



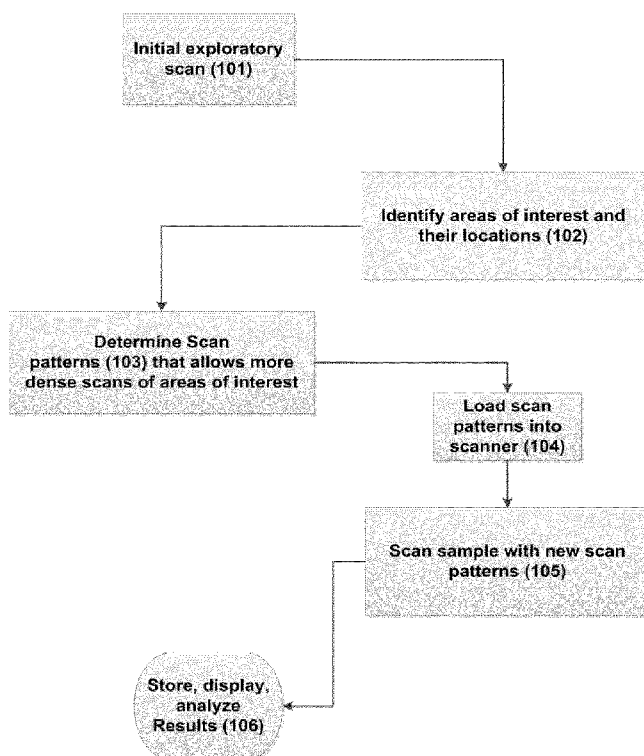
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- (54) Title: HIGH TEMPORAL RESOLUTION DOPPLER OCT IMAGING OF RETINAL BLOOD FLOW

FIG. 2



- (57) Abstract: Techniques are introduced to improve the ability of OCT to determine more accurately the nature of the flow of fluids in the eye, including faster measurements of the flow and a method to reduce geometric uncertainties due to eye movements.

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5 **HIGH TEMPORAL RESOLUTION DOPPLER OCT IMAGING
 OF RETINAL BLOOD FLOW**

FIELD OF THE INVENTION

10 The present application concerns Doppler optical coherence tomography
 and the improvement in the accuracy of measuring blood flow in the retina.

BACKGROUND

15 Optical Coherence Tomography (OCT) is a technique for performing high-
 resolution cross-sectional imaging that can provide images of tissue
 structure on the micron scale in situ and in real time (see, e.g., Huang et al.
 1991). OCT is a method of interferometry that determines the scattering
 profile of a sample along the OCT beam. Each scattering profile in the
 depth direction (z) is called an axial scan, or A-scan. Cross-sectional
 images (B-scans), and by extension 3D volumes, are built up from many A-
20 scans, with the OCT beam moved to a set of transverse (x and y) locations
 on the sample. One of the principle advantages of OCT is its ability to
 image the various layers of the retina of the eye. Technical improvements
 in this modality permit data sets to be obtained in very short times. Doppler
 OCT can be used to determine flow velocity by measuring phase shifts
25 between temporally separated measurements.

 The ability to measure total retinal blood flow can provide an important
 diagnosis between healthy and pathological retinal tissue. Doppler OCT is
 applicable to the measurement of blood flow in the retina and in retinal
30 vascular perfusion. The optimum area to measure total ocular blood flow is
 centered on the optical nerve head, as this is where most vessels enter and
 exit the retina. It is the current state of technology that even fast OCT
 systems have a difficulty acquiring temporally densely-sampled blood flow
 data of these vessels.

35

 Important to proper determination of blood flow or velocities is knowledge of
 the angle or angular orientation between the vessel (or blood flow) and that

5 of the beam probing the vessel (the Doppler angle). If these directions are perpendicular, then Doppler techniques, as historically practiced, yield no measurable shift. In cases where the Doppler angle is close to 90 degrees, accurate knowledge of the Doppler angle is critical to proper velocity determinations, because the absolute velocity is proportional to $1/\cosine$ of
10 the Doppler angle. There are, however, different OCT velocity measurement methods, using either phase or intensity variation measurements, which are influenced differently by the geometric arrangement between blood flow vector and the probe beam direction.

15 Doppler OCT has been successfully utilized in ophthalmologic diagnostic investigations as well as in functional imaging. (For a general introductory reference to Doppler OCT, see, e.g., Chen & Zhang 2008.) The recent advances in Fourier-domain OCT sensitivity and speed have been remarkable and have impacted the capabilities of Doppler OCT
20 measurement capacity. The results can, however, be limited by various physical and technical reasons, such as phase de-correlation due to high velocity, Brownian motion of the fluid itself, phase wrapping, large or poorly determined Doppler angles, inappropriate scan timescales, and low spatial sampling as will be described in more detail below.

25 There are a variety of measurements that can obtain a frequency shift. Most of these involve measurement of phases or phase differences between normally adjacent A-scans and/or intensity or amplitude information or combinations of these various observables. There are
30 sensitivity variations amongst these techniques, dependent upon the aforementioned geometric configuration, minimum and maximum velocities to be measured, temporal and spatial sampling, as well as variations in resolution and contrast. Other techniques used to determine a frequency shift include speckle variance, logarithmic intensity variance, differential
35 logarithmic intensity variance, 2D correlation mapping, split spectra amplitude de-correlation, and filtering of the original fringe data. A popular

5 technique, known as Doppler variance, uses autocorrelation which involves complex OCT data at each location (see, e.g., Zhao et al. 2000).

Circumpapillary Doppler OCT scans have been employed to provide quantitative information about the total retinal blood flow in vivo (see, e.g.,
 10 Tan et al. 2012). They have typically used two concentric circular scans and determined a vessel's angle by measuring the position of its cross-section at two separate positions or locations. The drawback to this approach is that the centers of the vessel cross-sections for the two interleaved circular scans with different diameters have to be precisely
 15 detected within each individual scan. This is time consuming, especially as there has not been an automated method introduced so far. Furthermore, it is often difficult to define the center of the vessel cross-sections, leading to inaccuracies in the determination of the vessel's orientation relative to the scan or probing beam. This is of interest as small changes in this
 20 orientation with angles approaching orthogonality (in certain measurement styles) may lead to very large differences in blood flow.

The temporal resolution of the scans is limited by two factors. On the one hand, the sampling of the circumpapillary scan has to be sufficiently dense
 25 in order to avoid phase de-correlation. On the other hand, one may not arbitrarily increase the A-scan rate as this reduces the sensitivity for lower flow speeds.

Some of the constraining factors of Doppler OCT are outlined below:

30 **Phase noise:** The phase noise limits the minimum quantifiable velocity. It is limited by two factors, the signal to noise ratio (SNR) and the oversampling factor. The SNR limited phase noise of an OCT system is described by (Park et al. 2005):

$$\Phi_{err_{SNR}} = \frac{1}{\sqrt{SNR}}.$$

In most cases the phase noise is limited by the oversampling of the
 35 scanning system. Ideally the two measurements used to calculate the

5 phase difference should be taken at the exact same location. In practice, one often uses scanning patterns, which don't allow 100% overlap between the two measurements. This causes phase de-correlation between the two measurements and, therefore, an increase in phase noise. The phase noise limited by the sampling density is described by (Park et al. 2005):

$$\Phi_{err_{sampling}} = \sqrt{\frac{4\pi}{3} \left(1 - \exp \left(-2 \left(\frac{\Delta x}{d} \right)^2 \right) \right)},$$

10 where Δx denotes the lateral distance between two measurements, and d the $1/e^2$ beam width at the focus. Besides the scanning pattern, sample motion may significantly contribute to the phase noise in a similar fashion.

Time difference between two measurements: The time between the two
15 measurements used to calculate the phase difference influences the quantifiable velocity range. Larger time differences enable the detection of slower velocities, smaller time differences on the other hand shift the detectable velocity range towards higher speeds.

20 **Fringe wash-out:** Fringe wash-out is mainly a problem of spectral domain OCT (SD-OCT). The phase shift introduced by moving scatterers during the integration time of the camera, causes a blurring of the interference fringe signal. This wash-out causes a reduction in the interference fringe amplitude and therefore a reduction of SNR of the signal from moving
25 scatterers. The fringe wash-out scales with the magnitude of the phase shift. For high velocities, the fringe wash-out may be so strong, that the SNR (signal-to-noise ratio) drops below one. Since as mentioned above, the phase noise is also limited by the SNR, this is a significant problem for Doppler OCT measurements.

30 **Doppler angle:** Doppler OCT is only sensitive to axial motion. In order to determine the absolute velocity of a moving scatterer, it is essential to know the angle between its velocity vector and the probing beam. A precise angle

determination is paramount due to the secant term in the expression for velocity from phase shift (see, e.g., Chen & Zhang 2008 review article, op. cit.). Since most of the vessels in the inner retina lie almost perpendicular to the probing beam, already small errors in the Doppler angle may significantly influence the resulting absolute velocity measurement.

SUMMARY

Many of the aforementioned problems with Doppler OCT can be reduced or even overcome if the scan timescales can be made shorter. One embodiment of the present application presents a technique to enhance the temporal resolution of measuring circumpapillary Doppler optical coherence tomography (OCT) scans. The OCT beam would be moved faster over those parts where no data are to be collected relative to the areas of interest where OCT are to be obtained. This can be achieved by scanning those areas that are known to contain principally blood vessels or other areas of interest and doing so via a dynamically or adaptively determined, real-time adjusted scan pattern, thus increasing the effective temporal resolution. Because no or very limited time is spent scanning between the vessels, the temporal resolution of the scan is improved, i.e., is finer.

In a four millimeter diameter circular scan only about 10-20% of the A-scans are actually sampling a blood vessel, while 80-90% of the A-scans sample static tissue. This implies that it is possible to increase adaptively the scan density across the vessels by about a factor of five, when information about the location of the vessel cross-sections is available. A real time adjustment of the scan pattern or scan density can be used to adjust dynamically or adaptively the location and density of samples taken per unit time during an individual scan. The ability will then exist to scan mostly, if not exclusively, the areas of the blood vessels. Another advantage of shorter measurement timescales will be the reduction in deleterious effects of eye movements, which can result in reducing the errors in vessel depth determination which can then alter the vessel's computed orientation. A finer spatial density of scans is thus achievable over blood vessels or other areas of interest.

5

Difficulty of adequately sampling the heart's pulsation cycle exists given the long-time scale for a single scan to occur. It is an embodiment of this invention, that the scan time of a single scan can be shortened by knowing in advance where the vessels are located, thus Doppler OCT scans can be directed to these specific areas. This directly results in an increased frame rate and, consequently, a higher temporal sampling of the heart's pulsation cycle.

10

15

In one embodiment, the positions of the vessels can be detected by one or more fully sampled circumpapillary scan(s). In those scans either the phase data or the intensity data may be used to determine the positions of the blood vessels. Alternatively the vessel locations may also be determined by a full volumetric scan. In this case, the phase data as well as the intensity data may be used to determine the positions of the blood vessels. In both cases the use of retinal tracking may help to improve the precision and repeatability. Alternatively, the vessels may be located by inspection of an image from a fundus camera (such as SLO, LSO, cLSO, or BLFI).

20

25

The use of a full volume scan to extract vessel positions also has the advantage to be able to extract the geometric orientation of the blood vessels relative to a probing beam over a larger course of each vessel (see, e.g., Michaely et al. 2007, Singh et al. 2010). Having this information at hand, there is the possibility to direct the scanning beam to the vessel cross sections and, moreover, scan particular regions of each vessel, which exhibit a favorable geometric angle orientation. This avoids measuring vessels at angles approaching orthogonality where the axial (parallel) velocity component is very small. It may, of course, also allow to avoid measuring in very steep regions of the vessels, where the axial velocity component is very high, and thus fringe washout, phase de-correlation, or phase wraps may influence measurement outcomes.

30

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5 **BRIEF DESCRIPTION OF THE DRAWINGS**

Fig. 1 is a schematic of an optical coherence tomographic instrument based on Fourier-domain technology.

Fig. 2 is a flow chart of one of the embodiments revealed in the present application which services to improve the frame rate of OCT sampling within
10 blood vessels in order to measure flowrate changes due to the cardiac cycle.

Fig. 3 illustrates a circumpapillary scan (302) with non-linear scanning speed. Triangles (304) indicate densely sampled regions across blood vessels (301). The ad hoc boundary of the ONH is indicated by 303.

15 Fig. 4 illustrates an arbitrary scan sampling all vessels (401) entering or exiting the optic nerve head (403). Sampling positions are chosen by a vessel's angle relative to the probing beam in order to optimize the Doppler angle. The dotted lines (402) indicate regions where a scan moves more quickly. Small circles (404) indicate densely-sampled regions across blood
20 vessels.

Fig. 5 schematically depicts a lateral view of a blood vessel (501) which varies in depth and one in which the blood flow vector (502) continuously changes as a function of depth (z). With a measurement beam (503) parallel to the vertical, it can be seen in this graphic, that the Doppler angle, which is the angle between flow vector (502) and the direction of the probe
25 beam, will be too small for steep (near parallel) flow (504); optimal when the angle between the blood flow vector (502) and measurement beams are neither close to parallel nor close to perpendicular; and too large when the two vectors (blood flow and probing beam) are essentially orthogonal (506).

30 Fig. 6 illustrates a circumpapillary scan (602), where three positions (small circles, 604) are being used for detecting sample orientation changes. The ad hoc boundary of the ONH is indicated by (603). Blood vessels are indicated by (601).

Fig. 7 shows a circumpapillary scan with non-linear scanning speed (702),
35 where three positions (small circles, 704) are being used for detecting sample orientation changes. Blood vessels are indicated by (701). The ad

5 hoc boundary of the ONH is indicated by (703). The triangles (705) and circles (704) are densely-scanned regions.

Fig. 8 illustrates an arbitrary scan sampling all vessels (801) entering or exiting the optic nerve head (803), where three positions (804) are analyzed via geometric methods and derive changes in the sample. The triangles
10 (805) and circles (804) are densely-scanned regions.

Fig. 9 presents the flow diagram of another embodiment of the present application. It allows the monitoring of orientation changes of a sample due to anatomical movements and the correction of angular measurements, or directions of areas of interest found within the sample.

15 **DETAILED DESCRIPTION**

A generalized Fourier Domain optical coherence tomography (FD-OCT) system used to collect an OCT dataset suitable for use with the present set of embodiments, disclosed herein, is illustrated in Fig. 1. A FD-OCT system
20 includes a light source, 201, typical sources including but not limited to broadband light sources with short temporal coherence lengths or swept laser sources.

Light from source (201) is routed, typically by optical fiber (205), to
25 illuminate the sample (210), a typical sample being tissues at the back of the human eye. The light is scanned, typically with a scanner (207) between the output of the fiber and the sample, so that the beam of light or probe beam (dashed line 208) is scanned over the area or volume to be imaged. Light scattered from the sample is collected, typically into the same
30 fiber (205) used to route the light for illumination. Reference light derived from the same source (201) travels a separate path, in this case involving fiber (203) and retro-reflector (204). Those skilled in the art recognize that a transmissive reference path can also be used. Collected sample light is combined with reference light, typically in a fiber coupler (202), to form light
35 interference in a detector (220). The output from the detector is supplied to a processor (221). The results can be stored in the processor (221) or displayed on display (222). The processing and storing functions may be

5 localized within the OCT instrument or functions may be performed on an
external processing unit to which the collected data is transferred. This unit
could be dedicated to data processing or perform other tasks which are
quite general and not dedicated to the OCT device. The display can also
provide a user interface for the instrument operator to control the collection
10 and analysis of the data.

The interference causes the intensity of the interfered light to vary across
the spectrum. The Fourier transform of the interference light reveals the
profile of scattering intensities at different path lengths, and therefore
15 scattering as a function of depth (z-direction) in the sample.

The profile of scattering as a function of depth along the probe beam is
called an axial scan (A-scan). A dataset of A-scans measured at
neighboring locations in the sample produces a cross-sectional image
20 (slice, tomogram, or B-scan) of the sample. A collection of B-scans
collected at different transverse locations on the sample comprises a 3D
volumetric dataset. Typically a B-scan is collected along a straight line but
B-scans generated from scans of other geometries including circular and
spiral patterns are also possible.

25 The sample and reference arms in the interferometer could consist of bulk-
optics, fiber-optics, photonic integrated circuits (PIC) or hybrid bulk-optic
systems and could have different architectures such as Michelson, Mach-
Zehnder, or common-path based designs as would be known by those
30 skilled in the art. Light beam as used herein should be interpreted as any
carefully directed light path. In time-domain systems, the reference arm
needs to have a tunable optical delay to generate interference. Balanced
detection systems are typically used in TD-OCT (time-domain OCT) and
SS-OCT systems (swept-source OCT), while spectrometers are typically
35 used at the detection port for SD-OCT (spectral domain OCT) systems.
The latter two OCT systems are collectively known as Fourier-domain OCT

5 (FD-OCT). The embodiments described herein could be applied to any type of OCT system.

In one common incorporation of Doppler OCT, one makes use of the easy access to interferometric phase information as a function of depth by the
 10 FD-OCT signal reconstruction. This information has per se no absolute value, but the difference of two temporally separated phase measurements at the same location yields an absolute value for small axial motion. For unambiguous velocity determination the phase difference $\Delta\varphi$ needs to be confined to $[-\pi, \pi]$:

$$\Delta\Phi = \begin{cases} \Delta\varphi, & |\Delta\varphi| < \pi \\ \Delta\varphi - \text{sign}(\Delta\varphi)2\pi, & |\Delta\varphi| > \pi \end{cases}$$

15 where $\Delta\Phi$ is the unwrapped phase difference. The axial velocity of a moving scatterer may then be determined by:

$$v = \frac{\lambda}{4\pi\tau} \tan^{-1} \left(\frac{\text{Im} \sum_m \exp(i\Delta\Phi_m)}{\text{Re} \sum_m \exp(i\Delta\Phi_m)} \right) \frac{1}{\cos \alpha},$$

where λ is the central wavelength, τ the time between two measurements, m the number of averaged phase differences, and α is the Doppler angle.

The maximum unambiguously quantifiable axial velocity is:

$$v_{max} = \pm \frac{\lambda}{4\tau}.$$

20 The minimum quantifiable axial velocity is limited by the phase noise Φ_{err} of the system:

$$v_{min} = \frac{\lambda \Delta \Phi_{err}}{4\pi\tau}.$$

Alternative to the described velocity extraction method, there are other methods described in the literature see, e.g., Szkulmowska et al. 2009, Ren et al. 2002, Y. Wang et al. 2010, R. K. Wang et al. 2009, and Liu et al. 2012.

25 The advantage of the embodiments described in the present application is that they allow for higher temporal resolution circumpapillary scans without increasing phase de-correlation or reducing the sensitivity for lower flow speeds.

5

In one embodiment of the present application, the basic idea is to increase the frame or acquisition rate of circumpapillary Doppler OCT scans, by dynamically or adaptively adjusting the scan density and location throughout the scan so that the movement of the probe beam in the OCT system between the areas of interest is faster than the movement of the OCT probe beam over the areas of interest. In a system with retinal eye tracking (see, e.g., Ferguson et al. 2004, US6325512, US6726325, US7365856, and US20120249956, all are hereby incorporated by reference) the repeated scans may be locked to the same position on the retina.

15

This embodiment can be summarized by the flow chart in Fig. 2. An initial exploratory scan (101) with a certain set of scan parameters (integration time, step speed, path, etc.) is conducted and from these data, areas of interest (e.g., blood vessels) are identified (102). The exploratory scan can for example be one or more circumpapillary OCT scan(s), a volume OCT scan or one or more images from a fundus imaging capability such as a fundus camera, LSO (laser scanning ophthalmoscope), SLO (scanning laser ophthalmoscope), BLFI (broad-line fundus imager), or cSLO (confocal SLO), or a combination instrument possessing a fundus imaging capability and an OCT system. (Such systems are described in Bernardes et al. 2011.). Initial locations of areas of interest can be determined (102) from these image data, and, a new set of scan parameters are determined (103) and are then communicated (104) to the scanner (207) and a set of OCT scans then are conducted concentrating on the locations of the areas of interest (105). After acquisition, the results can be stored or displayed or analyzed further (106).

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Reference is given to Fig. 3, where an exploratory OCT scan (circular or volume) with uniform sampling is performed indicated by dashed circle (302), just outside the limit of the optical nerve head (303). This scan can be used to identify the positions (304) of the vessels (301) on the circle (302) using its phase and/or intensity data (see, e.g., Wang et al. 2008).

5 Such detection methodologies would be known to the person having ordinary skill in the art.

With this information, additional circular scans (or scans of arbitrary path configuration) can be performed at the same or approximately same
10 locations, but this time, with uneven or non-uniform transverse and/or temporal sampling. In order to increase the frame rate while maintaining dense sampling of the vessels (301), these scans will have denser sampling across the vessels and very sparse or no sampling in the regions where only static tissue is scanned. This can increase the effective frame rate of
15 the circumpapillary scans approximately by a factor of five, resulting in a frame rate of approximately 50 Hz. Such a sampling rate will comprehensively resolve the cardiac cycle even in patients with higher pulse rates and ultimately lead to more precise blood flow measurements.

20 A similar method can also be used for Doppler OCT non-circumpapillary scans of vessels (401 in Fig. 4), where higher sampling densities are desired for some parts of the scan (404), while other parts of the retina may be scanned less densely (402). The regions to be scanned are chosen due to having more desirable angular relationship to the probe beam (explained
25 below). The limit of the ONH in this figure is indicated as 403.

Such applications could, for example, be an imaging mode, in which parts of a volume scan, containing pathologies (e.g., Srinivasan et al. 2006), are sampled more densely in order to improve image quality in these regions,
30 whereas in other regions of lesser interest, are sampled less densely.

Another embodiment also contemplated in Fig. 4 would not only make use of prior knowledge of the vessel positions (401), but takes into account the relative geometric orientations of the scan direction with respect to each
35 vessel and position the scan within a region that exhibits a favorable geometric orientation for the measurement. In other words, there should be a choice of a position where there is a preferred geometric orientation that

5 lies within a desired range, and allows an axial velocity measurement with optimal sensitivity. The axial velocity could be considered optimum if it lies well within the minimum measurable velocity, V_{min} , and the maximum unambiguously measurable velocity, V_{max} .

10 Fig. 5 illustrates a side view of a vessel (501) exiting the optic nerve head. This schematic vessel has significant curvature and, therefore, the blood flow velocity vectors (502) have different angles or angular orientations with respect to the probing beam (503). One would like to avoid scanning in regions where the Doppler angles are too small (504) or too large (506).

15 (505) shows a section of the vessel, where the angles between velocity vector and measurement beam lie within a desired range. Since the sections of each vessel do not necessarily lie on a circle, the circumpapillary scan may have an arbitrary shape (Fig. 4). In order to determine the Doppler angle along a range of each vessel, one may, for example, apply methods described by Michaely et al. 2007 or Singh et al. 2010. Because
20 the vessels in the optic nerve head region lie very close to the retinal surface one may alternatively use a topography map, generated from a volumetric scan, to generate a rough estimate of these angles. While these angles determined from the topography map may not be accurate enough
25 to be used for the absolute velocity calculations, they may suffice the requirements of finding suitable scanning regions.

Another embodiment of the present application is to avoid repetitive angle measurements throughout the course of the Doppler OCT measurement.
30 This can be achieved by first measuring the orientations of the vessels of interest with an angle determination method of choice, e.g. double circular scan (see, e.g., Wang et al. 2008; Huang & Wang WO2008124845), reference volume (Singh et al. 2010), vectorial reconstruction (Michaely et al. 2007), and then subsequently monitoring only changes in the orientation
35 of the full sample with respect to the probing beam.

5 In the case of circumpapillary Doppler OCT scans this approach is straightforward to implement. In Fig.6, blood vessels are indicated by (601) and (603) is an outline of the ONH. For circular measurements/scans (602) on the retina, there exists the possibility to extract at least three A-scans (604) from the circle and use their depth position for geometric
10 determination of the retina's orientation with respect to the probing beam (via detection of the inner limiting membrane or the retinal pigment epithelium). By performing this geometric analysis continuously for each circumpapillary scan, it is possible to detect changes in the orientation of the retina with respect to the probing beam and is, therefore, also able to
15 quantify changes in the angle between vessel and probing beam.

It is, therefore, no longer required to continuously use a double circular scan pattern. Instead it is sufficient to use only initially a vessel angle
20 determination and then switch to a circular scan pattern with a fixed diameter (Fig. 7, 702). Moreover, the image processing effort is reduced since now only the surface of the retina at three positions of the circular scan has to be detected, which is an easier task in contrast to determining the centers of the vessel's (701) cross sections (704 and 705) in each
25 circular scan.

As depicted in Fig. 8, as long as at least three measurement points (804) are acollinear, their three-dimensional coordinates may be used to determine changes in orientation of the sample between consecutive
30 measurements geometrically. The detected change in sample orientation may be used to update the initially-determined angle of each vessel (805) relative to the measurement beam. The changes in orientation could include tip and tilt or both.

Using the spatial coordinates $(x_i, y_i, z_i, i = 1, 2, 3)$ of the three points one can
35 determine the normal vector of the plane, which contains all three measurement points:

$$\vec{n} = \begin{pmatrix} x_2 - x_1 \\ y_2 - y_1 \\ z_2 - z_1 \end{pmatrix} \times \begin{pmatrix} x_3 - x_1 \\ y_3 - y_1 \\ z_3 - z_1 \end{pmatrix}$$

- 5 The mathematical operation $\times$ is the vector cross product. The normal vector to this plane provides a measure for the orientation of the sample at the time when the original Doppler angles were calculated. In a later measurement one can again use the updated coordinates of the three points to calculate the updated normal vector, which provides a measure for
- 10 the new orientation of the sample:

$$\vec{n}' = \begin{pmatrix} x_2' - x_1' \\ y_2' - y_1' \\ z_2' - z_1' \end{pmatrix} \times \begin{pmatrix} x_3' - x_1' \\ y_3' - y_1' \\ z_3' - z_1' \end{pmatrix}$$

Since this method is ideally applied with retinal tracking enabled, one can assume that:

$$x_i' = x_i$$

and

$$y_i' = y_i.$$

One would then normalize the obtained normal vectors:

$$\vec{e}_n = \frac{\vec{n}}{|\vec{n}|}$$

- 15 and

$$\vec{e}_n' = \frac{\vec{n}'}{|\vec{n}'|}$$

The difference between the two unit vectors then provides a measure of a change of orientation between the first measurement and the second measurement:

$$\Delta \vec{e} = \vec{e}_n' - \vec{e}_n$$

- 20 $\Delta \vec{e}$ is then added to each unit velocity vector, which is then used to calculate an updated angle between the updated unit velocity vector and the direction vector of the probing beam.

5 Fig. 9 presents the basic methodology of this embodiment. An exploratory scan (901) of a sample is (or samples are) conducted and the fluidic flows of interest are located and measured (902). Based upon a favorite algorithm (see above), the directions of the flows are determined (903). From this information, the orientation of the sample (904) relative to the
10 probing beam direction can be derived. The orientation determination could include the angles of tip and tilt relative to the probe beam. The procedure could be used to monitor the orientation changes of the sample (904). The sample orientation is then used to determine the corrections to the flow directions due to anatomical movements (905). The process can be
15 repeated as desired (907). Additional actions, such as further processing, storing, and displaying the results (906) are options. The corrected directions of flows can then be used to determine more accurate flow velocities. An alternative to an exploratory OCT scan is one using images from a fundus imaging capability such as a fundus camera, LSO (laser
20 scanning ophthalmoscope), SLO (scanning laser ophthalmoscope), BLFI (broad-line fundus imager), or cSLO (confocal SLO), or a combination instrument possessing a fundus imaging capability and an OCT system. (Such systems are described in Bernardes et al. 2011.)

25 The method may also be equally implemented for non-circular scan patterns (Fig. 8). In this embodiment, similar to the aforementioned geometric approach, will consist of a subset of a full scan, and will contain at least three measurements at different locations (804).

30 If only one vessel is to be evaluated and therefore only measurements at a single location are acquired, one may interleave additional scans for geometric determinations with the regular measurements. Since as few as three A-scans are sufficient for such a geometric measurement, it hardly adds to the total acquisition time. The scans for geometric determination
35 can then be used in the same manner to detect the orientation of the sample and continuously monitor changes in the orientation as was previously described for circular and arbitrary scan patterns (see Fig. 9).

5 The changes in the orientation of the full sample are again fully applicable to the predetermined angles between probing beam and blood vessel. The areas of interest (805) can then be scanned with a different set of scan parameters. Retinal tracking again helps to improve the accuracy of this method.

10

Other areas of interest for the monitoring of flow would include the flow and flow rate of aqueous humor in the anterior segment of the eye, or any other fluidic movements within the eye.

15

The current preferred optical coherence tomography method is Fourier Domain optical coherence tomography, principally due to the faster scan and data rates possible. Thus based upon this modality, it is estimated that scans of blood vessels can occur on the order of at least 25 Hz, which is at the sub-cardiac cycle level, measuring both diastole and systole components, total blood flow, and the presence or absence of any pathologies.

20

Although various applications and embodiments that incorporate the teachings of the present invention have been shown and described in detail herein, those skilled in the art can readily devise other varied embodiments that still incorporate these teachings.

25

REFERENCES

30 The following references are hereby incorporated by reference:

US6325512, US6726325, US7365856, US20120249956

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35

5 US Patent No. 7,884,945 Srinivasan et al. "Methods and apparatus for optical coherence tomography scanning"

US Patent Publication No. 2007/0291277 Everett et al. "Spectral domain optical coherence tomography system"

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US Patent No. 7,365,856 Everett et al. "Method of motion correction in optical coherence tomography imaging"

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5 **CLAIMS**

1. A method comprising:

obtaining image data of the eye using an OCT or fundus instrument;

processing said image data to identify two or more areas of interest;

10 and,

obtaining one or more scans of said areas of interest with an OCT system, in which the movement of the probe beam of the OCT system between said areas of interest is faster than the movement of the probe beam of the OCT system within said areas of interest.

15

2. A method according to claim 1, in which said areas of interest include blood vessels.

3. A method according to claim 2, further comprising:

20 determining flow velocities within said blood vessels.

4. A method according to claim 1, in which said areas of interest are pathological.

5. A method as recited in claim 1, further comprising:

identifying locations of said two or more areas of interest; and,

obtaining said one or more scans of said locations with a finer temporal and/or spatial density.

25

6. A method as recited in claim 5, in which the image data is volumetric and the areas of interest are of two or more blood vessels.

30

7. A method as recited in claim 6, further comprising:

monitoring the locations of these two or more blood vessels; and,

storing, or further processing said locations, in which the further processing includes determining a Doppler angle between each of the locations of the two or more blood vessels.

35

5

8. A method as recited in claim 7, in which said one or more scans are obtained of those blood vessels that possess a blood flow that are within a range of detection by the OCT instrument.

10

9. A method as recited in either of claims 7 or 8, further comprising: determining angular orientations of each of the two or more blood vessels at said locations;

processing said one or more scans to obtain flow rates and/or velocities of flow of the two or more blood vessels; and,

15

correcting said flow rates and/or velocities of flow for each of the two or more blood vessels using said angular orientation determinations for each of the two or more blood vessels.

20

10. A method of monitoring flow within a sample using an OCT system, comprising:

determining the directions of flow within the sample using a probe beam;

determining orientation of the sample relative to said probe beam;

monitoring changes in said orientation;

correcting said direction of flow based on changes in said orientation;

25

and,

storing, displaying, or further processing said corrected direction.

30

11. A method as recited in claim 10, further comprising: using corrected direction of flow in determining flow velocity.

12. A method as recited in claim 10, wherein the flow is in blood vessels.

35

13. A method as recited in claim 10, wherein orientation is tip and/or tilt.

5 14. A method as recited in claim 10, wherein the flow is from aqueous humor.

 15. A method of monitoring blood flow in the eye using an optical coherence tomography (OCT) system, said system including a scanner
10 for scanning a measurement beam across the eye, said method comprising:

 obtaining a first set of measurements by scanning the beam across the eye;

 identifying the locations of blood vessels based on the first set
15 of measurements;

 obtaining a second set of measurements by scanning the beam across the eye based on the identified locations of the blood vessels and wherein the density of the measurements in the second set of
20 measurements is higher in the regions of the blood vessels than in regions without blood vessels;

 determining the blood flow based on the second set of measurements; and
 displaying or storing information related to the determined blood flow

25 16. A method as recited in claim 15, in which said first set of measurements yields a volumetric dataset.

 17. A method as recited in either of claims 15 or 16, further comprising:
30 determining orientations of the blood vessels relative to said beam;
 monitoring changes in said orientations;
 correcting said direction of flow based on changes in said orientations;
 and,
 storing, displaying, or further processing said corrected direction.

35 18. A method as recited in any one of claims 15-17, further comprising:

5 monitoring the locations of the blood vessels; and,
storing, or further processing said locations, in which the further
processing includes determining a Doppler angle between each of the
locations of the blood vessels.

10 19. An optical coherence tomographic (OCT) system for imaging a
sample, comprising:
a source for generating a beam of light;
a divider for splitting the beam along separate sample and reference
paths;
15 optics for directing the beam over one or more locations on the sample;
a detector for receiving interfered light returned from both the sample
and reference paths; and,
a processor for analyzing image data of the sample taken by the OCT
system or a fundus imaging modality and also functions to position
20 adaptively said beam based on the results of the analysis.

20. A system as recited in claim 19, in which said processor also
functions to identify areas of interest and locations of said areas of
interest.

25 21. A system as recited in claim 20, in which the processor uses a
first speed to control the beam during scan acquisition at said locations
and a second speed of said beam between said locations.

30

FIGURES

FIG. 1

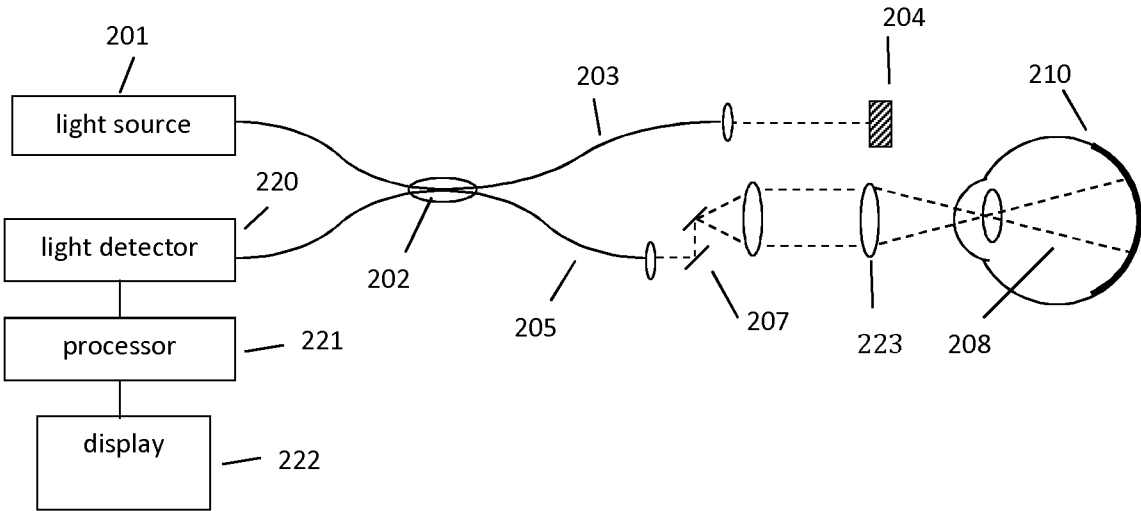


FIG. 2

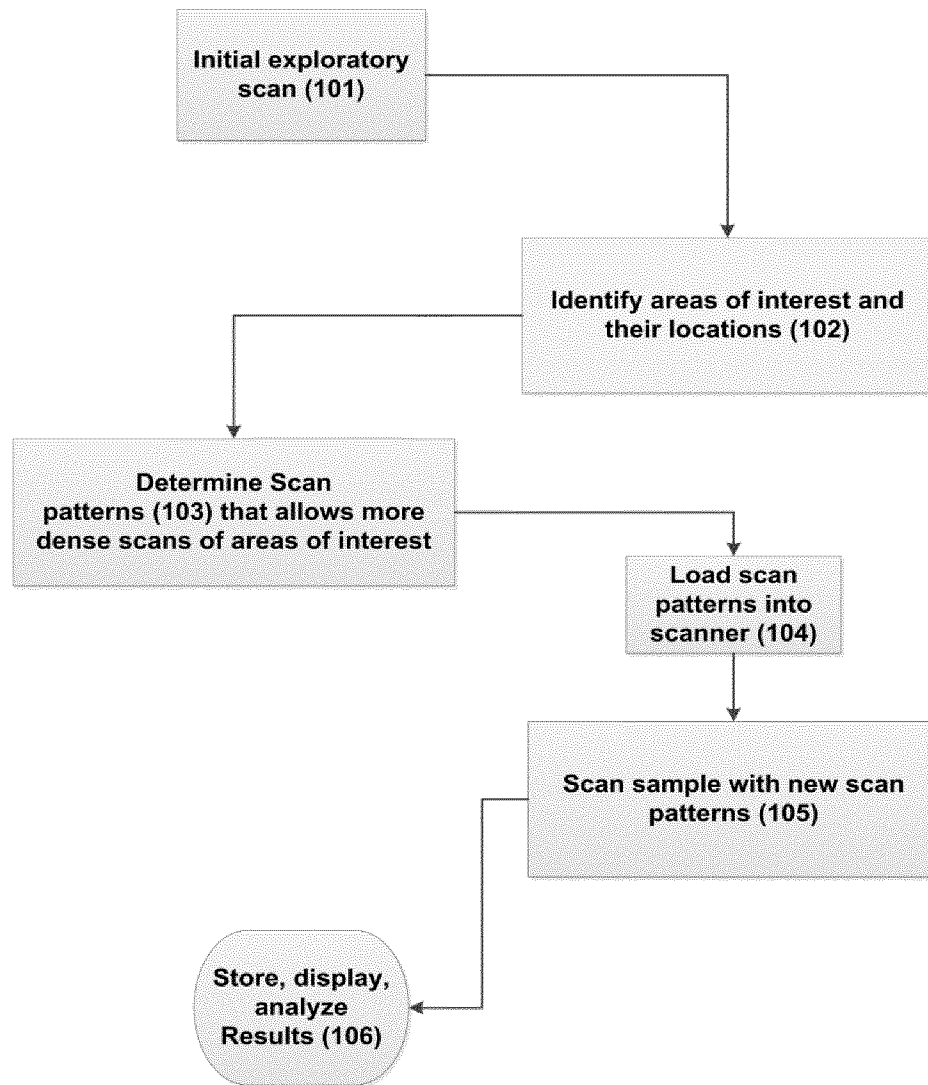


FIG. 3

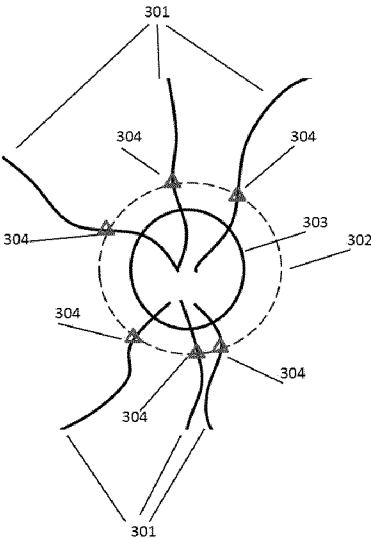


FIG. 4

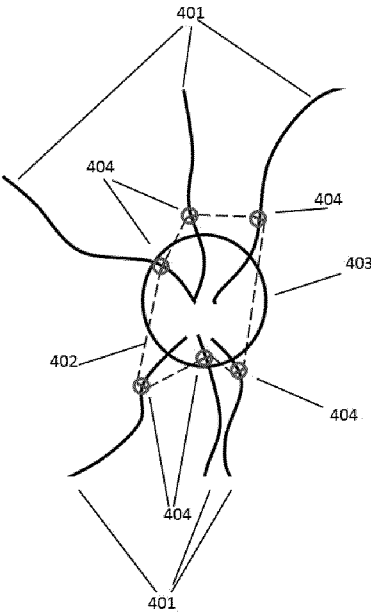


FIG. 5

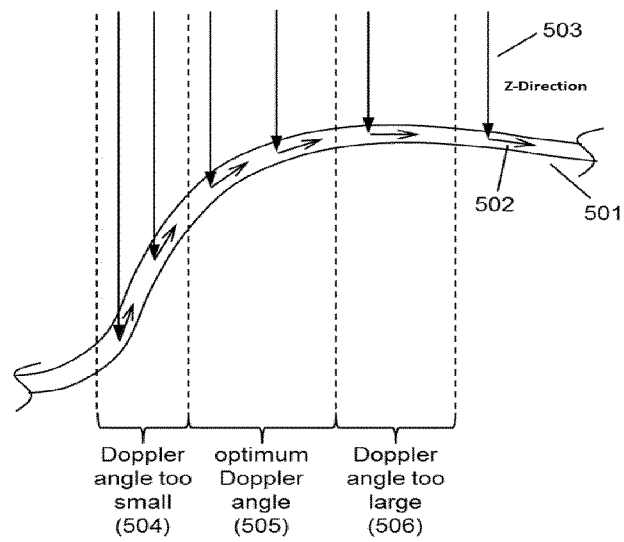


FIG. 6

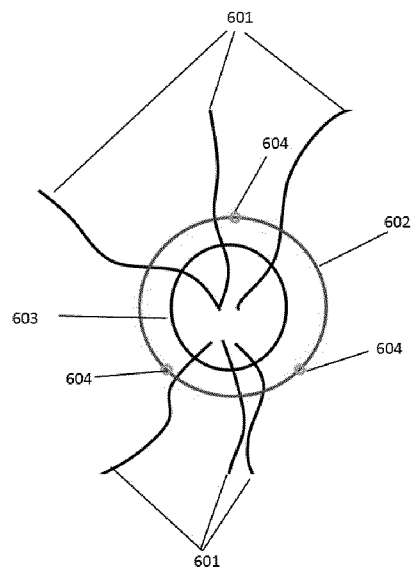


FIG. 7

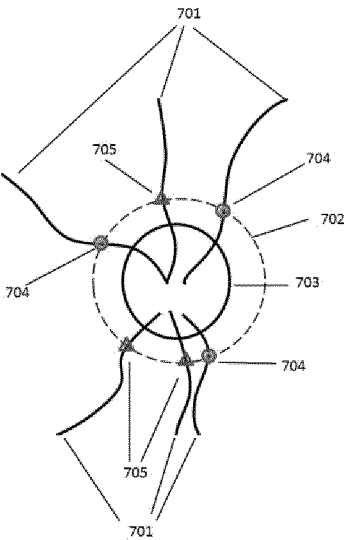


FIG. 8

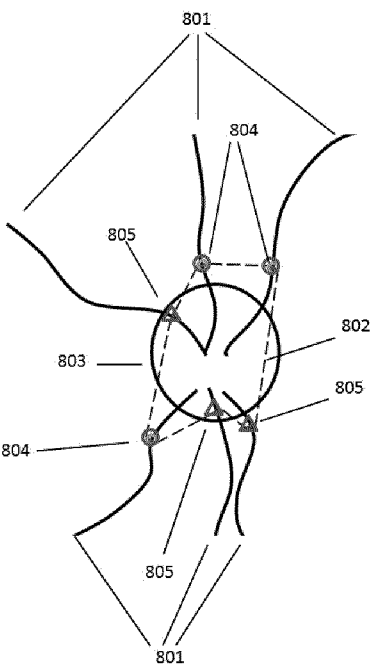
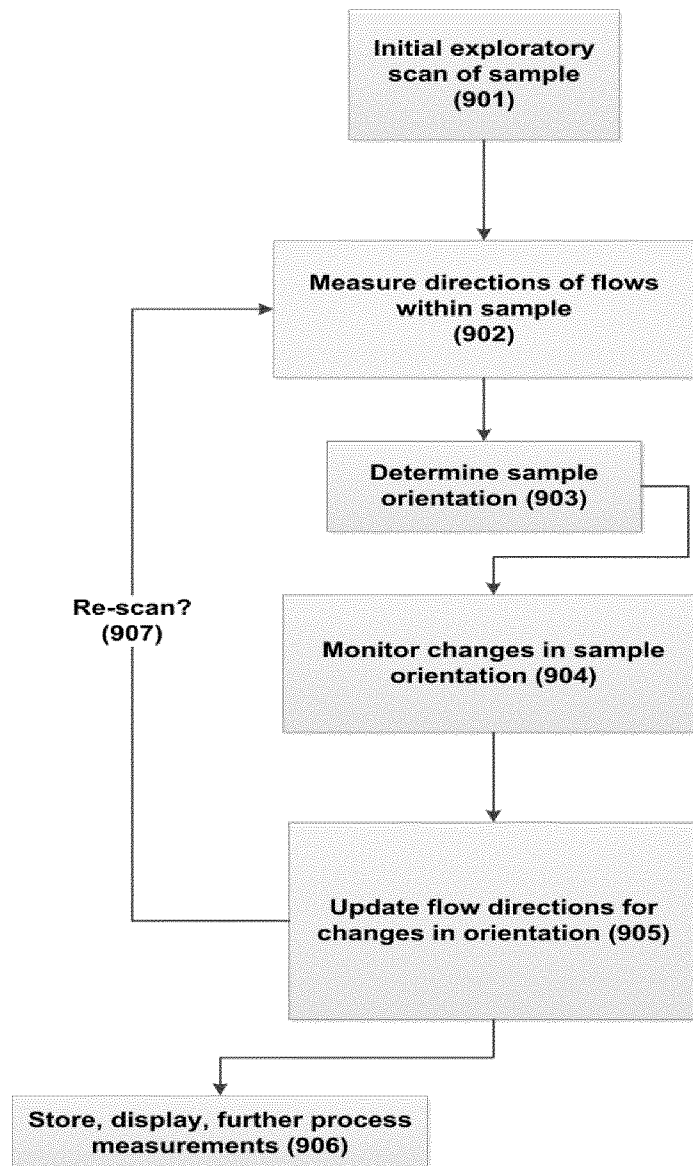


FIG. 9



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/070644

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61B3/10 A61B3/12
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)

A61B

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/078802 A1 (MASSACHUSETTS INST TECHNOLOGY [US]; SRINIVASAN VIVEK [US]; FUJIMOTO JA) 27 July 2006 (2006-07-27)	1-6
Y	paragraph [0134] - paragraph [0194]	7-9, 15-18
X	WO 2008/124845 A2 (UNIV SOUTHERN CALIFORNIA [US]; HUANG DAVID [US]; WANG YIMIN [US]) 16 October 2008 (2008-10-16)	10-14
Y	the whole document	7-9, 15-18
A	US 2011/267340 A1 (KRAUS MARTIN F G [DE] ET AL) 3 November 2011 (2011-11-03) paragraph [0134] paragraph [0207]	1-9



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search

25 February 2015

Date of mailing of the international search report

06/03/2015

Name and mailing address of the ISA/

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Authorized officer

Alvazzi Delfrate, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/070644

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-18
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9

Method for obtaining image data of areas of interest of the eye

2. claims: 10-18

Method of monitoring blood flow within a sample using OCT

3. claims: 19-21

OCT system for imaging a sample

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/070644

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2011139895 A1 10-11-2011	