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Wavelength-modulated differential photothermal radiometry for non-Invasive blood glucose detection

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Glucose detection is vital for diabetes management. The development of clinically viable noninvasive glucose biosensors has been hampered by lack of specificity and sensitivity. We introduce Wavelength-Modulated Differential Laser Photothermal Radiometry (WM-DPTR) for noninvasive blood glucose monitoring. WM-DPTR features unprecedented glucose-specificity and sensitivity by combining laser excitation by two out-of-phase modulated beams at wavelengths near the peak (9.5 mm) and the baseline (10.4 mm) of a prominent and isolated mid-IR glucose absorption band. Figure 1 shows the experimental set-up of the WM-DPTR system. Two out-of-phase modulated MIR laser beams (Laser A, 9.5 mm, and Laser B, 10.4 mm), are steered onto a sample with a pair of flat mirrors. The generated two out-of-phase photothermal signals S_A S_B are collected and focused onto the MCZT detector through a pair of off-axis paraboloidal mirrors. The signal from the detector is then sent to a lock-in amplifier for demodulation. The laser intensity ratio $I_R = I_A/I_B$ on the sample is strictly controlled with a pair of irises (Iris A and Iris B). Iris B is critical to the performance of the instrument and is motorized with diameter resolution 1.7 mm. The resulting differential signal $S_{AB} = S_A - S_B$ minimizes the background (water absorption/emission) effects, suppresses the overall signal range (from several hundred mV to several mV) and is related to the glucose concentration of the sample with much higher sensitivity than single-ended signal S_A or S_B. S_{AB} can be expressed by two parameters: amplitude A_{AB} and phase P_{AB}.

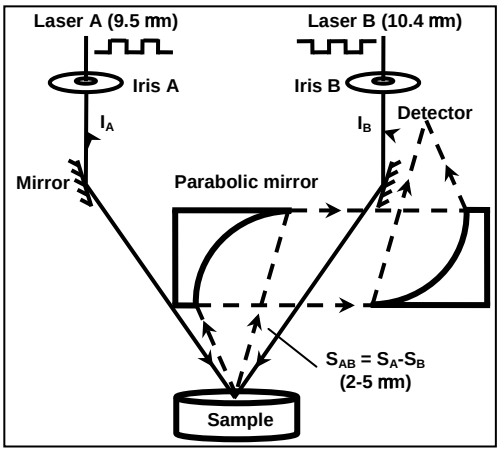

Fig. 1 *Schematic diagram of the WM-DPTR system. Two out-of-phase modulated mid-IR laser beams (Laser A and Laser B) are steered by two flat mirrors onto a sample. The generated IR emission is collected and focused onto a MCZT (HgCdZnTe) detector by a pair of parabolic mirrors. Laser intensity ratio I_R on the sample is controlled by a pair of irises (Iris A and Iris B).*

Measurements on water-glucose phantoms 0-20 mmol/l (0-360 mg/dl) demonstrate high sensitivity (up to 60% signal change due to 5.5 mmol/l (100 mg/dl) change in glucose) and resolution (0.07 mmol/l (1.3 mg/dl)) to meet wide clinical detection requirements ranging from hypoglycemia to hyperglycemia. Fig. 2 is the measured WM-DPTR amplitude and phase vs. glucose concentration at intensity ratios I_R = 1.01, 0.99 and 0.98 and modulation frequency 49 Hz. It is seen that both amplitude and phase can be used for optimally reliable glucose concentration diagnosis in a clinical setting. It is further observed that with decreasing intensity ratio, the sensitivity increases greatly at the expense of signal dynamic range. The highly sensitive measurement capability in low glucose concentration range is very attractive due to the lack of non-invasive methods for hypoglycemia monitoring below 3.85 mmol/l (70 mg/dl) for adults and around 1.65-2.2 mmol/l (30-40 mg/dl) for newborn infants . Shown in Fig. 3 are measurements at fixed laser intensity ratio I_R = 1.01 and two modulation

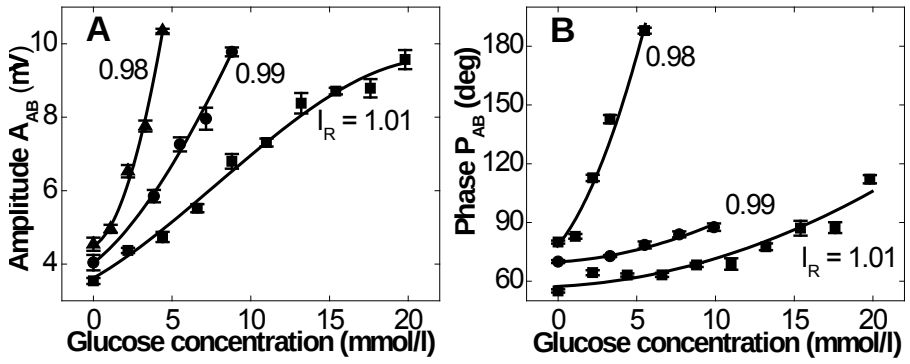

Fig. 2 *Effect of laser intensity ratio on glucose measurement sensitivity and detection range at modulation frequency f = 49 Hz. I_R = 0.98, 0.99 and 1.01. (A) amplitude vs. glucose concentration. (B) phase vs. glucose concentration. Each datum is an average of five measurements. Changes in I_R were made through fine adjustment of iris B, Fig. 1.*

frequencies, 67 Hz and 20 Hz. Both amplitude and phase are more sensitive at higher frequency. Fig. 3 also shows very complementary sensitivity to glucose between amplitude and phase across the full range of concentration.

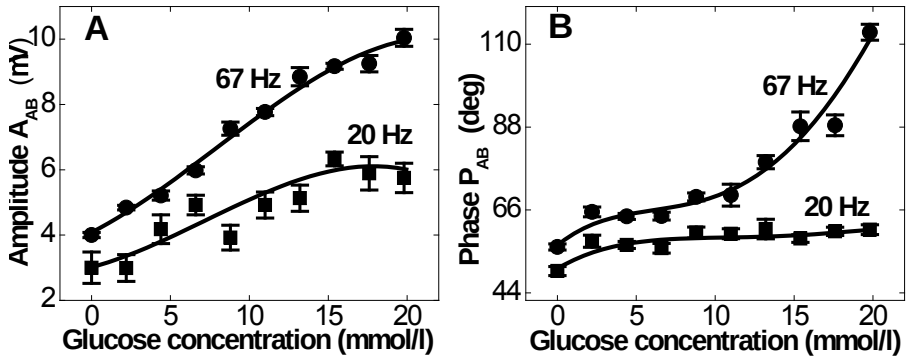

Fig. 3 *Effect of modulation frequency on glucose measurement sensitivity at intensity ratio I_R = 1.01. f = 20 Hz and 67 Hz. (A) amplitude vs. glucose concentration. (B) phase vs. glucose concentration. Each datum is an average of five measurements.*

The glucose sensing capability of the WM-DPTR method is rooted in the optical and thermal property (absorption coefficient η_a and thermal effusivity e) changes of the blood sample with glucose concentration. However, purely optical methods (such as transmission measurements) and purely thermal-wave methods (thermal effusivity measurements) are much less sensitive than WM-DPTR. This is so because the WM-DPTR method is based on the optical and thermal property change interdependence which greatly enhances differential signals: The thermal effusivity change acts as an amplifying factor of the optical absorption coefficient change. This is very important because optical changes add chromophore selectivity to WM-DPTR, whereas thermal changes alone are not selective at a molecular level.

We have introduced WM-DPTR for glucose detection in aqueous phantoms in the clinically relevant range. The amplitude and phase of the WM-DPTR signal act as two complementary glucose metrics and yield reliable results. Through proper selection of the excitation laser intensity ratio and the corresponding optimal modulation frequency, the WM-DPTR glucose measurement mode can be adjusted for maximum sensitivity to the glucose range of interest for accurate evaluation of biologically relevant glucose concentrations, from hypoglycemia to hyperglycemia. In practice, glucose detection instrumentation based on WM-DPTR is able to perform preliminary (coarse) measurements in the maximum dynamic range and relatively low sensitivity mode to locate a patent's glucose concentration range and then use appropriate intensity ratio to switch to the high-resolution mode for precise glucose measurements.