Bruce J. Wecker (SBN 78530)
Christopher L. Lebsock (SBN 184546)
HAUSFELD LLP
44 Montgomery Street, Suite 3400
San Francisco, CA 94104
Tel: (415) 633-1908
Fax: (415) 358-4980

Robert J. Yorio (SBN 93178)
CARR & FERRELL LLP
120 Constitution Drive,
Menlo Park, CA 94025
Tel: (650) 812-3400
Fax: (650) 812-3444

Attorneys for Plaintiff Dominion Assets LLC

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

DOMINION ASSETS LLC, a Delaware limited liability company,

Plaintiff,

vs.

MASIMO CORPORATION, a Delaware corporation, and CERCACOR LABORATORIES, INC., a Delaware corporation;

Defendant.

Case No.: CV 12 2773 NC

ORIGINAL COMPLAINT FOR PATENT INFRINGEMENT

DEMAND FOR JURY TRIAL

ORIGINAL COMPLAINT

Plaintiff Dominion Assets LLC. ("Plaintiff" or "Dominion"), files this Original Complaint for patent infringement against Masimo Corporation ("Masimo") and Cercacor Laboratories, Inc. ("Cercacor") (collectively "Defendants") alleging as follows:

1. Dominion is a development stage company employing scientists to develop its non-invasive monitor for the determination of the concentration of blood constituents. Dominion owns a portfolio of patents arising from its predecessors' path-breaking work in the area of non-invasive measurement of blood constituents. This Complaint concerns patents directed to the use of visible

and invisible light radiation to passing through body tissue to measure constituents of the blood, such as oxygen saturation, hemoglobin, carboxyhemoglobin, and methemoglobin.

2. Defendants' infringing products are sold throughout the United States. They provide market leading pulse oximeters and pulse CO-oximeters to hospitals and the alternate care market for patient monitoring of a variety of blood constituents.

3. Beginning in 2005, on information and belief, Masimo introduced a series of improvements to its pulse oximeters based on measuring the absorption of light at multiple wavelengths beyond the two used in conventional pulse oximetry. In 2005, Masimo introduced its rainbow SET platform, leveraging and incorporating rainbow technology licensed from Cercacor to provide reliable, real-time monitoring of additional measurements beyond arterial blood oxygen saturation and pulse rate. The Masimo rainbow SET platform has the ability to distinguish oxygenated hemoglobins from certain dyshemoglobins, hemoglobin incapable of transporting oxygen, and allows for the rapid, non-invasive monitoring of hemoglobin, carboxyhemoglobin, methemoglobin, and pleth variability index, which it refers to as Pulse CO-Oximetry.

4. Along with the release of the rainbow SET Pulse CO-Oximetry products, Masimo developed multi-wavelength sensors that have the ability to monitor twelve wavelength measurements with a single sensor. Thus, this case concerns the Defendants' infringement of patents that cover a fundamental piece of the products that Defendants sell and license.

THE PARTIES

5. Plaintiff Dominion Assets, LLC is a limited liability company organized under the laws of the state of Delaware with its principal place of business in Potomac Falls, Virginia. It is the owner of United States Patent Nos. 5,360,004, 5,460,177, and 5,379,764 ("Patents-in-Suit")

6. Defendant Masimo, on information and belief, is a corporation organized under the laws of the State of Delaware. Masimo is doing business in Northern California, and has its principal place of business at 40 Parker, in Irvine, California.

7. Defendant Cercacor, on information and belief, is a Delaware corporation having its principal place of business in Irvine, California. It was founded in 1998, and is formerly

known as Masimo Laboratories, Inc.

JURISDICTION & VENUE

8. This is an action for infringement of a United States patent. Accordingly, this action arises under the patent laws of the United States of America, 35 U.S.C. § 1 *et seq.*, and jurisdiction is properly based on 35 U.S.C. § 271 and 28 U.S.C. § 1338(a).

9. Venue is proper in this district under 28 U.S.C. §§ 1391(b-c) and 1400(b). Upon information and belief, each of the Defendants transacts or has transacted business in this judicial district, or committed and/or induced acts of patent infringement in this district.

INTRADISTRICT ASSIGNMENT

10. This action is an intellectual property action subject to district-wide assignment.

FACTUAL BACKGROUND

11. Biocontrol Technology (BICO) was a medical products company formed in 1972. In 1986 and 1987, BICO and its scientists invested in their hypothesis that blood glucose levels could be detected noninvasively by correlating points on the infrared spectrum that are reflected by electromagnetic energy through the skin. BICO studied this method in its own laboratory together with consultants at Battelle Memorial Institute in Columbus, Ohio. Information from these studies, and additional information acquired over years of refinement and further research, formed the building blocks upon which BICO filed a series of patent applications. BICO incorporated Diasense, Inc. in 1989, as its wholly owned subsidiary. Diasense was to serve as the marketing entity for BICO's non-invasive blood glucose monitor device while BICO focused on R&D and manufacturing functions. In December 1991, Diasense and BICO entered into a purchase agreement and BICO conveyed to Diasense its entire right, title and interest in the noninvasive glucose sensor and its development, including its extensive knowledge, technology and proprietary information. In December 1992, Diasense and BICO executed an amendment to the purchase agreement, which clarified certain terms and defined the "sensors" subject to transfer to include all devices for the noninvasive detection of analytes in mammals or in other biological materials. Diasense, thus, took assignments from all of the inventors of the patents at issue in this case. In 2006, Dominion acquired all of Diasense's intellectual property and recruited some of the

scientists, along with a leading scientist in the field, to meet its business objective to improve on the Diasense non-invasive monitor and bring devices for the non-invasive determination of analyte concentration to market. Dominion took assignment of the patents at issue in this suit in furtherance of this objective.

12. On November 1, 1994, United States Patent No. 5,360,004 ("the '004 patent") entitled "Non-invasive determination of analyte concentration using non-continuous radiation" was duly and legally issued. Dominion holds the title by assignment from the company that employed the inventors, Diasense, Inc., including the right to sue for past, present and future damages. A copy of the '004 patent is attached as Exhibit A.

13. On January 10, 1995, United States Patent No. 5,379,764 ("the '764 patent") entitled "Non-invasive determination of analyte concentration in body of mammals" was duly and legally issued. Dominion holds the title by assignment from the company that employed the inventors, Diasense, Inc., including the right to sue for past, present and future damages. A copy of the '764 patent is attached as Exhibit B.

14. On October 24, 1995, United States Patent No. 5,460,177 ("the '177 patent") entitled "Method for non-invasive measurement of concentration of analytes in blood using continuous spectrum radiation" was duly and legally issued. Dominion holds the title by assignment from the company that employed the inventors, Diasense, Inc., including the right to sue for past, present and future damages. A copy of the '177 patent is attached as Exhibit C.

15. The ''004, '764, and '177 patents ("Patents-in-Suit") are directed to methods and apparatus for measuring non-invasively components in the blood of humans by projecting near-infrared radiation on a portion of the subjects body, sensing the radiation at a plurality of wavelengths, and calculating the concentration of particular constituents of the patient's blood.

16. Pursuant to 35 U.S.C. § 282, the Patents-in-Suit are presumed valid.

17. On information and belief, Defendant Masimo develops manufactures and markets non-invasive patient monitoring products, including ones measuring a variety of constituents in the patient's blood. Such products include Masimo's pulse oximetry devices such as sensors, monitors, circuit boards and software. Masimo sells monitors, such as its Radical-7, Rad-87, Rad-

57, Pronto-7 and Pronto to hospitals and the alternate care market. Masimo sells circuit boards to original equipment manufacturers ("OEMs"), such as its MX-1 and MS-2011. It sells sensors, such as its SET and rainbow SEDline sensors to hospitals and the alternate care market. Masimo also sells software to upgrade installed monitors to add new features such as its Rainbow measurements.

18. On information and belief, Defendant Cercacor contracted the services of Masimo employees to develop a non-invasive blood constituent monitoring platform that measures hemoglobin, carboxyhemoglobin, methemoglobin and other blood constituents. That platform is known as, or incorporated into Masimo's "Rainbow SET" products.

19. On information and belief, Defendant Masimo and Defendant Cercacor entered cross-licensing agreements that provide for the joint development of "Rainbow SET" products and technologies, and for the sharing of profits from the sale and licensing of such products and technologies.

20. On information and belief, Defendants have known of Dominion's patents, at least since November 1, 2010. On that date, Masimo's Chief Executive Officer, its General Counsel, and its outside counsel were advised of the patents and provided access to a website containing detailed information about the patents, their prosecution and how Masimo's "Rainbow SET" products infringed a variety of claims in the Patents-in-Suit. It nonetheless continued the development and sale of its infringing products using the ideas disclosed the Dominion patents.

COUNT I
(Defendants' Patent Infringement)

21. Plaintiff incorporates by reference the allegations of paragraphs 1 through 20 above.

22. Dominion is the owner of the Patents-in-Suit.

23. Defendants have infringed and are still infringing the Patents-in-Suit, by, without authority, consent, right or license, and in direct infringement of the patents, making, using, offering for sale and/or selling patient monitoring products using the methods, processes and

apparatuses claimed in the patent in this country. This conduct constitutes infringement under 35 U.S.C. § 271(a).

24. In addition, Defendants have infringed and are still infringing the Patents-in-Suit in this country, through, inter alia, its active inducement of others to make, use, and/or sell the products and methods claimed in one or more claims of the patent. This conduct constitutes infringement under 35 U.S.C. § 271(b).

25. In addition, Defendants have infringed and are still infringing the 'Patents-in-Suit in this country through, inter alia, providing and selling goods and services including products designed for use in practicing one or more claims of the Patents-in-Suit, where the goods and services constitute a material part of the invention and are not staple articles of commerce, and which have no use other than infringing one or more claims of the Patents-in-Suit. Defendants have committed these acts with knowledge that the goods and services it provides are specially made for use in a manner that directly infringes the Patents-in-Suit. This conduct constitutes infringement under 35 U.S.C. § 271(c).

26. Defendants' infringing conduct is unlawful and willful. Defendants' willful conduct makes this an exceptional case as provided in 35 U.S.C. § 285.

27. As a result of Defendants' infringement, Plaintiff has been damaged, and will continue to be damaged, until they are enjoined from further acts of infringement.

28. Defendants will continue to infringe the Patents-in-Suit unless enjoined by this Court. Plaintiff faces real, substantial and irreparable damage and injury of a continuing nature from Defendant Defendants' infringement for which Plaintiff has no adequate remedy at law.

PRAYER FOR RELIEF

Wherefore, Plaintiff prays for entry of judgment:

A. declaring that Defendants have infringed one or more claims, specifically including claim 1, of each of the Patents-in-Suit;

B. that Defendants be permanently enjoined from further infringement, including contributory infringement and/or inducing infringement, of the Patents-in-Suit, or in the alternative awarding a royalty for post-judgment infringement;

C. that Defendants account for and pay to Plaintiff all damages caused by their infringement of the Patents-in-Suit, which by statute can be no less than a reasonable royalty;

D. that Plaintiff be granted pre-judgment and post-judgment interest on the damages caused to it by reason of Defendants' infringement of the Patents-in-Suit;

E. that Defendants' infringement of the Patents-in-Suit be adjudged willful and that the damages to Plaintiff be increased by three times the amount found or assessed pursuant to 35 U.S.C. § 284;

F. that this be adjudged an exceptional case and that Plaintiff be awarded its attorney's fees in this action pursuant to 35 U.S.C. § 285;

G. that costs be awarded to Plaintiff; and

H. that Plaintiff be granted such other and further relief as the Court may deem just and proper under the current circumstances.

DEMAND FOR JURY TRIAL

Plaintiff, by its undersigned attorneys, demands a trial by jury on all issues so triable.

Dated: May 30 2012

Respectfully submitted,

By: Bruce Wecker
BRUCE J. WECKER (SBN 78530)

Bruce J. Wecker (SBN) 78530
Christopher L. Lebsock (SBN 184546)
HAUSFELD LLP
44 Montgomery Street, Suite 3400
San Francisco, CA 94104
Tel: (415) 633-1908
Fax: (415) 358-4980
Email: bwecker@hausfeldllp.com
clebsock@hausfeldllp.com

Robert J. Yorio (SBN 93178)
CARR & FERRELL LLP
120 Constitution Drive,
Menlo Park, CA 94025
Tel: (650) 812-3400
Fax: (650) 812-3444

Attorneys for Plaintiff Dominion Assets LLC

EXHIBIT A

US005360004A

United States Patent [19]

Purdy et al.

[11] Patent Number: 5,360,004

[45] Date of Patent: Nov. 1, 1994

[54] **NON-INVASIVE DETERMINATION OF ANALYTE CONCENTRATION USING NON-CONTINUOUS RADIATION**

[75] Inventors: **David L. Purdy**, Marion Center; **Richard L. Wiggins; Paul Castro**, both of Indiana, all of Pa.

[73] Assignee: **Diasense, Inc.**, Pittsburgh, Pa.

[21] Appl. No.: **59,164**

[22] Filed: **May 7, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 987,766, Dec. 9, 1992.

[51] **Int. Cl.**[5] **A61B 5/00**

[52] **U.S. Cl.** **128/633**; 128/664; 356/39

[58] **Field of Search** 128/633–634, 128/664–667; 356/39–41

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,463,142	8/1969	Harte	128/633
4,655,225	4/1987	Dahne et al.	128/664 X
4,882,492	11/1989	Schlager	128/633 X
5,070,874	12/1991	Barnes et al.	128/633

Primary Examiner—Angela D. Sykes

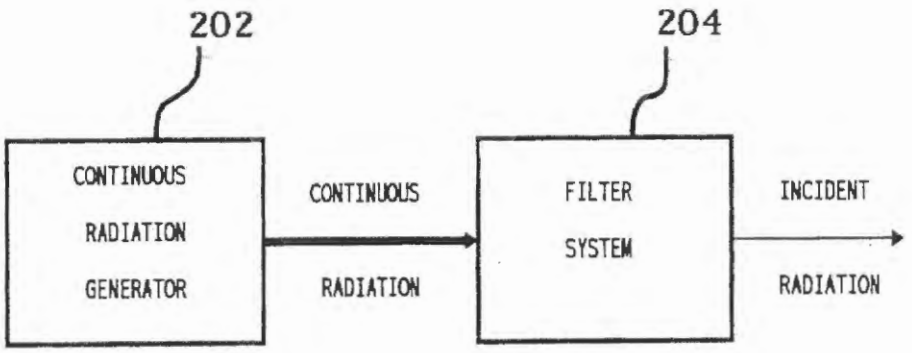
Attorney, Agent, or Firm—William H. Murray; Robert E. Rosenthal; Steve Mendelsohn

[57] **ABSTRACT**

A method and apparatus for non-invasive determination of the concentration of at least one analyte in a mammal. A portion of the body of the mammal is irradiated with incident radiation, where the incident radiation includes two or more distinct bands of continuous-wavelength incident radiation. The resulting radiation emitted from the portion of the body is sensed and a value for the concentration of the analyte is derived therefrom.

20 Claims, 5 Drawing Sheets

13



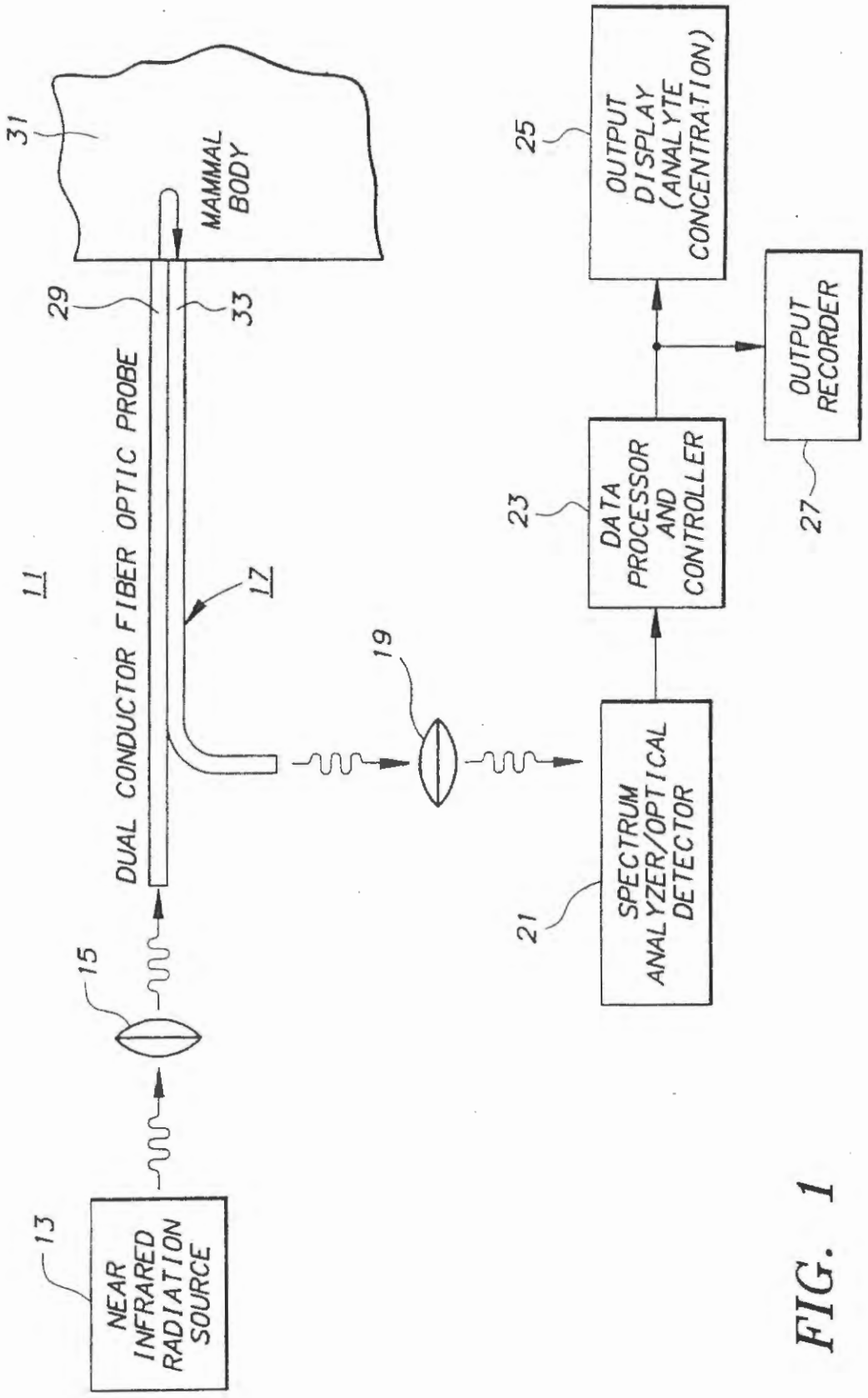
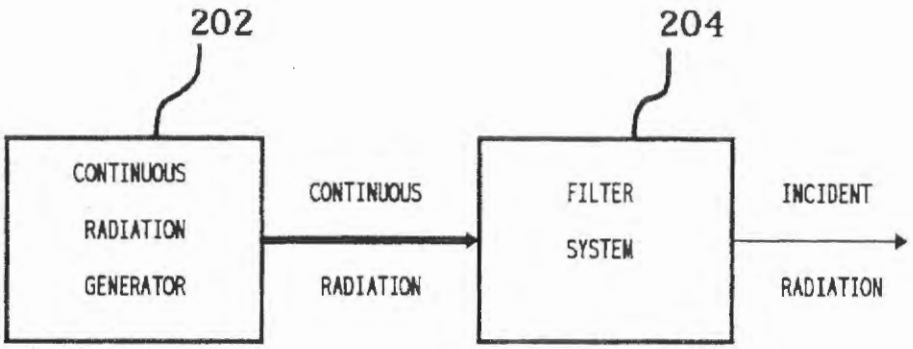

31
MAMMAL BODY
29
33
DUAL CONDUCTOR FIBER OPTIC PROBE
11
17
19
15
13
NEAR INFRARED RADIATION SOURCE
SPECTRUM ANALYZER/OPTICAL DETECTOR
21
DATA PROCESSOR AND CONTROLLER
23
OUTPUT DISPLAY (ANALYTE CONCENTRATION)
25
OUTPUT RECORDER
27

FIG. 1

FIGURE 2. 13


202
204
CONTINUOUS
RADIATION
GENERATOR
CONTINUOUS
RADIATION
FILTER
SYSTEM
INCIDENT
RADIATION

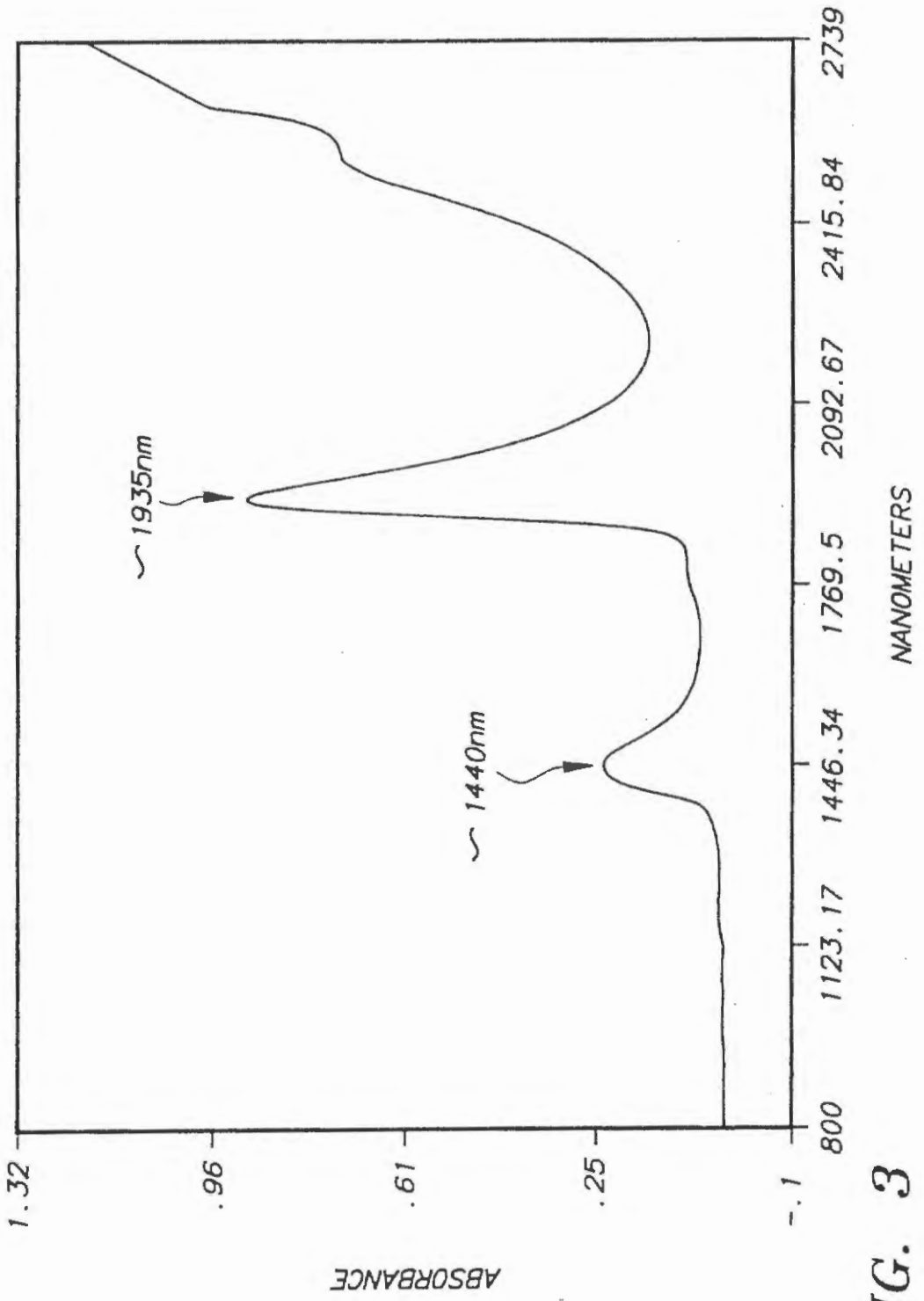

1935nm
1440nm
1.32
.96
.61
.25
-.1
ABSORBANCE
800
1123.17
1446.34
1769.5
2092.67
2415.84
2739
NANOMETERS

FIG. 3

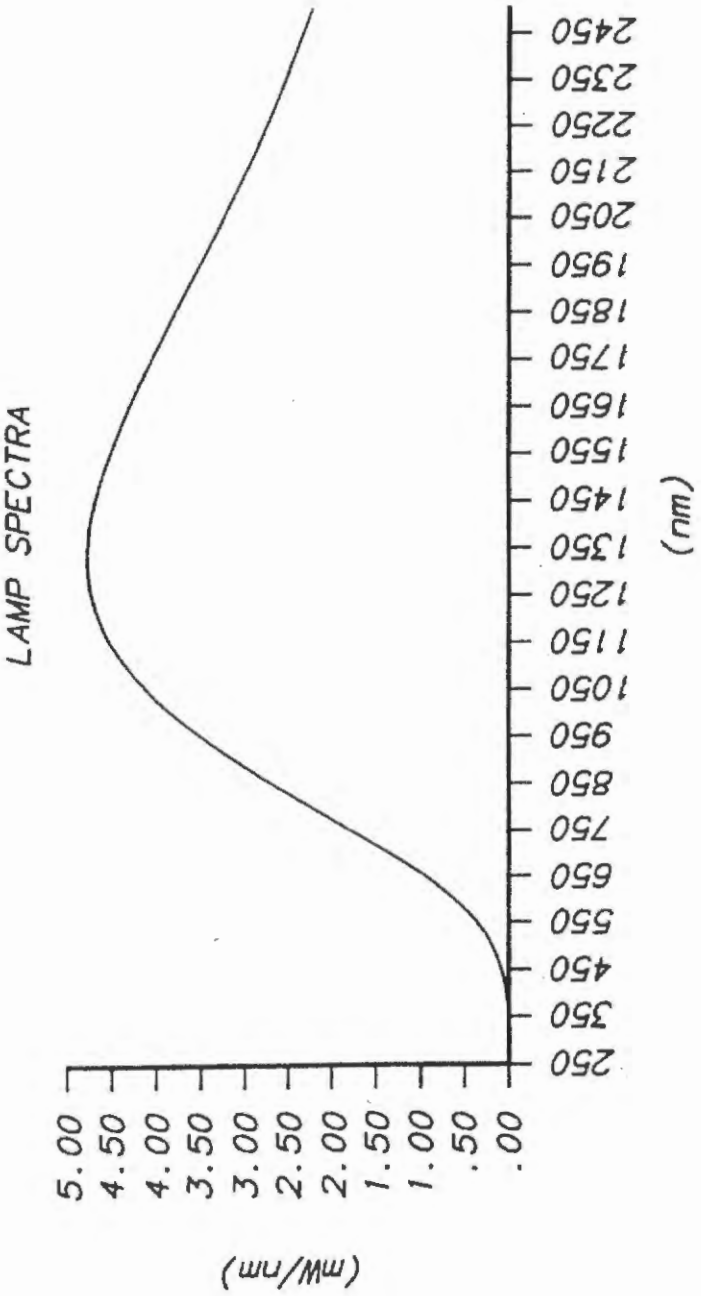

LAMP SPECTRA
(mW/nm)
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
.00
250
350
450
550
650
750
850
950
1050
1150
1250
1350
1450
1550
1650
1750
1850
1950
2050
2150
2250
2350
2450
(nm)

FIG. 4

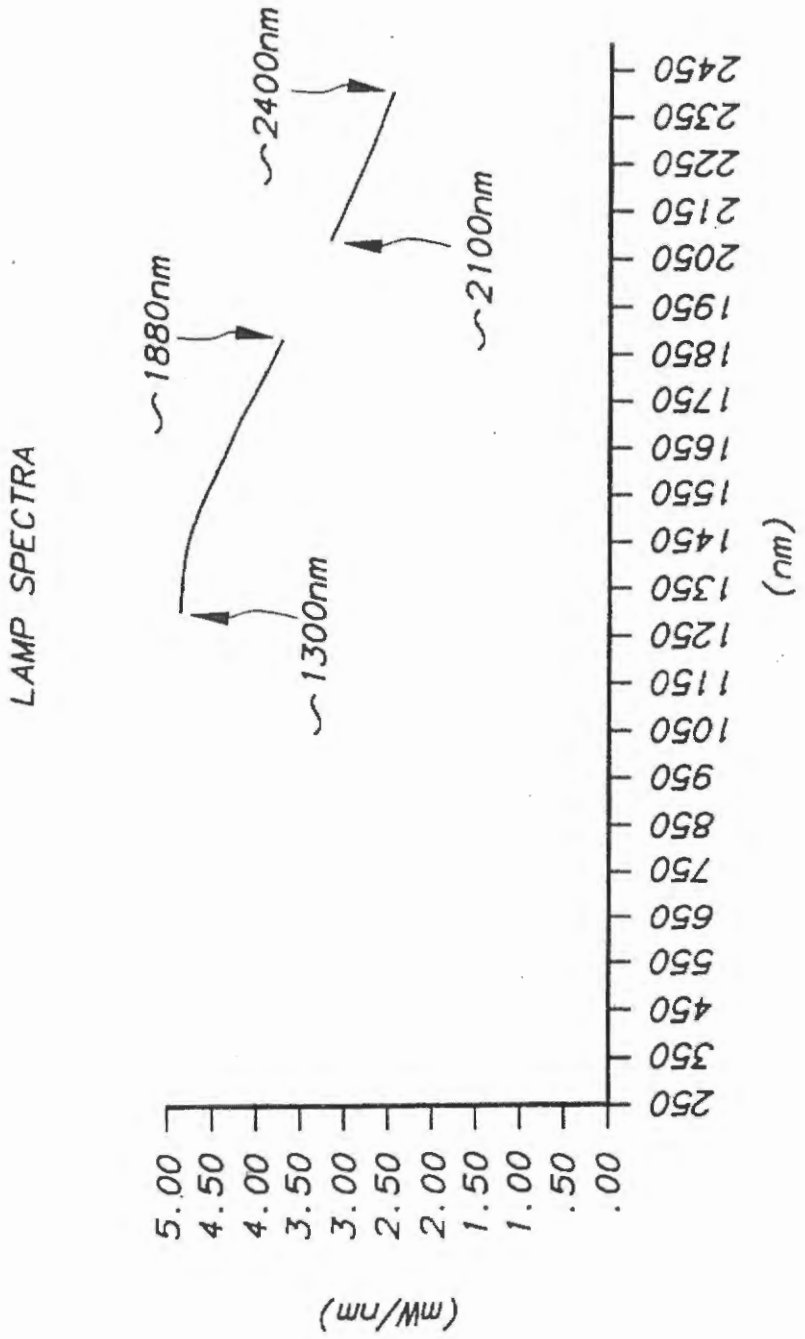

LAMP SPECTRA
2400nm
2100nm
1880nm
1300nm
250
350
450
550
650
750
850
950
1050
1150
1250
1350
1450
1550
1650
1750
1850
1950
2050
2150
2250
2350
2450
(nm)
.00
.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
(mW/nm)

FIG. 5

NON-INVASIVE DETERMINATION OF ANALYTE CONCENTRATION USING NON-CONTINUOUS RADIATION

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of copending application Ser. No. 07/987,766, filed Dec. 9, 1992, pending.

This invention relates to techniques for non-invasively detecting the concentration of analytes in living animals, and in particular to the use of infrared and near-infrared spectroscopic techniques for the non-invasive detection of glucose concentrations in the blood of humans.

In the diagnosis and treatment of various conditions, it is important to measure the concentration of various constituents in the blood. For example, in the treatment of diabetes, the concentration of glucose in the blood must be measured on a periodic basis. For persons experiencing insulin-dependent or Type I diabetes, it is often necessary or desirable to measure blood glucose concentration several times each day. Obtaining accurate readings of cholesterol concentrations is important in the prevention of coronary artery disease. The measurement of the concentration of other blood analytes, such as bilirubin and alcohol, is also important for various diagnostic purposes.

The accurate measurement of concentrations of such blood constituents, as it is now practiced, requires obtaining a blood sample, such as by pricking a finger. The obtaining of blood samples by such invasive techniques is both painful and inconvenient. In the case of diabetics, the need to lance a finger several times a day to monitor glucose levels results in a build-up of substantial scar tissue. Indeed, many diabetics are believed not to monitor their glucose level as frequently as recommended because of the pain and inconvenience of the invasive method. The result of such a failure to monitor glucose levels is a greater risk of experiencing the long-term health effects of diabetes. These health effects include damage to the eyes, resulting in partial and often total loss of vision, and damage to the extremities, which can result in the need to amputate. Millions of individuals in the United States alone suffer from diabetes. As a result, the failure of individuals afflicted with diabetes reliably to monitor their glucose levels is a significant public health problem.

In order to provide an alternative to the existing invasive blood glucose monitoring techniques, various non-invasive blood glucose detection techniques have been proposed. One of the most promising of these techniques is the non-invasive infrared spectroscopic technique. In this technique, a portion of the patient's skin is irradiated with infrared or near-infrared radiation. The resulting radiation that is either back-scattered or transmitted through a body part such as the finger, is then measured. By appropriate spectroscopic analysis techniques, it has been hoped that the concentration of glucose in the blood can be determined.

The ability to determine accurately the concentration of analytes in mammals, such as glucose in the blood of a diabetic, is directly related to the signal-to-noise ratio in the radiation resulting from the interaction of the incident radiation with the patient's body. One way to increase the signal-to-noise ratio of the resulting radiation, and thereby improve the accuracy of the determination of glucose concentration, is to increase the intensity (i.e., brightness) of the incident radiation. However, increasing the intensity of the incident radiation also increases the heating effect resulting from absorption by water in the body of incident radiation. The heating effect causes discomfort to the patient and even involves a risk of burning the patient.

It is accordingly an object of this invention to overcome the disadvantages and drawbacks of the prior art and to provide for the precise effective non-invasive determination of the concentration of analytes in a mammal, and particularly glucose in the blood of a human patient.

It is a specific object of this invention to provide a method for accurately determining analyte concentration without burning the patient's body.

Further objects and advantages of this invention will become apparent from the detailed description of a preferred embodiment which follows.

SUMMARY OF THE INVENTION

The present invention is a method and an apparatus for non-invasive determination of the concentration of at least one analyte in a mammal. According to the invention, a portion of the body of the mammal is irradiated with incident radiation, where the incident radiation includes two or more distinct bands of continuous-wavelength incident radiation. The resulting radiation emitted from the portion of the body is sensed and a value for the concentration of the analyte is derived from the sensed resulting radiation.

BRIEF DESCRIPTION OF THE DRAWINGS

For a better understanding of this invention, both as to its organization and as to its method of operation, together with additional objects and advantages thereof, reference is made to the following description, taken in connection with the accompanying drawings, in which:

FIG. **1** is a block diagram showing an embodiment of this invention with which the method of invention is practiced;

FIG. **2** is a block diagram of a preferred radiation source of the embodiment of FIG. **1**;

FIG. **3** depicts the absorbance spectrum of water in the near infrared wavelength range;

FIG. **4** depicts the continuous-wavelength radiation emitted by a continuous radiation generator of the radiation source of FIG. **2**; and

FIG. **5** depicts the incident radiation transmitted by the filter system of the radiation source of FIG. **2**.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

FIG. **1** shows apparatus **11** for the non-invasive determination of the concentration of at least one analyte in a mammal. This apparatus includes a source **13** of near-infrared radiation, a first lens system **15**, a dual conductor fiber-optic probe **17**, a second lens system **19**, a spectrum analyzer/detector **21**, a data processor and controller **23**, an output display device **25**, and an output recorder **27**.

Incident radiation from source **13** is focused by first lens system **15** onto fiber-optic probe **17**, which transmits the incident radiation onto a portion **31** of the mammal's body. Probe **17** also receives and transmits resulting radiation from portion **31** to second lens system **19**, which focuses the resulting radiation onto spec-

trum analyzer/detector **21**. Spectrum analyzer/detector **21** analyzes the resulting radiation and data processor and controller **23** determines analyte concentration, which may be displayed on output display device **25** and/or recorded on output recorder **27**.

Referring now to FIG. **2**, there is shown a block diagram of radiation source **13** of FIG. **1** according to the present invention. Source **13** generates radiation that includes two or more distinct bands of continuous-wavelength radiation in the near-infrared range (i.e., between about 1300 nm and about 2400 nm). Radiation source **13** includes continuous-wavelength radiation generator **202** and filter system **204**.

Continuous-wavelength radiation generator **202** may be a tungsten filament bulb. In order to maintain radiation intensity constant over time, the continuous-wavelength radiation generator **202** may be thermally isolated from its surroundings and the current through the filament may be maintained constant. Continuous-wavelength radiation generator **202** emits electromagnetic radiation across a continuous range of wavelengths. This continuous-wavelength radiation is transmitted from continuous-wavelength radiation generator **202** to filter system **204**.

Filter system **204** filters the received continuous-wavelength radiation and transmits incident radiation. The incident radiation irradiates a portion of the body of a mammal. The incident radiation includes two or more distinct bands of continuous-wavelength radiation. That is, the incident radiation includes electromagnetic radiation in two or more distinct bands, each band having a continuous range of wavelengths.

Two bands of electromagnetic radiation are distinct if their respective continuous ranges of wavelengths do not overlap. For example, a first band having continuous radiation between band limits of 1650 nm and 1750 nm is distinct from a second band having continuous radiation between band limits of 1850 nm and 1950 nm, but the first band is not distinct from a third band having continuous radiation between band limits of 1700 nm and 1800 nm. Furthermore, radiation at a wavelength of 1790 nm, for example, may be said to "fall between" the first and second bands of continuous-wavelength radiation, because 1790 nm is greater than the wavelengths of the first band and less than the wavelengths of the second band.

For purposes of this specification, a band of radiation is considered continuous, (1) if the band contains all wavelengths between the band limits or (2) if, between the band limits, there are a sufficient number of discrete wavelengths that are separated by sufficiently small increments to permit pretreatment as described in further detail later in this specification. Thus, a band of continuous radiation may be generated by a single source (such as a single tungsten lamp) or by multiple sources (such as an appropriate set of infrared emitting diodes).

In a preferred embodiment, continuous-wavelength radiation generator **202** is a 35-watt tungsten filament bulb that generates radiation ranging from about 300 nm to about 3000 nm when operated at 9.7 watts. Filter system **204** preferably filters all radiation in the received continuous-wavelength radiation having wavelengths less than about 1300 nm and greater than about 2400 nm. Those skilled in the art will also understand that the term "filter" as used in this specification refers to any appropriate device that either blocks or attenuates electromagnetic radiation in specified wavelength ranges.

In addition to filtering wavelengths less than about 1300 nm and greater than about 2400 nm, filter system **204** filters radiation in one or more selected wavelength ranges within the 1300 nm to 2400 nm range, thereby defining two or more distinct bands of continuous-wavelength radiation. It is preferred that the selected wavelength ranges correspond to peaks in the spectrum of radiation absorption by water. The absorption of radiation by water in the body is believed to be a primary source of heating of the body during conventional methods of non-invasive determination of analyte concentration in mammals. Thus, by filtering radiation corresponding to water-absorption according to the present invention, the risk of burning the mammal is reduced.

By filtering radiation around the water-absorption peaks, the heating effect can be reduced with least reduction of data points. For example, by filtering out about 20% of the range from 1300 nm to 2400 nm, one may reduce the heating effect by about 70%.

In addition, because the water-absorption wavelengths are filtered, the intensity of the incident radiation at the transmitted wavelengths can be increased relative to the intensities employed in conventional non-invasive glucose determination methods. As a result, the signal-to-noise ratio and therefore the accuracy of the determination of analyte concentration are improved, without increasing the risk of burning the mammal.

For example, as shown in FIG. **3**, two peaks in the near-infrared absorption spectrum for water occur at about 1440 nm and 1935 nm. In a preferred embodiment of the present invention, filter system **204** filters radiation having wavelengths (a) less than 1300 nm, (b) between 1880 nm and 2100 nm, and (c) greater than 2400 nm. In this preferred embodiment, filter system **204** transmits incident radiation having two distinct bands of continuous-wavelength radiation: (i) from 1300 nm to 1880 nm and (ii) from 2100 nm to 2400 nm. FIG. **4** depicts the continuous-wavelength radiation emitted by continuous radiation generator **202** and FIG. **5** depicts the incident radiation transmitted by filter system **204**.

Those skilled in the art will understand that filter system **204** may include combinations of appropriate wide-band interference filters and colored glass or dyed plastic to filter the continuous-wavelength radiation generated by continuous-wavelength radiation generator **202**. The wide-band interference filters may be coatings applied to the glass or plastic components.

It will also be understood by those skilled in the art that radiation source **13** may be implemented using two or more different radiation sources with appropriate filtering to generate incident radiation according to the present invention. For example, two or more sets of infrared emitting diodes may be used to generate incident radiation having two or more distinct bands of continuous-wavelength radiation.

Referring again to FIG. **1**, the lens systems **15** and **19** are represented by single-lens symbols. In actual practice, they are appropriate combinations of lenses including focusing lenses and collimators on the outlet side. Lens system **19** may include a spectrometer in a Czerny-Turner configuration. The fiber-optic probe **17** includes an input radiation conductor **29** for transmitting radiation to a portion **31**, for example, an ear lobe or wrist, of the patient's body and pickup or sensing radiation conductor **33** for receiving the resulting radiation from the portion **31**. The output end of the input conductor **29**

and the input or sensing end of the pickup conductor **33** are preferably in firm contact with the outer surface of the portion **31** of the subject's body. While each conductor **29** and **33** is represented by a symbol for a single conductor, each radiation conductor, in actual practice of this invention, includes bundles of optical fibers.

Radiation from the source **13** is directed by the lens system **15** into conductor **29** and, at its outlet, is projected into the portion **31**. This incident radiation induces scattered radiation within the body portion **31**, some of which passes through the end of conductor **33** and through the conductor and is directed by lens system **19** into spectrum analyzer/detector **21**. Spectrum analyzer/detector **21** may be a Model 6500 System Near Infrared Spectrometer acquired from Pacific Scientific Instrument Division, Pacific Scientific, Ltd., 2431 Linden Lane, Silver Spring, Md. 20910.

While FIG. **1** discloses apparatus in which scattered radiation is analyzed, the analysis of transmitted radiation, i.e., the input radiation less the back scattered and absorbed radiation, plus any forward scattered radiation, is within the scope of equivalents of this invention. In this case, the ends of conductors **29** and **33**, instead of being side-by-side in contact with adjacent surfaces of the body portion **31**, would be in contact with the outer surfaces on opposite sides of the body portion **31**, for example, with opposite surfaces of the ear lobe. The radiation, which is in this case passed through conductor **33**, is predominantly the radiation from the source **13** less the radiation scattered and absorbed by the molecules of the water in the blood, the glucose and other constituents of the blood. The skin also contributes to the scattering and absorption.

With the apparatus as shown in FIG. **1**, the resulting back scattered radiation emitted by the body portion **31** is passed by pickup conductor **33** and lens system **19** to the spectrum analyzer/detector **21** where this radiation is spread into a spectrum. The spectrum is focused on an array of optical detectors. A selected wavelength range is focused on each detector. For example, a range of 15 nanometers may be focused on each detector. The detectors may be lead-sulfide detectors, which are well-known in the field of infrared spectroscopy of grains and other agricultural products. Each detector converts the radiation in the corresponding selected wavelength range to electrical signals which are transmitted to the data processor **23**. In a preferred embodiment, intermediate each detector and the data processor, there is a pre-amplifier, an amplifier, and an analog-to-digital converter. It should be noted that, to reduce noise effects, a chopper is preferably provided before the detector to modulate the infrared beam. The amplifier is a lock-in amplifier, so that only the portion of the signal containing data is transmitted to the analog-to-digital converter.

The data processor then applies a step of pretreatment to the function of the magnitude of the radiation intensity versus wavelength. The step of pretreatment has the effect of minimizing, or eliminating, the effects of detector offset and drift. In a preferred embodiment, the pretreatment step comprises taking the nth derivative, and in particular, the second derivative, of the intensity vs. wavelength function. Alternatively, the pretreatment step may comprise the steps of subtracting the mean of the whole spectrum from each data point in the spectrum and then dividing each data point by the standard deviation of the whole spectrum.

The pretreated data is then subject to multivariate analysis. The result of the step of multivariate analysis is a glucose concentration. Various techniques of multivariate analysis are known in the chemical arts. A preferred multivariate analysis technique is partial least squares (PLS). The technique of partial least squares is taught in, for example, Geladi & Kowalski, Partial Least Squares Regression: A Tutorial, Analytica Chimica Acta, 185 (1986) 1–17. Various commercial software packages are available for implementation of the partial least squares technique. Such software packages are sold, for example, by NIR Systems, of Silver Spring, Md., under the name NSAS, (together with certain equipment), and in the Spectra Calc, Lab-Calc, and GRAMS software packages of Galactic Industries, of Salem, N.H. Other techniques such as principal component regression, principal component analysis, and multiple regression analysis (also called multiple linear regression analysis or ordinary least squares analysis) may also be used. Those skilled in the art of constructing models using these techniques will be able to do so using appropriate commercial software packages. The techniques of multiple regression analysis would ordinarily be employed if the number of data points is relatively small.

The first step in using multivariate techniques is the development of a model. The model relates various values of pretreated transmittance and reflectance with respect to wavelength to analyte concentrations. In developing the model, the device of the invention is employed to take measurements of reflected or transmitted light intensity on a subject. Simultaneously, invasive, highly-accurate methods are used to determine analyte concentrations. This process is accomplished over a range of analyte concentrations for two sets of data. One of these sets of data is the calibration set, and the other set is a prediction set.

The intensity values of the calibration set are pretreated, and are used as input for the multivariate model-developing software, together with the invasively-measured analyte concentrations. The software calculates, in the PLS technique, an initial set of factors, which make up an initial model. The initial model is then employed to obtain an analyte concentration from the prediction set infrared intensity values. This predicted value is then compared to the invasively determined analyte concentration obtained simultaneously with the prediction set infrared intensity values. A person suitably skilled in the art of constructing PLS models then reviews and analyzes the factors of the initial model and makes appropriate adjustments to develop an improved model. The techniques employed by a person skilled in the art of constructing multivariate statistical models are set forth in, for example, in Mark, Principles and Practice of Spectroscopic Calibration (1992). After an acceptable model has been iteratively developed, the model is employed in analyzing real data to obtain analyte concentrations.

One possible application of the present invention is to determine the concentration of glucose in the blood of a mammal. Glucose occurs in non-negligible concentrations in mammal tissue (i.e., the living cells) as well as in mammal blood. In living cells, glucose is metabolized into glucose phosphate which has an absorbance spectrum very similar to that of glucose. Accordingly, glucose phosphate will, by instruments using present technology, be detected as glucose.

Moreover, the concentrations of glucose in the blood stream and in the cells may differ from one another and may vary over time. In particular, in persons suffering from diabetes, who are most likely to employ non-invasive glucose sensing techniques, it has been observed that there is little predictable relation between the concentration of glucose in blood and the concentration of glucose in tissue. As a result, conventional non-invasive glucose sensors are difficult to calibrate accurately.

According to a preferred embodiment of the present invention, a calibration procedure employing a blood-volume modulation technique is performed to provide accurate determination of the blood glucose concentration in mammals. The calibration procedure preferably employs the following steps:

(1) employ the present invention to determine non-invasively the glucose concentration in a blood-rich body part of the mammal by irradiating the blood-rich body part of the mammal and detecting the resulting radiation;

(2) employ the present invention to determine non-invasively the glucose concentration in a blood-poor body part of the mammal by irradiating the blood-poor body part of the mammal and detecting the resulting radiation;

(3) employ a conventional technique to determine invasively the glucose concentration in the blood; and

(4) perform the multi-variate analysis of the present invention to process the absorbance spectra from the blood-rich and blood-poor body parts and the blood glucose concentration determined invasively, to generate a set of factors that provide, when multiplied by a given spectrum, the blood glucose concentration.

After calibration, a blood-volume modulation technique, whereby radiation measurements are taken from both blood-rich and blood-poor body parts, is then preferably employed to determine the blood glucose concentration in the mammal non-invasively.

It will be appreciated that there are considerable variations that can be accomplished in a method and apparatus of the invention without departing from its scope. As a result, although a preferred embodiment of a method and apparatus of the invention has been described above, it is emphasized that the invention is not limited to a preferred embodiment and there exist other alternative embodiments that are fully encompassed within the invention's scope, which is intended to be limited only by the scope of the appended claims.

What is claimed is:

1. A method for non-invasive determination of the concentration of at least one analyte in a mammal, comprising the steps of:

(a) concurrently irradiating a portion of the body of the mammal with incident radiation, said incident radiation including two or more distinct bands of continuous-wavelength incident radiation;

(b) sensing the resulting radiation emitted from said portion of the body; and

(c) deriving from the sensed resulting radiation a value for the concentration of said analyte.

2. The method of claim **1**, wherein step (a) comprises the steps of:

(1) generating continuous-wavelength source radiation; and

(2) filtering said continuous-wavelength source radiation to generate said two or more distinct bands of continuous-wavelength incident radiation.

3. The method of claim **2**, wherein said step of filtering decreases the intensity of said incident radiation relative to the intensity of said source radiation in a selected range of wavelengths intermediate a first and a second of said distinct bands and corresponding to a peak in the spectrum of radiation absorption by water.

4. The method of claim **1**, wherein said incident radiation comprises near infrared radiation.

5. The method of claim **1**, wherein radiation corresponding to a peak in the spectrum of radiation absorption by water falls outside of said two or more distinct bands of continuous-wavelength incident radiation.

6. The method of claim **1**, wherein step (c) comprises the steps of:

(1) deriving from the sensed resulting radiation a first expression for the magnitude of said sensed radiation as a function of wavelength of the sensed radiation;

(2) pretreating said first expression to minimize the influence of instrument offset and drift to obtain a second expression for the magnitude of said sensed radiation as a function of wavelength; and

(3) performing multivariate analysis of said second expression to obtain a value for the concentration of said analyte.

7. The method of claim **6**, wherein said step of pretreating said first expression comprises the step of obtaining the nth derivative of said first expression.

8. The method of claim **6**, wherein said step (c)(3) comprises the step of using the technique of partial least squares.

9. The method of claim **6**, wherein said step (c)(3) comprises the step of using the technique of principal component analysis.

10. The method of claim **1**, wherein step (b) comprises the step of concurrently sensing the resulting radiation emitted from said portion of the body with a plurality of detectors, wherein the resulting radiation comprises a plurality of wavelengths.

11. An apparatus for non-invasive determination of the concentration of at least one analyte in a mammal, comprising:

(a) means for concurrently irradiating a portion of the body of the mammal with incident radiation, said incident radiation including two or more distinct bands of continuous-wavelength incident radiation;

(b) means for sensing the resulting radiation emitted from said portion of the body; and

(c) means for deriving from the sensed resulting radiation a value for the concentration of said analyte.

12. The apparatus of claim **11**, wherein said irradiating means comprises:

(1) means for generating continuous-wavelength source radiation; and

(2) means for filtering said continuous-wavelength source radiation to generate said two or more distinct bands of continuous-wavelength incident radiation.

13. The apparatus of claim **12**, wherein said filtering means decreases the intensity of said incident radiation relative to the intensity of said source radiation in a selected range of wavelengths intermediate a first and a second of said distinct bands and corresponding to a peak in the spectrum of radiation absorption by water.

14. The apparatus of claim 11, wherein said incident radiation comprises near infrared radiation.

15. The apparatus of claim 11, wherein radiation corresponding to a peak in the spectrum of radiation absorption by water falls outside of said two or more distinct bands of continuous-wavelength incident radiation.

16. The apparatus of claim 11, wherein said deriving means comprises:

(1) means for deriving from the sensed resulting radiation a first expression for the magnitude of said sensed radiation as a function of wavelength of the sensed radiation; and

(2) data processing means adapted to (i) pretreat said first expression to minimize the influence of instrument offset and drift to obtain a second expression for the magnitude of said sensed radiation as a function of wavelength and (ii) perform multivariate analysis of said second expression to obtain a value for the concentration of said analyte.

17. The apparatus of claim 16, wherein said data processing means is adapted to pretreat said first expression by obtaining the nth derivative of said first expression.

18. The apparatus of claim 16, wherein said data processing means is adapted to perform multivariate analysis of said second expression using the technique of partial least squares.

19. The apparatus of claim 16, wherein said data processing means is adapted to perform multivariate analysis of said second expression using the technique of principal component analysis.

20. The apparatus of claim 11, wherein said means for sensing the resulting radiation emitted from said portion of the body comprises a plurality of detectors for concurrently sensing radiation at a plurality of wavelengths.

* * * * *

EXHIBIT B

US005379764A

United States Patent [19]

Barnes et al.

[11] Patent Number: 5,379,764

[45] Date of Patent: Jan. 10, 1995

[54] **NON-INVASIVE DETERMINATION OF ANALYTE CONCENTRATION IN BODY OF MAMMALS**

[75] Inventors: **Russell H. Barnes; Jimmie W. Brasch, Sr.**, both of Columbus, Ohio; **David L. Purdy**, Marion Center, Pa.; **William D. Longheed**, Toronto, Canada

[73] Assignee: **Diasense, Inc.**, Pittsburgh, Pa.

[21] Appl. No.: **987,766**

[22] Filed: **Dec. 9, 1992**

[51] **Int. Cl.**[6] **A61B 5/00**

[52] **U.S. Cl.** **128/633**; 128/664; 356/39

[58] **Field of Search** 128/633–635, 128/664–665, 666–667; 356/39–41

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,958,560	5/1976	March .	
3,973,118	8/1976	La Montaigne	250/226
4,014,321	3/1978	March .	
4,102,646	7/1978	Sleeter	23/230 R
4,169,676	10/1979	Kaiser	356/39
4,260,262	4/1981	Webster	356/418
4,404,642	9/1983	Rosenthal	364/571
4,427,889	1/1984	Muller	250/339
4,509,522	4/1985	Manuccia et al.	128/634
4,642,778	2/1987	Hieftje et al.	364/498
4,655,225	4/1987	Dahne et al.	128/633
4,798,954	1/1989	Stevenson	250/341
4,800,279	1/1989	Hieftje et al.	250/339
4,801,805	1/1989	Butler et al.	250/343
4,882,492	11/1989	Schlager	250/346
4,883,953	11/1989	Koashi et al.	250/226
4,975,581	12/1990	Robinson et al.	250/339
5,009,230	4/1991	Hutchinson	128/633
5,028,787	7/1991	Rosenthal et al.	250/341
5,054,487	10/1991	Clarke	128/633
5,068,536	11/1991	Rosenthal	250/341
5,070,874	12/1991	Barnes et al.	128/664
5,077,476	12/1991	Rosenthal	250/341
5,086,229	2/1992	Rosenthal et al.	250/341
5,222,495	6/1993	Clarke et al.	128/633

FOREIGN PATENT DOCUMENTS

0160768	11/1985	European Pat. Off. .
0317121	5/1989	European Pat. Off. .
9111136	8/1991	WIPO .

OTHER PUBLICATIONS

J. Drennen, et al. Near-Infrared Spectrometric Determination of Hydrogen Ion, Glucose, and Human Serum Albumin in a Simulated Biological Matrix, Spectroscopy, vol. 6, No. 2, p. 28 (1990).

K. Beebe & B. Kowalski, An Introduction to Multivariate Colibration and Analysis, Anal. Chem. 1987, 59, p. 1007A.

P. Geladi & B. Kowalski, Partial Least-Squares Regression: A Tutorial, Analytical Chimica Acta, 185 (1986) 1–17.

D. L. Wetzel, Near Infrared Reflectance Analysis: Sleeper Among Spectroscopic Techniques, Analytical Chemistry, vol. 55, p. 1165A (1983).

R. D. Rosenthal, An Introduction to Near Infrared Quantitative Analysis (1978).

(List continued on next page.)

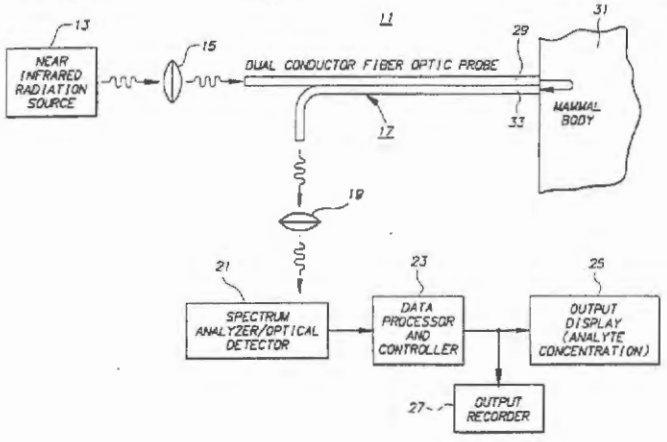
Primary Examiner—Angela D. Sykes

Attorney, Agent, or Firm—William H. Murray; Robert E. Rosenthal

[57] **ABSTRACT**

A method of non-invasive determination of the concentration of at least one analyte in the blood of a mammal, includes the steps of projecting near-infrared radiation on a portion of the body of the mammal, the radiation including a plurality of wavelengths; sensing the resulting radiation emitted from the portion of the body; deriving from the sensed resulting radiation emitted from the portion of the body a first expression for the magnitude of the sensed radiation as a function of wavelength of the sensed radiation; pretreating the first expression to minimize the influence of offset and drift to obtain a second expression for the magnitude of the sensed radiation as a function of wavelength; and performing multivariate analysis of the second expression to obtain a value for the concentration of the analyte.

8 Claims, 11 Drawing Sheets



OTHER PUBLICATIONS

N. Wang, et al., Determination of neodymium in rare earth mixtures by fourth–derivative spectrophotometry, Analytica Chimica Acta, 2541 (1991) 153–157.

C. E. Miller & B. E. Eichinger, Analysis of Rigid Polyurethane Foams by Near–Infrared Diffuse Reflectance Spectroscopy, Applied Spectroscopy, vol. 44, No. 5, p. 887 (1990).

T. Isaksson & T. Naes, Selection of Samples in Near–Infrared Spectroscopy, Part II: Selection Based on Spectral Measurements, Applied Spectroscopy, vol. 44, No. 7, p. 1152 (1990).

N. Kaiser, Laser Absorption Spectroscopy with an ATR Prism–Noninvasive in Vivo Determination of Glucose, in Feedback–controlled and preprogrammed insulin infusion in diabetes mellifus: Workshop Schloss Reisenburg 1978 (1979), at 30.

A. Miller, In Vivo Measurement of Glucose Concentrations with Lasers, in Feedback–controlled and preprogrammed insulin infusion in diabetes mellitus: Workshop held at Schloss Reisenburg 1978 (1979) at p. 33.

D. Haaland, Quantitative Infrared Analysis of Borophosphosilicate Films Using Multivariate Statistical Methods, Analytical Chemistry, 1988, 60, 1208.

D. Haaland & E. Thomas, Outlier Detection During Multivariate Quantative Analyses of Spectroscopic Data.

D. Haaland & E. Thomas, Partial Least–Squares Methods for Spectral Analyses, 1. Relation to other Quantitative Calibration Methods and the Extraction of Qualitative Information, Analytical Chemistry, 1988, 60, 1193.

D. Haaland & E. Thomas, Partial Least–Squares Methods for Spectra Analyses. 2. Application to Simulated and Glass Spectral Data, Analytical Chemistry, 1988, 60, 1202.

E. Thomas and D. Haaland, Comparison of Multivariate Calibration Methods for Quantitative Spectral Analysis, Analytical Chemistry, 1990, 62, 1091.

W. Lindberg & J. A. Persson, Partial Least–Squares Method for Spectrofluorimetric Analysis of Mixtures of Humic Acid and Lignin Sulforate, Analytic Chemistry, 1983, 55, 643.

H. Zeller, et al., Blood Glucose Measurement by Infrared Spectroscopy, The International Journal of Artificial Organs, vol. 12, No. 2, 1969, p. 129.

E. Penchant, C. Sulles & R. Jensen, Determination of Serum Cholesterol by Near–Infrared Reflectance Spectrometry, Anal. Chem. 1987, 59, 1816.

I Yoshiya, et al., Spectrophotometric monitoring of arterial oxygen saturation in the fingertip, Med. & Biol. Eng. & Comput., 1980, 18, 27–32.

M. Martens & H. Martens, Near–Infrared Reflectance Determination of Sensory Quality of Peas, Applied Spectroscopy, vol. 40, p. 303 (1985).

B. Bauer & T. Floyd, Monitoring of Glucose in Biological Fluids by Fourier Transform Infrared Spectrometry with a Cylindrical Internal Reflectance Cell, Analytical Chimica Acta, 197 (1987) 295–301.

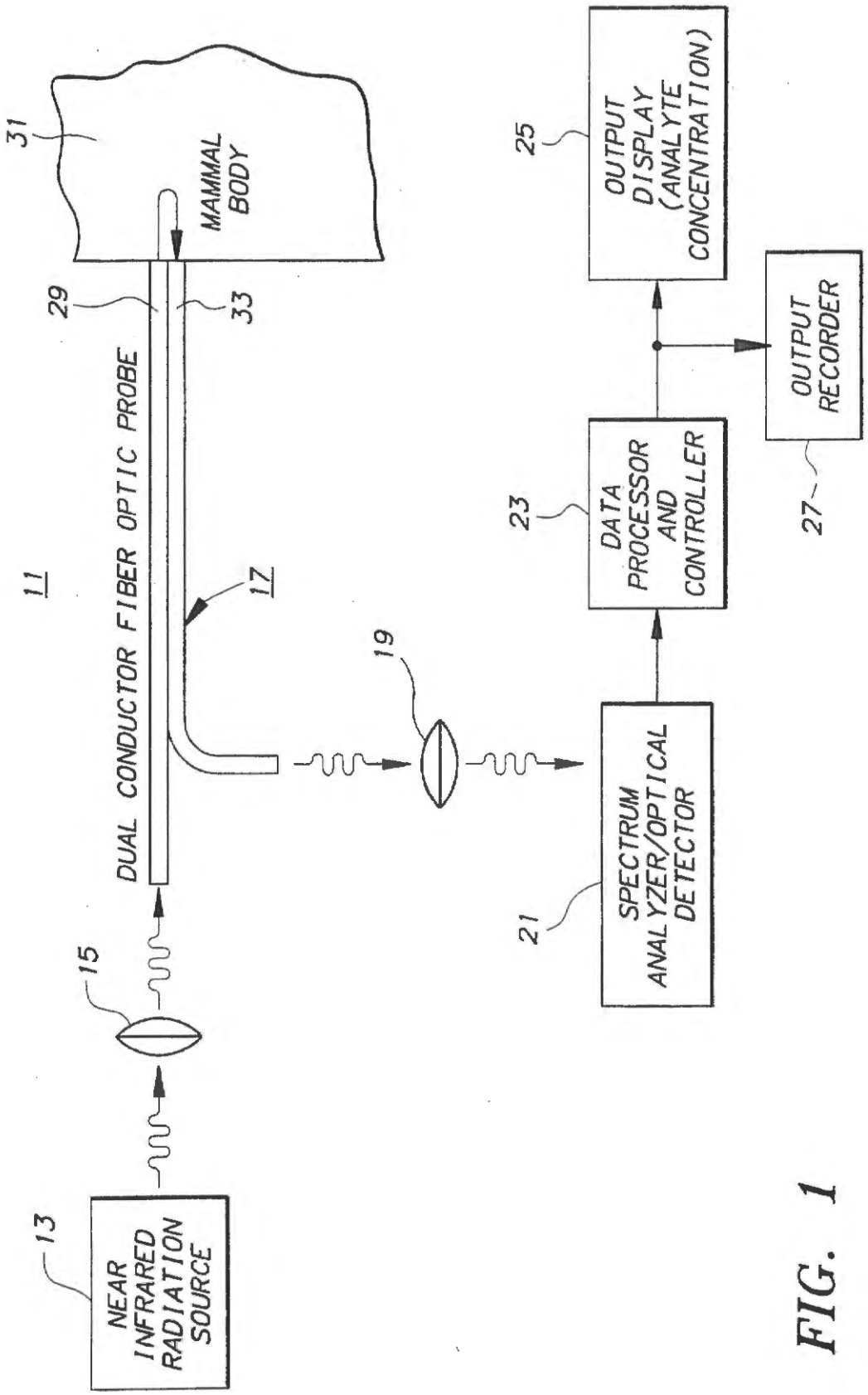

31
MAMMAL BODY
29
33
DUAL CONDUCTOR FIBER OPTIC PROBE
11
17
19
25
OUTPUT DISPLAY (ANALYTE CONCENTRATION)
23
DATA PROCESSOR AND CONTROLLER
27
OUTPUT RECORDER
15
21
SPECTRUM ANALYZER/OPTICAL DETECTOR
13
NEAR INFRARED RADIATION SOURCE

FIG. 1

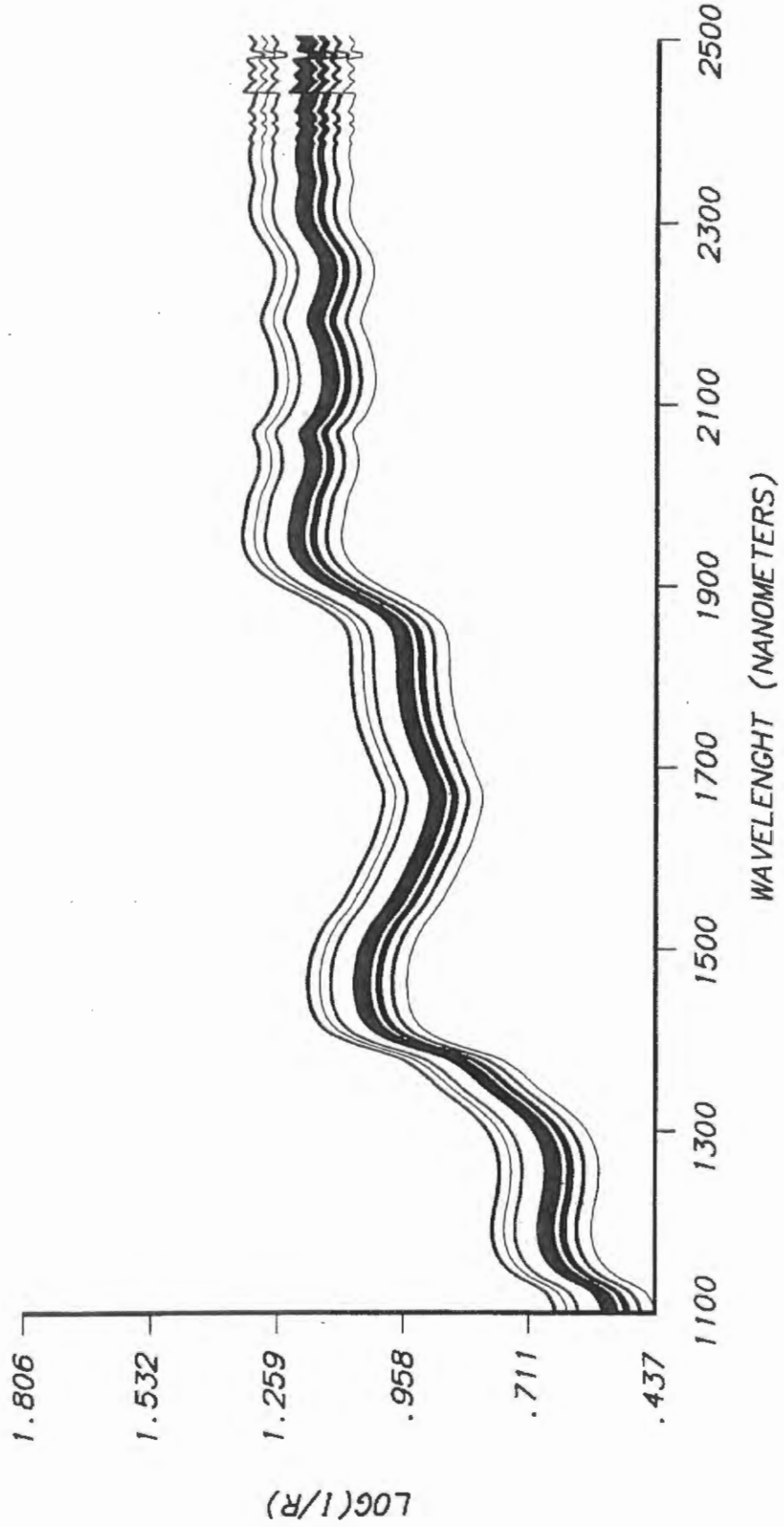

1.806
1.532
1.259
.958
.711
.437
LOG(1/R)
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGHT (NANOMETERS)

FIG. 2

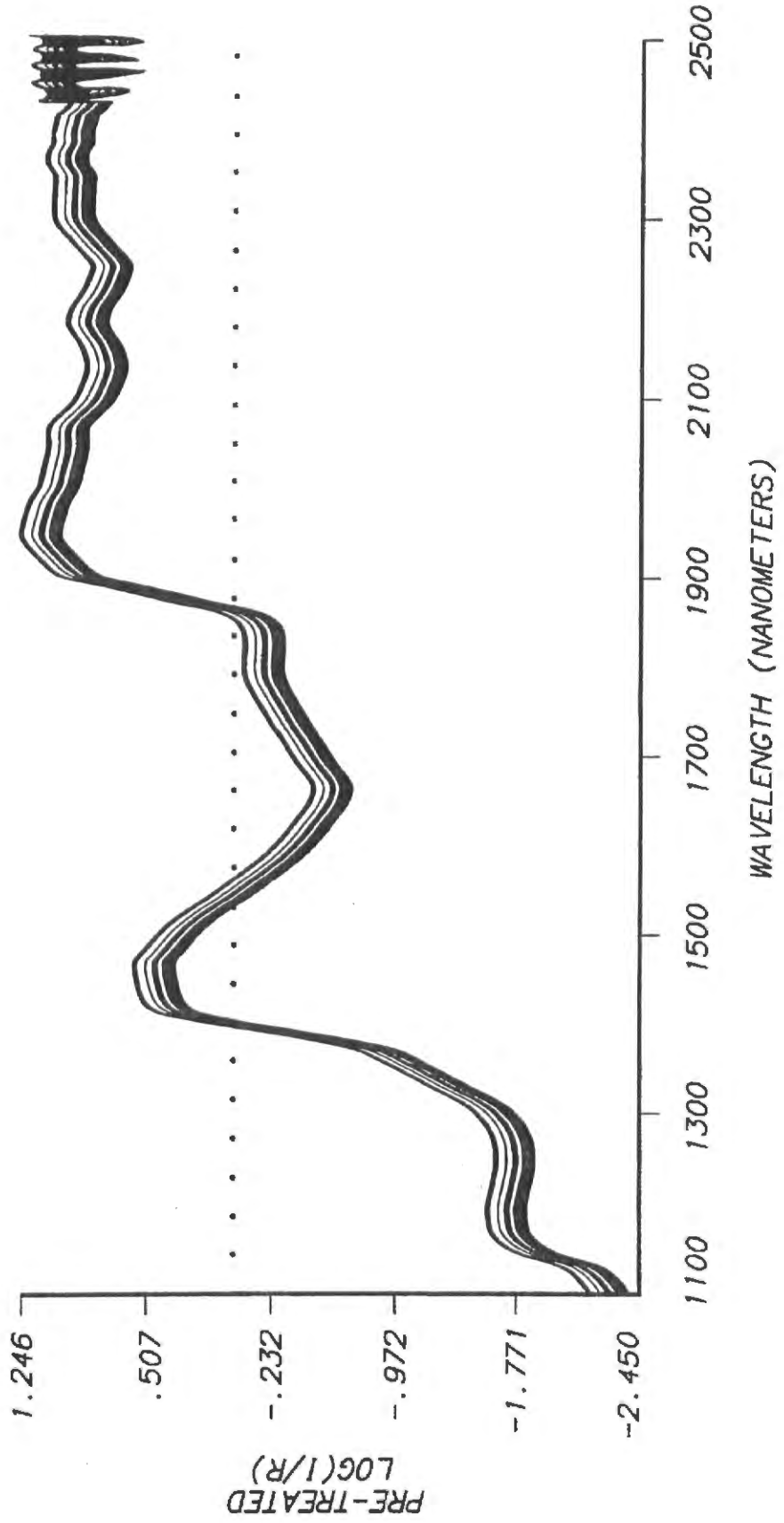

PRE-TREATED
LOG(1/R)
1.246
.507
-.232
-.972
-1.771
-2.450
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 3

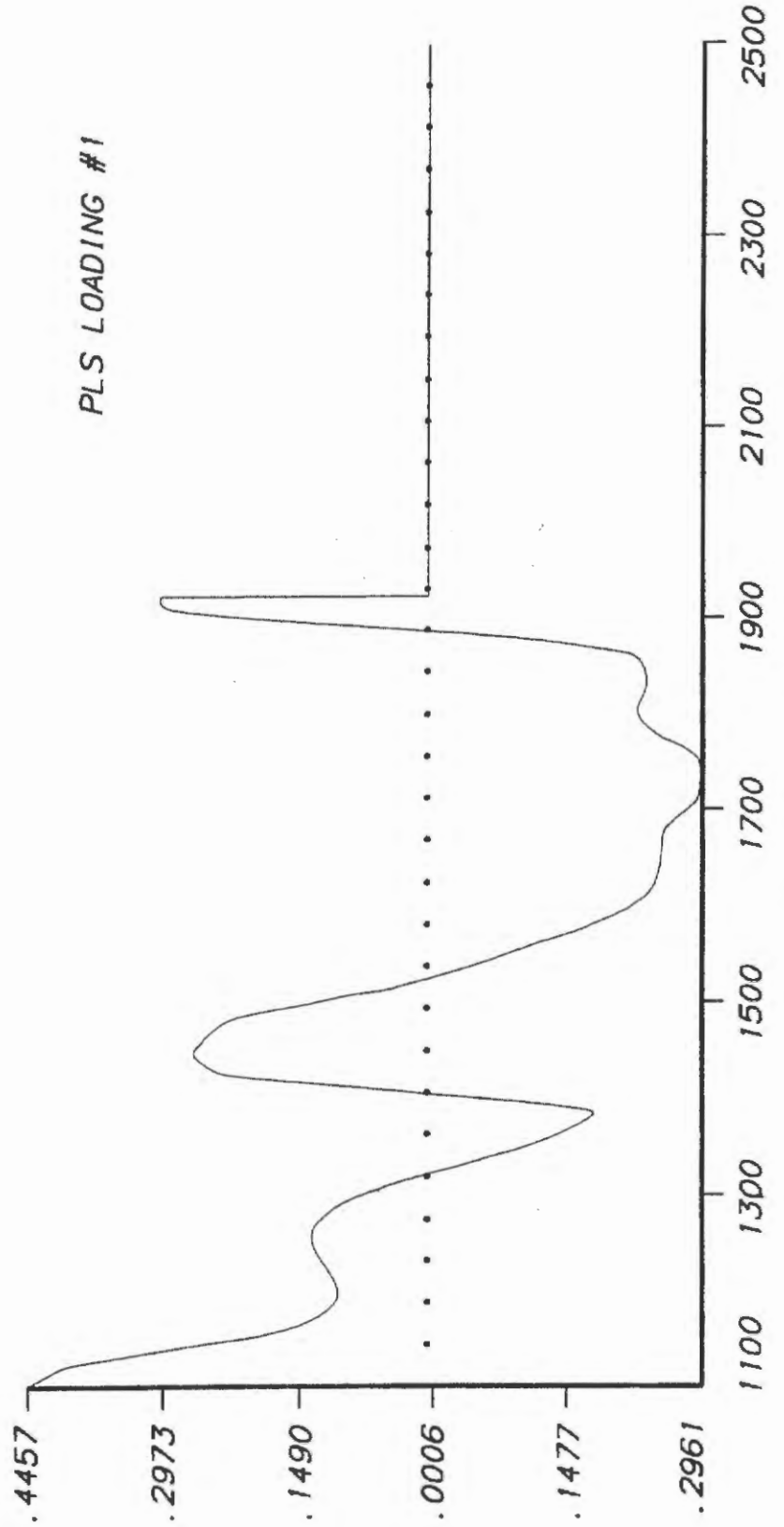

PLS LOADING #1
.4457
.2973
.1490
.0006
.1477
.2961
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 4A

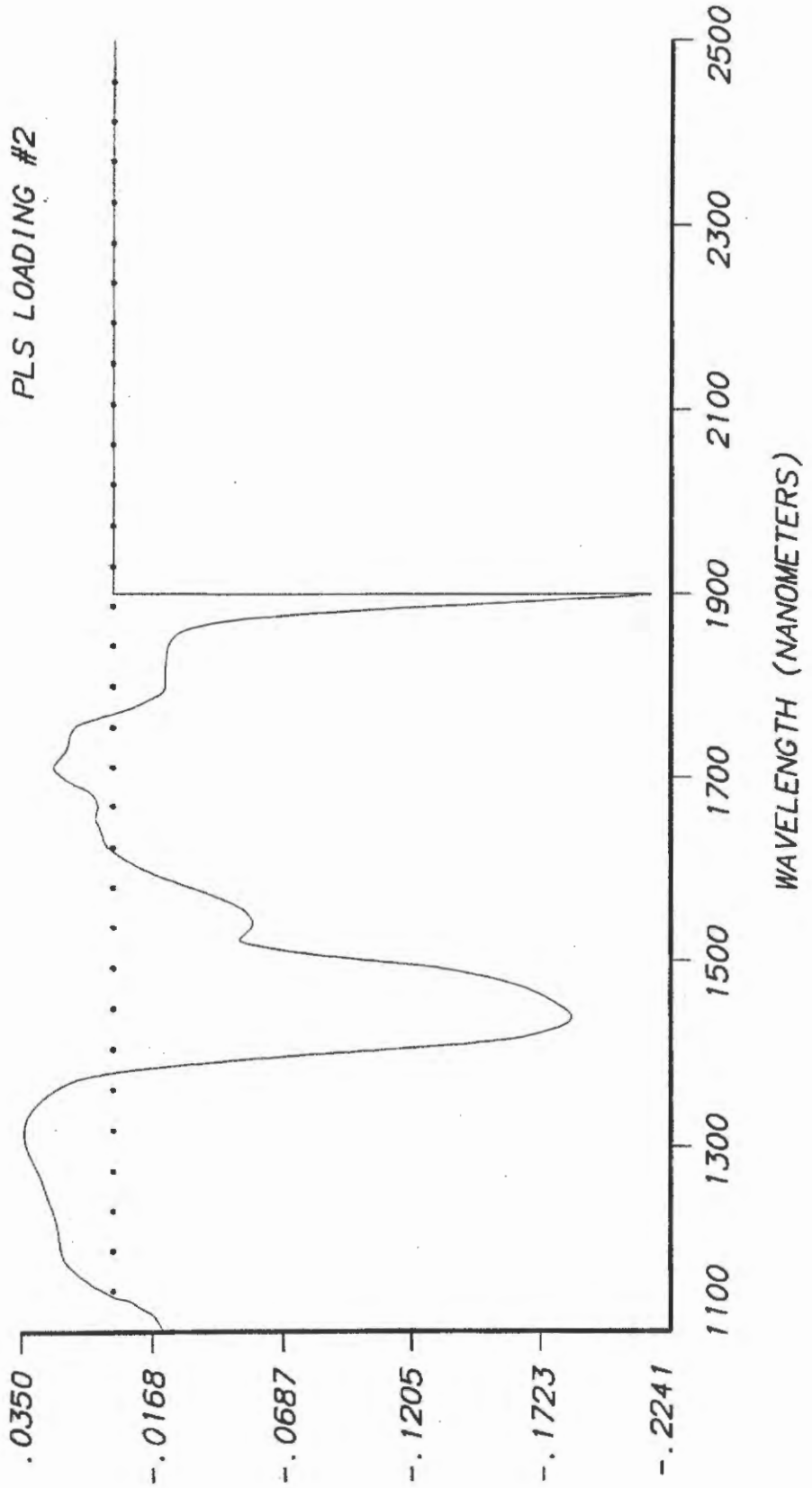

PLS LOADING #2
.0350
-.0168
-.0687
-.1205
-.1723
-.2241
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 4B

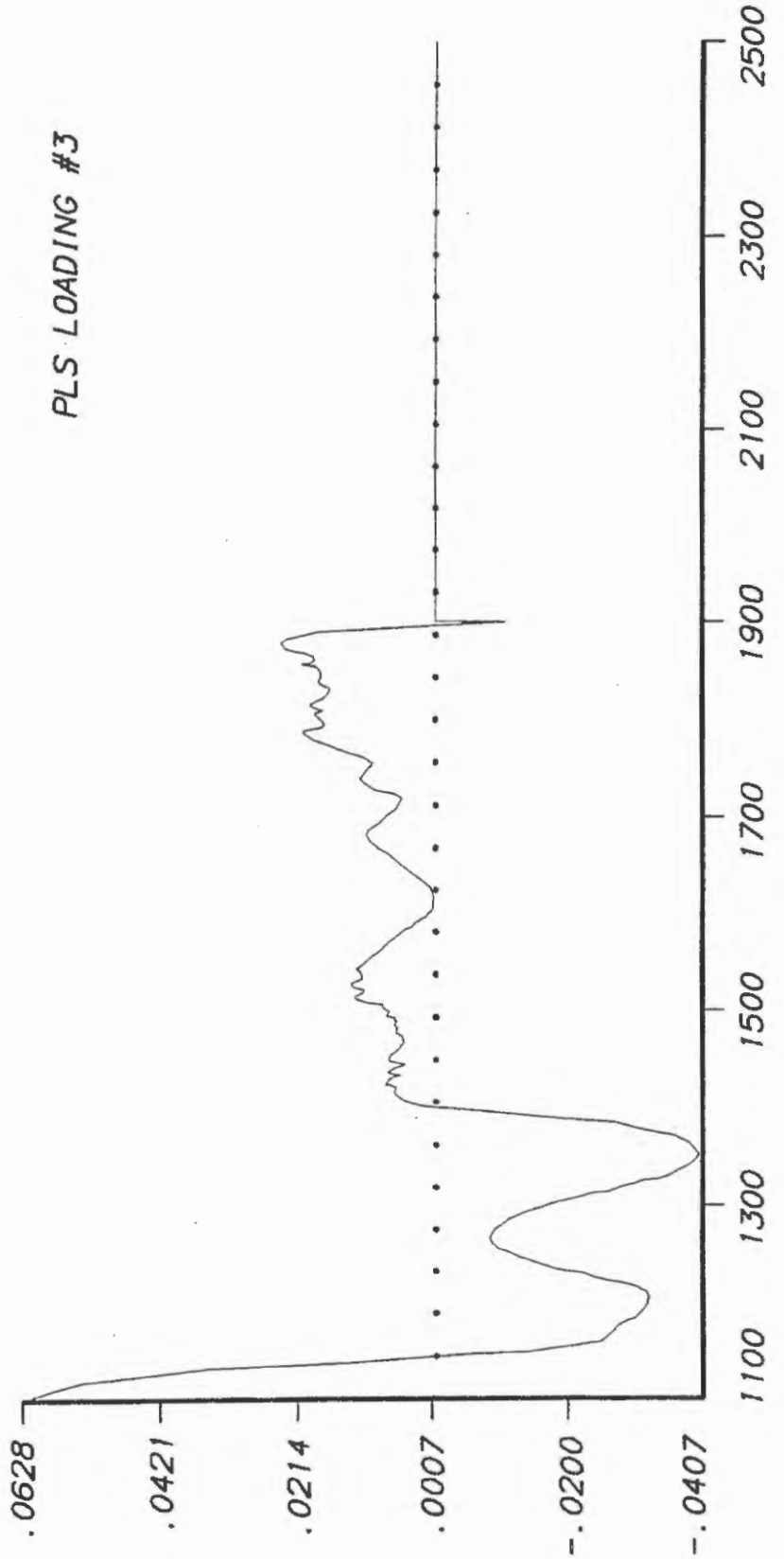

PLS LOADING #3
.0628
.0421
.0214
.0007
-.0200
-.0407
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 4C

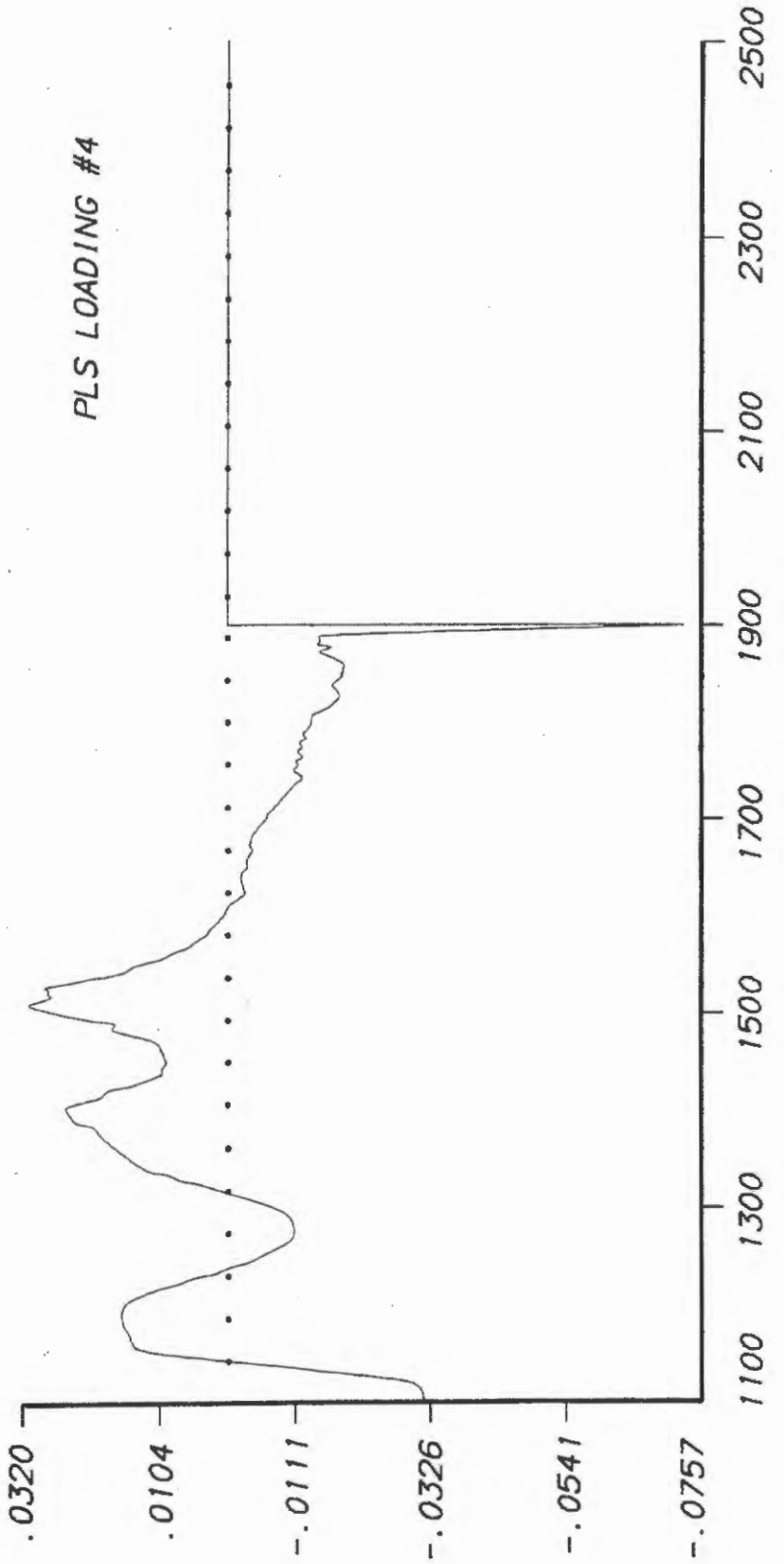

PLS LOADING #4
.0320
.0104
-.0111
-.0326
-.0541
-.0757
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 4D

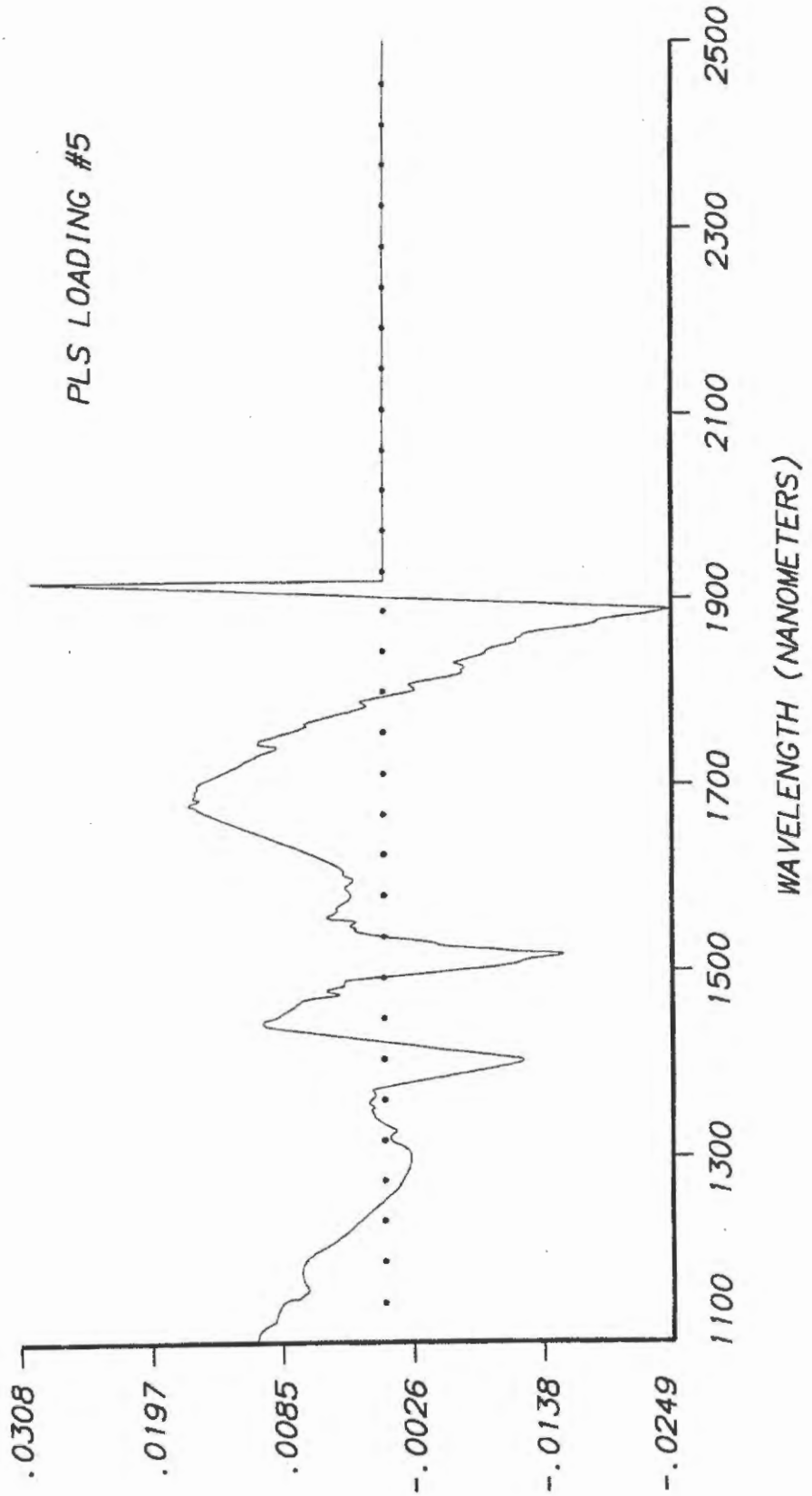

PLS LOADING #5
.0308
.0197
.0085
-.0026
-.0138
-.0249
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 4E

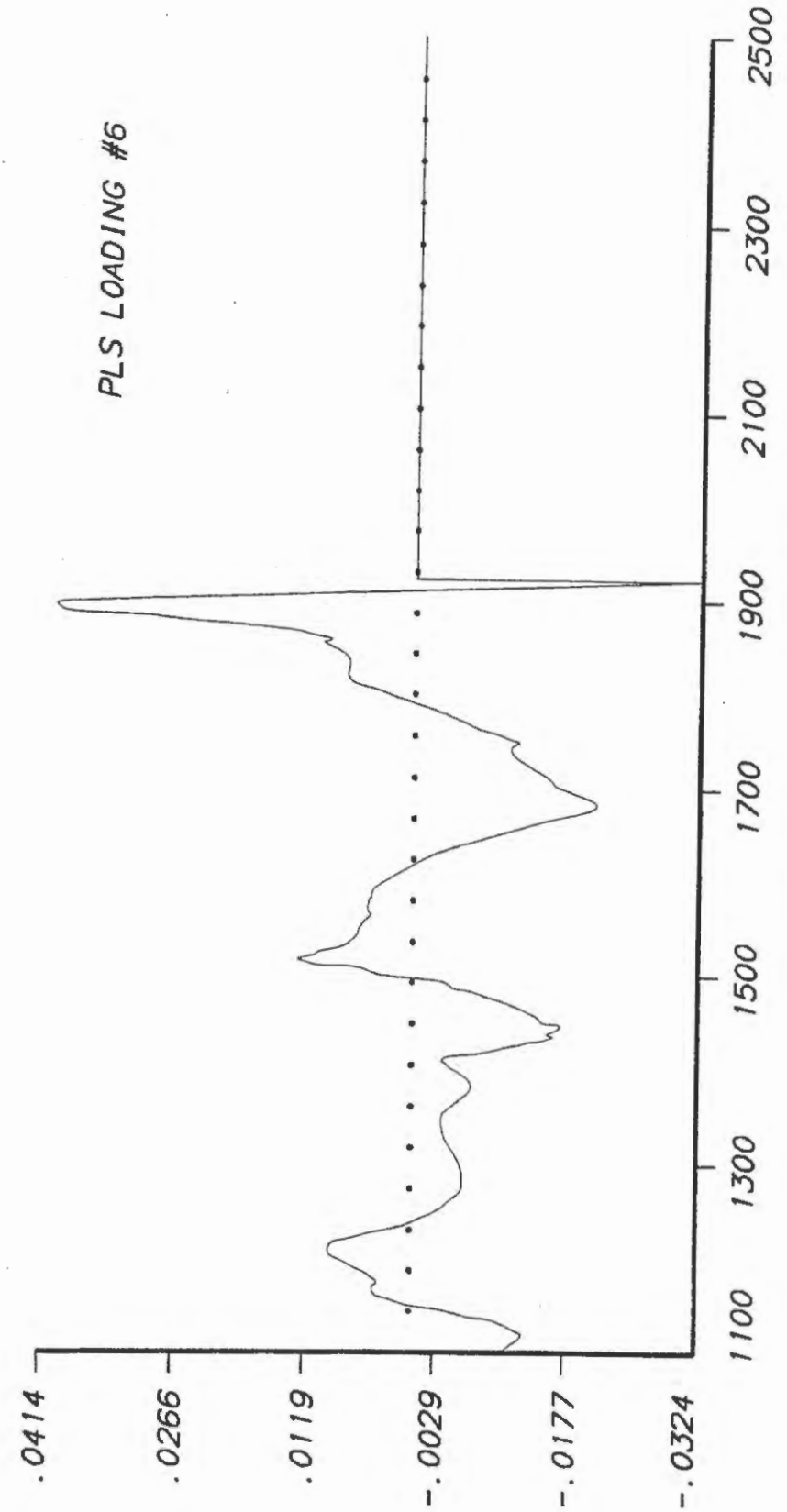

PLS LOADING #6
.0414
.0266
.0119
-.0029
-.0177
-.0324
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 4F

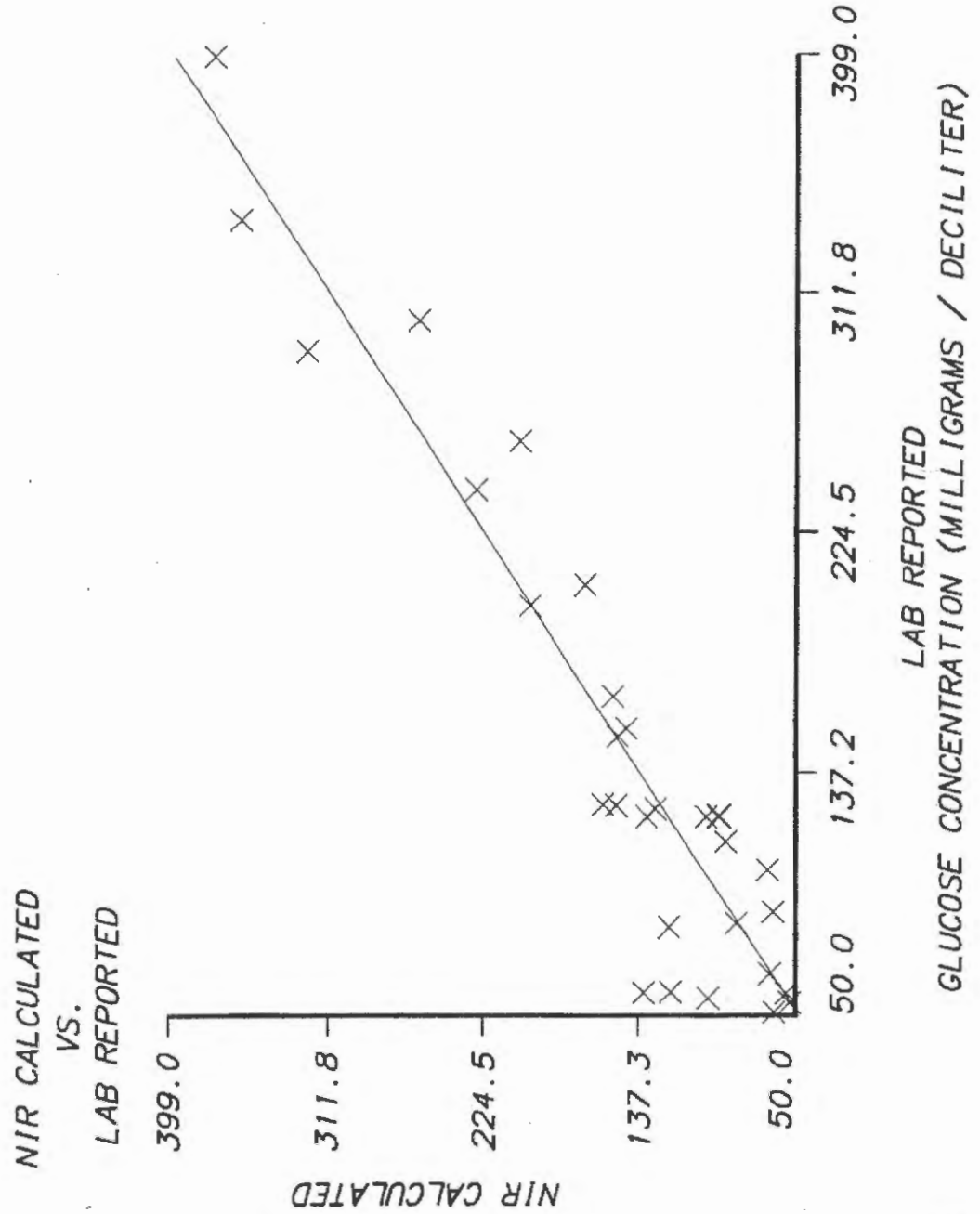

NIR CALCULATED
VS.
LAB REPORTED
399.0
311.8
224.5
137.3
50.0
NIR CALCULATED
50.0
137.2
224.5
311.8
399.0
LAB REPORTED
GLUCOSE CONCENTRATION (MILLIGRAMS / DECILITER)

FIG. 5

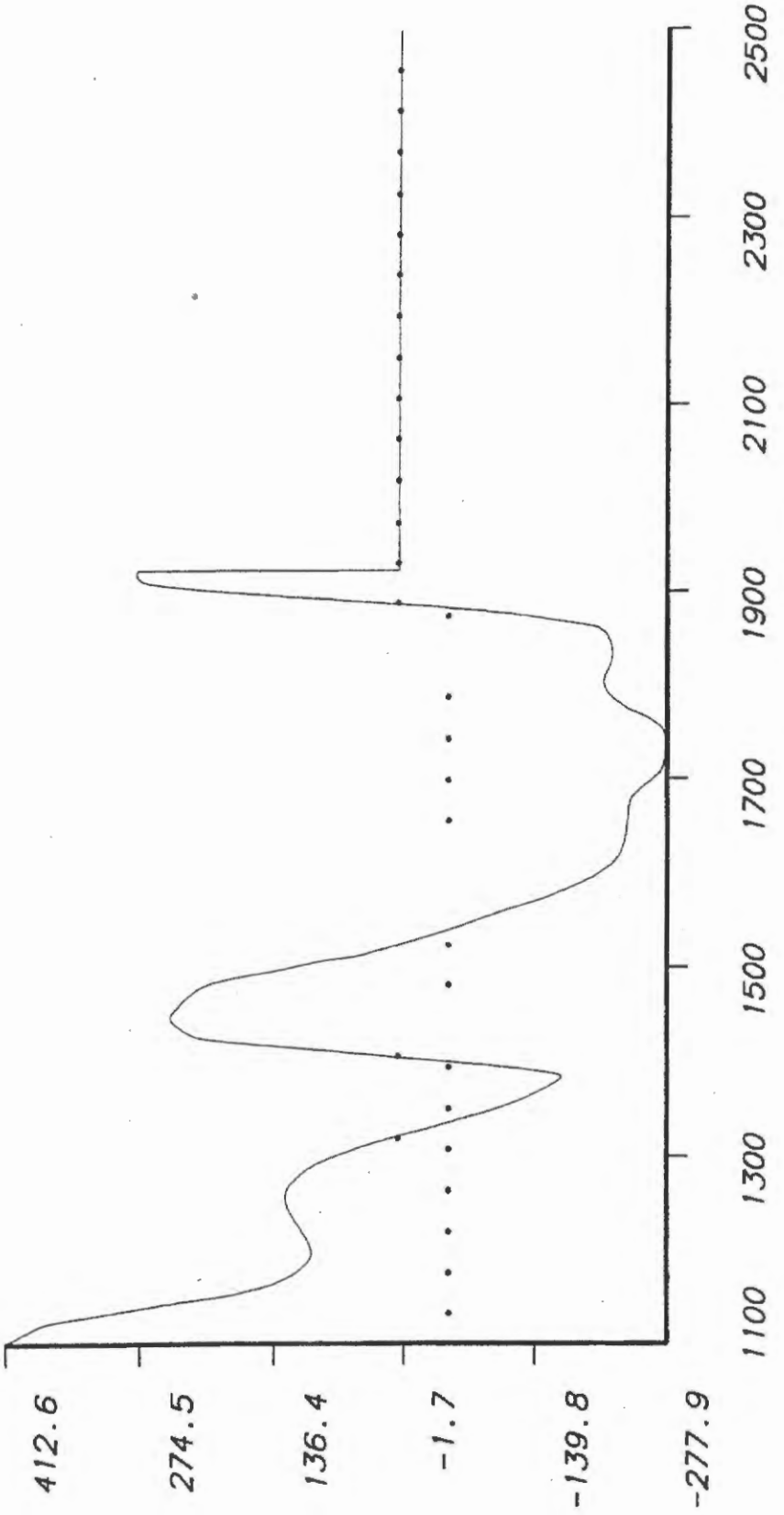

412.6
274.5
136.4
-1.7
-139.8
-277.9
1100
1300
1500
1700
1900
2100
2300
2500
WAVELENGTH (NANOMETERS)

FIG. 6

NON-INVASIVE DETERMINATION OF ANALYTE CONCENTRATION IN BODY OF MAMMALS

BACKGROUND OF THE INVENTION

Applicants herein are the inventors of U.S. Pat. No. 5,070,874, issued Dec. 10, 1991, for "Non-invasive Determination of Glucose Concentration in Body of Patient."

This invention relates to the determination of the concentration of analytes in the body of a mammal, and in particular to the determination of the concentration of glucose in the blood of a patient who is suspected of suffering from diabetes or to control the treatment or medication of patients who already suffer from diabetes. It has particular relationship to such determination without drawing blood from the patient, i.e., by a non-invasive process and by non-invasive means.

There is widespread demand for non-invasive determination of glucose in patients. In the United States there are approximately ten million diabetics. Two million of these are Type 1 Diabetics, whose pancreas secretes no insulin; and eight million of these are Type 2 Diabetics, whose pancreas secretes insufficient insulin or secretes it too late. Most of the Type 2 Diabetics can be controlled with proper diet and weight control. Some of the Type 2 Diabetics and all of the Type 1 Diabetics require one or more shots of insulin per day. Insulin controls the body's utilization of glucose or sugar in the blood and, in the correct concentrations, prevents hyperglycemia (excess glucose) which, if left uncorrected, can lead to ketosis, coma and death. Glucose determination is also indispensable for sufferers from hypoglycemia who must ingest glucose containing fluids, such as orange juice, if the glucose in their blood decreases to a low level.

Hyperglycemia in the diabetic is strongly suspected of being responsible for the long-term effects of diabetes which include heart disease, arteriosclerosis, blindness, stroke, hypertension, kidney failure, and premature death. Severe hypoglycemia has similar drastic consequences. In a normal person, the blood glucose level may vary between 60 and 130 milligrams per deciliter, a variance exceeding 100%; whereas, in a diabetic, the levels may vary from time to time from 40 to 500 milligrams per deciliter, a variance of 1150% for hyperglycemia. For hypoglycemia, 60 milligrams per deciliter indicates that treatment is necessary; the glucose may reach a dangerous level of 20 milligrams per deciliter. These large swings of glucose levels must be avoided to prevent the symptoms and complications of the disease. To avoid the swings, the diabetic must be able to conveniently monitor his blood glucose level, and then vary his caloric intake, diet and insulin to control the level. For effective control, frequent blood glucose monitoring is necessary.

The only practicable, reliable method currently available for monitoring blood glucose is by means of blood sampling. The diabetic pricks his epidermis with a needle or lance, usually in the finger, draws a drop of blood, and absorbs the blood on a chemically treated strip of paper. He can then read the glucose level by placing the strip in a glucometer (a spectrophotometer which reads glucose concentrations); or he can compare the color change of the strip with a calibrated color chart. The direct reading instruments are more accurate. Other methods include measuring the electrical resistance of the strip with a glucometer which is an ohmmeter calibrated in milligrams per deciliter. For effective control, some diabetics must utilize a finger prick four or more times a day.

It is desirable to dispense with the drawing and analyzing of blood and it is an object of this invention to achieve this purpose, providing for effective non-invasive determination of analyte concentration in the body of a mammal, and in particular glucose concentration in a patient suspected to suffer from, or already suffering from, diabetes.

European Publication 0 160 768, dated Nov. 13, 1985, to Clause Dahne and Daniel Cross, discloses one prior art technique for the non-invasive determination of glucose concentration. In Dahne, a beam of radiation in selected bands, 1575, 1765, 2100 and 2270±15 nanometers is impinged on a portion of the patient's body, penetrating into the portion, and the radiation resulting from the reaction within the body on the incident radiation is analyzed photometrically for the presence quantitatively of glucose. The resulting radiation which is analyzed may be scattered radiation or the transmitted radiation which, in effect, is the incident radiation less the predominant fraction of the scattered radiation and the radiation absorbed by the portion of the body.

Dahne suffers from the disadvantage that its process lacks the precision demanded for the effective monitoring of glucose concentration. The range of concentration over which the glucose is in practice monitored for effective control of the patient is between 40 and 500 milligrams per deciliter, but even lower concentrations may be encountered in hyperglycemia or hypoglycemia. A concentration appreciably greater than 120 milligrams per deciliter indicates a diabetic condition and treatment by diet or insulin. In the actual practice of Dahne's process, the highest concentration of glucose which was measured was one molar (1M) and the lowest concentration of glucose which was measured was 0.05 molar (page 18). The chemical formula for glucose is $C_6H_{12}O_6$. In a 1M solution of glucose, there are 180.16 grams per liter or 18,000 milligrams per deciliter. In 0.05 mole, there are 0.9 grams or 900 milligrams per deciliter. This is far out of the range of glucose concentrations which must be measured for effective control and, indeed, out of the range which is compatible with life. There is no evidence in Dahne that its process is more effective than is indicated by its tests.

It is accordingly an object of this invention to overcome the disadvantages and drawbacks of the prior art and to provide for the precise effective non-invasive determination of the concentration of blood analytes in a mammal, and particularly glucose in a human patient, taking into consideration the concentrations actually involved in such determination.

SUMMARY OF THE INVENTION

This invention arises from the realization that in any expression, for example, in a graph, of the concentration of glucose in blood as a function of the wavelengths over which an analysis is carried out, the measure of the maximum concentration, which must be precisely determined, is often obscured by the presence of other chemical species. It has been realized in arriving at this invention that the specific spectral features associated with species which must be measured may be emphasized and readily determined by appropriate mathematical techniques. In particular, such mathematical techniques may involve a step of pretreatment, followed by

a step of multivariate analysis. The step of pretreatment serves to eliminate or minimize the effects of detector offset and optical scattering drift. In particular, the step of pretreatment may also include deriving a new function, the nth derivative with respect to wavelength of the expression defining the concentration of glucose as a function of wavelength, over a defined region of this nth derivative. The nth derivative with respect to wavelength is then used as an input for multivariate analysis. Using multivariate analysis techniques, the glucose concentration is then determined. As is conventional in the use of multivariate techniques in chemical analysis, the multivariate analysis uses a model developed by comparing predicted concentrations of the species to be measured in specimens to the known concentrations of the species in that specimen.

Specifically, the non-invasive measurement of the concentration of glucose in blood is performed with a near-infrared radiation source, a probe, a spectrum analyzer with a detector and a data processor. The probe may include a dual fiber-optic conductor of near infrared radiation which is used in either the transmission or scattering mode. Radiation from the near infrared source is transmitted through one of the dual conductors, the end of which is placed near or in contact with a portion of the patient's body. The radiation transmitted into the body undergoes scattering and characteristic absorption depending on the identity of the species present. A portion of the radiation having undergone scattering and absorption is back scattered from the body and collected and transmitted back to the spectral analyzer/detector system by the other fiber-optic conductor, which is referred to as the sensing or pick-up conductor. The end of the sensing or pick-up fiber-optic conductor, placed near or in contact with the body, is arranged so that either a transmission or a scattering measurement is performed. In the transmission mode, the end of the pick-up fiber-optic conductor is arranged so that the near infrared radiation from the source can be passed through the portion of the body, which may be the ear lobe, tongue or webbing between the fingers or toes, and its spectral absorption characteristics measured. This is accomplished by placing the body section between the ends of the dual conductor so that radiation from the fiber-optic conductor connected to the near infrared source passes through the body section to the pick-up fiber-optic conductor which transmits the attenuated radiation to the spectral analyzer/detector. In the scattering mode, a bifurcated fiberoptic probe is preferably used. The bifurcated probe includes two separate bundles of fibers, one bundle being connected to the near infrared source, and the other bundle being connected to the spectral analyzer/detector system. The pick-up bundle may be, for example, centrally located and the source conductor bundle may be disposed in any configuration surrounding the central bundle. Alternatively, individual pick-up fibers may be disposed at selected locations in a bundle of conductors connected to the source. To measure blood glucose, the sensing end of the probe is placed near or in direct contact with an outer surface of the body. Near infrared radiation from the fibers connected to the source is transmitted through that portion of the body undergoing both characteristic spectral absorption and scattering. Some of the scattered radiation which has traveled through the body experiencing absorption is collected by the pick-up fibers in this configuration and then transmitted to the spectrum analyzer/detector.

The spectrum analyzer for this application can include a dispersive spectrometer with a prism or diffraction grating, a spectrometer in a Czerny-Turner configuration, a set of optical filters, a scanning interferometer, a stationary interferometer, or it may include a Hadamard transform spectrometer. Hadamard transform spectroscopy is described in a paper by Hammaker et al. in *Vibrational Spectra and Structure*, Vol. 15, Nov. 1986, edited by J. R. Durig, Elsevier Press, Amsterdam, Holland. The purpose of the spectrum analyzer is to disperse the near infrared radiation passing through the body into its spectral components. Selected wavelength ranges are focused on detector cells, which provide an analog signal proportional to the intensity of radiation in the selected wavelength ranges.

The data processor receives the output signal from the spectral analyzer. This output signal may be a reflected light intensity as a function of wavelength. The reflectance, R, is given by

$$R = I_0/I$$

where I_0 is the intensity of the radiation incident on the portion of the patient's body and I is the resulting radiation reflected back or scattered by the portion. When the reflectance is graphically presented, the quantity log (1/R) is customarily presented and called absorbance.

The data processor then calculates the concentration of blood glucose, and formats the output to a display or recording device giving blood glucose concentration in selected units. Preferably, a microprocessor in the data processor is used to perform data processing and control the operation of the spectral analyzer.

To investigate and demonstrate the practical utility of the invention, near infrared measurements were performed in different concentrations of glucose in rabbit ears. It was found that the intensity of the reflected radiation as a function of wavelength in the near infrared band of glucose between 1100 and 1900 nm. yielded effective data from which glucose concentrations could be derived. In the practice of this invention, in its broad aspects, measurements are made over the range of wavelengths from 700 to 3000 nm.

BRIEF DESCRIPTION OF THE DRAWINGS

For a better understanding of this invention, both as to its organization and as to its method of operation, together with additional objects and advantages thereof, reference is made to the following description, taken in connection with the accompanying drawings, in which:

FIG. 1 is a block diagram showing an embodiment of this invention with which the method of invention is practiced;

FIG. 2 is a graph presenting 31 spectra of the log of the reciprocal of the reflectance of radiation from a rabbit used as a test subject, i.e., the absorption for the subject, as a function of the wavelength in the near infrared;

FIG. 3 is a graph presenting the functions shown in FIG. 2 as a function of wavelength after a step of data pretreatment;

FIG. 4A through 4F are graphs showing six factors in a multivariate analysis model developed using the data of FIG. 2 and 3.

FIG. 5 is a graph in which concentrations of glucose in rabbit blood were determined in vivo and non-invasively in the practice of this invention from the data

derived from the graphs shown in FIGS. 2 and 3, using the model of FIGS. 4A–4F, is plotted against the corresponding known concentrations;

FIG. 6 is a graph in which the model of FIGS. 4A–4F is plotted on a single graph.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

FIG. 1 shows apparatus 11 for the non-invasive determination of the glucose concentration in a patient. This apparatus includes a source 13 of near-infrared radiation, a first lens system 15, a dual conductor fiber-optic probe 17, a second lens system 19, a spectrum analyzer/detector 21, a data processor and controller 23, an output display device 25 and an output recorder 27. As stated the source may produce radiation over the range from 700 to 3000 nm. The data presented in this application were produced using a Model 6500 System Near Infrared Spectrometer acquired from Pacific Scientific Instrument Division of Pacific Scientific, Ltd. The address of this Instrument Division is 2431 Linden Lane, Silver Spring, Md. 20910. The source may be an appropriate tungsten filament bulb, with an infrared filter disposed intermediate the bulb and the input radiation conductor 29. The intensity of the radiation of the source over the wavelengths of interest must be maintained constant. This may be achieved, for example, by thermally isolating the bulb from its surroundings and maintaining the current through the filament constant. The lens systems 15 and 19 are represented by single-lens symbols. In actual practice, they are appropriate combinations of lenses including focusing lenses and collimators on the outlet side. The fiber-optic probe 17 includes an input radiation conductor 29 for transmitting radiation to a portion 31, for example, an ear lobe or wrist, of the patient's body and pickup or sensing radiation conductor 33 for receiving the resulting radiation from the portion 31. The output end of the input conductor 29 and the input or sensing end of the pickup conductor 33 are preferably in firm contact with the outer surface of the portion 31 of the subject's body. While each conductor 29 and 33 is represented by a symbol for a single conductor, each radiation conductor, in actual practice of this invention, includes bundles of optical fibers.

Radiation from the source 13 is directed by the lens system 15 into conductor 29 and, at its outlet, is projected into the portion 31. This incident radiation induces scattered radiation within the body portion 31, some of which passes through the end of conductor 33 and through the conductor and is directed by lens system 19 into the spectrum analyzer/detector. While FIG. 1 discloses apparatus in which scattered radiation is analyzed, the analysis of transmitted radiation, i.e., the input radiation less the back scattered and absorbed radiation, plus any forward scattered radiation, is within the scope of equivalents of this invention. In this case, the ends of conductors 29 and 33, instead of being side-by-side in contact with adjacent surfaces of the body portion 31, would be in contact with the outer surfaces on opposite sides of the body portion 31, for example, with opposite surfaces of the ear lobe. The radiation, which is in this case passed through conductor 33, is predominantly the radiation from the source 13 less the radiation scattered and absorbed by the molecules of the water in the blood, the glucose and other constituents of the blood. The skin also contributes to the scattering and absorption.

With the apparatus as shown in FIG. 1, the resulting back scattered radiation emitted by the body portion 31 is passed by pickup conductor 33 and lens system 19 to the spectrum analyzer/detector 21 where this radiation is spread into a spectrum. The spectrum is focused on an array of optical detectors. A selected wavelength range is focused on each detector. For example, a range of 15 nanometers may be focused on each detector. The detectors may be lead-sulfide detectors, which are well-known in the field of infrared spectroscopy of grains and other agricultural products. Each detector converts the radiation in the corresponding selected wavelength range to electrical signals which are transmitted to the data processor 23. In a preferred embodiment, intermediate each detector and the data processor, there is a pre-amplifier, an amplifier, and an analog-to-digital converter. It should be noted that, to reduce noise effects, a chopper is preferably provided before the spectrometer to modulate the infrared beam. The amplifier is a lock-in amplifier, so that only the portion of the signal containing data is transmitted to the analog-to-digital converter.

The data processor then applies a step of pretreatment to the function of the magnitude of the radiation intensity versus wavelength. The step of pretreatment has the effect of minimizing, or eliminating the effects of detector offset and drift. In a preferred embodiment, the pretreatment step comprises taking the nth derivative, and in particular, the second derivative, of the intensity vs. wavelength function. Alternatively, the pretreatment step may comprise the steps of subtracting the mean of the whole spectrum from each data point in the spectrum and then dividing each data point by the standard deviation of the whole spectrum.

The pretreated data is then subjected to multivariate analysis. The result of the step of multivariate analysis is a glucose concentration. Various techniques of multivariate analysis are known in the chemical arts. A preferred multivariate analysis technique is partial least squares (PLS). The technique of partial least squares is taught in, for example, Geladi & Kowalski, Partial Least Squares Regression: A Tutorial, Analytica Chimica Acta, 185 (1986) 1–17. Various commercial software packages are available for implementation of the partial least squares technique. Such software packages are sold, for example, by NIR Systems, of Silver Spring, Md., under the name NSAS, (together with certain equipment), and in the Spectra Calc, Lab-Calc, and GRAMS software packages of Galactic Industries, of Salem, N.H. Other techniques such as principal component regression, principal component analysis, and multiple regression analysis (also called multiple linear regression analysis or ordinary least squares analysis) may also be used. Those skilled in the art of constructing models using these techniques will be able to do so using appropriate commercial software packages. The techniques of multiple regression analysis would ordinarily be employed if the number of data points is relatively small.

The first step in using multivariate techniques is the development of a model. The model relates various values of pretreated transmittance and reflectance with respect to wavelength to analyte concentrations. In developing the model, the device of the invention is employed to take measurements of reflected or transmitted light intensity on a subject. Simultaneously, invasive, highly-accurate methods are used to determine analyte concentrations. This process is accomplished

over a range of analyte concentrations for two sets of data. One of these sets of data is the calibration set, and the other set is a prediction set.

The intensity values of the calibration set are pretreated, and are used as input for the multivariate model-developing software, together with the invasively-measured analyte concentrations. The software calculates, in the PLS technique, an initial set of factors, which make up an initial model. The initial model is then employed to obtain an analyte concentration from the prediction set infrared intensity values. This predicted value is then compared to the invasively-determined analyte concentration obtained simultaneously with the prediction set infrared intensity values. A person suitably skilled in the art of constructing PLS models then reviews and analyzes the factors of the initial model and makes appropriate adjustments, to develop an improved model. The techniques employed by a person skilled in the art of constructing multivariate statistical models are set forth in, for example, in Mark, Principles and Practice of spectroscopic Calibration (1992). After an acceptable model has been iteratively developed, the model is employed in analyzing real data to obtain analyte concentrations.

As an example, the foregoing technique was employed in developing an multivariate statistical model using data on glucose concentrations in the blood of rabbits. Infrared intensity data were obtained by performing non-invasive near-infrared reflectance, using a device according to the invention on the abdomen of a rabbit. Simultaneously with the reflectance readings, blood samples were taken, and glucose concentrations were obtained by a clinical glucose analyzer manufactured by Yellow Springs Instruments. Initially, readings were taken from the rabbit in a normal state. The rabbit then received an intravenous insulin injection, and further measurements were taken, to obtain sensed intensity values corresponding to lower glucose concentrations. The rabbit was then injected with a glucose solution, and a further set of reflectance and invasive measurements were taken, at elevated blood glucose concentrations. A final set of measurements were taken after the rabbit's blood glucose concentration had returned to normal.

Certain data obtained above were designated a calibration set, to be used in building the PLS model. Other readings were designated a prediction set, to be used for testing the model.

Referring to FIG. 2, there is shown the reflectance intensity vs. wavelength over a range of wavelengths from 1100 nanometers to 2500 nanometers, for 31 readings taken from the rabbit in the calibration set. These data were then pretreated by the data processor, to eliminate the effects of offset and drift. The spectra, after a step of pretreatment, are shown in FIG. 3. As can be seen, the 31 spectra are much closer together than in FIG. 2, indicating the relatively large magnitude of the effects of offset and drift. The method of pretreatment used to obtain the intensity vs. wavelength data of FIG. 3 is that of subtracting the mean of the whole spectrum from each data point in the spectrum and then dividing each data point by the standard deviation of the whole spectrum. This pretreatment step is known as mean-centering and variance scaling. However, it is believed that obtaining the nth derivative, and specifically the second derivative, of the intensity vs. wavelength function, will provide satisfactory results.

The data of FIG. 3 were then reformatted in a conventional manner and employed by a skilled analyst using NIS Systems PLS software, to develop a model. The model contains six factor loadings. Only the data obtained in the range from 1100 to 1900 nanometers were found useful. The six factor loadings are displayed graphically in FIGS. 4A through 4F.

This model was then tested against a prediction set of data, obtained simultaneously with the calibration set. The results of this test of the model of FIGS. 4A–4F is shown in FIG. 5. FIG. 5 illustrates calculated glucose concentrations versus actual glucose concentrations. It will be seen that, for higher glucose concentrations, results of very good accuracy were obtained. At lower glucose concentrations, certain readings were very accurate, while others, probably due to the effects of noise, were less accurate.

Referring to FIG. 6, there is shown the 6-factor PLS model of FIGS. 4A to 4F plotted with respect to wavelength on a single graph, giving weighted averages to each. By multiplying the pretreated absorbance at each wavelength by the value for that wavelength given in FIG. 6, and then adding the products of that calculation, one obtains the concentration value for the analyte. The values shown in FIG. 6 are known as weighting factors or calibration values.

While a preferred embodiment and preferred practice of this invention has been disclosed herein, many modifications thereof are feasible. This invention is not to be restricted except insofar as is necessitated by the spirit of the prior art.

What is claimed is:

1. A method of non-invasive determination of the concentration of at least one analyte in the blood of a mammal, comprising the steps of:

(a) projecting near infrared radiation on a portion of the body of the mammal, said radiation including a plurality of wavelengths;

(b) sensing the resulting radiation emitted from said portion of the body;

(c) deriving from the sensed resulting radiation a first expression for the magnitude of said sensed radiation as a function of wavelength of the sensed radiation;

(d) pretreating said first expression to minimize the influence of instrument offset and drift to obtain a second expression for the magnitude of said sensed radiation as a function of wavelength; and

(e) performing multivariate analysis of said second expression to obtain a value for the concentration of said analyte.

2. The method of claim 1, wherein said step of pretreating said first expression comprises the step of obtaining the nth derivative of said first expression.

3. The method of claim 1, wherein said step (e) comprises the step of using the technique of partial least squares.

4. The method of claim 1, wherein said step (e) comprises the step of using the technique of principal component analysis.

5. An apparatus for non-invasive determination of the concentration of at least one analyte in the blood of a mammal, comprising:

(a) means for projecting near-infrared radiation on a portion of the body of the mammal, said radiation including a plurality of wavelengths;

(b) means for sensing the resulting radiation emitted from said portion of the body;

(c) means for deriving from the sensed resulting radiation a first expression for the magnitude of said sensed radiation as a function of wavelength of the sensed radiation; and

(d) data processing means adapted to (i) pretreat said first expression to minimize the influence of instrument offset and drift to obtain a second expression for the magnitude of said sensed radiation as a function of wavelength and (ii) perform multivariate analysis of said second expression to obtain a value for the concentration of said analyte.

6. The apparatus of claim 5, wherein said data processing means is adapted to pretreat said first expression by obtaining the nth derivative of said first expression.

7. The apparatus of claim 5, wherein said data processing means is adapted to perform multivariate analysis of said second expression using the technique of partial least squares.

8. The apparatus of claim 5, wherein said data processing means is adapted to perform multivariate analysis of said second expression using the technique of principal component analysis.

* * * * *

EXHIBIT C

US005460177A

United States Patent [19]

Purdy et al.

[11] Patent Number: 5,460,177

[45] Date of Patent: Oct. 24, 1995

[54] METHOD FOR NON-INVASIVE MEASUREMENT OF CONCENTRATION OF ANALYTES IN BLOOD USING CONTINUOUS SPECTRUM RADIATION

[75] Inventors: **David L. Purdy**, Marion Center; **Perry Palumbo**, New Kingston; **Mark DiFrancesco**, Indiana, all of Pa.

[73] Assignee: **Diasense, Inc.**, Indiana, Pa.

[21] Appl. No.: **59,162**

[22] Filed: **May 7, 1993**

[51] **Int. Cl.**[5] **A61B 5/00**

[52] **U.S. Cl.** **128/633**; 356/39

[58] **Field of Search** 128/633–634, 128/664–667; 356/39–41

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,948,248	8/1990	Lehman	128/633 X
5,119,815	6/1992	Chance	128/665 X
5,187,672	2/1993	Chance et al.	128/633 X
5,213,105	5/1993	Gratton et al.	128/665 X
5,303,026	4/1994	Strobl et al.	128/665 X

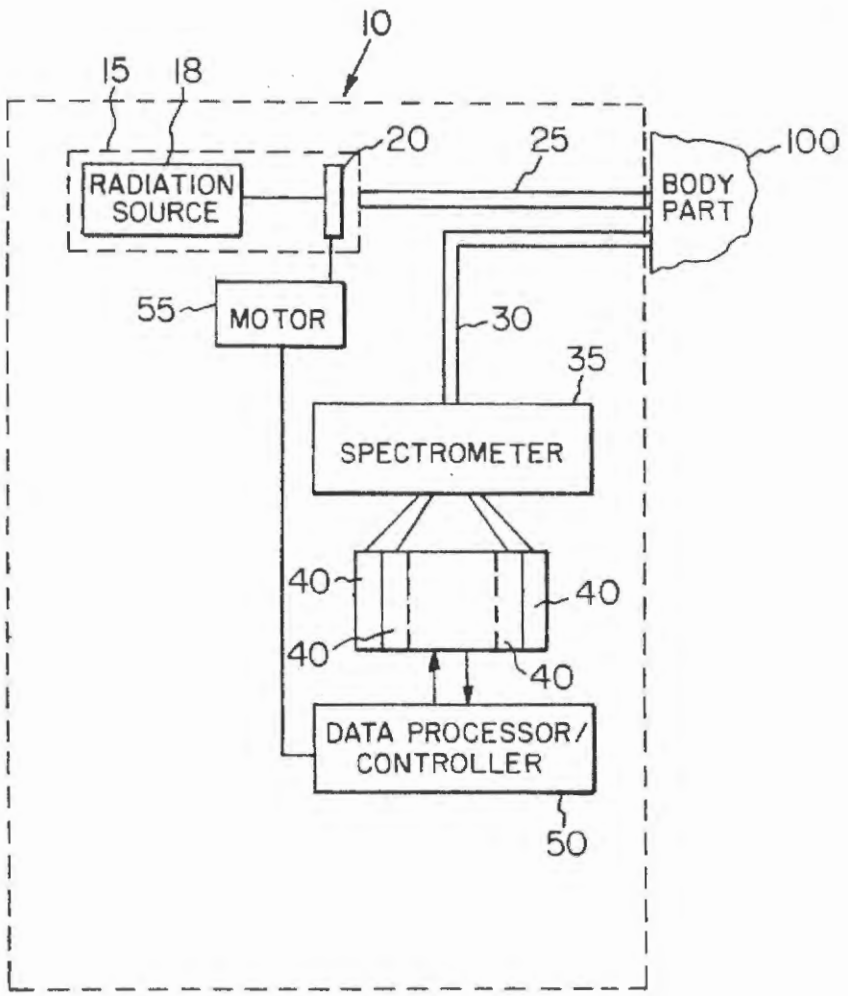
Primary Examiner—Angela D. Sykes

Attorney, Agent, or Firm—Webb Ziesenheim Bruening Logsdon Orkin & Hanson

[57] **ABSTRACT**

Method for non-invasive detection of the concentration of a constituent in blood of a living animal includes the steps of irradiating a body part of the animal with intensity-modulated radiation over a continuous spectrum; determining the intensity of radiation emitted from the body part at wavelength ranges within the continuous spectrum; and using the determined intensity to calculate the concentration of the constituent. A radiation source including a radiating bulb and a chopper for periodically interrupting radiation emitted from the bulb may be provided.

13 Claims, 1 Drawing Sheet



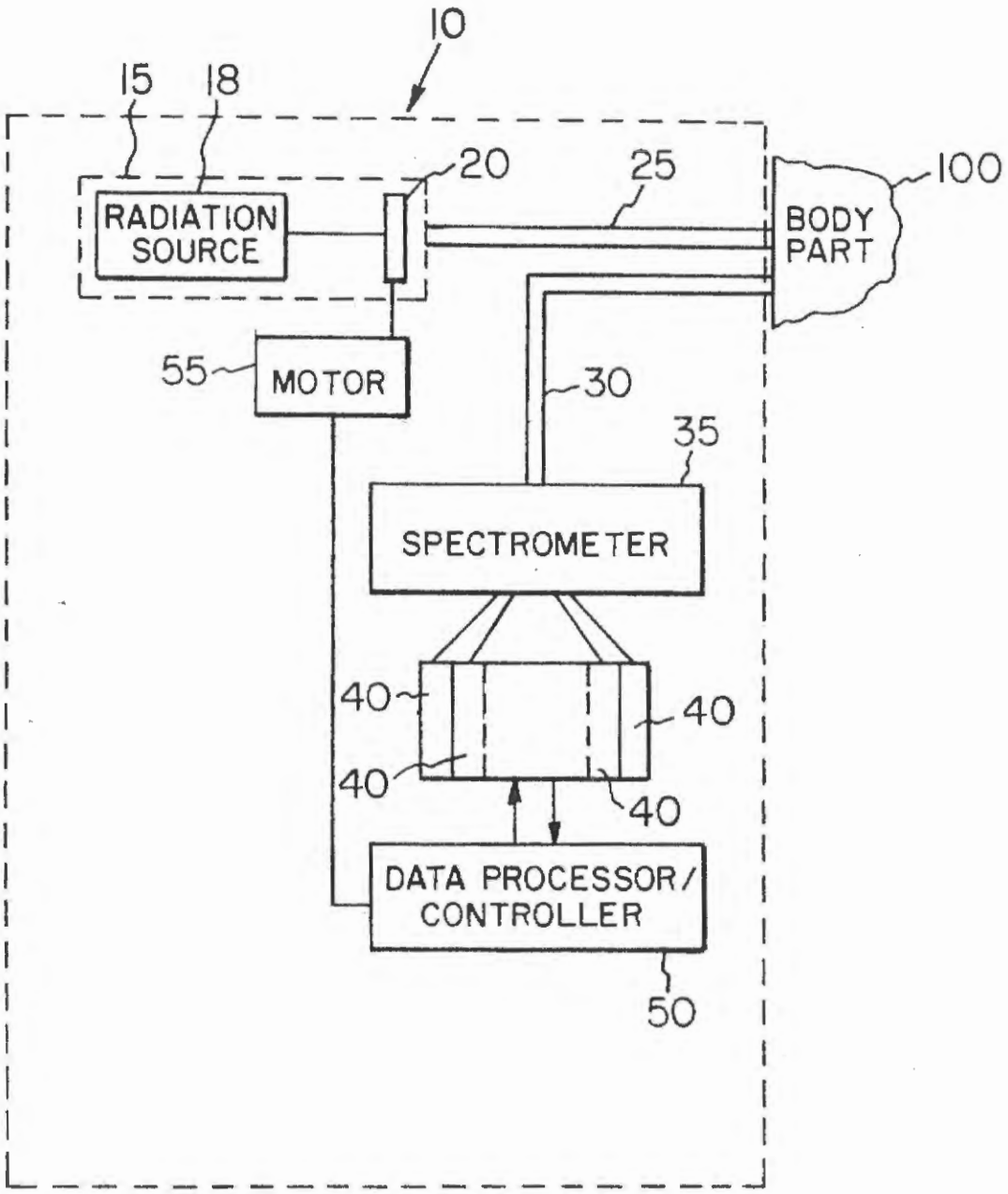

10
15
18
20
25
100
RADIATION SOURCE
BODY PART
55
MOTOR
30
35
SPECTROMETER
40
40
40
40
DATA PROCESSOR/ CONTROLLER
50

FIG. 1

METHOD FOR NON-INVASIVE MEASUREMENT OF CONCENTRATION OF ANALYTES IN BLOOD USING CONTINUOUS SPECTRUM RADIATION

BACKGROUND OF THE INVENTION

This invention relates to techniques for non-invasively detecting the concentration of analytes in the blood of living animals, and in particular to the use of continuous spectrum infrared spectroscopic techniques for the non-invasive detection of glucose concentrations in the blood of humans.

In the diagnosis and treatment of various conditions, it is important to measure the concentration of various constituents in the blood. For example, in the treatment of diabetes, the concentration of glucose in the blood must be measured on a periodic basis. For persons experiencing insulin-dependent or Type I diabetes, it is often necessary or desirable to measure blood glucose concentrations several times each day. Obtaining accurate readings of cholesterol concentrations is important in the prevention of coronary artery disease. The measurement of the concentration of other blood analytes, such as bilirubin and alcohol, is also important for various diagnostic purposes.

The accurate measurement of concentrations of such blood constituents, as it is now practiced, requires obtaining a blood sample, such as by pricking a finger. The obtaining of blood samples by invasive techniques, such as pricking the finger, is both painful and inconvenient. In the case of diabetics, the need to lance a finger several times a day to monitor glucose levels result in a buildup of scar tissue. Indeed, many diabetics are believed not to monitor their glucose levels as frequently as recommended because of the pain and inconvenience of the invasive method. The result of such a failure to monitor glucose levels is a greater risk of experiencing the long-term health effects of diabetes. These health effects include damage to the eyes, resulting in partial and often total loss of vision, as well as other serious health problems. Millions of individuals in the United States alone suffer from diabetes. As a result, the failure of an individual afflicted with diabetes reliably to monitor their glucose levels is a significant public health problem.

In order to provide an alternative to the existing invasive blood glucose monitoring techniques, non-invasive blood glucose detection techniques have been proposed. One such technique is the non-invasive continuous spectrum infrared spectroscopic technique. One example of such a technique is given in U.S. Pat. No. 5,070,874 (Barnes, et al.) In this technique, a portion of the patient's body is non-invasively irradiated with infrared radiation across a continuous spectrum. Radiation emitted from the body part, which radiation has been either transflected or transmitted, is then detected, to obtain signals representing the intensity of radiation at numerous wavelength ranges within the continuous spectrum. The signals are then processed to obtain an absorbance spectrum. Appropriate analytical techniques are applied to the detected absorbance spectrum in order to obtain a blood glucose level. Concentrations of other blood analytes may also be measured in this manner.

No device using the non-invasive infrared technique has achieved accuracy sufficient to match that of existing invasive techniques. A significant difficulty in obtaining sufficient accuracy is a low signal-to-noise ratio. Continuous-spectrum noninvasive techniques make use of radiation in the near-infrared portion of the spectrum. However, in this portion of the spectrum, the absorption of radiation by water

is very high. In addition, the concentrations of the analyte of interest in the bloodstream is typically low. As a result, the contribution of the analyte of interest to the signal intensity is only a relatively small change in the total signal intensity obtained by this technique. It has been found that detector noise is of the same order of magnitude as the change in intensity signal resulting from variations in analyte concentration. The variations in signal intensity as a result of variations in concentration of the analyte of interest are so small that, at intensities that have been used in the past, the detector's sensitivity may not be high enough to obtain sufficiently accurate readings.

A possible solution to this problem would be to increase the intensity of the radiation incident on the body part of the subject. However, an increase in the intensity of incident radiation increases the amount of energy absorbed by the body part. Increases in the energy absorbed by the body part result in greater heating of the body part the amount of heat produced. Excessive heating can cause discomfort and even burns to the subject, which obviously would be undesirable.

It is accordingly an object of this invention to provide a method for the continuous spectrum non-invasive spectroscopic detection of analytes in the bloodstream of living animals with increased signal-to-noise ratio.

Further objects and advantages of the invention will become apparent from the detailed description of a preferred embodiment which follows.

SUMMARY OF THE INVENTION

A method for non-invasive detection of the concentration of an analyte in the blood of a living animal includes the steps of irradiating a body part of the animal with intensity-modulated radiation over a continuous spectrum; detecting the intensity of radiation emitted from the body part at a plurality of discrete wavelength ranges within the continuous spectrum; and using the detected intensity to calculate the concentration of the blood analyte.

An apparatus for non-invasive detection of the concentrations of an analyte in the bloodstream of a living animal includes a source of intensity-modulated radiation over a continuous spectrum for irradiating a body part of the animal; detectors for detecting the intensity of radiation emitted by the body part at wavelength ranges within the continuous spectrum and providing an output signal representative of the detected radiation intensity; and an apparatus for calculating the concentration of the analyte from the detected intensity.

BRIEF DESCRIPTION OF THE FIGURE

FIG. **1** is a schematic representation of an apparatus for non-invasive detection of analyte concentration in the blood.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Referring to FIG. **1**, there is shown, schematically, an apparatus **10** for non-invasively detecting the concentration of an analyte in the bloodstream of an animal. Apparatus **10** includes radiation source **15** which emits intensity-modulated radiation over a continuous spectrum into an input end of incident optical fiber, or bundle of optical fibers **25**. An output end of optical fiber bundle **25** is coupled to body part **100**. Radiation source **15** preferably alternately repeatedly irradiates body part **100** for a selected interval and does not emit radiation for the selected interval. Radiation source **15**

includes a continuously-emitting radiation generator **18**, which is preferably a tungsten filament bulb. The temperature of the bulb and current provided to the filament of the tungsten filament bulb are preferably carefully controlled to obtain a constant radiation spectrum. Radiation source **15** also includes chopper **20**. Chopper **20** is interposed between radiation generator **18** and body part **100**, and preferably between radiation generator **18** and incident optical fiber bundle **25**. Chopper **20** alternately interrupts and non-interrupts radiation emitted by radiation generator **18**, thereby causing radiation emitted by radiation source **15** to be intensity-modulated, with the intensity vs. time having a square-wave pattern. Chopper **20** is preferably an arm on a pivot. Chopper **20** may also be a selected chopper wheel, such as is known in the art.

A source that provides radiation over a continuous spectrum provides radiation at every wavelength within a range, or at a large number of closely-spaced discrete wavelengths within a range. For example, to provide radiation over a continuous spectrum, at every wavelength within the range from 1100 to 2500 nanometers, a tungsten filament bulb may be used. Alternatively, there could be provided a large number of discrete wavelength radiation sources emitting simultaneously and separated in wavelength, preferably equally, across the spectrum. For example, there could be provided discrete wavelength radiation sources at intervals of about 10–15 nm, to provide radiation over a continuous spectrum.

Chopper **20** is driven by motor **55**. Motor **55** is controlled by data processor/controller **50**. Motor **55** drives chopper **20** to interrupt radiation from radiation generator **18** at a constant frequency. The frequency may be from about 250 Hz to about 1000 Hz, and in a preferred embodiment, the frequency is about 500 Hertz. The selected interval for which radiation source **15** alternately irradiates body part **100** and does not emit radiation is thus between about 1/500 seconds and 1/2000 seconds, and preferably about 1/1000 seconds. However, the frequency may be selected by those of skill in the art as desired. In the embodiment where chopper **20** is a motor-driven arm, motor **55** is preferably a synchronous, fixed frequency motor.

A portion of the radiation transmitted by incident optical fiber bundle **25** into body part **100** is emitted by body part **100** into pick up optical fiber, or bundle of optical fibers, **30**. Pick up optical fiber bundle **30** transmits radiation emitted from body part **100** to spectrometer **35**. Spectrometer **35** spectrally separates the radiation, and focuses the radiation on detectors **40**. Spectrometer **35** may be, for example, a unitary block of appropriate glass in a Czerny-Turner configuration. Detectors **40** may be, as is conventional in infrared and near-infrared detection, lead-sulfide detectors. A selected wavelength range within the continuous spectrum is focused by spectrometer **35** on each of detectors **40**. For example, detectors **40** may be 64 individual detectors, each covering a wavelength range of about 15 nanometers. Each one of detectors **40** produces an output electrical signal whose intensity represents the intensity of the detected radiation. Output electrical signals from detectors **40** are transmitted to pre-amplifier **45**. The portion of the signal representing radiation emitted from body part **100** has a known frequency as a result of pulsed or intensity-modulated radiation employed to irradiate body part **100**. At pre-amplifier **45**, appropriate electronic signal analytical techniques, particularly lock-in modulation techniques, are employed to isolate the portion of the signal which represents radiation emitted from body part **100**. Thus, noise, and in particular detector noise, can be filtered out from the signal. It will be understood that pre-amplifier **45** is controlled by data processor/controller **50**. After pre-amplifier **45** has removed at least a portion of the noise, the signal is transmitted to data processor/controller **50**. In accordance with conventional data processing techniques, data processor/controller **50** obtains an absorbance spectrum, showing absorbance plotted against wavelength.

Upon obtaining an absorbance spectrum, if calibrating apparatus **10**, the next step is to determine the analyte concentration in the blood in accordance with conventional invasive techniques. This step is performed by lancing a body part, such as a finger, to obtain a small quantity of blood, and then analyzing the blood in a high accuracy instrument. For example, in order to obtain the concentration of glucose invasively, an analyzer manufactured by Yellow Spring Instruments may be employed. The calibration of the instrument is preferably carried out by data processor/controller **50** using multivariate analytical techniques, employing as data input the absorbance spectrum obtained from the instrument, and the analyte concentration determined from analysis of the invasively-obtained blood sample.

It is also believed to be advantageous to use two absorbance spectra obtained at two different blood volume to tissue volume ratios. This may be done by taking two readings simultaneously at blood rich and blood poor portions of the skin, such as the inside of the wrist and the upper inside of the forearm, or by taking a first reading in a body part such as the finger or the ear lobe, and a second reading with the body part compressed to reduce the blood volume. In the technique either using two different blood volume to tissue volume ratios, or using only one non-invasive set of readings, the multivariate analytical technique may be the method of partial least squares. Various commercial software packages are available that will perform the computations required for partial least squares analysis. Such software packages include, for example, NSAS by NIR Systems of Silver Spring, Md., and Spectra Calc, Lab-Calc and GRAMS by Galactor Industries of Salem, N.H. Those of skill in the art of performing partial least squares analysis will be able to input properly the absorbance spectrum data and the analyte concentration determined from the invasively-obtained blood samples, in order to obtain a set of factors. The set of factors will, when multiplied by given spectrum, provide the concentration of the desired analyte in the blood.

In using the calibrated instrument to obtain an analyte concentration, data processor/controller **50** will, in accordance with conventional techniques, calculate the concentration of the analyte in blood, using the set of factors calculated during calibration of the instrument as discussed above. The concentration is preferably displayed on a suitable display, and may also be stored in an appropriate memory device. The detection step may employ either readings taken at a single blood volume to tissue volume ratio, or may employ readings taken at two different blood volume to tissue volume ratios.

It will be understood that an advantage of the present invention is the reduction in heating of body part **100** as a result of the irradiation of body part **100** with the continuous-spectrum pulsed radiation. In the illustrated embodiment, this is achieved by the location of chopper **20** intermediate radiation generator **18** and body part **100**. By locating chopper **20** intermediate radiation generator **18** and body part **100**, rather than, for example, intermediate body part **100** and detectors **40**, the time average radiation flux on body part **100** is reduced by one-half. Consequently, the

intensity of radiation incident on body part **100** may be increased by 100 percent, with no increase in time-average radiation flux and consequently no increase in heating effect. This increase in the intensity of incident radiation results in an increase in the intensity of radiation emitted from body part **100**. As a result, the signal-to-noise ratio is improved.

It will be understood that other techniques may be employed to obtain intensity-modulated incident radiation. For example, a radiation source **15** may be provided which can be continuously flashed to obtain a pulsed signal. However, flashing a tungsten-filament bulb, which is the preferred radiation source in the near-infrared, is not practical.

It will be appreciated that there are considerable variations that can be accomplished in a method and apparatus of the intention without departing from its scope. As a result, although a preferred embodiment of a method and apparatus of the invention have been described above, it is emphasized that the invention is not limited to a preferred embodiment and there exists other alternative embodiments that are fully encompassed within the invention's scope, which is intended to be limited only by the scope of the appended claims.

What is claimed is:

1. A method for non-invasive detection of the concentration of a constituent of blood of a living animal, comprising the steps of:

(a) irradiating a body part of the animal with intensity-modulated radiation over a continuous spectrum;

(b) detecting the intensity of radiation emitted from the body part at a plurality of wavelength ranges within said continuous spectrum; and

(c) using said detected intensity to calculate the concentration of the constituent.

2. The method of claim **1**, wherein said step (c) comprises using lock-in modulation techniques synchronized with the modulation of said radiation simultaneously in said step (a) to filter out noise.

3. The method of claim **1**, wherein said step (a) comprises repeatedly alternately irradiating and not irradiating the body part for a selected interval.

4. The method of claim **3**, wherein said selected interval is between about 1/2000 seconds and about 1/500 seconds.

5. The method of claim **1**, wherein said step (a) comprises providing a continuously emitting radiation generator and a chopper periodically to interrupt the irradiation of said body part by said radiation.

6. The method of claim **1**, herein said step (b) comprises focusing radiation emitted from the body part corresponding to each of said wavelength ranges on one of a plurality of detectors.

7. An apparatus for non-invasive detection of the concentration of an analyte in the bloodstream of a living animal, comprising:

(a) a source of intensity-modulated radiation over a continuous spectrum for irradiating a body part of the animal simultaneously over the continuous spectrum;

(b) a plurality of detectors for detecting the intensity of radiation emitted by the body part at a plurality of wavelength ranges within said continuous spectrum and providing an output signal representative of the detected radiation intensity; and

(c) means for calculating the concentration of the analyte from said detected intensity.

8. The apparatus of claim **7**, further comprising a preamplifier, for receiving said detector output signal and using lock-in modulation techniques synchronized with modulation of said radiation, to isolate the portion of said detector output signal which represents the radiation emitted from the body part.

9. The apparatus of claim **8**, wherein said source comprises a continuously-emitting lamp and a chopper positioned intermediate said lamp and the body part to periodically interrupt the irradiation of said body part.

10. The apparatus of claim **7**, wherein said radiation source alternately repeatedly emits radiation for a selected interval and non-emits for the selected interval.

11. The apparatus of claim **9**, wherein said selected interval is between about 1/500 seconds and 1/2000 seconds.

12. The apparatus of claim **7**, further comprising means for focusing radiation emitted from the body part at each of said wavelength ranges on one of said detectors.

13. The apparatus of claim **12**, wherein said focusing means comprises a spectrometer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,460,177

DATED : October 24, 1995

INVENTOR(S) : David L. Purdy, Perry Palumbo and Mark DiFrancesco

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 2 Line 18 after "part" insert --and--.

Column 5 Line 16 "intention" should read --invention--.

Claim 4 Line 44 Column 5 "between about 1/2000 seconds and about 1/500 seconds." should read --between about 1/500 seconds and about 1/2000 seconds.--.

Claim 6 Line 5 Column 6 "herein" should read --wherein--.

Claim 11 Line 36 Column 6 "claim 9," should read --claim 10,--.

Signed and Sealed this

Eleventh Day of June, 1996

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks