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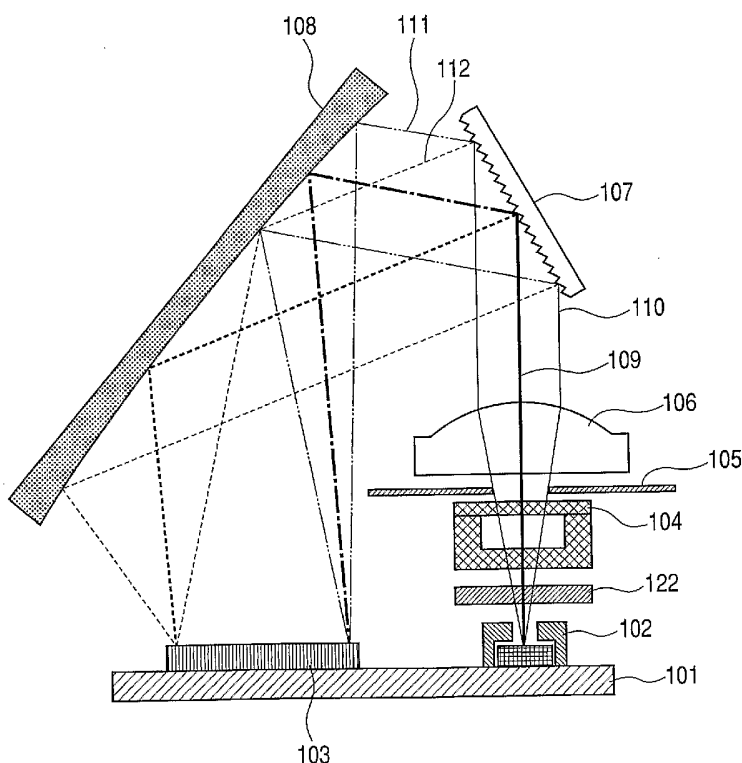
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(54) Title: DEVICE AND METHOD FOR ACQUIRING INFORMATION ON OBJECTIVE SUBSTANCE TO BE DETECTED BY DETECTING A CHANGE OF WAVELENGTH CHARACTERISTICS ON THE OPTICAL TRANSMITTANCE



(57) Abstract: An information-acquiring device for acquiring information on an objective substance to be detected, which is provided with a sensing element (104) that has a surface capable of fixing the objective substance to be detected thereon, and makes applied light change its wavelength characteristics in response to the fixed state of the objective substance to be detected onto the surface, a light source (102), and light-receiving means (103) for receiving light (111, 112) emitted from the light source (102) through the sensing element (104), has the light-receiving means (103) and the light source (102) arranged on the same substrate (101) so that the light which has been emitted from the light source (102) and has been transmitted through the sensing element (104) can be led to the light-receiving means (103), and has means (107) for varying the wavelength regions of each light incident on each of a plurality of the light-receiving means (103) installed in an optical path from the light source (102) to the light-receiving means (103).



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DESCRIPTION

DEVICE AND METHOD FOR ACQUIRING INFORMATION ON OBJECTIVE SUBSTANCE TO BE
DETECTED BY DETECTING A CHANGE OF WAVELENGTH CHARACTERISTICS ON THE OPTICAL
TRANSMITTANCE

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TECHNICAL FIELD

The present invention relates to a device for
acquiring information on an objective substance to be
detected by detecting a change of wavelength
10 characteristics on an optical transmittance in a
system containing the objective substance to be
detected, and to a method for acquiring the
information on the objective substance to be detected
by using the device.

15

BACKGROUND ART

In recent years, with increasing awareness of
health issues, environmental issues and security
issues, techniques for detecting trace amounts of
20 biological substances and chemical substances
relating to these issues have been demanded. As the
techniques for detecting these objective substances
to be detected, many techniques are suggested which
measure the change of optical properties of a liquid
25 specimen caused by the interaction of the specimen
including the substances to be detected with a
reagent or a sensor element. As for the methods for

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optically detecting these substances to be detected, many techniques of detecting the change of spectrum are proposed and/or developed as followings:

(1) a technique for detecting the change of an
5 absorption spectrum caused by a reaction product produced through a chemical reaction including an enzyme reaction, or detecting the change of an absorbance for a particular wavelength; and

(2) a technique for detecting the change of the
10 absorption spectrum or the absorbance for the particular wavelength by an agglomerate, through forming the agglomerate of fine particles through the substances to be detected, with the use of fine particles which immobilize a capturing body
15 specifically coupled with the substances to be detected thereon.

These techniques acquire information by measuring spectrum with the use of a spectroscope, and accordingly have a problem of needing a period of
20 time for scanning a necessary region of wavelengths. The problem can be improved by using a polychromator and an arrayed type detecting element, which eliminating the need for scanning the wavelengths. However, the device has constraint in the disposition
25 of a light source, a sensing part for introducing a specimen and treating it for measurement, the polychromator and a detecting element for detecting

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the optical properties, and leaves the problem unsolved that the device is hardly miniaturized.

In addition, there is a sensor by using a surface plasmon resonance technique as is described in USP 6,183,696, as an example of solving the above described miniaturization problem by adopting a detecting technique without depending on the change of an absorption spectrum. The invention according to USP 6,183,696 has a characteristic in solving a problem of a mechanism for detecting a resonance angle, which has been a problem of the conventional surface plasmon resonance technique, by diffusive incident light and adopting a photodiode array. An advantage of this sensor is a point of simplifying a configuration of a detecting device, because of having a light-emitting element and a light-receiving element formed on the same plane. However, the device needs a length corresponding to a resonance angle in a contacting part with a specimen, or equivalently, needs a large size of a sensor surface for detecting one objective substance to be detected, and accordingly has a constraint for simultaneously detecting a plurality of the substances to be detected.

As a technique of solving the problem of a sensor area for detecting the above described one objective substance to be detected, among techniques

using plasmon resonance, Japanese Patent No. 3452837 describes a sensor with the use of a localized plasmon resonance of metallic nanoparticles. A sensor element with the use of the localized plasmon resonance has an advantage of needing a very small area for a detecting element because of using metallic nanoparticles. However, the sensor element needs to detect a transmission spectrum or a reflection spectrum, and accordingly still leaves the same problem as in the above described technique of detecting the spectrum.

In addition, EP 1157266A1 discloses a sensor provided with a sensor chip having sensor chip units integrated crosswise and a phototransducer having the arrays of the phototransducer integrated crosswise, as a compact surface plasmon resonance sensor. Figure 4 (a) shows a disclosed sensor having a light source and a detecting element array arranged on the same substrate, and a perception region of a sensor chip and a diffraction grating installed in an optical path between the light source and the detecting element array. The sensor disclosed here is persistently the surface plasmon sensor which reflects an emitted light from a light source by the sensor chip and introduces the reflected light to the detecting element array. In addition, the document does not describe a method of detecting a light which

has been transmitted through the sensor chip and an application to the localized plasmon resonance.

DISCLOSURE OF THE INVENTION

5 The present invention is designed for miniaturizing both a sensing element portion and a detecting device, in a technique for detecting an objective substance to be detected with the use of spectrum characteristics for wavelengths.

10 Furthermore, the present invention provides a device for acquiring information on the objective substance to be detected, which is suitable for using localized plasmon resonance.

 According to an aspect of the present invention,

15 there is provided an information-acquiring device for acquiring information as to an objective substance to be detected, comprising a sensing element which has a surface capable of fixing the objective substance to be detected thereon and makes an applied light change

20 its wavelength characteristics in response to a fixed state of the objective substance to be detected onto the surface, a light source, and a plurality of light-receiving means for receiving light emitted from the light source through the sensing element,

25 wherein

 the device has the light-receiving means and the light source arranged on the same substrate, the

light emitted from the light source and transmitted through the sensing element is led to the light-receiving means, and

a means for varying the wavelength regions of
5 each light incident on each of a plurality of the light-receiving means is installed in an optical path from the light source to the light-receiving means.

The means for varying the wavelength region of each light incident on each of a plurality of the
10 light-receiving means is preferably a spectral means.

The sensing element may be arranged in a light path between the spectral means and the light source.

Alternatively, the sensing element may be arranged in a light path between the spectral means
15 and a plurality of the light-receiving means.

The information-acquiring device may have further a reflecting means for leading light from the light source to the light-receiving means through the sensing element. The reflecting means may be made of
20 a concave mirror which focuses spectral light made by the spectral means on the light-receiving means.

The device may have a plurality of the light sources, enables each of a plurality of the light sources to selectively emit light by using a means
25 for switching the light source and varies the wavelength of the light to be received by the light-receiving means by using the spectral means.

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The means for varying the wavelength region of each light incident on each of a plurality of the light-receiving means may be an optical filter.

The device may acquire information on the
5 objective substance to be detected by using plasmon resonance. The sensing element preferably has a surface which can fix a metallic nanoparticle capable of capturing the objective substance to be detected thereon, and the plasmon resonance is a localized
10 plasmon occurring around the metallic nanoparticle fixed on the surface.

The light source and the light-receiving means may be formed on the same semiconductor substrate.

According to another aspect of the present
15 invention, there is provided an information-acquiring method for acquiring information on an objective substance to be detected in a specimen by using a sensing element characterized in that the method comprises the steps of:

20 preparing the sensing element having the objective substance to be detected fixed thereon;

when light emitted from the light source illuminates the sensing element having the objective substance to be detected fixed thereon, and the
25 transmitted light of emitted light is led to a plurality of the light-receiving means placed on the same substrate as the light source is placed, varying

the wavelength of each light to be received by each
of a plurality of light-receiving means, through a
wavelength-varying means installed in an optical path
from a light source to the light-receiving means, and
5 acquiring the wavelength characteristics on the
transmittance of every wavelength of the light which
has passed through the sensing element and has been
received by each light-receiving means; and

determining the coupled amount of the objective
10 substance to be detected which has been coupled with
the sensing element, on the basis of the wavelength
characteristics.

The wavelengths of light to be received may be
varied by a spectral means. In the method, a
15 plurality of the light sources may be prepared, and
the wavelengths of the light to be received by the
light-receiving means are varied according to the
positions of a plurality of the light sources.

In the method for acquiring information on the
20 objective substance to be detected, the wavelength of
the light to be received may be varied by an optical
filter.

The present invention provides a device which
acquires information on an objective substance to be
25 detected by using a transmitted light that has been
transmitted through a sensing element, and which is
suitable for a sensor that uses localized plasmon

resonance. The device can be miniaturized because of arranging a light source and light-receiving means on the same substrate, and installing means for changing a wavelength region of a light incident on each of a plurality of light-receiving means in an optical path
5 from the light source to the light-receiving means. Furthermore, the device does not need a mechanical drive in acquiring a wavelength spectrum, and accordingly can shorten a period of time necessary
10 for acquiring the spectrum, or equivalently, an analysis period of time. In addition, the device arranges electric elements of the light source and the light-receiving means on a single substrate, and accordingly simplifies an electric interface and a
15 device configuration. Furthermore, the device has improved workability when performing maintenance.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic block diagram showing
20 one example of an information-acquiring device;

Figure 2 is a schematic block diagram showing one example of an information-acquiring device;

Figure 3 is a schematic block diagram showing one example of an information-acquiring device;

25 Figure 4 is a schematic block diagram showing one example of an information-acquiring device;

Figure 5 is a schematic block diagram showing

one example of an information-acquiring device;

Figure 6 is a schematic block diagram showing one example of an information-acquiring device;

Figure 7 is a schematic block diagram showing
5 one example of an information-acquiring device;

Figure 8 is a schematic block diagram showing wavelength characteristics of a transmitted light through a filter;

Figure 9 is a schematic block diagram showing
10 one example of an information-acquiring device;

Figures 10A, 10B, 10C and 10D are views showing a sensing element using localized plasmon resonance;

Figure 11 is a view showing a sensing element using an enzyme label;

15 Figure 12 is a view showing a sensing element using a fluorescent label;

Figure 13 is a view showing a spectral change caused by localized plasmon resonance; and

Figure 14 is a block diagram showing one
20 example of a configuration of a device according to the present invention.

In each drawing, the same reference characters are used for the same parts.

25 BEST MODE FOR CARRYING OUT THE INVENTION

Summaries of an information-acquiring device and an information-acquiring method for acquiring

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information on an objective substance to be detected provided by the present invention will be now described referring to Figures 1, 2, 4 and 7.

A sensing element 104 has a surface capable of
5 fixing the objective substance to be detected thereon. The objective substance to be detected is introduced into the sensing element mainly in a form of a liquid specimen containing the substance, and is fixed to the surface of the sensing element. The substances
10 to be detected are roughly classified into non-biological and biological substances. The non-biological substance among the objective substances to be detected, which increase an industrial utility value of the present invention, include PCB, dioxins
15 and endocrine disrupting chemicals so-called environmental hormones. The biological substances include nucleic acid, protein, sugar chain, lipid and complexes thereof, such as deoxyribonucleic acid, ribonucleic acid, an aptamer, a gene, a chromosome, a
20 cell membrane, a virus, an antigen, an antibody, a lectin, a hapten, a hormone, a receptor, an enzyme, a peptide, a sphingoglycolipid and a sphingolipid. Furthermore, bacteria and cells themselves can be the biological substances to be detected by the device
25 according to the present invention.

A light source 102 emits a light for illuminating a sensing element; of which the

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wavelength characteristics change corresponding to a captured state of the objective substance to be detected. The emitted light is transmitted through the sensing element, and is led to a light-receiving means 103 installed on the same substrate as the light source.

Means for varying each wavelength region (hereafter called "wavelength-varying means") is installed in a light path between the light source and the light-receiving means. The wavelength-varying means varies each wavelength or wavelength region of the light incident on each of the light-receiving means 103. By varying the wavelength, the sensing element can determine the transmittance of the light in each wavelength or wavelength region. Specifically, the present invention provides a device which can know the presence or absence of absorption in the predetermined wavelength regions and an absorbed amount, by making the wavelength-varying means divide a wavelength region relating to a wavelength absorption spectrum, and making a plurality of the light-receiving means receive a plurality of the obtained wavelengths or wavelength regions.

In the present invention, there are two aspects of arranging the sensing element 104 in the light path from the light source 102 to spectral means 107

as shown in Figure 1, and of arranging the sensing element 104 in the light path from spectral means 108 to the light-receiving means 103 as shown in Figure 2.

Aspects according to the present invention will
5 be now described under the sensing element and an optical configuration except it.

(Sensing Element)

It is known that when a metallic nanoparticle exists on the surface of a transparent substrate, an
10 applied light onto the substrate is greatly absorbed in a particular wavelength due to localized plasmon resonance. The absorbed peak wavelength changes according to a refractive index around the metallic nanoparticle.

15 When a metallic nanoparticle changes the surface condition through capturing a substance to be detected onto its surface, the refractive index around the metallic nanoparticle is changed, and an absorbed peak wavelength of the applied light is
20 shifted. By detecting the shifted amount, a sensing element can determine the presence or absence and the captured amount of the substance to be detected.

Figures 10A to 10D show an example of a sensing element with the use of a localized plasmon resonance
25 technique using the metallic nanoparticle. The sensing element is composed of: a main body consisting of a substrate 401 having a groove 403 of

a channel for passing a liquid specimen formed thereon and a lid 404 of the groove; and the metallic nanoparticle 402 fixed in the main body.

Figure 10A is a side view showing the state of the metallic nanoparticle fixed in the main body of the sensing element. Figures 10B and 10C show the state of a metallic nanoparticle 402 fixed on the bottom face of a groove 403 of a substrate 401. However, an aspect of fixing the metal nanoparticle not on the groove surface but on the surface which composes the channel of a channel lid 404 is acceptable. The substrate 401 and the lid 404 are preferably made of an optically transparent material, but are not always required to be transparent and have to have the surface which reflects an enough light for measurement when used in a configuration of detecting a reflected light.

A metallic element constituting a metallic nanoparticle 402 may be any element as long as it can cause a localized plasmon resonance phenomenon, but is preferably gold or silver. Figure 10D is an enlarged view showing the state of the metallic nanoparticle fixed in the main body of the sensing element. A capturing body 405 which forms a specific coupled pair with the objective substance to be detected, such as antigen/antibody, complementary DNA, receptor/ligand and enzyme/substrate, is immobilized

on the metallic nanoparticle 402, and the substance 406 to be detected is captured by the capturing body 405.

Figure 11 shows one example of a detecting
5 technique using an enzyme label. The capturing body 604 which specifically is coupled to the objective substance to be detected is prepared, and is labeled with an enzyme 605. On the other hand, the capturing body 405 is immobilized on a substrate 601 such as
10 substrate 401 and lid 404 in Figure 10C with a usual method. The sensing element makes the capturing body capture the objective substance to be detected, and then makes the objective substance coupled with the labeled capturing body 604. The sensing element
15 reacts the enzyme 605 with an enzyme substrate 606 corresponding to the enzyme 605 to produce an enzyme reaction product 607.

The above described components which can be adopted in the example of a detecting technique will
20 be described below. A substrate 601 comprises a material transparent sufficient for measuring a transmitting light in the case of measuring the transmitting light, and a material having a reflective face sufficient for measuring a reflective
25 light in the case of measuring the reflective light. A capturing body 405 and 604 includes an antibody which is specifically coupled with the objective

substance to be detected. An enzyme 605 includes horseradish peroxidase, alkaline phosphatase and β -galactosidase, but is not limited to only the enzyme as long as the enzyme can produce an enzyme reaction product 607 which has optical characteristics of having absorption in a particular wavelength, for instance, 491 nm. An enzyme substrate 606 to be used can be a substance which is usually used in combination with these enzymes. The substance is, for instance, 1,2-phenylenediamine. When the enzyme reaction product has an optical characteristic of having absorption in a particular wavelength, the absorption spectrum of a transmitted light has the characteristic originated in the enzyme reaction product. By using the characteristic, the information-acquiring device can acquire the fixed state of the objective substance to be detected on the surface of the sensing element, or equivalently, the presence or absence and the amount of the objective substance to be detected on the surface of the sensing element in more detail or more sensitively.

Figure 12 shows a detecting technique with the use of a fluorescence label. This technique employs a capturing body 604 indicated with a fluorescent dye 705, in the place of the capturing body 604 indicated with an enzyme 605 used in a detecting technique with

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the use of the enzyme label as is described in the example in Figure 11. As the fluorescent dye, fluorescein isothiocyanate, Cy3 and Cy5 are often used. The fluorescent dye 705 absorbs exciting light 706 and emits fluorescent light 707. The fluorescence 707 changes the spectrum intensity of the light which the sensing element receives, so that the sensing element can determine the fixed state of the objective substance to be detected on the surface of the sensing element, or equivalently, the presence or absence and the fixed amount of the objective substance to be detected on the surface. In the above detecting technique, a wavelength-limiting light filter for blocking the exciting light may be arranged at a suitable position, so that the exciting light 706 cannot affect a light-receiving element 103.

(Optical Configuration)

An optical configuration will be now described with reference to Figure 1.

A substrate 101 may be a printed circuit board or a semiconductor substrate. A preferable substrate material includes Si (silicon) and GaAs (gallium arsenic).

A light Source 102 is installed on the substrate 101. The light source 102 is not particularly limited as long as it emits a sufficient quantity of light in an objective wavelength region,

but a light-emitting element, particularly, a light emitting diode and a semiconductor laser are preferable. Further preferable is a LED made of a compound containing at least one of Ga (gallium), N
5 (nitrogen), In (indium), Al (aluminum) and P (phosphorus).

Light 109 emitted from a light source 102 reaches light-receiving means 103 via wavelength-varying means. Usable wavelength-varying means is
10 mainly conventional spectral means such as a diffraction grating. The examples of such spectral means include a transmission grating, a reflecting diffraction grating and a prism. Figure 1 shows an example using the reflecting diffraction grating.

15 Though depending on a diffraction efficiency, it is preferable to use a blaze type reflecting diffraction grating, and use the free spectral region of primary diffraction rays for detection. In addition, it is more preferable to place a filter for limiting
20 wavelengths, which is not shown in Figure 1, above the light source, so as to avoid stray light originating in light having wavelengths other than the free spectrum. The device shown in Figure 1 further employs a concave mirror 108 as wavelength-
25 varying means, which leads/focuses spectral light reflected by a diffraction grating 107 to/on a light-receiving element 103. The concave mirror narrows a

detecting wavelength range for every light-receiving means, and improves the overall accuracy of spectrometry. The device shown in Figure 1 also can employ a concave diffraction grating in place of the concave mirror 108 and a plane mirror in place of a planar plane diffraction grating 107, which configuration can be adopted as one aspect according to the present invention. The power of the concave diffraction grating 107 is preferably set so that the spectral light reflected by the concave diffraction grating can form an image on the light-receiving element 103.

Light-receiving means 103 has light-receiving elements. More specifically, the light-receiving element is preferably a photodiode made of Si when a receiving light has wavelengths in a visible light region, a photodiode made of GaAsP when having only to detect wavelengths only in a blue region out of a visible light region, and a photodiode made of InGaAs when having only to detect wavelengths only in an infrared region. In addition, the light-receiving means 103 has preferably a configuration in which light-receiving elements are arrayed. The preferable combination of the materials of a substrate 101, a light-emitting element 102 and the light-receiving means 103 should be selected in accordance with an operating wavelength region, but the substrate 101 is

preferably a Si substrate from the viewpoint of a cost.

When means for each varying the wavelength regions of light incident on each of a plurality of the light-receiving means is noted, an information-acquiring device according to the present invention can be divided into two aspects of (1) using spectral means (Figures 1, 2, 3, 4 and 5) and (2) using an optical filter (Figures 7 and 9), from the viewpoint of the above means.

(1) First of all, an aspect of using spectral means will be described. The aspect can be divided into two aspects of (i) an aspect having one light source (Figures 1, 2, 3, 7 and 9) and (ii) an aspect of switching a plurality of the light sources (Figures 4 and 5).

(i) Aspect having one light source

In an aspect described here, light emitted from one light source is divided into several wavelength ranges by spectral means, and a plurality of light-receiving means receive each divided light having each different wavelength range.

Light emitted from a light source 102, as shown in Figures 1, 2, 7 and 9, is narrowed by a light shield 105, is converted to parallel rays by a collimating lens 106, and reaches light-receiving means 103 via the above described wavelength-varying

means and sensing element 104 according to the present invention. The light-receiving means 103 is a sensor array in which light-receiving elements are linearly placed and configured.

5 The aspect is preferably configured to have a filter 122 for limiting wavelengths (hereafter called a "stray-light-avoiding filter") on a light-emitting element, in order to avoid the stray light due to the light having the wavelengths other than a free
10 spectral region.

(ii) Aspect of arranging a plurality of light sources and switching them

In an aspect described here, an information-acquiring device has a plurality of light sources,
15 can make selectively each light source emit light by using means for switching the light sources, divides each light into several wavelength ranges by spectral means, and make a plurality of light-receiving means receive the light having different wavelength ranges.
20 The aspect will be now described with reference to Figures 4, 5 and 6.

In every aspect in each figure, a light-emitting element is used as a light source 102. A plurality of light-emitting elements are linearly
25 placed on a substrate. A plurality of the light-emitting elements can sequentially emit light in a preset order through a function of switching means

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which has a control circuit installed on the substrate 101 or separately installed. Each light-emitting element may have its wavelengths or wavelength region optimally set so as to fit the
5 wavelengths of the light which will be received by a corresponding light-receiving element, but a plurality of light-emitting elements may employ the same light-emitting element if it has wide wavelengths.

10 Light-receiving means 103 has a plurality of light-receiving elements arrayed. Light emitted from a light-emitting element is divided into several wavelength regions by a diffraction grating 107. For the diffraction grating, a blaze type reflection
15 grating is preferably used.

The optimal arrangement of a light-emitting element 102, a light-receiving element 103 and a diffraction grating 107 will be now described with reference to Figure 6. Each of light sources 102a to
20 102e respectively corresponds to each of light-receiving elements 103a to 103e one-on-one. A pair of corresponding elements is called an "element pair". A pair of the light-emitting element 102a and the light-receiving element 103a is called an "element
25 pair (a)". Each of light-emitting elements 102a to 102e and each of light-receiving elements 103a to 103e are arranged so that an angle formed by a line

which connects each former element with the center of a diffraction grating 107 and a line which connects each latter element with the center can have a constant deflection angle $2K$. For instance, the
5 angle formed by the line 504 which connects the light-emitting element 102a and the center of the diffraction grating of 107 and the line 505 which connects the light-receiving element 103a and the center becomes $2K$. Thus formed angle by the lines
10 which connect each of the element pair and the center of the diffraction grating is hereafter called an "angle by element pair". A dashed line 502 is a line which divides the angle into equal halves (hereafter called a "bisector line"). Accordingly, each angle
15 formed by a line 502 and the lines 504 and 505 is K . The angle θ formed by each bisector line in the element pairs (a) to (e) and the normal line 501 of the diffraction grating is respectively determined to be θ_a to θ_e . When the light sources of emitting
20 light are sequentially switched from the light-emitting elements 102a to 102e in the arrangement, the wavelength λ of the light which the corresponding light-receiving element receives becomes
$$\lambda = (2 \sin \theta \cdot \cos K) / mN.$$
 In the above expression, N is the
25 number of the teeth of the diffraction grating and is constant, and m is an order of diffraction, while light by ± 1 order of diffraction is generally used.

It is clear from the expression that when θ is sequentially switched from θ_a to θ_e by switching the light-emitting elements, the wavelength is also switched. The light-emitting elements having optimal
5 characteristics for emitting the light with each wavelength are preferably arranged for the light sources 102(a) to 102(e) so as to correspond to each wavelength.

A configuration in a specific system will be
10 now described. The present aspect employs a detecting method using localized plasmon resonance caused by gold nanoparticles. An absorption spectrum by the localized plasmon of gold nanoparticles has a shape as shown in Figure 13. When the gold
15 nanoparticles have the diameter of 40 nm, the peak absorption wavelength in an aqueous solution is around 530 nm. In order to acquire the waveform of absorbed light, it is sufficient to acquire only a spectrum in a wavelength region between 450 nm and
20 600 nm. One example of the diffraction grating, the above described angle K and the range of above described angle θ was designed, and is described below.

When N is 600 Line/mm, K is 61.6 degree and m
25 is -1, θ corresponding to 450 nm is -9.04 degree, and θ corresponding to 600 nm is -12.10 degree.. An optical system can be composed by arranging the

light-emitting element and the light-receiving element at each corresponding position. When a LED is used for the light-emitting element in the above arrangement, a single LED is difficult to cover 450
5 to 600 nm because a general LED has a half-width of a wavelength of about 50 nm, so that a plurality of LEDs are preferably employed in order to cover the wavelength range. For instance, by using a blue LED for a wavelength zone of 450 nm to 500 nm, using a
10 green LED for 500 nm to 550 nm, and using a yellow LED for a wavelength zone of 550 nm to 600 nm, the device according to the aspect can cope with spectrometry requiring a wide wavelength range by using a light-emitting diode.

15 (2) Aspect of using optical filter

A device according to the present aspect varies the wavelength or the wavelength region of light incident on each of a plurality of light-receiving elements, by using an optical filter. The aspect
20 will be now described with reference to Figure 7. In the present aspect as well, other components than being described here can employ the components previously described in other aspects.

Reference numerals 708 and 709 are reflecting
25 mirrors of reflecting means for changing a traveling direction of light emitted from a light-emitting element.

Reference numeral 113 is an optical filter for limiting the wavelength of light input to a light-receiving element array, divides light into several wavelength regions light, and inputs a particular wavelength or a wavelength region into each light-receiving element. The optical filter is not particularly limited as long as it provides a desired zone, but an interference filter using a dielectric multilayer film is preferable. The optical filter 113 varies wavelengths of lights which a plurality of optical elements receive, and enables a sensing element to determine optical transmittance in each wavelength or wavelength region. Specifically, the optical filter makes each light-receiving element receive each of a plurality of the wavelengths or the wavelength regions provided by dividing the predetermined wavelength region necessary for forming a wavelength-absorption spectrum. Thereby, the device can obtain an absorption spectrum over the predetermined wavelength region.

Embodiments

The present invention will be now described below with reference to embodiments, but the present invention is not limited to these embodiments. In addition, repeated description on common matters to each embodiment is omitted.

(Embodiment 1)

Embodiment 1 will be now described with reference to Figure 1. A white light-emitting diode 102 and a photodiode array 103 are placed on a printed circuit board 101.

5 A sensing element 104 which is made of a flow cell made of an optically transparent glass, uses localized plasmon resonance, and has a structure shown in Figure 10, is manufactured by the following steps of: treating a detecting region of an inner
10 face of a channel of the flow cell with an aminosilane coupling agent to form the inner face having an amino group exposed thereon, filling it with an aqueous solution containing gold nanoparticles with diameters of 20 to 40 nm (made by
15 Tanaka Kikinzoku Kogyo K. K. Corporation) to fix gold nanoparticles thereon; subsequently, immobilizing an antibody on the gold nanoparticles as a capturing body; specifically, surface-modifying the gold nanoparticles with an ethanol solution of 11-
20 Mercaptoundecanoic acid having a thiol group having a high affinity for gold, by contacting the solution with the detecting region of the flow cell having the gold nanoparticles fixed thereon, to thereby expose a carboxyl group on the surfaces of the gold
25 nanoparticles; in the state, adding an aqueous solution of N-Hydroxysulfosuccinimide (made by Dojindo Laboratories Corporation) and an aqueous

solution of 1-Ethyl-3-[3-dimethylamino]propyl]carbodiimide hydrochloride (made in Dojindo Laboratories Corporation) dropwise into the detecting region, to thereby expose a succinimide group on the surfaces of the gold nanoparticles;
5 subsequently, putting a solution of rabbit antimouse IgG antibody buffered by phosphoric acid (pH 8.0), which is an antibody to be immobilized and has specificity for a substance to be detected, in the flow cell; and immobilizing the rabbit antimouse IgG
10 antibody on the gold surface, by reacting the above described succinimide group arranged on the gold surface with the amino group of the rabbit antimouse IgG antibody. With the above method, the sensing
15 element was prepared.

A sensing element 104 was arranged in an optical path from a light emitting diode 102 to a diffraction grating 107.

A collimating lens 106 converts the light into
20 parallel rays, which has been emitted from a light-emitting diode 102, has been transmitted through a stray-light-avoiding filter 122 and a sensing element 104, and has passed through a light shield 105. The parallel rays are incident on a diffraction grating
25 107. The diffraction grating 107 diffracts a ray of light with the longest wavelength to the ray of the light shown by 111, and diffracts the ray of light

with the shortest wavelength to the ray of the light shown by 112. A concave mirror of 108 focuses thus divided light onto a photodiode array 103, and narrows a wavelength range to be detected by every
5 photodiode of a light-receiving element to improve the overall accuracy of spectrometry. Thereby, the light with various wavelength ranges is incident on each photodiode of the photodiode array 103. By detecting output signals from all elements of the
10 photodiode array 103, the device acquires an absorption spectrum of localized plasmon resonance in a sensing element 104. A method for treating the signals output from the photodiode will be now described with reference to Figure 14. It is
15 presumed that each output from the photodiodes 103 has been already converted to voltage by a current-voltage converter circuit. In the figure, the current-voltage converter circuit is not shown, but generally a circuit using an operational amplifier is
20 used for it. A hold circuit 1010 holds the output from each photodiode. The hold circuit plays a role of simultaneously sampling each photodiode and holding the obtained output. A multiplexer 1009 inputs the output held by the hold circuit into an AD
25 converter 1008. Here, the multiplexer is used, but a shift register may be used. The AD converter converts input data into digital data, and a CPU 1001

processes the converted values and converts them into spectral data. The above described signal processing method is common in each embodiment.

Because of detecting light by using localized
5 plasmon resonance in each embodiment, the device can acquire spectral data described in Figure 13. A processing method will be described below.

Now, a change in a sensing element 104 will be described with reference to Figures 10A to 10D. A
10 metallic nanoparticle 402 has capturing bodies 405 immobilized on its surface. In the present embodiment, an antibody specifically coupled with an objective substance to be detected is used for the capturing body. When the antibody captures the
15 objective substance 406 to be detected, a refractive index around the metal nanoparticle 402 is changed. Thereby, as is shown in Figure 13, a peak absorption wavelength by localized plasmon resonance around the metal nanoparticle 402 is shifted from 131 measured
20 before capturing to 132 measured after capturing. The amount of the objective substance to be detected in an unknown specimen can be determined, on the basis of a working curve which has been determined from the variation of the absorption peak and the
25 known amount of the objective substance to be detected.

(Embodiment 2)

Embodiment 2 will be now described with reference to Figure 2.

A sensing element 104 according to the present embodiment uses localized plasmon resonance shown in
5 Figure 10, as in the case of the first embodiment, but in the present embodiment, the sensing element 104 is placed in an optical path from a concave mirror 108 to a photodiode array 103 as shown in Figure 2. Reference numeral 114 shows a sensing
10 portion in the sensing element 104. The device can acquire an absorption spectrum of localized plasmon, by making the photodiode array 103 detect spectral light after having passed through the sensing portion 114. When the sensing portion is smaller than the
15 photodiode array 103 as shown in Figure 2, it cannot acquire the all spectrum of the whole sensing portion. Accordingly, the device can acquire the spectrum in the whole objective wavelength range at the sensing portion 114, by acquiring the signals of the
20 photodiode while moving the sensing element 104 in the direction of the photodiode 103.

(Embodiment 3)

Embodiment 3 will be now described with reference to Figure 3. A device according to the
25 present embodiment has a concave diffraction grating 107 arranged in a position of a concave mirror 108 in Figure 1; the concave mirror 108 arranged in a

position of a plane diffraction grating 107 in Figure 1; and sensing means 104 arranged between them.

A concave mirror 108 is arranged so as to reflect light which has passed through a light shield 105, and focus the light on a sensing element 104. The sensing element 104 reflects the light so as to be incident on a concave diffraction grating 107. The concave diffraction grating 107 diffracts a ray of light with the longest wavelength to the ray of the light shown by 111, and the ray of the light with the shortest wavelength to the ray of the light shown by 112. The concave power of the diffraction grating 107 makes spectral light diffracted here focus on a photodiode array 103, and specifically makes the light with each different wavelength range incident on each photodiode of the photodiode array 103. As described above, the concave diffraction grating 107 narrows the wavelength range to be detected by every light-receiving element, and improves the overall accuracy of spectrometry.

A sensing element 104 is an element with a sensing label using an enzyme as shown in Figure 11. Alternatively, the sensing element using fluorescence as shown in Figure 12 may be used. The sensing element employs horseradish peroxidase as an enzyme 605, and 1,2-phenylenediamine as an enzyme substrate 606. Consequently, an enzyme product 607 is produced.

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which has absorption in 491 nm. The amount of an objective substance to be detected can be determined by measuring the absorption in 491 nm.

(Embodiment 4)

5 Embodiment 4 will be now described with reference to Figure 4. This device has white light emitting diodes 102a to 102e and photodiode arrays 103a to 103e arranged on a printed circuit board 101. Here, five light-emitting elements 102 and five
10 light-receiving elements 103 are shown in a diagram, for reasons of description, but are not always limited to the configuration. The positions of the elements are set so that the angles formed by element pairs (a) to (e) with respect to a diffraction
15 grating have the same constant deflection angle. The device employs the same sensing element 104 using localized plasmon resonance, which has been prepared with the same method as in Embodiment 1. Light emitted from each light-emitting element passes
20 through the sensing element and is incident on a concave diffraction grating 107. The used diffraction grating 107 is a concave grating for an aberration correction type constant deflection angle monochrometer made by Shimadzu Corporation, which is
25 a blaze type diffraction grating and is suitable for the present embodiment. The concave diffraction grating diffracts a ray of light with the longest

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wavelength to the ray of the light shown by 111, and diffracts the ray of light with the shortest wavelength to the ray of the light shown by 112. Then, the device sequentially switches the light-emitting elements 102a to 102e from which the light with the fixed wavelength corresponding to each light-emitting element can be taken out, and simultaneously detects the signals output from the light-receiving elements 103e to 103a to acquire the absorption spectrum due to the localized plasmon resonance which occurs in the sensing element 104.

In the above, an embodiment was described while referring to a configuration in Figure 4, but an optical system with the use of a reflecting mirror 108 in an optical path may be configured as shown in Figure 5.

(Embodiment 5)

Embodiment 5 will be now described with reference to Figure 7. This device employs the same sensing element 104 using localized plasmon resonance, which has been prepared with the same method as in Embodiment 1. The device makes light sequentially transmitted through the sensing element 104 and a light shield 105, and converted into parallel rays by a collimating lens 106, and makes the parallel rays sequentially incident on reflecting mirrors 708 and 709 to change the traveling direction of the rays,

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and the changed rays incident on an interference filter 113. The interference filter 113 leads incident lights having each desired wavelength to each element of a photodiode array 103, so that the sensing element 104 can detect them. Figure 8 shows the spectral characteristics of the interference filter 113. Each filter having the characteristics corresponding to the number 1 to N is placed at the front of each corresponding photodiode. Thereby, the light having each different wavelength range is incident on each photodiode of the photodiode array 103. Accordingly, the device can acquire an absorption spectrum of localized plasmon resonance which occurs in the sensing element 104, through detecting signals of all picture elements output from the photodiode array 103.

This application claims priority from Japanese Patent Application Nos. 2004-270501 filed September 16, 2004, 2004-270572 filed September 16, 2004 and 2004-270574 filed September 16, 2004, which are hereby incorporated by reference herein.

CLAIMS

1. An information-acquiring device for acquiring information as to an objective substance to be detected, comprising a sensing element which has a surface capable of fixing the objective substance to be detected thereon and makes an applied light change its wavelength characteristics in response to a fixed state of the objective substance to be detected onto the surface, a light source, and a plurality of light-receiving means for receiving light emitted from the light source through the sensing element, wherein

the device has the light-receiving means and the light source arranged on the same substrate, the light emitted from the light source and transmitted through the sensing element is led to the light-receiving means, and

a means for varying the wavelength regions of each light incident on each of a plurality of the light-receiving means is installed in an optical path from the light source to the light-receiving means.

2. The information-acquiring device according to claim 1, wherein the means for varying the wavelength region of each light incident on each of a plurality of the light-receiving means is a spectral means.

3. The information-acquiring device according

to claim 2, wherein the sensing element is arranged in a light path between the spectral means and the light source.

4. The information-acquiring device according to claim 2, wherein the sensing element is arranged in a light path between the spectral means and a plurality of the light-receiving means.

5. The information-acquiring device according to claim 2, further having a reflecting means for leading light from the light source to the light-receiving means through the sensing element.

6. The information-acquiring device according to claim 5, wherein the reflecting means is made of a concave mirror which focuses spectral light made by the spectral means on the light-receiving means.

7. The information-acquiring device according to claim 2, wherein the device has a plurality of the light sources, enables each of a plurality of the light sources to selectively emit light by using a means for switching the light source and varies the wavelength of the light to be received by the light-receiving means by using the spectral means.

8. The information-acquiring device according to claim 1, wherein the means for varying the wavelength region of each light incident on each of a plurality of the light-receiving means is an optical filter.

9. The information-acquiring device according to claim 1, wherein the device acquires information on the objective substance to be detected by using plasmon resonance.

5 10. The information-acquiring device according to claim 9, wherein the sensing element has a surface which can fix a metallic nanoparticle capable of capturing the objective substance to be detected thereon, and the plasmon resonance is a localized
10 plasmon occurring around the metallic nanoparticle fixed on the surface.

11. The information-acquiring device according to claim 1, wherein the light source and the light-receiving means are formed on the same semiconductor
15 substrate.

12. An information-acquiring method for acquiring information on an objective substance to be detected in a specimen by using a sensing element characterized in that the method comprises the steps
20 of:

preparing the sensing element having the objective substance to be detected fixed thereon;

when light emitted from the light source illuminates the sensing element having the objective
25 substance to be detected fixed thereon, and the transmitted light of emitted light is led to a plurality of the light-receiving means placed on the

same substrate as the light source is placed, varying the wavelength of each light to be received by each of a plurality of light-receiving means, through a wavelength-varying means installed in an optical path from a light source to the light-receiving means, and acquiring the wavelength characteristics on the transmittance of every wavelength of the light which has passed through the sensing element and has been received by each light-receiving means; and

10 determining the coupled amount of the objective substance to be detected which has been coupled with the sensing element, on the basis of the wavelength characteristics.

13. The method for acquiring information on the objective substance to be detected according to claim 15 12, wherein the wavelengths of light to be received are varied by a spectral means.

14. The method for acquiring information on the objective substance to be detected according to claim 20 13, wherein a plurality of the light sources are prepared, and the wavelengths of the light to be received by the light-receiving means are varied according to the positions of a plurality of the light sources.

25 15. The method for acquiring information on the objective substance to be detected according to claim 12, wherein the wavelength of the light to be received is varied by an optical filter.

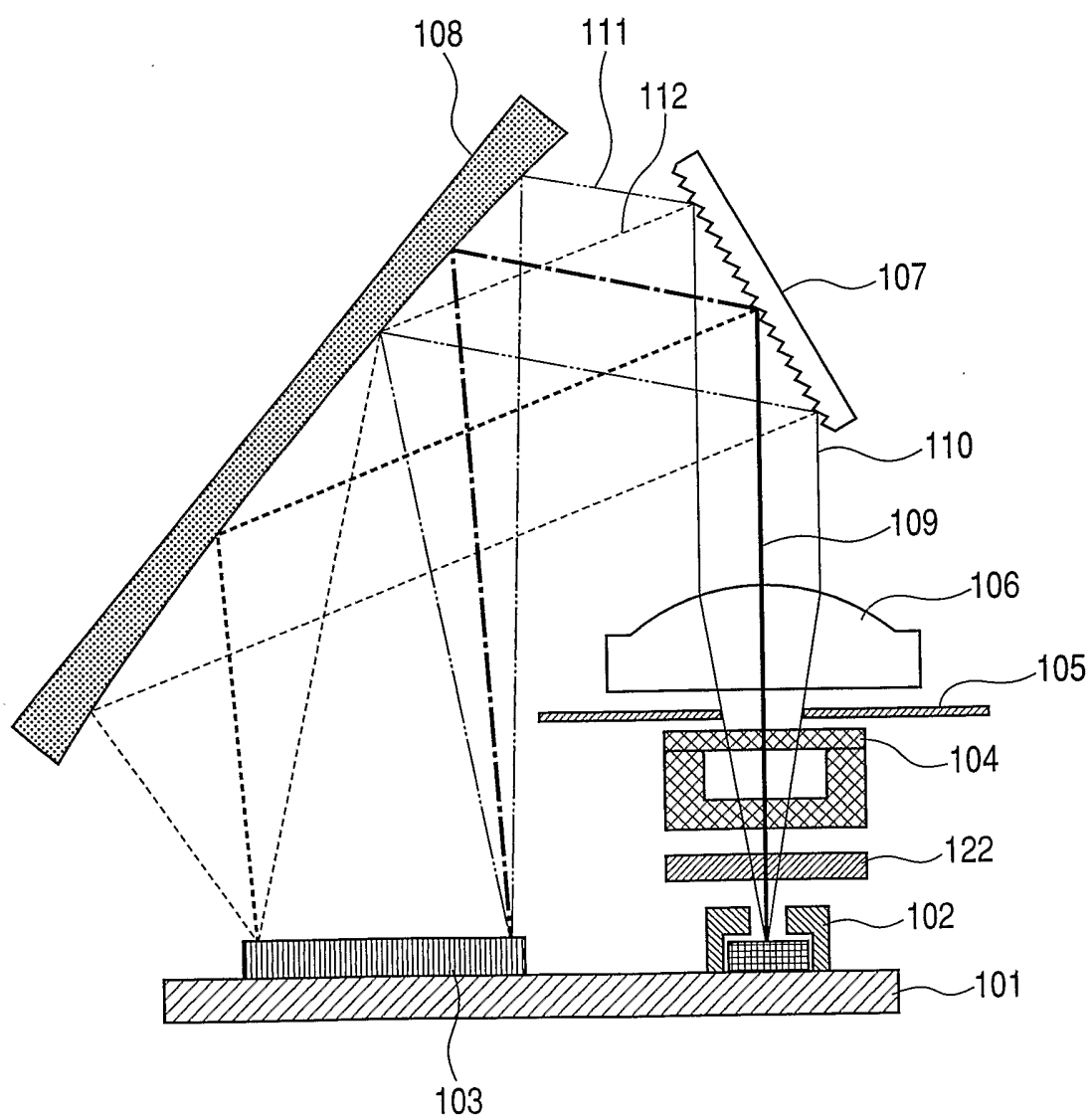
FIG. 1

FIG. 2

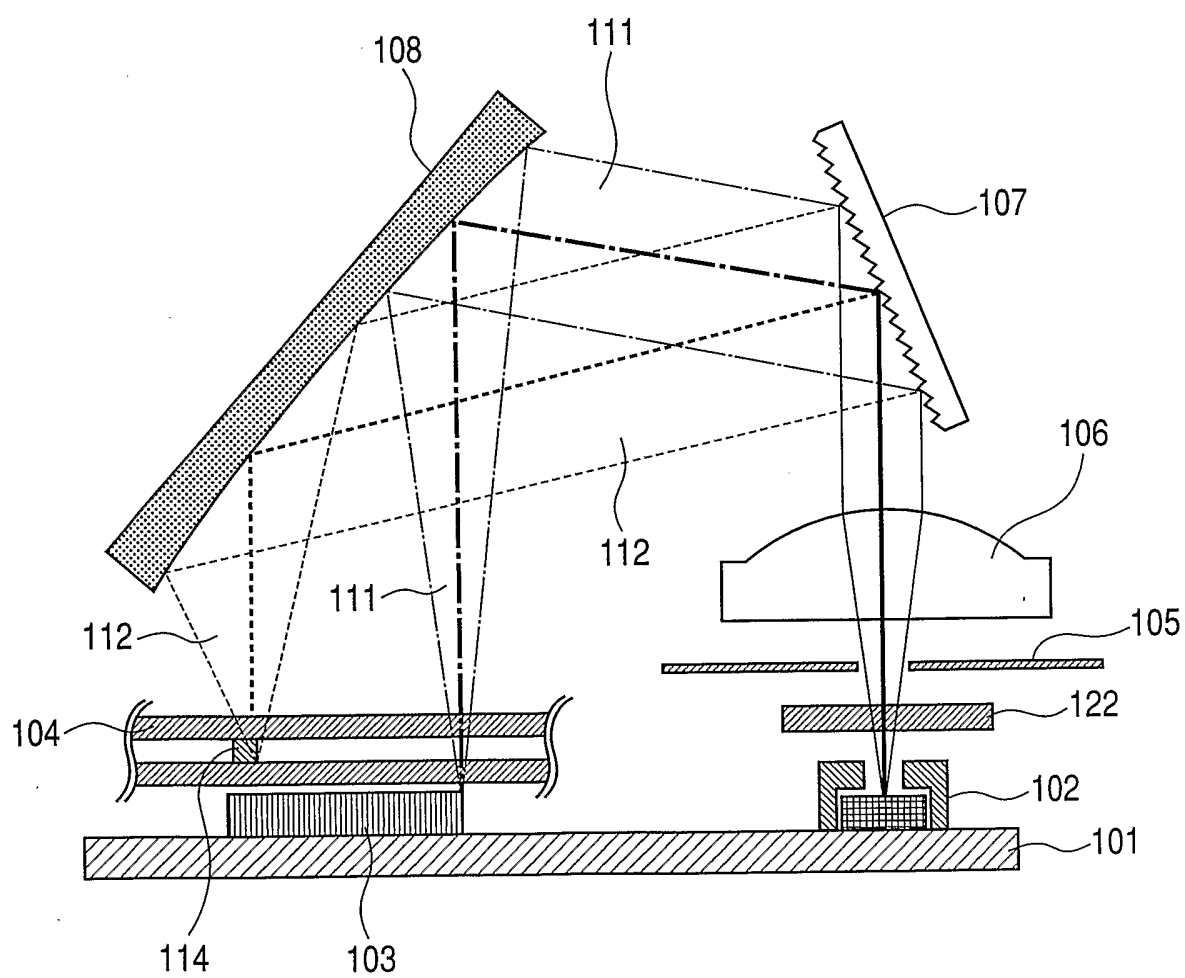


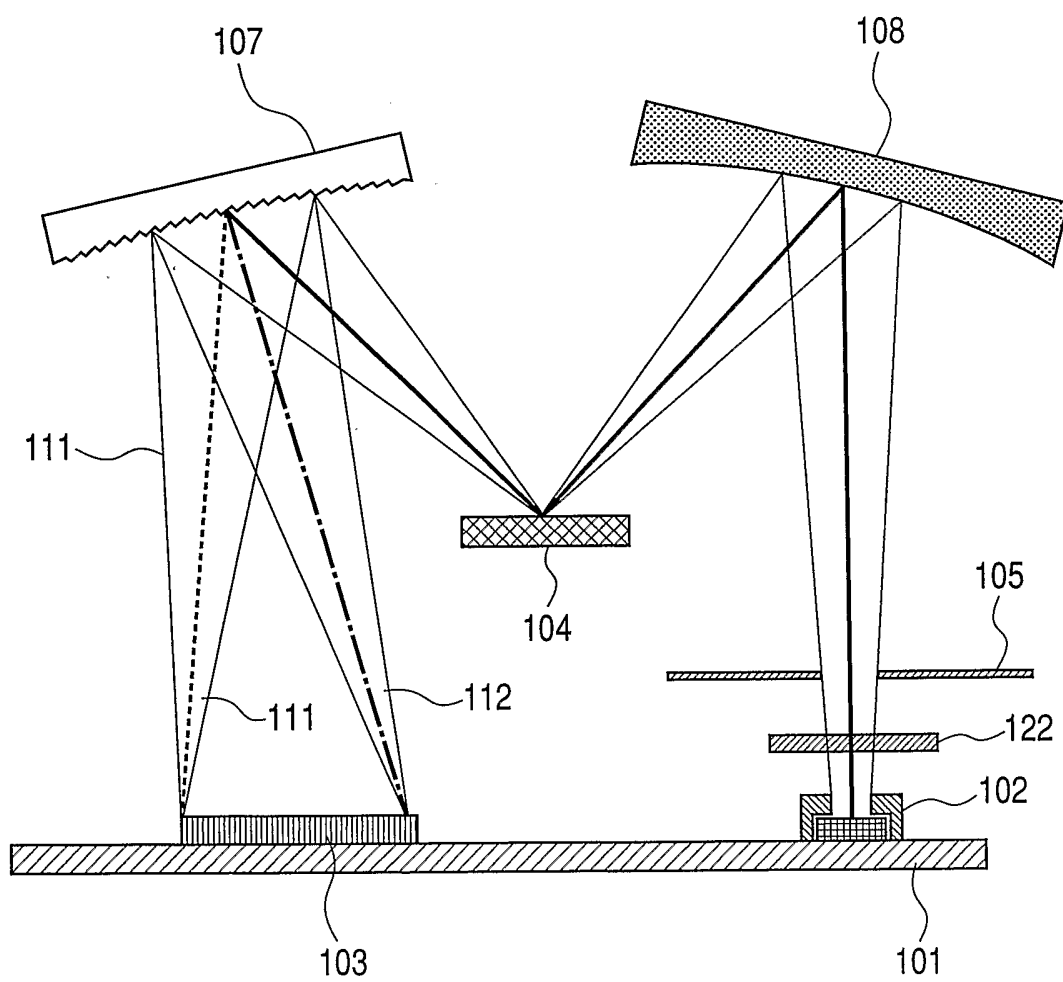
FIG. 3

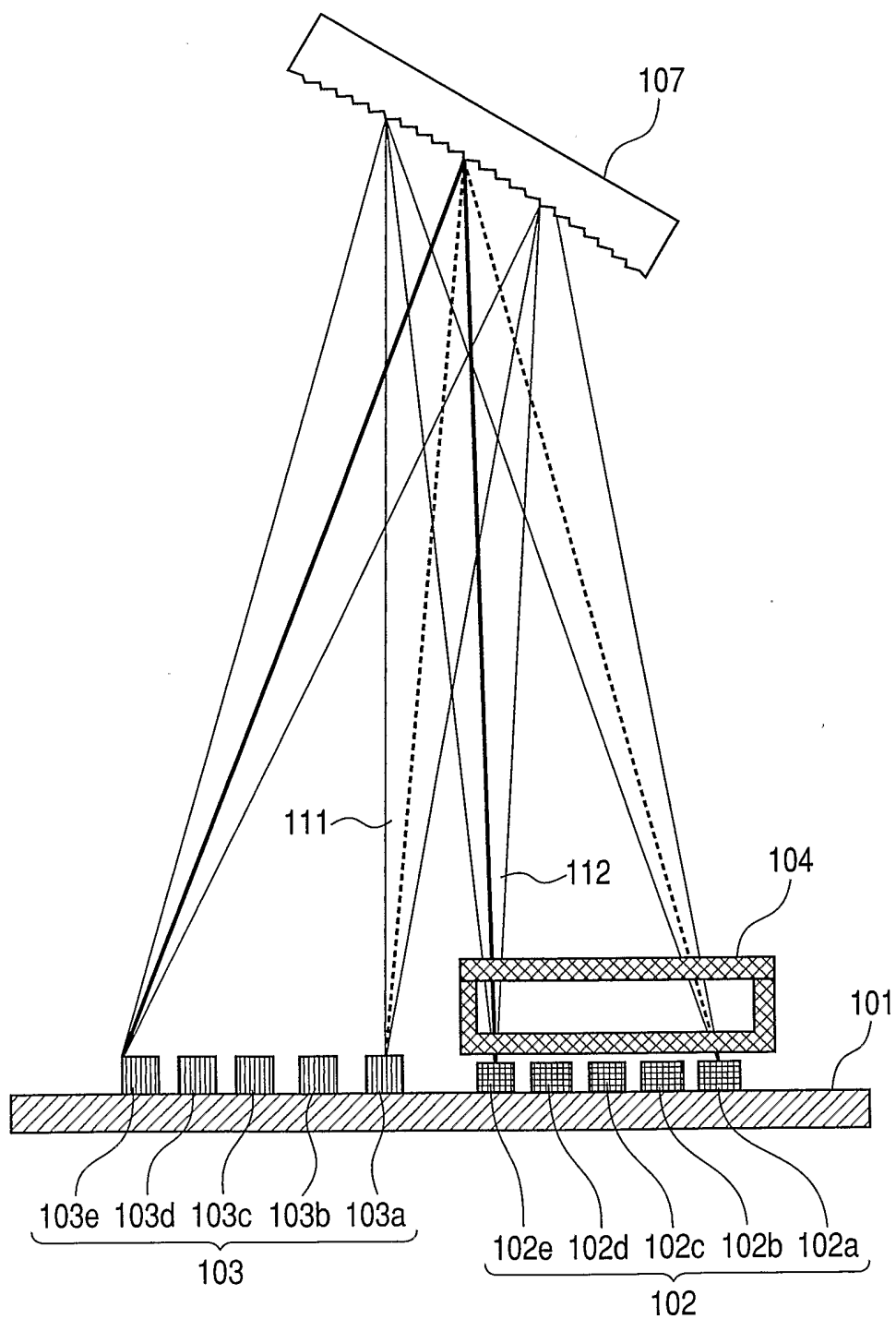
FIG. 4

FIG. 5

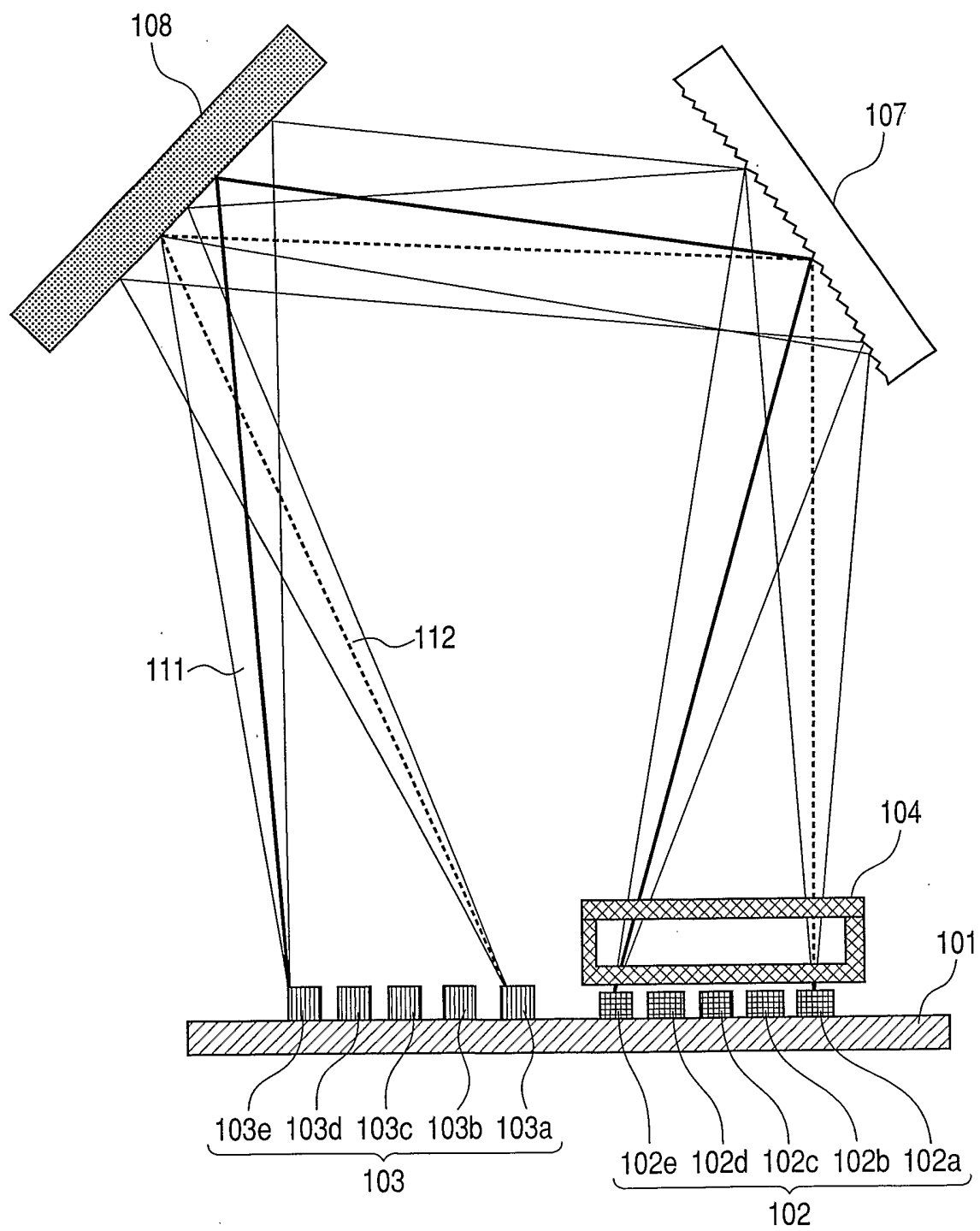
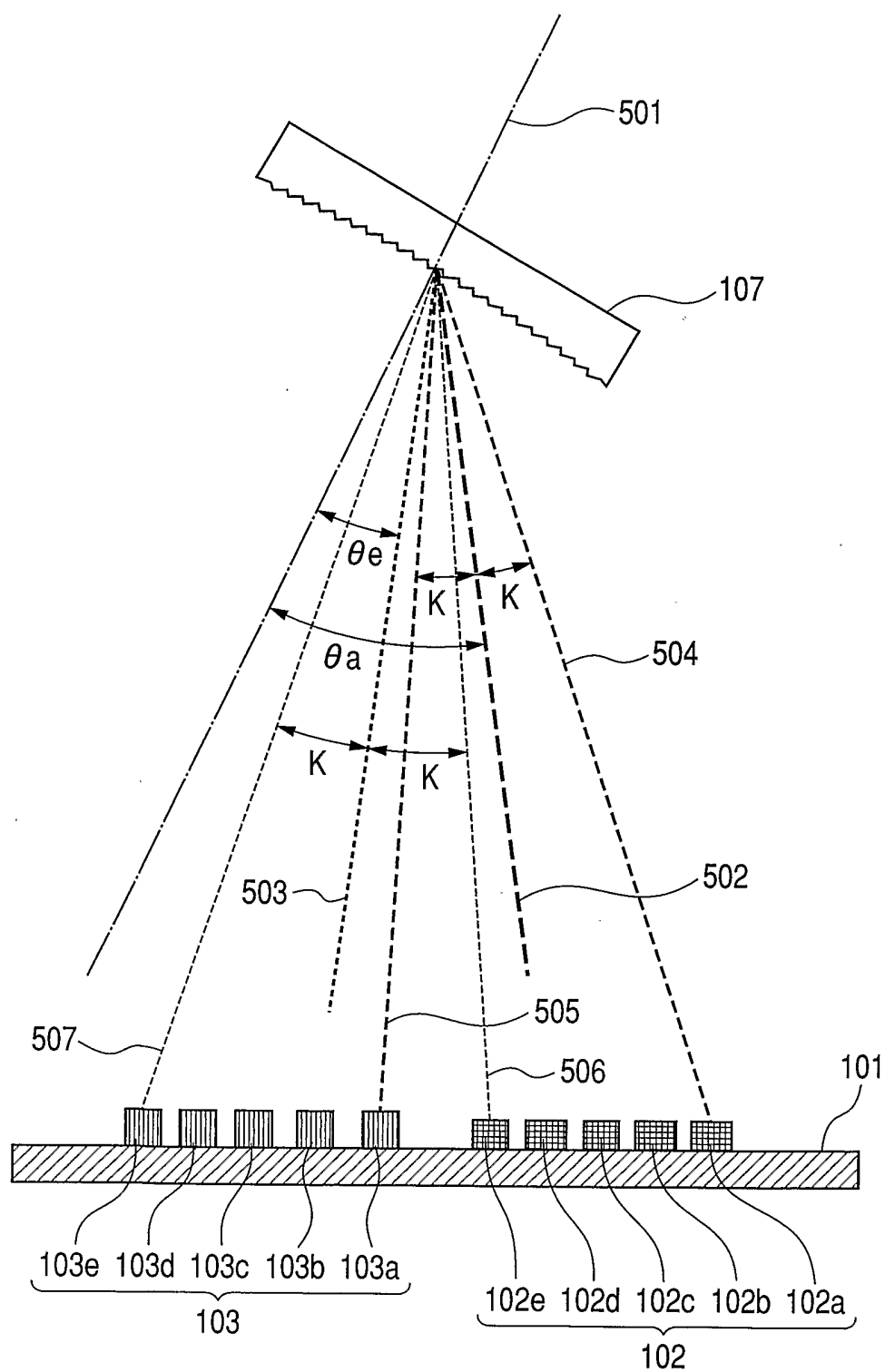


FIG. 6



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FIG. 7

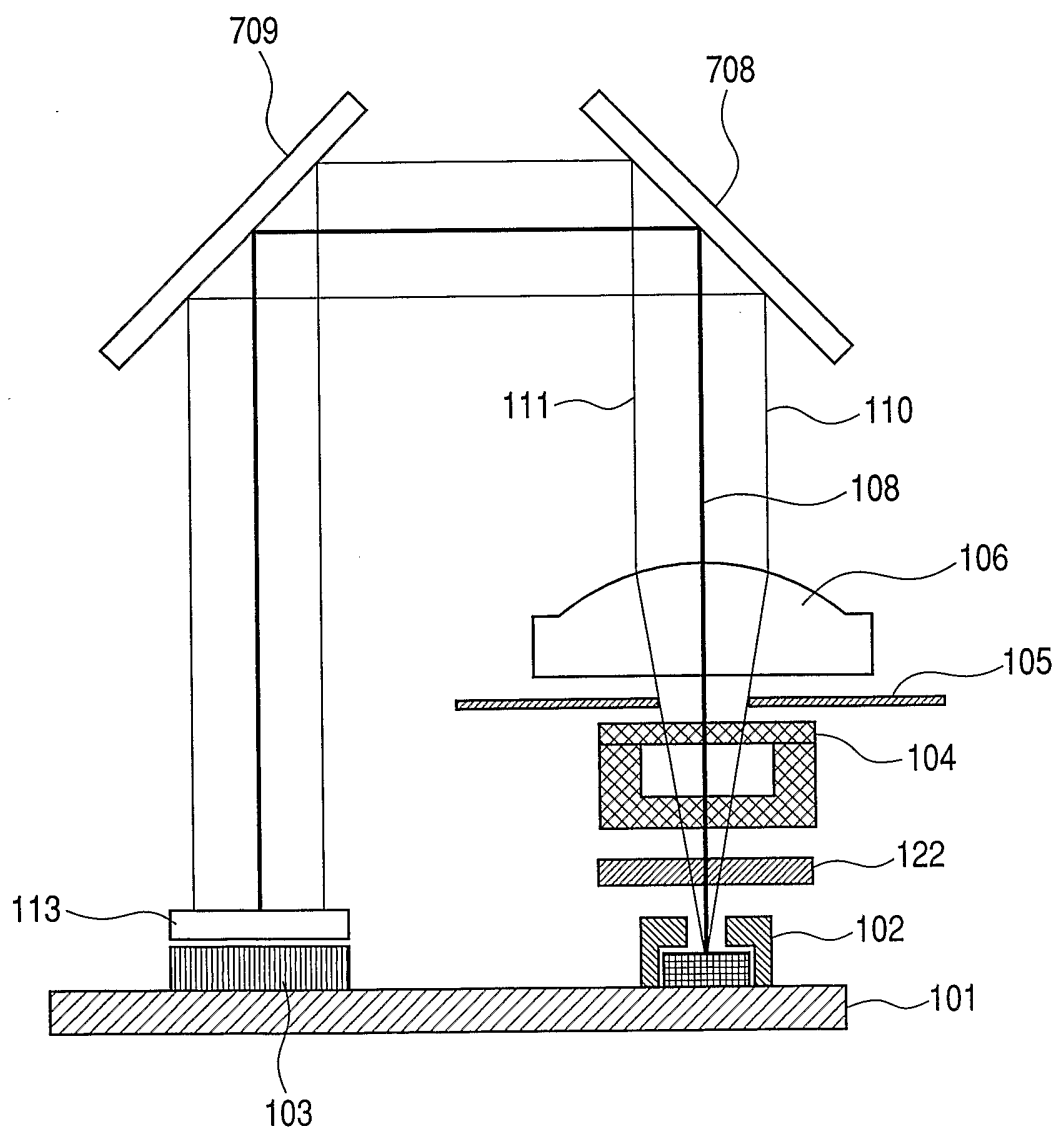


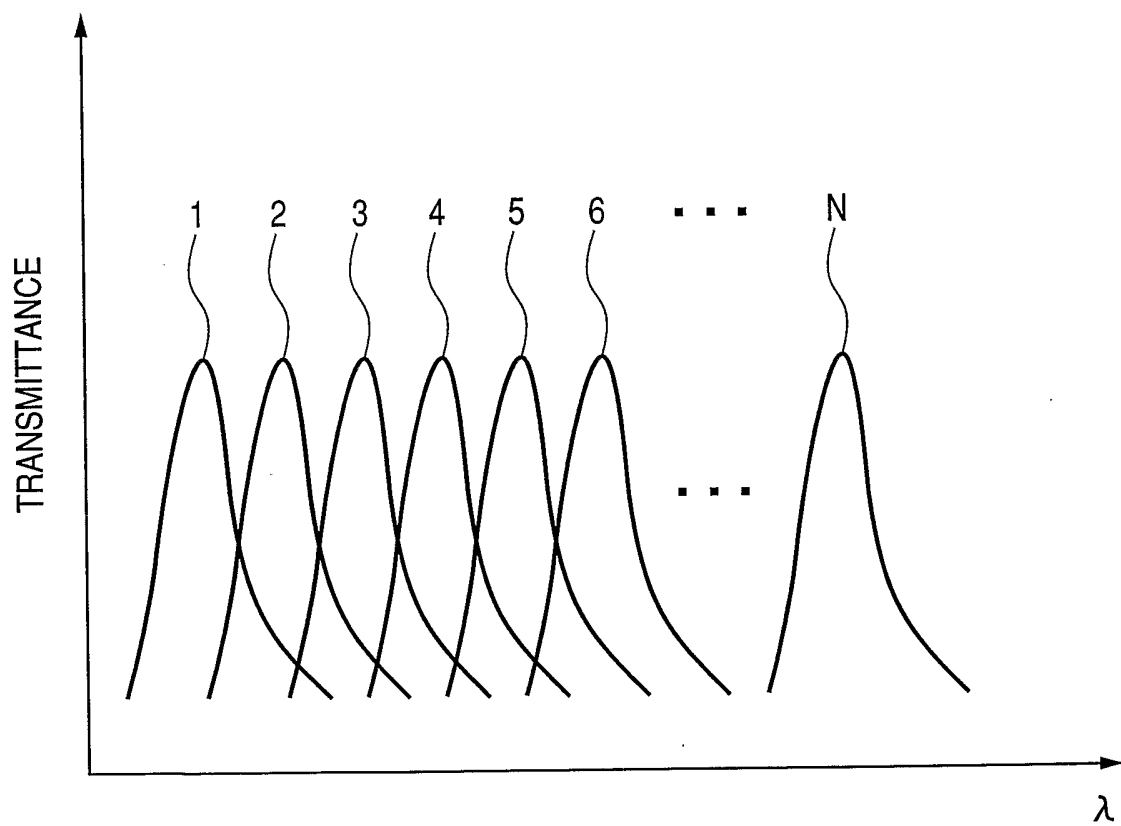
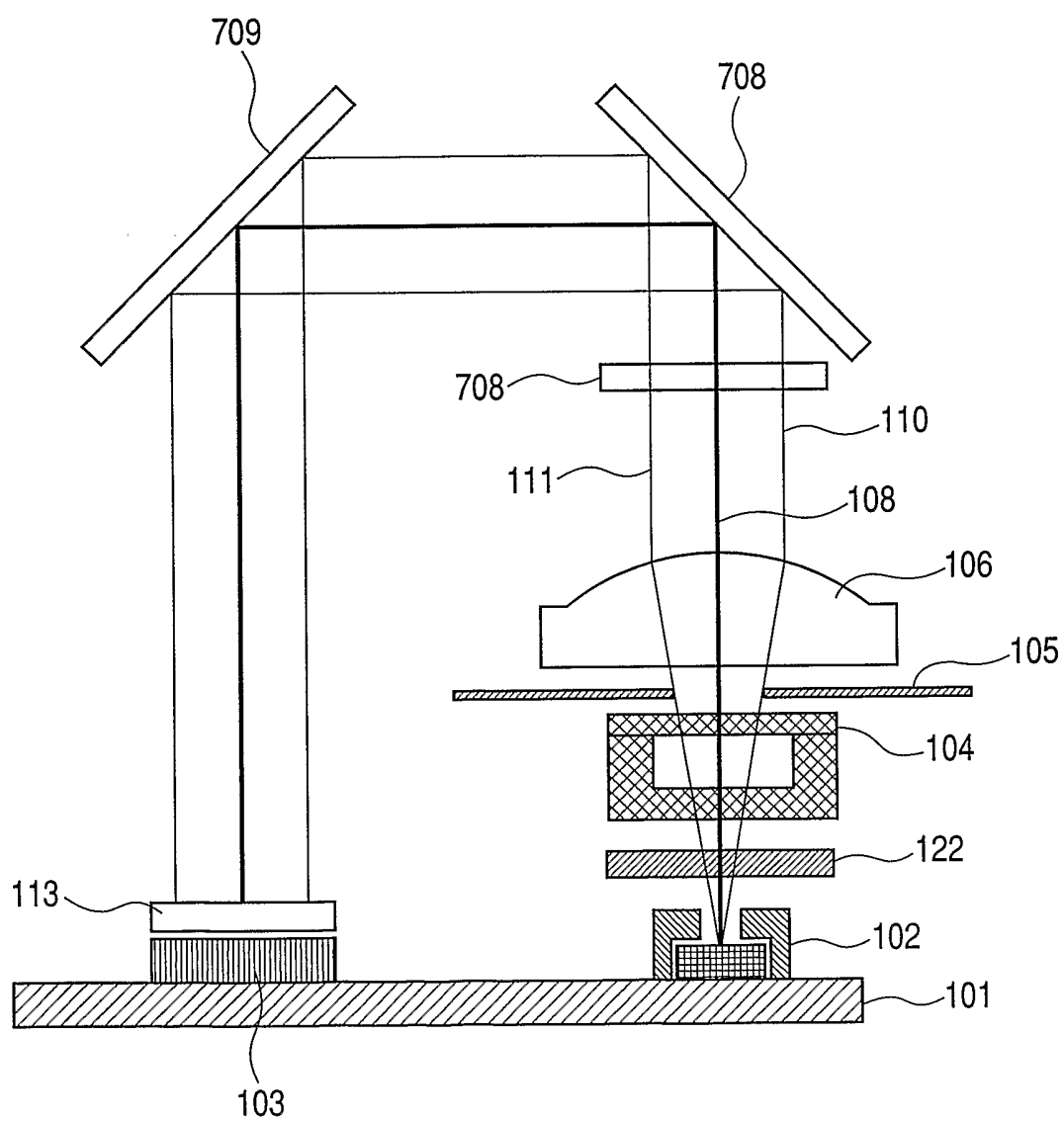
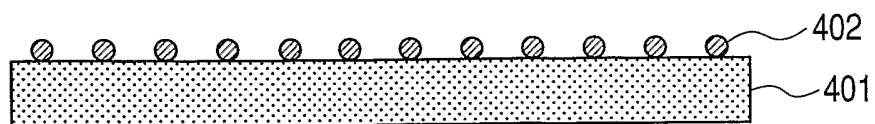
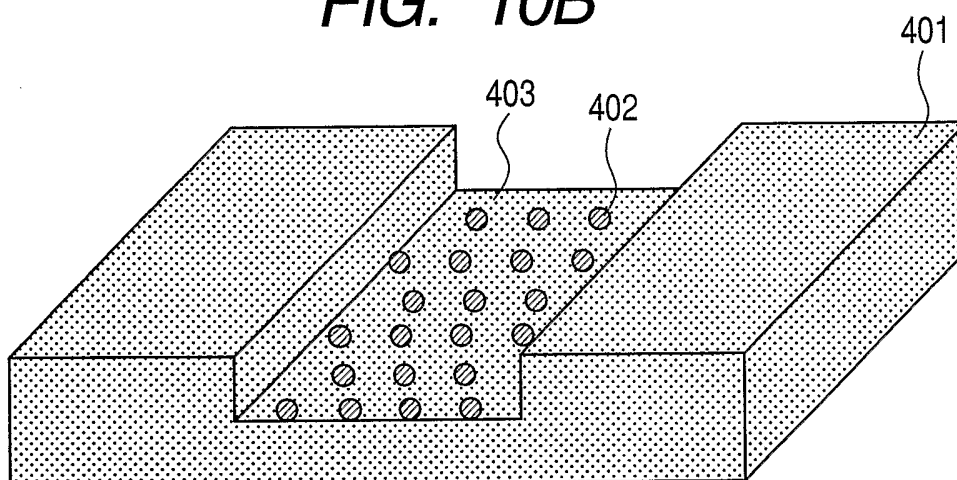
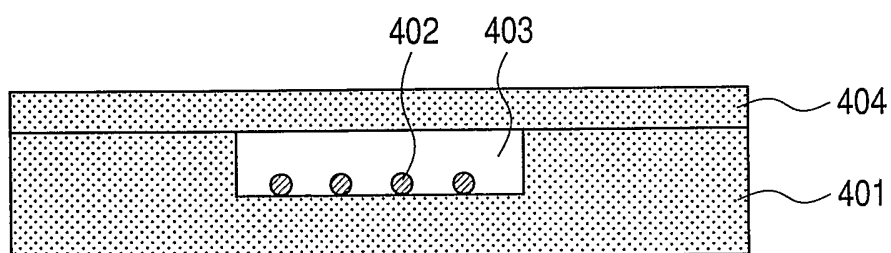
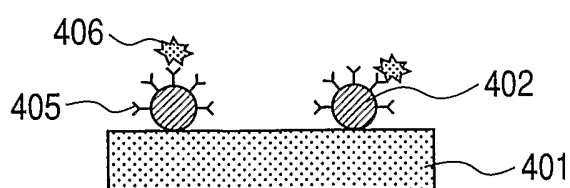
FIG. 8

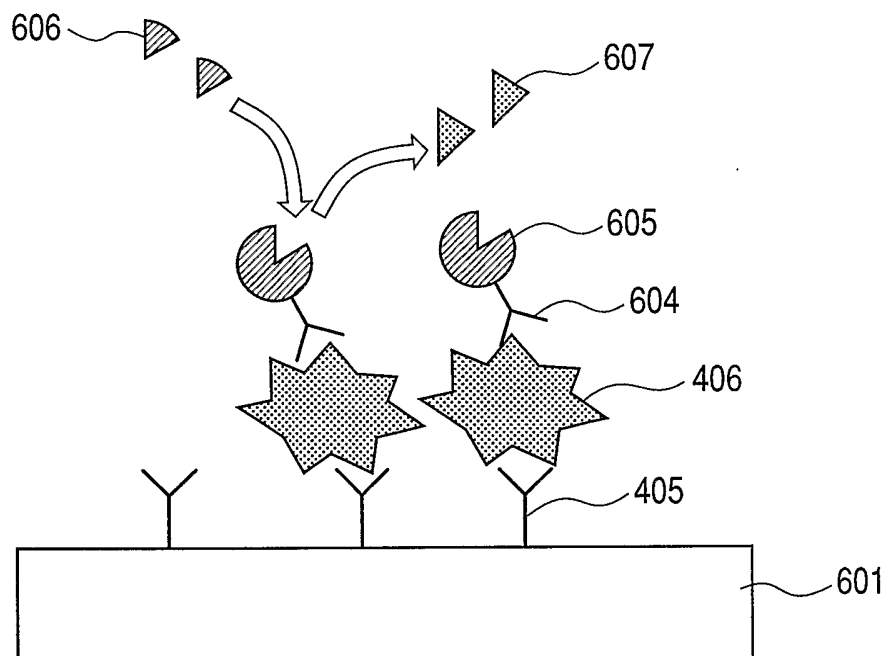
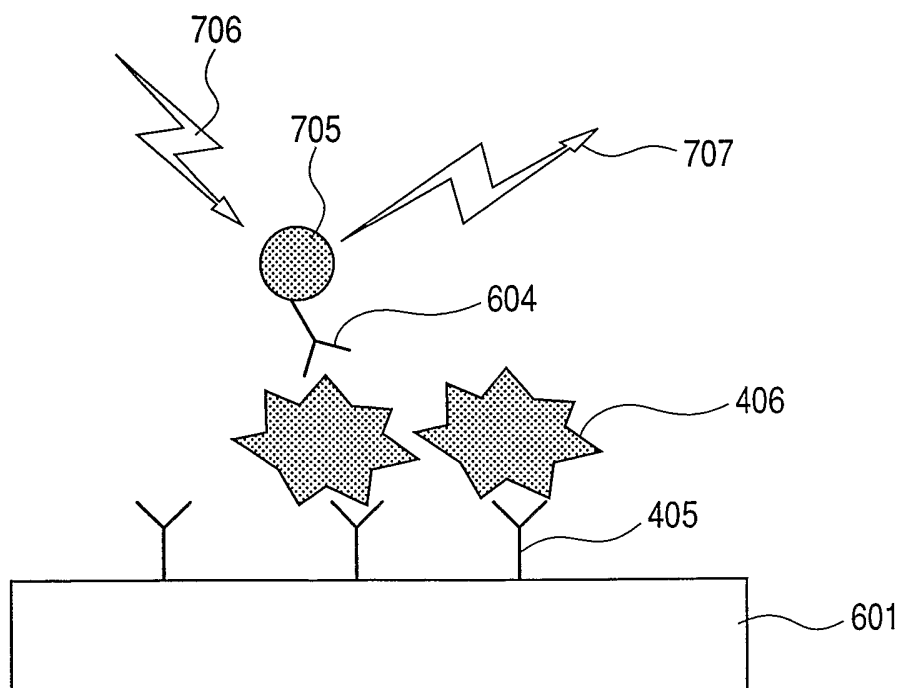
FIG. 9



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FIG. 10A*FIG. 10B**FIG. 10C**FIG. 10D*

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FIG. 11**FIG. 12**

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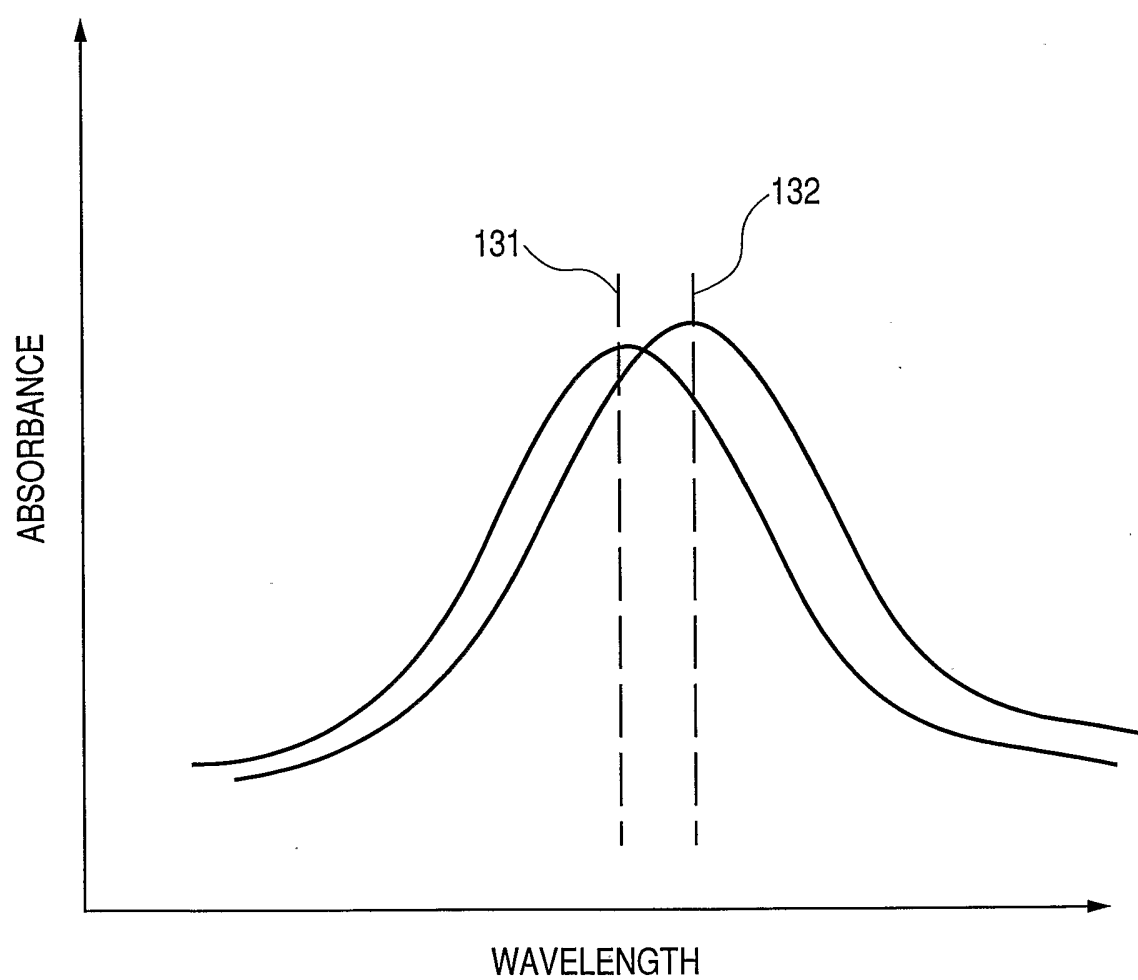
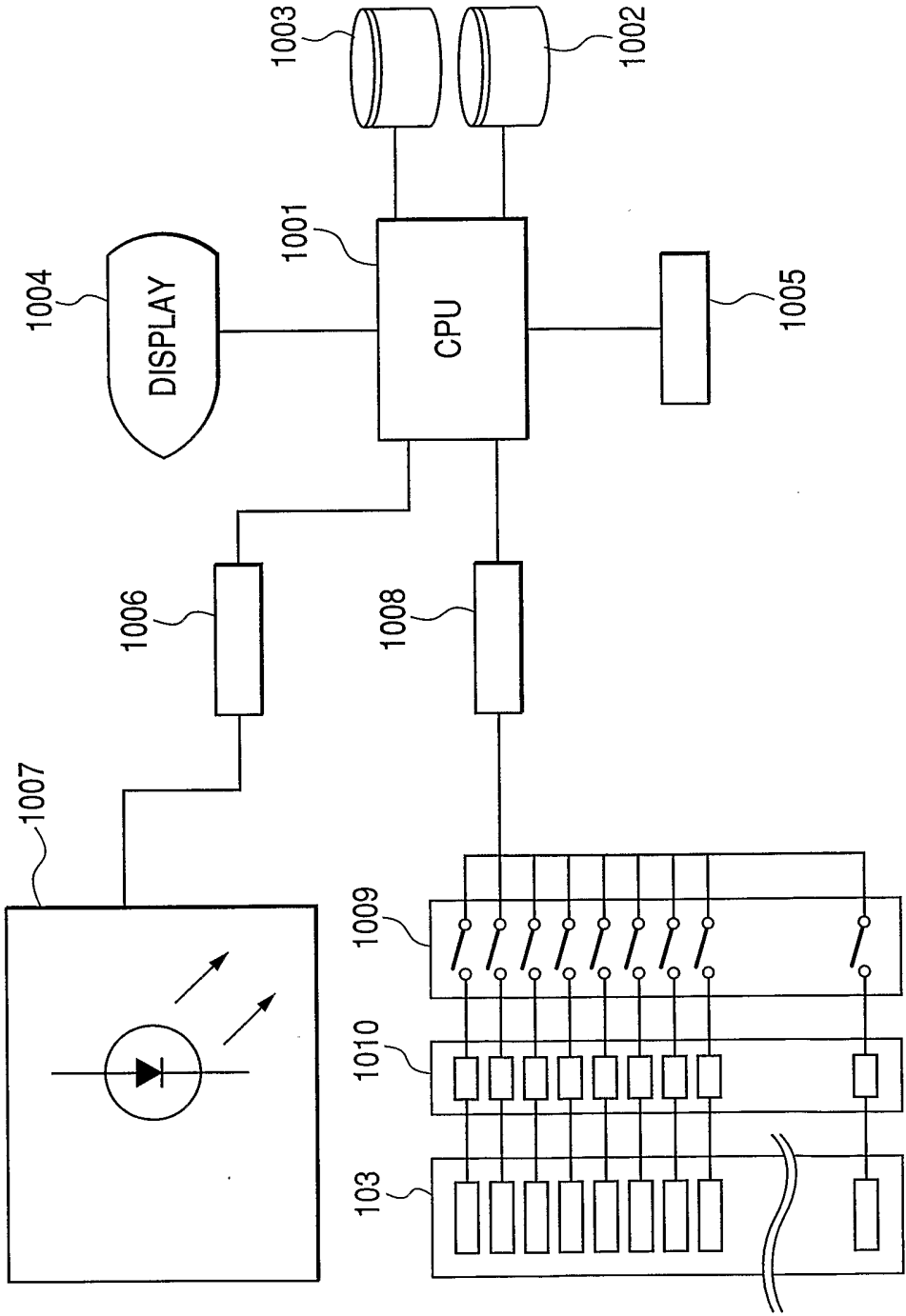
FIG. 13

FIG. 14



INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2005/017326

A. CLASSIFICATION OF SUBJECT MATTER
G01N21/55

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, INSPEC, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

21 December 2005

Date of mailing of the international search report

12/01/2006

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Duijs, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2005/017326

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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