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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 September 2017 (14.09.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/156232 A1

(51) International Patent Classification:
A61N 1/05 (2006.01) *A61B 5/00* (2006.01)

(21) International Application Number:
PCT/US2017/021516

(22) International Filing Date:
9 March 2017 (09.03.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/306,909 11 March 2016 (11.03.2016) US

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(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, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, 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, 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).

Published:

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

(54) Title: APPARATUS AND METHOD FOR NERVE STIMULATION AND/OR MONITORING

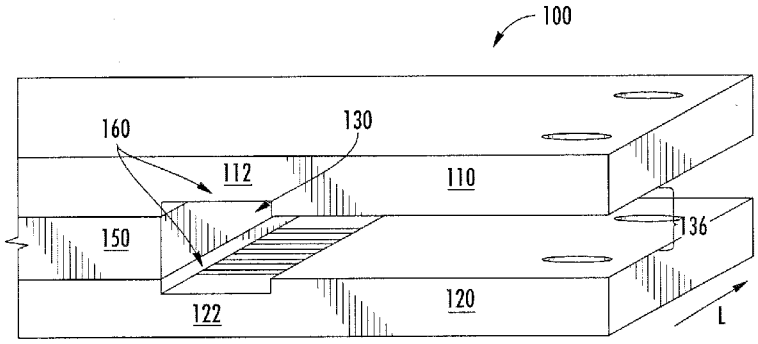

FIG. 1A

(57) Abstract: In one aspect, an apparatus for stimulating and/or monitoring a nerve is described herein. In some embodiments, the apparatus comprises a top substrate layer, a bottom substrate layer in facing opposition to the top substrate layer, and a channel disposed between the top substrate layer and the bottom substrate layer. The apparatus further comprises a plurality of electrodes disposed on one or more interior surfaces of the channel. Additionally, the channel is defined by the top substrate layer, the bottom substrate layer, and a retaining wall extending at least partially between the top substrate layer and the bottom substrate layer. The retaining wall retains the nerve within the channel.

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APPARATUS AND METHOD FOR NERVE STIMULATION AND/OR MONITORING

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority pursuant to 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Ser. No. 62/306,909, filed on March 11, 2016, which is hereby incorporated by reference in its entirety.

FIELD

[002] The present disclosure relates broadly to implantable medical devices and, more particularly, to bioelectronics devices for nerve stimulation and/or monitoring (recording).

BACKGROUND

[003] Virtually all physiological functions are regulated by neural activity. Accordingly, in the field of bioelectronics, it is frequently desirable to interface nerves in a living organism with an apparatus or device that may be used to stimulate or monitor the nerves. Unfortunately, some current bioelectronics devices suffer from one or more disadvantages. For example, some existing devices can be used only with large nerve branches and/or must be placed on the cortical brain surface. Such locations within the patient can be associated with the regulation of many different physiological functions. Accordingly, some existing devices can provide inconsistent results and/or obscure specific pathways of neural control. Additionally, some current devices are invasively penetrating of the nerve, suitable for use with only severed nerves, and/or difficult to use with nerves having a small diameter, such as a diameter of less than 500 μm. Therefore, there exists a need for improved bioelectronics devices and methods of stimulating and/or monitoring nerves that overcome one or more of the foregoing deficiencies of previous devices and methods.

SUMMARY

[004] In one aspect, apparatuses for nerve stimulation and/or monitoring are described herein which, in some cases, can provide one or more advantages compared to other apparatuses. For example, in some embodiments, an apparatus described herein is non-penetrating and removable. An apparatus described herein may also be "closeable" or otherwise able to retain or secure an

intact (non-severed) nerve, including an intact nerve having a small diameter. Additionally, in some cases, an apparatus described herein can be made by cost-effective microfabrication techniques and can have small and highly reproducible features. Moreover, an apparatus described herein, in some instances, is able to retain and stimulate and/or monitor an intact nerve while also permitting the nerve freedom of motion within the apparatus, thus preventing or reducing mechanical strain on the nerve.

[005] In some embodiments, an apparatus for nerve stimulation and/or monitoring described herein comprises a top substrate layer, a bottom substrate layer in facing opposition to the top substrate layer, and a channel disposed between the top substrate layer and the bottom substrate layer. Additionally, a plurality of electrodes is disposed on one or more interior surfaces of the channel. Further, the channel can be defined by the top substrate layer, the bottom substrate layer, and a retaining wall that extends at least partially between the top substrate layer and the bottom substrate layer. Moreover, this retaining wall can retain the nerve within the channel of the apparatus. The retaining wall may also retain the nerve in contact with the electrodes. In some implementations, the apparatus further comprises a spacer layer disposed between the top substrate layer and the bottom substrate layer.

[006] In another aspect, methods of stimulating and/or monitoring a nerve are described herein. In some embodiments, such a method comprises placing the nerve in the channel of an apparatus described hereinabove. Moreover, the nerve can be placed in contact with the plurality of electrodes of the apparatus. The method can further comprise sending electrical signals from the electrodes to the nerve and/or receiving electrical signals from the nerve to the electrodes. In addition, in some instances, the top substrate layer and the bottom substrate layer of the apparatus define an opening of the channel at a proximal end of the apparatus, and the method further comprises joining the top substrate layer and the bottom substrate layer to close the opening of the channel at the proximal end of the apparatus following placement of the nerve in the channel. Further, in some cases, the nerve is an intact nerve. Moreover, in some embodiments, the apparatus does not penetrate the nerve when the nerve is placed or retained in the channel. Additionally, in some instances, the nerve is a nerve of a living patient, and the method further comprises placing the apparatus within a biological compartment of the patient. In some such embodiments, the apparatus is sealed within the biological compartment of the patient after the nerve is placed in the channel of the apparatus. Further, such a method can also

comprise removing the nerve from the apparatus and removing the apparatus from the patient after sealing the apparatus within the biological compartment of the patient. Additionally, in some embodiments, a method described herein further comprises sending and/or receiving electrical signals to and/or from the nerve, including while the nerve is disposed within a channel of an apparatus described herein.

[007] These and other embodiments are described in greater detail in the detailed description which follows.

BRIEF DESCRIPTION OF THE FIGURES

[008] **FIG. 1A** illustrates a perspective view of an apparatus according to one embodiment described herein.

[009] **FIG. 1B** illustrates an exploded view of the apparatus of **FIG. 1A**.

[0010] **FIG. 2** illustrates a sectional view of the apparatus of **FIG. 1A**.

[0011] **FIG. 3A** illustrates a top plan view of an apparatus according to one embodiment described herein.

[0012] **FIG. 3B** illustrates an enlarged view of a portion of the apparatus of **FIG. 3A**.

[0013] **FIG. 3C** illustrates a perspective view of a portion of the apparatus of **FIG. 3A**.

[0014] **FIGS. 4A-4C** each illustrates a step of a method according to one embodiment described herein.

[0015] **FIG. 5** illustrates a perspective view of a tool used to perform steps of a method according to some embodiments described herein.

[0016] **FIGS. 6A-6D** each illustrates a step of a method according to one embodiment described herein.

[0017] **FIG. 7** illustrates a perspective view of portions of apparatuses according to one embodiment described herein.

[0018] **FIG. 8** illustrates a sectional view of an apparatus according to one embodiment described herein.

[0019] **FIGS. 9A-9D** each illustrates a step of a method according to one embodiment described herein.

DETAILED DESCRIPTION

[0020] Embodiments described herein can be understood more readily by reference to the following detailed description, examples, and figures. Elements, apparatus, and methods described herein, however, are not limited to the specific embodiments presented in the detailed description, examples, and figures. It should be recognized that these embodiments are merely illustrative of the principles of the present invention. Numerous modifications and adaptations will be readily apparent to those of skill in the art without departing from the spirit and scope of the invention.

[0021] In addition, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a stated range of "1.0 to 10.0" should be considered to include any and all subranges beginning with a minimum value of 1.0 or more and ending with a maximum value of 10.0 or less, e.g., 1.0 to 5.3, or 4.7 to 10.0, or 3.6 to 7.9.

[0022] All ranges disclosed herein are also to be considered to include the end points of the range, unless expressly stated otherwise. For example, a range of "between 5 and 10" or "from 5 to 10" or "5-10" should generally be considered to include the end points 5 and 10.

[0023] Further, when the phrase "up to" is used in connection with an amount or quantity, it is to be understood that the amount is at least a detectable amount or quantity. For example, a material present in an amount "up to" a specified amount can be present from a detectable amount and up to and including the specified amount.

I. Apparatuses for Nerve Stimulation and/or Monitoring

[0024] In one aspect, apparatuses for nerve stimulation and/or monitoring are described herein. In some embodiments, such an apparatus comprises a top substrate layer, a bottom substrate layer in facing opposition to the top substrate layer, and a channel disposed between the top substrate layer and the bottom substrate layer. Additionally, a plurality of electrodes can be disposed on one or more interior surfaces of the channel. For example, in some embodiments, top electrodes are disposed on an interior surface of the top surface layer, and bottom electrodes are disposed on an interior surface of the bottom substrate layer.

[0025] As described further hereinbelow, the channel of the apparatus can be defined by the top substrate layer, the bottom substrate layer, and a retaining wall extending at least partially between the top substrate layer and the bottom substrate layer. Moreover, the retaining wall can be operable to or can be configured to retain or secure the nerve within the channel of the

apparatus. The retaining wall can also retain the nerve in contact with the plurality of electrodes. In addition, in some cases, an apparatus described herein further comprises a spacer layer disposed between the top substrate layer and the bottom substrate layer. The height of this spacer layer can at least partially define a height of the channel. Moreover, in some cases, the top substrate layer and/or the bottom substrate layer comprises a recess, cavity, groove, trough, or furrow. Such a recess can have an elongated shape and define an interior surface of the channel. Thus, in some such instances, the channel of the apparatus is defined by the recess of the top substrate layer, the recess of the bottom substrate layer, and the retaining wall.

[0026] Specific components and features of apparatuses according to the present disclosure will now be further described with reference to the figures. It is to be understood that the same reference numerals used in differing figures generally correspond to the same features of an apparatus.

[0027] **FIG. 1A** illustrates a perspective view of an apparatus according to one embodiment described herein. **FIG. 1B** illustrates an exploded view of the apparatus of **FIG. 1A**. **FIG. 2** illustrates a sectional view of the apparatus of **FIG. 1A**. With reference to **FIG. 1A**, **FIG. 1B**, and **FIG. 2**, an apparatus (100) described herein comprises a top substrate layer (110) and a bottom substrate layer (120). The top substrate layer (110) is in facing opposition to the bottom substrate layer (120). In addition, a channel (130) is disposed between the top substrate layer (110) and the bottom substrate layer (120). The channel (130) is partially defined by the space between the top substrate layer (110) and the bottom substrate layer (120). The channel (130) is also defined by a retaining wall (140) extending partially between the top substrate layer (110) and the bottom substrate layer (120). As illustrated in **FIGS. 1A** and **1B**, the retaining wall (140) can be considered to be a single retaining wall having two discontinuous portions (141, 142). Alternatively, the apparatus (100) can be considered to include two retaining walls (141, 142). This structure is due to the presence of recesses (112, 122) in both the top substrate layer (110) and the bottom substrate layer (120). However, it is also possible for an apparatus described herein to include only one continuous retaining wall (such as only retaining wall portion 142), such as may occur if only one of the top substrate layer and the bottom substrate layer included a recess. In any event, it is to be understood that the retaining wall (140) can be operable to retain a nerve (not shown) within the channel (130).

[0028] Further, the apparatus (100) also comprises a spacer layer (150) disposed between the top substrate layer (110) and the bottom substrate layer (120). As described further herein, a height of the spacer layer (150) can at least partially define a height (132) of the channel (130) of the apparatus. Additionally, the spacer layer (150) can bond, attach, or affix the top substrate layer (110) to the bottom substrate layer (120). The spacer layer (150) may be formed separately from the top substrate layer (110) and the bottom substrate layer (120), or it may be incorporated into or formed integrally with the top substrate layer (110) and/or the bottom substrate layer (120). In some instances, though not necessarily in the embodiment illustrated in **FIG. 1A**, the top substrate layer (110) and the bottom substrate layer (120) may be formed from a single, continuous substrate layer that is folded over upon itself to create the top (110) and bottom (120) substrate layers in facing opposition to each other and separated by the spacer layer (150).

[0029] Moreover, in the embodiment of **FIG. 1A**, the top substrate layer (110) and the bottom substrate layer (120) define an opening (136) of the channel (130) at a proximal end (101) of the apparatus (100). Additionally, the opening (136) of the channel (130) at the proximal end (101) extends along a length (L) of the apparatus (100). The opening (136) can thus permit a nerve (not shown) having a long axis extending generally parallel to the length (L) to be inserted laterally or "sideways" into the channel (130) of the apparatus (100). The retaining wall (140) of the apparatus (100) can then retain the nerve within the channel (130) by partially obstructing the opening (136) of the apparatus (100). For reference purposes herein, the "proximal" end of an apparatus is the end opposite the spacer layer, or, in embodiments lacking a distinct spacer layer, the end opposite an end where the top substrate layer and the bottom substrate layer are joined.

[0030] It is to be understood that the height of the retaining wall (140), in conjunction with the height (132) and width (134) of the channel (130), can be selected based on the diameter of the nerve, and can be controlled with sub-micron precision. As used herein, a "height of the retaining wall" refers to the sum of the heights of a plurality of aligned retaining walls or the sum of the heights of any subportions of the retaining wall, when a discontinuous retaining wall or a plurality of collinear or "stacked" retaining walls is used. The nerve, once positioned in the channel (130), may experience movement within the channel (130), such that the apparatus does not penetrate the nerve or otherwise damage the nerve if the apparatus is subjected to movement during movement of muscles or other surrounding tissue. Thus, the apparatus need not be mechanically fastened to the nerve; rather, the nerve can be held inside the apparatus by the

retaining wall. Additionally, in some cases, the top substrate layer and the bottom substrate layer of an apparatus can be joined or attached at the proximal end of the apparatus to close the opening of the channel, thereby further retaining or securing a nerve within the channel without damaging the nerve. Thus, an apparatus described herein can be non-penetrating to the nerve. "Penetration" of a nerve, for reference purposes herein, can refer to the nerve's entanglement with or growth into a component of a device, or the piercing of the surface of the nerve by an external component. When penetration occurs, it can be very difficult if not impossible to remove the device without damaging the nerve.

[0031] Turning again to the channel (130) of the apparatus (100), the channel (130) has a height (132) and a width (134). The height (132) and width (134) may be approximately equal. As shown in **FIG. 2**, the height of the retaining wall (140) is less than the height (132) of the channel (130), thus allowing the nerve to be placed in the channel (130) and then to be retained in the channel (130) by the retaining wall (140). The height of the retaining wall (140), in some cases, may equal approximately one-quarter to one-third the height of the channel (130). Additionally, in some instances, the average or maximum height of the channel is less than about 1000 μm, less than about 500 μm, less than about 250 μm, less than about 100 μm, or less than about 50 μm. In some instances, the average or maximum height of the channel is 10-1000 μm, 50-1000 μm, 10-500 μm, 10-300 μm, 10-100 μm, 50-500 μm, 50-300 μm, or 50-100 μm. Further, in some embodiments, the height of the channel is equal to or slightly greater than the diameter of the nerve to be disposed in the channel. The nerve may be any nerve, such as an intact or un-severed small nerve, an organ-modulating nerve fascicle, or a peripheral nerve. In some cases, the nerve may have a diameter of about 25-500 μm, 50-400 μm, 100-300 μm, or 25-200 μm. Other sizes are also possible. Additionally, in some instances, the width of the channel has a value described above for the height of the channel. In some embodiments, for example, the width of the channel is less than 1000 μm, less than 500 μm, less than 250 μm, less than 100 μm, or less than 50 μm.

[0032] Further, as described above, the size of the retaining wall used to define the channel of an apparatus described herein can be selected based on the height and/or width of the channel, and/or based on the diameter of the nerve to be disposed in the channel. For example, in some cases, the retaining wall is selected to be low enough to permit insertion of the nerve, but high enough to retain the nerve following insertion. As a non-limiting example of proportions, for an

apparatus with a channel height of 600 μm and a channel width of 600 μm, a retaining wall height of 200 μm may be appropriate to retain a nerve having a diameter of 500 to 600 μm. In other cases, the retaining wall height may be less than 200 μm or greater than 200 μm. In some embodiments, the retaining wall height is up to 300 μm. Moreover, as described above, it is to be understood that the height of the retaining wall can be the total height of more than one portion of a discontinuous retaining wall or of a plurality of aligned retaining walls that operate cooperatively to retain a nerve. It is further to be understood that an apparatus having only a single 200 μm retaining wall may be functionally equivalent to an apparatus having two 100 μm, aligned retaining walls.

[0033] Additionally, in some instances, the height of the channel is 1.5 to 4 times, 2 to 3 times, or 1.75 to 3.5 times the height of the retaining wall. In some embodiments, the channel opening defined by the top substrate layer, the bottom substrate layer, and the retaining wall may be about 1/3 to 1/2 the height of the channel. In some cases, the width of the channel is 1.5 to 4 times, 2 to 3 times, or 1.75 to 3.5 times a height of the retaining wall. In some embodiments, the channel opening defined by the top substrate layer, the bottom substrate layer, and the retaining wall or walls may be about 1/3 to 1/2 the width of the channel. Further, in some embodiments, the height of the channel is 1.5 to 3 times a diameter of the nerve. In some cases, the width of the channel is 1.5 to 3 times a diameter of the nerve. Moreover, in some instances, the height of the channel and the width of the channel are substantially equal. Channel height and width may be adjusted independently, but in many cases have similar dimensions. However, the channel cross-section need not be square. Any channel cross-section (square, trapezoidal, rectangular, round, ovoid, etc.) may be used.

[0034] The apparatus of **FIG. 1A** also includes a plurality of electrodes (160) disposed on interior surfaces (111, 121) of the channel (130). As depicted in **FIGS. 1A** and **1B**, the interior surfaces (111, 121) are interior surfaces of recesses (112, 122) in the top substrate layer (110) and the bottom substrate layer (120). In particular, the interior surface (111) is an interior surface of the first recess (112) in the top substrate layer (110), and the interior surface (121) is an interior surface of the second recess (122) in the bottom substrate layer (120). Thus, in some embodiments, top electrodes are disposed on the surface of the recess of the top surface layer and bottom electrodes are disposed on the surface of the recess of the bottom substrate layer. Additionally, as illustrated in **FIG. 1A**, the plurality of electrodes (160) are substantially parallel

to one another and are oriented substantially perpendicular to a length of the channel (130). However, other arrangements of electrodes are also possible. Moreover, in some cases, the top electrodes of an apparatus are aligned with the bottom electrodes in an x-direction and/or in a y-direction, where the xy-plane can refer to the plane of an interior surface of the channel on which the electrodes are disposed (such that, for example, the x-direction corresponds to the L-direction in **FIG. 1A**). Further, in some embodiments, a height of the channel (as described above) is defined by a distance, such as a shortest distance, in the z-direction between the top electrodes and the bottom electrodes, wherein the z-direction is understood to be orthogonal to the xy-plane. Electrodes configured in a manner described herein can be operable to detect an electrical signal transmitted by the nerve along a length of the nerve, in particular a length of the nerve corresponding to the L-direction in **FIG. 1A**. In addition, as described further herein, the retaining wall of an apparatus described herein can retain the nerve in contact with one or more of the electrodes, including when the electrodes have a configuration described hereinabove.

[0035] Further, electrodes having an arrangement described herein, such as a longitudinal arrangement of electrodes along the channel length, can provide a means of determining the type of nerve disposed in the channel. As understood by a person of ordinary skill in the art, nerves transmit electrical signals or electrical impulse along a length of the nerve. The known distance between electrodes can thus be correlated with time series data of electrical recordings to estimate conduction velocity along the length of the nerve. Differing nerve fiber types such as alpha motor neuron and group A, B, or C nerve fibers can be classified by conduction velocity. As the signal is transmitted, it will cross each electrode in the plurality of electrodes at a slightly different time, permitting detection of the velocity and intensity of the electrical signal. Further, detecting electrical signals along the same nerve over a period of time (such as a period of time of up to 1 month or greater than 1 month) may be used to monitor the nerve's health and condition over time.

[0036] An apparatus described herein may also include one or more electrical interconnects coupling electrodes of the apparatus to an additional component of the apparatus or to an external device, such as a power supply, detector, and/or controller. Such electrical interconnects are illustrated in **FIG. 3**. **FIG. 3A** illustrates a top plan view of an apparatus according to one embodiment described herein. **FIG. 3B** illustrates an enlarged view of a portion of the apparatus of **FIG. 3A**. **FIG. 3C** illustrates a perspective view of this same portion

of the apparatus. With reference to **FIG. 3**, electrical interconnects (162) conduct electrical signals between the plurality of electrodes (160) and additional electrical instrumentation (not shown).

[0037] Turning again to details of specific components of apparatuses described herein, apparatuses described herein comprise top and bottom substrate layers. The top substrate layer and the bottom substrate layer may be formed from any material not inconsistent with the objectives of the invention. For example, in some cases, the top substrate layer and the bottom substrate layer may be formed from, comprise, consist of, or consist essentially of a flexible material, including a flexible biocompatible polymer. Flexibility of the top substrate layer and the bottom substrate layer may facilitate insertion of the nerve into the channel of the apparatus, allowing for ease of manipulation of the apparatus for placement on the nerve and then for subsequent removal from the nerve. Further, it is to be understood that a "flexible" substrate layer can be elastically or reversibly bent or flexed, without breaking or permanent deformation, from a planar position to a non-planar position through at least 15 degrees, at least 20 degrees, at least 30 degrees, or at least 45 degrees. In some instances, a flexible substrate layer can be flexed or bent through 10-45, 10-30, 15-45, 15-30, 20-45, or 20-30 degrees without breaking or permanently deforming. In some embodiments, the top and/or bottom substrate layer is formed from a polyimide, parylene, a silicone, a polyurethane, or a combination thereof. In some cases, the top and/or bottom substrate layer is formed from poly (4,4′-oxydiphenylene-pyromellitimide), which may be referred to by the trade name KAPTON. Additionally, the top substrate layer and the bottom substrate layer of an apparatus described herein may be fabricated or formed from the same materials, and may have the same or similar shapes and/or sizes. However, the top substrate layer and the bottom substrate layer may also be formed from different materials, and may have dissimilar shapes and sizes.

[0038] Further, in some embodiments, the top substrate layer and/or the bottom substrate layer is substantially transparent to light of wavelengths from 400 nm to 700 nm. When the top substrate layer and/or the bottom substrate layer are substantially transparent, visual inspection can determine if there is a nerve in the channel of the apparatus. The substantially transparent top substrate layer and/or the substantially transparent bottom substrate layer can transmit at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% of

visible light having wavelengths from 400 nm to 700 nm, from 425 nm to 675 nm, or from 450 nm to 650 nm.

[0039] Apparatuses described herein, in some cases, also comprise a spacer layer. The spacer layer may comprise or be formed from any material not inconsistent with the objectives of the present invention, including a material described hereinabove for the top and bottom substrate layers. In some embodiments, the spacer layer may comprise, consist, or consist essentially of a polyimide film with a thermosetting acrylate adhesive film. Additionally, the spacer layer may comprise electronic components such as a miniature wireless module or electrical stimulator circuitry.

[0040] Further, a top substrate layer, a bottom substrate layer, and/or a spacer layer of an apparatus described herein may be coated or surface treated to improve the biocompatibility of the apparatus or to reduce inflammation near the apparatus. Any coating not inconsistent with the objectives of the present invention may be used. Coating materials may include, but are not limited to, controlled-release drugs, polyethylene glycol, biomolecules such as proteins, peptides, amino acids, nucleic acids, antibodies or aptamers, or growth factors such as neural growth factor, brain derived growth factor, or any neurotrophins.

[0041] In addition, apparatuses described herein comprise electrodes and/or additional electrical interconnects. The electrodes and/or electrical interconnects may be formed from any electrically conductive material not inconsistent with the objectives of the present invention. In some cases, for example, the electrodes comprise, consist of, consist essentially of, or are formed from an inorganic material such as a metal or metal oxide, which may include platinum, copper, gold, or iridium oxide. Electrodes and/or interconnects may also be formed from an organic material such as poly(3,4-ethylenedioxythiophene), polypyrrole, carbon nanotubes, graphene, or a combination thereof. The electrical impedance and charge storage capacity of the electrodes may also have any values not inconsistent with the objectives of the present disclosure. Moreover, the foregoing values may be selected based in part on the exposed area of the electrodes. In some cases, the exposed area of the electrodes can be varied by changing the width of each electrode or by changing the width of the channel in which the electrodes are disposed. In some implementations, the electrodes may be insulated except where they are exposed in the channel. Further, in some cases, the thickness of the insulation corresponds to the retaining wall height. Moreover, any desired number of electrodes may be disposed in a channel

of an apparatus described herein. In some embodiments, the number of electrodes ranges from 1 to 64, 2 to 32, or 4 to 20 electrodes. Other numbers of electrodes may also be used.

[0042] In addition, in some cases, the flexible nature of the top substrate layer and/or the bottom substrate layer may result in cracking or delamination of an electrode material from the substrate during bending and stretching of the apparatus. In some such embodiments, this difficulty may be overcome by patterning electrode materials in a serpentine pattern to accommodate torsion due to both in plane and out of plane bending. In other embodiments, liquid metal interconnects encapsulated within microfluidic channels may be used to prevent breaking and electrical shorts due to torsion.

[0043] It is to be understood that apparatuses described herein can have any combination of features, components, or properties described hereinabove not inconsistent with the objectives of the present invention.

II. Methods of Nerve Stimulation and/or Monitoring

[0044] In another aspect, methods of stimulating and/or monitoring a nerve are described herein. In some implementations, such a method comprises placing a nerve in the channel of an apparatus described hereinabove in Section I. Any apparatus described hereinabove in Section I may be used. For example, the apparatus can comprise a top substrate layer, a bottom substrate layer in facing opposition to the top substrate layer, and a channel disposed between the top substrate layer and the bottom substrate layer. The apparatus can further comprise a plurality of electrodes disposed on one or more interior surfaces of the channel. Additionally, the channel is defined by the top substrate layer, the bottom substrate layer, and a retaining wall extending at least partially between the top substrate layer and the bottom substrate layer. The retaining wall retains the nerve within the channel. Moreover, placing the nerve in the channel of the apparatus comprises placing the nerve in contact with the plurality of electrodes. The method further comprises sending electrical signals from the electrodes to the nerve and/or receiving electrical signals from the nerve to the electrodes.

[0045] In addition, in some cases, the top substrate layer and the bottom substrate layer of the apparatus define an opening of the channel at a proximal end of the apparatus, and placing the nerve in the channel of the apparatus comprises first flexing an end of the top substrate layer away from a corresponding end of the bottom substrate layer to increase the size of the opening

of the channel, and subsequently placing the nerve in the channel through the opening of the channel. A method described herein may also comprise joining the top substrate layer and the bottom substrate layer to close the opening of the channel at the proximal end of the apparatus.

[0046] As described further herein, the nerve placed in the channel of the apparatus can be an intact or non-severed nerve. Additionally, a method described herein can be carried out without penetrating the nerve within the channel of the apparatus. Moreover, in some cases, the nerve is a nerve of a living patient, and the method further comprises placing the apparatus within a biological compartment of the patient. The biological compartment can be an interior region of the patient's body. A method described herein may also comprise sealing the apparatus within the biological compartment of the patient after placing the nerve in the channel of the apparatus, including by sealing or closing the biological compartment, such as by using sutures or staples. In addition, in some cases, the apparatus is not permanently implanted within the patient, but may instead be removed from the patient following a desired or therapeutic time period. Such an apparatus may accordingly not be solubilized, degraded, or otherwise decomposed in situ, but may instead be removed from the patient intact after a desired time period. In some implementations, the apparatus may be left in the body of the patient for up to a week, a month, a year, a decade, several decades, or many decades. Further, it is generally to be understood that the nerve may not grow into or become physically attached to the apparatus while the apparatus is disposed in the biological compartment, other than being retained within the channel in a manner described herein. Moreover, in some embodiments, removing the apparatus from the patient after a period of time does not damage the nerve. Thus, in some cases, a method described herein further comprises removing the apparatus from the patient after sealing the apparatus within the biological compartment of the patient, and removing the nerve from the apparatus, both without damaging or severing the nerve.

[0047] Additionally, in some embodiments, a method described herein further comprises sending and/or receiving electrical signals to and/or from the nerve, including while the nerve is disposed within a channel of an apparatus described herein. Such electrical signals can be sent from and/or received by electrodes of the apparatus. Further, electrical signals exchanged between a nerve and an apparatus can be used to stimulate, monitor, and/or characterize the nerve. For example, in some instances, a method described herein comprises sending electrical signals from electrodes of an apparatus to the nerve disposed in a channel of the apparatus, thereby

stimulating the nerve. Electrical signals can be sent to the nerve a plurality of times, including in a temporally periodic, regular, or irregular manner. In other implementations, a method comprises receiving electrical signals with electrodes of an apparatus from a nerve disposed in contact with the electrodes within a channel of the apparatus. As in the case of sending electrical signals, electrical signals may also be received by the electrodes a plurality of times or over a desired period of time. Further, in some embodiments, a method described herein comprises measuring the velocity and/or intensity of an electrical signal or series of electrical signals received from a nerve, including as a function of time and/or distance along the length of the nerve. Moreover, in some cases, comparing time series data between two electrode sites to calculate conduction velocity can be used to identify or distinguish different nerve fiber types, such as sensory or motor neurons.

[0048] More generally, methods described herein can be useful for electrical stimulation of a peripheral nerve intended to cause a physiological response or to provide therapy to the nerve. In addition, methods described herein can be useful for the diagnosis of conditions by combinations of electrical stimulation, recording of neural activity, and monitoring changes of other biometrics caused by stimulation. Further, some methods can provide electrical stimulation intended to mimic sensory perception such as touch feedback from a prosthetic device. Further still, some methods described herein can be useful for monitoring either endogenous or stimulated neural activity for the purpose of determining appropriate electrical stimulation to be delivered through an apparatus described herein either manually or by a feedback control mechanism. In addition, methods described herein can be useful for recording neural activity to be used as a control signal for driving prosthetics or any other electronic or mechanical device.

[0049] Specific steps of methods according to the present disclosure will now be further described with reference to the figures. It is to be understood that the same reference numerals used in differing figures generally correspond to the same steps of a method or features of an apparatus.

[0050] **FIGS. 4A-4C** each illustrates a step of a method according to one embodiment described herein. As illustrated in **FIGS. 4A-4C**, a top substrate layer (110) and a bottom substrate layer (120) of an apparatus (100) together define an opening (136) of a channel (130) of the apparatus (100) at a proximal end (101) of the apparatus (100). The method depicted in **FIGS. 4A-4C**

comprises placing a nerve (200) in the channel (130) of the apparatus (100). Specifically, to place the nerve (200) within the channel (130), an end (113) of the top substrate layer (110) is flexed or bent away from a corresponding end (123) of the bottom substrate layer (120) in order to increase the size of the opening (136). The nerve (200) is then placed in the channel (130) laterally or sideways through the opening (136) of the apparatus (100). The flexed or bent ends (113, 123) of the top and bottom substrate layers (110, 120) are depicted in **FIG. 4A**. Additionally, as illustrated in **FIG. 4A**, the nerve (200) has already been inserted into the channel (130) following flexing of the ends (113, 123) of the top and bottom substrate layers (110, 120). As illustrated in **FIG. 4B**, the ends (113, 123) of the top and bottom substrate layers (110, 120) have been moved back to their original planar or unflexed position following insertion of the nerve (200) into the channel (130).

[0051] In the step illustrated in **FIG. 4C**, the top substrate layer (110) and the bottom substrate layer (120) have been joined or attached to one another to close the opening (136) of the channel (130) at the proximal end (101) of the apparatus (100), following insertion of the nerve (200). The top substrate layer (110) and the bottom substrate layer (120) may be joined in any manner not inconsistent with the objectives of this invention. For example, closing or joining may be accomplished with a mechanical interlocking mechanism, staples, clamps, or sutures (not shown). Moreover, the top substrate layer (110) and/or the bottom substrate layer (120) may include closure guidance markings, indentations, or holes (170). Such closure guidance markings (170) can be used to align the top and bottom substrate layers (110, 120) and to facilitate accurate and efficient closing of the opening (136). However, it is again to be understood that closing the opening (136) as described above is optional and may provide only secondary containment or retention of the nerve (200) within the channel (130). The retaining wall (140) may serve as the primary means of retaining the nerve (200) within the channel (130).

[0052] Further, although not illustrated in **FIG. 4**, it is to be understood that the nerve (200) may be removed from the channel (130) of the apparatus (100) by sliding or otherwise moving the nerve (200) past the retaining wall (140) and through the opening (136) after the first and second substrate layers (110, 120) are detached or unjoined from one another. The first and second substrate layers (110, 120) may also be flexed open following detaching or unjoining of the layers (110, 120) from one another.

[0053] In addition, in some implementations, a vacuum tool may be used to carry out one or more of the steps illustrated in **FIGS. 4A-4C**. **FIG. 5** illustrates a perspective view of such a tool, and **FIGS. 6A-6D** illustrate the use of the tool of **FIG. 5** in steps of a method similar to the steps depicted in **FIGS. 4A-4C**. As depicted in **FIG. 5**, a vacuum tool (300) comprises a first vacuum gripper (310) and a second vacuum gripper (320) in facing opposition to one another. As illustrated in **FIGS. 6A-6D**, the vacuum grippers (310, 320) can be applied to the top substrate layer (110) and to the bottom substrate layer (120), and a vacuum can be applied to bend or pull back the ends (113, 123) of the first and second layers (110, 120) to widen the opening (136) of the channel (130) for insertion of the nerve (200). In **FIG. 6A**, the nerve (200) is partially inserted, while in **FIG. 6B** the nerve (200) is fully inserted into the channel (130).

[0054] It is to be understood that methods described herein can include any combination of steps and/or any combination of apparatus features, components, or properties described hereinabove not inconsistent with the objectives of the present invention.

EXAMPLE 1

Apparatus for Nerve Stimulation and/or Monitoring

[0055] An apparatus for nerve stimulation and/or monitoring according to one embodiment described herein was prepared as follows. A top substrate layer having electrodes and a bottom substrate layer having electrodes were made using conventional microfabrication methods, including photolithographic patterning and sputter deposition of thin films. Specifically, to form a substrate layer, a pre-fabricated substrate formed from a KAPTON polyimide film (thickness = 75 μm) was mounted on a silicon wafer for processing. A metal pattern forming the electrodes and metal interconnects was then deposited using platinum as the metal. A spinnable polyimide solution was next applied to achieve a desired recess depth, followed by selective etching to expose the metal electrodes along the channel. Finally, the polyimide film was cured in a nitrogen environment. **FIG. 7** is a photograph of ten copies of a coated substrate layer (110 and/or 120) with a plurality of electrodes (160) and interconnects (162). The substrate layers were separated by cutting the desired layer outline using a laser cutting/engraving tool.

[0056] A spacer layer (150) was fabricated from an alternating stack of polyimide film and thermosetting polymer to achieve a desired total thickness of the spacer layer (150), as shown in

FIG. 8. The dry stack was then cut to the desired length and width to form a spacer layer that could be disposed between a top substrate layer and a bottom substrate layer fabricated as described above. In particular, the spacer layer was permanently bonded to the top substrate layer and to the bottom substrate layer using a Flip-Chip-Bonding system to allow precise alignment, pressure control, and multi-stage temperature control.

[0057] An apparatus described herein may also be formed by depositing electrode material or otherwise forming electrodes or metal contacts on a substrate, such as a silicon wafer, followed by applying or forming a polyimide film over the functional substrate. In particular, a polyimide solution can be spun on the substrate. In one approach, after spinning the polyimide, the substrate is soft baked to evaporate solvents. Using a photoresist mask, selective wet or dry etching is used to expose the metal pads/contacts/electrodes and to define the channel of the apparatus, lined with electrodes. The polyimide is then further cured in a nitrogen environment to complete the apparatus.

[0058] In a second approach, after spinning the polyimide, the substrate is soft baked to evaporate solvents. Photodefinable polyimide is then patterned using a photomask and standard lithography processing. After photolithography patterning and development, the polyimide is then further cured in a nitrogen environment. Finally, a plasma etching process is used to remove residual polyimide from the patterned channel and fully expose the electrode surfaces.

EXAMPLE 2

Method for Nerve Stimulation and/or Monitoring

[0059] A method for stimulating and/or monitoring a nerve according to one embodiment described herein was carried out as follows. The apparatus of Example 1 was surgically placed on the isolated cutaneous branch of the sciatic nerve of an anesthetized rat. The nerve was specifically placed in the channel of the apparatus in contact with the plurality of electrodes, and 9-0 sutures were inserted through the closure guidance holes to "close" the channel by joining the proximal ends of the top substrate layer and the bottom substrate layer. An electrical signal was then sent from the electrodes to the nerve. The nerve was then removed from the apparatus without causing damage to the nerve, and the apparatus was then removed from the rat. **FIGS. 9A-9D** illustrate this process. Specifically, **FIG. 9A** illustrates the apparatus (100) and the nerve (200) prior to placement of the nerve (200) within the apparatus (100). **FIG. 9B** illustrates the

nerve (200) within the apparatus (100). **FIG. 9C** illustrates the appearance of the biological compartment during electrical stimulation of the nerve. **FIG. 9D** illustrates the nerve (200) in the biological compartment following removal of the nerve (200) from the apparatus (100), and the removal of the apparatus (100) from the biological compartment.

[0060] Various implementations of the disclosure have been described in fulfillment of the various objectives of the disclosure. It should be recognized that these implementations are merely illustrative of the principles of the present disclosure. Numerous modifications and adaptations thereof will be readily apparent to those skilled in the art without departing from the spirit and scope of the disclosure.

CLAIMS

1. An apparatus for nerve stimulation and/or monitoring comprising:

a top substrate layer;

a bottom substrate layer in facing opposition to the top substrate layer;

a channel disposed between the top substrate layer and the bottom substrate layer; and

a plurality of electrodes disposed on one or more interior surfaces of the channel,

wherein the channel is defined by the top substrate layer, the bottom substrate layer, and a retaining wall extending at least partially between the top substrate layer and the bottom substrate layer; and

wherein the retaining wall retains the nerve within the channel.

2. The apparatus of claim 1 further comprising a spacer layer disposed between the top substrate layer and the bottom substrate layer.

3. The apparatus of claim 2, wherein a height of the spacer layer at least partially defines a height of the channel.

4. The apparatus of any of the preceding claims, wherein the top substrate layer and the bottom substrate layer define an opening of the channel at a proximal end of the apparatus.

5. The apparatus of claim 4, wherein the opening of the channel at the proximal end of the apparatus extends along a length of the apparatus.

6. The apparatus of claim 5, wherein the top substrate layer and the bottom substrate layer are joined at a proximal end of the apparatus to close the opening.

7. The apparatus of any of the preceding claims, wherein the top substrate layer and the bottom substrate layer are formed from a flexible material.

8. The apparatus of any of the preceding claims, wherein the top substrate layer and the bottom substrate layer are formed from a biocompatible polymer.

9. The apparatus of any of the preceding claims, wherein the biocompatible polymer comprises one or more of a polyimide, parylene, a silicone, and a polyurethane.

10. The apparatus of claim 9, wherein the biocompatible polymer comprises poly (4,4′-oxydiphenylene-pyromellitimide).

11. The apparatus of any of the preceding claims, wherein the top substrate layer and the bottom substrate layer are substantially transparent to light of wavelengths from 400 nm to 700 nm.

12. The apparatus of any of the preceding claims, wherein the electrodes are formed from one or more of platinum, poly(3,4-ethylenedioxythiophene), polypyrrole, carbon nanotubes, graphene, and iridium oxide.

13. The apparatus of claim 12, wherein the electrodes are formed from platinum.

14. The apparatus of any of the preceding claims, wherein a height of the channel is up to 1000 μm.

15. The apparatus of any of the preceding claims, wherein a width of the channel is up to 1000 μm.

16. The apparatus of any of the preceding claims, wherein a height of the retaining wall is up to 300 μm.

17. The apparatus of any of the preceding claims, wherein a height of the channel is 1.5 to 4 times a height of the retaining wall.

18. The apparatus of any of the preceding claims, wherein a width of the channel is 1.5 to 4 times a height of the retaining wall.

19. The apparatus of any of the preceding claims, wherein a height of the channel and a width of the channel are substantially equal.

20. The apparatus of any of the preceding claims, wherein a height of the channel is 1.5 to 3 times a diameter of the nerve.

21. The apparatus of any of the preceding claims, wherein the retaining wall retains the nerve in contact with the electrodes.

22. The apparatus of any of the preceding claims, wherein the plurality of electrodes are substantially parallel to one another.

23. The apparatus of any of the preceding claims, wherein the plurality of electrodes are oriented substantially perpendicular to a length of the channel.

24. The apparatus of any of the preceding claims, wherein the top substrate layer comprises a recess.

25. The apparatus of any of the preceding claims, wherein the bottom substrate layer comprises a recess.

26. The apparatus of any of the preceding claims, wherein the top substrate layer comprises a recess and the bottom substrate layer comprises a recess.

27. The apparatus of claim 26, wherein the channel is defined by the recess of the top substrate layer, the recess of the bottom substrate layer, and the retaining wall.

28. The apparatus of claim 27, wherein the plurality of electrodes are disposed on a surface of the recess of the top substrate layer and/or on a surface of the recess of the bottom substrate layer.

29. The apparatus of claim 28, wherein top electrodes are disposed on the surface of the recess of the top surface layer and bottom electrodes are disposed on the surface of the recess of the bottom substrate layer.

30. The apparatus of claim 29, wherein the top electrodes are aligned with the bottom electrodes in an x-direction and/or in a y-direction.

31. The apparatus of claim 29 or claim 30, wherein a height of the channel is defined by a distance in the z-direction between the top electrodes and the bottom electrodes.

32. The apparatus of any of the preceding claims, wherein the plurality of electrodes is operable to detect an electrical signal transmitted by the nerve along a length of the nerve.

33. The apparatus of any of the preceding claims, wherein the top substrate layer and the bottom substrate layer have the same size and shape and/or are formed from the same material.

34. The apparatus of any of the preceding claims, wherein the apparatus is non-penetrating to the nerve.

35. A method of stimulating and/or monitoring a nerve comprising:

placing the nerve in the channel of the apparatus of claim 1 in contact with the plurality of electrodes; and

sending electrical signals from the electrodes to the nerve and/or receiving electrical signals from the nerve to the electrodes.

36. The method of claim 35, wherein the top substrate layer and the bottom substrate layer of the apparatus define an opening of the channel at a proximal end of the apparatus, and placing the nerve in the channel of the apparatus comprises:

flexing an end of the top substrate layer away from a corresponding end of the bottom substrate layer to increase the size of the opening of the channel; and

placing the nerve in the channel through the opening of the channel.

37. The method of claim 36 further comprising:

joining the top substrate layer and the bottom substrate layer to close the opening of the channel at the proximal end of the apparatus.

38. The method of any of claims 35-37, wherein the nerve is an intact nerve.

39. The method of any of claims 35-38, wherein the apparatus does not penetrate the nerve.

40. The method of any of claims 35-39, wherein the nerve is a nerve of a living patient, and the method further comprises placing the apparatus within a biological compartment of the patient.

41. The method of claim 40 further comprising:

sealing the apparatus within the biological compartment of the patient after placing the nerve in the channel of the apparatus.

42. The method of claim 41 further comprising:

removing the apparatus from the patient after sealing the apparatus within the biological compartment of the patient; and

removing the nerve from the apparatus.

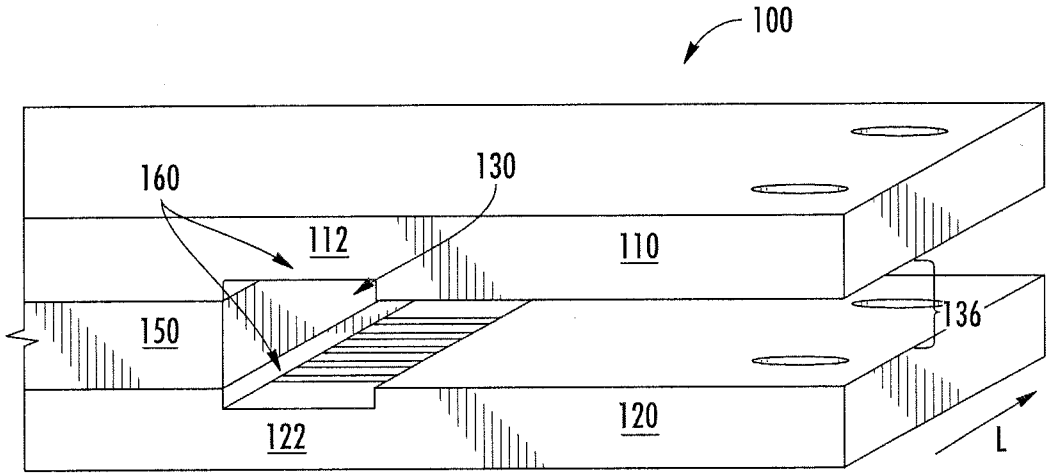
100
160
130
112
110
150
136
120
122
L

FIG. 1A

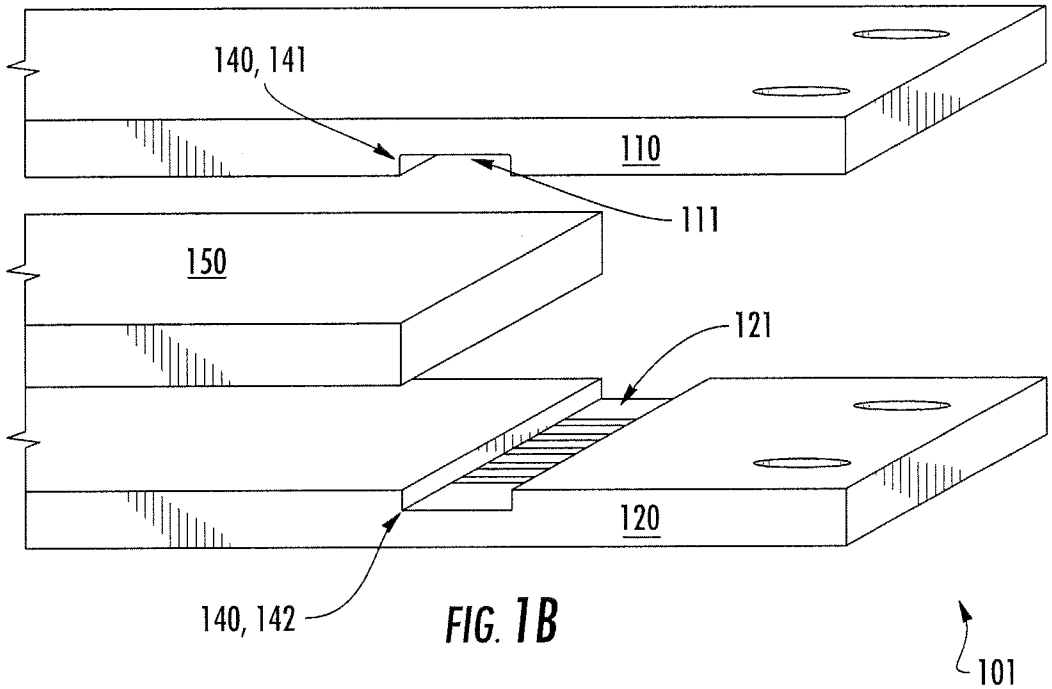
140, 141
110
111
150
121
120
140, 142
101

FIG. 1B

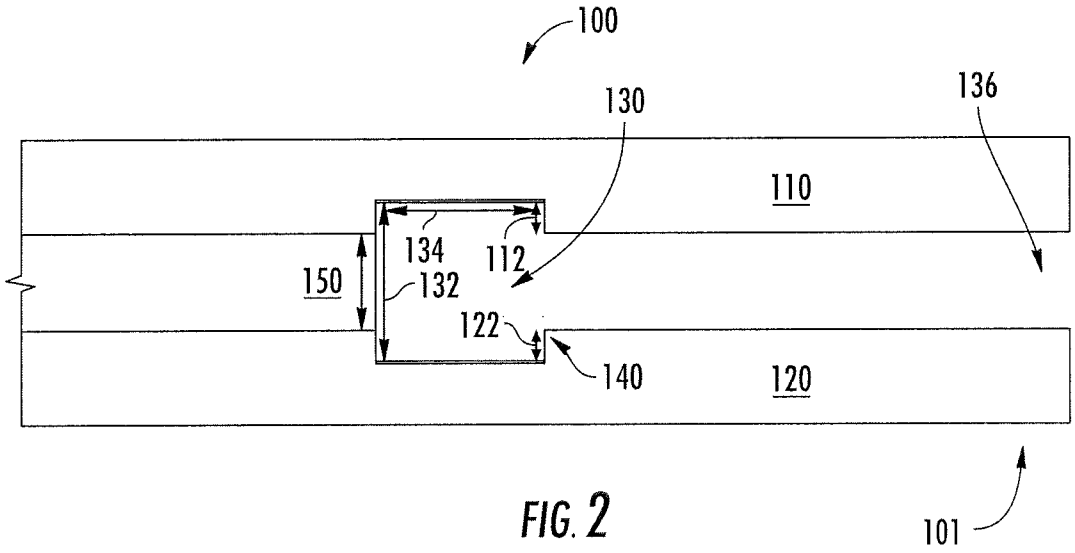

FIG. 2

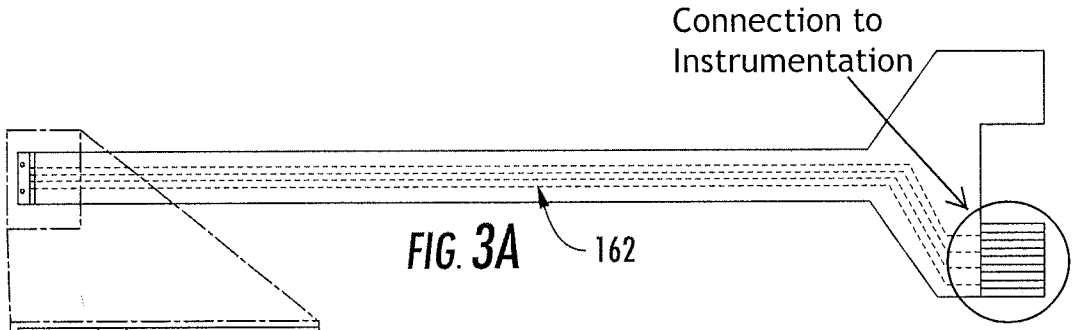

FIG. 3A

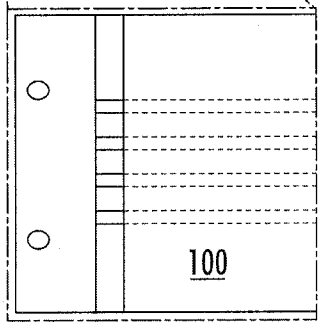

FIG. 3B

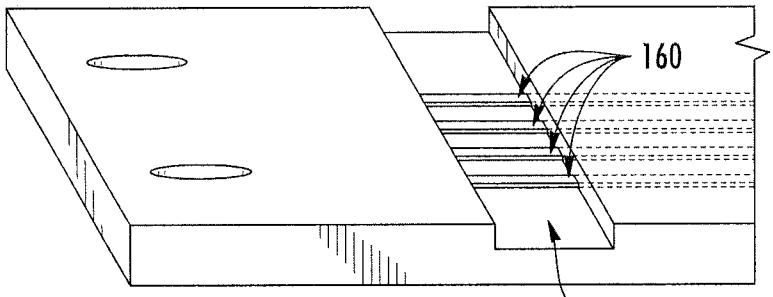

FIG. 3C

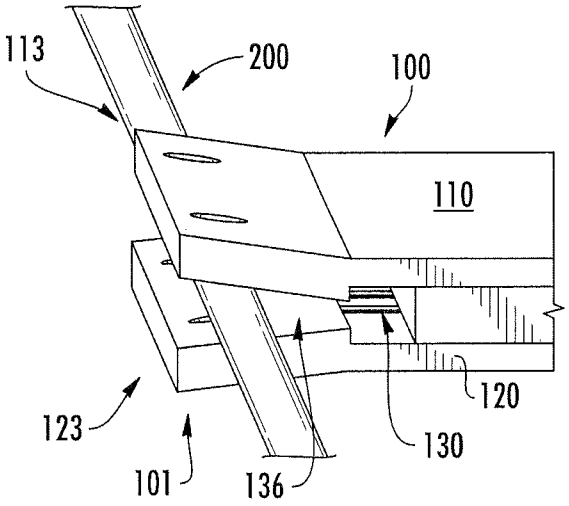

FIG. 4A

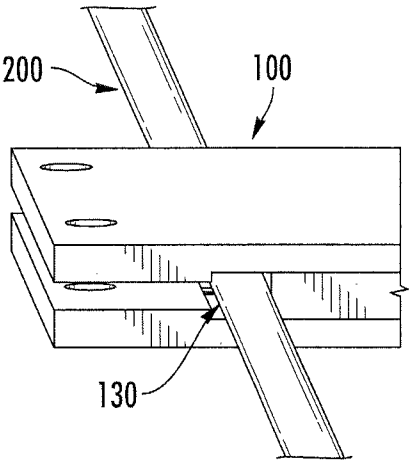

FIG. 4B

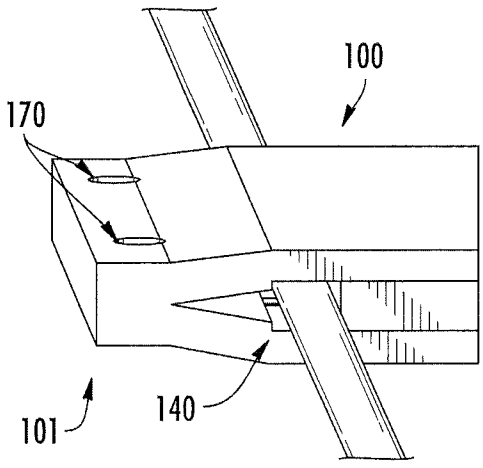

FIG. 4C

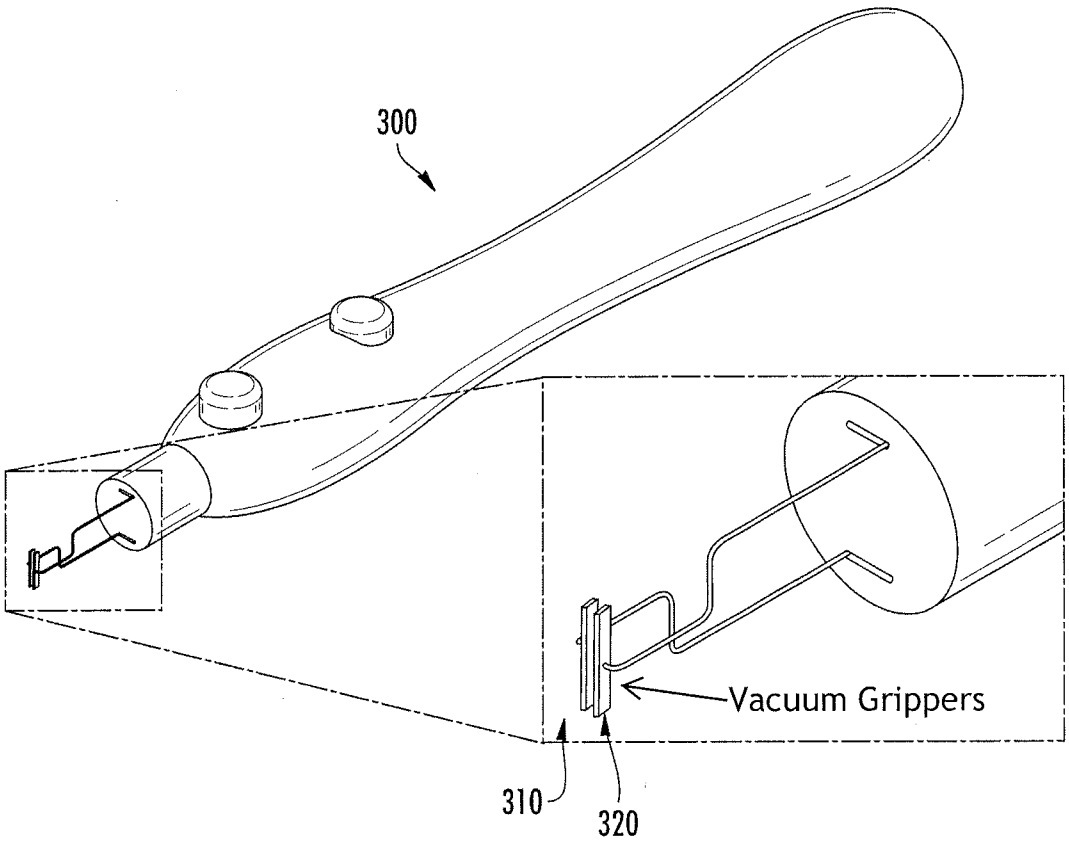

FIG. 5

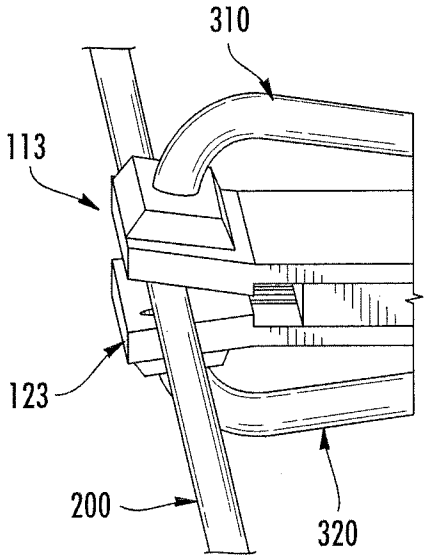

FIG. 6A

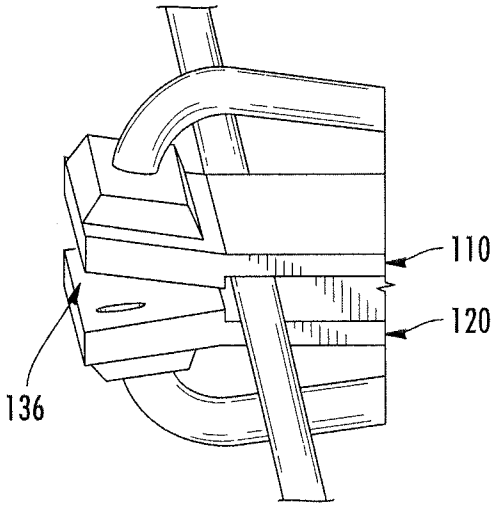

FIG. 6B

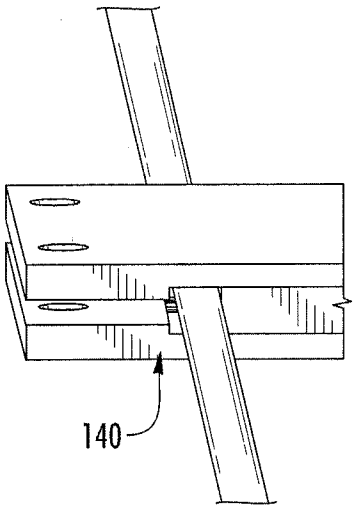

FIG. 6C

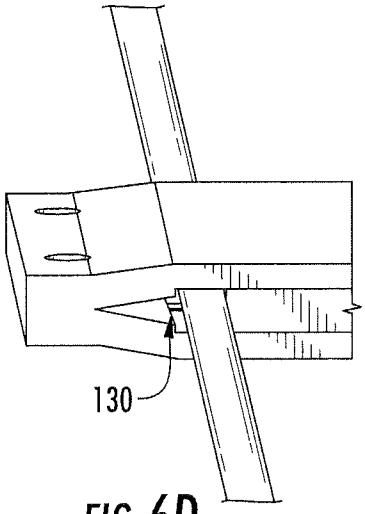

FIG. 6D

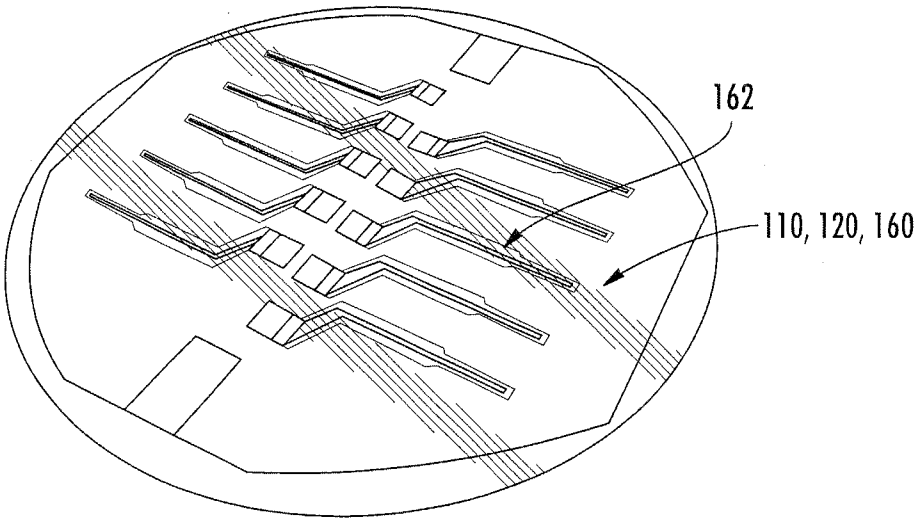
162
110, 120, 160

FIG. 7

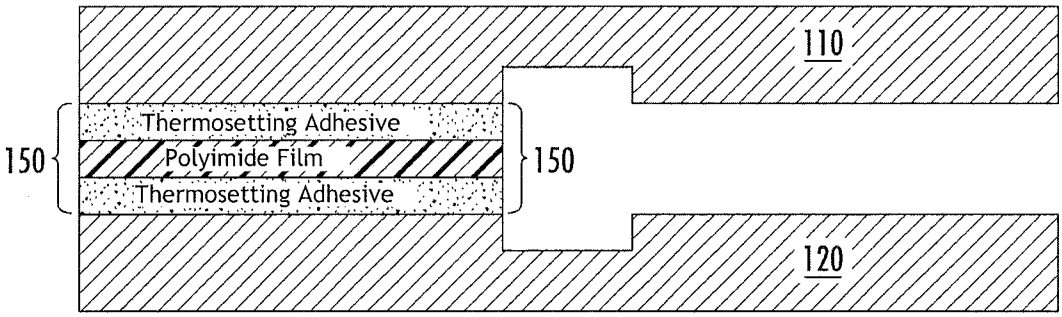
110
Thermosetting Adhesive
150
Polyimide Film
150
Thermosetting Adhesive
120

FIG. 8

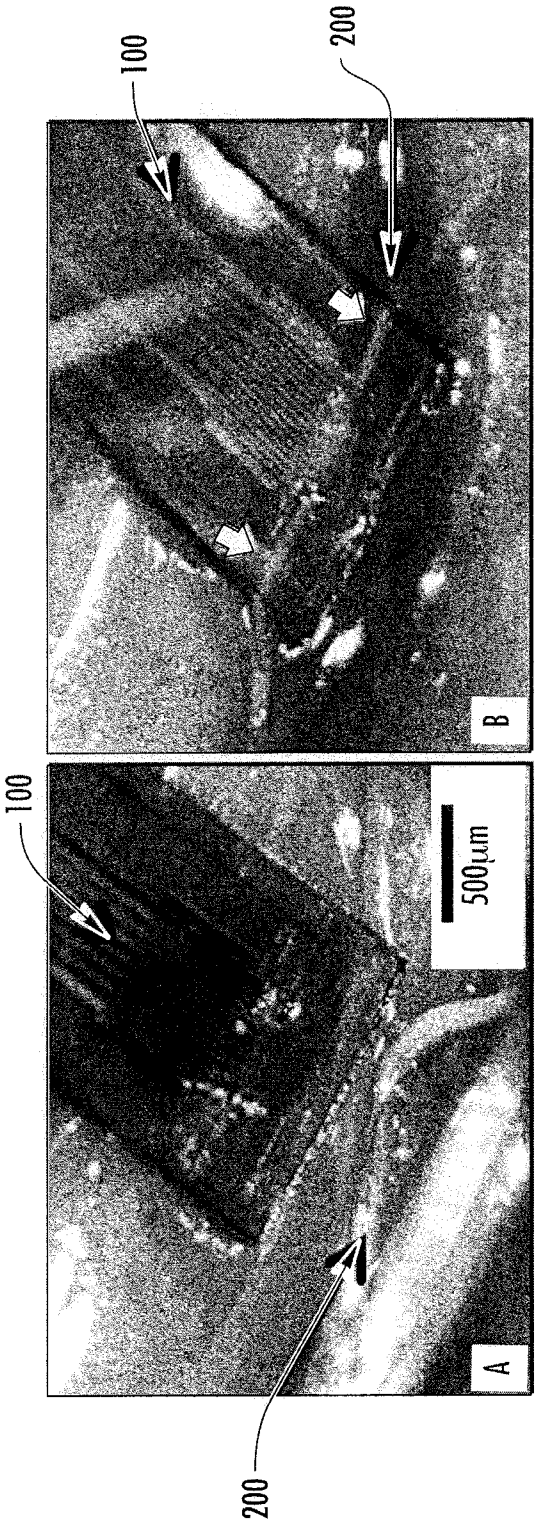

FIG. 9A

FIG. 9B

FIG. 9D

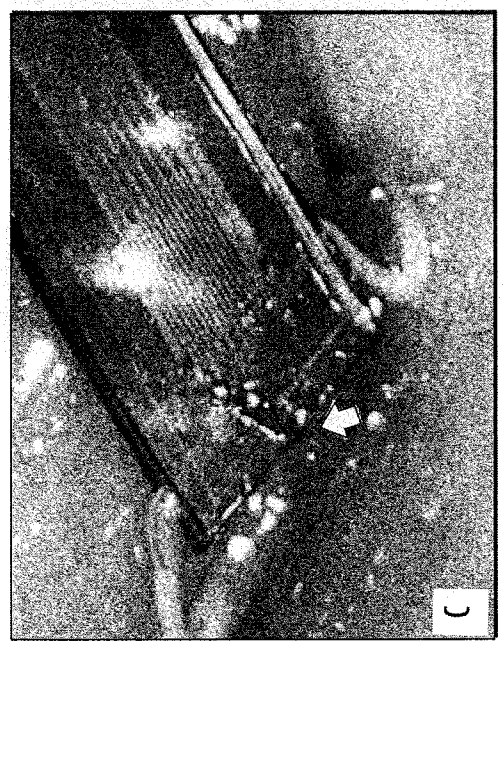

FIG. 9C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/021516

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 35-42
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/021516

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/05 A61B5/00
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 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/217109 A1 (ACHYUTA ANILKUMAR H [US] ET AL) 6 August 2015 (2015-08-06) paragraphs [0057] - [0060]; figures 6-7	1
X	WO 2015/109342 A2 (UNIV TEXAS [US]) 23 July 2015 (2015-07-23) paragraphs [0043] - [0058]; claim 1; figures 2,5-6	1-34
A	US 2010/312320 A1 (FALTYS MICHAEL A [US] ET AL) 9 December 2010 (2010-12-09) figures 15A-15D	1-34
A	WO 98/57699 A1 (AXON ENGINEERING INC [US]; BHADRA NARENDRA [US]; MORTIMER J THOMAS [US]) 23 December 1998 (1998-12-23) figures 5-9	1-34

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"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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Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2017	15/05/2017

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	Gentil, Cédric

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/021516

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Continuation of Box II.1

Claims Nos.: 35-42

Rule 39.1(iv) PCT - Method of treatment of the human or animal being by therapy. The method for stimulating a nerve, as defined in claims 35-42, comprises the step of sending electrical signals to the nerve to provide therapy (see e.g. description par. 48) and therefore relates to the curing of diseases or malfunctions of the body in order to restore or maintain health. It is therefore considered that claims 35-42 define a method of treatment of the human or animal body by therapy, for which no international search needs to be carried out (Rule 39.1(iv) PCT).