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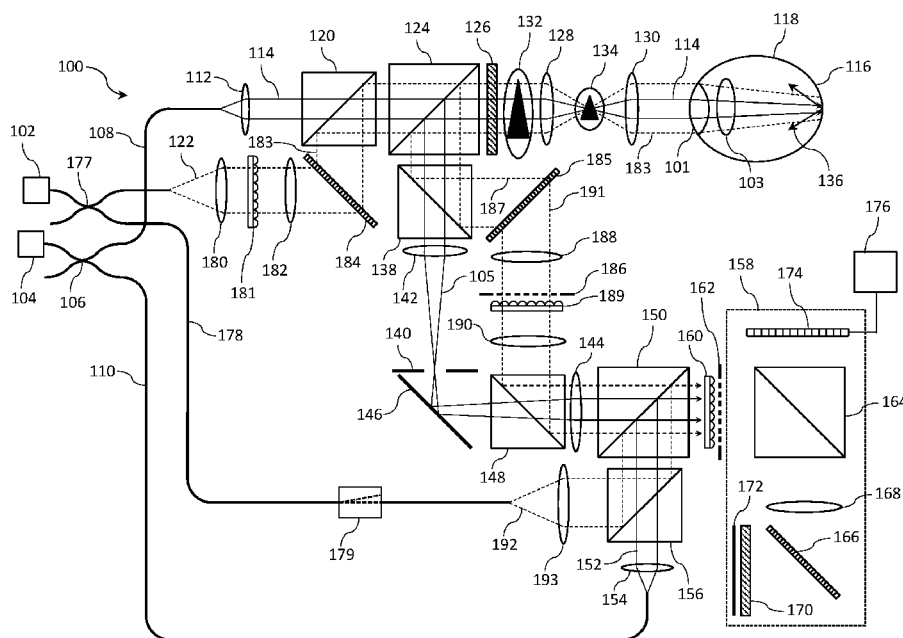


Fig. 1

(57) Abstract: Methods and apparatus are presented for confocal microscopy using dispersed structured illumination. In certain embodiments the apparatus also comprises an optical coherence tomography (OCT) system, and OCT images acquired from two or more regions of a sample are registered using a corresponding set of two or more larger area images acquired with the confocal microscopy system. In preferred embodiments the apparatus is suitable for analysing the retina of an eye. The confocal microscopy system can be operated in a purely intensity mode or in a coherent mode. In other embodiments a confocal microscopy system using dispersed structured illumination is utilised for surface metrology.



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APPARATUS AND METHOD FOR CONFOCAL MICROSCOPY USING DISPERSED STRUCTURED ILLUMINATION

Field of the Invention

The present invention relates to apparatus and methods for confocal microscopy using dispersed
5 structured illumination, in particular for the registration of co-acquired optical coherence
tomography (OCT) images. However it will be appreciated that the invention is not limited to
this particular field of use.

Related Applications

The present application claims priority from Australian Provisional Patent Application No
10 2016902602 entitled 'Apparatus and method for confocal microscopy using dispersed structured
illumination' filed on 1 July 2016, the contents of which are incorporated herein by reference.

Background of the Invention

Any discussion of the prior art throughout the specification should in no way be considered as
an admission that such prior art is widely known or forms part of the common general
15 knowledge in the field.

Optical coherence tomography (OCT) is a widely used interferometric technique for studying
biological samples including *in vivo* tissue such as the human eye, with lateral and depth
resolution, using information contained within the amplitude and phase of reflected or scattered
light. OCT systems generally utilise a Michelson interferometer configuration, with two main
20 approaches being employed: time domain OCT and spectral domain OCT.

In time domain OCT coherence properties of a partially coherent source such as a
superluminescent light emitting diode (SLED) with a coherence length of several microns are
utilised by interfering light reflected from a sample with a reference beam provided by the same
source, but with a time-varying path length. At a specific depth in the sample corresponding to
25 the path length delay in the reference arm, an interference envelope of fringes will be detected in
the combined back-reflected signal, allowing the reflection profile in the depth dimension to be
reconstructed. Commonly this is done for only a single sample point at a time, and the
corresponding scan of depth is known as an 'A-scan'.

Instead of scanning a delay line, spectral domain OCT techniques analyse the reflected light by
30 interfering it with a reference beam, either as a time-varying function of wavelength (swept
source OCT) or by dispersing the different wavelengths with a grating or other spectral

demultiplexer and detecting them simultaneously along a detector array. The spectral domain information is the Fourier transform of the spatial (depth) reflection profile, so the spatial profile can be recovered by a Fast Fourier Transform (FFT). Generally speaking, spectral domain OCT systems are preferred over time domain OCT systems because they have a ~20 to 30 dB
5 sensitivity advantage.

OCT techniques can be adapted to provide a laterally resolved 'B-scan' by scanning the sample beam relative to the sample in one axis, or a 'C-scan' by scanning in two axes. Faster acquisition is generally desirable irrespective of the type of scan, especially for reducing motion-induced artefacts with *in vivo* samples, and has been greatly improved over the previous
10 20 to 25 years by advances in several fields including faster swept source scanning rates and photodetector array readout speeds. However a fundamental limitation with scanning spot schemes, especially for *in vivo* applications, is presented by laser safety regulations: reducing dwell time to increase scanning speed without being able to increase the applied power will inevitably degrade the signal to noise ratio.

15 Consequently there has also been research into 'parallelised' OCT systems in which an extended sample area is probed with lateral resolution, or an array of sample spots probed simultaneously. It is relatively straightforward to parallelise time domain OCT, e.g. by utilising a CCD camera and imaging optics as described in US Patent No 5,465,147 entitled 'Method and apparatus for acquiring images using a CCD detector array and no transverse scanner'. This provides a two
20 dimensional (2-D) *en face* image, with depth resolution provided by scanning the reference mirror as usual in time domain OCT.

Swept source spectral domain OCT can be parallelised in similar fashion, as described in Bonin *et al* 'In vivo Fourier-domain full-field OCT of the human retina with 1.5 million A-lines/s', *Optics Letters* 35(20), 3432-3434 (2010). However because each frame corresponds to a single
25 wavelength, the acquisition time for each A-scan is equal to the frame period times the number of *k*-points (wavelength samples) acquired. Even for very high speed cameras with frame rates of 100s of kHz, this can lead to A-scan acquisition times of many ms which can lead to motion artefacts especially with *in vivo* samples. Published PCT patent application No WO
30 2016/094940 A1, entitled 'Multichannel optical receivers', discloses an alternative parallelised swept source OCT scheme that enables faster acquisition. In one particular implementation a plurality of spots on a sample are illuminated simultaneously and the reflected or scattered signal light mixed with a reference beam to form a plurality of interferograms with unique carrier frequencies.

Spectrometer-based spectral domain OCT is somewhat more difficult to parallelise because of the necessity to disperse wavelength across many pixels of a 2-D sensor array. In a configuration described in published US patent application No 2014/0028974 A1 entitled 'Line-field holoscopy', cylindrical lenses are used to produce a line illumination on a sample and on a reference mirror. Dispersion of the combined return sample and reference beams along one axis of a 2-D sensor array enables single shot B-scan acquisition. However for full three-dimensional (C-scan) imaging the illuminated line needs to be scanned in the orthogonal direction and the 2-D sensor array read out repeatedly, and it is generally difficult to retain phase coherence between the repeated linear scans.

Single shot C-scan acquisition can be achieved if a 2-D sample area is illuminated and the combined returning sample and reference wavefronts sampled in the two lateral dimensions, e.g. with a 2-D lenslet array, and the resulting sampling points dispersed onto separate sets of pixels of a 2-D sensor array. The effect of this general scheme is to squeeze data from three spatial dimensions, equivalent to two lateral dimensions and one spectral dimension, onto a 2-D sensor array. A mapping of dispersed sampling points onto separate sets of pixels can be ensured by appropriate positioning of the sampling points with respect to the wavelength dispersive element. US patent No US 9,243,888 entitled 'Image mapped optical coherence tomography' discloses an alternative approach in which an 'image mapper' having a number of differently angled facets reflects light from different portions of an image onto different areas of a dispersive element and thence onto separate sets of pixels of a 2-D sensor array.

Configurations for applying a lenslet-based sampling technique to single shot acquisition of images from small volumes of order $100\ \mu\text{m} \times 100\ \mu\text{m} \times 1000\ \mu\text{m}$ from retinal and other samples are disclosed in published US patent application No 2016/0345820 A1 entitled 'High resolution 3-D spectral domain optical imaging apparatus and method' and Anderson *et al* '3D-spectral domain computational imaging', Proc SPIE 9697 (8 March 2016) <http://dx.doi.org/10.1117/12.2214801>. The combined returning wavefronts are sampled with a rectilinear lenslet array angled with respect to the dispersive axis of a dispersive element, with the sampling being in either the Fourier plane, i.e. the far field, providing a form of 'holoscopy', i.e. holographic OCT, or the image plane, i.e. the near field. In either case the spatial resolution depends largely on the NA of the objective lens, and may for example be around $3\ \mu\text{m}$. Illuminated areas on the sample are preferably kept relatively small, of order $100\ \mu\text{m} \times 100\ \mu\text{m}$, to reduce the impact of multiple scattering and also because of the limited number of sampling points offered by commercially available lenslet arrays. Images of multiple adjacent or

overlapping volumes can in principle be acquired and stitched together to image larger sample volumes, but the total acquisition speed is limited by the frame rate of the 2-D sensor array.

Although acquisition of individual volumes can be fast, of order 0.1 ms, for reasonably cost effective electronics the frame rate currently limits the acquisition rate to a few 100 Hz. Since

5 eye motion can be significant on the ms time scale, improved registration techniques are required to allow a larger area of a retina to be acquired by stitching together frames without loss of registration. Improved registration techniques would also be advantageous to provide a clinical user with a broader view of a retina during setup, while identifying areas of interest. While a separate optical image of the retina could be obtained and multiplexed into an OCT
10 image, this would provide inferior resolution detail and the separate imaging systems are not tightly integrated.

Unless the context clearly requires otherwise, throughout the description and the claims the words ‘comprising’, ‘comprises’ and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense. That is, they are to be construed in the sense of

15 ‘including, but not limited to’.

Object of the Invention

It is an object of the present invention to overcome or ameliorate at least one of the limitations of the prior art, or to provide a useful alternative. It is an object of the present invention in a preferred form to provide apparatus and methods for acquiring optical coherence tomography
20 images of extended sample volumes by stitching together two or more images without loss of registration. It is another object of the present invention in a preferred form to provide apparatus and methods for analysing a sample using a dispersed structured illumination field.

Summary of the Invention

According to a first aspect of the present invention there is provided an apparatus for analysing a
25 sample, said apparatus comprising a confocal microscopy system comprising:

a first optical system comprising one or more optical sources for emitting light in a first wavelength band and a wavelength dispersive element for generating, at a first region of a sample, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;

30 a second optical system for collecting light from said dispersed structured illumination field reflected or scattered from said first region of said sample, compensating for the spectral dispersion imposed by said wavelength dispersive element and passing the dispersion compensated collected light through at least one aperture; and

a spectrometer comprising a two-dimensional sensor array for spectrally analysing the collected light reflected or scattered from said first region of said sample.

In certain embodiments the confocal microscopy system is configured to analyse a structure in the posterior segment of an eye such that, in use, the optical power elements of the eye cooperate with the first optical system to generate the dispersed structured illumination field at the structure. In a preferred embodiment the confocal microscopy system is configured to analyse the retina of an eye.

In certain embodiments the first optical system is configured to disperse the light in the first wavelength band along a direction at an angle to an axis of a grid of beamlets, for generating a dispersed structured illumination field that is substantially contiguous over the first region.

In certain embodiments the apparatus comprises an optical coherence tomography (OCT) system for performing an OCT analysis of the sample at a second region that is at least partially overlapping with the first region. In preferred embodiments the OCT system utilises light in a second wavelength band, different from the first wavelength band, for dispersion onto different portions of the two-dimensional sensor array.

Preferably, the OCT system is configured to sample in the Fourier field light reflected or scattered from the second region of the sample.

In preferred embodiments the apparatus is configured to move the dispersed structured illumination field and a sample beam of the OCT system relative to the sample, for acquiring a plurality of confocal microscopy and OCT images of successive first and second regions of the sample. The apparatus is preferably configured to acquire, for each position of the dispersed structured illumination field and the sample beam on the sample, a confocal microscopy image and an OCT image in a single frame of the two-dimensional sensor array. Preferably, the apparatus comprises a processor adapted to register the plurality of OCT images using information obtained from the plurality of confocal microscopy images. In preferred embodiments each of the second regions is wholly within a respective first region.

Preferably, the apparatus comprises an optical splitter for splitting off a portion of light from the one or more optical sources to form a reference beam for interfering with light in the first wavelength band reflected or scattered from the sample.

In certain embodiments the first optical system is configured to disperse the light in the first wavelength band along a direction substantially parallel to an axis of a grid of beamlets, for generating a dispersed structured illumination field comprising one or more overlapping sequences of dispersed wavelengths spaced apart on the sample.

In certain embodiments the first optical system comprises an optical source and a lenslet array for producing a grid of beamlets containing light in the first wavelength band.

According to a second aspect of the present invention there is provided a method for analysing a sample, said method comprising the steps of:

generating at a first region of said sample, using one or more optical sources emitting light in a first wavelength band and a wavelength dispersive element, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;

collecting light from said dispersed structured illumination field reflected or scattered from said first region of said sample;

compensating for the spectral dispersion imposed by said wavelength dispersive element;

passing the dispersion compensated collected light through at least one aperture; and spectrally analysing the collected light reflected or scattered from said first region of said sample using a spectrometer comprising a two-dimensional sensor array.

In certain embodiments the sample comprises a structure in the posterior segment of an eye.

In preferred embodiments the method further comprises the step of performing an OCT analysis of the sample at a second region that is at least partially overlapping with the first region.

According to a third aspect of the present invention there is provided an apparatus for performing optical coherence tomography (OCT) imaging across an extended region of a sample, said apparatus comprising:

5 a first optical system comprising one or more optical sources for emitting light in a first wavelength band and a wavelength dispersive element for generating, at a first region of a sample, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;

0 a second optical system for collecting light from said dispersed structured illumination field reflected or scattered from said first region of said sample and compensating for the spectral dispersion imposed by said wavelength dispersive element;

a spectrometer comprising a two-dimensional sensor array for spectrally analysing the collected light reflected or scattered from said first region of said sample;

5 an OCT system for acquiring an OCT image of said sample at a second region that is at least partially overlapping with said first region;

0 a mechanism for moving said dispersed structured illumination field and a sample beam of said OCT system across said sample so as to collect light reflected or scattered from at least one additional first region and to acquire an OCT image from at least one additional second region; and

a processor adapted to use information obtained from the spectral analysis of the collected light from two or more first regions to register OCT images acquired from two or more second regions.

According to a fourth aspect of the present invention there is provided a method for performing optical coherence tomography (OCT) imaging across an extended area of a sample, said method comprising the steps of:

(i) generating at a first region of said sample, using one or more optical sources emitting light in a first wavelength band and a wavelength dispersive element, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;

(ii) collecting light from said dispersed structured illumination field reflected or scattered from said first region;

(iii) compensating for the spectral dispersion imposed by said wavelength dispersive element;

(iv) spectrally analysing the collected light reflected or scattered from said first region;

(v) obtaining, with an OCT system having a sample beam that illuminates said sample, an OCT image of a second region of said sample, wherein said second region is at least partially overlapping with said first region;

(vi) moving said dispersed structured illumination field and said sample beam relative to said sample and repeating steps (i) to (v) for at least one additional first region and at least one additional second region; and

(vii) using information obtained from the spectral analysis of the collected light from two or more first regions to register the OCT images acquired from two or more second regions.

5
0 According to a fifth aspect of the present invention there is provided an article of manufacture comprising a computer usable medium having a computer readable program code configured to operate the apparatus according to the first or third aspect, or to implement the method according to the second or fourth aspect.

Brief Description of the Drawings

5 Preferred embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figure 1 illustrates in schematic form an apparatus comprising integrated confocal microscopy and spectral domain OCT systems for examining the retina of an eye;

10 Figure 2A shows in schematic form a preferred illumination pattern on a sample retina formed by light from the integrated confocal microscopy and spectral domain OCT systems shown in Figure 1;

Figure 2B shows in schematic form another illumination pattern formed by light from the integrated confocal microscopy and spectral domain OCT systems shown in Figure 1;

Figure 3 shows in schematic form a surface metrology apparatus;

25 Figure 4 depicts a spaced-apart set of overlapping wavelength-dispersed lines produced by the Figure 3 apparatus, for interaction with a sample; and

Figure 5 shows a mapping of a 2-D grid of beamlets dispersed onto a 2-D sensor array.

Detailed Description of the Invention

30 As mentioned in the Background section, OCT-based techniques for acquiring single snapshot 3-D images of relatively small volumes of a sample such as a retina, typically with illuminated areas of order $100\ \mu\text{m} \times 100\ \mu\text{m}$, have been disclosed in Anderson *et al* Proc SPIE 9697 (8 March 2016) <http://dx.doi.org/10.1117/12.2214801> and published US patent application No 2016/0345820 A1. Larger volumes can in principle be imaged by stitching together images of adjacent or slightly overlapping volumes, but this can be adversely affected by sample

movement especially for *in vivo* samples such as the human eye. To overcome this limitation we present a registration and viewing technique that provides snapshot measurements with spatial resolution comparable to that offered by confocal microscopy systems such as scanning laser ophthalmoscopes (SLOs), but without requiring high speed laser sampling which can have
5 its own motion artefacts.

Figure 1 shows in schematic form an apparatus **100** comprising integrated confocal microscopy and spectral domain OCT systems for examining one or more structures in the posterior segment of an eye **118**. The apparatus is particularly suitable for examining the retina **116** and will be described with reference to this application, but it is also suitable for examining other posterior
10 segment structures such as the choroid. In this example embodiment we employ wavelength multiplexing for the two systems, with first and second optical sources **102**, **104** emitting light in first and second wavelength bands that are different from each other for dispersion onto different portions of a 2-D sensor array **174**. In an alternative embodiment different wavelength bands are obtained from a single optical source using wavelength-selective optics such as an
15 optical fibre or bulk optics dichroic splitter. Wavelength multiplexing enables confocal microscopy and OCT data to be acquired simultaneously, which is preferred for reliable compensation of ocular motion as described below. In preferred embodiments each of the first and second wavelength bands comprises a single range of wavelengths, while in other embodiments they are interleaved. In other embodiments not described in detail herein,
20 orthogonal polarisation states or fast time multiplexing could be used instead of wavelength multiplexing for the confocal microscopy and OCT systems. For example polarisation demultiplexing could be used to separate an illumination beam into two polarisation states and encode the angularly dispersed confocal microscopy portion of the light into one polarisation state before a polarisation recombining element recombines the light which is subsequently
25 directed to the sample. In this embodiment, not further described herein, the detection system resolves both polarisation states in the reflected light to enable an integrated confocal microscopy and OCT system.

In preferred embodiments the optical sources emit light in the near IR spectral region, however in general light in the IR, visible or UV spectral regions could be used depending on the
30 application.

We first describe the operation of a high-resolution spectral domain OCT imaging system operating with light of wavelength around 870 nm. In the system as described, an OCT image of a retina **116** is obtained using a ‘holoscopic’ technique in which the Fourier plane of the

image is captured and a fast Fourier transform (FFT) employed to simulate mathematically the role of a physical lens to construct a high-resolution image of the retina. Near field techniques can alternatively be used. Light from a second optical source **104** in the form of an optical fibre coupled superluminescent diode (SLD) with centre wavelength 870 nm and bandwidth of

5 approximately 40 nm is split by a 90/10 ratio 2x2 coupler **106** into a sample path **108** (90%) and a reference path **110** (10%). Path length matching conditions will generally be required for the interference portion of the OCT system, and can be achieved by adjusting the lengths of the respective optical fibre paths during manufacture or by providing length adjusting means such as switchable delay lines for example. Light from the sample path fibre **108** is collimated by a

10 lens **112** to form a relatively small diameter sample beam **114** of, say, several 100 μm FWHM, corresponding inversely proportionally to the desired illumination spot size on the retina **116** of a sample eye **118**. That is, a smaller diameter sample beam will produce a larger illumination spot size on the retina. A dichroic optic in the form of a dichroic beam splitter **120** designed to pass light of 870 ± 18 nm and reflect light of 840 ± 8 nm allows the sample beam **114** to be

15 combined with light **122** from a first optical source **102** to be described later. Other dichroic beam splitters **138**, **148** and **156** in the apparatus are of similar design to the dichroic beam splitter **120**.

The sample beam **114** passes through a polarisation beam splitter (PBS) **124** and a quarter wave plate **126** before being relayed to the sample eye **118** via a 4F lens system comprising lenses **128**

20 and **130**. In certain embodiments the polarisation of light from the second optical source **104** is controlled, e.g. with a fibre optic polarisation controller or a linear polariser (not shown), to maximise its transmission through the PBS **124** towards the sample eye **118**. Adjustment of the position and angle of light incident on the retina **116** can be achieved via beam steering optics such as angular deflection devices **132** and **134**, which for convenience are depicted here as

25 transmissive devices such as prisms although non-dispersive reflective devices such as angularly adjustable mirrors are generally to be preferred. The first deflection device **132** allows the sample beam **114**, and the corresponding reflected beam that returns along the same path, to be moved to different positions on the retina **116**. The second deflection device **134** allows the angle of illumination on the retina to be adjusted, which can be important in achieving improved

30 image quality through reduction of speckle and enhancement of resolving power. Additional power elements may be inserted into the relay to accommodate for variations of the eye under test as would be well understood in the art.

A portion of the light **136** from the sample beam **114** reflected or scattered from the retina **116** is collected and passes back through the relay. The returning light then traverses the quarter wave plate **126** a second time so that a significant fraction of it is polarised orthogonally to the incoming sample beam **114**, for direction by the PBS **124** through a dichroic beam splitter **138**

5 towards an optional holoscopy aperture **140** located at a position that, in use, corresponds to the 8F retinal plane as defined by the combination of lenses **142**, **128**, **130** and the optical power elements of the eye **118**, i.e. its lens **103** and cornea **101**. Although optional, this aperture **140** advantageously serves to filter out light that is outside the spatial Nyquist limit of the subsequent analysis system and might otherwise contribute to phantom signals or noise.

10 Although the holoscopy aperture **140** is shown as being located at the 8F retinal plane, it could alternatively be positioned elsewhere, for example at the 12F retinal plane.

The relayed retinal image is then collimated by a lens **144** after being reflected by a mirror **146** and transmitted through a dichroic beam splitter **148**. A beam splitter **150**, preferably but not necessarily a polarisation beam splitter (PBS), allows the far field of the retinal image to be

15 combined with a suitably path length adjusted reference beam **152** that is collimated by a lens **154** and passes through a dichroic beam splitter **156**. The far field of the retinal image is then compared to the reference beam **152** using a spectrometer **158** capable of analysing the polarisation state of the combined beams at a grid of spatial positions determined by a spatial sampling element such as a two-dimensional (2-D) lenslet array **160**, preferably in combination

20 with a corresponding 2-D aperture array **162** for reducing stray light. The polarisation state of the combined beams is analysed by a PBS **164** which is adjusted to be at an angle to both polarisation states, thereby creating an interference between the reference and signal paths which can provide information on the relative phase across the far field of the retinal image.

The spectrometer **158** used here is a compact reflective spectrometer able to analyse a plurality

25 of grid points, beams or beamlets simultaneously as they are dispersed at an angle to the grid by an appropriately oriented wavelength dispersive element in the form of a transmissive grating **166**. A focusing element such as a lens **168** or an off-axis parabolic mirror collimates the grid of points for dispersion by the grating **166**, followed by double passage through a quarter wave plate **170** via reflection from a mirror **172** to rotate the polarisation state by 90 degrees. In

30 combination the quarter wave plate **170** and the mirror **172** form a polarisation transformation system, which in this particular example effects a polarisation transformation comprising a 90 degree rotation. The dispersed spectral components of the reflected light are imaged by the lens **168** onto a 2-D sensor array **174** such as a CMOS camera after passing through the PBS **164**. The interferogram detected by the 2-D sensor array is read out in a single frame for subsequent

analysis by a processor **176** equipped with suitable machine-readable program code. The processor may for example apply well-known Fourier transform techniques to obtain a depth-resolved image, i.e. a three-dimensional (3-D) image of a volume corresponding to the area of the retina **116** illuminated by the sample beam **114**. In preferred embodiments the grating **166** is oriented with respect to the grid of spatial positions determined by the 2-D lenslet array **160** and the corresponding 2-D aperture array **162** such that each of the combined beams entering the spectrometer **158** is dispersed onto a separate set of pixels of the two-dimensional sensor array **174**.

In broad terms the spectrometer **158** is configured for dispersion and polarisation transformation of light at a grid of sampling points, where the dispersion allows analysis of different wavelengths and the polarisation transformation enables redirection of optical power at a polarisation beam splitter. Advantageously, it provides a low-loss and compact realisation of a grid-sampling spectrometer where the polarisation beam splitter can provide the additional function of the interference analyser.

We now describe the operation of a confocal microscopy system using dispersed structured illumination, and its integration with the above-described holoscopic spectral domain OCT imaging system. In the particular embodiment described with reference to Figure 1 the confocal microscopy system utilises light **122** from a first optical source **102** in the form of an optical fibre coupled SLD with centre wavelength 840 nm and bandwidth of approximately 16 nm.

Optionally, a portion e.g. 10% of the light from this source is split off with a 2x2 coupler **177** into a reference path **178** if interferometric measurement is desired, e.g. for higher sensitivity or to obtain relative phase measurements for example for angiographic phase contrast measurements. This optional reference path **178** may also include an optical switch **179** to block the reference beam for non-interferometric measurements, as well as path length adjustment means such as switchable delay lines for interferometric measurements.

Light **122** from the first source **102** is collimated by a lens **180** into a relatively large beam, e.g. several mm in diameter and preferably larger in diameter than the OCT sample beam **114**, then launched into a spatial sampling element such as a 2-D lenslet array **181** and Fourier transformed by a subsequent lens **182**. The Fourier transformed sample beamlets are dispersed by a wavelength dispersive element in the form of a transmissive grating **184** and coupled into the same train as the holoscopic OCT system by the dichroic beam splitter **120**. Importantly, the lenslet array **181** and the grating **184** are preferably angled with respect to each other so that, as described below, the grid of dispersed sample beamlets **183** will provide a dispersed structured

illumination field that covers an extended and preferably substantially contiguous region when reimaged onto the retina **116** of the sample eye **118**. The grid of wavelength-dispersed Fourier transformed sample beamlets, represented schematically by the envelope **183**, is relayed to the eye **118**, analogously to the OCT sample beam **114**, by the optical relay system comprising

5 lenses **128**, **130** and deflectors **132**, **134**. The optical power elements of the eye then act on the dispersed sample beamlets to generate at the retina **116**, as shown in Figure 2A, a dispersed structured illumination field **200** in the form of a grid of beamlets for each wavelength within the first wavelength band, i.e. within the wavelength band emitted by the first source **102**.

Representative grids of beamlets for two particular wavelengths within the dispersion envelope

10 **202** of the first wavelength band are indicated by the arrays of points **204** and **206**. When the lenslet array **181** and the grating **184** are suitably angled with respect to each other as noted above, the dispersed structured illumination field **200** can be made substantially contiguous over a first region **208** on the retina. That is, within this first region there are few or no parts of the retina not illuminated by the dispersed structured illumination field. Each combination of grid

15 point plus wavelength defines a specific location **210** on the retina, with some redundancy since the dispersion envelopes **202** are partially overlapping at least within a portion of the first region **208**. The sample beam **114** of the OCT imaging system illuminates a second region **212** of the retina that is at least partially overlapping with the first region **208**. Preferably the second region **212** is wholly within a larger first region **208** as shown, so that every point on the retina

20 illuminated by the OCT beam **114** is also illuminated by the dispersed structured illumination field **200** of the confocal microscopy system. In certain embodiments the first region **208** may be ten to several hundred times larger than the cumulative area of the second region **212**. The second region may be contiguous as shown, or a grid of sampling points (A-scans), generated for example by a lenslet array or other spatial sampling element in the OCT optics train (not

25 shown in Figure 1), each of a given area, providing a cumulative area. Returning to Figure 1, in certain embodiments some optical power can be provided by appropriate design of the grating **184**, e.g. a degree of chirp, which would allow the redundant wavelengths to be imaged at different depths to give greater tolerance to variations in the ocular power of the eye **118** being analysed.

30 When the apparatus **100** is being used to analyse the retina **116** an eye **118** as shown in Figure 1, the optical power elements of the eye, i.e. the cornea **101** and the lens **103**, cooperate with the lenslet array **181**, the Fourier transforming lens **182**, the grating **184** and other optical components in the train to generate the dispersed structured illumination field at the retina **116**. For analysing a non-ocular sample the apparatus **100** may include an additional focusing

element in lieu of the optical power elements of the eye. Similarly, for analysing a structure in the anterior segment of an eye, such as the sclera, the anterior or posterior corneal surface or the anterior or posterior lens surface, the apparatus **100** may include an additional focusing element in lieu of some or all of the optical power elements of the eye as appropriate. These additional
5 focusing elements would also serve to focus the OCT sample beam **114** onto the sample.

As opposed to the 3-D holoscopic measurement provided by the OCT imaging system, the dispersed structured illumination field **200** as shown in Figure 2A enables a confocal measurement at each illuminated point **210** on the retina **116**. However to obtain the confocal measurement we need to create a pinhole or aperture array that can act on all wavelengths
10 simultaneously. This is provided by a second optical system comprising a dispersive element in the form of a transmissive grating **185** for unwinding the dispersion imposed by the grating **184**, and an aperture array **186** that is preferably tightly correlated with the sampling grid that was created by the lenslet array **181**. More broadly, the aperture array **186** needs to have at least one aperture correlated tightly with at least part of the sampling grid generated by the lenslet array
15 **181**. The dispersion compensation from the grating **185** occurs after the confocal beamlets **187** collected from the retina **116** have been separated from the returning holoscopic OCT beam **105** by the dichroic beam splitter **138**. The lens **188** used to focus the confocal beamlets **187** onto the aperture array **186** may require active focal length adjustment in production to ensure registration at the aperture array **186** over the whole wavelength range and grid points. The
20 second grating **185** also needs to be designed to reverse any optical power that may have been designed into the first grating **184**. An optional lenslet array **189** can be used to optimise the projection of the aperture array **186** through the lenslet array **160** and onto the subsequent aperture array **162** with low coupling loss, although adjustments of the lenses **190** and **144** may prove adequate in practice with reasonable efficiency. The grid of dispersion compensated
25 beamlets **191** is recombined with the returning OCT beam **105** in the dichroic beam splitter **148**, for analysis by the spectrometer **158**. This spectrometer is capable of analysing the grid of confocal microscopy points and the lenslet array **160**-sampled returning OCT beam **105** over a range of 830 to 890 nm through design of the dispersive element **166** and the focusing lens **168**. It will be appreciated that because the confocal microscopy and OCT systems use light in
30 different wavelength bands, the grid of confocal microscopy points and the sampled returning OCT beam will be projected onto different portions of the 2-D sensor array **174**, enabling acquisition of both confocal microscopy and OCT data within a single frame of the 2-D sensor array.

As mentioned above and with reference to Figure 2A, adjustment of the angular deflection device **132** enables the region **212** illuminated by the OCT sample beam **114** to be moved to different positions on the retina **116**, enabling examination of larger areas. Since the OCT and confocal microscopy systems are integrated, this adjustment also moves the region **208** illuminated by the dispersed structured illumination field **200** of the confocal microscopy system. Importantly, because the region **212** is at least partially overlapping with, and preferably wholly within a larger region **208**, the confocal microscopy system can be utilised to ensure accurate registration of successive volumes illuminated by the OCT sample beam **114**. For example the processor **176** may use autocorrelation techniques to determine displacement vectors based on the overlapping images of the larger region **208**. If eye movement, say, causes an error in the positioning of the OCT sample beam **114** on the retina, this error can be detected and corrected by matching the larger area retinal images acquired by the confocal microscopy system. It is for the purpose of ensuring accurate registration of successive OCT volumes that the dispersed structured illumination field **200** is preferably angled with respect to the beamlet grids **204**, **206** as described above with reference to Figure 2A. If the dispersion axis of the grating **184** were parallel to an axis of the lenslet array **181** the dispersed structured illumination field **200** at the retina may appear as shown in Figure 2B. It will be appreciated that in this situation there are gaps **214** in the dispersed structured illumination field **200** where significant portions of a region **212** illuminated by the OCT sample beam would have no overlap with the dispersion envelopes **202**.

Within each frame of the 2-D sensor array **174** the actual illumination time can be quite brief, of the order of 100 μ s, to reduce any fringe fading due to motion artefacts. For maximum accuracy of registration, a grid of confocal microscopy points and a lenslet-sampled OCT beam are preferably acquired substantially simultaneously e.g. with respective OCT and confocal microscopy images acquired in a single frame of the 2-D sensor array **174**. It is also possible for confocal microscopy and OCT images to be acquired in successive frames, e.g. by shuttering of the different wavelength bands obtained from a single broadband source or by pulsing of separate optical sources, although the time between frames should be short so that ocular motion can be reliably compensated. The ability to choose independently the timing of the illumination for the confocal microscopy and OCT systems can be beneficial. In one example, pulsing the confocal microscopy system source **102** at the end of a frame provides the ability to adjust the exact registration of the next frame of the holoscopic OCT measurement through a fine adjustment of the deflection device **132** from the position anticipated based on the shift of the confocal microscopy measurement. The ability to measure and correlate across a large field of

the retina **116** allows us to ensure that there are no gaps or stitching errors between separate volumes induced by eye motion. Furthermore we can accurately return to any retinal areas if required for reacquisition. Because the region **208** illuminated by the confocal microscopy system is usually considerably larger than the region **212** illuminated by the OCT system, points
5 on the retina will often appear in several confocal images, possibly hundreds of images. Advantageously, these multiple exposures enable a highly averaged image to be generated by having measured each point multiple times with different illumination wavelengths, increasing the quality of the image and reducing any speckle artefacts.

The confocal microscopy system can be operated in either a purely intensity mode, i.e. without
10 employing the reference arm **178**, as would be the case for a conventional SLO or scanning confocal microscope, or in a coherent mode where the grid of beamlets **191** reflected from the retina **116** is interfered with a reference beam **192** collimated by a lens **193**. Noting that a coherent signal can be more easily interpreted if its intensity is known, acquisition in both modes in sequential frames is possible via operation of the optical switch **179**. In many cases
15 the purely intensity mode will be preferred, since the interference in the coherent mode can be an unnecessary complication for the registration process. Alternatively it is possible to acquire a phase-resolved interference spectrum to interpret or determine the relative phase and amplitude of the confocal microscopy signal.

It will be appreciated that several elements in the apparatus of Figure 1 may need to be operated
20 in coordinated fashion, including for example the optical sources **102** and **104**, the angular deflection devices **132** and **134**, the optical switch **179** and the 2-D sensor array **174**. This overall level of control may for example be provided by equipping the processor **176** with suitable machine-readable program code.

In preferred embodiments the spectrometer **158** is common to the integrated OCT and confocal
25 microscopy systems as shown in Figure 1, to increase integration of the componentry and ensure enhanced registration of the OCT images. However it would be advantageous in some circumstances to have two independent spectrometers, e.g. to enable individual optimisation of each spectrometer.

We note that, for the purposes of registration of successive volumes illuminated by the OCT
30 system, it is not essential for the integrated microscopy system to be confocal. That is, the aperture array **186** and the lenslet array **189** could be omitted from the apparatus **100** to yield an OCT imaging system integrated with a non-confocal microscopy system. However a confocal

microscopy system is preferred because of the improved noise rejection and the improved accuracy of registration in the presence of axial displacements.

It will be appreciated that the confocal microscopy and OCT systems of the apparatus **100** can be operated in isolation. For example the confocal microscopy system alone may be used to
5 analyse one or more regions of the retina **116** or other structure in the posterior segment of an eye **118**.

The ability to generate a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within a wavelength band, used for registration of repeated snapshot 3-D OCT images as described above, can also be used for metrology applications. Figure 3 shows in
10 schematic form an apparatus **300** for surface metrology of an object **320**. Light from an optical source **302** in the form of a polarised superluminescent light emitting diode (SLED) with centre wavelength 840 nm and a bandwidth of approximately 20 nm is collimated by an off-axis parabolic mirror **304** then passed through a spatial sampling element such as a 2-D lenslet array **310** or an array of diffractive optical elements (DOEs) to produce a grid of sample beamlets.

15 The sample beamlets are relayed through a system of lenses **311** and **312** which can be magnifying or reducing, depending on the application, through choice of focal length. A wavelength dispersive element in the form of a transmissive grating **306** having, say, 1500 lines/mm, is provided within the lens relay. The optical source **302**, lenslet array **310**, grating **306** and lenses **311**, **312** in combination form an optical system that generates a dispersed
20 structured illumination field **314** in the form of a grid of beamlets for each wavelength within the emission band of the source. That is, each wavelength component of the source **302** will have a corresponding grid which is offset in the dispersive axis of the grating **306**. In an alternative embodiment a grid of sample beamlets for generating the dispersed structured illumination field is provided by a plurality of optical sources such as an array of LEDs. The
25 dispersed structured illumination field **314** proceeds to the sample **320** via a beam splitter, preferably but not necessarily a polarisation beam splitter (PBS) **322**, that splits it into a sample arm **324** and a reference arm **326**, and the reflections from the sample **320** and the reference arm mirror **328** are recombined by the PBS **322** after rotation of their respective polarisations by the quarter wave plates **330** and **332**.

30 In certain embodiments the transmissive grating **306** is designed to provide optical power in one or two axes through curvature of the lines or a chirped line spacing, or both, as is known in the art. In this case the optical power of the grating is a function of wavelength, so that any subsequent focusing of the light will have an effective wavelength-dependent focal plane as

represented by the curved wavefronts **309**. This feature is particularly advantageous for an industrial metrology system where samples may have large surface fluctuations, as it permits high transverse resolution over an extended depth of focus by using the chromatic focusing in combination with the phase information of the light at multiple wavelengths, which can be
5 accessed through an interferometric OCT measurement described below.

In the metrology apparatus **300** the grating **306** and lenslet array **310** are preferably oriented with respect to each other such that the dispersive axis of the grating is aligned with an axis of the lenslet array. This is in contrast to the previously described confocal microscopy/OCT apparatus **100** shown in Figure 1, where the dispersive axis of the grating **184** is preferably at an
10 angle to an axis of the lenslet array **181**. As depicted schematically in Figure 4, dispersion along an axis of the lenslet array results in a dispersed structured illumination field **400** having overlapping sequences of dispersed wavelengths **402** spaced apart on a series of projection lines **404**, for interaction with a sample. Similar to the situations shown in Figures 2A and 2B, the arrays of points **406** and **408** represent grids of beamlets for two particular wavelengths within
15 the dispersion envelope **410** of the wavelength band emitted by the source **302**.

The combined reflected reference and sample light fields are transformed through a dispersive optical relay **334** comprising relay lenses **336** and **338** and a numerical aperture limiting grating **340** designed to compensate the spectral dispersion and any chromatic focusing imposed by the grating **306**. This enables all wavelengths in the grid of dispersion compensated beamlets **341** to
20 be simultaneously apertured by an aperture grid **342** designed to correspond to the illuminating grid produced by the lenslet array **310**. The size of the apertures in the aperture grid **342** and the size of the dispersive relay aperture defined by the grating **340** are chosen to optimise collection of light from a sufficient depth of field at the sample **320** and reduce crosstalk from multiply-scattered light. Generally, smaller apertures provide enhanced depth of field and reduced lateral
25 resolution, along with lower signal levels. In one particular example the combination of a 4 mm long grating **340** and a lens **336** with 70 mm long focal length would provide a numerical aperture of approximately 0.02 depending on the angle of the grating **340**. An optional lenslet array **344** can be used to adjust the numerical aperture of the incident beamlets **341** to match the aperture size and hence the required resolution of the spectrometer **346**. In certain embodiments
30 an adjustable polariser **348** can be included to capture a fraction of the power in the combined sample and reference beams according to the expected power levels in each arm, and so interfere the sample and reference light according to their relative phases. Alternatively the polarisation state of the combined beams can be analysed by the polarisation beam splitter

(PBS) **350**, as is the case with the spectrometer **158** in the apparatus shown in Figure 1. Inclusion of the polariser **348** allows the polarisations to be analysed substantially independently of the PBS **350**.

The dispersion compensated grid of sampling points entering the spectrometer **346** contains
5 sample information derived from reflection or scattering from the illuminated portions of the
sample **320**, and can be analysed by 2-D spectrometer techniques as described in published US
patent application Nos US 2016/0135679 A1 entitled 'Ocular metrology employing spectral
wavefront analysis of reflected light' and US 2016/0135680 A1 entitled 'Wavefront analyser',
the contents of which are incorporated herein by reference. In the example embodiment
10 depicted in Figure 3 a compact spectrometer **346** comprises a PBS **350**, a flat field relay lens
352 or other focusing element, a wavelength dispersive element in the form of a transmissive
grating **356** and a polarisation transformation system **354** comprising a quarter wave plate **358**
and a mirror **360**. The polarisation transformation system rotates the polarisation state of the
dispersed light by 90 degrees to allow re-direction at the PBS **350** onto a 2-D sensor array **362**
15 such as a CMOS camera for analysis by a processor **364** equipped with suitable machine-
readable program code. The grating **356** is preferably oriented such that the dispersion is at an
angle to the sampling grid corresponding to the aperture grid **342**, to allow independent
interferometry of each resolvable wavelength for each point in the sampling grid. That is, each
grid point **500** is dispersed onto a separate set of pixels **502** of a 2-D sensor array **504** as shown
20 in Figure 5.

The dimensions of the on-sample dispersed structured illumination field **400** shown in Figure 4
will depend on the details of the optical components that generate it. In one exemplary
embodiment each overlapping sequence of dispersed wavelengths **402** has a length **412** of about
10 mm and a width **414** of about 20 μm , on a centre-to-centre spacing **416** of about 200 μm ,
25 with the number of projection lines **404** determined by the number of rows of lenslets in the
lenslet array **310**. Each point **418** on the sample within one of the overlapping sequences of
dispersed wavelengths **402** will be illuminated by multiple wavelengths, which enables
interferometric techniques to determine an unambiguous measurement of each axial reflection
point over a certain depth using a subsampled spectrum. In embodiments where the grating **306**
30 has optical power, the relative power in the reflection points will be significantly determined by
the wavelength dependent focusing. This can provide further information on the reflection
points to extend further the range over which an unambiguous determination of depth can be

made. Additionally, continuity constraints can often be employed to enhance the relative accuracy of measurements.

We now consider the effect of scanning the dispersed structured illumination field **400** in a controlled fashion relative to the sample **320**, e.g. by translating the sample on a stage or by
5 using beam steering optics. After the 2-D sensor array **362** and the processor **364** have acquired and analysed the sample volume corresponding to the spaced apart overlapping sequences of dispersed wavelengths **402** at one set position, the acquisition can be repeated with steps of, say, 10 μm until the spaces **420** between the overlapping sequences are filled, to acquire a complete contiguous volume. A large jump can then be made onto an adjacent sample region and the
10 process repeated. Preferably the steps are made at a small angle to the perpendicular of the projection lines **404** to allow oversampling of each sample point **418** at a different set of wavelengths. It is not essential for the dispersed structured illumination field **400** to have a plurality of overlapping sequences of dispersed wavelengths **402** as shown in Figure 4, although this would be advantageous for faster measurement of a sample over an extended area. On the
15 other hand the use of a dispersed structured illumination field having only one overlapping sequence of dispersed wavelengths **402**, which could for example be produced with a 1-D lenslet array or other 1-D spatial sampling element, may be advantageous for more rapid data readout.

In an alternative embodiment a wavelength-dispersed structured illumination field is generated
20 by interfering an array of wavelength-dispersed beamlets generated for example with a 2-D lenslet array. As described in Besold *et al* 'Fractional Talbot effect for periodic microlens arrays', *Optical Engineering* 36(4), 1099-1105 (1997), the coherent superposition of multiple dispersed beamlets forms a grid of high intensity 'rods' which can propagate with coherent superposition over a distance much longer than the corresponding Rayleigh length of an
25 equivalently sized array of individual beamlets.

Although the invention has been described with reference to specific examples, it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

The claims defining the invention are as follows:

1. An apparatus for analysing a sample, said apparatus comprising a confocal microscopy system comprising:

a first optical system comprising one or more optical sources for emitting light in a first wavelength band and a wavelength dispersive element for generating, at a first region of a sample, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;

a second optical system for collecting light from said dispersed structured illumination field reflected or scattered from said first region of said sample, compensating for the spectral dispersion imposed by said wavelength dispersive element and passing the dispersion compensated collected light through at least one aperture; and

a spectrometer comprising a two-dimensional sensor array for spectrally analysing the collected light reflected or scattered from said first region of said sample.

2. The apparatus according to claim 1, wherein said confocal microscopy system is configured to analyse a structure in the posterior segment of an eye such that, in use, the optical power elements of said eye cooperate with said first optical system to generate said dispersed structured illumination field at said structure.

3. The apparatus according to claim 2, wherein said confocal microscopy system is configured to analyse the retina of an eye.

4. The apparatus according to any one of claims 1 to 3, wherein said first optical system is configured to disperse the light in said first wavelength band along a direction at an angle to an axis of a grid of beamlets, for generating a dispersed structured illumination field that is substantially contiguous over said first region.

5. The apparatus according to any one of claims 1 to 4, comprising an optical coherence tomography (OCT) system for performing an OCT analysis of said sample at a second region that is at least partially overlapping with said first region.

6. The apparatus according to claim 5, wherein said OCT system utilises light in a second wavelength band, different from said first wavelength band, for dispersion onto different portions of said two-dimensional sensor array.

7. The apparatus according to claim 5 or claim 6, wherein said OCT system is configured to sample in the Fourier field light reflected or scattered from said second region of said sample.

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8. The apparatus according to any one of claims 5 to 7, wherein said apparatus is configured to move said dispersed structured illumination field and a sample beam of said OCT system relative to said sample, for acquiring a plurality of confocal microscopy and OCT images of successive first and second regions of said sample.
- 5 9. The apparatus according to claim 8, wherein said apparatus is configured to acquire, for each position of said dispersed structured illumination field and said sample beam on said sample, a confocal microscopy image and an OCT image in a single frame of said two-dimensional sensor array.
10. The apparatus according to claim 8 or claim 9, wherein said apparatus comprises a processor adapted to register the plurality of OCT images using information obtained from the plurality of confocal microscopy images.
11. The apparatus according to any one of claims 8 to 10, wherein each of the second regions is wholly within a respective first region.
12. The apparatus according to any one of claims 1 to 11, comprising an optical splitter for splitting off a portion of light from said one or more optical sources to form a reference beam for interfering with light in said first wavelength band reflected or scattered from said sample.
13. The apparatus according to any one of claims 1 to 3, wherein said first optical system is configured to disperse the light in said first wavelength band along a direction substantially parallel to an axis of a grid of beamlets, for generating a dispersed structured illumination field comprising one or more overlapping sequences of dispersed wavelengths spaced apart on said sample.
14. The apparatus according to any one of the preceding claims, wherein said first optical system comprises an optical source and a lenslet array for producing a grid of beamlets containing light in said first wavelength band.
- 25 15. A method for analysing a sample, said method comprising the steps of:
generating at a first region of said sample, using one or more optical sources emitting light in a first wavelength band and a wavelength dispersive element, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;
30 collecting light from said dispersed structured illumination field reflected or scattered from said first region of said sample;

compensating for the spectral dispersion imposed by said wavelength dispersive element;

passing the dispersion compensated collected light through at least one aperture; and spectrally analysing the collected light reflected or scattered from said first region of said sample using a spectrometer comprising a two-dimensional sensor array.

16. The method according to claim 15, wherein said sample comprises a structure in the posterior segment of an eye.

17. The method according to claim 15 or claim 16, further comprising the step of performing an OCT analysis of said sample at a second region that is at least partially overlapping with said first region.

18. An apparatus for performing optical coherence tomography (OCT) imaging across an extended region of a sample, said apparatus comprising:

a first optical system comprising one or more optical sources for emitting light in a first wavelength band and a wavelength dispersive element for generating, at a first region of a sample, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;

a second optical system for collecting light from said dispersed structured illumination field reflected or scattered from said first region of said sample and compensating for the spectral dispersion imposed by said wavelength dispersive element;

a spectrometer comprising a two-dimensional sensor array for spectrally analysing the collected light reflected or scattered from said first region of said sample;

an OCT system for acquiring an OCT image of said sample at a second region that is at least partially overlapping with said first region;

a mechanism for moving said dispersed structured illumination field and a sample beam of said OCT system across said sample so as to collect light reflected or scattered from at least one additional first region and to acquire an OCT image from at least one additional second region; and

a processor adapted to use information obtained from the spectral analysis of the collected light from two or more first regions to register OCT images acquired from two or more second regions.

19. A method for performing optical coherence tomography (OCT) imaging across an extended area of a sample, said method comprising the steps of:

(i) generating at a first region of said sample, using one or more optical sources emitting light in a first wavelength band and a wavelength dispersive element, a dispersed structured illumination field in the form of a grid of beamlets for each wavelength within said first wavelength band;

(ii) collecting light from said dispersed structured illumination field reflected or scattered from said first region;

(iii) compensating for the spectral dispersion imposed by said wavelength dispersive element;

(iv) spectrally analysing the collected light reflected or scattered from said first region;

(v) obtaining, with an OCT system having a sample beam that illuminates said sample, an OCT image of a second region of said sample, wherein said second region is at least partially overlapping with said first region;

(vi) moving said dispersed structured illumination field and said sample beam relative to said sample and repeating steps (i) to (v) for at least one additional first region and at least one additional second region; and

(vii) using information obtained from the spectral analysis of the collected light from two or more first regions to register the OCT images acquired from two or more second regions.

20. An article of manufacture comprising a computer usable medium having a computer readable program code configured to operate the apparatus of any one of claims 1 to 14 or claim 18, or to implement the method of any one of claims 15 to 17 or claim 19.

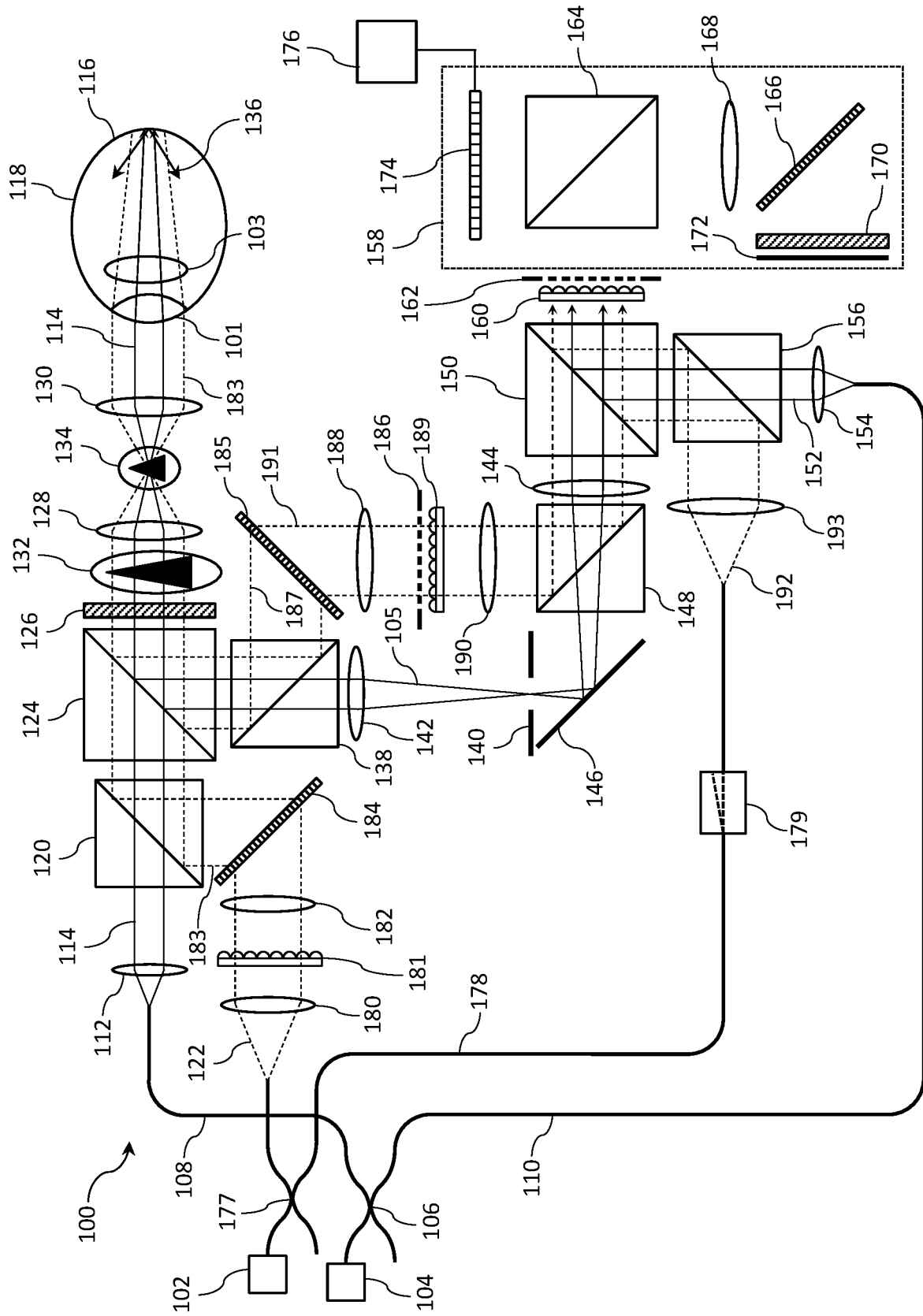


Fig. 1

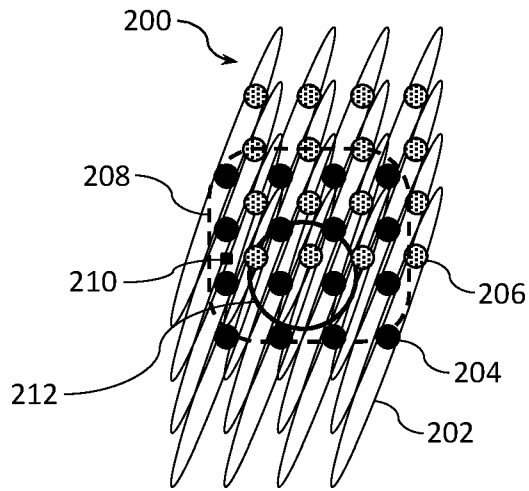


Fig. 2A

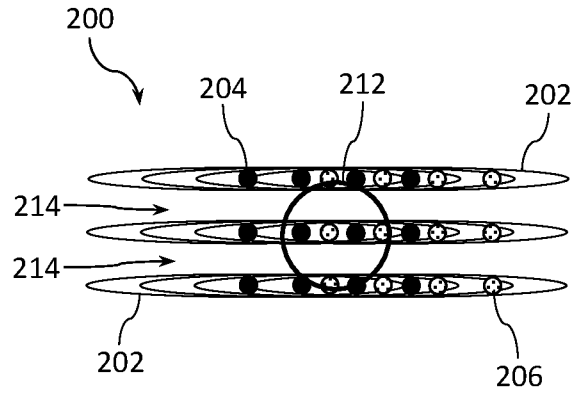


Fig. 2B

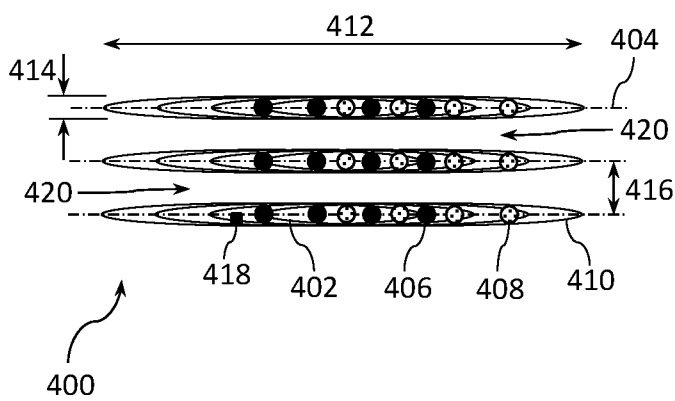


Fig. 4

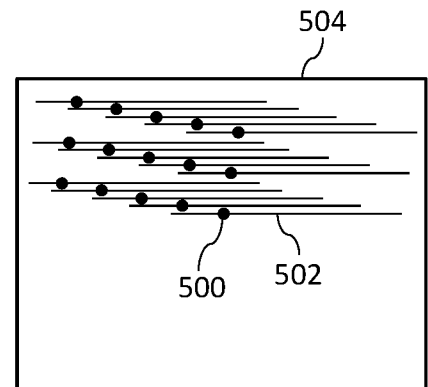


Fig. 5

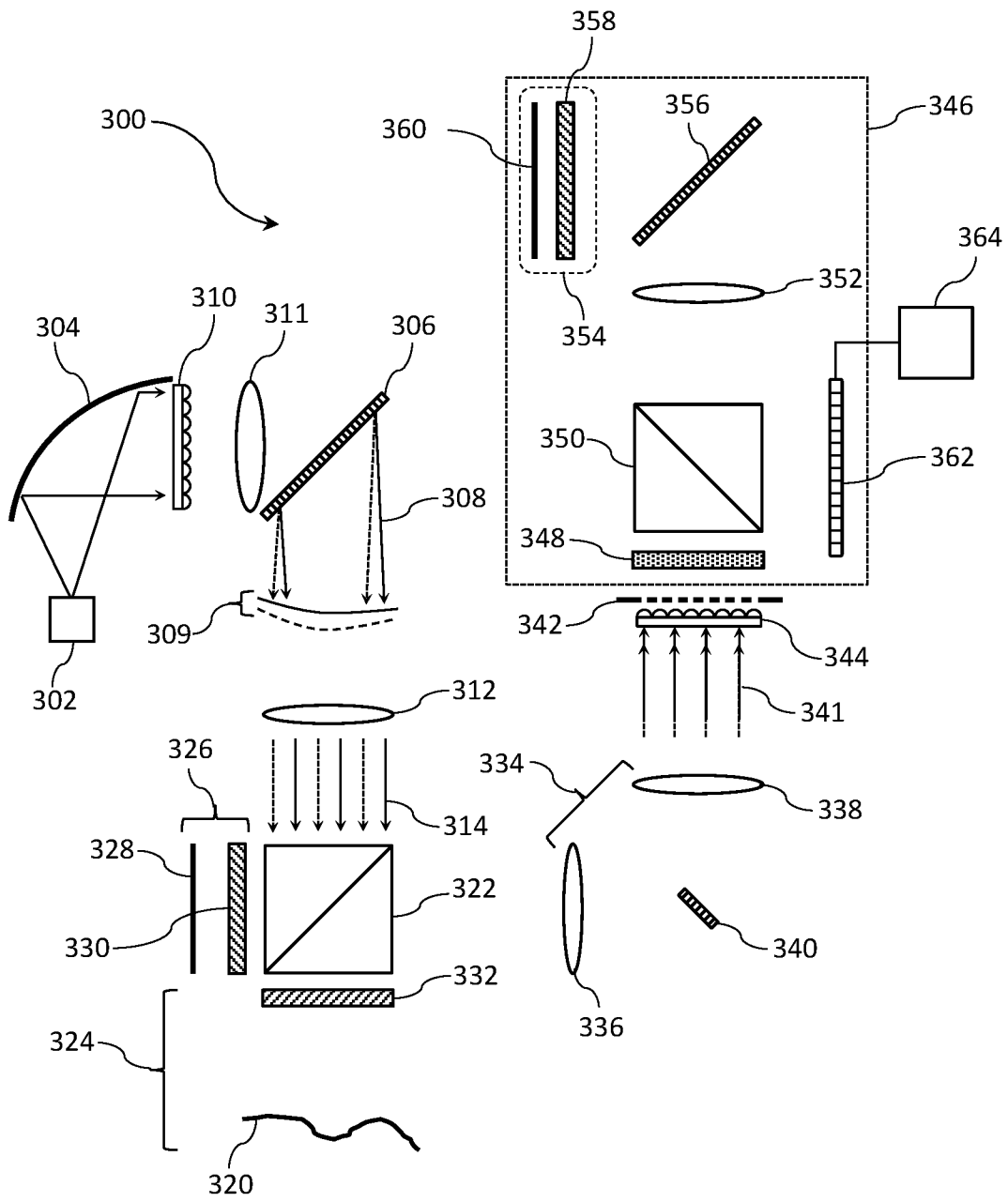


Fig. 3