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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 December 2015 (10.12.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/186087 A1

(51) International Patent Classification:
A61N 1/04 (2006.01) *A61N 1/36* (2006.01)

(21) International Application Number:
PCT/IB2015/054228

(22) International Filing Date:
4 June 2015 (04.06.2015)

(25) Filing Language: Italian

(26) Publication Language: English

(30) Priority Data:
TO2014A000451 5 June 2014 (05.06.2014) IT

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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, 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, KN, KP, KR, 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.

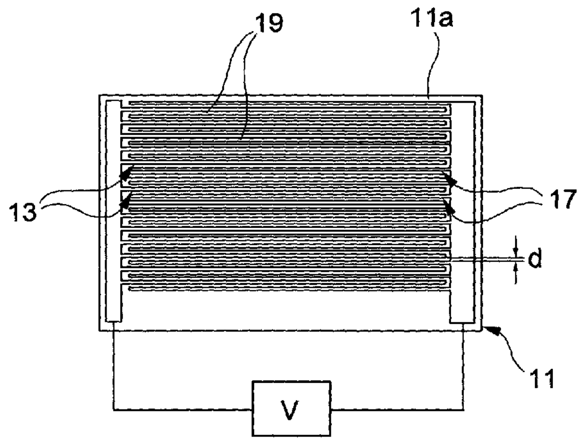
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

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

(54) Title: ELECTRODE PLATE WITH CONDUCTORS DEFINING GAPS AND A METHOD FOR ITS USE

FIG.2



(57) Abstract: Electrode plate comprising an electrically insulating supporting plate (11) having a front face (11a) and a rear face and a pattern of surface electrodes disposed on the front face for electrical stimulation of cutaneous nerve fibres. The pattern of surface electrodes comprises a first and second set of conductors (13, 17), whereby a gap region (19) of sinuous and/or arrayed configuration is defined between the first and second set of conductors. Each point of the gap region lies at a distance D_1 from the first set of conductors (13) and at a distance D_2 from the second set of conductors (17) such that the sum $D = D_1 + D_2$ is equal to or less than 250 μm, whereby the area of the gap region is of the order of magnitude of 1 mm^2 or greater.

WO 2015/186087 A1

ELECTRODE PLATE WITH CONDUCTORS DEFINING GAPS AND A METHOD FOR ITS USE

The present invention generally refers to non-chemical delivering electrode devices for electrical stimulation of cutaneous nerve fibres. Within the purposes of the present invention, “non-chemical delivering electrode devices” are those electrode devices for treatment of the human or animal body that are not configured for delivering a medicine or other chemicals to the body. In particular, the present invention refers to an electrode plate comprising an electrically insulating supporting plate having a front face and a rear face and a pattern of surface electrodes for electrical stimulation of cutaneous nerve fibres disposed on the front face of the supporting plate.

Excitable tissues are biological structures with membranes that can be depolarized by suitable electric current. The said current must have specific characteristics in order that depolarization takes place. Such characteristics are summarized in the strength duration curve, which determines the minimum duration and intensity (or strength) of the stimulating rectangular impulse for a given membrane. One most important parameter described by the curve is the rheobase, that is the minimum intensity that a stimulus of infinite duration must have in order to depolarize the membrane. Recent data have shown that depolarization is impossible not only if a stimulus amplitude is below rheobase, but also if its amplitude is above 20 time the rheobase level [1]. Another important parameter defined by the curve is the chronaxie. This is the duration of the stimulus required to stimulate the nerve at twice the rheobase. From the formula $I=Ir\cdot(1+C/t)$ where I is the current required, Ir is the rheobase, C is the chronaxie, and t is the duration of stimulus, it is evident that the current needed to stimulate the nerve will depend on the pulse width or duration of the stimulus. The chronaxie can be used as a measure of the threshold for any particular nerve and it is useful when comparing different nerves or nerve fiber types. Certain nerves have a different chronaxie based on their physical properties (myelination, size, etc).

Sensory nerves in the human and animal body are formed up by a number of fibres of different sizes and function:

1) Aβ fibres, i.e. large sized fibres that are covered by an insulating sheath (myelin)

and fast conducting (70-40 m/s); they convey senses of proprioception, touch and pressure;

2) Aδ fibres, i.e. medium sized fibres that are still myelinated and conduct at intermediate velocity (30-5 m/s). They convey senses of gross touch, cold and pricking or fast pain;

3) C fibres (2-0.5 m/s). They convey senses of warmth, heath and slow or burning pain.

Large Aβ sensory fibres are more easily stimulated than the smaller nociceptive Aδ and C fibres.

Typical pulse duration values suitable to stimulate different groups of fibres are the following:
50-100 microseconds for Aβ fibres, 200 microseconds for Aδ fibres, 500-1000 microseconds for C fibres.

Depolarization of the membrane occurs at the cathode.

It is important to add that one single depolarization in a nerve membrane is useless as to conveying information or to a neurophysiological recording. To such ends, the depolarization must be repeated a number of times per second. The time and intensity characteristics of impulses suitable to membrane depolarization and to convey information are therefore not apt to transport ions through tissues, as such transportation needs continuous currents applied for a large amount of time.

Clinical neurophysiologists have so far developed several methods to study objectively and reliably the Aβ nerve fibres, but the means to study Aδ and C fibres are scarce, costly, prone to errors and far from objective. Thus, while tests for evaluation of Aβ fibres are widely used, very few laboratories attempt to assess the function of Aδ and C fibres. Therefore, neurological conditions affecting Aβ fibres can reliably be diagnosed, but the much more widespread diseases involving Aδ and C fibres remain without the possibility of instrumental diagnosis.

The few methods so far employed for the electrophysiological study of the Aδ and C fibres are based upon a peculiar characteristic of such fibres: they, and they only, are embedded into the epidermal layer of the skin. Their endings, so called “free nerve endings”, terminate in such a layer, while endings of Aβ fibres terminate in deeper dermal layers of the skin.

So far, the only method recognized as reliable for selective activation of the nerve fibres lying within epidermal layer of the skin is infrared laser light. The best type of laser for the purpose is the CO_2 laser, with a wavelength almost completely absorbed by the first 50-100 μm of the skin. Because of some technical difficulties in focusing and conveying the beam with CO_2 another type of laser is nowadays preferred, the NdYAP. This has deeper penetration into the skin and is far less selective, but, because of its ease of use, it is now widely employed [2]. The effect of infrared laser onto the skin is a rise in temperature, hence depolarization of the axonal membranes is involved [3]. But the use of lasers has several drawbacks: it may cause burns, it is expensive, the stimulus characteristics cannot be easily controlled, there is a small but unpredictable delay in fibre activation and, as hinted above, its selectivity may be debatable. Such reasons have made the US researchers refrain from using lasers in the clinical setting for the purpose of nerve stimulation.

The traditional and most effective method of nerve stimulation is, since Galvani’s times, a pulse of electric current. This is very easily and precisely controlled in all its parameters, it is cheap to produce, it suffers no delay in triggering the fibre depolarization and generation of the action potential. This could be the ideal method for stimulating Aδ and C fibres, were it not for its lack of selectivity if applied through traditional surface electrodes. Electric pulses could be used for selective stimulation of Aδ and C fibres only if delivered through surface electrodes ensuring a current density profile properly suited to activate nerve membrane that would not spread deeper than 100 μm from the surface.

So, special electrodes have to be designed in order to accomplish such requirements. Some types of approach have been performed to this end:

i) Circular electrode where the cathode (the stimulating polarity) is a small dot with diameter of the order of 0.5 mm placed at the centre, surrounded by an isolation insert with diameter of 5 mm and by an outer conductive ring with diameter of 6 mm, the latter acting as anode [4]. As will be shown in the following, it has been demonstrated by computer simulation that the electric field has a shallow gradient, so the nerve fibres embedded in deep layers of the skin are also activated. At the same time, even if a selective stimulation of Aδ and C fibres were obtained, the amount of these fibres would be very small indeed, as the stimulating region only lies along the border of the central dot electrode. Matter of fact, it has been demonstrated in patients and through deep recordings from the central nervous system that such electrodes do not perform selective activation of the Aδ and C fibres, but mainly activate Aβ fibres [5].

ii) US 2013/0053933 discloses a device having multiple needles acting as cathodes, and penetrating the skin for about 0.3 mm. Such configuration achieves high enough current density and allows activation of higher amount of nerve fibres. There has been no scientific demonstration of its selectivity, but one objection is that the depth of 0.3 mm is far too much and the needle points are likely to penetrate the dermal layer, hence activating Aβ fibres also. Another major objection to the method is that it is invasive, based upon skin penetration.

iii) US 2006/0085056 discloses a device having an array of a large number of needles, penetrating the skin about 0.3 mm. It has the feature of being able to stimulate even more nerve fibres, but it has the drawbacks of penetrating down to the dermis (hence jeopardizing selectivity) and invasiveness. Again, there is no scientific demonstration of its selectivity.

Therefore, an aim of the invention is to provide a device that allows selective stimulation of nerve fibres located within the epidermal layer of the skin (Aδ and C terminals) without undesired activation of deeper fibres (Aβ).

A further aim of the invention is to provide a device that allows activations of a large number of the epidermal nerve fibres, proportional to the size of the device.

A still further aim of the invention is to provide a device that is not invasive, as the desired stimulation is just performed by applying the device on intact skin.

A further aim is to provide a device that is devoid as much as possible of electrical coupling with the recording electrodes employed in electrophysiological recordings.

In view of such aims, it is the object of the invention an electrode plate of the type defined above, wherein the pattern of surface electrodes comprises a first and second set of coplanar conductors which are positionable into mechanical and electrical contact with the skin of a human or animal body, characterized in that the first set consists of a plurality of conductors electrically connected to one another, and the second set consists of a single conductor or a plurality of conductors electrically connected to one another, said first and second set of conductors being connectable to a voltage generator so as that the first set of conductors has a first electric potential and the second set of conductors has a second electric potential different from the first electric potential, wherein a gap region of sinuous and/or arrayed configuration is defined between said first and second set of conductors, wherein when viewed in plan, each point of the gap region lies at a distance D_1 from the first set of conductors and at a distance D_2 from the second set of conductors such that the sum $D = D_1 + D_2$ is equal to or less than 250 μm, the area of the gap region being of the order of magnitude of 1 mm^2 or greater, said electrode plate thereby being capable of stimulating Aδ and C fibres selectively with respect to Aβ fibres.

The device according to the invention is capable of stimulating the nociceptive afferents only (i.e. Aδ and C fibres), by using electrical stimuli, without coactivation, or with negligible activation, of non-nociceptive fibres (Aβ fibres). By means of its specific technical features, the device according to the invention is capable to obtain the injection of high density current into a very superficial layer of the skin (epidermis, i.e. < 100 μm from the surface), distributed to an area as wide as possible (from several mm^2 up to few cm^2 or greater), and at the same avoiding current spreading into the deeper layer of the dermis (i.e. > 100 μm from the surface). Such features permit the desired selective activation because epidermis is only innervated by nociceptive afferents.

Another advantage of the invention in comparison with previous devices lies in its capability of greatly reducing the spread of electric stimulus to the recording electrodes commonly used in electrophysiology. Thereby the obtained recordings will be much less subject to interference, that otherwise may obscure the relevant parts of the trace. Such advantage has been found by the inventors in experiments even when the distance d between nearest conductors of different electric potential was increased to values greater than 250 □m, hence deprived of their selective property. Therefore, the electrode plate may be employed even in applications where Aβ fibres have to be stimulated but low interference from the stimulus is desirable.

Further characteristics and advantages of the electrode plate according to the invention will be apparent from the following detailed description, given with reference to the appended drawings, provided by way of non-limiting example only, in which:

- Fig. 1 is a schematic plan view illustrating a conventional, circular electrode plate;
- Fig. 2 is a schematic plan view illustrating an electrode plate according to the invention;
- Fig. 3 is a schematic plan view illustrating a portion of a gap region of an electrode plate according to the invention;
- Fig. 4 shows a cross-sectional view of distribution of second order spatial derivative of the electrical potential along the vertical direction for the conventional electrode plate (left side panel) and for the electrode plate of figure 2 according to the invention (right side panel). The X-scale is the distance from the centre of the electrode as indicated in figure. The skin model [7] consists of 4 layers (stratum corneum (SC) (thickness 29 μm), epidermis (60 μm), dermis (1300 μm), hypodermis (5000 μm) having different electrical conductance values (SC σ=5e-3 S/m, epidermis σx=0.95 S/m σz=0.15 S/m, dermis σx=2.57 S/m σz=1.62 S/m, hypodermis σ=2e-2 S/m). Conductivity of SC has been adapted to the experimental conditions. White regions in the SC indicate values of the spatial derivative above the colour scale, but irrelevant to our interest as nervous fibres are located in the epidermis and dermis layers. Values of the spatial derivative are negative under the cathode and positive in its neighbourhood (circular electrode) or under the anode (interdigitated electrode). Spatial scale is in meters. Only half the electrode is shown, with the central pin polarized as a cathode at -50V. The anodic pad for the concentric electrode is far away in the right direction at 2.5 mm distance;
- Fig. 5 shows: in left side panel, a table with numerical values of the integral of the activation function "f" calculated for the conventional and invention electrode plate at dif-

ferent depths along line profiles (integral path) of the cross-sectional plot of figure 4; in right side panel, a normalized plot of the integral values;

- Fig. 6 is a graph depicting the scalp recorded evoked potential after stimulation of epidermal nerve endings with the device of the invention. During the first 25 ms the electrical “artefact” of the electrical stimuli can be seen, due to the stimuli delivered in train of 5 pulses, with total duration of 25ms (the actual artefact linked to each single pulse is much smaller than with conventional electrodes). Subsequently there are no relevant deflections before the N2-P2 complex, reflecting cortical activation by the painful afferents;
- Figs. 7 and 8 are schematic plan view illustrating further embodiments of the electrode plate according to the invention; and
- Figs. 9a to 9d are graphs showing exemplary configurations of stimuli which can be delivered according to the invention.

Fig. 1 shows a conventional electrode plate as disclosed in [4]. This electrode plate comprises a supporting plate 1 carrying, on its front face, a small dot 3 acting as cathode, an insulation insert 5 and an outer conductive ring 7 acting as anode. The dot 3 is placed at the centre of the supporting plate 1, and is surrounded by the insulation insert 5 and by the outer conductive ring 7.

Fig. 2 shows an electrode plate according to the invention. This electrode plate comprises a supporting plate 11 of electrically insulating material that can be stiff or flexible. For example, the electrode plate may be of ceramic material, such as alumina or Macor®, fiberglass or plastic, such as Kapton®. The supporting plate 11 carries, on its front face 11a, a pattern of surface electrodes for electrical transcutaneous stimulation of nerve fibres. The electrode plate is suitable for being attached to the skin of a human or animal body. In this application the front face 11a is the face of the plate 11 that is positioned on the skin, whereas the opposite face, which is not visible in the drawings, is termed rear face.

The electrode plate can be set in mechanical and electrical contact to the subject skin with a sticking tape. According to an alternative embodiment, the electrode plate may have adhesive material applied on its front face.

The pattern of surface electrodes applied on the supporting plate 11 comprises a first and second set of conductors 13, 17, particularly in form of narrow strips, having different electric potentials when connected to a voltage generator V, and interdigitated with one another. More particularly, the first and second set of conductors 13, 17 are arranged in a comb-like pattern as shown in Fig. 2.

However, other geometries are possible according to the invention. Examples of further geometries are disclosed in the following.

A gap region 19 is defined between the first and second set of conductors 13, 17 for separating the first set of conductors from the second set of conductors. In the embodiment of Figure 2 the gap region 19 is of sinuous, particularly serpentine configuration.

From a geometrical point of view (see fig. 3), the gap region 19 is defined as the locus of points (P) that lie at a distance D_1 from the first set of conductors 13 and at a distance D_2 from the second set of conductors 17 such that the sum $D = D_1 + D_2$ is equal to or less than 250 μm. In the interdigitated embodiment of Figure 2, the sum D is equal to the distance d between nearest conductors of different electric potential; this means that distances d between nearest conductors of different electric potential are equal to or less than 250 μm.

Furthermore, the area of the gap region 19 is of the order of magnitude of 1 mm^2 or greater, when measured in plan view.

As will be shown in the following, in view of these features the electrode plate according to the invention is capable of selective stimulation of Aδ and C fibres, and is large enough to stimulate a suitable number of nerve fibres.

The selective stimulation is performed through a sequence of pulses with magnitude able to depolarize membranes of nociceptive fibres following their specific strength duration relationship, while minimizing the total amount of energy transmitted to the human or animal body. Each stimulus comprises a single electrical pulse or a burst of pulses, for example 5 pulses separated by a pulse period υ of 5ms. Typically, pulses may have duration T in the 0.2 ms-1 ms range (see Fig. 9a). For optimization of signal to noise ratio in recordings from nerves or EEG, stimuli may be repeated up to 1000 times, so that a maximum of 5000 pulses may be delivered, for a current application total time of 5s and a total session time of a few minutes.

Each pulse may be a rectangular, triangular pulse or any other shape pulse. Alternatively, it may contain a radiofrequency wave packet with spectral distribution within approximately 50-500 kHz. For example, the pulse may be the said radiofrequency wave packet summed with a DC or low frequency signal (see Fig. 9c).

In some applications, the average of the effective applied voltage or current is approximately zero value so as to promote membrane depolarization while minimizing transport of ions through tissues (see Figs. 9b and 9d).

The conductors 13, 17 may be fabricated with conventional lithographic methods by depositing a thin conductive layer over an insulating substrate. Deposition may be performed by sputtering and patterning by optical lithography. In particular, the inventors have fabricated some prototypes by depositing a 200 nm-thick gold layer over an insulating ceramic substrate, and patterning the interdigitated geometry by means of optical lithography and Argon milling. Alternatively, the inventors fabricated prototypes depositing the metallic (gold) layer over a negative-tone patterned photoresist interdigitated geometry, the final structure being obtained by lift-off technique. The prototypes have been wired by conducting paste or through ultrasonic bonding wires that were immersed in (insulating) Epoxy glue in order to mechanically sustain hard contact with human skin. The large conducting areas outside the interdigitated region of the device were electrically insulated from the skin by insulating varnish or glue. The area covered by the whole device had typical dimension of 6 x 10 mm^2, allowing the simultaneous activation of a very large number of epidermal fibres (density of nerve fibres is estimated to be around 60-120 /mm^2, depending on the skin zone).

The samples were subjected to experiments using, as electrical stimuli, a burst of 5 pulses each with duration of 1 ms, and interpulse interval of 4 ms (so the whole burst had duration of 25 ms). According to F. Rattay [6], the activating function “f” of unmyelinated fibres - which is strongly related to the firing of the action potential of the neuron - is proportional to the second order derivative of the electrical potential along fibre’s length, in this case d^2V/dz^2 as epidermal nerve fibres are mainly aligned along skin thickness (z direction). By evaluating the activating function, important information about stimulated (depolarized) regions (where f >0) and hyperpolarized regions (f <0) of the fibre can be extracted. Figure 4 shows the distribution of the second order potential derivative along z direction for the concentric electrode plate presented by Mørch et al. [7] and the electrode plate of the invention. Modelling is performed by Finite Element Analysis using a layered model for the skin reported by Mørch et al. [7]. Thus, plots of figure 4 well describe the regions where small fibres are mainly stimulated. The advantage of the invention clearly appears from these plots. It appears that circular electrodes used so far have a much smaller stimulating area mainly evidenced by the darker regions in the epidermis layer. Also, increasing the diameter of the circular electrode would not result in any relevant improvement of the stimulating area (see also Mørch et al.[7]). Thus, the final effect is stimulation of too small a number of epidermal fibres. On the contrary, the invention offers the possibility to extend the stimulating area at will by increasing the size of the device. The approach of the invention offers a larger stimulating area, as the electrode surface is characterized by a high edge/surface area ratio. Matter of fact, from the calculation of the inventors it appears that the activation function is peaked under the edges of the microstructured electrode and due to the very short interdigital distance, the efficacious electric field is limited to the epidermal region of the skin, approximately 100 µm below the surface. Darker area in the epidermis layer are a sequence of regions with maximum value of “f” and alternate sign. Table and plot of figure 5 describe the efficiency of the two types of electrodes in terms of average stimulation under the skin. Four profiles of the activation function “f” at different depths under the skin (-10 µm, -59 µm (middle of the epidermis) -100 µm, -200 µm) for a total length of 1 mm along the cross sections (integral path) of figure 4 were considered for the two electrodes (see dotted line of Figure 4 right). The table of Fig. 5 shows the values of the integrals of the activation function over these cross sections for the electrode plate of the invention and the circular one. Due to the symmetry of the electrode geometry, for the electrode plate of the invention only one sign (positive) values of “f” have been considered, while for the case of the circular electrode plate both signs of “f” have been considered, as the user could change voltage bias polarity. The total amount of the integral for each line thus represents the efficiency of fibres activation, a sort of average product between the value of the activation function and its spatial extension. Instead, the dependence of this integral along skin depth represents the selectivity of the electrode for deep fibres stimulation. Plot of Figure 5 shows this dependence; the plot is normalized to the integral value calculated just below the electrodes (-10 µm), as the voltage bias (-50 V) has been arbitrarily chosen. Plot and table well demonstrate that the electrode geometry of the invention allows better selectivity for fibres situated in the epidermal layers. The depth of efficient stimulation is a function of the electrode conductor distance and width and can be further optimized with respect to the realized prototypes.

Two prototype devices have been tested on volunteers:
Device 100. The device had surface of approximately 6 x 10 mm^2 and comb-like structure, with n. 16 teeth for the negative pole (cathode) and n. 16 teeth for the positive. Length of the teeth was 10 mm each. Distance between teeth of different electric potential was 100 µm.
Device 50. The device had surface of approximately 6 x 10 mm^2 and comb-like structure, with n. 31 teeth for the negative pole (cathode) and n. 31 teeth for the positive. Length of the teeth was 10 mm each. Distance between teeth of different electric potential was 50 µm.

Each device was applied in turn onto dry skin in the area between first and second metacarpal of the non-dominant hand of each subject. The site of application was chosen because it is in the area of distribution of the radial nerve, and because cutaneous branches of the radial nerve, at that site, run just underneath the epidermis. If enough current spreads to the dermis or subcutaneous, then the felt perception would be radiated, usually down to the second finger. Otherwise, if current is only spread to the epidermis, just the embedded nerve fibres will be stimulated, and a painful prick should be felt just beneath the device. A burst of 5 electrical pulses of 1 ms duration each, with interpulse interval of 4 ms was passed through the electrode; one single burst was delivered every 2 s. A constant voltage isolated pulse generator was used; current and voltage delivered to the device were monitored on oscilloscope. Starting from 0 V, the stimulator output was increased in steps of 5

V every two bursts, until the faintest sensation was felt by the subject. The very first sensation felt by the subject has always been a pin prick. Perception thresholds were assessed between 40 and 100 V approximately, according to the subject. In order to ascertain that epidermal nociceptive fibres were selectively stimulated, two experiments were set up.

1) Perception of touch and pin prick before and after application of local anaesthetic. Before the electrode was positioned, and on the same site, perception threshold of touch sense was assessed by means of Semmes Weinstein Von Frey Aesthesiometers®, and the pin prick threshold by means of the prototype device. The electrode was then removed and Emla® cream (mixture of local anaesthetics for transdermal anaesthesia, selectively blocking pain fibres while comparatively unaffecting touch fibres) was applied on the investigated skin spot. After 15 minutes, the excess cream was removed, and the two thresholds assessed again. Whilst the touch threshold remained the same, the pin prick threshold was increased by at least 100% the voltage value.

2) Pain related evoked potentials were recorded from the scalp after stimulation through the prototype device. The waveform obtained was very similar to the one obtained after stimulation with laser pulse, with the only difference that the time latency was shorter, indicating a faster activation of the epidermal nerve endings. The graph obtained is shown in Fig. 6, where the N2 component has latency of approximately 100 ms. Such component is considered to be linked to Aδ fibre activity when laser stimuli are used. It may safely be considered reflection of Aδ afferents even in our case. It is noteworthy that no previous peaks are visible in the graph of Fig. 5, thus ruling out activity by Aβ fibres, which obviously had not been stimulated.

Figure 7 shows a further embodiment of the electrode plate according to the invention.

In this embodiment, the pattern of surface electrodes comprises a first and second set of conductors 13', 17', particularly in form of narrow strips, having different electric potentials and interdigitated with one another. More particularly, the first and second set of conductors 13', 17' are arranged in a curvilinear pattern as shown in Fig. 7.

A gap region 19’ is defined between the first and second set of conductors 13’, 17’ for separating the first set of conductors from the second set of conductors. In the embodiment of Figure 7 the gap region 19’ is of sinuous (serpentine) configuration.

From a geometrical point of view, the gap region 19’ is defined as the locus of points that lie at a distance D_1 from the first set of conductors 13’ and at a distance D_2 from the second set of conductors 17’ such that the sum $D = D_1 + D_2$ is equal to or less than 250 µm (see Fig. 3 for clarification). In the interdigitated embodiment of Figure 7, the sum D is equal to the distance d’ between nearest conductors of different electric potential; this means that distances d’ between nearest conductors of different electric potential are equal to or less than 250 µm.

Furthermore, the area of the gap region 19’ is of the order of magnitude of 1 mm^2 or greater, when measured in plan view.

Figure 8 shows another embodiment of the electrode plate according to the invention.

In this embodiment, the pattern of surface electrodes comprises a first and second set of conductors 13’’, 17’’ having different electric potentials, wherein the second set of conductors 17’’ is in form of an enveloping electrode that surrounds the first set of conductors 13’’.

A gap region 19’’ is defined between the first and second set of conductors 13’’, 17’’ for separating the first set of conductors from the second set of conductors. Due to the enveloping arrangement of the second set of conductors 17’’, the gap region 19’’ is in form of closed loop. In particular, in Figure 8 the first set of conductors 13’’ is in form of an array of dots surrounded by the enveloping electrode 17’’, and the gap region 19’’ is in form of a plurality of ring-shaped regions, each of which is interposed between a corresponding dot and the enveloping electrode.

Electrical connection between the dots is provided by conductor parts (not shown) that are arranged on the back face of the electrode plate. According to another embodiment (not shown), the dots may be connected to one another by conductor parts formed on the front face of the electrode plate. However, further geometries are possible for the first set of conductors, such as for example narrow strips or more complex shapes.

From a geometrical point of view, the gap re-gion 19'' is defined as the locus of points that lie at a distance D_1 from the first set of conductors 13'' and at a distance D_2 from the second set of conductors 17'' such that the sum $D = D_1 + D_2$ is equal to or less than 250 μm (see Fig. 3 for clarification). In the embodiment of Figure 8, the sum D is equal to the distance d'' between nearest conductors of different electric potential; this means that each ring-shaped region has a width d'' equal to or less than 250 μm.

Furthermore, the area of the gap region 19'' (i.e. the sum of the areas of the individual ring-shaped regions) is of the order of magnitude of 1 mm^2 or greater, when measured in plan view.

Returning to the comb-like electrode plate of Figure 2, this arrangement may be used even in applications where Aβ fibres have to be stimulated but low interference from the stimulus is desirable.

As a matter of fact the inventors found that, when the distance d between nearest conductors of different electric potential was increased to values greater than 250 μm, the electrode plate was able to activate the entire fibres spectrum (Aβ, Aδ and C fibres), and therefore lost its selectivity, but still obtained reduced stimulus spread to recording electrodes. These recording electrodes are usually placed on the skin at some distance away from the stimulating electrode plate. This low interference feature may be advantageous in some applications, such as for example in clinical neurophysiology. However, it is believed that such an effect can be obtained also with interdigitated, circular geometry (an example of which is shown in Figure 7), and with arrayed geometry in which the first set of conductors is in form of an array of regions surrounded by the second set of conductors in form of an enveloping electrode (an example of which is shown in Figure 8).

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CLAIMS

1. Non-chemical delivering electrode plate comprising an electrically insulating supporting plate (11) having a front face (11a) and a rear face and a pattern of surface electrodes for electrical stimulation of cutaneous nerve fibres disposed on the front face (11a) of the supporting plate (11), wherein the pattern of surface electrodes comprises a first and second set of coplanar conductors (13, 17; 13', 17'; 13'', 17'') which are positionable into mechanical and electrical contact with the skin of a human or animal body, characterized in that the first set consists of a plurality of conductors electrically connected to one another, and the second set consists of a single conductor or a plurality of conductors electrically connected to one another, said first and second set of conductors being connectable to a voltage generator (V) so as that the first set of conductors has a first electric potential and the second set of conductors has a second electric potential different from the first electric potential, wherein a gap region (19; 19'; 19'') of sinuous and/or arrayed configuration is defined between said first and second set of conductors (13, 17; 13', 17'; 13'', 17''), wherein when viewed in plan, each point of the gap region lies at a distance D_1 from the first set of conductors (13; 13'; 13'') and at a distance D_2 from the second set of conductors (17; 17'; 17'') such that the sum $D = D_1 + D_2$ is equal to or less than 250 μm, the area of the gap region (19; 19'; 19'') being of the order of magnitude of 1 mm^2 or greater, said electrode plate thereby being capable of stimulating Aδ and C fibres selectively with respect to Aβ fibres.

2. Plate according to claim 1, wherein the sum D = D1 + D2 is equal to or less than 100 μm.

3. Plate according to claim 1 or 2, wherein said first and second set of conductors (13, 17; 13', 17') are in form of narrow strips of conductive material.

4. Plate according to any of claims 1 to 3, wherein said first and second set of conductors (13, 17; 13', 17') are interdigitated with one another, and wherein distances (d, d') between nearest conductors of different electric potential are equal to or less than 250 μm.

5. Plate according to claim 4, wherein distances (d, d') between nearest conductors of different electric potential are equal to or less than 100 μm.

6. Plate according to claim 4 or 5, wherein said first and second set of conductors (13, 17) are arranged in a comb-like pattern.

7. Plate according to claim 1 or 2, wherein said second set of conductors (17'') is in form of an enveloping electrode that surrounds said first set of conductors (13''), the gap region (19'') being in form of closed loop.

8. Plate according to claim 7, wherein said first set of conductors (13'') is in form of an array of dots surrounded by the enveloping electrode, the gap region (19'') being in form of a plurality of ring-shaped regions, each of which is interposed between a corresponding dot and the enveloping electrode.

9. Plate according to claim 8, wherein each ring-shaped region has a width (d'') equal to or less than 250 μm.

10. Plate according to claim 9, wherein each ring- shaped region has a width (d'') equal to or less than 100 μm.

11. Method for electrical stimulation of cutaneous nerve fibres using an electrode plate according to any of the preceding claims, wherein the method comprises:

- attaching the electrode plate onto the skin of a human or animal body to position the surface electrodes into electrical contact with the skin, and
- stimulating cutaneous nerve fibres by providing an electrical stimulus via the surface electrodes to the skin, wherein Aδ and C fibres are stimulated selectively with respect to Aβ fibres.

12. Method according to claim 11, wherein the stimulus comprises a single electrical pulse or a sequence of pulses whose magnitude is defined according to a strength duration relationship for the Aδ or C fibres, while minimizing the total energy transmitted to the

human or animal body.

13. Method according to claim 12, wherein each pulse contains also a radiofrequency wave packet with spectral distribution within approximately 50-500 kHz.

14. Method according to claim 12 or 13, wherein the time average of the applied electrical stimulus over its duration is approximately zero.

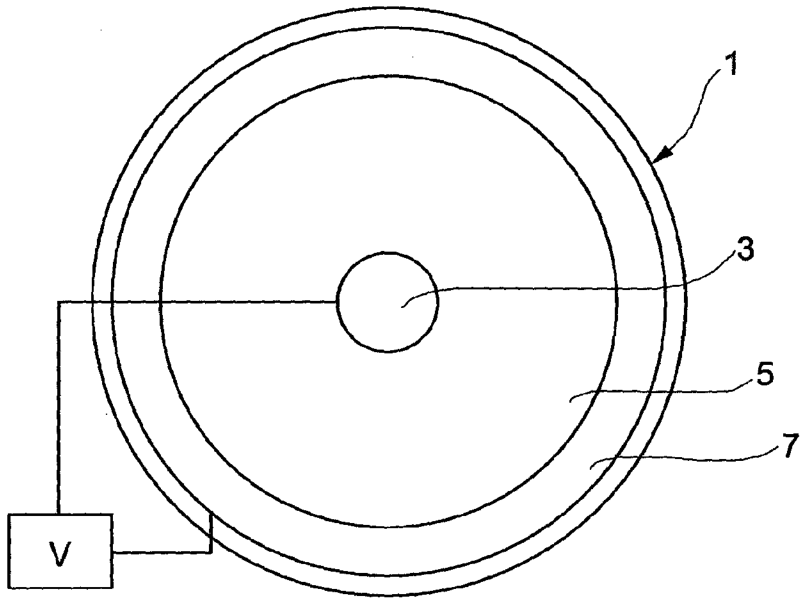
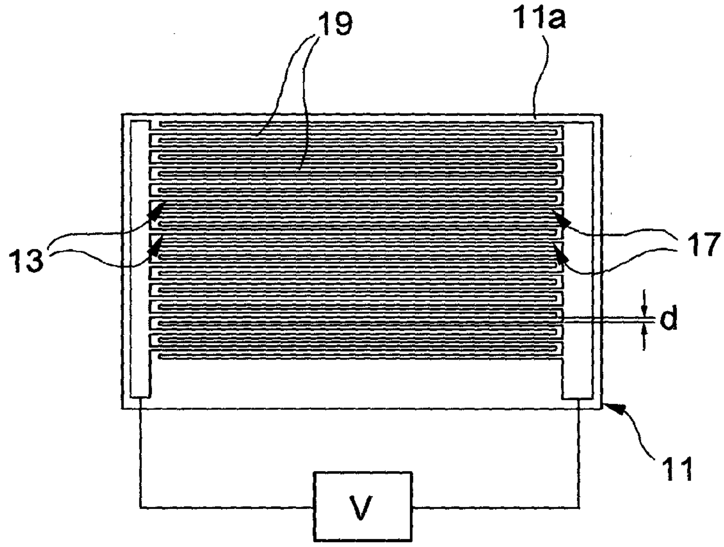


FIG.1

FIG.2



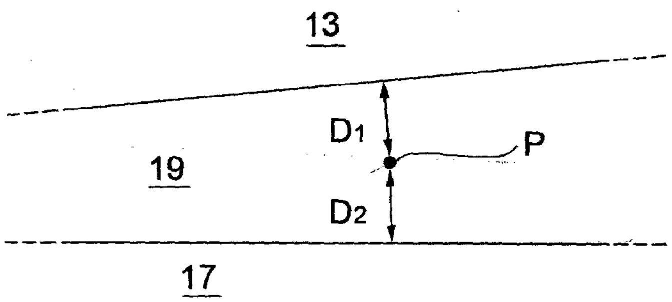


FIG.3

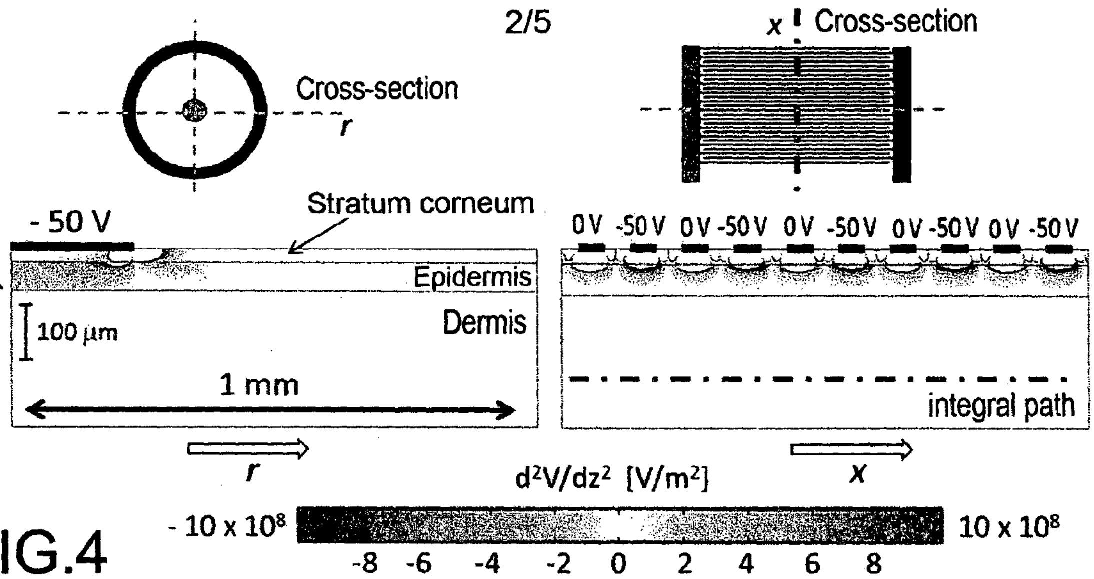


FIG.4

	Line depth	Total integral Value (V/m)	Normalized integral Value (V/m)
Circular Electrode (d2V/dx2 positivo)	10 µm	8.6E+05	1.0E+00
	59 µm	2.3E+04	2.7E-02
	100 µm	6.5E+02	7.5E+04
	200 µm	1.8E+02	2.1E+04
Circular Electrode (d2V/dx2 negativo)	10 µm	-9.8E+05	1.0E+00
	59 µm	-7.8E+04	8.0E-02
	100 µm	-4.9E+03	5.0E-03
	200 µm	-2.5E+03	2.6E-03
Interdigitated Electrode	10 µm	6.9E+06	1.0E+00
	59 µm	6.2E+04	8.9E-03
	100 µm	3.0E+02	4.4E-05
	200 µm	7.0E+00	1.0E-06

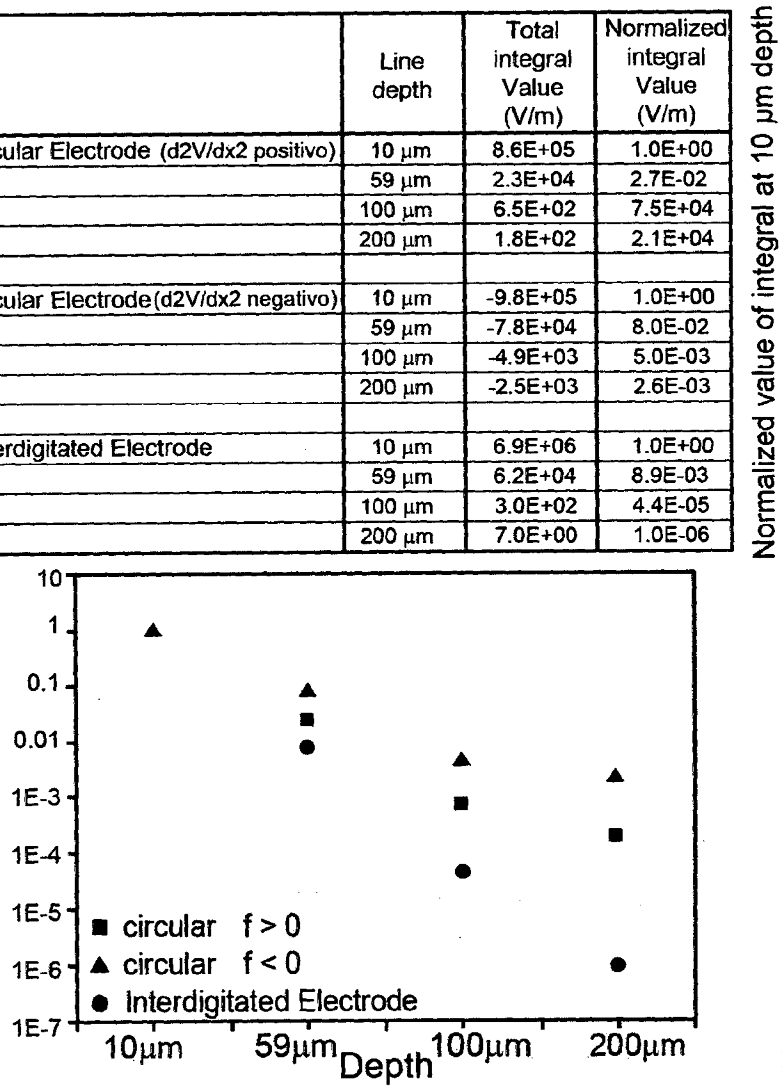


FIG.5

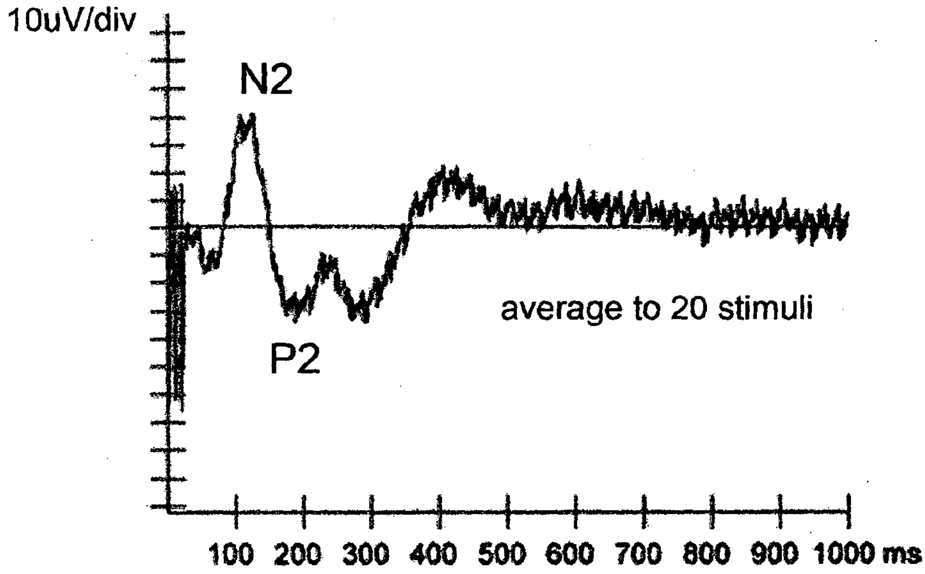

10uV/div
N2
P2
average to 20 stimuli
100 200 300 400 500 600 700 800 900 1000 ms

FIG.6

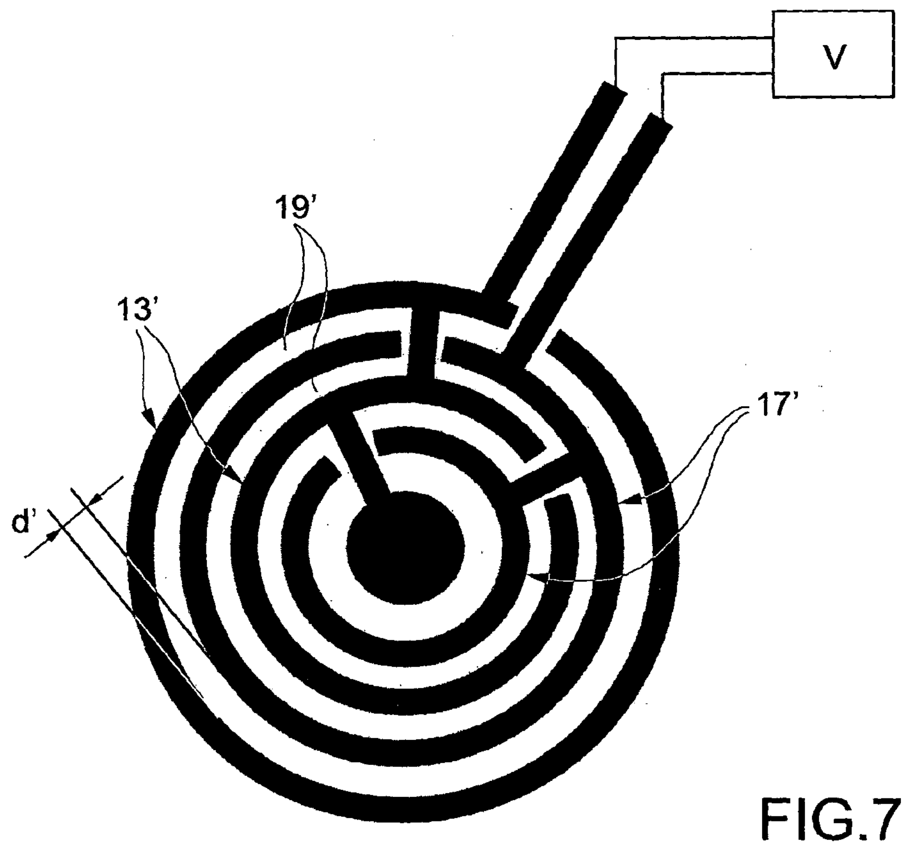

V
19'
13'
17'
d'

FIG.7

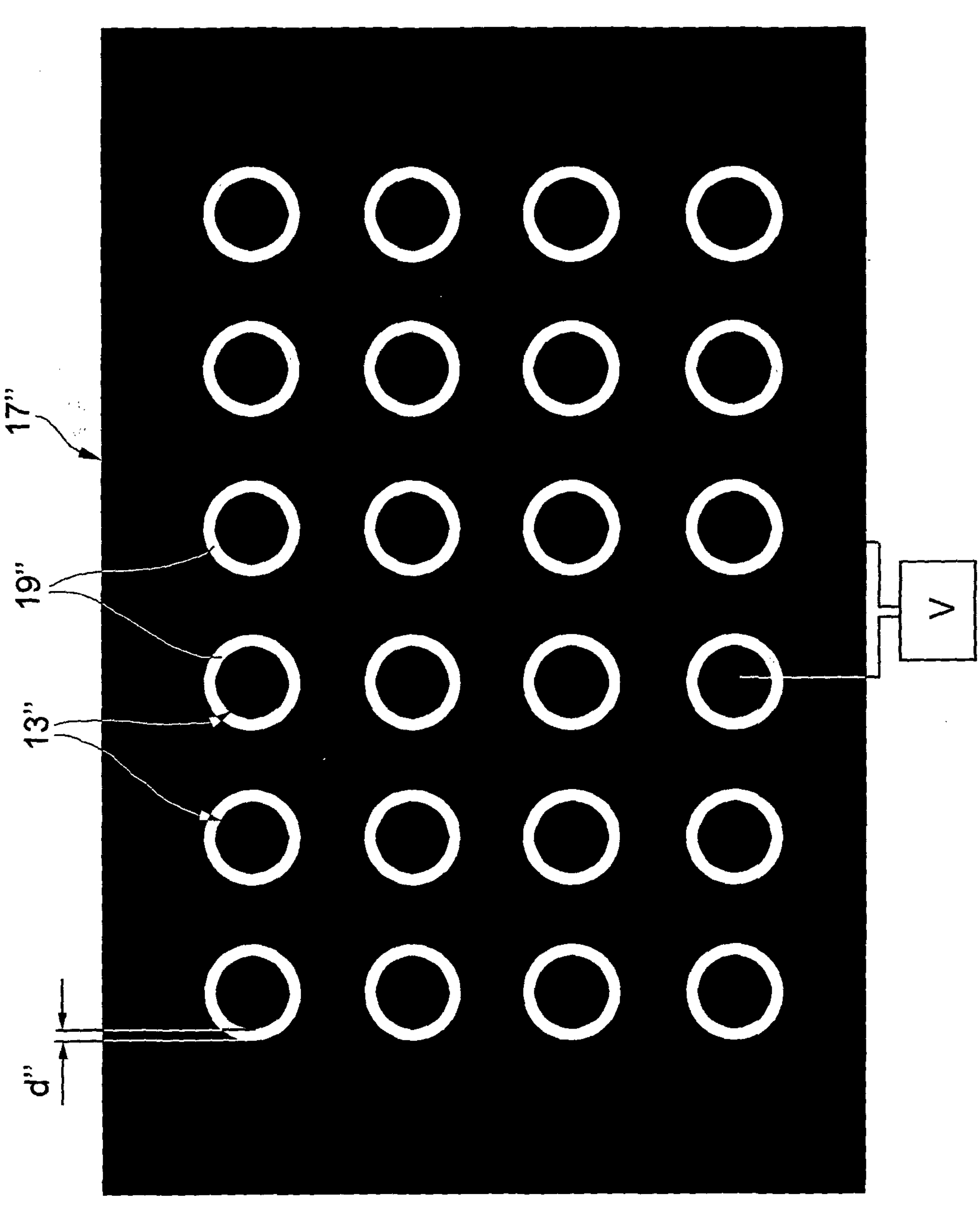


FIG.8

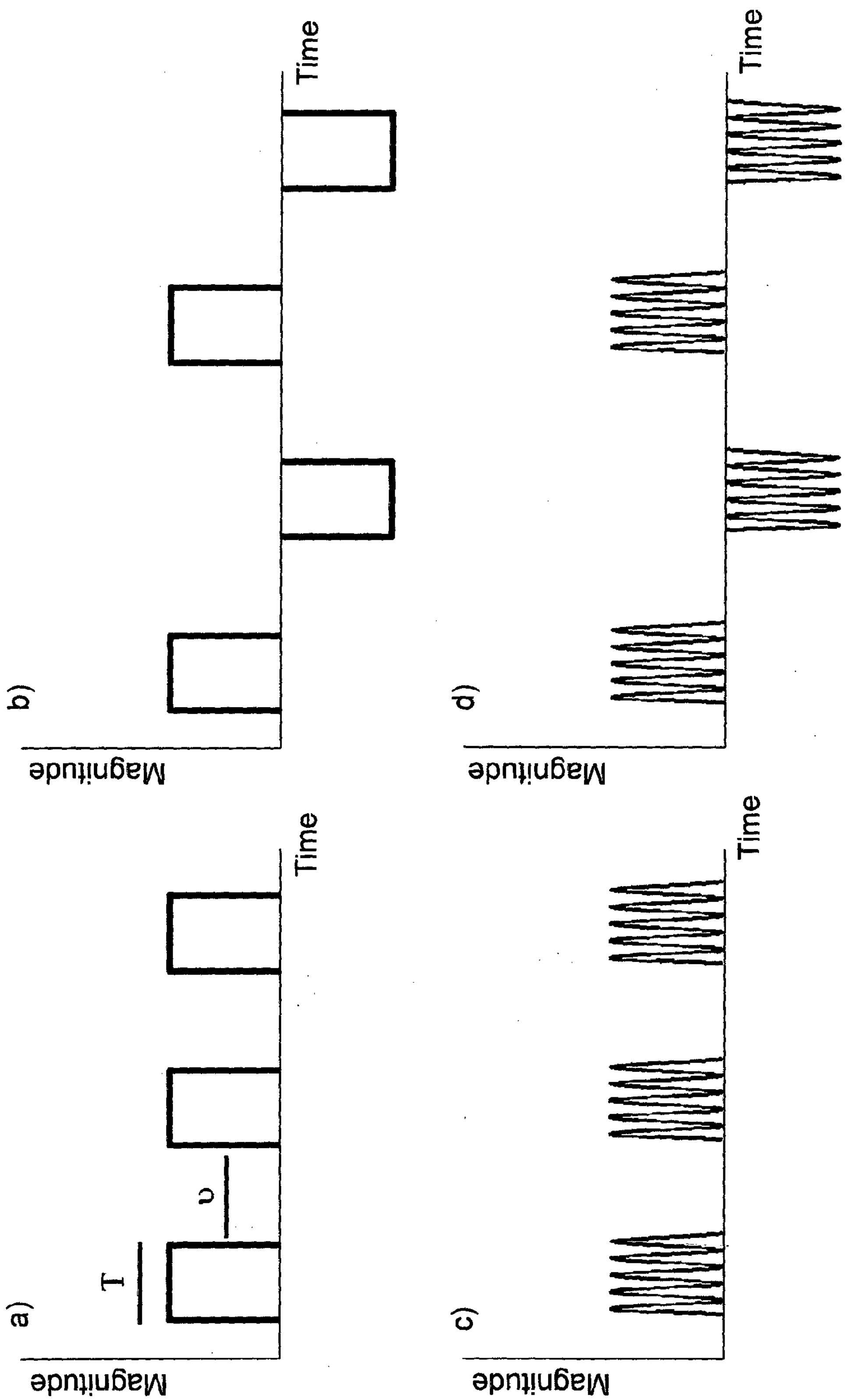


FIG.9

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Electrode plate comprising an electrically insulating supporting plate (11) having a front face (11a) and a rear face and a pattern of surface electrodes disposed on the front face for electrical stimulation of cutaneous nerve fibres. The pattern of surface electrodes comprises a first and second set of conductors (13, 17), whereby a gap region (19) of sinuous and/or arrayed configuration is defined between the first and second set of conductors. Each point of the gap region lies at a distance D_1 from the first set of conductors (13) and at a distance D_2 from the second set of conductors (17) such that the sum $D = D_1 + D_2$ is equal to or less than 250 µm, whereby the area of the gap region is of the order of magnitude of 1 mm^2 or greater.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/054228

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.: 11-14(partially)
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 11-14 relate to a method for electrical stimulation of cutaneous nerve fibres. To the extent that this is a method for treatment of the human or animal body by therapy, the International Searching Authority is not required to search the subject-matter of claims 11-14 according to Rule 39.1(iv) PCT.

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/IB2015/054228

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/04 A61N1/36
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 2002/183685 A1 (CRAWFORD NEVILLE [GB] ET AL CRAWFORD NEVILLE [US] ET AL) 5 December 2002 (2002-12-05)	1-6
Y	paragraph [0014] paragraph [0032] paragraph [0035] - paragraph [0046]; figure 1A -----	7-10
A	US 2012/101405 A1 (ANDERSEN OLE KAESELER [DK] ET AL) 26 April 2012 (2012-04-26) paragraph [0041] - paragraph [0044] paragraph [0064] - paragraph [0067] paragraph [0085] - paragraph [0090] -----	11-14
	-/--	

[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)

"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	Date of mailing of the international search report
11 August 2015	26/08/2015

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	Sigurd, Karin

4

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 337 642 A2 (INVENTOR S FUNDING CORP LTD [IL]) 18 October 1989 (1989-10-18) column 5, line 36 - column 6, line 8 column 8, line 45 - column 9, line 21; figures 3, 4	7-10
A	US 2010/087903 A1 (VAN HERK JOHANNES JOHANNA [NL] ET AL) 8 April 2010 (2010-04-08) paragraph [0022] - paragraph [0023] paragraph [0044] - paragraph [0046] paragraph [0079] - paragraph [0081]; figures 1, 4a, 4b	1-14
A	US 2010/152794 A1 (RADIVOJEVIC ZORAN [GB] ET AL) 17 June 2010 (2010-06-17) paragraph [0034] - paragraph [0045] paragraph [0054] paragraph [0087] - paragraph [0088]; figures 2, 3A	1-14

4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/054228

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