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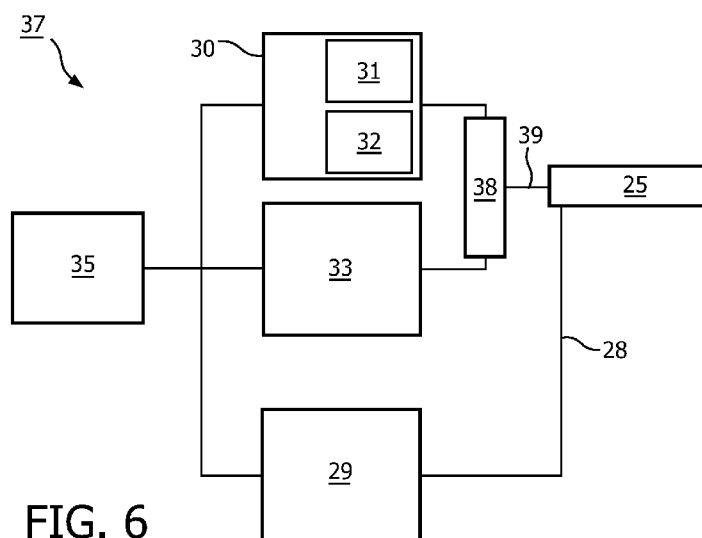


FIG. 6

(57) Abstract: The invention relates to identification and stimulation of nerve tissues, and more in particular to a method, apparatus and probe for optical nerve localization and optical nerve stimulation. The invention combines in a single apparatus the localization and the verification of the presence of nerve tissue by optical stimulation. The stimulation is detected by monitoring the variations based on thermal sensitive spectroscopic features of light scattering from the area of the stimulated nervous tissue.



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Device for optical nerve localization and optical nerve stimulation

FIELD OF THE INVENTION

The invention relates to localization and stimulation of nerve tissues, and more in particular to a method, apparatus and probe for optical nerve localization and optical nerve stimulation and treatment.

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BACKGROUND OF THE INVENTION

In various clinical interventions, it is important that nerves can be localized accurately prior to the intervention. For examples finding nerves may preserve or prevent resection during surgical procedures and allows for localized injection of pain relieving medicaments nearby nerves. Currently localization procedures consist of localizing nerves in imaging modalities such as ultrasound or magnetic resonant imaging (MRI), whereby it may be sometimes difficult to find and identify tissue as being nerves.

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There is a clinical desire for confirmation of the presence of the nerve in order to prevent complications. The gold standard for confirmation of this presence is stimulation of the nerves by using an electrical stimulation.

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US 5,284,154 describes a method and apparatus for locating and identifying the function of specific peripheral nerves. The apparatus of US 5,284,154 includes a stimulus delivery means and a response-detecting means. Electrical stimulation is used for example to locate, identify the function of, and guard against the inadvertent cutting of specific nerves during surgical procedures.

20

Electrical stimulation has several disadvantages, for example it may induce electrical burns on patients, which if unseen by surgeons can result in perforated organs and can also lead to peritonitis.

Recently, stimulation of nerves using optical energy has got increased intention in the literature. However, no practical device is known for in-vivo application.

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The inventor of the present invention has appreciated that an improved apparatus and method for nerve localization and detection is of benefit, and has in consequence devised the present invention.

SUMMARY OF THE INVENTION

It would be advantageous to achieve an improved in vivo nerve localization and detection so as to identify nerve tissues from the surrounding tissues without physically interacting with the nerve tissues. Physically interacting is herein defined as when the probe surface is in contact with the surface of the nerve tissue, e.g. when probe and nerve tissue touch each other.

It would also be advantageous to limit the number of different devices used for in vivo localization and treatment of nervous tissues in minimally invasive surgery.

In general, the invention preferably seeks to mitigate, alleviate or eliminate one or more of the above mentioned disadvantages singly or in any combination. In particular, it may be seen as an object of the present invention to provide a method that solves the above mentioned problems, or other problems, of the prior art.

For the purpose of this application the word “nerve” is referred herein also as “nervous”, e.g. nerve tissue and nervous tissue are used as synonymous. Nervous tissue is intended as the main component of the nervous system, e.g. in the brain, spinal cord, and nerves which regulate and control body functions.

To better address one or more of these concerns, in a first aspect of the invention an optical probe assembly is presented that comprises a housing comprising: one or more optical guides for guiding electromagnetic (EM) radiation towards a region of interest (ROI) and/or for detecting EM radiation scattered or emitted from the ROI.

In some embodiments the housing is or further comprises one or more fluid transport means for delivering a fluid towards the ROI.

The optical probe assembly may be a disposable probe for use in an endoscope or more generally for uses related to laparoscopic surgery. It should be mentioned that the optical probe assembly according to the present invention is particularly suited for relative simple and large scale manufacturing which may in turn lower the unit-price per probe assembly. This is advantageous as the probe assembly due to sanitary requirements may be disposed after single use.

The housing may be a flexible hollow tube. In some embodiments the tip of the housing towards the ROI may have a needle shape form. In some other embodiments the housing is a needle, e.g. a photonic needle.

In the context of the present invention it is to be understood that the term “optical guide” may include, and is not limited to, optical fibers (multi-mode and single-mode), thin film optical paths, photonic crystal fibers, photonic band-gap fibers (PBG),

polarization maintaining fibers, and the like. The optical probe assembly may also comprise more than one fiber i.e. a plurality of fibers or a fiber bundle.

The fluid transport means may be channels, e.g. micro-channels (μ channels) allowing for fluid transport from an external fluid reservoir to the region of interest.

5 The fluid is allowed to flow through the transporting means towards the region of interest to deliver fluid contained in an external fluid reservoir.

In some embodiments the ROI comprises nervous tissue. This is generally when the optical probe assembly is used in combination with an apparatus for minimally invasive surgery.

10 In some embodiments the fluid transported through the fluid transport means may comprise light absorbing materials. An example of light absorbing materials may be chromophores, liposomes, shells, nanoparticles and coated nanoparticles that contain absorbing dye molecules.

15 In some other embodiments the fluid may comprise nerve blocks. Nerve blocks are herein defined as compositions for regional nerve blockade such as local anesthetic for injection onto or near nerve tissue, for example for pain control.

Examples of nerve block may be lidocaine, epinephrine, steroid, and/or opioids.

20 In some embodiments according to the first aspect the one or more optical guides for guiding EM radiations comprises: at least one optical guide for guiding EM radiations towards the ROI; at least one optical guide for detecting EM radiations scattered or emitted from the ROI.

25 In some embodiments the illumination and the detection of EM radiations is carried out by separate optical fibers, i.e. one or more optical fibers guides the EM radiations towards a ROI and some other one or more optical fibers detects EM radiations scattered or emitted from said ROI.

30 In this way, spectroscopic localization of a nervous tissue is possible, as by illuminating through at least one optical guide for guiding EM radiations the nervous tissue, the light scattered or emitted from the area around the nervous tissue can be detected by the at least one optical guide for detecting EM radiations. In vivo spectroscopic analysis of the tissues allows for identification of the nervous tissue. This can be done for example by using a single optical channel monitoring a single wavelength or a narrow range of wavelengths and/or by using multiple optical channels monitoring a single wavelength or narrow ranges of wavelengths simultaneously.

In some embodiments according to the first aspect of the invention the EM radiations are within the UV/ Vis (Ultraviolet/Visible), NIR (Near-infrared) wavelength range.

This use of EM radiations, e.g. within the Vis wavelength range, may be used for the illumination of the area of interest or for detection purposes so as to identify the areas where fluid may be delivered and/or for localizing the nervous tissue through optical spectroscopy.

In some embodiments according to the first aspect of the invention the EM radiations are light amplified by stimulated emission of radiation (LASER) beams.

In some embodiments according to the first aspect of the invention the EM radiations are narrow band light emitting diode (LED) beams.

The LASER radiation or a LED beam induces the optical stimulation of the nerve tissue. Absorption of the LASER beam may cause photochemical, photomechanical effects causing stimulation of the nervous tissue. Stimulation may occur through irradiation with a LASER beam having a wavelength range which is at least partially absorbed by the light absorbing materials contained in the fluid delivered in the area of the nerve tissue. Indeed, in some embodiments the light absorbing materials absorb EM radiations within the wavelength range of said LASER beam. Advantageously the LASER beam, when light absorbing materials are present, may have a minimal absorption on the nervous tissue, maximum absorption in the light absorbing material and not significant absorption from other tissues around the nervous tissue. Indeed, the LASER beam stimulation and light absorption can be tuned so as to match minimizing absorption of the beam from the nervous tissues. In this way collateral damage of the nervous tissues, such as thermal damage are minimized if not completely avoided. In general independently from the mechanism causing transfer of energy between the light absorbing materials and the nerve tissue causing its stimulation, one important feature of the invention is that irradiation with LASER beam of the light absorbing materials causes in turn stimulation of the nerve tissue.

A further advantage of the single apparatus and probe assembly of the invention is that the LASER beam guided through the probe assembly towards the region of interest may be used also for ablation surgery operation. The presence of an optical guide for guiding LASER beam towards the ROI in the probe assembly allows for detection and/or for further use of the LASER beam. In this way localization of nervous tissue, treatment and ablation in the area of interest can be conducted through the same single apparatus and probe assembly.

In some embodiments according to the first aspect of the invention the one or more optical guides for guiding EM radiations comprises at least one optical guide for guiding EM radiations in the UV/ Vis, NIR wavelength range towards the ROI and for guiding a LASER beam towards the ROI.

5 In some embodiments according to the first aspect of the invention the one or more optical guides for guiding EM radiations comprises at least one optical guide for guiding EM radiations in the UV/ Vis, NIR wavelength range towards the ROI and for guiding a LED beam towards the ROI.

10 In some embodiments the illumination of the ROI for localization purposes and stimulation of the nerve tissue may be carried out by a single optical guide.

A single optical guide may guide the EM radiations for illumination of the nerve tissue. The same optical guide may also guide more powerful EM radiations, such as a LASER beam and therefore provide the mean for stimulating the nerve tissue directly or through previous interaction with the light adsorbing materials. In these embodiments
15 detection of the light scattered and/or emitted from the ROI may or may not be collected by the same optical guide.

In some other embodiments according to the first aspect of the invention the one or more optical guides for guiding EM radiations comprises at least one optical guide for guiding EM radiations in the UV/ Vis, NIR wavelength range towards said ROI, and at least
20 one optical guide for guiding LASER beam towards said ROI.

In some other embodiments according to the first aspect of the invention the one or more optical guides for guiding EM radiations comprises at least one optical guide for guiding EM radiations in the UV/ Vis, NIR wavelength range towards said ROI, and at least one optical guide for guiding LED beam towards said ROI.

25 Stimulation by LASER and illumination may be achieved by irradiation from at least two different optical guides. At least one optical guide provides illumination of the region of interest by guiding EM radiations in the UV/ Vis, NIR wavelength range. At least another optical guide provides optical stimulation of the region of interest by guiding a LASER beam towards the nerve tissue.

30 In some embodiments illumination of the region of interest may be carried out by several optical guides such as optical fibers guiding EM radiations within the same wavelength range. In some other embodiments the illumination of the ROI may be carried out by several optical guides such as optical fibers guiding EM radiations in different wavelength ranges. For example, it may be so that specific wavelength or wavelength ranges

of interest for optical spectroscopy monitoring of the ROI may be provided by separate optical guides.

In some other embodiments the stimulation of the ROI may be carried out by more optical guides guiding LASER beam within the same or with different wavelength or narrow wavelengths range.

In some embodiments the optical probe assembly according to first aspect further comprises at its distal end one or more lens systems.

To better address one or more of previous cited concerns, in a second aspect of the invention an apparatus for in vivo optical localization of a region of interest (ROI), is presented that comprises: an optical probe assembly; at least one first radiation source for generating an EM radiations beam, the at least one first radiation source optically coupled to the optical probe assembly, the probe being arranged to guide the radiation beam from said the radiation source towards said ROI, thereby providing illumination of the ROI; at least one second radiation source for generating an EM radiations beam, the at least one second radiation source optically coupled to the optical probe assembly, the probe being arranged to guide the radiation beam from the second radiation source towards the ROI, thereby providing stimulation of the ROI; at least one detector optically coupled to the optical probe assembly, the detector being arranged for detecting the ROI through the analysis of scattered or emitted radiation from the stimulated ROI.

In some embodiments according to the second aspect of the invention the at least one second radiation source optically coupled to the optical probe assembly, provides illumination and/or stimulation of the ROI.

In some embodiments according to the second aspect of the invention the at least one second radiation source is a source for generating light amplified by stimulated emission of radiation (LASER) beams.

Examples of LASER sources that may be used are sources capable of generating a beam having either a fixed wavelength or tunable wavelength: pulsed infrared LASER, ruby LASER, Alexandrite LASER, solid state LASER, CO₂ LASER, N₂ LASER, excimer LASER, tunable optical parametric oscillator (OPO) LASER system, Holmium-doped:Yttrium Aluminum Garnet (Ho:YAG) LASER, or an Erbium doped: Yttrium Aluminum Garnet (Er:YAG) LASER.

In some embodiments according to the second aspect of the invention the at least one second radiation source is a narrow band light emitting diode (LED).

Examples of radiation sources for illumination are radiation sources used for optical spectroscopy such as continuum sources producing a broad range of wavelength, e.g. D₂ lamp, Hg lamp, Xe lamp, W lamp, Nerst Glower, Ni/Ch wire and globar (SiC) or line sources producing few discrete wavelengths, e.g. hollow cathode lamps, LED.

5 LASER or EM radiations sources for illumination are coupled, e.g. thorough optical fibers, to the optical probe assembly.

In those embodiments, where a single optical guide guides both LASER beam and UV/Vis/NIR radiations for illumination purposes, the apparatus further comprises an optical coupler, such as a beam splitter, so that illumination and stimulation can be alternated
10 by alternatively selecting the source of radiation to be guided in the optical guide towards the nerve tissue.

The detector may be any light detector, such as photo-transducers used for spectroscopic analysis in the UV/Vis and NIR spectral region, e.g. photodiodes arrays, photomultiplier, phototubes, thermal detectors, charge-coupled device (CCD) or
15 complementary metal-oxide-semiconductor (CMOS).

In some embodiments the at least one detector is a spectrophotometer.

In some embodiments the apparatus according to the second aspect of the invention further comprises one or more fluid transport means for delivering a fluid towards the ROI.

20 Fluid transport means may be connecting means such as tubing.

In further embodiments the apparatus according to the second aspect of the invention further comprises a fluidic control unit for dispensing fluid towards the ROI, the fluidic control unit coupled to the optical probe assembly.

The fluidic control unit may be coupled through connecting means, for
25 example tubing, with the fluid transport means, such as μ channels, for delivering a fluid towards the ROI.

In further embodiments the fluidic control unit for dispensing the fluid may comprise at least one fluid reservoir.

In some embodiments the fluidic control unit may dispense more than one
30 fluid. For example dispensing of fluids comprising light absorbing materials may precede or follow dispensation of fluids comprising nerve blocks. Simultaneous delivery of fluids may be also envisaged through the action of the fluidic control unit.

In some further embodiments the apparatus according to the second aspect of the invention further comprises an electronic processing unit, a memory unit and a display

unit operatively coupled with each other and with the probe assembly, radiation sources and/or with the fluidic control unit for controlling the apparatus functions.

In some embodiments the apparatus according to the second aspect of the invention comprises a probe assembly according to the first aspect of the invention.

5 To better address one or more of previous cited concerns, in a third aspect of the invention a method for in vivo optical localization of nervous tissue is presented. The method comprises: localizing a nervous tissue by means of optical spectroscopy; optically stimulating said nervous tissue by exposing said nervous tissue to a LASER beam or a narrow band light emitting diode (LED) beam; detecting the presence of the stimulated
10 nervous tissue by spectroscopic analysis of EM radiations emitted or scattered by the area of the stimulated nervous tissue.

In a further aspect of the invention a method for in-vivo optical localization of nervous tissue using a probe assembly according to the first aspect is presented.

In a further aspect of the invention a method for optical localization of nervous
15 tissue using an apparatus according to the second aspect of the invention is presented.

In further embodiments according to the third aspect of the invention optically stimulating the nervous tissue comprises providing light absorbing materials at the nervous tissue before exposing the nervous tissue to a LASER beam or a narrow band light emitting diode (LED) beam.

20 In some embodiments according the third aspect of the invention light absorbing materials absorb EM radiations within the wavelength range of the LASER beam, i.e. the LASER beam used for stimulation or within the wavelength range of the narrow band light emitting diode (LED) beam.

In some other embodiments according the third aspect of the invention
25 optically stimulating said nervous tissue comprises providing laser light to perform treatment to said nervous tissue.

In some embodiments the detection of the presence of the stimulated nervous tissue comprises the detection of stimulated nerves through temperature sensitive spectral bands.

30 Generally, the absorption coefficient of water is sensitive to temperature. By determining the absorption of water from the light collected by the optical probe assembly, the temperature in front of the tip of the optical probe can be determined. Details can be found in *J. Biomed. Opt.* 15, 037015 and are included herein by reference.

In the method of the invention the basic idea is to locate and confirm the location of nerve tissues by stimulating and monitoring the response of the nerve tissues. Therefore the method comprises approaching of the probe assembly to the nerve tissue to firstly localize the area where the nerve tissue of interest is located. This approaching does not involve a physical contact between the probe assembly and the nerve tissue and may be carried out, for example, under image guidance.

The method then comprises the illumination of the nerve tissue, for example by a broad band light or a LASER beam to which follow the detection of the diffuse reflectance, fluorescence or Raman spectrum of the nerve tissue. Confirmation of the localization of the nerve tissue may include the application of an algorithm to spectrally distinguish nerve tissue from surrounding tissue. Once localized the nerve tissue can be optically stimulated by exposing it to a LASER beam. The response to the optical stimulation may be detected optically by monitoring the temperature dependent absorption bands of the nerve tissue, e.g. water absorption or fat absorption. Generally these bands lay in the NIR spectral region. In particular, the temperature dependence of characteristic fundamental vibrational modes of water may be taken as indication of the stimulation of the target nervous tissue. For example, in a NIR spectrum at least one of the characteristic absorption peaks of water may be monitored so that its variations induced by a temperature difference before and after optical stimulation of the nervous tissue may be taken as indication of nerve tissue stimulation. In some embodiments other temperature sensitive absorption peaks may used to detect optical stimulation of nervous tissue.

In some embodiments a LASER beam may also be used for optical spectroscopic detection of the nerve using Fluorescence or Raman spectroscopy. In that one LASER beam is used for e.g. excitation of Fluorescence usually in the UV or Vis wavelength range, or another LASER for excitation of Raman spectroscopy usually in the Vis to NIR wavelength range. The LASER beam for stimulation of nerves usually has a wavelength in the NIR 1800-1900 nm wavelength range.

In some embodiments according to the third aspect of the invention optically stimulating the nervous tissue comprises providing LASER light to perform treatment to the nervous tissue.

The method for in vivo optical localization of nervous tissue according to the third aspect of the invention may further comprise monitoring of the muscle activity resulting from nerve tissue stimulation. This has the advantage of further confirming the presence and location of nerve tissue.

Monitoring of the optical stimulation has also the advantage of preventing damages to the nerve tissue as if undesired values of light scattering are detected, for example due to rapid and excessive increase of temperature of the region of interest, ceasing of the stimulation may rapidly occur.

5 Accordingly, the method for in vivo optical localization of nervous tissue according to the third aspect of the invention may further comprise monitoring of the optical stimulation and ceasing of stimulation if non-nervous tissues are detected and/or if values associated to potential harm of the nervous tissue are encountered during the monitoring.

10 For the purpose of the application light scattering and reflectance are commonly used to indicate light beams detected by the detector in response to light illumination or LASER illumination of the region of interest.

A further advantage of the method is that in-situ, in vivo, LASER treatment may follow nerve location without the need of inserting further apparatus.

15 A further advantage of the method is that by using focused LASER light the nerve stimulation can be performed with higher spatial resolution compared to the electrical stimulation, which might be preferable for selective stimulation of different types of nerves, e.g. sensory and motor nerves or even specific fascicles in a nerve bundle and to prevent damage to other tissue outside of the nerve.

20 Following the localization of a nerve tissue, it may be so that treatment of the localized nerve tissue is needed, e.g. ablation by laser treatment. It is therefore possible to use the optical probe assembly, already used for nervous tissue localization, for LASER ablation in situ. Depending on the LASER wavelength needed, the LASER used for localization may be employed. Alternatively a second LASER source may be couple to the optical probe assembly, e.g. an Infra-Red (IR) LASER.

25 Accordingly, the method for in vivo optical localization of nervous tissue may further comprise LASER treating the area of interest, i.e. the area around the nerve tissue, by using the optical probe assembly and/or the apparatus according to the first and second aspect of the invention, respectively.

30 Accordingly the optical probe assembly according to the first aspect of the invention may further comprise at least an optical guide for guiding LASER beam towards the nervous tissue, thereby providing ablation of at least part of the nervous tissue and/or of the tissues in the area around the nervous tissue of interest. A separate optical guide dedicated to the guiding of a LASER beam to provide ablation may be needed if the LASER used for ablation has different characteristics than the LASER used for stimulation, e.g. an IR LASER

has a sharp band in the infrared spectral region, e.g. between 1.8 and 2.3 micrometer, and therefore this LASER may require specific infrared-transmitting fibers as optical guides.

Following the localization of a nerve tissue, it may be so that treatment of the localized nerve tissue is needed, for example exposure to composition which may affect it function such as nerve blocks or other chemicals which may interact with the nervous tissue.

Accordingly the method for in vivo optical localization of nervous tissue according to the third aspect of the invention may further comprise providing fluids comprising chemicals which interact with the nervous tissue before or after exposing the nervous tissue to a LASER beam.

One of the advantages of the invention is that a single probe and/or a single apparatus can be used to monitor a nerve response during and after the optical stimulus.

In some other embodiments the use of a single probe and/or a single apparatus to monitor a nerve response during and after the optical stimulus is done in conjunction with other neural activity responses detection, i.e. muscle movement, pain indicator and/or electrical response.

In those embodiments in addition to optical guides and μ channels, one or multiple electrically conductive fibers may be embedded in the probe assembly. If one electrically conductive fiber is used, a grounding pad is in contact with the patient at a location away from the needle location. If multiple electrically conductive fibers are used, the grounding pad may be optional.

The electrically conductive fibers may be used as an alternative to either electrically stimulate the nerve tissue and/or to record the nerve stimulation response alone or in combination with the optical fibers embedded in the probe assembly.

The basic idea of the invention is to combine in a single probe and a single apparatus the ability of localizing nervous tissue and confirming this localization by optical stimulation of the localized nervous tissue. This stimulation is detected by monitoring the variations based on thermal sensitive spectroscopic features of light scattering from the area of the stimulated nervous tissue.

Stimulation leading to a positive or negative nerve response is detected and discriminated by monitoring the spectroscopic features of light scattering from the area of the stimulated nervous tissue.

In general the various aspects of the invention may be combined and coupled in any way possible within the scope of the invention. These and other aspects, features

and/or advantages of the invention will be apparent from and elucidated with reference to the embodiments described hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

5 Embodiments of the invention will be described, by way of example only, with reference to the drawings, in which

Figure 1 is a schematic cross-sectional drawing of an optical probe assembly according to the present invention.

10 Figure 2 is a schematic cross-sectional drawing of an optical probe assembly according to possible embodiments of the present invention.

Figure 3 is a schematic cross-sectional drawing of an optical probe assembly according to other possible embodiments of the present invention.

15 Figure 4 is a schematic cross-sectional drawing of an optical probe assembly according to other possible embodiments of the present invention where the optical guide for guiding a LASER beam comprises a focusing lens system.

Figure 5 is a schematic drawing of an apparatus for in vivo optical localization of nervous tissue according to the present invention.

Figure 6 is a schematic drawing of an apparatus for in vivo optical localization of nervous tissue according to embodiments of the present invention.

20 Figure 7 is a flow chart for a method according to the invention.

Figure 8 is a log plot of the absorption spectra of blood, water and fat.

DESCRIPTION OF EMBODIMENTS

25 An embodiment of the invention is illustrated in figure 1. Figure 1 shows the cross section of an optical probe assembly 1 comprising a housing 2 confining a μ channel 3 as fluid transport means and a fiber optic 4, as optical guide for guiding EM radiations towards a nerve tissue while the probe assembly is located in the vicinity of a nerve tissue.

30 Figure 2 shows the cross section of an optical probe assembly 5 comprising a housing 6 confining a μ channel 7 as fluid transport means and two optical fibers 8 and 9. Optical fiber 8 guides EM radiations towards a nerve tissue while optical guide 9 detects the EM radiations scattered or emitted from the area of the nerve tissue.

Figure 3 shows the cross section of an optical probe assembly 10 comprising a housing 11 comprising fiber optics and μ channels for fluid transport. Fiber optic 12 guides EM radiations towards the nerve tissue, while fiber optic 13 detects EM radiations scattered

from the nerve tissue area. In housing 11, μ channels 14 and 15 may be used to transport the same fluid or different fluids towards the nerve tissue. μ channels 14 and 15 in this embodiment are located at the periphery of optical guide 16 for guiding LASER beam towards the nerve tissue for stimulation purposes. However, any other geometry combining fiber optics and μ channels embedded in the housing may be envisaged. For example it may be so that μ channels and fiber optics surround each other, such as an inner fiber optic is surrounded by an outer μ channel sharing the same geometric axis.

Figures 1-3 do not show the tip of the probe assembly. An example of a tip for the probe assembly 10 is shown in figure 4. The housing 11 has a tip 17 having the shape of a needle. Figure 4 shows flat end faced optical guide 19 for illumination of the nervous tissue and flat end faced optical guide 20 for detection of light scattered from the nerve tissue. Figure 5 shows also μ channels 21 and 22 for fluid transport and optical guide 23 for guiding LASER beam towards the nerve tissue. In this embodiment optical guide 23 has at its distal or sampling end part towards the ROI a lens system 24. This is advantageous so as to focus the LASER beam in a specific spot on the nerve tissue. Indeed, in some embodiments the optical probe assembly comprises at least one optical guide for guiding a LASER beam, having a lens system at its distal end part, thereby focusing the LASER beam towards the ROI.

Figure 5 is a schematic drawing of an apparatus for in vivo optical localization of nervous tissue according to the present invention. The apparatus 27 comprises an optical probe assembly 25 optically connected through an optical guide 26, e.g. one or more optical fibers, to a device 30 for measuring light intensity, i.e. a device that can measure light intensity as a function of its wavelength, e.g. a spectrophotometer. Device 30 comprises a source of EM radiations in the UV/Vis or NIR region 31 and a detector 32 for detecting the light. Optical probe assembly 25 is also optically connected through optical guide 34 to a LASER source 33. A fluidic control unit 29 connected via, e.g. tubing 28, to optical probe assembly 25 may control the release and delivery of desired fluids towards the nervous tissue. Fluidic control unit 29, LASER source 33 and spectrophotometer 30 may all be connected to an electronic processing unit 35 for controlling the apparatus functions.

The fluidic control unit 29 is also connected to a reservoir of fluids (not shown).

In some embodiments as shown in figure 6, the apparatus 37 comprises an optical probe assembly 25 which is connected via a single optical fiber to an optical

coupler/beam splitter 38. The beam splitter 38 is connected to the EM source of light 31 of spectrophotometer 30 and to the LASER source 33 so that illumination from the LASER source and from the EM source of light can be alternated selectively.

Figure 7 is a flow chart for a method according to the invention. The method comprise: localizing a nervous tissue by means of optical spectroscopy (S1); optically stimulating the nervous tissue by exposing said nervous tissue to a LASER beam (S2); detecting the presence of the stimulated nervous tissue by spectroscopic analysis of EM radiations emitted or scattered by the stimulated nervous tissue (S3).

In some embodiments the probe assembly may contain a system for acquiring images, in 2 or 3 dimensions, of nerve tissue microstructure, e.g. by means of confocal detection through a optical fiber scanning microscope. In these embodiments, the at least one optical guide is used to guide LASER beam for nervous tissue stimulation and to illuminate the tissue for images acquisition. Automated image segmentation algorithms may be used to detect nerve tissue from the images. The output of these algorithms may be used to direct LASER beam stimulation towards a precise location.

In some embodiments the housing may be used as a fluid transport means for delivering a fluid towards the ROI. For example, the housing of the optical probe assembly may be a hollow tube and a stylet, e.g. mandrin may be located inside the hollow tube filling up the entire volume of the hollow tube. The stylet may contain the one or more optical guides according to the invention. During the process for optical detection and stimulation of the nervous tissue, the assembly probe may be brought close to a nerve tissue to stimulate it so as to confirm that indeed the location is correct. At this stage the stylet may be removed while keeping the hollow tube at its location. By connecting a pumping means, such a syringe to the hollow tube, a fluid, comprising, e.g. steroid or the like, is allowed to flow towards the nerve tissue of interest via the housing, i.e. the hollow tube. In this way the fluid transport means may be the housing in itself after removing at least part of the probe assembly.

Figure 8 is a log plot of the absorption spectra of blood, water and fat.

In figure 8 the characteristic absorption peaks of Hemoglobin 42, Oxygenated Hemoglobin 43, Water 40 and Fat 41 may be observed.

Algorithm

As mentioned confirmation of the localization of the nerve tissue may include the application of an algorithm to spectrally distinguish nerve tissue from surrounding tissue.

This algorithm has been developed that can be used to derive optical tissue properties such as the scattering coefficient and absorption coefficient of different tissue chromophores: e.g. hemoglobin, oxygenated hemoglobin, water, fat etc. These properties are different between different tissue types, such as subcutaneous fat, muscle and nervous tissue.

- 5 In more detail the algorithm can be described as follows. The spectral fitting may be performed by making use of the analytically derived formula for reflectance spectroscopy e.g. from T.J. Farrel *et alter*, Med. Phys. 19 (1992) p879-888 or R. Nachabé, *et alter*, J. Biomed. Opt. 15, 037015 (2010).

This reflectance distribution R is given by

$$R(\rho) = \int_0^{\infty} R(\rho, z_0) \delta(z_0 - 1/\mu_t') dz_0$$

$$= \frac{a'}{4\pi} \left[\frac{1}{\mu_t'} \left(\mu_{eff} + \frac{1}{\tilde{r}_1} \right) \frac{e^{-\mu_{eff}\tilde{r}_1}}{\tilde{r}_1^2} + \left(\frac{1}{\mu_t'} + 2z_b \right) \left(\mu_{eff} + \frac{1}{\tilde{r}_2} \right) \frac{e^{-\mu_{eff}\tilde{r}_2}}{\tilde{r}_2^2} \right]$$

where

$$\tilde{r}_1 = [x^2 + y^2 + (1/\mu_t')^2]^{1/2}$$

$$\tilde{r}_2 = [x^2 + y^2 + ((1/\mu_t') + 2z_b)^2]^{1/2}$$

$$\mu_{eff} = \sqrt{3\mu_a[\mu_a + \mu_s(1-g)]}$$

(1)

- 10 In this formula the three macroscopic parameters describing the probability of interaction with tissue are: the *absorption coefficient* μ_a and the *scattering coefficient* μ_s both in cm^{-1} as well as by g which is the mean cosine of the scattering angle. Furthermore, we have the total reduced attenuation coefficient μ_t' that gives the total chance for interaction with tissue

$$\mu_t' = \mu_a + \mu_s(1-g).$$

(2)

- 15 The *albedo* a' is the probability of scattering relative to the total probability of interaction

$$a' = \mu_s / \mu_t'.$$

(3)

We assume a point source at a depth $z_0 = 1/\mu_t'$ and no boundary mismatch hence $z_b = 2/(3\mu_t')$. Furthermore, we assume that the scattering coefficient can be written as

$$\mu_s'(\lambda) = a\lambda^{-b}.$$

(4)

- 20 The main absorbing constituents in normal tissue dominating the absorption in the visible and near-infrared range are blood (i.e. hemoglobin), water and fat. In figure 8 the absorption coefficient of these chromophores as a function of the wavelength are presented.

Note that blood dominates the absorption in the visible range, while water and fat dominate in the near infrared range.

In some other embodiments the probe assembly may contain a phase-sensitive reflectometry system with interferometric detection to optically monitor the expansions of axons or dendrites resulting from LASER beam stimulation.

The total absorption coefficient is a linear combination of the absorption coefficients of for instance blood, water and fat (hence for each component the value of that shown in figure 8 multiplied by its volume fraction). By fitting the above formula while using the power law for scattering we can determine the volume fractions of the blood, water and fat as well as the scattering coefficient. With this method we can now translate the measured spectra in physiological parameters that can be used to discriminate different tissues.

Another way to discriminate differences in spectra is by making use of a principal components analysis. This method allows classification of differences in spectra and thus allows discrimination between tissues. How to extract the intrinsic fluorescence from the measured fluorescence can be found for instance in Zhang *et al.*, Optics Letters 25 (2000) p.1451.

In some further embodiments optical stimulation is performed by means of stimulating light-sensitive ionic channels like for example Channelrhodopsin-2, a light-sensitive cation channel that can be used to photo-stimulate mammalian neurons, e.g. see Nat Neurosci. 2005 Sep;8(9):1263-8.

While the invention has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive; the invention is not limited to the disclosed embodiments.

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

CLAIMS:

1. An apparatus for in vivo optical localization of a region of interest (ROI), the apparatus comprising:

- an optical probe assembly;
- at least one first radiation source for generating an EM radiations beam, said at least one first radiation source optically coupled to said optical probe assembly, the probe being arranged to guide said radiation beam from said first radiation source towards said ROI, thereby providing illumination of said ROI;
- at least one second radiation source for generating an EM radiations beam, said at least one second radiation source optically coupled to said optical probe assembly, the probe being arranged to guide said radiation beam from said second radiation source towards said ROI, thereby providing stimulation of said ROI;
- at least one detector optically coupled to said optical probe assembly, the detector being arranged for detecting said ROI through the analysis of scattered or emitted radiation from said stimulated ROI.

2. An apparatus for in vivo optical localization of a ROI according to claim 1, wherein said at least one second radiation source is a source for generating light amplified by stimulated emission of radiation (LASER) beams.

3. An apparatus for in vivo optical localization of a ROI according to claim 1, the apparatus further comprising one or more fluid transport means for delivering a fluid towards said ROI.

4. An apparatus for in vivo optical localization of a ROI according to claim 1, the apparatus further comprising:

- a fluidic control unit for dispensing fluid towards said ROI, said fluidic control unit coupled to said optical probe assembly.

5. An apparatus for in vivo optical localization of a ROI according to claim 1 wherein said optical probe assembly comprises:

a housing comprising:

- one or more optical guides for guiding EM radiations towards a ROI

and/or for detecting EM radiations scattered or emitted from said ROI.

6. An apparatus for in vivo optical localization of a ROI according to claim 5 wherein said housing is or further comprises:

- one or more fluid transport means for delivering a fluid towards said ROI.

7. An apparatus for in vivo optical localization of a ROI according to claim 5 wherein said one or more optical guides for guiding EM radiations comprises:

- at least one optical guide for guiding EM radiations towards said ROI;

- at least one optical guide for detecting EM radiations scattered or emitted from said ROI.

8. An apparatus for in vivo optical localization of a ROI according to claim 5 wherein said EM radiations are within the UV/ Vis, NIR wavelength range.

9. An apparatus for in vivo optical localization of a ROI according to claim 5 wherein said EM radiations are LASER beams.

10. An apparatus for in vivo optical localization of a ROI according to claim 5 wherein said one or more optical guides for guiding EM radiations comprises:

- at least one optical guide for guiding EM radiations in the UV/ Vis, NIR wavelength range towards said ROI and for guiding a LASER beam towards said ROI.

11. An apparatus for in vivo optical localization of a ROI according to claim 5 wherein said one or more optical guides for guiding EM radiations comprises:

- at least one optical guide for guiding EM radiations in the UV/ Vis, NIR wavelength range towards said ROI, and

- at least one optical guide for guiding LASER beam towards said ROI.

12. An apparatus for in vivo optical localization of a ROI according to claim 1 wherein said ROI comprises nervous tissue.

13. An apparatus for in vivo optical localization of nervous tissue according to claim 5 said optical probe assembly further comprises at its distal end one or more lens systems.

14. A method for in vivo optical localization of nervous tissue, the method comprising:

- localizing a nervous tissue by means of optical spectroscopy
- optically stimulating said nervous tissue by exposing said nervous tissue to a stimulating beam, such as a LASER beam or a narrow band light emitting diode (LED) beam,
- detecting the presence of said stimulated nervous tissue by spectroscopic analysis of EM radiations emitted or scattered by said stimulated nervous tissue.

15. A method according to claim 14 wherein optically stimulating said nervous tissue comprises providing LASER light to perform treatment to said nervous tissue.

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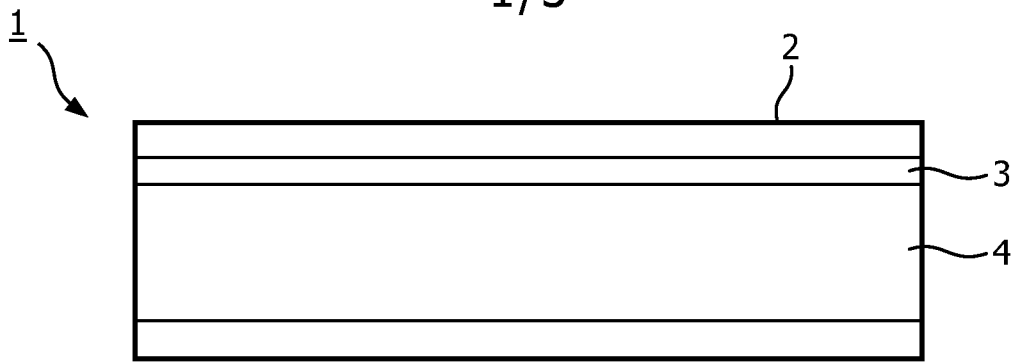


FIG. 1

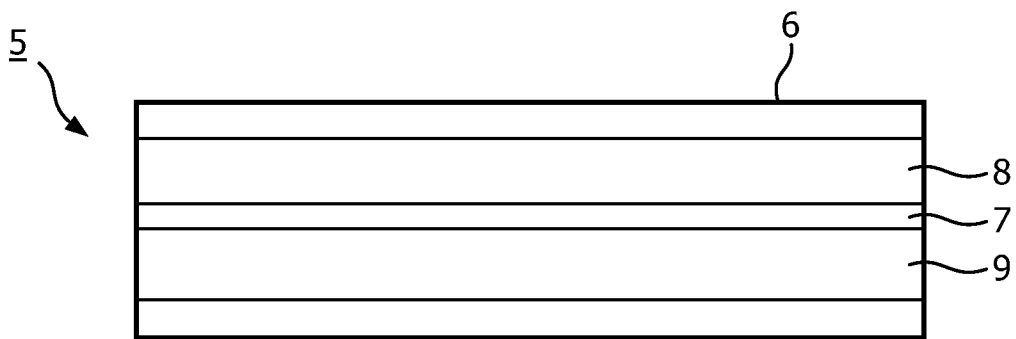


FIG. 2

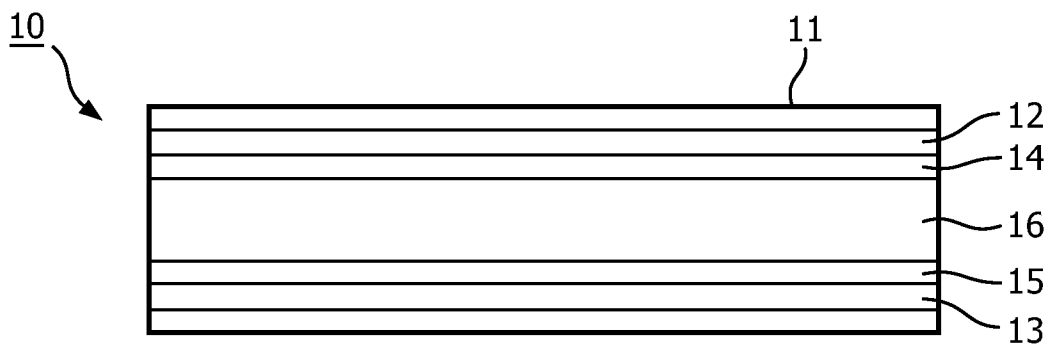


FIG. 3

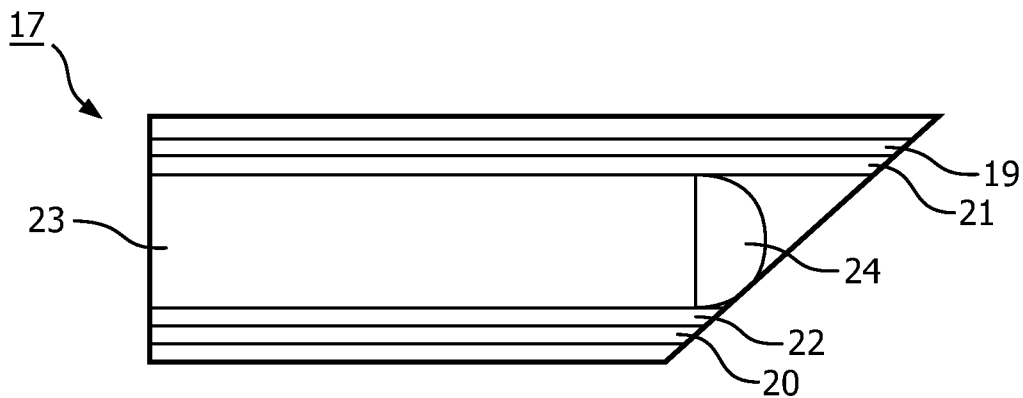


FIG. 4

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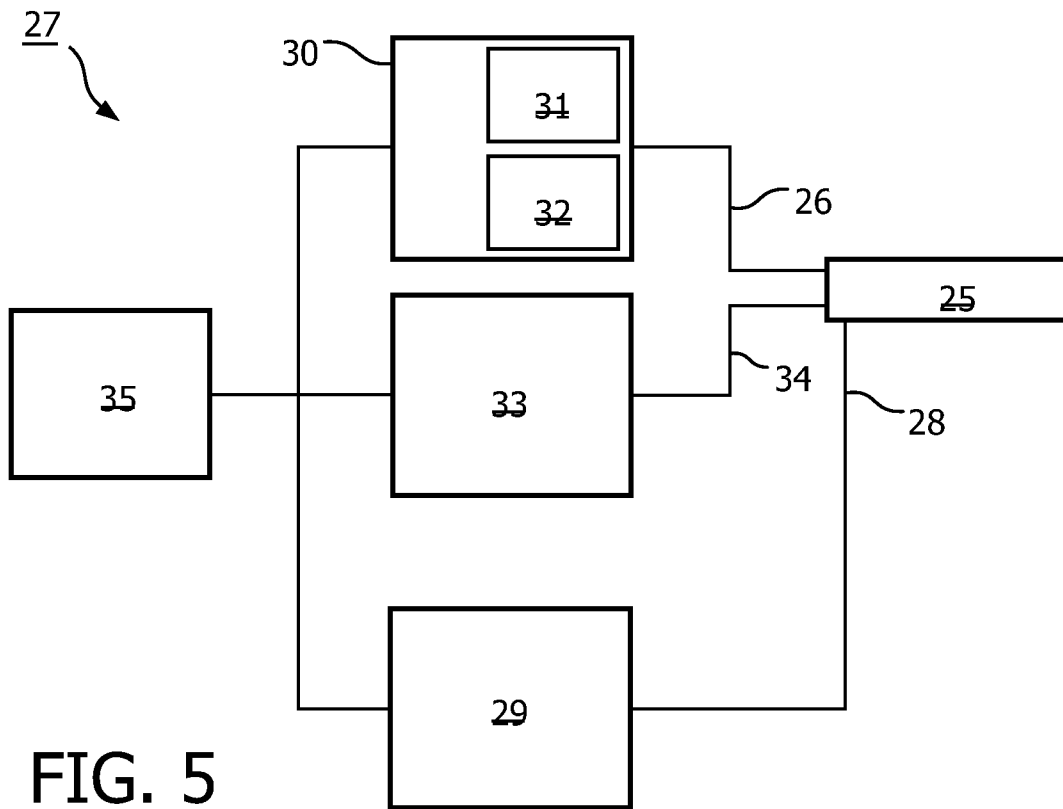


FIG. 5

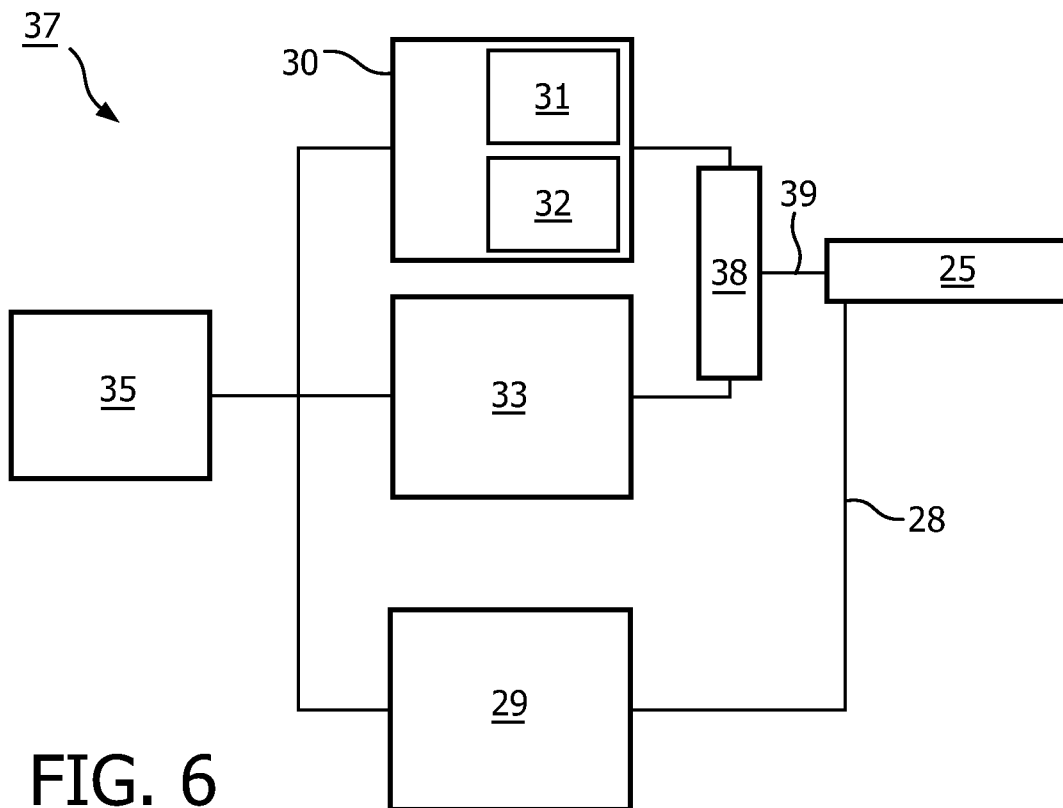


FIG. 6

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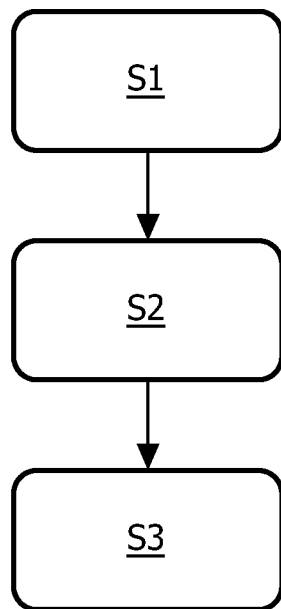


FIG. 7

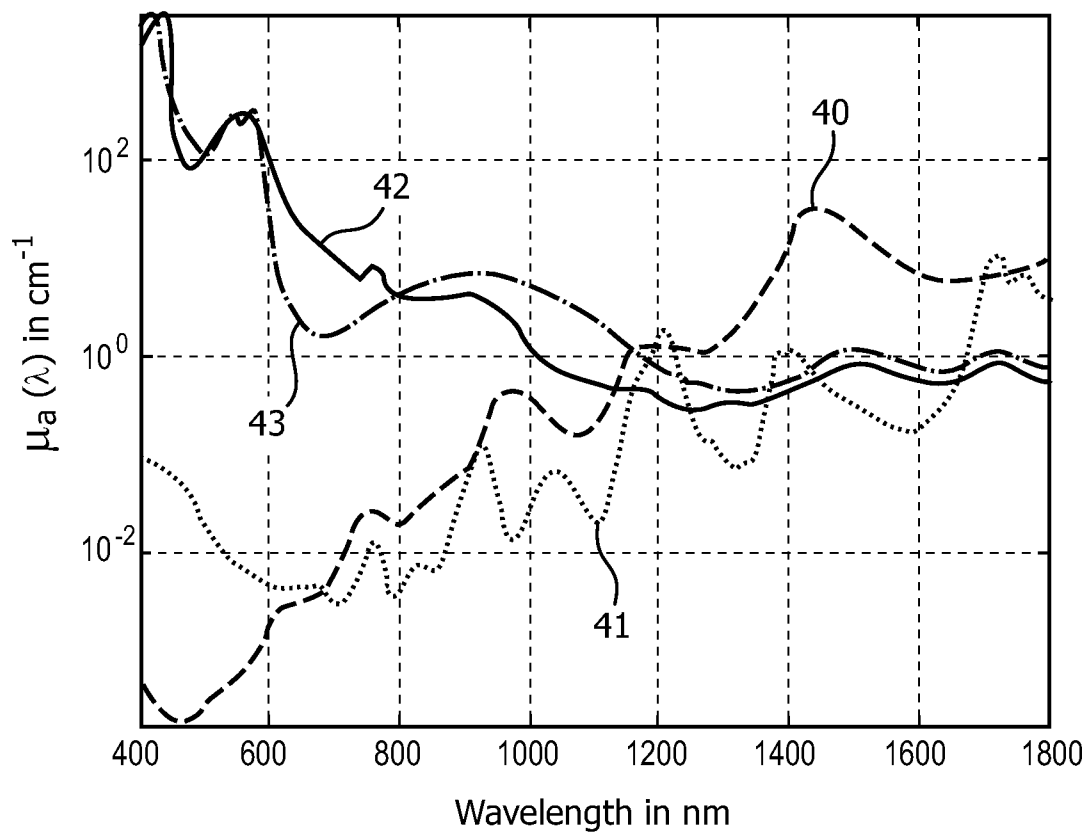


FIG. 8