

(51) International Patent Classification:
G01N 21/55 (2006.01) **G01N 21/77** (2006.01)(21) International Application Number:
PCT/US2010/056112(22) International Filing Date:
10 November 2010 (10.11.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

[Continued on next page]

(54) Title: NON-SPECTROSCOPIC LABEL-INDEPENDENT OPTICAL READER SYSTEM AND METHODS

(57) Abstract: A non-spectroscopic, label-independent optical reader system is disclosed, where an exemplary system includes a broadband light source that generates broadband light made incident upon the resonant waveguide grating (RWG) biosensor. The light reflects from the RWG biosensor to form biosensor-reflected light. A photodetector receives the reflected light and generates a first detector signal representative of the reflected light intensity. An optical-edge filter can filter the broadband light, the reflected light, or both. A processor calculates a resonant wavelength for the RWG biosensor based on the detector signal.

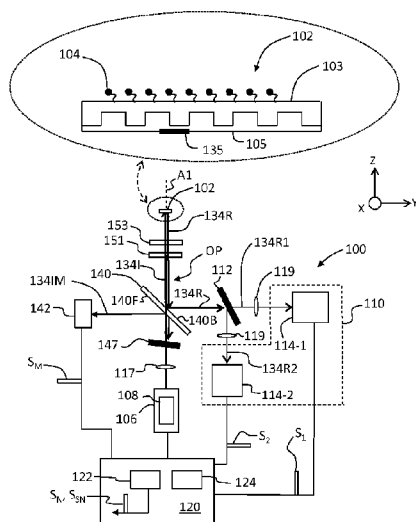


FIG. 5D



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- *before the expiration of the time limit for amending the
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NON-SPECTROSCOPIC LABEL-INDEPENDENT OPTICAL READER SYSTEM AND METHODS

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CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Provisional Application Serial No. 61/261,543 filed on November 16, 2009.

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FIELD

[0002] The present disclosure relates to label-independent optical readers, and in particular to optical reader systems and methods that do not use a spectrometer.

BACKGROUND

15 [0003] Label-independent detection (LID) optical readers can be used to detect drug molecule binding to a target molecule such as a protein and to detect the interaction of drug molecules with cells. Certain types of LID optical readers measure changes in refractive index on the surface of an individual resonant waveguide grating (RWG) biosensor, for arrays of RWG biosensors, and for RWG biosensors integrated
20 in the individual wells of a microplate.

[0004] In the general operation of a LID optical reader, spectrally broadband light from a broadband optical light source is directed to each RWG biosensor. Only light whose wavelength is resonant with the RWG biosensor is strongly reflected. The reflected light is collected and spectrally analyzed to determine the RWG biosensor
25 resonance wavelength. A measured shift in the resonance wavelength is representative of a refractive index change and thus biochemical/cell/drug interaction occurring at the surface of the RWG biosensor.

[0005] Most optical readers use one or more spectrometers to analyze light reflected from the biosensor. This makes such optical reader systems relatively
30 expensive and complex. Further, the resonant wavelength is determined indirectly by processing the spectra obtained from the one or more spectrometers. This typically includes having to use an algorithm, such as a centroid-finding algorithm.

SUMMARY

[0006] An aspect of the disclosure is a non-spectroscopic optical reader system for reading a RWG biosensor. The system includes a broadband light source that generates broadband light that is incident the RWG biosensor and that reflects therefrom to form biosensor-reflected light having an intensity. A first photodetector receives the biosensor-reflected light and generates a first detector signal representative of the first intensity. An optical edge filter filters either the broadband light or the biosensor-reflected light. A processor receives the first detector signal and calculates therefrom a resonant wavelength for the RWG biosensor.

[0007] Another aspect of the disclosure is a non-spectroscopic optical system for label-independent reading of a RWG biosensor. The system includes a broadband light source that generates broadband light that is incident upon the RWG biosensor and that reflects therefrom. The system also includes an optical edge filter that transmits and reflects respective portions of the reflected light from the RWG biosensor. The system also has first and second photodetectors disposed relative to the optical edge filter to respectively receive the transmitted and reflected light portions and to generate therefrom respective first and second detector signals. The system further includes a processor connected to the first and second photodetectors. The processor receives the first and second detector signals and generates therefrom a signal representative of a resonant wavelength of the RWG biosensor.

[0008] Another aspect of the disclosure is a non-spectroscopic method of label-independent reading of a RWG biosensor operably supported by a support structure. The method includes directing broadband light to be incident upon the RWG biosensor and generating reflected light therefrom. The method also includes transmitting the incident broadband light or the reflected light through an optical edge filter. The method further includes detecting the transmitted and filtered portion of the reflected light with a first photodetector and generating a first detector signal representative of a first intensity of the first detected light. The method additionally includes determining a resonant wavelength based on the first detector signal.

[0009] These and other advantages of the disclosure will be further understood and appreciated by those skilled in the art by reference to the following written specification, claims and appended drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] A more complete understanding of the present disclosure may be had by reference to the following detailed description when taken in conjunction with the accompanying drawings, wherein:

5 [0011] **FIG. 1** is a generalized schematic diagram of an example non-spectroscopic optical reader system used to interrogate one or more RWG biosensors;

[0012] **FIG. 2** is a plot of an example optical edge filter transmission T vs. wavelength (nm);

10 [0013] **FIG. 3** is a plot of the intensity (relative units) versus wavelength (nm) for light reflected from the RWG biosensor, illustrating the resonant wavelength and the shift therein (as indicated by arrow **139**) when biological material is present on the surface of the RWG biosensor;

[0014] **FIG. 4** is a plan view of a RWG biosensor support structure in the form of a microplate that comprises a support plate with a surface having a plurality of wells
15 formed therein that each contain a RWG biosensor;

[0015] **FIG. 5A** is a schematic diagram of an example embodiment of the non-spectroscopic optical reader system that utilizes a single photodetector disposed in the optical path adjacent and downstream of an optical edge filter;

[0016] **FIG. 5B** is similar to **FIG. 5A** and illustrates an example embodiment of the
20 non-spectroscopic optical reader system wherein the optical edge filter is disposed in the optical path between the light source unit and the RWG biosensor, and that includes a monitoring photodetector for normalizing the system signal;

[0017] **FIG. 5C** is similar to **FIG. 5A**, and illustrates an example embodiment of the non-spectroscopic optical reader system that utilizes two photodetectors
25 respectively arranged to receive transmitted and reflected light from the optical edge filter and generate respective detector signals;

[0018] **FIG. 5D** is similar to **FIG. 5C** and illustrates an example embodiment of the non-spectroscopic optical reader system that utilizes two photodetectors and where a beamsplitter enables a portion of the optical path to lie along the system axis, and
30 wherein a polarizer and quarter-wave wave plate serve to optically isolate the two photodetectors;

[0019] FIG. 6A is a schematic diagram of an example embodiment of the optical-fiber-based non-spectroscopic optical reader system that utilizes a single photodetector;

[0020] FIG. 6B is similar to FIG. 6A and illustrates an embodiment of a single-photodetector optical-fiber-based non-spectroscopic optical reader system wherein the optical edge filter is arranged adjacent the light source unit;

[0021] FIG. 6C is similar to FIG. 6A and illustrates an embodiment of a two-photodetector optical-fiber-based non-spectroscopic optical reader system;

[0022] FIG. 7 is a plot of the splitting ratio (SR) of the WDM edge filter for the two output ports (solid line) and (dashed line) for the optical-fiber-based non-spectroscopic optical reader system of FIG. 6C;

[0023] FIG. 8 is a schematic diagram similar to FIG. 5C and illustrates an example imaging-based non-spectroscopic optical reader system; and

[0024] FIG. 9 is a schematic diagram of an example signal-processing system for calculating a system signal representative of a resonance wavelength based on input signals from the two photodetectors of a two-photodetector non-spectroscopic optical reader system.

DETAILED DESCRIPTION

[0025] Reference is now to embodiments of the disclosure, exemplary embodiments of which are illustrated in the accompanying drawings.

[0026] FIG. 1 is a generalized schematic diagram of an example non-spectroscopic optical reader system ("system") 100 used to interrogate one or more RWG biosensors 102 each having a sensor surface 103 and a substrate bottom surface 105, to determine if a biological interaction has occurred with biological substance 104 present on the RWG biosensor. System 100 includes a light source unit 106, a photodetector unit 110, an optical edge filter 112, and a controller/signal processor 120. A system axis A1 normally intersects RWG biosensor 102.

[0027] An example light source unit 106 includes a broadband light source 108, such as super luminous diode (SLD). An example wavelength band $\Delta\lambda$ for broadband light source 108 ranges from about 820 nm to about 840 nm.

[0028] Controller/signal processor 120 includes a processor unit ("processor") 122 operably coupled to a memory unit ("memory") 124. In an example embodiment,

processor **122** is adapted (e.g., is programmed or is programmable) to process information provided to controller/signal processor **120** from photodetector unit **110** or from memory **124**. In an example embodiment, controller/signal processor **120** is or includes a programmable computer. The term “processor” includes a general purpose processor, a microcontroller (i.e., an execution unit with memory, etc., integrated within a single integrated circuit), or a digital signal processor. Memory **124** may include any of the common forms of digital memory used in electronic systems and computers. Memory **124** is used, for example, to store data, including resonant wavelength information obtained as described below, and computer-readable instructions (e.g., software) for carrying out signal-processing methods in processor **122**.

[0029] **FIG. 2** is a plot of transmittance T vs. wavelength (nm) showing the characteristic linear transmittance of an example optical edge filter **112**. An example wavelength range of optical edge filter is between about 825 nm ($T = 0$) and 835 nm ($T = 1$). An example slope of the T vs. wavelength curve is $1/10 \text{ nm}^{-1}$.

[0030] With reference again to **FIG. 1**, in the general operation of system **100**, light source **106** generates an incident light **134I**. This light is incident upon RWG biosensor **102** at substrate bottom surface **105** and forms a light spot **135** thereon. Incident light **134I** penetrates surface **105** and interacts with the biological substance **104** on sensor surface **103** and reflects therefrom, forming a reflected light **134R**. Example RWG biosensors **102** make use of changes in the refractive index at sensor surface **103** that affect the waveguide coupling properties of incident light **134I** and reflected light **134R** from the RWG biosensor to enable label-free detection of biological substance **104** (e.g., cell, molecule, protein, drug, chemical compound, nucleic acid, peptide, carbohydrate, etc.) on the RWG biosensor. Biological substance **104** may be located within a bulk fluid deposited on sensor surface **103**, and the presence of this biological substance alters the index of refraction at the RWG biosensor surface. In embodiments, sensor surface **103** can be coated with, for example, biochemical compounds (not shown) that only allow surface attachment of specific complementary biological substances **104**, thereby enabling RWG biosensor **102** to be both highly sensitive and highly specific.

[0031] FIG. 3 is a plot of the intensity (relative units) versus wavelength for reflected light **134R**. When chemical binding occurs at RWG biosensor surface **103**, the resonant wavelength λ_R shifts slightly, as indicated by arrow **139**. In this way, system **100** and RWG biosensor **102** can be used to detect a wide variety of biological substances **104** and changes thereof. Likewise, RWG biosensor **102** can be used to detect the movements or changes in cells immobilized to sensor surface **103**. For example, when the cells move relative to RWG biosensor **102**, or when they incorporate or eject material, a refractive index change occurs.

[0032] With reference again to FIG. 1, reflected light **134R** passes through optical edge filter **112** and can be detected by photodetector unit **110**. Incident and reflected light **134I** and **134R** define an optical path **OP**. Optical edge filter **112** can be located anywhere in the optical path **OP** between light source **106** and photodetector unit **110**. In some example embodiments of system **100**, optical path **OP** is symmetric about system axis **A1**, while in other embodiments the optical path lies along at least a portion of the system axis.

[0033] Controller/signal processor **120** receives from photodetector unit **110** a detector photocurrent signal S_1 or detector photocurrent signals S_1 and S_2 (depending on the number of photodetectors **114** in the photodetector unit), and processor **122** processes these signals according to the methods described below. Controller/signal processor **120** is configured to determine if there are any changes (e.g., 1 part per million) in the RWG biosensor resonance wavelength λ_R caused by the presence of biological substance and changes thereof. The output of this signal processing is a power-normalized system signal S_N for each RWG biosensor **102** representative of a value for the resonant wavelength λ_R . In an example where normalized system signal is self-normalized (as described below), the system signal is denoted S_{SN} .

[0034] In embodiments, one or more RWG biosensors **102** can be supported by a support structure **168** that facilitates reading of one or more RWG biosensors by system **100**. FIG. 4 is a plan view of an example support structure **168** in the form of a microplate **170** that comprises a support plate **171** with a surface **173** having a plurality of wells **175** formed therein. An example support plate **171** has a two-part construction of an upper plate and a lower plate (not shown), as described for example in U.S. Patent Application Publication No. 2007/0211245.

[0035] Microplate **170** of **FIG. 4** illustrates an exemplary configuration where RWG biosensors **102** are arranged in an array **102A** and operably supported in respective wells **175**. An exemplary RWG biosensor array **102A** has a 4.5 mm pitch for RWG biosensors **102** that are 2 mm square, and includes 16 RWG biosensors per column and 24 RWG biosensors in each row. A microplate holder **174** is also shown holding microplate **170**. Many different types of plate holders can be used as microplate holder **174**.

[0036] It is noted here that system **100** of the present disclosure is not limited to the use of microplates, and generally can be used with any support structure **168** capable of holding one or more RWG biosensors **102**. Other suitable support structures include, for instance, microscope slides, microfluidic structures, micro-arrays, petri dishes, custom single and multiple biosensor support structures, and the like

[0037] In the case where multiple RWG biosensors **102** are operably supported (e.g., as an array **102A**), then they can be used to enable high-throughput drug or chemical screening studies. For a more detailed discussion about the detection of a biological substance **104** (or a biomolecular binding event) using scanning optical reader systems, reference is made to U.S. Patent Application Ser. No. 11/027,547. Other optical reader systems are disclosed in, for example, U.S. Patent No. 7,424,187 and U.S. Patent Application Publications No. 2006/0205058 and 2007/0202543.

Example system embodiments

[0038] **FIG. 5A** is similar to **FIG. 1** and illustrates an example embodiment of system **100** wherein photodetector unit **110** includes a photodetector **114** disposed to receive reflected light **134R** transmitted through optical edge filter **112**. Optical edge filter **112** is shown disposed in optical path **OP** between RWG biosensor **102** and detector unit **110**. An optional collecting lens **119** is provided in optical path **OP** between optical edge filter **112** and photodetector **114** to assist in collecting reflected light **134R** and directing it to the photodetector. Photodetector **114** generates detector signals **S₁** that are received and processed by controller/signal processor **120** as described below.

[0039] **FIG. 5B** illustrates a single-detector embodiment of system **100** similar to that shown in **FIG. 5A**, but with the optical edge filter **112** disposed between the

broadband light source and RWG biosensor. System **100** of **FIG. 5B** includes a power monitoring system in the form of a beamsplitter **140** of known reflectivity/transmittance arranged in the optical path **OP** in incident light **134I**, and a monitoring photodetector **142** arranged to receive a known portion **134IM** of incident light **134I** redirected to the photodetector. Monitoring photodetector **142** sends a monitoring signal S_M to controller/signal processor **120** to provide a measure of the power in “monitoring” incident light **134IM** and thus a measure of the power in incident light **134I**.

[0040] **FIG. 5C** illustrates an alternate embodiment of system **100** similar to that shown in **FIG. 5A**, but where the photodetector unit **110** includes two photodetectors **114-1** and **114-2** disposed relative to optical edge filter **112** to respectively receive transmitted and reflected light **134R1** and **134R2** therefrom. Photodetectors **114-1** and **114-2** generate respective detector signals S_1 and S_2 , which are received and processed by the controller/signal processor **120** as described below.

[0041] **FIG. 5D** illustrates an example embodiment of system **100** similar to **FIG. 5C** wherein a portion of the optical path **OP**, as defined by incident and reflected light **134I** and **134R**, lies along system axis **A1**. System **100** of **FIG. 5D** includes, disposed along the system axis in order from light source unit **106** and RWG biosensor **102**: optional lens **117**, a band-pass filter **147**, a beamsplitter **140**, a polarizer **151** and a quarter-wave waveplate **153**.

[0042] Band-pass filter **147** is used to narrow the bandwidth of broadband light source **108**, and can also be located in light source unit **106**. Beamsplitter **140** has front and back surfaces **140F** and **140B**. As incident light **134I** enters beamsplitter **140** at front surface **140F** and exits at back surface **140B**, a small portion of the incident light is reflected to form the aforementioned monitoring light **134IM**, as discussed in connection with **FIG. 5B**. Example beamsplitters **140** include a beamsplitter cube, a beamsplitter plate and a pellicle beamsplitter. A 20X reduction in the amount of power measured in monitoring light **134IM** was observed when using a pellicle beamsplitter versus using a cube beamsplitter.

[0043] In an example embodiment, monitoring photodetector **142** is arranged to receive and detect monitoring light **134IM** and transmit a corresponding monitoring signal S_M to controller/signal processor **120**. As in the example shown in **FIG. 5B**,

monitoring signal S_M can be used to monitor the performance of light source unit **106** (e.g., power levels, fluctuations, etc.), and this information can be used to improve the overall performance of system **100**.

[0044] Polarizer **151** and quarter-wave waveplate **153** are configured to optically
 5 isolate photodetectors **114-1** and **114-2** and to mitigate a non-resonant sensor response. A portion of reflected light **135R** traveling along system axis **A1** is reflected by beamsplitter **140** and travels to edge filter **112**, which directs first and second reflected light **134R1** and **134R2** to respective photodetectors **114-1** and **114-2**. Photodetectors **114-1** and **114-2** generate respective detector signals S_1 and S_2 , which are received and
 10 processed by the controller/signal processor **120** as described below.

[0045] With reference to **FIG. 5C** and **FIG. 5D**, in the general operation of the two-detector embodiments of system **100**, light source unit **106** (and optional lens **117**) generates broadband incident light **134I** that reflects from RWG biosensor **102**, to form reflected light **134R**. Reflected light **134R** is incident upon optical edge filter **112**,
 15 which forms from this reflected light a “transmitted” reflected light **134R1** and a “reflected” reflected light **134R2**. Optional lens **119** can be used to help collect and direct reflected light **134R**. Light **134R1** is detected by photodetector **114-1**, while light **134R2** is detected by photodetector **114-2**.

[0046] Photodetectors **114-1** and **114-2** generate respective detectors signals S_1 and
 20 S_2 having respective photocurrents I_1 and I_2 that are representative of the intensity of light detected. Detector signals S_1 and S_2 travel to controller **120**. Processor **122** receives detector signals S_1 and S_2 and processes these signals according to the methods described below to generate system signal S_{SN} representative of a value for resonant wavelength λ_R . In embodiments, information from detector signals S_1 and S_2 is stored
 25 in memory **124** and then provided to processor **122**.

[0047] The operation of single-detector embodiments of system **100** of **FIGS. 5A** and **5B** is similar to that of the two-detector embodiments of **FIG. 5C** and **FIG. 5D**, except that there is only one detector signal S_1 generated and processed to calculate the system signal S_N . An advantage of using a two-detector system **100** is that such a
 30 system generates two detector signals S_1 and S_2 that provide for a more accurate determination of system signal S , as described below.

[0048] FIGS. 5A through 5D describe example “free space” systems wherein the light travels through free space rather than waveguides. FIGS. 6A through 6C are schematic diagrams of fiber-based “guided wave” systems 100 where the light travels mostly through optical waveguides, which are shown by way of example as being in the form of optical fibers.

[0049] FIG. 6A is a schematic diagram of an example guided-wave system 100 that uses a single photodetector 114 in photodetector unit 110. Fiber-based system 100 includes a first optical fiber section F1 that connects light source unit 106 to a 1x2 coupler 125 having a “1x” end 125-1 and a “2x” end 125-2. A second optical fiber section F2 connects the “1x” coupler end 125-1 to an optical fiber collimator 126. Optical fiber collimator 126 includes a lens 118 to facilitate forming incident light 134I. A third optical fiber section F3 connects the “2x” coupler end 125-2 to optical edge filter 112, which in embodiments can be the same, but appropriately packaged, optical edge filter used in the free-space embodiments of system 100 described in FIGS. 5A through 5D. Optical edge filter 112 as shown in FIG. 6A is in the form of a coarse wavelength division multiplexer (hereinafter, “WDM edge filter 112”). An optical fiber section F4 connects the WDM edge filter 112 to photodetector unit 110 having the single photodetector 114. Photodetector 114 can be electrically connected to the controller/signal processor 120.

[0050] FIG. 6B illustrates an embodiment of the single-photodetector guided-wave system 100 similar to that shown in FIG 6A, but where the edge filter 112 is located between the light source 106 and the RWG biosensor 102.

[0051] FIG. 6C illustrates an embodiment of a guided-wave system 100 similar to that shown in FIG. 6A, but that illustrates a two-photodetector embodiment with two optical fiber sections F4-1 and F4-2, respectively, connecting the two output ports 112-1 and 112-2 of WDM edge filter 112 to photodetectors 114-1 and 114-2 in photodetector unit 110. FIG. 7 is a plot of the splitting ratio (SR) of WDM edge filter 112 for the two output ports 112-1 (solid line) and 112-2 (dashed line). A variety of fiber-optic and micro-optic based components can be selected to implement the fiber-based system. These can include, for example, optical circulators, dual fiber collimators, etc.

[0052] With reference again to **FIG. 6C**, the two-photodetector fiber-optic embodiment of system **100** works in essentially the same manner as the two-detector free-space embodiment of the system as shown in **FIGS. 5C** and **5D**. Light source unit **106** generates light **107I** that travels over first optical fiber section **F1** to the “2x” coupler end **125-2**. The 1x2 coupler **125** couples light **107I** into second optical fiber section **F2** and travels to optical fiber collimator **126**, which is configured (e.g., with lens **118**) to form incident light **134I** along system axis **A1**. This light is incident upon RWG biosensor **102** and is reflected therefrom along system axis **A1** to form reflected light **134R**. Thus, the optical path **OP** of system **100** lies along system axis **A1**.

[0053] Optical fiber collimator **126** receives reflected light **134R** and converts it to guided light **107R** that travels over optical fiber section **F2** to the “1x” coupler end **125-1**. The 1x2 coupler **125** outputs guided light **107R** at the “2x” coupler end **125-2** to optical fiber section **F3**. Guided light **107R** travels over optical fiber section **F3** to WDM edge filter **112**, which transmits a portion **107R1** of guided light **107R** to photodetector **114-1** and another portion **107R2** to photodetector **114-2** according to the splitting ratio plot of **FIG. 7**. The guided light portions **107R1** and **107R2** created by WDM edge filter **112** are equivalent light **134R1** and light **134R2** of the free-space embodiments of system **100** of **FIGS. 5C** and **5D**.

[0054] As with the free-space embodiment of system **100** of **FIG. 5C**, in the optical fiber embodiment of system **100** of **FIG. 6C**, photodetectors **114-1** and **114-2** generate respective detectors signals **S₁** and **S₂** having respective photocurrents I_1 and I_2 that are representative of the intensity of light detected. Detector signals **S₁** and **S₂** travel to controller **120**. Processor **122** receives detector signals **S₁** and **S₂** and processes these signals according to the methods described below to generate system signal **S_{SN}** representative of a value for resonant wavelength λ_R .

[0055] **FIG. 8** is a schematic diagram of an example imaging-based system **100**. System **100** of **FIG. 8** includes photodetectors **114-1** and **114-2** in the form of image sensors such as charge-coupled device (CCD) cameras. An image of a single RWG biosensor **102** or of multiple RWG biosensors can be formed on image sensors **114-1** and **114-2** via reflected light **134R** (dashed lines). The pixels (not shown) of the image sensors **114-1** and **114-2** capture respective images of the one or more RWG biosensors **102** and provide respective detector signals **S₁** and **S₂** representative of the

captured images. Controller/signal processor **120** then processes the detector signals **S₁** and **S₂** and generates system signal **S_N** or **S_{SN}** (depending on if one or two image sensors are used) representative of one or more resonant wavelengths λ_R associated with the one or more imaged RWG biosensors **102**. As in the embodiments shown in
 5 **FIGS. 5A** through **5D**, one or two image sensors can be selected.

Mathematical Analysis

[0056] As described above, system **100** does not rely on using a spectrometer to analyze reflected light **134R** to ascertain a value for the resonant wavelength λ_R . Rather, the two-photodetector system **100** detects the intensity of the reflected light
 10 **134R** as passed through optical edge filter **112** and converts the detected intensity, as represented by signals **S₁** and **S₂** from photodetectors **114-1** and **114-2**, into a resonant wavelength λ_R . The following mathematical analysis describes how signals **S₁** and **S₂** are processed to calculate the normalized (or self-normalized) system signal **S_N** (or **S_{SN}**) representative of resonant wavelength λ_R .

15 [0057] It is assumed that both the broadband optical source power spectral density P_{BBS} of light source unit **106** and the responsivity $\mathcal{R}_{PD}$ of the one or more photodetectors **114** are constant over the spectral region of interest, i.e.,

$$P_{BBS}(\lambda) = P_o \quad W/nm \quad (1)$$

$$\mathcal{R}_{PD}(\lambda) = \mathcal{R}_o \quad A/W \quad (2)$$

20 [0058] It is also assumed that the entire system **100** is uniform in the spatial Cartesian coordinate system (x, y, z). Optical edge filter **112** is characterized by a linear change in transmittance over the spectral region of interest, i.e.

$$T_F(\lambda) = \begin{cases} 0 & \lambda \leq \lambda_e \\ S_F(\lambda - \lambda_e) & \lambda_e < \lambda \leq \lambda_e + S_F^{-1} \\ 1 & \lambda > \lambda_e + S_F^{-1} \end{cases} \quad (3)$$

where S_F is the slope of the filter edge in units of nm^{-1} and λ_e is the spectral position of
 25 the filter edge. The edge filter shape for $S_F = 1/10 \text{ nm}^{-1}$ and $\lambda_e = 825 \text{ nm}$ is shown in **FIG. 2**.

[0059] The reflectance spectrum of RWG biosensor **102** can be characterized by the general function

$$R(\lambda, \lambda_R) = R_o(\lambda - \lambda_R) \quad (4)$$

where λ_R is the resonance wavelength, i.e., the spectral location of the resonance peak and shifts with refractive index changes at the sensor surface. For mathematical simplicity it is assumed that $R(\lambda, \lambda_R)$ is normalized to unity, i.e.

$$\int_{-\infty}^{+\infty} R(\lambda, \lambda_R) d\lambda = 1 \quad (5)$$

and has units of wavelength (nm). Finally, each photodetector **114** integrates over all incident optical wavelengths to yield the system response when the reflected resonance is located at λ_R :

$$I_1(\lambda_R) = \int_{-\infty}^{+\infty} P_{BBS}(\lambda) R(\lambda, \lambda_R) T_F(\lambda) \Re_{PD}(\lambda) d\lambda \quad (6)$$

[0060] Using the above definitions and substituting in the edge filter functional response results in the following expression for the system photocurrent:

$$I_1(\lambda_R) = \begin{cases} 0 & \lambda_R \leq \lambda_e \\ P_o \Re_o S_F \int_{\lambda_e}^{\lambda_e + S_F^{-1}} (\lambda - \lambda_e) R_o(\lambda - \lambda_R) d\lambda & \lambda_e < \lambda_R \leq \lambda_e + S_F^{-1} \\ P_o \Re_o & \lambda_R \geq \lambda_e + S_F^{-1} \end{cases} \quad (7)$$

This expression is only valid when the resonant wavelength λ_R is sufficiently far away from the transition regions of the edge filter function relative to the spectral width of the $R(\lambda, \lambda_R)$. The spectral regions where the photocurrent is constant do not contain any useful information and can be ignored. As a result, the above expression for the photocurrent simplifies to

$$I_1(\lambda_R) = P_o \Re_o S_F \left[\int_{\lambda_e}^{\lambda_e + S_F^{-1}} \lambda R_o(\lambda - \lambda_R) d\lambda - \lambda_e \right] \quad (8)$$

[0061] The photocurrent is proportional to the expectation value, or center of mass, centroid, etc., of the biosensor reflectance spectrum. The expectation value of $R(\lambda, \lambda_R)$ is given by the expression

$$\langle R(\lambda, \lambda_R) \rangle = \int_{-\infty}^{+\infty} \lambda R_o(\lambda - \lambda_R) d\lambda \quad (9)$$

This is precisely what is measured in optical reader systems that use traditional spectroscopic means to measure the resonance wavelength. However, system **100** of the present disclosure generates the same information without ever having to directly spectrally measure and resolve the biosensor reflectance spectrum via spectroscopic means. Further, it avoids the need to implement complex centroid algorithms to determine the resonance wavelength.

[0062] Certain conditions are required to ensure that system **100** only measures changes in the resonant wavelength. First, the power P_o from light source unit **106** and the detector responsivity $\mathcal{R}_o$ must be stable. Typically, at constant temperature the photodiode responsivity is stable. However, the power produced by light source unit **106** may drift with time. As a result, the optical power of light source unit **106** is preferably monitored and used to normalize the measured signal S_1 .

[0063] Systems **100** of **FIG. 5B** and **FIG. 5D** include a power monitoring system in the form of a beamsplitter **140** of known reflectivity/transmittance arranged in the optical path **OP** in incident light **134I**, and a monitoring photodetector **142** arranged to receive a known portion or fraction (α) of incident light **134I** redirected to the photodetector in the form of measurement light **134IM**. Monitoring photodetector **142** sends a monitoring signal S_M to controller/signal processor **120** to provide a measure of the power in incident light **134I**.

[0064] Hence, the power-normalized system signal S_N is defined by dividing by $\alpha P_o \mathcal{R}_o \Delta_{BBS}$, where it is assumed that the responsivity of monitoring photodetector **142** is the same as the measuring photodetector **114**, α is the fraction of the source power split off for monitoring purposes by beamsplitter **140**, and Δ_{BBS} is the spectral width of the optical source:

$$S_N(\lambda_R) = \left[\frac{(1-\alpha)}{\alpha \Delta_{BBS}} \right] S_F \left[\int_{\lambda_e}^{\lambda_e + S_F^{-1}} \lambda R_o (\lambda - \lambda_R) d\lambda - \lambda_e \right] \quad (10)$$

[0065] This method negates the detrimental effects of power drift in light source unit **106**. However, even with this improvement in the overall stability of system **100**, the system is still sensitive to perturbations that change the optical power detected by photodetector unit **110**. For example, if during operation a defect appears (a smudge, water droplet, fingerprint, a piece of debris, etc.) on the RWG biosensor **102** between

readings, the defect will reduce the received optical power and decrease the signal $S_N(\lambda_R)$, and hence, be interpreted as an erroneous wavelength change. This is illustrated mathematically by including a scale factor γ . The photodetector **114** not only performs a spectral integration as shown in Eq. 6, it also performs a spatial
 5 integration. As a result, γ is expressed as:

$$\gamma = \left(\frac{1}{A_{PD}} \right) \iint_{\substack{\text{Detector} \\ \text{Dimension}}} T_D(x, y) dx dy \quad (11)$$

where $T_D(x, y)$ is the spatial “transmission” function of the defect and A_{PD} is the area of photodetector **114**. With the assumption that a defect impacts all wavelengths equally, the expression for $S_N(\lambda_R)$ now becomes:

$$S_N(\lambda_R, \gamma) = \left[\frac{\gamma(1-\alpha)}{\alpha \Delta_{BBS}} \right] S_F \left[\int_{\lambda_e}^{\lambda_e + S_F^{-1}} \lambda R_o(\lambda - \lambda_R) d\lambda - \lambda_e \right] \quad (12)$$

[0066] Finally, the impact of the “spectral shape” of both real light source units
 106 and real photodetectors **114** are considered. To examine the impact of spectral non-uniformity, Eq. 12 is written to include the wavelength dependent terms in Eq. 6:

$$S_N^{Real}(\lambda_R, \gamma) = \left[\frac{\gamma(1-\alpha)}{\alpha I_{BBS}^{Tot}} \right] S_F \left[\int_{\lambda_e}^{\lambda_e + S_F^{-1}} \lambda P_{BBS}(\lambda) \Re_{PD}(\lambda) R_o(\lambda - \lambda_R) d\lambda - \lambda_e \int_{\lambda_e}^{\lambda_e + S_F^{-1}} P_{BBS}(\lambda) \Re_{PD}(\lambda) R_o(\lambda - \lambda_R) d\lambda \right] \quad (13)$$

where

$$I_{BBS}^{Tot} = \int_{\substack{\text{All} \\ \text{Wavelengths}}} \Re_{PD}(\lambda) P_{BBS}(\lambda) d\lambda \quad (14)$$

[0067] If the width of the $R(\lambda, \lambda_R)$ is small compared to the spectral variation of the components in the system then $R(\lambda, \lambda_R)$ can be approximated by the dirac delta
 20 function:

$$R(\lambda, \lambda_R) \approx \delta(\lambda - \lambda_R) \quad (15)$$

With this approximation Eq. 13 reduces to

$$S_N^{Real}(\lambda_R, \gamma) = \left[\frac{\gamma(1-\alpha)}{\alpha I_{BBS}^{Tot}} \right] S_F P_{BBS}(\lambda_R) \Re_{PD}(\lambda_R) (\lambda_R - \lambda_e) \quad (16)$$

The expression for the “real” signal generated by system **100** is complex and requires the careful control of the system components.

[0068] Example systems **100** as discussed above include the use of two photodetectors **114** in photodetector unit **110**. The two-photodetector embodiments of system **100** generate detector signals S_1 and S_2 that can be used to form a self-normalized signal S_{SN} that is proportional to the wavelength shift of the RWG biosensor.

[0069] In most cases, optical filters generate both a transmitted signal and reflected signal and are optically lossless such that

$$T_F(\lambda) + R_F(\lambda) = 1 \quad (17)$$

The reflectance of the optical edge filter **112** can be represented by $R_F(\lambda) = 1 - T_F(\lambda)$:

$$R_F(\lambda) = \begin{cases} 1 & \lambda \leq \lambda_e \\ 1 - S_F(\lambda - \lambda_e) & \lambda_e < \lambda \leq \lambda_e + S_F^{-1} \\ 0 & \lambda > \lambda_e + S_F^{-1} \end{cases} \quad (18)$$

The photocurrent generated by photodetector **114-2** is given by the expression

$$I_2(\lambda_R) = P_o \Re_o \int_{-\infty}^{+\infty} R_F(\lambda) R_o(\lambda - \lambda_R) d\lambda \quad (19)$$

15 where it is assumed that both photodetectors **114-1** and **114-2** have the same responsivity. Again, ignoring the photocurrent generated in the “constant” spectral regions results in the following simplified expression for I_2

$$I_2(\lambda_R) = P_o \Re_o - P_o \Re_o S_F \left[\int_{\lambda_e}^{\lambda_e + S_F^{-1}} \lambda R_o(\lambda - \lambda_R) d\lambda - \lambda_e \right] \quad (20)$$

[0070] The photocurrent generated by photodetector **114-1** is the same as the single- photodiode system **100** shown in **FIG. 5A** and given by Eq. 8. Both photocurrents I_1 and I_2 can be used to generate a self-normalized output signal S_{SN} for the system. Thus, the following output signal is defined:

$$S_{SN}(\lambda_R) = \frac{I_2(\lambda_R) - I_1(\lambda_R)}{I_2(\lambda_R) + I_1(\lambda_R)} \quad (21)$$

Substituting the expressions for I_1 and I_2 into the expression for S_{SN} and simplifying yields the self-normalized signal produced by the system:

$$S_{SN}(\lambda_R) = 1 - 2S_F \left[\int_{\lambda_e}^{\lambda_e + S_F^{-1}} \lambda R_o(\lambda - \lambda_R) d\lambda - \lambda_e \right] \quad (22)$$

[0071] There are two benefits from using the self-normalized signal S_{SN} . First, power fluctuations in light source unit **106** are normalized out of the final signal, and second, the response of system **100** is increased by a factor of two as compared to the response of the single detector case that generates signal S_N .

[0072] In the case of a non-ideal system the signals $I_1(\lambda_R)$ and $I_2(\lambda_R)$ can be rewritten as

$$I_1(\lambda_R, \gamma) = \gamma S_F \int_{\lambda_e}^{\lambda_e + S_F^{-1}} (\lambda - \lambda_e) P_{BBS}(\lambda) \Re_{PD}(\lambda) R_o(\lambda - \lambda_R) d\lambda \quad (23)$$

$$I_2(\lambda_R, \gamma) = \gamma \left[\int_{\lambda_e}^{\lambda_e + S_F^{-1}} P_{BBS}(\lambda) \Re_{PD}(\lambda) R_o(\lambda - \lambda_R) d\lambda - S_F \int_{\lambda_e}^{\lambda_e + S_F^{-1}} (\lambda - \lambda_e) P_{BBS}(\lambda) \Re_{PD}(\lambda) R_o(\lambda - \lambda_R) d\lambda \right] \quad (24)$$

Invoking Eq. 15 again yields the simplified expression for the two signals

$$I_1(\lambda_R, \gamma) = \gamma S_F P_{BBS}(\lambda_R) \Re_{PD}(\lambda_R) (\lambda_R - \lambda_e) \quad (25)$$

$$I_2(\lambda_R, \gamma) = \gamma P_{BBS}(\lambda_R) \Re_{PD}(\lambda_R) - \gamma S_F P_{BBS}(\lambda_R) \Re_{PD}(\lambda_R) (\lambda_R - \lambda_e) \quad (26)$$

Substituting these expressions into Eq. 21 and simplifying yields the “real” self-normalized signal:

$$S_{SN}^{Real}(\lambda_R) = 1 - 2S_F (\lambda_R - \lambda_e) \quad (27)$$

which is equivalent to Eq. 22 in the delta function limit.

[0073] Equation 22 shows that when non-ideal aspects of system **100** are included, such as light source unit power fluctuations, optical fringes due to multi-path interference, defects present on the microplate, the spectral dependence of the photodetector, etc, the final self-normalized signal S_{SN} produced by the system is independent of these perturbations. The result is therefore a robust and accurate measurement of the resonance wavelength without having to spectrally decompose the reflected light **134R** from RWG biosensor **102**.

[0074] In practical situations, the detector signals S_1 and S_2 are converted to voltages V_1 and V_2 , and in embodiments, processor **122** is configured to: a) determine the first and second voltages V_1 and V_2 from the respective first and second detector signals S_1 and S_2 ; b) determine a difference $V_2 - V_1$ between the first and second voltages; c) determine a sum $V_1 + V_2$ of the first and second voltages; and d) divide the voltage difference by the voltage sum, i.e. $S_{SN} = (V_2 - V_1) / (V_2 + V_1)$.

[0075] **FIG. 9** is a schematic diagram of an example embodiment of a signal processing circuit **300** for processor **122** used to process detector signals S_1 and S_2 and the corresponding voltages V_1 and V_2 . Signal processing circuitry **300** includes two branches **302-1** and **302-2** that each include in series a transimpedance amplifier (TIA) **310**, an analog-to-digital converter (ADC) **316** and a low-pass filter (LPF) **320**. Signals **SL1** and **SL2** are outputted by respective LPFs **320-1** and **320-2**. The two circuit branches are connected at their respective LPF outputs to difference and sum logic circuitry **330** and **332**, which are each connected to division logic circuitry **340**.

[0076] LPF output signals **SL1** and **SL2** are inputted to difference and sum logic circuitry **330** and **332** to generate the difference and sum signals **SD** and **SS**, respectively. The difference and sum signals **SD** and **SS** are inputted into division logic circuitry **340** to form the self-normalized output signal S_{SN} of the system by dividing **SD** by **SS**.

[0077] It will be apparent to those skilled in the art that various modifications to the preferred embodiment of the disclosure as described herein can be made without departing from the scope of the disclosure as defined in the appended claims. Thus, the disclosure covers the modifications and variations provided they come within the scope of the appended claims and the equivalents thereto.

What is claimed is:

1. A non-spectroscopic optical reader system for reading a resonant waveguide grating (RWG) biosensor, comprising:

a broadband light source that generates broadband light that is incident on the RWG biosensor and that reflects therefrom to form biosensor-reflected light having an intensity;

a first photodetector arranged to receive the biosensor-reflected light and generate a first detector signal representative of the first intensity;

an optical edge filter to filter the broadband light, the biosensor-reflected light, or both; and

a signal processor to receive at least one first detector signal and to calculate therefrom a resonant wavelength for the RWG biosensor.

2. The system of claim 1, when the optical edge filter filters the biosensor-reflected light, then further comprising:

a second photodetector, with the first and second photodetectors disposed relative to the optical edge filter to respectively receive biosensor-reflected light transmitted through and reflected by the optical edge filter,

the second photodetector generates a second detector signal representative of a second intensity, and the signal processor calculates a resonant wavelength for the RWG biosensor based on the first and second detector signals.

3. The system of claim 2, further comprising:

a system axis that normally intersects the RWG biosensor;

a beamsplitter arranged along the system axis and configured so that the broadband light incident on the RWG biosensor and biosensor reflected light travel along a portion of the system axis; and

a polarizer and quarter-wave waveplate disposed along the system axis between the beamsplitter and the RWG biosensor to optically isolate the biosensor reflected light.

4. The system of any of claims 2 or 3, wherein the signal processor:
determines first and second voltages from the first and second detector signals;
determines a difference between the first and second voltages;
determines a sum of the first and second voltages; and
divides the voltage difference by the voltage sum.
5. The system of any of claims 1 to 4, further comprising an optical fiber section that optically connects either the broadband light source or the first photodetector to the optical edge filter.
6. The system of any of claims 2 to 5, further comprising first and second optical fiber sections that respectively optically connect the optical edge filter to the first and second photodetectors.
7. A non-spectroscopic optical system for label-independent reading of a resonant-waveguide (RWG) biosensor, comprising:
a broadband light source that generates broadband light that is incident on the RWG biosensor and reflects from the RWG biosensor;
an optical edge filter to transmit and reflect respective portions of light reflected from the RWG biosensor;
first and second photodetectors disposed relative to the optical edge filter to respectively receive the transmitted and reflected light portions and to generate respective first and second signals; and
a processor connected to the first and second photodetectors to receive the first and second signals and to generate a signal representative of a resonant wavelength of the RWG biosensor.
8. The system of claim 7, wherein the processor:
determines first and second voltages from the first and second signals;
determines a difference between the first and second voltages;
determines a sum of the first and second voltages; and
divides the voltage difference by the voltage sum.

9. The system of any of claims 7 to 8, further comprising an optical fiber section that optically connects the broadband light source or the first and second photodetectors to the optical edge filter.
10. The system of any of claims 7 to 9, further comprising an optical fiber section optically connected to the broadband light source.
11. The system of claim 10, further comprising at least one additional optical fiber section to guide reflected light from the optical edge filter to the first and second photodetectors.
12. A non-spectroscopic method of label-independent reading of a resonant-waveguide (RWG) biosensor operably supported by a support structure, comprising:
 - directing broadband light to a RWG biosensor to generate reflected light;
 - transmitting the incident broadband light or the reflected light through an optical edge filter;
 - detecting the transmitted and filtered portion of the reflected light with a first photodetector to generate a first signal representative of a first intensity of the reflected light; and
 - determining a resonant wavelength based on the first signal.
13. The method of claim 12, further comprising disposing the optical edge filter in the reflected light from the RWG biosensor.
14. The method of any of claims 12 to 13, further comprising directing the broadband light to the biosensor through at least one optical fiber section.
15. The method of any of claims 12 to 14, wherein directing the broadband light comprises scanning the broadband light over the RWG biosensor.
16. The method of any of claims 12 to 15, further comprising providing the support structure as a microplate having a plurality of wells that each support a RWG biosensor to form an array of RWG biosensors.

17. The method of any of claims 12 to 16, further comprising:
reflecting at least a portion of the reflected light from the optical edge filter;
detecting the reflected portion with a second photodetector to generate a second signal representative of a second intensity; and
determining the resonant wavelength based on the first and second detector signals.
18. The method of claim 17, further comprising:
directing the incident broadband light and the reflected light along a portion of a system axis that is normal to the RWG biosensor; and
optically isolating the reflected light by passing the incident broadband light and the reflected light through a quarter-wave waveplate and a polarizer.
19. The method of any of claims 17 to 18, further comprising:
determining first and second voltages from the first and second signals;
determining a difference between the first and second voltages;
determining a sum of the first and second voltages; and
dividing the voltage difference by the voltage sum.
20. The method of any of claims 17 to 19, wherein the first and second photodetectors respectively comprise first and second image sensors, and respectively detecting the transmitted and reflected light portions with the first and second image sensors.
21. The method of any of claims 17 to 20, wherein the first and second photodetectors comprise at least one charge-coupled device (CCD).
22. The method of any of claims 17 to 21, wherein the first and second signals are representative of first and second voltages, and further comprising processing the first and second signals with a signal processor to calculate the resonant wavelength based on the first and second voltages.

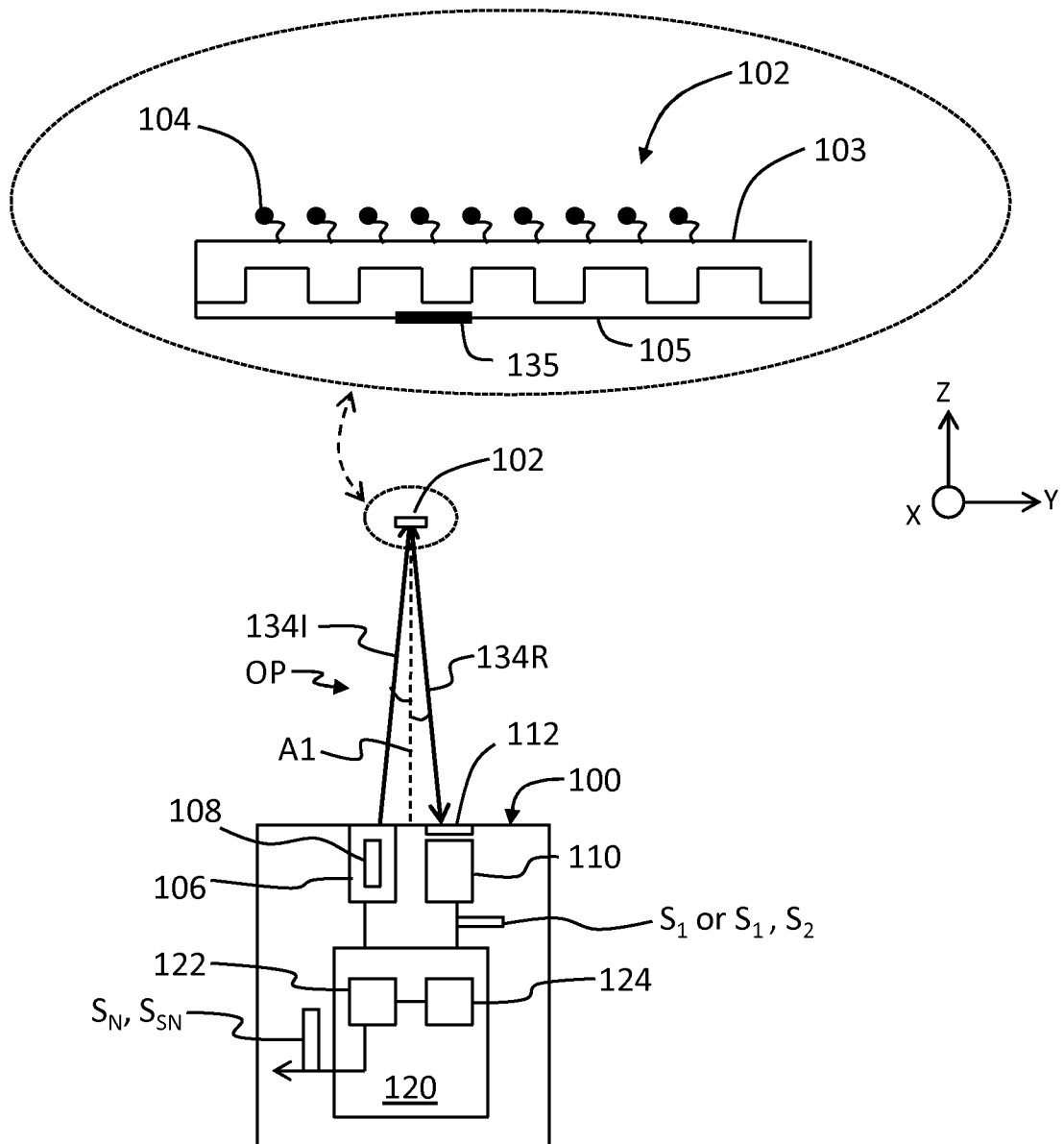


FIG. 1

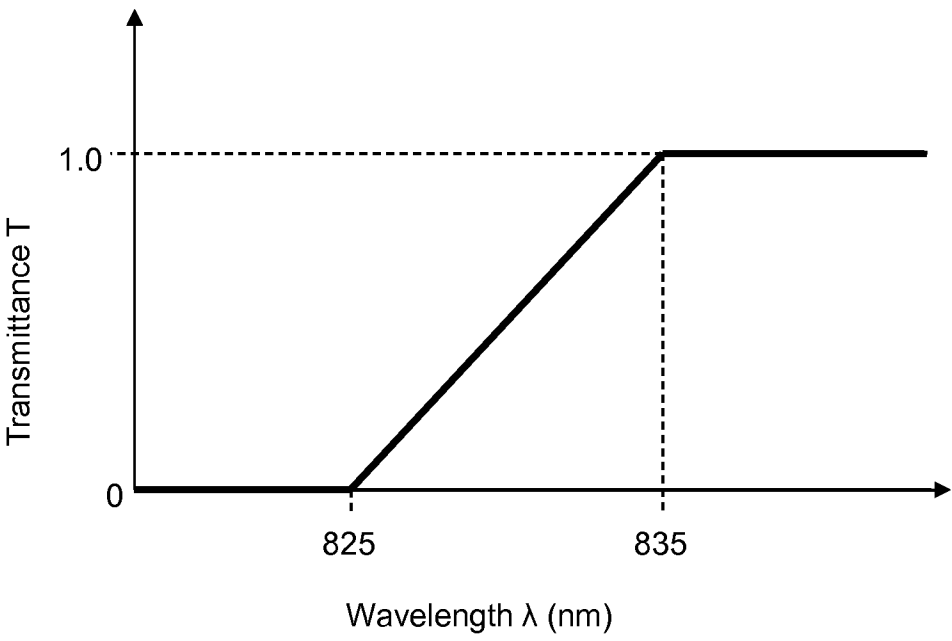


FIG. 2

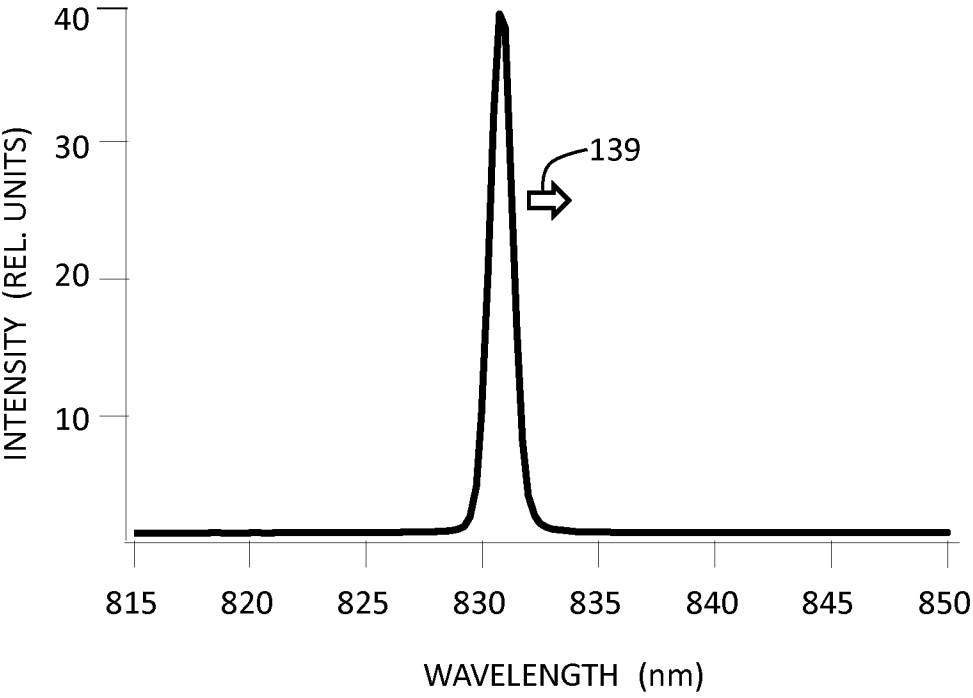


FIG. 3

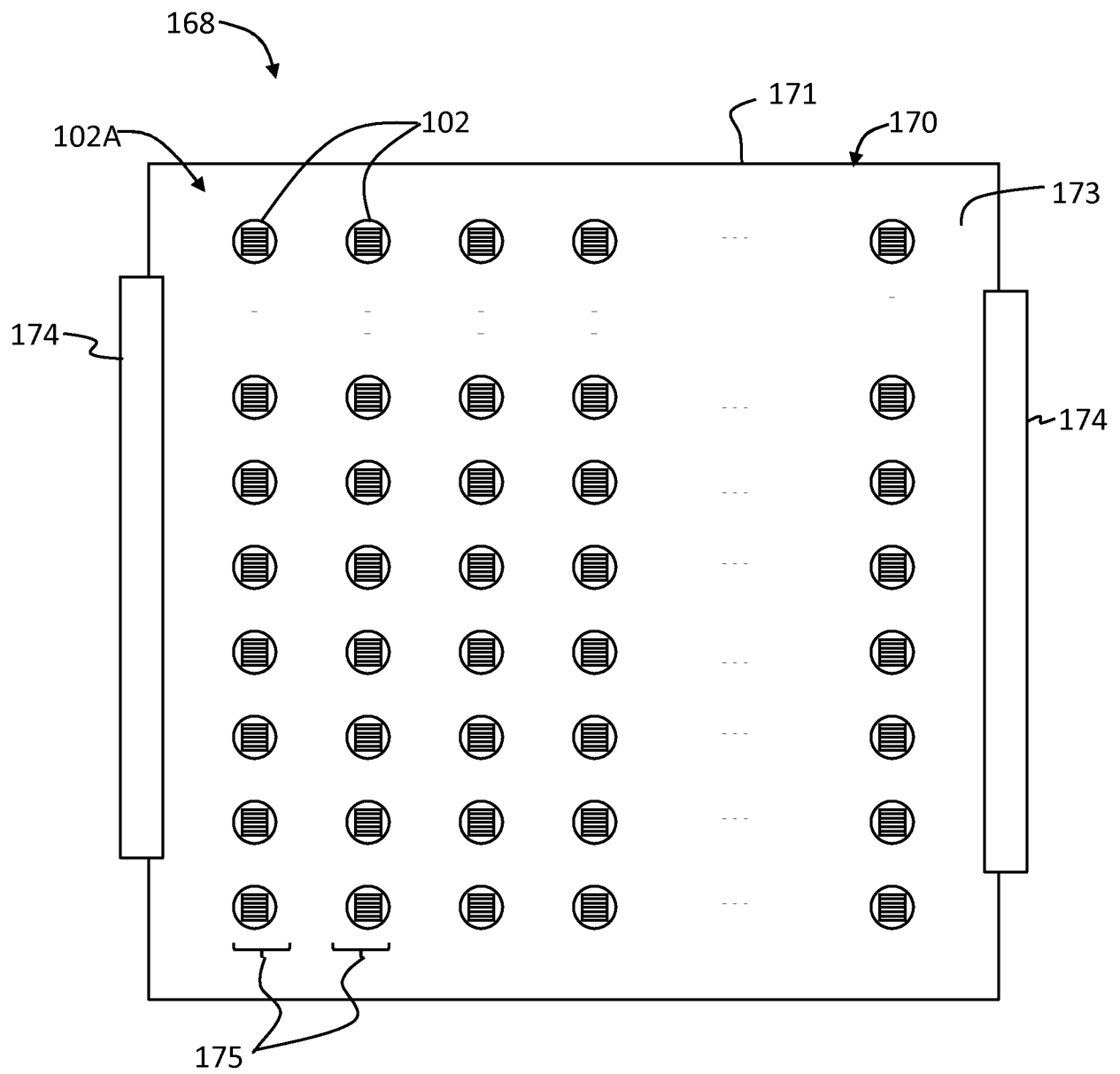
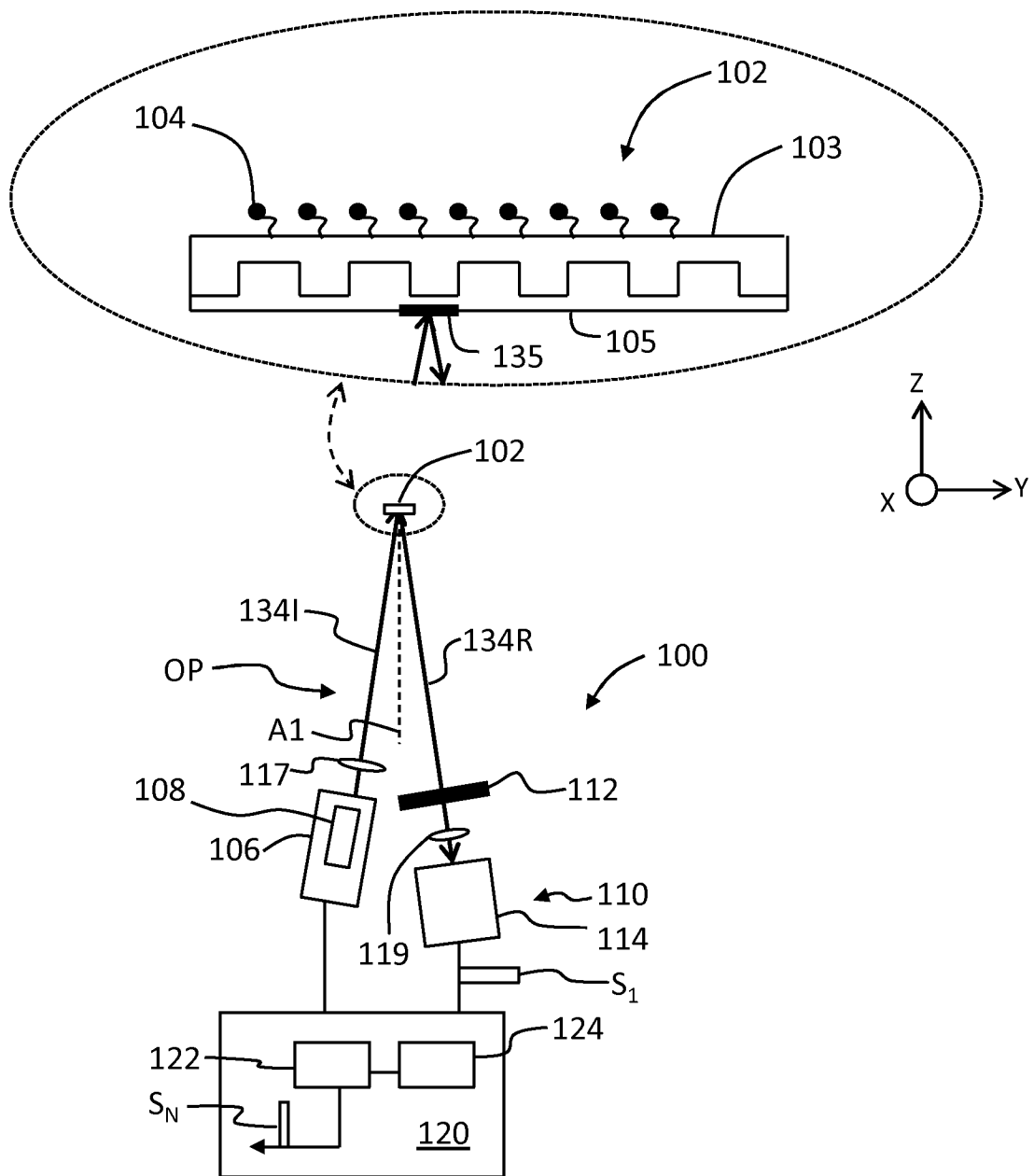


FIG. 4

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**FIG. 5A**

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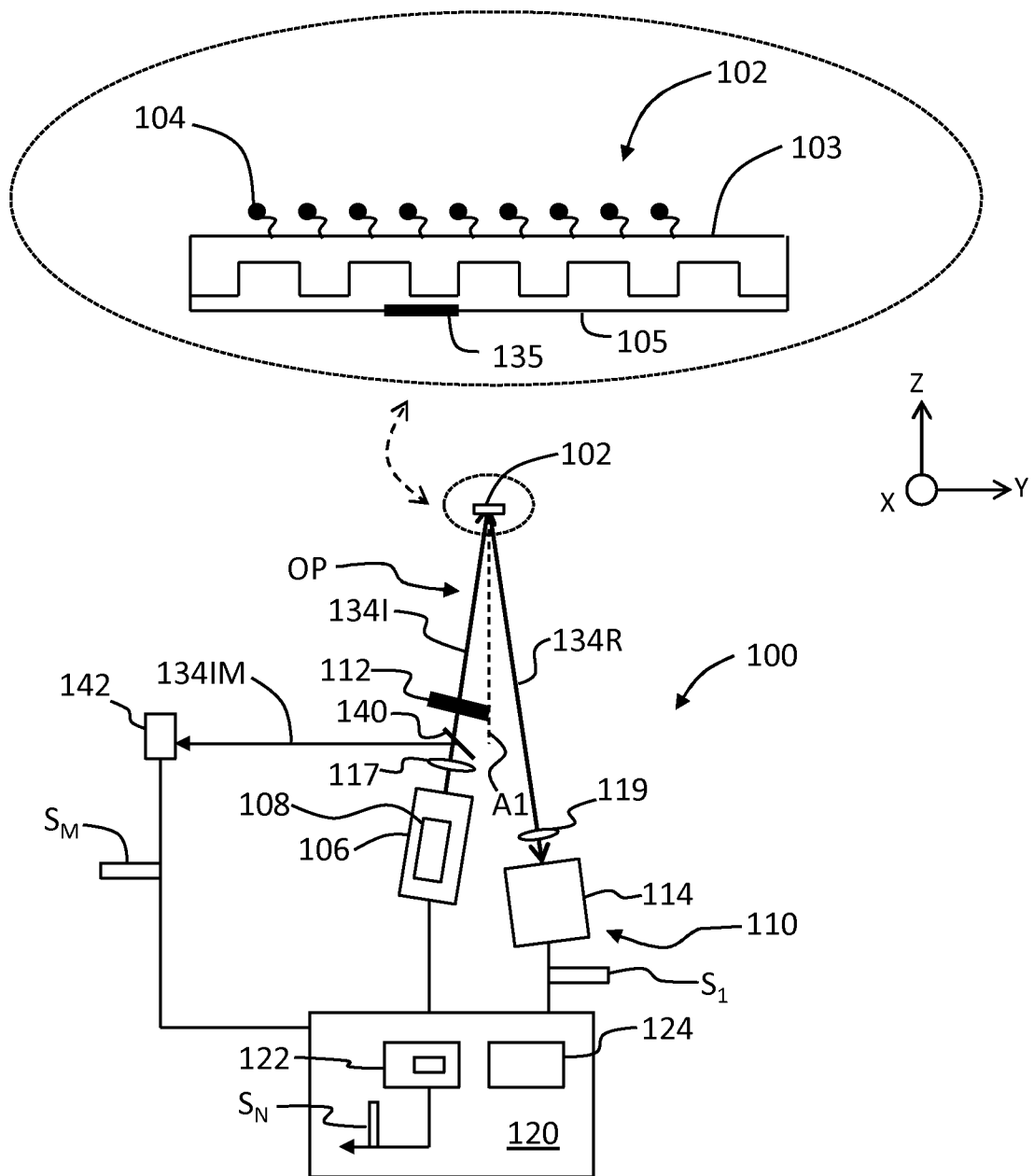
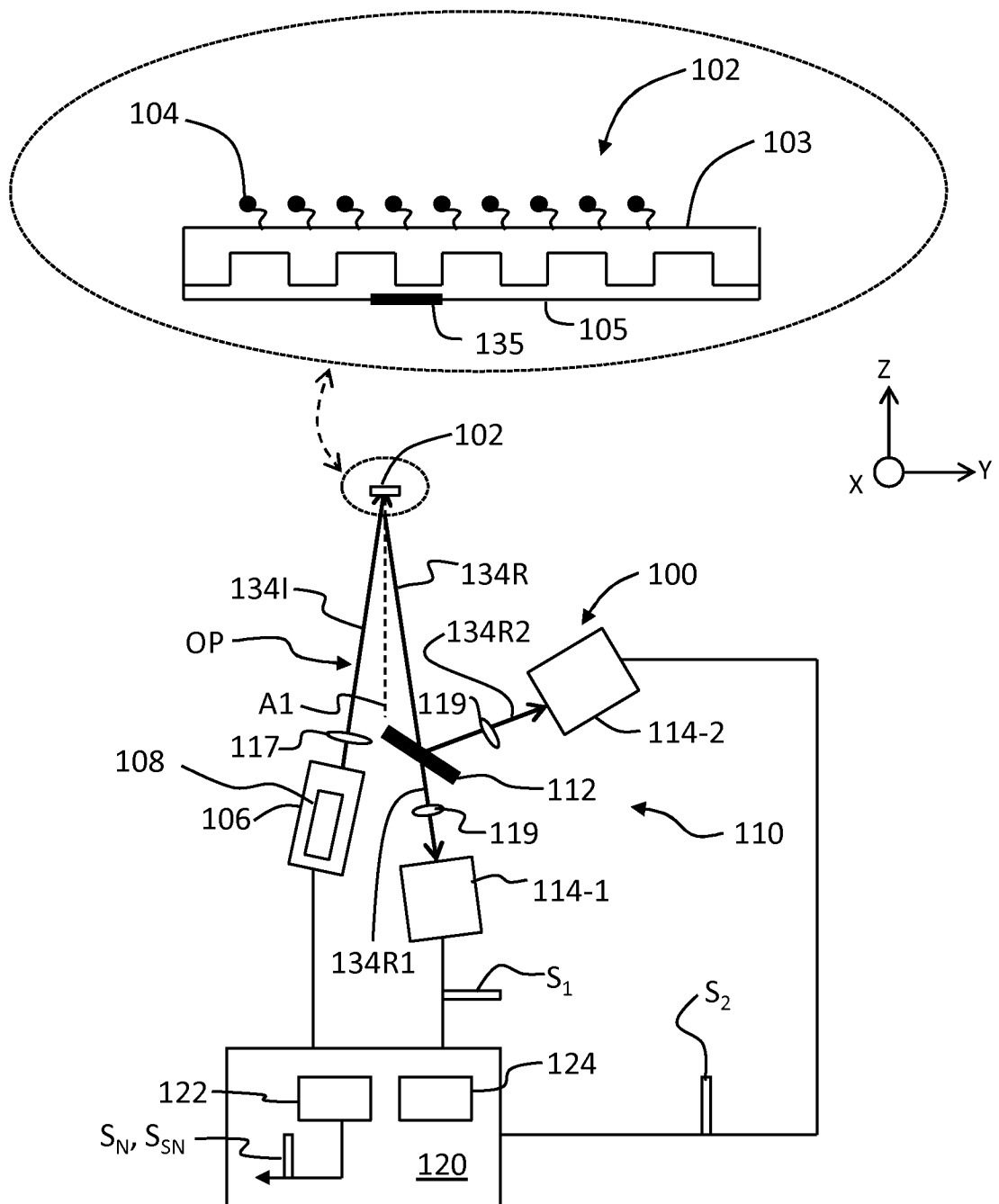


FIG. 5B

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**FIG. 5C**

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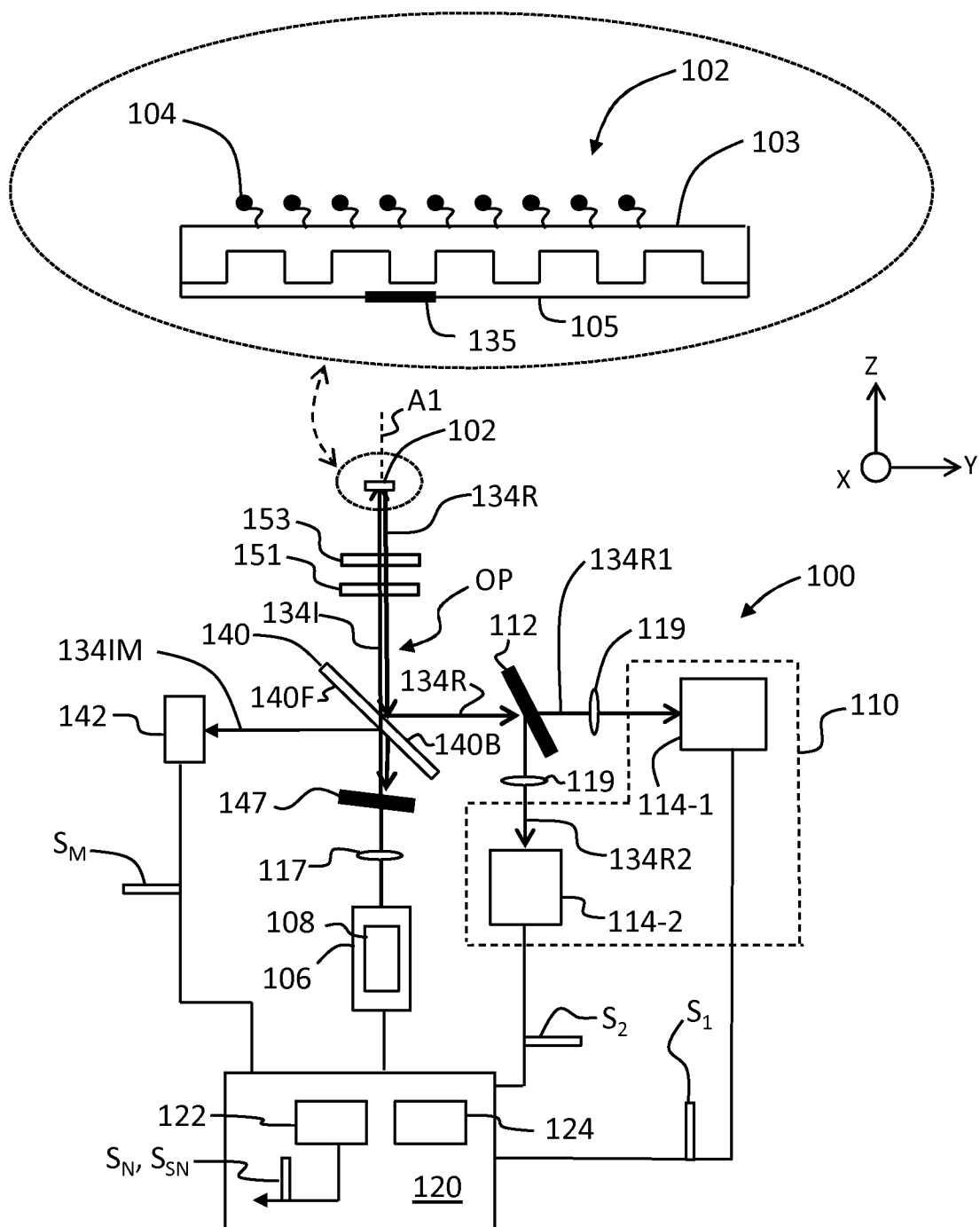


FIG. 5D

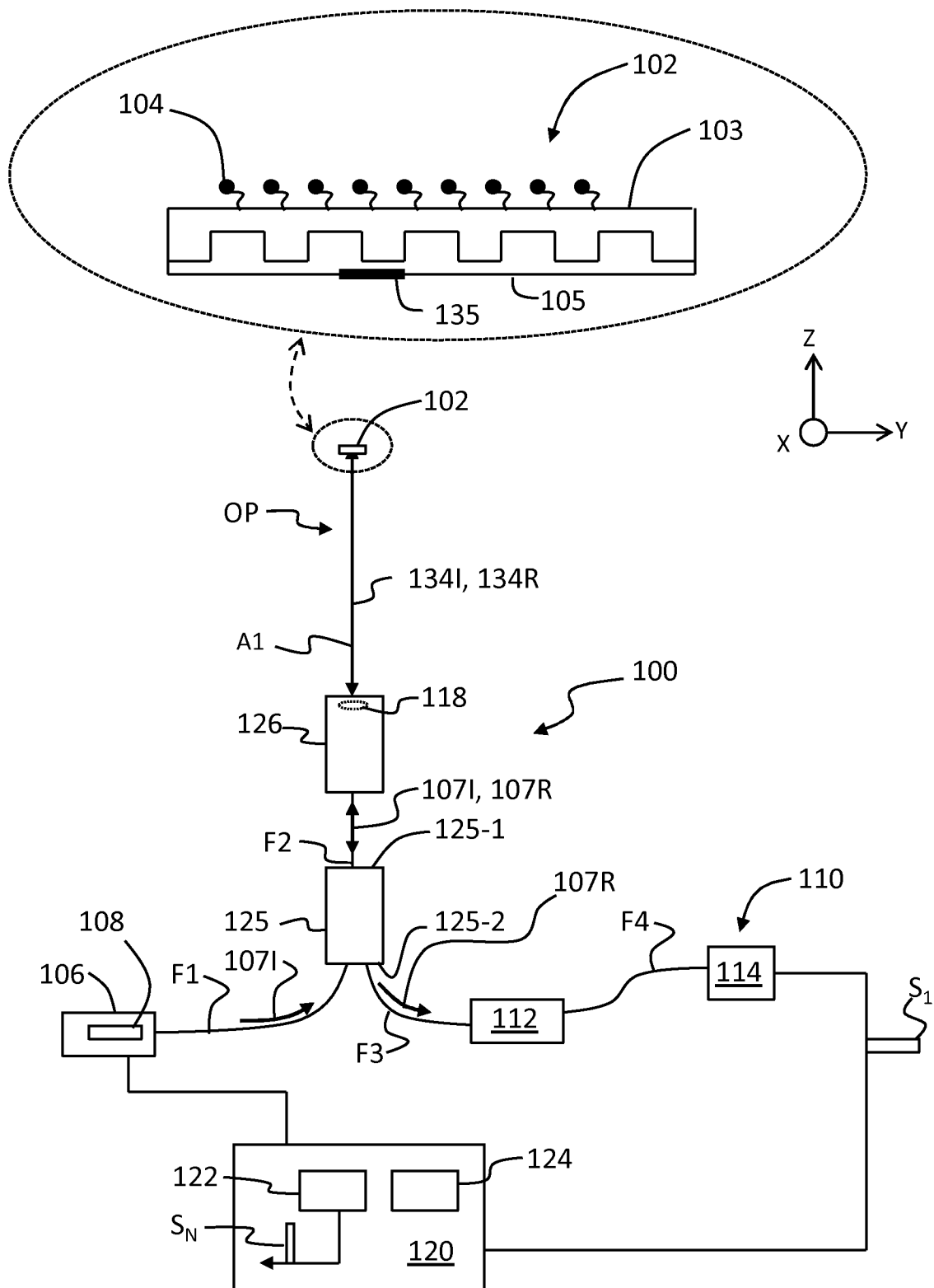


FIG. 6A

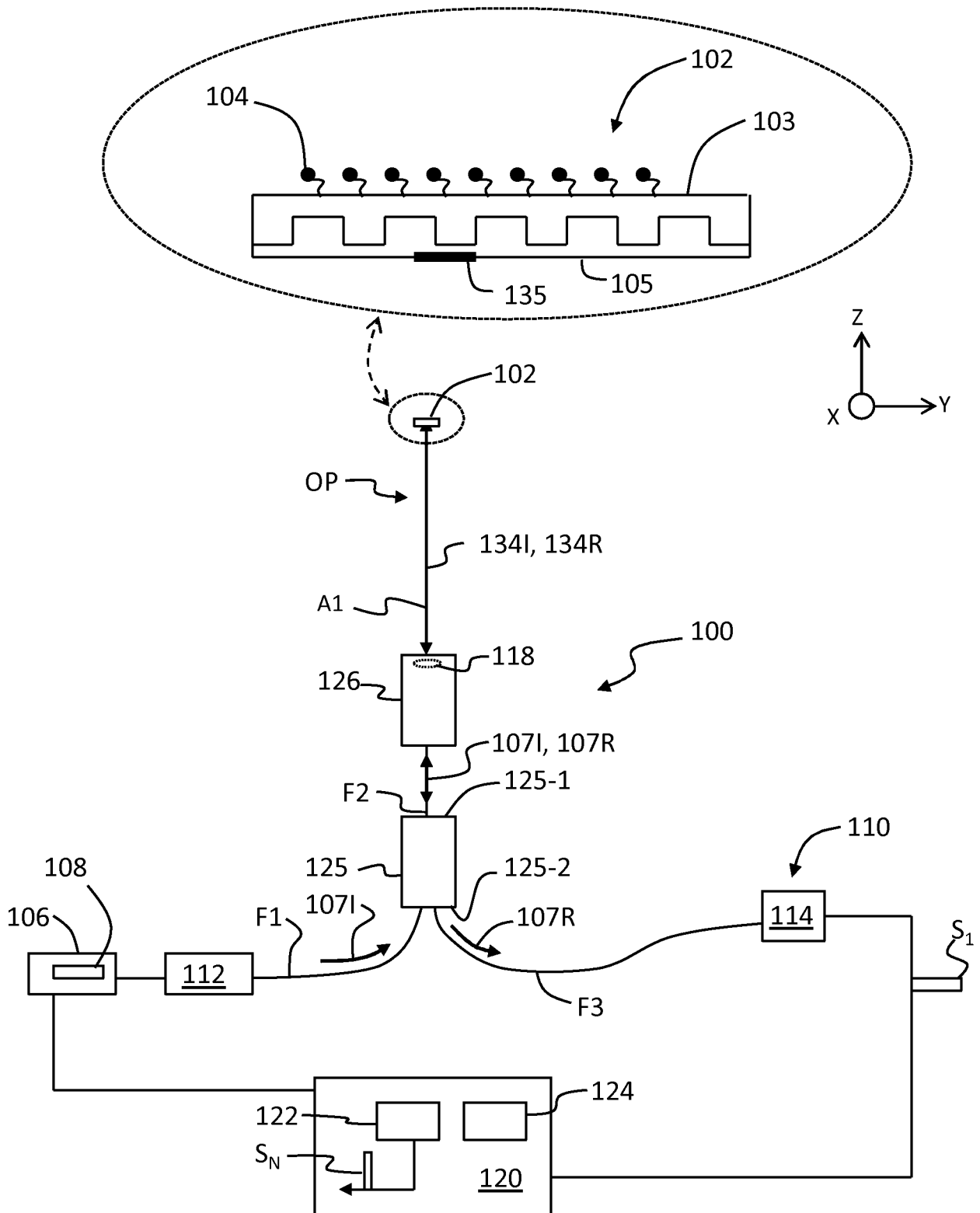


FIG. 6B

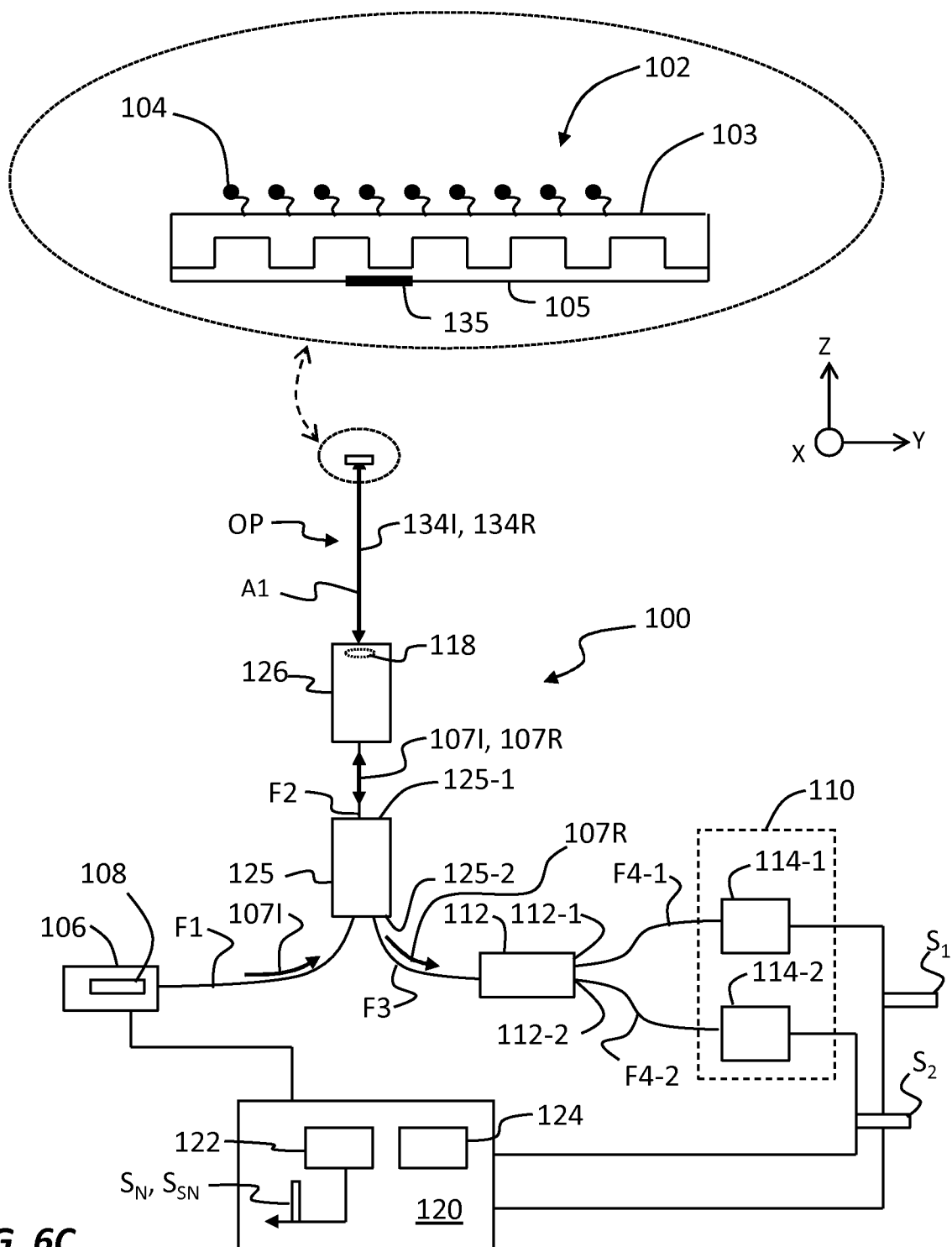
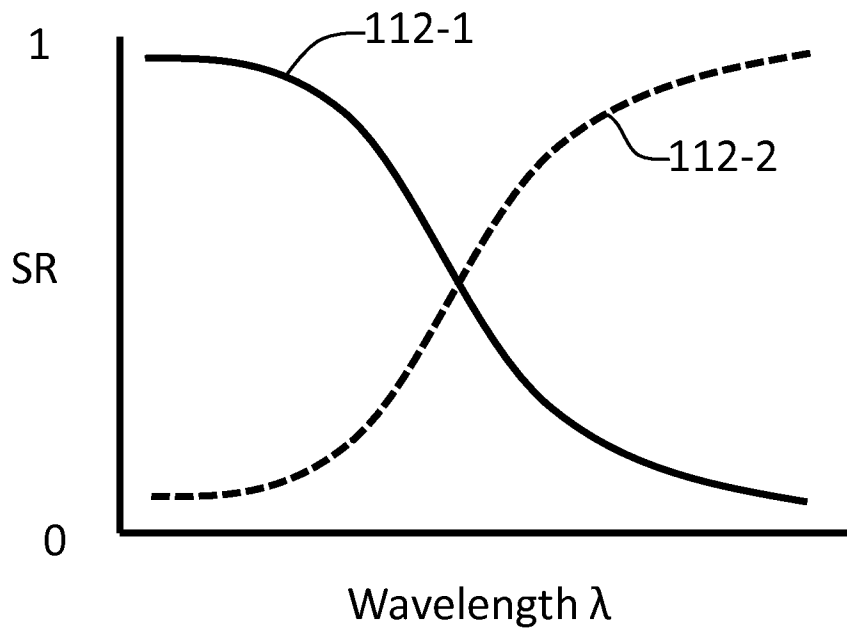
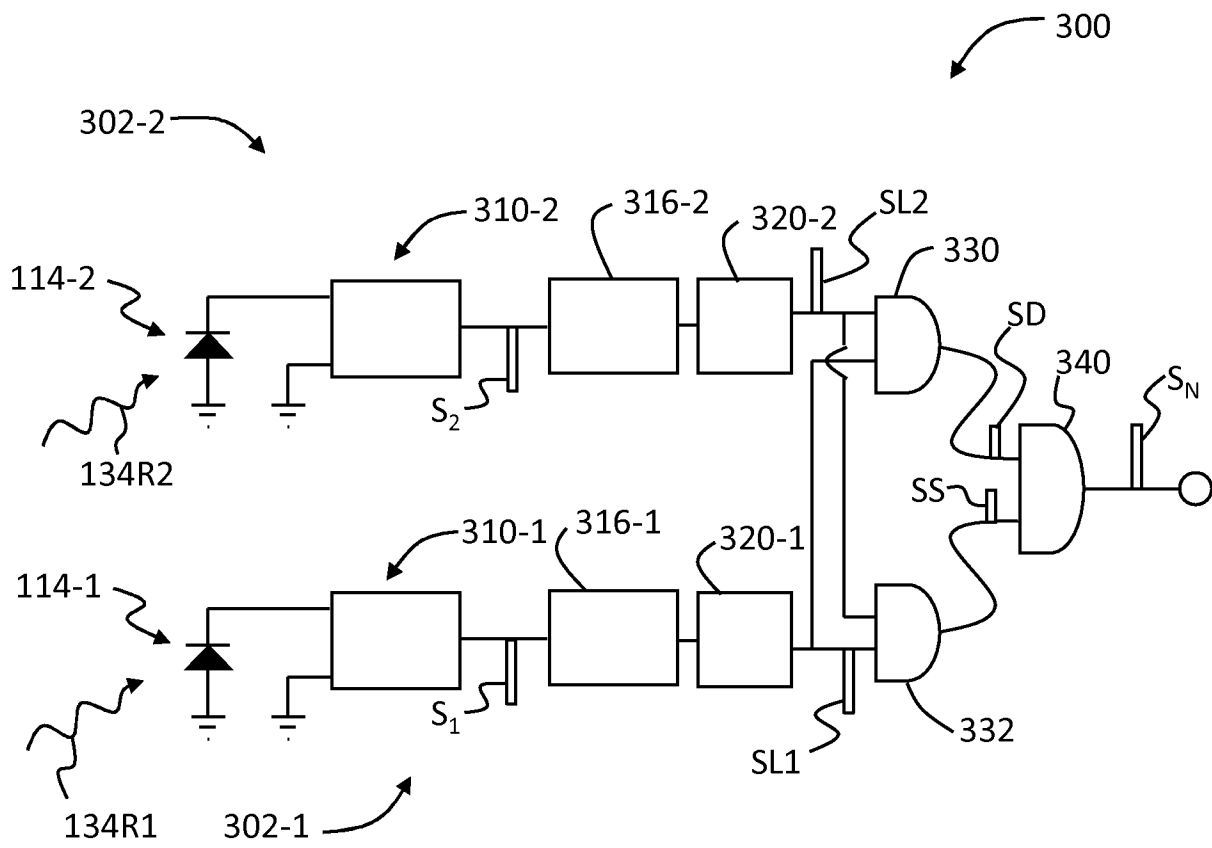


FIG. 6C

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**FIG. 7**

**FIG. 9**

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/056112

A. CLASSIFICATION OF SUBJECT MATTER

INV. G01N21/55 G01N21/77
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G01N

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

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

EPO-Internal, COMPENDEX, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/141611 A1 (FRUTOS ANTHONY G [US] ET AL) 29 June 2006 (2006-06-29) cited in the application paragraphs [0017], [0024], [0025], [0027]; figures 1,5 -----	1,5, 12-16
Y	Y.-J. RAO: "In-fibre Bragg grating sensors", MEAS. SCI. TECHNOL., vol. 8, no. 4, 1 April 2007 (2007-04-01), pages 355-375, XP002618866, DOI: 10.1088/0957-0233/8/4/002 figures 8a,10a paragraphs [04.1], [4.2.1] -----	1,5, 12-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/056112

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006141611 A1	29-06-2006	US 2006205058 A1 WO 2006071992 A1	14-09-2006 06-07-2006
