NIR wavelength windows are 700 – 1100 nm, 1500 – 1850 nm, and 2000 – 2400 nm, all of which can be used to measure glucose. However, the absorption peaks for water are between 1350 and 1520 nm, and the other between 1790 and 2000 nm (Maruo *et al.*, 2015; Liu *et al.*, 2015; Yadav *et al.*, 2014; Tang *et al.*, 2020b). In the shorter wavelength in the NIR range, water has a lower light absorption, hence, the use of LED as an emitter with shorter wavelengths; 940 nm will allow NIR spectroscopy to be more selective as it does not interfere with the absorption peak of water; 1450 nm, 1787 nm (Arefin *et al.*, 2018). In practice, NIR LEDs are employed in technologies such as pulse oximetry, which measures oxygen saturation in the blood and assists in detecting inorganic and/or organic contaminants (Yang *et al.*, 2022) and adulterants (Mazivila *et al.*, 2020), ensuring food safety and consumer protection.

2.3.2 Photodiode

A photodiode is a semiconductor-based electrical device that converts photonic energy, in the form of electromagnetic radiation, to a detectable electrical signal in the form of current or voltage (Damulira *et al.*, 2019). PIN photodiode is one of the photodiode types, consisting of N-type and P-type semiconductor layers and one layer of intrinsic material or undoped semiconductor layer in between them (Kaur *et al.*, 2020) in order to increase detection volume. (Oliveira *et al.*, 2016; Damulira *et al.*, 2019b). The basic operation of a silicon photodiode is to convert light energy into electrical energy in which electron-hole pairs are generated via reverse bias voltage to increase the depletion region. Due to the carrier drifting in opposite directions, a signal is generated towards the collecting electrodes. (Ahmad *et al.*, 2018). For the detection of photons in the 430 nm to 1100 nm range, BPW34 silicon PIN photodiode is commonly used as optical detectors in biophotonic instrumentation due to their high sensitivity to light in the visible and near-infrared spectra.

In a study by Dzundza *et al*. (2022), even though the VEML6030 photodetector (Vishay Semiconductors, USA) has an almost uniform sensitivity in the range of 400 – 800 nm, which gradually decreases and still allows measurements up to a wavelength of 900 nm, however, this sensor has a low measurement frequency of 10 Hz, which is not enough for a complete analysis in the study. Therefore, the author proposed the use of several photodiodes simultaneously, with the combination of BPW34 infrared photodiode (OSRAM, Germany) to extend the range and equalize the sensitivity in the infrared region of the spectrum. Additionally, this type of compact-sized photodiode offers rapid response times and high precision (Wei *et al*., 2024) making them suitable for real-time monitoring and sensitive detection in biological assays.

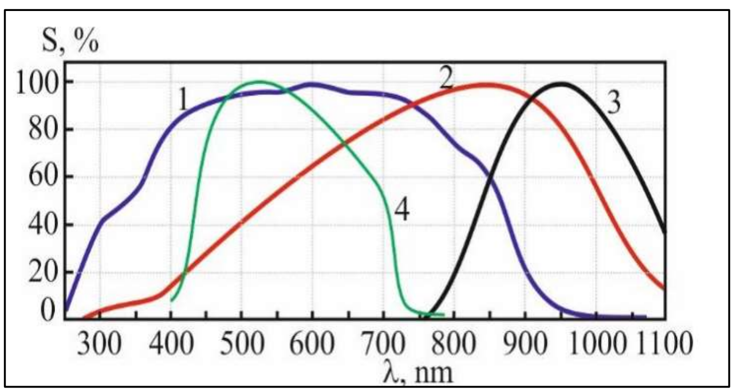

Figure 2.5 Spectral sensitivity of different photodetectors: VEML6030 (1), OPT101(2), BPW34 (3), TMD37003M (4) (Dzunda *et al*., 2022).

2.3.3 Microcontroller board

In biophotonic instrumentation, a microcontroller board (MB) is a fundamental component, by providing the necessary control and processing capabilities for various biophotonic applications. Microcontroller boards are compact, single-chip microcomputers that integrate a range of essential components within a single integrated circuit. These boards typically include a central processing unit (CPU), random access memory (RAM), specialized function registers, program and data read-only memory, multiple input/output ports, and various peripheral functions such as analogue-to-digital converters (ADC), digital-to-analogue converters (DAC), timers, voltage reference, pulse width modulation (PWM), serial peripheral interface, universal serial bus (USB) port, ethernet port, along with a host of other peripherals (Hodgson, 2021). The principle behind their usage lies in their ability to perform real-time processing and control tasks, essential for the precise operation and data handling required in biophotonic applications.

In general, the input and output ports of the microcontroller can receive data or information through the input port and send the output via the internet or Wi-Fi server (in some cases, the microcontroller itself can act as a Wi-Fi server) (Ismailov & Jo'Rayev, 2022). Furthermore, C, C++ and MicroPython are popular programming languages that run on microcontroller. These languages are widely used in embedded systems development and offer a range of features that make the microcontroller suitable for various applications. There are several types of microcontroller boards available in the market nowadays, such as Arduino introduced in 2005, Raspberry Pi launched in 2012, and Adafruit founded in 2005. All microcontrollers mentioned have undergone several iterations and variations were released since then. The function of each microcontroller is distinctly the same even though they have different specifications and capabilities, but the proper board is chosen depending on the project intended. Di Nonno and Ulber (2022) developed an Arduino-controlled photo- and fluorimeter, and Sweeney *et al*. (2019) developed a Raspberry Pi-based device for microfluidic blood coagulation assay.

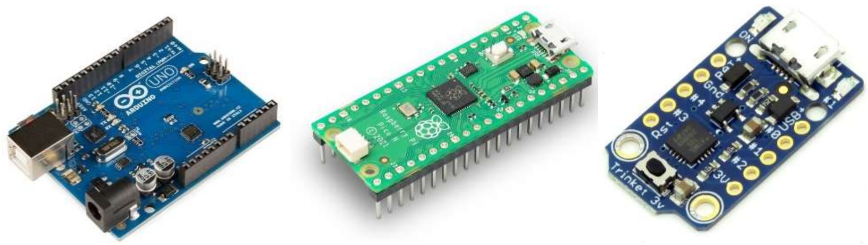

Figure 2.6 Different types of microcontroller boards in the market. Left: Arduino Uno. Middle: Raspberry Pi Pico. Right: Adafruit Trinket.

2.3.4 Android app

An Android app is a software application that runs on mobile devices powered by the Android operating system (OS). However, every OS has its own minimum requirements on smartphone to guarantee that the hardware can support the basic operations of the OS, such as running essential apps, handling multiple tasks, and maintaining smooth performance. The minimum requirements for an OS on a smartphone can vary according to the OS itself. As for Android OS, the minimum hardware specifications have evolved over time to accommodate new features and ensure optimal performance. For instance, earlier versions of Android, such as Android version 1.5 or known as Android Cupcake (Bhatt, 2024), required at least 256 MB of RAM and a single-core processor, whereas latest versions like Android version 14.0 was released on 2023, typically need at least 4 GB of RAM and an octa-core processor. As for internal storage, at least 64 GB is required (PhoneMore, 2023), though higher storage is preferable for installing apps and storing data. Additionally, modern Android versions often necessitate specific screen resolutions, hardware sensors, and security features. The storage requirements have also increased, with a minimum of 64 GB becoming more common to handle the larger size of apps and the OS itself. These minimum requirements ensure that the device can run the OS smoothly, support essential applications, and provide a satisfactory user experience.

In addition, Android apps are built for mobile devices such as smartphones and tablets and can be installed from the Google Play Store or other Android-app-focused websites. They were designed to utilise the device's hardware capabilities, including touchscreen, camera, Global Positioning System (GPS), microphone, and more, to provide a wide range of functionalities and services to users. Common alternative programming languages used to develop an Android app are Java, Kotlin, C/C++, and Python (Petrecolla, 2023). In biophotonic instrumentation, an Android app can be developed and integrated into a single, user-friendly interface. These apps can be designed to control and interact with various biophotonic devices such as spectrometers, oscilloscopes, microscopes, and sensors, to facilitate data acquisition, processing, and analysis.

As in biophotonic instrumentation using photometric method, Android apps such as AR-Oscilloscope and Scoppy can be used to visualize the frequency or voltage signals from the samples, and analyse the signals related to the samples' concentration. One recent example of an Android app in biophotonic is the bioluminescent-based analyte quantitation by smartphone (BAQS) developed by Kim *et al*. (2017), which utilised the default CMOS sensors in smartphone to detect bioluminescence signals from biological samples. The app includes a software algorithm called noise reduction by ensemble averaging (NREA) to enhance the signal-to-noise ratio (SNR) and improve the detection sensitivity.

2.4 Review of previous studies related to optical sensing of glucose

In recent years, researchers have shown a growing interest in the integration of biophotonic instrumentation with smartphones for various purposes, employing diverse methodologies. The studies discussed below demonstrate that smartphones can effectively be implemented as tools in biophotonic instrumentation, exhibiting a high degree of correlation when compared to the conventional methods. However, many of these studies utilise the built-in camera as a detector, presenting challenges in alignment to accommodate the varying positions of the rear camera across different smartphone models. Additionally, only white light that is composed of multiple wavelengths will be emitted from the smartphone's flashlight, resulting in variations in intensity when different smartphone brands are taken into account.

2.4.1 Colorimetric detection system with a smartphone for self-monitoring blood glucose

The study by Wang *et al*. (2019) focuses on the design, fabrication, and feasibility analysis of a colorimetric detection system with a smartphone for self-monitoring blood glucose. The researchers developed a portable and convenient system that utilised a smartphone to capture and analyse blood glucose levels using colorimetric strips. The system comprises an Integrated Blood Glucose Detection Device (IBGDD) that consist of a blood glucose test site, a disposable lancet, a cover and baseplate set, and a light guide channel and a smartphone. Optical simulation was conducted to optimize the design of the IBGDD for efficient light guidance. Then, the smartphone's camera captures images of colorimetric strips, and an automatic glucose concentration analysis software installed on the smartphone analyses the blood glucose concentration. The designed system was tested with blood samples from diabetic patients and compared with a commercial Yellow Springs Instrument (YSI) biochemical blood glucose analyser equipment (YSI-2300). Results showed that all measured data fell within the acceptable accuracy criteria of ±15 mg/dL or ±15% according to ISO 15197:2013 standards. The system demonstrated high accuracy and stability in blood