DEVELOPING WEARABLE 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

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, the development of wearable Raman-based SMBGs is underexplored. There are several challenges regarding this development. First, the most suitable measuring sites (wrist, forearm, nail fold, fingertip, and thenar) to directly measure glucose scattering remains unknown. Although past work reported high accuracy of glucose prediction from all these five sites, the high accuracy may be attributable to the use of the full spectrum which may contain unintended signal artifacts that correlated with glycemic (Kang et al., 2020). Second, proper features (engineering) remain underexplored. Although past work proposed feature engineering techniques such as principal component analysis (Li et al., 2019) or protein/hemoglobin normalization (Kang et al., 2020; Shao et al., 2012), the lack of formal comparison makes it difficult to understand what works. Third, no work has considered the development of wearable Raman-based SMBGs. The key challenge here is to achieve practicality in the real world while preserving/not losing too much accuracy (e.g., accuracy may drop when the wearable is worn as a watch but is more practical and usable). Thus, a comprehensive comparison between measuring sites and feature engineering 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 measurement achieves correlation with blood glucose over $R^2 = 0.8$ comparable to reputable wearable SpO2 sensors in the market. Our results contribute to (1) comparing the measuring sites for direct measurement of glucose in the blood, (2) find the proper feature engineering for predicting the glycemic, (3) prototyping and evaluating the wearable Raman-based SMBGs as a means for daily CGM.

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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 times. 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

First, it remains unknown of the effective measuring sites. Due to methodological variations, it is challenging to compare previous findings. In addition, past works have a questionable methodology, i.e., it might be claimed that the great accuracy of glucose prediction may be attributable to the use of the full spectrum which may contain unintended signal artifacts that correlated with glycemic (Kang et al., 2020). Five successful measuring locations on the human body have been documented. However, only the wrist, fingertip, and forearm were compared with the same methodology (González Viveros et al., 2022). The nail fold is a promising measuring site because its thin epidermis layer makes it easier for the laser to penetrate the microvessel in the dermis (Li et al., 2019). Thenar has been chosen as a measuring site for a portable Raman-based SMBG device

(Lundsgaard-Nielsen et al., 2018). This work seeks to identify the strongest correlation between glucose fingerprint and glycemic using the direct measurement of glucose technique (Kang et al., 2020).

Second, valid feature engineering approach remains to be investigated. Particularly, past work used primarily two different approaches. The first approach uses statistical-based analysis on full spectrum data with additional preprocessing such as dimension reduction or feature importance (Enejder et al., 2005; González Viveros et al., 2022; Li et al., 2019; Scholtes-Timmerman et al., 2014). The second method is to normalize the spectrum with either hemoglobin peak (1549 cm^{-1}) (Shao et al., 2012) or protein and lipid peak (1450 cm^{-1}) (Kang et al., 2020) and handpick a smaller set of spectra for modeling (Kang et al., 2020; Shao et al., 2012). This work seeks to compare these two methodological approaches on human subjects.

Third, no work has considered the development of wearable Raman-based SMBG. Developing wearable has several challenges. Regrading measuring site, the wrist is the ideal option for measuring sites because it can be easily adopted in the widely use platform (smart band/watch). This option yields the best pervasiveness but not the accuracy. The similar situation applies to modeling. A more complex model may fit the data more accurately in exchange for efficiency. This work seeks to both develop a practical wearable Raman-based SMBG in daily use to achieve CGM and evaluate the level of compromise in order to archives this goal.

1.3 Objectives

We separate this works into four studies.

1.3.1 Study 1: Measuring sites

Objective: To study the measuring site.

Independent Variables:

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

Dependent Variables: The strongest direct measurement of glucose spectra (1125 cm^{-1}).

Outcome: Ranking of measuring sites.

1.3.2 Study 2: Feature engineering

Objective: Study the effect of feature engineering and selection.

Independent Variables:

1. Feature engineering technique
   (a) No engineering
   (b) PCA (baseline)
   (c) Normalization with protein and lipid peak (1450 cm^{-1})
   (d) Normalization with hemoglobin peak (1549 cm^{-1})
2. Feature selection and modeling
   (a) Full spectrum + PLS (baseline)
   (b) single 1125 cm^{-1} peak + LR
   (c) 911, 1060, 1125 cm^{-1} peak + MLR

Dependent Variables: Glycemic

Outcome: The effect of feature engineering, selection, and modeling on prediction accuracy.

1.3.3 Study 3: Designing and developing wearable Raman-based SMBG

Objective: Design and develop a prototype of a wearable Raman-based SMBG.

Outcome: A prototype.

1.3.4 Study 4: Device Evaluation

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

Independent Variables: Measured Raman scattering

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 of amorphous glucose (glucose fingerprint) when combined with water (glucose solution) and blood (blood glucose). Then, we go into measuring sites and preprocessing techniques, and data modeling.

2.1 Glucose fingerprint

The "glucose fingerprint" is a characteristic Raman scattering spectrum that appears when glucose is present in the analyte. The Raman scattering in glucose solution (glucose and water) exhibits peaks at 796, 1060, 1125, and 1366 cm^{-1} (Figure 2.1). These peaks increase as a function of glucose concentration showing the quantitative property of Raman spectroscopy (Shao et al., 2012). The glucose fingerprint also exhibits in a more complex analyte as blood when measuring Raman scattering of ISF (Enejder et al., 2005; González Viveros et al., 2022; Kang et al., 2020; Scholtes-Timmerman et al., 2014) as show in Figure 2.4.

Kang et al. (2020) extracts the glucose fingerprint which has a peak at 1125 cm^{-1} from two noisy Raman signals. As a result, Raman spectroscopy can measure blood glucose.

2.2 Measuring Sites

Because the thickness of the human skin varies from place to place, Raman scattering measurements taken at several sites might provide varied results (González Viveros et al., 2022; Li et al., 2019). The glucose fingerprint signal will be stronger if the laser

Figure 2.1

Raman spectra of glucose solution at different concentration (Shao et al., 2012).

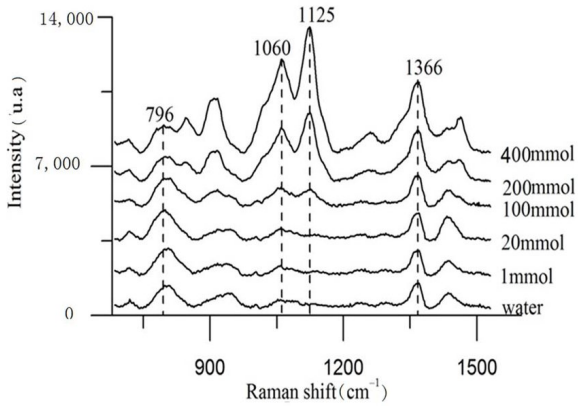


Table 2.1

Assignments of Raman peaks that are identified in the spectra of the microvessels and blood (Chaiken et al., 2001; Enejder et al., 2005; Lemler et al., 2014; Magnussen et al., 2017)

Peak Position (cm^{-1})		Assignments	Components
Microvessels	Blood		
650	643	P:C-S str	Ascorbic acid
758	752	ν_{15}	Trp
837	827	$\gamma 10$	Fructose
858	855	$\nu(C-C)$	Tyr, lac
885	-	-	-
902	898	p:C-C skeletal	Tyr
945	940	$\nu(C-C)$	Crtic acid
978	971	p: Skeletal vibr	Fibrin
1004	1004	ν-ring	Phe
1027	1026	$\delta(=C_bH_2)$asym	Lac
1130	1129	ν_5,	Lac
1163	1157	ν_{44}	Heme
1217	1212	$\nu_5+\nu_{18}$	Heme
1320	1321	p: CH2 twist	Try
1332	1341	ν_{41}	Trp
1424	1423	ν_{28}	Acetates
1448	1450	$\delta(=CH_2/CH_3)$	Trp
1551	1546	ν_{11}	Heme
1608	1603	$\nu(C=C)_{\text{venyl}}$	Heme
1660	1653	Amide I	Heme

Figure 2.2

A trace of glucose fingerprint in Raman scattering of in vivo blood (Shao et al., 2012).

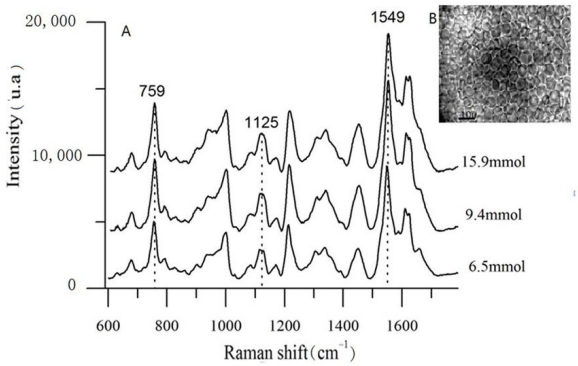
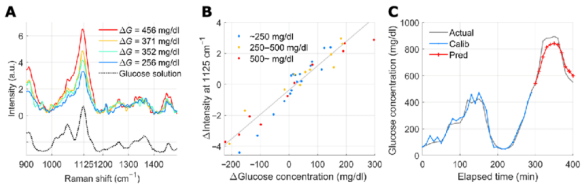


Figure 2.3

*(**A**) Raman spectra of blood glucose obtained by subtracting two Raman signals (Kang et al., 2020).*



focuses on the blood vessels (Shao et al., 2012). Human skin consists of multiple layers called the stratum corneum (SC), epidermis, and dermis (Li et al., 2019). In most sites (e.g., wrist, forearm, fingertip), the assessed Raman signal is from ISF of SC and epidermis layer (Li et al., 2019). The following problems may arise when measuring glucose in ISF rather than blood, (1) ISF glucose is lag when compared to blood glucose (Cengiz & Tamborlane, 2009; Steil et al., 2005), (2) concentration of glucose in ISF is significantly lower than blood (O'Kane, 2012). As a result, the signal of glucose Raman scattering is weak (Li et al., 2019). A better strategy is to measure the Raman signal in areas where the laser can reach the dermis better. Because the dermis contains microvessels (Cutolo, Grassi, & Matucci Cerinic, 2003; Ingegnoli, Smith, Sulli, & Cutolo, 2018), if the site (nailfold) is picked carefully, we can obtain the glucose signal directly from the blood.

Li et al. (2019) reports the greater $R^2 = 0.98$ prediction correlation when use nailfold as a measuring site. The result is better than the forearm ($R^2 = 0.83$) (Enejder et al., 2005; Scholtes-Timmerman et al., 2014) and fingertip ($R^2 = 0.91$) (Oh et al., 2011). Recently, González Viveros et al. (2022) measures Raman glucose at forearm, wrist, and index fingertip and achieves the root-mean-square error (RMSE) of 56.31 ± 4.28,

Figure 2.4

*(**A**) Blood glucose value with 1125 cm^{-1} relative intensity. (**B**) Concentration-dependent Raman relative intensities of glucose (1125 cm^{-1}) (Shao et al., 2012)*

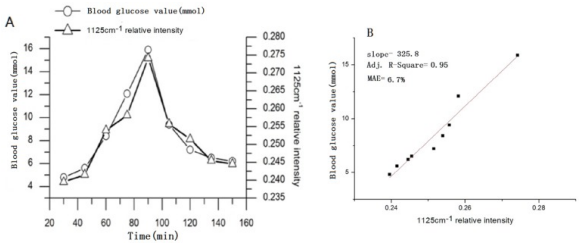
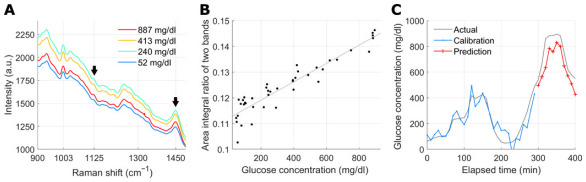


Figure 2.5

*(**B**) Showing the linear relationship between normalized 1125 cm^{-1} with blood glucose ($R^2 = 0.94$) (Kang et al., 2020)*



58.22 ± 1.03, and 56.65 ± 8.99 ml/dL respectively.

2.3 Preprocessing techniques and Data modeling

There are primarily two preprocessing options. Either extracting the features or utilize the complete Raman spectrum as an input. The full spectrum analysis pair with 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 results vary from $R^2 = 0.62$ (Kang et al., 2020), $R^2 = 0.83$ (Enejder et al., 2005; Scholtes-Timmerman et al., 2014), and RMSE of around 65 $\pm$ 0.4 ml/dL in González Viveros et al. (2022). The preprocessing can be done by hand-pick (Kang et al., 2020; Shao et al., 2012) or automatically (González Viveros et al., 2022; Li et al., 2019) pick the features. Hand-pick features were performed by normalizing the spectra with either protein and lipid peaks (1450 cm^{-1}) (Kang et al., 2020) or hemoglobin peaks (1549 cm^{-1}) (Shao et al., 2012). It is demonstrated that the normalized 1125 cm^{-1} has a linear correlation with in vivo blood glucose at $R^2 = 0.95$ (Shao et al., 2012). In Kang et al. (2020), normalized 911, 1060, 1125 cm^{-1} with 1450 cm^{-1} were utilized as inputs of the more complex multiple linear regression (MLR) which achieved $R^2 = 0.91$. The automatic feature extraction was demonstrated with PCA (Li et al., 2019) and SOM (González Viveros et al., 2022).

CHAPTER 3
METHODOLOGY

3.1 Study 1: Confirming the parameters

The purpose of this study is to clarify how measurement sites and schemes affect Raman spectra. The outcome of this study will be used to design the experiment in Section 3.2.

3.1.1 Equipment

The Raman instrument equipped with a 785 nm laser and 10x objective lens will be used to assess the Raman spectra. The Accu-Chek® Guide Meter is representing a standard blood glucose meter for SMBG (*Accu-Chek Guide meter | Accu-Chek*, 2022) and will be used for assessing glycemic.

3.1.2 Studying Measuring schemes

We will evaluate the Raman spectroscopy at four measurement sites: the wrist, forearm, index fingertip, and index nail fold. The measuring schemes will be put to the test to see which one produces the strongest scattering signal without introducing a fluorescence interference. The optimal measuring schemes will be used for the rest of the Raman scattering assessment.

3.1.3 Data collection

The Oral Glucose tolerance Test (OGTT) will be used to manipulate glycemic of the three healthy participants. The participants have to conduct fasting at least eight hours before the test. Once the participants arrived at the experiment area, they will be instructed to acclimate for 30 minutes. During the acclimation, instructor will repeat the experiment procedure. Both Raman Instrument and conventional SMBG equipment will be used to collect data at the interested measuring site. When the acclimation is completed, the first sample will be drawn. The participants begin the OGTT by consume a 250 ml of water containing 75 g of glucose in five minutes. Then, for the next two hours; (1) collecting Raman spectra at the interested measuring site every five minutes; (2) collecting blood sample at the interested measuring site every 20 minutes. In total, there will be 25 Raman samples and eight blood samples.

Each participant has to repeat the experiment until all four measuring sites are measured. The experiment has to be done on another day.

3.1.4 Metric

The subtraction of two Raman signals will be used to extract the glucose fingerprint. The remaining signal is the change of glucose concentration as showed in the following derivation.

The Raman spectra (RS) contains glucose fingerprint (G) and tissue spectra (T).

$$\mathrm{RS} = \mathrm{G} + \mathrm{T} \tag{3.1}$$

Then, the subtraction of two Raman signal can be represented as follows;

$$\Delta\mathrm{RS} = \mathrm{RS}_1 - \mathrm{RS}_2 \tag{3.2}$$

where RS_i is the Raman spectra measured at time i. Then, substituting Equation 3.2 with Equation 3.1 will derive the follows

$$\Delta\mathrm{RS} = \Delta\mathrm{G} + \Delta\mathrm{T} \tag{3.3}$$

Given the measuring site is the same, the tissue spectra will also be the same. Thus, ΔT is 0. Then, it is obvious that

$$\Delta\mathrm{RS} = \Delta\mathrm{G} \tag{3.4}$$

Therefore, the best measuring site is the one that produces the greatest correlation between ΔG and the actual changes in blood glucose.

3.2 Study 2: Raman scattering of blood glucose study

The purpose of this study is to model the relationship between Raman spectra and blood glucose. The same equipment from Section 3.1 will be used. The measuring site and scheme are chosen based on the result of Section 3.1.

Figure 3.1

*An example of wearable (*Measure blood oxygen levels on Apple Watch*, 2022).*

3.3 Data Collection

The same data collection and experiment procedure from Section 3.1 will also be used. In this study, we increase the number of participants to 15 participants. The participants shall be from three different age groups (5 each from 20 to 35 years, 36 to 50 years, and 51 to 65 years).

A total of $15 \times 25 = 375$ Raman samples and $15 \times 8 = 120$ blood samples are collected.

3.4 Preprocessing and Data Modeling

The acquired Raman spectra will be normalized by their intensity of 1450 or 1549 cm^{-1}. Thus, there are three preprocessing options: (1) without normalization, (2) normalize with 1450 cm^{-1}, and (3) normalized with 1549 cm^{-1}. The Linear Regression (LR) model will be used to assess the linearity of 1125 cm^{-1} with glucose concentration. The MLR model with 911, 1060, 1125 cm^{-1} as inputs we will use for multivariate analysis. As a baseline model, full spectrum with PLS will also be employed.

In total, there will be $3 \times 3 = 9$ combinations to compare.

3.5 Metric

The model performance will be assessed using the Pearson correlation. Additionally, resource usage during prediction will be tracked.

3.6 Study 3: Designing and developing wearable blood glucose device

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

Outcome: A prototype.

3.7 Study 4: Device Evaluation

Objective: To evaluate the prototype, we redo Section 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.

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