DEVELOPING WEARABLE BLOOD GLUCOSE METER USING RAMAN SPECTROSCOPY TECHNIQUE FOR CONTINUOUS GLUCOSE MONITORING

by

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ABSTRACT

Continuous glucose monitoring (CGM) systems have been identified as a crucial component of successful glycemic management in diabetic patients (Lee, Probst, Klonoff, & Sode, 2021). Currently, the commercial CGM approach involves implanting a sensor (Keenan, Mastrototaro, Voskanyan, & Steil, 2009). Its minimally-invasive nature prevents the pervasiveness of monitoring glucose. The non-invasive approach such as Raman spectroscopy has been studied as a means to measure glycemic in vivo. Thus, wearable (continuous, non-invasive, pervasive) self-monitoring blood glucose (SMBG) is possible. However, wearable has its limitation and previous works do not study the aspect of this usage. Thus, a comprehensive comparison between measuring sites, measuring schemes, preprocessing techniques, and models is studied here. Furthermore, a prototype of wearable SMBG is developed and evaluated. We found that the wrist is the best site to measure glycemic. When use normalized 1125 cm^{-1}, it achieved $R^2 = 0.9$ with blood glucose. Our prototype achieves correlation with blood glucose over $R^2 = 0.8$ comparable to reputable wearable SpO2 sensors in the market. Our results contribute to (1) the best site to measure glycemic in the human and measuring scheme, (2) effective preprocessing technique and model for predicting the glycemic, (3) prototyping the wearable SMBG using Raman spectroscopy.

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CHAPTER 1
INTRODUCTION

1.1 Background of the Study

Continuous glucose monitoring (CGM) systems have been recognized as a key factor for effective glycemic control of diabetic patients (Lee et al., 2021). CGM refers to automatic, continuous (real-time or periodic) monitoring of users' glucose through invasive, minimally invasive (e.g., small incisions), and non-invasive means. To date, the acceptable and commercialized CGM approach is through sensor implantation, but it requires lengthy calibrations, sometimes unreliable and minimally-invasive (Keenan et al., 2009).

Non-invasive techniques through analyte (e.g., glucose solution, interstitial fluid (ISF)) analysis have attracted much interest. Optical-based methods were proven to yield superior results, achieving strong selectivity of glucose fingerprints on complex analytes such as blood (Alsunaidi, Althobaiti, Tamal, Albaker, & Al-Naib, 2021). Among the optical-based methods (e.g., far infrared to fluorescence spectroscopy), Raman spectroscopy appears promising due to its insensitivity to water (e.g., as compared to near-infrared) and its ability to accurately measure glucose quantitatively and transcutaneously (Kang et al., 2020). Anyhow, Raman spectroscopy comes with challenge, as is often confounded with fluorescence artifacts, but of which is commonly countered by adjusting the laser intensity or measuring schemes. The rise of Raman spectroscopy is also timely due to its recent advancement of laser technology (*Discover 50 years of Raman innovation by HORIBA*, 2018).

The use of Raman spectroscopy for measuring blood glucose can be dated back as far as 2005. Enejder et al. (2005) found a strong association ($R^2 = 0.83$) on Raman spectra between crystallized glucose and ISF measured at human forearm. Shao et al. (2012) confirmed a strong association ($R^2 = 0.91$) on Raman spectra between concentration on glucose solution and ISF measured at mouse ear. Kang et al. (2020) demonstrated a new approach to extract glucose scattering by subtracting two Raman signals from two different time points as a direct measurement of glucose in blood. In addition, they validated that to reliably measure the glucose concentration in blood, the glucose peak (1125cm^{-1}) should be normalized with protein and lipid peak (1450cm^{-1}). They

achieved an $R^2 = 0.91$ between actual glycemic and predicted glycemic using Raman spectra measured from a pig's ear. The measuring site is another important variable. 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 chosen as promising measurement sites. While González Viveros et al. (2022) indicates that the forearm is the most effective site when compared to the wrist and index finger, it remains unclear which site is the best due to varying equipment, parameters, and methodology (e.g., how to preprocess) across the papers. Due to the portability of wearables, there has also been some very recent attempt to deploy Raman spectroscopy on wearable (e.g., smartwatch) commercially *Quantum Operation Inc.* (2022) but the research is still in its infancy.

This research aims to build on previous work by (1) confirming the use of Raman scatterings for measuring blood glucose, (2) comparing models, and (3) developing the first wearable (continuous, non-invasive, pervasive) Raman-based self-monitoring blood glucose (SMBG) system, primarily for daily users for widespread use. The accuracy of the glycemic measurement should be comparable to that of the well-respected SpO2 wearable sensor (Apple Watch 6) of ($R^2 = 0.81$, $p < 0.001$) (Pipek, Nascimento, Acencio, & Teixeira, 2021). This justification was made because Raman spectroscopy was demonstrated to have at most 90% association with blood glucose. In addition, body movements may potentially confound the measurements, so it is advisable to set the objective for daily users rather than for clinical use.

1.2 Statement of the Problem

The difficulty of this work is brought on by the wearable's general limitations, limited power and battery. Therefore, the measuring site, scheme, and model have to be chosen carefully. In addition, comparing previous results is difficult since they all used different equipment, parameters, and methodology.

The measuring site (forearm, wrist, nail fold, and fingertip) may yield different Raman scattering signals. In terms of design, the wrist is the ideal site since it can be employed in the wearable such as smartwatches which are already widely daily driven and adopted. If other sites are chosen then another form of wearable has to be considered which will raise the usability question. Although the forearm is a superior option when compared to the wrist and fingertip in the indirect measurement (González Viveros et

al., 2022), proof of direct glucose measurement is absent. Furthermore, each site has a different skin structure, thus the appropriate measuring scheme should also be different. As a result, it is necessary to research the measuring sites and their optimal scheme in order to assess the direct glucose measurement and evaluate the sites based to their correlation with glycemic, Signal-to-noise ratio (SNR), and total measuring duration. The measuring scheme will be benchmarked with Apple Watch SpO2 sensor which uses a total measuring time of 15 seconds (*Measure blood oxygen levels on Apple Watch*, 2022).

The choice of model should be based on both resource consumption (model complexity) and accuracy (predictability). Earlier studies demonstrated that the normalized 1125 cm^{-1} has a linear relationship with in vivo blood glucose concentration ($R^2 = 0.95$) (Shao et al., 2012). However, the normalization-based works did not measure Raman from human subjects (Kang et al., 2020; Shao et al., 2012). Other works that involve human subjects use various preprocessing methods, such as principal component analysis (PCA) (Li et al., 2019) and self-organizing maps (SOM) (González Viveros et al., 2022). The aforementioned factors make it impossible to compare models. In addition, resource consumption should be assessed as its impacts the wearable battery life. Therefore, a thorough comparison of preprocessing and model selection is required.

1.3 Objectives

Our objective is to develop a wearable SMBG. To achieve this, we separate the project into four studies.

1.3.1 Study 1: Confirming the parameters

Objective: To study the measuring site, schemes.

Independent Variables:

1. Measuring Scheme
2. Measuring Site
    (a) Wrist
    (b) Forearm
    (c) Index fingertip
    (d) Index nail fold

Dependent Variables: Glucose peaks around 1125 cm^{-1} with the lowest total measuring time.

Outcome: Confirm the suited measuring site and scheme.

1.3.2 Study 2: Raman scattering of blood glucose study

Objective: Study Raman scattering of blood glucose and build a model to predict the glycemic for a wearable device.

Independent Variables: Raman scattering of blood

Dependent Variables: Glycemic

Outcome: The model that results in glycemic prediction correlation $R^2 > 0.8$ with actual glycemic, and resource usage.

1.3.3 Study 3: Designing and developing wearable blood glucose device

Objective: Design and develop a prototype of a wearable SMBG.

Outcome: A prototype.

1.3.4 Study 4: Device Evaluation

Objective: To evaluate the prototype, we redo the 1.3.2 experiment with our prototype.

Independent Variables: Raman scattering of blood

Dependent Variables: Glycemic

Outcome: Prototype achieves glycemic prediction correlation $R^2 > 0.8$ with actual glycemic.

1.4 Organization of the Study

The document is organized as following. Chapter 2 as Literature Review and Chapter 3 as Methodology.

CHAPTER 2
LITERATURE REVIEW

We review the result of Raman spectra when measuring glucose as a solution (mix with water) and blood (glycemic), the linearity relationship of glucose peaks with glucose concentration, and the data modeling.

2.1 Glucose fingerprint

Once the incident photons hit the glucose, the inelastic scattering occurs and known as a Raman scattering. In glucose solution (glucose + water), Raman scattering peak at 796, 1060, 1125, and 1366 cm^{-1}. The intensity of scattered light increase as the concentration of glucose increase (Shao et al., 2012). This same phenomena occur when measuring Raman scattering of blood (Enejder et al., 2005; González Viveros et al., 2022; Kang et al., 2020; Scholtes-Timmerman et al., 2014). In Kang et al. (2020), after subtracting the two Raman spectra measure at two different time points, the spectra peaks at 1125 cm^{-1}. Unlike the glucose solution, Raman signal of blood is noisy because of blood contains various substance (Li et al., 2019). To extract the linearity relationship, the 1125 cm^{-1} has to be normalized with the peaks of protein and lipid (1450 cm^{-1} (Kang et al., 2020), 1549 cm^{-1} (Shao et al., 2012)).

2.2 Data modeling

Full spectrum analysis using partial least squares (PLS) is widely used (Enejder et al., 2005; González Viveros et al., 2022; Kang et al., 2020; Scholtes-Timmerman et al., 2014). The result range from

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). Full spectrum analysis using partial least squares (PLS) (Enejder et al., 2005; González Viveros et al., 2022; Kang et al., 2020; Scholtes-Timmerman et al., 2014) is widely used, and a few neural network approach (González Viveros et al., 2022; Li et al., 2019). However, comparing model performance is difficult since each paper employs a different preprocessing technique. For a wearable with power and battery constraints, the suited model should provide good prediction accuracy (over 80% of Clarke error grid (CEG) zone A)

with low usage of resources.

In glucose solution, the concentration of 0.1 - 40 mmol/L of glucose in water and Raman shift at 1125 cm^{-1} has a linear relationship Shao et al. (2012). The same case can not be said with blood glucose. Since blood contains multiple components, using 1125 cm^{-1} directly will not work. Kang et al. (2020) shows that the ratio of 1125 and 1450 (protein/lipid peak) cm^{-1} yield a linear relationship. Figure **??** shows that the normalized 1125 cm^{-1} has a linear relationship with the glucose concentration. This same procedure is also presented in (Shao et al., 2012) where 1549 cm^{-1} is used to normalize the spectrum. On the other hand, Li et al. (2019) uses PCA and BP-ANN with an input layer of 3, a hidden layer of 4, and an output layer of 1. While the model achieved an RMSE of 0.27 in intersubject modeling, using PCA is not necessarily means the features in use is a glucose-related feature (Kang et al., 2020). Adding to the neural network, FFNN is primarily used in modeling glucose in (González Viveros et al., 2022). Without any feature selection, the RMSE of glucose prediction is 3.1 mmol/L and 30.12 mmol after implementing SOM and RReliefF as automatic feature selection.

2.3 Concentration Limitation

The usual blood glucose range of a healthy person can be as low as 0.3 - 1 mmol/L and $<$3 mmol/L for diabeties (Shao et al., 2012).

CHAPTER 3
METHODOLOGY

3.1 Study 1: Confirming the parameters

Kang et al. (2020)

3.2 Study 2: Raman scattering of blood glucose study

3.3 Study 3: Designing and developing wearable blood glucose device

3.4 Study 4: Device Evaluation

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