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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2024 (19.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/256494 A1

(51) International Patent Classification:
A61N 5/06 (2006.01) *A61N 1/18* (2006.01)

(21) International Application Number:
PCT/EP2024/066284

(22) International Filing Date:
12 June 2024 (12.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
23386049.3 16 June 2023 (16.06.2023) EP
23194138.6 30 August 2023 (30.08.2023) EP

(71) Applicant: **DANMARKS TEKNISKE UNIVERSITET** [DK/DK]; Anker Engelunds Vej 101, 2800 Kongens Lyngby (DK).

(72) Inventors: **MARKOS, Christos**; c/o Danmarks Tekniske Universitet, Anker Engelunds Vej 101, 2800 Kongens Lyngby (DK). **SUI, Kunyang**; c/o Danmarks Tekniske Universitet, Anker Engelunds Vej 101, 2800 Kongens Lyngby (DK).

(74) Agent: **PLOUGMANN VINGTOFT A/S**; Strandvejen 70, 2900 Hellerup (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

(54) Title: ANGLED FIBER-BASED NEURAL IMPLANT FOR NEUROMODULATION

(57) Abstract: An angled fiber-based neural implant for neuromodulation and a method to manufacture such a neural implant is presented. The angled fiber-based neural implant comprises a fiber shank for inserting in neural tissue. The fiber shank comprises an optical waveguide, and the optical waveguide comprises a core and a cladding adapted so that light is able to propagate along the length of the optical waveguide. The shape of the core is arranged for providing a substantially uniform intensity distribution of light radiation from the core at the fiber tip, and the fiber tip comprises an angled surface. The end of the core and the end of the plurality of conduits are exposed at the angled surface, so that the plurality of conduits emanates at two, or more, different levels, where each level comprises a different depth into the tissue.

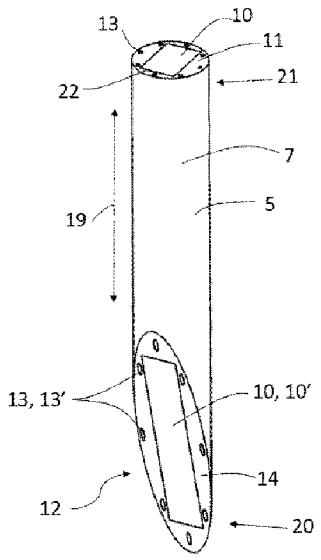

Fig. 1

WO 2024/256494 A1

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Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

ANGLED FIBER-BASED NEURAL IMPLANT FOR NEUROMODULATION

FIELD OF THE INVENTION

The present invention relates to an angled optical fiber-based neural implant for neuromodulation of different brain regions and a method for manufacturing such neural implant.

BACKGROUND OF THE INVENTION

The field of neuroscience has witnessed remarkable progress in recent years, fuelled by technological advancement that allows us to delve deeper into the complexities of the human brain. Among these breakthroughs, implantable neural interfaces utilizing electrophysical signals and incorporating optical neuromodulation modalities have emerged as transformative tools. These devices enable researchers and clinicians to achieve bi-directional neural interfacing, offering unprecedented insights into the functional networks of the brain and improving the treatment of neurological diseases.

An optical fiber-based neural implant is an optoelectronic device used in neuroscience and medical applications to study and manipulate the activity of neurons in the central and peripheral nervous systems. It is a tiny implantable device made up of a thin fiber optic cable, which is typically coated with a polymer material, such as silicone or polyimide, to prevent damage to surrounding brain tissue.

The implant is designed to be inserted into a brain or other neural tissue and can record electrical signals from individual or populations of neurons, provide optical stimulation to manipulate neuron activity, or deliver drugs to specific regions of the brain. Fiber-based neural implants are often used in deep-brain stimulation, a therapy used to treat conditions such as Parkinson's disease, chronic pain, and epilepsy.

Advances in technology have allowed for the integration of multiple functionalities into a single fiber-based neural implant, making it a versatile tool for neuromodulation research and clinical applications.

By harnessing electrophysiological and photo-pharmacology signals, neural implants provide researchers with the means to modulate and decode neural activity at a local level.

By exerting control over neural activity, researchers gain insights into the underlying mechanisms governing cognition, perception, and behaviour or any physical action of a living organism.

The use of optogenetics with neural implants marks a milestone in the field of implantable neural interfaces. Optogenetics leverages light-sensitive proteins to selectively control and monitor neural activity with precision. By incorporating optogenetics into implantable devices, researchers can achieve bidirectional neural interfacing, facilitating real-time communication between neural circuits and external control systems. This capability opens up new avenues for investigating complex brain dynamics and developing advanced therapeutic interventions.

A second optical modality is infrared neuromodulation. Infrared neuromodulation uses infrared light to manipulate neural activity in the central or peripheral nervous system. This method does not require virus and genetic modification. Infrared light is absorbed by the tissue without causing damage, interacting with molecules in the cells to trigger physiological responses. This can be achieved through photo thermal effects, optogenetics with infrared-sensitive opsins, or temperature-sensitive ion channels.

The impact of implantable neural interfaces, utilizing electrophysical signals and using optogenetics and infrared neuromodulation extends beyond the realm of scientific research. These devices hold promise in the treatment of neurological diseases, providing innovative approaches to address conditions that were once deemed untreatable. By establishing bidirectional communication with the brain, implantable neural interfaces enable targeted interventions and personalized therapies. From neurodegenerative disorders to psychiatric conditions and epilepsy, these devices are transforming our ability to manage and improve the lives of individuals affected by neurological diseases.

Fiber-based neural implants have been proven to be effective in providing deep-brain neuromodulation. These implants are now integrated with multi-functional microstructures that allow for optical stimulation, electric signal recording, and drug delivery all at the same time. Despite these advancements, the device's output is limited to a flat fiber end, which means that the interface can only probe a specific location/depth within the brain. In other words, the device can only interact with a small area of the brain, which limits its overall efficacy. While the integrated microstructures allow for multiple functionalities, the design of the device remains a barrier to a more comprehensive and effective neuromodulation across different brain and/or neural regions.

Hence, an improved fiber-based implantable neural implant for deep-brain neuromodulation would be advantageous, and in particular a more efficient and/or reliable neural implant for deep-brain neuromodulation at different depths into the brain would be advantageous.

OBJECT OF THE INVENTION

It is an object of the invention to provide a neural implant for neuromodulation at different depths into the brain or other tissue.

It is a further object of the present invention to provide an alternative to the prior art.

In particular, it may be seen as an object of the present invention to provide a neural implant for deep-brain neuromodulation that solves the above mentioned problems of the prior art.

SUMMARY OF THE INVENTION

Thus, the above described object and several other objects are intended to be obtained in a first aspect of the invention by providing an angled fiber-based neural implant for neuromodulation in tissue, wherein

- the neural implant comprises

- a fiber shank, and
- an adaptor, for setup connectorization and light source connectorization,

- the fiber shank comprises
  - a proximal end connected to the adaptor,
  - an implanted end for implantation into tissue, and
  - a fiber tip at the implanted end,
  - an optical waveguide for optical neuromodulation,
  - a plurality of conduits, and
  - electrodes may be inserted into one, or more, of the plurality of conduits for electrical neuromodulation,
- the optical waveguide comprises a core and a cladding, adapted so that light is able to propagate along the length of the waveguide,
- the cladding comprises a central hole, the core is placed in the central hole and is going from the proximal end to the fiber tip, and
- the plurality of conduits are embedded in the fiber shank, each conduit going from the proximal end to the fiber tip;

wherein the non-circular shape of the core is arranged for providing a substantially uniform intensity distribution of light radiation from the core at the fiber tip; and

wherein the fiber tip comprises an angled surface, the end of the core and the end of the plurality of conduits are exposed at the angled surface, so that the plurality of conduits emanates at two, or more, different levels, where each level comprises a different depth into the tissue.

The invention relates to an optical fiber-based neural implant with an angled tip. Fiber-based neural implants are effective devices for deep-brain neuromodulation. Integrated multi-functional microstructures can provide optical stimulation, electric signal recording, imaging and drug delivery at the same time. However, in the prior art, all the output conduits of the device end at a flat fiber end, and therefore can only achieve interrogate at one specific location/depth in the tissue, which may be brain tissue. To be able to conduct depth-resolved neuromodulation, the invention presents a new structure by controllably angling the tip of the fiber neural device with integrated functional microstructure conduits the longitudinal length of the fiber direction.

There are two main innovations in the implant. Firstly, the tip of the fiber comprises an angle that is introduced either by the mechanic cutting or grinding method in a controllable way. All the functional microstructures, including but not limited to the electrodes and microfluidic channels, are placed along the length of the fiber. The depth between each microstructure can be adjusted by the diameter of the fiber shank and the angle at the tip of the fiber. In this way, depth-resolved neural activity recording or chemical stimulation can be achieved. Secondly, for traditional circular-core optical fiber most delivered power is located at the center of the fiber core since the light guided by optical fiber has a Gaussian profile. The result being that the depth-resolved implant having different optical stimulation efficiency at different depths in the tissue. From figure 4a, it can be seen that the light profile at the output end of a 30° tip angle fiber has a very uneven/non-uniform distribution. In the present invention, instead of using a circular fiber core, the shape of the fiber core used is square. The square core would make the guided light modes mix and form an extremely even light distribution at the implanted end of the fiber as seen in figure 4b. These results are based on the accurate modeling and ray trace analysis in Zemax OpticStudfio.

Fiber-based neural implants have the advantage of low production costs and high reliability. However, in the prior art fiber implant, all the electrodes emanate at the flat end surface of the fiber shank. This makes the implant activate or record from the neurons at one specific cortical layer in the brain. To achieve depth-resolved neural activity recording, longitudinal distributed electrodes have to be added by some very complicated methods, such as micro-fabrication, and photolithography. This lead to a high development production cost.

For the proposed fiber-based neural implant of the invention, the longitudinal distributed electrodes are introduced to the angled fiber tip with a blade cutting or fiber polishing method providing a fiber shank having a depth-resolved neural recording function with a very low fabrication cost.

In addition, the existing implantable fiber-based neural implants have a round core shape and an uneven light distribution at the output end of the optical

waveguide. By contrast, the proposed fiber implant has a square core shape, which can make the guiding mode mix and form a uniform emission pattern.

To obtain a substantially uniform intensity distribution of light radiation from the core at the fiber tip, the core may be formed as a square, a rectangle, quadrangle, or any non-circular form from which a substantially uniform intensity distribution of light radiation from the core is obtained.

The setup connectorization may comprise an electrophysiology setup connectorization or a photopharmacology setup connectorization or an optical setup.

Neuromodulation refers to the process of using various techniques to modify or regulate the activity of the nervous system. It involves the application of electrical, chemical, or physical stimulation to specific neural structures in order to modulate their function.

Neuromodulation techniques are primarily used for therapeutic purposes to treat neurological and psychiatric conditions that involve abnormal neural activity. These techniques aim to restore or normalize neural activity, alleviate symptoms, and improve the overall functioning of the nervous system.

Electrophysiology is a branch of physiology that studies the electrical activity of biological cells and tissues. It involves the measurement and analysis of electrical signals generated by living organisms, particularly the electrical properties of cells, such as neurons and muscle cells.

Photopharmacology is a field of research that involves the development and use of photosensitive molecules - photopharmaceuticals - to control biological processes with light. It combines principles from pharmacology and optics to enable precise spatiotemporal control over cellular processes and signalling pathways.

Traditional pharmacology relies on the use of drugs that interact with specific molecular targets in the body, such as receptors or enzymes, to modulate their activity and produce a desired effect. In photopharmacology, photosensitive

molecules are designed to undergo specific chemical or structural changes upon exposure to light, allowing them to switch their activity on or off in a controlled manner.

The fiber-based implantable neural implant comprises several components, including:

Fiber shank: This is the main body of the implant housing the optical waveguide and any associated electronics or sensors. The fiber shank may be 10 cm long when used in humans but may also be as small as 1-4 mm for instance when used in small animals. The diameter of the fiber shank may be 0.1 - 1 mm.

The optical waveguide: The waveguide transmits light and comprises a core and a cladding. The optical waveguide is substantially identical to the fiber shank with the exception of additions of conduits and electrodes to the fiber shank.

The core: The core is an optical material that is designed to transmit light signals. It can be used to both stimulate and monitor neural activity. The core is made of material of a different refractive index than the cladding. Typically, the refractive index of the core is higher than the refractive index of the cladding, but the refractive index of the core may alternatively be lower than the refractive index of the cladding through bandgap/antiresonant mechanism, the core and cladding are constructed so that the transmitted light substantially propagates in the core.

When the refractive index of the core is higher than the refractive index of the cladding, the core may be made of polycarbonate with a refractive index of 1.57 while the cladding may by made of poly methyl methacrylate with a refractive index of 1.48. In the case when the refractive index of the core is lower than the refractive index of the cladding, the core may be air with a refractive index of 1.00.

The cladding: The cladding houses the core which is placed in a central hole in the cladding and the conduits which are electrodes, microfluidic channels, and other possible sensors. The cladding may be made from a variety of materials, such as,

glass, polymers, or a combination hereof. The cladding will typically have the form of a tube.

Conduits: The conduits are channels going from the proximal end of the fiber shank to the inserted end, where they emanate in the angled surface. The conduits are holding electrodes to measure electrical neuronal activities at the outlet end of the conduit, or the conduits may be used as channels for delivering drugs.

Electrodes: The electrodes are small conductive elements that are used to detect or stimulate electrical activity in the brain. They are integrated into microstructure conduits in the cladding and may be used in conjunction with the optical core to provide a more complete picture of neural activity.

Sensors: The implant may also include various types of sensors, such as temperature sensors, pressure sensors, or chemical sensors. These sensors can be used to monitor changes in the environment surrounding the implant, providing additional context for the neural activity being recorded.

Electronics: The neural implant may include various types of electronics, such as amplifiers or signal processors, which are used to amplify and analyse the signals collected by the optical fibers, electrodes, and microfluidic channels.

Adapter: The proximal end of the fiber shank is connected to an adaptor. The adaptor may be connected to external equipment, such as data acquisition systems or stimulation devices. Especially the adaptor may be connected to a light source, so that the adapter ensures the light is transmitted into the core of the optical waveguide. The adaptor may also be connected to the microfluidic channels ensuring that drugs are delivered into the microfluidic channels.

According to an embodiment, the angled surface of the fiber tip comprises an angle relative to the longitudinal direction of the fiber shank so that the angled surface is not perpendicular relative to the longitudinal direction of the fiber shank.

A further advantage of the invention is that using a fiber tip with an angle relative to the longitudinal direction of the fiber shank is that the use of the implant will causes less inflammation in the brain in chronic application than a fiber tip with is perpendicular to the longitudinal direction of the fiber shank.

According to an embodiment, the angle of the fiber tip relative to the longitudinal direction of the fiber shank is between 0° and 90° degrees, more preferable between 15° and 75°, or even more preferable between 30° and 60°.

In a typical embodiment, the angle may preferably be 30° ensuring that the channels emanate at different depths in the tissue. However, the angle may be selected to ensure the different depths are suitable for the task to be performed.

According to an embodiment, the cross-section of the core is substantially formed as a rectangle, a square, or any non-circular geometry.

Preferably, the cross-section of the core is formed as a square, but other forms may also be used. The cross-section may be a rectangle, a quadrangle, or any other form providing a substantially uniform intensity distribution of light radiation from the core at the fiber tip. That the core is substantially formed as a square or a rectangle is to be understood that the square or rectangle may have rounded corners.

According to an embodiment, the cladding surrounds the core so that the optical waveguide and electrodes in the fiber tip are in contact with tissue when implanted.

The fiber shank is formed so the core is inside the cladding, so the only part of the core in contact with the tissue when implanted is exposed at the angled surface end.

According to an embodiment, the cladding comprises microfluidic channels for drug delivery in photopharmacology.

The microfluidic channels are conduits wherein no electrode is inserted, or from which an electrode has been removed.

According to an embodiment, the core and the cladding are made of polymer materials with a Young's modulus less than 10 GPa.

Alternatively, the cladding may be made of polymer and the core may be made of glass.

The neural implant is inserted in neural tissue and therefore the implant may preferably be made of soft material to reduce possible damage to the neural tissue.

According to an embodiment, the proximal end is attached to the adaptor, and by connecting the adaptor with a light source, light is delivered to the fiber tip.

According to an embodiment, the electrodes are exposed at the proximal end for the connectorization with an electrophysiology setup for neural activity recording.

In a second aspect, the invention relates to a method for manufacturing an angled fiber-based neural implant for neuromodulation in tissue, wherein

the neural implant comprises

- a fiber shank, and
- an adaptor, for setup connectorization and light source connectorization,

- the fiber shank comprises
  - a proximal end connected to the adaptor,
  - an implanted end for implantation into tissue,
  - a fiber tip at the implanted end,
  - an optical waveguide for optical neuromodulation;
- the optical waveguide comprises a core and a cladding, adapted so that light is able to propagate along the length of the waveguide,

wherein the method comprises:

- providing core material for the core of the optical waveguide,
- providing cladding material for the cladding of the optical waveguide,

- forming a preform comprising the core material and the cladding material so that the core material is inserted into the cladding material, so that a structure is formed in a preform,
- scaling down the preform into a fiber shank by using a thermal drawing method, namely, by loading the preform into a furnace and drawing such preform to fiber by a tractor, adjusting the implant size by varying the feeding and drawing speed,
- cutting the fiber in a suitable length to form a fiber shank, and
- adjusting the fiber tip to comprise an angled surface,

the method is performed so that the fiber shank comprises an optical waveguide, the optical waveguide comprises

- a core comprising a non-circular shape for providing a substantially uniform intensity distribution of light radiation from the core at the fiber tip of the fiber shank when guiding light from a light source at the proximal end, and
- a cladding comprising a central hole, for holding the core, and a plurality of conduits, electrodes may be inserted into one, or more, of the plurality of conduits for electrical neuromodulation,
- the core and the plurality of conduits are placed from the proximal end to the fiber tip,

the optical waveguide is manufactured so that light is able to propagate in the core of the optical waveguide by the total internal reflection principle.

This aspect of the invention is particularly, but not exclusively, advantageous in that the method according to the present invention may be used to manufacture a neural implant with a core comprising a non-circular shape for providing a substantially uniform intensity distribution of light radiation from the core at the fiber tip of the fiber shank and further by providing a fiber tip with an angled surface, the surface being angled relative to the longitudinal direction of the fiber shank, hereby providing conduits emanating at different depth in the tissue when implanted.

According to an embodiment, the method further comprises introducing electrodes by either

- a modified thermal drawing method, namely, loading electrodes into the conduits in the cladding during the drawing process, or
- a post-insertion method comprising exposing the conduits in the cladding followed by the insertion of the electrodes.

According to an embodiment, the method further comprises adjusting the fiber tip of the fiber shank by mechanical cutting, focused ion beam cutting, chemical etching, and/or femtosecond laser micromachining of the fiber tip, so that the plurality of conduits emanates at two, or more, different levels, where each level comprises a different depth into the tissue.

The fiber tip may be adjusted by many different methods, it may be by mechanical cutting, focused ion beam cutting, chemical etching, and/or femtosecond laser micromachining, but any other method to form an angled surface with outlets for the core and the conduits may be used.

According to an embodiment, the method further comprises adjusting the fiber tip at an angle between an angled surface of the fiber tip relative to the longitudinal direction of the fiber shank between 0° and 90° degrees, more preferably between 15° and 75°, or even more preferable between 30° and 60°.

According to an embodiment, the method further comprises

- attaching the proximal end to an adaptor, so that light entering the core from the light source at the proximal end is exiting the core at the fiber tip at the implanted end.

The first and second aspects of the present invention may each be combined with any other aspects. These and other aspects of the invention will be apparent from and elucidated with reference to the embodiments described hereinafter.

BRIEF DESCRIPTION OF THE FIGURES

The neural implant according to the invention will now be described in more detail with regard to the accompanying figures. The figures show one way of

implementing the present invention and are not to be construed as being limiting to other possible embodiments falling within the scope of the attached claim set.

Fig. 1 illustrates the fiber shank of the neural implant.
Fig. 2 illustrates the side view of the fiber implant with microstructure conduits illustrated in dashed lines for neuromodulation at different depths.
Fig. 3 illustrates the neural implant inserted in a brain of a mouse.
Fig. 4a and 4b illustrate the difference between using a circular or a square core in the fiber shank.
Fig. 5a and 5b illustrate a method for manufacturing the fiber shank for the neural implant.
Fig. 6a and 6b illustrate two different methods for adding electrodes in the microstructure conduits.
Fig. 7 illustrates cutting the angled surface at the implanted end.
Fig. 8 is a flowchart of a method according to the invention.
Fig. 9 shows a diagram illustrating that there is less tissue inflammation using an angled fiber tip compared to flat-cleaved implant.

DETAILED DESCRIPTION OF AN EMBODIMENT

Fig. 1 shows the fiber shank 5 of the neural implant 1. The optical waveguide 7 comprises a core 10 surrounded by a cladding 11. The fiber shank further comprises a fiber tip 12 at an implanted end 20. The fiber tip comprises a flat angled surface 14; the angled surface is angled relative to the longitudinal direction 19 of the fiber shank. The core 10 emanates in the centre of the fiber tip 12. In the cladding 11 there are microstructure conduits 13 going from the proximal end 21 to the tip 12 at the implanted end 20 and the microstructure conduits 13 comprises outlets 13' in the angled surface 14 of the fiber tip. Also, the core 10 comprises an outlet 10' in the angled surface 14 of the fiber tip.

Fig. 2 shows in (a) the neural implant from the side with the location of the microstructure conduits 13 in the cladding 11 are illustrated with dashed lines. (b) shows the neural implant from the front, so the angled surface 14 of the fiber tip 12 can be viewed. Fig. 2b shows the angled surface 14 of the fiber tip 12 with the core 10 surrounded by the cladding 11, and the outlets 13' of the microstructure

conduits 13. The outlets 13' of the microstructure conduits 13 are at different levels 25, so different microstructure conduits with outlets at different levels emanates at different depth into the tissue, which may be brain tissue.

Fig. 3 shows the neural implant 1, comprising the fiber shank 5 and the adaptor 6, inserted in a brain 32 of a mouse 35. The implanted end 20 with the angled surface 14 is located in the brain of the mouse, while the proximal end is outside the skull of the mouse and is connected through the adaptor 6 to a light source 30 so the core is guiding light from the light source to the fiber tip. Further, the microstructure conduits are connected through the adaptor 6 to an electrophysiology setup 31, where some conduits may hold electrodes and other conduits may be microfluidic channels.

An enlarged section of Fig. 3 shows the tip of the fiber shank and illustrates that the outlets 13' of the microstructure conduits emanate at different levels 25 of the angled surface 14 of the implanted end 20.

Fig. 4a and 4b show the difference between using a circular or a square core in the fiber shank. Fig. 4a and 4b show the light distribution profile at the output end of the 30° tip angle fiber with circular and square cores, respectively. The intensity has been normalized. Clearly, the light intensity is much more evenly distributed using a square core. When using a circular core, the light intensity is highest in the center of the circular core, whereas using a square core, the light intensity is evenly distributed all over the square core.

Fig. 5a illustrates a method for manufacturing the fiber shank for the neural implant. When manufacturing the fiber shank, a square core of core material 51 is inserted in a structured tube of cladding material 52 creating a preform 53. Fig. 5b shows that the preform 53 is then heated by a furnace 54 and attached to a tractor 55, which draws a fiber 56 out of the preform. The fiber 56 maintains the same structure as the preform with a core, a cladding, and microstructure conduits.

Fig. 6a and 6b show two different methods for adding electrodes in the microstructure conduits. Fig. 6a shows that the electrodes may be added during

the drawing process by pulling metal wires 61 from a feeder 62 and inserting the metal wires in the preform. The tractor 55 is used for pulling the metal wires feeder 62 and the preform feeder 53 during the manufacturing process of the fiber shank. Alternatively, as shown in fig. 6b, metal wires 61, which work as electrodes 63, may be inserted in the microstructure conduits 13 after the fiber shank 5 has been formed.

Fig. 7 shows that after the fiber shank 5 has been formed, a blade 71 is used to cut the angled surface at the implanted end 20 so that the outlets 13' of the microstructure conduits 13 are at different levels.

Fig. 8 illustrates the method of manufacturing the neural implant by providing (S1) core material for the core of the optical waveguide and providing (S2) cladding material for the cladding of the optical waveguide. The core material and the cladding material are used to form (S3) a preform where the core material is inserted into the cladding material so that basically the preform is formed with a core with a square cross-section surrounded by a tube-formed cladding material. In addition, the conduits are formed in the cladding material. Then the preform is scaled down (S4) by a thermal drawing method by loading the preform into a furnace and the preform is then drawn into a fiber by a tractor drawing the fiber so that the preform is stretched into a fiber of a desired size by varying the speed of the tractor.

Furthermore, the method comprises cutting (S5) the fiber into a suitable length to form a fiber shank of a required length and finally adjusting (S6) the fiber tip to comprise an angled surface. The surface being angled relative to the longitudinal direction of the fiber shank.

A further advantage of using a fiber tip (12) with an angled surface (14) is that the reduced materials when introducing the angled tip by cutting method would cause less inflammation in chronic application compared with flat end face fiber. Fig. 9 shows a diagram with a comparison between the mean values for fluorescent intensity (arbitrary units) which is indication the degree of inflammation in the brain four weeks after the implantation. Fig. 9 is showing a control mean florescence intensity value 91, where the fluorescent intensity is

measured where there is no implant, a mean florescence intensity value 92 for the fluorescent intensity measured using an angled implant of the invention, and a mean florescence intensity value 93 for the fluorescent intensity measured using an implant with a flat end face fiber. The mean florescence intensity measured for the flat end shows a higher intensity than the mean florescence intensity measured for the angled surface. This is an experimental verification that the implant with an angled surface causes less inflammation.

Although the present invention has been described in connection with the specified embodiments, it should not be construed as being in any way limited to the presented examples. The scope of the present invention is set out by the accompanying claim set. In the context of the claims, the terms "comprising" or "comprises" do not exclude other possible elements or steps. Also, the mentioning of references such as "a" or "an" etc. should not be construed as excluding a plurality. The use of reference signs in the claims with respect to elements indicated in the figures shall also not be construed as limiting the scope of the invention. Furthermore, individual features mentioned in different claims, may possibly be advantageously combined, and the mentioning of these features in different claims does not exclude that a combination of features is not possible and advantageous.

In exemplary embodiments E1-E14, the invention may relate to:

E1. An angled fiber-based neural implant for neuromodulation in tissue, wherein

- the neural implant (1) comprises
  - a fiber shank (5), and
  - an adaptor (6), for setup connectorization and light source connectorization,
- the fiber shank comprises
  - a proximal end (21) connected to the adaptor,
  - an implanted end (20) for implantation into tissue, and
  - a fiber tip (12) at the implanted end,
  - an optical waveguide (7) for optical neuromodulation,
  - a plurality of conduits (13), and

- electrodes (63) may be inserted into one, or more, of the plurality of conduits for electrical neuromodulation,

- the optical waveguide (7) comprises a core (10) and a cladding (11), adapted so that light is able to propagate along the length of the optical waveguide,
- the cladding (11) comprises a central hole (22), the core (10) is placed in the central hole and is going from the proximal end (21) to the fiber tip (12), and
- the plurality of conduits (13) are embedded in the fiber shank (5), each conduit going from the proximal end (21) to the fiber tip (12);

wherein the non-circular shape of the core (10) is arranged for providing a substantially uniform intensity distribution of light radiation from the core at the fiber tip (12); and

wherein the fiber tip comprises an angled surface (14), the end (10') of the core and the end (13') of the plurality of conduits are exposed at the angled surface so that the plurality of conduits (13) emanates at two or more different levels (25), where each level comprises a different depth into the tissue.

E2. The neural implant according to embodiment E1, wherein the angled surface (14) of the fiber tip (12) comprises an angle relative to the longitudinal direction (19) of the fiber shank (5) so that the angled surface is not perpendicular relative to the longitudinal direction of the fiber shank.

E3. The neural implant according to any of the embodiments E1-E2, wherein the angle of the fiber tip (12) relative to the longitudinal direction (19) of the fiber shank (5) is between 0° and 90° degrees, more preferable between 15° and 75°, or even more preferable between 30° and 60°.

E4. The neural implant according to any of the embodiments E1-E3, wherein the cross-section of the core (10) is substantially formed as a rectangle, a square or any non-circular geometry.

E5. The neural implant according to any of the embodiments E1-E4, wherein the cladding (11) surrounds the core (10) so that the optical waveguide (7) and electrodes (63) in the fiber tip (12) are in contact with tissue when implanted.

E6. The neural implant according to any of the embodiments E1-E5, wherein the cladding (11) comprises microfluidic channels for drug delivery in photopharmacology.

E7. The neural implant according to any of the embodiments E1-E6, wherein the core (10) and cladding (11) are made of polymer materials with a Young's modulus less than 10 GPa.

E8. The neural implant according to any of the embodiments E1-E7, wherein the proximal end (21) is attached to the adaptor (6), and by connecting the adaptor with a light source, light is delivered to the fiber tip (12).

E9. The neural implant according to any of the embodiments E1-E8, wherein the electrodes (63) are exposed at the proximal end (21) for the connectorization with an electrophysiology setup for neural activity recording.

E10. A method for manufacturing an angled fiber-based neural implant for neuromodulation in tissue, wherein

the neural implant (1) comprises
- a fiber shank (5), and
- an adaptor (6), for setup connectorization and light source connectorization,

- the fiber shank (5) comprises
  - a proximal end (21) connected to the adaptor,
  - an implanted end (20) for implantation into tissue,
  - a fiber tip (12) at the implanted end,

- an optical waveguide (7) for optical neuromodulation;

- the optical waveguide comprises a core (10) and a cladding (11), adapted so that light is able to propagate along the length of the waveguide,

wherein the method comprises:

- providing (S1) core material (51) for the core (10) of the optical waveguide (7),
- providing (S2) cladding material (52) for the cladding (11) of the optical waveguide (7),
- forming (S3) a preform (53) comprising the core material and the cladding material so that the core material is inserted into the cladding material so that a structure is formed in a preform,
- scaling (S4) down the preform (53) into a fiber shank (5) by using a thermal drawing method, namely, by loading the preform (53) into a furnace (54) and drawing such preform (53) to fiber (56) by a tractor (55), adjusting the implant size by varying the feeding and drawing speed,
- cutting (S5) the fiber (56) in a suitable length to form a fiber shank (5), and
- adjusting (S6) the fiber tip (12) to comprise an angled surface (14),

the method is performed so that the fiber shank (5) comprises an optical waveguide (7), the optical waveguide comprises

- a core (10) comprising a non-circular shape for providing a substantially uniform intensity distribution of light radiation from the core (10) at the fiber tip (12) of the fiber shank (5) when guiding light from a light source (30) at the proximal end (21), and
- a cladding (11) comprising a central hole (22) for holding the core (10), and a plurality of conduits (13), electrodes (63) may be inserted into one, or more, of the plurality of conduits (13) for electrical neuromodulation,
- the core (10) and the plurality of conduits (13) are placed from the proximal end (21) to the fiber tip (12),

the optical waveguide is manufactured so that light is able to propagate in the core (10) of the optical waveguide (7) by the total internal reflection principle.

E11. The method for manufacturing a neural implant according to embodiment E10, wherein the method further comprises introducing electrodes (63) by either

- a modified thermal drawing method, namely, loading electrodes (63) into the conduits (13) in the cladding (11) during the drawing process, or
- a post-insertion method comprising exposing the conduits (13) in the cladding (11) followed by the insertion of the electrodes (63).

E12. The method for manufacturing a neural implant according to any of the embodiments E10-E11, wherein the method further comprises adjusting the fiber tip (12) of the fiber shank (5) by mechanical cutting, focused ion beam cutting, chemical etching, and/or femtosecond laser micromachining of the fiber tip, so that the plurality of conduits (13) emanates at two, or more, different levels (25), where each level comprises a different depth into the tissue.

E13. The method for manufacturing a neural implant according to any of the embodiments E10-E12, wherein the method further comprises adjusting the fiber tip (12) at an angle between an angled surface (14) of the fiber tip (12) relative to the longitudinal direction (19) of the fiber shank (5) between 0° and 90° degrees, more preferably between 15° and 75°, or even more preferable between 30° and 60°.

E14. The method for manufacturing a neural implant according to any of the embodiments E10-E13, wherein the method further comprises

- attaching the proximal end (21) to an adaptor (6), so that light entering the core (10) from the light source (30) at the proximal end is exiting the core at the fiber tip (12) at the implanted end (20).

CLAIMS:

1. An angled fiber-based neural implant for neuromodulation in tissue, wherein
   - the neural implant (1) comprises
     - a fiber shank (5), and
     - an adaptor (6), for setup connectorization and light source connectorization,
   - the fiber shank comprises
     - a proximal end (21) connected to the adaptor,
     - an implanted end (20) for implantation into tissue, and
     - a fiber tip (12) at the implanted end,
     - an optical waveguide (7) for optical neuromodulation,
     - a plurality of conduits (13), and
     - electrodes (63) may be inserted into one, or more, of the plurality of conduits for electrical neuromodulation,
   - the optical waveguide (7) comprises a core (10) and a cladding (11), adapted so that light is able to propagate along the length of the optical waveguide,
   - the cladding (11) comprises a central hole (22), the core (10) is placed in the central hole and is going from the proximal end (21) to the fiber tip (12), and
   - the plurality of conduits (13) are embedded in the fiber shank (5), each conduit going from the proximal end (21) to the fiber tip (12);

   wherein the non-circular shape of the core (10) is arranged for providing a substantially uniform intensity distribution of light radiation from the core at the fiber tip (12);

   wherein the fiber tip comprises an angled surface (14), the end (10') of the core and the end (13') of the plurality of conduits are exposed at the angled surface so that the plurality of conduits (13) emanates at two or more different levels (25), where each level comprises a different depth into the tissue; and

   wherein the angled surface (14) of the fiber tip (12) comprises an angle relative to the longitudinal direction (19) of the fiber shank (5) so that the angled surface is not perpendicular relative to the longitudinal direction of the fiber shank.

2. The neural implant according to claim 1, wherein the angle of the fiber tip (12) relative to the longitudinal direction (19) of the fiber shank (5) is between 0° and 90° degrees, more preferable between 15° and 75°, or even more preferable between 30° and 60°.

3. The neural implant according to any of the claims 1-2, wherein the cross-section of the core (10) is substantially formed as a rectangle, a square or any non-circular geometry.

4. The neural implant according to any of the claims 1-3, wherein the cladding (11) surrounds the core (10) so that the optical waveguide (7) and electrodes (63) in the fiber tip (12) are in contact with tissue when implanted.

5. The neural implant according to any of the claims 1-4, wherein the cladding (11) comprises microfluidic channels for drug delivery in photopharmacology.

6. The neural implant according to any of the claims 1-5, wherein the core (10) and cladding (11) are made of polymer materials with a Young's modulus less than 10 GPa.

7. The neural implant according to any of the claims 1-6, wherein the proximal end (21) is attached to the adaptor (6), and by connecting the adaptor with a light source, light is delivered to the fiber tip (12).

8. The neural implant according to any of the claims 1-7, wherein the electrodes (63) are exposed at the proximal end (21) for the connectorization with an electrophysiology setup for neural activity recording.

9. A method for manufacturing an angled fiber-based neural implant for neuromodulation in tissue, wherein
the neural implant (1) comprises
    - a fiber shank (5), and
    - an adaptor (6), for setup connectorization and light source connectorization,
- the fiber shank (5) comprises
    - a proximal end (21) connected to the adaptor,
    - an implanted end (20) for implantation into tissue,
    - a fiber tip (12) at the implanted end,
    - an optical waveguide (7) for optical neuromodulation;
- the optical waveguide comprises a core (10) and a cladding (11), adapted so that light is able to propagate along the length of the waveguide,

wherein the method comprises:

- providing (S1) core material (51) for the core (10) of the optical waveguide (7),
- providing (S2) cladding material (52) for the cladding (11) of the optical waveguide (7),
- forming (S3) a preform (53) comprising the core material and the cladding material so that the core material is inserted into the cladding material so that a structure is formed in a preform,
- scaling (S4) down the preform (53) into a fiber shank (5) by using a thermal drawing method, namely, by loading the preform (53) into a furnace (54) and drawing such preform (53) to fiber (56) by a tractor (55), adjusting the implant size by varying the feeding and drawing speed,
- cutting (S5) the fiber (56) in a suitable length to form a fiber shank (5), and
- adjusting (S6) the fiber tip (12) to comprise an angled surface (14),

the method is performed so that the fiber shank (5) comprises an optical waveguide (7), the optical waveguide comprises

- a core (10) comprising a non-circular shape for providing a substantially uniform intensity distribution of light radiation from the core (10) at the

fiber tip (12) of the fiber shank (5) when guiding light from a light source (30) at the proximal end (21), and

- a cladding (11) comprising a central hole (22) for holding the core (10), and a plurality of conduits (13), electrodes (63) may be inserted into one, or more, of the plurality of conduits (13) for electrical neuromodulation,
- the core (10) and the plurality of conduits (13) are placed from the proximal end (21) to the fiber tip (12),

the optical waveguide is manufactured so that light is able to propagate in the core (10) of the optical waveguide (7) by the total internal reflection principle, and

the angled surface (14) of the fiber tip (12) comprises an angle relative to the longitudinal direction (19) of the fiber shank (5) so that the angled surface is not perpendicular relative to the longitudinal direction of the fiber shank.

10. The method for manufacturing a neural implant according to claim 9, wherein the method further comprises introducing electrodes (63) by either
    - a modified thermal drawing method, namely, loading electrodes (63) into the conduits (13) in the cladding (11) during the drawing process, or
    - a post-insertion method comprising exposing the conduits (13) in the cladding (11) followed by the insertion of the electrodes (63).

11. The method for manufacturing a neural implant according to any of the claims 9-10, wherein the method further comprises adjusting the fiber tip (12) of the fiber shank (5) by mechanical cutting, focused ion beam cutting, chemical etching, and/or femtosecond laser micromachining of the fiber tip, so that the plurality of conduits (13) emanates at two, or more, different levels (25), where each level comprises a different depth into the tissue.

12. The method for manufacturing a neural implant according to any of the claims 9-11, wherein the method further comprises adjusting the fiber tip (12) at an angle between an angled surface (14) of the fiber tip (12) relative to the

longitudinal direction (19) of the fiber shank (5) between 0° and 90° degrees, more preferably between 15° and 75°, or even more preferable between 30° and 60°.

13. The method for manufacturing a neural implant according to any of the claims 9-12, wherein the method further comprises
    - attaching the proximal end (21) to an adaptor (6), so that light entering the core (10) from the light source (30) at the proximal end is exiting the core at the fiber tip (12) at the implanted end (20).

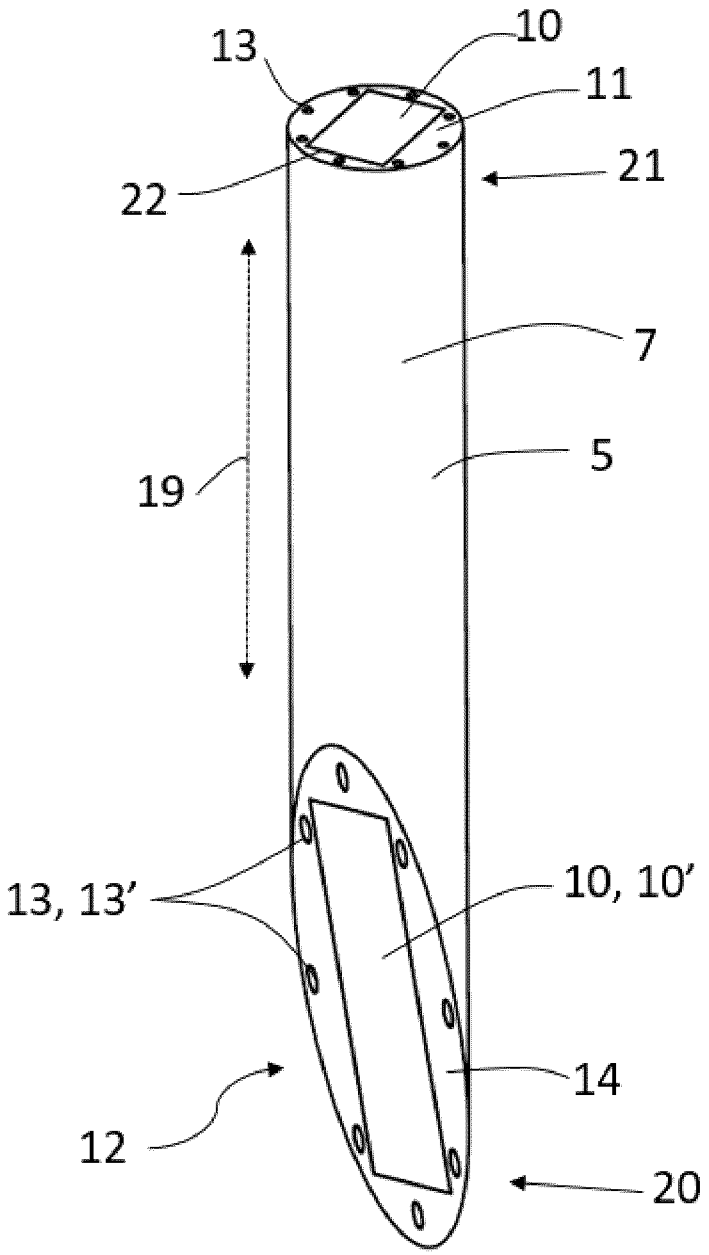


Fig. 1

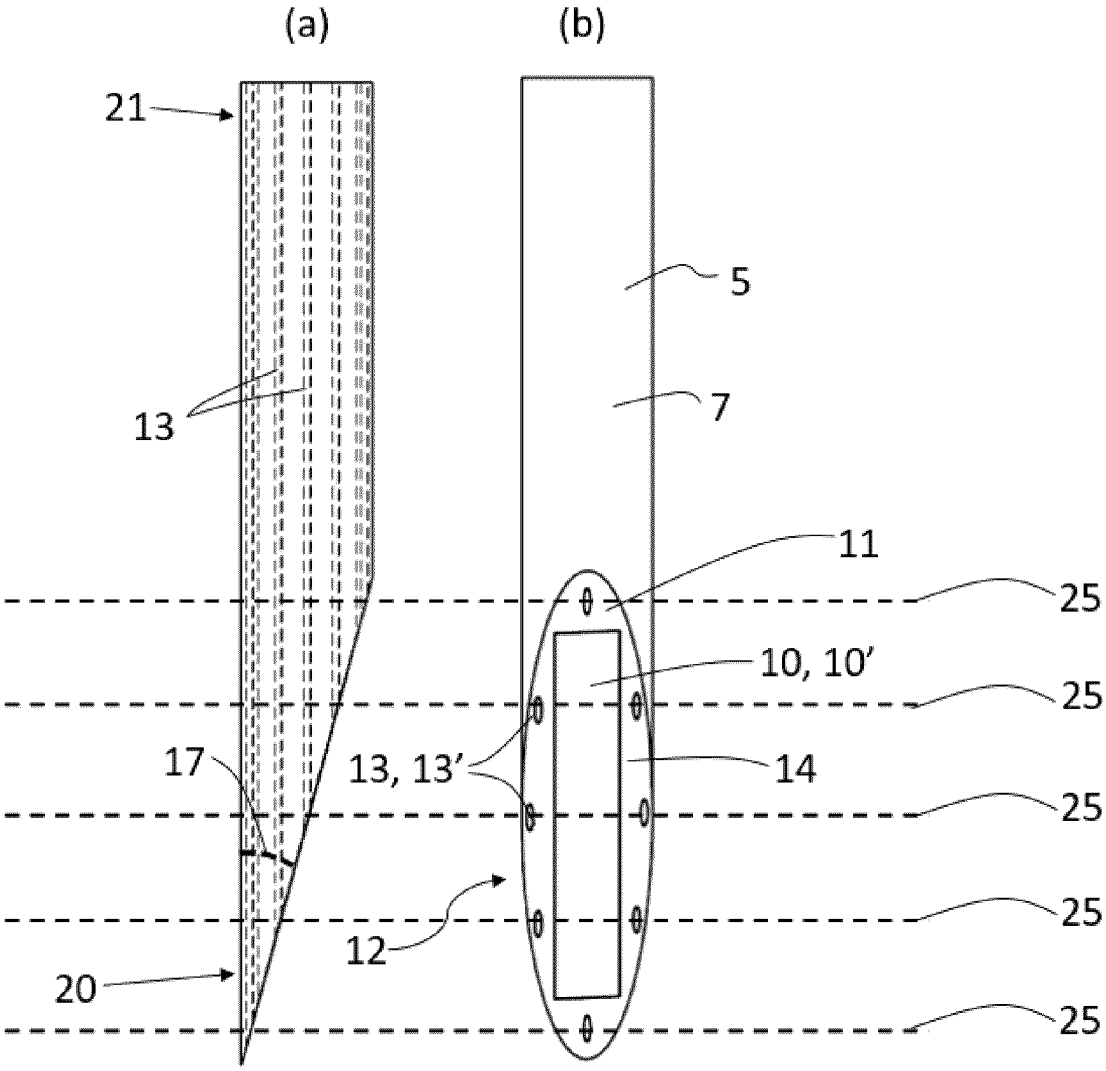


Fig. 2

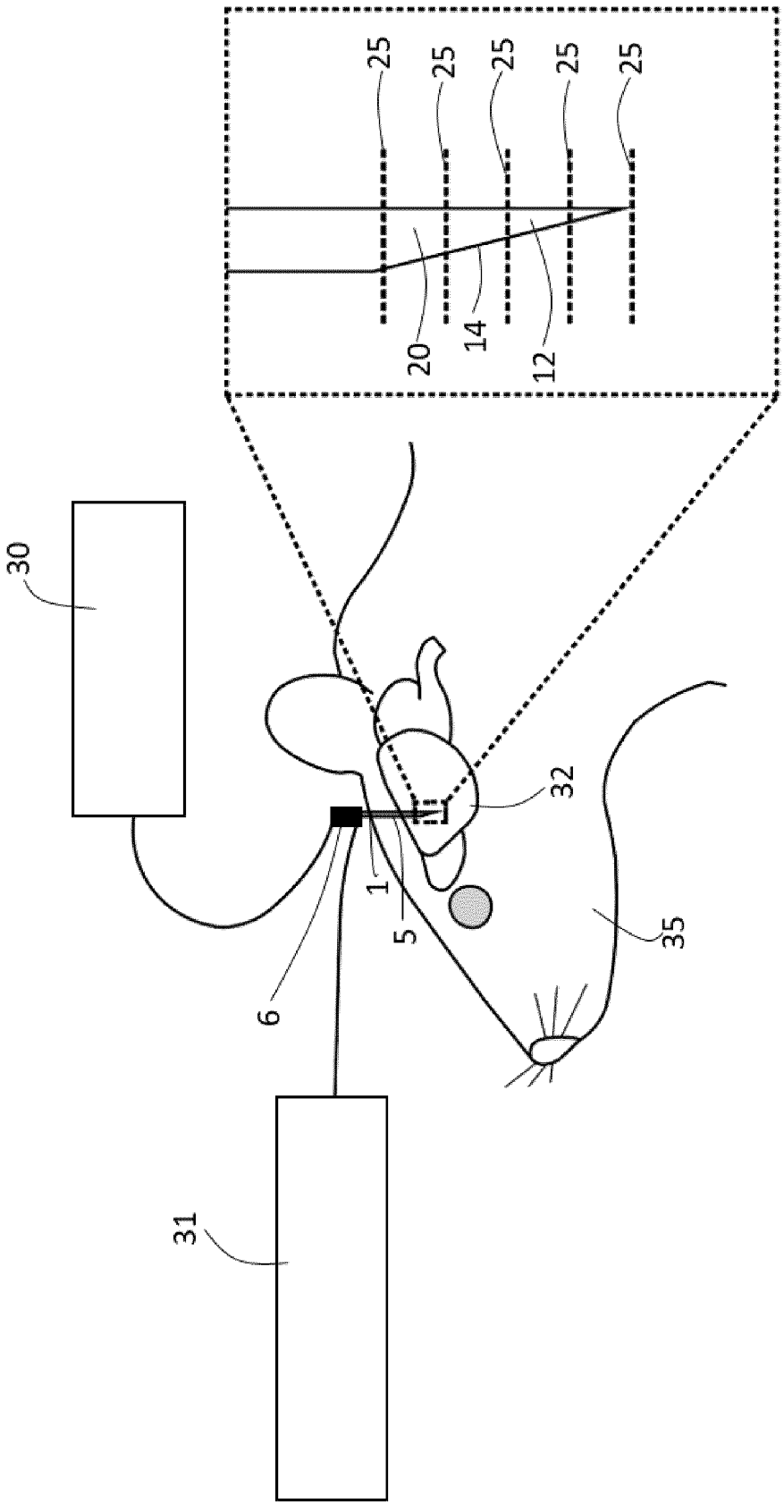
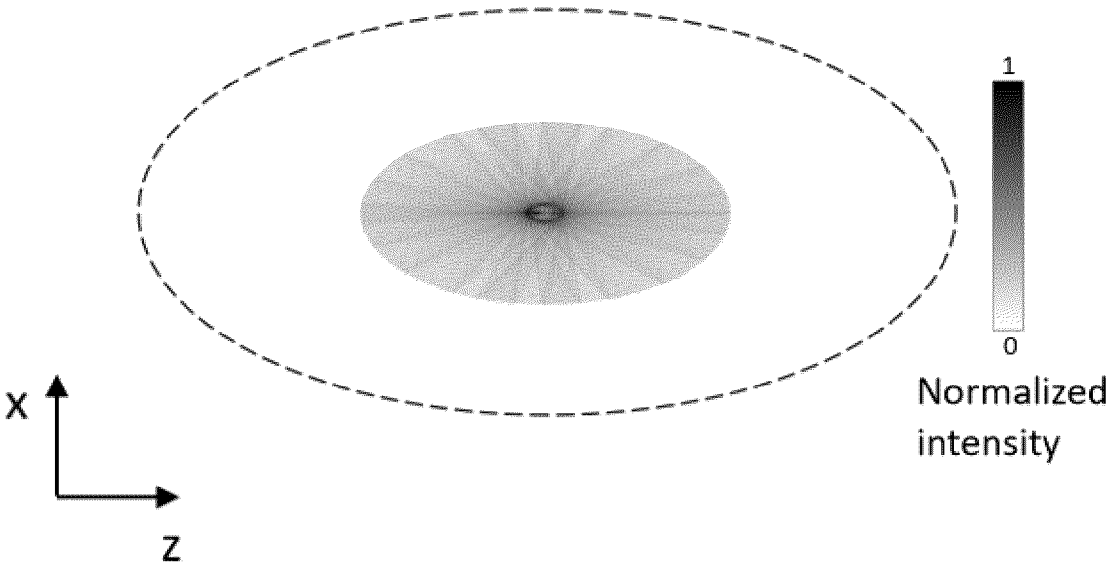


Fig. 3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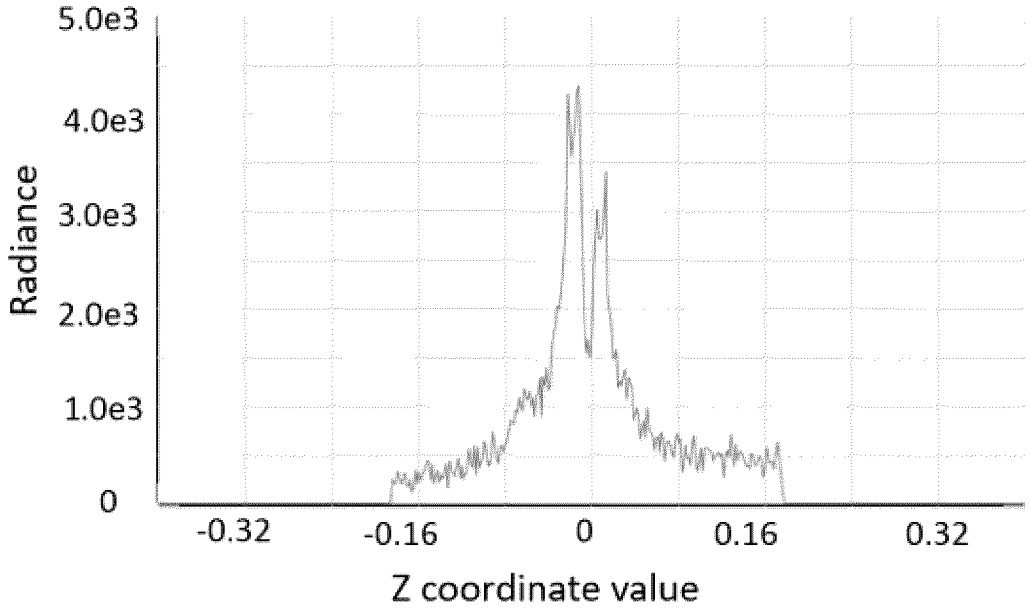
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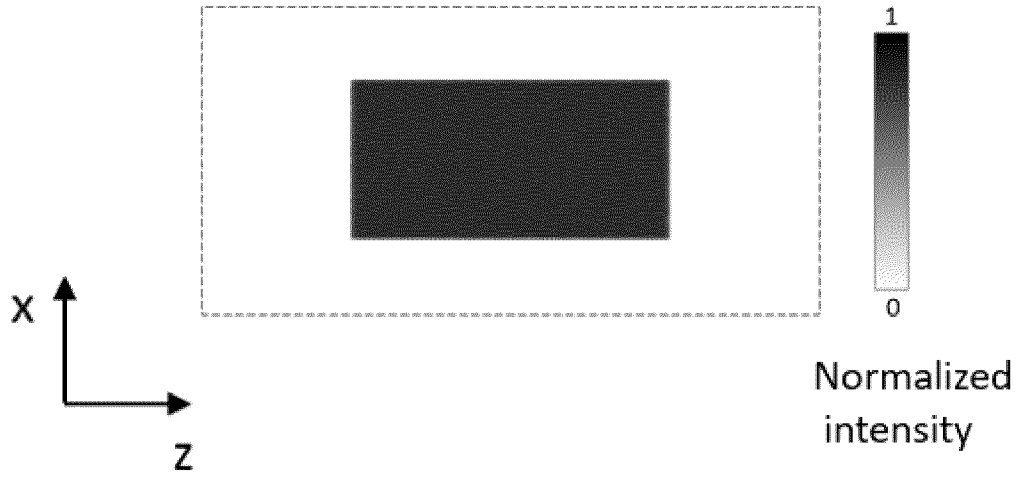
Fig. 4a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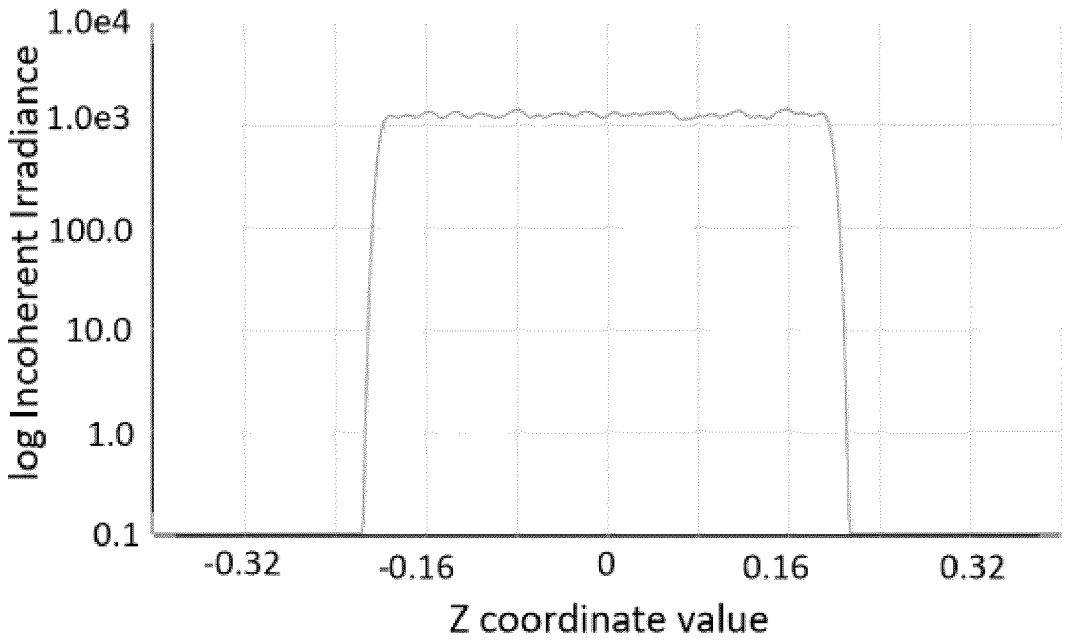
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Fig. 4b

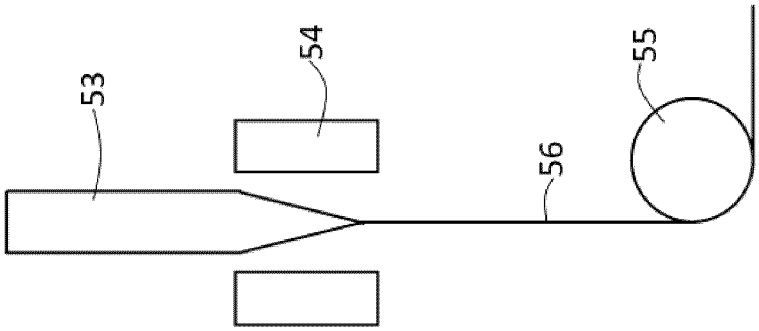


Fig. 5b

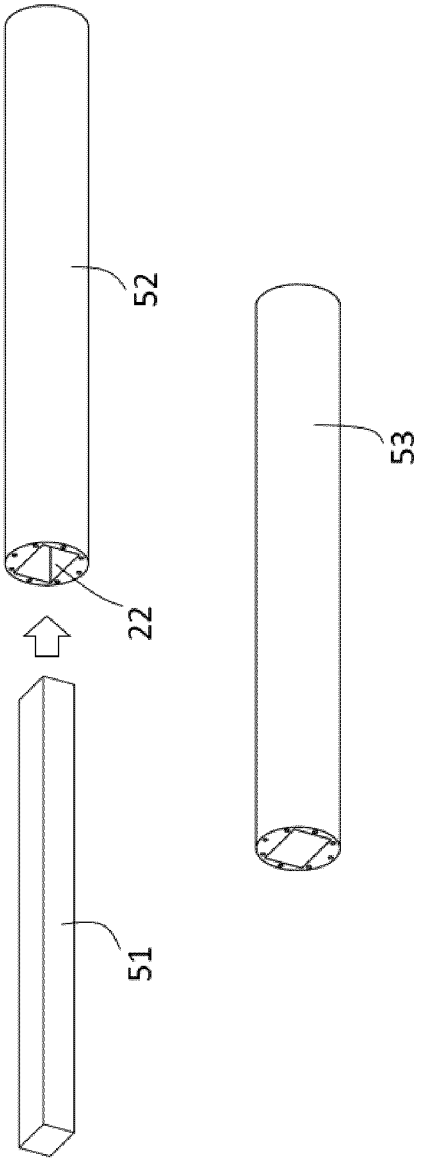


Fig. 5a

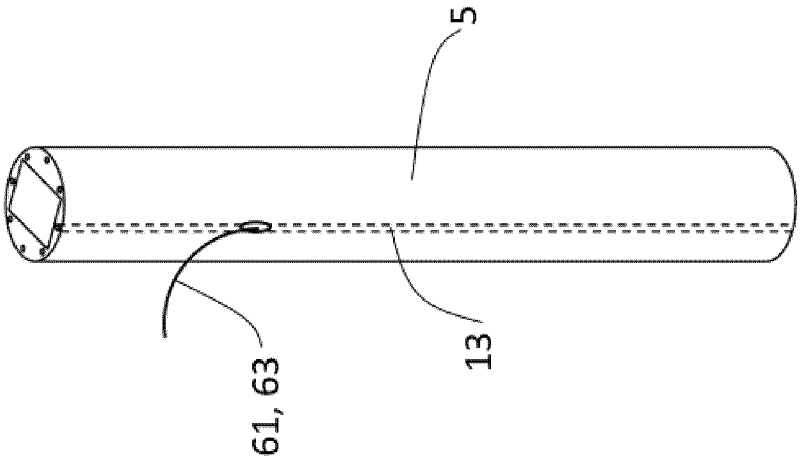


Fig. 6b

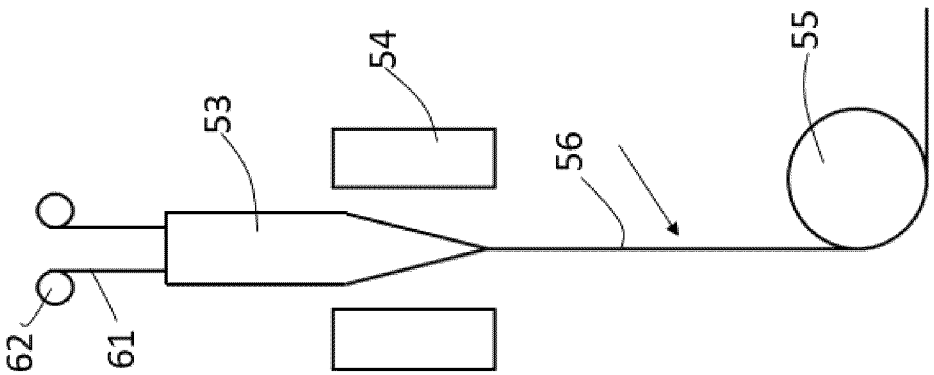


Fig. 6a

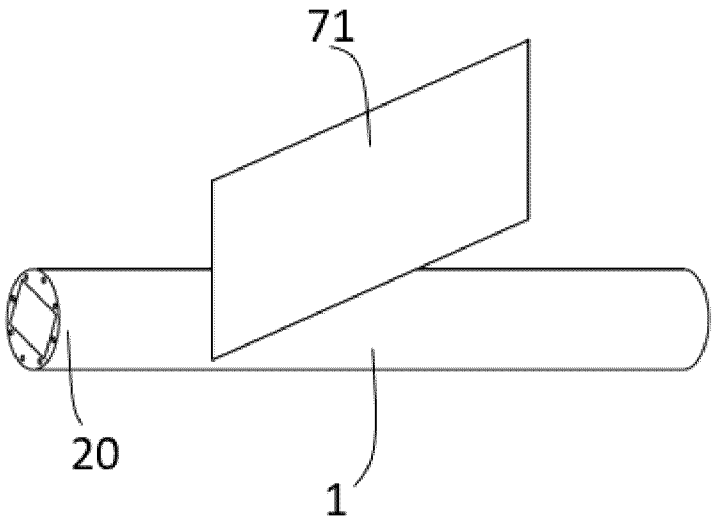


Fig. 7

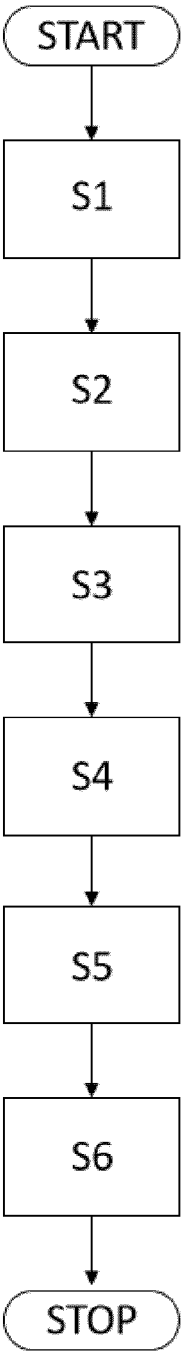
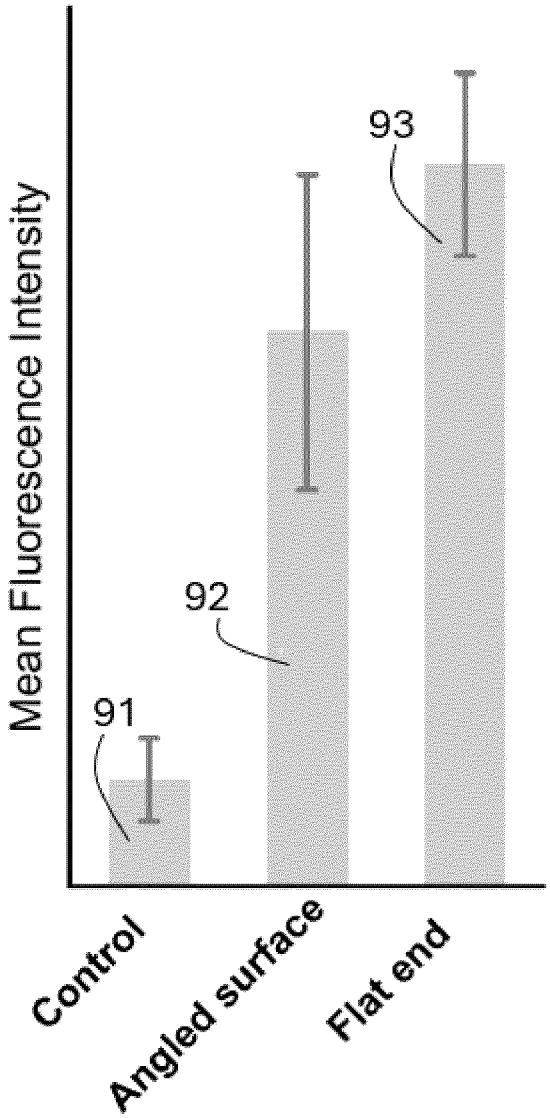


Fig. 8


Mean Fluorescence Intensity
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92
93
Control
Angled surface
Flat end

Fig. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/066284

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N5/06 A61N1/18
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)
A61N A61M

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAN ZHENG ET AL: "Multifunctional fiber-based optoacoustic emitter for non-genetic bidirectional neural communication", ARXIV.ORG, CORNELL UNIVERSITY LIBRARY, 201 OLIN LIBRARY CORNELL UNIVERSITY ITHACA, NY 14853, 9 January 2023 (2023-01-09), XP091411462, description of figures 1 and 3; figures 1,3	1-13
A	US 2018/296243 A1 (HANSON TIMOTHY L [US] ET AL) 18 October 2018 (2018-10-18) paragraph [0057]; claims 1,3	1-13
A	US 2013/030352 A1 (SEYMOUR JOHN P [US] ET AL) 31 January 2013 (2013-01-31) the whole document	1-13

-/--

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2024	08/08/2024

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	Beck, Ewa

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/066284

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KIRTI SHARMA ET AL: "Multifunctional optrode for opsin delivery, optical stimulation, and electrophysiological recordings in freely moving rats", JOURNAL OF NEURAL ENGINEERING, INSTITUTE OF PHYSICS PUBLISHING, BRISTOL, GB, vol. 18, no. 6, 15 November 2021 (2021-11-15), page 66013, XP020371731, ISSN: 1741-2552, DOI: 10.1088/1741-2552/AC3206 [retrieved on 2021-11-15] figure 1 -----	1-13

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/066284

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		US 2018296243 A1	18-10-2018
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		WO 2016126340 A2	11-08-2016
US 2013030352 A1	31-01-2013	EP 2736406 A1	04-06-2014
		US 2013030352 A1	31-01-2013
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