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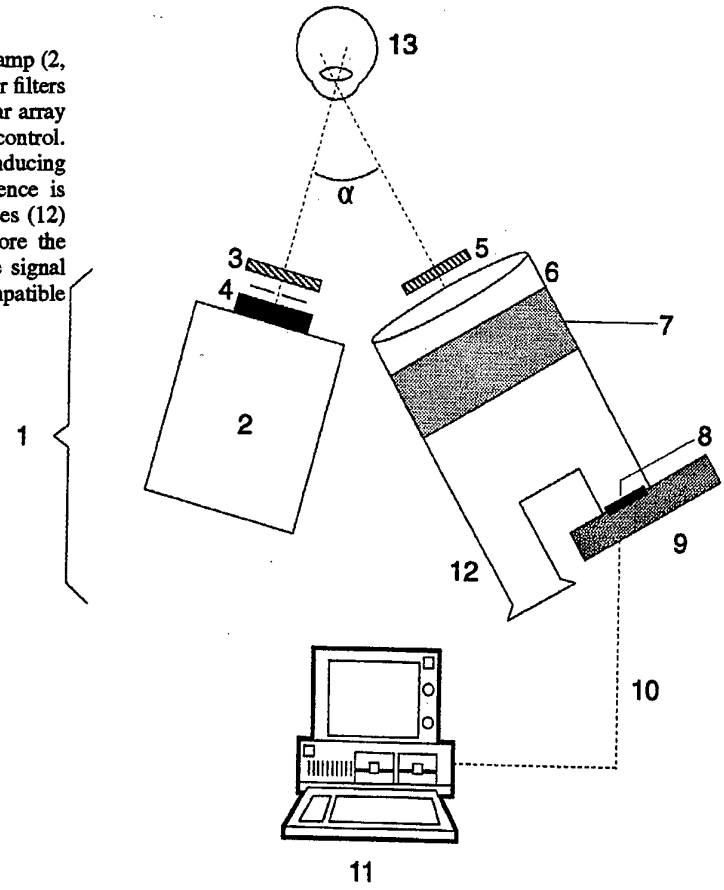
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(54) Title: OCULAR FLUOROMETER

(57) Abstract

The instrument is to be adapted to an ophthalmic slit-lamp (2, 6) and includes holders for fluorescence excitation and barrier filters (3, 5) in the light path and a detector system made of a linear array of photodiodes (8) with respective circuitry for reading and control. The light is focused in a chosen zone of the eye (13) inducing fluorescence by using specific wavelength. The fluorescence is measured by the detector (8) coupled to one of the eyepieces (12) of the slit-lamp (26), or to a beam-splitter (7) placed before the eyepieces (12). There is a system for digitalization of the signal from the detector (8) which is connected to an IBM compatible computer (11) where the data is stored and analysed.



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DESCRIPTION

OCULAR FLUOROMETER

This invent is a new ocular fluorometer.

The instrument is to be adapted to an ophthalmic slit-lamp and includes holders for fluorescence excitation and barrier filters in the light path and a detector system made of a linear array of photodiodes with respective circuitry for reading and control. The ligth is focused in a chosen zone of the eye inducing fluorescence by using specific wavelengths. The fluorescence is measured by the detector coupled to one of the eyepieces of the slit-lamp, or to a beam-splitter placed before the eyepieces.

There is a system for digitalization of the signal from the detector which is connected to an **IBM** compatible computer where the data is stored and analysed.

The instrument has a spatial resolution 50 μ (corresponding to the spacing between the photodiodes) and a sensitivity (lower level of detection) equivalent to the fluorescence of a fluorescein solution of 1 ng/mg. The excellent reproducibility and linearity of the instrument and its design are particularly appropriate for performing the most sophisticated ocular fluorometry measurements in the clinical ophtahlmological practice, including studies of permeability of the blood-retinal barrier.

The present invention regards a new ocular fluorometer. The instrument is based in an ophthalmic slit-lamp using specific pairs of fluorescence excitation

and barrier filters in the light path and a detector system made by a photodiode linear array with respective circuitry for reading and control. The incoming light from the slit is focused in the eye location where it is desired to measure the induced fluorescence. This in turn is measured using a detector system placed in one of the eyepieces of the slit-lamp microscope or using a beam-splitter, the other eyepieces is used for focusing. There is also a system for digitalization of the signal from the detector which is connected to an **IBM** compatible computer where the data is stored and analysed.

DESCRIPTION OF PRIOR ART

Since 1975, when the technique of vitreous fluorophotometry was proposed for the first time, as a method designed to measure low concentrations of fluorescein in the eye, and more specifically, in the vitreous body, different ocular fluorometers have been proposed.

The ocular fluorometers presently available have serious limitations. Among them:

- instrument dedicated optically to posterior segment examination
- fixed angle of measurement
- automatic scanning of the whole axis of the eye
- fixed filter system dedicated only to fluorescein detection

These equipments are described in detail in: Early Breakdown of the Blood-Retinal Barrier in Diabetes, José G. Cunha-Vaz, J.R. Faria de Abreu, António J. Campos and Grabiela M. Figo, British Journal of Ophthalmology, volume 59, nº. 11, pages 649-656, November 1975; - Vitreous Fluorophotometry for clinical research, Ran C. Zeimer, Norman P. Blair, José G. Cunha-Vaz, Arch.

Ophthalmol, vol. 101, pages 1753-1756, November 1983; A Scanning Ocular Spectrofluorophotometer, Jay W. Mclaren and Richard F. Brubaker, Investigative Ophthalmology & Visual Science, vol., 29, n°.8, pages 1285-1292, August 1988.

SUMMARY OF THE INVENTION

The fluorometer here described solves the technical problems referred previously and minimises costs of production. It is an instrument to be adapted to an ophthalmic slit-lamp (a biomicroscope using slit illumination) where excitation and barrier filters have been in the light path and a detector based on an array of photodiodes with respective circuitry for reading and control. The illumination slit is focused in the eye location where the induced fluorescence is to be measured. this measurement is performed by a detector placed in one of the eyepieces of the slit-lamp; the other eyepieces is used for focusing. The equipment includes also a system for digitalization of the signal from the detector which is connected to a **IBM** compatible computer where the data is stored and analysed.

One of the objectives of the invention if the conception of an instrument that is an accessory for adaptation to an ordinary ophthalmic slit-lamp, it is compact and more flexible for examination in various locations in the eye and not dedicated for posterior segment analysis.

Another objective is the possibility of utilisation using different angles of measurement. The instrument proposed is based on another original concept it has a system that allows automatic or manual positioning in selected areas of the eye of major clinical interest, the interfaces cornea/aqueous, aqueous/lens and vitreous/retina, performing electronic scanning in each of these areas.

It is, therefore, possible to obtain with this new system improved resolution and more rapid positioning in the areas of clinical interest.

Another objective of the invent is the possibility of quick changing of filters, both excitation and barrier. Such a device allows for detection of both exogenous and endogenous fluorescence, i.e., autofluorescence of ocular tissues.

This instrument offers also, when compared to the ocular fluorometers available, excellent computational capabilities.

Finally, this invent involves production costs which are calculated as at least four times inferior to available instrumentation.

BRIEF DESCRIPTION DRAWINGS

For information and, therefore, without imposing undue restrictions we include 2 drawings (fig. 1 and fig.2). Figure 1 shows schematically the ocular fluorometer, figure 2 shows the acquisition process block diagram.

DETAILED DESCRIPTION A SELECTED SOLUTION

The invent is a fluorometric accessory to be adapted to an ophthalmic silt-lamp (biomicroscope with slit illumination) which is an equipment that is present in every ophthalmic examination room.

The fluorometric accessory must be coupled and installed without difficulties, must allow the use of the slit-lamp when not in use for ocular fluorometry and must allow fluorometric measurements to be performed with

high precision, reproducibility and liability, competing in is technical performance with the best existing ocular fluorometers available.

The conditions are, therefore:

1st Easy installation of the unit, easy coupling and uncoupling to an ordinary ophthalmic slit-lamp without the need of a specialised technician.

2nd Allow normal use of the slit-lamp when the fluorometric accessory is in place, without major hindrance.

3rd Perform fluorometric measurements at the level of the cornea, anterior chamber, lens, vitreous and retina with the required resolution and liability.

4th Easy interchange and placement of new filter pairs in order to be able to measure exogenous and endogenous fluorophores.

5th Perform fluorometric measurements in a reproducible manner with the sensitivity and linearity at least comparable to instrumentation available in the market.

In order to fulfil these conditions the conception of the instrument took into consideration:

1st - Adaptation to the optical plane of the more distant eyepiece of the binocular system of the slit-lamp.

2nd - No interference with the optical system of the slit-lamp.

3rd - Good resolution, even better than in presently available instrumentation.

A photodiode array with a resolution between detectors of 50 μm was chosen. This corresponds "in vivo" to a resolution of 0,5 mm in the interfaces cornea-aqueous and aqueous-lens. This resolution is obtained using a measurement angle of 45°.

The instrument has the capacity of measuring in various angles, which open its fields of application for specular and light scattering examination of the ocular structures. These different angles may also be keep constant if so desired, in order to maintain measurement reproducibility.

- Successive measurements in the cornea, lens and retina.

The existing alternatives to perform fluorometric measurements in different locations of the eye were based either in the capacity for mechanical automatic scanning along the axis of the eye or isolated measurements in restricted areas of the eye (extent depending on resolution density of photodetectors).

Recognising the limitation associated both with scanning of the entire eye, increasing the duration of the examination and resulting in a variety of artefacts and problems with eye fixation, and with examination of only restricted areas of the eye, we have made an original option based on the average size of the human eye.

Three zones of measurement are chosen: cornea, lens and retina, the eye being approximately 24 mm long. This distance as well as the location of the anterior surfaces of the cornea, lens and retina may be determined experimentally using their specular reflection.

It was possible to develop a mechanical system for positioning by automatic control using three main positions:

Cornea (I), lens (II) and retina (III), after initial positioning of the slit-lamp focusing the anterior surface of the lens. After the initial focusing step on the

Cornea (I), lens (II) and retina (III), after initial positioning of the slit-lamp focusing the anterior surface of the lens. After the initial focusing step on the anterior surface of the lens, the examiner only has to press positioning button I in order to focus in the cornea and by pressing button III it will bring into focus the detection system on the retinal region, changing also in this last situation, the instrumentation angle between incident light and reflecting light angle to 14°, using a contact lens or special 60D lens.

In these conditions it is possible to obtain fluorometric measurements characterised by very good resolution in the areas of principal clinical significance (interfaces cornea-aqueous, aqueous-lens and vitreous-retina).

The fluorescence packs obtained in the recordings performed before administration of any exogenous fluorophore indicate the autofluorescence of the cornea, lens and retina and serve as references when reading the results.

Figure 1 shows the ocular fluorometer composed essentially by a module for excitation, a module for detection, a module for reading and control, a processing module and a computer which are the electronic component of the instrument.

The module of excitation is composed essentially by a slit-lamp with a device to receive appropriate excitation filters.

The electronics of the instruments starts at the detector chip and ends at the computer following the usual block diagram of any data acquisition and control systems:

Transducer

Transducer readout circuit

Transducer driver and control circuit

Analogue to digital conversion

A DSP based PC processor module for data pre-processing and storage and direct control measurements

A computer for general supervision, disk storage and graphical analysis of results.

The photodetector is a solid state Self-Scanning Linear Photodiode Array from Hamamatsu, series S3921/S3924. It offers high performance and good flexibility and all members of the series are pin compatible. Those sensors feature an integrated signal processing circuit providing and output signal with a boxcar waveform thus allowing signal readout with a simple external circuit. Low dark current, large spectral range, good sensitivity and pixel pitch 50 μm (S3921) are some other important characteristics (see Hamamatsu MOS Linear Image Sensors for more technical details).

Driver/Readout circuit. The driver circuit provides all the clock and control signals needed for the sensor to work properly (see technical data from Hamamatsu) with the timing parameters adjusted to the experiment requirements. The main part of this circuit is the software programmable Intel 8254 Timer. The readout circuit includes signal conditioning, amplification and quantification by the **ADC (BURR BROWN AD** 7800). There is a clear interconnection between control and readout as the conversion timing of the **ADC** must be synchronised with sensor driving determining the pulse output frequency and width.

The sensor exposure time is determined by the overall timing of the Driver/Readout circuit.

PC Module. This a **DSP** (Digital Signal Processing) board containing the Texas Instruments **TMS320C25** digital signal processor and specially developed

for this Ocular Fluorometer. It is to be plugged in a free slot of an ordinary **PC** compatible computer and is connected to the detector module (located at the ocular eye end of the slit-lamp) by a 50-way flat cable. It has local memory accessed by both the **TMS** and the **PC** processor. It drives the sensor module and reads the converted data in a "stand alone" mode. It also performs some data pre-processing using some software noise reduction algorithms. An important element of this module is the before referred 8254 Timer programmable by the **PC** but gated by the **TMS** which allows for acquisition timing maximum flexibility- one of the key features of the Instrument.

The Computer is the interface between the user and the system. It gives the user the possibility of defining in a friendly environment some of the measurements parameters. After the acquisition starts, the computer reads the pre processed data and we can follow on the monitor, in real time, the acquisition results and decide whether the data is to be stored on disk for posterior analysis. We can also introduce some correction factors to compensate for eventual non-uniformities and/or non-linearities. Finally the user can utilise the program for post-processing and to analyse data that has been stored on disk.

In fig. 2 the acquisition process block diagram is presented summarising the functions of the instruments and stating which modules are responsible for them.

This description is not intended to be a complete one and some minor modification are possible and may be introduced. This invention should be considered limited to be following requests.

CLAIMS

1ª. - Ocular Fluorometer characterised for being based on an ordinary ophthalmic slit-lamp, including special filter holders for excitation and barrier functions, and an electronic component, including a multiple photodiode detector, reading and a computer that makes general supervision and performs disk storage and graphic analysis of the results.

2ª. - Ocular Fluorometer which has all the characteristics stated in 1. and by being adapted as an accessory to the plane of the eyepiece or to the beam-spliter does not interfere with the optical system of the slit-lamp allowing its simultaneous normal use.

3ª. - Ocular Fluorometer according to the previous claims including also a mechanical device which allows for automated positioning in three main positions of focusing, centred respectively on the anterior surface of the cornea, anterior surface of the lens and retina-vitreous interface; this automated positioning is initiated by an manual focusing step to be performed by the examiner which first focus the slit-lamp on the anterior surface of the lens; after this initial step the examiner has only to press a positioning button (I) which brings automatically into focus the area of the cornea or a positioning button (III) which brings into focus the interface vitreous-retina; to perform measurements in this area the angle of the instrument is changed to 14°, the pupil must be dilated and an accessory lens of 60 D or a plane contact lens must be used.

4ª. - Ocular Fluorometer according to the previous claims and which is characterised by identifying by specular reflection the anterior surfaces of the cornea, lens and retina.

5ª. - Ocular Fluorometer according to the previous claims characterised by having a linear array of photodiodes with respective circuitry for reading and control. The photodiodes detect the excited light from the area in focus, allowing high resolution fluorescence measurements in the areas of major clinical interest, i.e., cornea, aqueous, lens, and vitreous-retina.

6ª. - Ocular Fluorometer according to the previous claims characterised by the detector having an integrated signal processing circuit allowing for readout by a simple external circuit as the video line presents a boxcar waveform with pulse amplitudes proportional to the light exposure.

7ª. - Ocular Fluorometer according to the previous claims characterised by a inner spatial resolution 50 μm corresponding to the pixel pitch and a Lower Level of Detection of 1 ng/ml fluorescein equivalent concentration.

8ª. - Ocular Fluorometer according to the previous claims characterised by a driver/readout circuit that provides the clock and control signal needed for sensor driving with timing parameters adjusted to the experiment requirements which the main part is the software programmable Intel 8254 timer and integrates all the electronics for signal conditioning, amplification and quantification.

9ª. - Ocular Fluorometer according to the previous claims characterised by having a **PC** module based on a Digital Signal Processor (**TI TMS 320C25**) that is to be plugged in a **IBM** compatible free slot that drives the detector module through a 50 - way flat cable and reads the converted data in a "stand alone" mode. It also performs some data pre-processing using software noise reduction algorithms.

AMENDED CLAIMS

[received by the International Bureau on 9 December 1994 (09.12.94); original claims 1-9 replaced by amended claims 1-8 (3 pages)]

1. Ocular Fluorometer characterised for being based on an ordinary ophthalmic slit-lamp, adapted as an accessory to the plane of the eyepiece or to the modified beam-splitter does not interfere with the optical system of the slit-lamp allowing its simultaneous normal use, including special filter holders for excitation and barrier functions, and an electronic component, including a multiple photodiode detector, reading and a computer that makes general supervision and performs disk storage and graphic analysis of the results.

2. Ocular Flurometer according to the previous claim including also a mechanical device which allows for automated positioning in three main positions of focusing, centered respectively on the anterior surface of the cornea, anterior surface of the lens and retina-vitreous interface; this automated positioning is initiated by an manual focusing step to be performed by the examiner which first focus the slit-lamp on the anterior surface of the lens; after this initial step the examiner has only to press a positioning button (I) which brings automatically into focus the area of the cornea or a positioning button (III) which brings into focus the interface vitreous-retina; perform measurements in this area the angle of the instrument is changed to 14°, the pupil must be dilated and an accessory lens of 60 D or a plane contact lens must be used.

3. Ocular Fluorometer according to the previous claims which is characterised by identifying, by specular reflection, the anterior surfaces of the cornea, lens and retina.

4. Ocular Fluorometer according to the previous claims characterised by having a linear array of photodiodes with respective circuitry for reading and

control; this driver/readout circuit provides the clock and control signal needed for sensor driving with timing parameters adjusted to the experiment requirements which the main part is the software programmable Intel 8254 timer and integrates all the electronics for signal conditioning, amplification and quantification; that is controlled by a DSP that maximises the ADC data rate in order to drastically reduce noise; the photodiodes detect the excited light from the area in focus, allowing high resolution fluorescence measurements in the areas of major clinical interest, i.e., cornea, aqueous, lens, and vitreous-retina.

5. Ocular Fluorometer according to the previous claims characterised by a inner spatial resolution 50 mm corresponding to the pixel pitch and a Lower Level of Detection of 1 ng/ml fluorescein equivalent concentration.

6. Ocular Fluorometer according to the previous claims characterised by having a PC module based on a Digital Signal Processor (TI TMS 320C25) and with local memory that is to be plugged in a IBM compatible free slot that drives the detector module through a 50 - way flat cable and reads the converted data in a "stand alone" mode; it also performs some data pre-processing using software noise reduction algorithms and assures an efficient connection to the host computer for measurement supervision, data storage and analysis and graphical friendly interface with the user.

7. Ocular Fluorometer accordind to the previous claims characterised by being based on the articulated action of two programs running simultaneously, one at the host PC level and the other at the DSP module.

8. Ocular Fluorometer according to the previous claims characterised by allowing for photodiode array rotation to act as both spot and sccaning fluorometer, a feature that is particularly important in the anterior chamber.

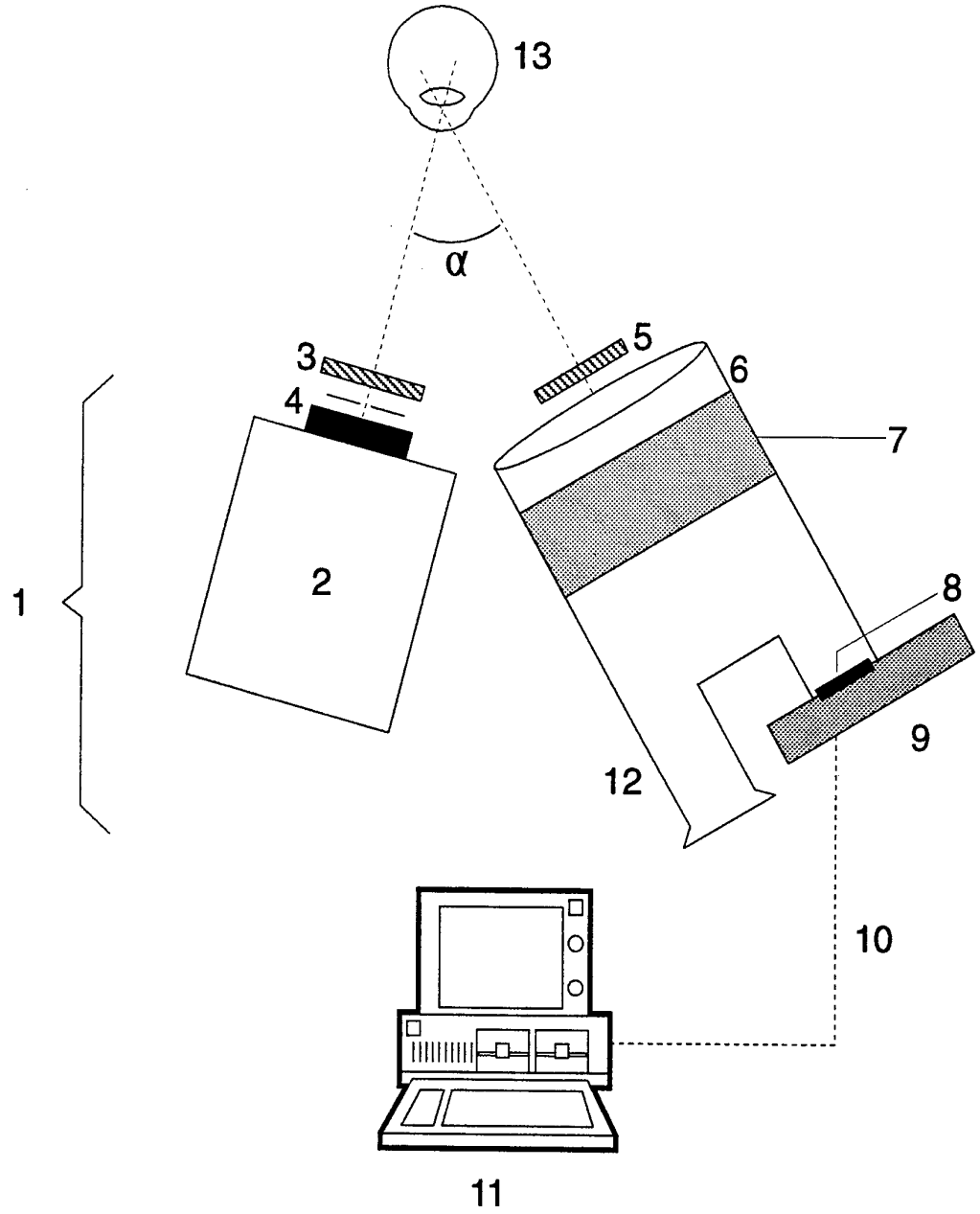


FIG. 1

ACQUISITION PROCESS BLOCK DIAGRAM

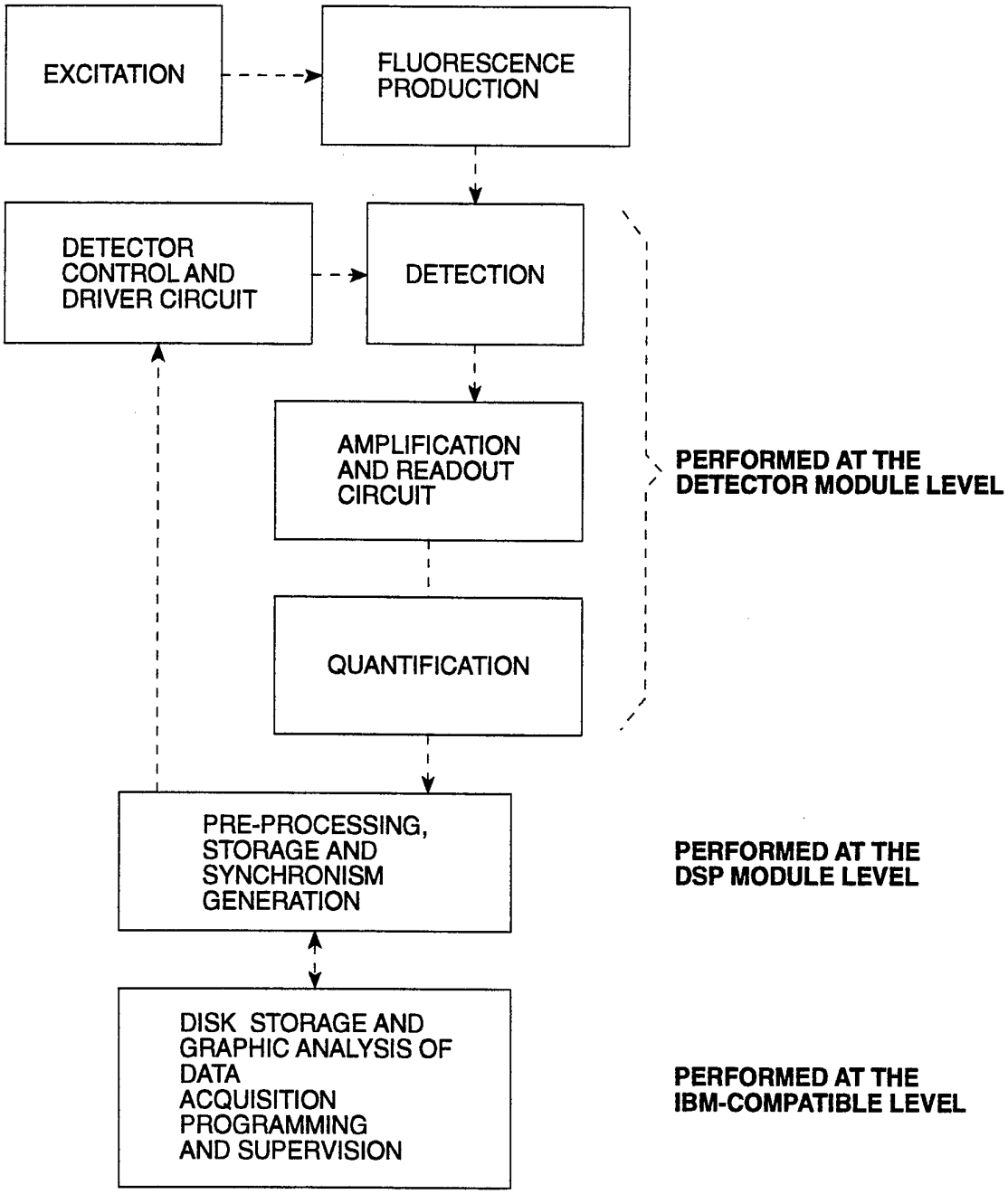


FIG. 2

INTERNATIONAL SEARCH REPORT

Int. al Application No
PCT/PT 94/00005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61B3/12 A61B3/135

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)
IPC 5 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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,31 17 699 (METRICON LTD.) 28 October 1982 see page 15, line 5 - page 19, line 3 see page 26, line 4 - page 29, line 10	1,2,5,6,8
A	see page 31, line 23 - page 35, line 25	4
A	ARCHIVES OF OPHTHALMOLOGY, vol.101, no.11, November 1983 pages 1753 - 1756 R.C. ZEIMER ET AL. 'Vitreous Fluorophotometry for Clinical Research' cited in the application see page 1753 - page 1754; figures 1,2	1,3,4,8
A	WO,A,93 05699 (ALLERGAN, INC.) 1 April 1993 see page 7, line 25 - page 9, line 21	1,2

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

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1994	05. 10. 94

Name and mailing address of the ISA	Authorized officer
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I nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 512 518 (NIKON CORP.) 11 November 1992 see column 2, line 40 - column 4, line 15; figure 2.	1-3
A	INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol.29, no.8, August 1988 pages 1285 - 1293 J.W. MC LAREN ET AL. 'A Scanning Ocular Spectrofluorophotometer' cited in the application see page 1285 - page 1287; figures 1,2	1,3,8
P,A	WO,A,93 20743 (ALCON SURGICAL, INC.) 28 October 1993 see page 5, line 30 - page 8, line 19	3-5,8,9

INTERNATIONAL SEARCH REPORT

nal Application No
PCT/PT 94/00005

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