(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) Title: QUANTITATIVE RETINAL IMAGING

FIG 2

(57) **Abstract:** A method and system are proposed for imaging the retinal structure of an eye. A light source is provided and a repetitive pattern is projected on the retina by said light source having illuminated and non-illuminated portions with a spatial frequency larger than 0.5 mm-1. For the illuminated and non-illuminated portions a fluorescence level is measured; and a fluorescence level is derived as a corrected value for illuminated and non -illuminated areas.

WO 2018/097723 A1

Title: Quantitative Retinal Imaging

FIELD

5 The invention relates to a method of obtaining an image of the human retina for the purpose of analysing tissue structure, function and biochemistry.

BACKGROUND

10 In the prior art, fundus imaging is a technique for obtaining high resolution images of the interior of the eye, in particular, the human retina. This can be done for many diagnostic reasons, e.g. to identify glaucoma, diabetic retinopathy, and age related macula degeneration. Fundus imaging can be performed with high resolution fundus cameras in multispectral images.

15 Another technique is scanning laser ophthalmoscopy. Here, the retina is scanned by a point or line source, that is imaged on a photodiode or line camera. Since the only light that is received is directly related to the imaged point itself, diffraction and scattering is minimal and the resolution of the images is high. This technique can be applied for many different

20 wavelengths, and can be combined with fluorescence measurements. However, the technique is cumbersome and expensive. Another technique is optical coherence tomography, wherein a reflected beam is optically combined with an incoming scanning point source beam, and scattering behaviour can be made visible. 2D high resolution cross sections can be

25 produced, inter alia, to visualize structures in the retina, such as cysts, ruptures, or determining the retinal nerve fibre layer thickness. Angiography is another application area of optical coherence tomography. Multiple images can be used to distinguish differences attributed to blood flow. In this way blood vessels can be analysed.

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Although the eye is primarily imaged for studying the function of the eye itself, the prior art has also mentioned studies, e.g. wherein the vessel diameter is correlated to e.g. a risk of a myocardial infarct in patients. Also fluorescence markers can be used to label individual substances. In relation

5 to this studies were performed to image beta amyloid aggregates in the retina. These aggregates are associated with Alzheimer's disease, and it is contemplated that the optical nerve system is physically closely linked to the brain.

While these techniques are promising, there is a problem in providing

10 quantitative data on these images. For example, there is a problem on how to relate the fluorescence in quantitative sense to the aggregates.

A technique to optically measure tissue structure, function and biochemistry is so called spatial frequency domain imaging (SFDI). This is a modulated illumination technique wherein a spatial frequency is used for imaging a

15 sinusoid or other repetitive shape on tissue, for example, by means of a spatial light modulator or digital mirror device. SFDI has typically been used in geometries where large areas of tissue can be exposed, such as skin. The retina is a very thin curved tissue with a water/tissue refractive index interface offering limited optical access to measure optical characteristics.

20 For retinal imaging SFDI, is considered not useful due to its low spatial resolution, large imaging depth that significantly extends beyond the retina, and small size of the retina compared to the spatial frequencies usually employed for SFDI (typically 0 - 0.2 mm^{-1}, or 0 - 0.33μ_{tr} where 1/μ_{tr} is the transport mean free path).

25   From US20160157723 a technique called sub diffuse spatial frequency imaging is known (sd-SFDI). sd-SFDI has shown promise in quantifying the subdiffuse scattering properties of easily accessible turbid media such as skin. However, the water-tissue interface of the retina; the curvature of the retina and the maximum projectable extent of the

patterned illumination in the retina vs. skin are not comparable with the
flat geometry of air-tissue interface. Furthermore, US20160157723 shows
quantification of the absorption properties of easily accessible turbid media
using spatial frequencies usually employed for SFDI, which are not

5   appropriate for imaging the absorption properties of the retina.The
invention has as an object to provide an imaging technique that does not
suffer from the afore described problems and that is able to provide an
enhanced, quantitative image of the retina.

10   SUMMARY OF THE INVENTION
             This can be done by a method and system for imaging the retinal
structure of an eye according to the referenced claims. A light source is
provided and a repetitive pattern is projected on the retina by said light
source having illuminated and non-illuminated portions with a spatial

15   frequency larger than $0.33\mu_{tr}$. The periodic signal is shifted in phase and the
phase-shifted images are combined to form a demodulated image, for which
a tissue optical transport model is used to determine the tissue optical
properties. A high spatial frequency of the phase shifted images induces an
additional sensitivity to the angular scattering distribution related to sub-

20   diffuse light transport. In an embodiment, a fluorescence level is measured;
and a fluorescence level is derived as a corrected value for the effects of
optical properties on measured fluorescence level, thereby allowing
measurement of undistorted, intrinsic fluorescence and distinguishing
autofluorescence from labeled fluorescence.

25   By projecting the phase shifted images with spatial frequencies in
a sub-diffuse region, such high spatial frequencies are utilized as a wide-
field equivalent of spatially resolved diffuse reflectance measurements at
short source-detector separations. This sub diffuse technique has the
following advantages for obtaining an optical characteristic of the retina.

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The limited penetration depth of the sub-diffuse light that is required due to the small thickness of the retina, enables to accurately recover optical property maps of the retina without any distorting effects from the underlying choroid. Second, the spatial frequencies employed ($>0.33\mu_{tr}$) are

5   useful in the limited-area geometry of the retina, which has a typical retinal image sizes of about 15 mm in diameter. It is noted that μ_{tr} is the transport coefficient, which is the sum of an absorption coefficient μ_a and a reduced scattering coefficient μ'_s measured in mm^{-1}. In addition, implementation of the projection technique in the retina is particularly advantageous since

10   specular reflections that are problematic for current application areas are not present in the retina due to a combination of annular illumination (or other optical solutions) used in fundus camera's to reduce the corneal reflections, and the relatively small specular reflectance of the retina due to the small vitreous-retina refractive index mismatch.

15   In US2016/0157723 A1 a structured light imaging method is described to measure sub-diffuse scattering parameters, being reduced scattering coefficient and backscatter likelihood. It is the objective of the current invention to measure sub-diffuse scattering, absorption and fluorescence parameters in the thin top-layer of a 2-layer medium, i.e. the

20   retina on top of the choroid. Although in US2016/0157723 A1 it is understood that absorption and fluorescence of a material can be measured using SFDI, it is suggested to do so with low spatial frequency modulated patterns which is not appropriate for separating retinal absorption and fluorescence from choroid absorption and fluorescence.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an example of spatially varying patterns that can be projected onto the retina;

Figure 2 shows a configuration of a narrow banded n-color source;

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Figure 3 shows a configuration of the broad band light source

DETAILED DESCRIPTION OF THE DRAWINGS

There has been significant success in performing quantitative fiber-optic

5   probe measurements during clinical procedures to quantify sub-diffuse
scattering, absorption and fluorescence in small tissue volumes outside the
eye. This single-point contact approach of contact fibers is however not
compatible with wide-field retinal imaging.

Current state-of-the-art retinal imaging devices are unable to

10   relate collected images to the retinal tissue optical properties (scattering
and absorption). When light enters tissue it is scattered due to fluctuations
in the optical refractive index related to tissue structure, and it is absorbed
due to the presence of chromophores such as bilirubin, carotenoids and
hemoglobin. Quantification of these scattering and absorption properties of

15   tissue is likely to be diagnostically valuable, as changes in light scattering
can be directly correlated to changes in tissue microstructure while changes
in absorption can be directly correlated to changes in pigmentation,
bilirubin/carotenoid concentration and vascular properties such as
microvascular blood oxygenation.

20   Moreover, differences in tissue optical properties have been shown
to have a strong influence on the amount of fluorescence signal that is
collected under wide-field optical imaging. Unless these differences are
appropriately corrected for, this can lead to misinterpretation of
fluorescence molecular imaging signatures. This can be overcome by

25   measuring the tissue optical properties and using this knowledge e.g. to
correct the raw fluorescence to recover the intrinsic, undistorted
fluorescence from naturally present fluorophores such as lipofuscin or from
labeled fluorophores such as curcumin or targeted fluorescent tracers such
as Bevacizumab-IRDye800CW.

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In further embodiments, the retinal image is spectrally analysed. Spectral analysis of the sub-diffuse scattering and absorption properties is particularly advantageous for accurate determination of molecular concentrations of absorbing and fluorescent molecules through spectral

5   unmixing, as is known from the prior art. In another embodiment a scattering coefficient μ_s is measured as average number of scattering events per unit distance [mm^{-1}]. Also a phase function p(Θ) is measured as an angular scattering distribution of tissue.

For spatial frequency responses two regimes exist in tissue,

10   without a clear regime boundary. But for patterns with a pitch smaller than $3/\mu_{tr}$ i.e. a spatial frequency larger than $0.33\mu_{tr}$, a sub diffuse regime has a smaller interrogation depth and provides more information on scattering since phase information remains preserved, in contrast to the diffuse region. This is a critical aspect of imaging the retina, wherein the retina including

15   its blood saturation level and vascular structure must be discriminated from the underlying choroid. These values are of significant importance for analyzing the tissue structure and function of the retina, since accordingly one can determine absolute absorbance values indicative of the presence of (molecular concentrations of) certain chromophores and fluorophores.

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Figure 1 shows an example of spatially varying patterns that can be projected onto the retina. For example, a sinusoid pattern can be provided at a certain pitch, e.g. 2 mm, for a first spectral wavelength, e.g. in the 450-600 nm range. In the following, the spectral spreading can be very

25   small, e.g. less than 1 nm, or can be larger, eg. 50 nm.

For another wavelength, e.g. 700 nm, another pitch can be used, e.g. of 1.7 mm. In this way, overlapping patterns of different colors can be projected simultaneously at different pitches, which can be deconvoluted by applying a Fourier transform as is known from the prior art. By providing a

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repetitive pattern for a plurality of spectral bands, each having its own spatial frequency, simultaneous projection of such repetitive patterns is possible, that can be detected independently. In this way, increasing the spectral resolution will not go to the detriment of the camera's framerate.

5   The patterns are spatially varying, and can be temporally varying as well, for instance, for a scanning sinusoid pattern that is moved over the retina. Alternatively a scanning point source, or scanning patterns of various dimensions in the form of circles lines or ellipses can be provided.

        Figure 2 shows a configuration of a narrow banded n-color source,
10   e.g. RGB source. In the Fourier plane of a lens system (not depicted), a high frequency spatial light modulator 2 is arranged, that is able to project n-numbered patterns, e.g. a blue pattern, red pattern and green pattern, as depicted in Figure 1.

        Figure 3 shows a configuration of the broad band light source 1,
15   that is capable of projecting various patterns, via a spatial light modulator 2 and a dichroic mirror 3, to the eye 4. Such patterns can be provided by projecting said repetitive pattern by a scanning light beam from said light source derived from a DMD or SLM and using a photodiode or camera 5 as an optical detector. The detector 5 is capable of registering light from the
20   illuminated pattern on the retina, as well as light from neighbouring parts. This light contains information on the tissue through which it travelled. The detector may be multispectral, divided over several channels. In this way simultaneous spectral detection of several wavelengths is feasible. The application of a multispectral camera that images a large number of spectral
25   bands at the expense of a low spatial resolution, by e.g. creating a mosaic pattern of pixel-based color filters on the imaging chip, is appropriate for sd-SFDI since the spatial resolution achieved by sd-SFDI is fundamentally limited by the tissue light transport properties anyway, allowing to use a large number of imaging wavelengths at the expense of a low spatial pixel

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resolution on the imaging chip. The camera can also be a monochrome camera, providing an instantaneous multispectral image, without necessarily projecting multiple colors sequentially.

By flash projection or continuous illumination, an optical response

5   of for example biomarkers in the retina can be influenced.

The invention is not limited to the projection of patterned images, but can be used with other techniques as well, such as Raman scattering, 2 photon fluorescence lifetime measurement. In addition, instead of a (pinhole) camera a photodiode array can be used to provide a detection

10   similar to scanning laser ophthalmoscopy (SLO). A difference with regular SLO is that here information on the scatter path is used (via scattering and absorption). Annular projection in combination with a polarizing filter may prevent specular reflection in the air- lens surface or in the pupil. Variations are a full illumination of the pupil, a halve illumination, ring illumination or

15   point illumination. These variations will alter the optical transfer path through the retina to the camera.

An example of an optical transport model is given as follows:

$$R_{SF}^{Model}\left(\mu_a, \mu_s, \gamma, d_{fib}, NA, n_{medium}\right) =$$

$$\frac{NA^2}{n_{medium}^2}\left(1 + 0.62\gamma^2 e^{-15\gamma^2\left(\mu_s d_{fib}\right)}\right)\left[\frac{\left(\mu_s d_{fib}\right)^{0.57\gamma}}{2.3\gamma^2 + \left(\mu_s d_{fib}\right)^{0.57\gamma}}\right]e^{-\mu_a\frac{1.35\gamma^{0.9}d_{fib}}{\left(\mu_s d_{fib}\right)^{0.9}\left(8.64 + \mu_s d_{fib}\right)^{0.48}}}$$

20

In a preferred embodiment, the retina is illuminated with spatial patterns of the form:

$$S = \frac{S_0}{2}\left[1 + M_0 \cos(2\pi f_x x + \alpha)\right]$$

25

where S_0, M_0, f_x, and α (alpha) are the illumination source intensity, modulation depth, spatial frequency, and spatial phase, respectively. In this simple case, the pattern is constant in the orthogonal y direction. In reflection mode, the sub-diffusely reflected intensity, I, is a sum of AC and DC components, $I = I_{AC} + I_{DC}$, where the measured AC component of the reflected intensity, I_{AC}, can be modeled as:

$$I_{AC} = M_{AC}(x, f_x) \cdot \cos(2\pi f_x x + \alpha)$$

Here, $M_{AC}(x, fx)$ represents the amplitude envelope of the reflected photon density standing wave at frequency f_x. Note that multiple $M_{AC}(x, f_x)$ curves can be sampled in parallel at each y pixel row using a 2-D camera, allowing spatial sampling of millions of reflectance values simultaneously.

It is known from the prior art to employ a simple time-domain amplitude demodulation method, illuminating a sinusoid pattern three times at the same spatial frequency, with phase offsets $\alpha=0$, $2/3\pi$, and $4/3\pi$ radians. $M_{AC}(x, f_x)$ can then be calculated algebraically at each spatial location, x_i, by:

$$M_{AC}(x_i, f_x) = \frac{2^{1/2}}{3}\{[I_1(x_i) - I_2(x_i)]^2 + [I_2(x_i) - I_3(x_i)]^2 + [I_3(x_i) - I_1(x_i)]^2\}^{1/2},$$

where I_1, I_2, and I_3 represent the I_{AC} image values at each location with shifted spatial phases. This differencing approach is convenient, as it automatically removes features common to all three images, including the average image noise and digitization offset.

The spatially varying DC amplitude, $M_{DC}(x_i)$, can be calculated as earlier with $f_x=0$, or at any frequency of illumination using:

$$M_{DC}(x_i) = \frac{1}{3}[I_1(x_i) + I_2(x_i) + I_3(x_i)]$$

In the frequency domain, a measurement $M_{AC}(x, f_x)$ is the product
of the source intensity, I_0; the modulation transfer function (MTF) of the
illumination and imaging optical system, MTF_{system}; and the true turbid
system MTF, $R_d(x_i, f_x)$:

$$M_{AC}(x_i, f_x) = I_0 \cdot MTF_{system}(x_i, f_x) \cdot R_d(x_i, f_x)$$

Therefore, we can simultaneously calibrate for the absolute
intensity of the source and the MTF of the imaging system by performing a
reference measurement, $M_{AC,ref}(x, f_x)$, on a turbid phantom of known optical
properties. Using a model prediction for the phantom diffuse reflectance,
$R_{d,ref,pred}(f_x)$, we can write the sub-diffuse reflectance at each spatial location
as:

$$R_d(x_i, f_x) = \frac{M_{AC}(x_i, f_x)}{M_{AC,ref}(x_i, f_x)} \cdot R_{d,ref,pred}(f_x).$$

This direct division-based correction for the system frequency
response is an advantage of SFD measurement over other spatially resolved
measurements, avoiding system PSF deconvolution in the real spatial
domain, which can amplify measurement noise and uncertainties. Ideally,
the surface contours of the sample and the phantom should be identical or
be compensated numerically using surface profilometry. Note that in sub-
diffuse imaging, the exact phase function of the calibration phantom must
be known in order to correctly calculate $R_{d,ref,pred}(f_x)$.

In a preferred embodiment, multiple spatial frequencies will be used and multiple wavelengths will be used in order to obtain sufficient information to fit the data $R_d(x_i, f_x)$ to a reflectance model that describes the dependence of the signal $R_d(x_i, f_x)$ on the tissue optical properties μ'_s, γ, and μ_a. As an initial guess, the reflectance model dependence on scattering properties μ'_s and γ is based on the idea that R_d exhibits a γ-specific proportionality vs. dimensionless scattering given as the product of $(\mu_s' \, f_x^{-1})$:

$$R_d(\mu'_s, \gamma, f_x) = \eta\left(1 + \left(\zeta_4\gamma^{-2}\right)\left(\mu'_s f_x^{-1}\right)^{(1-\zeta_2\gamma)}\right)\left[\frac{\left(\mu'_s f_x^{-1}\right)^{(1-\zeta_3\gamma)}}{\zeta_1\gamma^2 + \left(\mu'_s f_x^{-1}\right)^{(1-\zeta_3\gamma)}}\right] \qquad (1)$$

Here the fitted parameters include η, which represents the collection efficiency of the detector, and ζ_i , for i = [1,2,3,4] , which are fitted coefficients used to capture the dynamics in demodulated reflectance observed in response to changes in $\mu_s' \, f_x^{-1}$ and γ . Note that equation (1) is the wide-field non-contact equivalent of reflectance collected with a single fiber in contact with tissue. Model coefficients can be estimated by minimizing the difference between simulated and model estimated values of demodulated reflectance. Monte Carlo simulations of light transport can be used, using the repetitive patterns that are projected onto the retinal tissue, which is a curved turbid medium, to derive the map of retinal optical properties, including the absorption coefficient μ_a and a reduced scattering coefficient μ'_s measured in mm^{-1}.

The effect of absorption on remitted reflectance can also be specified for sd-SFDI. As an initial guess, the model structure follows from expressions for

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effective photon path length in the sub-diffuse single fiber reflectance
geometry,

$$R_d(f_x, \mu_s', \gamma, \mu_a) = R_d(f_x, \mu_s', \gamma)e^{-\mu_a\langle L\rangle}$$

(2)

$$\langle L\rangle = f_x^{-1}\frac{p_1 C_{PF}}{(\mu_s' f_x^{-1})^{p_2}(p_3 + (\mu_a f_x^{-1})^{p_3})}$$

(3)

Here C_{PF} and p_1-p_3 are fitted coefficients used to capture the
dynamics in attenuation of demodulated reflectance observed in response to
changes in μ_s', f_x^{-1}, γ and μ_a. Model coefficients can be estimated by
minimizing the difference between simulated and model estimated values of
demodulated reflectance. Other expressions than Eq. (2,3) may also be
investigated to describe the effect of attenuation due to absorbing molecules
on the collected signals.

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Claims

1.   A method of obtaining an image of the retinal structure of an eye,
comprising:
 - providing a light source;
 - projecting a plurality of repetitive patterns on the retina by said light
5   source, each pattern having illuminated and non-illuminated portions
      with a spatial frequency larger than $0.33\mu_{tr}$;
 - measuring for each pattern an optical response for the illuminated and
      non-illuminated portions; and
 - deriving a retina tissue absorption value by combining the optical
10   responses from the plurality of phase shifted repetitive patterns of
      illuminated and non-illuminated areas.

2.   A method according to claim 1 wherein said repetitive pattern is
simultaneously provided for a plurality of spectral bands, each having its own
spatial frequency.

15   3.   A method according to claim 1 wherein wherein for the illuminated and
non-illuminated portions a tissue optical transport model is used for
determining the retina tissue absorption value, a retina tissue scattering value
or a retina tissue fluorescence value.

4.   A method according to claim 1, wherein a fluorescence level is measured
20   and a real fluorescence level is derived for illuminated and non-illuminated
areas.

5.   A method according to claim 1, wherein said image is obtained by
projecting said repetitive pattern by a scanning light beam from said light
source derived from a DMD or SLM and using a photodiode or camera as an
25   optical detector.

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6. A method according to claim 1, wherein said patterns are sinusoidal patterns line patterns, dot patterns or concentric patterns.

7. A method according to any of the preceding claims, wherein a scattering coefficient μs is measured as average number of scattering events per unit distance [mm-1]

8. A method according to any of the preceding claims, wherein a phase function is measured as an angular scattering distribution of tissue.

9. A method according to any of the preceding claims, wherein said retinal image is spectrally analysed for chromofores including any of oxygenated or desoxygenated hemoglobin, melanin, bilirubin, beta-carotene, lipids and water.

10. System for imaging the retinal structure of an eye, comprising:
   - a light source and projector, (7) the projector arranged to projecting the light source in a repetitive pattern on the retina thus having illuminated and non-illuminated portions with a spatial frequency larger than $0.33\mu_t$;
   - an optical detector arranged for detecting the projected repetitive pattern of the retina;
   - a processing device arranged to deriving a retina tissue absorption value by combining optical responses measured by the optical detector, from a plurality of phase shifted repetitive patterns of illuminated and non-illuminated areas projected on the retina.
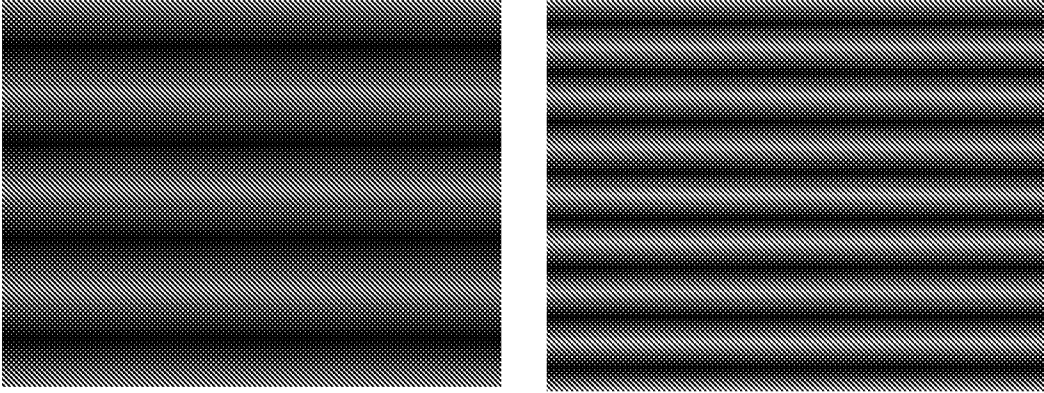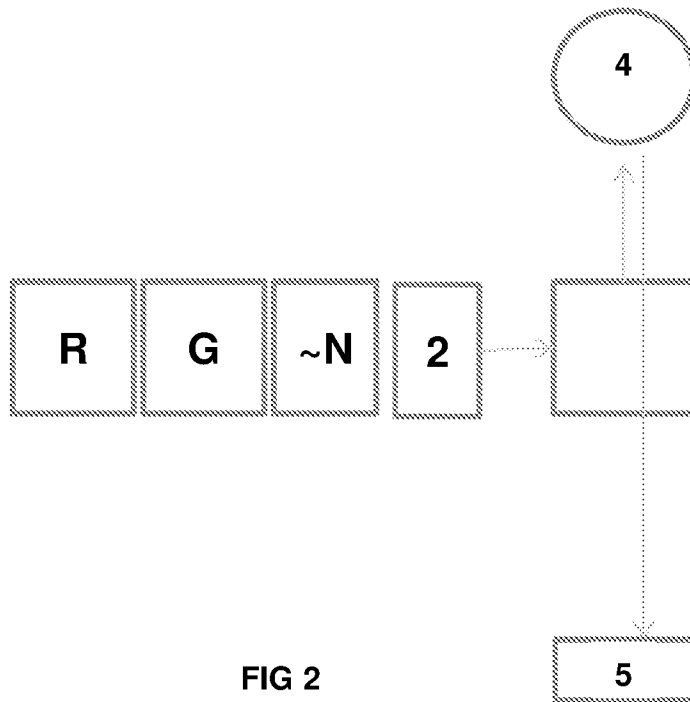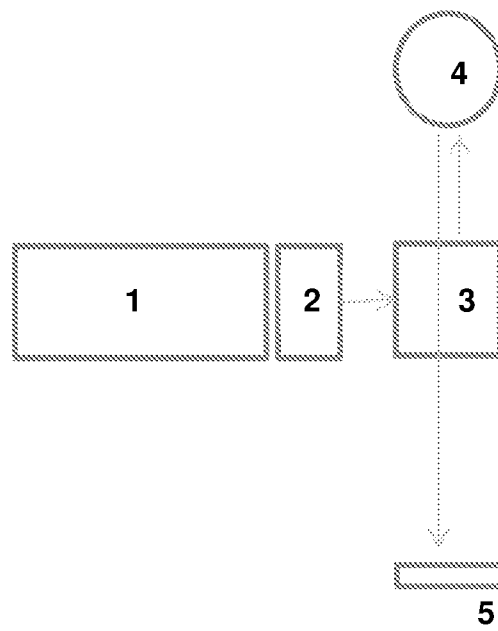
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FIG 1

FIG 2

FIG 3

INTERNATIONAL SEARCH REPORT

	International application No
	PCT/NL2017/050772

A. CLASSIFICATION OF SUBJECT MATTER
INV. 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

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Y	WO 2011/012646 A2 (HOFFMANN LA ROCHE [CH]; DOBOSZ MICHAEL [DE]; SCHEUER WERNER [DE]; STRO) 3 February 2011 (2011-02-03) page 17, line 3 - page 22, line 22	4,8,9

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| [X] | Further documents are listed in the continuation of Box C. | [X] | See patent family annex. |

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Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2018	22/02/2018

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

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International application No
PCT/NL2017/050772

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