



(51) International Patent Classification:

A61B 5/0478 (2006.01) A61N 1/04 (2006.01)
A61B 5/05 (2006.01) A61N 5/06 (2006.01)

(21) International Application Number:

PCT/US2017/051387

(22) International Filing Date:

13 September 2017 (13.09.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/394,041 13 September 2016 (13.09.2016) US
62/503,189 08 May 2017 (08.05.2017) US

(71) Applicant: UNIVERSITY OF UTAH RESEARCH-
FOUNDATION [US/US]; 615 Arapeen Drive, Suite 310,
Salt Lake City, UT 84108 (US).

(72) Inventors: LEBER, Moritz; 615 Arapeen Drive, Suite
310, Salt Lake City, UT 84108 (US). NEGLI, Sandeep; 615
Arapeen Drive, Suite 310, Salt Lake City, UT 84108 (US).
SOLZBACHER, Florian; 615 Arapeen Drive, Suite 310,
Salt Lake City, UT 84108 (US).

(74) Agent: ERICKSEN, Erik, S. et al.; Thorpe North & West-
ern, LLP, 8180 S. 700 E., Suite 350, Sandy, UT 84070 (US).

(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, JO, 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: MICRONEEDLE ARRAYS HAVING A BIO-ERODIBLE SUBSTRATE

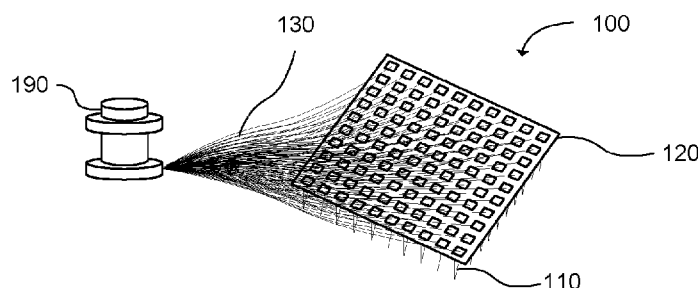


FIG. 1A

(57) Abstract: A microneedle array (100) can include a plurality of microneedles (110) secured in a common bio-erodible substrate (120) in an array of microneedles (110) distributed in a two-dimensional pattern. At least a portion of the plurality of microneedles (110) can be independently addressable.



MICRONEEDLE ARRAYS HAVING A BIO-ERODIBLE SUBSTRATE**RELATED APPLICATION(S)**

This application claims the benefit of U.S. Provisional Application No. 62/394,041 filed on September 13, 2016, which is incorporated herein by reference. This application also claims the benefit of U.S. Provisional Application No. 62/503,189 filed on May 8, 2017, entitled MICROELECTRODE ARRAYS, which is incorporated herein by reference.

GOVERNMENT INTEREST

This invention was made with government support under R01 NS085213 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Various neural interface devices are under development for numerous applications involving restoration of lost function due to traumatic injury or neurological disease, monitoring neural activity, controlling pain perception, and the like. Often the neural interface approaches place sensors or electrodes in a specific area of the brain or peripheral nerve such that a stimulus or electrical signal sent to the electrode can produce a response, such as a movement of a particular muscle group and/or sensations. For example, the electrodes can enable voluntary movement of body parts, restoration of sensation, bowel control, vision, hearing, and the like.

In application, the electrodes can be used to control affected paralyzed regions, artificial limbs or prosthetic devices, as well as a number of other devices such as computers, robots, and the like. Paralysis, loss of limbs, and various other afflictions can result in a reduced quality of life. However, neural interfaces can assist an afflicted person with regaining functionality and with improving the quality of life. Despite significant advances in neural electrical interface devices, challenges remain in terms of longevity, reliability, degree of restoration, and other factors.

SUMMARY

A microneedle array can include a plurality of microneedles secured in a bio-erodible substrate where the microneedles are arranged as an array of microneedles distributed in a two-dimensional pattern. At least a portion of the plurality of microneedles
5 can also be independently electrically addressable. The bio-erodible substrate can be configured to erode after implantation such that the microneedles are free floating within implanted tissue. In one example, the microneedles are microelectrodes. In an alternative, the microneedles are micro-optrodes.

A method of monitoring or stimulating a neural region can include inserting a
10 microneedle array as described herein into the neural region. After implantation, the bio-erodible substrate can be allowed to bio-erode to provide free-floating microneedles in the neural region. The free-floating microneedles can be used to monitor or stimulate the neural region with reduced trauma and inflammation to adjacent tissue.

A method of manufacturing a microneedle array can include preparing a plurality of
15 microneedles and securing the plurality of microneedles in a bio-erodible substrate. A lead can be wire bonded to at least a portion of the plurality of microneedles.

There has thus been outlined, rather broadly, the more important features of the invention so that the detailed description thereof that follows may be better understood, and so that the present contribution to the art may be better appreciated. Other features of the
20 present invention will become clearer from the following detailed description of the invention, taken with the accompanying drawings and claims, or may be learned by the practice of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A illustrates a microelectrode array having a bio-erodible substrate and a
25 connector interface, in accordance with examples of the present disclosure.

FIG. 1B illustrates a microelectrode array in place within tissue where the bio-erodible substrate has been removed, in accordance with examples of the present disclosure.

FIG. 1C illustrates a microelectrode array where the bio-erodible substrate has been
30 removed, in accordance with examples of the present disclosure.

FIG. 2A illustrates perspective view of an electrode array attached to tape and

placed in a mold, in accordance with examples of the present disclosure.

FIG. 2B illustrates a perspective view of the mold of FIG. 2A with the electrode array submerged in the mold, in accordance with examples of the present disclosure.

5 FIG. 2C illustrates a back side view of the electrode array of FIG. 2B with the tape removed, in accordance with examples of the present disclosure.

FIG. 2D illustrates a back side view of the electrode array of FIG. 2C after etching such that the microelectrodes are detached and held in place, in accordance with examples of the present disclosure.

10 FIG. 2E illustrates a perspective view of the electrode array of FIG. 2D with tape re-attached to the back side thereof, and a new insulating layer has been deposited onto the side walls of the individual microelectrodes with the tips de-insulated, , in accordance with examples of the present disclosure.

15 FIG. 2F illustrates a back side view of the electrode array of FIG. 2E prior to wire bonding and detachment of the microelectrode array from the mold, in accordance with examples of the present disclosure.

FIG. 3A illustrates an electrode array embedded in a polymer, in accordance with examples of the present disclosure.

FIG. 3B illustrates the electrode array of FIG. 4A with the tips of the electrodes exposed, in accordance with examples of the present disclosure.

20 FIG. 4 is a flowchart illustrating a method of monitoring or stimulating a neural region, in accordance with examples of the present disclosure.

FIG. 5 is a flowchart illustrating a method of manufacturing a microelectrode array, in accordance with examples of the present disclosure.

25 These drawings are provided to illustrate various aspects of the invention and are not intended to be limiting of the scope in terms of dimensions, materials, configurations, arrangements or proportions unless otherwise limited by the claims.

DETAILED DESCRIPTION

While these exemplary embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, it should be understood that other embodiments may be realized and that various changes to the invention may be made without departing from the spirit and scope of the present invention. Thus, the following more detailed description of the embodiments of the present invention is not intended to limit the scope of the invention, as claimed, but is presented for purposes of illustration only and not limitation to describe the features and characteristics of the present invention, to set forth the best mode of operation of the invention, and to sufficiently enable one skilled in the art to practice the invention. Accordingly, the scope of the present invention is to be defined solely by the appended claims.

Definitions

In describing and claiming the present invention, the following terminology will be used.

The singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a microelectrode” includes reference to one or more of such structures and reference to “monitoring” refers to one or more such steps.

As used herein, the term “about” is used to provide flexibility and imprecision associated with a given term, metric or value. The degree of flexibility for a particular variable can be readily determined by one skilled in the art. However, unless otherwise enunciated, the term “about” generally connotes flexibility of less than 5%, and most often less than 1%, and in some cases less than 0.01%.

As used herein with respect to an identified property or circumstance, “substantially” refers to a degree of deviation that is sufficiently small so as to not measurably detract from the identified property or circumstance. The exact degree of deviation allowable may in some cases depend on the specific context.

As used herein, “adjacent” refers to the proximity of two structures or elements. Particularly, elements that are identified as being “adjacent” may be either abutting or connected. Such elements may also be near or close to each other without necessarily

contacting each other. The exact degree of proximity may in some cases depend on the specific context.

As used herein, a plurality of items, structural elements, compositional elements, and/or materials may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a *de facto* equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

As used herein, the term “at least one of” is intended to be synonymous with “one or more of.” For example, “at least one of A, B and C” explicitly includes only A, only B, only C, and combinations of each.

Concentrations, amounts, and other numerical data may be presented herein in a range format. It is to be understood that such range format is used merely for convenience and brevity and should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. For example, a numerical range of about 1 to about 4.5 should be interpreted to include not only the explicitly recited limits of 1 to about 4.5, but also to include individual numerals such as 2, 3, 4, and sub-ranges such as 1 to 3, 2 to 4, etc. The same principle applies to ranges reciting only one numerical value, such as “less than about 4.5,” which should be interpreted to include all of the above-recited values and ranges. Further, such an interpretation should apply regardless of the breadth of the range or the characteristic being described.

Any steps recited in any method or process claims may be executed in any order and are not limited to the order presented in the claims. Means-plus-function or step-plus-function limitations will only be employed where for a specific claim limitation all of the following conditions are present in that limitation: a) “means for” or “step for” is expressly recited; and b) a corresponding function is expressly recited. The structure, material or acts that support the means-plus function are expressly recited in the description herein. Accordingly, the scope of the invention should be determined solely by the appended

claims and their legal equivalents, rather than by the descriptions and examples given herein.

Microneedle Arrays

Chronically implantable microfabricated devices for neural stimulation and recording are important technologies with several emerging applications in substitution of motor, sensory, and cognitive function, such as when these modalities are compromised due to injury or disease. The implantable microfabricated devices may be used for accurate measurements of physiological signals within a body and can be used to provide control of artificial and biological devices. For example, measurements of motor neural signals sent to or travelling down a nerve within a body can be used to control an artificial device such as an artificial appendage, or distal body parts. The neural interface can be designed to address some of the major issues affecting the long-term recording and/or stimulation performance and the foreign body response to implanted microelectrodes. Similar stimulation can also be achieved via micro-optrodes which deliver light along a microneedle shaft from a suitable light source. The shape, size, electrode material, tethering forces, as well as the implantation technique, can each be important factors that can play a role in the foreign body response to chronically implanted neural electrodes. However, a few studies done in a rat model have suggested that one of the most significant factors that influences and increases the reaction of the brain to an implanted neural device is the manner in which it is anchored to the skull. For example, the tethering forces generated by the wires that are used to connect the neural interface to a skull-mounted electrical connector can trigger an immunological reaction and increase the encapsulation radius (neural dead zone) up to a few hundred microns around each microelectrode. This large encapsulation radius can substantially degrade recording performance as it is generally well accepted that an electrode be positioned within $\sim 100\ \mu\text{m}$ of a neuron for adequate detection.

Thus, multi-needle arrays that can record from and stimulate neurons without causing tissue damage or deterioration of the electrodes and/or optrodes are becoming increasingly valuable tools for many neuroscience investigators. Multi-needle arrays can require the use of arrays of needles maintained in a stable mechanical position relative to the associated neuronal structures for prolonged time periods. For example, the Utah

Electrode Array (UEA) and the Utah Slanted Electrode Array (USEA) have been in experimental use for two decades and are the standard in neural microelectrode technology. Yet, the UEA has only been partially able to provide reliable and useful signals over extended periods of time. In some studies, it has been demonstrated that as many as 80% of
5 UEAs fail acutely. Of those that failed, approximately 50% failed due to mechanical failures such as wire breakage and/or damage caused by the tethering force of the device.

Furthermore, where the UEA assembly survives the acute period, the recording performance of the UEA typically degrades over time. A primary cause of signal degradation can be continuous tissue inflammation around the UEA. For example,
10 tethering of the microelectrode array to the skull can increase the brain tissue inflammation significantly. The present technology seeks to provide a robust microneedle array that eliminates mechanical failures, but also has buoyancy that allows the device to float in the targeted tissue. A floating device can decrease the dead zone and improve the chronic recording performance of the device. For large neuronal mapping, the interconnect
15 technology can be scalable (to 1000+ channels) without compromising flexibility, robustness, and chronic performance of the device.

Typically, microfabricated arrays are made of a silicon substrate and are very rigid. For example, the UEA has a silicon base. The vast wire bonding work, which is used to connect the cables with the electrode arrays, can severely limit the flexibility and can lead
20 to unacceptable tethering forces and subsequent tissue irritation. In some cases, micro-fabricated polymer (e.g. polyimide) can be a good substitute to silicon or metal. However, a vast bonding work is still needed to connect the polymer cables with the silicon probes. Thus, while typical polymeric substrates include polyimide and liquid crystal polymers, the associated cables are normally used in relatively dry environments whereas an implantable
25 ribbon cable can require further design to resist an aqueous and biologically active medium. Furthermore, these ribbon cables often fail due to water penetration after a short period of time. Overall, conventional polymer/metal thin film based approaches for flexible and implantable devices continue to suffer from significant technical limitations such as aging under flexing, damage during surgery and implantation or use.

30 Given the highly convoluted structure of the human brain and the need to access a variety of surface and deep areas, the microelectrode arrays can include electrodes that can

record from neurons that lie deep in the sulci and from neurons that lie on the surface of the brain. The novel microneedle array is further designed to “float” (i.e. needles are not anchored directly to the skull) on the brain. As such, the needles within the microneedle array are generally not tethered or anchored to one another. In one example, the electrodes
5 can be attached to the skull via a ribbon cable. Alternatively, a corresponding waveguide can be provide to connect optrodes within an array. The proposed floating device can have several advantages: (1) the proposed technology can provide a microneedle array that can float in brain tissue, which can mitigate the relative micro-motion of the needles of the array with the brain tissue resulting in decreased tissue inflammation and increased chronic
10 performance of the array, and (2) the fabrication process can use semiconductor manufacturing processes. Thus, the pitch and dimensions of the electrical connection can be precise (within a micrometer) yielding a highly repeatable and reproducible floating device.

In further detail, the arrays described herein can include a plurality of microneedles
15 secured in a bio-erodible substrate. The bio-erodible substrate can be a common erodible substrate where all of the microneedles are secured within a monolithic (e.g. single) shared substrate. Typically, the array can have microneedles distributed in a two-dimensional pattern within a plane of the substrate. Further, at least a portion of the plurality of microneedles can be independently electrically and/or optically addressable. Although
20 described in detail with respect to a microelectrode array, these principles can be equally applied to a micro-optrode array where a waveguide is oriented within one or more of the microneedles of the array. In some cases, the array can have a portion of microelectrodes, a distinct portion of micro-optrodes, or a portion of microneedles having both electrical and optical pathways.

This is further illustrated in FIGs. 1A-1C. FIG. 1A illustrates a microelectrode
25 array 100 connected to a connector 190. Individual microelectrodes 110 of the microelectrode array 100 are secured in a bio-erodible substrate 120. In this particular example, each of the microelectrodes 110 of the microelectrode array 100 also include an electrical connection 130 associated therewith. As illustrated in FIGs. 1B and 1C, once the
30 microelectrode array 100 is brought into contact with biological tissue 105, the bio-erodible substrate 120 erodes away leaving a plurality of free-floating microelectrodes 110. In this

manner, each microelectrode 110 is free to move independent of neighboring microelectrodes. The result is to limit potential trauma to tissue to a single location.

The microneedle arrays can be designed to include a large number of microneedles. For example, the microneedle arrays can typically include from about 16 microneedles to about 2000 microneedles. In other examples, the microneedle array can include from about 25 microneedles to about 225 microneedles. In yet other examples, the microneedle arrays can include from about 81 to about 400 microneedles.

The microneedles of the microneedle array can be arranged in a variety of two-dimensional patterns across the bio-erodible substrate. When referring to a “two-dimensional pattern,” it is to be understood that the microneedles themselves are arranged in a two-dimensional pattern across the substrate, such as in the x and y directions with the tips of the microneedles extending away from the substrate into the z direction, for example. Thus, a microneedle array as described herein is a three-dimensional structure with microneedles distributed in a two-dimensional placement pattern (i.e. a non-linear, non-one-dimensional pattern) across the bio-erodible substrate in x and y directions. As such, the base of each microneedle is oriented within the two-dimensional placement pattern, regardless of tip location, height or geometry of the microneedle shaft. In other examples, the microneedles may be placed in a three-dimensional pattern. For example, the microneedles may be secured to a substrate that forms a surface that is not planar or two dimensional.

In some examples, the two-dimensional pattern can be a pre-determined non-uniform pattern. In such cases, the spacing between at least some of the microneedles can be non-uniform. In yet other examples, the two-dimensional pattern can be a pre-determined uniform pattern. In such examples, the spacing between each of the microneedles can be uniform or substantially uniform. In some specific examples, the microneedles can be spaced in a regular grid of parallel columns and rows. However, where this is the case, it is noted that the number of columns and the number of rows can be greater than or equal to 2, so as to provide a two-dimensional pattern. Thus, in a few examples, the microneedle array can include a 2x2, 2x10, 4x4, 3x6, 8x12, 10x10, 15x20, or other suitable array having any other suitable arrangement of columns and rows of microneedles.

In some specific examples, the plurality of microneedles can be secured in the common bio-erodible substrate at a density of from about 1 microneedle per mm^2 to about 25 microneedles per mm^2 . In other examples, the plurality of microneedles can be spaced at a density of from about 2 microneedles per mm^2 to about 10 microneedles per mm^2 . In yet other examples, the plurality of microneedles can be spaced at a density of from about 4 microneedles per mm^2 to about 25 microneedles per mm^2 .

In some additional examples, the plurality of microneedles can be spaced from one another at a distance of from about 200 μm to about 1200 μm . In other examples, the microneedles can be spaced from one another at a distance of from about 100 μm to about 500 μm or from about 200 μm to about 1200 μm .

The microneedles can generally include a base portion, a shaft portion, and a tip portion. The microneedles can most often have a tapered needle shape. Regardless, the microneedles can have a variety of lengths. In some examples, each of the plurality of microneedles can have the same length, or substantially the same length. In yet other examples, at least a first portion of the microneedles can have a length that is different than a second portion of the microneedles. Varying lengths can allow for penetration at different depths into neural tissue which may provide additional improvement in signal acquisition or stimulation, depending on tissue location. In some examples, the plurality of microneedles can have tips oriented, or substantially oriented, in a common plane. In some examples, the common plane can be parallel to the bio-erodible substrate. In other examples, the plane can be non-parallel to the bio-erodible substrate, such as in a slanted pattern, for example. In yet other examples, the tips of the plurality of electrodes can be oriented in a concave pattern, a convex pattern, a contoured pattern, or the like.

The microneedles can have a variety of heights, which can depend on whether the electrodes are intended to be monitor/stimulate surface neurons or non-surface neurons. Thus, in some examples, at least a portion of the microneedles can be penetrating microneedles. In yet other examples, at least a portion of the microneedles can be non-penetrating microneedles. In some specific examples, the plurality of microneedles can have a length of from about 200 μm to about 1800 μm , or from about 800 μm to about 1500 μm .

In some further examples, the plurality of microneedles can be high aspect ratio

microneedles (i.e. the lengths/heights of the microneedles can be large relative to the widths of the microneedles). Typically, the plurality of microneedles can have an aspect ratio of from about 2 to about 20. In other examples, the plurality of microneedles can have an aspect ratio of from about 3 to about 8. In some specific examples, the microneedles can have a width of from about 2 μm to about 200 μm , and often from 10 μm to 50 μm . Further, in some additional examples, at least a portion of the microneedles can be high aspect ratio microneedles having sharpened tips for penetrating biological tissue while minimizing damage upon insertion.

As previously discussed, the plurality of microneedles can be secured in a common bio-erodible substrate. The bio-erodible substrate can be formulated to have sufficient structural integrity to secure the plurality of microneedles to the substrate prior to and during positioning of the microneedles in a neural region. Further, the bio-erodible substrate can be formulated to bio-erode within a suitable period of time after placement of the microneedles. In some specific examples, the bio-erodible substrate can be formulated to bio-erode within a period of from about 30 minutes to about 240 minutes upon exposure to fluid environment (e.g. cerebral fluid). In yet other examples, the bio-erodible substrate can be formulated to bio-erode within a period of from about 45 minutes to about 90 minutes or 120 minutes. After the bio-erodible substrate erodes away, the microelectrodes are left free-floating in the tissue. For example, FIG. 1C (and FIG. 1B) depicts the microelectrodes without the bio-erodible substrate. After the bio-erodible substrate has eroded, the microelectrodes that are free floating can move relative to one another independently. This movement can be due to external impact, adjacent tissue movement (e.g. neighboring muscles) or growth of the tissue in which the microelectrodes are implanted. By allowing the microelectrodes to be free floating, the tissue in which the microelectrodes are implanted is less likely to be damaged due to a rigid structure of microelectrodes that are tethered together or to a skull of the patient.

Typically, the bio-erodible substrate can be relatively thin so as to facilitate rapid bio-erosion of the substrate. Thickness can be limited by the mechanical stability as an array base (e.g. withstand handling and insertion/implantation procedures). For example, in some cases, the bio-erodible substrate can have a thickness of from about 100 μm to

about 2000 μm , and in some cases from 20 μm to 250 μm .

The bio-erodible substrate can be made of a variety of materials. Non-limiting examples can include polyethylene glycol, polyglycolic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, polyoxyethylene/polyoxypropylene copolymers, polylactides, polyglycolides, polydioxanones, polysaccharides, hyaluronic acid polymers, starches, acacia gum, agar, alginates, carrageenan, cassia gums, cellulose gums, chitin, chitosan, curdlan, gelatin, dextran, fibrin, fulcelleran, gellan gum, ghatti gum, guar gum, tragacanth, karaya gum, locust bean gum, pectin, tara gum, xanthan gum, the like, or combinations thereof. For polymeric materials, the degree of cross-linking can be adjusted in order to vary the degradation rates. Additives such as degradation accelerators, anti-inflammatory agents, therapeutic agents, antibiotics, neural growth factors, and the like. Additives can be included in the substrate in order to adjust degradation rates, provide pharmaceutical benefits, and the like. Of particular interest are bio-erodible substrates formed of polymer based hydrogels. In one example, the bio-erodible substrate can be polyethylene glycol. Biomaterials such as polymer based hydrogels can also be used as delivery tools to deliver drugs such as neuronal growth factors and other therapeutics with precise delivery into defined brain region and specified temporal release.

The bio-erodible substrate can be prepared to have a variety of shapes and sizes. In some examples, the bio-erodible substrate can have a square or rectangular shape. In other examples, the bio-erodible substrate can have a circular or elliptical shape. In yet other examples, the bio-erodible substrate can have a triangular, polygonal, trapezoidal, rhomboidal, irregular, or other suitable shape. The particular shape of the bio-erodible substrate can depend on a number of factors, such as the desired application of the microneedle array, the number and positioning of the microneedles, and other factors.

In some examples, the bio-erodible substrate can have a length or diameter of from about 1 mm to about 10 mm. In yet other examples, the bio-erodible substrate can have a length or diameter of from about 2 mm to about 6 mm. Similarly, in some examples, the bio-erodible substrate can have a width of from about 1 mm to about 10 mm. In yet other examples, the bio-erodible substrate can have a width of from about 2 mm to about 6 mm.

As described above, at least a portion of the plurality of microelectrodes can be

independently electrically addressable. In some additional examples, each of the plurality of microelectrodes can be independently electrically addressable. In some examples, the microelectrodes can be electrically addressable by wire bonding a lead or electrical connection to respective microelectrodes, or equivalent. The lead can include or be made of any electrically conductive material. Non-limiting examples of conductive materials can include titanium, iridium, platinum, tungsten, gold, copper, aluminum, silver, conductive polymers, alloys thereof, or combinations thereof.

It is noted that the leads can typically have a relatively small diameter so as to increase the flexibility of the lead and minimize any trauma associated with positioning of the microelectrode on or in biological tissue. However, the leads can also be sufficiently thick so as to minimize mechanical failures due to wire breakage or the like (e.g. have a high fatigue resistance). Thus, in some examples, the leads can have a diameter of from about 5 μm to about 40 μm , or from about 20 μm to about 50 μm . In some specific examples, the leads can have a diameter from about 20 μm to about 30 μm . In one example, the leads include a ribbon cable. For example, the ribbon cable can have 1 μm metal width (metal thickness to be $< 1 \mu\text{m}$) and polyimide thickness = 12 μm with an overall width of 2 mm.

Furthermore, the leads can be operably connected to the connector 190. The connector 190 can provide a physical base which can be secured to a skull or epidermal layer to provide stability and external electrical connections. In one example, the connector can be a printed circuit board (PCB) which has electrical circuits to have electrical connection to the array (e.g. UEA) through the wires/ribbon cable.

In one alternative, the leads can be electrically connected to a wireless transceiver to allow communication with an external transceiver. In such cases, the device can further include a power source and control circuitry which can be oriented on a control base remote from the plurality of microelectrodes. Thus, referring to FIG. 1A, the connector 190 may be replaced by an implantable base unit which includes at least a wireless transceiver, a power supply, and control circuitry.

In some additional examples, the microneedle array can include one or more fluidic channels and associated connections for sampling of biological fluids and/or administration of a diagnostic agent, therapeutic agent, stimulatory agent, or the like. In some examples,

such fluidic connections can be operably associated with a microfluidic pump or the like to facilitate movement of the fluids to and/or from the microneedle array. These microfluidics connections (channels) can be used for precise delivery into a defined brain region and with a specified temporal release. The degree of cross-linking in the polymer can be adjusted in order to vary the degradation rates. The delivery drugs can be neuronal growth factors, degradation accelerators, anti-inflammatory agents, therapeutic agents, antibiotics, and the like

In yet other examples, the microneedle array can include one or more waveguides and associated connections for delivering an optical signal to the neural region. In such examples, the waveguides can be operably associated with a suitable source of electromagnetic radiation to transmit the optical signal to the neural region. The channels can also be used as waveguides to transmit light. In such cases, the microneedles can be micro-optrodes. Although micro-optrode arrays can be formed in a variety of ways, processing similar to the UEA processes can be used where the shaft portion is formed of an erodible, etchable material which can be removed. Alternatively, the shafts can be formed of an optically transparent material. See U.S. Application Publication No. 2013-0046148-A1 which is incorporated herein by reference. In some cases, all of the plurality of microneedles are optically independently addressable micro-optrodes.

The present disclosure also describes methods of monitoring and/or stimulating a neural region. The method can include inserting a microneedle array as described herein into a neural region. The bio-erodible substrate can be allowed to bio-erode to provide free-floating microneedles in the neural region. The neural region can be monitored and/or stimulated via one or more of the free-floating microneedles.

The microneedle array can be inserted into the neural region in a variety of suitable ways. However, chronically implanted microneedle arrays can demand high standards. For example, blood pulsation, inertial movements, adjacent muscle movements, and the like can cause relative motions of the neural tissue with respect to surrounding tissue. For example, where the microneedle array is implanted in a small space between the skull and the brain, the array is subjected to the relative movements of the skull and brain. Therefore, in some examples, the microneedle array can be mechanically decoupled from the surrounding tissue, such as the skull, to allow the microneedle array to float on the

neural tissue, such as the cerebral cortex, and minimize tissue damage associated with relative movements between the neural tissue and surrounding tissue. Additionally, the microneedle array can be implanted within peripheral nerves.

Additionally, to further minimize tissue damage, the substrate to which the microneedles of the microneedle array are initially secured can be allowed to bio-erode. Thus, each of the individual microneedles can be free-floating in the neural tissue such that the microneedles are mechanically decoupled from one another within the neural tissue to allow microneedles to move independent of one another. As such, movement of one of the individual microneedles will be isolated to the individual microneedle rather than being cumulative across the entire array. This can both minimize tissue damage in the neural region and strain on the fragile microneedles and associated electrical, optical, and/or fluidic connections.

Once in position, each of the microneedles can be used to monitor and/or stimulate the neural region via one or more of the microneedles. Monitoring and/or stimulating can be performed prior to the bio-erosion of the substrate, and after bio-erosion of the substrate via the plurality of free-floating microneedles, as desired. As previously discussed, the neural region can be monitored by recording electrical stimuli at the neural region, sampling of biological fluids from the neural region, or the like. Further, stimulating the neural region can be performed by delivering an electrical stimulus, a chemical agent, an optical signal, the like, or a combination thereof to the neural region via one or more microneedle of the microneedle array.

The present disclosure also provides a method of manufacturing a microneedle array. The method can include preparing a plurality of microneedles and securing the microneedles in a bio-erodible substrate. A lead can be wire bonded, or otherwise connected, to at least a portion of the plurality of microneedles. Further, the lead can be electrically conductively attached. For example, for a ribbon-cable, anisotropic conductive film (ACF) bonding can be used.

The plurality of microneedle arrays can be prepared in a variety of manners. In some examples, the plurality of microelectrodes can be prepared via a Michigan Electrode Array (MEA) process. In other examples, the plurality of microelectrodes can be prepared via a Utah Electrode Array (UEA) process (e.g. U.S. Patent Nos. 5,215,088; 7,951,300; and

8,865,288 which are each incorporated herein by reference). For example, the UEA can be manufactured by first providing a three-dimensional body of a first material. A first surface of the body is cut to form trenches to a preselected depth (e.g. via a dicing wheel). The trenches are filled with a second material to provide isolating regions of the second material and isolated regions of the first material between the isolating regions. The second material is adapted to provide electrical isolation between the isolated regions. A second surface of the body is sawed opposite the first surface at a preselected depth in criss-crossing channels to provide pillars of the first material between the channels. The channels typically have a bottom that reaches the second material deposited on the opposite side. In this manner, the pillars are electrically isolated from each other by means of the isolating second material. The pillars can then be etched to form tapered needles to reduce their cross-sectional size toward their distal ends. The distal ends can optionally be metallized, portions insulated or otherwise coated to create electrical contact pads and surface properties appropriate for stimulation and recording.

Where the UEA process is employed, the plurality of microneedles can be held in place using a photoresist material or other suitable material while the initial substrate is removed via etching or other suitable process and replaced with a bio-reducible substrate. The photoresist material, or the other suitable material, can then be removed to provide a plurality of microneedles secured in a common bio-erodible substrate. Leads and/or other suitable connections can be bonded to microelectrodes of the microneedle array in any suitable manner, such as via wire bonding, the like, or other suitable manner.

The electrode array can optionally have multi-site electrodes (e.g. U.S. Patent Application No. 15/271,062, published as U.S. Application Publication No. 2017-0007813-A1, which is incorporated herein by reference is known as a UMEA). A multi-site electrode is an electrode or micro needle with a plurality of active sites on each microelectrode that are electrically isolated from one another. Thus, an array of microneedles can further include multiple electrode active sites on each microneedle. In one example, a 10x10 microneedle array having 8 active sites per microneedle could provide up to 800 independent electrical signals to or from 800 unique tissue locations. Regardless, the set of electrically active sites can be arranged at and/or near the tip of each microneedle, and in many cases along a shaft of the microneedles. A portion or all of the

active sites can be independently electrically addressable. The microneedles can also be insulated with an insulator such that at least one, and in some cases all, active sites of each set are exposed.

Example

5 The present example describes one method of fabricating a floating microelectrode array where a 10x10 matrix of electrodes is held together with a biocompatible dissolvable polyethylene glycol (PEG) material. The PEG provides the array a temporary rigid mechanical substrate for insertion of the microelectrode array into neural tissue. Once the 10x10 (or 4x4, etc.) matrix of electrodes are inside the tissue, the PEG dissolves on its own
10 after it gets in contact with biological fluid. At that point each electrode will be independently floating of each other.

 The fabrication method can be performed in few simple steps without changing the entire process flow of the Utah array fabrication. The technology can use the same well-established methods for wire bonding, packaging, handling, implantation, and testing as the
15 standard UEA. These all serve to reduce experimental risk given the present experience in implanting and using standard UEAs.

 FIGS. 2A-F illustrate various stages or steps in the fabrication method. It should be appreciated that not all steps or components of the method are illustrated in FIGS. 2A-F. FIG. 2A illustrates a perspective view of an electrode array 220 in a mold 230. The
20 electrode array 220 can be a microelectrode array and have all the features and capabilities of the microelectrodes 110 of FIGS. 1A-C. In one example, the electrode array 220 is a standard Utah Electrode Array (UEA). The individual electrodes of the electrode array 220 can initially be connected by a substrate 210 where the substrate is not bio-erodible. For example, the substrate 210 may be composed of glass.

25 An initial step in the fabrication of an electrode array where the microelectrodes are secured using a bio-erodible substrate can be removal of the glass lines in between the different shafts of the electrode array 220 while keeping the array in place. The back of the electrode array 220 can be attached to tape 240. In one specific example, the tape 240 can be Kapton tape. The tape 240 is fastened to the back of the electrode array 220 such that
30 the tips of the electrodes protrude away from the tape. It should be appreciated that suitable structures other than tape may be employed to temporarily fix the microelectrodes

relative to one another. The electrode array 220 attached to the tape 240 can be positioned in a mold 230. The mold 230 can be ring shaped such that the electrode array 220 is surrounded by the mold 230. In one example, the mold 230 is composed of an etch resistant polymer. In one aspect, the mold 230 is composed of polyethylene (PE). The glass lines of the substrate 210 can be etched in Hydrofluoric acid (HF). In preparation for the etching process, the electrode array 220 can first be coated with standard photoresist (S1813 or AZ9260, for example). This maintains the electrode array 220 in place and protects the shafts and tips of the microelectrodes from the HF.

FIG. 2B illustrates a perspective view of FIG. 2A after a photoresist 250 has filled the mold 230. For example, the photoresist 250 can be pipetted onto the electrode array 220 until the mold 230 is entirely filled to the top. In one example, the assembly was then left under vacuum in a desiccator in order to remove bubbles from the photoresist. The assembly can be left in vacuum for about 60 minutes. In one example, after the desiccation, the assembly was placed on a hotplate at 110°C for 30 min and subsequently hard baked in an atmospheric environment in an oven for 4 h at 90°C and 10 h at 60°C.

FIG. 2C illustrates a back view of FIG. 2B after the tape 240 was removed. Removing the tape 240 exposes the pad side and the glass lines on the back of the electrode array 220 embedded in the photoresist 250. The tape 240 can typically be removed once the photoresist 250 has cured.

FIG. 2D illustrates a back view of FIG. 2C after the substrate 210 has been removed. For example, the substrate 210 can be removed using a 60 min etching step in HF 49% can be performed. The etching step can remove the glass lines of the substrate 210. The etching allows all shafts of the electrode array 220 to be detached and held in place by the photoresist 250. The assembly can be inspected to ensure that all glass lines were removed. Subsequent to etching, a metal mold can be used for deposition of bio-erodible material and subsequent steps.

In one embodiment, if all the glass lines of the substrate 210 have been removed, then a thin gold layer may be sputtered on the back of the electrode array 220 to form bonding pads for the individual electrodes. In one embodiment, if Pt bonding pads are employed then a sputtering step may be omitted.

FIG. 2E illustrates a perspective view of FIG. 2D after the tape 240 is reattached,

photoresist 250 is ablated, and a new layers are deposited to the front side of the electrode array 220. First, the tape 240 can be applied to the back side of the electrode array 220 still positioned in the mold 230. The tape 240 of FIG. 2E can be the same tape as FIG. 2A or can be a new piece of tape. Next, the photoresist 250 can be removed thus releasing the electrode array 220. The individual electrodes of the electrode array 220 can be held together using only a thin protective layer. For example, the thin layer can be a 3 μm thick parylene-C layer. The protective layer can be deposited prior to packaging for use or after exposure of tips. The electrode array 220 can be immersed in acetone to dissolve the photoresist 250. The electrode array 220 may be rinsed with isopropyl alcohol (IPA) in order to remove any residual acetone. In one embodiment, this step is performed with only slow stirring of the solution in order to keep the electrode array 220 in place on the tape 240. For example, the adhesive power of a silicone based adhesive may have been compromised by the previous acetone treatment. The electrode array 220 may then be air dried before being processed by an excimer laser. The laser may be a KrF with $\lambda=248.35$ nm. The ablation of the thin layer may remove the last remaining connection between the single electrodes of the electrode array 220. The electrodes may be rinsed again in IPA to remove any ablation residuals.

Next, the electrode array 220 may be coated with another thin layer to encapsulate the entire surface of the electrodes. The thin layer may be a 3 μm thick Parylene-C layer. This thin layer can be deposited using chemical vapor deposition (CVD) or techniques such as sputtering or the like. Next, the active sites, meaning the tips of the electrodes, may be deinsulated by selectively removing the thin layer. The thin layer may be removed using the previously described laser ablation. The thin layer on the substrate connecting the electrodes may also be removed using the laser ablation. The mold 230 may be replaced by a metal ring. The front side of the electrode array 220 within the mold 230 may be embedded in Polyethylene Glycol (PEG). The PEG may be deposited under vacuum to prevent the formation of bubbles.

FIG. 2F illustrates a back view of FIG. 2E after the tape 240 has been removed. The tape 240 may be removed once the PEG has solidified. With the tape 240 removed, the back of each electrode of the electrode array 220 is exposed and each electrode is bonded to a wire. The wires may be employed to connect the electrodes to a connector such as the

connector 190 of FIG. 1A. For example, the wires may be insulated gold wires. The wires may be 25 μm in diameter. In one embodiment, after each wire bonded column of 10 electrodes, silicone can be applied using a thin platinum wire onto the bond sites in order to provide additional mechanical strength to the bonds and to encapsulate the remaining gold thin film. The silicone can then be cured at 65°C. In one example, temperatures higher than 65°C may not be used in order to prevent the PEG from melting. For an electrode array 220 with 100 electrodes, such as a UEA, this process may be repeated iteratively for each of the additional 9 columns of 10 electrodes each until each of the 100 electrodes is wire bonded and encapsulated.

FIG. 3A illustrates a side view or cross section view of an electrode array 310 embedded in polymer in accordance with embodiments of the present technology. The electrode array 310 can be a microelectrode array and have all the features and capabilities of the microelectrodes 110 of FIGS. 1A-C and the electrode array 220 of FIGS. 2A-F. In one example, a layer 330 can be applied to cover the entire electrode array 310 after the electrode array 310 has been wire bonded to the back side of the electrode array 300. FIG. 3A depicts a portion of the wires 320 being covered by the layer 330. The layer 330 can be composed of PEG and may be several millimeters thick.

FIG. 3B illustrates a side view or cross section view of the electrode array 310 of FIG. 3A after a portion of the layer 330 has been removed. For example, the layer 340 is depicted as exposing the tips 350 of the electrodes in the electrode array 340. The layer 340 may be the same layer as the layer 330 of FIG. 3A having a portion removed. The layer 340 may be composed of PEG. The portion of the layer surrounding the tips 350 can be removed by dipping the assembly into deionized water. In this case, the coating can increase mechanical stability and reduce mechanical stress on bonding pads during implantation.

The electrode array 330 of FIGS. 3A and 3B may be positioned in a mold such as the mold 230 of FIGS. 2A-F. In order to release the electrode array 330, the mold can be heated, such as on a hotplate, melting only the PEG that connects the mold to the array.

In one embodiment, phosphate buffered saline can be employed to dissolve the PEG. For example, the phosphate buffered saline may dissolve the PEG in less than 60 min at 37°C.

One advantage of the present technology with a bio-erodible substrate is to start with an already existing electrode array such as the UEA. The implantation of the electrodes and its geometrical dimensions can remain the same as for the non-dissolving electrode array. In one embodiment, a polymer or non-noble metal can be used instead of the glass lines between the electrodes during the fabrication of the electrode array. The use of the polymer would not only facilitate the separation of the electrodes by using solvents or weaker acids than HF 49%, but also avoid the sputtering step for the pad metallization since the existing bond pads can remain sound during the separation process. In one embodiment, ultra-flexible Parylene-C based ribbon cables may be used instead of gold wires for electrical connections. This can remove additional stress from the wires as well as accelerate the bonding process, as the process would move from serial to batch.

The present technology also extends to methods of monitoring or stimulating a neural region using an electrode array of the present technology. In one embodiment illustrated as a flow chart in FIG. 4, a method 400, can include inserting a microneedle array into the neural region, as in block 410. The method can further include, allowing the bio-erodible substrate to bio-erode to provide free-floating microneedles in the neural region, as in block 420. The method can further include, monitoring or stimulating the neural region via one or more of the free-floating microneedles, as in block 430.

The method 400 can further include, monitoring the neural region by recording an electrical stimulus in the neural region. The method 400 can further include, stimulating the neural region by delivering an electrical signal to the neural region. The method 400 can further include, delivering a therapeutically active agent from the bio-erodible substrate.

The present technology also extends to methods of manufacturing a microneedle array of the present technology. In one embodiment illustrated as a flow chart in FIG. 5, a method 500, can include preparing a plurality of microneedles, as in block 510. The method can further include, securing the plurality of microneedles in a bio-erodible substrate in an array having microneedles distributed in a two-dimensional pattern, as in block 520. The method can further include, wire bonding a lead to at least a portion of the plurality of microneedles, as in block 530.

The foregoing detailed description describes the invention with reference to specific exemplary embodiments. However, it will be appreciated that various modifications and

changes can be made without departing from the scope of the present invention as set forth in the appended claims. The detailed description and accompanying drawings are to be regarded as merely illustrative, rather than as restrictive, and all such modifications or changes, if any, are intended to fall within the scope of the present invention as described

5 and set forth herein.

CLAIMS

What is claimed is:

1. A microneedle array, comprising:

5 a plurality of microneedles in an array having microneedles distributed in a two-dimensional pattern, wherein at least a portion of the plurality of microneedles are independently addressable; and

a bio-erodible substrate securing the plurality of microneedles and configured to degrade after implantation such that the plurality of microneedles are free floating.

- 10 2. The microneedle array of claim 1, comprising from 16 to 2000 microneedles.

3. The microneedle array of claim 1, wherein the plurality of microneedles are secured in the bio-erodible substrate at a density of from about 1 microneedle per mm² to about 20 microneedles per mm².

4. The microneedle array of claim 1, wherein the plurality of microneedles are spaced from one another at a distance of from about 200 μm to about 1200 μm.

- 20 5. The microneedle array of claim 1, wherein the array includes a regular grid of parallel columns and rows.

6. The microneedle array of claim 1, wherein each of the plurality of microneedles have a length of from about 200 μm to about 1800 μm.

- 25 7. The microneedle array of claim 1, wherein the plurality of microneedles have tips oriented in a common plane.

8. The microneedle array of claim 1, wherein the plurality of microneedles are high aspect ratio microneedles having sharpened tips for penetrating biological tissue.

9. The microneedle array of claim 1, wherein the bio-erodible substrate comprises a material selected from the group consisting of: polyethylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, polyoxyethylene/polyoxypropylene copolymers, starches, acacia gum, agar, alginates, carrageenan, cassia gums, cellulose gums, chitin, chitosan, curdlan, gelatin, dextran, fibrin, fulcelleran, gellan gum, ghatti gum, guar gum, tragacanth, karaya gum, locust bean gum, pectin, tara gum, xanthan gum, and combinations thereof.
10. The microneedle array of claim 1, wherein the bio-erodible substrate has a width of from about 1 mm to about 10 mm.
11. The microneedle array of claim 1, wherein the bio-erodible substrate has a length of from about 1 mm to about 10 mm.
12. The microneedle array of claim 1, wherein each of the plurality of microneedles is a microelectrode which is independently electrically addressable.
13. The microneedle array of claim 1, wherein each of the plurality of microneedles is a micro-optrode which is independently optically addressable.
14. The microneedle array of claim 1, wherein the bio-erodible substrate further comprises a therapeutically agent.
15. A method of monitoring or stimulating a neural region, comprising:
 inserting a microneedle array according to claim 1 into the neural region;
 allowing the bio-erodible substrate to bio-erode to provide free-floating microneedles in the neural region; and
 monitoring or stimulating the neural region via one or more of the free-floating microneedles.

16. The method of claim 15, wherein the bio-erodible substrate is formulated to bio-erode within a period of from 5 minutes to 240 minutes.

17. The method of claim 15, further comprising:

5 monitoring the neural region by recording an electrical stimulus in the neural region.

18. The method of claim 15, further comprising:

10 stimulating the neural region by delivering an electrical signal to the neural region.

19. The method of claim 15, further comprising:

 delivering a therapeutically active agent from the bio-erodible substrate.

15 20. A method of manufacturing a microneedle array, comprising:

 preparing a plurality of microneedles;

 securing the plurality of microneedles in a bio-erodible substrate in an array

 having microneedles distributed in a two-dimensional pattern; and

20 optionally wire bonding a lead to at least a portion of the plurality of microneedles.

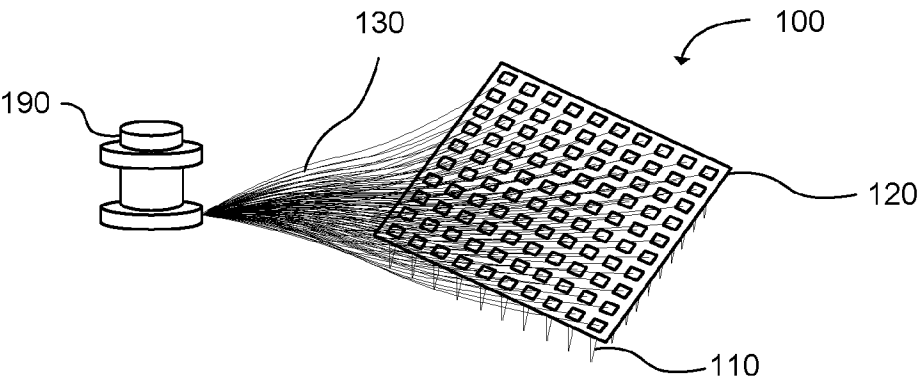


FIG. 1A

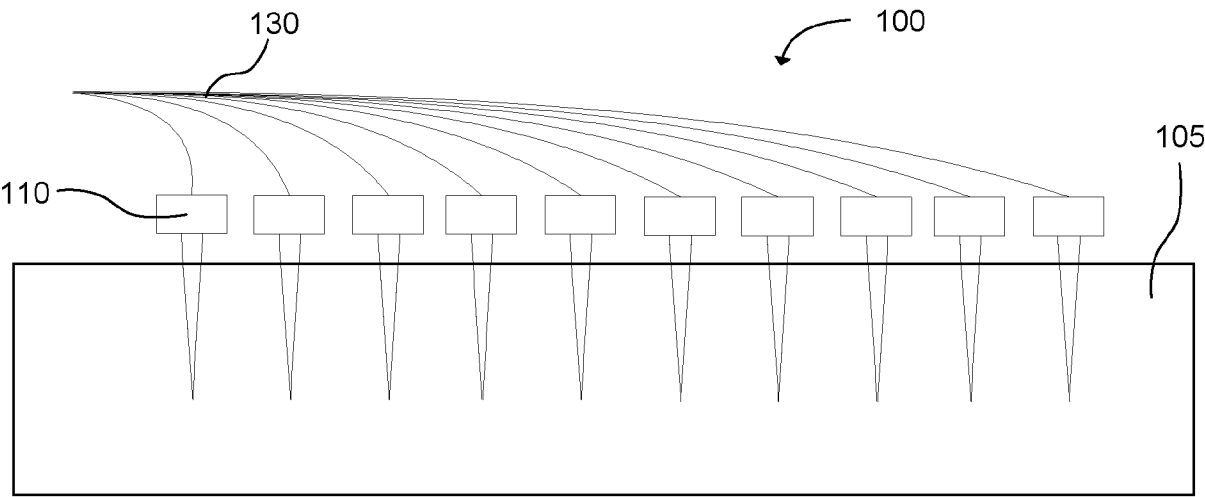


FIG. 1B

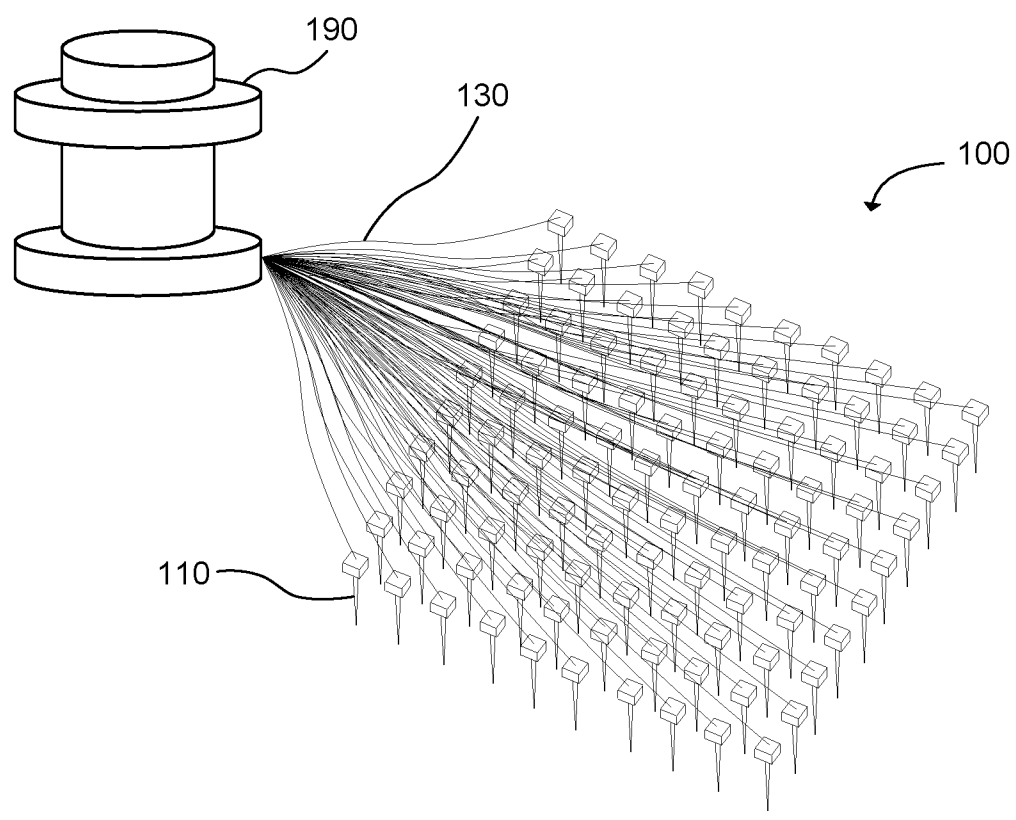


FIG. 1C

3/8

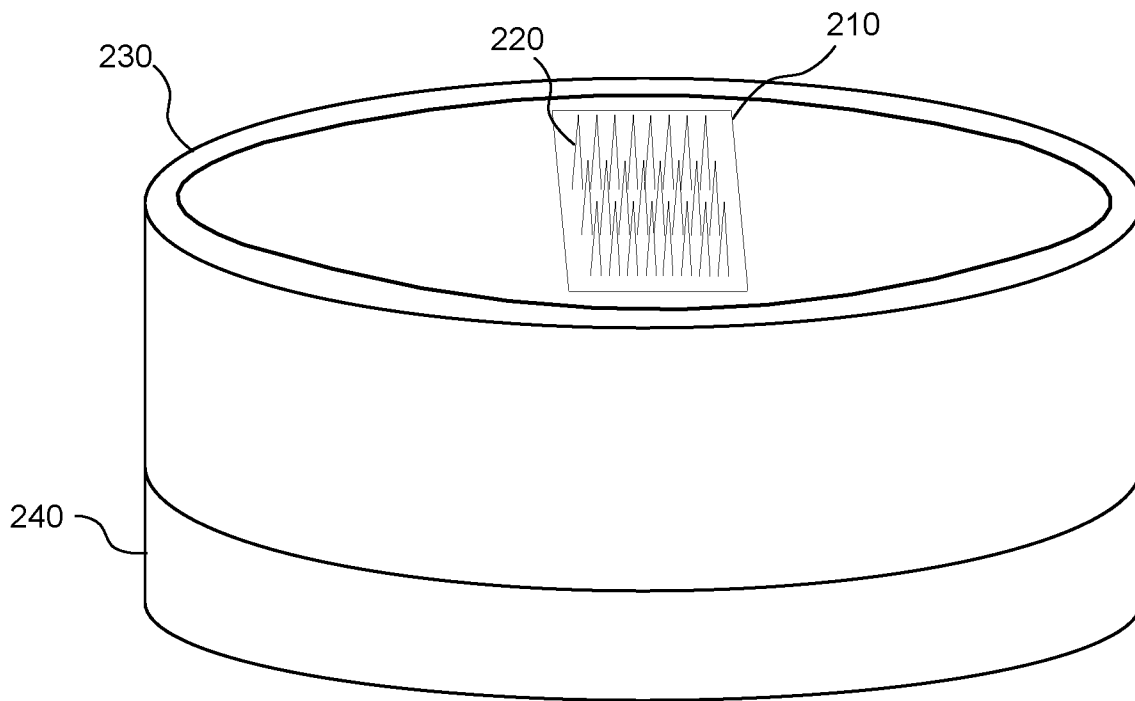


FIG. 2A

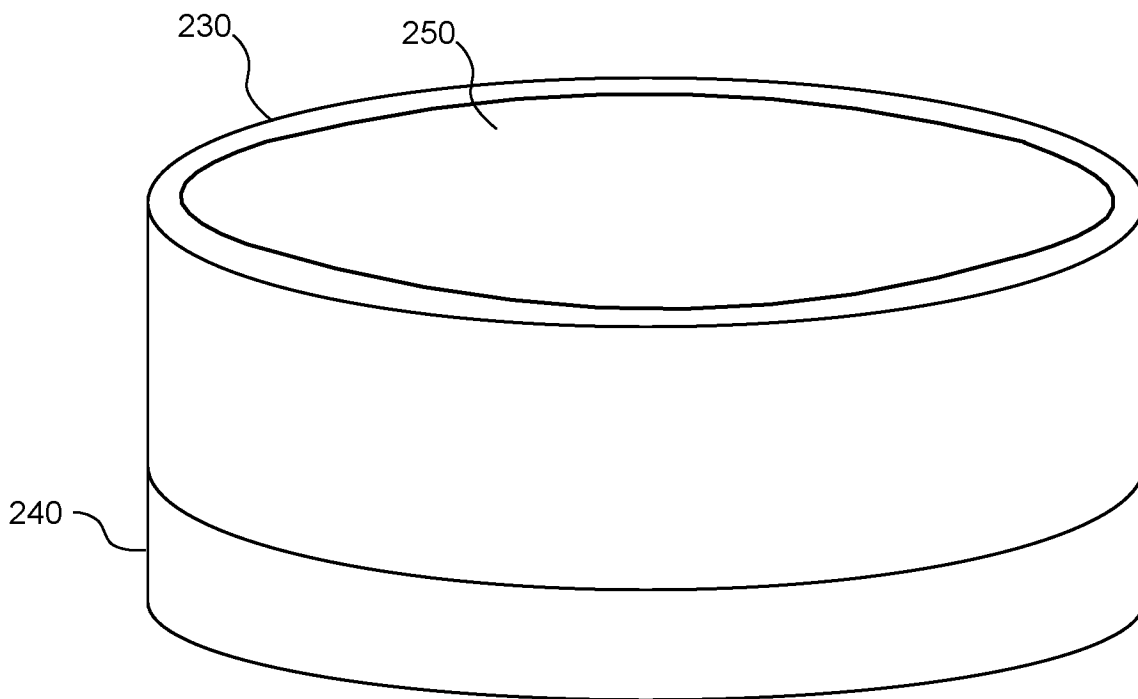


FIG. 2B

4/8

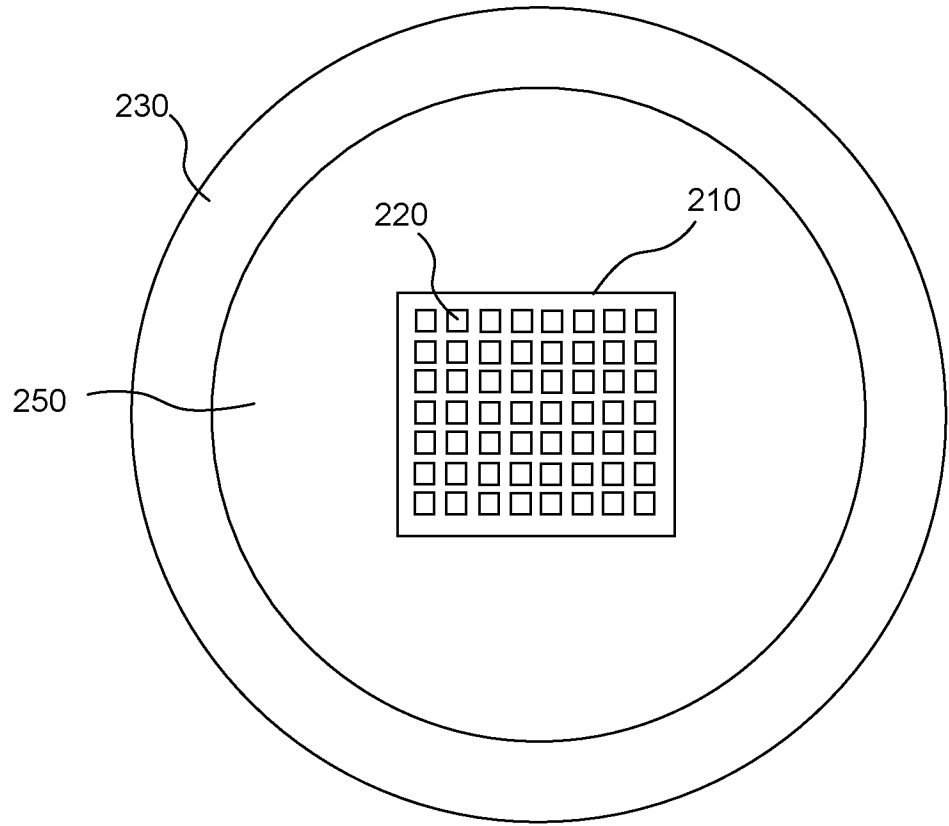


FIG. 2C

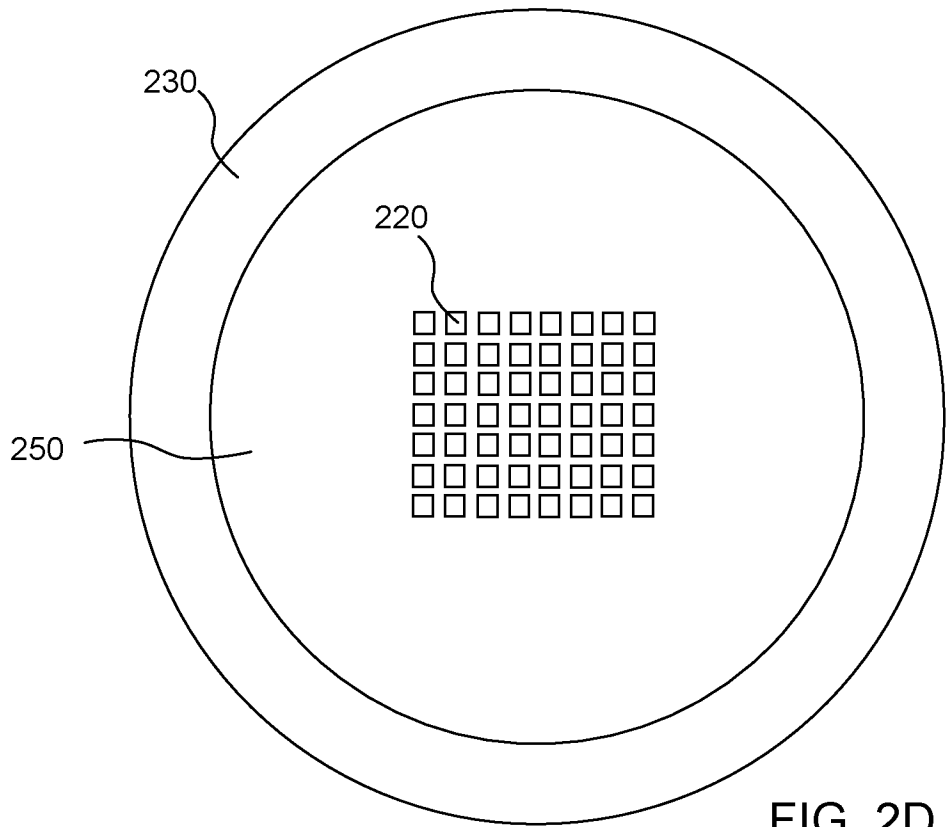


FIG. 2D

5/8

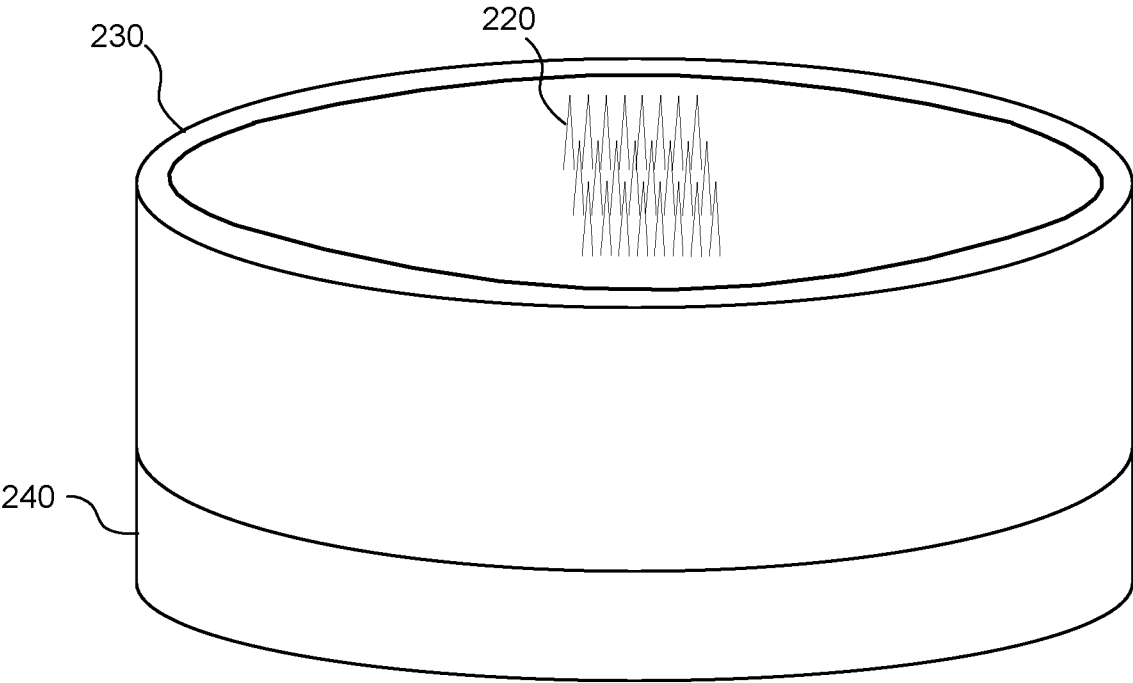


FIG. 2E

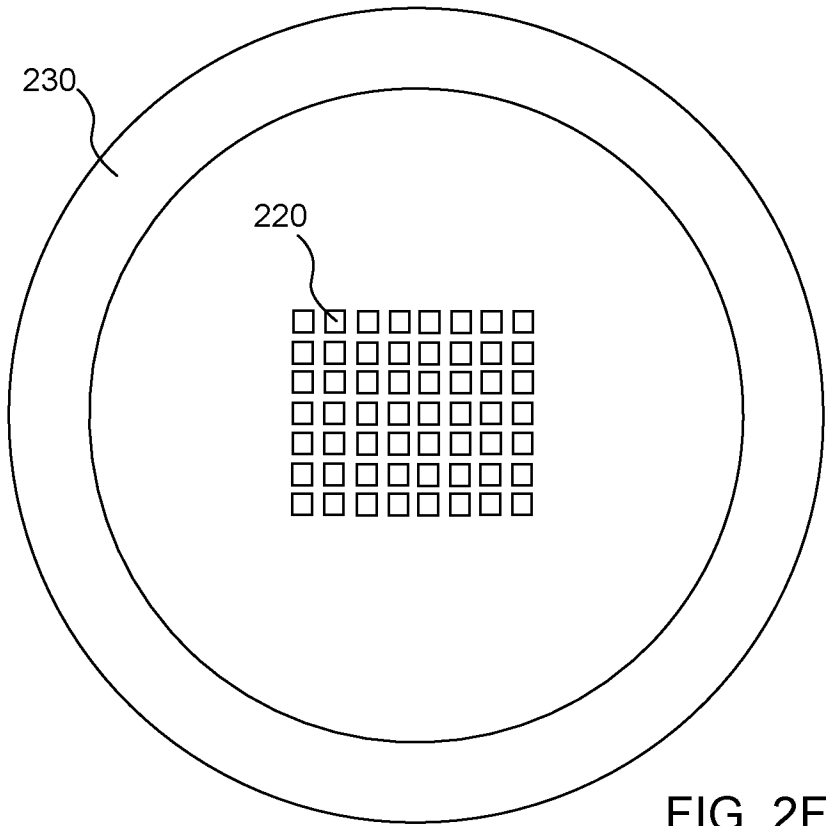


FIG. 2F

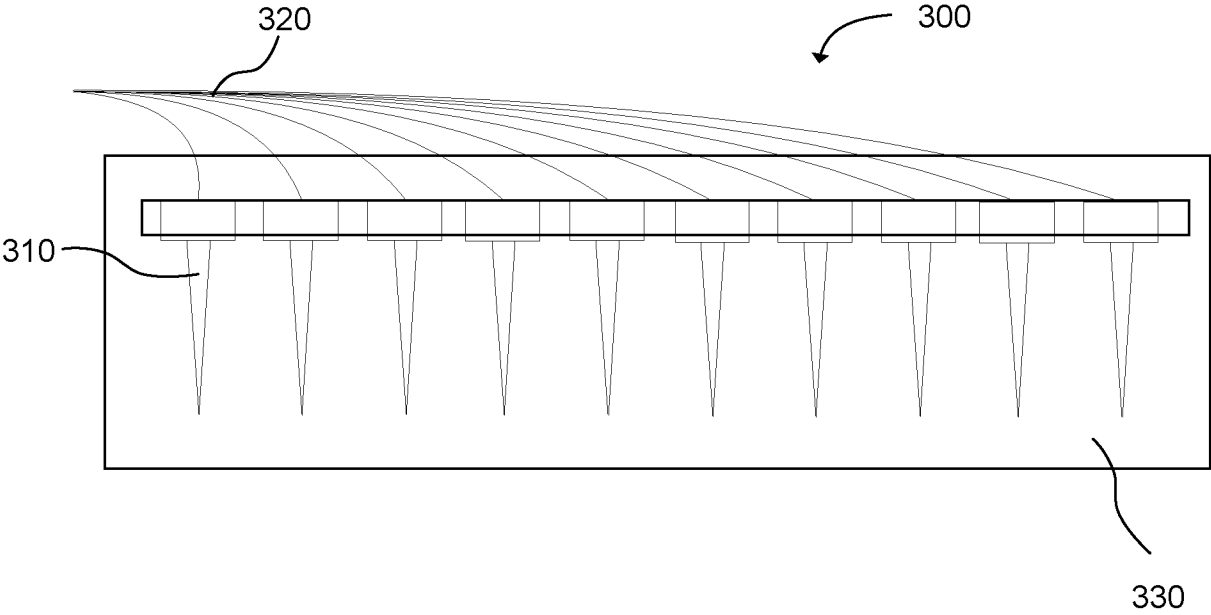


FIG. 3A

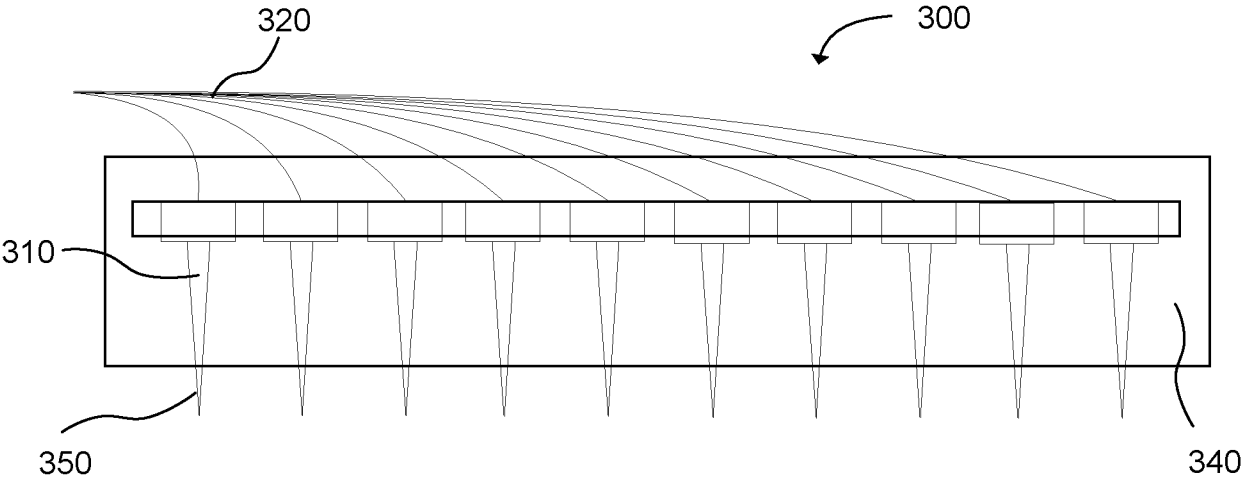


FIG. 3B

7/8

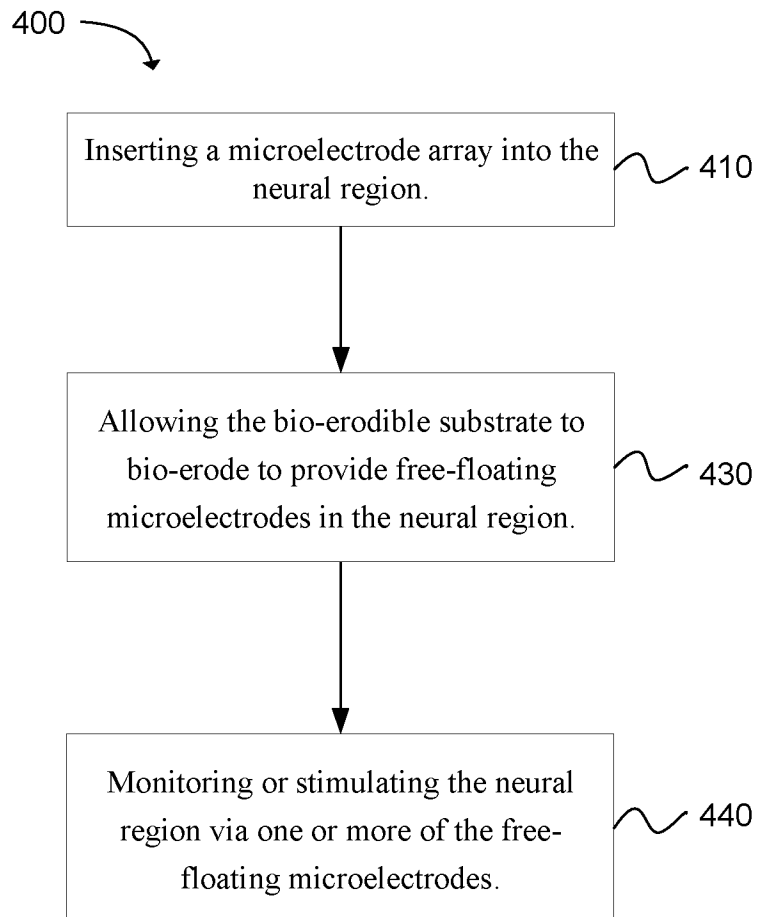


FIG. 4

8/8

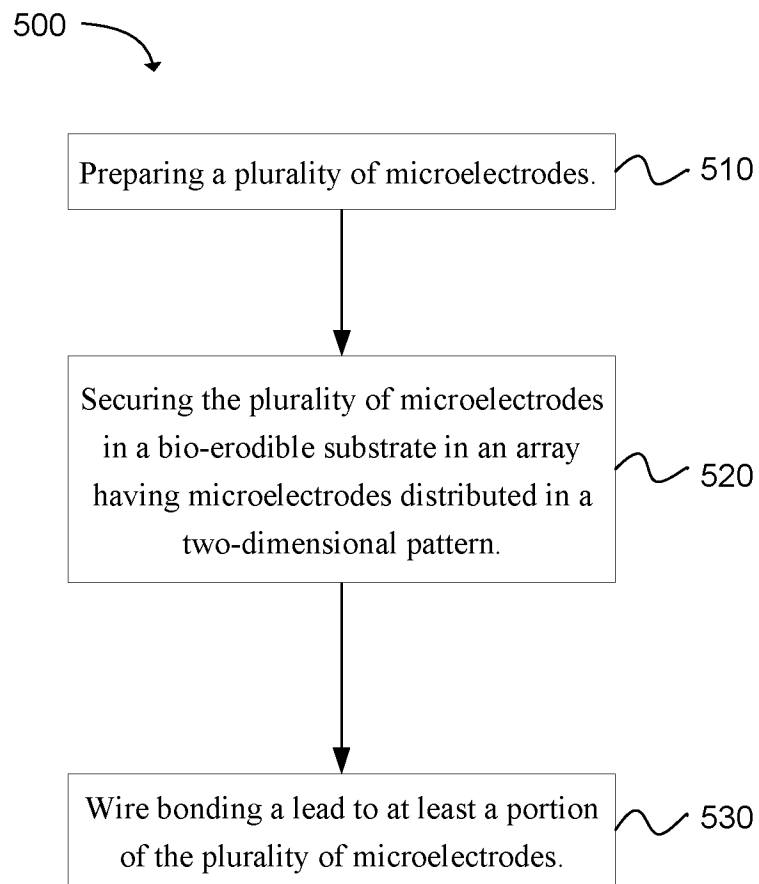


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/051387

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 5/0478; A61B 5/05; A61N 1/04; A61N 5/06 (2017.01)

CPC - A61B 5/04001; A61B 5/0082; A61B 5/4029; A61B 5/4058; A61B 5/4076; A61B 2562/0209; A61B 2562/0285; A61B 2562/046; A61N 5/0601; A61N 5/0622; A61N 2005/0652; G01N 33/4836 (2017.08)

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)

See Search History document

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

USPC - 435/288.7; 600/300; 607/88 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/0046148 A1 (TATHIREDDY et al) 21 February 2013 (21.02.2013) entire document	1-20
Y	US 2011/0093052 A1 (ANDERSON et al) 21 April 2011 (21.04.2011) entire document	1-20
Y	US 2013/0273135 A1 (UNIVERSITY OF UTAH RESEARCH FOUNDATION) 17 October 2013 (17.10.2013) entire document	14, 19

☐ Further documents are listed in the continuation of Box C.☐ 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)

"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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 October 2017

Date of mailing of the international search report

16 NOV 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774