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(54) POLARIZATION MODULATION INTERROGATION OF GRATING-COUPLED WAVEGUIDE SENSORS

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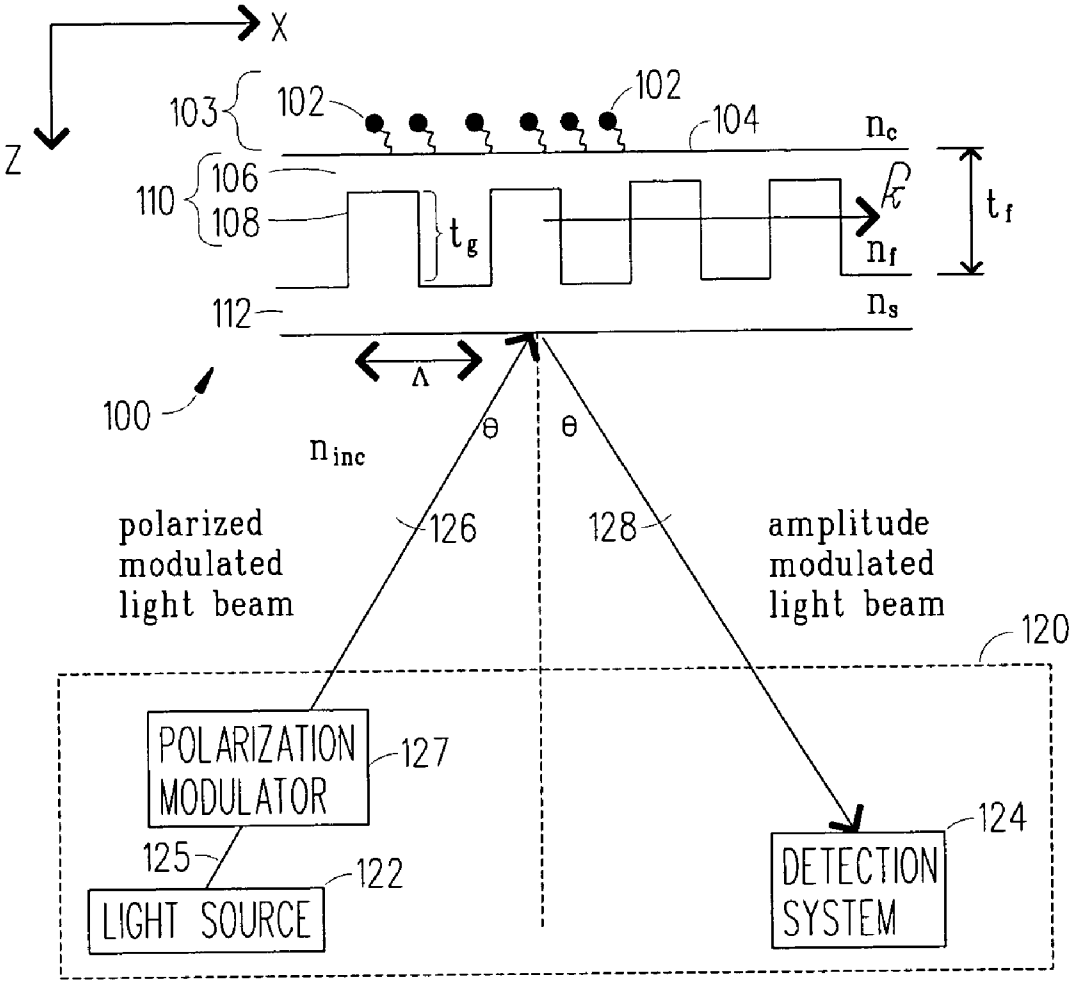
(57) ABSTRACT

An optical interrogation system and a GCW sensor are described herein that are used to determine whether a biological substance (e.g., cell, molecule, protein, drug) is located in a sensing region of the GCW sensor. The optical interrogation system includes a light source, a polarization modulator and a detection system. The light source outputs a polarized light beam and the polarization modulator modulates the polarized light beam and outputs a polarization-modulated light beam. The GCW sensor receives and converts the polarization-modulated light beam into an amplitude modulated light beam that is directed towards the detection system. The detection system receives the amplitude modulated light beam and demodulates the received amplitude modulated light beam by responding to signals at a modulation frequency of the polarization-modulated light beam and ignoring noise affecting the signals outside the modulation frequency to detect a resonant condition (e.g., resonant angle, resonant wavelength). The detected resonant condition that has a one-to-one relationship with the refractive index of the superstrate containing the biological substance is analyzed to determine whether or not the biological substance is located in the sensing region of the GCW sensor.



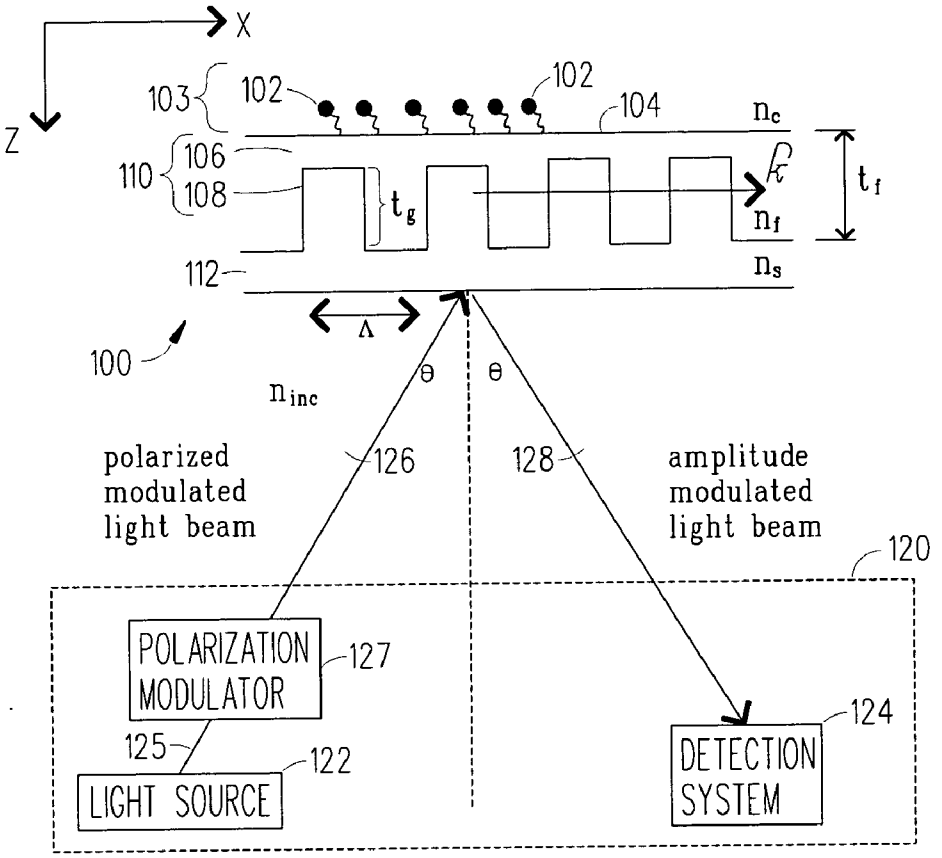

X
Z
103
102
102
104
n_c
110
106
108
t_g
t_f
n_f
n_s
112
Λ
100
n_{inc}
θ
θ
polarized
modulated
light beam
126
128
amplitude
modulated
light beam
120
POLARIZATION
MODULATOR
127
125
122
LIGHT SOURCE
DETECTION
SYSTEM
124

FIG. 1

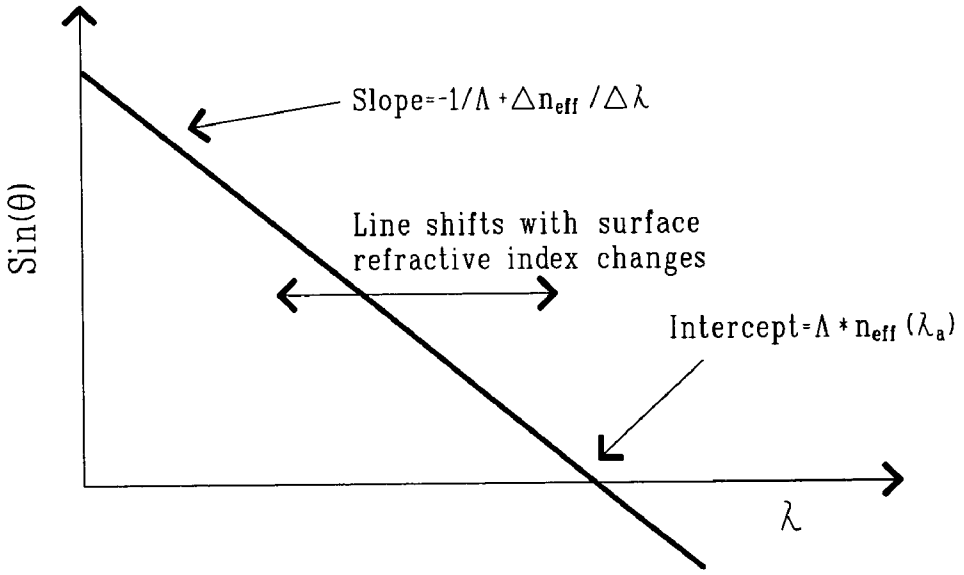

Slope=-1/Λ+Δn_{eff}/Δλ
Sin(θ)
Line shifts with surface
refractive index changes
Intercept=Λ*n_{eff}(λ_a)
λ

FIG. 2

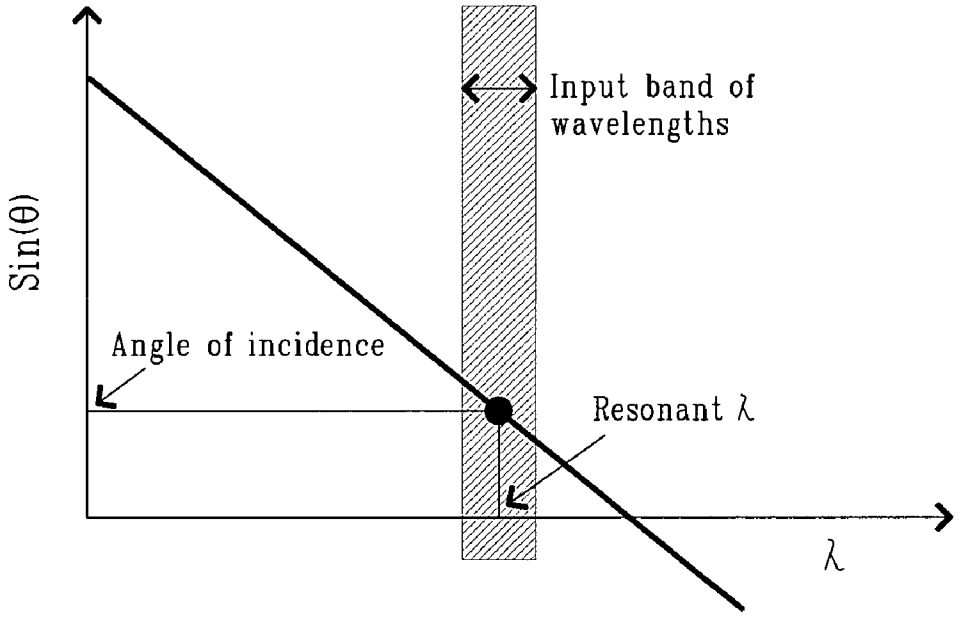

Input band of
wavelengths
Sin(θ)
Angle of incidence
Resonant λ
λ

FIG. 3

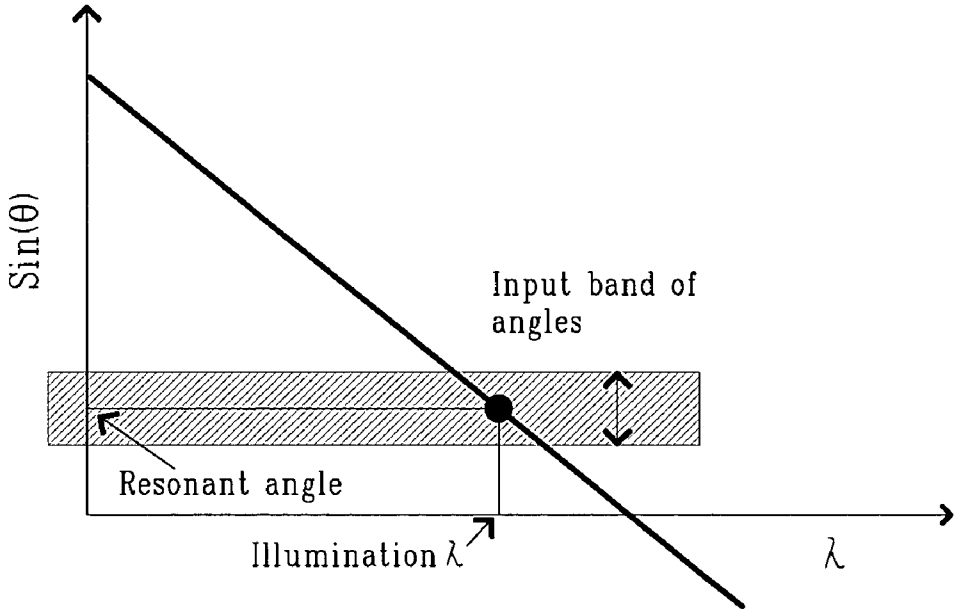

Sin(θ)
Input band of
angles
Resonant angle
Illumination λ
λ

FIG. 4

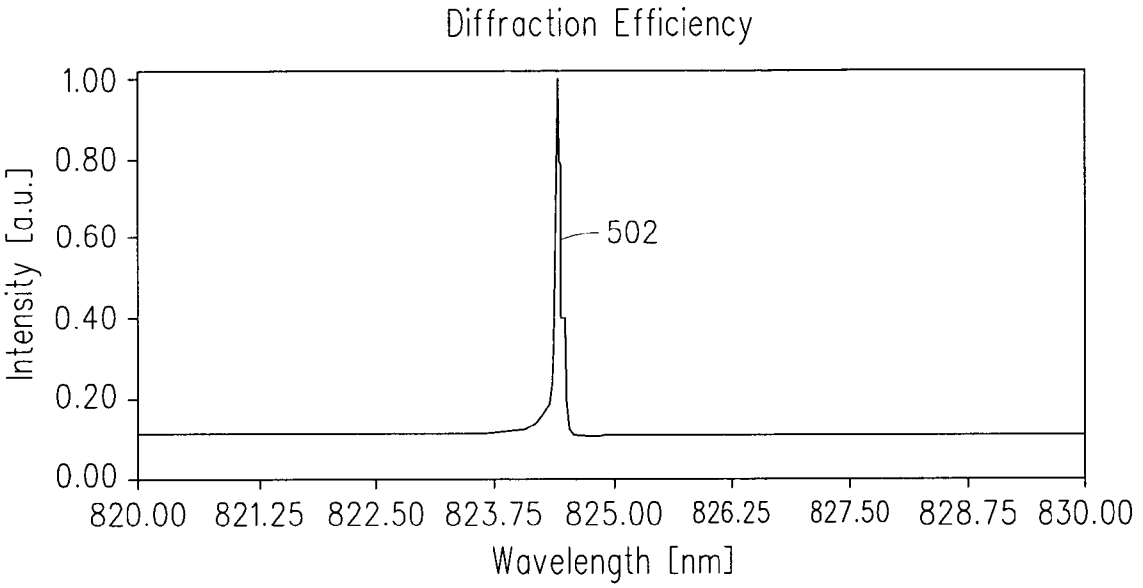

Diffraction Efficiency
1.00
0.80
0.60
0.40
0.20
0.00
Intensity [a.u.]
502
820.00
821.25
822.50
823.75
825.00
826.25
827.50
828.75
830.00
Wavelength [nm]

FIG. 5

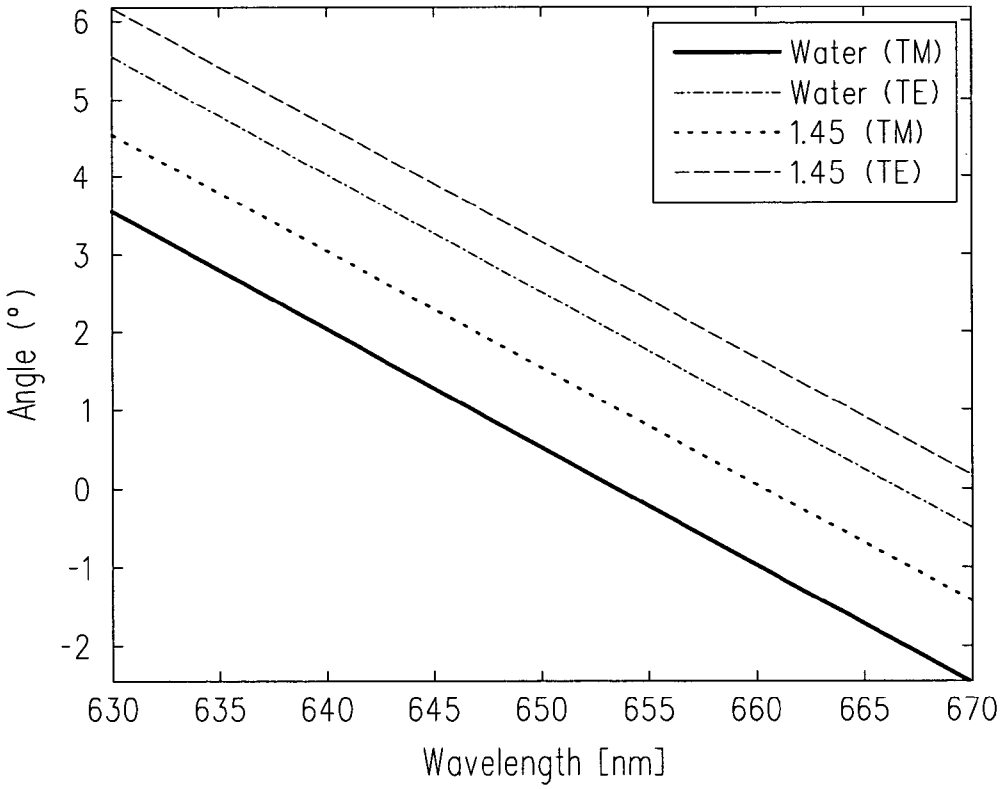

Water (TM)
Water (TE)
1.45 (TM)
1.45 (TE)
6
5
4
3
2
1
0
-1
-2
Angle (°)
630
635
640
645
650
655
660
665
670
Wavelength [nm]

FIG. 6

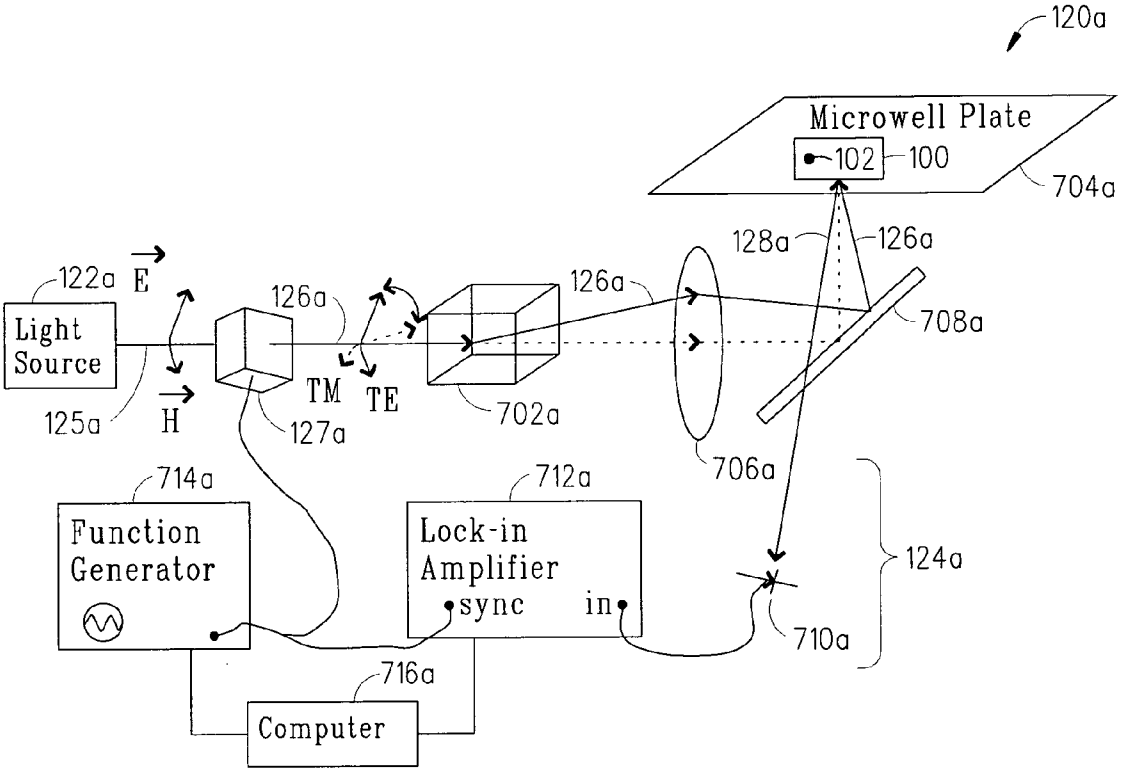

120a
Microwell Plate
102
100
704a
128a
126a
122a
E
126a
126a
Light Source
708a
125a
H
TM
TE
127a
702a
706a
714a
712a
Function Generator
Lock-in Amplifier
sync
in
124a
710a
716a
Computer

FIG. 7

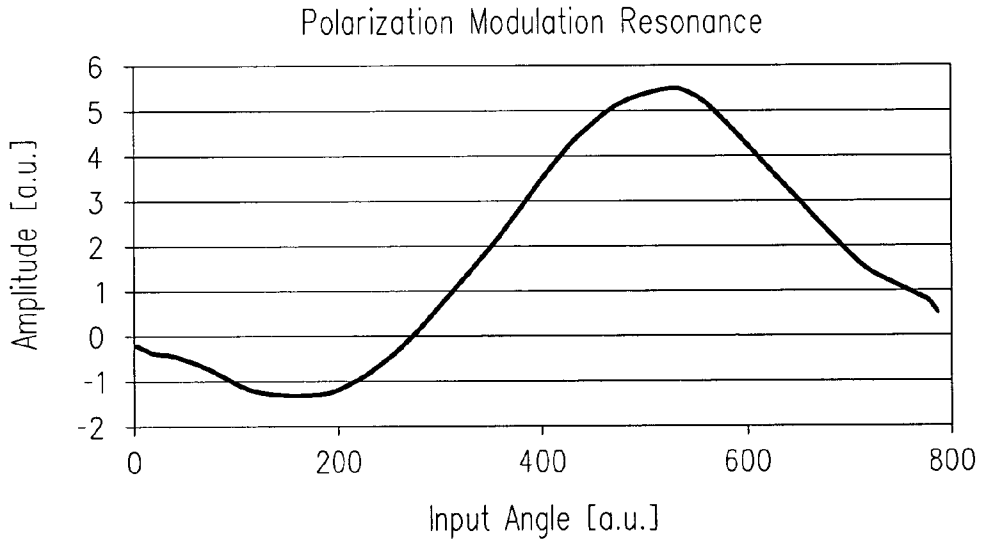

Polarization Modulation Resonance
Amplitude [a.u.]
6
5
4
3
2
1
0
-1
-2
0
200
400
600
800
Input Angle [a.u.]

FIG. 8

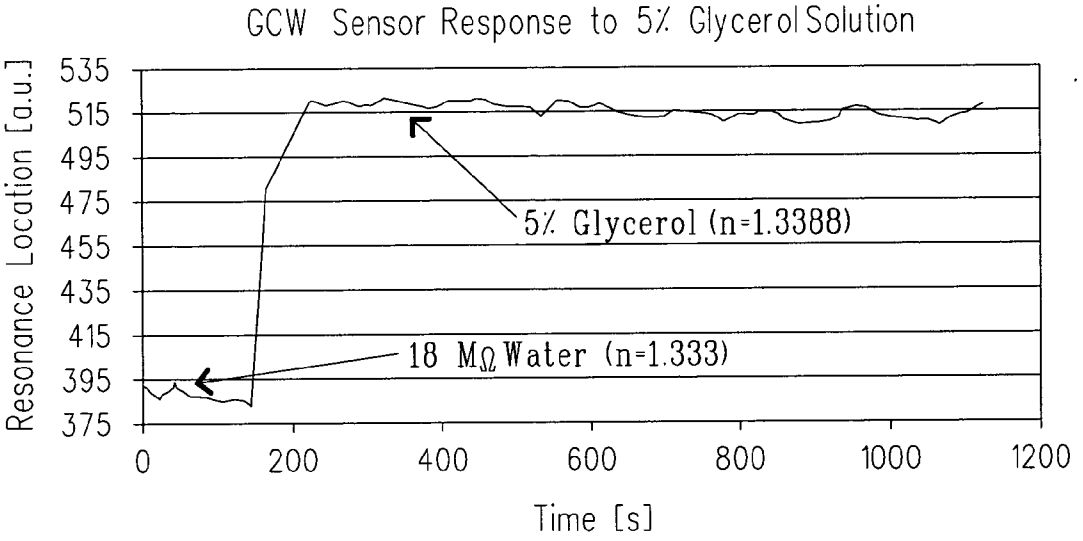

GCW Sensor Response to 5% Glycerol Solution
Resonance Location [a.u.]
535
515
495
475
455
435
415
395
375
0
200
400
600
800
1000
1200
Time [s]
5% Glycerol (n=1.3388)
18 MΩ Water (n=1.333)

FIG. 9

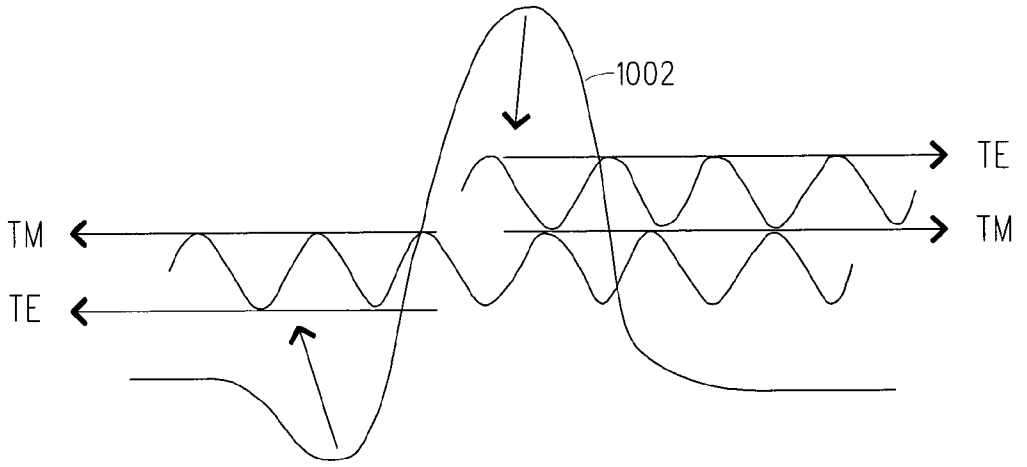

1002
TE
TM
TM
TE

FIG. 10

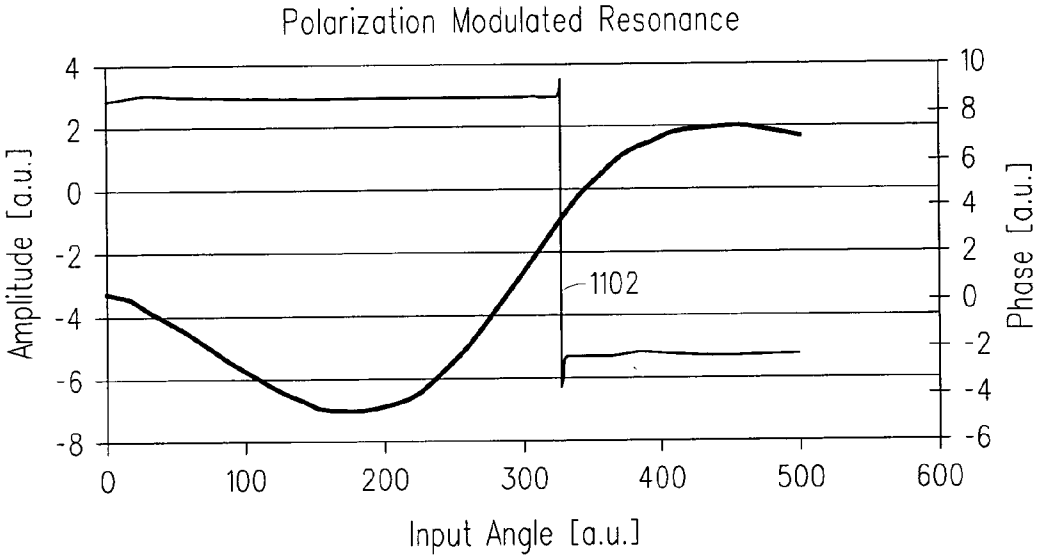

Polarization Modulated Resonance
Amplitude [a.u.]
Phase [a.u.]
Input Angle [a.u.]
1102
4
2
0
-2
-4
-6
-8
10
8
6
4
2
0
-2
-4
-6
0
100
200
300
400
500
600

FIG. 11

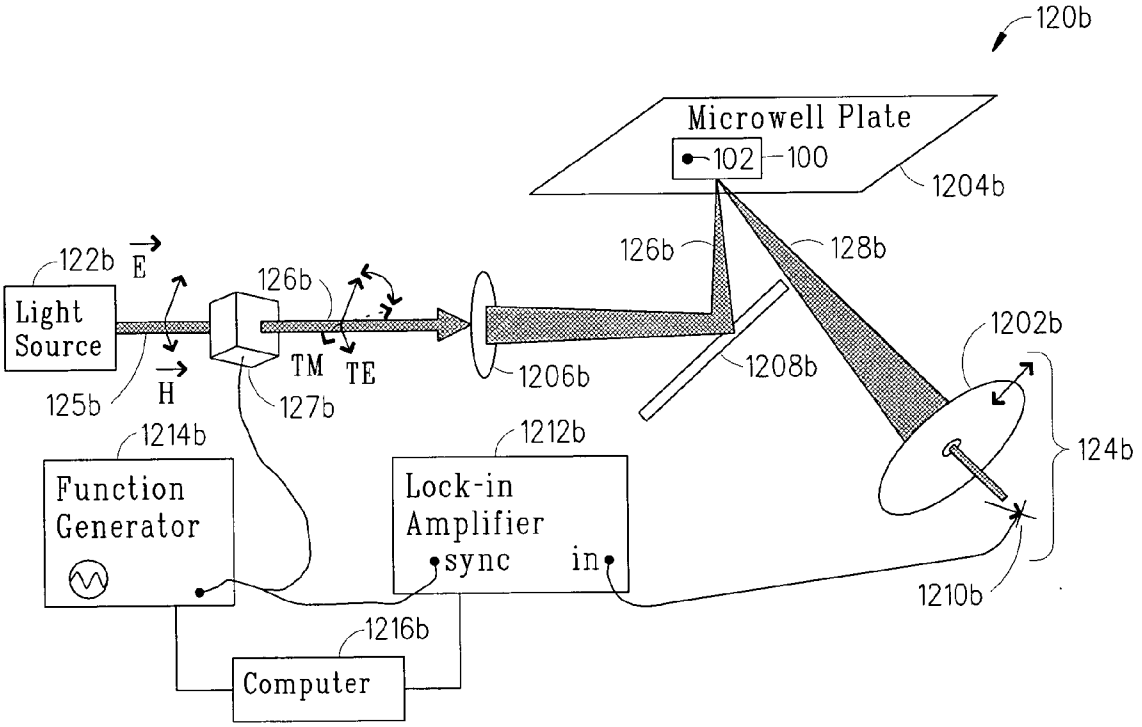

120b
Microwell Plate
102
100
1204b
122b
E
Light Source
125b
H
126b
TM
TE
127b
126b
128b
1206b
1208b
1202b
124b
1214b
Function Generator
1212b
Lock-in Amplifier
sync
in
1210b
1216b
Computer

FIG. 12

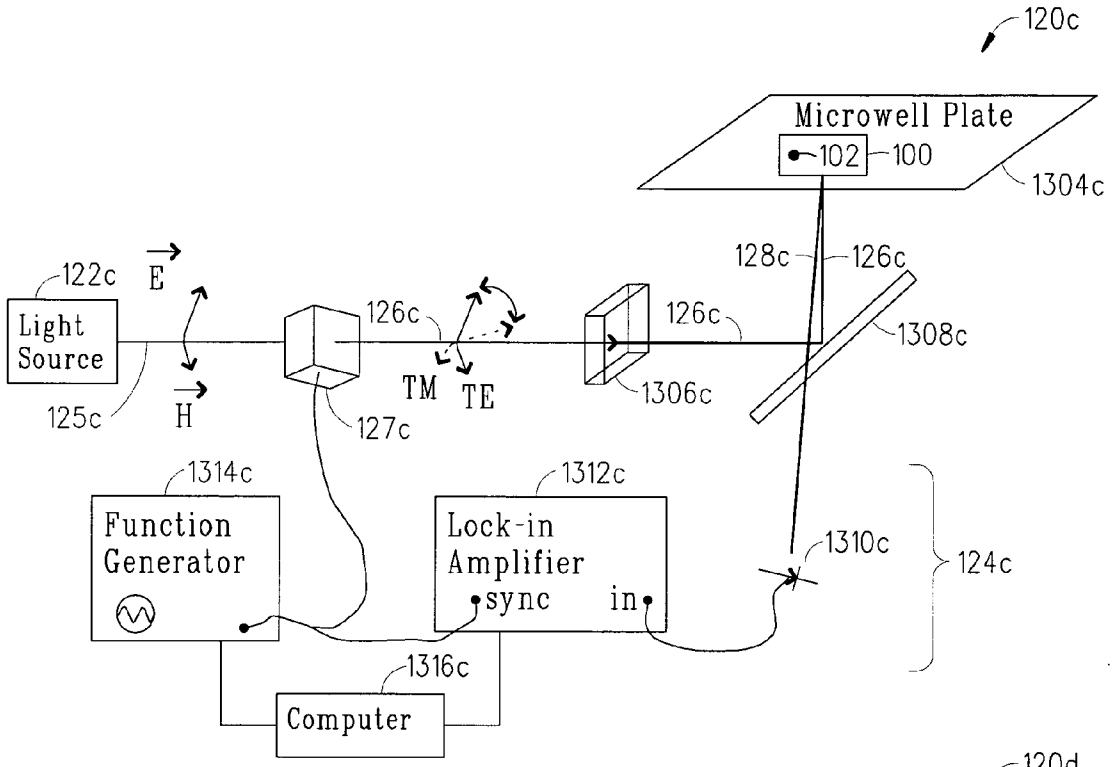

120c
Microwell Plate
102
100
1304c
128c
126c
122c
E
Light Source
125c
H
126c
TM
TE
126c
1306c
1308c
127c
1314c
Function Generator
1312c
Lock-in Amplifier
sync
in
1310c
124c
1316c
Computer

FIG. 13

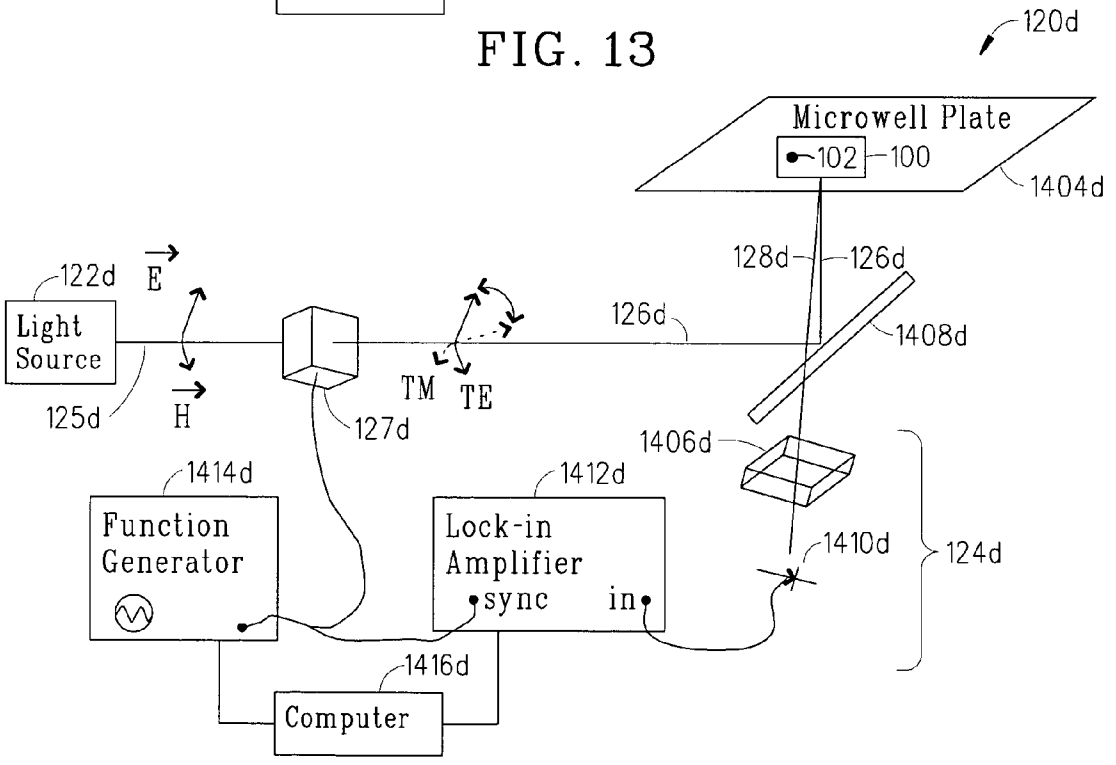

120d
Microwell Plate
102
100
1404d
128d
126d
122d
E
Light Source
125d
H
126d
TM
TE
1408d
127d
1406d
1414d
Function Generator
1412d
Lock-in Amplifier
sync
in
1410d
124d
1416d
Computer

FIG. 14

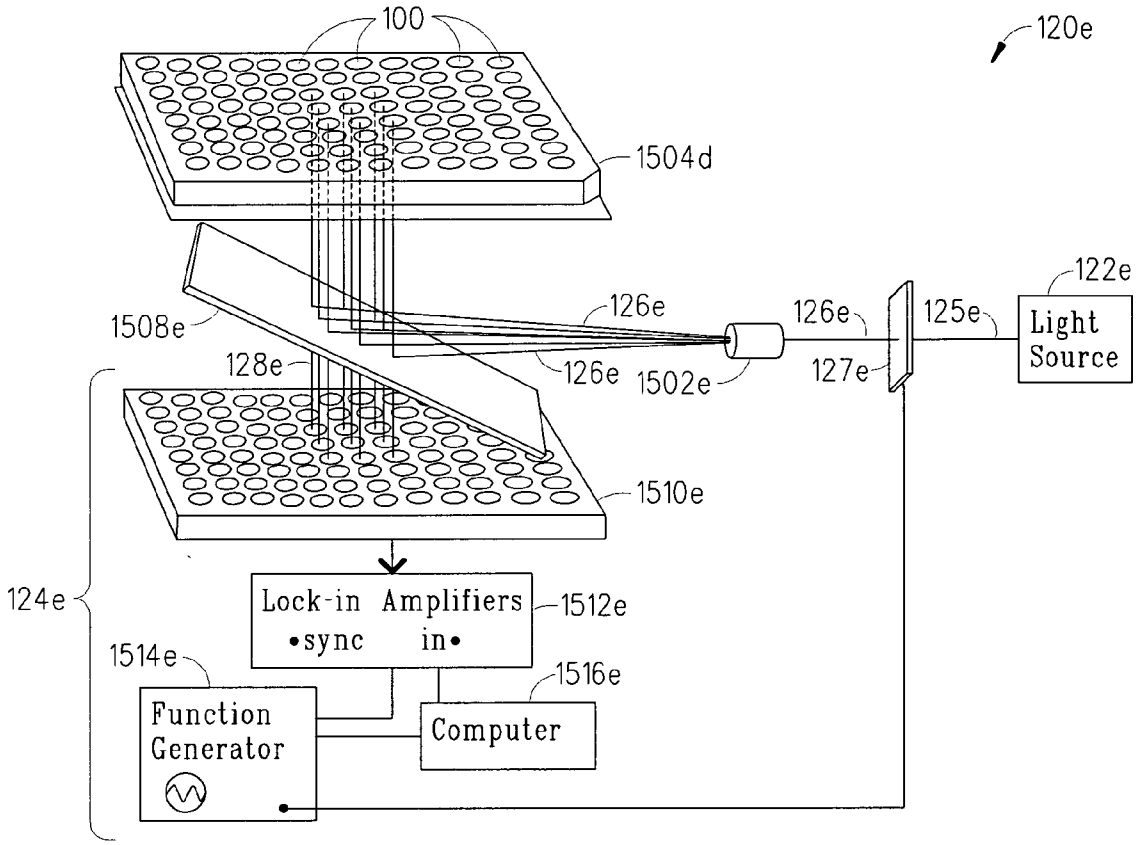

100
120e
1504d
122e
126e
126e
125e
Light Source
1508e
128e
126e
1502e
127e
1510e
124e
Lock-in Amplifiers
•sync in•
1512e
1514e
1516e
Function Generator
Computer

FIG. 15

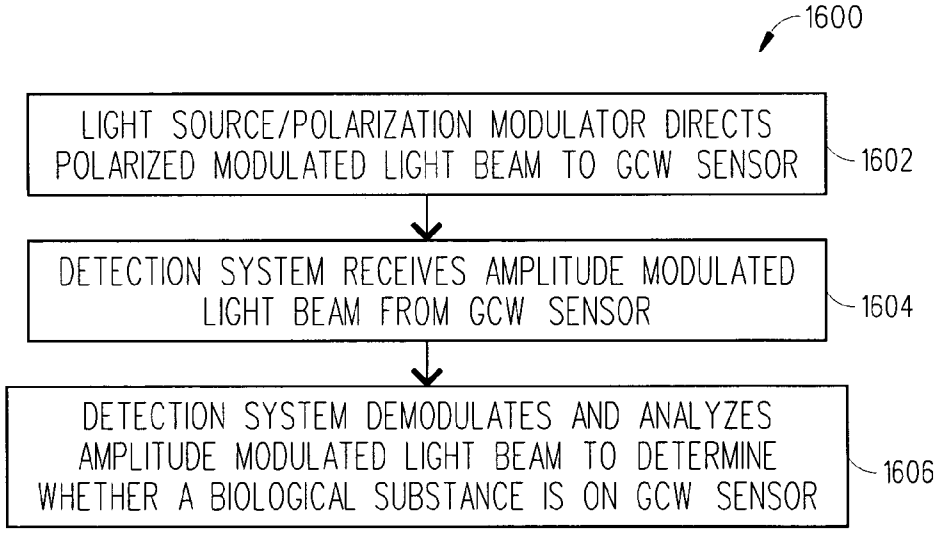

1600
LIGHT SOURCE/POLARIZATION MODULATOR DIRECTS POLARIZED MODULATED LIGHT BEAM TO GCW SENSOR
1602
DETECTION SYSTEM RECEIVES AMPLITUDE MODULATED LIGHT BEAM FROM GCW SENSOR
1604
DETECTION SYSTEM DEMODULATES AND ANALYZES AMPLITUDE MODULATED LIGHT BEAM TO DETERMINE WHETHER A BIOLOGICAL SUBSTANCE IS ON GCW SENSOR
1606

FIG. 16

POLARIZATION MODULATION INTERROGATION OF GRATING-COUPLED WAVEGUIDE SENSORS

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention relates in general to a grating-coupled waveguide (GCW) sensor and, in particular, to an optical interrogation system and method for using polarization-modulated light beams to interrogate a GCW sensor in order to determine whether or not a biological substance is located within a sensing region of the GCW sensor.

[0003] 2. Description of Related Art

[0004] Grating-coupled waveguide (GCW) sensors are fast becoming the technology of choice to enable accurate label-free detection of a biological substance (e.g., cell, drug, chemical compound). This technology typically involves the use of a waveguide evanescent field to sense changes in the refractive index of a GCW sensor caused by the presence of a biological substance in a sensing region of the GCW sensor. To generate the evanescent field, an optical interrogation system is used which has a light source that couples a light beam into a waveguide of the GCW sensor. The optical interrogation system also includes a detector that receives a light beam coupled out from the waveguide that is analyzed to determine the effective refractive index of the waveguide. In determining the effective refractive index of the GCW sensor it should be understood that the light beam received by the detector had interacted with the waveguide under a resonant condition, where the wavevectors of a diffraction grating, incoming light beam, and guided mode all sum to zero. And, that this resonant condition occurs only for a specific wavelength and angle of the incoming light where changes in this angle or wavelength corresponds to changes in the effective refractive index of the waveguide caused by the presence of the biological substance in the sensing region of the GCW sensor. Thus, the optical interrogation system is used to sense a change in the effective index of the GCW sensor which enables one to determine whether or not a biological substance is located within the sensing region of the GCW sensor.

[0005] For this technology to be viable, one must have an optical interrogation system and in particular a detector capable of accurately monitoring the resonant angle, wavelength, or both. In particular, the optical interrogation system must emit a light beam that interacts with the GCW sensor, and must in turn receive the light beam coupled-out off the GCW sensor and process that light beam to detect in real time any changes in it's resonant angle and/or wavelength. While there are many approaches for accomplishing these tasks, each has unique implementation challenges, since the light beam output from the GCW sensor is relatively weak and there are multiple sources of noise that degrade this light beam especially in high-throughput screening applications.

[0006] GCW sensors are particularly attractive for use in high-throughput screening applications, where the absence of fluorescent tags and the possibility of reduced false-negatives would provide a large cost advantage. For this reason, the microplate has been targeted as the platform for such sensors, where 96 or 384 individual wells provide the high-throughput access demanded by the industry. In this application, the waveguide and diffraction grating of the GCW sensor are located in the bottom of each well; e.g., the diffraction grating may be stamped into the well bottom, and the waveguide subsequently grown on top of the diffraction grating. The wells themselves are typically composed of an optically transparent, low-birefringence, low-cost plastic that is typically several millimeters thick. To probe the GCW sensor in the well bottom while leaving the tops of the wells open for fluid handling, etc., the optical light beam is emitted into the bottom of the microplate and passes through the well plastic before striking the GCW sensor. One source of noise for this type of optical interrogation system is produced by the Fresnel reflection emanating from the bottom surface of each well. Due to the large number of wells, one ideally tries to design the GCW sensor to operate with incoming light beams near normal incidence. As a result, this spurious Fresnel reflection which acts as noise is often inextricably mixed with the light beam output from the GCW sensor that contains the desired information about the resonant angle and/or wavelength. In addition to the Fresnel reflection caused by the bottom surface of the microplate, the top surface of the waveguide inserts yet another Fresnel reflection into the output light beam that mingled with the light beam that propagated as a waveguide mode and exited the GCW sensor through the diffraction grating.

[0007] In addition to these direct optical noise sources, the traditional optical interrogation system is susceptible to other electrical and optical noises. For example, the wavelength or angle of the output light beam is often monitored with detectors such as charge-coupled device (CCD) cameras or spectrographs that observe the signal in a DC fashion. All of the DC electrical and optical (stray light) noise can impede the detection of the resonant angle and/or wavelength in the output light beam. Accordingly, there is a need for an optical interrogation system and method that can avoid the aforementioned problematical noise sources when interrogating one or more GCW sensors. This need and other needs are satisfied by the optical interrogation system, GCW sensor and method of the present invention.

BRIEF DESCRIPTION OF THE INVENTION

[0008] The present invention includes an optical interrogation system capable of interrogating a GCW sensor to determine whether a biological substance (e.g., cell, molecule, protein, drug) is located in a sensing region of the GCW sensor. The optical interrogation system includes a light source, a polarization modulator and a detection system. The light source outputs a polarized light beam and the polarization modulator modulates the polarized light beam and outputs a polarization-modulated light beam. The GCW sensor receives and converts the polarization-modulated light beam into an amplitude modulated light beam that is directed towards the detection system. The detection system receives the amplitude modulated light beam and demodulates the received amplitude modulated light beam by responding to signals at a modulation frequency of the polarization-modulated light beam and ignoring noise affecting the signals outside the modulation frequency to detect a resonant condition (e.g., resonant angle, resonant wavelength). The detected resonant condition that has a one-to-one relationship with the refractive index of the superstrate containing the biological substance is analyzed to determine whether or not the biological substance is located in the sensing region of the GCW sensor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] A more complete understanding of the present invention may be had by reference to the following detailed description when taken in conjunction with the accompanying drawings wherein:

[0010] **FIG. 1** is a diagram of the basic components of an optical interrogation system and GCW sensor in accordance with the present invention;

[0011] **FIG. 2** is a graph that illustrates the relationship between the resonant angle and resonant wavelength of the GCW sensor shown in **FIG. 1**;

[0012] **FIG. 3** is a graph used to help describe how a spectral interrogation approach can be used by the optical interrogation system to determine the resonant wavelength of the GCW sensor shown in **FIG. 1**;

[0013] **FIG. 4** is a graph used to help describe how an angular interrogation approach can be used by the optical interrogation system to determine the resonant angle of the GCW sensor shown in **FIG. 1**;

[0014] **FIG. 5** is a graph generated by GSOLVER that illustrates the resonant wavelength (reflection anomaly) of an exemplary GCW sensor having a substrate made from cyclic-olefin copolymer (COC) and a waveguide film made from Ta_2O_5;

[0015] **FIG. 6** is a graph illustrating the relationship between the resonant angle and wavelength of an exemplary GCW sensor that has two different cover indices;

[0016] **FIG. 7** is a diagram illustrating the basic components of a first embodiment of the optical interrogation system shown in **FIG. 1** that utilizes an angular scanning approach to scan a polarization-modulated light beam that is directed into the GCW sensor in order to detect a biological substance in accordance with the present invention;

[0017] **FIG. 8** is a graph that shows the amplitude resonance of an exemplary GCW sensor that was observed when testing the optical interrogation system shown in **FIG. 7**;

[0018] **FIG. 9** is a graph that shows the resonance location observed when 5% glycerol solution is placed on top of an exemplary GCW sensor to test the optical interrogation system shown in **FIG. 7**;

[0019] **FIG. 10** is a diagram the shows the amplitude resonance of an exemplary GCW sensor that has the characteristic trough/peak shape seen during the testing of the optical interrogation system shown in **FIG. 7**;

[0020] **FIG. 11** is a graph that shows the phase of a resonance superimposed on the amplitude plot shown in **FIG. 8** when testing the optical interrogation system shown in **FIG. 7**;

[0021] **FIG. 12** is a diagram illustrating the basic components of a second embodiment of the optical interrogation system shown in **FIG. 1** that utilizes an angular scanning approach to scan an amplitude modulated light beam emitted from the GCW sensor in order to detect a biological substance in accordance with the present invention;

[0022] **FIG. 13** is a diagram illustrating the basic components of a third embodiment of the optical interrogation system shown in **FIG. 1** that utilizes a wavelength scanning approach to scan a polarization-modulated light beam that is directed into the GCW sensor in order to detect a biological substance in accordance with the present invention;

[0023] **FIG. 14** is a diagram illustrating the basic components of a fourth embodiment of the optical interrogation system shown in **FIG. 1** that utilizes a wavelength scanning approach to scan an amplitude modulated light beam emitted from the GCW sensor in order to detect a biological substance in accordance with the present invention;

[0024] **FIG. 15** is a diagram illustrating the basic components of a fifth embodiment of the optical interrogation system shown in **FIG. 1** that can utilize an angular or wavelength scanning approach to scan an array of GCW sensors incorporated within a microplate in accordance with the present invention; and

[0025] **FIG. 16** is a flowchart illustrating the basic steps of a preferred method for using the optical interrogation system and GCW sensor shown in **FIG. 1** to detect a biological substance in accordance with the present invention.

DETAILED DESCRIPTION OF THE DRAWINGS

[0026] Referring to **FIG. 1**, there is shown a diagram of the basic components of a GCW sensor **100** and an optical interrogation system **120** in accordance with the present invention. Basically, the optical interrogation system **120** interrogates the GCW sensor **100** to determine whether a biological substance **102** (e.g., cell, molecule, protein, drug, chemical compound, nucleic acid, peptide, carbohydrate) is located in a sensing region **103** (superstrate **103**) of the GCW sensor **100**. The optical interrogation system **120** includes a light source **122**, a polarization modulator **127** (e.g., photoelastic modulator **127**, photorefractive modulator **127**, liquid crystal modulator **127**) and a detection system **124**. The light source **122** outputs a polarized light beam **125** and the polarization modulator **127** modulates the polarized light beam **125** and outputs a polarization-modulated light beam **126**. The GCW sensor **100** receives and converts the polarization-modulated light beam **126** into an amplitude modulated light beam **128** that is directed towards the detection system **124**. The detection system **124** receives the amplitude modulated light beam **128** and demodulates the received amplitude modulated light beam **128** by responding to signals at a modulation frequency of the polarization-modulated light beam **125** and ignoring noise affecting the signals outside the modulation frequency to detect a resonant condition (e.g., resonant angle, resonant wavelength). The detected resonant condition has a one-to-one relationship with the refractive index of the superstrate containing the biological substance **102** that indicates whether the biological substance **102** is located in the sensing region **103** of the GCW sensor **100**. How the GCW sensor **100** converts the polarization-modulated light beam **126** into the amplitude modulated light beam **128** which enables the optical interrogation system **120** to demodulate the amplitude modulated light beam **128** in a manner that avoids the problems caused by noise sources (e.g., Fresnel reflections, DC electrical and stray light noise) is described in greater detail below after a brief discussion about the basic structure and functionality of the GCW sensor **100**.

[0027] As shown in **FIG. 1**, the GCW sensor **100** includes a thin (~100 nm) layer of material **106** (e.g., waveguide film **106**) deposited on the surface of a diffraction grating **108**

which together form a waveguide **110**. The waveguide film **106** is preferably made of a dielectric material such as Ta_2O_5, TiO_2, TiO_2-SiO_2, HfO_2, ZrO_2, Al_2O_3, Si_3N_4, HfON, SiON, scandium oxides or mixtures thereof. The diffraction grating **108** is formed within a substrate **112** or waveguide film **106** by embossing, holography, or other methods. The diffraction grating **108** can thereby be located above, below, or even within the waveguide film **106**. Moreover, the diffraction grating **108** need not be in direct physical contact with a waveguide film **106**, simply near enough to cause optical influence on the waveguide mode. Furthermore, due to effective-index waveguiding, the diffraction grating **108** itself can be fabricated with appropriately high enough index to serve as the waveguide itself without the need for an additional waveguide film deposition. The substrate **112** is preferably made of glass or plastic such as cyclic-olefin copolymer (COC). For example, the GCW sensor **100** can have a cyclic-olefin substrate **112** which has an index n_s=1.53, a grating pitch Λ=538 nm, a grating thickness is t_g=10 nm, a waveguide index n_f=2.01, a waveguide thickness t_f=110 nm, and a superstrate index that is nominally the index of water (the solvent in which most experiments are performed, $n_c \geqq 1.33$). This GCW sensor **100** is referred to herein as the exemplary GCW sensor **100**.

[**0028**] The biological substance **102** which may be located within a bulk fluid is introduced to the superstrate **103** (sensing region) of the GCW sensor **100** and it is the presence of this biological substance **102** that alters the index of refraction at the surface **104** of the GCW sensor **100**. Thus, to detect the biological substance **102**, the GCW sensor **100** is probed with a light beam **126** emitted from the light source **122** and then a reflected light beam **128** received at the detection system **124** is analyzed to determine if there are any changes (~1 part per million) in the refractive index caused by the presence of the biological substance **102** in the sensing region **103** of the GCW sensor **100**. In one embodiment, the top surface **104** may be coated with biochemical compounds (not shown) that only allow surface attachment of specific complementary biological substances **102** which enables an GCW sensor **100** to be created that is both highly sensitive and highly specific. In this way, the optical interrogation system **120** and GCW sensors **100** may be used to detect a wide variety of biological substances **102** and if the GCW sensors **100** are arranged in arrays they may be used to enable high throughput drug or chemical screening studies (see **FIG. 15**).

[**0029**] The sensitivity of the GCW sensor **100** may be best understood by analyzing the structure of the diffraction grating **108** and the waveguide **110**. The light beam **126** shone on the diffraction grating **108** can only be coupled into the waveguide **110** if its wave vector satisfies the following resonant condition as shown in equation no. 1:

$$k'_x = k_x \kappa \quad [1]$$

[**0030**] where k_x' is the x-component of the incident wave vector, k_x is the guided mode wave vector, and κ is the grating vector. The grating vector κ is defined as a vector having a direction perpendicular to the lines of the diffraction grating **108** and a magnitude given by $2\pi/\Lambda$ where Λ is the grating period (pitch). This expression may also be written in terms of wavelength λ and incident angle θ as shown in equation no. 2:

$$\frac{2\pi n_{inc}}{\lambda}\sin\theta = \frac{2\pi n_{eff}}{\lambda} - \frac{2\pi}{\Lambda} \quad [2]$$

[**0031**] Where θ is the angle of incidence of the light beam **126**, n_{inc} is the index of refraction of the incident medium, λ is the wavelength of the light **126**, and n_{eff} is the effective index of refraction of the waveguide **110**. The effective index of the waveguide **110** is a weighted average of the indices of refraction that the optical waveguide mode field or fundamental mode "sees" as it propagates through the waveguide **110**. The fundamental mode preferably has a spatial extent that is much wider than the waveguide **110** itself, the extent depending on the refractive index difference between the waveguide **110** and the substrate **112**, as well as between the waveguide **110** and the superstrate **103**. In particular, the fundamental mode has an evanescent wave/tail that extends into the superstrate **103** (sensing region) which "sees" any surface changes created when the biological substance **102** approaches or comes in contact with the top surface **104** of the GCW sensor **100**.

[**0032**] The previous expression shown in equation no. 2 may be rewritten in the more convenient form shown in equation no. 3:

$$\sin\theta = n_{eff} - \frac{\lambda}{\Lambda} \quad [3]$$

[**0033**] which is the equation of a line where sin θ being the y axis, λ being the x-axis, Λn_{eff} the x-intercept, and $-1/\Lambda$ the slope. To obtain equation no. 3, n_{inc} has been set to 1 so that it could be removed from equation no. 2. This approximation is used since air (n~1.0003) is the most common incident medium. This relation is pictured in the graph shown in **FIG. 2**. When a biological substance **102** binds to the surface **104**, the effective index of the waveguide **110** is altered which leads to the shifting the resonant wavelength or resonant angle of the GCW sensor **100**. This shifting can be seen as a shift of the x-intercept in the line shown in **FIG. 2**.

[**0034**] The resonant condition (e.g., resonant wavelength or resonant angle) of such a GCW sensor **100** may be interrogated to determine refractive index changes by observing the reflected light **128** from the GCW sensor **100** (see **FIG. 1**). There are two different modes of operation for monitoring refractive index changes-spectral interrogation or angular interrogation. In spectral interrogation, a nominally collimated, scanned-wavelength beam of modulated polarized light **126** is sent into the GCW sensor **100** and the reflected amplitude modulated light **128** is collected and monitored by a photodiode (for example) within a detection system **124**. By observing the spectral location of the resonant wavelength (peak), one can monitor binding or refractive index changes on or near the surface **104** of the GCW sensor **100**. The spectral interrogation concept is graphically represented in the graph shown in **FIG. 3**. Conversely, in angular interrogation, a nominally single wavelength of modulated polarized light **126** is angle-scanned to create a range of illumination angles and directed into the GCW sensor **100**. The reflected amplitude modu-

lated light **128** is monitored by a photodiode (for example) within the detection system **124**. By monitoring the position of the resonant angle reflected by the GCW sensor **100**, one can monitor binding or refractive index changes on or near the surface **104** of the GCW sensor **100**. The angular interrogation concept is graphically represented in the graph shown in **FIG. 4**.

[**0035**] To maintain simplicity and efficiency of operation, the GCW sensors **100** employed in biosensing applications can be designed such that only the zeroth diffracted orders of the incident light **126** propagate in free space, while what would be the ±1 orders couple to the fundamental mode of the waveguide **110**. The higher diffraction orders are avoided by designing a sub-wavelength diffraction grating **108** which has a grating pitch A smaller than the desired operating wavelength λ of the incident light **126**. In this case, the coupling efficiency of the waveguide **110** is large since multiple orders do not remove power from the GCW sensor **100**. Moreover, since only the zeroth reflected and transmitted beams exist in free space, the GCW sensor **100** can thereby produce nearly total reflection or transmission of the desired (anomalous) wavelength λ of the incident light **126**. **FIG. 5** shows a GSOLVER (rigorous coupled-wave analysis, or RCWA code) analysis of an exemplary GCW **100** where the TE input light **126** angle is 3° and the reflected light beam **128** which is at 3° from the normal has a resonance **502** in the vicinity of 824 nm when the substance (water) in the superstrate **103** has an index of 1.33.

[**0036**] As mentioned above, GCW sensors **100** are used in biosensing applications because they enable one to determine the location of the resonance angle/wavelength **502** which directly corresponds to the refractive index of the superstrate **103** and thereby allows the monitoring of biological substance **102** binding on the GCW sensor **100**. This is all possible because the evanescent tail of the propagating fundamental mode in the waveguide **110** senses index changes in the superstrate **103** caused by the presence of the biological substance **102**. The index change in the supersrate **103** changes the resonance condition of the GCW **100** according equation no. 1 and then the resonance **502** shifts to a new wavelength or angle location. The location of the shifted resonance indicates the current index of the superstrate **103** which indicates whether or not the biological substance **102** is in the superstrate **103** of the GCW **100**. It has been shown that the resonance **502** can shift hundreds of nanometers for a unit change in the refractive index of the superstrate **103** (see **FIG. 2**). The relationship between angle and wavelength is displayed in the graph shown in **FIG. 6** for a BIOS-1 GCW sensor **100**. The different curves in the graph show behavior for both TE and TM polarizations with two different cover indices.

[**0037**] Referring to **FIGS. 7-15**, there are illustrated five embodiments of the optical interrogation system **120** shown in **FIG. 1** that utilize different approaches to interact with one or more GCW sensors **100** in order to detect the presence of a biological substance **102**. Although only five embodiments of the optical interrogation system **120** are described herein, it should be understood that other configurations of the optical interrogation system **120** could be used to interact with the GCW sensor **100** in order to detect the presence of the biological substance **102**. Accordingly, the optical interrogation system **120** should not be construed in a limited manner.

[**0038**] Referring to **FIG. 7**, there is a diagram illustrating the basic components of a first embodiment of the optical interrogation system **120***a* in accordance with the present invention. The optical interrogation system **120***a* utilizes an angular scanning approach to scan the polarization-modulated light beam **126** that is directed into the GCW sensor **100** in order to enable the detection of the biological substance **102**.

[**0039**] As shown, the optical interrogation system **120***a* includes a light source **122***a* that outputs a polarized light beam **125***a* that is received by a polarization modulator **127***a* (e.g., photoelastic modulator **127***a*). The polarization modulator **127***a* modulates the polarized light beam **125***a* by causing a time-varying polarization alternation between TE and TM modes (see the wobbling vectors in **FIG. 7**). The polarization modulator **127***a* outputs the polarization-modulated light beam **126***a* to an acousto-optic modulator **702***a* which changes the angle of the polarization-modulated light beam **125***a* by mixing it with an acoustic wave. The magnitude of the angular deflection depends upon the drive frequency of the acousto-optic modulator **702***a* and therefore the acoustic wave. In effect, the acousto-optic modulator **702***a* enables one to control the angular scanning of the polarization-modulated light beam **126***a*. Since the polarization-modulated light beam **126** should intersect the microwell plate **704***a* in a constant location, a lens **706***a* and beamsplitter **708***a* are placed between the acousto-optic modulator **702***a* and the microwell plate **704***a*, where the distance from the lens **706***a* to each GCW sensor **100** is a focal length. In this manner, the angle of the polarization-modulated light beam **126***a* incident upon the microwell plate **704***a* changes with the frequency of the acousto-optic modulator **702***a*, while the location of the incidence remains constant. After interacting with the GCW sensor **100** in the microwell plate **704***a*, the polarization-modulated light beam **126***a* which has only one of the two polarization states resonant within the GCW sensor **100** is converted into the amplitude modulated light beam **128***a* that is modulated at the same frequency as the polarization-modulated light beam **126***a*. The amplitude modulated light beam **128***a* is received by the detection system **124***a* and in particular by a detector **710***a* (e.g., photodiode **710***a*) which converts the amplitude modulated light beam **128***a* into an electrical signal that is then demodulated by a lock-in amplifier **712***a* or *a* similar instrument capable of detecting electrical signals at specific frequencies (e.g., an RF mixer). The lock-in amplifier **712***a* demodulates the electrical signal by responding to signals at the modulation frequency of the polarization-modulated light beam **126***a* and ignoring noise affecting the signals outside the modulation frequency. A computer **716***a* then analyzes the demodulated electrical signal (e.g., a DC voltage proportional to the original modulated reflected optical signal strength) to determine a resonant angle that correlates to the superstrate **103** refractive index and therefore the biological substance content **102** at the sensing region **103** of the GCW sensor **100**. The frequency being detected by the lock-in amplifier **712***a* can be derived from a function generator **714***a* that also drives the polarization modulator **127***a*.

[**0040**] The use of the acousto-optic modulator **702***a* is attractive since it utilizes no moving parts, however other angular scanning techniques can be used in the present invention. For example, a simple rotating plate of glass could be used that deflects the polarization-modulated light

beam **126***a* through refraction at the glass/air interface. The deflection angle depends upon the rotation angle of the glass plate such that the rotating plate causes a smoothly varying angle. The results of several experiments using the optical interrogation system **120***a* and the exemplary GCW sensor **100** are provided below with respect to **FIGS. 8-11**.

[**0041**] Referring to **FIG. 8**, there is a graph that shows the resonance observed when testing an experimental optical interrogation system **120***a* where the amplitude recorded by the lock-in amplifier **712***a* versus the frequency of the acousto-optic modulator **702***a* represents the signal. This scan took 0.5 s-2 min. to acquire, and resulted in the very high signal-to-noise curve shown in **FIG. 8**. It should be noted that the light source **122***a* (e.g., He/Ne laser **122***a*) had to be attenuated greatly to avoid saturating the detector **710***a* (e.g., Si photodiode **710***a*) and the lock-in amplifier **712***a* still had many (>5) orders of magnitude of input gain settings to accommodate still lower laser levels.

[**0042**] It should be appreciated that the actual sensitivity of the optical interrogation system **120***a* to biological events depends upon the GCW sensor **100**, instrument, angular stability, etc. Thus, to obtain some estimate of the performance of the experimental optical interrogation system **120***a*, index fluids were placed on the top surface **104** of the GCW sensor **100** to illicit a change in the resonant angle and thereby determine the refractive index unit sensitivity. **FIG. 9** shows the result of this study. Noise levels were determined to be as low as ~10^{-5} (single standard deviation), and further work indicates that the desired 10^{-6} sensitivity is easily achieved with more accurate scanning electronics.

[**0043**] Another important aspect of the present invention, is that the lock-in amplifier **712***a* provides an extra observable beyond the simple amplitude resonance pictured above in **FIG. 8**. As a phase-locked technique, the lock-in amplifier **712***a* provides not only the amplitude of the resonant signal, but also its phase, as referenced to a stable frequency signal such as the electrical function driving the polarization modulator **127***a*. It should be noted that this information could be obtained with most phase-sensitive detectors (other than a lock-in amplifier **112**), or even with a device that can separately monitor the TE and TM polarizations of the amplitude modulated light beam **128***a* output from the GCW sensor **100**.

[**0044**] To understand what information the phase signal might present, one can examine the amplitude signal more closely. **FIG. 10** shows a diagram of the amplitude resonance **1002** with the characteristic trough/peak shape seen in experiments and theory, where the TE mode has been phase-matched to the GCW sensor **100**. The negatively valued dip (source of the arrow on the bottom left of the figure) represents a region where the TE power is below the TM ambient signal, caused by resonantly transmitting the TE light through the GCW sensor **100** (see **FIG. 1**).) The peak represents the region where the TE light resonantly reflects from the GCW sensor **100**, enhancing the power on the detector **710***a*. Since the TM mode does not interact with the waveguide **110**, its level is constant for both the trough and peak. Remembering that the light is modulated between TE and TM modes in time, the curves drawn in **FIG. 10** therefore represent the time-varying signal present at the lock-in amplifier **712***a* at the modulation frequency. By comparing the signals from the peak and trough regions, one can see that the waves are 180° phase-shifted from one another. Moreover, this phase shift should occur at the instant that the amplitude crosses from negative to positive in the center of the resonance.

[**0045**] This simple understanding serves to accurately predict what was observed during the experiments with the experimental optical interrogation system **120***a*. **FIG. 11** shows the phase of the resonance **1102** superimposed on the amplitude plot shown in **FIG. 8**. Since the lock-in amplifier **712***a* outputs a −10-10 volt signal to the computer **716***a* to register 360° in phase, the change from ~8 V to ~−2 V represents the 180° phase change indicated in **FIG. 11**. The transition occurs very close to zero amplitude, where the small difference is actually due to filtering of the amplitude signal that shifts it relative to the phase signal that is acquired at a different time. It should be noticed that this phase transition is extremely steep compared to the resonance amplitude. Moreover, it is akin to a digital indication (on/off) of the resonance location, and therefore represents the simplest signal to detect from a signal processing standpoint. The steepness results from the fact that the transition occurs in a trigger fashion, depending on the relative intensities of the TE/TM modes. Because this signal is so narrow, it could possibly relax the constraints on the resonance width as they relate to detection and location of the resonance. Because the phase signal is inextricably related to the amplitude resonance however, it is not apparent that the localization of the resonance peak will improve using the phase signature, but one may be able to take advantage of signal processing techniques (e.g. a Schmidt trigger) to derive some sensitivity advantage from this phase signal **1102**. Assuming this is the case, the width of the amplitude resonance may become less relevant, and allow a whole new class of sensor designs where the width constraints are greatly relaxed.

[**0046**] Referring to **FIG. 12**, there is a diagram illustrating the basic components of a second embodiment of the optical interrogation system **120***b*. The optical interrogation system **120***b* utilizes an angular scanning approach to scan the amplitude modulated light beam **128***b* emitted from the GCW sensor **100** in order to enable the detection of the biological substance **102**. As shown, the optical interrogation system **120***b* includes a light source **122***b* that outputs a polarized light beam **125***b* that is received by a polarization modulator **127***b* (e.g., photoelastic modulator **127***b*). The polarization modulator **127***b* modulates the polarized light beam **125***b* by causing a time-varying polarization alternation between TE and TM modes (see the wobbling vectors in **FIG. 12**). The polarization modulator **127***b* outputs the polarization-modulated light beam **126***b* to a lens **1206***b* and beamsplitter **1208***b*. The lens **1206***b* and beamsplitter **1208***b* direct the polarization-modulated light beam **126***b* to the GCW sensor **100** within the microwell plate **1204***b*. After interacting with the GCW sensor **100** in the microwell plate **1204***b*, the polarization-modulated light beam **126***b* which has only one of the two polarization states resonant within the GCW sensor **100** is converted into the amplitude modulated light beam **128***b* that is modulated at the same frequency as the polarization-modulated light beam **126***b*. The amplitude modulated light beam **128***b* is received by the detection system **124***b* and in particular by a scanning pinhole plate **1202***b* that scans the angle of the amplitude modulated light beam **128***b*. The detector **1210***b* (e.g., photodiode **1210***b*) converts the scanned amplitude modulated

light beam **128***b* into an electrical signal that is then demodulated by a lock-in amplifier **1212***b*. The lock-in amplifier **1212***b* demodulates the electrical signal by responding to signals at the modulation frequency of the polarization-modulated light beam **126***b* and ignoring noise affecting the signals outside the modulation frequency. A computer **1216***b* then analyzes the demodulated electrical signal (e.g., a DC voltage proportional to the original modulated reflected optical signal strength) to determine a resonant angle that correlates to the superstrate **103** refractive index and therefore the biological substance content **102** at the sensing region **103** of the GCW sensor **100**. The frequency being detected by the lock-in amplifier **1212***b* can be derived from a function generator **1214***b* that also drives the polarization modulator **127***b*.

[**0047**] Referring to **FIG. 13**, there is a diagram illustrating the basic components of a third embodiment of the optical interrogation system **120***c*. The optical interrogation system **120***c* utilizes a wavelength scanning approach to scan the polarization-modulated light beam **126***c* directed into the GCW sensor **100** in order to enable the detection of the biological substance **102**. As shown, the optical interrogation system **120***c* includes a broadband light source **122***c* that outputs a polarized light beam **125***c* that is received by a polarization modulator **127***c* (e.g., photoelastic modulator **127***c*). The polarization modulator **127***c* modulates the polarized light beam **125***c* by causing a time-varying polarization alternation between TE and TM modes (see the wobbling vectors in **FIG. 13**). The polarization modulator **127***c* outputs the polarization-modulated light beam **126***c* to a tunable filter **1306***c*. The tunable filter **1306***c* scans the wavelength of the polarization-modulated light beam **126***c* and directs the scanned polarization-modulated light beam **126***c* to a beamsplitter **1308***c*. The beamsplitter **1308***c* directs the polarization-modulated light beam **126***c* to the GCW sensor **100** within the microwell plate **1304***c*. After interacting with the GCW sensor **100** in the microwell plate **1304***c*, the polarization-modulated light beam **126***c* which has only one of the two polarization states resonant within the GCW sensor **100** is converted into the amplitude modulated light beam **128***c* that is modulated at the same frequency as the polarization-modulated light beam **126***c*. The amplitude modulated light beam **128***c* is received by the detection system **124***b* and in particular by a detector **1310***c* (e.g., photodiode **1310***c*) which converts the amplitude modulated light beam **128***c* into an electrical signal that is then demodulated by a lock-in amplifier **1312***c*. The lock-in amplifier **1212***c* demodulates the electrical signal by responding to signals at the modulation frequency of the polarization-modulated light beam **126***c* and ignoring noise affecting the signals outside the modulation frequency. A computer **1316***c* then analyzes the demodulated electrical signal (e.g., a DC voltage proportional to the original modulated reflected optical signal strength) to determine a resonant angle that correlates to the superstrate **103** refractive index and therefore the biological substance content **102** at the sensing region **103** of the GCW sensor **100**. The frequency being detected by the lock-in amplifier **1312***c* can be derived from a function generator **1314***c* that also drives the polarization modulator **127***c*.

[**0048**] Referring to **FIG. 14**, there is a diagram illustrating the basic components of a fourth embodiment of the optical interrogation system **120***d*. The optical interrogation system **120***d* utilizes an wavelength scanning approach to scan the amplitude modulated light beam **128***d* emitted from the GCW sensor **100** in order to enable the detection of the biological substance **102**. As shown, the optical interrogation system **120***d* includes a broadband light source **122***d* that outputs a polarized light beam **125***d* that is received by a polarization modulator **127***d* (e.g., photoelastic modulator **127***d*). The polarization modulator **127***d* modulates the polarized light beam **125***d* by causing a time-varying polarization alternation between TE and TM modes (see the wobbling vectors in **FIG. 14**). The polarization modulator **127***d* outputs the polarization-modulated light beam **126***d* to a beamsplitter **1408***d*. The beamsplitter **1408***d* directs the polarization-modulated light beam **126***d* to the GCW sensor **100** within the microwell plate **1404***d*. After interacting with the GCW sensor **100** in the microwell plate **1404***d*, the polarization-modulated light beam **126***d* which has only one of the two polarization states resonant within the GCW sensor **100** is converted into the amplitude modulated light beam **128***d* that is modulated at the same frequency as the polarization-modulated light beam **126***d*. The amplitude modulated light beam **128***d* is received by the detection system **124***d* and in particular by a scanning filter **1406***d* that scans the wavelength of the amplitude modulated light beam **128***d*. The detector **1410***d* (e.g., photodiode **1210***d*) converts the scanned amplitude modulated light beam **128***d* into an electrical signal that is then demodulated by a lock-in amplifier **1412***d*. The lock-in amplifier **1412***d* demodulates the electrical signal by responding to signals at the modulation frequency of the polarization-modulated light beam **126***d* and ignoring noise affecting the signals outside the modulation frequency. A computer **1416***d* then analyzes the demodulated electrical signal (e.g., a DC voltage proportional to the original modulated reflected optical signal strength) to determine a resonant angle that correlates to the superstrate **103** refractive index and therefore the biological substance content **102** at the sensing region **103** of the GCW sensor **100**. The frequency being detected by the lock-in amplifier **1412***d* can be derived from a function generator **1414***d* that also drives the polarization modulator **127***d*.

[**0049**] Referring to **FIG. 15**, there is a diagram illustrating the basic components of a fifth embodiment of the optical interrogation system **120***e*. The optical interrogation system **120***e* utilizes a parallel angle/wavelength scanning approach to scan multiple polarization-modulated light beams **126***e* directed to multiple GCW sensors **100** to enable the high-throughput detection of biological substances **102**. As shown, the optical interrogation system **120***e* includes a light source **122***e* that outputs a polarized light beam **125***e* that is received by a polarization modulator **127***e* (e.g., photoelastic modulator **127***e*). The polarization modulator **127***e* modulates the polarized light beam **125***e* by causing a time-varying polarization alternation between TE and TM modes and outputs the polarization-modulated light beam **126***e* to a diffractive optic **1502***e*. The diffractive optic **1502***e* emits an array of polarization-modulated light beams **126***e* to a beamsplitter **1508***e*. The beamsplitter **1508***e* directs the polarization-modulated light beams **126***e* to the GCW sensors **110** within the microwell plate **1504***d*. After interacting with the GCW sensors **100** in the microwell plate **1504***e*, the polarization-modulated light beams **126***d* are converted into the amplitude modulated light beams **128***e* that are modulated at the same frequency as the polarization-modulated light beams **126***e*. The amplitude modulated light beams **128***e* are received by the detection system **124***e* and in particular by

an array of detectors **1510***e* (e.g., photodiodes **1510***e*) which converts the scanned amplitude modulated light beams **128***e* into electrical signals that are then demodulated by an array of lock-in amplifiers **1512***e*. The lock-in amplifiers **1512***e* demodulate the electrical signals by responding to signals at the modulation frequency of the polarization-modulated light beam **126***e* and ignoring noise affecting the signals outside the modulation frequency. A computer **1516***e* then analyzes the demodulated electrical signal (e.g., a DC voltage proportional to the original modulated reflected optical signal strength) to determine a resonant angle that correlates to the superstrate **103** refractive index and therefore the biological substance content **102** at the sensing region **103** of the GCW sensor **100**. The frequency being detected by the lock-in amplifiers **1512***e* can be derived from a function generator **1514***e* that also drives the polarization modulator **127***e*. It should be appreciated that the configuration of this optical interrogation system **120***e* is only one of many different possible configurations that can be used in high-throughput screening applications. Basically, this invention can be applied to all multiplexed, scanning, etc. systems that are compatible with polarization modulation.

[**0050**] Although **FIG. 15** does not explicitly show the components required to scan the angle or wavelength as per one of the many embodiments shown in **FIGS. 7, 12, 13**, or **14**. It is assumed that one of these scanning techniques (or a suitable substitute) would be employed together with the components of **FIG. 15** to achieve a system that scans the GCW **100** resonance over every well. For the embodiments of **FIGS. 7 and 13**, only one scanning element (acousto-optic modulator or filter) need be placed before the diffractive optic, thereby copying the scanning behavior to each separate beam. In the embodiments of **FIGS. 12 and 14**, the scanning apparatus (pinhole or filter) would likely be required in duplicate for each beam reflected from each well of the plate.

[**0051**] Referring to **FIG. 16**, there is a flowchart illustrating the basic steps of a preferred method for using the optical interrogation system **120** and GCW sensor **100** to detect a biological substance **102** in accordance with the present invention. Although the GCW sensor **100** and optical interrogation system **120** are described herein as being used to detect the presence of biological substances **102** like cells, molecules, proteins, drugs, chemical compounds, nucleic acids, peptides or carbohydrates on the surfaces **104** of the GWC sensor **100**, it should be understood that the GCW sensor **100** and optical interrogation system **120** can be used to perform a wide variety of studies. For example, the GCW sensor **100** and optical interrogation system **120** can be used to perform cell migration assays, drug permeability assays, drug solubility studies, virus detection studies and protein secretion studies.

[**0052**] Beginning at step **1602**, the light source **122** and polarization modulator **127** are used to direct a polarization-modulated light beam **126** to the GCW sensor **100**. At step **1604**, the detection system **124** receives an amplitude modulated light beam **128** from the GCW sensor **100**. Then at step **1606**, the detection system **124** demodulates and analyzes the received amplitude modulated light beam **128** to detect a resonant wavelength or resonant angle which corresponds to a superstrate **103** refractive index that indicates whether a biological substance **102** is located on the surface **104** of the GCW sensor **100**.

[**0053**] Following are some advantages and uses of the optical interrogation system **120** and GCW sensors **100** of the present invention:

[**0054**] The use of polarization modulation in accordance with the present invention enables one to use large-area photodiodes that provides a cost advantage and robustness to the instrument design not currently available with traditional optical interrogation systems. Moreover, the use of large area detectors greatly relaxes the performance (flatness, etc.) required from the sensor wellplate. Basically, the reflected beam simply has to hit the photodiode somewhere in its area to be correctly detected and decoded. The only constraint in this situation is that the beams from separate wells do not "cross" each other in the farfield. In other words, each beam should retain its relationship relative to its neighbors, although neighbor proximity may vary from well to well. This is a much less stringent condition than would be required for coupling back into optical fiber, for example, or imaging the reflections onto CCDs used by traditional optical interrogation systems.

[**0055**] The use of polarization modulation in accordance with the present invention can be applied to nearly every instrument designed to interrogate grating-coupled biosensors. The invention involves the overlay of polarization modulation and coherent (phase-sensitive) detection onto the structures of the traditional optical interrogation systems. This is true regardless of whether angle, wavelength or some other parameter is being scanned, either on the input or output of the GCW sensor **100**.

[**0056**] The present invention removes a large number of noise sources by taking advantage of optical beam polarization.

[**0057**] The present invention drastically reduces the required power for detection of biological substances. As a result, the milliwatts of power typically required of the output beam for sensitive detection by a CCD element is reduced several orders of magnitude under this invention. This is very important for the high-throughput screening market, since 96, 384, or even 1536 wells may be interrogated in parallel with the same optical (laser) source.

[**0058**] In addition to the signal-to-noise improvements associated with the present invention, there are several other equally important benefits of the technology. First, because the polarization modulation technique obtains high signal-to-noise data from ordinary photodiodes, the cost and complexity of the instrumentation can be greatly reduced compared to the expensive CCD or spectrograph solutions used by traditional optical interrogation systems. Moreover, the scale-up of the optical interrogation system **120** to accommodate 96 or 384 wells in a plate becomes much easier since one only needs to use more inexpensive detectors and lock-in amplifiers.

[**0059**] In addition to the cost and complexity advantage of the present invention, the use of lock-in amplifiers provides phase information about the

resonance previously unavailable. The presence of both amplitude and phase information from the phase-sensitive detection provides an extra observable. As discussed above, this phase information actually contains a convenient and unique signal that indicates the resonance location.

[0060] The polarization modulation concept of the present invention can be implemented within most interrogation schemes (e.g., angular or wavelength-based approaches). It simply requires that the polarization be modulated in order to distinguish the waveguide output from noise, somewhat independent of the other variables of the system. In one embodiment of this invention, one could modulate the input beam polarization much faster than the angular scanning rate, such that the angular position is essentially constant during the demodulation process for each angular step.

[0061] As described above, the preferred modulation method is photoelastic, where a quartz plate is vibrated to produce time-variable birefringence due to the photoelastic effect. This technology is preferred both for the purity of polarization modulation as well as high available modulation frequency, 100 kHz.

[0062] Although the preferred embodiments of the present invention described above utilized a reflected light beam to enable the detection of the biological substance, it should be readily appreciated that a transmitted beam and even a beam exiting the side of the sensor could also be used to detect the biological substance. Of course, minor changes to the set-up of the system would be required to detect the transmitted beam or the beam exiting the side of the sensor.

[0063] Although several embodiments of the present invention has been illustrated in the accompanying Drawings and described in the foregoing Detailed Description, it should be understood that the invention is not limited to the embodiments disclosed, but is capable of numerous rearrangements, modifications and substitutions without departing from the spirit of the invention as set forth and defined by the following claims.

What is claimed is:

1. A grating-coupled waveguide sensor comprising:

a substrate;

a diffraction grating; and

a waveguide film, wherein a waveguide formed by said diffraction grating and said waveguide film receives a polarization-modulated light beam and outputs an amplitude modulated light beam that is analyzed by an optical interrogation system which demodulates the amplitude modulated light beam by responding to signals at a modulation frequency of the polarization-modulated light beam and ignoring noise affecting the signals outside the modulation frequency to determine whether a biological substance is located in a sensing region above said waveguide film.

2. The grating-coupled waveguide sensor of claim 1, wherein said biological substance is a cell, molecule, protein, drug, chemical compound, nucleic acid, peptide or carbohydrate.

3. The grating-coupled waveguide sensor of claim 1, wherein said optical interrogation system utilizes an angular scanning approach to scan the polarization-modulated light beam to enable the detection of a resonant angle which indicates whether the biological substance is located in the sensing region above said waveguide film.

4. The grating-coupled waveguide sensor of claim 1, wherein said optical interrogation system utilizes an angular scanning approach to scan the amplitude modulated light beam to enable the detection of a resonant angle which indicates whether the biological substance is located in the sensing region above said waveguide film.

5. The grating-coupled waveguide sensor of claim 1, wherein said optical interrogation system utilizes a wavelength scanning approach to scan the polarization-modulated light beam to enable the detection of a resonant wavelength which indicates whether the biological substance is located in the sensing region above said waveguide film.

6. The grating-coupled waveguide sensor of claim 1, wherein said optical interrogation system utilizes a wavelength scanning approach to scan the amplitude modulated light beam to enable the detection of a resonant wavelength which indicates whether the biological substance is located in the sensing region above said waveguide film.

7. An optical interrogation system for interrogating a grating-coupled waveguide sensor, said optical interrogation system comprising:

a light source capable of outputting a polarized light beam;

a polarization modulator capable of modulating the polarized light beam and outputting a polarization-modulated light beam;

said grating-coupled waveguide sensor capable of receiving the polarization-modulated light beam and converting the polarization-modulated light beam into an amplitude modulated light beam;

a detection system capable of receiving the amplitude modulated light beam and further capable of demodulating the received amplitude modulated light beam by responding to signals at a modulation frequency of the polarization-modulated light beam and ignoring noise affecting the signals outside the modulation frequency to detect a resonant condition which corresponds to a predetermined refractive index that indicates whether a biological substance is located in a sensing region of said grating-based waveguide sensor.

8. The optical interrogation system of claim 7, wherein said biological substance is a cell, molecule, protein, drug, chemical compound, nucleic acid, peptide or carbohydrate.

9. The optical interrogation system of claim 7, wherein said polarization modulator is a photoelastic modulator.

10. The optical interrogation system of claim 7, wherein said polarization modulator is a photorefractive modulator.

11. The optical interrogation system of claim 7, wherein said polarization modulator is a liquid crystal modulator.

12. The optical interrogation system of claim 7, wherein said grating-coupled waveguide sensor is located within a microplate.

13. The optical interrogation system of claim 7, wherein said detection system includes a photodiode capable of receiving the amplitude modulated light beam and converting the amplitude modulated light beam into an electrical signal that is demodulated by a lock-in amplifier.

14. The optical interrogation system of claim 13, wherein phase information within said demodulated electrical signal is used to identify the resonant condition which indicates whether the biological substance is located in the sensing region of said grating-coupled waveguide sensor.

15. The optical interrogation system of claim 13, wherein amplitude information within said demodulated electrical signal is used to identify the resonant condition which indicates whether the biological substance is located in the sensing region of said grating-coupled waveguide sensor.

16. The optical interrogation system of claim 7, further comprising:

an acousto-optic modulator capable of receiving the polarization-modulated light beam from said polarization modulator and further capable of scanning the angle of the polarization-modulated light beam;

a lens capable of receiving the polarization-modulated light beam from said acousto-optic modulator and further capable of directing the polarization-modulated light beam into said grating-coupled waveguide sensor; and

said detection system including:

a detector capable of receiving the amplitude modulated light beam from said grating-coupled waveguide sensor and further capable of converting the amplitude modulated light beam into an electrical signal; and

a lock-in amplifier capable of receiving the electrical signal from said detector and further capable of demodulating the electrical signal to detect the resonant condition which indicates whether the biological substance is located in the sensing region of said grating-based waveguide sensor; and

a function generator capable of synchronizing said polarization modulator and said lock-in amplifier.

17. The optical interrogation system of claim 7, further comprising:

a lens capable of receiving the polarization-modulated light beam from said polarization modulator and further capable of directing the polarization-modulated light beam into said grating-coupled waveguide sensor; and

said detection system including:

a scanning pinhole plate capable of receiving the amplitude modulated light beam from said grating-coupled waveguide sensor and further capable of scanning the angle of amplitude modulated light beam;

a detector capable of receiving the amplitude modulated light beam from said scanning pinhole plate and further capable of converting the amplitude modulated light beam into an electrical signal; and

a lock-in amplifier capable of receiving the electrical signal from said detector and further capable of demodulating the electrical signal to detect the resonant condition which indicates whether the biological substance is located in the sensing region of said grating-based waveguide sensor; and

a function generator capable of synchronizing said polarization modulator and said lock-in amplifier.

18. The optical interrogation system of claim 7, further comprising:

a tunable filter capable of receiving the broadband polarization-modulated light beam from said polarization modulator and further capable of scanning the wavelength of the polarization-modulated light beam;

a beam splitter capable of receiving the polarization-modulated light beam from said tunable filter and further capable of directing the polarization-modulated light beam into said grating-coupled waveguide sensor; and

said detection system including:

a detector capable of receiving the amplitude modulated light beam from said grating-coupled waveguide sensor and further capable of converting the amplitude modulated light beam into an electrical signal; and

a lock-in amplifier capable of receiving the electrical signal from said detector and further capable of demodulating the electrical signal to detect the resonant condition which indicates whether the biological substance is located in the sensing region of said grating-based waveguide sensor; and

a function generator capable of synchronizing said polarization modulator and said lock-in amplifier.

19. The optical interrogation system of claim 7, further comprising:

a beam splitter capable of receiving the polarization-modulated light beam from said polarization modulator and further capable of directing the polarization-modulated light beam into said grating-coupled waveguide sensor; and

said detection system including:

a scanning filter capable of receiving the amplitude modulated light beam from said grating-coupled waveguide sensor and further capable of scanning the wavelength of the amplitude modulated light beam;

a detector capable of receiving the amplitude modulated light beam from said scanning filter and further capable of converting the amplitude modulated light beam into an electrical signal; and

a lock-in amplifier capable of receiving the electrical signal from said detector and further capable of demodulating the electrical signal to detect the resonant condition which indicates whether the biological substance is located in the sensing region of said grating-based waveguide sensor; and

a function generator capable of synchronizing said polarization modulator and said lock-in amplifier.

20. A method for interrogating one or more grating-coupled waveguide sensors, said method comprising the steps of:

directing a polarization-modulated light beam into each grating-coupled waveguide sensor;

receiving an amplitude modulated light beam from each grating-coupled waveguide sensor; and

analyzing each received amplitude modulated light beam to detect a resonant condition which corresponds to a superstrate refractive index that indicates whether a biological substance is located in a sensing region of the respective grating-coupled waveguide sensor.

21. The method of claim 20, wherein said biological substance is a cell, molecule, protein, drug, chemical compound, nucleic acid, peptide or carbohydrate.

22. The method of claim 20, wherein said analyzing step further includes:

converting each received amplitude modulated light beam into an electrical signal; and

demodulating each electrical signal to identify the resonant condition which indicates whether the biological substance is located in the sensing region of the respective grating-coupled waveguide sensor.

23. The method of claim 22, wherein phase information within said demodulated electrical signal is used to identify the resonant condition which indicates whether the biological substance is located in the sensing region of the respective grating-coupled waveguide sensor.

24. The method of claim 22, wherein amplitude information within said demodulated electrical signal is used to identify the resonant condition which indicates whether the biological substance is located in the sensing region of the respective grating-coupled waveguide sensor.

25. The method of claim 20, wherein said analyzing step utilizes an angular scanning approach to scan the polarization-modulated light beam to enable the detection of a resonant angle which indicates whether the biological substance is located in the sensing region of the respective grating-coupled waveguide sensor.

26. The method of claim 20, wherein said analyzing step utilizes an angular scanning approach to scan the amplitude modulated light beam to enable the detection of a resonant angle which indicates whether the biological substance is located in the sensing region of the respective grating-coupled waveguide sensor.

27. The method of claim 20, wherein said analyzing step utilizes a wavelength scanning approach to scan the polarization-modulated light beam to enable the detection of a resonant wavelength which indicates whether the biological substance is located in the sensing region of the respective grating-coupled waveguide sensor.

28. The method of claim 20, wherein said analyzing step utilizes a wavelength scanning approach to scan the amplitude modulated light beam to enable the detection of a resonant wavelength which indicates whether the biological substance is located in the sensing region of the respective grating-coupled waveguide sensor

29. The method of claim 20, wherein said grating-coupled waveguide sensor is located within a microplate.

30. A microplate comprising:

a frame including a plurality of wells formed therein, each well incorporating a grating-based waveguide that includes:

a substrate;

a diffraction grating;

a waveguide film;

wherein said substrate receives a polarization-modulated light beam that is converted into an amplitude modulated light beam after the polarization-modulated light beam interacts with said diffraction grating, said waveguide film and a sensing region of said waveguide film; and

wherein said substrate outputs the amplitude modulated light beam that is received by an optical interrogation system that demodulates the amplitude modulated light beam by responding to signals at a modulation frequency of the polarization-modulated light beam and ignoring noise affecting the signals outside the modulation frequency to determine whether a biological substance is located in the sensing region of said waveguide film.

31. The microplate of claim 30, wherein said biological substance is a cell, molecule, protein, drug, chemical compound, nucleic acid, peptide or carbohydrate.

32. The microplate of claim 30, wherein said optical interrogation system utilizes an angular scanning approach to scan the polarization-modulated light beam to enable the detection of a resonant angle which indicates whether the biological substance is located in the sensing region of said waveguide film.

33. The microplate of claim 30, wherein said optical interrogation system utilizes an angular scanning approach to scan the amplitude modulated light beam to enable the detection of a resonant angle which indicates whether the biological substance is located in the sensing region of said waveguide film.

34. The microplate of claim 30, wherein said optical interrogation system utilizes a wavelength scanning approach to scan the polarization-modulated light beam to enable the detection of a resonant wavelength which indicates whether the biological substance is located in the sensing region of said waveguide film.

35. The microplate of claim 30, wherein said optical interrogation system utilizes a wavelength scanning approach to scan the amplitude modulated light beam to enable the detection of a resonant wavelength which indicates whether the biological substance is located in the sensing region of said waveguide film.

36. The microplate of claim 30, wherein said optical interrogation system utilizes a diffractive optic to generate the multiple polarization-modulated light beams that are directed towards the wells.

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