DEVELOPING A PORTABLE BLOOD GLUCOSE METER USING RAMAN SPECTROSCOPY TECHNIQUE

by

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Engineering in Data Science and Artificial Intelligence

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ABSTRACT

Self-monitoring of blood glucose (SMBG) is essential for diabetics to monitor their glycemia (the concentration of sugar or glucose in the blood). By measuring glycemia continuously, the treatment and patient lifestyle can be adjusted according to the report. The solution would be a wearable device that collects blood glucose continuously throughout the day. However, building a complete non-invasive one is challenging. Multiple techniques employing non-optical and optical methods have been studied. One technique that showing to be promising for this task is Raman Spectroscopy due to its low sensitivity to water and temperature, and great specificity. Fortunately, researchers have shown that glycemia can be measured by observing the light scattering such as the Raman Spectroscopy technique. With this method, it is possible to develop portable blood glucose meter equipment that is not only non-invasive but also a continuous method. Our portable equipment has an accuracy comparable to the clinical glucose meter of choice with an error of less than $\pm$ 0.83 mmol/L. The portable aspect enables continuous sampling throughout the day. With our equipment, continuous non-invasive SMBG is possible. Not only this will help to improve the treatment plan for diabetics but also enables individuals to monitor their glycemia which in turn may improve their diet selection.

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CHAPTER 1
INTRODUCTION

1.1 Background of the Study

Building a wearable blood glucose device can help diabetes to monitor their glycemic throughout the day. The term "wearable" could be seen as a combination of non-invasive, continuous, and portable devices. Currently, continuous glucose monitoring (CGM) systems have been recognized as the ideal monitoring systems for glycemic control of diabetic patients (Lee, Probst, Klonoff, & Sode, 2021). However, current CGM devices are not reliable in terms of accuracy and required sensor implantation which considers being a minimally invasive (Keenan, Mastrototaro, Voskanyan, & Steil, 2009)

Fortunately, the analyte analysis noninvasive techniques have been studied as a means to measure glycemic continuously. Among techniques, the ones using optical methods yield a better result (Sim, Ahn, Jeong, & Kim, 2018). Ranging from far infrared to fluorescence spectroscopy, Raman spectroscopy is the most interesting technique. Not only it is insensitive to water, but it is also shown to be able to quantitatively measure glucose transcutaneously (Kang et al., 2020). Recently, *Quantum Operation Inc.* (2022) shows the prototype of a wearable blood glucose smartwatch that employs Raman spectroscopy. However, evidence of a workable device is absent.

1.2 Statement of the Problem

One important variable that impact the overall design of the wearable device is the measuring site. Forearm (Enejder et al., 2005; Scholtes-Timmerman, Bijlsma, Fokkert, Slingerland, & Veen, 2014), thenar (Lundsgaard-Nielsen et al., 2018), and nail fold (Li et al., 2019) have been selected as measuring sites with promising results. While González Viveros et al. (2022) shows that the forearm is the most effective site compared to the wrist and index finger, it remains unclear which site is the best due to different equipment, parameters, methodology, and analysis styles across the papers.

The experiment must be conducted to finalize and confirm the measuring scheme. Raman spectroscopy with 785 nm laser was used in (González Viveros et al., 2022; Li et al., 2019; Scholtes-Timmerman et al., 2014) and showed success. However, the schemes were different. Measuring configuration is 10 times accumulation of 10 seconds exposure in Scholtes-Timmerman et al. (2014), nine times accumulation of 30 seconds exposure in (González Viveros et al., 2022), and six times accumulation of 40 seconds exposure in (Li et al., 2019). Since we want to develop a wearable device, a benchmark of 15 seconds is chosen following the SpO2 measuring of the Apple Watch 8 (*Measure blood oxygen levels on Apple Watch*, 2022).

Data were obtained using the oral glucose tolerance test (OGTT) from 12 volunteers for 10 days in (Li et al., 2019), a single collection from 46 volunteers (including 32 type-2 diabetes, 10 prediabetes) in (González Viveros et al., 2022) and from 166 patients in (Scholtes-Timmerman et al., 2014). All labels were obtained by drawing a blood sample from the subject.

Modeling the data with multiple linear regression (MLR) + hand-pick features (911, 1060, 1125, 1450 cm^{-1}) result in prediction correlation $R = 0.85$ for intrasubject cross-validation (CV) and $R = 0.91$ for intersubject CV (Kang et al., 2020), a back propagation artificial neural network (BP-ANN) + principal component analysis (PCA) achieved root-means-square error (RMSE) of 0.45 mmol/L and R^2 of 0.95 for intrasubject modeling and RMSE of 0.27 and R^2 of 0.98 for intersubject modeling (Li et al., 2019). González Viveros et al. (2022) showed the use of self-organizing maps (SOM) + RReliefF as automatic feature selection and feed-forward artificial neural networks (FFNN) can achieve up to RMSE of 30.12 mg/dL (1.7 mmol/L).

1.3 Objectives

Our objective is to develop a wearable self-monitoring blood glucose meter. To achieve this, we separate the project into two studies.

1.3.1 Study 1: Confirming the parameters

The first study aims to confirm the parameters starting from laser selection (wavelength), measuring time, and measuring site. For now, we pre-select the laser to 785 nm as it offers (1) good skin penetration the skin compared to 830 nm (Sim et al., 2018), (2) availability of cost-efficient and compact, high-quality laser sources (Photonics, 2021). The measuring time has to be tested with the actual Raman Instrument. The measuring site will be the index fingertip, index nail fold, wrist, and forearm.

Metric: A fingerprint of glucose should be presented (high correlation) with minimal fluorescence and total time.

Outcome: Ranking measuring sites by correlation. Confirm measuring time.

1.3.2 Study 2: Raman scattering of blood glucose study

The second study aims to understand and reproduce the Raman scattering of blood glucose. This study will require 15 subjects for data collection using the OGTT scheme. The preprocessing and modeling will be done following the previous works. At this stage, the performance and power consumption of models will be recorded for the next study.

Metric: Selected features are agreed to in prior works. Modeling achieves over 80% of Clarke error grid (CEG) zone A.

Outcome: By performing ΔG (Kang et al., 2020), we confirm the peak of glucose in the blood. Confirm the model to use.

1.3.3 Study 3: Designing and developing wearable blood glucose device

The third study aims to finalize the design of our wearable device and develop a prototype. The feature will include storage for self-data collection and upload to the cloud.

Metric: Workable device with blood glucose prediction similar to the 1.3.2.

Outcome: Prototype device.

1.3.4 Study 4: Device Evaluation

The fourth study aims to evaluate the prototype. We repeat the 1.3.2 experiment but this time with substituting Raman instrument with our prototype.

Metric: CEG zone A.

Outcome: The prototype achieve over 80% of CEG zone A.

1.4 Organization of the Study

Start your paragraph here.

CHAPTER 2
TITLE

Write your introductory paragraph/s to give an overview of the chapter (except for Chapter 1). Limit this section to two paragraphs. Follow the appropriate structure of writing paragraphs. Paragraphs should have at least four sentences (8 lines). Paragraphs with more than 6 sentences (12 lines) must be split into two paragraphs. Maintain one blank line between paragraphs.

2.1 Heading, Level 2

This section presents some guidelines on how to create and format tables and figures following the APA Style with some examples. Every table and figure should serve a purpose. A table or figure can be referred to in the text by its number [e.g., As shown in Table 2.1..., as can be seen in the results of the testing (see Figure 2.1)]. Avoid writing "the table above" or "the figure below" as the position of a figure or table might change during the writing process.

Tables and figures can be generated in different ways using many programs. Table 2.1 presents the format of a table following the APA style. Align all tables and figures with the left margin and place a table or figure after a paragraph where it is first mentioned. Separate the paragraph and the table or figure title by a double-spaced blank line. Titles should be brief, clear, and explanatory.

Repeat the column headings on the second page of the table (see Table 2.1). Separate

Figure 2.1

Doge.

Note. Additional notes goes here.

this paragraph from the table by a double-spaced line. Tables and figures can be placed at the start or end of a page. Fit the table or figure between the margins and in one page.

As there is very little space left for the table on this page, present the table on the next page. You can add more content in this section. The description should be as close to the table or figure as possible. (There should be one blank double-spaced line between the last line of the paragraph and the table or figure number, and between the table / figure number and the title.)

You can cite stuff in references.bib like this (Author, 2024). y is as follows.

$$y = mx + b \tag{2.1}$$

2.2 Heading, Level 2

Add a short introductory sentence/s here.

2.2.1 Heading, Level 3

Start your paragraph here. Table 2.2 presents a sample of a qualitative table with variable descriptions. Separate the paragraph and the table or figure title by a double-spaced blank line. Titles should be brief, clear, and explanatory. Check the Language Center website for more examples.

2.2.2 Heading, Level 3

(1 space between the last line of this section and the next Level 2 heading)

2.3 Heading, Level 2

As for figures, the figure title should also be written in italics below the figure number (in bold) separated by a double-spaced blank line as shown in Figure 2.1. The size and density of the elements in a figure must be considered when deciding on the font size and spacing. Continue with the paragraph here.

Continue with the paragraph here. The table or figure should be as close to the description as possible or when it is first mentioned. Fit the tables and figures between the margins. (There should be one blank double-spaced line between the previous paragraph and the figure number, and between the figure number and the title.)

Table 2.1

An example table in latex.

Methods	Metric
Method A	153.3
Method B	2.4

Note. Add notes here.

CHAPTER 3

METHODOLOGY

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