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**Cornsweet**(10) **Pub. No.: US 2005/0070772 A1**(43) **Pub. Date: Mar. 31, 2005**(54) **OPTICAL ALIGNMENT APPARATUS****Publication Classification**(75) Inventor: **Tom N. Cornsweet, Prescott, AZ (US)**(51) **Int. Cl.<sup>7</sup> ..... A61B 5/00; G01N 21/43**(52) **U.S. Cl. .... 600/319; 356/517**

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**Phoenix, AZ 85016 (US)**(57) **ABSTRACT**

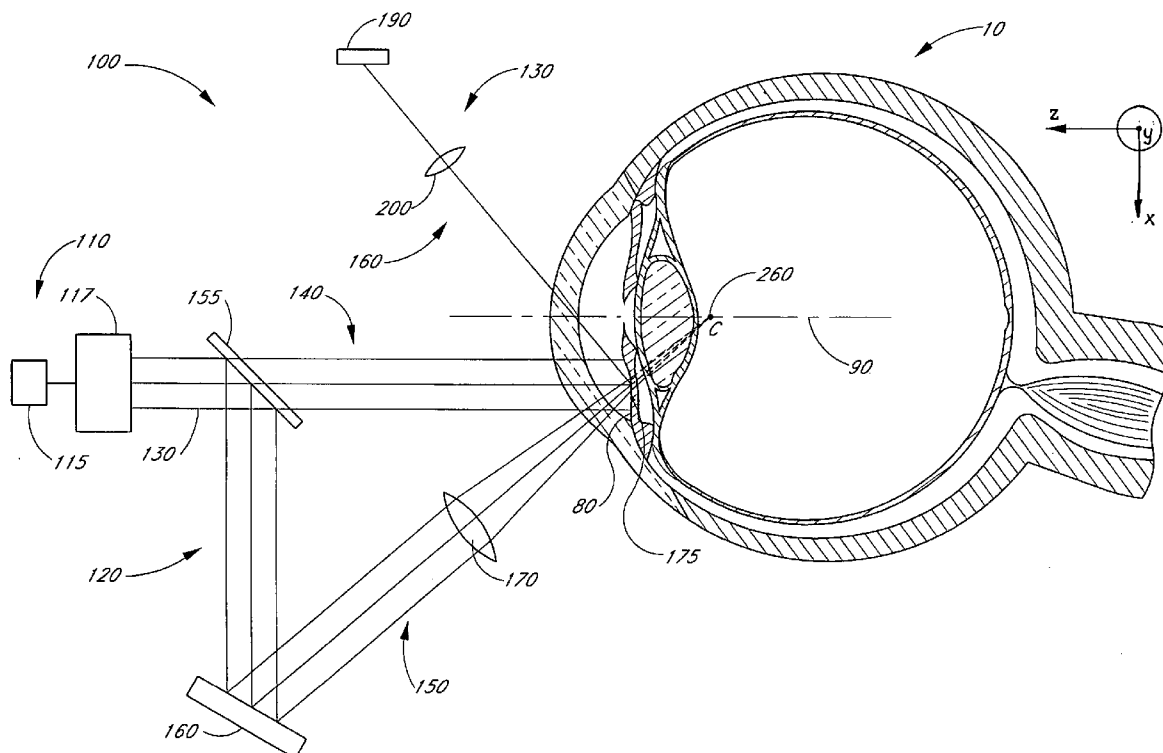
The glucose concentration in the bloodstream is directly correlated to the concentration of glucose in the aqueous humor. Furthermore, variation in the glucose concentration in the aqueous humor will cause like variations in its index of refraction. Thus, by measuring the refractive index of the aqueous humor, the glucose concentration in the blood can be determined.

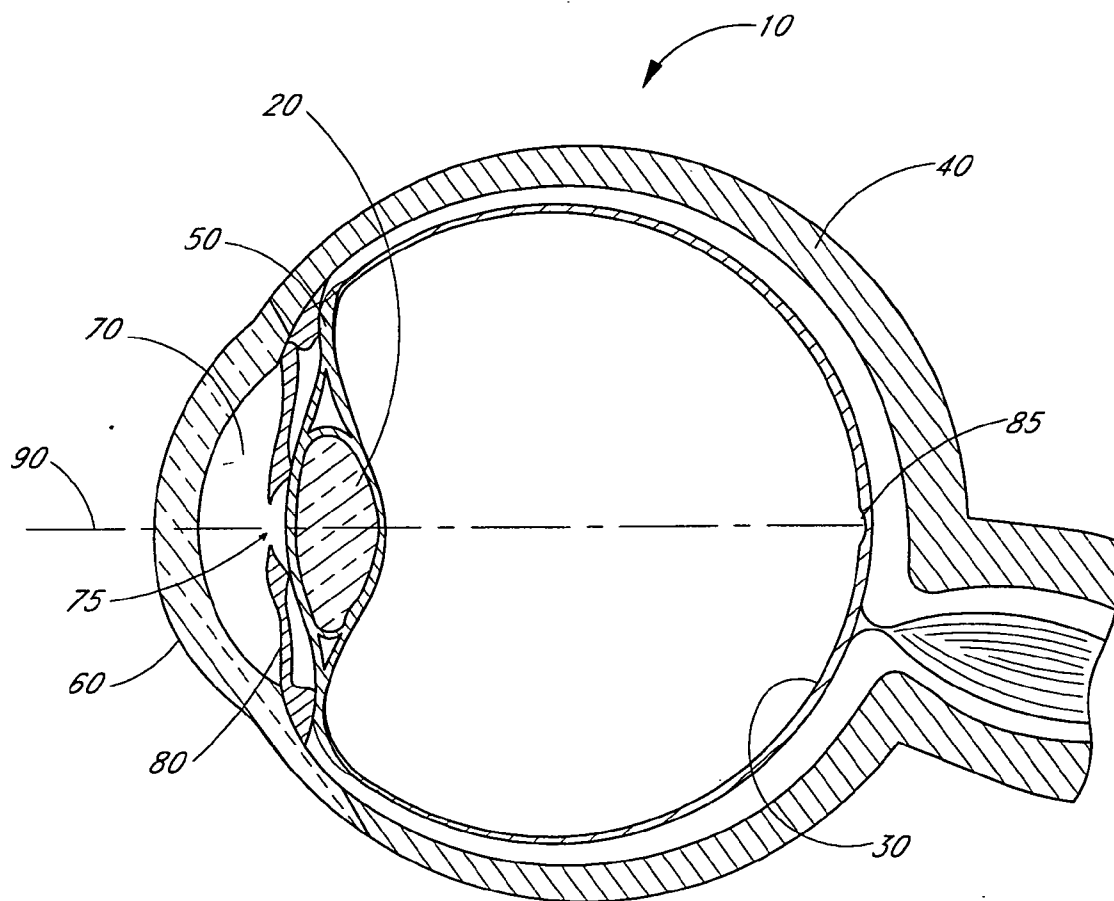
The refractive index of the aqueous humor can be measured by interferometry. In various embodiments of the invention that employ interferometry, two beams may be directed onto the eye and caused to interfere, thereby producing a fringe pattern. The fringe pattern may be analyzed to determine the index of refraction of the aqueous humor in the eye and the glucose concentration therein. The glucose level in the blood can be ascertained from this information.

(73) Assignee: **VISUAL PATHWAYS, INC.**(21) Appl. No.: **10/983,924**(22) Filed: **Nov. 8, 2004****Related U.S. Application Data**

(62) Division of application No. 10/247,753, filed on Sep. 19, 2002, now Pat. No. 6,836,337.

(60) Provisional application No. 60/323,939, filed on Sep. 20, 2001.





*FIG. 1*

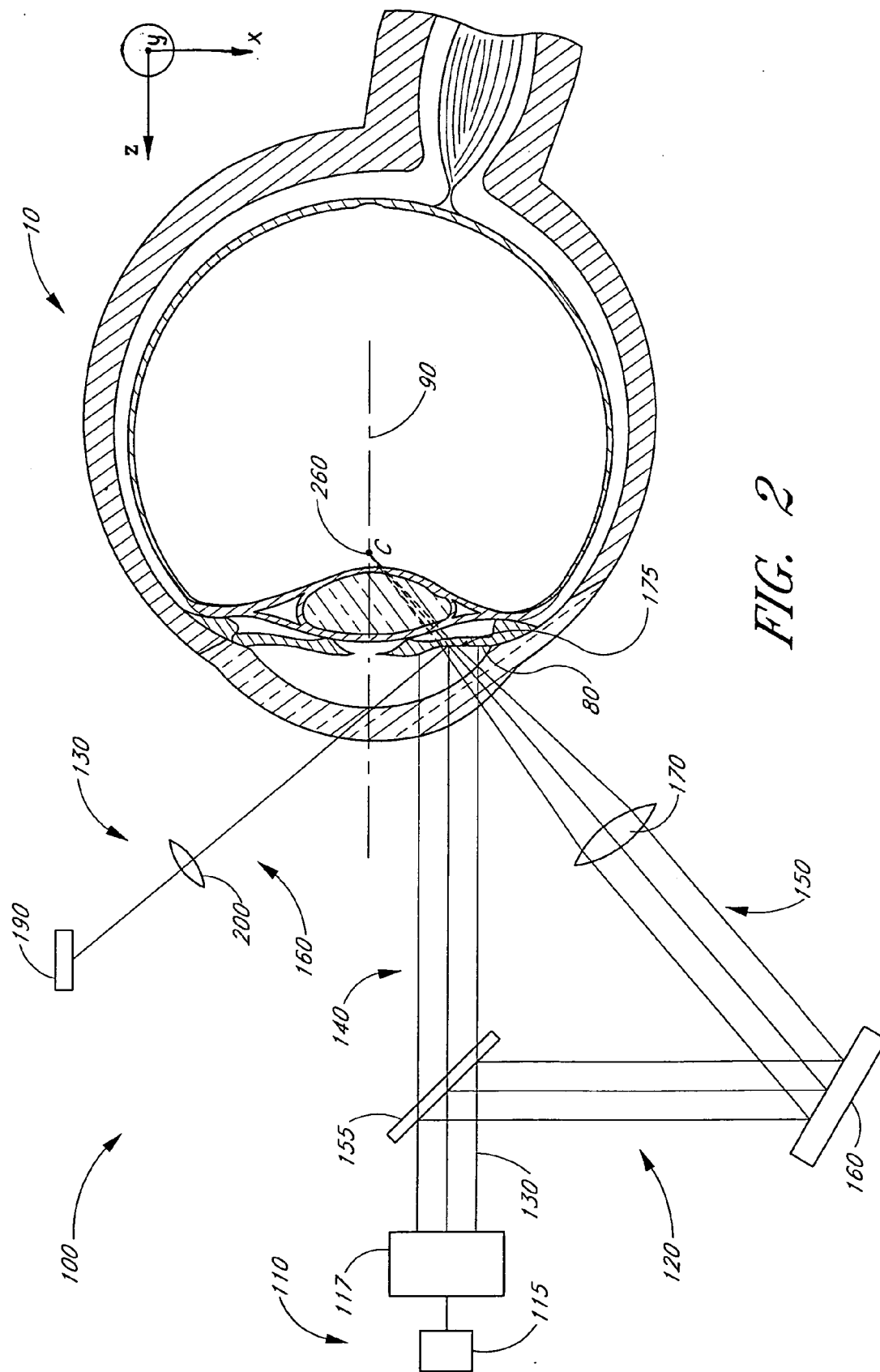


FIG. 2

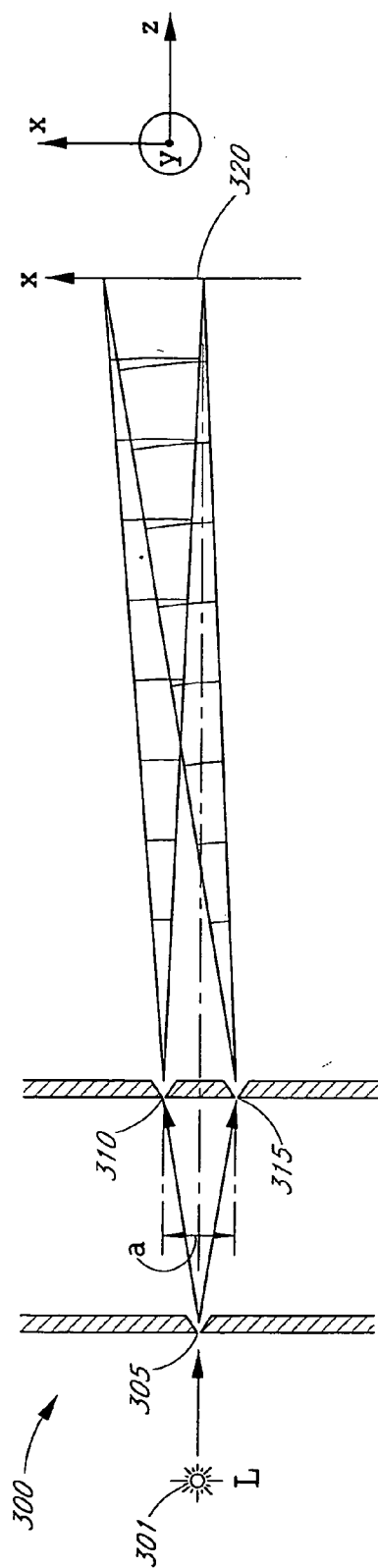


FIG. 3A

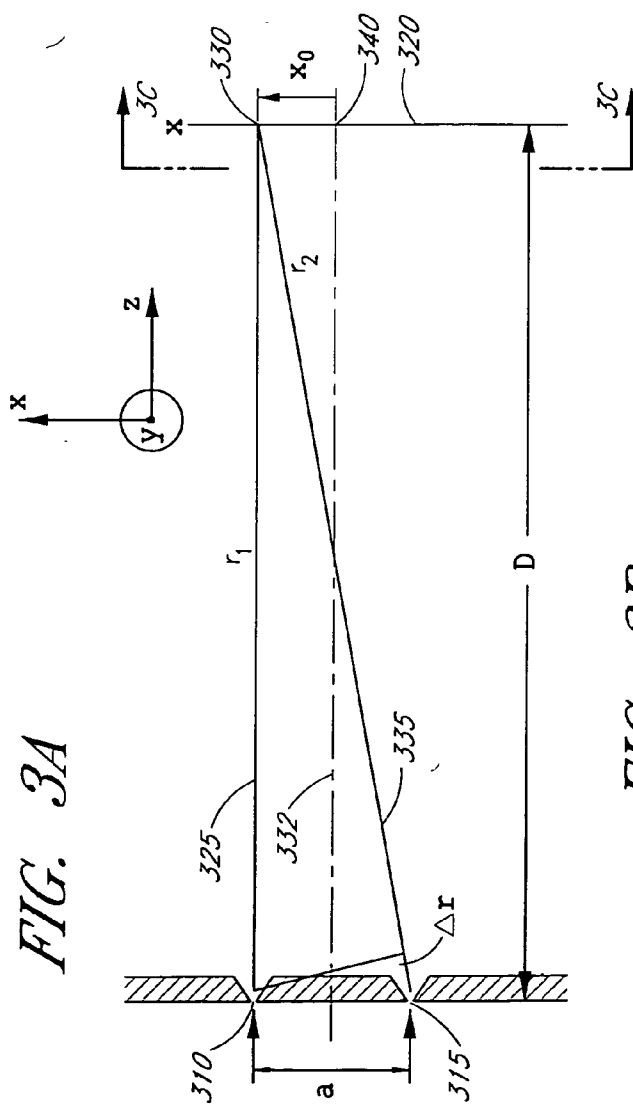


FIG. 3B

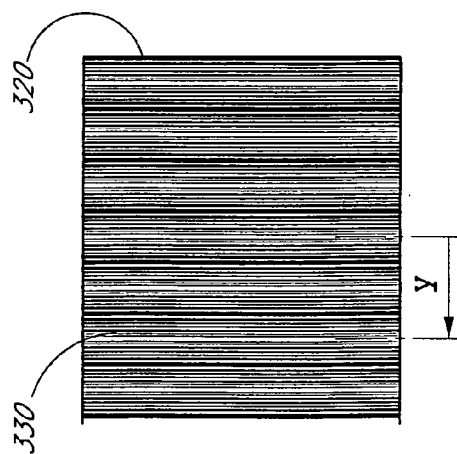
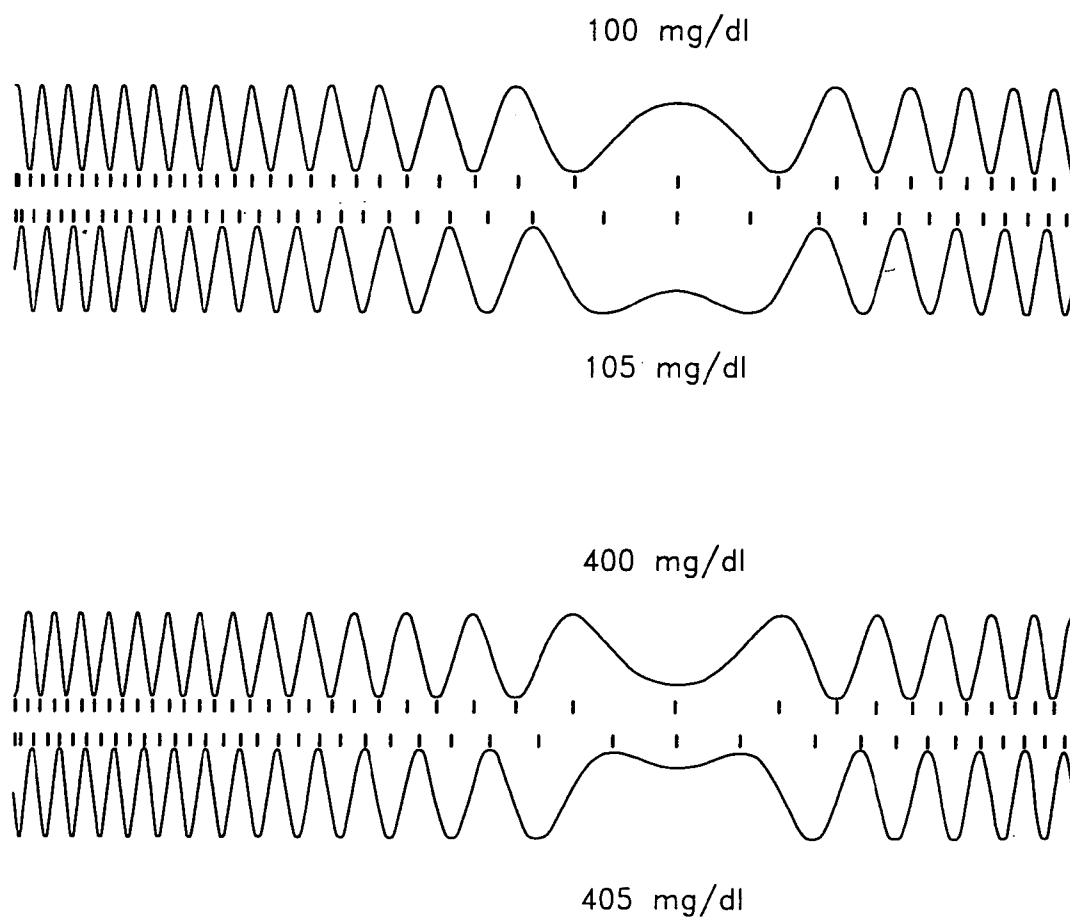


FIG. 3C



*FIG. 4*

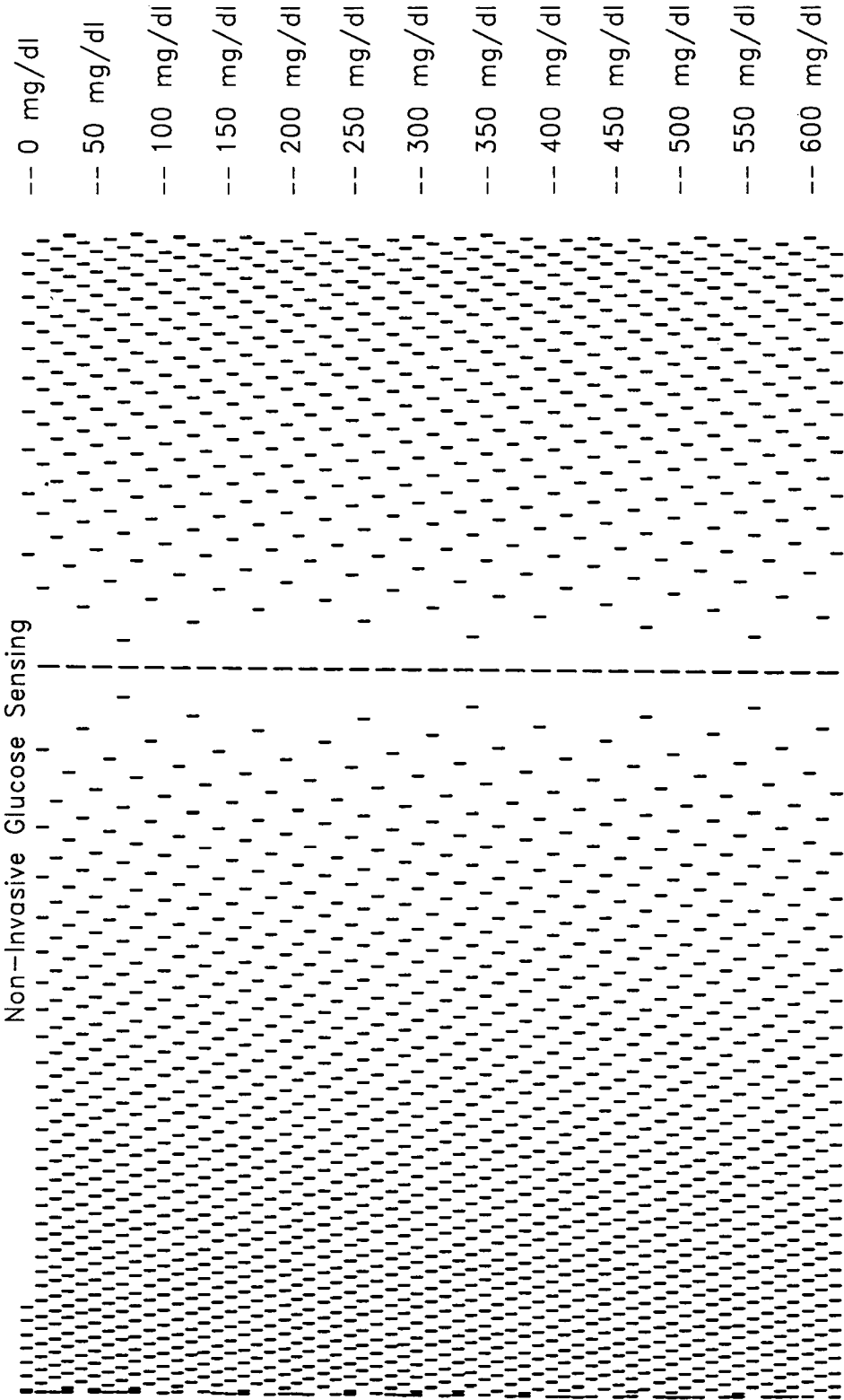


FIG. 5

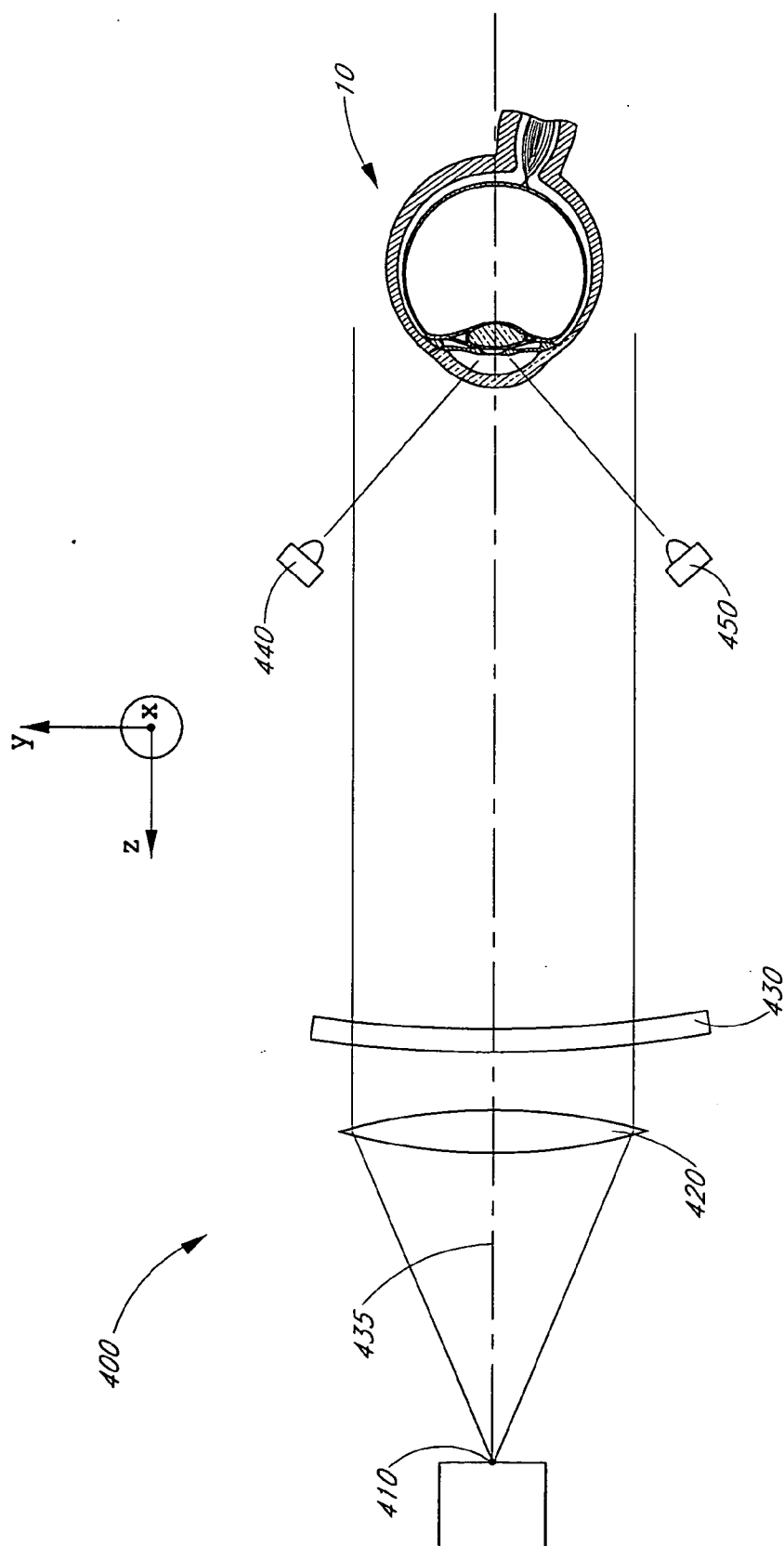
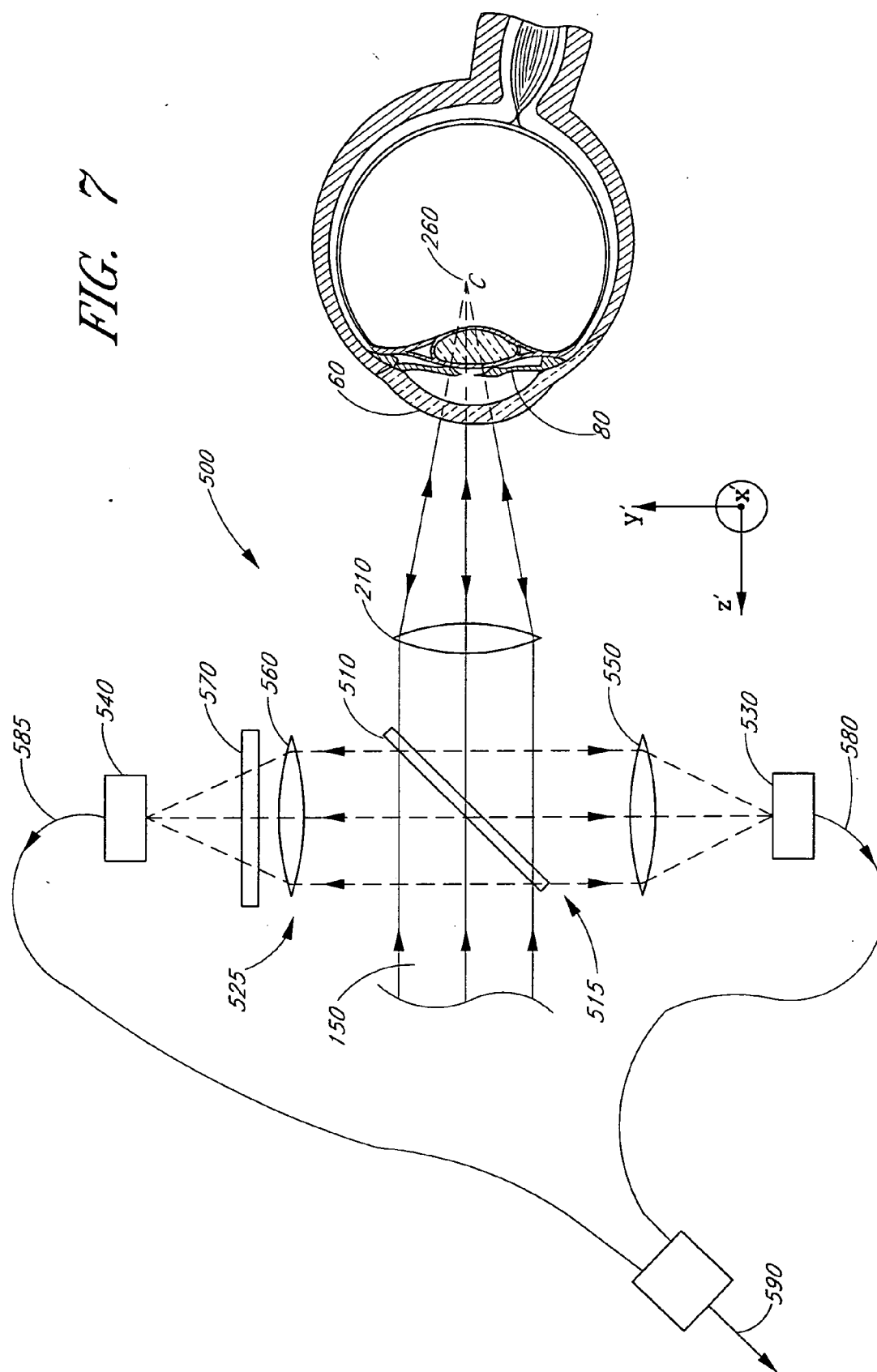


FIG. 6

FIG. 7





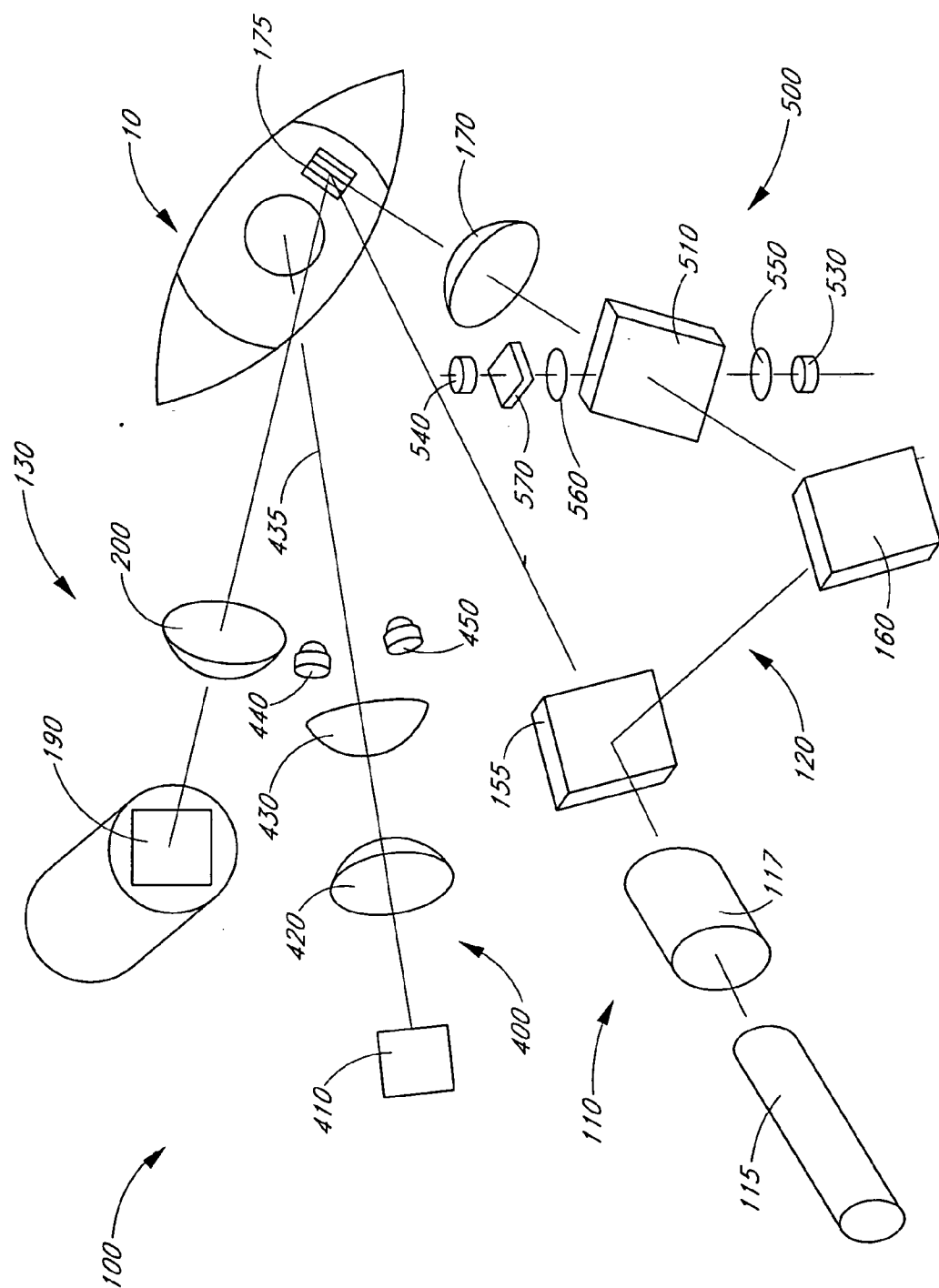
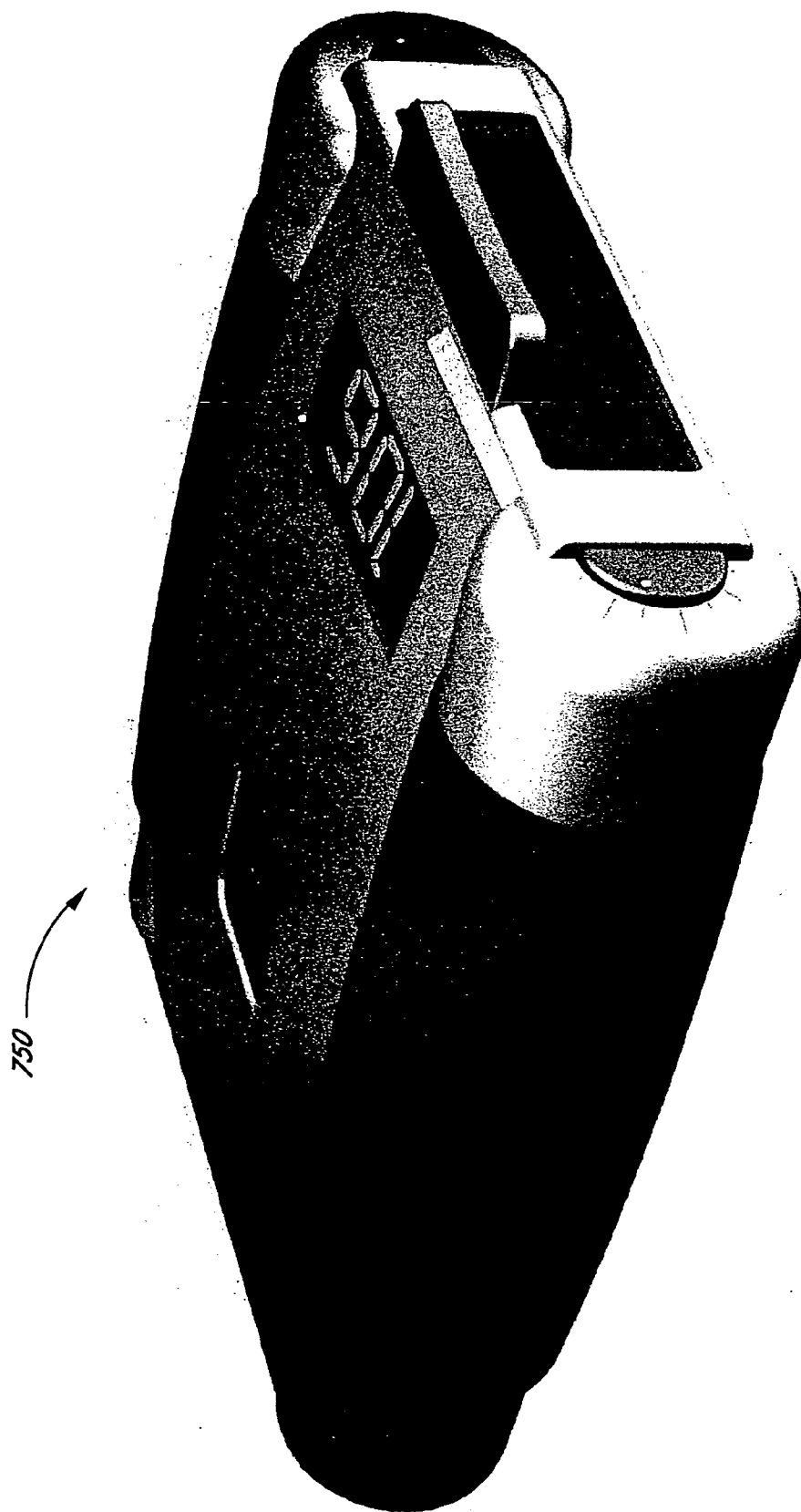


FIG. 8



*FIG. 9*

## OPTICAL ALIGNMENT APPARATUS

### RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. § 119(e) from U.S. Provisional Patent Application No. 60/323, 939, filed Sep. 20, 2001, entitled "Non-Invasive Blood Glucose Monitoring by Interferometry", which is hereby incorporated herein by reference in its entirety.

### BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention is directed to glucose monitoring, and more specifically, to apparatus and methods for monitoring glucose using interferometry.

[0004] 2. Description of the Related Art

[0005] Diabetics are advised to closely monitor the concentration of glucose in their bloodstream. If the concentration is outside of a normal healthy range, the patient needs to adjust his or her insulin dosage or sugar intake to counter the risk of diabetic complications. Current monitoring methods involve drawing blood from the patient several times a day, which is costly, painful, and poses the risk of infection. As a result, many diabetics test their blood glucose less frequently than would be desirable, increasing the possibility of diabetic related health problems. Thus, what is needed is a painless, non-invasive approach for determining the glucose level within the bloodstream.

### SUMMARY OF THE INVENTION

[0006] One aspect of the invention comprises a method of measuring glucose levels in blood of a living being having an eye. The eye comprises a cornea and a lens, which together form an anterior chamber. The eye further comprises an iris and aqueous humor in the anterior chamber of the eye. The aqueous humor has an index of refraction that is correlated to the glucose level in the blood. To measure the glucose levels in the blood, two substantially coherent beams of light are propagated through the cornea to illuminate a region of the iris. The two substantially coherent beams of light propagate through the aqueous humor to reach the iris. The two beams are overlapped on the region of the iris. These two beams are sufficiently coherent so as to produce an interference pattern in this region of the iris where they overlap. The interference pattern comprises a plurality of fringes having a spatial arrangement that depends on the index of refraction of the aqueous humor. The interference pattern is imaged onto a light sensitive optical detector, and the glucose level in the blood is determined from the spatial arrangement of the fringes in the interference pattern.

[0007] Another aspect of the invention comprises an apparatus for monitoring glucose fluctuations by measuring optical properties of an eye. The apparatus comprises a light source which emits a beam of light, an optical element, an optical detector and imaging optics. The optical element is situated to receive this beam of light from the light source and to split the beam of light into first and second probe beams that propagate along respective first and second optical paths. The apparatus further includes at least one optical element in one of the optical paths to alter the optical path such that first and second probe beams intersect at a

target plane. The optical detector and imaging optics are arranged to image the target plane onto the optical detector.

[0008] Another aspect of the invention comprises a method of monitoring glucose levels in blood of a living being having an eye. In this method, light is propagated through a portion of the eye comprising aqueous humor having an index of refraction that varies with glucose concentration. Phase information associated with the light is obtained through optical interference. The phase information depends at least in part on the index of refraction of the aqueous humor. The phase information is used to determine the glucose levels in the blood.

[0009] Yet another aspect of the invention comprises an alignment apparatus for lateral aligning an eye with respect to the apparatus. The apparatus comprises a central light source, a partially reflecting concave mirror, and first and second offset light sources. The partially reflecting concave mirror has an optical axis passing therethrough. The central light source is centrally disposed along this optical axis such that at least a portion of the light from the central light source propagates through the partially reflecting concave mirror along the optical axis. The first and second offset light sources are disposed in a plane passing through the optical axis. The first and second offset light sources are on opposite sides of the optical axis and emit light at an oblique angle toward the optical axis.

[0010] Still another aspect of the invention comprises a method of aligning a device with respect to a cornea wherein the cornea has a substantially spherical curvature defined by a center of curvature. In this method light is propagated toward the cornea. This light has substantially spherical wavefronts defined by a center of curvature that is substantially coincident with the center of curvature of the cornea. A portion of the light from the cornea is retroreflect, collected, and focusing onto an optical detector having a photosensitive area. When the center of curvature of the wavefronts is substantially coincident with the center of curvature of the eye, the light focused on the photosensitive area has a different intensity than when the respective centers of curvature are non-coincident.

### BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. 1 is a schematic illustration of the anatomy of the eye including the cornea, iris, lens, and anterior chamber containing aqueous humor.

[0012] FIG. 2 schematically illustrates a device for measuring the concentration of glucose in the bloodstream of a subject by measuring optical properties of the aqueous humor within the eye.

[0013] FIGS. 3A and 3B schematically illustrates the interference of two cylindrical wavefronts produced by Young's double slit configuration.

[0014] FIG. 3C is an exemplary interference pattern comprising a plurality of fringes resulting from the interference of the two cylindrical wavefronts produced in the configuration schematically illustrated in FIGS. 3A and 3B.

[0015] FIG. 4 shows profiles of the fringe patterns obtained using the device schematically illustrated in FIG. 2 for four different aqueous glucose concentrations.

[0016] FIG. 5 illustrates how the peak locations change with refractive index over a range of glucose concentrations from zero to about 600 milligrams per deciliter (mg/dl) or about six times the typical level found in healthy human beings.

[0017] FIG. 6 schematically illustrates a subsystem used for lateral alignment of the probe beams with respect to the eye in two orthogonal directions (x, y) that are normal to the visual axis.

[0018] FIG. 7 schematically illustrates a side view of subsystem used for longitudinal alignment along an axis through the center of curvature of the cornea, such that the distance separating the optical system and the eye is appropriate for accurate measurement of the glucose concentration.

[0019] FIG. 8 schematically illustrates a system for measuring the concentration of glucose in the bloodstream of a subject together with the aligning subsystems shown in FIGS. 6 and 7.

[0020] FIG. 9 is an artistic rendering of a compact instrument for measuring the concentration of glucose in the bloodstream of a subject.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0021] These and other embodiments of the present invention will also become readily apparent to those skilled in the art from the following detailed description of the preferred embodiments having reference to the attached figures, the invention not being limited to any particular embodiment(s) disclosed. Accordingly, the scope of the present invention is intended to be defined only by reference to the appended claims.

[0022] As is well known and illustrated in FIG. 1, an eye 10 includes a lens 20 for imaging onto a retina 30 located at the back of the eyeball. Dense relatively opaque tissue, the sclera 40, together with a curved transparent window, the cornea 60, forms a chamber inside of which is the ocular lens 20. This lens 20 is held in place by the ciliary body 50 and fibrous muscle included therewith. An iris 80 comprising opaque diffusely reflecting tissue that includes a central opening, i.e., the pupil 75, lies on an anterior surface of the lens 20. The refractive powers of the lens 20 and the cornea 60 combine to focus light on the retina 30. A tiny region approximately at the center of the retina 30 known as the fovea 85, comprises densely packed photoreceptor, which provides vision for fine detail. When the eye 10 peers at a distant object, such as for example a star, the eye 10 rotates until an image of the distant object falls on the fovea 85. A straight line drawn through the center of the pupil 75 and the fovea 85 is known as the visual axis 90, sometimes referred to as the line of sight. The cornea 60 and the lens 20 together form a cavity 70 called the anterior chamber 70. The anterior chamber 70 is filled with a transparent liquid known as aqueous humor.

[0023] Advantageously, the glucose concentration in the aqueous humor closely tracks the glucose concentration in the bloodstream to within a delay of only minutes. Increases in the glucose level of the blood are mimicked by proportional rises in the glucose level in the aqueous humor.

Accordingly, by monitoring the glucose concentration of the aqueous humor, changes in the glucose concentration in the blood can be sensed.

[0024] Fluctuations in the glucose concentration of the aqueous humor have also been shown to produce a corresponding shift, in the index of refractive of the aqueous humor. Therefore, devices and methods for measurements of the refractive index of the aqueous humor can be used to quantify variations in the concentration of glucose in the aqueous humor. By measuring this aqueous glucose concentration in this manner, patients can determine the concentration of glucose in the blood and adjust their insulin and sugar intake accordingly.

[0025] Interferometry can be employed to measure the index of refraction of the aqueous humor. Other optical methods can be used that monitor optical properties that are dependant on the refractive index of this fluid in the eye 10. Identifying and quantifying fluctuations in the index of refraction of the aqueous humor using light is preferred as it is clean, non-invasive, and relatively precise. Interferometers offer one approach for optically determining the refractive index of the aqueous humor, however, other well known techniques as well as those yet devised are possible alternatives.

[0026] An optical instrument 100 for measuring the refractive index of the aqueous humor is schematically illustrated in FIG. 2. This optical instrument 100 comprises a light source 110, an interferometer 120, and a detection system 130. The light source 110 preferably comprises a coherent source 115 such as a laser. This light source 110 preferably outputs invisible radiation such as infrared but is not limited to any particular wavelength range. The wavelength of the light may, for example, be between about 500 to 950 nanometers (nm). Other types of light sources may also be used.

[0027] The light source 110 may further include beam shaping optics 117 for producing a beam 130 possessing suitable properties such as intensity and diameter. In one preferred embodiment, the beam shaping optics 117 includes a beam expander. An exemplary beam expander comprises an afocal system similar to a telescope in which a substantially collimated input beam entering the beam expander exits with substantially the same degree of collimation, but with a diameter different from that of the input beam. The beam expander may increase or decrease the diameter of the beam 130 depending on the desired spatial extent and the beam size of the coherent source 115. The beam shaping optics 117 may further include a neutral density filter as well as possibly polarizers and apertures to suite the particular application. Other optics may be included in the beam shaping optics 117 and elsewhere in the instrument 100.

[0028] The interferometer 120 comprises two arms, a first and second with corresponding first and second probe beams 140, 150 that are interfered. The interferometer 120 includes a beamsplitter 155 which splits the optical beam 130 from the light source 110 into the two probe beams 140, 150. Other methods and devices (such as, other splitters comprising for example a prism) may also be employed for creating the two probe beams 140, 150 from the original beam 130. Since the first and second probe beams 140, 150 are interfered, the coherent light source 115 preferably has a coherence length that is longer than the optical path length

difference between the two optical paths **140**, **150**. A relatively long coherence length may advantageously increase the optical contrast of the resultant interference pattern.

[0029] The interferometer **120** further comprises optics, such as a mirror or reflector **160** and a lens **170** to direct light in the second probe beam **150** towards the eye **10** and to focus this beam. The lens **170** causes the beam **150** to be converging when incident on the eye **10**, which in certain embodiments is beneficial; such a configuration, however, is not required and may vary in other designs. The use of the mirror **160** in FIG. 2 is illustrative of a preferred embodiment for directing light and should not be construed as limiting since other optical components and configurations may be used. For example, a different number of mirrors or reflectors may otherwise be employed.

[0030] The interferometer **120** is preferably adjusted such that the first probe beam **140** and the second probe beam **150** are incident on the eye **10** and, more particularly, overlap each other over a region **175** of the iris **80**. A fringe pattern is formed where the two beams **140**, **150** overlap.

[0031] The detection system **130** in the instrument **100** comprises an optical sensor **190** and an imaging element **200** such as a lens. In one preferred embodiment, the lens **200** has a power and is positioned appropriately to produce an image of the iris **80** on the optical detector **190**.

[0032] Preferably, the principle plane of the imaging lens **200** is oriented at an angle to satisfy the Scheimpflug condition. The Scheimpflug condition is met when three lines through the plane of the iris **80**, the principle plane of the imaging lens **200**, and the plane of the sensor **190** all intersect at a common point. Under these circumstances, in theory all the points in the plane of the iris **80** may be simultaneously focused in the plane of the sensor **190** by the imaging lens **200**.

[0033] In certain preferred embodiments, the optical sensor **190** comprises a one or two dimensional sensor array such as a charge coupled device (CCD) or a complementary metal oxide semiconductor (CMOS) detector array. Other types of optical detectors **190** may also be used. In certain embodiments, the sensor **190** produces an image signal that is received by a computer and/or other electronics for processing the image signal.

[0034] In one preferred embodiment, an image is obtained of the interference fringes formed in the region **175** in the iris **80** where the first and second beams **140**, **150** intersect. The interference fringes formed on the iris **80** in the region **175** are produced due to mutual coherence of the two intersecting probe beams **140**, **150**. Phase differences resulting from the optical path difference traveled by the first and second probe beam **140**, **150** cause constructive and destructive interference which varies with position within the overlap region **175**. Consequently, bright and dark regions, i.e., a fringe pattern, are produced in the overlap region **175** on the iris **80**.

[0035] As stated previously, variations in the glucose concentration of the aqueous humor alter the refractive index of the aqueous humor **20**. Since the probe beams **140**, **150** both pass through the aqueous humor, the interference fringes formed on the iris **80** are affected by changes in the refractive index of the aqueous humor. More particularly, the optical path length of the first and second probe beams **140**,

**150** varies with the index of refraction of the aqueous humor in the anterior chamber **70** of the eye **10**. The fringe pattern varies as well. Thus, variations in the glucose concentration of the aqueous humor are directly correlated to quantitative changes in the fringes formed on the iris **80** in the overlap region **175**.

[0036] The nature of the fringes formed on the iris **80** may be generally understood by reference to FIGS. 3A-3C, which schematically illustrate the formation of interference fringes using Young's double slit configuration **300**. In this optical arrangement, a monochromatic light source **301** emits light that is transmitted through a narrow vertically oriented elongated slit **305**, which diffracts the light incident thereon. The result is an optical beam having cylindrical wavefronts. These cylindrical wavefronts illuminate two other vertically oriented elongated slits **310**, **315** which are laterally (i.e., horizontally) separated from each other by a distance  $a$ . Light is diffracted by the two slits **310**, **315**, the output of which is a pair of beams also characterized by vertically oriented cylindrical wavefronts. The two beams illuminate a diffuse screen **320** where they interfere constructively and destructively producing vertical fringes such as the ones schematically illustrated in FIG. 3C.

[0037] The cause of the elongated bright and dark regions in FIG. 3C has been well characterized and may be understood as follows. Constructive or destructive interference results when the two beams are overlapped. The interference at a given location on the diffuse screen **320** is determined by the respective optical path distance from the two slits **310**, **315** to that specific location on the diffuse screen. For example, a ray **325** shown in FIG. 3B that is transmitted through the first slit **310**, travels a distance  $r_1$ , and illuminates the diffuse screen **320** at a point **330**, which is located a distance  $x_0$  from a centerline **332**. The centerline **332** through the system is defined as a line normal to the diffuse screen **320** that bisects the two slits **310**, **315**. The distance from the diffuse screen **320** to the plane containing the two slits **310**, **315** is defined as  $D$ . A second ray **335** is transmitted through the second slit **315**, travels a distance  $r_2$ , and illuminates the diffuse screen **320** at the same point **330**. The distances through which the two rays travel may differ, as indicated in FIG. 3B, by the distance  $\Delta r = r_1 - r_2$ . If the original slit **305** is sufficiently narrow, the light emerging from it (in the  $x$ - $z$  plane) is substantially coherent and the waves associated with rays produced by the light source **301** oscillate in phase with one another. The phase of the two rays **325**, **335** at the point **330** on the screen **320** is determined in part by the respective path lengths  $r_1$  and  $r_2$ . More particularly, the relative phase between the two rays **325**, **335** is proportional to the difference in the two path lengths, i.e.,  $\Delta r$ . If the two rays **325**, **335** have the same intensity  $I_1 = I_2 = I_0$ , then the intensity at the point **330** is given by the well known relation,

$$I = I_0(1 + I_0 \cos(\delta)) \quad (1)$$

[0038] where  $I_0$  is the intensities of rays **325**, **335** and  $\delta$  the relative phase between the rays **325**, **335** given by the relation  $(\delta = 2\pi\Delta r/\lambda)$ , where  $\lambda$  is the wavelength of the source **301**. In this case, the light emitted from the slits **310**, **315** propagates through air or vacuum to the diffusely reflecting screen **320**.

[0039] Accordingly, if for example the distance  $\Delta r$  corresponds to an optical path difference over which light at the

wavelength  $\lambda$  oscillates through precisely one-half of a cycle ( $\pi$  radians in phase), then the two rays **325**, **335** will be  $\pi$  radians out of phase with each other at point **330** and the two rays **325**, **335** will cancel each other, resulting in a reflected intensity of zero at point **330**. If  $\Delta r$  is exactly an integer number of cycles (i.e., an integer multiple of  $2\pi$  radians), the two rays will be in phase at the point **330**, and under ideal conditions, the resulting reflected intensity will equal the sum of the intensities of the two individual rays.

[0040] For points **330** on the screen **320** closer to the centerline **332** (i.e., for smaller values of  $x$ ),  $\Delta r$  is reduced, reaching a value of zero at a center point **340** where the centerline intersects the screen. The optical path difference  $\Delta r$  increases again for positions below the centerline (i.e., negative values on the  $x$ -axis). The intensity on the screen **320** oscillates between high and low on both sides of the centerline **332** as illustrated in FIG. 3C. Specifically, the reflected intensity  $I$  fluctuates along the diffusing surface **320** accordingly to the relation,

$$I = 4A_0 \cos^2[a\pi x/(D\lambda)] \quad (2)$$

[0041] where  $A_0$  is the amplitude of the rays **325**, **335** at the diffuse screen **320**,  $x$  is the distance along the  $x$ -axis across the diffuse screen **320** as measured from the centerline **332** where  $x=0$ ,  $a$  is the lateral distance separating the two slits **310**, **315**,  $D$  is the distance from the diffuse screen **320** to the plane containing the two slits **310**, **315**, and  $\lambda$  is the wavelength of the source **301**. Since the difference in path lengths,  $\Delta r$ , is substantially the same for the plurality of points on the screen **320** in the  $\pm y$ -direction, the interference fringes produced by the elongated slits **310**, **315**, which are oriented lengthwise parallel to the  $y$ -axis, are linear and also oriented along the  $y$ -direction.

[0042] The relations derived based on FIGS. 3A and 3B assume that the region between the slits **310**, **315** and the diffuse screen **320** is filled with air or vacuum. Constructive or destructive interference, however, does not depend solely on the distance traveled by the light and, more specifically, the difference in the distance between the two physical paths,  $\Delta r$ . Rather, the time it takes the light to travel through that optical path difference determines the result of the interference. The phase of the light depends upon time, not distance. Accordingly, the index of refraction of the medium through which the light propagates along the optical paths will affect the resultant fringe pattern as the refractive index determines the phase of the light.

[0043] If the region between the slits **310**, **315** and the diffuse screen **320** is filled, instead, with a liquid such as water, the velocity of the light waves is reduced. The index of refraction of water is 1.5. Accordingly, the speed of light in the region between the slits **310**, **315** and the diffuse screen **320** is approximately three quarters of that in air. Under these conditions, the value of  $\Delta r$  between two rays transmitted from slits **310**, **315** will produce a phase difference that is  $\frac{4}{3}$  larger than when the region between the slits **310**, **315** and the diffuse screen **320** is filled with air. Likewise, there will be  $\frac{4}{3}$  as many fringes per unit distance formed on the diffuse screen **320** than when the region between the slits **310**, **315** and the diffuse screen **320** is filled with air. The number of fringes per unit distance across the screen **320** is therefore directly proportional to the speed of light in the medium. In certain embodiments, this relationship between refractive index of a media and the spacing

between fringes may be used to determine the refractive index of that media. Other effects on the fringe pattern can also be measured and quantified to determine the index of refraction of the medium.

[0044] Referring again to FIG. 2, light from light source **115** is transmitted through the beam shaping optics **117** and is incident on the beamsplitter **155**. A fraction of the light is transmitted through the beamsplitter **155** to produce the first probe beam **140**. This probe beam **140** is preferably substantially parallel to the visual axis **90** of the eye **10**. When light from the probe beam **140** illuminates the cornea **60**, the light is refracted toward the pupil **75** and illuminates the iris **80**.

[0045] Another fraction of the light, i.e., the remainder, is reflected from the beamsplitter **155** forming the second probe beam **150**. In certain embodiments, the fraction of the light that is transmitted through the beamsplitter **155** to produce the first probe beam **140** and the fraction of light is reflected by the beamsplitter **155** to produce the second probe beam **150** are selected so that they have substantially equal intensity when they are interfered on the front surface of the iris **80**. Favorable contrast can thereby be achieved.

[0046] This reflected beam **150** is directed by the mirror or reflector **160** through the focusing lens **170** towards the eye **10**. In certain embodiments, the focal length of the lens **170** is substantially equal to the distance from the focusing lens **170** to a point **260** located at the center of curvature,  $C$  of the front corneal surface of the cornea **60**. The light transmitted through the lens **170** converges toward the center point **260** however is incident on the cornea **60** before reaching its center,  $C$ . As discussed above, the focal length of the focusing lens **170** is preferably selected to substantially correspond to the distance from the lens to the radius of curvature of the cornea **60**. When this condition is satisfied and the lens **170** is positioned such that its focal point and this center of curvature are coincident, then the rays associated with the second beam **150** that are incident on the corneal surface will be substantially perpendicular thereto. With an angle of incidence of substantially zero, the converging rays are not refracted by the cornea **60**.

[0047] As discussed above, the converging rays associated with this second probe beam **150** preferably illuminate a substantially similar region **175** of the iris **80** as the first probe beam **140**. The overlap of the two beams **140**, **150** produces interference fringes on the iris **80** as a consequence of constructive and destructive interference. The interference process is generally similar to the optical phenomena related to the Young's double slit configuration **300** discussed above with reference to FIGS. 3A-3C. The configuration in FIGS. 3A and 3B, however, differs from the interferometer **120** shown FIG. 2. The fringes formed in the Young's double slit configuration **300** were produced by two probe beams each having cylindrical wavefronts defined by substantially equal radii of curvature. The first and second probe beams **140**, **150** in the interferometer **120** depicted in FIG. 2 comprise wavefronts having different radii of curvature. In various preferred embodiments, first probe beam **140** is has a radius of curvature of about 25 millimeter. The refractive power of the cornea **60** will cause the probe beam **140** to be convergent such that spherical wavefronts are incident on the iris **80**. At the iris **80**, the second probe beam **150** also comprises substantially spherical wavefronts.

These spherical wavefronts are defined by a radius of curvature that is approximately equal to the distance from the focusing lens **170** to the center of curvature **260** of the cornea **60**. The result of interfering substantially planar waves with substantially spherical wavefronts is a plurality of annular shaped fringes. In various preferred embodiments, the overlap region **175** corresponds to a portion of these annular shaped fringes. Accordingly, the fringes may not be complete rings but only portions of annuli. An intensity profile across a cross-section of these fringes corresponding, for example, to the x-z plane is shown in **FIG. 4**. These fringes in **FIG. 4** are for a variety of glucose concentrations and respective refractive index values. As shown, these fringe patterns have a point of symmetry and the frequency of the fringes increases to either side of the point of symmetry with distance away from the point of symmetry.

[0048] **FIG. 4** shows profiles of the fringe patterns for four different aqueous glucose concentrations. Short vertical lines are included to mark the locations of the peaks and troughs in the interference pattern. Differences in the refractive index between the aqueous humor solutions shown in the different profiles produce variation in the plot pattern. For example, the shape of the profile in the region near the point of symmetry as well as the rate of change of fringe spacing varies. In contrast, the location of the point of symmetry is substantially fixed over a wide range of refractive indices.

[0049] An analytical expression can be derived that characterizes the fringe pattern. In one exemplary case, the radius of curvature of the cornea **60** is approximately 8.0 millimeters (mm) and the distance from the corneal vertex to the plane of the iris **80** is approximately 4 mm. (As used herein, and consistent with conventional usage, the corneal vertex corresponds to the foremost point of the cornea **60**, where the cornea intersects the visual axis.) Under these circumstance, the signal strength,  $I$ , of the light reflected by the iris **80** is given by,

$$I = \sin^2 \left( \frac{1}{180} \pi \left( 580645g \sqrt{\tan^2 \left( \sin^{-1} \left( \frac{r}{8} \right) - \sin^{-1} \left( \frac{r}{8g} \right) \right) (u)^2 + (u)^2 - 580645g \left( 8 - \sqrt{\left( r - u \tan \left( \sin^{-1} \left( \frac{r}{8} \right) - \sin^{-1} \left( \frac{r}{8g} \right) \right)^2 + 16} \right)} \right) \right) \right)$$

$$\text{where } u = 8 \sqrt{1 - \frac{r^2}{64}} - 4,$$

[0050]  $g$  is glucose concentration, and  $r$  is the distance in the plane of the iris **80** between the visual axis **90** of the eye **10** and the point where the strength is evaluated. This expression quantifies the variation in intensity of light across region **175** of the iris **80** illuminated by the two overlapping probe beams **140**, **150**. More specifically, this expression characterizes the variation in intensity corresponding to the fringe pattern that results from the interference of these two beams **140**, **150**. Accordingly, equations such as these could be used to determine the index of refraction and the relative glucose concentration from a given fringe pattern. These equations, however, are complex and other techniques may be preferred for ascertaining the relative levels of glucose concentration.

[0051] In **FIG. 5**, a series of plots illustrates how the peak locations move with increase in glucose concentration. The plurality of plots corresponds to a range of glucose concentrations from zero to about 600 milligram per deciliter (mg/dl), the later value of which is about six times the normal level found in healthy human beings. No two of these patterns are alike. Accordingly, analysis of the pattern yields a sensitive and substantially unambiguous reading of the refractive index over the entire range. Thus, in various preferred embodiments, the signal from the sensor **190** may be processed to determine the location of the peaks and troughs. The set of locations of the various peaks and troughs is like a fingerprint which can be used to determine the relative index of refraction and glucose concentration. In certain preferred embodiments, the pattern of peaks and troughs, i.e., their relative location and spacing with respect to each other and to the center of symmetry, can be compared to a database of similar patterns for different glucose concentrations. By looking up the pattern in electronic look-up tables, a value of the refractive index can be obtained from which the relative glucose concentration can be calculated after calibrating the instrument **100**. The look-up tables may include glucose concentrations in other embodiments.

[0052] For example, in some embodiments, the signal from the sensor **190** may be digitized and sent to a computer, microprocessor, or other electronics, which determines the point of symmetry and locates the peaks and troughs within a range of this point of symmetry. For instance, peaks and troughs within about 0.5 mm of the point of symmetry can be determined. This mapping of the peaks and valleys can be compared with a set of patterns computed from analytical expressions for a range of plausible glucose levels. One or more of the computed patterns from the set that substantially matches the fringe pattern produced by the measurement can be used to arrive at the measured value of relative glucose concentration. Averaging and/or other signal processing techniques may be employed to reduce noise or otherwise improve accuracy and precision.

[0053] In other preferred embodiments, the intensity of the fringe pattern imaged on the sensor **190** can be fit to a curve, e.g., using a least squares fits or other fitting techniques. Based on the curve to which the intensity pattern is fit, unknowns such as the index of refraction or glucose concentration in the aqueous humor can be determined.

[0054] Still other techniques for ascertaining the index of refraction of the aqueous humor from the intensity pattern of the overlapping probe beams **140**, **150** may be utilized, both those well known and well as those yet to be devised. Also, variations and additional processes, such as for example digital signal processing, filtering, and noise reduction techniques, may be used to yield more accurate or precise results or to simplify or accelerate the analysis.

[0055] Thus, in various embodiments, light from the two probe beams **140**, **150** is diffusely reflected off the iris **80**, some of that light being collected by the imaging lens **200** and focused onto the sensor **190**. An image of the fringe pattern resulting from interfering the two beams **140**, **150** is thereby formed on the sensor **190**. The signal output from the sensor **190** is analyzed, for example, as described above, to determine the glucose concentration based on the rela-

tionship established between refractive index and glucose concentration by calibrating the instrument with independent measurements.

[0056] The profiles in the FIGS. 4 and 5 were computed using a model wherein the iris 80 was assumed to be a smooth, reflecting surface. In certain cases, however, the iris 80 is more accurately represented as a surface that is rough compared to the dimensions of the wavelength of the light from the coherent light source 115. The roughness of the iris 80 gives rise to several effects. First, the distance from the cornea 60 to different locations on the iris 80 does not change smoothly, but includes an additional random perturbation added to it. Second, when illuminated by coherent light, the iris roughness generates speckle. Speckle, which is well known in the art, is a random-appearing variation in the intensity of the reflected light that is superimposed upon or multiplied by to the underlying fringe pattern.

[0057] In certain cases, errors that may be introduced by these effects can be reduced by employing various instrument configurations and measurement techniques. For example, the optical sensor 190 may comprise a two-dimensional detector array, which detects a plurality of elongated fringes corresponding to the fringe pattern. Instead of simply obtaining a single intensity distribution across a cross-section of the fringe pattern, a plurality of such cross-sections can be taken at different locations along the length of the fringes. In this manner, the variations caused by the roughness of the iris 80 may be averaged out over the length of the fringes. For example, if the fringes are oriented substantially vertically (i.e., along the y-direction), a separate estimate of the fringe location and spacing can be produced for each horizontal scan line (i.e., along the x-direction) of the array 190. The results of averaging over several horizontal scan lines produces an average value of fringe spacing that may be more accurate than the value produced by a single horizontal scan across the array 190. The variations due to the iris 80 being a rough surface, can thereby be reduced.

[0058] In certain embodiments, the device 100 additionally comprises a lateral alignment subsystem 400 schematically illustrated in FIG. 6 that is used to align the device 100 with respect to the eye 10. The subsystem 400 is preferably used for "lateral" alignment, i.e., positioning along two orthogonal axes (e.g., x, y) normal to the visual axis 90. The lateral alignment subsystem 400 comprises a central light source 410, a lens 420, and a curved mirror 430 aligned along an optical axis 435. The lateral alignment subsystem further includes two additional light sources 440, 450 offset from and on opposite sides of the optical axis 435. Other configurations and designs, however, are possible.

[0059] In one preferred embodiment, the central light source 410 comprises a light emitting diode (LED) that produces light in the green portion of the light spectrum. Green is preferred since it is easily detected by the eye, although the choice herein does not preclude the use of other colors or other types of light sources. The lateral spatial extent of the light produced by light source 410 preferably has a diameter that is relatively small in relation to other dimensions of the subsystem 400, namely the focal length of the lens 420, and approaches the characteristics of an idealized point source. A pin hole or other aperture may be included to reduce the effective spatial extent of the source of light 410.

[0060] The off-centered light sources 440, 450 may also comprise light emitting diodes LEDs but may comprise other types of light sources in other embodiments. In various preferred embodiments, the light sources 440, 450 are white light-emitting diodes that diffusely illuminate of the eye 10. The lateral spatial extent of the light produced by these two light sources 440, 450 also is preferably small in relation to other dimensions of the subsystem 400 and may approach the characteristics of an idealized point source. A pin hole or other aperture may be included to reduce the effective spatial extent of these light sources 440, 450. The two offset light sources 440, 450 are preferably arranged on opposite sides of the optical axis 435. In one preferred embodiment, the two offset light sources 440, 450 are disposed above and below the optical axis 435, in a vertical plane (e.g., the y-z plane) through the optical axis. More preferably, the two offset light sources 440, 450 are equally distant from the optical axis 435 and are also equally distant from the eye 10. In such a configuration, the two light sources 440, 450 are disposed symmetrically about the optical axis 435. Accordingly, the angle from the eye 10 to the first offset source 440, as measured with respect to the optical axis 435, is equal and opposite to the angle from the eye to the second offset source 450. Other arrangements are possible, however, the first and second offset light sources 440, 450 are preferably on opposite sides of the central light source 410 as seen by the eye 10. Preferably, the offset light sources 440, 450 are close to the eye such that the images of these light sources move independently of the image of the green light source which appears to the eye 10 to be at infinity. For instance, the offset light sources 440, 450 may be a distance of about one inch (i.e., about 25 mm) from the cornea.

[0061] Preferably, the lens 420 comprises a collimating lens. More specifically, the lens 420 has a focal length and is positioned a distance from the central light source 410 so as to provide a substantially collimated beam that is directed toward the eye 10. In other embodiments, other types of optical elements may provide collimation such as, for example, concave mirrors and diffractive optic elements.

[0062] The curved mirror 430 is partly transparent, which may be accomplished with a partially silvered mirror 430. Some of the light from the central light source 410 therefore is transmitted through the mirror, while some of the light from the offset light sources 440, 450 is reflected as will be discussed below. Preferably, the mirror 430 is concave from the perspective of the eye 10 and of uniform thickness such that it possesses substantially zero refractive power. The use of the collimating lens 420 and the curved mirror 430 is illustrative and does not preclude the use of other optical elements in other configurations.

[0063] In certain embodiments, the subsystem 400 is used to correctly position the eye 10 laterally relative to the device 100 in two directions. This task may involve for example aligning the apparatus 100 with respect to the eye 10 vertically and horizontally. Light from the light source 410 is substantially collimated by the lens 420, is transmitted through the curved mirror 430, and enters the eye 10 through the cornea 60. Using this configuration, a patient observes a small green spot of light that is substantially centered on the optical axis 435 defined by the source 410, the lens 420.

[0064] The additional offset light sources 440, 450, which are preferably white light sources, diffusely illuminate the



front of the eye **10**. Some of the light from the offset light sources **440**, **450** is reflected from the surface of the eye **10** to the curved mirror **430**, which is approximately located at its focal distance from the eye, or more specifically from the ocular lens. This provides the patient with a view of the eye **10** that appears at optical infinity. The view includes the iris **80**, pupil **75**, and lids, etc. Moreover, light that is specularly reflected from the steeply convex surface of the cornea **60** forms two tiny virtual images of the offset light sources **440**, **450**, which appear to the patient as bright white points approximately in the plane of the iris **80**. Similarly, the light from the central source **410** that is reflected from the cornea **60** appears as a tiny green point. During alignment, the patient moves laterally, e.g., horizontally and vertically, with respect to the instrument **100** that includes the alignment subsystem **400**. The patient adjusts his or her lateral position until the green dot image produced by the central light source **410** is centered between the two images of the offset white light sources **440**, **450**. The instrument **100** is considered to be aligned in two orthogonal directions, e.g., the vertical and horizontal axes, when the images of the two light sources **440**, **450** are collinear with and bisected by the green dot image produced by the central light source **410**, and the green point reflected from the cornea **60** is centered on the green source **410** seen directly through the partially transparent mirror **430**.

[0065] The above alignment procedure is based on an assumption that the patient's vision is approximately emmetropic, that is that the patient's eye is focused on a target at infinity and that he or she is neither nearsighted nor farsighted. If the patient were, for example, nearsighted, the image of the patient's eye **10** in the above procedure would appear defocused, as would small green spot image produced by the central light source **410**. In certain embodiments, such non-emmetropic conditions may be corrected by adjusting the longitudinal position of the central light source **410** towards or away from the collimating lens **420** until the small green spot image produced by the light source **410** appears sharp to the patient. Correction may also be provided by positioning the curved mirror **430** towards or away from the patient until the image of the patient's eye appears sharp. To adjust the positioning, the subsystem **400** may further comprise, for example, micrometers or other translation devices mechanically coupled to the source **410**, collimating lens **420**, and/or the curved mirror **430**. In this configuration, the patient adjusts the position of the source **410**, collimating lens **420**, and/or the curved mirror **430** by adjusting the translation devices. In other embodiments, after appropriate adjustment has been reached, e.g., once the proper non-emmetropic corrections have been made, the position is locked in place. In still other embodiments, the amount of correction can be recorded and made available so that several patients requiring different non-emmetropic correction settings may easily use the same instrument. Manual or electronic positioning and translation components can be used. In the case where positioning is by electronic apparatus, the one or more correction setting can be stored in memory and adjustment can be automatic.

[0066] In addition to providing correct lateral, e.g., horizontal and vertical, alignment, the instrument **100** is preferably located an appropriate distance away from the eye **10**. Most preferably, the instrument **100** is positioned such that

the focal point of the focusing lens **170** in the second arm of the interferometer **150** corresponds to the center of curvature **260** of the cornea **80**.

[0067] In certain embodiments, for example, the instrument **100** further comprises an alignment subsystem **500**, such as schematically illustrated in FIG. 7, that facilitates longitudinal positioning of the instrument **100** with respect to the eye **10** as well as fine adjustment of the lateral alignment. This subsystem **500** is for establishing the appropriate distance between the optical device **100** and the eye **10**. More specifically, the separation of the instrument **100** from the eye **10** as measured along an axis through the center of curvature, C, of the cornea **60** (i.e., along the z'-axis shown in FIG. 7), is preferably such that accurate measurement of the glucose concentration can be obtained. This z'-axis is preferably offset from the visual axis **90** by a small angle.

[0068] The fine longitudinal and lateral alignment subsystem **500** comprises a beamsplitter **510** which introduces two (i.e., third and fourth) additional optical paths **515**, **525** into the instrument **100** and two optical detectors **530**, **540**, one in each of these optical paths. Two lenses **550**, **560** are associated with the two detectors **530**, **540** in the third and fourth optical paths **515**, **525**. The fine lateral/longitudinal alignment subsystem **500** further includes an optical filter **570** in the fourth path **525** for filtering light directed to the detector **540**. The detectors **530**, **540** respectively produce alignment and reference signals **580**, **585**, which together enable substantially precise longitudinal as well as lateral alignment.

[0069] The beamsplitter **510** may comprise a beamsplitter cube or a plate with a partially reflective coating formed thereon. Other types of beam separators may also be used. In certain embodiments, the detectors **530**, **540** may comprise photodiodes, which preferably have a small light sensitive area. The detector **530** may further include a pinhole that is used to decrease the effective photosensitive area of the detector **530**. In one preferred embodiment, the pinhole aperture is less than about 0.2 millimeters in diameter. In other embodiments, the detectors **530**, **540** may comprise two dimensional sensor arrays such as CCD or CMOS detector arrays. The lenses **550**, **560** focus light to a small spot on the detectors **530**, **540**. Other types of detectors and optical elements may be employed as well. The filter **570** may comprise a neutral density filter or other type of filter or attenuator.

[0070] The subsystem **500** for fine longitudinal/lateral alignment is inserted in the second arm of the instrument **100** such that the second probe beam **150** from the coherent light source **115** propagating towards the focusing lens **170** is received by the beamsplitter **510**. A portion of the light in the second probe beam **150** is reflected by the beamsplitter **510** and is focused on a small area of the detector **540** by the associated collecting lens **560**. The portion of the light in the beam **150** that is not reflected by the beamsplitter **510** is transmitted and received by the focusing lens **170** which directs the light into the eye **10**. Of the light incident on the eye **10**, about 3% will be specularly reflected by the outer corneal surface for a typical human eye. When the focusing lens **170** is properly aligned, the light reflected by the corneal surface propagates back toward the beamsplitter **510** along the same path by which it arrived at the cornea **30**. The

retroreflected light traverses substantially the same path on return because, when properly aligned, the center of curvature **260** of the cornea **30** is in the focal plane of the lens **170**. Under these conditions substantially all the rays in the beam **150** are normal to the corneal surface and, therefore, propagate back along the same path.

[0071] Thus, when the instrument **100** is properly aligned, some of the light reflected by the cornea **60** is additionally directed by the beamsplitter **510** toward the detector **530**. This light is focused by the lens **550** onto a small area of the detector **530** for measurement. The magnitude of the alignment signal **580** is directly related to the intensity of the spot falling on the detector **530**. Preferably, proper alignment produces the highest relative intensity of the alignment signal **580** output by the detector **560**. A normalized signal **590** is produced by dividing the alignment signal **580** by the reference signal **585**. This reference signal **585** corresponds to a fraction of the output emitted by the coherent light source **115** that is transferred to the second probe beam **150** of the interferometer **120**. Accordingly, normalization adjusts for fluctuations in the power output of the coherent light source **110**.

[0072] If the instrument **100** is not correctly aligned so that the focal point of the focusing lens **170** is not coincident with the center of curvature, C, of the cornea **60**, the rays in the second probe beam **150** that are reflected off the corneal surface will have non-normal reflection angles. These retroreflected rays will therefore not follow the same path back to the lens **170** and the beamsplitter **510**. The deviations will result in a spot on the detector **530** that is dimmer or one that partially or totally misses the effective photosensitive region of the detector. Under non-ideal conditions, when the longitudinal or lateral alignment is off, the normalized alignment signal **590** is correspondingly smaller than the aligned case where the alignment in all three orthogonal directions is substantially correct.

[0073] Thus, in one preferred embodiment, when the instrument **100** is properly aligned, the alignment subsystem **500** preferably produces the maximum normalized alignment signal **590**. A small audio speaker may be included to emit an audio verification when the normalized signal **590** reaches its aligned value. The detector electronics can be designed to automatically capture an image of the fringes produced at the iris **80** at this time when suitable alignment is achieved.

[0074] Under preferred alignment conditions, the light in the second probe beam **150** that is reflected by the beamsplitter **510** and directed onto the reference detector **540** is more intense than the light reflected from the cornea **60**. In certain embodiments, the filter **570** is used to attenuate the intensity of the light focused onto this detector **540**. This filter **570** may reduce the intensity so that the reference signal **585** is approximately equal to the alignment signal **580** and the normalized signal **590** is approximately one when suitable alignment is achieved. Other methods of compensating for the higher intensity light received by the detector **540** are also possible. For example, the light incident on the detector **540** may be defocused to produce a lower value of the reference signal **585**.

[0075] In certain embodiments, such as schematically illustrated in FIG. 8, the device **100** for measuring the concentration of glucose in the bloodstream preferably

includes both the rough lateral alignment subsystem **400** as well as the fine lateral/longitudinal alignment system **500**. The lateral alignment subsystem **400** is particularly well suited for aligning the instrument **100** laterally with respect to the eye **10**, i.e., in the x and y direction. The fine lateral/longitudinal alignment subsystem **500** may be utilized to position the device **100** at the appropriately in all three directions, i.e., x, y, and z. Although alignment systems **400**, **500** such as those described with reference to FIGS. 6 and 7 are shown, other types of systems for aligning the instrument **100** may be employed as well. Alignment systems both well known as well as those yet to be devised are considered possible.

[0076] In various preferred embodiments, however, substantially all the optical components are included in a common structure and may be contained within an enclosure to produce a compact instrument **750** such as illustrated in FIG. 9. In the embodiment shown in FIG. 9, the compact enclosed instrument **750** is about the size of a small book or pair of binoculars or preferably smaller. The particular design, however, should not be so restricted and may take other shapes and forms.

[0077] In certain embodiments of the device **750**, the patient activates the instrument using for example a switch. The light sources **410**, **440**, **450**, the detectors **190**, **530**, **540**, and supporting electronic are powered. The coherent light source **115** may be set at a relatively low level. The patient then peers into an eyepiece (e.g., a window) and sees his or her eye reflected from the curved mirror **430**. The patient proceeds to move the instrument **750** laterally in a plane normal to the visual axis **90**, e.g., vertically and horizontally, or in two other orthogonal directions depending on the design. The patient endeavors to center the small green spot of light produced by the central light source **410** between the two images of the two offset light sources **440**, **450**. While maintaining alignment in the plane normal to the visual axis **90**, the patient translates the instrument **750** toward or away from his or her eye **10** until an audio alignment signal is heard. The fringe pattern on the iris **80** is captured and a reading appears on a display included in the instrument **750**.

[0078] As discussed above, an audio alignment signal may be triggered when the normalized alignment signal **590** is maximized. In certain embodiments, the instrument **750** may be configured such that when this condition is satisfied, the coherent light source **115** momentarily brightens. Also, one video frame or field may be captured by the detector **190**. Subsequently, the coherent light source **115** is turn off or otherwise powered down and the processing or computations are performed. When the signal processing is complete, the result can be displayed.

[0079] The fringes produced at the iris **80** are not an absolute measure of glucose concentration. Fringe spacing, for example, has a slight dependence on the shape of the particular patient's eye, which, in turn, affects the various path lengths within the aqueous humor. Therefore, in certain embodiments, the devices **100**, **750** are preferably calibrated to individual users. In various embodiments, such as instruments **100**, **750** used by a diabetic family, a single instrument is calibrated separately for different users.

[0080] The calibration procedure may be as follows. For a period of time, e.g. a few days, the user measures blood glucose one or more times a day using one or more methods

that provide an independent accurate measure of glucose concentration. Methods well known in the art such as the finger stick method may be suitable. The user also performs a measurement of the index of refraction of the aqueous humor with the instrument **100, 750** described above. The user enters the results of both readings into the device **100, 750** possibly using an interface such as a keypad that plugs into the instrument for such purposes. By storing measurements obtained over a period of time, the instrument **100, 750** can be calibrated with suitable accuracy. In various embodiments, the data are analyzed automatically and the instrument **100, 750** indicates when sufficient data have been obtained to generate a reliable calibration. The appropriate constant or set of constants can be automatically recorded by the instrument **100, 750**. A display or other interface can be used to indicate that the instrument **100, 750** is properly calibrated and ready for regular use. In other embodiments, a single measurement may be employed to calibrate the instrument **100, 750** although multiple measurements may improve accuracy.

[0081] Based on the independently measured glucose levels, the values obtained by of the instrument **100** are preferably calibrated so that the output produced by the instrument can be correlated with the appropriate glucose level. As different eyes **10** are physically different, the instrument **100** is preferably calibrated separately for different patients.

[0082] Glucose, however, may not be the only substance dissolved in the aqueous humor, and these other substances may affect the index of refraction and the fringes produced on the iris **80**. The effect of such substances is expected to be sufficiently small so as not to significantly alter the fringes produced on the iris **80** and interfere with accurate measurements of glucose levels. Nevertheless, the effect of such substances can be reduced or substantially eliminated by employing various techniques. For instance, the measurements can be performed at the appropriate wavelengths to reduce the effect of other solutes on the measured index of refraction. A given solute, such as for example glucose, may cause a change in refractive index that varies with the wavelength of the incident light. The variation in refractive index with wavelength is called dispersion. Different solutes have different dispersion characteristics. Therefore, in certain embodiments, a suitable wavelength can be chosen such that variations in glucose concentrations causes a significant change in the refractive index, while any interfering substances do not. For example, the concentration of sodium chloride in the aqueous humor may fluctuate. However, such changes have a negligible effect on the refractive index in the near infrared wavelengths where variations in the glucose level do significantly affect the refractive index.

[0083] In other embodiments, the measurement of the spacing and locations of the fringes produced at the iris **80** can be performed at two or more different wavelengths. Preferably, different wavelengths are selected that manifest different variations in refractive index with concentration of glucose and the interfering material. Measurements of the fringe spacing or location at these two wavelengths provides sufficient information to distinguish between the effects of the two solutes. Two measurements are performed, one at each wavelength and two values of refractive index are obtained. The glucose concentration in the aqueous humor can be determined from the two refractive index changes at

the two wavelengths. In general, if there are N solutes, the contribution of one of the solutes, e.g., glucose, can be determined by measuring the fringe pattern at N properly chosen wavelengths. Other methods and variations, however, may be employed to ascertain the level of glucose concentration.

[0084] In certain cases, the physical distance between the cornea **60** and the iris **80** varies. Such variations cause the fringe pattern produced at the iris **80** to change, thus interfering with accurate refractive index measurements. Such changes in this physical distance, however, may be accounted for by various techniques.

[0085] In various embodiments, the effects of changes in the physical length of the light paths can be separated out. These optical path lengths govern in part the times required for light to travel over the physical paths. To account for variations in length, additional measurements can be obtained at different wavelengths. In one preferred embodiment, for example, a second coherent light source of different wavelength may be included in the instrument **100, 750**. Preferably, the refractive index of glucose is different for the two wavelengths. Using the second coherent light source, a second set of measurements of the resulting fringe pattern can be obtained. This second set of measurements will have the same pair of physical path lengths but a different pair of optical path lengths as the index of refraction is different for the two wavelengths. Thus, the difference between the two fringe patterns is a measure of the difference in refractive indices at the two wavelengths, which, in turn, can be use to establish the physical path length. In this manner, the measurement of glucose concentration can be calibrated for varying thicknesses between the cornea **60** and the iris **80**.

[0086] Other variations of the instrument design and configuration are considered possible. For example, instead of using a video camera, the image of the fringes could be swept across a vertical slit or set of slits in front of one or more photodetectors, thus converting the fringe spacing into temporal frequencies that could be measured. The alignment might also be performed entirely automatically, using, for example, a video image of the eye and corneal reflection to drive motors that position the optical system with respect to the eye. The instrument may also be interfaced to a computer as well. Still other variations of the instrument and techniques for measuring glucose concentration may be employed. The methods and designs should not be limited only to those embodiments disclosed herein.

[0087] Those skilled in the art will appreciate that the methods and designs described above have additional applications and that the relevant applications are not limited to those specifically recited above. Also, the present invention may be embodied in other specific forms without departing from the essential characteristics as described herein. The embodiments described above are to be considered in all respects as illustrative only and not restrictive in any manner.

1-18. (Cancelled)

19. An alignment apparatus for lateral aligning an eye with respect to said apparatus comprising:

- a) a central light source;
- b) a partially reflecting concave mirror having an optical axis passing therethrough, said central light source

centrally disposed along said optical axis such that at least a portion of said light from said central light source propagates through said partially reflecting concave mirror along said optical axis; and

- c) first and second offset light sources disposed in a plane passing through said optical axis, said first and second offset light sources on opposite sides of said optical axis, said first and second offset light sources emitting light at an oblique angle toward said optical axis.

**20.** The alignment apparatus of claim 19, wherein said central light source comprises a light emitting diode.

**21.** The alignment apparatus of claim 19, wherein said partially reflecting concave mirror comprises a metalized mirror.

**22.** The alignment apparatus of claim 19, wherein said first and second offset light sources comprise light emitting diodes.

**23.** The alignment apparatus of claim 19, wherein said first and second offset light sources are spaced apart from said optical axis by equal distances.

**24.** The alignment apparatus of claim 19, wherein said first and second offset light source have respective positions and orientations such that said light emitted from said light sources is substantially directed toward a common point on said optical axis.

**25.** A method of aligning a device with respect to a cornea, said cornea having a substantially spherical curvature defined by a center of curvature, said method comprising:

- a) propagating light toward said cornea, said light having substantially spherical wavefronts defined by a center of curvature that is substantially coincident with said center of curvature of said cornea;

- b) retroreflecting a portion of said light from said cornea;

- c) collecting said retroreflected light; and

- d) focusing said collected light on an optical detector having a photosensitive area such that when said center of curvature of said wavefronts is substantially coincident with said center of curvature of said eye, said light focused on said photosensitive area has a different intensity than when said respective centers of curvature are non-coincident.

**26.** The method of claim 25, further comprising covering at least a portion of said optical detector such that when said center of curvature of said wavefronts is non-coincident with said center of curvature of said eye, said light incident on said photosensitive area is reduced.

\* \* \* \* \*