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(71) Applicant: UNIVERSITY OF CONNECTICUT [US/US]; 263 Farmington Avenue, Suite MC 5355, Farmington, CT 06030–5355 (US).

(72) Inventors: FOX, Martin, D.; 1 Storr Heights Road, Storrs, CT 06268 (US). JANG, Sunghoon; 25 Cameo Drive, Willimantic, CT 06226 (US).

(74) Agent: REIMER, Leah, M.; Cantor Colburn LLP, 55 Griffin Road South, Bloomfield, CT 06002 (US).

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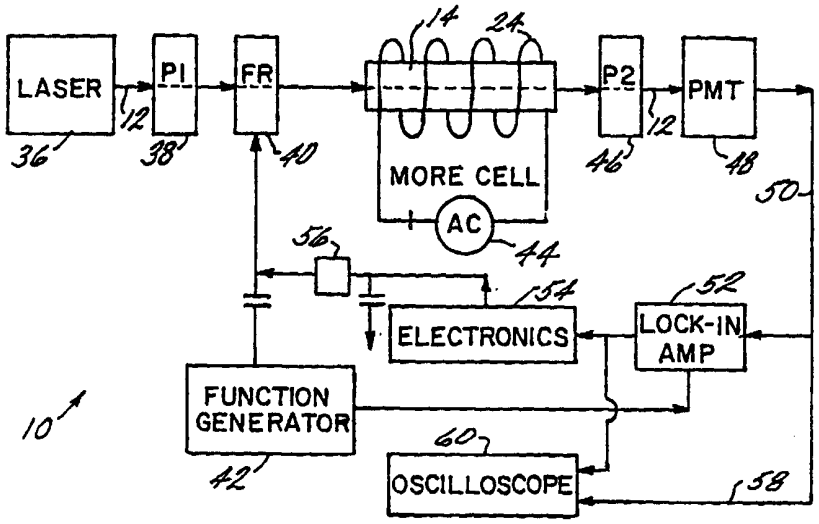

(57) Abstract

A non–invasive apparatus and method of optically sensing the glucose concentration of a solution is provided. The optical glucose sensor is based on the fact that glucose solutions have a magnetic optical rotatory effect (MORE) such that when a magnetic field is set up in a glucose solution there is a rotation of the polarization vector of the incident light that is proportional to the path length, magnetic field strength, and the concentration of glucose in the solution. The optical glucose sensor includes a laser that passes a beam of polarized light through the glucose solution (i.e. aqueous humor or an eye) while a coil sets up a magnetic field (B) in the solution. A photomultiplier tube provides an output signal indicative of the rotation of the polarization vector of incident light. The beam of light is also modulated by a Faraday rotator, which is controlled by a lock–in amplifier that closes a feed back loop. The output of the lock–in amplifier generates a signal indicative of the glucose concentration in the solution, which may be displayed on an oscilloscope or provided to a processor, which displays a readout indicative of the glucose concentration.

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OPTICAL GLUCOSE SENSOR APPARATUS AND METHOD

FIELD OF THE INVENTION

The present invention relates to apparatus and methods of determining the glucose concentration of a glucose solution and more particularly, to an apparatus and method for non-invasive testing of the blood glucose of an individual based on measuring the optical rotation of glucose in the aqueous humor of the eye by optical methods.

BACKGROUND OF THE INVENTION

Diabetes mellitus represents one of the major health problems today. Often, diabetes leads to such problems as renal failure and vision impairment. Estimated costs of diabetes related health care range between $20 to $40 billion annually. However, a recent multi-center NIH study has indicated that the health risks associated with diabetes are significantly reduced when the blood glucose levels are tightly controlled, indicating that it is prudent to measures the blood glucose as often as five or six times a day. Thus it is important that proper monitoring be done by diabetics at home or work.

Presently, existing methods of home blood glucose monitoring require obtaining a blood sample by pricking the fingertip with a needle or lancet (referred to as a "stick"), allowing the puncture to bleed until a testing strip is adequately covered with blood, and then placing the coated strip into a glucose monitor for testing. This method strongly discourages patient compliance and has the following serious drawbacks. First, this procedure is invasive. For many people, the prospect of performing 5 or 6 "sticks" daily is intimidating and painful. In addition, it provides a

significant opportunity for infection for a population, which is pre-disposed to infection of the extremities.

Second, this procedure for testing is laborious and involved. Many people have trouble learning how to test their own blood glucose. In addition, the procedure can become a nuisance, since it requires thorough hygiene (washing the hands, cleaning the area which is to be "stuck", etc.) and an involved testing procedure using strips and monitoring devices in the exact same manner. Third, there is little margin for error in the testing procedure, and thus many individuals do not necessarily obtain accurate results due to poor testing practices. Fourth, this procedure is expensive. Although the current marketing strategy employed by most manufacturers is to sell the monitor rather cheaply, the testing remains expensive and is the real source of profit, routinely costing 80 cents each. Thus tight blood sugar controls, requiring 5 or 6 strips daily, can cost patients over $1,000 annually.

Alternatively, a non-invasive method of testing an individuals blood glucose presently exists. This non-invasive method reflects a beam of light through the aqueous humor glucose. The method measures the polarization rotation of the beam to determine the concentration of the blood glucose.

Problems with previous noninvasive optical glucose measuring devices include the lack of spatial resolution of the rotatory effect, i.e. all tissues traversed by the beam affect the rotatory status of the light field. Second, the signal-to-noise ratio of optical rotatory effect is limited by the DC frequency of the conventional rotatory effect. Third, conventional optical rotatory effect is cancelled upon reflection from a dielectric mirror surface (the aqueous/lens interface is an example of such a surface).

SUMMARY OF THE INVENTION

In accordance with the present invention, an apparatus for determining the concentration of optically active substances in a solution comprises a laser for producing a beam of light. The beam of light passes through a coil having a predetermined number of turns. The coil is disposed about at least a portion of the solution, preferably the aqueous humor of an eye. An alternating current source is electrically connected to the coil to generate a magnetic field through the solution disposed therein. An optical detector receives the beam of light after the beam passes through the portion of the solution and the coil. The optical detector provides an output

signal indicative of the optical rotation of the solution, wherein the optical rotation is proportional to the concentration of the optically active substance.

In accordance with another embodiment of the present invention, a method for optically sensing concentration of optically active substance in a solution comprises generating a polarized beam of light and passing the beam through the solution. A magnetic field is set up through the solution to provide a polarization of the vector of incident light, which is proportional to the concentration of the optically active substance in the solution. The rotation of the polarization of the received polarized beam of light is determined.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figure 1 is a functional diagram of an optical glucose sensor embodying the present invention;

Figure 2 is a diagrammatic view illustrative of reflective characteristics from a dielectric mirror of light passing through an optical rotatory medium;

Figure 3 is a diagrammatic view illustrative of reflective characteristics from a dielectric mirror of light passing through a magnetic optical rotatory effect cell embodying the present invention;

Figure 4 is an enlarged diagrammatic view of an eye with a detector beam reflecting off the aqueous humor passing through a magnetic field provided by the optical glucose sensor of Figure 1;

Figure 5 is a graphical illustration of the voltage output of the optical glucose sensor of Figure 1 for a single pass through the MORE cell;

Figure 6 is a graphical illustration of the voltage output of the optical glucose sensor of Figure 1 for a double pass through the MORE cell; and

Figure 7 is a functional diagram of an alternative embodiment of an optical glucose sensor embodying the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Referring to Figure 1, a non-invasive optical glucose sensor 10 embodying the present invention is illustrated. The glucose sensor 10 passes a beam of

polarized light 12 through a glucose solution 14, which is reflected back through the solution. The glucose solution has a Faraday effect, thus providing an optical rotatory medium (e.g., Faraday Rotator) that rotates the polarization of light passing therethrough. The optical sensor 10 measures the polarization rotation of the reflected beam of light after passing through the glucose solution 14. It has been found that when a magnetic field (B) is set up in the glucose solution there is a rotation of the polarization of the vector of the incident light that is proportional to the path length, magnetic field strength and the concentration of the glucose in the solution. This relationship between the glucose concentration of the solution 14 and the rotation of the polarized light 12 passing therethrough permits non-invasive measurement of the glucose contrention of the solution. This magnetic optical rotatory effect (MORE) of a glucose solution 14 was found to be linearly proportional with the glucose concentration with a negative slope at physiologic concentrations, as will be described hereinafter.

Figure 2 illustrates the reflection of a beam of light 12 passing through a cell of an optical rotatory medium 14 (i.e., a glucose solution) and reflecting back therethrough off a reflective surface 16, such as a dielectric surface. The geometry of the passage of the polarized beam 12 reflected through the cell 14 is shown graphically by the vector of the electric field (E) 18. The direction of the E vector of the transmitted beam is shown at 20. The effect of the beam of light 12 reflected from the dielectric mirror 16 is similar to that of a conventional optical rotatory effect as is well know in the art. Generally, the resulting rotation of the **E** vector 16, as shown at 22, is 180°, and thus cancels the reflection resulting in zero net optical rotation. Graphically shown at 20 and 22, the direction of rotation is given by **k x E,** and both **k** and **E** show no net rotation of the reflective beam. This cancellation of the conventional optical rotatory effect upon reflection from a dielectric mirror surface is discussed in the article "Polarimetry in the Presence of Chiral and Gyrotropic Media and Various Reflection and Retrodirection Mirroring" published in Journal of Electromagnetic Waves and Applications, v.11 297-313, 1997, which is hereinafter incorporated by reference.

Figure 3 illustrates the reflection of a beam of light 12 through a cell 14 of a similar optical medium, as shown in Figure 2, wherein a magnetic field (B) is set up in the optical rotatory medium by conducting an alternating current through the coil 24 disposed about the medium. In contrast to the method illustrated in Figure 2, the

cell of Figure 3 uses the magnetic Optical Rotator Effect ("MORE") to achieve double the rotation (2θ) in the same geometry. This double rotation is achieved because the direction of rotation is dependent on the vector cross product B x E, and the direction of B remains in the same direction as indicated by arrows 26. The direction of the E vector 18 of the transmitted beam is shown at 28. As shown, the reflection of the light beam 12 from the dielectric mirror 16 and magnetic optical rotatory effect cell 14 with glucose solution results in 180 degree rotation of **E** vector 18 (due to the mirror reflection) with an additional 2θ phase shift, as shown at 30. This method eliminates the cancellation of the conventional optical rotation effect that occurs upon reflection from a dielectric [E field inverting] mirror.

This method of optically sensing the concentration of glucose in a solution 14 disposed in the aqueous humor 31 in accordance with the present invention may be used to provide a non-invasive procedure to determine the glucose level of an individual by reflecting the beam of light 12 off the lens 32 in the human eye 34 as illustrated in Figure 4. The lens/aqueous interface can be characterized as a dielectric mirror 16. For such an interface, the magnetic optical rotation effect should double the detected rotation. The double rotation is due to the light beam 12 passing twice through the glucose in the aqueous humor 14 with magnetic field (B) after reflection of the light beam 12 from the aqueous/lens interface.

Referring again to Figure 1, a detailed description of the optical glucose sensor 10 is provided. The sensor is similar in a number aspects as that disclosed in the articles "Multiple Wavelength Non-Invasive Ocular Polarimetry for Glucose Measurement for Managing of Diabetes", published in SBIR Program Final Report, 1995; and "Optical Glucose Sensor Using a Single Faraday Rotator, published in Proceedings of the 23rd Annual Northeast Bioengineering Conference, May 21-22, 1997; each of which are hereinafter incorporated by reference. A coherent light source 36, currently a helium neon (HeNe) laser, emits a collimated beam 12. In the alternative, the light source may be a white light source. This could be a laser operating at a different frequency (i.e., infrared diode) or a coherent light source with a collimating lens. The beam 12 is then passed through a first polarizer (P1) 38, which linearly polarizes the light of the beam to produce a field (E). The laser 36 provides approximately 2 mW effective output after the first polarizer 38 of 633 nm.

The light beam 12 then passes through a Faraday rotator (FR) 40 which rotates the polarization of the beam approximately 5°. This degree of rotation is dependent on the level of the voltage, which may be increased by increasing the voltage provided to the Faraday rotator. On skilled in the art that a poeckel cells, liquid crystals and kerr cell may also be used to rotate the polarization of the beam. A function generator 42 provides an approximately 1.2 Hz drive signal to the Faraday rotator 40. The light beam 12 then passes through the cell 14 (MORE cell) of glucose solution (e.g., the aqueous solution of the aqueous humor 31) and reflects back through the cell, as shown in Figure 3. A coil 24 of a predetermined number of turns is electrically connected to an alternating current (ac) source 44. The number of turns of the coil is based on the desired magnitude of the magnetic field (B). In one embodiment, the number of turns is greater than 100. The frequency of the ac source, for example, may be approximately 10 Hz, however, one skilled in the art will appreciate that signal to noise ratio improves as the frequency of the ac source increases. The coil 24 winds about the cell 14, such that the longitudinal axis of the coil is generally perpendicular to the reflective interface 16. The ac source 44 and the coil 24 generate a magnetic field (B) throughout the glucose solution, which can be precisely controlled. In a one embodiment of the present invention, the inner diameter of the coil 24 is substantially equal to the diameter of the human eye (i.e., the cell). In the operation of the optical sensor 10, the coil 24 is place within the user's eye socket so that a portion of the eye 34 is disposed within the coil. The reflected beam 12 then passes through the coil and the glucose solution of the aqueous humor 31 within the eye 34 and reflects off the lens 32 and back through the solution and coil.

The light beam 12 then passes through a second polarizer (P2) 46, which is disposed at 90 degrees to the first polarizer 38. The resulting rotation of the polarized beam passing through the second polarizer 46 is determined by a photomultiplier tube (PMT) 48 that generates an electrical output signal at lead 50 representative of the rotational position of the beam 12. The output signal is fed back to the Faraday rotator 40 through a lock-in or phase lock amplifier 52, an electronic circuit 54 and a two (2) Henry inductor 56 to close the loop. The output signal is also provided to an oscilloscope 60 via lead 58 for displaying the output signal. In the alternative, the output signal from the photomultiplier tube 48 and the lock-in amplifier

52 may be provided to a processor that generates a phase signal indicative of the phase rotation of the glucose in the aqueous humor 31. The phase signal is provided to a readout, which displays a result indicative of the concentration of the glucose in the aqueous humor.

The lock-in amplifier 52 provides an output signal which is a dc voltage proportional to the amplitude of the 1.2 kHz present in the output signal from the photomultiplier 48. This dc output voltage is fed back to the an integrator of the electronic circuit 54 and the Faraday rotator 40 through the inductor 56 to close the loop. The lock-in amplifier 52 therefore provides phase and frequency locked detection of the 1.2 kHz component, which is proportional to the net rotation between the two polarizers 38 and 46 disposed at 90° to each other. The bandpass of the feedback loop also limits the lock-in frequency. As described hereinbefore, increasing the lock in frequency increase the signal to noise ratio of the system. The MORE cell 14, varies or modulates this net rotation at the frequency of the magnetic field (B), which may be set at approximately 10 Hz (frequency of the ac source 44). The resultant signal is picked up as a 10 Hz p-p ac signal on the oscilloscope 60. The function generator also provides the 1.2 kHz signal to the lock-in amplifier. This AC modulation of the desired signal, which can be detected using the lock-in amplifier 52 for phase coherent detection, results in improved signal to noise ratio. This lock-in technique can actually pull a signal out of over 100 db of additive random noise.

In the sensing of the glucose level of the glucose solution with the aqueous humor 31 of the eye 34, the beam of light 12 passes through the magnetic optical rotatory cell 14 after reflection from the dielectric mirror 16, the magnitude of rotation due to the MORE cell is proportional to the concentration of the glucose, the path length of the cell, and the magnitude of the magnetic field (B) in the cell.

In an alternative embodiment, a single magnetic optical rotatory effect (MORE) cell may be used to sense the optical rotation of a glucose solution. A single MORE cell is similar to that described hereinabove except the light 12 is not reflected back through the cell 14 (glucose solution), but reflected directly to the second polarizer 46.

Figures 5 and 6 illustrate graphically the peak to peak voltage of the output signal of the optical sensor 10 versus the glucose concentration of the solution for a single MORE cell and double MORE cell, respectively. The output slopes 66, 68

for both single and double MORE, respectively, are shown in equations (1) and (2) below;

$$\left|\frac{\Delta Vp - p(mV)}{\Delta G(mg/dl)}\right|_{1MORE} = 0.242\,(mV/(mg/dl)) \qquad (1)$$

$$\left|\frac{\Delta Vp - p(mV)}{\Delta G(mg/dl)}\right|_{2MORE} = 0.476\,(mV/(mg/dl)) \qquad (2)$$

Where Vp-p is peak-peak voltage output is from the lock-in amplifier 52; and

G is the concentration of glucose solution in mg/dl.

As shown by equations (1) and (2), the double MORE cell provides twice the optical rotation of the single pass of the single MORE cell, and thus showing that the double MORE had 99.7% greater slope (close to the predicted 100% greater slope) indicating twice the sensitivity of single MORE cell.

Referring to Figure 7, an alternative embodiment of an optical glucose sensor 70 is shown. Like numbered components of the sensor 10 illustrated in Figure 1 and described hereinbefore are similar to sensor 70 shown in Figure 7. The glucose sensor 70 of Figure 7 further includes an additional lock in amplifier 72 for a second feedback loop to improve the signal to noise ratio of the sensor. The output signal of the first lock in amplifier 52 is provided to the input of the second lock in amplifier 70. Further, the ac source 44 is provided to the input of the second lock in amplifier 70. The output of the second lock in amplifier is then provided to the oscilloscope 60 (or processor).

The present invention described hereinbefore for optically sensing glucose using the fact that magnetically induced optical rotation in glucose solutions is linearly proportional to glucose concentration at physiologic levels has many advantages over the prior art. This non-invasive method of testing blood glucose is fast and simple, and is more economical than existing methods. The cost to patients of such a method would be significantly less over time than existing methods because only a monitor 10 would be required, and the high monthly expense of testing strips would be avoided. In addition, patient acceptance would be very high because of the non-invasive nature and the simple use of the procedure.

In addition, the present invention produces improved spatial resolution since the effect only occurs in regions of space where the magnetic field distribution can be precisely controlled. Improved signal to noise ratio can also be achieved due to an AC modulation of the desired signal which can be detected using a lock in amplifier for phase coherent detection. This lock-in technique can actually pull a signal out of over 100 db of additive random noise. Further, the magnetic field (B) provided about the cell 14 of glucose solution eliminates the cancellation of the conventional optical rotation effect that occurs upon reflection from a dielectric [E field inverting] mirror 16. This makes possible glucose measurements after reflection from the aqueous/lens interface.

While the present invention has been described to determine the blood glucose level of an individual, one will appreciate that this could also be useful in glucose detection in biotechnology applications, where non-invasive methods to determine the concentration of glucose in a solution is required.

Although the foregoing detailed description has been directed to the measurement of glucose in the aqueous humor 34, the apparatus and method are adaptable to other applications where an optically active substance is to be measured. As one example, some biogenetic processes have optically active materials either as reactants or products, and the apparatus and method may be used as a non-invasive tool to follow the progress of the reaction without the potential for contamination presented by sampling devices.

It will be understood that a person skilled in the art may make modifications to the preferred embodiment shown herein within the scope and intent of the claims. While the present invention has been described as carried out in a specific embodiment thereof, it is not intended to cover the invention broadly within the scope and spirit of the claims.

CLAIMS

What is claimed is:

1. An apparatus for determining concentration of optically active substances in a solution, the apparatus comprising:

a laser for producing a beam of light;

a coil having a predetermined number of turns about at least a portion of the solution;

an alternating current source electrically connected to the coil to generate a magnetic field through the solution;

an optical detector for receiving the beam of light after the beam passes through the portion of the solution and the coil, the optical detector providing an output signal indicative of the optical rotation of the solution, wherein the optical rotation is proportional to the concentration of the optically active substance.

2. The apparatus of claim 1 further includes:

a first polarizer disposed upstream from the coil for linearly polarizing the beam of light; and

a second polarizer disposed downstream from the coil for linearly polarizing the beam of light.

3. The apparatus of claim 1 the first polarizer and second polarizer are disposed at approximately 90 degrees from each other.

4. The apparatus of claim 1 wherein the optical detector comprises a photomultiplier tube.

5. The apparatus of claim 1 further includes:

an optical beam modulator for electronically modulating the beam of light to null the observed phase shift resulting from elements other than the optically observed active substance, thereby providing a closed loop.

6. The apparatus of claim 5 wherein the optical beam modulator comprises a Faraday rotator.

7. The apparatus of claim 5 further includes a function generator for driving the optical beam modulator at a predetermined frequency.

8. The apparatus of claim 5 further includes a lock-in amplifier to provided phase and frequency locked detection signal at a predetermined frequency of the output signal.

9. The apparatus of claim 8 wherein the detection is provided to the optical beam modulator to provide a closed loop.

10. The apparatus of claim 1 further includes a reflector disposed downstream from the coil to reflect the beam of light to the optical detector.

11. The apparatus of claim 10 wherein the reflector reflects the beam of light back through the solution to the coil to reflect the beam of light to the optical detector.

12. The apparatus of claim 1 wherein the solution is disposed in an aqueous humor of an eye.

13. The apparatus of claim 1 wherein the optically active substance is glucose.

14. The apparatus of claim 1 further includes a processor for displaying a readout indicative of the concentration of the optically active substance in response to the output signal.

15. A method for optically sensing concentration of optically active substance in a solution; the method comprising:

generating a polarized beam of light;

generating a magnetic field through the solution;

passing the polarized beam of light through the solution;

receiving the polarized beam of light from the solution; and

determining the rotation of polarization of the received polarized beam of light due to the optically active substance in the solution.

16. The method of claim 15 further comprising passing the beam of light through a first polarizer disposed upstream from the solution.

17. The method of claim 16 further comprising passing the beam of light through a second polarizer disposed downstream from the solution.

18. The method of claim 15 further comprising modulating the polarized beam of light at a predetermined frequency.

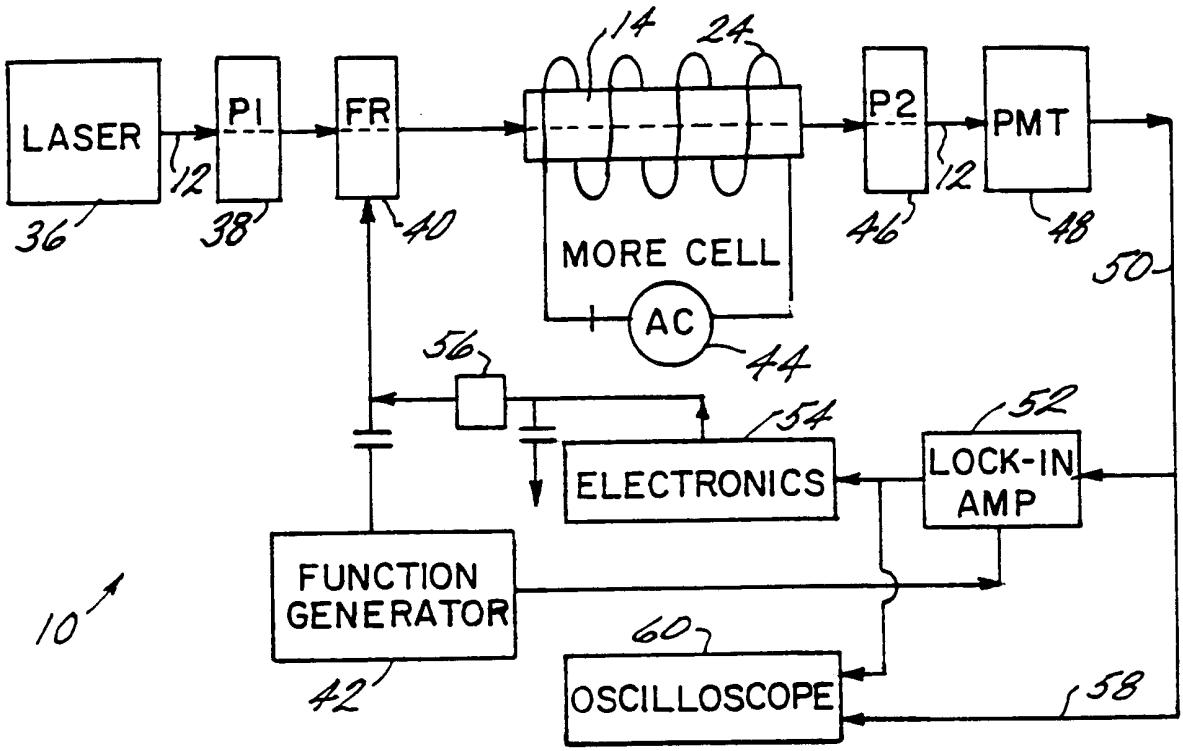
19. The method of claim 18 wherein the beam of light is modulated using a Faraday rotator.

20. The method of claim 18 further comprising generating a phase and frequency locked detection signal in response to the output signal to provide feedback to a beam modulator.

21. The method of claim 15 further comprising reflecting the beam of light back through the solution and coil to the optical detector.

22. The method of claim 15 is further comprising displaying a readout indicative of the concentration of the optically active substance in the solution based on the rotation of polarization.

23. The method of claim 15 wherein the solution is disposed in an aqueous humor of the eye.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P2
PMT
MORE CELL
AC
ELECTRONICS
LOCK-IN AMP
FUNCTION GENERATOR
OSCILLOSCOPE
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FIG. 1

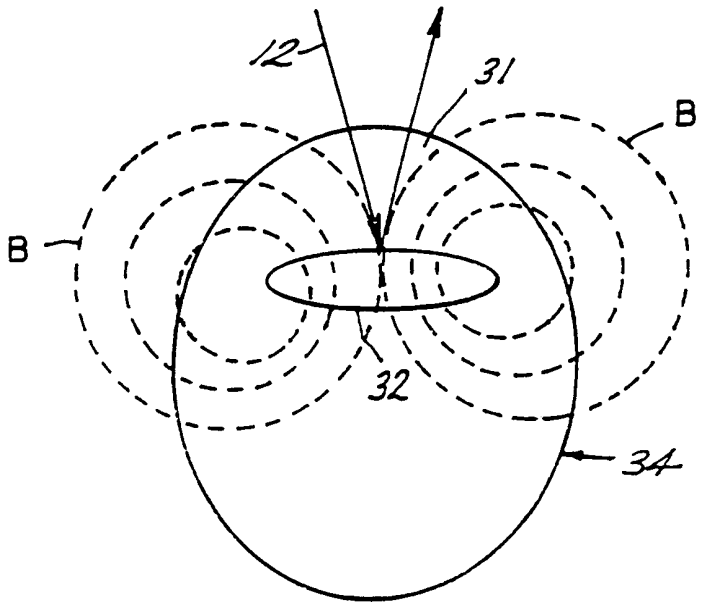
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FIG. 4

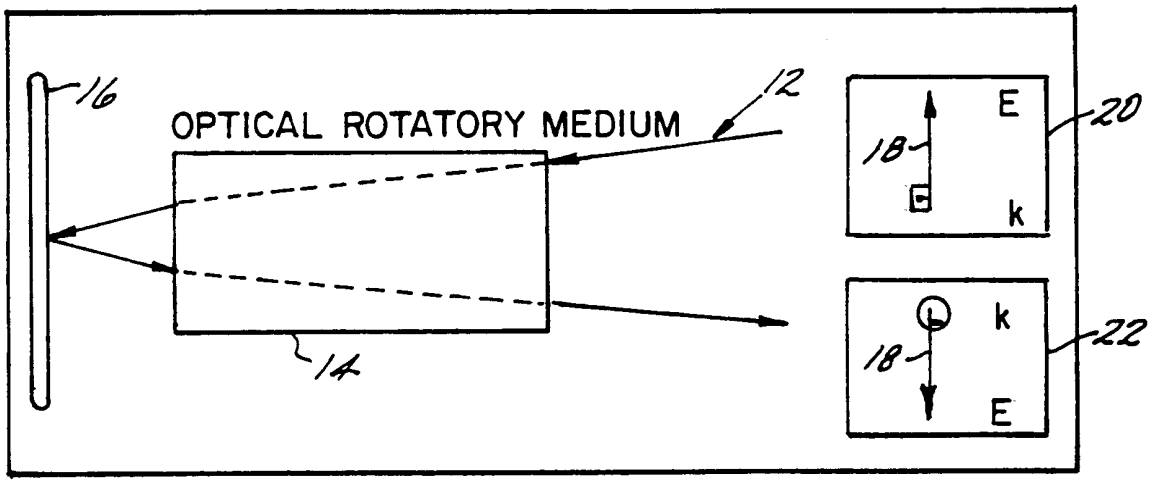
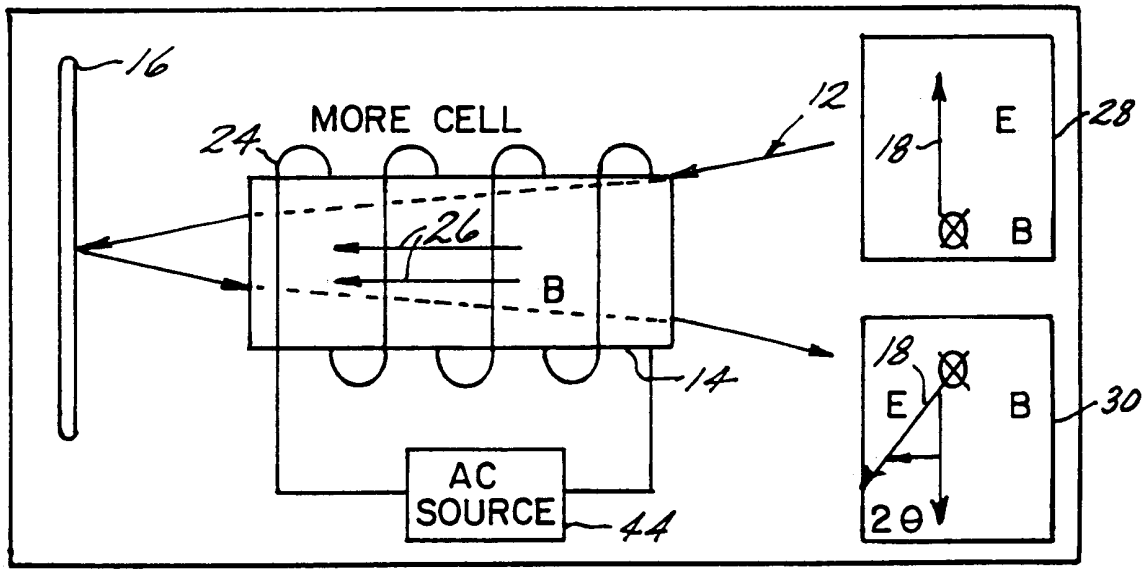

16
OPTICAL ROTATORY MEDIUM
12
14
E
18
k
20
k
18
E
22

FIG. 2


16
MORE CELL
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14
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SOURCE
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18
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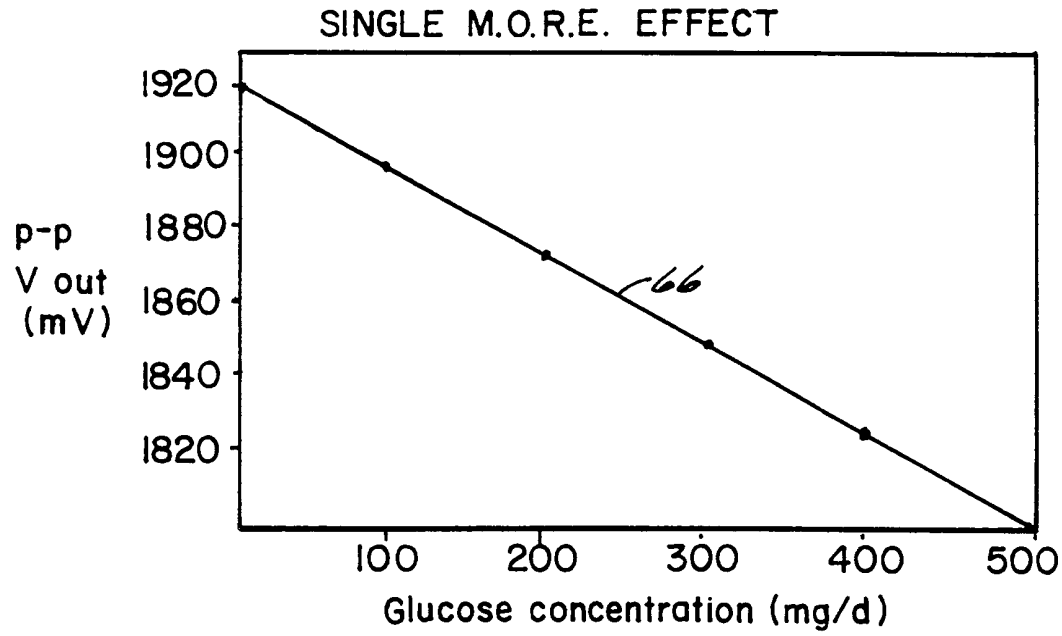
28
18
E
B
30
2θ

FIG. 3


SINGLE M.O.R.E. EFFECT
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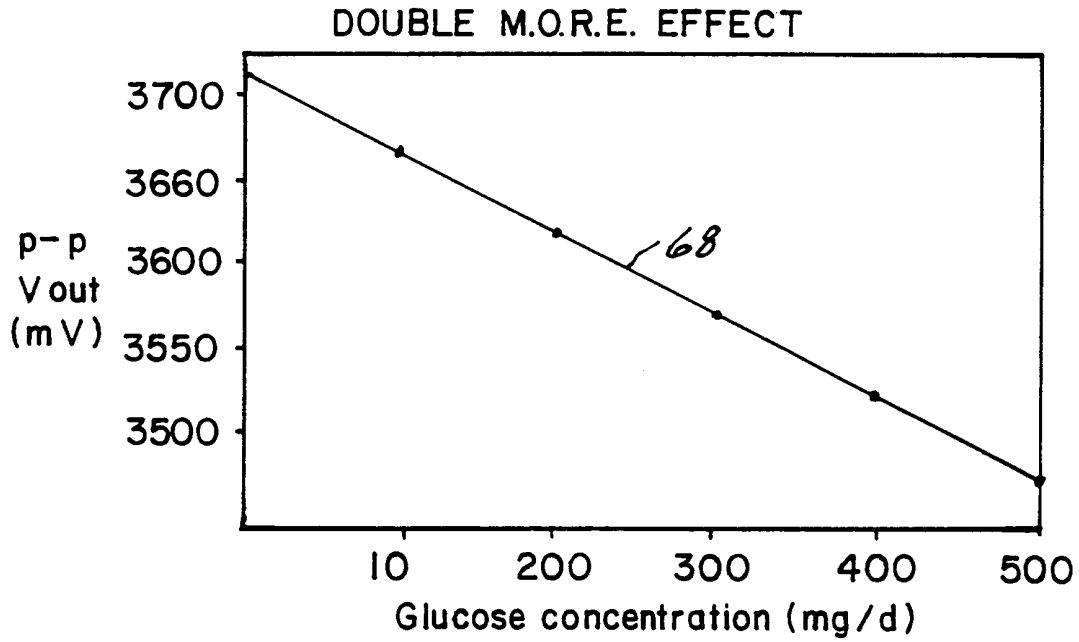
1900
1880
1860
1840
1820
p-p
V out
(mV)
66
100
200
300
400
500
Glucose concentration (mg/d)

FIG. 5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3660
3600
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p-p
Vout
(mV)
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200
300
400
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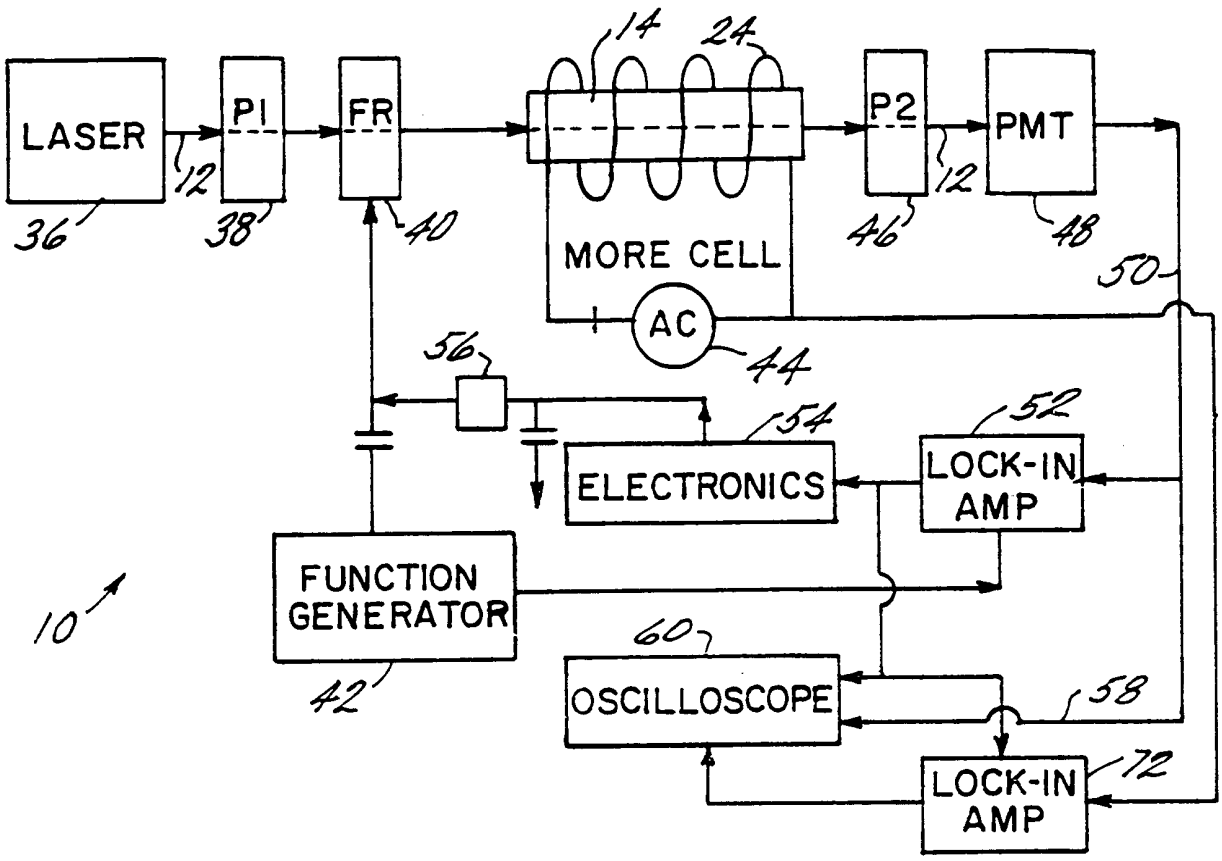
Glucose concentration (mg/d)

FIG. 6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46
48
MORE CELL
AC
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50
56
54
52
ELECTRONICS
LOCK-IN AMP
FUNCTION GENERATOR
10
60
OSCILLOSCOPE
58
LOCK-IN AMP
72
42

FIG. 7