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Continuous glucose determination using fiber-based tunable mid-infrared laser spectroscopy

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ABSTRACT

Wavelength-tunable laser spectroscopy in combination with a small-sized fiber-optic attenuated total reflection (ATR) sensor (fiber-based evanescent field analysis, FEFA) is reported for the continuous measurement of the glucose level. We propose a method of controlling and stabilizing the wavelength and power of laser emission and present a newly developed mid-infrared wavelength-tunable laser with a broad emission spectrum band of 9.19–9.77 μm (1024–1088 cm^{-1}). The novel small-sized flow-through fiber-optic ATR sensor with long optical sensing length was used for glucose level determination. The experimental results indicate that the noise-equivalent concentration of this laser measurement system is as low as 3.8 mg/dL, which is among the most precise glucose measurements using mid-infrared spectroscopy. The sensitivity, which is three times that of conventional Fourier transform infrared spectrometer, was acquired because of the higher laser power and higher spectral resolution. The best prediction of the glucose concentration in phosphate buffered saline solution was achieved using the five-variable partial least-squares model, yielding a root-mean-square error of prediction as small as 3.5 mg/dL. The high sensitivity, multiple tunable wavelengths and small fiber-based sensor with long optical sensing length make glucose determination possible in blood or interstitial fluid in vivo.

1. Introduction

Diabetes mellitus is a serious human disease for which there is currently no cure. The general method of controlling the disease is to inject insulin by monitoring the blood glucose concentration. It is thus important to closely monitor the change in the blood glucose level, which can provide a reference value for the indication and treatment of diabetes. The widely used method of a fingertip prick combined with biomedical analysis is unable to provide a continuous glucose measurement. Meanwhile, non-invasive glucose measurements are currently in the research stage.

Many papers have surveyed measurements of glucose made with an enzyme electrode implanted in the body, and several products, such as SEVEN® Plus (DexCom, Inc.) [1], Paradigm® REAL-Time (Medtronic, Inc.) [2,3], and FreeStyle Navigator® (Abbott Laboratories) [4–6] have acquired certification from the Food and Drug Administration in the United States. However, the glucose level around the position of the implanted enzyme electrode is irreversibly depleted, which affects the local glucose concentration. Hence, the value monitored does not represent the true glucose concentration in the interstitial fluid in real time. At the same time, significant drift due to bioelectricity caused by electrolytes in the body fluid and electrochemical reaction under hypoxia reduces the accuracy of glucose determination, especially in the case of a low glucose concentration. Corrections are often required to obtain an accurate glucose concentration using an enzyme electrode, and the useful lifetime of the implanted enzyme electrode in the body is generally 3–7 days [7,8]. In contrast, a fiber-based sensor is not affected by bioelectricity in the body, making it a promising sensor to be implanted for glucose measurement. Implanted fiber sensors based on fluorescence resonance energy transfer (FRET) have received attention recently. Meadows [9], Dweik [10] and BioTex Company [11] have promoted this technology, and fiber-optic sensors have been implanted into the bodies of small animals for glucose determination. However, the poor long-term stability of fluorescent molecules banded on fibers and the slow response time makes it impossible for this technology to be used clinically. Compared with FRET technology, mid-infrared spectroscopy does not require a banded fluorescent substance, and the specific absorbance in the mid-infrared band allows a substance to be distinguished from various chemical species; mid-infrared spectroscopy based on attenuated total reflection (ATR) technique has been widely applied to determine the glucose concentration in vitro [12–14]. There is the potential for the fiber-optic ATR sensor to be implanted for continuous glucose monitoring.

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Previous research has demonstrated the applicability of a Fourier transform infrared (FT-IR) spectrometer. However, practical shortcomings, such as low spectral resolution and low spectral intensity for a traditional source, which restrict the detection limit and application of the FT-IR spectrometer in the detection of weak signals, are difficult to overcome. The high power and high spectral resolution of a laser source improve the measurement resolution, which has been successfully used in spectral analysis [15–17]. Kaiser [18,19], Mendelson [20] and Meinke [21] revealed the possibility of measuring glucose using a carbon dioxide (CO_2) laser with either one or two emission wavelengths in combination with a horizontal attenuated total reflection (HATR) sensor cell. Because of the overlap of the absorption spectrum of glucose and the absorption spectra of urea, urea acid, creatinine, phosphate and other materials in body fluid [22,23], it is impossible to measure the glucose concentration using spectral analysis and the single- or double-wavelength spectrometer. Gotshal [24] attempted to use a wavelength-tunable CO_2 laser combined with an ATR sensor for glucose measurement; however, the experimental results suffered from the low stability of the laser emission wavelengths and power. At the same time, because of the weak signal of glucose in the body, a fiber-optic ATR sensor with long optical sensing length is required to improve the resolution and sensitivity. Therefore, it is important to develop a light source with high power, high spectral resolution and multiple emission wavelengths combined with a small-sized fiber-optic ATR sensor with long optical sensing length for glucose measurement in vivo. This paper proposes a method of controlling and stabilizing the laser emission wavelength and power and presents a wavelength-tunable pulsed CO_2 laser with a broad emission band. Furthermore, the design of a novel small-sized flow-through fiber-optic ATR sensor is presented. The experimental results indicate that the proposed laser spectroscopy using a fiber-optic ATR sensor has the potential for continuous glucose determination in vivo.

2. Materials and methods

2.1. Experimental system

Fig. 1 shows the dual paths used to overcome the fluctuation of the laser power. To avoid heating and/or damaging the sample and to avoid exceeding the detector threshold (maximum incidence power: 2 mW) by high-power (hundreds of mW) laser excitation during the experiment, the laser output power was attenuated by an infrared attenuator (Model 401, Lasnix, Berg, Germany) with an adjustable transmittance from 0.01% to 100%. A zinc selenide (ZnSe) beam splitter was used to divide the laser beam into dual paths, one for sample measurement and the other for reference. A ZnSe lens was used to focus the incident light on a fiber-optic ATR sensor, and the emerging light was detected by a pyroelectric detector (LME-353-63, InfraTec GmbH, Dresden, Germany). The reference-path light was focused onto the same model of detector directly by a ZnSe lens, and the two detectors were connected to the same model of lock-in amplifier circuit (SR830, Stanford Research Systems, Inc., California, USA), for which a synchronous reference frequency (750 Hz) was offered by the RF circuit of the laser device. The lock-in signals of the reference and sample paths were then synchronously recorded by a data acquisition system. The "sandwich" measurement method was used to overcome instrument drift. Phosphate buffered saline (PBS) solution was first pumped into the flow-through fiber-optic ATR sensor, and the two lock-in voltages of the dual paths were recorded. The sensor chamber was then flushed by the sample solution having a different glucose concentration, and the lock-in voltages were recorded again. The relative intensity is defined as

$$r_s = \frac{u_G^R/u_G^S}{u_P^R/u_P^S}, \qquad (1)$$

where u is the lock-in voltage, the superscripts "S" and "R" denote the sample and reference paths, respectively, and the subscripts "P" and "G" denote PBS and glucose solution, respectively. r_s is the relative intensity correlated with the glucose concentration.

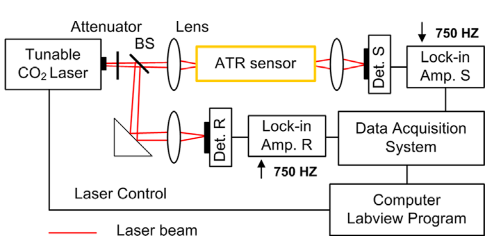

Fig. 1. Schematic diagram of the experimental set up. The reference frequency of the lock-in amplifier (750 Hz) was supplied by the laser RF circuit.

2.2. Method of stabilizing the laser emission wavelengths and power

A method of controlling and stabilizing the laser emission wavelengths and power is proposed, and a wavelength-tunable CO_2 laser (Access Laser Co., Washington, USA) with a broad emission spectrum of 9.19–9.77 μm (1024–1088 cm^{-1}) is presented; the laser works in TEM_{00} mode, with air-cooled operation. The polarization state of the laser beam is perpendicular to the horizontal plane, with a waist diameter of <2 mm and divergence angle of <5 mrad. Fig. 2 shows that the laser pulsed at 750 Hz (duty cycle of 0.5) and was driven by a RF driver, with the emission wavelength regulated by a linear motor and a piezo actuator. The output light was divided by a beam splitter (yellow), and approximately 5% of the laser light was reflected and detected by an IR detector (green) as the sampling signal, which provides a feedback signal to stabilize the laser power and wavelength. The linear motor and its drive can be considered as a module for selecting the wavelength during wavelength scanning and selection of the laser spectrum line. To control the laser emission wavelength and stabilize the power, a piezoelectric ceramic and its drive circuit were used to adjust the length of the laser resonant cavity. A linear stepping motor was first used to coarsely adjust the emission wavelength, and the piezoelectric ceramic was then used for fine adjustment. All these operations were controlled by a control board with LabView software installed on a computer.

2.3. Structural design of the fiber-optic ATR sensor

AgCl/Br was chosen as the fiber material because of its broad transmission band (4–18 μm) and low loss in the mid-infrared region. Other characteristics of the material, such as its non-toxic, non-hygroscopic and non-brittle properties, allow it to be bent

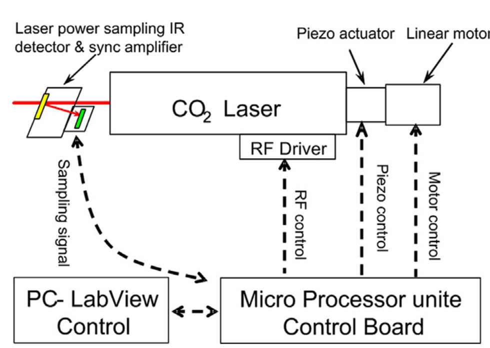

Fig. 2. Control scheme of the CO_2 laser.