Wavelength-modulated differential laser photothermal radiometry for blood glucose measurements

X. Guo\textsuperscript{a}, A. Mandelis\textsuperscript{a}, A. Matvienko\textsuperscript{a}, K. Sivagurunathan\textsuperscript{a} and B. Zinman\textsuperscript{b}
\textsuperscript{a}Department of MIE, University Toronto, 5 King’s College Road, Toronto, ON M5S 3G8, Canada
\textsuperscript{b}Samuel Luenfeld Research Institute, Mount Sinai Hospital, University of Toronto, 60 Murray Street, Toronto, ON M5T 3L9, Canada

Email: guox@mie.utoronto.ca

Abstract. A Wavelength-Modulated Differential Laser Photothermal Radiometer (WM-DPTR) technique was used for non-invasive blood glucose monitoring in the mid-IR range, where the prominent absorption peak is glucose specific and isolated from other interfering peaks in human blood. The WM-DPTR method consists of the out-of-phase modulated excitation at two discrete wavelengths 9.5 $\mu$m and 10.4 $\mu$m (near the peak and the baseline of glucose absorption), generated from two quantum cascade lasers (QCL) and the differential emission detection through a thermal-wave upconversion process via a HgCdZnTe (MCZT) detector (2-5 $\mu$m). The differential method suppresses the background signal and reduces source-detection interference, thus enhancing glucose detection sensitivity. The results from aqueous glucose phantom (0–440 mg/dl) measurements demonstrate that both amplitude and phase of the WM-DPTR signal can be used for glucose detection. The dynamic range and the sensitivity of the glucose detection are influenced greatly by the laser intensity ratio and modulation frequency. The optimal intensity ratio for high sensitivity is ~1. Other laser intensity ratios increase dynamic range but reduce sensitivity. Sensitivity increases with frequency.

1. Introduction
Diabetes has become one of the leading causes of death and disability in the world. In order to effectively manage this health condition, frequent monitoring of blood glucose is often required, particularly in patients who require regular insulin injections. The current standard technique for self-monitoring of blood glucose requires a skin puncture to draw a small blood sample. Discomfort and pain reduce its effective implementation. Over the past two decades, the pursuit for non-invasive methods of glucose monitoring has resulted in the development of a number of optical technologies [1]. The NIR spectral range has been well explored because of the relatively low water absorption. However, the glucose absorption bands in NIR are weak and overlapped with other blood constituents. Separation often requires sophisticated processing algorithms. In comparison, there are several prominent glucose absorption peaks in the MIR ‘finger-print’ region (8.3-12.5 $\mu$m). The strongest of them is at ~ 9.6 $\mu$m due to the C-O-C bending. The peak is well isolated from other interfering peaks in human blood [2,3]. A major difficulty in MIR is the intrinsic high-background absorption coefficient of water which tends to fully dominate the relatively low normal glucose concentration in human blood.

In this paper we present a novel wavelength modulated differential laser photothermal radiometer (WM-DPTR) for blood glucose monitoring in the MIR range. The mechanism of WM-DPTR glucose detection lies in the differential absorption of two laser lines at the glucose specific
peak around 9.6 μm. The elimination of water background yields high glucose sensitivity of the differential signal.

2. Theory

In the WM-DPTR method, two out-of-phase modulated laser beams (λ_A near the peak and λ_B at the baseline of glucose absorption) generate two out-of-phase photothermal signals S_A and S_B dependent on the optical and thermal properties of the sample: optical absorption coefficient μ_a and thermal effusivity e, as well as on the background. μ_A and μ_B are glucose-concentration-dependent, while μ_B is background-dependent but glucose-independent. Thus the resulting differential signal S_AB eliminates the background and is related to the glucose concentration of the sample with much higher sensitivity than either signal S_A or S_B.

A theoretical analysis of the WM-DPTR signal generation in tissue can be given using a 1-D heat conduction equation in the frequency domain [4], with a harmonic laser-induced heat source at subsurface depth z of tissue following optical absorption at wavelength λ_IR with absorption coefficient μ_a(λ_IR). The resulting IR radiometric flux (signal) can be written as

\[ \mathcal{S}(\omega) = \int M(\lambda_{ir}, T_0) \frac{\partial M(\lambda_{ir}, T_0)}{\partial T} \frac{\mu_{air}\mu_a(\lambda_{ir})I_0}{\kappa(\sigma^2 - \mu_a(\lambda_{ir})^2)} \left[ \frac{1}{\mu_a(\lambda_{IR}) + \mu_{air}} \left[ \frac{\kappa\mu_a(\lambda_{IR}) + h}{\sigma + \mu_{air}} \right] \right] d\lambda_{ir} \]  

(1)

where \( M(\lambda_{ir}, T_0) \) is the Plank distribution function at the ambient temperature \( T_0 \), \( \kappa \) the thermal conductivity of tissue, \( I_0 \) (W/cm\(^2\)) the laser intensity, \( \omega \) is the angular frequency of modulation \( \sigma(\omega) = \sqrt{i\omega/D} \) the complex thermal wave number; \( D \) the thermal diffusivity; \( h \) the heat loss coefficient. \( \lambda_{ir} \) and \( \mu_{air} \) are emission wavelength and absorption coefficient of the tissue. \( \lambda_{ir1} \sim \lambda_{ir2} \) is the detected emission wavelength range. For WM-DPTR system, excitation wavelengths \( \lambda_A = 9.5 \) μm, \( \lambda_B = 10.4 \) μm, the absorption coefficient at the excitation wavelength are \( \mu_A \) (glucose dependent) and \( \mu_B \) (glucose independent). The emission wavelength range is the spectral bandwidth of a Mercury-Cadmium-Zinc-Telluride (MCZT) detector: 2-5 μm. Thermal effusivity \( e \) (glucose dependent) is related to thermal conductivity \( \kappa \) and thermal diffusivity \( D \) in Eq. (1) through \( e = \kappa/\sqrt{D} \).

![Figure 1](image-url)  

**Figure 1.** Simulated frequency dependence of sensitivity in glucose detection for 300 mg/dl glucose concentration change. The modulation frequencies are 16, 49 and 150 Hz. (a) relative amplitude change \( \Delta A_{AB} \) vs. \( I_R \). (b) phase change \( \Delta P_{AB} \) vs. \( I_R \).  

WM-DPTR glucose detection was modelled for aqueous glucose solutions in the 0 to 300 mg/dl range to study the effects on detection sensitivity and dynamic range. The glucose dependent parameters (μ_A, κ and D) used in the simulation were determined from the literature [3, 5-7]. The glucose effect on absorption coefficient μ_a around 3 μm was ignored owing to the extremely strong water absorption there. \( h \) was set to zero due to minimal temperature difference between sample and ambient. Fig. 1 presents the effect of laser intensity ratio \( I_R = I_A/I_B \) and modulation frequency on sensitivity to glucose in the 0-300 mg/dl range. It is seen that both amplitude A_{AB} and phase P_{AB} are sensitive to glucose, but the sensitivity and dynamic range are greatly influenced...
by the laser intensity ratio. In general, I_R close to 1 is optimal. Frequency doesn’t affect the peak sensitivity, but affects the optimal ratio position and high sensitivity range. Higher frequencies tend to shift the optimal ratio to larger value and broaden the laser intensity ratio range.

3. Materials and method
Aqueous glucose solutions of 0–440 mg/dl concentration were used in the WM-DPTR measurements. Fig. 2 is the experimental set up of WM-DPTR system. Two out-of-phase modulated mid-IR laser (QCLs Pranalytica System, Pranalytica Inc. CA, USA) beams from laser A and laser B are focused onto a sample by a pair of identical lenses. The generated IR emission is collected by a 45° mirror and focused onto a MCZT (HgCdZnTe) (PVI-2TE-5, Vigo System, Poland) detector through a pair of parabolic mirrors. The signal from the detector is then sent to a lock-in amplifier for demodulation. The laser intensity ratio on the sample is controlled by a pair of irises in front of the lasers. Iris 2 is motorized with diameter resolution 1.7 μm.

Figure 2. Schematic diagram of the WM-DPTR system. Two out-of-phase modulated mid-IR laser beams (laser A and laser B) controlled by a laser controller are steered by two flat mirrors and a 45° mirror and focused onto a sample by a pair of identical lenses. The generated IR emission is collected by the same 45° mirror and focused onto a MCZT (HgCdZnTe) detector by a pair of parabolic mirrors. The converted electrical signal is sent to a lock-in amplifier. Laser intensity ratio on the sample is controlled by a pair of irises in front of the lasers.

4. Results and discussion
WM-DPTR glucose measurements showed the similar trend to the simulations. Fig. 3 presents the strong laser intensity ratio dependence of the glucose sensitivity and detection dynamic range. Both amplitude and phase exhibit increase in dynamic range at the cost of sensitivity. However, this might be an advantage of WM-DPTR for new-born baby and hypoglycemia monitoring: sensitive glucose measurements below 80 mg/dl are critical and are hard to achieve with today’s technologies. Shown in Fig. 4 is the frequency dependence of the signal. In agreement with our simulations, both amplitude and phase are more sensitive at higher frequencies. This might be due to offsetting photothermal saturation.

Figure 3. Measured laser intensity ratio dependence of sensitivity to glucose detection (0 – 440 mg/dl) at 50 Hz. Laser intensity ratio I_R = 0.99 and 1.01. (a) A_{AB} vs. I_R. (b) P_{AB} vs. I_R.
Figure 4. Frequency dependence of sensitivity in glucose detection (0 – 440 mg/dl) with laser intensity ratio $I_0 = 1.01$. The frequencies are 20 and 67 Hz. The data point is an average of 5 measurements. (a) Normalized amplitude vs. glucose concentration. (b) phase vs. glucose concentration

5. Conclusion
WM-DPTR was used to measure aqueous glucose solutions in the concentration range 0-440 mg/dl. It was demonstrated that WM-DPTR is a very sensitive method for glucose detection, especially compared with current non-invasive techniques. It was found that both amplitude and phase can be used for glucose sensing. This improves the reliability of the technique over other, single-signal-channel based methods. In WM-DPTR precise control of iris size, and thus laser intensity ratio, is critical for sensitive and monotonic glucose measurements. Work is continuing on measurements with fluids closer to clinical practice such as serum, plasma and interstitial fluid.

Acknowledgements
The authors thank the NSERC-CIHR CHRP program, the Ontario Ministry of Research and Innovation (MRI) and the NSERC Discovery Program for financial support of this research. We are grateful to Dr. K. Patel (Pranalytica, Inc.) for helpful discussions on, and partial support of, the QCL system.

References
[1] R. McNichols and G. Coté, “Optical glucose sensing in biological fluids: an overview,” J. Biomed. Opt. 5, 5-16 (2000).
[2] W. Martin, S. Mirov, and R. Venugopalan, “Middle infrared, quantum cascade laser optoelectronic absorption system for monitoring glucose in serum,” J. Biomed. Opt. 7, 613-617 (2002).
[3] W. Martin, S. Mirov, and R. Venugopalan, “Middle infrared, quantum cascade laser optoelectronic absorption system for monitoring glucose in serum,” Appl. Spec. 59, 881-884 (2005).
[4] A. Mandelis, “Green’s functions in thermal-wave physics: Cartesian coordinate representations,” J. Appl. Phys., 78, 647-655 (1995).
[5] CRC handbook of chemistry and physics, editor-in-chief, Robert C. Weast ; editor, David R. Lide. Boca Raton, Fla. : CRC Press, c1989. 70th ed.
[6] Y. Zhang and S. Tadigadapa, “A novel immunosensing technique based on the thermal properties of biochemicals,” Sensors, 2005 IEEE, 41-44 (2005).
[7] R. Darros-Barbosa, M. Balaban and A. Teixeira, “Temperature and concentration dependence of heat capacity of model aqueous solutions,” Int. J. Food Prop. 6, 239-58 (2003).