US 20070213607A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2007/0213607 A1

Mandelis et al. (43) Pub. Date: Sep. 13, 2007

(54) NON-INVASIVE BIOTHERMOPHOTONIC SENSOR FOR BLOOD GLUCOSE MONITORING

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(21) Appl. No.: 11/368,698

(22) Filed: Mar. 7, 2006

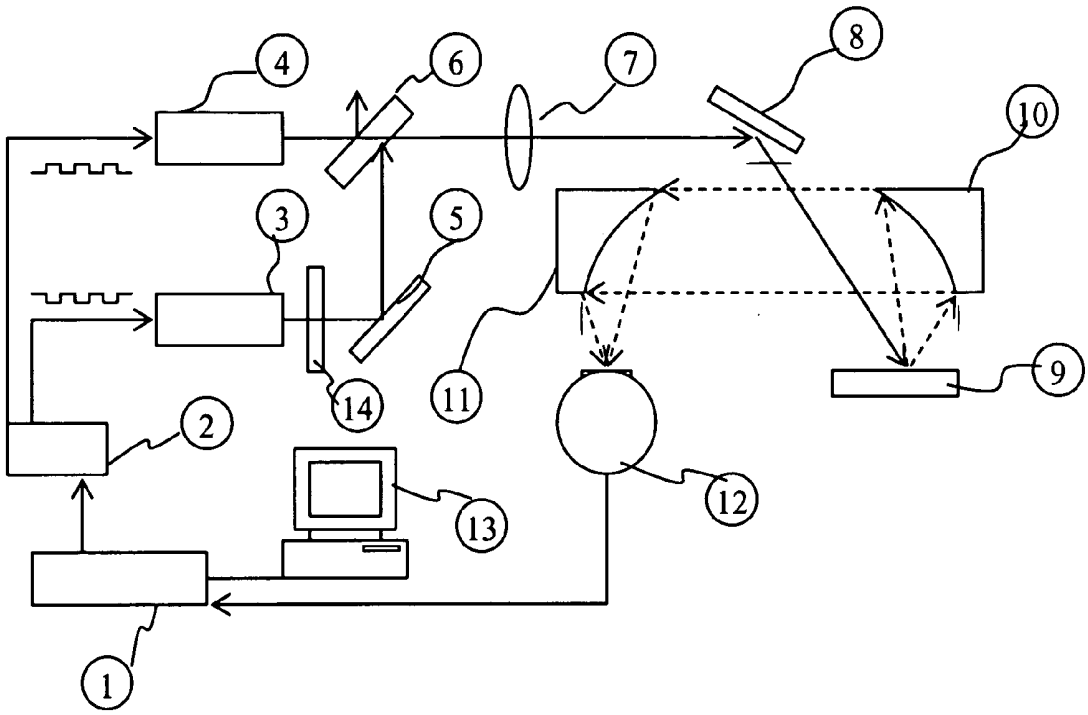
Publication Classification

(51) Int. Cl.
A61B 5/00 (2006.01)

(52) U.S. Cl. 600/316

(57) ABSTRACT

There is provided a glucose monitoring method and apparatus based on the principle of Wavelength-Modulated Differential Laser Photothermal Radiometry (WM-DPTR). Two intensity modulated laser beams operating in tandem at specific mid-infrared (IR) wavelengths and current-modulated synchronously by two electrical waveforms 180 degrees out-of-phase, are used to interrogate the tissue surface. The laser wavelengths are selected to absorb in the mid infrared range (8.5-10.5 μm) where the glucose spectrum exhibits a discrete absorption band. The differential thermal-wave signal generated by the tissue sample through modulated absorption between two specific wavelengths within the band (for example, the peak at 9.6 and the nearest baseline at 10.5 μm) lead to minute changes in sample temperature and to non-equilibrium blackbody radiation emission. This modulated emission is measured with a broadband infrared detector. The detector is coupled to a lock-in amplifier for signal demodulation. Any glucose concentration increases will be registered as differential photothermal signals above the fully suppressed signal baseline due to increased absorption at the probed peak or near-peak of the band at 9.6 μm at the selected wavelength modulation frequency. The emphasis is on the ability to monitor blood glucose levels in diabetic patients in a non-invasive, non-contacting manner with differential signal generation methods for real-time baseline corrections, a crucial feature toward precise and universal calibration (independent of person-to-person contact, skin, temperature or IR-emission variations) in order to offer accurate absolute glucose concentration readings.



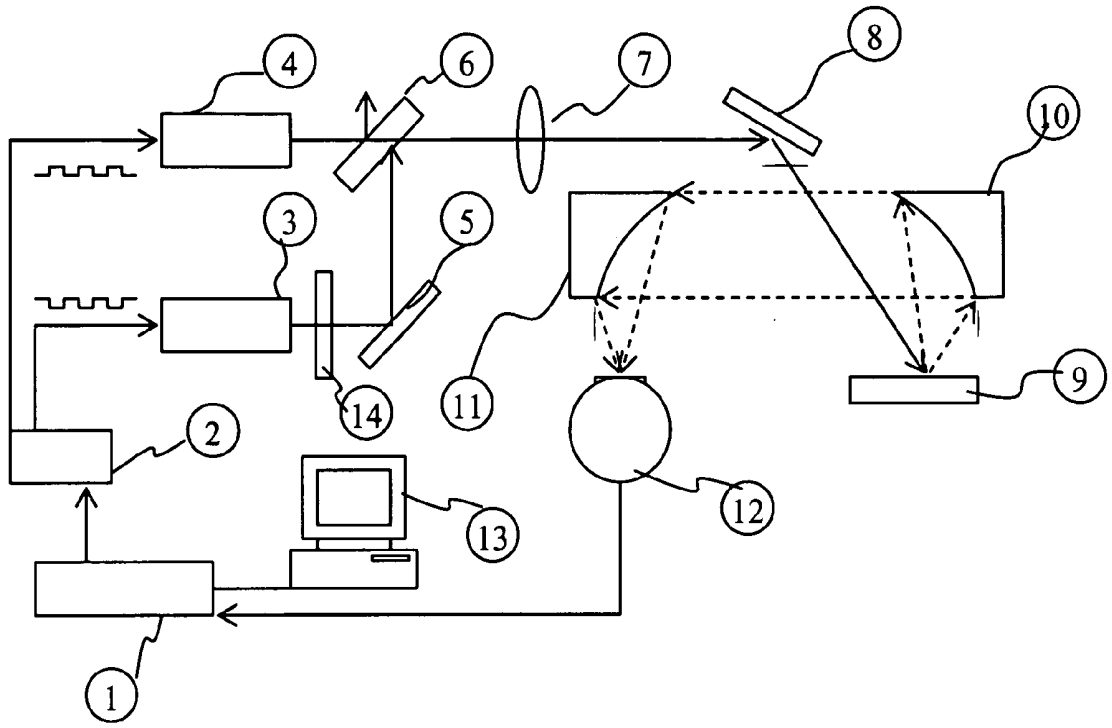


Figure 1

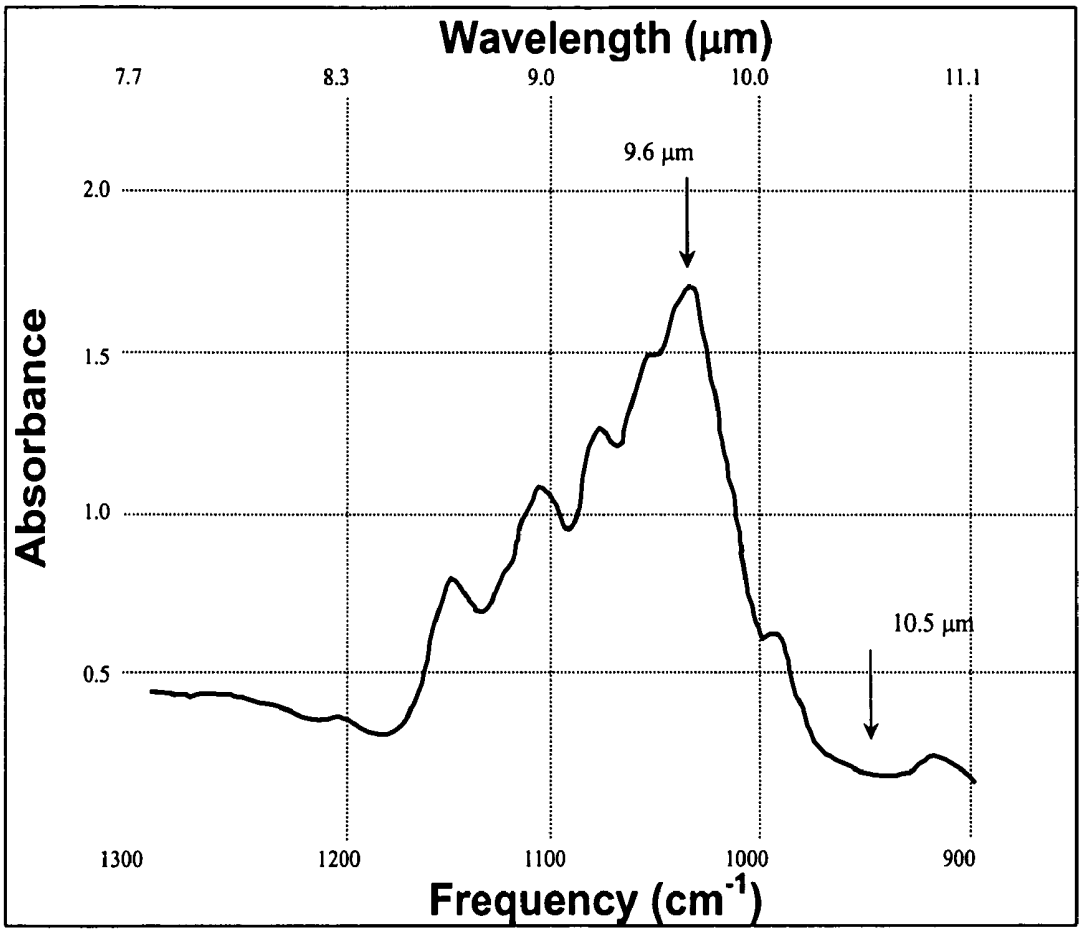

Wavelength (μm)
7.7
8.3
9.0
10.0
11.1
9.6 μm
2.0
1.5
1.0
0.5
Absorbance
10.5 μm
1300
1200
1100
1000
900
Frequency (cm-1)

Figure 2

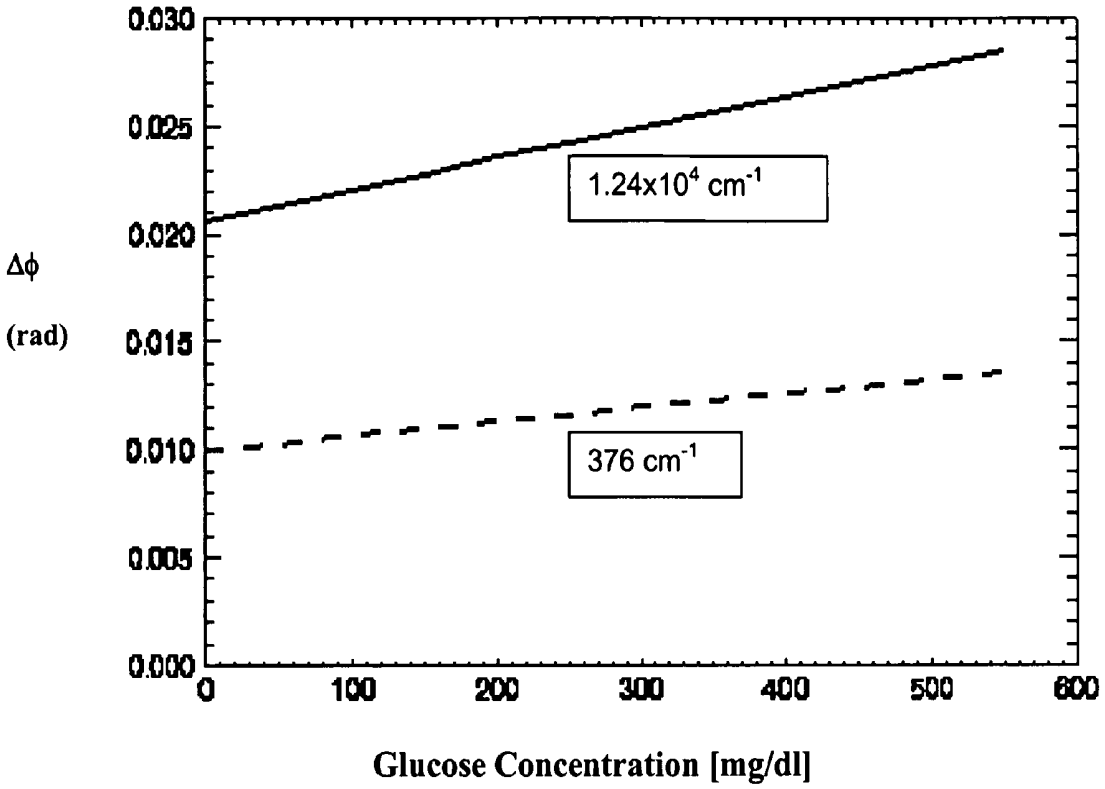

0.030
0.025
0.020
0.015
0.010
0.005
0.000
Δϕ
(rad)
1.24x10^4 cm^-1
376 cm^-1
0
100
200
300
400
500
600
Glucose Concentration [mg/dl]

Figure 3

NON-INVASIVE BIOTHERMOPHOTONIC SENSOR FOR BLOOD GLUCOSE MONITORING

FIELD OF INVENTION

[0001] The present invention relates to a method and device to monitor blood glucose in diabetic patients in a non-invasive manner.

BACKGROUND OF THE INVENTION

[0002] The metabolic disease known as diabetes mellitus afflicts a large and growing number of people worldwide. In order to manage this health condition, frequent monitoring of blood glucose level is essential, especially for the patients who require regular insulin injections. To reduce risk of severe long-term health complications, it is recommended that diabetes patients check blood sugar level up to five times a day to maintain physiological glucose concentration between 90 and 120 mg/dl [A. C. Guyton and J. E. Hall, *Textbook of medical physiology* 10th ed. Philadelphia, Ch.78 (2000)]. The standard technique for measurement of glucose concentration requires skin puncture to draw a small blood sample (typically microliter volume) which can be examined using a test strip and automated meter to report the results. Although this technique provides accurate glucose concentration data, frequent skin puncture is associated with significant discomfort, pain and risk of infection. Besides, it cannot be used for continuously monitoring glucose levels, an essential requirement especially for some categories of diabetics, including juvenile diabetes. Continuous monitoring also enables the creation of a real-time insulin pump—a much sought after mode of insulin delivery that better mimics the normal physiological condition. Over the past two decades, search for alternative methods of glucose monitoring resulted in development of a number of optical technologies including an IR absorption technique [H. Zeller, P. Novak and R. Landgraf, *Int. J. Art. Org.* 12, 129 (1989)], the pulsed photoacoustic method [H. A. MacKenzie, H. S. Ashton, S. Spiers, Y. Shen, S. S. Freeborn, J. Hannigan, J. Lindberg and P. Rae *Clinical Chem.* 45, 1587 (1999); K. M. Quan, G. B. Christison, H. A. MacKenzie and P. Hodgson, *Phys. Med. Biol.* 38, 1911 (1993)], polarimetry [G. L. Cote, M. D. Fox and R. B. Northrop, *IEEE Trans. Biomed. Eng.* 44, 1221 (1992)] and Raman spectroscopy [A. J. Berger, Y. Wang and M. S. Feld, *Appi. Opt.* 35, 209 (1996)].

[0003] Despite significant effort directed towards the development of non-invasive and minimally-invasive techniques for glucose monitoring [O, S. Khalil, *Clinical Chem.* 45, 165 (1999); G. L. Cote and R. J. McNichols, *Biomedical Photonics Handbook*, Ed.: Tuan Vo-Dinh, Ch. 18 (CRC Press) (2003)], no completely non-invasive sensor satisfying sensitivity and specificity conditions similar to intrusive sensors is available at the moment. [R. W. Waynant and V. M. Chenault (April 1998), "*Overview of Non-Invasive Fluid Glucose Measurement Using Optical Techniques to Maintain Glucose Control in Diabetes Mellitus*", at http://www.ieee.org/organizations /pubs/newsletters/ leos/apr98/overview. htm (LEOS Newsletter, Vol. 12)]. Traditionally, the near-IR spectral range (0.8-3 μm) has been explored for the development of optical technologies for glucose monitoring because of relatively low water absorption [M. Robinson, R. P. Eaton, D. M. Haaland, D. W. Koepp, E. V. Thomas, B. R. Stallard, and P. L. Robinson, *Clin. Chem.* 38, 1618 (1992); M. A. Arnold and G. W. Small, *Anal. Chem.* 62, 1457 (1990); D. Kajiwara, T. Uemura, H. Kishikawa, K. Nishida, Y. Hashiguchi, M. Uehara, M. Sakakida, K. Ilchinose and M. Shichiri, *Med. Biol. Eng. Comput.* 31, S17 (1993); R. Marbach, Th. Koschinsky, F. A. Gries and H. M. Heise, *Appl. Spectrosc.* 47, 875 (1993)]. Quantitative interpretation of spectroscopic data in the near-IR often requires sophisticated processing algorithms due to overlap of glucose molecule overtones and absorption bands of other tissue analytes. Farther into the mid-IR region (2.5-10 μm), the spectrum of anhydrous glucose has more than 20 absorption peaks, not all of which are specific to this molecule. Of particular significance, however, is the prominent absorption peak in the 8.5-10.5 μm band which is due to the carbon-oxygen-carbon bond in the pyrane ring of glucose. This feature is peaked at ca. 9.7 μm, and is isolated from other interfering peaks in human blood [C. J. Pouchert, *The Aldrich Library of Infrared Spectra, 3rd. ed.*, Aldrich Chemical Co. (1981)]. This peak is within the spectral range of the CO_2 laser which emits at several discrete wavelengths between 9.2 and 10.8 μm. A major difficulty for practical monitoring of glucose in human tissue within this spectral range is the intrinsic high-background absorption coefficient of water (640 cm^{-1} at 9.7 μm), which tends to fully dominate the relatively low normal concentration of glucose in human blood (typically 90 to 120 mg/dl). Nevertheless, a modulated CO_2 laser emission at 9.6 μm and a multiple attenuated total reflection (ATR) plate, both sides of which were immersed in the sample solution for signal enhancement (unrealistic for practical devices), was successfully used in obtaining definite correlations between ATR signal and glucose concentration in the range of 50-280 mg/dl [Y. Mendelson, C. Clermont, R. A. Peura and B-C. Lin, *IEEE Trans. Biomed. Eng.* 37, 458 (1990)]. Unfortunately, the data scatter in the critical 50 to 120 mg/dl range was on the order of 50-90% which is unacceptable for a practical device implementation. Several factors contributed to this: ATR plate heating, high signal sensitivity to the angle of incidence of the laser beam on the plate, the inherent depth inadequacy of the evanescent electromagnetic (EM) field probing only ca. 1.3 μm into the adjacent fluid zone, and the small, yet interfering, background absorptions (e.g. proteins) which cannot be eliminated using single-ended optical techniques. Besides, any practical implementation of this method would stumble on serious difficulties with regard to signal variations due to contact interface variations of the ATR prism from patient to patient and the presence of the glucose-deficient tissue surface epidermis layer (~80 μm).

SUMMARY OF THE INVENTION

[0004] The present invention provides a non-invasive glucose monitoring apparatus ("Spectroscopic Glucose Radiometer—SGR") based on a modality utilizing Wavelength-Modulated Differential Laser Photothermal Radiometry (WM-DPTR). In one aspect, the present method comprises:

[0005] 1) irradiating the tissue surface with two specialty low-power (~200 mW) radiation emitting sources (CO_2 lasers or other appropriate sources).

[0006] 2) operating the said sources in tandem and modulated synchronously at angular modulation frequency $\omega=2\pi f$ with f in the 0.1-10000 Hz range by two electrical waveforms 180 degrees out-of-phase.

[0007] 3) producing periodic frequency pulses of the irradiating sources (laser beams) in the range covering 0.1 Hz to 10 kHz, especially in the vicinity of (but not confined to) 700 Hz.

[0008] 4) making the two spatially separated beams at the desired wavelengths co-incident on the sample surface using appropriate optical elements.

[0009] 5) equalizing the intensities of the two beams via a neutral density filter and monitoring sub-surface tissue fluid differential absorption at the pre-determined wavelengths in the presence of glucose concentration within the normal human range (90-120 mg/dl) in order to determine the healthy band for normal residual glucose of the emissive infrared signal and/or adjust the said signal to zero to null the differential absorption from the healthy band.

[0010] 6) generating out-of-phase photothermal-wave signals at both wavelengths leading to minute changes in net sample temperature (<1K) due to differential absorption.

[0011] 7) using photothermal-wave superposition (destructive interference) over one modulation period in the tissue leading to net differential blackbody radiation emission at the said two wavelengths.

[0012] 8) collecting said emission signal with suitable mid-IR collecting optics including solid-angle and reflectivity optimized curved mirrors and specialty fiber-optic delivery systems (e.g. silver halide optical fibers).

[0013] 9) detecting said collected signal with a wide-bandwidth (dc-MHz) cryogenic broadband HgCdTe (MCT) detector (2-12 μm), or any other solid-state detector in the mid-IR capable of fast signal modulation, such as room-temperature or thermoelectrically-cooled HgCdZnTe detector (2-6 μm), ZnSe, Ge, or other commercially available or specially designed and engineered detectors. This list is understood not to be exclusive but inclusive of any current or future state-of-the art mid-IR detector device.

[0014] 10) outfitting the said detector with a narrow bandpass IR filter to block the CO_2 laser emission line range, if so required by possible overlap of the spectral bandwidth of the detector with the source emission range.

[0015] 11) demodulating the said detector signal by an appropriate demodulating device (lock-in amplifier)

[0016] 12) recording the signals by a computer

[0017] 13) processing said recorded signal and correlating it to glucose concentration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The device for monitoring blood glucose according to the present invention will now be described by way of example only, reference being had to the accompanying drawings in which:

[0019] FIG. **1** illustrates a schematic diagram of an embodiment of the Spectroscopic Glucose Radiometer.

[0020] FIG. **2** illustrates a section of the mid-IR absorption spectrum of glucose showing the two proposed detection wavelengths.

[0021] FIG. **3** illustrates differential photothermal-wave phase as a function of glucose concentration for $\alpha=1.24\times10^4$ cm^{-1} (modulation frequency 70 Hz) and $\alpha=376$ cm^{-1} (modulation frequency 30 Hz). These are values of optical absorption coefficient corresponding to the peak of glucose band and to human skin, at wavelengths 9.6 μm and 10.5 μm, respectively (FIG. **2**).

DETAILED DESCRIPTION OF THE INVENTION

[0022] The present invention provides a device based on non-invasive, non-contacting measurements with differential signal generation methods for real-time baseline corrections, a crucial feature toward precise and universal calibration (independent of person-to-person mid-IR spectral baseline variations, skin and subcutaneous absorption, body temperature or IR-emission variations) in order to offer accurate absolute glucose concentration readings. In addition, spectroscopic baseline suppression, coupled to maximally high signal dynamic range afforded by differential lock-in amplifier detection, is very promising for detection of both hyperglycemia and hypoglycemia.

[0023] FIG. **1** shows an embodiment of the apparatus for non-invasive glucose monitoring, using two specialty low-power (~200 mW) CO_2 lasers **3** and **4**. The lasers are operating in tandem and are current-modulated synchronously at modulation frequency $f=\omega/2\pi$ in the 0.1-10000 Hz range by out-of-phase electrical waveforms generated by a wave generator **2**. The two spatially separated laser beams at the desired wavelengths are made co-incident by directing the beams through mirror **5**, beam combiner **6**, lens **7** and mirror **8** on the sample surface **9** as shown in FIG. **1**. The intensities of the beams are equalized by a variable neutral density filter **14** or by current adjustment of one of the two laser power supplies. The beams are modulated at the same frequency but 180 degrees out-of-phase. This wavelength modulation arrangement gives rise to destructive interference over one modulation period between the two thermal waves generated through optical absorption at the two chosen wavelengths at the peak and trough (baseline) of the glucose 8.5-10.5 μm absorption band. This amounts to a differential thermal-wave signal generated in the tissue sample. Thermal waves are minute oscillatory changes of sample temperature (<1 K) leading to differential blackbody radiation emission modulated at the common frequency of the wavelength modulation. The emission is collected by paraboloidal mirrors **10** and **11** and measured with a broadband HgCdTe (MCT) detector **12** (2-12 μm bandwidth) outfitted with a narrow bandpass IR filter to block the CO_2 laser emission line range. It is to be understood that other clinically convenient embodiments of the mid-IR detector and blackbody emission power can be substituted for the aforementioned devices within the scope of the invention. These comprise, but are not limited to, fiber optic delivery systems (e.g. Silver halide mid-IR fibers), room-temperature or thermoelectrically-cooled HgCdZnTe (MCZT) detector (2-6 μm), ZnSe, Ge, or other commercially available or specially designed and engineered detectors. The MCT detector **12** is coupled to a lock-in amplifier **1** for signal demodulation, referenced at the wavelength modulation

frequency f=ω/2π The demodulated signal from the lock-in amplifier **1** is sent to a personal computer **13** for recording and processing. If the intensities of the two beams are properly equalized a zero signal is expected from equal (background) absorption coefficients at the two wavelengths in the absence of any glucose concentration. Normal physiological glucose concentration range signals (90-120 mg/dl) lead to a healthy differential thermal-wave signal calibration band recorded by the lock-in amplifier. Any glucose concentration increases are registered as excess photothermal signals above the healthy base band, the said healthy base band signals possibly been fully suppressed. Differential signals as a result of increased absorption at 9.6 μm at a modulation frequency in the range between 0.1 Hz and 10 kHz, are judiciously selected near the peak and baseline of the absorption band in FIG. **2** so as to maximize the differential photothermal-wave signal.

[**0024**] The biothermophotonic device relies on judiciously chosen differential CO_2 laser line absorption in tissue in the 8.5-10.5 μm glucose IR absorption band, thermal-wave generation in tissue and dual wavelength phase-sensitive detection of radiometric signals (detection of photothermal blackbody photons) in the mid-IR spectral band away from the absorption region. The spectrally differential thermal-wave signal of the mid-IR response recorded at the peak and off-peak of glucose absorption can be related to glucose concentration in the tissue specimen. This biosensor device may be applied for measurements of glucose concentration in the interstitial fluid (ISF) of the superficial skin layers to establish correlation with glucose concentration in the blood. Since it measures only one absorption band through its own generated infrared emissions at two infrared absorption locations (maximum and minimum), the biosensor is self referenced, featuring real-time baseline normalization, and in relative isolation from interfering tissue absorptions. Therefore, it can yield absolute measurements of glucose concentration within, below or above the healthy base-band, unlike many other optical and near-IR techniques introduced to-date [M. Robinson, R. P. Eaton, D. M. Haaland, D. W. Koepp, E. V. Thomas, B. R. Stallard, and P. L. Robinson, *Clin. Chem.* 38, 1618 (1992); M. A. Arnold and G. W. Small, *Anal. Chem.* 62, 1457 (1990); D. Kajiwara, T. Uemura, H. Kishikawa, K. Nishida, Y. Hashiguchi, M. Uehara, M. Sakakida, K. Ilchinose and M. Shichiri, *Med. Biol. Eng. Comput.* 31, S17 (1993); R. Marbach, Th. Koschinsky, F. A. Gries and H. M. Heise, *Appl. Spectrosc.* 47, 875 (1993)].

[**0025**] This differential method will give at least one order-of-magnitude higher signal resolution and signal-to-noise ratio increase over conventional single-ended optical methods [C. H. Wang and A. Mandelis, Rev. Sci. Instrum. 71, 1961 (2000)] and thus yield resolution superior to existing optical methods within the physiological glucose concentration range. The separation of source and detection wavelengths is also very important in providing effective isolation of the glucose peak with minimum interferences from nuisance absorptions including interference from the incident laser beams. In future in-vitro or in-vivo tissue applications, the frequency-dependent thermal penetration depth can be adjusted through appropriate frequency tuning to maximize the differential signal collected from subsurface depths well beyond the epidermis layer: from dermis (>500 μm) and from interstitial fluid or blood layers. This is an important feature of thermal-wave based methods, as the strong water absorption will allow effective optical penetration down to only 20-30 μm inside the glucose containing layers below the epidermis. It is important to emphasize that the differential spectroscopic scheme of signal generation of this device subtracts out automatically the strong water absorption baseline (640 cm^{-1} at 9.7 μm). The power of laser irradiation will be strictly controlled and maintained within regulatory-body-approved safe exposure level at all times.

Theory of Spectroscopic Differential Radiometry with Applications to Glucose Detection

[**0026**] The SGR instrument is based on Wavelength-Modulated Differential Laser Photothermal Radiometry (WM-DPTR). It takes advantage of characteristic spectral features of glucose (spectral "fingerprints") in the mid-IR spectral range (8.5-12 μm). The glucose absorption spectrum has several fundamental absorption bands in the mid-IR that can be used to distinguish glucose molecules from other tissue analytes. Specifically, the absorption peak at 9.6 μm is the most prominent and it is not obstructed by spectral features of other substances [C. J. Pouchert, *The Aldrich Library of Infrared Spectra,* 3*rd. ed.*, Aldrich Chemical Co. (1981)] (FIG. **2**). The principle of the WM-DPTR method consists in phase-sensitive measurements of oscillating IR radiation emitted by a laser-heated tissue specimen at two discrete wavelengths (at the peak and off-peak of glucose absorption) and relating the observed phase shift to changes of glucose concentration. Dual wavelength detection is required to ensure selectivity of measurements. In our studies, the radiometric signals will be recorded at the peak of the glucose absorption (9.6 μm) and at the reference wavelength of 10.5 μm, near the minimum of glucose absorption (FIG. **2**) to isolate the glucose contributions from contributions of water and other tissue substances. To create periodic thermal sources (thermal waves) near the tissue surface, intensity-modulated laser radiation is considered. A theoretical analysis of the thermal wave generation and IR emission can be given using a one-dimensional heat conduction equation in frequency domain [A. Mandelis, *J. Appl. Phys.* 78, 647 (1995); A. Mandelis, *Diffusion-Wave Fields. Mathematical Methods and Green Functions* (New York: Springer, 2001) p. 3] with a harmonic laser-induced heat source following optical absorption at wavelength λ_{IR1} with tissue absorption coefficient $\alpha(\lambda_{IR1})$:

$$Q(z,\omega)=\alpha(\lambda_{IR1})I_0 e^{-\alpha(\lambda IR1)z}\cdot e^{i\omega t} \quad (1)$$

where $I_0(W/cm^2)$ is the laser radiation intensity entering a sample, and ω is the angular frequency of laser modulation. The harmonic component of the spatial temperature distribution $\tilde{T}(z, \omega)$ and the resulting increase in IR radiometric flux $\tilde{R}(\lambda_{ir},\omega)$ detected at the wavelength λ_{ir} within a narrow spectral band δ_λ can be written as:

$$\tilde{T}(z,\omega)=\frac{\alpha I_0}{\kappa(\sigma^2-\alpha^2)}\left[e^{-\alpha z}-\frac{\kappa\alpha+h}{\kappa\sigma+h}e^{-\sigma z}\right] \quad (2)$$

$$\tilde{R}(\lambda_{ir},\omega)=\left(\frac{\partial M(\lambda_{ir},T_0)}{\partial T}\right)\frac{\delta_\lambda\alpha_{ir}\alpha I_0}{\kappa(\sigma^2-\alpha^2)}\left[\frac{1}{\alpha+\alpha_{ir}}-\frac{\kappa\alpha+h}{\kappa\sigma+h}\cdot\frac{1}{\sigma+\alpha_{ir}}\right] \quad (3)$$

where $M(\lambda_{ir}, T_0)$ is the Plank distribution function for blackbody radiation at the ambient temperature T_0, κ is the thermal conductivity of tissue, $\sigma(\omega)=\sqrt{i\omega/D}$ is the complex thermal wavenumber; D is tissue thermal diffusivity; the

coefficient h describes convective heat loss at the air-tissue interface. Equation (3) shows that the radiometric response $\tilde{R}(\lambda_{ir}, \omega)$ depends on absorption coefficients $\alpha(\lambda_{IR1})$ at the excitation wavelength and $\alpha(\lambda_{ir})$ at the detection wavelength (ca. 5 μm). Therefore, spectroscopic data can be obtained from radiometric measurements if the IR signal is recorded at different excitation wavelengths. The dual wavelength WM-DPTR technique records radiometric signals obtained at λ_{IR1}, =9.6 μm and λ_{IR2}=10.5 μm. The response at each wavelength is detected at the same spectral bandwidth ($\lambda_{ir}\delta_{\lambda}$). A narrow-band signal processing algorithm (lock-in) computes the corresponding phases and the differential phase is related to glucose concentration in a tissue specimen. Quantitative estimates of the radiometric signal amplitude and phase can be done using optical properties of human skin assuming water content approximately 70%. The effect of glucose concentration on the absorption coefficient at 9.6 μm was investigated recently [W. B. Martin, S. Mirov and R. Venugopalan, *J. Biomed. Opt.* 7, 613 (2002)]. It was shown that the peak absorption coefficient λ_{IR1} depends linearly on glucose concentration, c_g, in the range 0-500 mg/dl with slope $d\alpha_{IR1}/dc_g=4.2\times10^{-2}$ $cm^{-1}/(mg/dl)$. At the same time, the baseline absorption coefficient α_{IR2} is unaffected by glucose. Using, this value of the slope to model linear variations of the absorption coefficient $\alpha(\lambda_{IR1})=\alpha_{IR1}$ as:

$$\alpha_{IR1}(c_g) = \alpha_{IR1}(c_g = 0) + \left(\frac{d\alpha_{IR1}}{dc_g}\right)\cdot c_g \qquad (4)$$

where glucose-free absorption coefficient is taken $\alpha_{IR1}(c_g=0)=598$ cm^{-1}. The differential phase of radiometric signals at the two wavelengths computed for different values of the absorption coefficient, corresponding to a possible maximum and a minimum value of the glucose peak, is shown in FIG. **3**. This plot shows a linear increase of differential phase with increase of glucose concentration, however sensitivity (slope of straight lines) is greater for the strong light absorption ($\alpha_{IR1}=1.24\times10^4$ cm^{-1}). Estimates of the differential phase sensitivity suggest that glucose concentration increase of Δc_g=100 mg/dl should result in the relative phase shift $\Delta\phi\approx4.4\times10^{-3}$ rad for superficial light absorption in tissue. This amounts to a 0.1° phase resolution, which should be quite feasible with today's lock-in technology. Experimental work [P. Zheng, C. E. Kramer, C. W. Barnes, J. R. Braig and B. B. Sterling, *Diabetes Tech. and Therap.* 2, 17 (2000)] reports differential phase measurements with sensitivity $\Delta\phi\approx3.5\times10^{-6}$ rad/(mg/dl) achieved with a thermoelectric cooler. This degree of sensitivity is approx. two orders of magnitude higher than a low absorption peak with $\alpha_{IR1}=376$ cm^{-1}, FIG. **3**. Note that this 376 cm^{-1} peak was intentionally underestimated compared to the water background absorption of 640 cm^{-1} at 9.7 μm, so as to be taken as a worst case scenario.

[**0027**] In conclusion, these theoretical estimates demonstrate definite feasibility of the Wavelength-Modulated Differential Laser Photothermal Radiometric technique and of the proposed SGR device to detect variations of glucose concentration typical of diabetes patients, with the model indicating phase resolution requirements of $\Delta\phi\sim10^{-3}$ rad.

[**0028**] While this apparatus and its application has been described and illustrated with respect to a one particular embodiment, it will be appreciated that numerous embodiments of the instrument may be made without departing from the scope of this invention. Some such alternative components and devices to enhance clinical convenience and applicability have already been suggested in the detailed description of the invention.

Therefore what is claimed is:

1) A glucose monitoring method based on the principle of Wavelength-Modulated Differential Laser Photothermal Radiometry (WM-DPTR), comprising:

a) irradiating the tissue surface with two specialty low-power (~200 mW) radiation emitting sources.

b) modulating the said sources in tandem and synchronously at angular modulation frequency $\omega=2\pi f$ with fin the 0.1-10000 Hz range by appropriate modulating means.

c) producing periodic frequency pulses of the irradiating sources (laser beams) in the range covering 0.1 Hz to 10 kHz, especially in the vicinity of (but not confined to) 700 Hz.

d) making the two spatially separated beams at the desired wavelengths co-incident on the sample surface using appropriate optical elements.

e) equalizing the intensities of the two beams and monitoring sub-surface tissue fluid differential absorption at the pre-determined wavelengths in the presence of glucose concentration within the normal human range (90-120 mg/dl) in order to determine the healthy band for normal residual glucose of the emissive infrared signal and/or adjust the said signal to zero to null the differential absorption from the healthy band.

f) generating out-of-phase photothermal-wave signals at both wavelengths leading to minute changes in net sample temperature (<1K) due to differential absorption.

g) using photothermal-wave superposition (destructive interference) over one modulation period in the tissue leading to net differential blackbody radiation emission.

h) collecting said emission signal with suitable mid-IR collecting optics including solid-angle and reflectivity optimized curved mirrors and specialty fiber-optic delivery systems.

i) detecting said collected signal with a wide-bandwidth (dc-MHz) detector.

j) outfitting the said detector with a narrow bandpass IR filter to block the CO_2 laser emission line range, if so required by possible overlap of the spectral bandwidth of the detector with the source emission range.

k) demodulating the said detector signal by an appropriate demodulating device (lock-in amplifier).

l) recording the said detector signals.

m) processing said recorded signal and correlating it to glucose concentration.

2) the method according to claim 1 wherein said irradiating sources are two specialty low-power (~200 mW) CO_2 lasers emitting in the vicinity of 9.6 and 10.5 μm wave-

length, respectively or two specialty low-power (~200 mW) halogen lamps with filters in the 9.6 to 10.7μ range.

3) the method according to claim 1 wherein said modulation of the said sources is done by electrical waveforms 180 degrees out-of-phase or by mechanical choppers 180 degrees out-of-phase or by opto-acoustic modulators 180 degrees out-of-phase or by electro-optical modulators 180 degrees out-of-phase.

4) the method according to claim 1 wherein said making the two spatially separated beams at the desired wavelengths co-incident on the sample surface with an appropriate beam combiner and mid-**1**R-transparent optical lens or with optical fibers fitted with a beam combiner and optical lens at the tip.

5) the method according to claim 1 wherein said equalizing the intensities of the two beams to obtain the baseline signal is done by using a variable neutral density filter or by adjusting the current amplitude driving one of the lasers.

6) the method according to claim 1 wherein said collecting the said emission signal is done with mid-IR collecting optics including solid-angle and reflectivity optimized curved mirrors or with a mid-IR collecting fiber optic system.

7) the method according to claim 1 wherein detecting said emission signal is done with a with a broadband HgCdTe (MCT) detector with sensitivity in the (2-12 μm) range or with a thermoelectrically cooled or room-temperature solid state HgCdZnTe (MCZT) detector (2-6 μm) or with a ZnSe, Ge, or other commercially available or specially designed engineered detector with sensitivity in the (2-12 μm) range.

8) the method according to claim 1 wherein said demodulating of the said detector signal is done by using a lock-in amplifier or by using a lock-in amplifier card or digital LIA (software) or by using an appropriate data acquisition card and digital LIA software.

9) the method according to claim 1 wherein said recording of the said signals is done by a personal computer or other storage and display device.

10) the method according to claim 1 wherein said processing of said recorded signal and correlating it to glucose concentration is done by proprietary software.

11) A glucose monitoring biothermophotonic apparatus based on the principle of Wavelength-Modulated Differential Laser Photothermal Radiometry (WM-DPTR), comprising:

n) irradiating the tissue surface with two specialty low-power (~200 mW) radiation emitting sources.

o) modulating the said sources in tandem and synchronously at angular modulation frequency $\omega=2\pi f$ with fin the 0.1-10000 Hz range by appropriate modulating means.

p) producing periodic frequency pulses of the irradiating sources (laser beams) in the range covering 0.1 Hz to 10 kHz, especially in the vicinity of (but not confined to) 700 Hz.

q) making the two spatially separated beams at the desired wavelengths co-incident on the sample surface using appropriate optical elements.

r) equalizing the intensities of the two beams and monitoring sub-surface tissue fluid differential absorption at the pre-determined wavelengths in the presence of glucose concentration within the normal human range (90-120 mg/dl) in order to determine the healthy band for normal residual glucose of the emissive infrared signal and/or adjust the said signal to zero to null the differential absorption from the healthy band.

s) generating out-of-phase photothermal-wave signals at both wavelengths leading to minute changes in net sample temperature (<1K) due to differential absorption.

t) using photothermal-wave superposition (destructive interference) over one modulation period in the tissue leading to net differential blackbody radiation emission.

u) collecting said emission signal with suitable mid-IR collecting optics including solid-angle and reflectivity optimized curved mirrors and specialty fiber-optic delivery systems.

v) detecting said collected signal with a wide-bandwidth (dc-MHz) detector.

w) outfitting the said detector with a narrow bandpass IR filter to block the CO_2 laser emission line range, if so required by possible overlap of the spectral bandwidth of the detector with the source emission range.

x) demodulating the said detector signal by an appropriate demodulating device (lock-in amplifier).

y) recording the said detector signals.

z) processing said recorded signal and correlating it to glucose concentration.

12) the apparatus according to claim 11 wherein said irradiating sources are two specialty low-power (~200 mW) CO_2 lasers emitting in the vicinity of 9.6 and 10.5 μm wavelength, respectively or two specialty low-power (~200 mW) halogen lamps with filters in the 9.6 to 10.7μ range.

13) the apparatus according to claim 11 wherein said modulation of the said sources is done by electrical waveforms 180 degrees out-of-phase or by mechanical choppers 180 degrees out-of-phase or by opto-acoustic modulators 180 degrees out-of-phase or by electro-optical modulators 180 degrees out-of-phase.

14) the apparatus according to claim 11 wherein said making the two spatially separated beams at the desired wavelengths co-incident on the sample surface with an appropriate beam combiner and mid-**1**R-transparent optical lens or with optical fibers fitted with a beam combiner and optical lens at the tip.

15) the apparatus according to claim 11 wherein said equalizing the intensities of the two beams to obtain the baseline signal is done by using a variable neutral density filter or by adjusting the current amplitude driving one of the lasers.

16) the apparatus according to claim 11 wherein said collecting the said emission signal is done with a mid-IR collecting optics including solid-angle and reflectivity optimized curved mirrors or with a mid-IR collecting fiber optic system.

17) the apparatus according to claim 11 wherein detecting said emission signal is done with a with a broadband HgCdTe (MCT) detector with sensitivity in the (2-12 μm) range or with a thermoelectrically cooled or room-temperature solid state HgCdZnTe (MCZT) detector (2-6 μm) or

with a ZnSe, Ge, or other commercially available or specially designed engineered detector with sensitivity in the (2-12 μm) range.

18) the apparatus according to claim 11 wherein said demodulating of the said detector signal is done by using a lock-in amplifier or by using a lock-in amplifier card or digital LIA (software) or by using an appropriate data acquisition card and digital LIA software.

19) the apparatus according to claim 11 wherein said recording of the said signals is done by a personal computer or other storage and display device.

20) the apparatus according to claim 11 wherein said processing of said recorded signal and correlating it to glucose concentration is done by proprietary software.

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专利名称(译)	用于血糖监测的无创生物热光电传感器		
公开(公告)号	US20070213607A1	公开(公告)日	2007-09-13
申请号	US11/368698	申请日	2006-03-07
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发明人	MANDELIS, ANDREAS TELENKOV, SERGEY		
IPC分类号	A61B5/00		
CPC分类号	A61B5/01 A61B5/0091 A61B5/7228 A61B5/14532		
其他公开文献	US7729734		
外部链接	Espacenet USPTO		

摘要(译)

提供了一种基于波长调制差分激光光热辐射测量（WM-DPTR）原理的葡萄糖监测方法和装置。两个强度调制激光束在特定的中红外（IR）波长下串联工作，并通过两个180度异相的电波同步电流调制，用于询问组织表面。选择激光波长以吸收中红外范围（8.5-10.5μm），其中葡萄糖光谱显示出离散的吸收带。由组织样本通过带内两个特定波长之间的调制吸收产生的差分热波信号（例如，9.6处的峰值和10.5μm处的最近基线）导致样品温度和非平衡黑体的微小变化。辐射发射。用宽带红外探测器测量该调制发射。检测器耦合到锁定放大器以进行信号解调。任何葡萄糖浓度增加将记录为高于完全抑制信号基线的差分光热信号，这是由于在所选波长调制频率下在9.6μm处的探测峰或近峰处的吸收增加。重点是能够以非侵入性，非接触方式监测糖尿病患者的血糖水平，使用差分信号生成方法进行实时基线校正，这是实现精确和通用校准的关键特征（独立于人与人之间）- 人员接触，皮肤，温度或IR发射变化），以提供准确的绝对葡萄糖浓度读数。