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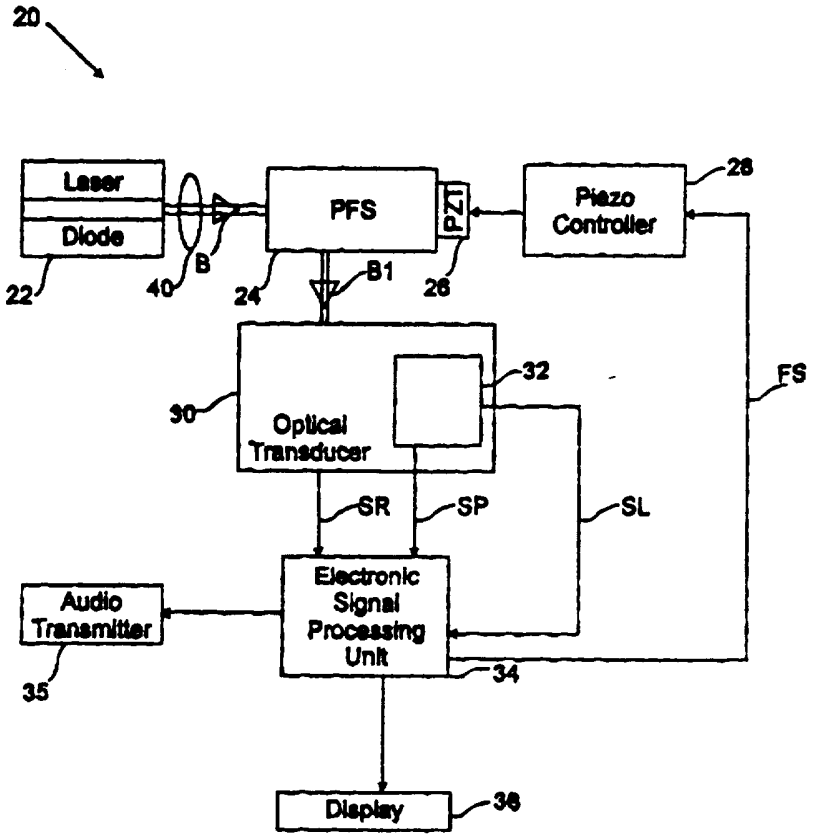
(54) Title: NON-INVASIVE BLOOD GLUCOSE MEASUREMENT

(57) Abstract

A method and apparatus for non-invasive measurement of blood glucose concentration based on producing a polarized-modulated laser beam, measuring a phase difference introduced, e.g., by a finger (F) or a ear lobule (E) of a subject, measuring the phase difference between a reference signal (SR) and a probe/measurement signal (SP, SM), and processing the obtained data which are then presented as blood glucose concentration. Apparatus includes an infrared laser source (22), a polarized frequency shifter (24) which produces a polarized-modulated infrared laser beam, a piezoelectric transducer (26) for driving the polarizing frequency shifter (24), and an optical transducer (30) with a glucose measuring head (32). The latter has an optical input for receiving the laser beam and a balanced receiver (62). The probe beam, after passing through the finger, is converted into a probe electrical signal, the reference beam is converted into a reference electrical signal, the probe and reference electrical signals are compared, and the obtained phase difference is processed by an electronic signal processing unit (34) which presents the results in the form of blood glucose concentration. Alternate embodiments based on measurement of circular dichroism caused by the presence of glucose in blood are included. The polarized frequency shifter may be crystal optic or fiber-optic based.



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NON-INVASIVE BLOOD GLUCOSE MEASUREMENT

Field of the Invention

The present invention relates to measuring the concentration of glucose, more particularly to the non-invasive, phase-sensitive measurement of the glucose concentration in blood.

Background of the Invention

As of 1992, more than ten million people in the United States of America suffer from diabetes (an increased level of glucose in the blood) and hypoglycemia (a reduced level of glucose in the blood). Individuals afflicted with either disease in a severe form typically perform an invasive blood glucose level analysis four or more times a day.

Invasive techniques require withdrawal of a blood sample from the patient each time an analysis is to be performed. An accurate laboratory blood analysis requires withdrawing from 5 to 10 ml of blood and analyzing it using a laboratory instrument designed for performing such a biochemical analysis. However, the results of the test often are not available for several hours, and sometimes days. In addition, the instruments necessary to perform such an analysis are expensive and require that the blood samples be taken and analyzed by trained technicians.

Another invasive technique, referred to as a "finger poke" or a "finger stick" uses an integrated, self-contained instrument that evaluates a much smaller blood sample (approximately 0.25 ml). The small blood sample is obtained by puncturing a finger with a small lancet. The sample is then placed on a chemically treated carrier and inserted

into the instrument. The finger poke devices normally provide the glucose concentration results in a few moments. However, they are still quite costly for private use, i.e., in the range of several thousand dollars.

More recently, portable finger poke instruments have become available which require the use of single use, disposable, chemically treated carrier "strips." Although the portable instruments have a relatively low cost (about $100 to $300 U.S.D.), the cumulative cost to diabetics for the normal supply of disposable carrier "strips" is considerable.

Invasive techniques for glucose analysis are problematic and suffer from poor patient compliance. Many people who would benefit from knowing their glucose concentration are reluctant to have blood withdrawn by a finger poke or a hypodermic needle or have a generalized fear of invasive medical procedures. Still others suffer anxiety in connection with the sampling and worry about the discomfort (pain) and possibility of infection. Another problem is that frequent invasive glucose testing uses up convenient sample sites and complicates further testing until the used convenient sites heal.

Non-invasive methods for measuring blood constituents, including glucose have been described. However, to date none of these techniques has resulted in a commercially useful instrument. The non-invasive monitoring methods are roughly divided into measurements based on either the intensity of light being transmitted through or reflected from the tissue, or the phase shift of modulated light transmitted through the tissue (the "phase-sensitive" measurement).

When light is transmitted through perfused tissue in vivo, e.g., through a patient's finger, it is differently absorbed by the various components illuminated, namely blood, with its many constituent parts, tissue (including protein, fat, water, cholesterol, etc.), cartilage, and

bone. The different components thus form an absorption spectrum for each wavelength. The total absorption of a given wavelength of light by all of the components is called "real absorption" and the absorption spectrum may vary for different wavelengths.

The known intensity sensing methods for measuring the level of a blood constituent, including glucose, are based on measuring a real absorption spectrum for blood perfused tissue at two or more different wavelengths, and subtracting therefrom the statistical absorption spectra for each of the various blood components, except for the one component being measured. It is assumed that after such subtraction, the remainder is a real spectrum of the constituent to be measured.

Rosenthal et al. U.S. Patent 5,086,229 refers to such a non-invasive, near-infrared quantitative analysis instrument for measuring blood glucose. The instrument contains a plurality of near-infrared laser sources having different wavelengths of emission and one or a plurality of photodetectors. A blood-containing part, e.g., a finger, is placed between the laser sources and photodetectors. The light sources are illuminated and the wavelengths then transmitted through the blood-containing part are detected. The real absorption spectrums obtained from the photodetector signals are compared with individual statistical absorption spectra of each constituent, which are stored in the memory of the instrument. A glucose level is derived from the comparison.

The intensity measuring instruments, including the Rosenthal instrument, suffer from the following disadvantages. First, because they measure intensity, the noise level of the measured signal is affected by components of the tissue other than blood, and variations in conditions such as background light, tissue temperature, ambient temperature, and the amplitude of the laser source. This results in a poor signal-to-noise ratio. Even the use of

the latest up-to-date low-noise electronics would not substantially improve this ratio.

Second, because the subtraction technique is based on statistically derived absorption data for each individual constituent, the results obtained are of necessity statistical. However, the differences between the actual glucose level in blood and the results of statistical measurements may be substantial and significant. In this regard, the absorption due to the glucose concentration is very small compared to other components such that statistical errors may be a greater component of the determined value than the actual glucose component.

The non-invasive phase sensitive measurement methods possess significantly higher sensitivity and a much higher signal-to-noise ratio than intensity-measurement methods. The higher sensitivity is the consequence of the noise sources affecting the amplitude, but not the phase, of a signal.

In phase sensitive techniques, an instrument compares a known reference signal, e.g., a sine wave, with a measurement signal that has been passed through the tissue. The measurement signal will have a time delay (phase shift) relative to the reference signal because of various factors, e.g., a fluorescence time delay, etc. Concentrations of blood constituents then may be obtained from a measurement of the time delay (phase shift).

Cote et al., "Noninvasive Optical Polarimetric Glucose Sensing Using A True Phase Measurement Technique," IEEE Transactions of Biomedical Engineering, Vol. 39, No. 7, July 1992, pp. 752-756 ("Cote") refers to passing linearly-polarized light through the anterior chamber of an excised human eye and determining the glucose level of the aqueous eye humor based on the phase shift between the reference signal and the measurement signal that was converted by the glucose. A helium-neon laser beam, coupled through a rotating linear polarizer along with two stationary linear

polarizers and two detectors, is used to produce reference and signal outputs. The polarizer was rotated by means of a synchronous electric motor. The amplitudes of these outputs varied sinusoidally with a frequency twice that of the angular velocity of the rotating polarizer. The phase difference of the outputs would be proportional to the rotation of the linear polarization vector passing through the anterior chamber of the eye.

One problem with the Cote apparatus is that it uses a synchronous motor which generates mechanical vibrations which cannot exceed, e.g., 200 Hz. Therefore, the frequency of rotation of the motor falls into the frequency range (1 Hz to 600 Hz) of mechanical vibrations produced by different sources, interferes with those mechanical vibrations, and produces high measurement noise. Consequently, the Cote technique can be implemented only under laboratory conditions where mechanical vibrations can be isolated, and is unsuitable for application in the form of a portable instrument for personal use.

Another problem with the Cote measurement system is that it is based on passing the light through the human eye. It is thus inconvenient for practical self-administration of the test. More important, however, is that the eye is subject to involuntary high-frequency movements (such as microsaccadic movements) which fall into the same frequency range as the rotating frequency of the driving motor of the system and have amplitudes of 1 to 3 min of arc. Should the apparatus be used in vivo, such involuntary eye movements would lead to interference with the measurement signals and would markedly increase the measurement noise.

Still another problem with the Cote system is that the axis of the synchronous motor can be fixed with respect to the direction of propagation of optical signals with an accuracy not exceeding several minutes of arc. This means that using the device requires that a calibration be carried out in real time.

Thus, there is a continuing need for improved non-invasive analytical instruments and methods that would provide essentially the same accuracy as conventional invasive blood glucose tests. There also is a need for non-invasive, low-cost methods and instruments for the measurement of glucose levels in diabetic or hypoglycemic patients. There also is a need for a durable, cost-effective, and environmentally conscious nondisposable apparatus for measuring blood glucose.

Summary of the Invention

It is, therefore, an object of the invention to overcome the disadvantages of existing non-invasive instruments and to provide improved methods and apparatus for the non-invasive phase-sensitive measurement of blood constituents such as glucose, based on phase-sensitive measurements.

It is another object to provide a portable, non-invasive blood glucose monitor that is suitable for personal use, at home or away, which obtains glucose level measurements through high-scattering (signal-depolarizing) tissue, operates in a frequency range beyond that of mechanical vibrations, and is not restricted for use with the eye.

Broadly, the invention concerns apparatus and methods for the non-invasive measurement of the concentration of a constituent in blood based on precision, phase sensitive and high signal to noise measurements.

One aspect of the invention is directed to methods and apparatus for producing a phase-modulated laser beam via a polarizing frequency shifter, measuring a phase difference introduced, e.g., by a finger or a ear lobule of a subject, measuring phase difference between a reference signal and a probe signal, and processing the obtained data which are then presented as blood glucose concentration. One such method is for the non-invasive precision phase sensitive

measurement of the glucose level in the blood and includes the steps of:

passing a beam emitted by an infrared laser beam source through a polarizing frequency shifter that is driven by a piezoelectric transducer and produces a polarized-modulated beam having a direction of polarization rotating in the plane of polarization with a frequency of rotation falling into a frequency range beyond that of mechanical vibrations;

passing the polarized-modulated beam through an optical transducer which splits the polarized-modulated beam into a reference optical beam and a probe optical beam;

passing the probe optical beam through a blood-carrying body part to form a passed probe optical beam, the above-mentioned optical transducer having a first sensor for measuring the reference optical beam and converting it into a reference electric signal having a phase corresponding to the polarized-modulated optical beam, and a second sensor for measuring the passed probe beam and converting it into a probe electric signal having a phase corresponding to the passed probe beam, the second sensor preferably being made in the form of a balanced receiver, the balanced receiver having means for dividing the passed probe optical beam into a polarized component and a depolarized component, and means for determining a scattering-free probe electric signal having a phase from the balanced receiver;

determining a phase difference between the reference electric signal and the probe electric signal; and

converting the phase difference into information relating to the concentration of glucose.

The phase difference is preferably measured by subtracting the phase of reference electric signal from the phase of the scattering-free probe electric signal. The blood-carrying body part may be any well perfused tissue in which blood vessels are distributed with high density such as an appendage, e.g., finger, earlobe, toe or bridge of the nose. In the case of a measurement carried out with a finger, the laser beam is preferably transmitted through the nail-bed, which is especially concentrated with blood vessels.

One such apparatus, disclosed herein, includes a polarizing frequency shifter which is based on the use of bulk optics (crystal optics). Although satisfactory, it is relatively expensive and cannot be easily produced in small dimensions because its polarizing frequency shifter cannot be manufactured in an integrated-optic implementation. Hence, the present invention also is directed to an improvement of the bulk optics methods and apparatus disclosed herein, namely, the non-invasive phase-sensitive measurement of blood glucose level which is small in size and can be produced in integrated-optic implementation.

Thus, another aspect of the invention is directed to a method and apparatus for the non-invasive precision phase sensitive measurement of the glucose level in the blood using integrated fiber optics. One such method includes the steps of:

passing a beam emitted by an infrared laser beam source through an optical phase modulator that is fiber-optic based and driven by a piezoceramic transducer and produces two polarized-modulated beams, each having a direction of polarization rotating in the plane of polarization with a frequency of rotation falling into a frequency range beyond that of mechanical vibrations, as a reference optical beam and a measurement optical beam;

passing the measurement optical beam through a blood-carrying body part to form a passed measurement optical beam;

measuring the reference optical beam and converting it into a electrical reference signal having a phase corresponding to the polarized-modulated optical beam;

measuring the passed measurement optical beam and converting it into a electrical measurement signal having a phase corresponding to the passed measurement beam, preferably using a balanced receiver having means for dividing the passed measurement optical beam into a polarized component and a depolarized component, and determining a scattering-free probe electric signal having a phase from the balanced receiver;

determining a phase difference between the reference electric signal and the probe electric signal; and

converting the phase difference into information relating to the concentration of glucose.

One such apparatus includes:

a laser beam source;

an optical phase modulator including a polarizer, an optic-fiber system that has an input coupler that couples the polarized laser beam into two polarization preserving fiber-optic conductors, a phase shifter that strains one of the fiber-optic conductors to modulate the beam propagating therein, an output optical coupler that recombines and coherently mixes the phase modulated beam and the unmodulated beam and then couples the combined beams into the outputs of the two fiber-optic conductors, a quarter-wave plate structure that converts the respective outputs of the two fiber-optic conductors into a polarized-modulated reference beam and a measurement beam;

a glucose measuring head that has an aperture to receive a blood-carrying tissue and a balanced receiver which receives the measurement optical beam after it passes through the tissue and produces an electrical measurement signal corresponding to the phase shift due to optical interaction with glucose in the blood; and

an electronic signal processing unit that converts the phase difference between the balanced receiver output and the reference beam into a measurement of the glucose concentration.

The phase difference is preferably measured by subtracting the phase of reference electric signal from the phase of the scattering-free probe electric signal. The blood-carrying body part may be any well perfused tissue in which blood vessels are distributed with high density such as an appendage, e.g., finger, earlobe, toe or bridge of the nose. In the case of a measurement carried out with a finger, the laser beam is preferably transmitted through the nail-bed, which is especially concentrated with blood vessels.

Other aspects of the invention are directed to the various methods and apparatus described in the following descriptions and their combinations.

Brief Description of Drawings

The above and other objects and advantages of the invention will be apparent upon consideration of the following detailed description taken in conjunction with the accompanying drawing, in which like reference characters refer like parts throughout, and in which:

Fig. 1 is a block diagram of an apparatus in accordance with a preferred embodiment of the present invention;

Fig. 2 is a schematic structural view of the polarizing frequency shifter of Fig. 1 for measuring polarization rotation angle;

Fig. 3 is a graph illustrating the rotating vector of polarization in the plane of travel;

Figs. 4 is a schematic structural view of the optical transducer of Fig. 1;

Figs. 4A and 4B are partial structural views of Fig. 4 showing the calibration cell cartridge in different positions;

Fig. 5 is a block diagram of the balanced receiver of Fig. 4;

Fig. 6 is a schematic structural view of an embodiment of a built-in glucose measuring head of Fig. 1;

Fig. 6A is a schematic structural view of another embodiment of a remotely-located glucose measuring unit of Fig. 1;

Fig. 6B is a schematic structural view of another embodiment of a glucose measuring head of Fig. 1;

Fig. 7 is a block diagram of the electronic signal processing unit of Fig. 1;

Fig. 8 is a graph illustrating a calibration procedure;

Fig. 9 is a schematic structural view of the polarizing frequency shifter in accordance with a second embodiment of the present invention;

Fig. 10 is a block diagram of the balanced receiver for operation in conjunction with polarizing frequency shifter of Fig. 9;

Fig. 11 is a block diagram of a third embodiment of the present invention utilizing direct frequency modulation of a laser diode;

Fig. 12 is a schematic structural view of a polarizing frequency shifter of Fig. 11;

Fig. 13 is a block diagram of an apparatus in accordance with an alternate preferred embodiment of the present invention;

Fig. 14 is a schematic structural view of the optical phase modulator of Fig. 13;

Fig. 15 is a perspective view of a section of the phase shifter of Fig. 14;

Figs. 16a, 16b, and 16c are graphs illustrating the positions of axes of polarization with respect to an X-Y reference coordinate plane at three locations in the optical phase modulator of Fig. 14, namely at the optical polarizer output, in a first arm of the phase modulator, and in a second arm of the phase modulator, respectively; and

Fig. 17 is a block diagram of the electronic signal processing unit of Fig. 13.

Detailed Description of the Invention

Embodiment of Non-Invasive Apparatus and Methods with Polarizing Frequency Shifter for Measuring Polarization Rotation Angle

A preferred embodiment of a non-invasive apparatus in accordance with the present invention is shown in Fig. 1. The apparatus, which is designated in general by reference numeral 20, including a light source 22, a polarized frequency shifter ("PFS") 24, an optical transducer unit 30, an electronic signal processing unit 34, and optionally, one or both of an audio transmitter 35 and a visual display device 36.

Visual display device 36 may be a conventional liquid crystal display or a paper printer. Audio transmitter 35 may be a speaker (or microphone transducer) that indicates audibly the measured value (and, optionally, some indication of the range of normal values) for visually-impaired individuals. In the drawings, optical signals are shown by double lines and electrical signals are shown by single lines.

Light source 22 is preferably a laser source which produces a laser beam, more preferably a laser diode. Laser source 22 has a power-supply unit (not shown) and a collimating lens 40 which produces a collimated optical beam B (1 to 3 mm) with low divergence. The wavelength range is selected to correspond to a known wavelength range that

includes a peak of the optical rotation characteristic of the component to be measured. For measuring blood glucose, laser source 22 operates in the wavelength of 750 to 1000 nm, e.g., 850 nm (the near-infrared range) and preferably with a low-noise intensity and phase variation. One such laser diode is available from Spectra Diode Labs, San Jose, California. It should be understood that other light sources and other wavelength ranges corresponding to other optical activity peaks for glucose (and similar peaks for other blood constituents) could be used.

PFS 24 receives collimated optical beam B and has a piezoelectric transducer ("PZT") 26, which is controlled by a piezoelectric controller 28. Piezoelectric controller 28 is a conventional circuit that generates a modulating signal, e.g., a sawtooth or triangular waveform at a selected frequency f, preferably responsive to a feedback control signal FS from electronic signal processing unit 34 (as described below), and causes PZT 26 to vibrate accordingly. PZT 26 is used to impart a phase modulation to a component of optical beam B and PFS 24 produces a linearly polarized-modulated optical beam B1 having a direction of polarization which rotates in the plane of polarization, which is perpendicular to the direction of its propagation with a frequency equal to one-half that of PZT 26. Optical beam B1 is sent to optical transducer 30.

Optical transducer 30 receives optical beam B1 and produces a reference electric signal SR corresponding to the phase of optical beam B1, a polarized electric signal SP corresponding to the phase of optical beam B1 after it has passed through blood-carrying tissue, which includes a phase shift introduced by glucose (described in detail below), and an electric signal SL, having an amplitude proportional to the thickness of the measured blood-carrying tissue, e.g., a finger. Optical transducer 30 also includes a glucose measuring head 32 which receives the blood-carrying tissue to be measured. Head 32 may be either securely attached to

optical transducer 30 (shown in Fig. 1) or physically disconnected from optical transducer 30 for remote use and coupled to transducer 30 by an optical fiber (shown in Fig. 6A).

Electronic signal processing unit 34 is connected to optical transducer 30, receives electric signals SR, SP, and SL and provides feedback signal FS. Unit 34 processes signals SR and SP and produces a measurement phase difference signal SΘ. The measurement signal phase difference Θ_M is then taken together with signal SL and calibration data (which provides information regarding the effective thickness of the blood-carrying body) and converted into information about the glucose concentration. The information may be displayed, e.g., in a decimal digital form on visual display 36, which is connected to electronic signal processing unit 34. Feedback signal FS is used to provide a linear motion of piezoelectric transducer 24 with a fixed frequency f and to avoid hysteresis.

Because in many cases people suffering from diabetes have poor vision, signal processing unit 34 also (or alternatively) may be connected to audio transmitter 35 having an audio output AO (see Fig. 6B). Audio transmitter 35 may repeat the glucose information in an audible form, e.g., by synthesized speech as is conventionally used in the telecommunications field.

Referring to Fig. 2, a preferred structure of PFS 24 includes a polarized-beam splitter cube (hereafter referred to as "PBSC") 42 which has an optical beam input side 42a and an optical beam output side 42b. PBSC 42 splits beam B, which can be unpolarized, into two optical beams BSP and BPP, preferably with a 50/50 ratio. Optical beams BSP and BPP are polarized and have orthogonal (mutually perpendicular) directions of polarizations. Optical beam BSP is a so-called S-polarized beam having a polarization direction which is perpendicular to the plane of incidence (i.e., to the plane of the drawing). Optical beam BPP is a

so-called P-polarized beam, having a polarization direction which is in the plane of incidence (i.e., in the plane of the drawing).

Located on two adjoining sides of PBSC 42 are quarter-wave plates 44 and 46, respectively. A quarter-wave plate is a well known optical element that introduces a phase delay equal to a quarter of the wavelength and which is characterized by a fast axis and a slow axis. Each quarter-wave plate 44 and 46 has an orientation of the direction of their fast axes so that they form a 45° angle with respect to the polarization direction of optical beams BPP and BSP.

Although in Fig. 2 plates 44 and 46 are illustrated separated from PBSC 42, in the actual construction of PFS 24 they may be cemented or bonded to the respective sides of PBSC 42. Mirrors 48 and 50 are respectively located outwardly of, and spaced distances L48 and L50 from the center C of PBSC 42. The difference between distances L48 and L50 is maintained at a value less than the coherent length of laser diode 22. In order to achieve a desired accuracy on the order of a few millidegrees, it is desirable that the above mentioned distance difference be less than 1.0 mm.

One of the mirrors, e.g., mirror 50, is attached, e.g., cemented to PZT 26. PZT 26 is operated at selected frequency f that is sufficiently high to not be affected by mechanical vibration frequencies, which are typically less than 600 Hz, and sufficiently low to measure a phase shift on the order of ones of millidegrees (e.g., 3 millidegrees). A suitable frequency range is 650 Hz to 15 kHz. A preferred frequency range is selected from between 700 Hz and 5 kHz.

Located on optical beam output side 42B of PBSC 42, is a quarter-wave plate 52 which has its fast axis parallel to that of quarter-wave plate 44. Plate 52 is preferably secured to PBSC 42.

In operation, the S-polarized beam BSP reflects off mirror 48, passes back through center C and exits side 42B

of PBSC 42. The P-polarized optical beam BPP reflects off vibrating mirror 50 and becomes phase-modulated, and passes back to center C of PBSC 42 where it is reflected through side 42B and combined with the reflected optical beam BSP. The combined or composite reflected optical beams BSP and BPP then pass through quarter-wave plate 52 to provide polarized-modulated optical beam B1.

The output optical beam B1 of PFS 24 is a vector $\vec{E}$ which is defined by an angle ϕ and an amplitude E_o, as described below, and which is illustrated as beam $\vec{E}(t)$ in Fig. 3. Fig. 3 illustrates an X-Y coordinate system and a vector $\vec{E}$ of polarization which rotates in the plane XY with a frequency f/2. Angle ϕ is an angle of rotation of vector $\vec{E}$, which varies with frequency f/2. Angle ϕ is determined by the following formula:

$$\vec{E}(t) = E_o \vec{e}(t)$$
$$\vec{e}(t) = \vec{e}_x \cos\phi + \vec{e}_y \sin\phi$$
$$\phi = \phi_o + \pi f t$$

where ϕ_o is a constant phase shift caused by the difference in the path lengths L48 and L50 between center C of PBSC 42 and respective mirrors 48 and 50, vector $\vec{e}(t)$ is a single vector of polarization, vectors $\vec{e}_x$ and $\vec{e}_y$ are single coordinate vectors which show the directions of the coordinate axes, and E_o is an amplitude of laser beam B. As will be explained below, the phase of the polarized-modulated optical beam B1, and the phase shift introduced by the glucose concentration, can be recovered by using the reference polarizer 58 (Fig. 4) and the measuring polarizer 68 in the balanced receiver 62 (Fig. 5).

Referring to Figs. 4, 5, and 6, optical transducer 30 includes an optical beam splitter cube 54 which has an optical beam input side 54a, a reference optical beam output side 54r, and a measurement optical beam output side 54m. It preferably has a ratio of 50/50, i.e., it is a

conventional optical element which splits an input optical beam, namely optical beam B1, into two mutually-perpendicular components, namely optical beams BR and BP with a 50:50 ratio. The one optical beam BR is passed through a reference channel including a neutral-density attenuator 56, a polarizer 58, and a photodetector 60. Attenuator 56, polarizer 58, and photodetector 60 are arranged on an axis with optical beam BR, spaced sequentially from reference optical output side 54r, as illustrated in Fig. 4. In as much as optical beam BR is used to provide a reference phase measurement, its intensity may be attenuated by attenuator 56 to optimize recovery of the phase portion of the optical beam. The attenuation may be on the order of 40-80%. Polarizer 58 is used to recover the reference signal phase information. Photodetector 60 produces electrical signal SR having a phase modulation corresponding to the reference optical beam BR.

A cartridge 59 is placed between attenuator 56 and polarizer 58 for calibration purposes. Cartridge 59 contains two reference cells 59a and 59b and a transparent window 61. Cell 59a contains a first concentration C_1 of a glucose solution and cell 59b contains a second concentration C_2 of a glucose solution. Each cell has an equal optical pathlength (i.e., the length through which optical beam BR passes), e.g., 1.0 cm. Window 61 has the same construction as cells 59a and 59b except that it is empty. Alternatively, window 61 may be an aperture.

In this embodiment, cell 59a, transparent window 61, and cell 59b are linearly arranged on a sliding structure with window 61 located between cells 59a and 59b. Cartridge 59 may be shifted from the "central" position, illustrated in Fig. 4, in the direction of either arrow A_1 or arrow A_2 to the positions respectively shown in Figs. 4A and 4B. The movement may be manual or automatic under control of microcontroller 116. In Fig. 4, cartridge 59 is in the central position and optical beam BR passes through window

61. In Fig. 4A, cartridge 59 is shifted so that optical beam BR passes through cell 59a. In Fig. 4B, cartridge 59 is shifted so that optical beam BR passes through cell 59b. It should be understood that other configurations for window 61 and cells 59a and 59b could be used, e.g., cells and window spaced about an axis so that cartridge 59 can be rotated from one position to the next.

The other optical beam, probe optical beam BP, is passed through glucose measuring head 32 to balance receiver 62, which are sequentially located on measurement optical output side 54m of beam splitter cube 54. Probe optical beam BP is passed through the glucose measuring head 32 which may contain the object being measured, e.g., a blood carrying body part (tissue) such as a patient's finger F and produces a passed probe optical beam illustrated in Figs. 4 and 5 as beam BP1. Optical beam BP1 contains a polarized component which carries phase shift information related to the glucose concentration and a depolarized scatter component which does not carry such glucose related information. These components are collectively illustrated as optical beam BP1 in Fig. 5. More specifically, the transmission of optical beam BP through blood-carrying body F changes the direction of polarization of optical beam BP. This introduces a phase shift θ_M with respect to reference optical beam BR. Furthermore, the transmission of optical beam BP through finger F is accompanied by the depolarization of part of optical beam BP, which is caused by the scattering of the optical beam in the finger. The depolarized component of optical beam BP1 has a time-constant average intensity and does not contain any information about the phase shift. Therefore, this component of the passed optical beam contributes only to the noise level of the signal. Typically, less than 5% of optical beam BP1 remains polarized after passage through the blood-carrying body. However, because only the polarized component of optical beam BP1 produces an AC signal, that

remaining 5% is sufficient data and may be used to recover the polarized signal.

Balanced receiver 62 functions to subtract out electronically the depolarized portion of the optical signal and to leave only the polarized component. It has as its output a probe electric signal SP corresponding to the polarized component of passed probe optical beam BP1.

The structure of a balanced receiver 62 in accordance with a preferred embodiment of the invention is shown in Fig. 5. Receiver 62 includes a beam-splitter plate 64 with a 50:50 splitting ratio. Beam splitter plate 64 receives passed probe optical beam BP1 and divides optical beam BP1 into two equal components BP1-A and BP1-B. One of these components is converted into a polarized component. In this regard, located on the path of optical beam component BP1-A are a polarizer 68 and a photodetector 70. The other component is used as a depolarized component. In this regard, located on the path of optical beam BP1-B is a photodetector 72. Photodetectors 70 and 72 are preferably identical and matched and produce polarized component electric signal S-A and depolarized component electric signal S-B on their respective outputs. Electrical signal S-A also is referred to as the polarized electric component. Electric signal S-B also is referred to as the depolarized electric component.

Balanced receiver 62 also includes a difference amplifier 74, a low-pass filter 76, and a division amplifier 78. Output electric signals S-A and S-B of photodetectors 70 and 72 are directed to the inputs of difference amplifier 74. The output of difference amplifier 74 is connected to an input of division amplifier 78. Low-pass filter 76 is located between photodetector 72 and division amplifier 78 and passes the DC signal components of signal S-B. The other input to division amplifier 78 is the low pass filtered output of photodetector 72. The signal SP output

of division amplifier 78 is the ratio of its inputs and provides probe electric signal SP.

One embodiment of the structure of glucose measuring head 32, in which an object, such as finger F, is inserted into an object-receiving recess, is shown in Fig. 6. Unit 32 includes a housing 80 which has a central cavity 82, a spring-loaded axial stop element 84, a side opening 85, and a spring-loaded pressure element 88 having a compression spring 86. Housing 80 also has a second side opening 90 that is closed with a glass plate 92. Central cavity 82 serves to receive a finger F as a measuring object. Opening 90 serves for directing optical beam BP onto a nail bed NB of finger F. Axial stop element 84 serves to adjust the position of finger F so that optical beam BP intersects nail bed NB. Pressure element 88 is intended for the fixation of finger F during measurement and for increasing the amount of blood in the measured portion of finger F. An increase in the amount of blood in the measured portion of finger F reduces the scattering of the light transmitted through finger F and increases the signal-to-noise ratio of the measurement.

On the side of finger F opposite to nail bed NB of finger F, housing 80 has a recess 94 accommodating balance receiver 62. Beam-splitter plate 64 of balance receiver 62 is located on the side of finger F opposite to nail bed NB, i.e., on the side of digital pulp DP of finger F. Beam-splitter plate 64 is protected by a glass plate 96.

Recess 94 also contains a sensor 98 which determines the thickness of finger F in the portion being measured and which generates the above-mentioned signal SL. Sensor 90 may be a capacity-type or a resistor-type sensor capable of determining variations in the capacity or in the resistance between the conditions as they are in the absence of finger F and once finger F has been inserted.

Referring to Fig. 6A, another embodiment of glucose measuring head 32A is shown. This embodiment is located

remotely from optical transducer 30 and is connected to it through a polarization-preserving fiber-optical link 100. In this case, a ferrule 102 is inserted into side opening 90 and supports a GRIN rod microlens ("GRIN lens") 104. GRIN lens 104 is a gradient index lens which has an index of refraction which varies in a predetermined relationship with the thickness of the lens. It is intended to produce an output optical beam BP in a collimated form at the output of optical fiber 100. This is used because optical beam BP loses its collimation properties when it is transmitted through optical fiber 100. Polarization preserving optical fibers and GRIN lenses are commercially available products. The remaining parts of unit 32A are the same as those of unit 32 shown in Fig. 6.

Referring to Fig. 6B, an embodiment of glucose measuring head 32B for using a patient's earlobe E as the blood-carrying body is shown. In this embodiment, glucose measuring head 32B is attached to a head appliance 106 such as an arc-shaped head holder or band or a head band or of the same type as are used in conventional head sets including earphones for supporting microphones on the head of a wearer. Head appliance 106 supports a speaker/microphone 35 for reproducing audio information about the glucose concentration, which is provided by suitable circuitry (not shown) associated with signal processing unit 34. Preferably, speaker/microphone 35 is supported at one end of head appliance 106. Head appliance 106 also supports a U-shaped clip 101 which, in turn, supports glucose measuring head 32b and which can be attached to earlobe E of the patient. One side of clip 101 holds a GRIN rod lens 104b with an optical fiber link 100b while the other side of clip 101 holds a balance receiver 62 with a thickness sensor (not shown). Structurally, GRIN rod lens 104b, balance receiver 62, and the sensor of the embodiment of Fig. 6B may be the same as those of Fig. 6a.

Referring to Fig. 7, electronic signal processing unit 34 includes a phase-sensitive homodyne receiver 114, which receives the reference electric signal SR and the probe electric signal SP and produces on its output an electric signal SΘ which is proportional to a blood glucose concentration, a microcontroller 116, which processes signal SΘ in order to convert it into a glucose-concentration signal S_G, and an analog-digital (A/D) converter 118 which receives, e.g., signal S_G and converts it into digital information C_G. The output of A/D converter 118 is passed to display 36 for displaying the obtained information about the concentration of glucose in the blood.

Phase-sensitive homodyne receiver 114 is a device which determines the phase difference between signals SR and SP. It may operate based on either a lock-in amplifier technique or a time-interval counter operating in a phase mode, in accordance with conventional techniques. One useful phase-sensitive homodyne receiver, with a resolution of 0.001° in phase difference, is available from Stanford Research Systems, Inc., Sunnyvale, CA.

Electronic signal processing unit 34 also contains a memory unit 115 which is connected to microcontroller 116 and which may store data required for custom calibration of apparatus 20, patient's measurement data, etc.

In order to exclude the effect of statical phase shift Θ_o, which may occur because of temperature (ambient or sample) variations, misalignment in the optical system, imperfect optics (designed not exactly for the given wavelength), etc., each measurement procedure preferably begins with calibration of apparatus 20. For this purpose, prior to actual measurement on the object, a reference calibration procedure is carried out by first passing optical beam BR through transparent window 61 (Fig. 4) and then sequentially through cells 59a and 59b. Ideally, the calibration procedure using cells 59a and 59b can be omitted. However, for manufacturability and use over long

periods of time, e.g., months and years, frequent calibration is desired for continued accuracy.

For the calibration, cells 59a and 59b are sequentially shifted (in any order) into the positions shown in Figs. 4A and 4B in which they alternatively interfere with the optical path of optical beam BR. The calibration procedure is the same as measuring the glucose concentration in object F, except that no tissue is inserted in measuring head 32, the meanings of signals SR and SP are reversed, and signal SL is not used because the sample cell path length is known, i.e., 1 cm. The details of the propagation of the optical beams and processing of the obtained information is discussed below with reference to the measurement of glucose in blood carrying body part F.

Both cells 59a and 59b contain glucose solution samples of different known glucose concentrations C_1 and C_2. The results of the calibration measurement will thus produce two points in a relationship between a reference phase difference θ_R (per 1 cm of the pathlength) and glucose concentration C_G. This is shown in Fig. 8. The results of the calibration are shown by the curve labelled D in Fig. 8. From this reference calibration, one can obtain statical phase shift θ_o per 1 cm of pathlength. It should be understood that cells 59a and 59b alternatively may contain or comprise some optically active material (in any state), other than two different solutions of glucose, which have the same effects on the polarized-modulated laser beam as do the glucose solutions at two different known concentrations, but have a longer useful life than solutions of glucose.

In measuring tissue F, however, the phase shift θ_M between probe electric signal SP and reference electric signal SR will depend on many factors, including effective pathlength L_{EFF} for beam BP. Effective length L_{EFF} is only that part of the optical path of beam BP which is passed only through the blood-filled portion of the measurement object and differs from actual thickness of the finger.

Therefore, in order to obtain the glucose-concentration information from the results of measurement, it is necessary to subtract all extraneous data.

Phase shift θ_M may be generally expressed by the following formula (1):

$$\theta_M = \alpha_{GL}\ C_{GL}\ L_{EFF} + \theta_{SUB} + \theta_O \qquad (1)$$

where θ_{SUB} is a phase shift introduced by other blood components which also are optically active, i.e., subject to optical rotation at the wavelength of light used, and α_{GL} is a known optical parameter which, for a given wavelength, may be obtained from spectroscopy data.

Each subject, however, has θ_{SUB} which is constant in time and does not depend on the changes in the glucose concentration. This parameter and effective path-length L_{EFF} may be obtained based on two (or more) measurements taken at different glucose concentrations for which the glucose concentrations are obtained by a conventional invasive procedure (e.g., a finger poke measurement, laboratory analysis, or other biochemical analysis method, preferably on the basis of finger poke measurements). For this purpose, the concentration of glucose is measured at least twice: for example, once on an empty stomach and once an hour after administration of a concentrated solution of dextrose (or any other substance which raises the blood glucose level). These calibrating measurements need be performed only once for each person, prior to using the apparatus for the first time, as part of a start-up calibration procedure. The results of such two calibrating measurements may be expressed by the following formulae (2.1) and (2.2):

$$\theta_{M1} = \alpha_{GL}\ C_{GL1}\ L_{EFF} + \theta_{SUB} + \theta_O \qquad (2.1)$$

$$\theta_{M2} = \alpha_{GL}\ C_{GL2}\ L_{EFF} + \theta_{SUB} + \theta_O \qquad (2.2)$$

where C_{GL1} and C_{GL2} are the measured concentrations of glucose and θ_{M1} and θ_{M2} are the phase shifts measured by apparatus 20 at approximately the same time that the two glucose samples are obtained, respectively. These values are introduced into and stored in memory unit 115. The more calibration measurements that are made during the one-time start-up calibration procedure, the more accurate the calibration information will be.

From formulae (2.1) and (2.2), effective length L_{EFF} can be expressed as follows:

$$L_{EFF} = \frac{\theta_{M2} - \theta_{M1}}{\alpha_{GL} (C_{GL2} - C_{GL1})}. \quad (3)$$

Substituting formulas (3) into (1), a general expression for θ_M is obtained as follows:

$$\theta_M = \frac{C_{GL} (\theta_{M2} - \theta_{M1})}{(C_{GL2} - C_{GL1})} + \theta_{SUB} + \theta_O \quad (4)$$

Now the curve corresponding to formula (4) should be compared with reference calibration curve D. In order to ensure meaningful comparison, both curves must be normalized against the pathlength, i.e., each curve is divided by its pathlength.

Fig. 8 shows the normalized curve D and curve K. For curve D, the ordinate represents θ_R/L (L = 1 cm). For curve K, the ordinate represents $(\theta_M-\theta_O)/L_{EFF}$. Theoretically, both curves are parallel and represented by straight lines. In reality, however, they may have some deviations from the theoretical condition. Accordingly, memory unit 115 contains a suitable algorithm, which can be derived from experimentally acquired data, for processing the above-mentioned data by known methods of correlation analysis so

as to minimize the above-mentioned deviations. One of the variables of such algorithm may be an actual thickness of the finger. It is understood that the above formulae are parts of the algorithm and that all calculations are performed automatically in microcontroller 116. Upon completion of the calibration procedures, including the one-time start-up calibration, apparatus 20 is ready for actual measurement.

Operation of apparatus 20 of the invention for measuring the blood-glucose concentration will be now described for the case of glucose measuring head 32 for a finger F built into the apparatus (i.e., for non-remote version of Figs. 4 and 6).

When apparatus 20 is switched on, laser diode 22 generates a laser beam B which is directed through collimating lens 40 to PFS 24. PFS 24 produces a polarization modulation of optical beam B via mirror 50 and PZT 26 which is driven by piezoelectric controller 28. The resulting polarized-modulated optical beam B1 is sent to optical transducer 30. Optical transducer 30 splits optical beam B1 into a polarized-modulated reference optical beam BR and a polarized-modulated probe optical beam BP. Reference optical beam BR is passed through optical attenuator 56, window 61, polarizer 58, and converted by photodetector 60 into reference electric signal SR. Probe optical beam BP is sent to glucose measuring head 32.

For measuring the blood glucose level, the patient inserts his/her finger F into opening 82 against spring-loaded stop element 84 and adjusts the position of finger F so that nail bed NB is aligned with the position of side opening 90. At the same time, spring-loaded pressure element 88 applies pressure to finger F behind the measurement portion, whereby the amount of blood in the finger flesh to be measured increases to increase the sensitivity of measurements.

Probe optical beam BP thus passes through the blood of finger F and becomes passed probe optical beam BP1. Transmission of probe optical beam BP through finger F changes the direction of polarization of the resulting optical beam BP1 because glucose is an optically active material for the wavelength of probe optical beam BP. This introduces a phase shift θ_M for optical beam BP1 with respect to reference optical beam BR. For a wavelength λ = 850 nm and a blood glucose concentration of 70mg/100ml, the phase shift is on the order of 4.7 millidegrees.

The transmitted optical beam BP1 passes through protective plate 96 to a beam-splitting plate 64 of balanced receiver 62. In balanced receiver 62, optical beam BP1 is split into two optical beams BP1-A and BP1-B. Component BP1-A is directed through polarizer 68 to photodetector 70. Photodetector 70 produces an electrical signal S-A corresponding to the polarized component of optical beam BP1-A, which is input to difference amplifier 74. At the same time, component BP1-B is directly passed to photodetector 72. Photodetector 72 produces an electric signal S-B corresponding to the non-polarized component of optical beam BP1-B, which is also input to difference amplifier 74.

Difference amplifier 74 then provides an output that is the difference between the electrical signals S-A and S-B corresponding to depolarized and polarized components of optical beams BP1-A and BP1-B. The output signal of difference amplifier 74 thus carries information only about the polarized component BP1-A. However, the amplitude of this difference signal still contains noise associated with light scattering. To further reduce this noise component, the amplitude of the output signal from difference amplifier 74 is divided, in division amplifier 78, by the amplitude of the signal from photodetector 72 which contains the same scattering noise. More specifically, the output of photodetector 72 is passed through low-pass filter 76 for

removing frequencies above 10 to 100 Hz and the filtered signal is provided as the denominator to the division amplifier 78. The resulting probe electric signal SP thus carries information about polarized component BP1-A, but the amplitude of signal SP is free of the noise influence.

Reference electric signal SR and probe electric signal SP are then passed to phase-sensitive homodyne receiver 114. An output of homodyne receiver 114 is provided as a feedback signal FS to piezoelectric controller 28. Receiver 114 extracts a phase-difference signal SΘ, which is sent to the input of microcontroller 116. At the same time, microcontroller 116 receives length measurement signal SL from sensor 98 and calibration data from memory unit 115.

On the basis of the algorithm, phase difference signal $S\theta$, length signal SL, and calibration data, microcontroller 116 produces a signal S_G proportional to the concentration of glucose. Signal S_G is converted by A/D converter 118 into a digital glucose-concentration information C_G which can be shown on display 36 and/or indicated on display 35. The apparatus uses averaging techniques for the measurements to extract the best signal to noise information and may require up to a minute to produce a glucose concentration measurement. Averaging will average out variations in blood volume due to pulsatile blood flow, motion artifact and other movements.

Apparatus 20 made in accordance with the embodiment of the remotely located glucose measuring head shown in Fig. 6A operates in the same manner as the apparatus of the embodiment of Fig. 6 except that optical beam BP is transmitted to finger F or another blood-carrying part, via optical-fiber link 100 and GRIN lens 104.

In the case of apparatus 20 made in accordance with the embodiment of glucose measuring head 32B shown in Fig. 6B, head appliance 106 is put on the patient's head as in the case of a conventional headphone so that transducer 108 is located near one ear of the wearer while the lobule E of the

other ear of the patient is clamped by clip 101. In this manner, ear lobule E is located on the optical path of optical beam BP between fiber-optical link 100b and balanced receiver 62b. All other parts operate on the same principle as similar parts of the previous embodiment.

In an actual construction, apparatus 20 may have small dimensions of about 40 cm x 15 cm x 20 cm, or less. This allows the use of the apparatus as a home and portable monitoring device. Use of customizable ASIC devices and/or customized integrated circuits will permit reducing the size further. A rechargeable battery (or replaceable battery) may be used to operate the system electronics to permit portable use.

Embodiment of Non-Invasive Apparatus and Methods with Polarizing Frequency Shifter for Measuring Circular Dichroism

The embodiments described above in connection with Figs. 1 through 8 relate to a method and apparatus based on the measurement of a polarization rotation angle of light transmitted through in vivo tissue. The above described method and apparatus are based in part on an assumption that dependence of an angle of rotation on a wavelength has a maximum and that in a preferred embodiment of the apparatus the operative wavelength corresponds to this particular maximum.

It is known, however, that any optically active medium, e.g., glucose, may interact with an incident polarized light in two different ways. In other words, the above medium may either change the angle polarization of the linear component of the polarized incident light, or (if the incident light contains left and right circular polarized components) it may absorb the left and right circular polarized components differently. The latter one is known as "circular dichroism".

Another aspect of the present invention concerns an apparatus for determining blood-glucose concentration by

measuring circular dichroism. In general, the apparatus is the same as the one described above with reference to Figs. 1 through 8. The main difference between both embodiments is in the structure of the polarizing frequency shifters. Therefore, in the following description of the apparatus based on measurement of circular dichroism, only those components and elements which are different will be described in detail. Furthermore, in the drawings of Figs. 9 and 10 the portions of the second embodiment having parts identical with the first embodiment will be designated by the same reference numerals with an addition of 100.

Referring to Fig. 9, a polarizing frequency shifter 142 for measuring circular dichroism is shown. Polarizing frequency shifter of Fig. 9 is identical to polarizing frequency shifter 42 of Fig. 2, with the exception that shifter 142 does not have output quarter-wave plate 52.

Similarly, Fig. 10 shows a block diagram of a photoreceiver 162 of Fig. 4 which is suitable for the embodiment of the shifter of Fig. 9. The parts identical with those of Fig. 5 will be designated by the same reference numerals, but with an addition of 100.

Receiver 162 includes a photodiode 170 which receives probe optical beam BP1 and converts it into a mixture of DC and AC electrical signals. An output of photodiode 170 is connected to a division amplifier 178 via a low-pass filter 174 and a high-pass filter 171 which are connected in parallel to each other. An output of division amplifier 178 is an AC signal S_{out} which may be represented by the following a formula:

$$S_{out} = (A_{RCD} - A_{LCD}) \sin(2\pi ft + \phi_o),$$
$$\text{where } (A_{RCD} - A_{LCD}) = C_{GL}(\alpha_{RCD} - \alpha_{LCD})/\alpha_o,$$

where α_{RCD} and α_{LCD} are absorption coefficients for right and left circular polarized lights, and α_o is an absorption coefficient for a non-polarized light.

Operation of the apparatus for measuring glucose concentration on the principle of circular dichroism will now be described with reference to the drawings of the previous embodiment, with the exception that Fig. 2 and 5 will be replaced by Figs. 9 and 10.

When apparatus 20 is switched on, laser diode 22 generates a laser beam B which is directed through collimating lens 40 to PFS 124 (Fig. 9). PFS 124 produces a polarization modulation of optical beam B via mirror 150 and PZT 126 which is driven by piezoelectric controller 28. The resulting polarized-modulated optical beam B1 constitutes a 50%:50% mixture of left and right circular polarized beams, which may be expressed as follows:

$$\vec{E}_{B1} = \vec{E}_{RCP} \ (1 - ie^{i2\ ft+1\ °}) + \vec{E}_{LCP} \ (1 + ie^{i2\ ft+1\ °})$$

where E_{RCP} is the amplitude of the right circular polarized component of beam B1, E_{LCP} is the amplitude of the left circular polarized component of beam B1, and E_{B1} is the amplitude of beam B1; ϕ_o and f are the same as defined in the first embodiment.

Optical transducer 30 splits optical beam B1 into a polarized-modulated reference optical beam BR and a polarized-modulated probe optical beam BP. Reference optical beam BR is passed through optical attenuator 56, window 61, polarizer 58, and converted by photodetector 60 into reference electric signal SR. Probe optical beam BP is sent to glucose measuring head 32.

For measuring the blood glucose level, the patient inserts his/her finger F into opening 82 against spring-loaded stop element 84 and adjusts the position of finger F so that nail bed NB is aligned with the position of side opening 90. At the same time, spring-loaded pressure element 88 applies pressure to finger F behind the measurement portion, whereby the amount of blood in the

finger flesh to be measured increases to increase the sensitivity of measurements.

Probe optical beam BP thus passes through the blood of finger F and becomes passed probe optical beam BP1. Transmission of probe optical beam BP through finger F changes the direction of polarization of the resulting optical beam BP1 because glucose is an optically active material for the wavelength of probe optical beam BP. As a result, an absorption difference occurs between the left and right circular polarized components of the incident light. For a wavelength λ = 850 nm and a blood glucose concentration of 70mg/100ml, the absorption difference is on the order of (2 to 5)x10^{-5}.

The transmitted optical beam BP1 passes through protective plate 96 to a photodiode 170. The output signal of photodiode 160 is sent via parallel filters 171 and 174 to division amplifier 178 which produces on its output an AC signal S_{out}. The output signal S_{out}, which carries information only about circular dichroism caused by glucose absorption of the light, constitutes a probe electrical signal SP.

Reference electric signal SR and probe electric signal SP are then passed to phase-sensitive homodyne receiver 114. An output of homodyne receiver 114 is provided as a feedback signal FS to piezoelectric controller 28. Receiver 114 extracts the amplitude of probe electrical signal SP, which is sent to the input of microcontroller 116. At the same time, microcontroller 116 receives length measurement signal SL from sensor 98 and calibration data from memory unit 115.

The signals are finally processed in a manner similar to the apparatus of the first embodiment.

Embodiment of Apparatus And Methods with Frequency Modulation of Laser Diode

The first and second embodiments of the apparatus described above with reference to Figs. 1 through 10 related

to phase modulation of a laser beam by passing it through PFSs 24 and 124 based on the use of piezoelectric transducers 26 and 126, respectively. Depending on the costs requirements and characteristics (power, wavelength, and spectral width) of the laser source used in the apparatus, it may appear more advantageous to utilize direct frequency modulation of laser diode 22, instead of the use of piezo movements of PFS 24.

Fig. 11 is a block diagram of an apparatus of a third embodiment utilizing direct frequency modulation of a laser diode. Fig. 12 is a schematic structural view of a polarizing frequency shifter of Fig. 11 for use in conjunction with the third embodiment. The parts identical with those of Figs. 1 and 2 will be designated by the same reference numerals but with an addition of 200. Furthermore, the description of identical parts will be omitted.

The apparatus shown in Fig. 11 is generally the same as the one of Fig. 1 with the following exceptions: piezo-transducer (PZT) 26, piezo controller 28, and feedback FS from electronic signal processing unit 34 to piezoelectric controller 28 are eliminated, while some new elements are introduced. The new elements are a current controller 227 and a triangular wave generator 229, and feedback FS1 from electronic signal processing unit 234 to current controller 227 (Fig. 11). Current controller 227 is connected to laser diode 222 and to triangular wave generator 229. In fact, current controller 227 is an element of apparatus of Fig. 1, as well, but it has not been shown.

A polarizing frequency shifter (PFS) 224 is the same as PFS 24 with the exception that PZT 26 is removed.

The apparatus of the third embodiment of Figs. 11 and 12 operates similarly to that of the first embodiment with the exception that phase modulation of laser beam B which is supplied to PFS 224 is produced by direct frequency

modulation of this beam in laser diode 222. In this case phase modulation in PFS 224 may be expressed by the following formula:

$$\phi(T) = \phi_o + 2\pi ft$$
$$f = 4\beta \cdot (\Delta L/C) I_a f_o$$
$$\phi_o = 2\pi (\Delta L/C) \nu_o,$$

where ϕ_o is a statical phase shift, f is a PFS frequency, ß is a frequency-to-current conversion factor of laser diode 222, ΔL is an optical-path difference in PFS 224, I_a is an amplitude of current modulation produced by triangular wave generator 229, f_o is a frequency of the triangular wave, and ν_o is an optical frequency of laser diode 222.

As far as PFS 224 is concerned, it operates in the same manner as PFS 24, with the exception that both mirrors 248 and 250 are not subject to vibrations because the beam is modulated not by vibration of the mirrors but by directly changing the frequency of laser diode 222.

Embodiment of Non-Invasive Apparatus and Methods Using Polarizing Frequency Shifter of Integrated Optic Implementation

A schematic block diagram of a fiber optic-based implementation of the invention is shown in Fig. 13. The apparatus, which is designated in general by reference numeral 320, includes a laser source 322 which produces a laser beam B, an optical phase modulator (OPM) 332 which receives laser beam B from laser source 322, a glucose measuring head 326 which contains a sensor in the form of a balanced receiver 328, and an electronic signal processing unit 330 connected to OPM 332 and to balanced receiver 328. Glucose measuring head 326 is connected to OPM 332 via a single-mode polarization-maintaining fiber-optic link 334.

Laser source 322 is preferably a laser diode which operates in the wavelength of 750 to 1000 nm (the near-infrared range), e.g., 850 nm, with a low-coherence

length and preferably with a low-noise intensity and phase variation. A laser source of such type is produced, e.g., by Spectra Diode Labs, San Jose, California. Laser source 322 has a corresponding power-supply unit (not shown). It should be understood that other light sources and other wavelength ranges corresponding to other optical activity peaks for glucose (and similar peaks for other blood constituents) could be used.

The structure of OPM 332 is schematically shown in Fig. 14. Referring to Figs. 3, 14, 15, 16a-16c and 17, OPM 332 comprises the following elements, arranged sequentially in the direction of propagation of laser beam B emanating from laser beam source 322: an optical isolator 336 which prevents back reflection of laser light to laser source 322, an input polarizer 338, two fiber-optic arms 340 and 342 which are interconnected by means of an input optical coupler 344 and an output optical coupler 346, an optical phase shifter 348 which is attached to fiber-optic arm 340, a quarter-wave plate 350, a glucose reference cartridge 352, an output polarizer 354, and a photodiode 356.

Optical polarizer 338 polarizes laser beam B so that the direction of its polarization forms a 45° angle to axis X, where, as shown in Fig. 16a, axis X is one of coordinate axes of the reference X-Y coordinate system. Fig. 16a is a graph illustrating position of the axis of polarization with respect to an X-Y reference coordinate plane at the output of polarizer 338.

Fiber-optic arms 340 and 342 are used to propagate light from laser source 322 to output quarter-wave plate 350. Each of fiber-optic arms 340 and 342 supports propagation of light in one of two orthogonally polarized modes. In particular, fiber-optic arm 340 is oriented so that it can support propagation of light mode with Y-axis direction of polarization, as illustrated in Fig. 16b, and fiber-optic arm 42 is oriented so that it can support

propagation of light mode with X-axis direction, as illustrated in Fig. 16c.

At its end facing optical polarizer 338, fiber-optic arm 340 has an optical lens 358 which is a GRIN rod microlens. From GRIN rod microlens 358, the laser beam is coupled into arm 340 and passes to input optical coupler 344.

Input optical coupler 344 is formed by fusing fiber-optic arms 340 and 342. Commercial optical couplers are available, e.g., from SEASTAR Optics, Inc., Seattle, Washington. It is analogous in its action to a beam splitter with a 50:50 ratio, and splits laser beam B into two components B1 and B2. Beam component B1 propagates along fiber-optic arm 340 and beam component B2 propagates along fiber-optic arm 342. However, in as much as each arm supports a different one mode of propagation, the components B1 and B2 are not identical.

Referring to Fig. 15, phase shifter 348 is made in the form of a thin-walled piezoceramic ring 360 around which fiber-optic arm 340 is wrapped to form a coil 362. Commercial phase shifters of this type are available from, e.g., Burleigh Instruments, Inc., Burleigh Park, Fisher, New York. Piezoceramic ring 360 is electrically connected to electronic signal processing unit 330 (not shown). Unit 330 sends to piezoelectric ring 360 a signal FS, preferably an AC voltage which causes alternating contractions of piezoceramic ring 360, and thus phase modulates optical beam B1.

Preferably, phase shifter 348 is controlled by a piezoelectric controller 421 (shown in Fig. 17). Piezoelectric controller 421 is a conventional circuit that generates a modulating signal FS, e.g., a sawtooth or triangular waveform at a selected frequency f, preferably responsive to a feedback control signal FB from electronic signal processing unit 330 (as described below), and causes ring 360 to vibrate accordingly.

Output optical coupler 346 also is formed by fusing optical fiber arms 340 and 342 to provide coherent mixing of the two light propagating modes of arms 340 and 342. As a result, each output portion 340a and 342a of a respective optical fiber arms 340 and 342 has a complementary coherent mixture of optical beams B1 and B2 with an orthogonal direction of polarization. Each output portion 340a and 342a is terminated in a GRIN rod microlens, lenses 343 and 345, respectively.

GRIN rod microlens 343 is aligned with quarter wave plate 350 window 350a and GRIN rod microlens 345 is aligned with quarter wave plate 350 window 50b. Quarter-wave plate 350 is a conventional device which introduces a phase delay equal to a quarter of the wavelength of the incident beam and is characterized by a fast axis and a slow axis. Quarter-wave plate 350 has a direction of its axis of polarization parallel to that of input polarizer 338. As a result, the beam emitted from GRIN rod microlens 343, after passing through window 350a, is a polarized-modulated optical beam which is used as a reference optical beam BR. Similarly, the beam emitted from GRIN rod microlens 345, after passing through window 350b, is a polarized-modulated optical beam which is used as a measurement optical beam BM. Reference optical beam BR is passed through a polarizer 354 and sensed by a photodetector 356 which produces an electrical reference signal SR corresponding to the phase of optical beam BR. It should be understood that measurement beam BM is used in the same manner as probe beam BP previously described.

Glucose measuring head 326, which receives the blood-carrying tissue to be measured, may be either securely attached to optical transducer 330 (not shown) or physically disconnected from optical transducer 330 for remote use and coupled to OPM 32 by an optical fiber link 334 (shown in Fig. 13, and shown in Figs. 6A and 6B as element 100 and 100B). It receives measurement optical beam BM and, as

discussed below, produces an output electrical measurement signal SM corresponding to the phase of the measurement optical beam BM after is has passed through the tissue. Signal SM is thus essentially the same as signal SP previously described.

Electronic signal processing unit 330 is connected to OPM 332, receives electric signals SR, SM, and a signal SL corresponding to the thickness of the tissue through which the optical beam BM passes and provides a piezoceramic control signal FS. Unit 330 processes signals SR and SM and produces a measurement phase difference signal SΘ in the same manner described above. Signal FS is used to provide a linear motion of piezoceramic ring 60 with a fixed frequency f and to avoid hysteresis.

Each output optical beam BR and BM is a polarized-modulated optical beam that is characterized by the strength of an electrical field E. As shown and previously described in connection with Fig. 3, each above-mentioned field E also can be represented by a coordinate system (axes X and Y) and a vector $\vec{E}$ of polarization which rotates in the plane XY with a frequency f/2.

Referring to Fig. 14, a cartridge 352 is preferably placed between quarterwave plate 350 and output polarizer 354 for calibration purposes, in the same manner as previously described with reference to Figs. 4, 4a and 4b.

Referring to Figs. 14, 5, 6, 6A and 6B, measurement optical beam BM is passed through glucose measuring head 326 to balance receiver 328. Glucose measuring head 326 and balanced receiver 328 operate in essentially the same manner as the different glucose heads and balanced receiver embodiments already discussed in connection with Figs. 1-8, with the understanding that beams BP, BP1, BP1-A and BP1-B of Figs. 1-8 correspond to beams BM, BM1, BM1-A and BM1-B in the embodiment of Fig. 14.

In the embodiment of Fig. 14, balanced receiver 328 functions to subtract out electronically the depolarized

portion of the optical signal BM1 and to leave only the polarized component. It has as its output an electrical measurement signal SM corresponding to the polarized component of passed measurement optical beam BM1.

Referring to Fig. 17, electronic signal processing unit 330 is similar to unit 30 already described in connection with Fig. 7 (the same elements given the same reference numbers are the same except as otherwise indicated) and includes a phase-sensitive homodyne receiver 114, which receives the reference electric signal SR and the measurement electric signal SM and produces on its output an electric signal SΘ which is proportional to a blood glucose concentration, a microcontroller 116, which processes signal SΘ in order to convert it into a glucose-concentration signal S_G, and an analog-digital (A/D) converter 118 which receives, e.g., signal S_G and converts it into digital information C_G. The output of A/D converter 118 is passed to display 119 for displaying the obtained information about the concentration of glucose in the blood.

Electronic signal processing unit 330 also contains a piezocontroller 421 which is connected via a feedback signal FB with phase-sensitive homodyne receiver 114. Piezocontroller 421, in turn, is connected to phase shifter 448 (Fig. 2). Piezocontroller 421 is a device which controls waveforms of an AC voltage signal FS supplied to phase shifter 448.

In order to exclude the effect of statical phase shift Θ_o, which may occur because of temperature (ambient or sample) variations, misalignment in the optical system, imperfect optics (designed not exactly for the given wavelength), etc., each measurement procedure preferably begins with calibration of apparatus 320 in any of the manners already described (substituting signal SM for SP, BM for BP, etc.).

Operation of apparatus 320 of the invention of Figs. 13 and 14 for measuring the blood-glucose concentration will be

now described for the case of glucose measuring head 326 built into the apparatus (i.e., for non-remote version).

When an apparatus 320 is switched on, laser diode 322 generates a laser beam B which is directed to fiber-optic arm 340. When beam B passes through input optical coupler 344, it is split into two mutually-orthogonal beam components B1 and B2. One of them, i.e., beam component B1, which propagates through arm 340, is subjected to phase modulation under the action of phase shifter 348. The other, i.e., beam component B2, which propagates through arm 342, remains unchanged. In output coupler 346 both beam components B1 and B2 are coherently mixed. As a result, after passing through output optical coupler 346, each output portion 340a and 342a of respective optical fiber arm 340 and 342 has a complementary coherent mixture of optical beams B1 and B2 with an orthogonal direction of polarization. These beams then pass through windows 350a and 350b of a quarter-wave plate 350 and are transformed into linear-polarized waves, respectively to form optical beams BR and BM. As shown in Fig. 3, the direction of polarization of these waves rotates with the frequency corresponding to that of phase shifter 348.

Measurement optical beam BM is sent directly to glucose measuring head 326. Reference optical beam BR is sent to reference photodetector 356 via cell cartridge 352 and polarizer 354. Reference photodetector 356 produces a reference electrical signal SR.

With reference to Fig. 6A, for measuring the blood glucose level, the patient inserts his/her finger F into opening 82 against spring-loaded stop element 84 and adjusts the position of finger F so that nail bed NB is aligned with the position of side opening 90. At the same time, spring-loaded pressure element 88 applies a pressure to finger F behind the measurement portion, whereby the amount of blood in the finger flesh to be measured is increased to increase the sensitivity of measurements.

Measuring beam BM passes out lens 104 and through the blood of finger F and becomes passed measurement beam BM1 (BP1 in Fig. 6A). Transmission of measuring beam BM (BP in Fig. 6A) through finger F changes the direction of polarization of the beam because glucose is an optically active material for the wavelength of measurement optical beam BM. This introduces a phase shift θ_M for optical beam BM1 (BP1) with respect to reference optical beam BR. The phase shift can be determined in the manner previously described with reference to Fig. 5, to obtain signal SM.

Reference electric signal SR and measuring electric signal SM are then passed to phase-sensitive homodyne receiver 114. See Fig. 17. An output of homodyne receiver 114 is provided as a feedback signal FB to piezoelectric controller 421. Receiver 114 extracts a phase-difference signal Sθ, which is sent to the input of microcontroller 116. At the same time, microcontroller 116 receives length measurement signal SL from sensor 98 and calibration data from memory unit 115.

On the basis of the algorithm, phase difference signal Sθ, length signal SL, and calibration data, microcontroller 116 produces a signal S_G proportional to the concentration of glucose. Signal S_G is converted by A/D converter 118 into a digital glucose concentration information C_G which can be shown and/or indicated on display 119. The apparatus uses averaging techniques for the measurements to extract the best signal to noise information and may require up to several seconds to produce a glucose concentration measurement. Averaging will average out variations in blood volume due to pulsatile blood flow, motion artifact and other movements.

In the case that the integrated optic embodiment is to be used in an embodiment for measuring the change in polarization based on circular dichroism, as previously described, then the optical phase modulator 332 is modified by deleting quarter wave plate 350. The thus modified

apparatus 320 can then be used to determine the phase shift due to, e.g., blood glucose, based on circular dichroism in the same manner as the system based on circular dichroism previously described.

In an actual construction, apparatus 320 may have small dimensions of about 40 cm x 15 cm x 20 cm, or less. This allows the use of the apparatus as a home and portable monitoring device. Use of customizable ASIC devices and/or customized integrated circuits will permit reducing the size further. A rechargeable battery (or replaceable battery) may be used to operate the system electronics to permit portable use.

Thus, it has been shown that the invention provides methods and apparatus for non-invasive precision phase-sensitive measurement of blood glucose. These methods and apparatus do not involve the use of mechanically moving parts, result in low-noise measurements, operate in the frequency range beyond that of mechanical vibrations, are suitable for use at home or as a portable blood monitoring device, utilize processing electronics which allow glucose-level measurements through high-scattering tissue, and are not restricted for use with an eye but applicable to other blood-carrying body parts. Advantageously also, the device and methods use a single near infrared light source, e.g., a single laser diode. In addition, the device obtains a measurement from perfused blood-carrying tissue in effective real time, rather than from aqueous eye humor in which changes in the glucose concentration may lag behind the blood glucose concentration by two hours.

Although the apparatus and the methods have been shown and described in the form of several specific embodiments, these embodiments, their parts, materials, and configurations have been given only as examples, and many other modifications of apparatus and method possible. For example, cartridge 59 may be removable, stored separately, and inserted when necessary, rather than be incorporated

into apparatus 20. The thin walled piezoceramic body 360 may have configurations other than a ring and can be made, e.g., as a strip to which the optic-fiber arm 340 may be attached. An LED (light-emitting diode) operating in a near-infrared region of the spectrum with adequate collimating lenses may be used instead of a laser diode. Apparatus 20 also may be equipped with memory 115 of sufficient capacity for storing a log of the patient's measurements, e.g., date, time and values. It also may be equipped for storing information regarding medication dosages administered, e.g., units of insulin, using a suitable keypad or other data entry system. In the case that apparatus 20 is constructed for use as a hospital or clinic-based unit, it may contain or be provided with more substantial computing functions such as calibration data for each patient it will service, maintain a log of each patient's measurements and also may include additional electronic circuitry for improving the accuracy of measurements. For example, a feedback signal may be sent to the laser source to stabilize amplitude and phase noise variation of the laser beam.

The present invention is particularly useful for monitoring blood constituents which undergo short term changes, such as glucose, in the presence of other optically active blood or tissue constituents (whether less dominant than, e.g., glucose), e.g., protein, which either do not change or change very slowly with time. In the case where the other optically active components do change somewhat with time, short term and long term averaging techniques may be used to control the effects of a change in the other optically active components. Similarly, the start-up calibration using two or more invasive glucose measurements could be infrequently used, e.g., once a year or when the patient's weight has changed significantly.

The invention also may be useful for identifying the concentration of an optically active substance that is added

to blood and selectively bonds to a desired blood constituent. For example, substances such as optically active monoclonal antibodies that bind to specific antigenic determinants of a selected blood constituent or cell subpopulation may be used. This provides for indirectly measuring noninvasively blood components that are not significantly or sufficiently optically active for diagnostic and therapeutic purposes.

One skilled in the art will appreciate that the present invention can be practiced by other than the described embodiments, which are presented for purposes of illustration and not of limitation.

CLAIMS

1. An apparatus for non-invasive precision phase-sensitive measurement of the blood glucose concentration having a source which produces an infrared laser beam characterized by:

a polarizing frequency shifter having a piezoelectric transducer for use in imparting phase modulation of a laser beam, an optical input for receiving an infrared laser beam, and an optical output which produces a polarized-modulated infrared laser beam;

a piezoelectric controller for operating the piezoelectric transducer at a selected modulation frequency;

an optical transducer which has a glucose measuring head and an optical input for receiving said polarized-modulated infrared laser beam from said output of said polarizing frequency shifter and an output providing a reference electric signal, said glucose measuring head having a space for receiving a blood-carrying body part and generating a probe electric signal corresponding to the polarized component of the polarized-modulated laser beam passing through the tissue and a thickness measurement signal corresponding to the thickness of said blood carrying body part; and

an electronic signal processing unit which has an input which is electrically connected to said optical transducer for receiving said reference electric signal and inputs which are electrically connected to said glucose measuring head for receiving said probe electric signal and thickness measurement signal, said electronic signal processing unit having a feedback loop to said piezoelectric controller for controlling the piezoelectric transducer.

2. The apparatus of claim 1 characterized in that the optical transducer is characterized by:

a beam splitter having an optical input for receiving said polarized-modulated infrared laser beam which is split

into a reference optical signal and a probe optical signal, a reference optical output, and a measurement optical output; and

a measurement sensor in the form of a balanced receiver which produces at its output a probe electrical signal, wherein the glucose measuring head and the measurement sensor are arranged sequentially from said measurement optical output side.

3. The apparatus of claim 2 characterized in that the polarizing frequency shifter is characterized by:

a polarizing beam splitter cube having a center, a beam input side and a beam output side which is perpendicular to said input side;

a first quarter-wave plate which is located on a side of said polarizing beam splitter cube which is opposite to said beam input plate;

a second quarter-wave plate located on a side of said polarizing beam splitter cube which is opposite to said beam output side;

a third quarter-wave plate located on said output side of said polarizing beam splitter cube;

a first mirror which is located on the outer side of said first quarter-wave plate and is attached to said piezoelectrical transducer; and

a second mirror which is located on an outer side of said second quarter-wave plate;

wherein the difference between distances of said first and said second mirrors and said center of said polarizing beam splitter cube is smaller than a coherent length of said infrared laser beam.

4. The apparatus of claim 2 characterized in that the polarizing frequency shifter is characterized by:

two lengths of polarization preserving fiber-optic conductors, each fiber-optic length having an input end and an output end;

an input optical coupler joining together the two fiber-optic conductors near their input ends for coupling light received at each fiber-optic input into both fiber-optic conductors;

an optical coupler output joining together the two fiber optic conductors near their output ends for mixing coherently the light propagating in each fiber-optic and coupling said mixture to each fiber-optic output;

a phase modulator, including the piezoelectric transducer, connected to one of the two fiber-optic conductors for imparting a phase modulation of a polarized beam components propagating therein; and

a polarizing element interposed between the laser beam source and one of the fiber-optic conductors so that a polarized optical laser beam component propagates in each fiber-optic conductor with a different direction of polarization, and the output coupler provides each fiber-optic conductor output with a complementary coherent mixture of the modulated and unmodulated beam components with an orthogonal direction of polarization;

a quarter-wave plate structure adjacent the fiber-optic conductor outputs so that the output laser beams pass therethrough, thereby providing the polarized-modulated reference and measurement optical beams;

and characterized in that the electronic signal processing unit has a feedback loop to said piezoelectric controller for controlling the piezoelectric transducer to vibrate at the selected modulation frequency to deform the one optical fiber to impart a phase modulation to the laser beam component propagating therein.

5. The apparatus of claim 4 characterized in that the piezoelectric transducer is characterized by a thin-walled

piezoceramic ring around which the one fiber-optic conductor is wound.

6. The apparatus of claims 3 or 4 in which the balanced receiver is characterized by:

a beam splitter plate which receives said probe optical signal from said glucose sensor unit and splits said probe optical signal into a first component and a second component;

a polarizer and first photodetector, said first component being passed to said first photodetector through said polarizer, said first photodetector having an output corresponding to the polarized component;

a second photodetector which receives said second component from said beam splitter plate having an output corresponding to the depolarized component;

a difference amplifier having a first input and a second input and an output, said first input of said difference amplifier being connected to said first photodetector output and said second input of said difference amplifier being connected to said second photodetector output;

a division amplifier having a first input, a second input, and an output that is the electric probe signal;

a low-pass filter electrically connected between said second photodetector and said second input of said division amplifier, said output of said difference amplifier being connected to said first input of said division amplifier.

7. The apparatus of claim 2 in which the balanced receiver is characterized by a photoreceiver, and the polarizing frequency shifter is further characterized by:

a polarizing beam splitter cube having a center, a beam input side and a beam output side which is perpendicular to said input side;

a first quarter-wave plate which is located on a side

of said polarizing beam splitter cube which is opposite to said beam input plate;

a second quarter-wave plate located on a side of said polarizing beam splitter cube which is opposite to said beam output side;

a first mirror which is located on the outer side of said first quarter-wave plate and is attached to said piezoelectrical transducer; and

a second mirror which is located on an outer side of said second quarter-wave plate;

wherein the difference between distances of said first and said second mirrors and said center of said polarizing beam splitter cube is smaller than a coherent length of said infrared laser beam.

8. The apparatus of claim 7 in which the photoreceiver is characterized by a photodiode which is connected via a low-pass filter and a high-pass filter to a division amplifier, said low-pass filter and said high-pass filter being connected in parallel, said photodiode receiving said probe optical signal from said glucose sensor unit, said division amplifier having an output.

9. The apparatus of any of claims 1-8 in which the electronic signal processing unit is characterized by a phase-sensitive homodyne receiver which receives said reference electrical signal and said probe electrical signal, a microcontroller connected to said phase-sensitive homodyne receiver, and memory means connected to said microcontroller.

10. The apparatus of claim 9 further characterized by:

an audio transmitter connected to said microcontroller;

an analog-to-digital converter connected to said microcontroller; and

a display unit connected to said analog-to-digital converter.

11. The apparatus of any of claims 1-10 in which the glucose measuring head is characterized by:

a housing having said space for receiving said blood-carrying body part;

an optical measurement signal input located on one side of said space for receiving said measurement optical signal, said balanced receiver being located on a side of said space opposite to said one side;

a sensor for measuring a thickness of said blood-carrying body part for producing said thickness measurement signal;

fixation means for fixing said blood-carrying body part; and

compression means for compressing said blood-carrying body part.

12. The apparatus of claim 11 characterized in that the glucose measuring head is located remotely from said optical transducer and the optical measurement signal input is connected to said optical transducer through a polarization preserving fiber optic link.

13. The apparatus of claim 11, characterized in that the glucose measuring head is located remotely from said optical transducer and said optical measurement signal input is connected to said optical transducer through a polarization preserving fiber optic link, and the apparatus is further characterized by a head appliance which can be attached to the subject's head and supports a microphone connected to an audio transmitter and located near one ear of said subject when said head appliance is attached to the subject's head, and wherein said glucose sensing unit is made in the form of a resilient U-shape clip for inserting

into said U-shaped clip an ear lobule of another ear of said subject, said U-shaped clip having a first leg and a second leg, said first leg supporting said polarization preserving fiber-optic link and said second leg supporting said balanced receiver and said thickness measurement sensor, so that during operation of said apparatus said phase-modulated infrared laser beam is transmitted to said balance receiver through said ear lobule.

14. The apparatus of any of claims 1-13 in which the optical transducer is further characterized by an optical attenuator, a reference calibration cartridge with at least two cells containing glucose solutions of different concentrations, a reference polarizer, and a reference sensor arranged sequentially from said reference optical outside side.

15. A method for determining non-invasively the concentration of glucose in a blood-carrying body part of a patient characterized by the steps of:

(a) providing a polarized-modulated laser beam having a modulation frequency above the range of mechanical vibrations and a phase;

(b) splitting the polarized-modulated laser beam into a reference optical beam and a probe optical beam;

(c) passing the reference optical beam through a polarizer and sensing the polarized reference optical beam with a photodetector for producing a reference electric signal corresponding to the phase of the polarized-modulated light beam;

(d) passing the probe optical beam through the blood carrying body part having glucose to be measured and

(i) splitting the passed probe optical beam into a polarized component and a depolarized component;

(ii) converting the depolarized component into a depolarized component electric signal;

(iii) converting the polarized component into a polarized component electric signal;

(iv) subtracting the depolarized component electric signal from the polarized component electric signal to obtain a first subtracted signal;

(v) low-pass filtering the depolarized component electric signal; and

(vi) dividing the first subtracted signal by the low-pass filtered signal, thereby providing the probe electric signal corresponding to the phase of the passed probe optical beam;

(e) determining a phase difference between the reference and probe electric signals; and

(f) determining the concentration of the glucose in the blood carrying body part illuminated by the probe optical beam based on the determined phase difference.

16. The method of claim 15 in which step (a) is further characterized by:

providing a first polarized laser beam and a second polarized laser beam with mutually orthogonal polarization directions,

imparting a phase modulation to one of the first and second polarized laser beams at the selected modulation frequency;

combining the one phase-modulated and other polarized laser beams; and

passing the combined laser beams through a quarter wave plate to provide the polarized-modulated laser beam.

17. The method of claim 15 in which step (a) is further characterized by:

generating a laser beam;

providing a polarizing beam splitter cube having a center for splitting an incident beam into an s-polarized beam and a p-polarized beam;

passing the laser beam into the center of the polarizing beam splitter cube to produce an s-polarized laser beam and a p-polarized laser beam having mutually orthogonal polarization directions;

providing a first mirror spaced a first distance from the cube center, interposing a first quarter wave plate between the cube center and the first mirror, and reflecting the s-polarized laser beam off the first mirror so that the s-polarized laser beam and reflected s-polarized laser beam pass through the first quarter wave plate;

providing a second mirror spaced a second distance from the cube center, interposing a second quarter wave plate between the center and the second mirror, vibrating the second mirror at the selected modulation frequency to vary the second distance and impart a phase modulation to the p-polarized laser beam, and reflecting the p-polarized laser beam off the vibrating second mirror so that the p-polarized laser beam and the reflected p-polarized laser beam pass through the second quarter wave plate; and

combining the reflected s- and p-polarized laser beams and passing the combined reflected beams through a third quarter wave plate, thereby to form the polarized-modulated laser beam.

18. The method of claim 17, in which in step (a), the step of vibrating the second mirror is further characterized by attaching a piezoelectric transducer to the second mirror and controlling the piezoelectric transducer to vibrate the second mirror at the modulation frequency.

19. The method of claim 15 in which step (a) is characterized by:

generating a laser beam;

producing direct frequency modulation of said laser beam by means of a waveform generator with a predetermined modulation frequency;

providing a polarizing beam splitter cube having a center for splitting an incident beam into an s-polarized beam and a p-polarized beam;

passing the laser beam into the center of the polarizing beam splitter cube to produce an s-polarized laser beam and a p-polarized laser beam having mutually orthogonal polarization directions;

providing a first mirror spaced a first distance from the cube center, interposing a first quarter wave plate between the cube center and the first mirror, and reflecting the s-polarized laser beam off the first mirror so that the s-polarized laser beam and reflected s-polarized laser beam pass through the first quarter wave plate;

providing a second mirror spaced a second distance from the cube center, interposing a second quarter wave plate between the center and the second mirror, and reflecting the polarized laser beam off the second mirror so that the polarized laser beam and the reflected p-polarized laser beam pass through the second quarter wave plate; and

maintaining a predetermined difference between said first distance and said second distance; and

combining the reflected s- and p-polarized laser beams and passing the combined reflected beams through a third quarter wave plate, thereby to form the polarized-modulated laser beam.

20. The method of claims 18 or 19, further characterized by selecting the laser beam to be a near infrared wavelength in the range of 750 to 1000 nm, and controlling the difference between the first and second distances to be less than 1.0 mm.

21. The method of claim 15 characterized in that steps (a) and (b) are further characterized by:

providing an optical phase modulator by joining together two lengths of polarization preserving fiber-optic

conductors so that each fiber-optic length has an input end and an output end, providing an input optical coupler for coupling light received at each fiber-optic input into both fiber-optic conductors, and providing an optical coupler output for mixing the light propagating in each fiber-optic and coupling said mixture to each fiber-optic output;

passing a laser beam through a polarizing element and into one of the fiber-optic conductors so that a polarized optical beam component propagates in each fiber-optic conductor with a different direction of polarization;

imparting a phase modulation to one of the two propagating polarized beam components;

combining coherently the modulated and unmodulated laser beam components at the output coupler and providing each fiber-optic conductor output with a complementary coherent mixture of the modulated and unmodulated beam components with an orthogonal direction of polarization; and

passing the outputs of the first and second fiber-optic conductors through respective quarter-wave plate windows, thereby providing the polarized-modulated reference and probe optical beams.

22. The method of claim 21 characterized in that the step of imparting a phase modulation further comprises attaching a piezoelectric body to the one fiber-optic conductor between the input and output optical couplers, and activating the piezoelectric body to vibrate at the selected modulation frequency to deform the optical fibers to impart a phase modulation to the laser beam component propagating therein.

23. The method of claim 22 characterized in that the piezoelectric body is a thin-walled piezoceramic ring around which the one fiber-optic conductor is wound, and the laser beam is a near infrared wavelength selected in the range of from 750 to 1000mm.

24. The method of any of claims 15-23, in which step (b) is further characterized by:

calibrating the reference and probe electrical signals before performing step (d), the calibrating step further comprising:

selecting one of the probe and reference optical beams as the calibrating optical beam;

passing the calibrating optical beam through a first cell containing a solution of glucose at a first known concentration and thickness and determining a first data point corresponding to the measured phase difference for the first known concentration;

passing the calibration optical beam through a second cell containing a solution of glucose at a second known concentration different from the first concentration and thickness and determining a second data point corresponding to the measured phase difference for the second known concentration; and

determining calibration data based on the first and second data points to calibrate a determined phase difference for the blood glucose to be measured in step (d).

25. The method of any of claims 15-23, in which step (c) is further characterized by:

passing the reference optical beam through an optical attenuator;

passing the attenuated reference optical beam through the polarizer; and

sensing the polarized attenuated reference optical beam with the photodetector for producing the reference electric signal.

26. The method of claim 25, in which step (c) includes measuring the path length of the probe optical beam through the blood carrying body part.

27. The method of any of claims 15-23 in which step (e) is further characterized by providing a phase sensitive homodyne receiver for receiving the reference and probe electric signals and producing therefrom a phase difference signal.

28. The method of any of claims 15-23 in which step (f) is further characterized by:

receiving calibration information corresponding to a first and second determined phase difference signals based on two known concentrations of glucose and a predetermined relationship between the said two phase difference signals and said two known concentrations;

receiving the determined phase difference signal from step (e); and

determining the concentration of the glucose in the blood carrying body part based upon the determined phase difference signal and the calibration information.

29. The method of any of claims 15-23 characterized by selecting the modulation frequency from between 650 Hz and 10 KHz.

30. The method of any of claims 15-23 in which step (f) is further characterized by:

receiving information for calibrating the determined phase difference signal to the concentration of blood glucose in the blood carrying tissue;

receiving the determined phase difference signal from step (e); and

determining the concentration of the blood glucose based upon the determined phase difference signal and the calibration information.

31. The method of any of claims 15-23 in which step (f) is further characterized by:

measuring the thickness of the blood carrying tissue being illuminated by the probe optical beam as a length signal;

receiving information for calibrating the determined phase difference signal to the concentration of blood glucose in the blood carrying body part;

receiving the determined phase difference signal from step (e); and

determining the concentration of the blood glucose based upon the determined phase difference signal, the calibration information, and the length signal.

32. A method for determining non-invasively the concentration of glucose in a blood-carrying body part of a patient characterized by the steps of:

(a) providing a polarized-modulated laser beam having a modulation frequency above the range of mechanical vibrations and a phase;

(b) splitting the polarized-modulated laser beam into a reference optical beam and a probe optical beam;

(c) passing the reference optical beam through a polarizer and sensing the polarized reference optical beam with a photodetector for producing a reference electric signal corresponding to the phase of the polarized-modulated light beam;

(d) passing the probe optical beam through the blood carrying body part having glucose to be measured and

(i) converting said probe optical beam component into a mixture of a DC and AC electrical signal components;

(ii) separating said DC and AC electrical signal components by passing said mixture through a low-pass filter and a high-pass filter;

(e) dividing said AC signal onto said DC signals and providing a ratio in the form of an output electrical signal proportional to circular dichroism which is developed in said probe optical beam when it passes through said blood carrying body part; and

(f) determining the concentration of the glucose in said blood carrying body part on the basis of the determined circular dichroism.

33. The method of claim 32 in which step (a) is further characterized by:

generating a laser beam;

providing a polarizing beam splitter cube having a center for splitting an incident beam into an s-polarized beam and a p-polarized beam;

passing the laser beam into the center of the polarizing beam splitter cube to produce an s-polarized laser beam and a p-polarized laser beam having mutually orthogonal polarization directions;

providing a first mirror spaced a first distance from the cube center, interposing a first quarter wave plate between the cube center and the first mirror, and reflecting the s-polarized laser beam off the first mirror so that the s-polarized laser beam and reflected s-polarized laser beam pass through the first quarter wave plate;

providing a second mirror spaced a second distance from the cube center, interposing a second quarter wave plate between the center and the second mirror, vibrating the second mirror at the selected modulation frequency to vary the second distance and impart a phase modulation to the polarized laser beam, and reflecting the p-polarized laser beam off the vibrating second mirror so that the p-polarized

laser beam and the reflected p-polarized laser beam pass through the second quarter wave plate; and

combining the reflected s- and p-polarized laser beams to form the polarized-modulated laser beam.

34. The method of claims 32 or 33, in which in step (a), the step of vibrating the second mirror is characterized by attaching a piezoelectric transducer to the second mirror and controlling the piezoelectric transducer to vibrate the second mirror at the modulation frequency.

35. The method of claim 34, further characterized by selecting the laser beam to be a near infrared wavelength in the range of 750 to 1000 nm, and controlling the difference between the first and second distances to be less than 1.0 mm.

36. The method of claim 32, in which step (b) is further characterized by:

calibrating the reference and probe electrical signals before performing step (d), the calibrating step further comprising:

selecting one of the probe and reference optical beams as the calibrating optical beam;

passing the calibrating optical beam through a first cell containing a solution of glucose at a first known concentration and thickness and determining a first data point corresponding to the measured phase difference for the first known concentration;

passing the calibration optical beam through a second cell containing a solution of glucose at a second known concentration different from the first concentration and thickness and determining a second data point corresponding to the measured phase difference for the second known concentration; and

determining calibration data based on the first and second data points to calibrate a determined phase difference for the blood glucose to be measured in step (d).

37. A polarizing frequency shifter for use in producing a polarized-modulated beam of collimated light from a laser beam source characterized by:

a polarizing beam splitter having a center, a beam input side, and a beam output side which is perpendicular to the beam input side;

a first quarter-wave plate located adjacent the beam output side of the polarizing beam splitter;

a first mirror located a first distance from the beam center opposite one of the beam input side and beam output side of the polarized beam splitter;

a second quarter wave plate interposed between the first mirror and the beam splitter center;

a second mirror which is located a second distance from the beam center opposite the other of the beam input side and beam output side, the first and second mirrors being positioned to reflect beams emanating from the center back to the center;

a third quarter wave plate interposed between the second mirror and the beam splitter center, the second and third quarter wave plates being oriented to produce respectively polarized beams having mutually orthogonal directions of polarization;

a piezoelectric transducer secured to one of the first and second mirrors;

a controller circuit for controlling the piezoelectric transducer to vibrate the one mirror with a selected frequency above that of mechanical vibration to vary the second distance and impart a phase modulation to the laser beam incident thereon;

wherein the difference between first and second distances is less than 1.0 mm.

38. The apparatus of claim 37 characterized in that the light source is a laser diode and the controller circuit causes the piezoelectric transducer to vibrate the one mirror with a frequency selected in the range of from 650 to 15 KHz.

39. The apparatus of claim 37 wherein the controller circuit receives a feedback signal to control the vibration and hysteresis of the piezoelectric transducer.

40. Apparatus for use in calibrating a non-invasive instrument for measuring the glucose concentration in blood carrying tissue using a laser beam and precise phase sensitive measurements characterized by:

a housing having therein a window, a first cell containing a solution of glucose at a first selected concentration, and a second cell containing a solution of glucose at a second selected concentration, the first and second cells having a defined thickness; and

means for selectively presenting one of the window, first cell, and second cell to a laser beam having a phase so that the laser beam is not phase shifted by the window, is phase shifted a first amount by the first cell, and is phase shifted a second amount by the second cell.

41. The apparatus of claim 40 characterized in that the selectively presenting means is responsive to a supplied control signal for advancing the housing to present selectively one of the window, first cell and second cell under automatic control.

42. The apparatus of claims 40 or 41 further characterized by:

an optical attenuator for attenuating the laser beam passing through the presented one of the window, first cell and second cell; and

a polarizer for polarizing the attenuated laser beam.

43. A method of calibrating an apparatus for non-invasively measuring a concentration of glucose in a blood carrying tissue having a source of laser light providing a collimated optical beam having a wavelength corresponding to the optical activity of the glucose, a polarizing frequency shifter for producing a polarized-modulated optical beam including a piezoelectric transducer for imparting the phase modulation and a controller for operating the piezoelectric transducer, a beam splitter device for splitting the polarized-modulated optical beam into a reference optical beam and a probe optical beam, an optical transducer for presenting blood carrying tissue to the probe optical beam having a reference polarizer and a first photodetector for converting the reference optical beam into a reference electric signal having a first phase, a balanced receiver for converting the probe optical beam passed through the tissue into a probe electric signal having a second phase, and a means for determining the concentration of the optically active blood constituent in response to the phase difference between the probe electric signal and the reference electric signal, characterized by the steps of:

(a) passing the probe optical beam through the blood carrying tissue having a first glucose concentration that is determined by an invasive procedure;

(b) passing the probe optical beam through the blood carrying tissue having a second glucose concentration that is determined by an invasive procedure;

(c) determining a first and a second phase difference based on the determined reference and probe electric signals corresponding to the first and second determined glucose concentrations;

(d) determining an effective thickness for the blood carrying tissue based on the first and second determined phase differences and the first and second measured glucose concentrations;

(e) determining a measurement relationship between a ratio of a measurement phase difference to the effective thickness and the glucose concentrations invasively measured;

(f) passing one of the reference and probe optical beams through a first cell of a known thickness having a first known concentration of a glucose solution and determining a first phase difference corresponding to the first known concentration;

(g) passing the one optical beam through a second cell of a known thickness having a second known concentration of a glucose solution and determining a second phase difference corresponding to the second known concentration;

(h) determining a reference linear relationship between the first phase difference and the second phase difference and the first and second known glucose concentrations;

(i) comparing, on the basis of a statistical correlation analysis, the reference linear relationship and the measurement relationship; and

(j) determining, on the basis of the comparison, an accuracy and resolution of measurement of glucose concentration.

44. The method of claim 43 wherein the calibration procedure is further characterized by repeating steps (f)-(i) prior to passing the probe optical beam through the blood carrying tissue to measure the glucose concentration thereof.

45. The method of claims 43 or 44 characterized in that the blood carrying tissue is an appendage selected from

among the group consisting of fingers, toes, nose bridge, ankles, elbows, and earlobes.

46. A tissue holding device for use in non-invasive measurement of blood glucose concentrations characterized by:

a housing having a first aperture for receiving a polarized-modulated collimated beam of light and a cavity for receiving blood carrying tissue;

a balanced receiver having a beam splitter element for receiving a probe optical beam of light after passage through the blood carrying tissue and splitting the beam into a first optical probe beam and a second optical probe beam;

a polarizing element interposed in the path of one of the first and second optical probe beams for producing a polarized component;

a first photodetector for converting the polarized component to a polarized component electric signal;

a second photodetector for converting the other of the first and second optical probe beams to a depolarized component electric signal;

a difference amplifier for producing a difference signal corresponding to the difference between the polarized and depolarized component electric signals;

a low pass filter for filtering the depolarized component electric signal; and

a division amplifier for producing the probe electric signal from a ratio of the difference signal and the filtered depolarized electric signal.

47. The apparatus of claim 41 further characterized by a sensor for measuring the thickness of the blood carrying tissue in the cavity.

48. The apparatus of claims 46 or 47 further characterized by a length of polarization preserving optical fiber for coupling the polarized-modulated measurement optical beam to the housing first aperture and a GRIN lens interposed between the polarization preserving optical fiber and the cavity.

49. The apparatus of any of claims 46-48 further characterized by a member for contacting the tissue and a force exerting element for urging the member against the tissue.

50. The apparatus of claim 46 characterized in that the blood carrying tissue is an earlobe and further characterized by a head appliance for supporting the housing with the earlobe positioned in the housing cavity.

51. The apparatus of claim 50 further characterized by a length of polarization preserving optical fiber for coupling the polarized-modulated measurement beam to the housing first aperture.

52. An apparatus for non-invasive precision phase-sensitive measurement of the blood glucose concentration characterized by:

a source which produces an infrared laser beam;

a current controller which is connected to said source for applying a bias current to said source;

a waveform generator connected to said current controller for interposing a modulation current onto said bias current, thus providing frequency modulation of said source;

a polarizing frequency shifter for use in imparting phase modulation of a laser beam, an optical input for receiving an infrared laser beam, and an optical output which produces a polarized-modulated infrared laser beam;

an optical transducer which has a glucose measuring head and an optical input for receiving said polarized-modulated infrared laser beam from said output of said polarizing frequency shifter and an output providing a reference electric signal, said glucose measuring head having a space for receiving a blood-carrying body part and generating a probe electric signal corresponding to the polarized component of the polarized-modulated laser beam passing through the tissue and a thickness measurement signal corresponding to the thickness of said blood carrying body part; and

an electronic signal processing unit which has an input which is electrically connected to said optical transducer for receiving said reference electric signal and inputs which are electrically connected to said glucose measuring head for receiving said probe electric signal and thickness measurement signal, said electronic signal processing unit having a feedback loop to said current controller for suppressing phase noise produced by said polarizing frequency shifter.

53. The apparatus of claim 52 characterized in that the optical transducer is characterized by:

a beam splitter cube having an optical input side for receiving said polarized-modulated infrared laser beam which is split into a reference optical signal and a probe optical signal, a reference optical output side, and a measurement optical output side; and

a measurement sensor in the form of a balanced receiver which produces at its output a probe electrical signal, wherein the glucose measuring head and the measurement sensor are arranged sequentially from said measurement optical output side.

54. The apparatus of claim 53 characterized in that the optical transducer is further characterized by an

optical attenuator, a reference calibration cartridge with at least two cells containing glucose solutions of different concentrations, a reference polarizer, and a reference sensor arranged sequentially from said reference optical output side.

55. The apparatus of claim 53 characterized in that the polarizing frequency shifter is characterized by:

a polarizing beam splitter cube having a center, a beam input side and a beam output side which is perpendicular to said input side;

a first quarter-wave plate which is located on a side of said polarizing beam splitter cube which is opposite to said beam input plate;

a second quarter-wave plate located on a side of said polarizing beam splitter cube which is opposite to said beam output side;

a third quarter-wave plate located on said output side of said polarizing beam splitter cube;

a first mirror which is located on the outer side of said first quarter-wave plate; and

a second mirror which is located on an outer side of said second quarter-wave plate;

wherein the difference between distances of said first and said second mirrors and said center of said polarizing beam splitter cube is smaller than a coherent length of said infrared laser beam.

56. The apparatus of claim 55 characterized in that the balanced receiver is characterized by:

a beam splitter plate which receives said probe optical signal from said glucose sensor unit and splits said probe optical signal into a first component and a second component;

a polarizer and first photodetector, said first component being passed to said first photodetector through

said polarizer, said first photodetector having an output corresponding to the polarized component;

a second photodetector which receives said second component from said beam splitter plate having an output corresponding to the depolarized component;

a difference amplifier having a first input and a second input and an output, said first input of said difference amplifier being connected to said first photodetector output and said second input of said difference amplifier being connected to said second photodetector output;

a division amplifier having a first input, a second input, and an output;

a low-pass filter electrically connected between said second photodetector and said second input of said division amplifier, said output of said difference amplifier being connected to said first input of said division amplifier.

57. The apparatus of claim 53 characterized in that the balanced receiver is a photoreceiver, and the polarizing frequency shifter is characterized by:

a polarizing beam splitter cube having a center, a beam input side and a beam output side which is perpendicular to said input side;

a first quarter-wave plate which is located on a side of said polarizing beam splitter cube which is opposite to said beam input plate;

a second quarter-wave plate located on a side of said polarizing beam splitter cube which is opposite to said beam output side;

a first mirror which is located on the outer side of said first quarter-wave plate and is attached to said piezoelectrical transducer; and

a second mirror which is located on an outer side of said second quarter-wave plate;

wherein the difference between distances of said first and said second mirrors and said center of said polarizing beam splitter cube is smaller than a coherent length of said infrared laser beam.

58. The apparatus of claim 57 characterized in that the photoreceiver is characterized by:

a photodiode which is connected via a low-pass filter and a high-pass filter to a division amplifier, said low-pass filter and said high-pass filter being connected in parallel, said photodiode receiving said probe optical signal from said glucose sensor unit, said division amplifier having an output.

59. The apparatus of any of claims 52-58 characterized in that the electronic signal processing unit is characterized by a phase-sensitive homodyne receiver which receives said reference electrical signal and said probe electrical signal, a microcontroller connected to said phase-sensitive homodyne receiver, and memory means connected to said microcontroller.

60. The apparatus of any of claims 52-58 characterized in that the glucose measuring head is characterized by:

a housing having said space for receiving said blood-carrying body part;

an optical measurement signal input located on one side of said space for receiving said measurement optical signal, said photoreceiver being located on a side of said space opposite to said one side;

fixation means for fixing said blood-carrying body part; and

compression means for compressing said blood-carrying body part.

61. A pocket-type instrument for non-invasive measurement of blood glucose concentration characterized by:

an infrared laser source which produces an infrared laser beam;

an optical phase modulator comprising:

a first fiber-optic arm having an input for receiving the laser beam and an output;

a second fiber-optic arm having an input and an output, in the course of propagation through said fiber-optic arms said laser beam forming light-propagating modes;

an optical isolator located between the laser source and the input of the first fiber-optic arm for minimizing back reflection of laser light to the laser source;

an input polarizer located between the optical isolator and the input of the first fiber-optic arm, the input polarizer polarizing the laser beam so that the direction of its polarization forms a 45° angle to an axis X in an orthogonal X-Y coordinates in the cross-section of said first fiber-optic arm;

an input optical coupler which connects the first and second fiber-optic arms, the input optical coupler having means for splitting the laser beam into a first component which further propagates through the first fiber-optic arm and a second component which further propagates through the second fiber-optic arm;

an optical phase shifter connected to said first fiber-optic arm for phase modulating the said first component;

an output optical coupler connecting the first and second fiber-optic arms having means for coherently mixing the light-propagating modes of the first and second fiber-optic arms so that each output of each fiber-optic arm has a complementary coherent mixture of said first component and said second component with an

orthogonal direction of linear polarization, the output of said first fiber-optic arm producing a reference beam and the output of the fiber-optic second arm producing a measuring beam;

a quarter-wave plate for introducing a phase delay, said quarter-wave plate having a first window and a second window, said first window being aligned with the output of said first fiber-optic arm for producing a polarized-modulated reference optical beam, the second window being aligned with the second fiber-optic arm for producing a polarized-modulated measurement optical beam;

a glucose reference cartridge comprising two reference cells corresponding to two known glucose concentrations, the cartridge being shiftable between positions of passing the reference optical beam through one, the other or none of the reference cells;

an output polarizer located after the glucose reference cartridge in the direction of propagation of said reference beam; and

a photodiode located after the output polarizer for converting the reference optical beam into an electrical reference signal;

a glucose measuring head comprising

an input for receiving the polarized modulated measuring beam,

a space for receiving a blood-carrying body part of a subject,

a balanced receiver having an output producing an electrical measurement signal, and

means for producing a thickness measurement signal proportional to the thickness of said blood carrying body; and

an electronic signal processing unit which has a first input which is electrically connected to said photodiode for receiving said electrical reference signal and a second

input which is electrically connected to said balanced receiver for receiving said electrical measurement signal, and a third input for receiving said thickness measurement signal.

62. The apparatus of claim 61 characterized in that the phase shifter is made in the form of a piezoelectric body to which said first fiber-optic arm is attached, said piezoelectric body being electrically connected to said electronic signal processing unit, and the electronic signal processing unit is further characterized by means for sending a voltage signal to said piezoelectric body for causing alternating contractions of the piezoelectric body to modulate phases of the first component of said laser beam.

63. The apparatus of claim 62 characterized in that the phase shifter piezoelectric body is characterized by a thin-walled piezoceramic ring around which a portion of the first fiber-optic arm is wound, said piezoceramic ring being electrically connected to the electronic signal processing unit.

64. The apparatus of claim 62 characterized in that the balanced receiver is further characterized by means for dividing said measurement signal into a polarized component and a depolarized component and means for determining a polarized portion of said measurement signal from said balance receiver.

65. The apparatus of claims 61-64 characterized in that the electronic signal processing unit is further characterized by a phase-sensitive homodyne receiver which receives said reference electrical signal and said measurement electrical signal, a microcontroller connected to said phase-sensitive homodyne receiver, memory means

connected to said microcontroller, a piezocontroller, said phase-sensitive homodyne receiver being connected to the piezocontroller via a feedback loop and the piezocontroller being electrically connected to said piezoelectric body;

an audio transmitter connected to said microcontroller;

an analog-to-digital converter connected to said microcontroller; and

a display unit connected to said analog-to-digital converter.

66. The apparatus of any of the claim 61-65 characterized in that the glucose measuring head is further characterized by:

a housing having said space for receiving said blood-carrying body part;

fixation means for fixing said blood-carrying body part; and

compression means for compressing said blood-carrying body part; and

wherein the input of said glucose measuring head is located on one side of the space for receiving said body-carrying part, and the balanced receiver is located on a side of said space opposite to said one side.

67. An optical phase modulator for producing two polarized-modulated laser beams from a laser source characterized by:

a first length of a polarization preserving fiber-optic conductor having an input for receiving a polarized laser beam and an output;

a second length of a polarization preserving fiber-optic conductor having an input and an output;

an input polarizer for polarizing a laser beam as it passes into the input of the first fiber-optic conductor so that the direction of its polarization forms a 45° angle to

an axis X in an orthogonal X-Y coordinates in the cross-section of said first fiber-optic arm;

an input optical coupler which connects together the first and second fiber-optic conductors, the input optical coupler having a means for splitting a polarized laser beam propagating into the first fiber-optic conductor input into a first component which further propagates through the first fiber-optic conductor and a second component which further propagates through the second fiber-optic arm;

an optical phase shifter connected to said first fiber-optic conductor for phase modulating the said first component;

an output optical coupler connecting the first and second fiber-optic conductors so that each output of each fiber-optic conductor has a complementary coherent mixture of said first component and said second component with an orthogonal direction of linear polarization, the output of said first fiber-optic conductor producing a first optical beam and the output of the fiber-optic second art producing a second optical beam; and

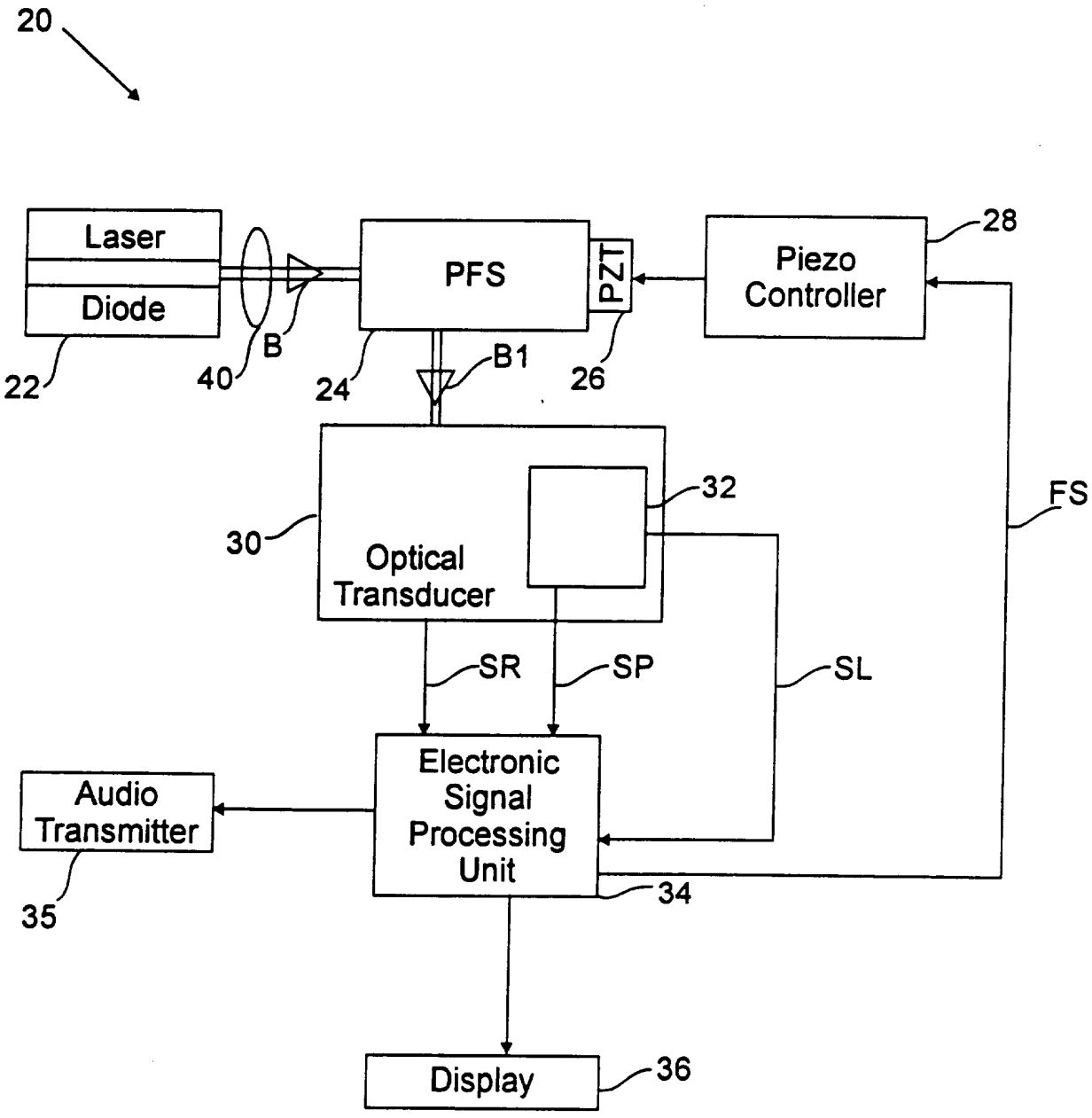
a quarter-wave plate structure for introducing a phase delay, said quarter-wave plate structure having a first window and a second window, said first window being aligned with the output of said first fiber-optic conductors for producing a first polarized-modulated optical beam and the second window being aligned with the second fiber-optic conductor for producing a second polarized modulated beam.

68. The apparatus of claim 67 characterized in that the phase modulator is further characterized by a piezoelectric body attached to a portion of the first fiber-optic conductor and a piezoelectric controller for operating the piezoelectric body to vibrate at a selected modulation frequency, thereby to deform the first fiber-optic conductor and phase modulate the component laser beam propagating therein.

69. The apparatus of claims 68 characterized in that the piezoelectric controller causes the piezoelectric body to vibrate with a frequency selected in the range of from 650Hz to 15 KHz.

70. The apparatus of claims 68 or 69 characterized in that the piezoelectric body is a thin-walled piezoceramic ring around which the portion of the first fiber-optic conductor is wound.

71. The apparatus of any of claims 68-70 characterized in that the piezoelectric controller circuit receives a feedback signal to control the vibration and hysteresis of the piezoelectric body.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Laser
Diode
22
40
B
PFS
PZT
24
B1
26
Piezo Controller
28
FS
30
Optical Transducer
32
SR
SP
SL
Electronic Signal Processing Unit
34
Audio Transmitter
35
Display
36

FIG. 1

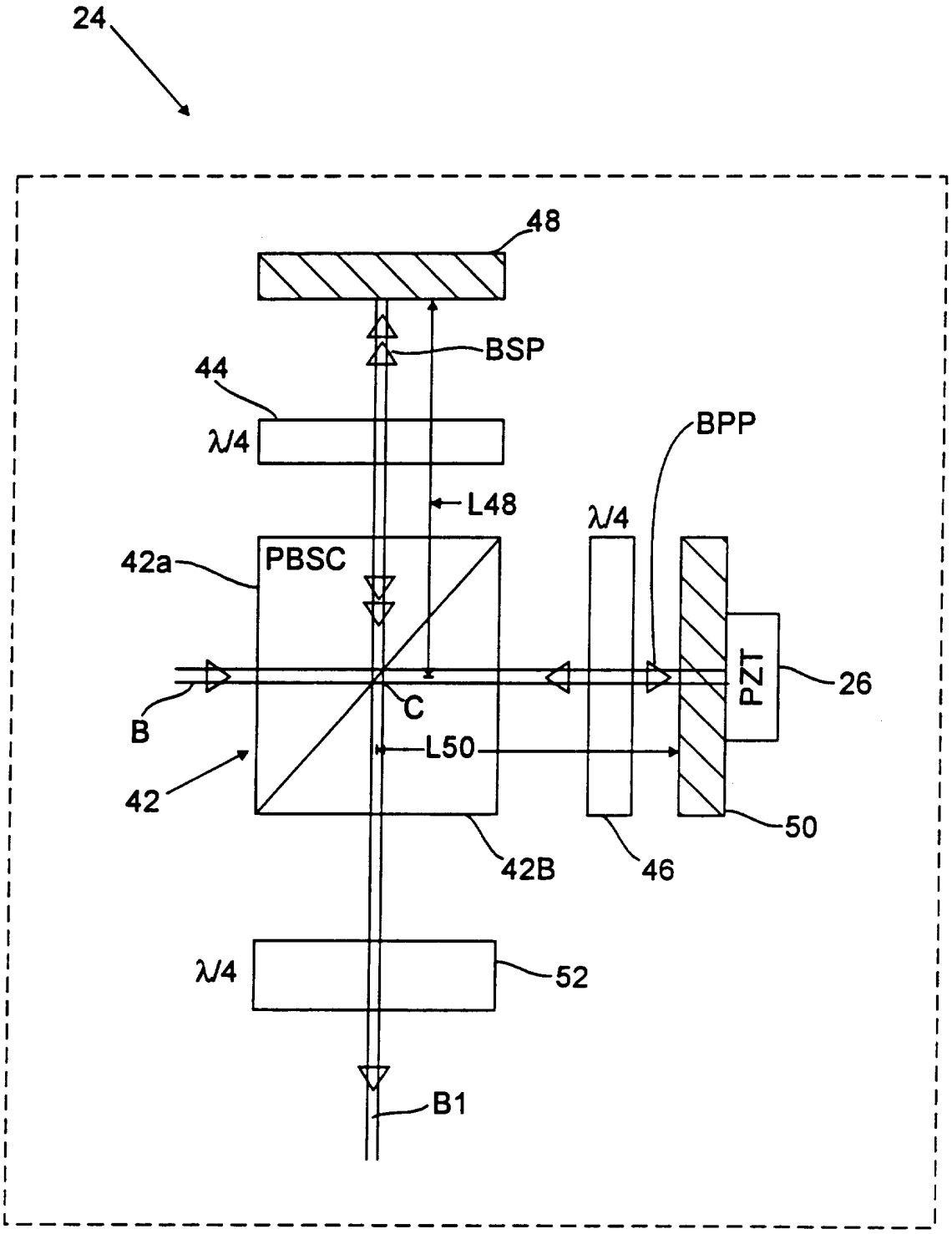

24
48
BSP
44
λ/4
BPP
L48
λ/4
42a
PBSC
PZT
26
B
C
L50
42
50
42B
46
λ/4
52
B1

FIG. 2

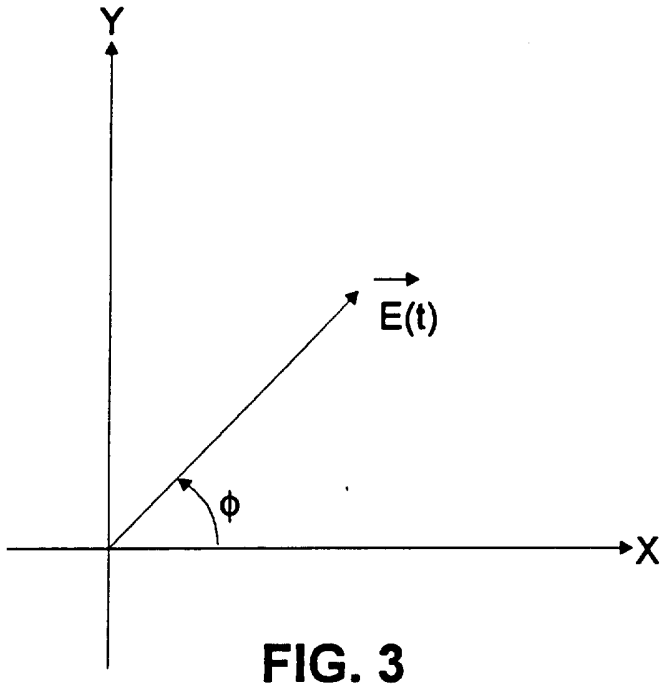


FIG. 3

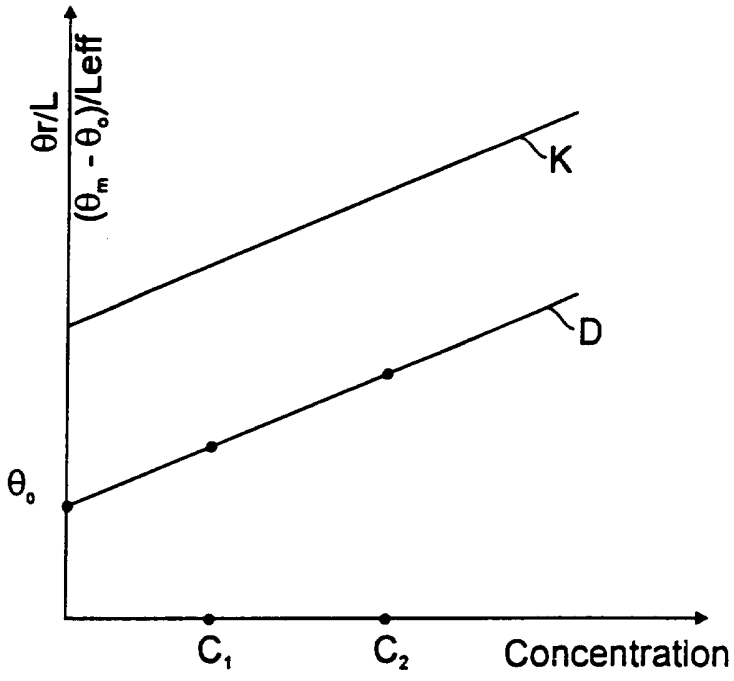


FIG. 8

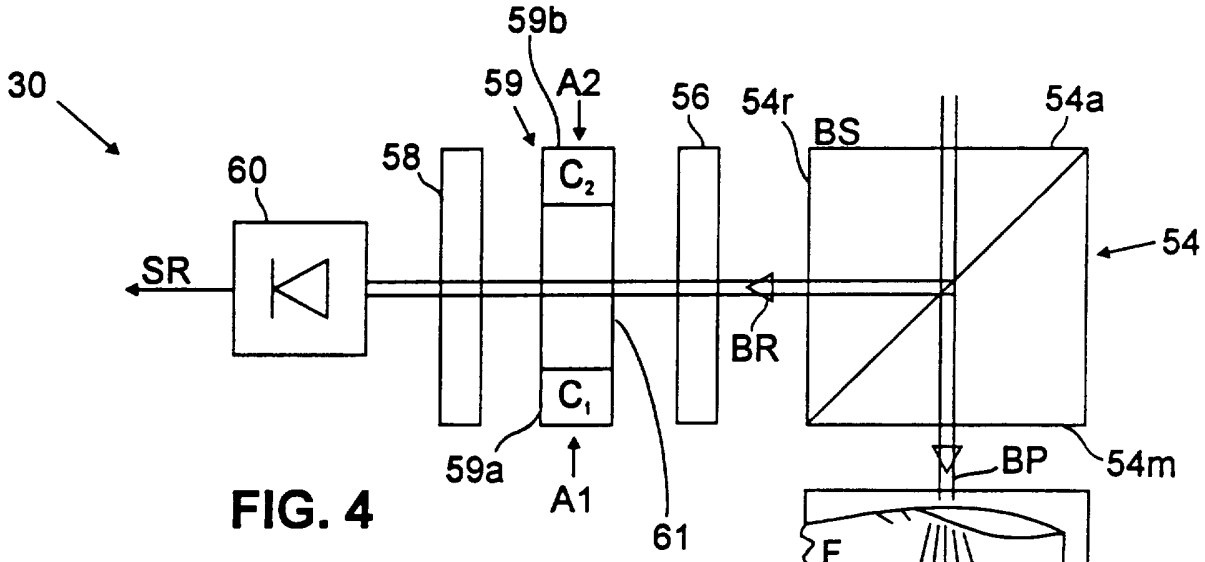


FIG. 4

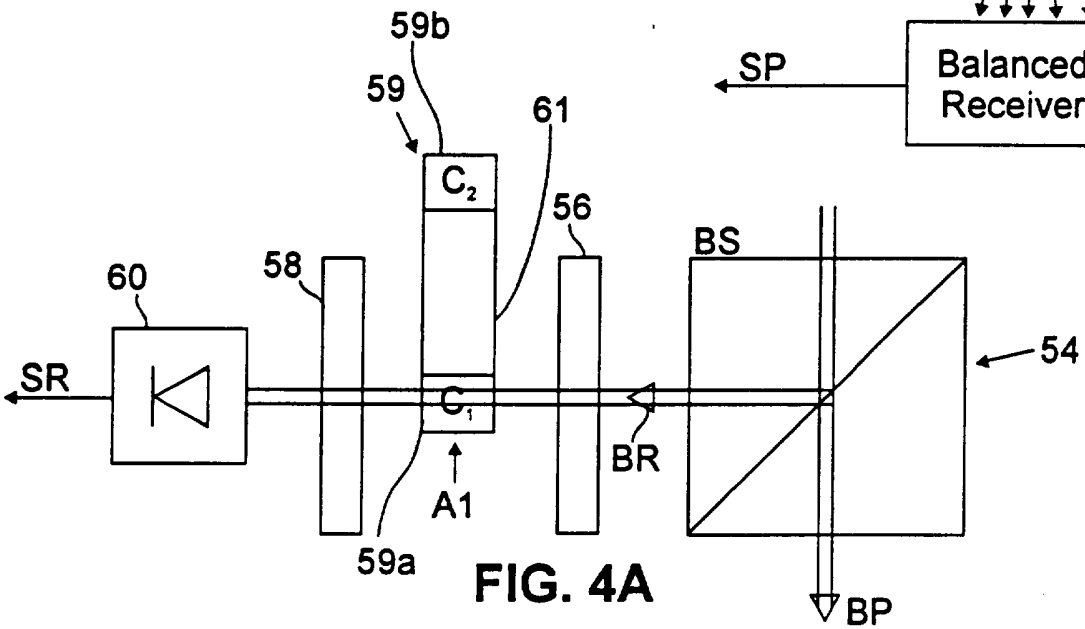


FIG. 4A

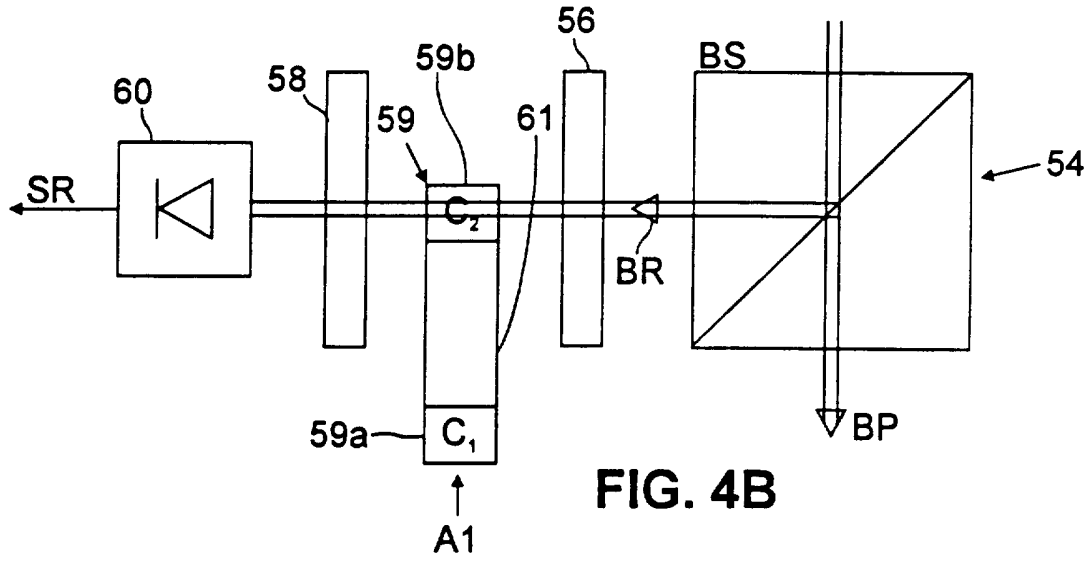


FIG. 4B

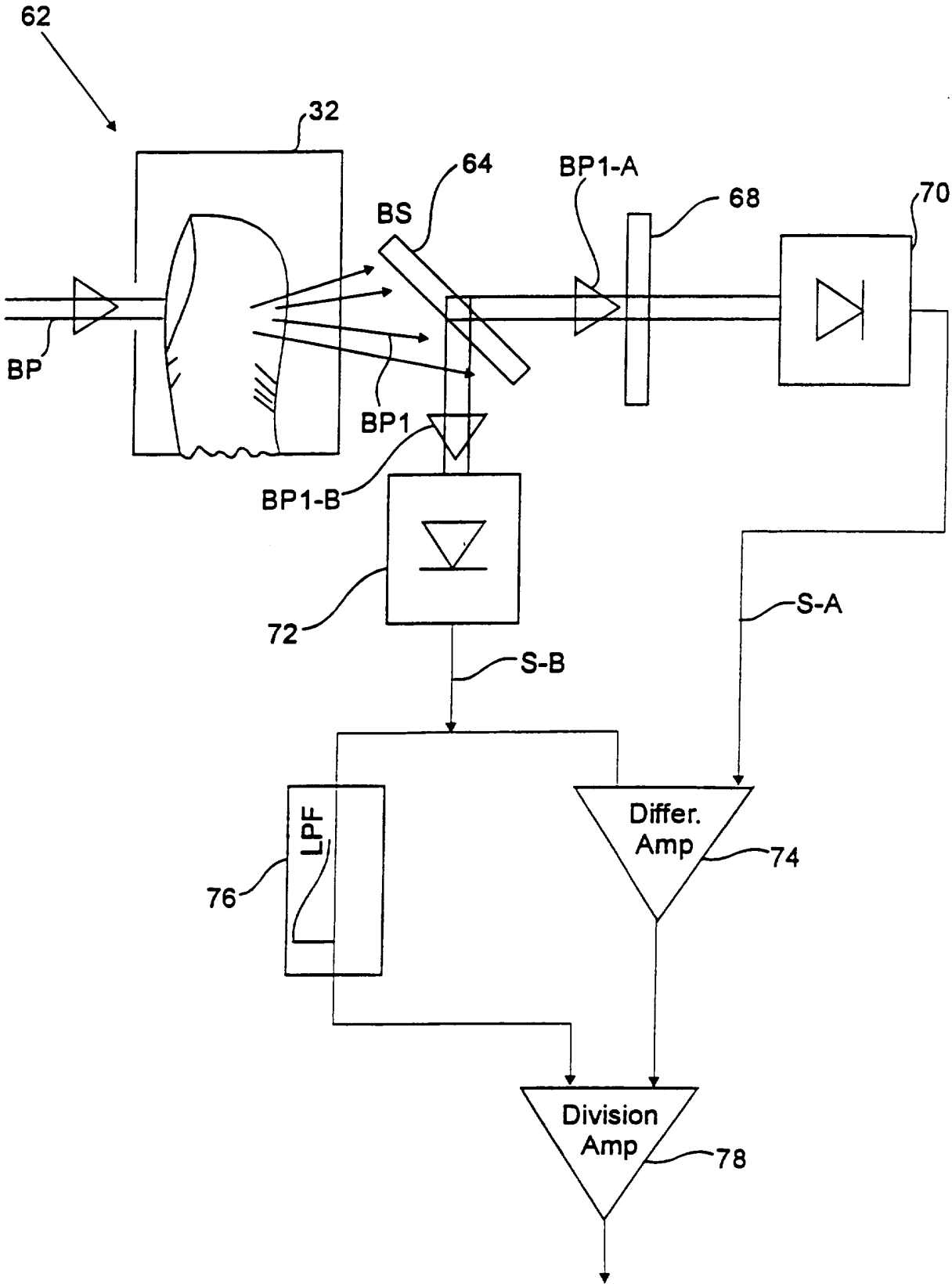

62
32
64
BS
BP1-A
68
70
BP
BP1
BP1-B
72
S-A
S-B
LPF
76
Differ.
Amp
74
Division
Amp
78

FIG.5

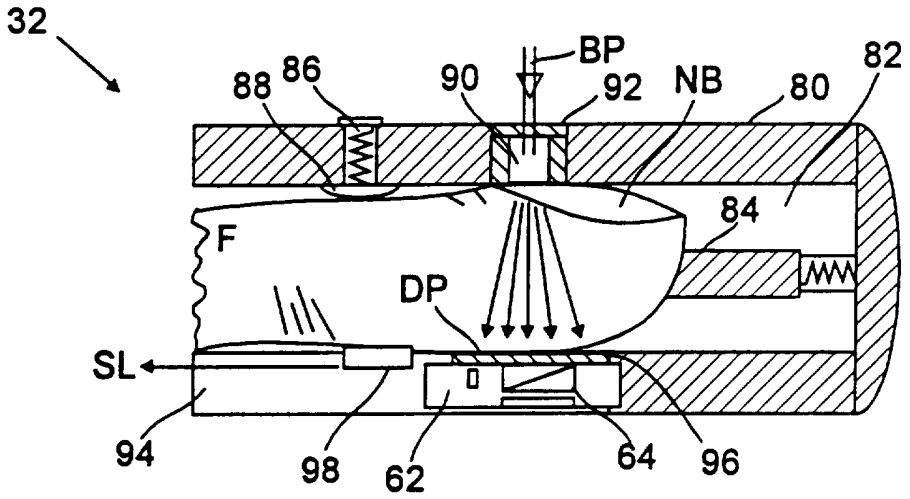


FIG. 6

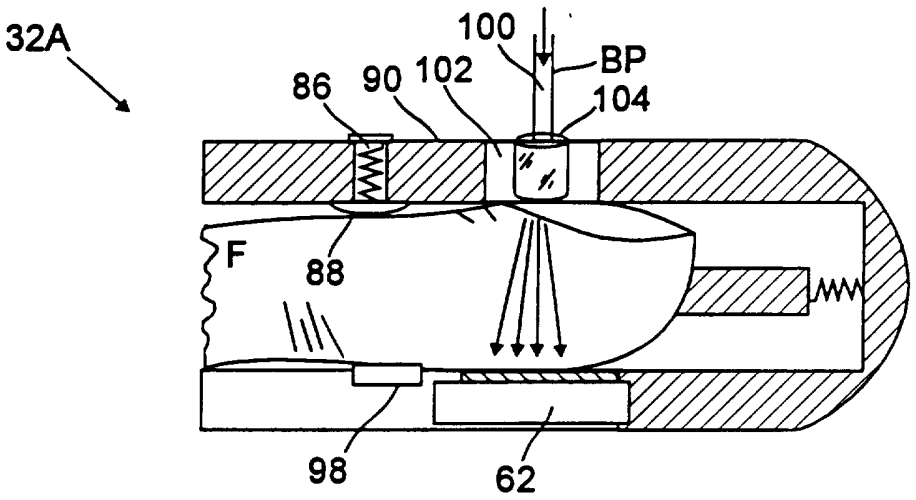


FIG. 6A

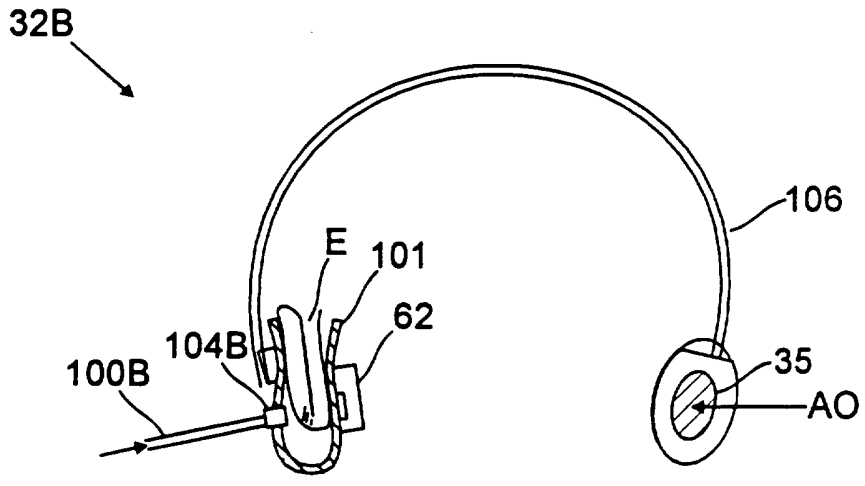


FIG. 6B

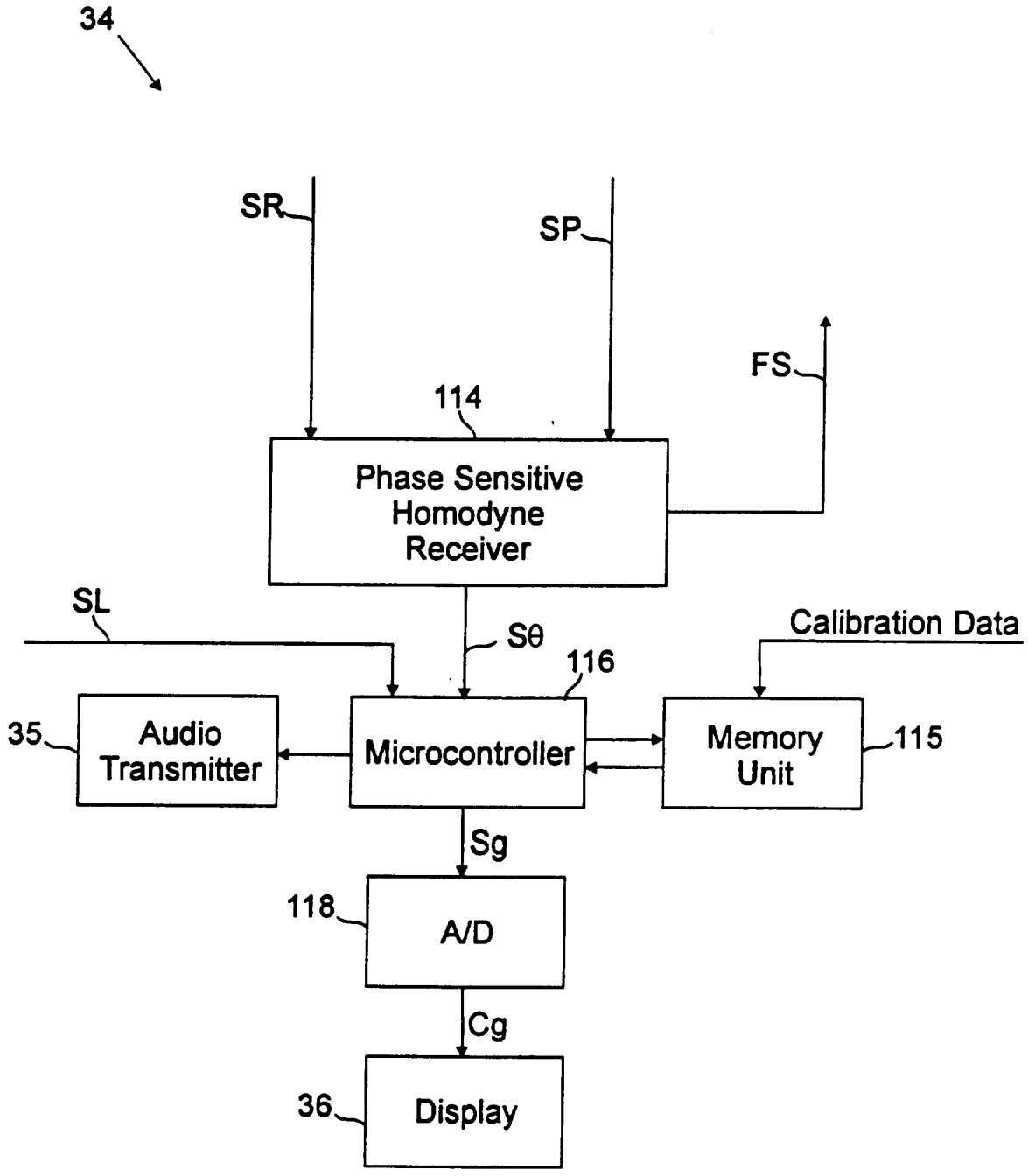
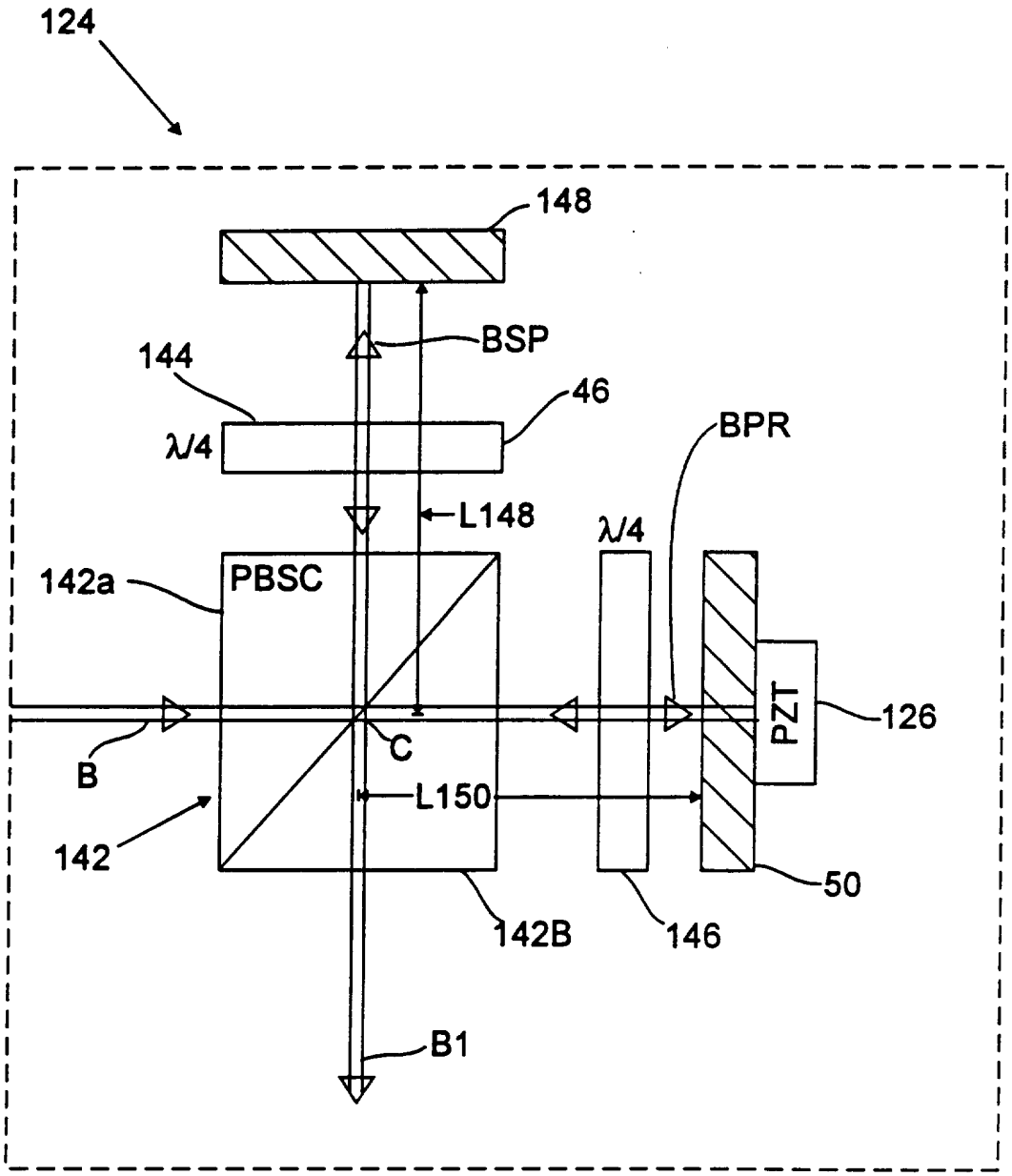

34
SR
SP
FS
114
Phase Sensitive Homodyne Receiver
SL
Sθ
Calibration Data
116
35
Audio Transmitter
Microcontroller
Memory Unit
115
Sg
118
A/D
Cg
36
Display

FIG. 7


124
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λ/4
BPR
L148
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PBSC
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B
C
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142
50
142B
146
B1

FIG. 9

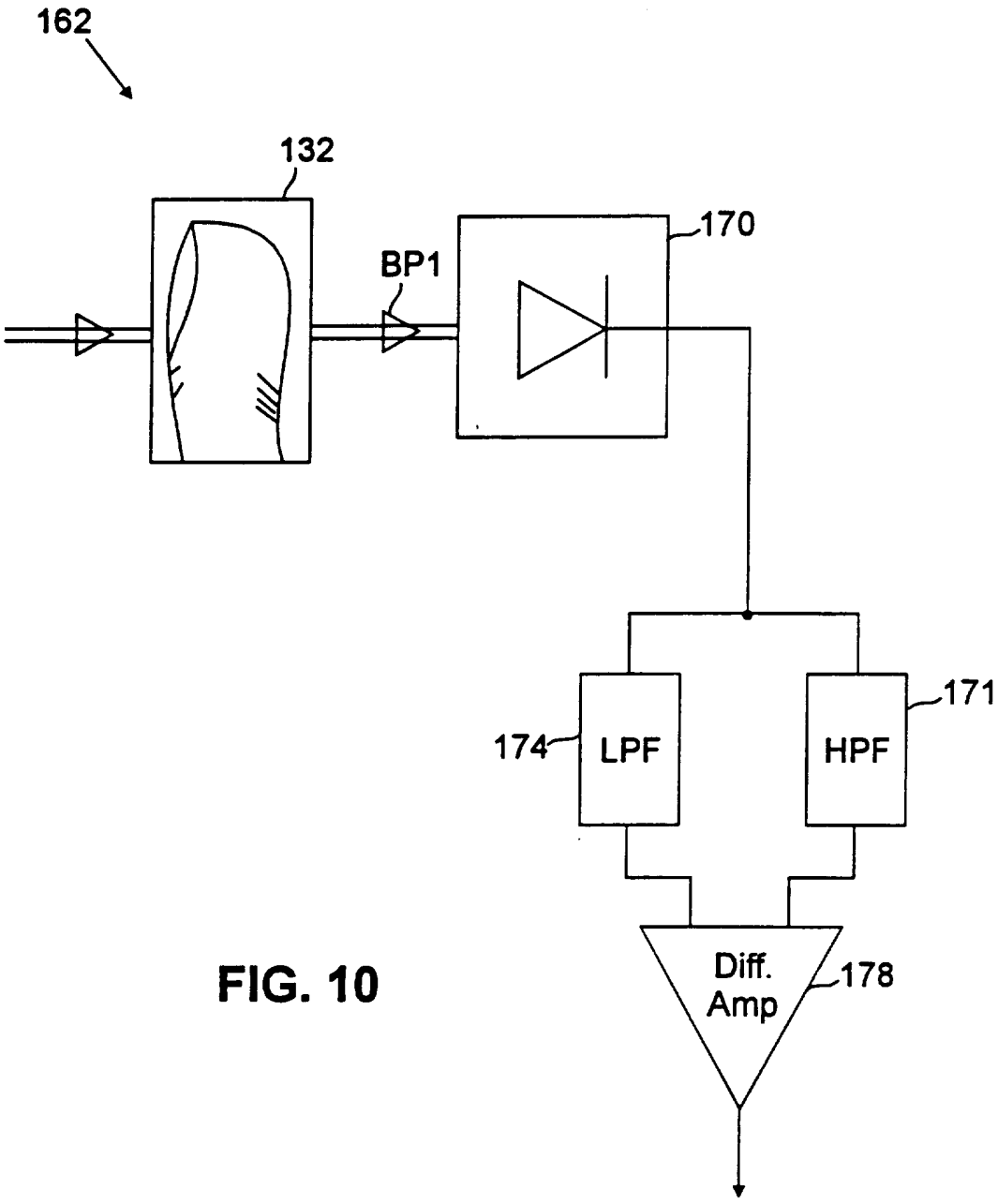
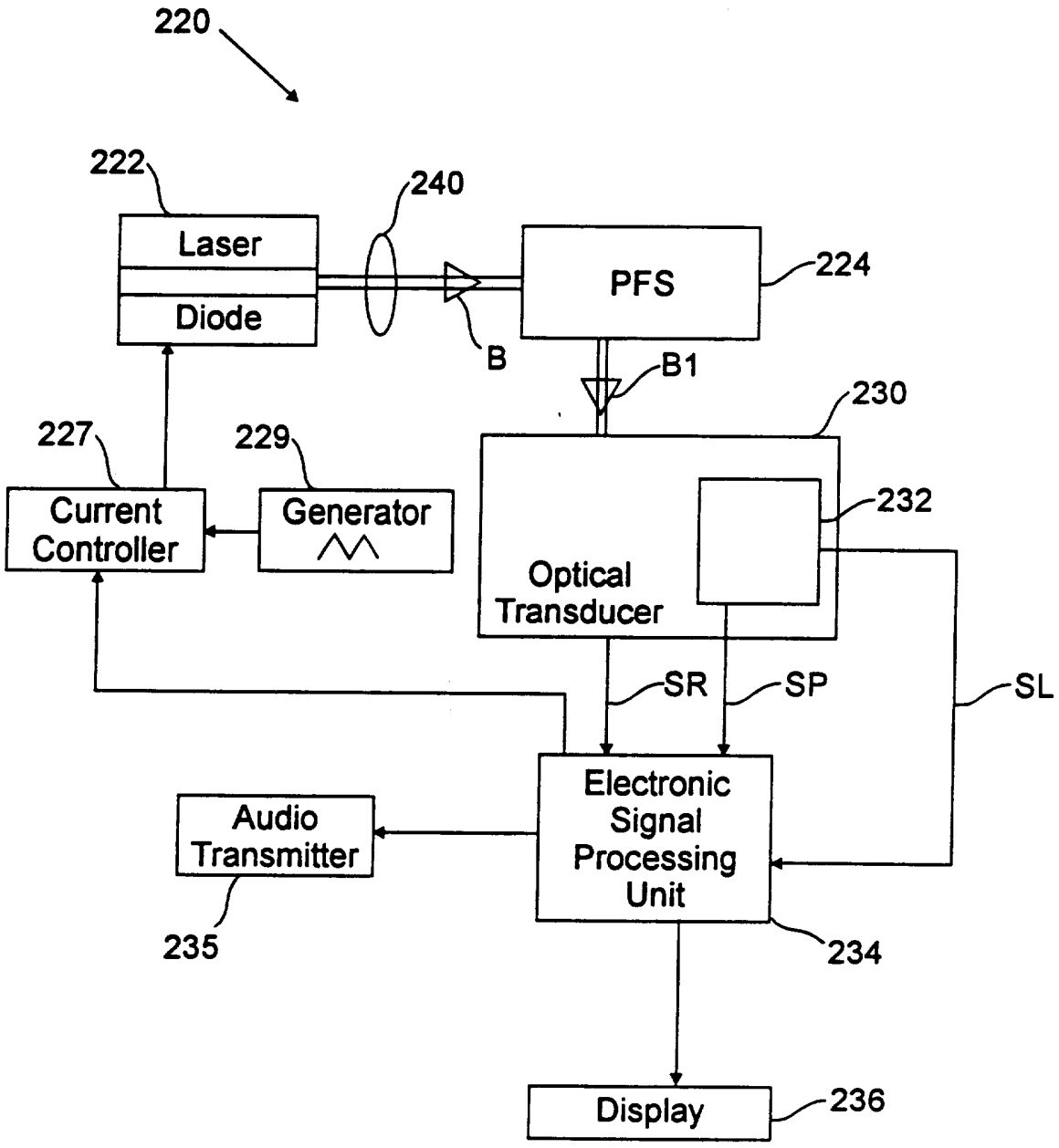


FIG. 10


220
222
240
Laser
Diode
PFS
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B
B1
230
227
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Current Controller
Generator
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Optical Transducer
SR
SP
SL
Electronic Signal Processing Unit
Audio Transmitter
235
234
Display
236

FIG. 11

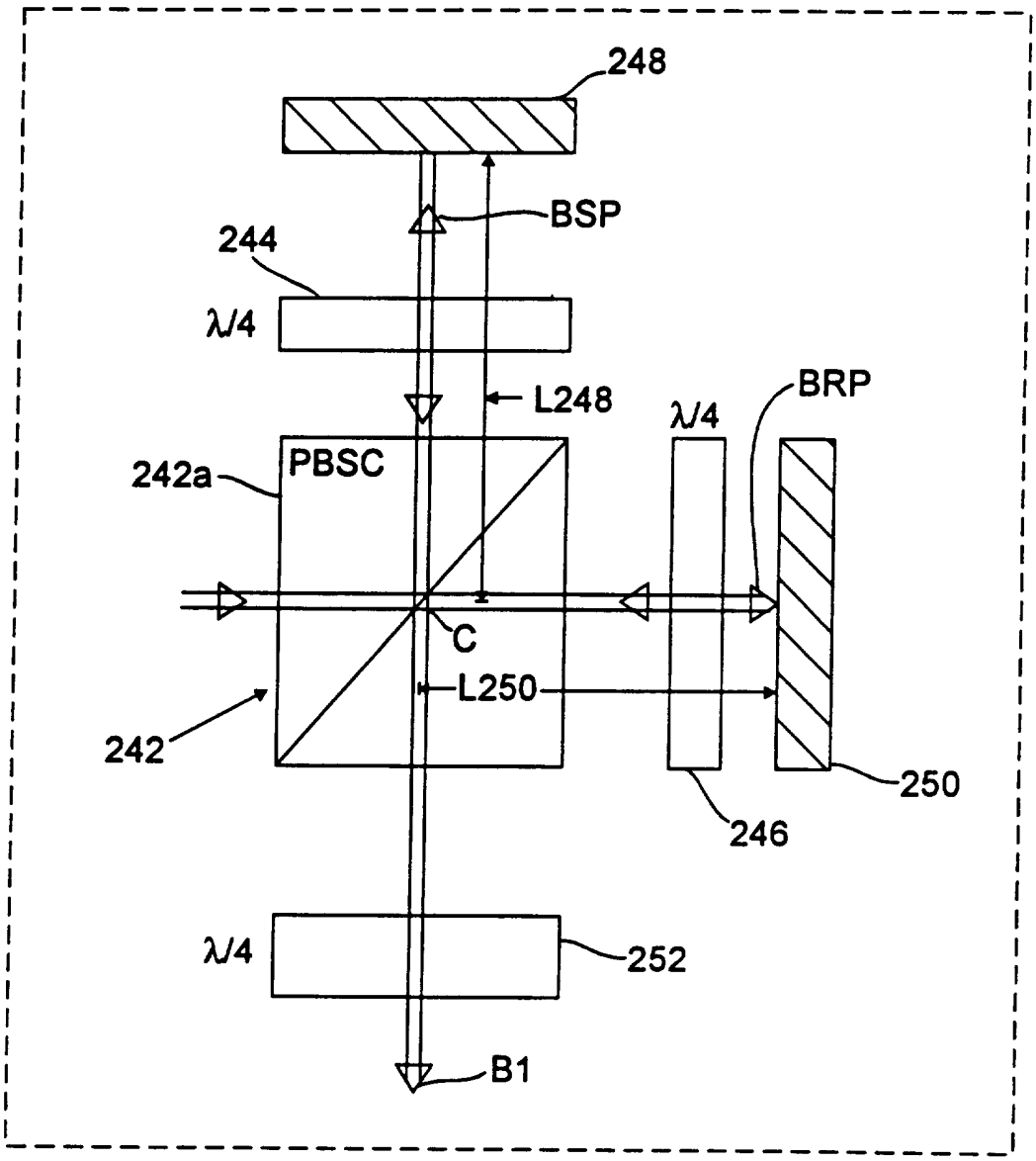
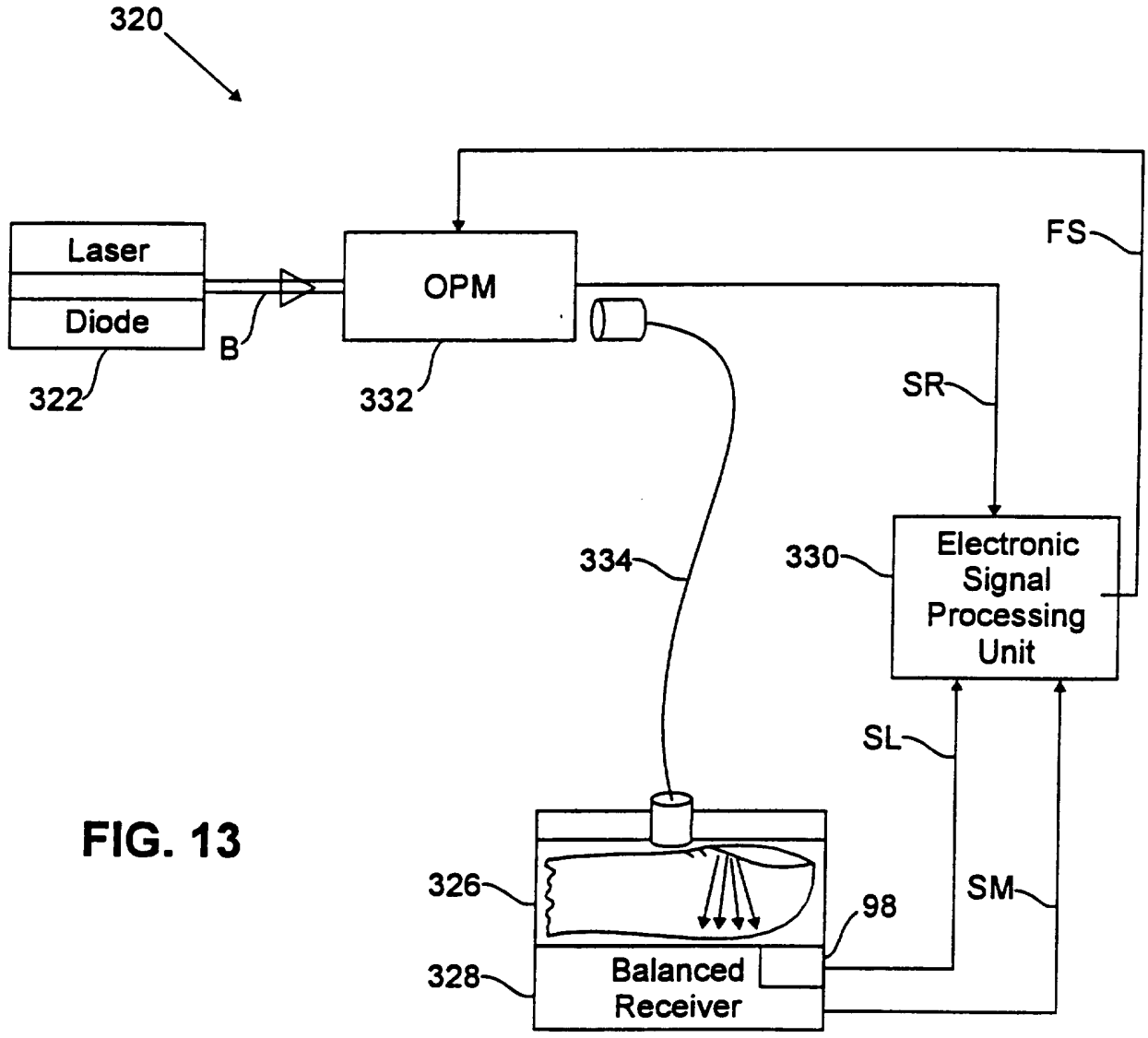


FIG. 12


320
Laser
Diode
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OPM
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FS
SR
334
330
Electronic
Signal
Processing
Unit
SL
326
98
SM
328
Balanced
Receiver

FIG. 13

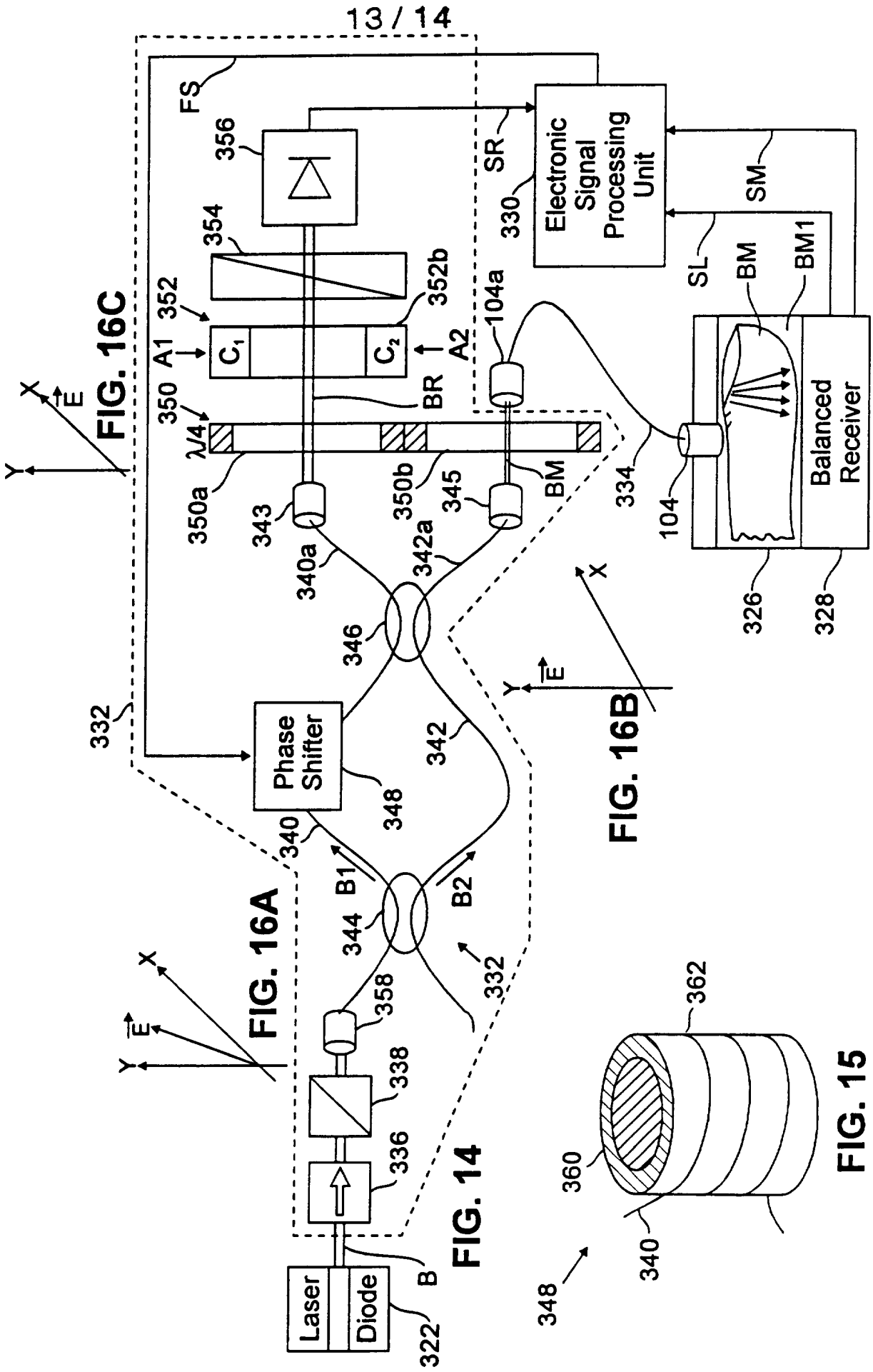


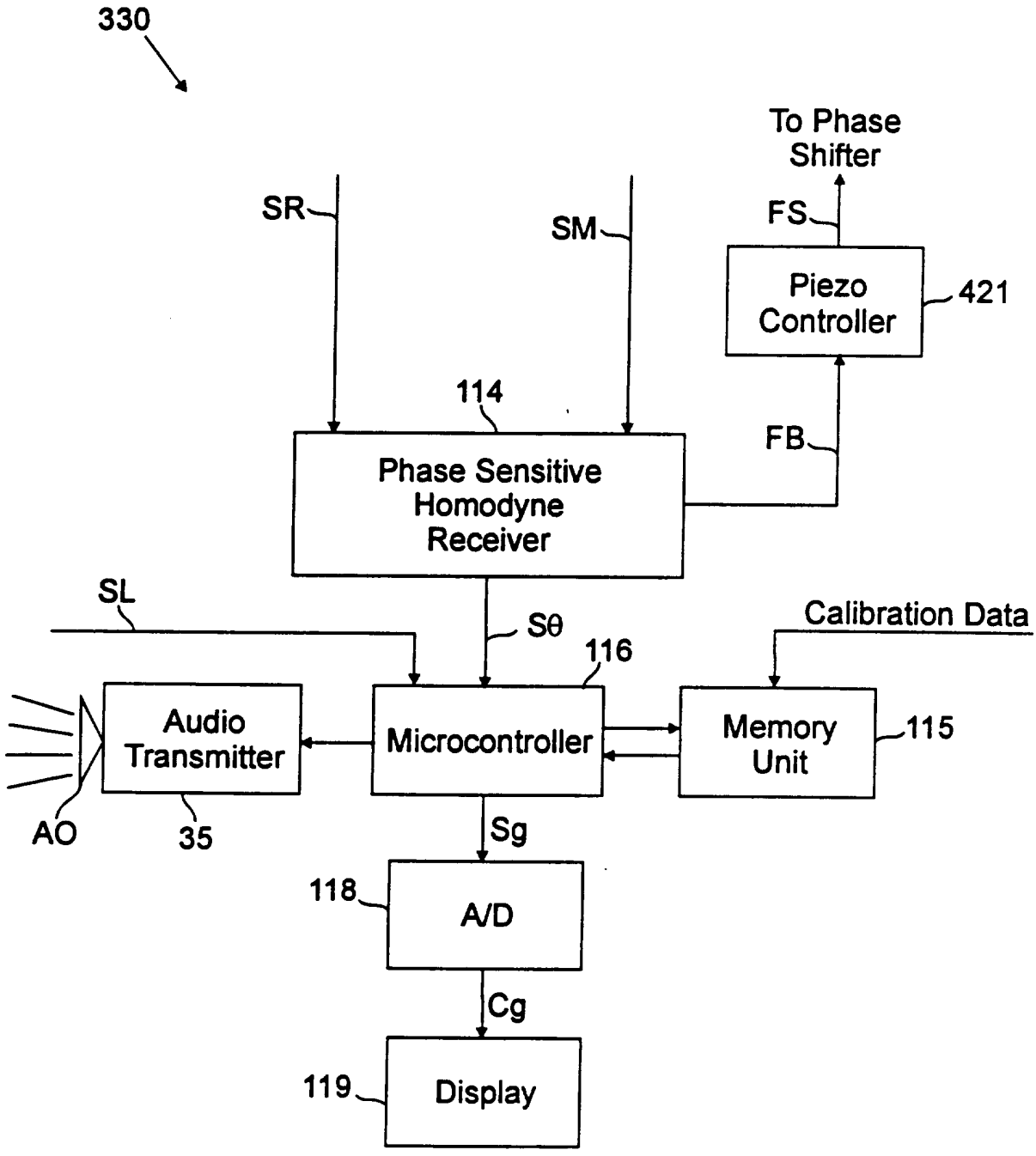
FIG. 16C

FIG. 16A

FIG. 14

FIG. 16B

FIG. 15


330
To Phase Shifter
SR
SM
FS
Piezo Controller
421
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FB
Phase Sensitive Homodyne Receiver
SL
Sθ
Calibration Data
116
Audio Transmitter
Microcontroller
Memory Unit
115
AO
35
Sg
118
A/D
Cg
119
Display

FIG. 17

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/US93/11807

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61B 05/02
US CL : 128/633
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/633, 664-666; 356/041, 364, 366, 368; 359/237-239, 278, 289

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y, P	US, A, 5,289,258 (Szafreniec et al) 22 February 1994, see figure 1.	67-71
A, P	US, A, 5,181,138 (Davis et al) 19 January 1993, see enitre document.	37-39
Y, P	US, A, 5,209,231 (Cote et al) 11 May 1993, see entire document.	40-42
Y	US, A, 4,834,532 (Yount) 30 May 1989, see entire document.	40-42
A	US, A, 4,704,029 (Van Heuvelen) 03 November 1987, see entire document.	1-8, 15-23, 32-36, 43-48, 50-59, and 61-65

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
20 APRIL 1994

Date of mailing of the international search report
MAY 19 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11807

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,901,728 (Hutchinson) 20 February 1990, see entire document.	1-8, 15-23, 32-36, 43-48, 50-59, 61-65

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/US93/11807

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-14, 24-31, 49, and 60
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Telephone Practice
Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int .tional application No.
PCT/US93/11807

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claims 1-31 and 52-60, drawn to a method and apparatus for measuring blood glucose, classified in class 128, subclass 633.
Group II, claims 32-36, drawn to a method of measuring blood glucose using circular dichroism, classified in class 128, subclass 633.
Group III, claims 37-39, drawn to a polarizing frequency shifter, classified in class 359, subclass 237.
Group IV, claims 40-45, drawn to a method and apparatus for calibrating a glucose monitor, classified in class 128, subclass 633.
Group V, claims 46-51, drawn to a tissue holding device, classified in class 128, subclass 666.
Group VI, claims 51-66, drawn to a pocket-type glucose monitor, classified in class 128, subclass 633.
Group VII, claim 67-71, drawn to an optical phase modulator, classified in class 359, subclass 238.