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(71) Applicant *(for all designated States except US):* **THE GOVERNMENT OF THE U.S.A., represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; 601 1 Executive Boulevard, Suite 325, Rockville, MD 20852 (US).

(72) Inventors; and

(75) Inventors/ Applicants *(for US only):* **SHROFF, Hari** [US/US]; 2725 Connecticut Ave NW #609, Washington, DC 20008 (US). **YORK, Andrew, Gregory** [US/US]; Building 13, 3N17, 13 South Drive, Bethesda, MD (US). **WU, Yicong** [CN/US]; Building 13, G800, 13 South Drive, Bethesda, MD (US).

(74) Agent: **PAUL, Jenny, A.;** Polsinelli Shughart PC, 161 North Clark Street, Suite 4200, Chicago, IL 60601 (US).

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(54) **Title:** SYSTEM AND METHOD OF PRODUCING NONDIFFRACTING LIGHT SHEETS BY A MULTIPLICITY OF SPATIALLY OVERLAPPING, MINIMALLY INTERFERING NONDIFFRACTING OPTICAL BEAMS

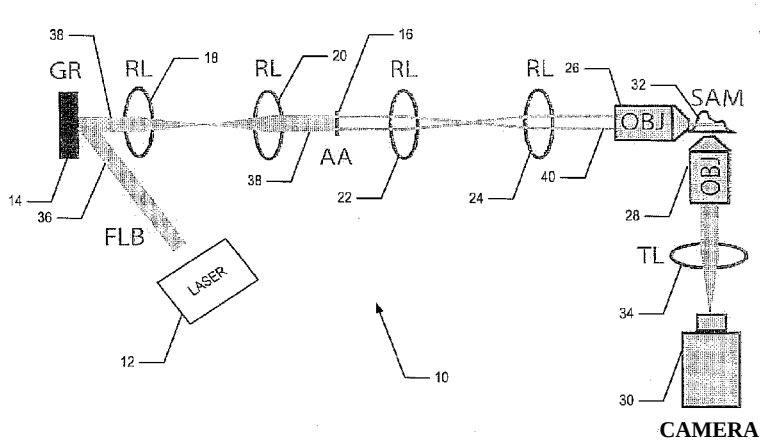

FIG. 1

(57) **Abstract:** A system and method of producing nondiffracting sheets of light that spatially overlap, but do not interfere with each other when intersecting the detection plane of an optical arrangement is disclosed. The system includes an illumination source for transmitting a beam of light through the optical arrangement that includes a diffraction grating for diffracting the light beam to produce beams of light having different wavelengths, which are then passed through an annular aperture that transforms the beams of light into nondiffracting beams having different wavelengths.

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RELATED APPLICATIONS

[0001] This application claims priority to U.S. Patent Application No. 61/360,352, filed June 30, 2010, and entitled SYSTEM AND METHOD OF PRODUCING NONDIFFRACTING LIGHT SHEETS BY A MULTIPLICITY OF SPATIALLY OVERLAPPING, MINIMALLY INTERFERING NONDIFFRACTING OPTICAL BEAMS, the entire contents of which are incorporated herein by reference.

FIELD

[0002] This application relates to a system of producing nondiffracting light sheets by a multiplicity of spatially overlapping optical beams, and in particular a selective plane illumination microscopy that utilizes such a system of producing nondiffracting light sheets.

BACKGROUND

[0003] Selective plane illumination microscopy (SPIM) is a technique that uses a thin sheet of light for the illumination of a sample at a detection plane of a detection objective lens that detects a fluorescence signal generated by the sample when illuminated. SPIM provides optical sectioning of the sample by illuminating only those fluorophores that are in the detection plane. The system combines the advantages of wide-field methods (speed, flexibility, and dynamic range) with those of a confocal arrangement (optical sectioning). SPIM also provides quantitative three-dimensional maps of the distribution of a fluorophore within the sample, for example, the expression pattern of GFP-labeled protein, with high spatiotemporal resolution and an excellent signal to noise ratio. However, the standard SPIM technique produces nonuniform axial resolution, which is caused by the diffraction of the laser beam through the sample. As diffraction causes the laser beam to spread and thicken at distances far from its center (beam waist), optical sectioning degrades, thereby forcing a compromise between field of view and axial resolution.

[0004] Other prior art techniques manipulate the phase of the laser beam by a spatial light modulator (SLM) to produce nondiffracting beams, such as Bessel beams, for sample illumination, in order to alleviate the problems mentioned above. However, the concentric rings of multiple nondiffracting beams produce regions of high intensity at points of overlap referred to as interference, thereby degrading both optical sectioning and the quality of the

image. Furthermore, scanning a single nondiffracting beam throughout the sample is much slower than producing a multiplicity of minimally interfering nondiffracting beams that illuminate the sample near-simultaneously. Accordingly, there is a need in the art for a SPIM microscope that addresses the problems of the prior art.

SUMMARY

[0005] In an embodiment, a system may include an illumination source that transmits a beam of light. A first optical arrangement transforms the beam of light into a plurality of beams with each of the plurality of beams having a different wavelength. A second optical arrangement transforms the plurality of beams into a plurality of nondiffracting beams with each of the plurality of nondiffracting beams having different wavelengths such that the plurality of nondiffracting beams spatially overlap with at least another one of the plurality of nondiffracting beams with reduced interference.

[0006] In another embodiment, a method for producing nondiffracting sheets of light may include:

transmitting a beam of pulsed light,

transforming the beam of pulsed light into a plurality of beams, each of the plurality of beams having a different wavelength, and

focusing the plurality of beams through an annular aperture for transforming the plurality of beams into a plurality of nondiffracting beams, each of the plurality of nondiffracting beams having different wavelengths such that the plurality of nondiffracting beams overlap with one another with reduced interference.

[0007] In yet another embodiment, a microscope may include a laser source that transmits a pulsed laser beam, a diffraction grating for causing the pulsed laser beam to be split into a plurality of pulsed laser beams with each of the plurality of pulsed laser beams having different wavelengths. A first optic arrangement magnifies the plurality of pulsed laser beams having different wavelengths from the diffraction grating and images the plurality of pulsed laser beams through an aperture for transforming the plurality of pulsed laser beams into a plurality of nondiffracting beams. Each of the plurality of nondiffracting beams has a different wavelength. A second optic arrangement demagnifies the plurality of nondiffracting beams, and then focuses the plurality of nondiffracting beams onto a sample at the detection plane of the second optic arrangement, wherein the plurality of nondiffracting beams spatially overlap at least one other of the plurality of nondiffracting beams, but with reduced interference.

[0008] Additional objectives, advantages and novel features will be set forth in the description which follows or will become apparent to those skilled in the art upon examination of the drawings and detailed description which follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 is a simplified illustration of an embodiment of a selective plane illumination microscopy system; and

[0010] FIGS. *2*A and **2B** are simplified illustrations showing the plurality of nondiffracting beams relative to a detection plane of the microscopy system.

[0011] Corresponding reference characters indicate corresponding elements among the view of the drawings. The headings used in the figures should not be interpreted to limit the scope of the claims.

DETAILED DESCRIPTION

[0012] Selective plane illumination microscopy (SPIM) is a technique that provides fast, 3-dimensional biological imaging with minimal photo-bleaching and photo-damage to a sample. However, the axial resolution of the image produced by conventional SPIM microscopes suffers increasing degradation at distances from the illumination beam waist due to diffractive spreading of the illumination source. Other techniques manipulate the phase of the laser beam by a spatial light modulator to produce non-diffracting beams, such as Bessel beams, for sample illumination; however, Bessel beams produce regions of high intensity outside the detection plane, caused by concentric rings ("ringing") or interference, thereby degrading the quality of the image.

[0013] In physics, interference is the addition (superposition) of two or more waves that produces a new wave pattern. Interference usually refers to the interaction of waves that are correlated or coherent with each other, either because these waves come from the same source or because they have the same or nearly the same frequency. The principle of superposition of waves states that the resultant displacement at a point is equal to the vector sum of the displacements of different waves at that point. For example, if a crest of a wave meets a crest of another wave at the same point then the crests interfere constructively and the resultant wave amplitude is increased. However, if a crest of a wave meets a trough of another wave then the waves interfere destructively, and the resultant wave amplitude is decreased.

[0014] Both destructive and constructive interference produce unwanted concentric ringing that degrades the quality of the image detected by a Bessel-beam based SPIM microscope as discussed above. In particular, constructive interference focuses energy into planes other than the detection plane of the microscope, thereby producing peaks in the rings, while destructive interference generates intensity nulls, which produces troughs in the rings. Accordingly, both constructive and destructive interference above and below the detection plane of the microscope create difficulties in measuring the fluorescence signal generated by the illumination of a sample under detection by the microscope. As used herein, the term "interference" will refer to both constructive and destructive interference as described above.

[0015] As such, embodiments of a system and method that produces nondiffracting sheets of light using a multiplicity of spatially overlapping optical beams as disclosed herein include particular properties and characteristics that address issues related to reducing interference. The system and method as described herein overcomes these deficiencies by producing beams of light having different wavelengths that are transformed into

nondiffracting beams that also have different wavelengths, which cause the nondiffracting beams to spatially overlap (causing a sheet) with minimal interference between the nondiffracting beams. Furthermore, the interference due to any individual nondiffracting beam, is reduced if the illumination source is a femtosecond laser beam, which produces multiphoton excitation of the sample and eliminates regions of high intensity that would otherwise exist due to the mechanism of linear absorption for generating fluorescence in a biological specimen under observation.

[0016] Referring to the drawings, one embodiment of the system and method for producing nondiffracting sheets of light using the multiplicity of spatially overlapping optical beams is embodied in a microscope is illustrated and generally indicated as **10** in FIG. **1.** In an embodiment, the microscope **10** may be a SPIM microscope that includes a laser device **12,** such as a femtosecond laser device that generates a pulsed laser beam **36,** which is reflected off a diffraction grating **14.** In a particular embodiment, the diffraction grating **14** may have the following characteristics: **830.8** grooves/mm, **19.7** degree blaze, input angle = **49.8** degrees and an output angle = **0** degrees. In a particular embodiment, the pulsed laser beam **36** may have an input beam diameter = **10** mm. The output angle of the diffraction grating **14** should be normal to the face of the diffraction grating **14** such that the groove distance, input angle, wavelength lambda, and the order "m" to satisfy the following equation **m(lambda) = d sine theta i**.

[0017] The plurality of beams **38** having different wavelengths imparted by the diffraction grating **14** is then imaged by a pair of relay lenses **18** and **20,** such as lenses **18** and **20** having focal lengths of **300** mm and **100** mm, respectively, through an annular aperture **16** that transforms the plurality of beams **38** having different wavelengths into a plurality of nondiffracting beams **40** with different wavelengths. However, the focal length of the relay lens **18** and **20** may be chosen so that the diameter of the pulsed laser beam **36** is demagnified (or magnified) to fill the annular aperture **16.** In an embodiment, the annular aperture **16** may have an inner radius between **2.33** mm to **2.63** mm and an outer radius of **2.66** mm. The value of the outer radius of the annular aperture **16** may be chosen so that, after magnification by the relay lenses **18, 20, 22,** and **24,** the back focal plane diameter of the first objective lens **26** is filled so as to produce the highest available numerical aperture. The value of the inner radius of the annular aperture **16** determines the length of the nondiffacting beam **40** with smaller values producing a shorter nondiffracting beam **40** while larger values producing a longer nondiffracting beam **40** Based on the characteristics of the first objective lens **26** and the relay lenses **18, 20, 22,** and **24** the range of values of the outer radius may be

between 2.0-2.66 mm, and the inner radius may be any value less than the range of values for the outer radius. In addition, other embodiments that transform the plurality of beams **38** into plurality of nondiffracting beams **40** may include an axicon, a spatial light modulator (SLM), or a binary phase mask.

[0018] As used herein, the term "nondiffracting beam" means any beam of electromagnetic light that shows little or no diffraction over a significant propagation distance (i.e. the transverse intensity distributions of the beam do not vary over a significant propagation distance), including but not limited to Bessel-like beams (i.e., those beams whose wave amplitude is approximated by a Bessel function).

[0019] The plurality of nondiffracting beams **40** are then reimaged by another pair of relay lenses **22** and **24,** for example lenses having focal lengths of **100** mm and **300** mm, respectively, onto the back detection plane of a first objective lens **26,** for example an excitation objective lens. In other embodiments, the relay lenses **22** and **24** may have any suitable focal length with the only constraint being that the nondiffracting beams **40** must cover the back focal plane of the first objective lens **26** In an example embodiment, the first objective lens **26** may be a Nikon 0.8 NA 40x water immersion objective lens. The annular aperture **16** may be replaced by an axicon plus additional lenses for increased power efficiency. In one embodiment, this arrangement transforms the energy into a series of nondiffracting beams **40** that overlap each other, but also reduces interference of the beams **40.** As shown in FIGS. **1, 2A** and **2B,** the resulting plurality of nondiffracting beams **40** may illuminate a biological sample **32** and induce a multiphoton fluorescence excitation in the sample **32** along the optical axis and in the vicinity of a detection plane **42** of the first objective lens **26.**

[0020] Referring to FIGS. **1** and **2A,** the microscope **10** further includes a focusing optic arrangement having a second objective lens **28,** for example a detection objective lens, positioned at a 90-degree angle relative to the sample **36** on the detection plane **42.** In one embodiment, the second or detection objective lens **28** may be a Nikon 0.8 NA 40x water immersion objective lens. The main constraint on the types of first and second objective lenses **26** and **28** is that these lenses must fit together at 90 degrees angle for a SPIM arrangement such that the 90 degree geometry imposes spatial constraints on the types of objective lenses that may be used. As shown in FIG. **1,** a tube lens **34** is positioned along the optic axis of the second objective lens **28** for imaging the fluorescence excitation signal emitted by the sample **32** onto a widefield detector **30.** In an embodiment, the tube lens **34** may be a 200 mm Nikon tube lens, however other focal lengths may be used to provide a

given magnification. For example, the 200 mm tube lens in the example embodiment provides a magnification of 40x when combined with the first objective lens **26.** In one embodiment, the widefield detector **30** may be a charge coupled detector (CCD), for example, an Andor iXon 888).

[0021] The optical overall arrangement of the microscope **10** described above creates a multiplicity of nondiffracting beams of light from an illumination source that overlap spatially with each other but with reduced interference, thereby producing sheets of light that resist diffraction along the optic axis. This arrangement results in better axial resolution of the image than is possible with conventional SPIM microscopes.

[0022] The concept of transforming a pulsed laser beam **36** generated from a laser source **12** that is split into a plurality of beams **38** having different wavelengths and then transformed into a plurality of nondiffracting beams **40** may be applied to other microscopy, such as fluorescence microscopy, where the application of nondiffracting sheets of light to illuminate a sample to generate the resulting excitation profile is desirable.

[0023] It should be understood from the foregoing that, while particular embodiments have been illustrated and described, various modifications can be made thereto without departing from the spirit and scope of the invention as will be apparent to those skilled in the art. Such changes and modifications are within the scope and teachings of this invention as defined in the claims appended hereto.

CLAIMS

What is claimed is:

1. A system comprising:

an illumination source that transmits a beam of light,

a first optical arrangement for transforming the beam of light into a plurality of beams, each of the plurality of beams having a different wavelength, and

a second optical arrangement for transforming the plurality of beams into a plurality of nondiffracting beams, each of the plurality of nondiffracting beams having different wavelengths such that the plurality of nondiffracting beams spatially overlap with at least another one of the plurality of nondiffracting beams with reduced interference.

2. The system of claim 1, wherein the first optical arrangement comprises:

a diffraction grating for transforming the beam of light into the plurality of beams having different wavelengths.

3. The system of claim 1, wherein the second optical arrangement comprises:

an annular aperture, a spatial light modulator, an axicon, or a binary phase mask for transforming the plurality of beams into a plurality of nondiffracting beams having different wavelengths.

4. The system of claim 3, wherein the first optical arrangement comprises:

a pair of lenses for magnifying the beam of light onto the annular aperture, spatial light modulator, axicon or binary phase mask.

5. The system of claim 1, wherein the second optical arrangement comprises:

a pair of lenses for demagnifying the plurality of nondiffracting beams and a first objective lens for focusing the plurality of nondiffracting beams along the detection plane.

6. The system of claim 1, further comprising:

a sample illuminated by the plurality of nondiffracting beams along the vicinity of the detection plane for generating a fluorescence signal, and

a second objective lens for detecting the fluorescence signal.

7. The system of claim 7, further comprising:

a detector for detecting the fluorescence signal generated by the sample such that the incidence of interference is reduced.

8. The system of claim 1, wherein the illumination source is a laser device.

9. The system of claim 8, wherein the laser device is a femtosecond laser device.

10. The system of claim 1, wherein the beam of light is a femtosecond laser beam.

11. A method for producing nondiffracting sheets of light comprising:

transmitting a beam of pulsed light,

transforming the beam of pulsed light into a plurality of beams, each of the plurality of beams having a different wavelength, and

focusing the plurality of beams through an annular aperture for transforming the plurality of beams into a plurality of nondiffracting beams, each of the plurality of nondiffracting beams having different wavelengths such that the plurality of nondiffracting beams overlap with one another with reduced interference.

12. The method of claim 11, further comprising:

focusing the plurality of nondiffracting beams through an optical arrangement to illuminate a sample along a detection plane of the optical arrangement.

13. The method of claim 12, wherein each of the plurality of nondiffracting beams intersects the detection plane at either different times and/or different locations along the detection plane relative to another of the plurality of nondiffracting beams.

14. The method of claim 12, wherein transforming the beam of pulsed light into a plurality of beams having different wavelengths comprises directing the beam of pulsed light onto a diffraction grating.

15. The method of claim 11, wherein transforming the plurality of beams into a plurality of nondiffracting beams comprises passing the plurality of beams through an aperture.

16. A microscope comprising:

a laser source that transmits a pulsed laser beam,

a diffraction grating for causing the pulsed laser beam to be split into a plurality of pulsed laser beams, each of the plurality of pulsed laser beams having different wavelengths,

a first optic arrangement for magnifying the plurality of pulsed laser beams having different wavelengths from the diffraction grating and imaging the plurality of pulsed laser beams through an aperture for transforming the plurality of pulsed laser beams into a plurality of nondiffracting beams, each of the plurality of nondiffracting beams having a different wavelength,

a second optic arrangement for demagnifying the plurality of nondiffracting beams, and focusing the plurality of nondiffracting beams onto a sample along a detection plane, wherein the plurality of nondiffracting beams overlap at least one other of the plurality of nondiffracting beams with reduced interference.

17. The microscope of claim 16, wherein the aperture is an annular aperture, spatial light modulator, axicon or binary phase mask .

18. The microscope of claim 16, wherein the first optic arrangement is a pair of relay lenses.

19. The microscope of claim 16, wherein the second optic arrangement is a pair of relay lenses in combination with a first objective lens, wherein the first objective lens focuses the plurality of nondiffracting beams onto the sample along the detection plane of the first objective lens.

20. The microscope of claim 16, further comprising:

a third optical arrangement including a second objective lens for imaging a fluorescence signal generated by the sample as the plurality of nondiffracting beams intersect the detection plane.

21. The microscope of claim 20, wherein the laser source is a femotsecond laser device.

22. The microscope of claim 16, wherein the microscope is a selective plane illumination (SPIM) microscope.

23. The microscope of claim, 20, further comprising:

a detector for detecting the fluorescence signal generated by the sample along the detection plane such that the interference that is detectable by the detector is reduced.

24. The microscope of claim 16, wherein the plurality of nondiffracting beams resists diffraction along an optic axis of the second optic arrangement.

25. The microscope of claim 16, the first optic arrangement comprises:

first and second relay lenses for magnifying the plurality of beams through the annular aperture.

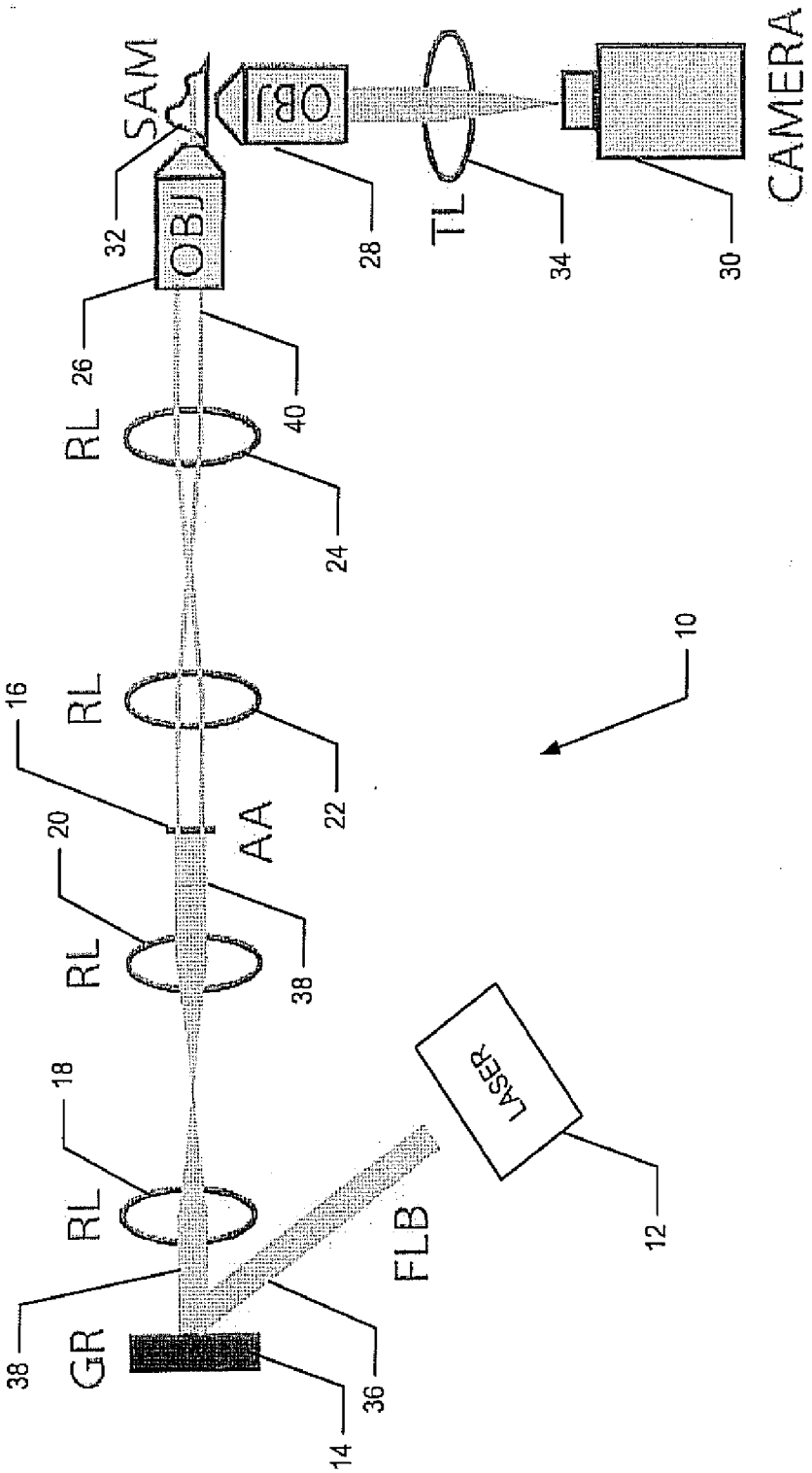
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FIG. 1

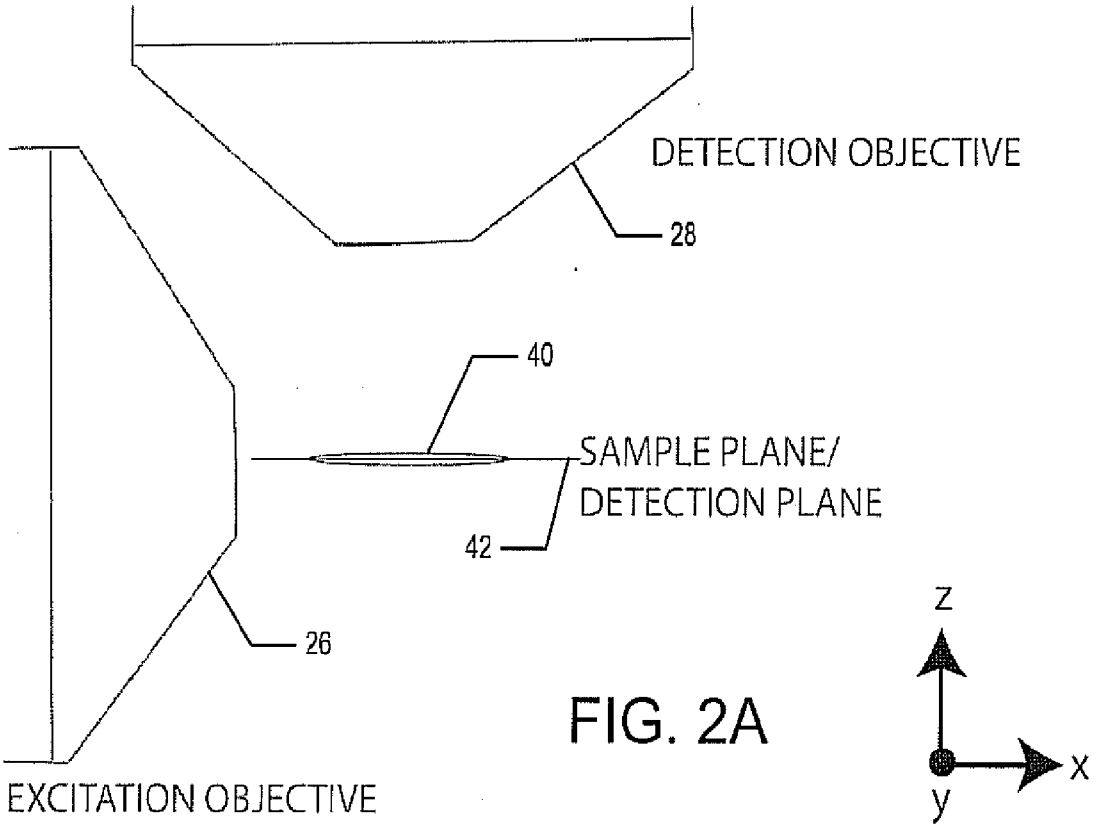
DETECTION OBJECTIVE
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FIG. 2A

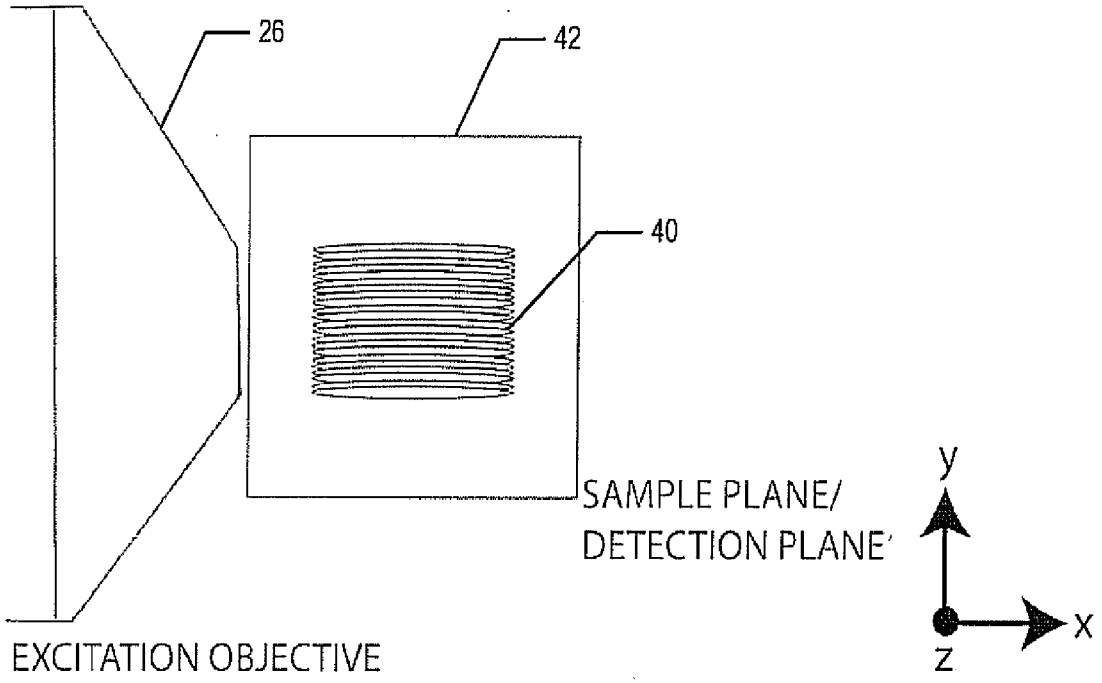
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FIG. 2B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/042495

A. CLASSIFICATION OF SUBJECT MATTER
INV. G02B21/00 G02B21/16 G02B27/58
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G02B

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , WPI Data, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Fischer P et al: "Wavelength dependent propagation andreconstruction of white light Bessel beams", JOURNAL OF OPTICS A: PURE AND APPLIED OPTICS, vol. 8 24 April 2006 (2006-04-24), pages 477-482, XP000002659023, DOI: 10.1088/1464-4258/8/5/018 Retrieved from the Internet: URL: http://iopscience.iop.org/1464-4258/8/5/018/pdf/1464-4258_8_5_018.pdf [retrieved on 2011-09-13]	1,3,4, 8-11
A	abstract; figure 3	2,5-7, 12-25

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2011	29/09/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ward, Seamus

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/042495

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Greger K et al: "Basic building units and properties of a fluorescence single plane illumination microscope", Review of Scientific Instruments, vol. 78, no. 2, 023705, 28 February 2007 (2007-02-28), pages 023705-1-023705-7, XP000002659024, DOI: 10.1063/1.2428277 Retrieved from the Internet: URL: http://scitation.aip.org/getpdf/servlet/GetPDFServlet?filetype=pdf&id=RSINAKOOOO78000002023705000001&idtype=cvips&doi=10.1063/1.2428277&prog=normal [retrieved on 2011-09-13] abstract; figures	1-25
Y	DE 10 2007 063274 A1 (UNIV ALBERT LUDWIGS FREIBURG [DE]; ZEISS CARL MICROIMAGING GMBH [DE]) 25 June 2009 (2009-06-25) abstract; figures	1-25
A	Fahrbach F et al: "Microscopy with non-diffracting beams", Abstract at Focus on Microscopy Conference 2009, 2009, XP000002659025, Retrieved from the Internet: URL: http://www.focusonmicroscopy.org/2009/PDF/281_Fahrbach.pdf [retrieved on 2011-09-13] abstract; figure	1-25
A	Huisken J et al: "Optical Sectioning Deep Inside Live Embryos by Selective Plane Illumination Microscopy", Science, vol. 305 13 August 2004 (2004-08-13), pages 1007-1009, XP000002659026, DOI: 10.1126/science.1100035 Retrieved from the Internet: URL: http://www.sciencemag.org/content/305/5686/1007.full.pdf [retrieved on 2011-09-13] abstract; figures	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/042495

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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