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(54) **STRUCTURED ILLUMINATION OF A SAMPLE**

(57) A system includes: a light source; first and second gratings; and at least one reflective component that in a first position forms a first light path originating at the light source and extending to the first grating and thereafter to a subsequent component in the system, and that in a second position forms a second light path originating at the light source and extending to the second grating and thereafter to the subsequent component.

Dit octrooi is verleend ongeacht het bijgevoegde resultaat van het onderzoek naar de stand van de techniek en schriftelijke opinie. Het octrooischrift komt overeen met de oorspronkelijk ingediende stukken.

STRUCTURED ILLUMINATION OF A SAMPLE

BACKGROUND

[0001] Structured illumination microscopy (SIM) has been used to increase the resolution of images obtained from a sample. SIM utilizes several images of a sample with differing fringe patterns so that different locations on the sample are exposed to a range of illumination intensities. In some instances, the procedure can be repeated by rotating the pattern orientation about the optical axis at separate angles. The captured images may be assembled into a single image having an extended spatial frequency bandwidth, which may be retransformed into real space to generate an image having a higher resolution than one captured by a conventional microscope. Existing approaches to SIM may have one or more characteristics that increase the complexity, size, manufacturing cost, and/or the cost of operation of the system.

SUMMARY

[0002] In a first aspect, a system includes: a light source; a first grating and a second grating; and at least one reflective component selectively positionable in a first position in which it forms a first light path originating at the light source and extending to the first grating and thereafter to a subsequent component in the system, and in a second position in which it forms a second light path originating at the light source and extending to the second grating and thereafter to the subsequent component.

[0003] Implementations can include any or all of the following features. The reflective component includes a rotatable mirror that assumes the first or second positions. The rotatable mirror is double-sided and comprises an elongate member, and wherein an axle is coupled to the elongate member substantially at a center of the elongate member. The axle is offset from and substantially parallel to a plane defined by the first and second light paths. When the rotatable mirror assumes the first position, a first end of the elongate member interrupts a first path originating at the light source and extending to the second grating, and reflects first light originating at the light source toward the first grating. When the rotatable mirror assumes the first position, a second end of the elongate member does not interrupt a second path from the first grating to the subsequent component. When the rotatable mirror assumes the second position, a second end of the elongate member interrupts a second path from the second grating, and reflects second light from the second grating toward the subsequent component. When the rotatable mirror assumes the second position, the first end of the elongate member does not interrupt the first path originating at the light source and extending to the second grating. The first and second gratings are oriented so that respective normals thereof are substantially antiparallel to each other, and wherein the axle is substantially aligned with the normals. The rotatable mirror reciprocates

between the first and second positions. The reflective component includes a first translatable mirror that undergoes first translation into the first position. The reflective component further includes a second translatable mirror that undergoes second translation into the second position. The first and second translations are substantially perpendicular to a plane defined by the first and second light paths. The first translation is substantially parallel to a plane defined by the first and second light paths. The first translatable mirror undergoes a second translation into the second position, and wherein the second translation is substantially parallel to the plane defined by the first and second light paths. The reflective component includes a rotatable prism that assumes the first or second positions. The first and second gratings are positioned adjacent each other, wherein the rotatable prism in the first position reflects first light along the first light path toward the first grating, and wherein the rotatable prism in the second position reflects second light along the second light path toward the second grating. The first and second gratings face toward the subsequent component. The first and second gratings are in a fixed position relative to the light source. The subsequent component is a phase selector. The system further comprises a phase selector positioned between the light source and the reflective component. The phase selector is in a fixed position relative to the light source.

[0004] In a second aspect, which may be but need not be combined with the first aspect, a system includes: a light source; a first grating and a second grating; and at least one reflective component including at least one mirror selectively positionable in a first position in which it interrupts a first path originating at the light source and extending to the second grating, and directs first light toward the first grating, while not interrupting a second path from the first grating to a subsequent component in the system, and in a second position in which it interrupts a third path from the second grating and directs second light from the second grating toward the subsequent component, while not interrupting the first path.

[0005] In a third aspect, the system described above forms the optical subsystem of a structured illumination microcopy device.

[0006] Implementations can include any or all of the following features. Respective grating orientations of the first and second gratings are substantially perpendicular to each other. The first and second gratings face toward each other. The subsequent component is a phase selector. The system further comprises a phase selector positioned between the light source and the at least one mirror.

[0007] In a fourth aspect, a method includes: positioning at least one reflective component to define a first light path originating at a light source and extending to a first grating and thereafter to a subsequent component; directing first phase-selected light from the first light path onto a sample; positioning the at least one reflective component to define a second light path originating at the light source and extending to a second grating and thereafter to the subsequent component;

and directing second phase-selected light from the second light path onto the sample.

[0008] Implementations can include any or all of the following features. Positioning the at least one reflective component to define the first light path comprises interrupting a first path originating at the light source and extending to the second grating and directing first light toward the first grating, while not interrupting a second path from the first grating to the subsequent component. Positioning the at least one reflective component to define the second light path comprises interrupting a third path from the second grating and directing second light from the second grating toward the subsequent component, while not interrupting the first path.

[0009] It should be appreciated that all combinations of the foregoing concepts and additional concepts discussed in greater detail below (provided such concepts are not mutually inconsistent) are contemplated as being part of the inventive subject matter disclosed herein. In particular, all combinations of claimed subject matter appearing at the end of this disclosure are contemplated as being part of the inventive subject matter disclosed herein.

BRIEF DESCRIPTION OF DRAWINGS

[0010] FIG. 1 is a schematic view of an example system that can facilitate structured illumination microscopy (SIM) and in which a phase selector is placed after a reflective component.

[0011] FIG. 2 shows an example of a rotating inline grating system (RIGS) having a rotatable mirror that may be implemented as part of the system of FIG. 1.

[0012] FIG. 3A is a top view of the system of FIG. 2 showing the rotatable mirror in a first position.

[0013] FIG. 3B is a perspective detailed view of the rotatable mirror in the first position shown in FIG. 3A.

[0014] FIG. 4A is a top view of the system of FIG. 2 showing the rotatable mirror in a second position.

[0015] FIG. 4B is a perspective detailed view of the rotatable mirror in the second position shown in FIG. 4A.

[0016] FIG. 5 is a schematic view of a system having one or more mirrors that may be implemented as part of the system of FIG. 1 to facilitate SIM.

[0017] FIG. 6 is a schematic view of an example system having a translatable mirror that may be implemented as part of the system of FIG. 1.

[0018] FIGS. 7A-B schematically show an example of vertically translating mirrors that may be implemented as part of the system in FIG. 6.

[0019] FIGS. 8A-B schematically show an example of horizontally translating mirrors

that may be implemented as part of the system in FIG. 6.

[0020] FIG. 9 is a schematic view of a system having a rotatable prism that may be implemented as part of the system of FIG. 1.

[0021] FIG. 10 shows an example of a method that can be used for positioning one or more reflective components for performing SIM.

[0022] FIG. 11 is a schematic view of an example system that can facilitate SIM and in which a phase selector is placed before a reflective component.

[0023] FIG. 12 is a schematic view of an example system that can be used for biological and/or chemical analysis; the system of FIG. 1 can be a part of the system in FIG. 12.

DETAILED DESCRIPTION

[0024] This document describes examples of systems and techniques that can provide structured illumination, including, but not limited to, by facilitating structured illumination microscopy (SIM). Such systems/techniques can provide one or more advantages over existing approaches, for example as will be described below.

[0025] Imaging (e.g., using SIM) can be performed to analyze a sample of any of multiple materials. In some implementations, SIM imaging or another type of imaging can be performed as part of biological or chemical analysis, such as a process of sequencing genetic material. In one example, the process can be a DNA sequencing process, e.g., sequencing-by-synthesis or next-generation sequencing (also known as high-throughput sequencing). In another example, the process may be used to enable genotyping. As one skilled in the art will know, genotyping involves determining differences in the genetic make-up (genotype) of an individual by examining the individual's DNA sequence using biological assays and comparing it to another individual's sequence or a reference sequence. Such processes can involve fluorescent imaging, where a sample of genetic material is subjected to light (e.g., a laser beam) to trigger a fluorescent response by one or more markers on the genetic material. Some nucleotides can have fluorescent tags associated with the nucleotide to fluoresce responsive to exposure to the energy source. A wavelength of the fluorescent response can be used to determine the presence of a corresponding nucleotide. Fluorescent responses can be detected over the course of the sequencing process and used to build a record of nucleotides in the sample.

[0026] SIM imaging is based on spatially structured light. For example, the structure can consist of or include a pattern in the illuminating light that helps increase the resolution of the obtained image(s). In some implementations, the structure can include patterns of fringes. Fringes of light can be generated by impinging a light beam on a diffraction grating (referred to as a grating for simplicity) such that reflective or transmissive diffraction occurs. The structured light can be impinged on the sample, illuminating the sample according to the respective fringes which may

occur according to some periodicity. For example, images of the sample can be acquired at different phases of the fringes in the structured light, sometimes referred to as the respective pattern phases of the images. This can allow various locations on the sample to be exposed to a multitude of illumination intensities. The pattern of the structured light can be rotated relative to the sample, and the images just mentioned can be captured for each of the rotation angles.

[0027] Different types of gratings can be used in various implementations. The grating(s) can include one or more forms of periodic structure. In some implementations, the gratings can be formed by removing or omitting physical material from a substrate. In other implementations, optical filters or other non-physical materials may be implemented to form the gratings. For example, the substrate can be provided with a set of slits and/or grooves therein to form the grating. In some implementations, the grating can be formed by adding material to the substrate. For example, periodically spaced structures can be formed on the substrate by the same or a different material.

[0028] With a SIM system, it can be preferable that the system is capable of rapidly processing samples so as to facilitate a high throughput. Faster SIM imaging can enable a greater throughput of the analysis system. That is, more chemical or biological samples can be imaged over the same time period. For high throughput, the system may illuminate a relatively large area of the sample with high-contrast fringes and/or rapidly switch between fringe orientations. For such a system to achieve a high throughput, the imaging should therefore be highly repeatable and reliable. High optical power may be useful to keep exposure times relatively short. As such, good optical efficiency and a powerful light source may be useful to achieve a high optical power.

[0029] In some SIM systems that project high-contrast fringes, a coherent light source may be used. In such systems, a single-mode laser may be such a coherent light source, but may be cost prohibitive in the context of the type of analysis being done and/or the amount of power required. Other types of light sources such as a light-emitting diode (LED) or an arc lamp may not provide sufficient coherence for the application. Thus, a multimode laser can be a viable candidate as a coherent light source but is associated with the characteristic of having spectral multimode patterns. To achieve a desired uniformity with a multimode laser, the multimode laser output can be mode-scrambled. However, use of mode-scrambled multimode lasers can result in multiple light sources to selectively excite multiple gratings unless an optical switch is used, which may increase cost and optical system complexity. In addition, use of mode-scrambled multimode lasers may also result in reliance on a relay lens system to obtain zero-order blocking for a desired fringe frequency and modulation contrast.

[0030] Described herein are implementations of structured illumination systems for analyzing samples, some such systems including a single light source, at least two fixed gratings, and a mechanism for directing the entire beam from the light source onto one or the other of the

gratings. A phase selector can be used for choosing the pattern phase. The mechanism can include either of a rotary double-sided mirror, non-rotating mirrors, or a rotatable prism mirror, to name a few examples. With a rotary double-sided mirror, a blade of the mirror can be placed in a first position for reflection only onto the first grating, and can be placed in a second position for reflection only onto the second grating. A non-rotating mirror can translate into the first or second positions. A rotatable prism mirror can selectively direct light from the light source onto the first or second grating.

[0031] The examples described herein can provide advantages compared to previous approaches. In some implementations, a rotatable mirror can be used to switch between excitation of the respective gratings. Such a rotatable mirror can switch between two optical paths using a single light source. In addition, such a rotatable mirror can be sized such that errors in rotational position and/or thermal effects do not appreciably alter the optical paths. Reduction of the effect of such rotational variations and/or thermal effects on the optical paths can allow the SIM imaging system to operate faster as the component moving the rotatable mirror (e.g., a motor) can operate faster as there is less reliance on fine tuning of the positioning compared to systems that implement moveable gratings or other components. If more than two optical paths are to be implemented, multiple rotatable mirrors can be implemented for a multiple optical paths. In some implementations, the gratings may be fixed in place rather than gratings that rotate, translate, or otherwise move as part of operation. This can provide angle precision and stability, to name just two examples, as the gratings also do not require fine positional tuning. In some implementations, a single light source may be used as the rotatable mirror can be rotated into or out of a respective light path to block or unblock a corresponding light path from the single light source. By implementing the currently proposed system, which includes this selectively positionable reflective component, as the optical subsystem of a SIM system, mode-blocking may be omitted for the multimode laser and the entire path of light may be either transmitted or blocked. Such a system can also eliminate having the orders of light emitted from a grating be separable from each other at some particular stage of the system (e.g., to require the orders of light to be in focus at some stage where one or more orders are blocked, and one or more orders are allowed to propagate). That is, a grating can emit light that is not diffracted and that is referred to as light of order 0, and also emit diffracted light that propagates on opposite sides of the 0-order light and is referred to as light of orders +/– 1, respectively. In a system that uses order-blocking, the orders 0 and +/– 1 of light can all be in focus at a blocking stage where, say, the 0-order light is blocked and the orders +/– 1 are not blocked. In systems that do not use order-blocking, some or all of the orders of light can come into focus elsewhere in the system (e.g., at an objective lens), and such a system can have a shorter optical path length. In addition, such a system with a selectively positionable reflective component may omit an optical switch, thereby reducing the components and complexity of the optical

system. Moreover, such a system can increase the overall compactness; for example, by omitting a relay lens system that facilitates recombining multiple grating paths.

[0032] FIG. 1 schematically shows an example of a system 100 that can facilitate SIM imaging. The system 100 can be used in combination with one or more other examples described herein. Some components in this and other examples are shown conceptually as a block or other generic component; such component(s) can be implemented in form of one or more separate or integrated components so as to perform the indicated function(s).

[0033] The system 100 includes a light source 102. The light source 102 can be selected based on the coherence and/or power output for which the system 100 is to be implemented. For example, a multimode laser can be used as the light source 102.

[0034] The system 100 includes a light-structuring component 104 that receives light from the light source 102. In some implementations, the light-structuring component 104 facilitates that the received light impinges on one or more gratings so as to generate a pattern of light fringes. For example, one or more reflective components can be used for directing the light onto the proper grating and/or to further guide the light toward a next stage in the system 100. Examples of the light-structuring component 104 are described below. A beam 106 extending between the light source 102 and the light-structuring component 104 schematically illustrates the propagation of light. The light-structuring component 104 can generate structured light and provide the structured light to a subsequent component in the system 100.

[0035] In some implementations, the subsequent component is a phase selector 108 in the system 100. The phase selector 108 can receive light from the light-structuring component 104. In some implementations, the phase selector 108 is used for selecting the pattern phase at which an image will be captured. For example, the phase selector 108 can facilitate selecting among multiple candidate pattern phases according to a desired illumination of the sample or to a required degree of resolution, as described in greater detail herein.

[0036] The system 100 includes a projection lens 110 that can receive light from the phase selector 108. Such light can be referred to as phase-selected light to indicate that the light corresponds to a selection of the particular pattern phase(s) having been done, such as by way of the phase selector 108. The projection lens 110 can include one or more optical elements such as lenses that condition the phase-selected light before it impinges on a next stage in the system 100.

[0037] The system 100 includes a mirror 112 that at least partially reflects light from the projection lens 110 toward an objective lens 114. In some implementations, the mirror 112 provides selective transmission, such as to reflect some part(s) of illuminating light arriving from the projection lens 110 and to transmit at least some part of imaging light arriving at the mirror 112 from the objective lens 114. For example, the mirror 112 can be a dichroic mirror.

[0038] The objective lens 114 receives illumination light from the mirror 112. The

objective lens 114 can include one or more optical elements such as lenses that condition light from the projection lens 110 (as reflected by the mirror 112) before light impinges on a next stage in the system 100.

[0039] The objective lens 114 directs light onto a sample 116. In some implementations, the sample 116 includes one or more materials to be analyzed. For example, the sample 116 can include genetic material to be illuminated for detection of fluorescent responses. The sample 116 can be held on a suitable substrate, including, but not limited to, a flowcell that allows liquids or other fluids to selectively be flowed relative to the sample. For example, the sample 116 can be subjected to reagent containing one or more nucleotides prior to illumination and thereafter image capturing and analysis.

[0040] The sample 116 can be held by a stage 118 in the system 100. The stage 118 can provide one or more types of manipulation relative to the sample 116. In some implementations, physical movement of the sample 116 can be provided. For example, the stage 118 can translationally and/or rotationally reposition the sample 116 relative to at least one other component of the system 100. In some implementations, thermal treatment of the sample 116 can be provided. For example, the stage 118 can heat and/or cool the sample 116.

[0041] Phase selection can be facilitated by the stage 118. In some implementations, the stage 118 can translate the sample 116 a distance relative to stationary light fringes to accomplish phase selection (e.g., using a piezo actuator in the stage 118). For example, the phase selector 108 can then be bypassed in, or eliminated from, the system 100.

[0042] That is, light originating in the light source 102, conditioned in the described components, can be directed at the sample 116 for illumination after propagating through the objective lens 114. Any light emitted by the sample 116 can traverse the objective lens 114 in an opposite direction and partially or entirely be transmitted through the mirror 112. The system 100 can include a filter component 120 receiving light from the objective lens 114 through the mirror 112. The filter component 120 can filter such light in one or more ways. For example, the filter component 120 can pass through some particular wavelength(s) and/or block (or reflect) some other particular wavelength(s). In some implementations, the mirror 112 can incorporate the filter component 120 as part of the mirror, such as by positioning the filter component 120 on a rear surface of the mirror 112.

[0043] Light traversing the filter component 120 can enter a camera system 122 in the system 100. The camera system 122 can include one or more image sensors capable of detecting electromagnetic radiation of the kind(s) relevant to the analysis to be performed. In some implementations, the camera system 122 is configured for capturing images using fluorescent light. For example, the camera system 122 can include a charge-coupled device, a complementary metal-oxide semiconductor device, or other image capture device. The camera system 122 can generate

output in digital and/or analog form. For example, data corresponding to an image captured by the camera system 122 can be stored by the camera system 122 or can be sent to a separate component (e.g., a computer system or other device) for storage and/or analysis.

[0044] Operation of the system 100 or other apparatuses or machines will be exemplified below. In some implementations, the light-structuring component 104 includes one or more reflective components and at least one grating. For example, the reflective component can redirect light toward, or arriving from, the grating(s) to generate light that is conditioned so as to provide one or more forms of illumination of the sample 116. In some implementations, the light-structuring component 104 can condition the light from the light source 102 to perform SIM imaging. For example, such structured light may not need to be in focus at a particular position within the light-structuring component 104; rather, the structured light (e.g., fringes of a diffraction pattern) can be focused at another stage of the system 100, including, but not limited to, at a back of the objective lens 114.

[0045] FIG. 2 shows an example of a system 200 having a rotatable mirror 202. The system 200 can be used in combination with one or more other examples described herein. An individual component of the system 200 can perform a similar or identical function to a corresponding component described with reference to another example in this description.

[0046] The system 200 includes a light source 204. In some implementations, the light source 204 provides light that it in turn receives through at least one fiber optic cable 206. For example, the light source 204 and the fiber optic cable 206 can collectively be considered a fiber launch module.

[0047] The system 200 includes a grating 208 and a grating 210. In some implementations, the grating 208 and/or 210 can serve as a diffractive component with regard to light from the light source 204. For example, the grating 208 and/or 210 can comprise a substrate with a periodic structure, the substrate combined with a prism. The gratings 208 and 210 can be positioned relative to each other according to one or more arrangements. Here, the gratings 208 and 210 face each other in the system 200. The gratings 208 and 210 can be substantially identical to each other or can have one or more differences. The size, periodicity or other spatial aspect of one of the gratings 208 and 210 can differ from that/those of the other. The grating orientation (i.e., the spatial orientation of the periodic structure) of one of the gratings 208 and 210 can differ from that/those of the other. In some implementations, the respective grating orientations of the gratings 208 and 210, which gratings themselves face toward each other, can be substantially perpendicular to each other or at any other angle relative to each other. In some implementations, the gratings 208 and 210 can be at offset positions relative to the rotatable mirror 202. In some implementations, the gratings 208 and/or 210 can be in a fixed position relative to the light source 204.

[0048] The system 200 can include one or more components (e.g., as a phase selector 108 of FIG. 1) to facilitate phase selection with regard to the light that should be applied to a sample (e.g., to the sample 116 in FIG. 1). Here, the system 200 includes a piezo fringe shifter 212. In some implementations, the piezo fringe shifter 212 can receive light from the grating 208 and/or 210 and can perform phase selection with regard to some or all of that light. For example, the piezo fringe shifter 212 can be used for controlling the pattern phase of the structured light using which a particular image should be captured. The piezo fringe shifter 212 can include a piezo actuator. For example, a piezo piston system can be used to effectuate phase selection. Other approaches can be used. For example, a tilting optical plate can be used for phase selection. For example, the system 200 is here implemented on a board 214, and one or more areas of the board 214 can be tilted to accomplish phase selection. As another example, one or more of the gratings 208 and 210 can be moved (e.g., translated) for the phase selection, such as by a piezo actuator. Light emanating from the piezo fringe shifter 212 is sometimes referred to as phase-selected light, to indicate that the light has been conditioned according to a particular phase selection. In some implementations, the gratings 208 and/or 210 can be in a fixed position relative to the light source 204.

[0049] The system includes a projection lens 216 that can include one or more optical components (e.g., a lens) to condition light that is received from the piezo fringe shifter 212. For example, the projection lens 216 can control the characteristics of the light before the light enters an objective lens (e.g., the objective lens 114 in FIG. 1).

[0050] The rotatable mirror 202 can be used to redirect at least one beam of light toward, and/or arriving from, one or more of the gratings 208 or 210. The rotatable mirror 202 can include one or more materials so as to be sufficiently reflective of the electromagnetic waves with which the sample is to be illuminated. In some implementations, the light from the light source 204 includes a laser beam of one or more wavelengths. For example, a metal-coated mirror and/or a dielectric mirror can be used. The rotatable mirror 202 can be double-sided. For example, the rotatable mirror 202 can be considered double-sided if it is capable of performing reflection on at least part of both its sides (e.g., reflective at a first end for a first beam path and reflective at a second end, opposite the first end, for a second beam path).

[0051] The rotatable mirror 202 can include an elongate member. The rotatable mirror 202 can have any of a variety of form factors or other shape characteristics. The rotatable mirror 202 can have a generally flat configuration. The rotatable mirror 202 can have a substantially square or otherwise rectangular shape. The rotatable mirror 202 can have rounded corners. The rotatable mirror 202 can have a substantially constant thickness. The reflective surfaces of the rotatable mirror 202 can be substantially planar.

[0052] The rotatable mirror 202 can be supported by an axle 218 of the system 200. The axle 218 can allow the rotatable mirror 202 to be rotated about the axle 218 in either or both

directions. The axle 218 can be made of a material with sufficient rigidity to hold and manipulate the rotatable mirror 202, such material(s) including, but not limited to, metal. The axle 218 can be coupled substantially at a center of the rotatable mirror 202. For example, the rotatable mirror 202 can have an opening at the center, or a cutout from one side that reaches the center, so as to facilitate coupling with the axle 218. As another example, the axle 218 can include separate axle portions that are coupled to respective faces of the rotatable mirror 202, without the need for any opening in the rotatable mirror 202. The axle 218 can have at least one suspension 220. Here, the suspension 220 is positioned at the ends of the axle 218 on both sides of the rotatable mirror 202. The suspension 220 can include a bearing or other feature that facilitates low-friction operation.

[0053] The rotatable mirror 202 can be actuated to assume one or more positions. Any form of motor or other actuator can be used for controlling the rotatable mirror 202. In some implementations, a stepper motor 222 is used. The stepper motor 222 can be coupled to the axle 218 and be used for causing the axle 218, and thereby the rotatable mirror 202, to rotate and assume the desired position(s). In some implementations, the rotatable mirror 202 rotates in the same direction toward the new positions (e.g., always clockwise, or always counter-clockwise, about the rotation axis of the axle 218). In some implementations, the rotatable mirror 202 reciprocates between two or more positions (e.g., alternatingly clockwise or counter-clockwise, about the rotation axis of the axle 218).

[0054] FIGS. 3A-B show an example relating to the system 200 in FIG. 2. FIG. 3A shows the system 200 in a top view, and FIG. 3B shows the system 200 in a perspective view. The rotatable mirror 202 is in the same position in each of FIGS. 3A-B.

[0055] The light source 204 here generates light 300 that propagates toward the grating 210. The rotatable mirror 202 is positioned (e.g., oriented about the rotational axis of the axle 218) so that a first end 302 of the rotatable mirror 202 does not interrupt the light 300. Currently, the first end 302 may be positioned closer to the viewer than is the light 300 which may propagate in the plane of the drawing. That is, a reflective surface 202A of the rotatable mirror 202 that faces toward the light source 204 currently does not interrupt the light 300 because the first end 302 does not block the path of the light 300. The light 300 therefore propagates (through air, vacuum, or another fluid) until reaching the grating 210.

[0056] The light 300 interacts with the grating 210 in one or more ways. In some implementations, the light 300 undergoes diffraction based on the grating 210. Here, light 304 is structured light (e.g., having one or more pattern fringes) that emanates from the grating 210 based on the interaction therewith by the light 300. The light 304 initially propagates substantially in a direction generally toward the projection lens 216. However, the position of the rotatable mirror 202 is such that a second end 306 of the rotatable mirror 202 does interrupt the light 304. The second end 306 can be opposite the first end 302. In some implementations, the first end 302 and

the second end 306 can be positioned at any angle relative to each other, such as any angle between 0 degrees and 180 degrees. Currently, the second end 306 may be positioned about as close to the viewer as is the light 304. That is, a reflective surface 202B of the rotatable mirror 202 that faces toward the grating 210 does interrupt the light 304 because the second end 306 blocks the path of the light 304. From the light 304, the rotatable mirror 202 therefore directs light 308 toward the piezo fringe shifter 212.

[0057] The piezo fringe shifter 212 performs phase selection on the light 308. For example, the piezo fringe shifter 212 selects the pattern phase to which the sample is to be subjected in the present illumination (e.g., for purposes of capturing one or more particular images). Light 310 emanates from the piezo fringe shifter 212 and propagates toward, and enters, the projection lens 216. The light 310 corresponds to a specific phase selection made using the piezo fringe shifter 212. The light 310 can therefore be characterized as phase-selected light. The light 310 can then continue to propagate through the system (e.g., as in the system 100 in FIG. 1), for example to illuminate the sample 116.

[0058] Here, the characteristics of the phase-selected electromagnetic waves of the light 310 correspond to the fact that the light 300 is diffracted by the grating 210 and that phase-selection is performed by the piezo fringe shifter 212. The involvement of the grating 210, moreover, was here a result of the positioning of the rotatable mirror 202 so that the second end 306 thereof interrupted the light 304, whereas the first end 302 did not interrupt the light 300.

[0059] Assume now that the rotatable mirror 202 instead is placed in a different position. FIGS. 4A-B show another example relating to the system 200 in FIG. 2. FIG. 4A shows the system 200 in a top view, and FIG. 4B shows the system 200 in a perspective view. The rotatable mirror 202 is in the same position in each of FIGS. 4A-B.

[0060] The light source 204 here generates the light 300 that initially propagates toward the grating 210. The rotatable mirror 202 is positioned (e.g., oriented about the rotational axis of the axle 218) so that the first end 302 of the rotatable mirror 202 does interrupt the light 300. Currently, the first end 302 may be positioned about as close to the viewer as is the light 300. That is, the reflective surface 202A of the rotatable mirror 202 that faces toward the light source 204 does interrupt the light 300 because the first end 302 blocks the path of the light 300. Light 312 therefore propagates (through air, vacuum, or another fluid) until reaching the grating 208.

[0061] The light 312 interacts with the grating 208 in one or more ways. In some implementations, the light 312 undergoes diffraction based on the grating 208. Here, light 314 is structured light (e.g., having one or more pattern fringes) that emanates from the grating 208 based on the interaction therewith by the light 312. The light 314 propagates substantially in a direction toward the piezo fringe shifter 212. The position of the rotatable mirror 202 is such that the second end 306 of the rotatable mirror 202 does not interrupt the light 314. Currently, the second end 306

may be positioned closer to the viewer than is the light 314. That is, neither the reflective surface 202B of the rotatable mirror 202, nor a reflective surface 202C that faces toward the grating 208, currently interrupts the light 314 because the second end 306 does not block the path of the light 314. The light 314 therefore propagates until reaching the piezo fringe shifter 212.

[0062] The piezo fringe shifter 212 performs phase selection on the light 314. For example, the piezo fringe shifter 212 selects the pattern phase to which the sample is to be subjected in the present illumination (e.g., for purposes of capturing one or more particular images). Light 316 emanates from the piezo fringe shifter 212 and propagates toward, and enters, the projection lens 216. The light 316 corresponds to a specific phase selection made using the piezo fringe shifter 212. The light 316 can therefore be characterized as phase-selected light. The light 316 can then continue to propagate through the system (e.g., as in the system 100 in FIG. 1), for example to illuminate the sample 116.

[0063] Here, the characteristics of the phase-selected electromagnetic waves of the light 316 correspond to the fact that the light 300 is diffracted by the grating 208 and that phase-selection is performed by the piezo fringe shifter 212. The involvement of the grating 208, moreover, was here a result of the positioning of the rotatable mirror 202 so that the first end 302 thereof interrupted the light 300, whereas the second end 306 did not interrupt the light 314. The rotatable mirror 202 can be caused to repeatedly assume different positions (e.g., the ones of FIG. 3A-B and FIGS. 4A-B, respectively) by various rotations. For example, the rotatable mirror 202 can reciprocate between the FIGS. 3A-B position and the FIGS. 4A-B position. As another example, the rotatable mirror 202 can rotate in the same direction (e.g., clockwise or counter-clockwise, from the perspective of the stepper motor 222) to repeatedly assume the FIGS. 3A-B position and the FIGS. 4A-B position.

[0064] As mentioned above, the gratings 208 and 210 can have different grating orientations with respect to each other. For example, the gratings 208 and 210 can have grating orientations that are substantially perpendicular to each other. The light 304 (FIG. 3A), emanating from the grating 210, and the light 314 (FIG. 4A), emanating from the grating 208, can therefore have different characteristics. For example, the pattern of fringes can be different in one of the lights 304 and 314 than in the other. Illuminating the sample (e.g., the sample 116 in FIG. 1) with differently structured light can facilitate use of the system 200 for SIM imaging.

[0065] The above examples illustrate a system that includes a light source (e.g., the light source 204); a first grating (e.g., the grating 210) and a second grating (e.g., the grating 208); a phase selector (e.g., the piezo fringe shifter 212); and at least one reflective component (e.g., the rotatable mirror 202). In a first position (e.g., as shown in FIGS. 3A-B) the reflective component forms a first light path from the light source to the first grating (e.g., by the first end 302 not interrupting the light 300) and thereafter to the phase selector (e.g., by the second end 306 blocking

the light 304). In a second position (e.g., as shown in FIGS. 4A-B), the reflective component forms a second light path from the light source to the second grating (e.g., by the first end 302 blocking the light 300) and thereafter to the phase selector (e.g., by the second end 306 not interrupting the light 304).

[0066] The above examples also illustrate a system that includes a light source (e.g., the light source 204); a first grating (e.g., the grating 208) and a second grating (e.g., the grating 210); a phase selector (e.g., the piezo fringe shifter 212); and at least one mirror (e.g., the rotatable mirror 202). Particularly, the mirror has a first position (e.g., as shown in FIGS. 4A-B) that interrupts (e.g., by the first end 302) a first path from the light source to the second grating, while not interrupting (e.g., by the second end 306 not blocking the light 314) a second path from the first grating to the phase selector. The mirror has a second position (e.g., as shown in FIGS. 3A-B) that interrupts (e.g., by the second end 306) a third path from the second grating and directs second light (e.g., the light 308) toward the phase selector, while not interrupting the first path (e.g., by the first end 302 not blocking the light 300).

[0067] Examples herein relate to using a reflective component and one or more gratings to provide structured light which can be used for SIM imaging. In some implementations, the mechanical motion can be significant (e.g., by rotating a mirror or another reflective component). However, reasonable mechanical and motion tolerances can be provided. For example, less or no precision may be needed regarding the start or stop positions of a reflective component (e.g., a mirror or a prism mirror); and stability and repeatability can be provided (e.g., with a rotatable mirror) by using precision bearings (e.g., in the suspension 220), a precision spindle (e.g., in the axle 218), and/or an accurate mirror (e.g., with the rotatable mirror 202 having low runout and/or good flatness). The stability and repeatability may be made independent of parts that can wear out (e.g., guide ways and/or end stops).

[0068] FIG. 5 schematically shows another example of a system 500 that can be used as part of a SIM imaging system. The system 500 can be used in combination with one or more other examples described herein. The system 500 includes a light source 502, a mirror 504, a grating 506 and a grating 508, a mirror 510, a phase selector 512, and a projection lens 514. An individual component of the system 500 can perform a similar or identical function to a corresponding component described with reference to another example in this description. Here, the gratings 506 and 508 face toward each other. In some implementations, the gratings 506 and 508 can have different grating orientations, including, but not limited to, ones that are substantially perpendicular to each other or at any other angle relative to each other. In some implementations, the gratings 506 and 508 can be at offset positions relative to the mirror 504 and/or mirror 510.

[0069] A Cartesian coordinate system having respective x-, y- and z-axes is shown. Here, the x- and y-axes extend in the plane of the illustration, and the z-axis extends perpendicularly to

the x- and y-axes in a direction toward the viewer.

[0070] A path 516 is marked between the light source 502 and the grating 508. In this and other examples, a path can indicate the way that a light beam can travel unless it is interrupted by some structure. A path 517 is marked between the mirror 504 and the grating 506. A path 518 is marked between the grating 506 and the phase selector 512. A path 520 is marked from the grating 508 extending, in this example, to the side of the projection lens 514. The paths 516, 517, 518, 520 are here illustrated using dashed lines.

[0071] The light source 502 here generates light 522 along at least part of the path 516. If the position of the mirror 504 is such that the mirror 504 does not interrupt the path 516 and does not block the light 522, then the light 522 can propagate along the path 516 and reach the grating 508. That is, the mirror 504 can then be considered as forming a light path of the light 522, the light path extending from the light source 502 to the grating 508. On the other hand, if the position of the mirror 504 is such that the mirror 504 interrupts the path 516 and blocks the light 522, then the mirror 504 can reflect the light 522, and light 524 can propagate along the path 517 toward the grating 506. The redirected light 524 is here indicated by a dot-dash line. That is, the mirror 504 can then be considered as forming a light path of the light 522 and the light 524, the light path extending from the light source 502 to the grating 506. Thus, the mirror 504 can selectively redirect the light 522 from the light source 502 between two paths toward a selected one of the gratings 506 or 508 based on the position of mirror 504.

[0072] The mirror 510 can selectively redirect light from a selected one of the gratings 506 or 508 toward the phase selector 512 based on the position of mirror 510. If the mirror 504 does not interrupt the path 516 such that light 526 is emanating from the grating 508 and the position of the mirror 510 is such that the mirror 510 interrupts the path 520 and blocks light 526 emanating from the grating 508, then the mirror 510 can reflect light 528 toward the phase selector 512. That is, the mirrors 504 and 510 can then be considered as cooperatively forming a light path of the light 522, the light 526 and the light 528, the light path extending from the light source 502 to the phase selector 512. On the other hand, if the mirror 504 does interrupt the path 516 such that light 524 is redirected toward the grating 506 and the position of the mirror 510 is such that the mirror 510 does not interrupt the path 518 and does not block light 530, then the light 530 can propagate along the path 518 and reach the phase selector 512. The light 530 is here indicated by a dot-dash line. That is, the mirrors 504 and 510 can then be considered as cooperatively forming a light path of the light 522, the light 524, and the light 530, the light path extending from the light source 502 to the phase selector 512.

[0073] The paths 516, 517, 518 and 520 can define one or more planes depending on the orientation of the components of the system 500. Here, the light path that includes the light 522, the light 526 and the light 528 extends substantially in the x-y-plane as illustrated (e.g., in the plane

of the drawing). Similarly, the light path that includes the light 522, the light 524 and the light 530 also extends substantially in the x-y-plane. At least one aspect of the system 500 can be substantially aligned with one or more such planes. In some implementations, the mirrors 504 and 510 are part of a rotatable mirror (e.g., the rotatable mirror 202 in FIG. 2). For example, such a rotatable mirror can revolve at least partially about an axis 532 here schematically indicated between the mirrors 504 and 510. The axis 532 can be substantially parallel to the plane of one or more of the light paths. For example, the axis 532 can be offset from the plane in some direction (e.g., toward the viewer, similar to the positioning of the axle 218 in FIG. 2). In some implementations, one or more of the lights 522, 524, 526, 528, and/or 530 can propagate along a plane forming an angle relative to the x-y plane (i.e., in a direction toward or away from the viewer) so as to form a light path having components in the x-, y-, and z-axes.

[0074] FIG. 6 schematically shows an example of a system 600 having a translatable mirror 602. The translatable mirror 602 is here schematically illustrated using a dashed outline. Examples of the translatable mirror 602 will be given below. The system 600 can be used in combination with one or more other examples described herein. The system 600 includes a light source 604, a grating 606 and a grating 608, and a phase selector 610. An individual component of the system 600 can perform a similar or identical function to a corresponding component described with reference to another example in this description.

[0075] The translatable mirror 602 can include one or more mirrors that can undergo translation (in one or more directions) as part of the operation of the system 600. The translatable mirror 602 can be translated into a first position where the translatable mirror 602 forms a light path 612 from the light source 604 to the grating 606 and thereafter to the phase selector 610. The translatable mirror 602 can be translated into a second position where the translatable mirror 602 forms a light path 614 from the light source 604 to the grating 608 and thereafter to the phase selector 610. Thus, the translatable mirror 602 can selectively redirect the light from the light source 604 between the two light paths 612 and 614 toward the phase selector 610.

[0076] The gratings 606 and 608 can be placed in any of various positions relative to each other. The orientation of the grating 606 can be characterized using a normal 616 of the grating 606. For example, the normal 616 can be a vector defined to be perpendicular to an optically active surface of the grating 606. The orientation of the grating 608 can be characterized using a normal 618 of the grating 608. For example, the normal 618 can be a vector defined to be perpendicular to an optically active surface of the grating 608. In some implementations, the normals 616 and 618 are substantially aligned with each other. For example, the normals 616 and 618 can be substantially antiparallel to each other (e.g., oriented toward each other). In other implementations, the normals 616 and 618 can form an angle between the normals 616 and 618.

[0077] The light paths 612 and 614 can define one or more planes depending on the

orientation of the components of the system 600. Here, each of the light paths 612 and 614 extends substantially in the plane of the drawing. In other implementations, the light paths 612 and/or 614 can have one or more portions that extend out of or in to the plane of the drawing. At least one aspect of the system 600 can be substantially aligned with one or more such planes of the light paths 612 or 614. In some implementations, the translatable mirror 602 can undergo translation that is substantially perpendicular to the plane of the light paths 612 and 614. In some implementations, the translatable mirror 602 can undergo translation that is substantially parallel to the plane of the light paths 612 and 614. Combinations of these approaches can be used. In some implementations, a first side of the translatable mirror 602 can have a first reflective angle (e.g., to form light path 612) and a second side of the translatable mirror 602 can have a second reflective angle (e.g., to form light path 614), where the first reflective angle is different from the second reflective angle.

[0078] FIGS. 7A-B schematically show an example relating to the system 600 in FIG. 6. The described examples can be used in combination with one or more other examples described herein. A translatable mirror 602' is here schematically illustrated. The translatable mirror 602' can be used as, or as part of, the translatable mirror 602 in FIG. 6. That is, a pair of mirrors 700 and 704 when in a first translated position shown in FIG. 7A can form light path 614 and the pair of mirrors 700 and 704 when in a second translated position shown in FIG. 7B can form light path 612. The translatable mirror 602' includes a mirror 700 coupled to a track 702. Here, the mirror 700 has a rectangular shape and a side 700A of the mirror 700 faces a side 702A of the track 702. The track 702 can facilitate translation of the mirror 700 vertically along the side 702A. For example, an actuator (not shown) can act on the mirror 700 and relocate it in either direction along the track 702. Similarly, the translatable mirror 602' includes a mirror 704 having a rectangular shape and coupled to a track 706 so that a side 704A of the mirror 704 faces a side 706A of the track 706. Accordingly, the track 706 can facilitate translation of the mirror 704 vertically along the side 706A. More than one track can be used for translation of the mirror 700 and/or 704. Other types of actuation can be used. For example, the mirror 700 and/or 704 can be manipulated by an actuator.

[0079] FIG. 7A shows a configuration of the translatable mirror 602' with the mirror 700 positioned toward an end 708 of the track 702, and the mirror 704 positioned toward an end 710 of the track 706. In some implementations, the position in FIG. 7A can correspond to the formation of one or more light paths. For example, with reference again also to FIG. 6, the position of the mirror 704 toward the end 710 can facilitate interruption of the light path 612 between the light source 604 and the grating 606. Due to the blocking, the mirror 704 can serve to redirect light from the light source 604 toward the grating 608 and in so doing can form the light path 614. The mirror 700, moreover, which is currently positioned toward the end 708, may not interrupt the light path 614 between the grating 608 and the phase selector 610. As such, the translation of the translatable mirror 602' into the shown configuration can form the light path 614 in the system 600.

[0080] FIG. 7B shows a configuration of the translatable mirror 602' with the mirror 700 positioned toward an end 712 of the track 702, and the mirror 704 positioned toward an end 714 of the track 706. The end 712 is here substantially opposite the end 708, and the end 714 is here substantially opposite the end 710. In some implementations, the position in FIG. 7B can correspond to the formation of one or more light paths. For example, with reference again also to FIG. 6, the position of the mirror 704 toward the end 714 may not interrupt the light path 612 from the light source 604, and the light may therefore reach the grating 606. The mirror 700, moreover, which is currently positioned toward the end 712, may interrupt the light path 612 emanating from the grating 606. Due to the blocking, the mirror 700 can serve to redirect light from the grating 606 toward the phase selector 610 and in so doing can form the light path 612. As such, the translation of the translatable mirror 602' into the shown configuration can form the light path 612 in the system 600. The translation to or from the positions shows in FIGS. 7A-B can occur in a direction that is substantially perpendicular to one or more of the planes of the light paths 612 and 614.

[0081] FIGS. 8A-B schematically show another example relating to the system 600 in FIG. 6. The described examples can be used in combination with one or more other examples described herein. A translatable mirror 602" is here schematically illustrated. The translatable mirror 602" can be used as, or as part of, the translatable mirror 602 in FIG. 6. The translatable mirror 602" includes a mirror 800 coupled to a track 802. Here, the mirror 800 has a rectangular shape and a side 800A of the mirror 800 faces a side 802A of the track 802. The track 802 can facilitate translation of the mirror 800 along the side 802A. For example, an actuator (not shown) can act on the mirror 800 and relocate it in either direction along the track 802.

[0082] FIG. 8A shows a configuration of the translatable mirror 602" with the mirror 800 positioned toward an end 804 of the track 802. In some implementations, the position in FIG. 8A can correspond to the formation of one or more light paths. For example, with reference again also to FIG. 6, the position of the mirror 800 toward the end 804 can facilitate interruption of the light path 612 between the light source 604 and the grating 606. Due to the blocking, the mirror 800 can serve to redirect light from the light source 604 toward the grating 608 and in so doing can form the light path 614. At an end 806 of the track 802 no mirror is currently positioned. As a result, the translatable mirror 602" may not interrupt the light path 614 between the grating 608 and the phase selector 610. As such, the translation of the translatable mirror 602" into the shown configuration can form the light path 614 in the system 600.

[0083] FIG. 8B shows a configuration of the translatable mirror 602" with the mirror 800 positioned toward the end 806 of the track 802. In some implementations, the position in FIG. 8B can correspond to the formation of one or more light paths. For example, with reference again also to FIG. 6, the absence of a mirror at the end 804 can facilitate propagation of the light from the light source 604 to the grating 606. Moreover, the position of the mirror 800 toward the end 806

can facilitate interruption of the light path 612 emanating from the grating 606. Due to the blocking, the mirror 800 can serve to redirect light from the grating 606 toward the phase selector 610 and in so doing can form the light path 612.

[0084] FIG. 9 schematically shows an example of a system 900 having a rotatable prism 902. The system 900 can be used in combination with one or more other examples described herein. The system 900 also includes a light source 904, a grating 906 and a grating 908, a phase selector 910, and a projection lens 912. An individual component of the system 900 can perform a similar or identical function to a corresponding component described with reference to another example in this description.

[0085] The rotatable prism 902 can undergo rotation about one or more rotational axes to assume one or more positions. Here, the rotatable prism 902 can be rotated about an axis perpendicular to the plane of the drawing, the rotation schematically indicated by an arrow 914. For simplicity, the rotatable prism 902 is here shown in a single orientation. However, the operation of the system 900 will be exemplified based on at least two different orientations of the rotatable prism 902. Here, the gratings 906 and 908 face toward the phase selector 910. Other placements or orientations can be used.

[0086] The light source 904 provides light 916 that propagates toward the rotatable prism 902. The light 916 will interact with the rotatable prism 902 and undergo reflection. Here, light 918 emanating from the rotatable prism 902 is the result of such reflection when the rotatable prism 902 is in a first position. The light 918 is directed toward the grating 906 and interacts therewith. Light 920 emanates from the grating 906 as a result of this interaction and propagates toward the phase selector 910 and interacts therewith. Light 922 emanates from the phase selector 910 as a result of this interaction and propagates toward the projection lens 912 and interacts therewith. That is, when the rotatable prism 902 is in the first position, it reflects the light 918 along a first light path from the rotatable prism 902 toward the grating 906.

[0087] Moreover, light 924 emanating from the rotatable prism 902 is the result of reflection of the light 916 when the rotatable prism 902 is in a second position. The light 924 is directed toward the grating 908 and interacts therewith. Light 926 emanates from the grating 908 as a result of this interaction and propagates toward the phase selector 910 and interacts therewith. The light 922 emanates from the phase selector 910 as a result of this interaction and propagates toward the projection lens 912 and interacts therewith. That is, when the rotatable prism 902 is in the second position, it reflects the light 924 along a second light path from the rotatable prism 902 toward the grating 908.

[0088] FIG. 10 shows an example of a method 1000 that can be used for performing SIM. The method 1000 can be performed in one or more of the systems exemplified herein. The method 1000 can include more or fewer operations than shown. Two or more of the operations of the

method 1000 can be performed in a different order unless otherwise indicated. Some aspects of other examples described herein will be referenced for illustrative purposes.

[0089] At 1010, the method 1000 includes positioning of a reflective component in a first position. The first position can facilitate definition of a first light path originating at a light source and extending to a first grating and thereafter to a subsequent component. For example, the rotatable mirror 202 can be placed in the position shown in FIGS. 3A-B to define the light path from the light source 204 to the grating 210 and thereafter to the piezo fringe shifter 212, the light path including the light 300, 304 and 308. As another example, the rotatable mirror 202 can be placed in the position shown in FIGS. 4A-B to define the light path from the light source 204 to the grating 208 and thereafter to the piezo fringe shifter 212, the light path including the light 300, 312 and 314. As another example, the mirrors 504 and 510 in FIG. 5 can be placed to define the light path that includes the light 522, 526 and 528. As another example, the mirrors 504 and 510 in FIG. 5 can be placed to define the light path that includes the light 522, 524 and 530. As another example, the translatable mirror 602' can be placed in the position shown in FIG. 7A to define the light path 614 in FIG. 6. As another example, the translatable mirror 602' can be placed in the position shown in FIG. 7B to define the light path 612 in FIG. 6. As another example, the translatable mirror 602" can be placed in the position shown in FIG. 8A to define the light path 614 in FIG. 6. As another example, the translatable mirror 602" can be placed in the position shown in FIG. 8B to define the light path 612 in FIG. 6. As another example, the rotatable prism 902 in FIG. 9 can be placed in the position that defines the light path that includes the light 916, 918, 920 and 922. As another example, the rotatable prism 902 in FIG. 9 can be placed in the position that defines the light path that includes the light 916, 924, 926 and 922. For example, the subsequent component can be the phase selector 108 in FIG. 1. As another example, the subsequent component can be the projection lens 110 in FIG. 11.

[0090] At 1020, the method 1000 includes directing first phase-selected light from the first light path onto a sample. For example, phase-selected light can be emanating from the piezo fringe shifter 212 (FIG. 2) and/or from one or more of the phase selectors 108 (FIG. 1), 512 (FIG. 5), 610 (FIG. 6) or 910 (FIG. 9). The phase-selected light can be directed onto the sample 116 in FIG. 1. Thus, the sample can be illuminated using the phase-selected light (e.g., structured light). The sample can be imaged (e.g., using the camera system 122 in FIG. 1) based on such illumination by the first phase-selected light and such operations are not explicitly discussed here for brevity.

[0091] At 1030, the method 1000 includes positioning of a reflective component in a second position. The second position can facilitate definition of a second light path originating at the light source and extending to a second grating and thereafter to the subsequent component. For example, the rotatable mirror 202 can be placed in the position shown in FIGS. 3A-B to define the

light path from the light source 204 to the grating 210 and thereafter to the piezo fringe shifter 212, the light path including the light 300, 304 and 308. As another example, the rotatable mirror 202 can be placed in the position shown in FIGS. 4A-B to define the light path from the light source 204 to the grating 208 and thereafter to the piezo fringe shifter 212, the light path including the light 300, 312 and 314. As another example, the mirrors 504 and 510 in FIG. 5 can be placed to define the light path that includes the light 522, 526 and 528. As another example, the mirrors 504 and 510 in FIG. 5 can be placed to define the light path that includes the light 522, 524 and 530. As another example, the translatable mirror 602' can be placed in the position shown in FIG. 7A to define the light path 614 in FIG. 6. As another example, the translatable mirror 602' can be placed in the position shown in FIG. 7B to define the light path 612 in FIG. 6. As another example, the translatable mirror 602" can be placed in the position shown in FIG. 8A to define the light path 614 in FIG. 6. As another example, the translatable mirror 602" can be placed in the position shown in FIG. 8B to define the light path 612 in FIG. 6. As another example, the rotatable prism 902 in FIG. 9 can be placed in the position that defines the light path that includes the light 916, 918, 920 and 922. As another example, the rotatable prism 902 in FIG. 9 can be placed in the position that defines the light path that includes the light 916, 924, 926 and 922.

[0092] At 1040, the method 1000 includes directing second phase-selected light from the second light path onto the sample. For example, phase-selected light can be emanating from the piezo fringe shifter 212 (FIG. 2) and/or from one or more of the phase selectors 108 (FIG. 1), 512 (FIG. 5), 610 (FIG. 6) or 910 (FIG. 9). The phase-selected light can be directed onto the sample 116 in FIG. 1. Thus, the sample can be illuminated using the phase-selected light (e.g., structured light). The sample can be imaged (e.g., using the camera system 122 in FIG. 1) based on such illumination by the second phase-selected light and such operations are not explicitly discussed here for brevity.

[0093] FIG. 11 schematically shows another example of a system 1100 that can facilitate SIM. The system 1100 can be used in combination with one or more other examples described herein. Some components in this and other examples are shown conceptually as a block or other generic component; such component(s) can be implemented in form of one or more separate or integrated components so as to perform the indicated function(s). Components corresponding to those of the system 100 (FIG. 1) that are not explicitly mentioned can serve the same or a similar role in the system 1100.

[0094] The system 1100 includes a phase selector 108' positioned before a light-structuring component 104'. In some implementations, the phase selector 108' can receive the beam 106 from the light source 102. The phase selector 108' can provide phase-selected light to the light-structuring component 104'. The light-structuring component 104' can generate structured light and provide the structured light to a subsequent component in the system 1100. In some

implementations, the subsequent component is the projection lens 110. Other approaches can be used.

[0095] In some implementations, the stage 118 can translate the sample 116 a distance relative to stationary light fringes to accomplish phase selection (e.g., using a piezo actuator in the stage 118). For example, the phase selector 108' can then be bypassed in, or eliminated from, the system 1100.

[0096] FIG. 12 is a schematic view of an example system 1200 that can be used for biological and/or chemical analysis. Systems and/or techniques described herein, including, but not limited to, the system 100 (FIG. 1) and/or the method 1000 (FIG. 10), can be part of the system 1200 in some implementations. The system 1200 can operate to obtain any information or data that relates to at least one biological and/or chemical substance. In some implementations, a carrier 1202 supplies material to be analyzed. For example, the carrier 1202 can include a cartridge or any other component holding the material. In some implementations, the system 1200 has a receptacle 1204 to receive the carrier 1202 at least during the analysis. The receptacle 1204 can form an opening in a housing 1206 of the system 1200. For example, some or all components of the system 1200 can be within the housing 1206.

[0097] The system 1200 can include an optical system 1208 for biological and/or chemical analysis of the material(s) of the carrier 1202. The optical system 1208 can perform one or more optical operations, including, but not limited to, illumination and/or imaging of the material(s). For example, the optical system 1208 can include any or all systems described elsewhere herein. As another example, the optical system 1208 can perform any or all operations described elsewhere herein.

[0098] The system 1200 can include a thermal system 1210 for providing thermal treatment relating to biological and/or chemical analysis. In some implementations, the thermal system 1210 thermally conditions at least part of the material(s) to be analyzed and/or the carrier 1202.

[0099] The system 1200 can include a fluid system 1212 for managing one or more fluids relating to biological and/or chemical analysis. In some implementations, the fluid(s) can be provided for the carrier 1202 or its material(s). For example, fluid can be added to and/or removed from the material of the carrier 1202.

[00100] The system 1200 includes a user interface 1214 that facilitates input and/or output relating to biological and/or chemical analysis. The user interface can be used to specify one or more parameters for the operation of the system 1200 and/or to output results of biological and/or chemical analysis, to name just a few examples. For example, the user interface 1214 can include one or more display screens (e.g., a touchscreen), a keyboard, and/or a pointing device (e.g., a mouse or a trackpad).

[00101] The system 1200 can include a system controller 1216 that can control one or more aspects of the system 1200 for performing biological and/or chemical analysis. The system controller 1216 can control the receptacle 1204, the optical system 1208, the thermal system 1210, the fluid system 1212, and/or the user interface 1214. The system controller 1216 can include at least one processor and at least one storage medium (e.g., a memory) with executable instructions for the processor.

[00102] The terms "substantially" and "about" used throughout this Specification are used to describe and account for small fluctuations, such as due to variations in processing. For example, they can refer to less than or equal to ±5%, such as less than or equal to ±2%, such as less than or equal to ±1%, such as less than or equal to ±0.5%, such as less than or equal to ±0.2%, such as less than or equal to ±0.1%, such as less than or equal to ±0.05%. Also, when used herein, an indefinite article such as "a" or "an" means "at least one."

[00103] It should be appreciated that all combinations of the foregoing concepts and additional concepts discussed in greater detail below (provided such concepts are not mutually inconsistent) are contemplated as being part of the inventive subject matter disclosed herein. In particular, all combinations of claimed subject matter appearing at the end of this disclosure are contemplated as being part of the inventive subject matter disclosed herein.

[00104] A number of implementations have been described. Nevertheless, it will be understood that various modifications may be made without departing from the scope of the specification.

[00105] In addition, the logic flows depicted in the figures do not require the particular order shown, or sequential order, to achieve desirable results. In addition, other processes may be provided, or processes may be eliminated, from the described flows, and other components may be added to, or removed from, the described systems. Accordingly, other implementations are within the scope of the following claims.

[00106] While certain features of the described implementations have been illustrated as described herein, many modifications, substitutions, changes and equivalents will now occur to those skilled in the art. It is, therefore, to be understood that appended claims are intended to cover all such modifications and changes as fall within the scope of the implementations. It should be understood that they have been presented by way of example only, not limitation, and various changes in form and details may be made. Any portion of the apparatus and/or methods described herein may be combined in any combination, except mutually exclusive combinations. The implementations described herein can include various combinations and/or sub-combinations of the functions, components and/or features of the different implementations described.

[00107] The disclosure also includes the following clauses:

1. A system for generating spatially structured light suitable for structured illumination

microscopy (SIM) comprising:

a light source;

a first grating and a second grating; and

at least one reflective component, selectively positionable in a first position in which it forms a first light path originating at the light source and extending to the first grating and thereafter to a subsequent component in the system, and in a second position in which it forms a second light path originating at the light source and extending to the second grating and thereafter to the subsequent component.

2. The system of clause 1, wherein the reflective component includes a rotatable mirror that assumes the first or second positions.

3. The system of clause 2, wherein the rotatable mirror is double-sided and comprises an elongate member, and wherein an axle is coupled to the elongate member substantially at a center of the elongate member.

4. The system of clause 3, wherein the axle is offset from and substantially parallel to a plane defined by the first and second light paths.

5. The system of any of clauses 3 or 4, wherein when the rotatable mirror assumes the first position, a first end of the elongate member interrupts a first path originating at the light source and extending to the second grating, and reflects first light originating at the light source toward the first grating.

6. The system of clause 5, wherein when the rotatable mirror assumes the first position, a second end of the elongate member does not interrupt a second path from the first grating to the subsequent component.

7. The system of any of clauses 5 or 6, wherein when the rotatable mirror assumes the second position, a second end of the elongate member interrupts a second path from the second grating, and reflects second light from the second grating toward the subsequent component.

8. The system of clause 7, wherein when the rotatable mirror assumes the second position, the first end of the elongate member does not interrupt the first path originating at the light source and extending to the second grating.

9. The system of any of clauses 3 to 8, wherein the first and second gratings are oriented so that respective normals thereof are substantially antiparallel to each other, and wherein the axle is substantially aligned with the normals.

10. The system of any of clauses 2 to 9, wherein the rotatable mirror reciprocates between the first and second positions.

11. The system of any preceding clause, wherein the reflective component includes a first translatable mirror that undergoes first translation into the first position.

12. The system of clause 11, wherein the reflective component further includes a second

translatable mirror that undergoes second translation into the second position.

13. The system of clause 12, wherein the first and second translations are substantially perpendicular to a plane defined by the first and second light paths.

14. The system of any of clauses 11 to 12, wherein the first translation is substantially parallel to a plane defined by the first and second light paths.

15. The system of clause 14, wherein the first translatable mirror undergoes a second translation into the second position, and wherein the second translation is substantially parallel to the plane defined by the first and second light paths.

16. The system of any preceding clause, wherein the reflective component includes a rotatable prism that assumes the first or second position.

17. The system of clause 16, wherein the first and second gratings are positioned adjacent each other, wherein the rotatable prism in the first position reflects first light along the first light path toward the first grating, and wherein the rotatable prism in the second position reflects second light along the second light path toward the second grating.

18. The system of any of clauses 16 or 17, wherein the first and second gratings face toward the subsequent component.

19. The system of any preceding clause, wherein the first and second gratings are in a fixed position relative to the light source.

20. The system of any preceding clause, wherein the subsequent component is a phase selector.

21. The system of any of clauses 1 to 19, further comprising a phase selector positioned between the light source and the reflective component.

22. The system of any of clauses 20 or 21, wherein the phase selector is in a fixed position relative to the light source.

23. A system for generating spatially structured light suitable for structured illumination microscopy (SIM), preferably the system of any of the preceding clauses, comprising:

a light source;

a first grating and a second grating; and

at least one reflective component, including at least one mirror selectively positionable in a first position in which it interrupts a first light path originating at the light source and extending to the second grating, and directs first light toward the first grating, while not interrupting a second light path from the first grating to a subsequent component in the system, and in a second position in which it interrupts a third light path from the second grating and directs second light from the second grating toward the subsequent component, while not interrupting the first light path.

24. The system of clause 23, wherein respective grating orientations of the first and second gratings are substantially perpendicular to each other.

25. The system of any of clauses 23 to 24, wherein the first and second gratings face toward each other.

26. The system of any of clauses 23 to 25, wherein the subsequent component is a phase selector.

27. The system of any of clauses 23 to 25, further comprising a phase selector positioned between the light source and the at least one mirror.

28. Structured illumination microscopy (SIM) device, comprising the system of any of the preceding clauses as an optical subsystem.

29. A method for generating spatially structured light suitable for structured illumination microscopy (SIM) of a sample comprising:

positioning at least one reflective component to define a first light path originating at a light source and extending to a first grating and thereafter to a subsequent component;

directing first phase-selected light from the first light path onto the sample;

positioning the at least one reflective component to define a second light path originating at the light source and extending to a second grating and thereafter to the subsequent component; and

directing second phase-selected light from the second light path onto the sample.

30. The method of clause 29, wherein positioning the at least one reflective component to define the first light path comprises interrupting a first path originating at the light source and extending to the second grating and directing first light toward the first grating, while not interrupting a second path from the first grating to the subsequent component.

31. The method of clause 30, wherein positioning the at least one reflective component to define the second light path comprises interrupting a third path from the second grating and directing second light from the second grating toward the subsequent component, while not interrupting the first path.

CONCLUSIES

1. Systeem voor het genereren van ruimtelijk gestructureerd licht dat geschikt is voor gestructureerd-licht microscopie (*Structured Light Microscopy, SIM*), omvattende;

een lichtbron;

een eerste rooster en een tweede rooster;

ten minste een reflecterende component, selectief positioneerbaar in een eerste positie waarin deze een eerste lichtpad vormt dat begint bij de lichtbron en zich uitstrekt naar het eerste rooster en daarna naar een volgende component in het systeem, en in een tweede positie waarin deze een tweede lichtpad vormt dat begint bij de lichtbron en zich uitstrekt naar het tweede rooster en daarna naar de volgende component.

2. Systeem volgens conclusie 1, waarbij de reflecterende component een draaibare spiegel omvat die de eerste of tweede positie aanneemt.

3. Systeem volgens conclusie 2, waarbij de draaibare spiegel tweezijdig is en een uitgerekt lid omvat, en waarbij een as gekoppeld is aan het uitgerekte lid hoofdzakelijk bij een middelpunt van het uitgerekte lid.

4. Systeem volgens conclusie 3, waarbij de as verschoven is ten opzichte van en hoofdzakelijk parallel is aan een vlak gedefinieerd door de eerste en tweede lichtpaden.

5. Systeem volgens een van de conclusies 3 of 4, waarbij, wanneer de draaibare spiegel de eerste positie aanneemt, een eerste uiteinde van het uitgerekte lid een eerste pad dat begint bij de lichtbron en zich uitstrekt naar het tweede rooster onderbreekt, en eerste licht dat begint bij de lichtbron reflecteert naar het eerste rooster.

6. Systeem volgens conclusie 5, waarbij, wanneer de draaibare spiegel de eerste positie aanneemt, een tweede uiteinde van het uitgerekte lig een tweede pad van het eerste rooster naar de volgende component niet onderbreekt.

7. Systeem volgens een van de conclusies 5 of 6, waarbij, wanneer de draaibare spiegel de tweede positie aanneemt, het tweede uiteinde van het uitgerekte lig een tweede pad vanaf het tweede rooster onderbreekt, en tweede licht reflecteert van het tweede rooster naar de volgende component.

8. Systeem volgens conclusie 7, waarbij, wanneer de draaibare spiegel de tweede positie aanneemt, het eerste uiteinde van het uitgerekte lig het eerste pad dat begint bij de lichtbron en zich uitstrekt naar het tweede rooster niet onderbreekt.

9. Systeem volgens een van de conclusies 3-8, waarbij de eerste en tweede rooster zodanig georiënteerd zijn dat respectievelijke loodlijnen ervan hoofdzakelijk antiparallel aan elkaar zijn, en waarbij de as hoofdzakelijk in lijn ligt met de loodlijnen.

10. Systeem volgens een van de conclusies 2-9, waarbij de draaibare spiegel heen en weer beweegt tussen de eerste en tweede posities.

11. Systeem volgens een van de voorgaande conclusies, waarbij de reflecterende component een eerste transleerbare spiegel omvat die een eerste translatie ondergaat naar de eerste positie.

12. Systeem volgens conclusie 11, waarbij de reflecterende component verder een tweede transleerbare spiegel omdat die een tweede translatie ondergaat naar de tweede positie.

13. Systeem volgens conclusie 12, waarbij de eerste en tweede translaties hoofdzakelijk dwars zijn op een vlak dat gedefinieerd wordt door de eerste en tweede lichtpaden.

14. Systeem volgens een van de conclusies 11-12, waarbij de eerste translatie hoofdzakelijk parallel is aan een vlak gedefinieerd door de eerste en tweede lichtpaden.

15. Systeem volgens conclusie 14, waarbij de eerste transleerbare spiegel een tweede translatie naar de tweede positie ondergaat, en waarbij de tweede translatie hoofdzakelijk parallel is aan het vlak gedefinieerd door de eerste en tweede lichtpaden.

16. Systeem volgens een van de voorgaande conclusies, waarbij de reflecterende component een draaibaar prisma omvat dat de eerste of tweede positie aanneemt.

17. Systeem volgens conclusie 16, waarbij de eerste en tweede roosters gepositioneerd zijn naast elkaar, waarbij de draaibare prisma in de eerste positie eerste licht reflecteert langs het eerste lichtpad naar het eerste rooster, en waarbij het draaibare prisma in de tweede positie tweede licht reflecteert langs het tweede lichtpad naar het tweede rooster.

18. Systeem volgens een van de conclusies 16 of 17, waarbij de eerste en tweede roosters gerangschikt zijn tegenover de volgende component.

19. Systeem volgens een van de voorgaande conclusies, waarbij de eerste en tweede roosters zich in een vaste positie bevinden ten opzichte van de lichtbron.

20. Systeem volgens een van de voorgaande conclusies, waarbij de volgende component een fase-selector is.

21. Systeem volgens een van de conclusies 1-19, verder omvattende een fase-selector gerangschikt tussen de lichtbron en de reflecterende component.

22. Systeem volgens conclusie 20 or 21, waarbij de fase-selector zich in een vaste positie bevindt ten opzichte van de lichtbron.

23. Systeem voor het genereren van ruimtelijk gestructureerd licht dat geschikt is voor gestructureerd-licht microscopie (*Structured Light Microscopy, SIM*), bij voorkeur het systeem volgens een van de voorgaande conclusies, omvattende:

een lichtbron;

een eerste rooster en een tweede rooster;

ten minste een reflecterende component, omvattende ten minste een spiegel die selectief positioneerbaar is in een eerste positie waarin deze een eerste lichtpad onderbreekt dat begint bij de lichtbron en zich uitstrekt naar het tweede rooster en het eerste licht richt naar het eerste rooster, terwijl deze een tweede lichtpad van het eerste rooster naar een volgende component in het systeem niet onderbreekt, en in een tweede positie waarin het een derde lichtpad vanaf de tweede rooster onderbreekt en tweede licht van het tweede rooster richt naar de volgende component, terwijl deze het eerste lichtpad niet onderbreekt.

24. Systeem volgens conclusie 23, waarbij respectievelijke roosteroriëntaties van de eerste en tweede roosters hoofdzakelijk dwars op elkaar staan.

25. Systeem volgens een van de conclusies 23-24, waarbij de eerste en tweede roosters tegenover elkaar gerangschikt zijn.

26. Systeem volgens een van de conclusies 23-25, waarbij de volgende component een fase-selector is.

27. Systeem volgens een van de conclusies 23-25, verder omvattende een fase-selector gerangschikt tussen de lichtbron en de ten minste een spiegel.

28. Inrichting voor gestructureerd-licht microscopie (*Structured Light Microscopy, SIM*), omvattende het systeem volgens een van de voorgaande conclusies als een optisch subsysteem.

29. Werkwijze voor het genereren van ruimtelijk gestructureerd licht geschikt voor gestructureerd-licht microscopie (*Structured Light Microscopy, SIM*) van een monster, omvattende:

het positioneren van ten minste een reflecterende component om een eerste lichtpad te definiëren dat begint bij een lichtbron en zich uitstrekt naar een eerste rooster en daarna naar een volgende component;

het richten van eerste fase-geselecteerd licht van het eerste lichtpad op het monster;

het positioneren van de ten minste een reflecterende component om een tweede lichtpad te definiëren dat begint bij de lichtbron en zich uitstrekt naar een tweede rooster en daarna naar de volgende component; en

het richten van tweede fase-geselecteerd licht van het tweede lichtpad op het monster.

30. Werkwijze volgens conclusie 29, waarbij het positioneren van de ten minste een reflecterende component om het eerste lichtpad te definiëren omvat het onderbreken van een eerste pad dat begint bij de lichtbron en zich uitstrekt naar het tweede rooster en het richten van eerste licht naar het eerste rooster, terwijl een tweede pad van het eerste rooster naar de volgende component niet onderbroken wordt.

31. Werkwijze volgens conclusie 30, waarbij het positioneren van de ten minste een reflecterende component om het tweede lichtpad te definiëren omvat het onderbreken van een derde pad vanaf het tweede rooster en het richten van tweede licht van het tweede rooster naar de volgende component, terwijl het eerste pad niet onderbroken wordt.

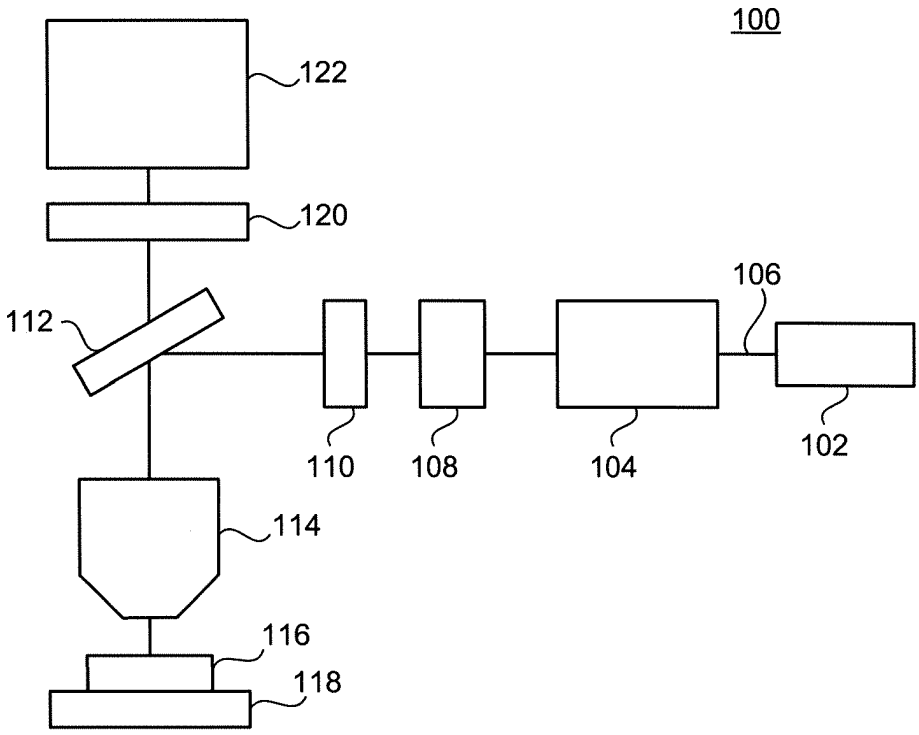


FIG. 1

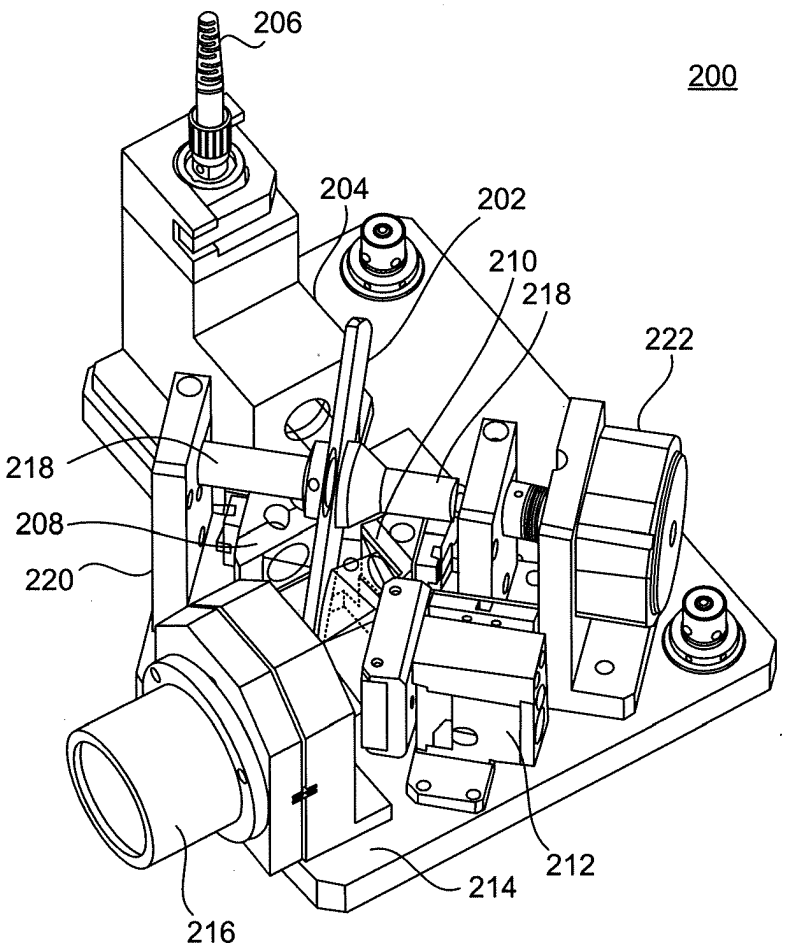


FIG. 2

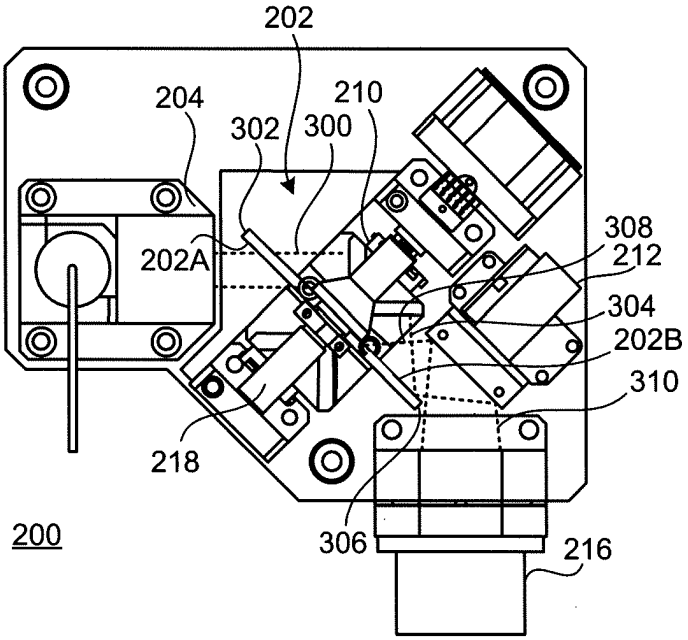

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202B
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FIG. 3A

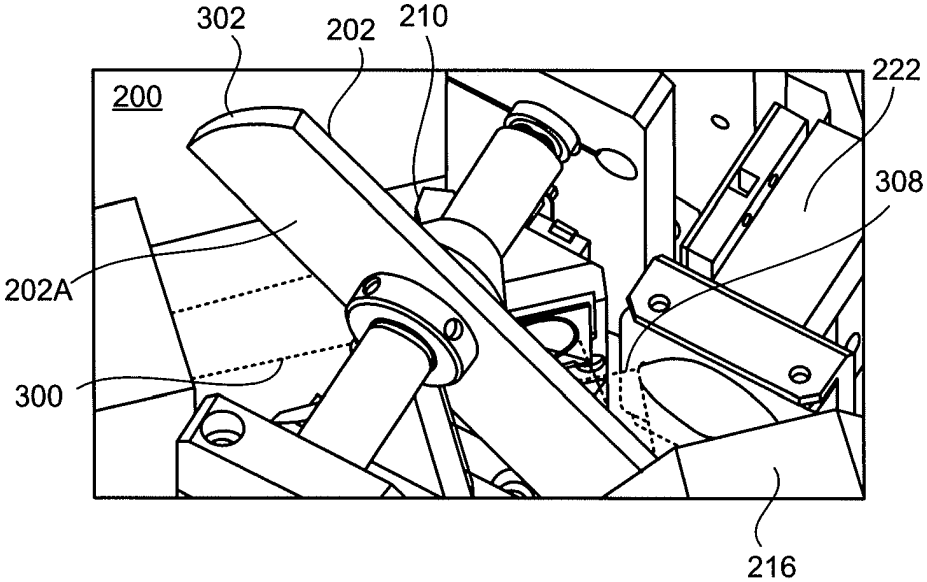

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222
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308
202A
300
216

FIG. 3B

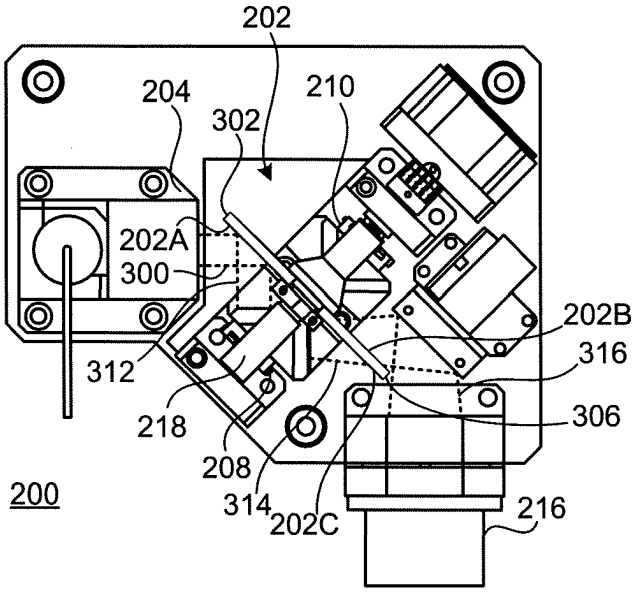

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302
202A
300
202B
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312
306
218
208
314
202C
216
200

FIG. 4A

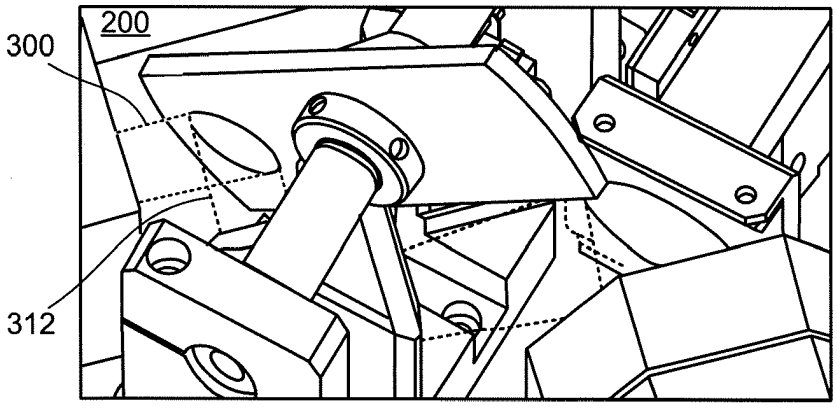

200
300
312

FIG. 4B

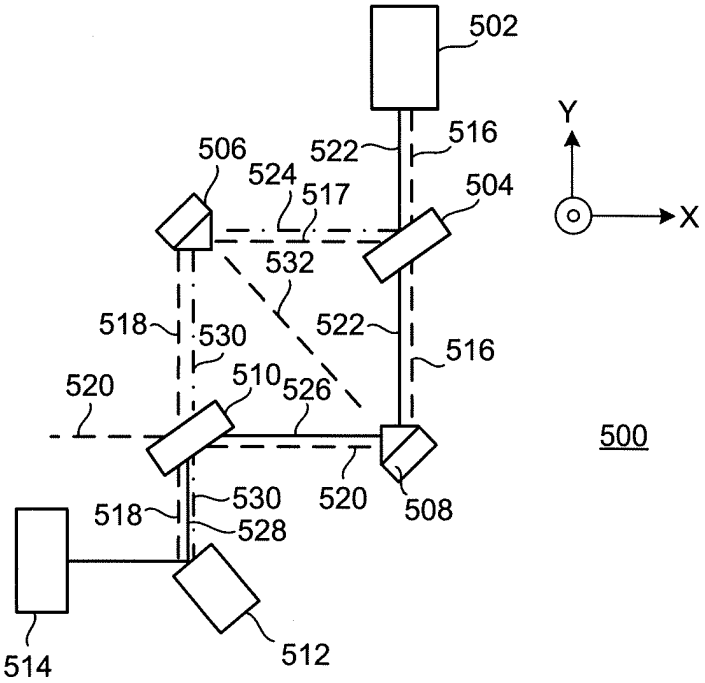

502
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X
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FIG. 5

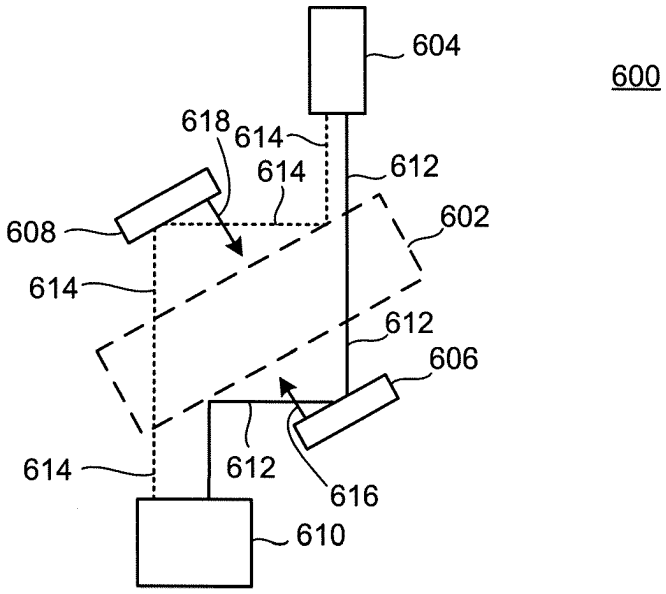

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616
610

FIG. 6

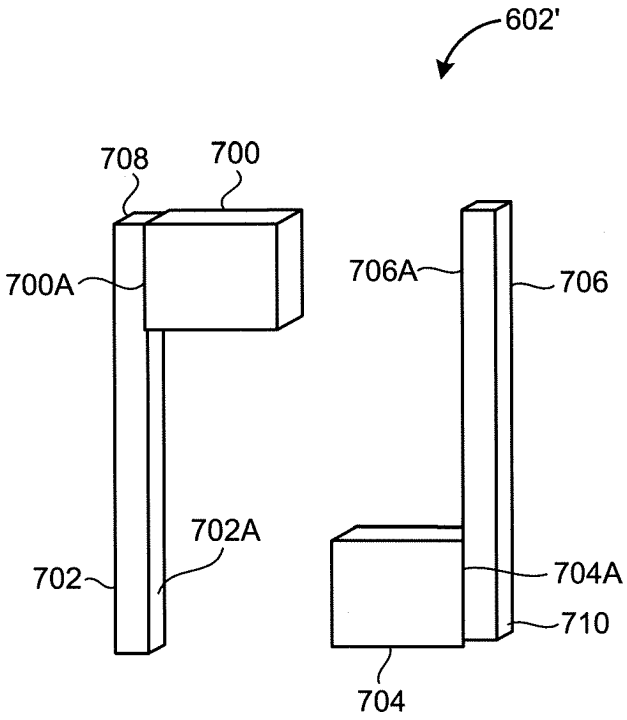

602'
708
700
700A
706A
706
702A
702
704A
710
704

FIG. 7A

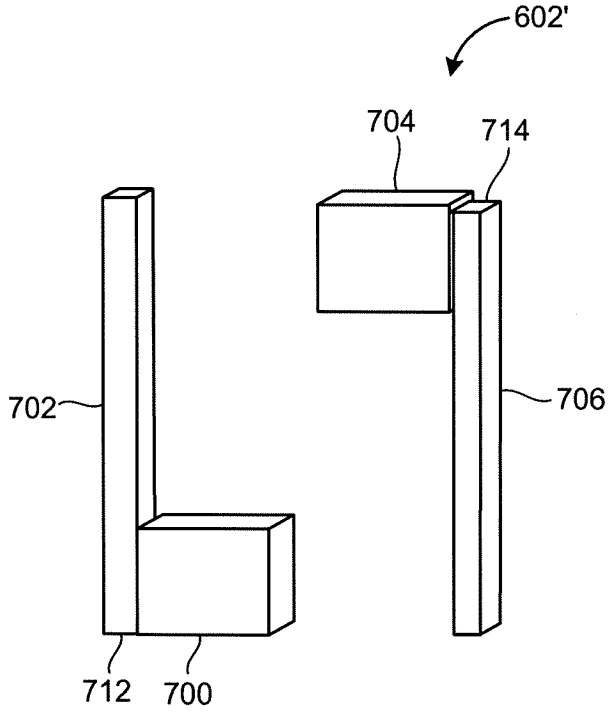

602'
704
714
702
706
712
700

FIG. 7B

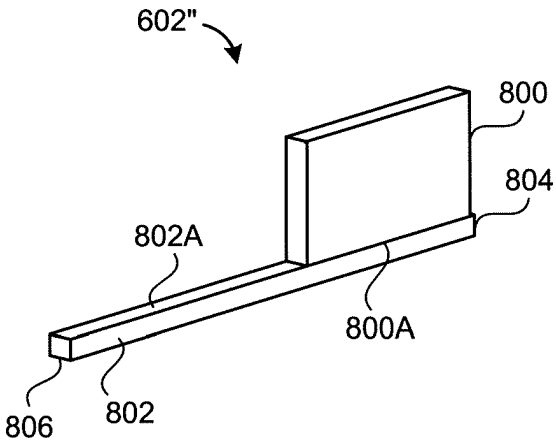


FIG. 8A

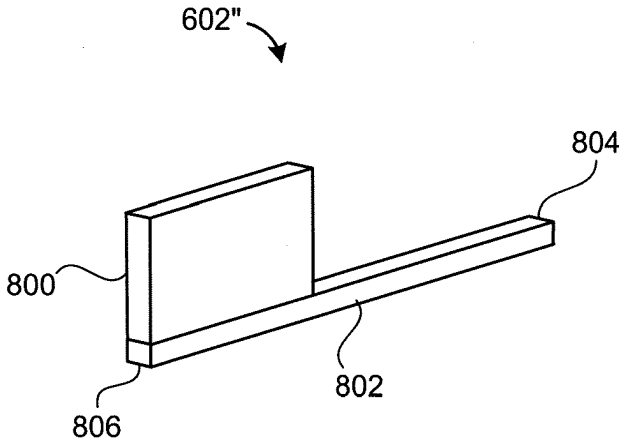


FIG. 8B

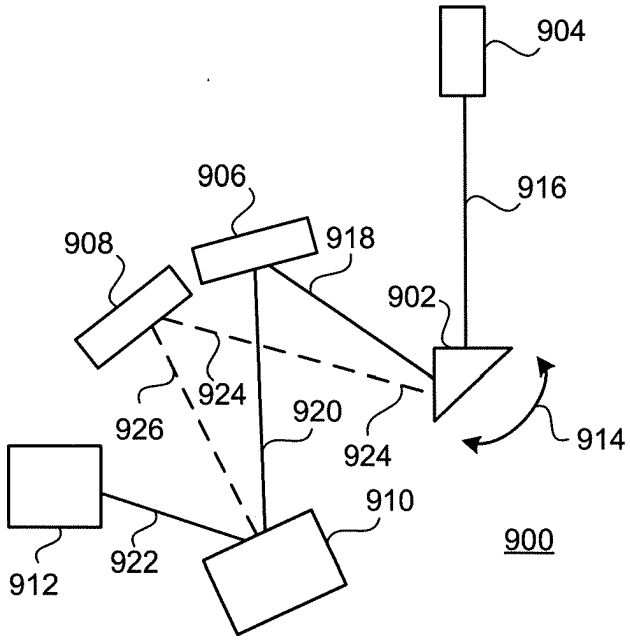


FIG. 9

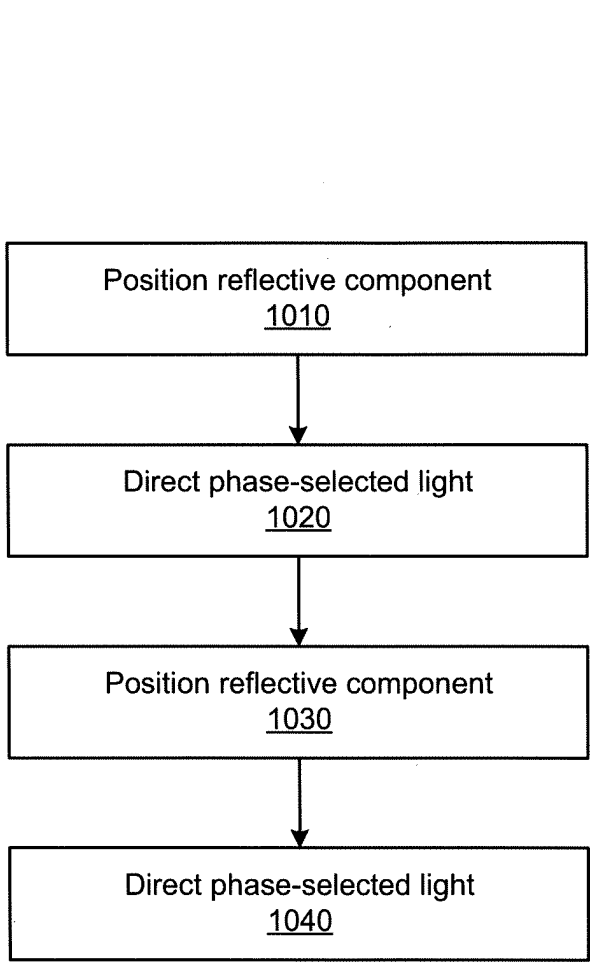

1000
Position reflective component
1010
Direct phase-selected light
1020
Position reflective component
1030
Direct phase-selected light
1040

FIG. 10

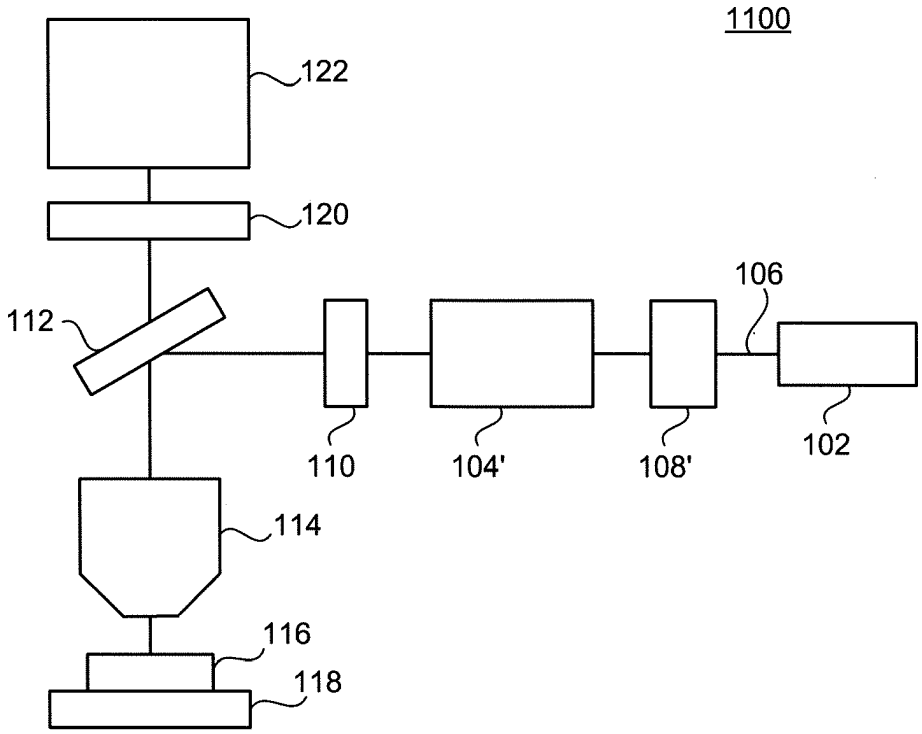

1100
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120
112
106
110
104'
108'
102
114
116
118

FIG. 11

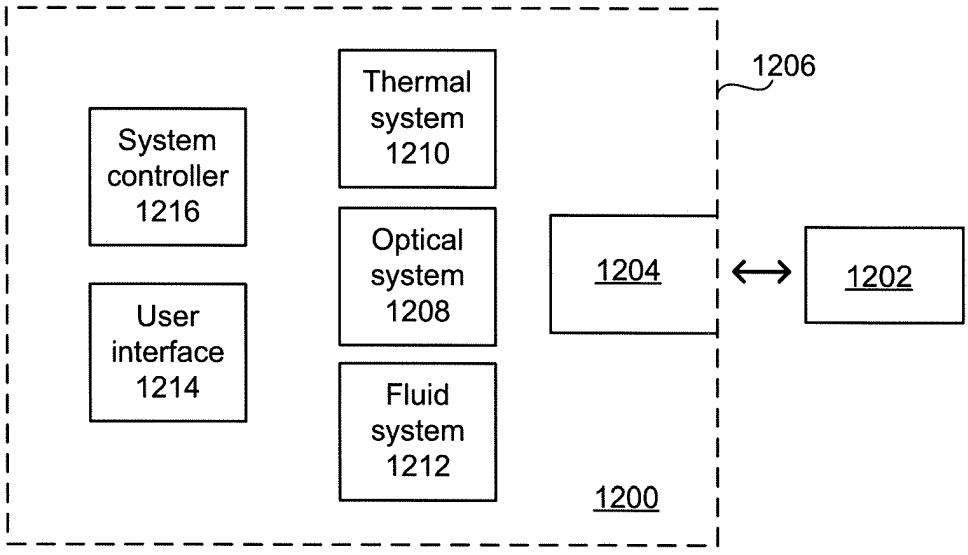

1206
System controller 1216
Thermal system 1210
Optical system 1208
Fluid system 1212
User interface 1214
1204
1202
1200

FIG. 12

SAMENWERKINGSVERDRAG (PCT)

RAPPORT BETREFFENDE NIEUWHEIDSONDERZOEK VAN INTERNATIONAAL TYPE

IDENTIFICATIE VAN DE NATIONALE AANVRAGE	KENMERK VAN DE AANVRAGER OF VAN DE GEMACHTIGDE
	4A/2YG64/24
Nederlands aanvraag nr. **2022286**	Indieningsdatum **21-12-2018**
	Ingeroepen voorrangsdatum
Aanvrager (Naam) **Illumina, Inc**	
Datum van het verzoek voor een onderzoek van internationaal type **19-01-2019**	Door de Instantie voor Internationaal Onderzoek aan het verzoek voor een onderzoek van internationaal type toegekend nr. **SN72772**

I. CLASSIFICATIE VAN HET ONDERWERP (bij toepassing van verschillende classificaties, alle classificatiesymbolen opgeven)

Volgens de internationale classificatie (IPC)

G02B26/08;G02B21/00;G02B21/06;G02B27/58

II. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte minimumdocumentatie

Classificatiesysteem	Classificatiesymbolen
IPC	**G02B**

Onderzochte andere documentatie dan de minimum documentatie, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

III. ☐	**GEEN ONDERZOEK MOGELIJK VOOR BEPAALDE CONCLUSIES**	(opmerkingen op aanvullingsblad)
IV. ☐	**GEBREK AAN EENHEID VAN UITVINDING**	(opmerkingen op aanvullingsblad)

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2022286

A. CLASSIFICATIE VAN HET ONDERWERP
INV. G02B26/08 G02B21/00 G02B21/06 G02B27/58
ADD.

Volgens de Internationale Classificatie van octrooien (IPC) of zowel volgens de nationale classificatie als volgens de IPC.

B. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte miminum documentatie (classificatie gevolgd door classificatiesymbolen)
G02B

Onderzochte andere documentatie dan de mimimum documentatie, voor dergelijke documenten, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

Tijdens het onderzoek geraadpleegde elektronische gegevensbestanden (naam van de gegevensbestanden en, waar uitvoerbaar, gebruikte trefwoorden)
EPO-Internal, WPI Data

C. VAN BELANG GEACHTE DOCUMENTEN

Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	WO 88/08631 A1 (HUGHES AIRCRAFT CO [US]) 3 november 1988 (1988-11-03)	1,2,10, 16-19
A	* bladzijde 12, regel 7 - bladzijde 13, regel 13; figuur 7 *	3-9, 23-27, 30,31

X	JP S60 68314 A (RICOH KK) 18 april 1985 (1985-04-18)	1,11-15
A	* samenvatting; figuren 1-7 *	3-9, 23-27, 30,31

X	WO 2014/040800 A1 (ZEISS CARL MICROSCOPY GMBH [DE]) 20 maart 2014 (2014-03-20)	1,2,10, 20-22, 28,29
A	* bladzijde 1, regel 14 - bladzijde 18, regel 18; figuren 1-3 *	3-9, 23-27, 30,31

	-/--	

[X] Verdere documenten worden vermeld in het vervolg van vak C.

[X] Leden van dezelfde octrooifamilie zijn vermeld in een bijlage

° Speciale categorieën van aangehaalde documenten

"A" niet tot de categorie X of Y behorende literatuur die de stand van de techniek beschrijft

"D" in de octrooiaanvrage vermeld

"E" eerdere octrooi(aanvrage), gepubliceerd op of na de indieningsdatum, waarin dezelfde uitvinding wordt beschreven

"L" om andere redenen vermelde literatuur

"O" niet-schriftelijke stand van de techniek

"P" tussen de voorrangsdatum en de indieningsdatum gepubliceerde literatuur

"T" na de indieningsdatum of de voorrangsdatum gepubliceerde literatuur die niet bezwarend is voor de octrooiaanvrage, maar wordt vermeld ter verheldering van de theorie of het principe dat ten grondslag ligt aan de uitvinding

"X" de conclusie wordt als niet nieuw of niet inventief beschouwd ten opzichte van deze literatuur

"Y" de conclusie wordt als niet inventief beschouwd ten opzichte van de combinatie van deze literatuur met andere geciteerde literatuur van dezelfde categorie, waarbij de combinatie voor de vakman voor de hand liggend wordt geacht

"&" lid van dezelfde octrooifamilie of overeenkomstige octrooipublicatie

Datum waarop het onderzoek naar de stand van de techniek van internationaal type werd voltooid	Verzenddatum van het rapport van het onderzoek naar de stand van de techniek van internationaal type
28 augustus 2019	

Naam en adres van de instantie	De bevoegde ambtenaar
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Frisch, Anna Maria

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ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2022286

C.(Vervolg). VAN BELANG GEACHTE DOCUMENTEN

Categorie °	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
A	CA 2 524 242 A1 (CA NAT RESEARCH COUNCIL [CA]) 21 april 2007 (2007-04-21) * alinea [0059] - alinea [0064]; figuur 7 * -----	3-9, 23-27, 30,31
A	CA 2 555 477 A1 (CA NAT RESEARCH COUNCIL [CA]) 21 april 2007 (2007-04-21) * alinea [0059] - alinea [0064]; figuur 7 * -----	3-9, 23-27, 30,31
A	US 2007/091401 A1 (DUFOUR MARC L [CA] ET AL) 26 april 2007 (2007-04-26) * alinea [0065] - alinea [0070]; figuur 7 * -----	3-9, 23-27, 30,31
A	WO 2004/030166 A1 (AGILENT TECHNOLOGIES INC [US]; STEFFENS WOLF [DE] ET AL.) 8 april 2004 (2004-04-08) * bladzijde 3, regel 13 - bladzijde 4, regel 8; figuur 1 * -----	3-9
X	DE 10 2012 017917 A1 (ZEISS CARL MICROSCOPY GMBH [DE]) 13 maart 2014 (2014-03-13)	1,2,10, 28,29
A	* alinea [0002] - alinea [0090]; figuren 1-4 * -----	3-9, 23-27, 30,31

ONDERZOEKSRAPPORT BETREFFENDE HET RESULTAAT VAN HET ONDERZOEK NAAR DE STAND VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE

Informatie over leden van dezelfde octrooifamilie

Nummer van het verzoek om een onderzoek naar de stand van de techniek
NL 2022286

In het rapport genoemd octrooigeschrift	Datum van publicatie	Overeenkomend(e) geschrift(en)	Datum van publicatie
WO 8808631	A1 03-11-1988	EP 0311664 A1	19-04-1989
		JP H01503582 A	30-11-1989
		US 4862468 A	29-08-1989
		WO 8808631 A1	03-11-1988
JP S6068314	A 18-04-1985	GEEN	
WO 2014040800	A1 20-03-2014	DE 102012017922 A1	15-05-2014
		EP 2895907 A1	22-07-2015
		JP 6310917 B2	11-04-2018
		JP 2015527618 A	17-09-2015
		US 2015253559 A1	10-09-2015
		WO 2014040800 A1	20-03-2014
CA 2524242	A1 21-04-2007	GEEN	
CA 2555477	A1 21-04-2007	GEEN	
US 2007091401	A1 26-04-2007	GEEN	
WO 2004030166	A1 08-04-2004	AU 2002342751 A1	19-04-2004
		DE 60217558 T2	03-05-2007
		EP 1547209 A1	29-06-2005
		JP 2006500776 A	05-01-2006
		US 2006274810 A1	07-12-2006
		WO 2004030166 A1	08-04-2004
DE 102012017917 A1	13-03-2014	DE 102012017917 A1	13-03-2014
		WO 2014040798 A1	20-03-2014

WRITTEN OPINION

File No.	Filing date *(day/month/year)*	Priority date *(day/month/year)*	Application No.
SN72772	21.12.2018		NL2022286

International Patent Classification (IPC)
INV. G02B26/08 G02B21/00 G02B21/06 G02B27/58

Applicant
Illumina, Inc

This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the application
- ☒ Box No. VIII Certain observations on the application

	Examiner
	Frisch, Anna Maria

Application number

WRITTEN OPINION

NL2022286

Box No. I Basis of this opinion

1. This opinion has been established on the basis of the latest set of claims filed before the start of the search.

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the application as filed.

   ☐ filed together with the application in electronic form.

   ☐ furnished subsequently for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes:	Claims	3-9, 23-27, 30, 31
	No:	Claims	1, 2, 10-22, 28, 29
Inventive step	Yes:	Claims	3-9, 23-27, 30, 31
	No:	Claims	1, 2, 10-22, 28, 29
Industrial applicability	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION

Box No. VIII Certain observations on the application

see separate sheet

Re Item V

Reference is made to the following documents:

D1: WO8808631

D2: JPS6068314

D3: WO2014040800

D4: CA2524242

D5: C2555477

D6: US20070091401

D7: WO2004030166

D8: DE102012017917

1.1 The subject-matter of claims 1, 2, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 28, as far as they are understood and construed, is not new:

Documents D1, D2, D3, and D8 describe a system suitable for the generation of spatially structured light which is suitable for a structured light microscope comprising a light source (D1: the laser rod 11, D2: implicit, D3: 10, D8: implicit), a first grating (D1: 81, D2: A, D3: 41, D8: 71) and a second grating (D1: 80, D2: B, D3: 42, 43, D8: 72), at least one reflecting component (D1: 71, D2: P1, D3: 20, D8: 50), which is selectively positionable in a first light path extending from the light source to the first grating and to the following component in the system, and in a second light path extending from the light source to the second grating and to the following component (D1: see figure 7, D2: see figure 6, D3: see figure 1, D8: see figure). The reflecting component of D1 is a rotatable mirror in the form of a prism (D1: see figure 7) which is moved between the first and the second position. The reflective component of D3 and D8 is a rotatable mirror which is moved into the first and the second position. The gratings of D1, D3, and D8 are located adjacent each other, are fixed towards the light source, and face the same direction/same following component (D1, D8: they face the reflective component, D3: they face a phase shifter, see figure 1). In D2, the reflective component comprises a first translatable mirror (left hand side of prism reflector P1) which can be positioned in the first position. In D2, the reflective component comprises a second translatable mirror which can be positioned in the second position (D2: right hand side of prism P1). The first and the second translations in D2 are parallel to the plane defined by the optical paths and the first translatable mirror is translated into both positions (D2: see figure 6).

The first and second grating of D1 - D3 and D8 are positioned behind the light source. The following component in D3 is a phase shifter (D3: 41, 42, 43). The system of D3 also comprises a phase selector between the light source and the reflector (D3: see

phase selector 14). D3 and D8 also describe a device for structured light microscopy which comprises a sub-system according to any of claims 1 - 27 (D3: see abstract, D8: see abstract and paragraph [0002]).

1.2 The above arguments translate into a corresponding novelty objection for the method of claim 29.

2. The additional features of claim 13 also do not appear to provide a basis for an inventive activity:

It is clear for the skilled person that the mirror P1 in D2 could also be moved out of the plane formed by the light paths.

3. Under the constraints for clarity mentioned below, it appears that the subject-matter of claims 3 - 9, 23 - 27, and 30, 31 are neither known from nor rendered obvious by the prior art:

The skilled person knows the selection of a grating by using a rotatable mirror or a translatable mirror pair from D1, D2, or D3, as shown above. It is thereby considered that he will contemplate on the replacement of the simple rotating mirror of D3 with the one of D2 or D1 in case the replacement of the fibres of D3 is needed or desired (e.g. due to unacceptable optical losses).

A system for selecting an optical path with a single double sided reflector element put in one of two positions as such is also known (see D4: figure 7, D5: figure 7, D6: figure 7). However, it is considered that the skilled person has no motivation to use this system as replacement of the single rotatable mirror of D1 or D3 or the translatable mirror pair of D2.

Re Item VIII

1. Two independent claims (claims 1 and 23) in the same category and with similar and overlapping scope render the nature of the invention unclear.

1.2 Since the configuration of the system is not clearly defined (e.g. by by stating that the gratings are parallel adjusted to each other and the single mirror with the two opossed reflecting sides is oriented at 45° to mirror planes), it is not clear from claims 3 - 9 and 23 - 27 that the the mirror interrupts the first light path via a reflection by its first mirror side to redirect the beam towards the first grating in its first position, and, in its second position, redirects the light coming from the second grating via reflection by the second mirror side towards the further component, as it is understood from the description and illustrated in the embodiments of figures 1 - 4 and 6.

The claims are thus unclear as such and not supported by the description.

Similar objections apply also to claims 30 and 31.