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(54) Title: MULTIPLE FIBER PROBE FOR LASER INDUCED SPECTROSCOPY

(57) Abstract: A multi-fiber probe (300) for Laser Induced Fluorescence spectroscopy to test biological tissue is described. The probe comprises a source optical fiber (313) through which the tissue to be tested is irradiated with laser radiation. Laser Induced Fluorescence is focused, by a lens (329) in the probe, on the end face (318) of a receiving optical fiber (315) of the probe. The fluorescence is analyzed to determine if its spectrum has peaks characteristic of the fluorescence of NADH and collagen. If the spectrum does not have the peak corresponding to collagen, the tissue under test is deemed to be not normal. The lens whose axial position in the probe or its focal length may be controlled such that the fluorescence from different depths of the tissue is focused on the receiving fiber is used to test the tissue comprehensively. The lens may be formed by a fluid lens. A system (500) using the disclosed probe and a method for testing tissue are also disclosed.

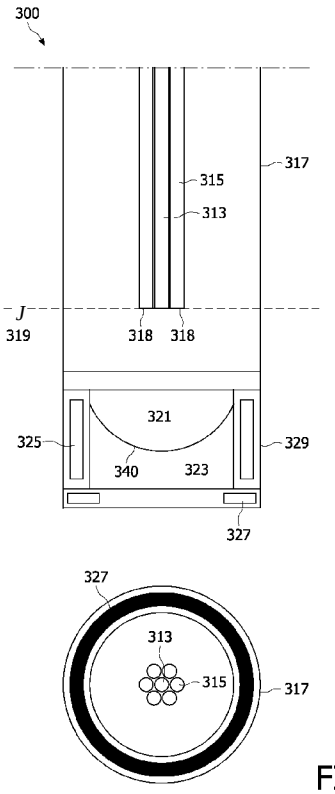

FIG. 3

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Multiple fiber probe for laser induced spectroscopy

FIELD OF THE INVENTION

The following belongs to the field of pathology using Laser Induced Fluorescence (LIF) Spectroscopy, in particular histopathology using Laser Induced Fluorescence (LIF) Spectroscopy.

BACKGROUND OF THE INVENTION

The principle involved in Laser Induced Fluorescence (LIF) Spectroscopy based histopathology is as follows. A tissue to be tested is irradiated with a laser radiation. Molecules in the tissue absorb the radiation and their energy level is increased. After a certain time, the molecules return to their previous energy state by re-emitting the absorbed energy either as thermal radiation or as light. Some compounds re-emit the energy as light radiation and this phenomenon is known as fluorescence. The wavelength of the re-emitted energy is different from the wavelength of the absorbed radiation. The wavelength of the energy re-emitted depends on the chemical compound that is re-emitting or fluorescing. Thus, when the spectrum of the re-emitted radiation is analyzed, the presence or absence of various compounds can be ascertained.

LIF Spectroscopy may be used to test a tissue to determine if it is normal or not normal. In particular, LIF Spectroscopy offers a convenient method of testing epithelial tissues in a non-invasive or minimally invasive manner since these tissues are often accessible without a surgical incision. However, with suitable modifications, the invention could also be used for testing endothelial tissues.

To carry out LIF Spectroscopy on a tissue, a probe is used, through which the tissue is irradiated and the resultant fluorescence is received for analysis. Known probes contain an optical fiber, called a source optical fiber, for irradiating the tissue under test with laser radiation. Near or around the source optical fiber are other optical fibers, called receiving optical fibers, for collecting the fluorescence induced in the tissue by the laser radiation for analysis. Such a probe, containing more than one optical fiber, is called a multi-fiber or multiple-fiber probe.

The publication "Multiple-Fiber Probe Design for Fluorescence Spectroscopy in Tissue" by T. Joshua Pfefer et al, Applied Optics, Vol. 41, No. 22, 1 August, 2002, describes such a probe. The publication provides theoretical evidence that probe design strongly affects tissue interrogation. Therefore, application-specific customization of probe design may lead to improvements in the efficacy of fluorescence-based diagnostic devices.

In the case of epithelial tissue, the thickness of the outermost keratinous layer varies considerably. In the case of the tongue - which is covered by an epithelial tissue - for example, the thickness of the white coating on it varies from person to person and in the same person from time to time.

SUMMARY OF THE INVENTION

Probes with different dimensional details are, hence, needed for testing a tissue comprehensively i.e. for collecting the fluorescence from different depths of the tissue for analysis. Thus, an improved optical fiber probe for carrying out LIF Spectroscopy is provided herein.

Such a probe finds application in detection of carcinomas of epithelial and endothelial tissues. Examples of epithelial tissues other than the tongue are mammalian skin - a dry, keratinized, stratified epithelial tissue and the lining of the oral cavity - an unkeratinized, stratified epithelial tissue. Further examples of epithelial and endothelial tissues are blood vessels (circulatory system), oesophagus and stomach (digestive system), cervix (female reproductive system), larynx (respiratory system), cornea (sensory system), urinary bladder (urinary system).

A fiber optic probe for Laser Induced Fluorescence Spectroscopy comprising a source optical fiber for irradiating a tissue with a laser radiation, a receiving optical fiber for receiving at its end face, a fluorescence induced in the tissue by the laser radiation, and a lens unit for varying a position of a plane of focus with reference to the end face, for focusing the fluorescence substantially from the plane of focus on the end face.

In the following description, the words above, below and depth are used. This is with the assumption that the surface of the tissue to be tested is positioned horizontally for the sake of ease of description. With suitable replacements of these descriptive words, the descriptions apply in whichever orientation the tissue is positioned.

By setting the plane of focus to a certain depth in the tissue, the fluorescence from a small volume of tissue on both sides of the plane of focus is focused on the end face of the receiving optical fibers. With this, the fluorescence from that volume of tissue on both

sides of the plane of focus can be analyzed. By setting the distance between any two consecutive positions of the plane of focus such that there is an overlap of the said small volumes of tissue between the planes of focus, the fluorescence from throughout the thickness of the tissue is tested, once the plane of focus has been incremented through the entire thickness of the tissue and the fluorescence from each position of the plane of focus has been analyzed.

The expression "plane of focus" is used herein to mean an imaginary plane the points on which are in focus in a real image formed by a lens on a plane surface. Conversely, none of the other points in the three dimensional space around the plane of focus is in focus in the real image formed by the lens. The plane surface on which the real image is formed is referred to as the "focal plane".

The disclosed probe provides an advantage that once the probe is placed on the surface of the tissue under test, it need not be replaced during the complete test.

In one embodiment, the lens is a fluid lens whose focal length can be varied. Such fluid lenses are known per se. The United States patent document US 7,126,903 B2 discloses a fluid lens with variable focal length. The focal length of such a fluid lens can be varied by applying suitable control voltages between its electrodes.

An advantage of the use of a fluid lens whose focal length can be varied is that the position of the plane of focus can be varied without any mechanical movement of the lens relative to the other parts of the probe.

Another embodiment includes a lens with a fixed focal length in addition to a fluid lens. With this arrangement, the focal length of the combination of lenses varies in a known way when the focal length of the fluid lens is varied. This arrangement has the advantage that it provides a designer flexibility in designing lens systems for varying the position of the plane of focus.

Another embodiment includes a lens with a fixed focal length, and a mechanism for varying its axial position. In this embodiment the axial position of the lens is varied such that the position of the plane of focus is varied.

Mechanisms suitable for varying the axial position of the lens include a rack and pinion arrangement, re-circulating ball screws or linear motors, to name a few.

Various combinations of fixed lenses with fixed focal lengths, movable lenses with fixed focal lengths or fluid lenses with variable focal lengths could be used for varying the position of the plane of focus. A multi-fiber probe using any such combination for varying the position of the plane of focus is deemed to be within the scope of this invention.

Further, a system for testing a tissue is provided herein. The system uses a multi-fiber probe according to the invention and comprises, a source of laser radiation for irradiating a tissue through a source optical fiber of the probe, an analyzer for analyzing a fluorescence received through the receiving optical fiber of the probe for obtaining the fluorescence spectrum, an evaluation unit for evaluating the spectrum, a decision unit for deciding on an action to be taken, the decision depending on a result of the evaluation of the spectrum, a control unit for controlling a position of a plane of focus based on the decision of the decision unit and a user interface (UI) to convey an information about the decision to a user.

A method of testing a tissue using a probe is hereby provided, the method comprising a step of irradiating a tissue with a laser radiation, a step of receiving, at an end face of a receiving optical fiber, a fluorescence induced in the tissue by the laser radiation and a control step of varying a position of a plane of focus for focusing the fluorescence on the end face of the receiving optical fiber.

Still further, a method of testing a tissue using a multi-fiber probe is provided. A method of testing a tissue using a system described above, comprising the steps of placing a multi-fiber probe on a tissue, a step of positioning a plane of focus at a first predetermined depth, a step of irradiating a tissue with a laser radiation, a step of analyzing a fluorescence received from the tissue and obtaining its fluorescence spectrum, a step of evaluating the spectrum, controlling the position of the plane of focus based on the evaluation, a step of comparing the position of the plane of focus with a second predetermined depth, a step of displaying a result of the test based either on the result of the evaluating step or of the step of comparing the position of the plane of focus.

An advantage of this method of testing the tissue is that the decision that the tissue is not normal is reached only after the tissue is tested at all depths and hence avoids any false decisions. However the decision that the tissue is normal can be reached at any position of the plane of focus at which the fluorescence spectrum substantially matches with the spectrum of fluorescence from normal tissue. This leads to shorter testing times when the tissue under test is a normal tissue.

A computer program is also hereby provided for testing a tissue using the disclosed system. The computer program comprises instructions for initiating a laser to irradiate a tissue, controlling the position of the plane of focus for focusing the fluorescence from the tissue on the end face of a receiving optical fiber, analyzing the fluorescence

focused on the end face of the receiving optical fiber and obtaining the fluorescence spectrum, evaluating the spectrum and displaying the result of the test.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other aspects will be described in detail hereinafter, by way of example, on the basis of the following embodiments, with reference to the accompanying drawings, wherein:

Fig. 1 is a diagram of an epithelial or endothelial tissue

Fig. 2 is a diagram of a fluorescence spectrum from a normal tissue

Fig. 3 is a diagram of a multi-fiber probe according to an embodiment of the invention

Fig. 4 is a diagram of a multi-fiber probe, according to an embodiment of the invention, in use

Fig. 5 is a diagram of a system using a multi-fiber probe according to the invention

Fig. 6 is a representation of the method of use of a multi-fiber probe according to the invention

DETAILED DESCRIPTION OF EMBODIMENTS

A tissue, as depicted in Fig. 1 (not drawn to scale) consists of three layers - a keratinous layer 101 which is the outermost layer, a cellular layer 103 containing epithelial cells, below the outermost layer 101 and a basement (or basal) layer 105 below the cellular layer 103. Below the basement layer is the connective tissue 107, which is not a part of the tissue. In normal tissue, the cellular layer 103 contains, among other things, Hydrogenated Nicotinamide Adenine Dinucleotide (NADH) and the basement layer 105 contains, among other things, Collagen.

Fig. 2 is an exemplary fluorescence spectrum of a normal tissue, with the wavelength (λ) on a first axis and the intensity of the fluorescence on a second axis perpendicular to the first axis. As shown in Fig. 2, the fluorescence spectrum of normal tissue has two peaks, 209 and 211, corresponding to the fluorescence of collagen and the fluorescence of NADH respectively.

It has been found that in cancerous tissue, the basement layer is deficient. Thus, the fluorescence spectrum of cancerous tissue does not have a peak corresponding to the fluorescence of collagen. In other words, a fluorescence spectrum of a tissue that does not

have a peak at the wavelength at which collagen fluoresces may be deemed to be cancerous or, in general, not normal.

Fig. 3 is a diagram of a probe 300 (not drawn to scale) according to an exemplary embodiment of the disclosed probe. A source optical fiber 313 and receiving optical fibers 315 are housed in an outer cover 317. The probe further contains a fluid lens 329 with a variable focal length. The fluid lens contains two immiscible liquids 321 and 323 with a meniscus 340 between them. The fluid lens is surrounded by an electrode 325 and has another electrode 327 at one end of the lens. By applying a suitable voltage across the two electrodes the focal length of the fluid lens can be set to a desired value.

In Fig. 3, a single source optical fiber 313 and six receiving optical fibers 315 have been shown. This is an exemplary construction and is not the only way to arrange the optical fibers. Many other arrangements are possible in which the variables could be the diameter of the source optical fiber, the number of source optical fibers, the diameter of the receiving optical fibers, the number of receiving optical fibers, the arrangement of the end faces of the fibers and such other parameters. It is also conceivable that a single fiber could be used for both irradiating the tissue and receiving the fluorescence.

Fluid lenses with variable focal lengths are well known and the Fig. 3 and the corresponding description are provided to facilitate an understanding of the disclosed probe and are in no way limiting to the scope of the present invention.

Fig. 4 is a diagram of an exemplary probe according to an embodiment of the invention. When the focal length of the fluid lens 329 is varied, the position of the plane of focus 431 is varied. In other words, the fluorescence from the points on the plane represented by 431 is made to focus substantially on the focal plane 319. The focal plane 319 is substantially the plane formed by the end faces of the receiving optical fibers 315. Even though the fluorescence that is focused on the focal plane is predominantly from the tissue lying on the plane of focus 431, the fluorescence reaching the focal plane 319 is from a volume of the tissue surrounding the plane of focus 431. This volume is shown exemplarily by the broken line 433.

By changing the position of the plane of focus, shown in the diagram exemplarily as 43Γ, the fluorescence from the tissue shown by dotted line 433' is made to reach the focal plane 319. It is to be noted that there is an overlap - the hatched portion 435 - of the volume of tissue between the two consecutive positions of the plane of focus. By incrementing the plane of focus in this manner, it can be ensured that the fluorescence from all depths of the tissue is received and analyzed.

Fig. 5 is a diagram of a system for testing a tissue, using a probe according to an embodiment of the device described herein. The system shown generally as 500 has a control part 537, an interconnection part 539 and a probe 300. The control part comprises a source of laser 541, an analyzer 543, an evaluation unit 545, a decision unit 547, a control unit 548 and a user interface 549. The interconnection part 539 carries, among other things, the conductors for controlling the focal length or the position of the lens 329 of the probe 300 and optical fiber interconnections between the control part 537 and the multi-fiber probe 300. In the following description, the probe end of the fibers is referred to as the proximal end and the control part end of the fibers is referred to as the distal end of the fibers.

The source of laser radiation 541 produces a laser radiation, preferably with a wavelength in the range invisible to humans. In particular, the laser radiation could be in the Ultraviolet (UV) range e.g. in the range of wavelengths between 290 nm and 351 nm, of the spectrum. The laser radiation is optically coupled to the distal end of the source optical fiber. The laser radiation travels through the source optical fiber in the interconnection part 539 and emerges from the proximal end of the source optical fiber in the probe. When the probe is placed on the tissue, the laser radiation irradiates the tissue. As explained with reference to Fig. 4, the fluorescence induced by the laser radiation in the tissue is focused on the proximal end of the receiving optical fibers. The received fluorescence travels to the distal end through the interconnection part 539. The fluorescence is analyzed by the analyzer 543. The result of the analysis is a fluorescence spectrum. The analyzer 543 measures and plots or tabulates the intensity of the fluorescence at various wavelengths. Even though, normally, a spectrum is depicted as a two dimensional graph with wavelengths represented on a first axis and the intensities of radiation represented by a second axis orthogonal to the first axis, it could take many other forms in practice. It could be in the form of matrices or tables or histograms, for instance.

This fluorescence spectrum is evaluated by the evaluation unit 545, by comparing it with a reference spectrum, for example, to determine if the spectrum has peaks at the wavelengths at which collagen and NADH fluoresce. Based on the result of the evaluation, the decision unit 547 either causes a UI 549 to convey to the user that the test is complete and the tissue is normal or decides to continue the test.

If the evaluation unit 545 finds that the spectrum of the received fluorescence has peaks corresponding to the fluorescence of collagen and NADH the decision unit 547 stops further testing and causes the UI 549 to convey to the user that the tissue under test is normal and that the test is concluded. If the evaluation unit 545, finds that the fluorescence

spectrum, with the position of the plane of focus at a certain depth in the tissue, does not have the peaks at the wavelengths at which collagen and NADH fluoresce, the decision unit 547 commands the control unit 548 to change the position of the plane of focus to a subsequent depth in the tissue. This process continues iteratively. The aim of this iteration is to ensure that the fluorescence from all depths of the tissue is tested. The final depth at which the fluorescence is analyzed could result in either the decision that the tissue is normal or that the tissue is not normal. Then the decision unit 547 causes the UI 549 to convey the result to the user and ends the tests.

The terms 'analyzer', 'evaluation unit', 'decision unit', 'control unit' and 'control part' are used herein to describe the units carrying out various functions to be carried out. They could be based on a microprocessor (μP) or microcontroller (μC) or a Digital Signal Processor (DSP) or an Application Specific Integrated Circuit (ASIC) or any other generic device or a dedicated device configured to carry out the tasks mentioned. Further, the term 'configured' as used here is meant in the sense that the controller could be hardwired or software driven or a combination of the two. Still further, even though the analyzer 543, evaluation unit 545, decision unit 547 and the control unit 548 are shown in the figure as separate blocks, physically they could reside in a common controller or be separate. The different blocks are enumerated only for describing the different functions or operations or tasks that are to be executed and not to imply that they reside in physically different blocks or units.

An advantage of the system described above is that the tissue is tested with a single probe and once placed on the tissue under test, it needs to be removed only when the test is complete. Further, with the system described above, the test is automatic and needs no human intervention, other than placing the probe on the tissue and removing it when the test is complete. However, this could also be automated, for example, with a robot. Another advantage is that the tests done with the system are reliable since the tissue is tested with the plane of focus at various depths in the tissue such that the total volume of the tissue below the probe is tested, before declaring that it is not normal. However, a single instance of the spectrum of the received fluorescence substantially matching with the fluorescence spectrum of normal tissue is sufficient to declare that the tissue is normal.

Fig. 6 shows a representation of a method of testing a tissue, using a probe disclosed herein.

In a placement step 651, the probe is placed on the tissue to be tested. The term placing, in this context, means placing the tip of the probe on the tissue to be tested such

that the probe is substantially perpendicular to the surface of the tissue, for example, as shown in Fig. 4. This step is typically carried out by a person, say a pathologist but, may also be automated, say by using a robot.

In an initial positioning step 653, the lens in the probe is controlled and the plane of focus is set to an initial position. The depth of the initial position is referred to as the first predetermined depth. This could be the smallest depth in the tissue or the largest. The smallest depth is chosen such that the plane of focus is in the keratinous layer. The largest depth may be chosen such that it is at the junction between the basement layer and the connective tissue below it or even in the connective tissue itself. When one of these depths is chosen as the initial position of the plane of focus, the other is referred to as the second predetermined depth.

In an irradiation step 655 the tissue is irradiated with a laser radiation, which induces fluorescence in the tissue. The fluorescence is generated throughout the depth of the tissue and a part of it is radiated towards the probe. However, when the plane of focus is set to a certain depth, the fluorescence that is focused on the end faces of the receiving optical fibers is predominantly from a volume of tissue on either side of the plane of focus, as explained with reference to Fig. 4.

In an analysis step 657 the fluorescence is analyzed and its spectrum obtained.

In an evaluation step 659, the fluorescence spectrum is either compared to a reference spectrum obtained from normal tissue or the spectrum is evaluated to determine if it has the characteristics of a spectrum from a normal tissue or not. If the characteristics of the spectrum matches with the characteristics of the fluorescence from a normal tissue or has peaks at the said wavelengths (Fig. 2), the tissue is deemed to be normal. This is conveyed to the user, through a suitable interface, in a "normal tissue" display step 661. In an end of test step 669, testing is ended.

If the tissue is deemed "not normal" at a position of the plane of focus, the position of the plane of focus is changed in a control step 663. The position of the plane of focus is changed by a predetermined distance towards the second predetermined depth. As explained before with reference to Fig. 4, the position of the plane of focus is so changed that there is an overlap in the volumes surrounding the tissue from which the fluorescence reaches the focal plane.

In a comparison step 665, the position of the plane of focus is compared with the second predetermined depth. If the position of the plane of focus has been set to the

second predetermined depth, the tissue is classified as not normal. This is conveyed to the user in a "not normal" display step 667 and the process of testing is ended in step 669.

If the plane of focus has not reached the second predetermined depth, the irradiation step 655, the analysis step 657 and the evaluation step 659 are repeated and the further processes follow as described earlier.

It is to be noted that the method as described here is an exemplary one and is only one of the ways of testing the tissue. The aim of the method is to set the plane of focus at various depths within the tissue and analyze the fluorescence received by the receiving optical fibers to decide if the tissue is normal or not normal and to ensure that the tissue is finally declared as not normal only after the tissue has been tested such that the fluorescence from all depths of the tissue has been analyzed. The tissue may be declared normal, if found so, at any depth of the plane of focus. Variations to the method can be thought of by a person skilled in the art to suit various needs or restrictions.

While the embodiments have been described in detail in the drawings and description, such drawings and description are to be considered exemplary and not restrictive; the invention is not limited to the disclosed embodiments.

For example, it is possible to operate the invention in an embodiment wherein the laser radiation from the source optical fiber does not pass through the lens and only the fluorescence from the tissue passes through the lens. It is also possible that there are more source optical fibers than one. Similarly, in the disclosed method of testing the tissue, the use of a first predetermined depth and a second predetermined depth is not essential. The method can be practiced with the initial position of the plane of focus set to any depth in the tissue. But it is to be ensured that the fluorescence from various depths is analyzed and that the tissue is tested comprehensively.

Other variations to the disclosed embodiments can be understood and effected by those skilled in the art, in practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims. In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality. A single processor or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. A computer program may be stored or distributed on a suitable medium, such as an optical storage medium or a solid-state medium supplied together with or as part of other hardware, but may also be distributed in other forms, such as via the Internet or other wired or wireless

telecommunication systems. Any reference signs in the claims should not be construed as limiting the scope.

CLAIMS:

1. A fiber optic probe (300) for Laser Induced Fluorescence Spectroscopy, comprising:

a source optical fiber (313) for irradiating a tissue with a laser radiation;

a receiving optical fiber (315) for receiving at its end face (318) a fluorescence induced in the tissue by the laser radiation; and

a lens unit (329) for varying a position of a plane of focus (431, 43Γ) with reference to the end face, for focusing the fluorescence substantially from the plane of focus (431, 431') on the end face (318).

2. A fiber optic probe (300) according to claim 1, wherein the lens unit includes a fluid lens (329) with a variable focal length.

3. A fiber optic probe (300) according to claim 1, wherein the lens unit includes a lens and a means for varying its position in the probe.

4. A fiber optic probe according to claim 1 comprising an additional stationary lens with a fixed focal length, for aiding the varying the position of the plane of focus.

5. A system (500) for testing a tissue using a fiber optic probe (300) according to claim 1, the system comprising;

a source of laser radiation (541) for irradiating the tissue through the source optical fiber (313) of the probe;

an analyzer (543) for analyzing a fluorescence, received through the receiving optical fiber (315) of the probe, for obtaining a fluorescence spectrum;

an evaluation unit (545) for evaluating the spectrum,

a decision unit (547) for deciding on an action to be taken, depending on a result of the evaluation of the spectrum;

a control unit (548) for controlling a position of the plane of focus (431, 43Γ) based on the decision of the decision unit (547); and

a user interface (549) to convey an information about the decision to a user.

6. A system according to claim 5, wherein the wavelength of the laser radiation is in the ultraviolet band.

7. A method of testing a tissue using a probe (300) according to claim 1, comprising;

an irradiation step (655) of irradiating the tissue with a laser radiation;

a receiving step of receiving, at an end face of a receiving optical fiber, a fluorescence induced in the tissue by the laser radiation; and

a control step of varying a position of a plane of focus for focusing the fluorescence on the end face of the receiving optical fiber.

8. The method of testing a tissue claim 7, using a system according to claim 5, the method comprising the steps of;

a placement step (651) of placing an optic fiber probe on the tissue under test;

an initial positioning step (653) of controlling the position of the plane of focus to a first predetermined depth;

an analysis step (657) of analyzing the fluorescence received from the tissue and obtaining a fluorescence spectrum;

an evaluation step (659) of evaluating the fluorescence spectrum;

a comparison step (665) of comparing the position of the plane of focus with a second predetermined depth;

either a normal tissue display step (661) of displaying a result of the test or a not normal tissue display step (667) of displaying an alternative result of the test; and

an end of test step (669).

9. The method according to claim 8, wherein the testing is terminated after a single instance of evaluating the spectrum.

10. A computer program for operating a system (500) according to Claim 5, for testing a tissue, the computer program comprising instructions for:

initiating a laser to irradiate a tissue; and

controlling a position of a plane of focus for focusing the fluorescence from a tissue on an end face of a receiving optical fiber.

analyzing the fluorescence focused on the end face of a receiving optical fiber and obtaining a fluorescence spectrum;

evaluating a spectrum; and

displaying a result of the test.

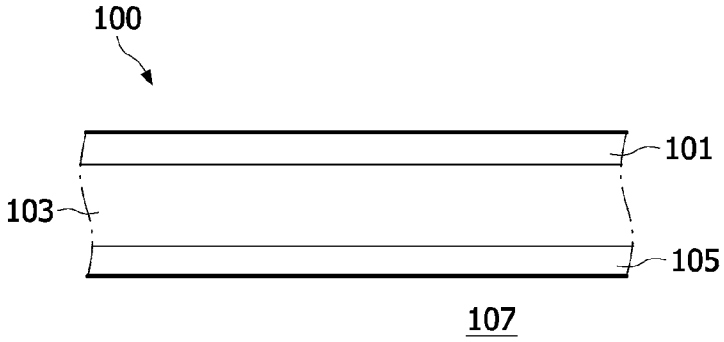

FIG. 1

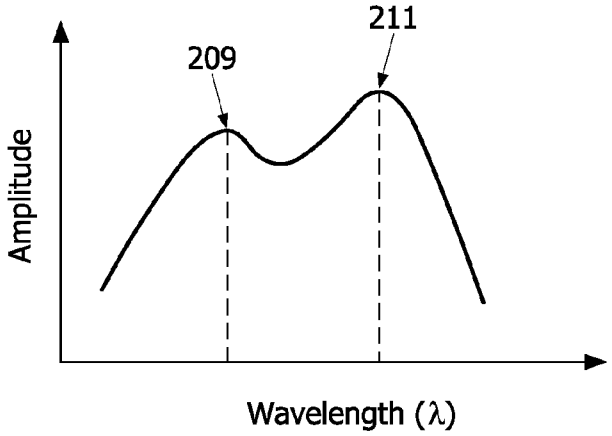

FIG. 2

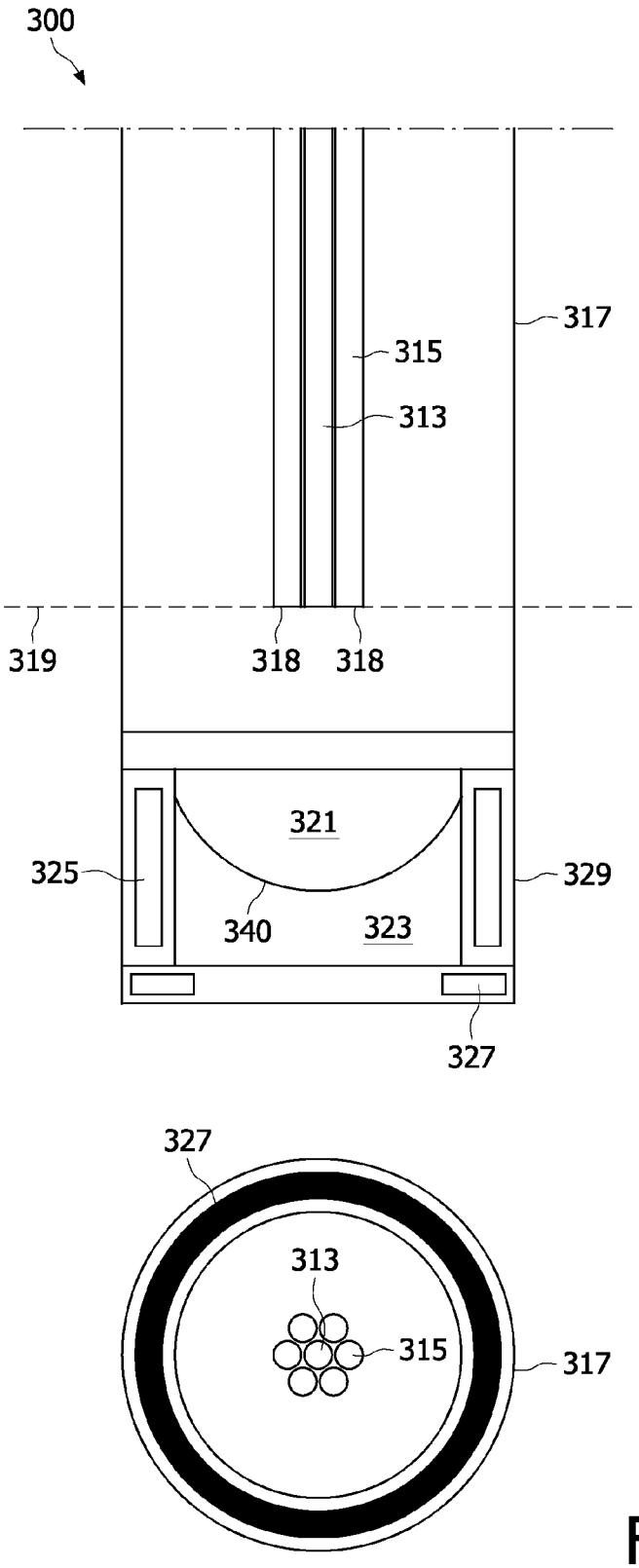
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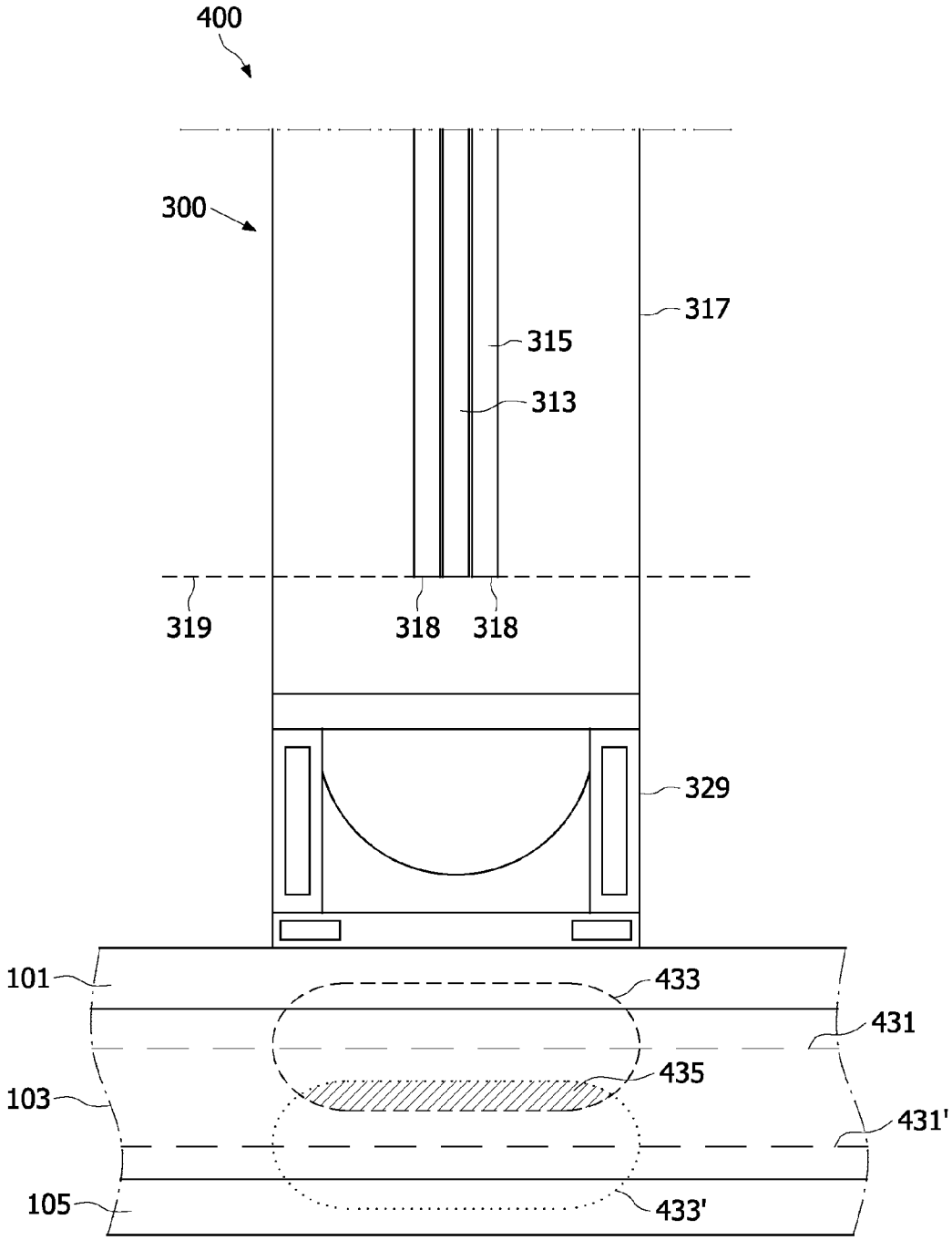
FIG. 3


400
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318
329
101
433
431
435
103
431'
105
433'

FIG. 4

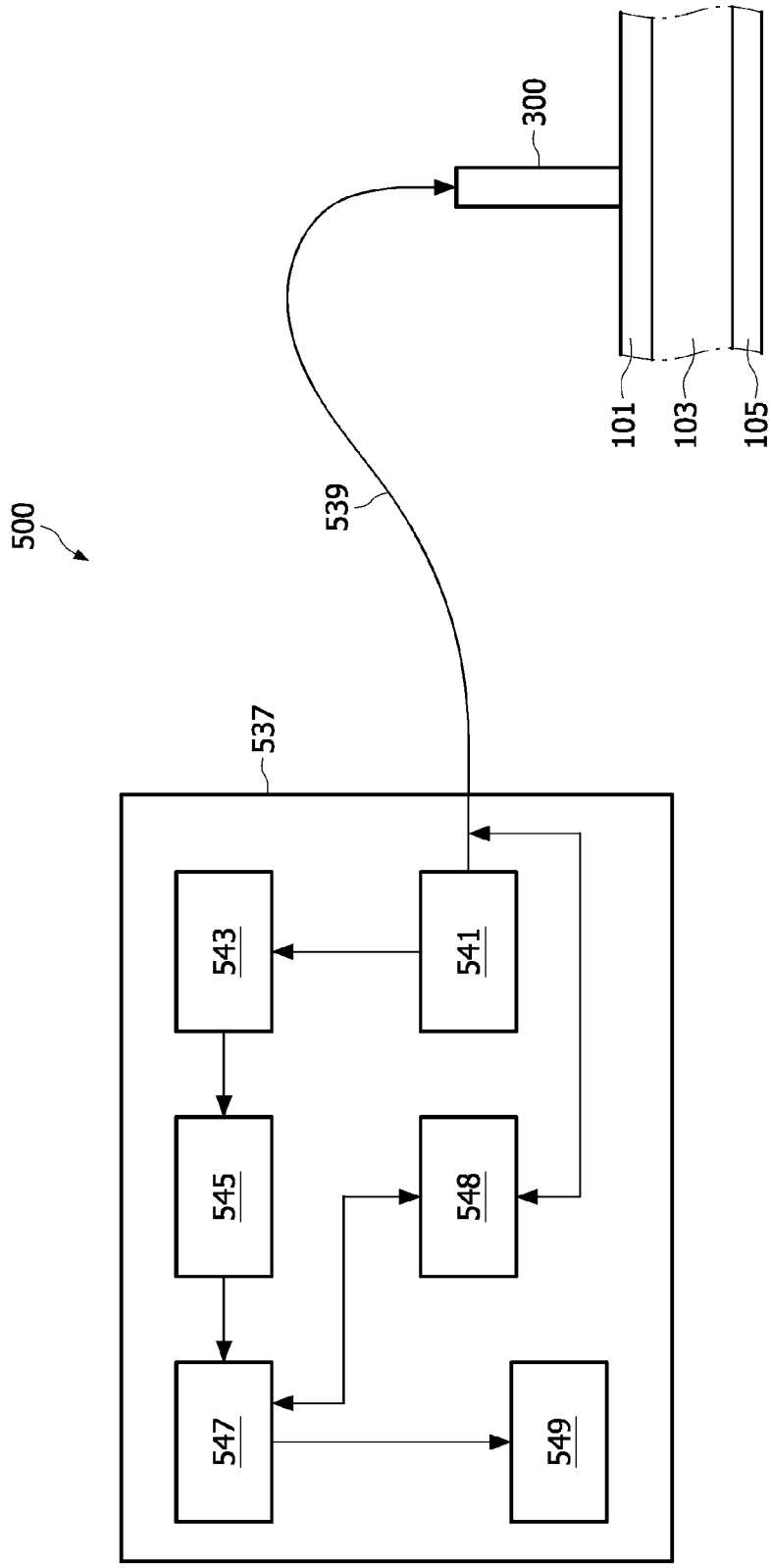

FIG. 5

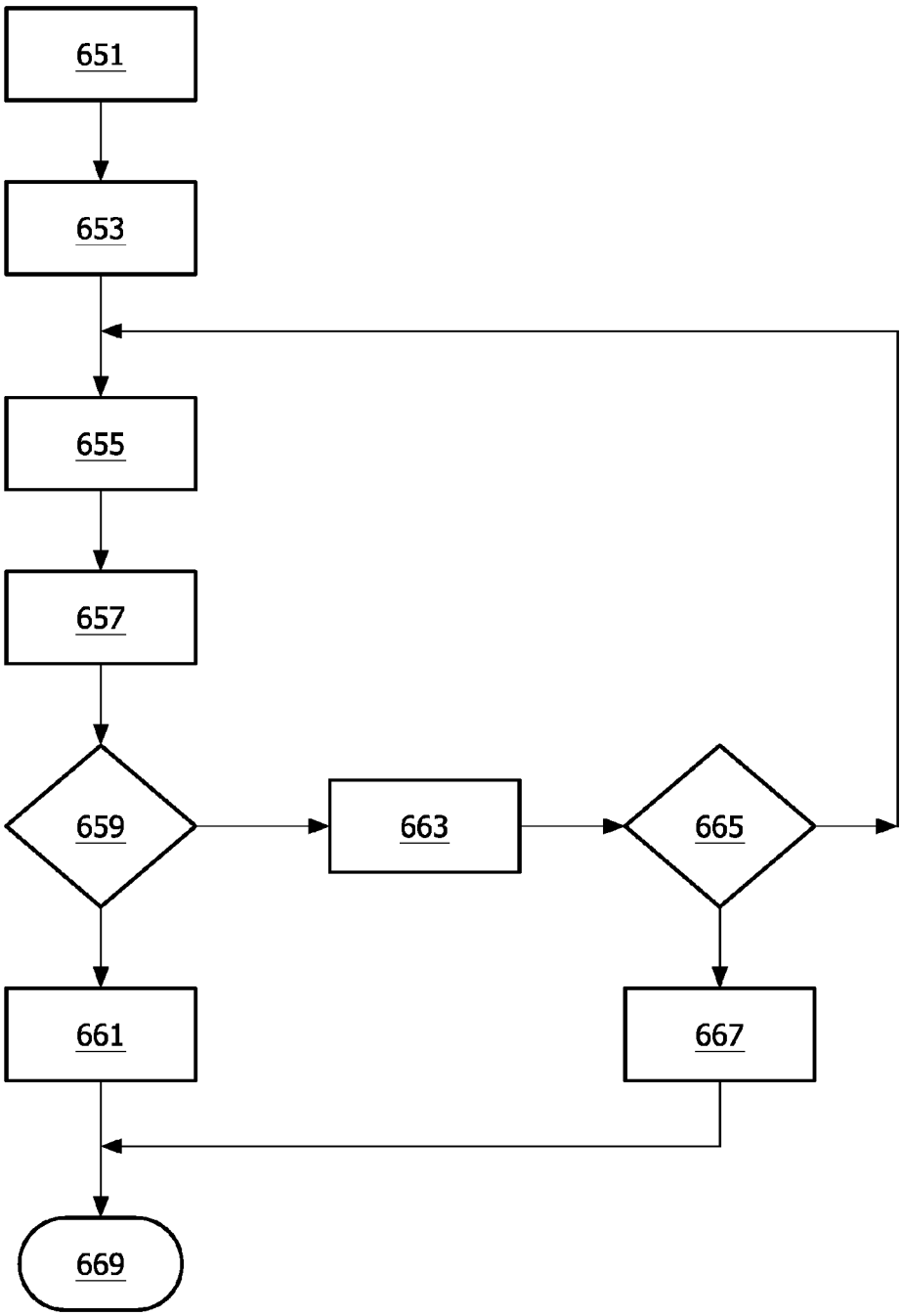

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/057515

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B1/Q7 A61B5/00 G01N21/64
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 G01N

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	US 2004/254474 Al (SEIBEL ERIC [US] ET AL) 16 December 2004 (2004-12-16) abstract; paragraphs [0002] , [0003] , [0010] , [0021] , [0052] , [0080] - [0082] , [0084] ; figures 1, 13, 16A, 16B	1-10
X	US 2008/081950 Al (K0ENIG KARSTEN [DE] ET AL) 3 April 2008 (2008-04-03) abstract; paragraphs [0033] , [0051] , [0071] , [0073] ; figures 1,2a, 2b	1,3,5-7
X	US 2010/282954 Al (HENDRIKS BERNARDUS HENDRIKUS WILHELMUS [NL] ET AL) 11 November 2010 (2010-11-11) paragraphs [0021] , [0034] , [0050] , [0055] - [0057] ; figure 1	1-3,7

-/ -

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

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

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

"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	Date of mailing of the international search report
29 April 2013	08/05/2013

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/057515

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/286476 A1 (JIANG HONGRUI [US] ET AL) 11 November 2010 (2010-11-11) paragraphs [0031], [0035] - [0039]; figures 1,10-12	1-3,7
X	US 6 066 245 A (TR0ST PETER [US]) 23 May 2000 (2000-05-23) column 4, line 14 - column 6, line 22; figure 2	1,7

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