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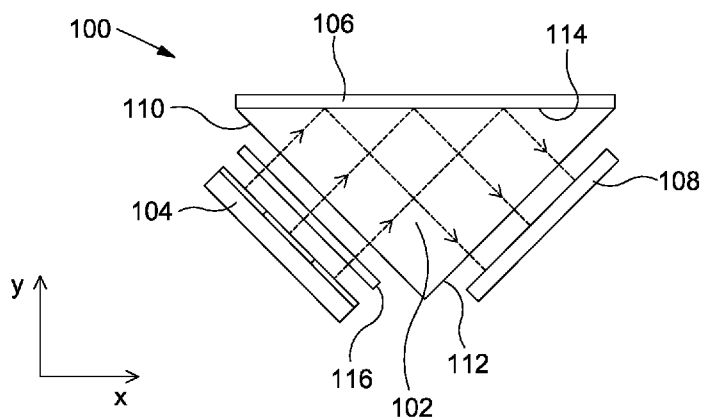


Fig. 1

(57) Abstract: An imaging surface plasmon resonance apparatus comprises: a prism; a two dimensional vertical-cavity surface-emitting laser array; a layer of metal; and a detector. The two dimensional vertical-cavity surface-emitting laser array is operable to produce a two dimensional array of beams of electromagnetic radiation and is arranged such that each one of said two dimensional array of beams of electromagnetic radiation is coupled into the prism and is incident on a different one of a plurality of regions on a surface of the prism. The beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may be generally mutually parallel. The layer of metal is disposed on or adjacent to the surface of the prism in the vicinity of each of the plurality of regions on the surface of the prism. The layer of metal may comprise a two dimensional array of receptor sites for supporting a receptor, each receptor site disposed on a surface of the layer of metal that is distal to the prism and adjacent one of the plurality of regions on the surface of the prism. The detector is arranged to receive a portion of each of the plurality of beams of electromagnetic radiation which is reflected from the interface between the prism and the layer of metal and operable to determine an intensity of said portion of each of the plurality of beams of electromagnetic radiation.

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Imaging surface plasmon resonance apparatus

Technical Field of the Disclosure

5 This disclosure relates to an imaging surface plasmon resonance apparatus. The imaging surface plasmon resonance apparatus may have application, for example, in an assay (also sometimes referred to as a molecular interaction assay), which is arranged to measure the presence or concentration of a specific target molecule.

10 Background of the Disclosure

There are known techniques that are able to report or visualize the specific interaction between biomolecules. Such a technique or test may be referred to as a molecular interaction assay, which is arranged to measure the presence or concentration of a
15 specific target molecule (which may be referred to as an analyte). A molecular interaction assay typically uses a bio-receptor which can bind to the analyte. Such interactions are extremely specific with the bio-receptor and analyte binding in a similar way to a key and a lock. Typically, only the correct analyte is able to bind to the bio-receptor.

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Many such assays require also use a reporter molecule. The reporter molecule is operable to bind to the analyte, typically only once the analyte has bound to the bio-receptor. The reporter molecule can report the presence of the analyte target molecule in some way. For example, the reporter molecule may use: an enzyme, as in an
25 enzyme linked immunosorbent assay (ELISA); radioactivity, as in a radio immunosorbent assay (RIA); or, more commonly, a fluorophore, as in a fluorescent immunosorbent assay (FIA).

As an alternative to the usage of reporter molecules, label-free detection assay
30 methods have been developed and are gaining popularity. One known label-free detection method is surface plasmon resonance (SPR). The present disclosure relates to such a label-free detection assay method, in particular to an imaging surface plasmon resonance apparatus.

One arrangement for using surface plasmon resonance as a label-free detection method (which may be referred to as a surface plasmon resonance apparatus) comprises a prism which is provided with a relatively thin layer of metal (for example gold) on one face thereof. Electromagnetic radiation is coupled into the prism and is incident on the interface between the prism and the metal such that total internal reflection occurs. This generates an evanescent wave in the metal layer which propagates parallel to the interface between the prism and the metal (and in the plane of incidence) and has an amplitude that decays exponentially in a direction perpendicular to the interface between the prism and the metal.

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At the interface between the metal layer and an adjacent (dielectric) medium, surface plasmon polaritons can be generated. Surface plasmon polaritons are a type of coupled oscillation of electrons (plasmons) within the metal layer and an electromagnetic oscillation (polaritons) in the dielectric medium. In particular, surface plasmons are collective conduction electron oscillations at the interface of two layers, one layer being a metal (usually a noble metal) and the second layer being a dielectric. If the thickness of the metal layer is sufficiently thin (with respect to a penetration depth of the evanescent wave) and a resonance condition is met, an evanescent wave can excite surface plasmon polaritons on an opposite side of the metal layer to the prism. This uses some of the energy from the incident electromagnetic radiation and therefore reduces the intensity of the electromagnetic radiation reflected from the interface between the prism and the metal layer.

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Reflected electromagnetic radiation is coupled out of the prism and is incident on a detector, which is arranged to determine an intensity of the reflected electromagnetic radiation (which, in turn, is dependent on whether or surface plasmon polaritons have been excited).

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The resonance condition is dependent on the wavelength and angle of incidence of the incident electromagnetic radiation. The resonance condition is also dependent on optical properties of both the metal and the adjacent (dielectric) medium. If the metal is provided with a bio-receptor on its surface then these optical properties (and therefore the resonance condition) may vary in dependence on the presence or absence of a specific target molecule (or analyte) being bound to the bio-receptor. Therefore, by measuring information related to the resonance condition, it is possible to determine

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information about the presence and/or quantity of the specific target molecule adjacent the metal layer.

5 In some systems, a plurality of different bio-receptors are provided on the metal layer; each one is irradiated with electromagnetic radiation and the electromagnetic radiation reflected from each is detected by a separate detector. Such an arrangement is known as imaging SPR (iSPR).

10 One challenge with the above-described imaging surface plasmon resonance apparatus is that the resonance condition is very narrow and therefore it is important to have adequate control over the wavelength and angle of incidence of the incident electromagnetic radiation.

15 In particular, one of the main design challenges in the above-described imaging surface plasmon resonance apparatus is the optical system. Typically, many lenses are required to project light properly onto the prism and to observe the reflected light on the imaging sensor. Each lens has a specific aligned optical path and focal distance to achieve the best illumination and image quality. In particular, the optics which illuminate the metal layer may be required to do so with a precision of the order of 0.1° in order to operate correctly.

20 In addition, in a traditional imaging surface plasmon resonance apparatus the measurement may involve scanning through different angles of incidence in order to identify the resonance condition (as a local minimum in the intensity of the reflected electromagnetic radiation), which further complicates the optical system.

25 Two relatively simple arrangements are disclosed in US5912456A and US6424418B2, wherein a metal layer is illuminated with electromagnetic radiation at a plurality of different angles and the amount of reflected radiation from each is determined by a separate detector so as to determine a resonance spectrum. These two simple
30 arrangements do not use optical prisms.

It is an aim of the present disclosure to provide an imaging surface plasmon resonance apparatus that address one or more of problems associated with prior art methods, whether identified above or otherwise.

Summary

In general, this disclosure proposes to overcome the problems in existing arrangements by providing an imaging surface plasmon resonance apparatus using a two dimensional vertical-cavity surface-emitting laser array. This arrangement is advantageous since it provides an apparatus with a very high degree of multiplexing and which is very compact.

According to a first aspect of the present disclosure, there is provided an imaging surface plasmon resonance apparatus comprising: a prism; a two dimensional vertical-cavity surface-emitting laser array operable to produce a two dimensional array of beams of electromagnetic radiation and arranged such that each one of said two dimensional array of beams of electromagnetic radiation is coupled into the prism and is incident on a different one of a plurality of regions on a surface of the prism at substantially the same angle of incidence; a layer of metal disposed on or adjacent to the surface of the prism in the vicinity of each of the plurality of regions on the surface of the prism; and a detector arranged to receive a portion of each of the two dimensional array of beams of electromagnetic radiation which is reflected from the interface between the prism and the layer of metal and operable to determine an intensity of said portion of each of the plurality of beams of electromagnetic radiation.

Advantageously, the two dimensional vertical-cavity surface-emitting laser array of the imaging surface plasmon resonance apparatus according to the first aspect of the disclosure provides an apparatus with a very high degree of multiplexing and which is very compact, as now discussed.

Prior art imaging surface plasmon resonance apparatuses which comprise a prism (upon which the metal layer is disposed) typically have illumination optics to couple radiation into the prism that this bulky and which must be accurately aligned. One known arrangement uses a single light source (for example a diode laser) with a single pinhole and a collimating lens to ensure that the (divergent) electromagnetic radiation from the pinhole is collimated and is incident on the metal layer at a suitable angle to observe the resonance. However, in order to do this, the light source (or pinhole) should be disposed at a focal point of the collimating lens. It will be appreciated that the desired dimension of the collimated beam will be of the order of the dimensions of

the prism. Furthermore, the focal length of the lens will typically scale with the size of the lens.

5 Compared to such known systems, the present imaging surface plasmon resonance apparatus disclosed here has the following advantages. By providing a two dimensional vertical-cavity surface-emitting laser array operable to produce a two dimensional array of beams of electromagnetic radiation no collimating illumination optics is required. Advantageously, this allows for a particularly compact apparatus. For example, the optical volume may be reduced by at least a factor of 10.

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Some prior art imaging surface plasmon resonance apparatuses are arranged to illuminate a metal layer with electromagnetic radiation at a plurality of different angles and the amount of reflected radiation from each is determined by a separate detector so as to determine a resonance spectrum. It will be appreciated that these prior art
15 arrangements are incompatible with an arrangement that has a two dimensional vertical-cavity surface-emitting laser array operable to produce a two dimensional array of beams of electromagnetic radiation that are generally mutually parallel.

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20 Compared to such known systems, the present imaging surface plasmon resonance apparatus disclosed here has the advantage that it allows for a two dimensional array of beams of electromagnetic radiation that are generally mutually parallel and therefore incident on the surface of the prism at substantially the same angle. This therefore allows for a two dimensional array of different receptors to be simultaneously monitored whilst all of these remain within a dynamic range of a detector for determining the
25 presence and/or concentration of a target molecule being bound to those receptors. Advantageously, this significantly increases the number of receptors that can be monitored simultaneously (i.e. it allows a significant increase in the amount of multiplexing).

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30 It will be appreciated that the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may be considered to be generally mutually parallel if the directions of all of the beams of electromagnetic radiation vary by less than 1° . For example, the directions of all of the beams of electromagnetic radiation may vary by less than 0.5° . For example, the directions of all
35 of the beams of electromagnetic radiation may vary by less than 0.1° . The direction of

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each beam of electromagnetic radiation may be the direction of a chief ray of that beam.

5 It will be appreciated that beams of electromagnetic radiation may be considered to be have the same angle of incidence at the surface of the prism if their angles of incidence vary by less than 1° . For example, the angles of incidence of all of the beams of electromagnetic radiation may vary by less than 0.5° . For example, the angles of incidence of all of the beams of electromagnetic radiation may vary by less than 0.1° .

10 As used herein, it will be appreciated that a receptor is intended to mean anything (for example a molecule) which can receive and bind to something else. Receptors can comprise any one of a number of biological molecules such as, for example, proteins, viruses and the like.

15 According to a second aspect of the present disclosure, there is provided an imaging surface plasmon resonance apparatus comprising: a prism; a two dimensional vertical-cavity surface-emitting laser array operable to produce a two dimensional array of beams of electromagnetic radiation and arranged such that each one of said two dimensional array of beams of electromagnetic radiation is coupled into the prism and
20 is incident on a different one of a plurality of regions on a surface of the prism; a layer of metal disposed on or adjacent to the surface of the prism in the vicinity of each of the plurality of regions on the surface of the prism and comprising a two dimensional array of receptor sites for supporting a receptor, each receptor site disposed on a surface of the layer of metal that is distal to the prism and adjacent one of the plurality of regions
25 on the surface of the prism; and a detector arranged to receive a portion of each of the two dimensional array of beams of electromagnetic radiation which is reflected from the interface between the prism and the layer of metal and operable to determine an intensity of said portion of each of the plurality of beams of electromagnetic radiation.

30 Advantageously, the combination of: a two-dimensional array of receptor sites disposed on the surface of the layer of metal that is distal to the prism; and a two dimensional vertical-cavity surface-emitting laser array operable to produce a two-dimensional array of beams of electromagnetic radiation provides an apparatus with a very high degree of multiplexing and which is very compact.

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The beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may be generally mutually parallel.

5 The imaging surface plasmon resonance apparatus may further comprise a plurality of receptors, each disposed on a surface of the layer of metal that is distal to the prism.

The plurality of receptors may be disposed as a two dimensional array. The receptors may be disposed at the receptor sites.

10 It will be appreciated that the two-dimensional array of receptors (which are disposed on a surface of the layer of metal that is distal to the prism) are on an opposite surface of the layer of metal to that which the electromagnetic radiation is incident on. It will be appreciated that a beam of electromagnetic radiation being incident on an interface between the prism and the layer of metal in the vicinity of one of the receptors from the
15 two-dimensional array of receptors means that that beam is incident on a position on one surface that generally corresponds to the position on the opposite surface where the receptor is (for example merely translated in a direction of the thickness of the layer of metal, which may be generally perpendicular to the two opposed surfaces). It will be further appreciated that in the vicinity is intended to mean close enough that the
20 evanescent wave generated in the metal layer when that beam of electromagnetic radiation is incident on the interface between the prism and the layer of metal can excite surface plasmon polaritons on the opposite side of the metal layer at the location of the receptor.

25 The imaging surface plasmon resonance apparatus may further comprise a pinhole array disposed between the two dimensional vertical-cavity surface-emitting laser and the prism. Each vertical-cavity surface-emitting laser in the two dimensional vertical-cavity surface-emitting laser array may be aligned with a different one of the pinholes in the pinhole array.

30 Each one of the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may be at least partially formed or controlled by a pinhole from the pinhole array.

The imaging surface plasmon resonance apparatus may further comprise a microlens array. Each microlens in the microlens array may be arranged to reduce a divergence of one of the two dimensional array of beams of electromagnetic radiation.

- 5 In particular, the two dimensional vertical-cavity surface-emitting laser may comprise a microlens array. Each microlens in the microlens array may be arranged to reduce a divergence of one of the two dimensional array of beams of electromagnetic radiation.

- 10 In general, each one of the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may be partially formed and/or directed by a pinhole from a pinhole array and/or a microlens from a microlens array.

- 15 The beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may each have a divergence of 1° or less.

- For example, the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation each have a divergence of 0.5° or less. For example, the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation each have a divergence of the order of 0.3° or less.

- 20 It will be appreciated that in order for the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation to each have a divergence of 1° or less some collimating optics may be provided (for example a microlens array)

- 25 The imaging surface plasmon resonance apparatus may further comprise a processor operable to determine a concentration of a target molecule from the intensity of the portion of each of the plurality of beams of electromagnetic radiation determined by the detector.

- 30 The detector may comprise any suitable electromagnetic radiation setector. Suitable detectors include, for example, a single-photon avalanche detectors (SPAD), photodiodes, complementary metal-oxide-semiconductor (CMOS) diode arrays and/or charge-coupled device (CCD) arrays.

- 35 The prism may be a right prism. The prism may be a 5x5x5 mm 90-degrees prism.

5 The layer of metal may comprise any type of metal. In some embodiments, the layer of metal may comprise a noble metal. Advantageously, noble metals are less prone to oxidization. For example the layer of metal may comprise gold. The layer of metal may have a thickness of the order of 50 nm.

10 The layer of metal may comprise a substantially continuous layer of metal disposed on or adjacent to the surface of the prism in the vicinity of all of the plurality of regions on the surface of the prism.

Alternatively, the layer of metal may comprise a plurality of discrete patches of metal disposed on or adjacent to the surface of the prism.

15 For example, the layer of metal may comprise a plurality of discrete patches of metal, each discrete patch of metal being disposed in the vicinity of a different one of the plurality of regions on the surface of the prism.

20 The imaging surface plasmon resonance apparatus may further comprise a polarizer arranged to polarize the two dimensional array of beams of electromagnetic radiation such that the electric field of each of the beams of electromagnetic radiation is parallel to the plane of incidence at the surface of the prism.

25 The imaging surface plasmon resonance apparatus may further comprise one or more sensors operable to determine one or more ambient conditions.

For example, the apparatus may comprise sensors operable to determine one or more of: a relative humidity, temperature and/or pressure adjacent the layer of metal.

30 The imaging surface plasmon resonance apparatus may further comprise a printed circuit board to which the two dimensional vertical-cavity surface-emitting laser array and the detector are mounted.

35 The imaging surface plasmon resonance apparatus may further comprise a user interface for providing signals to the two dimensional vertical-cavity surface-emitting laser array and/or receiving signals from the detector.

For example the printed circuit board may be provided with a USB port, which may form part of the user interface.

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Brief Description of the Preferred Embodiments

Some embodiments of the disclosure will now be described by way of example only and with reference to the accompanying drawings, in which:

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Figure 1 shows a schematic illustration of an imaging surface plasmon resonance apparatus according to the present disclosure;

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Figure 2 shows a plan (top) view of the imaging surface plasmon resonance apparatus shown in Figure 1, showing a layer of metal;

Figure 3 shows an example resonance curve for the intensity of the reflected radiation of one of a two dimensional array of beams of electromagnetic radiation within the imaging surface plasmon resonance apparatus shown in Figure 1 as a function of the angle of incidence of that beam of electromagnetic radiation;

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Figure 4 shows a schematic illustration of a known imaging surface plasmon resonance apparatus; and

Figure 5 shows a schematic illustration of another imaging surface plasmon resonance apparatus according to the present disclosure.

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Detailed Description of the Preferred Embodiments

Generally speaking, the disclosure provides an imaging surface plasmon resonance apparatus that uses a two dimensional vertical-cavity surface-emitting laser array operable to produce a two dimensional array of beams of electromagnetic radiation.

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Generally, each beam of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation is incident on a metal layer at substantially the same angle of incidence proximate to a different one of a plurality of receptor patches.

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Some examples of such an imaging surface plasmon resonance apparatus are shown in the accompanying figures, as now discussed.

Figure 1 is a schematic illustration of an imaging surface plasmon resonance apparatus 100 according to the present disclosure. The imaging surface plasmon resonance apparatus 100 comprises a prism 102, a two dimensional vertical-cavity surface-emitting laser array 104; a layer of metal 106 disposed on or adjacent to a surface of the prism 102; and a detector 108.

The prism 102 is a right prism. In particular, the prism 102 is in the form of a right triangular prism having three rectangular surfaces 110, 112, 114 (out of the plane of Figure 1) and two triangular surfaces (parallel to the plane of Figure 1). The triangular cross section of the prism 102 (see Figure 1) is an isosceles right triangle. That is, the triangle has two mutually perpendicular shorter sides (shorter surfaces 110, 112) that are equal in length and one longer side (longer surface 114) that is disposed at 45° to each of the shorter sides 110, 112.

It will be appreciated that the shape of the prism 102 is defined by two parallel, congruent triangular surfaces one being a copy of the other but translated in a direction perpendicular to the other triangular surface (out of the plane of Figure 1), with one rectangular surface extending between each pair of corresponding sides of the two triangular surfaces.

The prism 102 is formed from a light-transmitting material (for example glass). In particular, the prism 102 is formed from a material that is transmits radiation emitted by the two dimensional vertical-cavity surface-emitting laser array 104.

The prism 102 may have dimensions of 5x5x5 mm. That is, the dimensions of each of the shorter surfaces 110, 112 are 5 mm (in the plane of Figure 1) and 5 mm (perpendicular to the plane of Figure 1).

The two dimensional vertical-cavity surface-emitting laser array 104 is operable to produce a two dimensional array of beams of electromagnetic radiation. These are illustrated very schematically in Figure 1 by three dotted lines with arrows. It will be appreciated that there will also be beams of electromagnetic radiation not in the plane of Figure 1 but in parallel planes. It will be further appreciated that in each direction of the two dimensional array of beams of electromagnetic radiation there may be fewer

than or more than three beams of electromagnetic radiation. In general, the two dimensional array of beams of electromagnetic radiation can be an $n \times m$ array of parallel beams of electromagnetic radiation.

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The two dimensional vertical-cavity surface-emitting laser array 104 is arranged such that each one of said two dimensional array of beams of electromagnetic radiation is coupled into the prism 102. In particular, the two dimensional vertical-cavity surface-emitting laser array 104 is disposed adjacent a first one of the shorter surfaces 110 of the prism 102. The two dimensional vertical-cavity surface-emitting laser array 104 is orientated such that the two dimensional array of beams of electromagnetic radiation produced thereby is coupled into the prism 102 through the first shorter surface 110 and is incident on the longer surface 114 of the prism 102.

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The imaging surface plasmon resonance apparatus 100 further comprises a polarizer 116. The polarizer 116 is a plane polarizer, also referred to as a linear polarizer. The polarizer 116 is arranged to polarize the two dimensional array of beams of electromagnetic radiation output by the two dimensional vertical-cavity surface-emitting laser array 104. In particular, the radiation is polarized such that the electric field of each of the beams of electromagnetic radiation is parallel to the plane of incidence at the longer surface 114 of the prism 102 (i.e. parallel to the plane of Figure 1). This polarization state may be referred to as p-polarization.

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The beams of electromagnetic radiation output by the two dimensional vertical-cavity surface-emitting laser array 104 are generally parallel. Therefore, each of the beams of electromagnetic radiation output by the two dimensional vertical-cavity surface-emitting laser array 104 is incident on a different region on the longer surface 114 of the prism 102 at generally the same angle of incidence.

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As will be discussed further below, the longer surface 114 of the prism 102 may be considered to comprise a plurality of regions (each region, for example, defined by a position of each beam spot from the two dimensional array of beams of electromagnetic radiation).

The layer of metal 106 is disposed on the longer surface 114 of the prism 102 in the vicinity of each of the plurality of regions on the surface of the prism 102 (each region being defined by a position of each beam spot from the two dimensional array of beams of electromagnetic radiation on the longer surface). Although the layer of metal 106 is disposed on the longer surface 114 of the prism 102, in alternative embodiments it may be disposed adjacent to said longer surface 114. The layer of metal 106 comprises a layer of gold having a thickness of the order of 50 nm. However, it will be appreciated that in alternative embodiments other metals and thicknesses may be used. In general, the layer of metal may comprise a noble metal.

At least a portion of each of the two dimensional array of beams of electromagnetic radiation is reflected from the interface between the prism 102 and the layer of metal 106. These reflected portions are illustrated very schematically in Figure 1 by three dotted lines with arrows.

The detector 108 is arranged to receive a portion of each of the two dimensional array of beams of electromagnetic radiation which is reflected from the interface between the prism 102 and the layer of metal 106. The detector 108 is operable to determine an intensity of said portion of each of the plurality of beams of electromagnetic radiation.

The detector 108 may comprise any suitable electromagnetic radiation sensor. Suitable detectors include, for example, a single-photon avalanche detectors (SPAD), photodiodes, complementary metal-oxide-semiconductor (CMOS) diode arrays and/or charge-coupled device (CCD) arrays.

Figure 2 shows a plan (top) view of the layer of metal 106 in one embodiment. It will be appreciated that Figure 2 shows a surface of the layer of metal 106 that is distal to the prism 102 and which may be referred to herein as a distal surface of the layer of metal 106. The distal surface is opposite the surface the layer of metal 106 which is disposed on the prism 106, which may be referred to as a proximal surface of the layer of metal 106. It is the proximal surface which forms part of the interface from which the electromagnetic radiation is at least partially reflected. The positions of the beam spots of the two dimensional array of beams of electromagnetic radiation at the interface between the prism 102 and the layer of metal 106 are coincident with the plurality of regions on the longer surface 114 of the prism 102 defined by a position of each beam spot from the two dimensional array of beams of electromagnetic radiation. Also

shown in Figure 2 (in dotted lines) are the positions 200 on the distal surface that correspond to (i.e. are opposite to) the positions of the beam spots from the two dimensional array of beams of electromagnetic radiation at the interface between the prism 102 and the layer of metal 106.

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In use, a receptor (for example a bio-receptor) may be disposed on each of the positions 200 on the distal surface of the layer of metal 106 that correspond to the positions of the beam spots from the two dimensional array of beams of electromagnetic radiation at the interface between the prism 102 and the layer of metal 106. For example, in general, each of the positions 200 on the distal surface of the layer of metal 106 that correspond to the positions of the beam spots of one of the beams of electromagnetic radiation may be provided with a different type of bio-receptor such that the imaging surface plasmon resonance apparatus 100 can be used to identify the presence and/or concentration of a plurality of different target molecules or analytes.

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Each of the positions 200 on the distal surface of the layer of metal 106 that corresponds to the positions of a beam spot from the two dimensional array of beams of electromagnetic radiation at the interface between the prism 102 and the layer of metal 106 may be referred to as a receptor site 200. Therefore, the layer of metal 106 disposed on the longer surface 114 of the prism 102 may be considered to comprise a two dimensional array of receptor sites for supporting a receptor. Each such receptor site 200 being disposed on a surface of the layer of metal 106 that is distal to the prism 102 and adjacent one of the plurality of regions on the surface of the prism 102 defined by the beam spots.

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In the embodiment shown in Figure 2 there is an 8x8 array of 64 receptor sites 200 (each corresponding to a different one of an 8x8 two dimensional array of beams of electromagnetic radiation output by the two dimensional vertical-cavity surface-emitting laser array 104).

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In use, the imaging surface plasmon resonance apparatus 100 may have application in an assay (also sometimes referred to as an assay or a molecular interaction assay), which is arranged to measure the presence or concentration of a specific target molecule, as now discussed.

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In use, a plurality of receptors are provided, each on a different one of the receptor sites 200. The distal surface of the layer of metal 106 is disposed in a sample fluid (for example a gas or a liquid) to be analysed. If certain target molecules are present in the sample fluid they can bind to the receptors. It will be appreciated that these interactions are extremely specific with the receptor and target molecule (analyte) binding in a similar way to a key and a lock. Typically, only the correct analyte is able to bind to the receptor.

The receptor sites 200 may have dimensions of the order of 100-200 μm . A lower limit of the dimensions of the receptor sites 200 may be imposed by the smallest size of a patch of receptor that can be deposited on the layer of metal 106.

As the two dimensional array of beams of electromagnetic radiation is coupled into the prism 102 from the two dimensional vertical-cavity surface-emitting laser array 104 and is incident on the interface between the prism 102 and the layer of metal 106 they are reflected from the interface (and received by the detector 108). The optical properties of the prism 102 and the layer of metal 106 are such that total internal reflection can occur. However, this generates an evanescent wave in the layer of metal 106 which propagates parallel to the interface between the prism 102 and the layer of metal 106 (and in the plane of incidence) and has an amplitude that decays exponentially in a direction perpendicular to the interface between the prism 102 and the layer of metal 106.

At the interface between the layer of metal 106 and an adjacent (dielectric) medium, in this case the receptors at the receptor sites 200, surface plasmon polaritons can be generated. Surface plasmon polaritons are a type of coupled oscillation of electrons (plasmons) within the layer of metal 106 and an electromagnetic oscillation (polaritons) in the dielectric medium. In particular, surface plasmons are collective conduction electron oscillations at the interface of two layers, one layer being a metal (usually a noble metal) and the second layer being a dielectric. If the thickness of the layer of metal 106 is sufficiently thin (with respect to a penetration depth of the evanescent wave) and a resonance condition is met, it can excite surface plasmon polaritons on an opposite side of the layer of metal 106 to the prism 102 (i.e. on the distal surface of the layer of metal 106). This uses some of the energy from the incident electromagnetic

radiation and therefore reduces the intensity of the electromagnetic radiation that is reflected from the interface between the prism 102 and the layer of metal 106. In turn, this reduces the intensity of the reflected portion of each of the two dimensional array of beams of electromagnetic radiation determined by the detector 108.

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The resonance condition is dependent on the wavelength and angle of incidence of the incident electromagnetic radiation (generated by the two dimensional vertical-cavity surface-emitting laser array 104).

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The resonance condition is also dependent on optical properties of both the layer of metal 106 and the adjacent (dielectric) medium, i.e. the receptors at the receptor sites 200. The optical properties of the dielectric (and therefore the resonance condition) vary in dependence on the presence or absence of the specific target molecule (or analyte) that can bind to the receptor. In particular, the optical properties of the dielectric (and therefore the resonance condition) vary in dependence on the concentration of the specific target molecule (or analyte) that is bound to the receptor.

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Figure 3 shows an example resonance curve 300 for the intensity of the reflected radiation of one of the two dimensional array of beams of electromagnetic radiation as a function of the angle of incidence of that beam of electromagnetic radiation. As the concentration of the specific target molecule (or analyte) that is bound to the receptor at the receptor site corresponding to a particular beam of electromagnetic radiation varies, resonance curve 300 will also vary. For example, the resonance curve 300 may move to the left or right such that the angle at which the minimum 302 of the resonance curve 300 occurs varies.

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In some prior art arrangements, apparatus scan through a range of different angles of incidence in order to identify the position of a minimum 302 of the resonance curve 300. However, this can result in a bulky and complicated optical system and/or a reduction in the level of multiplexing that is possible.

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In contrast, the imaging surface plasmon resonance apparatus 100 uses an individual beam of radiation (from the two dimensional vertical-cavity surface-emitting laser array 104) for each receptor site 200 that has a fixed angle of incidence. Furthermore, the beams of electromagnetic radiation in the two dimensional array of beams of

electromagnetic radiation may typically each have a divergence of 0.5° or less (for example, less than 0.3°). Therefore, the detector 108 samples the resonance curve 300 at a fixed angle. Since this fixed angle is on the resonance trough, as the resonance curve 300 moves to the left or right the sampled value will increase or decrease.

The dynamic range of a typical detector 108 is illustrated in Figure 3 as a rectangle 304. The rectangle 304 has a non-zero width in the direction of the axis for the angle of incidence for a number of reasons. For example the electromagnetic radiation will have some non-zero bandwidth, some non-zero divergence and/or the detector 108 subtends a non-zero range of angles at which it can receive the reflected radiation. In addition, the rectangle 304 has a finite height which corresponds to the dynamic range of intensities over which the detector 108 can operate. It can be seen that if the resonance curve 300 moves by more than a few tenths of a degree the imaging surface plasmon resonance apparatus 100 can no longer operate (since the resonance curve 300 no longer overlaps the rectangle 304 representing the dynamic range). Increasing the range of angles of incidence (for example by increasing the divergence of the beams of electromagnetic radiation) or the bandwidth of the radiation will effectively broaden the thickness of the line in of the resonance curve 300, which reduces the resolution of the imaging surface plasmon resonance apparatus 100.

Advantageously, the two dimensional vertical-cavity surface-emitting laser array 104 of the imaging surface plasmon resonance apparatus 100 according to the present disclosure provides an apparatus with a very high degree of multiplexing and which is very compact, as now discussed.

Prior art imaging surface plasmon resonance apparatuses which comprise a prism (upon which the metal layer is disposed) typically have illumination optics to couple radiation into the prism that this bulky and which must be accurately aligned. One such known apparatus 400 is shown in Figure 4.

The known apparatus 400 shown in Figure 4 shares some features in common with the imaging surface plasmon resonance apparatus 100 according to the present disclosure. In particular, the known apparatus comprises: a prism 402, having two mutually perpendicular shorter surfaces 410, 412 and one longer surface 414; a layer

of metal 406 disposed on the longer surface 414 of the prism 102; a detector 408 adjacent one of the shorter surfaces 412; and a polarizer 416.

5 However, in order to illuminate the interface between the prism 402 and the layer of metal 406, the known apparatus 400 uses a different illumination system, as now discussed.

10 The known apparatus 400 uses a single light source 418 (for example a diode laser) which illuminates a single pinhole 420 in a screen 422. The single pinhole 420 acts as a point source and illuminates a collimating lens 424 to ensure that the (divergent) electromagnetic radiation from the pinhole 420 is collimated and is incident on the metal layer 406 at a suitable angle to observe the resonance. However, in order to do this, the pinhole 420 should be disposed at a focal point of the collimating lens 424. It will be appreciated that the desired dimension of the collimated beam will be of the order of the dimensions of the prism 402. Furthermore, the focal length of the lens will typically scale with the size of the lens 424. Therefore, with such an arrangement 400 the illumination system is at least the same size as the prism 402 or larger.

20 Compared to such known systems, the present imaging surface plasmon resonance apparatus 100 disclosed here has the following advantages. By providing a two dimensional vertical-cavity surface-emitting laser array 104 operable to produce a two dimensional array of beams of electromagnetic radiation no bulky collimating illumination optics is required. The two dimensional array of beams of electromagnetic radiation produced by a two dimensional vertical-cavity surface-emitting laser array 104 may have some divergence, however, due these can be collimated with significantly smaller optics (for example a microlens array and/or a pinhole array). Advantageously, this allows for a particularly compact apparatus. For example, the optical volume may be reduced by at least a factor of 10.

30 Some prior art imaging surface plasmon resonance apparatuses are arranged to illuminate a metal layer with electromagnetic radiation at a plurality of different angles and the amount of reflected radiation from each is determined by a separate detector so as to determine a resonance spectrum. It will be appreciated that these prior art arrangements are incompatible with an arrangement that has a two dimensional vertical-cavity surface-emitting laser array operable to produce a two dimensional array

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of beams of electromagnetic radiation that are generally mutually parallel and are incident on the interface between the prism 102 and the layer of metal 106 at substantially the same angle of incidence (since a range of angles of incidence is required).

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Compared to such known systems, the present imaging surface plasmon resonance apparatus 100 disclosed here has the advantage that it allows for a two dimensional array of beams of electromagnetic radiation that are generally mutually parallel and therefore incident on the surface 114 of the prism 402 at substantially the same angle.

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This therefore allows for a two dimensional array of different receptors to be simultaneously monitored whilst all of these remain within a dynamic range of a detector for determining the presence and/or concentration of a target molecule being bound to those receptors. Advantageously, this significantly increases the number of receptors that can be monitored simultaneously (i.e. it allows a significant increase in the amount of multiplexing).

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It will be appreciated that the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may be considered to be generally mutually parallel if the directions of all of the beams of electromagnetic radiation vary by less than 1° . For example, the directions of all of the beams of electromagnetic radiation may vary by less than 0.5° . For example, the directions of all of the beams of electromagnetic radiation may vary by less than 0.1° . The direction of each beam of electromagnetic radiation may be the direction of a chief ray of that beam.

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It will be appreciated that beams of electromagnetic radiation may be considered to be have the same angle of incidence if their angles of incidence vary by less than 1° . For example, the angles of incidence of all of the beams of electromagnetic radiation may vary by less than 0.5° . For example, the angles of incidence of all of the beams of electromagnetic radiation may vary by less than 0.1° .

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In some embodiments, the imaging surface plasmon resonance apparatus 100 may further comprise a pinhole array (not shown) disposed between the two dimensional vertical-cavity surface-emitting laser 104 and the prism 102. Each vertical-cavity surface-emitting laser in the two dimensional vertical-cavity surface-emitting laser array

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104 may be aligned with a different one of the pinholes in the pinhole array. Each one of the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation may be at least partially formed or controlled by a pinhole from the pinhole array. Advantageously, the pinhole array may improve control over the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation.

In some embodiments, as shown in Figure 2, the layer of metal 106 may comprise a substantially continuous layer of metal disposed on, or adjacent to, the surface 114 of the prism 102 in the vicinity of all of the plurality of regions on the surface of the prism 102 corresponding to one of the beam spots. That is, all of the receptor sites 200 shown in Figure 2 are provided on a single layer of metal 106.

Alternatively, in other embodiments, the layer of metal 106, may comprise a plurality of discrete patches of metal disposed on or adjacent to the surface 114 of the prism 102. For example, the layer of metal 106 may comprise a plurality of discrete patches of metal, each discrete patch of metal being disposed in the vicinity of a different one of the plurality of regions on the surface of the prism 102 corresponding to one of the beam spots. That is, each of the receptor sites 200 shown in Figure 2 may be provided on a different patch of metal 106.

Figure 5 is a schematic illustration of another imaging surface plasmon resonance apparatus 500 according to the present disclosure. The imaging surface plasmon resonance apparatus 500 shown in Figure 5 shares many features in common with the imaging surface plasmon resonance apparatus 100 shown in Figure 1. Such features share common reference numerals and will not be described further here unless a feature of the imaging surface plasmon resonance apparatus 500 shown in Figure 5 differs from the corresponding feature of the imaging surface plasmon resonance apparatus 100 shown in Figure 1.

In the following, the differences between the imaging surface plasmon resonance apparatus 500 shown in Figure 5 and the imaging surface plasmon resonance apparatus 100 shown in Figure 1 are described. In particular, the imaging surface plasmon resonance apparatus 500 shown in Figure 5 comprises some additional,

optional features, not present in the imaging surface plasmon resonance apparatus 100 shown in Figure 1.

5 The imaging surface plasmon resonance apparatus 500 further comprises a printed circuit board 502. The two dimensional vertical-cavity surface-emitting laser array 104 is mounted on the printed circuit board 502 via a support 504 and a contact 506 (for example one or more soldered contacts). Similarly, the detector 108 is mounted on the printed circuit board 502 via a support 508 and a contact 510 (for example one or more soldered contacts). The supports 504, 508 may comprise printed circuit boards.

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The imaging surface plasmon resonance apparatus 500 further comprising one or more sensors operable to determine one or more ambient conditions. In particular, the imaging surface plasmon resonance apparatus 500 further comprises a support 512 which is provided with one or more sensors operable to determine one or more ambient conditions. The support 512 may comprise, for example, sensors operable to determine one or more of: a relative humidity, temperature and/or pressure adjacent the layer of metal 106. The support 512 is connected to the support 508 of the detector 108 via a contact 514 (for example one or more soldered contacts).

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20 The imaging surface plasmon resonance apparatus 500 further comprises a universal serial bus (USB) port 516. The USB port 516 provides a user interface for providing signals to the two dimensional vertical-cavity surface-emitting laser array 104. The USB port 516 provides a user interface for receiving signals from the detector 108. The USB port 516 provides a user interface for receiving signals from the one or more sensors provided on the support 516.

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Optionally, the imaging surface plasmon resonance apparatus 500 may further comprise a processor 518 operable to determine a concentration of a target molecule from the intensity of the portion of each of the plurality of beams of electromagnetic radiation determined by the detector 108. The processor 518 may be operable to implement the methods described above with reference to Figure 3. Alternatively, signals from the detector 108 may be processed by a separate processor connected to the detector 108 via the USB port 516.

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Embodiments of the present disclosure can be employed in many different applications including any optical system or imaging system, for example, in the cellular telephone (mobile telephone) and other industries.

5 List of reference numerals:

- 100 imaging plasmon resonance apparatus
- 102 prism
- 104 two dimensional vertical-cavity surface-emitting laser array
- 106 layer of metal
- 108 detector
- 110 shorter rectangular surface of prism
- 112 shorter rectangular surface of prism
- 114 longer rectangular surface of prism
- 116 polarizer

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200 receptor sites

300 resonance curve

302 minimum

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304 rectangle representing dynamic range

400 known apparatus

402 prism

406 layer of metal

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408 detector

410 shorter rectangular surface of prism

412 shorter rectangular surface of prism

414 longer rectangular surface of prism

416 polarizer

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418 light source

420 single pinhole

422 screen

424 collimating lens

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500 imaging surface plasmon resonance apparatus

502 printed circuit board
504 support
506 contact
508 support
510 contact
512 support
514 contact
516 universal serial bus port
518 processor

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The skilled person will understand that in the preceding description and appended claims, positional terms such as 'above', 'along', 'side', etc. are made with reference to conceptual illustrations, such as those shown in the appended drawings. These terms are used for ease of reference but are not intended to be of limiting nature. These terms are therefore to be understood as referring to an object when in an orientation as shown in the accompanying drawings.

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Although the disclosure has been described in terms of preferred embodiments as set forth above, it should be understood that these embodiments are illustrative only and that the claims are not limited to those embodiments. Those skilled in the art will be able to make modifications and alternatives in view of the disclosure which are contemplated as falling within the scope of the appended claims. Each feature disclosed or illustrated in the present specification may be incorporated in any embodiments, whether alone or in any appropriate combination with any other feature disclosed or illustrated herein.

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CLAIMS:

1. An imaging surface plasmon resonance apparatus comprising:

a prism;

5 a two dimensional vertical-cavity surface-emitting laser array operable to produce a two dimensional array of beams of electromagnetic radiation and arranged such that each one of said two dimensional array of beams of electromagnetic radiation is coupled into the prism and is incident on a different one of a plurality of regions on a surface of the prism at substantially the same angle of incidence;

10 a layer of metal disposed on or adjacent to the surface of the prism in the vicinity of each of the plurality of regions on the surface of the prism; and

a detector arranged to receive a portion of each of the two dimensional array of beams of electromagnetic radiation which is reflected from the interface between the prism and the layer of metal and operable to determine an intensity of said portion of
15 each of the plurality of beams of electromagnetic radiation.

2. An imaging surface plasmon resonance apparatus comprising:

a prism;

a two dimensional vertical-cavity surface-emitting laser array operable to
20 produce a two dimensional array of beams of electromagnetic radiation and arranged such that each one of said two dimensional array of beams of electromagnetic radiation is coupled into the prism and is incident on a different one of a plurality of regions on a surface of the prism;

a layer of metal disposed on or adjacent to the surface of the prism in the
25 vicinity of each of the plurality of regions on the surface of the prism and comprising a two dimensional array of receptor sites for supporting a receptor, each receptor site disposed on a surface of the layer of metal that is distal to the prism and adjacent one of the plurality of regions on the surface of the prism; and

a detector arranged to receive a portion of each of the two dimensional array of
30 beams of electromagnetic radiation which is reflected from the interface between the prism and the layer of metal and operable to determine an intensity of said portion of each of the plurality of beams of electromagnetic radiation.

3. The imaging surface plasmon resonance apparatus of claim 1 or claim 2 further comprising a plurality of receptors, each disposed on a surface of the layer of metal that is distal to the prism.

5 4. The imaging surface plasmon resonance apparatus of any preceding claim further comprising a pinhole array disposed between the two dimensional vertical-cavity surface-emitting laser and the prism, each vertical-cavity surface-emitting laser in the two dimensional vertical-cavity surface-emitting laser array being aligned with a different one of the pinholes in the pinhole array.

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5. The imaging surface plasmon resonance apparatus of any preceding claim wherein the two dimensional vertical-cavity surface-emitting laser comprises a microlens array, each microlens in the microlens array being arranged to reduce a divergence of one of the two dimensional array of beams of electromagnetic radiation.

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6. The imaging surface plasmon resonance apparatus of any preceding claim wherein the beams of electromagnetic radiation in the two dimensional array of beams of electromagnetic radiation each have a divergence of 1° or less.

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7. The imaging surface plasmon resonance apparatus of any preceding claim further comprising a processor operable to determine a concentration of a target molecule from the intensity of the portion of each of the plurality of beams of electromagnetic radiation determined by the detector.

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8. The imaging surface plasmon resonance apparatus of any preceding claim wherein the layer of metal comprises a substantially continuous layer of metal disposed on or adjacent to the surface of the prism in the vicinity of all of the plurality of regions on the surface of the prism.

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9. The imaging surface plasmon resonance apparatus of any one of claims 1 to 8 wherein the layer of metal comprises a plurality of discrete patches of metal disposed on or adjacent to the surface of the prism.

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10. The imaging surface plasmon resonance apparatus of any preceding claim further comprising a polarizer arranged to polarize the two dimensional array of beams

of electromagnetic radiation such that the electric field of each of the beams of electromagnetic radiation is parallel to the plane of incidence at the surface of the prism.

5 11. The imaging surface plasmon resonance apparatus of any preceding claim further comprising one or more sensors operable to determine one or more ambient conditions.

10 12. The imaging surface plasmon resonance apparatus of any preceding claim further comprising a printed circuit board to which the two dimensional vertical-cavity surface-emitting laser array and the detector are mounted.

15 13. The imaging surface plasmon resonance apparatus of any preceding claim further comprising a user interface for providing signals to the two dimensional vertical-cavity surface-emitting laser array and/or receiving signals from the detector.

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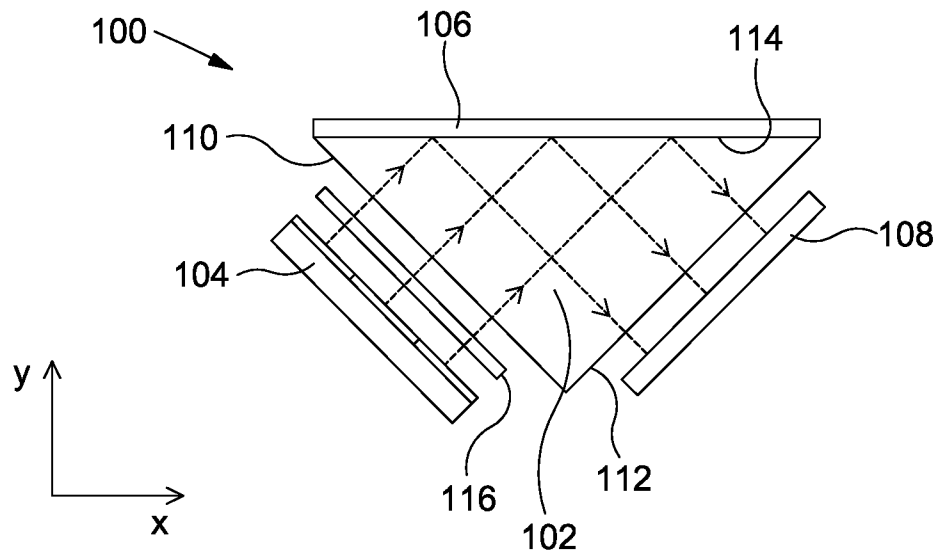


Fig. 1

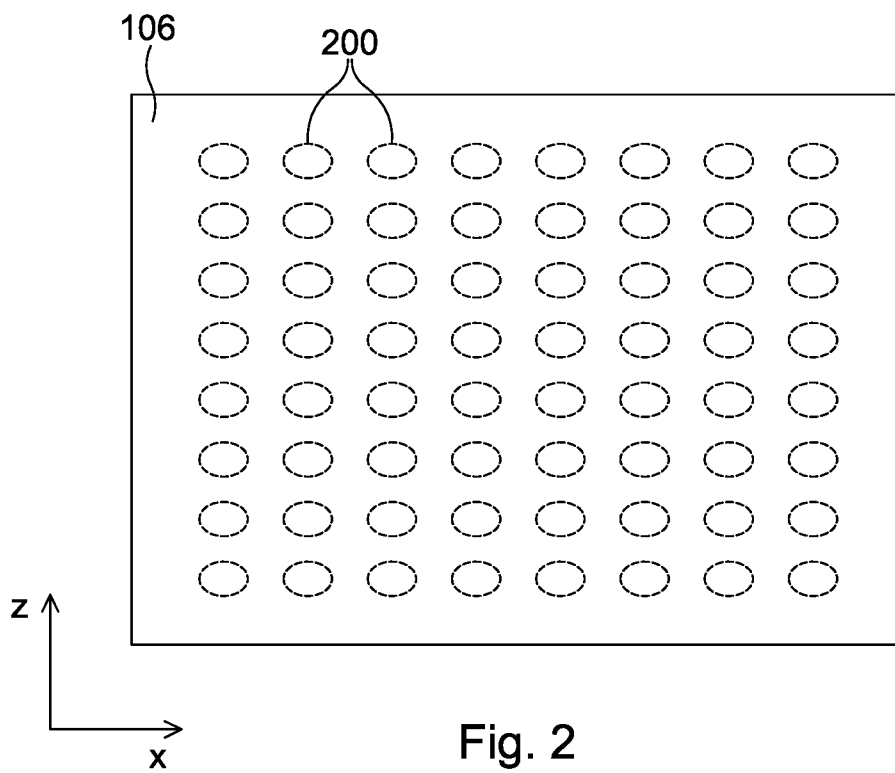


Fig. 2

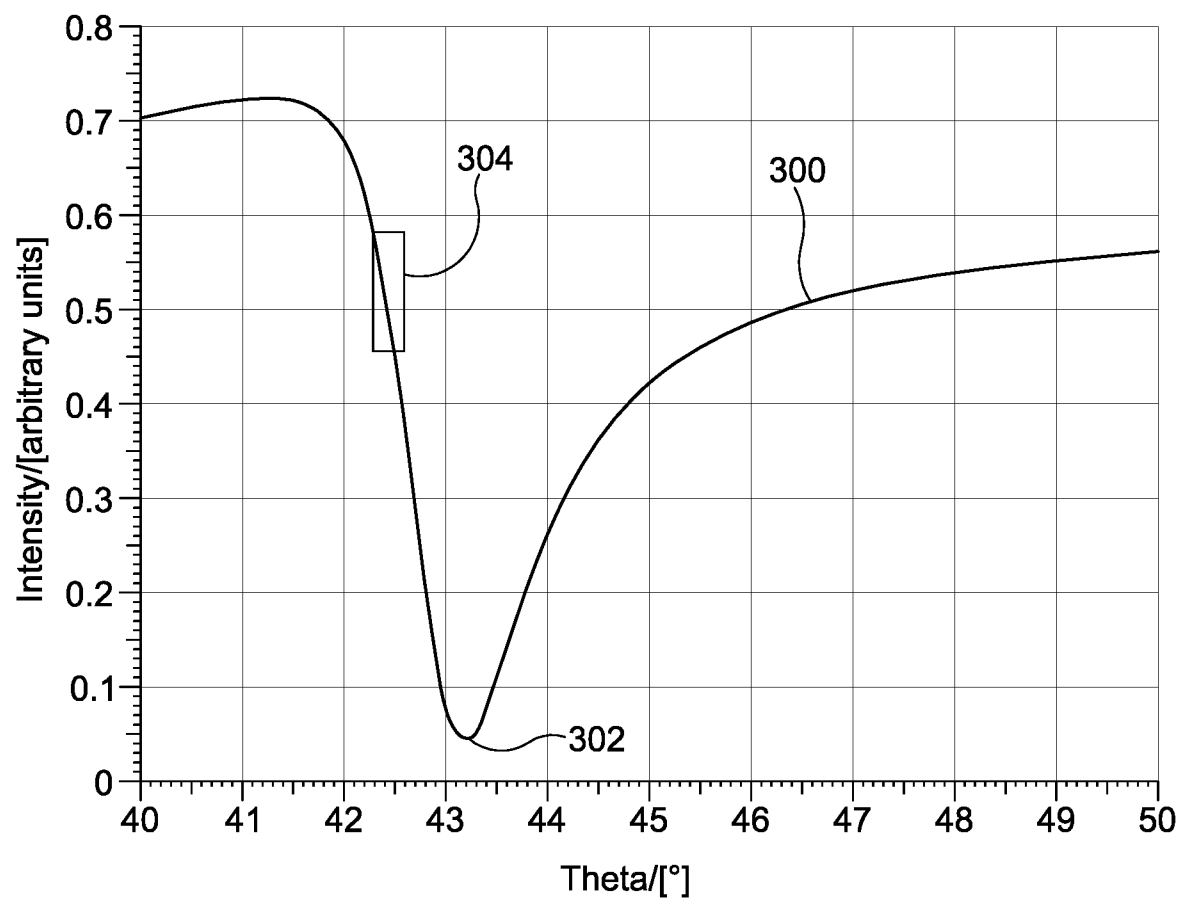


Fig. 3

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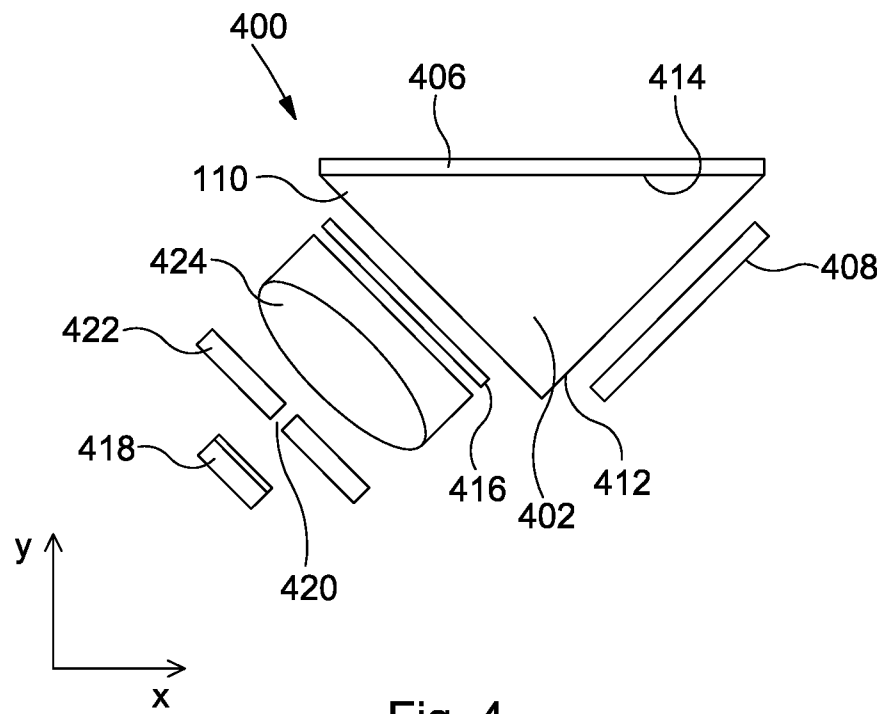


Fig. 4

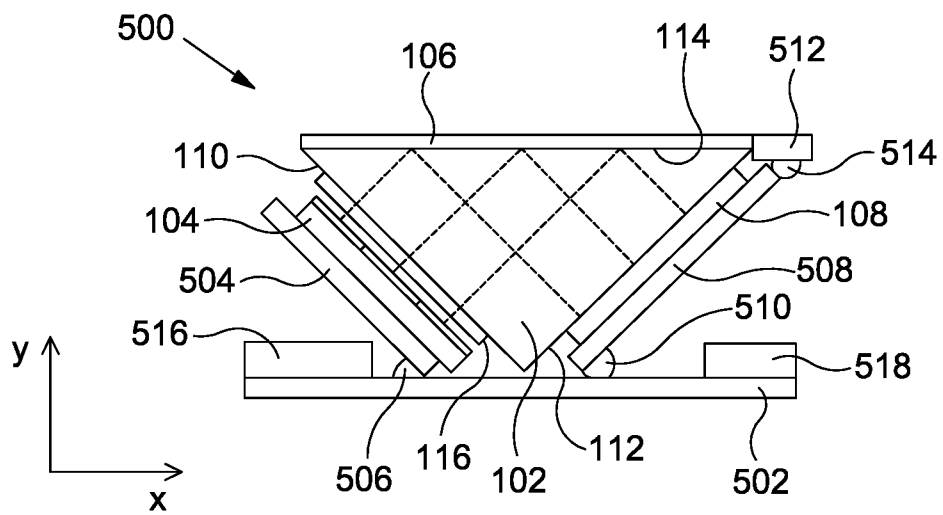


Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/067933

A. CLASSIFICATION OF SUBJECT MATTER

INV. G01N21/552 G01N21/25 G01N33/543
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 practicable, search terms used)

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Further documents are listed in the continuation of Box C.



See patent family annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 September 2021

Date of mailing of the international search report

15/09/2021

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INTERNATIONAL SEARCH REPORT

International application No

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