Measuring Blood Glucose Using Vertical Cavity Semiconductor Lasers (VCSELs)

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***Abstract*— As diabetes mellitus is becoming a more widespread serious disease, a more convenient and accurate way of controlling blood glucose, which improves the patient's life quality and adds savings for health care systems, is desirable. Optical methods are one of the painless and promising methods that can be used for blood glucose predictions. However, having accuracies lower than what is acceptable clinically has been a major concern. To improve on the accuracy of the predictions, the signal-to-noise ratio in the spectrum can be increased, for which the use of thermally tunable vertical cavity semiconductor lasers (VCSEL) is proposed. This paper will present and discuss the results of applying Partial Least Square (PLS) techniques on small wavelength windows with the goal of determining the number of VCSELs required to predict glucose concentration, and verify that with PLS it is possible to predict glucose concentration from a selected subset of absorption spectra.**

INTRODUCTION

The burden of care for patients suffering from diabetes mellitus has been increasing. Tight control of blood sugar is an important factor for effectively minimizing the complications associated with this disease. Since accurate blood glucose monitoring requires pricking of fingers for blood sampling, enhancing glucose measurement techniques to allow easy and continuous monitoring has received a lot of attention in the past decades. The goal of this research is to develop small and low power implantable glucose sensors. One promising technique is to use near-infrared spectroscopy, where an optical spectrum measurement is analyzed using multivariate techniques to determine glucose concentration. However, these techniques suffer from low signal-to-noise ratio (SNR), and the packaging for the implant is not straight forward. Therefore, we are proposing to use Vertical Cavity Surface Emitting Lasers (VCSELs) as the light source in the current research. VCSELs are semiconductor lasers with small dimensions and low power consumption. In addition, VCSELs operate within a small spectrum, and the high power spectral density provides a higher signal-to-noise ratio.

This paper discusses the results of our investigation in the wavelength range of $1.0\mu m$ to $1.7\mu m$. Our aim is to determine the minimum number of segments required to predict the glucose concentration within an acceptable clinical accuracy, and to analyze the accuracy of the partial least square technique given the absorption spectra at specific wavelength segments. Ultimately, the optimal VCSEL wavelengths will be selected for the integration of a laser-based implantable chip.

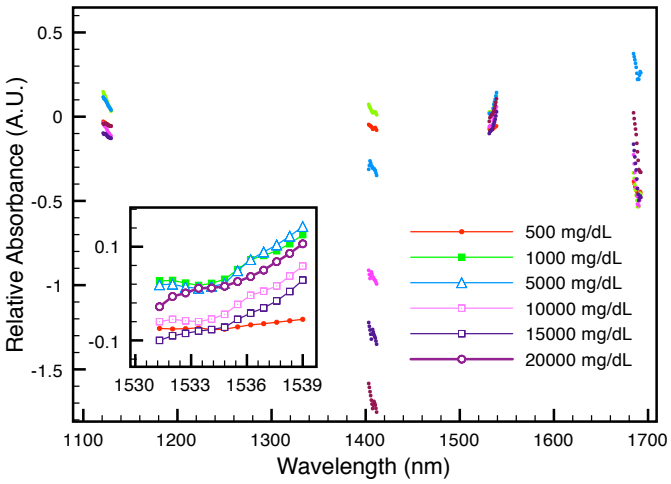

Figure 1: Glucose Absorption Spectrum for the 7 nm wide wavelength segments: 1126±3.5nm, 1408±3.5nm, 1536±3.5nm, 1689±3.5nm. Inset: zoom-in for the 1536±3.5nm segment.

GLUCOSE MONITORING

This section includes an overview of the glucose monitoring methods such as chemical-based glucose monitoring, and optical glucose monitoring techniques including lasers. In addition, some fundamentals of Vertical Cavity Surface Emitting Lasers

(VCSELs) are discussed.

Chemical-based Glucose Monitoring

Used as early as 1962 [1], enzymatic sensors are used clinically for glucose sensing, and the biochemistry is still a topic of research today [2]. Current reliable chemical-based biosensor devices are restricted by their limited life spans. Several companies and research groups are pursuing implantable chemical-based sensors, but commercially available sensors have a limit of up to 3 days use, a limitation due to the chemical sensors needing to interact with the blood directly.

Optical Glucose Monitoring

Optical sensors avoid chemical biosensor limitations because light remains largely unaffected when interacting with the blood. Several measurement techniques have been proposed, including polarimetry [3], Raman spectroscopy, optical coherence tomography, absorption [4] and reflectance [5] spectroscopy. Non-invasive sensors have challenges, however, due to interference, poor signal strength, and calibration issues, and these approaches are still not accurate enough for clinical use. These main challenges in accurate measurements would be significantly reduced if the optical sensor had close access to either interstitial fluid or preferably the blood plasma, so that the light did not have to interact with several layers of tissue. Water is the main component of the body and blood, and in the certain wavelength regions the absorption is too strong to transmit light. There are two wavelength regions in the near infrared that are commonly used for glucose monitoring: first-overtone ($1560-1850nm$), and combination band ($2080 - 2325nm$) region, where glucose has numerous absorption bands and water has relatively higher transmittance.

The light source can be a broad spectrum source such as a white light, or a tunable laser. Using a laser will bring about advantages such as higher signal-to-noise ratio in the absorption spectrum [6], which is considered as critical in improving glucose measurement accuracy.

Vertical Cavity Surface Emitting Lasers

Since their inception, semiconductor diode lasers have been unique light sources with excellent spectral and beam properties. Vertical Cavity Surface Emitting Lasers (VCSELs) are a type of semiconductor laser that have received tremendous attention because of their low-cost, small size, array operation, lower power consumption, and circular beam pattern; these properties make them attractive for optical communications and biomedical applications.

Spectroscopy applications require the use of multiple wavelengths. There are several approaches possible: using tunable lasers, using an array with different wavelength lasers, or by thermal tuning individual lasers. The most successful technique for fabricating tunable VCSELs involves micromechanically tunable mirrors [7], [8]. Such tunable VCSELs offer a tuning range of up to 40 nm, with the drawback that they require a tuning voltage to be applied. Alternatively, a fixed multi-wavelength array can be fabricated [9]–[11]. Finally, the easiest method of tuning is a laser is by changing it's temperature. Thermal tuning typically provides a tuning range of $7nm$, and can be achieved simply by varying the laser drive current [12]. The advantage of this approach is that a single laser can be swept over a molecule's vibrational resonance feature, for example, such as that of glucose.

In our proposed approach, an small array of single-mode VCSELs will be used for the emission source. The array will be used to acquire a multipoint (e.g., 5 bands) optical spectrum. The lasers will be operated one by one, and share one detector. These lasers will be thermally tuned by varying the bias current. This paper presents a feasibility study to determine if it will be possible to use VCSEL-based spectroscopy for glucose monitoring.

EXPERIMENTAL SETUP

This section includes a description of the apparatus used for the experiments. It describes how the sub-windows of the absorbtion spectrum have been selected to identify glucose concentration. Finally, the analysis of the measurements is discussed.

Description of Apparatus

The set up for the experiment consists of a container for the solution, fiber collimators, a light white source, and an optical spectrum analyzer. The container is made of two slides of glass, with $1mm$ thickness, separated by a $1mm$ gap. Hence, the path-length of light in the solution is $1mm$.

Determining sub-window

This paper proposes using VCSELs to improve the accuracy of the glucose prediction to a more clinically relevant accuracy and increasing the signal-to-noise ratio. It is required to determine the number of absorption spectra segments that can reveal enough information to predict the glucose concentration. As a result, the number of VCSELs required, in the wavelength range of $1.0\mu m$ to $1.7\mu m$, will be determined. The wavelength windows, which contain the glucose information, are selected to be centered on the glucose absorption peaks; namely these peaks are at $1126, 1408, 1536,$ and $1689nm$ [13]. As a result, the wavelength windows are approximately $1126 \pm 3.5nm$, $1408 \pm 3.5nm$, $1536 \pm 3.5nm$, $1689 \pm 3.5nm$. The partial least square (PLS) technique was applied to these spectral bands. Using all four windows, the PLS analysis is optimized with three principle components. It is noted that increasing the number of principle components further does not improve the model for glucose prediction, since noise gets incorporated into the model.

Absorption Spectroscopy

Solutions of glucose in distilled water for various concentrations have been used to construct absorption spectra for the wavelengths $1.0\mu m$ to $1.7\mu m$. The absorption spectra are collected and subtracted from the absorption spectrum of the pure water; hence the resultant spectra contains mostly the absorption characteristics of glucose with added noise. Figure 1 shows the average of these resultant spectrums for six different concentrations in the chosen wavelength segments discussed in previous section. As can be observed from the figure (inset), there is no obvious linear relationship between the absorption spectra at these glucose peaks and glucose concentration; this issue has also been discussed in previous reports dealing with optical glucose measurements [6], [14]. As a result, a multivariate analysis such as partial least square (PLS) is required to find the relationship between the measured absorption spectrum and glucose concentration.

The concentrations of the glucose solutions are made high since this project is at the stage of preliminary investigation. In the future, once the method is proven to be promising, these concentrations will be reduced to clinically relevant ranges.

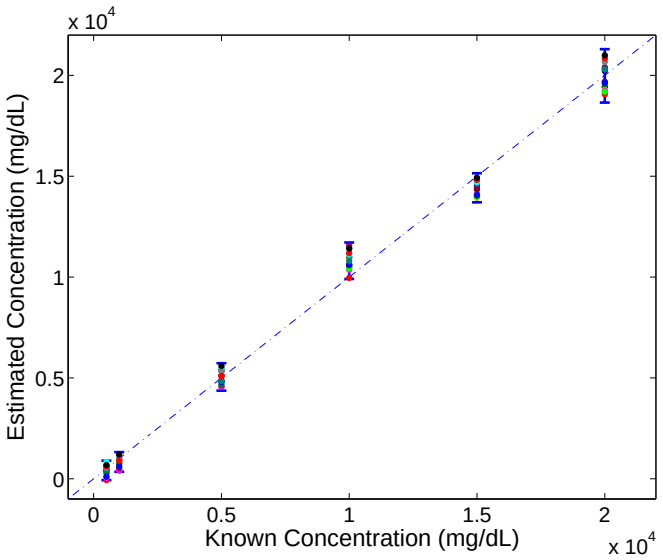

Figure 2: Predicted glucose vs. measured glucose. Error bars indicate 95% confidence interval defined by the 1st data set of spectra, which was used to build the model.

RESULTS

Absorption spectra are collected in two separate experiments. In each experiment, 16 sets of spectra for each concentration were recorded. The first data set (i.e. 16 sets of absorption spectra) was used to build the PLS model for predicting glucose concentration and for defining the 95% confidence interval. The 2nd data set was used to validate the model and estimate the accuracy of the technique.

Figure 2 shows the results of building the PLS model from the average of the first data set. The same 16 sets of spectra are used to define the 95% confidence interval for predicted glucose concentration, which is shown by error bars. These error bars are an indication of the noise and provide an estimation of the algorithm precision. In addition, on the same figure, the same 16 sets of spectra are plotted to illustrate the algorithm precision, when the input is the original data set. The figure shows that a good agreement between measured and predicted values was obtained.

Next, the model is validated with the 2nd data set, to test for accuracy. This is done by comparing the predicted concentrations from the 2nd experiments

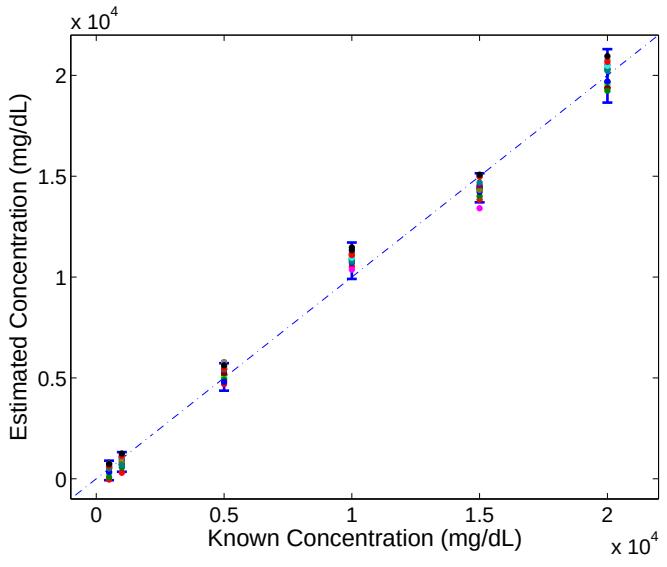

Figure 3: Predicted glucose vs. measured glucose, using the 2nd data set. 96% of the predictions fell within the 95% confidence intervals, as defined by the 1st data set.

with the 95% confidence interval defined by the the first data set. The results, shown in Figure 3, show that 96% of the predicted concentrations from the second data set fall within the 95% confidence interval. Finally, averaging of multiple spectra can be employed to increase the precision of the glucose prediction.

DISCUSSION

The results show that the chosen wavelength segments can be used to predict glucose concentration. In addition, the results show that the model built from one set of data can successfully make predictions on different data sets with a good accuracy. As a result, the PLS technique applied on a small number of segments (4), with segments spanning $7nm$, can be used to predict glucose concentration. Additional improvements are needed to increase the accuracy of the prediction. Specifically, using lasers on the specific windows, which are shown to be useful for predicting glucose concentration, will improve the results by reducing the noise.

CONCLUSION

Four wavelength segments, each $7nm$ wide, have been identified in the wavelength range of $1.0\mu m$ to $1.7\mu m$ as promising windows that contain useful glucose information. As a result, four VCSELs in this range can be used to predict glucose concentration. The PLS signal processing technique has been successfully applied to predict glucose based on the optical spectra. In future work, we will implement a system using VCSELs to demonstrate VCSEL-based glucose measurements of whole blood.

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