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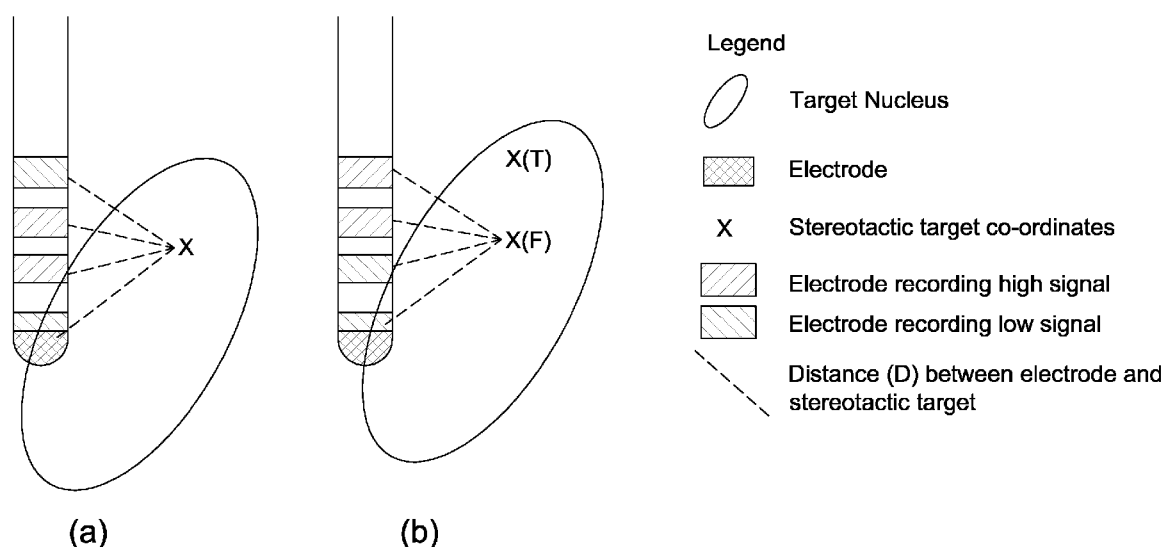


Fig. 5

(57) Abstract: A method of checking the location of implantation of a deep brain stimulation (DBS) lead comprising a plurality of electrodes is provided. The method comprises deriving a value representative of an electrophysiological signal obtained from two or more of the electrodes. The method also comprises comparing the derived values against the distance of the electrode from an intended stereotactic target location. The method further comprises calculating a mathematical function representative of how the signal varies with distance. On the basis of the calculated mathematical function, the proximity of an implanted DBS lead to a target implantation position is then determined. A system for checking the location of implantation of a deep brain stimulation (DBS) lead comprising a plurality of electrodes is also provided. A method of performing deep brain stimulation (DBS) is further provided.



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Checking the location of implantation of a deep brain stimulation (DBS) lead

Technical Field

5 The present invention relates to a method of and system for assessing the suitability of a target for deep brain stimulation (DBS) and/or the suitability of the implanted position of a DBS lead. In particular, the present invention relates to a method of and system for checking the location of implantation of a DBS lead. The present invention also relates to a method of performing deep brain stimulation (DBS).

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Background to the Invention

A variety of neurological conditions, such as Parkinson's Disease, can be treated with deep brain stimulation (DBS). This has been shown to be effective in reducing the symptoms associated with the condition, e.g. tremors, stiffness and mobility problems, leading to a better quality of life for the person affected by the condition. DBS is a surgical procedure where electrodes are implanted into a patient's brain. The electrodes are electrically connected to a pulse generator that is implanted in the patient's body e.g. in their chest. Activating the pulse generator causes the electrodes to deliver high frequency stimulation to the targeted area. This stimulation changes some of the electrical signals in the brain that cause the symptoms of Parkinson's and other neurological conditions. Advantageously, DBS is a non-destructive and reversible type of surgery. This becomes important where it transpires that the electrodes have been implanted incorrectly, at the wrong position in the brain, causing undesirable, possibly unpleasant, side effects. Ceasing the pulses, and therefore the stimulation, also ceases the (potentially adverse) effects that the stimulation has been providing. However, if the neurological condition still needs to be treated, correcting how the stimulation is applied, and possibly repositioning the implanted electrodes, can be difficult. It is clearly desirable to avoid repeat attempts at implantation due to the risks associated with brain lead insertion.

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The electrodes are typically located along and at or near the end of a lead (or probe) that is implanted into the patient's brain. Assuming the lead and electrode(s) are positioned correctly, pulses can be used to stimulate nearby neurons. Figure 1 shows a frequency-time log power spectrum where the dark peaks around 22 Hz are

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representative of high or over-activity in the brain. DBS is applied at a time interval, as shown by the bars on the time axis and it can be seen that, where DBS is utilized, the activity reduces. I.e. this demonstrates the advantageous effect DBS can have on the brain of a person suffering with a neurological condition. For example, DBS is believed to help to modulate the oscillatory activity which occurs between the cortex and the basal ganglia. High frequency DBS is believed to suppress the excess activity at low frequencies e.g. between about 12 and 28 Hz (the beta frequency band) that occurs in Parkinson's Disease. The signal attenuates with distance from the source. Suppressing the signal, using DBS, improves the symptoms of Parkinson's Disease, implying that implanting an electrode array spanning the source of this signal would be the most efficient way to suppress the symptoms.

Different sites in the brain will need to be targeted, depending on the condition and/or symptoms to be treated. For example, for treating Parkinson's, the subthalamic nucleus (STN) or the globus pallidus interna (GPi) are commonly targeted. When a DBS lead that is implanted in the brain is activated, it emits an electric field into the surrounding area which, if positioned well, will stimulate the correct part of the brain and provide beneficial effects. However, even correct positioning of the DBS lead, and especially incorrect positioning of the lead, can provide stimulation to parts of the brain that should not be stimulated. That can lead to adverse effects on the patient. If a DBS lead is implanted more than 1.5mm away from the target implantation location, DBS applied will be ineffective, however, for the reasons discussed herein, accurately locating a DBS lead is difficult.

Typically, a DBS lead 10, e.g. as shown in Figure 2, comprises a number of ring electrodes 12 that extend the entire circumference of a cylindrical lead. Electrical connections 14 provide for conveying the generated pulses to one or more of the electrodes. The electrodes emit stimulation current I in all directions, as depicted by the arrows. Split or segmented or non-circumferential electrode leads have also been developed, for example. Here, electrode portions 16 are provided around the periphery of the lead. When activated, the electric field produced is directional, rather than annular, dependent upon the size and positions of the electrode portions. This can help avoid stimulating areas of the brain that should not be stimulated (because that would cause unwanted side effects). It is possible to selectively activate one or more of the electrode portions.

Currently more than 80% of DBS therapy centres pick the “target” location for DBS using direct visualization on magnetic resonance imaging (MRI) or computerized tomography (CT) images, informed by typical stereotactic co-ordinates from anatomical atlases. Stereotaxy is a form of surgery utilizing a 3D coordinate system to locate a target inside the brain for DBS. CT scans involve X-ray imaging, whereas MRI scans use magnetic fields and radio frequency pulses to produce an image of the brain. It is, however, extremely difficult, just from CT or MRI images alone, to distinguish functional areas within a neurological structure. This is because the true physiological target is often some small part of the visible target structure. For example, the STN has three major functional divisions, of which motor control is one. For Parkinson’s Disease the part of the STN sub-serving motor control needs to be implanted for symptomatic benefit. Stimulation through a contact in the part of the STN sub-serving limbic function can induce neuropsychiatric side-effects. However, the limbic and motor areas of the STN are indistinguishable on routine clinical scans. In the treatment of Parkinson’s Disease, the STN or GPi is often targeted, but imaging using MRI or CT alone is insufficient to accurately locate the motor areas of within these brain structures to target with DBS – i.e. precise co-ordinates within the brain where DBS should be applied.

To address this issue, and increase the chance of correctly identifying a good implantation location, a plurality of micro-electrodes is often used in the determination phase. For example, between 3 and 7 multiple small probes can be inserted into the brain to assess multiple trajectories around the initial target selected using imaging and/ or stereotactic co-ordinates. These micro-electrodes can be used to “scope out” what the best trajectory might be and then a thicker DBS probe can be inserted along one of those trajectories in order to actually provide the DBS to the patient. By testing a higher number of possible trajectories, better results can be achieved compared with MRI or CT scanning alone. A Microdrive is used to place the DBS lead at a particular depth, typically such that the middle of the electrode array is at the target. However, inserting multiple leads into the brain increases the risk of bleeding and insertion into an area where insertion/stimulation is not required. Moreover, the process is time-consuming and prone to error in inexperienced hands. As a result, fewer centres use micro-electrode recordings compared to when DBS was first introduced in the modern era.

In order to perform the stereotactic surgery, a stereotactic frame is used. If the frame develops a fault e.g. due to wear and tear, or because it develops a slight twist in the structure etc., this can lead to large errors (e.g. up to 3mm) in determining the DBS implantation location. Incorrect implantation can lead to stimulation of other parts of the brain and corresponding unpleasant side effects.

Aspects and embodiments of the present invention have been devised with the foregoing in mind.

10 Summary of the invention

According to a first aspect of the present invention there is provided a method of checking the location of implantation of a deep brain stimulation (DBS) lead comprising a plurality of electrodes. A method of checking the location of implantation of a deep brain stimulation (DBS) lead comprising a plurality of electrodes comprises deriving a value representative of an electrophysiological signal obtained from two or more of the electrodes. The method may further comprise comparing the derived values against the distance of the electrode(s) from an intended stereotactic target location. The method may further comprise calculating a mathematical function representative of how the signal varies with distance. On the basis of the calculated mathematical function, the method may further comprise determining the proximity of an implanted DBS lead to a target implantation position. The plurality of electrodes is typically distributed over or across a DBS lead. It may be desirable for the centremost electrode(s) of the plurality to be within the vicinity of the target location, so that the array spans an intended target. Advantageously, the present invention provides a way to check the quality of placement of an implanted DBS lead by mathematically processing signals received at the electrodes and without the need for further invasive techniques.

30 In an embodiment, calculating the mathematical function comprises fitting the derived values against distance using a straight line fit or a curve. Calculating the mathematical function may comprise fitting the derived values against distance using a mathematical transformation on the derived values such as taking a natural logarithm. The method may further comprise determining whether there is a positive or negative correlation between the derived values and the distance. When there is a positive correlation between the derived values and the distance, this may indicate that the

DBS lead is not implanted at an optimal position; and where there is a negative correlation between the derived values and the distance, this may indicate the DBS lead is implanted at a correct and/or optimal location. The method may further comprise comparing the correlation between the derived values and the distance, for a particular electrode or DBS lead, over time and determining whether the DBS lead is still implanted at a correct or optimal position.

In an embodiment, comparing the derived values and the distance may comprise plotting the derived values against distance on a graph. The method may further comprise displaying or outputting one or more of the derived values, distance or fit, or parameters relating thereto.

It is beneficial to use the information signals emitted by the brain, but these first have to be interpreted in terms of a meaningful value. A useful value is electrical power. As such, in another embodiment, deriving the values representative of the LFP signal comprises deriving the power. In an embodiment, detecting an electrophysiological signal comprises detecting a local field potential (LFP). Preferably, LFP signals in the beta oscillation range (approximately 12-28Hz) emitted by the subthalamic nucleus (STN) of a person's brain are detected. Alternatively, other neurophysiological signals could be detected e.g. seizure activity.

According to a second aspect of the present invention there is provided a system for checking the location of implantation of a deep brain stimulation (DBS) lead comprising a plurality of electrodes.

The system may comprise a deep brain stimulation (DBS) lead comprising a plurality of electrodes, the electrodes being operational to emit a stimulation pulse and/or to detect an electrophysiological signal. The system may also comprise a pulse generator operational to command one or more of the electrodes to emit a stimulation pulse and/or to detect an electrophysiological signal. A remote control module operational to program the pulse generator to command one or more of the electrodes may also be provided. Software may also be provided, configured to run at the remote control module or other processor to perform the method of any of the first aspect.

In an embodiment, the DBS lead is of circular cross section and the electrodes are distributed around the circumference thereof in a pattern and/or in bands e.g. longitudinally separated along the DBS lead.

- 5 In another embodiment, the pulse generator and remote control module are configured for wireless communication and, optionally or preferably, by radio. Other suitable forms of communication may also/instead be used.

10 The same or different electrodes or contacts may be used for sensing and for stimulation. The electrodes may be configured to detect local field potentials (LFPs). In an embodiment, the electrodes are configured to detect local field potentials (LFPs) in the beta oscillation range (approximately 12-28Hz) emitted by the subthalamic nucleus (STN) of a person's brain. The electrodes may be configured to detect other signals and/or at other frequencies.

15 According to a third aspect of the present invention, there is provided a method of performing deep brain stimulation (DBS). The method may comprise inserting a DBS lead into a brain or using a DBS lead inserted into a brain. The DBS lead may comprise a plurality of electrodes. The method may also comprise coupling the DBS
20 lead to a remote control module. The method may further comprise performing the method of the first aspect. The method may further comprise using the control module to generate electrical stimulation signals at one or more of the electrodes.

25 Aspects and embodiments of the invention may be implemented on a computer. There may be provided a computer program, which when run on a computer, causes the computer to perform any method disclosed herein. The computer program may be a software implementation, and the computer may be considered as any appropriate hardware, including a digital signal processor, a microcontroller, and an implementation in read only memory (ROM), erasable programmable read only memory (EPROM) or
30 electronically erasable programmable read only memory (EEPROM), as non-limiting examples. The software implementation may be an assembly program.

The computer program may be provided on a computer readable medium, which may be a physical computer readable medium, such as a disc or a memory device, or may
35 be embodied as a transient signal. Such a transient signal may be a network download, including an internet download.

According to a fourth aspect there is provided a computer program configured to, when executed on a computing device, cause the computing device to perform the method according to the first aspect.

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Features of the aspects and embodiments described above and below may be used interchangeably and/or in combination, even if not expressly stated.

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As such, whilst it is known in the prior art to use LFP signals to guide DBS lead placement, it is desirable to improve upon known methods. For example, it is known to use a combination of MRI brain scans and brain maps made from data from cadavers in order to determine a DBS target location. However, whilst that indicates to a surgeon a theoretical position within the brain to be targeted, the surgeon then has to guess how and where to insert the DBS lead and effectively hope the final position matches with the theoretical/desired position.

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Aspects and embodiments of the invention involve comparing the derived values against the distance of the electrode(s) from an intended stereotactic target location (e.g. by plotting the values), calculating a mathematical function representative of how the signal varies with distance (e.g. taking a logarithm of the power values) and using that to determine the proximity of an implanted DBS lead to a target implantation position (e.g. by determining whether the fit gives a positive or negative slope). This advantageously gives a measure of the quality of the implantation, without the need for additional invasive techniques such as pre-determining the target location using microelectrodes.

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Aspects and embodiments of the invention utilise the LFP signals to assess the quality of the target "X" selected using imaging and/or a surgical atlas. Effectively, aspects and embodiments of the invention enable a surgeon to be able to determine whether "X" is good enough, based on the position of implanted DBS electrodes and recording physiological signals such as LFPs using the electrodes. I.e. after a DBS lead is inserted into a patient – e.g. following the MRI and atlas insertion location determination – is it in a good place, or should it be somewhere else? Advantageously aspects and embodiments of the invention enables determination of any significant discrepancies between an imaging based target implanted with a DBS electrode and the optimal physiological target, without the need for additional invasive probes.

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Advantageously, the present invention can indicate when a better physiological target may be available, using electrode position intra/post-operative imaging and physiological signals recorded directly through the DBS electrode. No additional invasive recording is required. Advantageously, the method uses recordings from the DBS lead itself to assess DBS lead placement intra-operatively.

It is known in the art to use microelectrodes to identify the target location. It is also possible to get a measure of the quality of the identified target location by determining the length (in mm) of the passage of the microelectrode through the target area using a microdrive. However, there is no comparable technique for LFP measurements using a macroelectrode. This is because macroelectrodes operate on a signal that summates spatially and as such is prone to volume conduction and an accurate length measurement is not possible due to the spread of the signal. The power of a signal recorded by a macroelectrode alone is not an indicator of implantation in an optimal target, as this can vary with location, disease state, severity and duration. Aspects and embodiments of the present invention both avoid the use of microelectrodes (and the disadvantages associated therewith as already discussed) and give a measure of the quality of the implant location.

Aspects and embodiments of the invention will now be described with reference to the Figures of the accompanying drawings in which:

Figure 3 is a schematic view of a system according to an embodiment of the invention;
Figure 4 is a schematic view of a DBS lead implanted near a stereotactic target of a patient's brain;

Figure 5(a) is a schematic view of a DBS lead implanted near a stereotactic target of a patient's brain;

Figure 5(b) is a schematic view of a DBS lead implanted near a stereotactic target of a patient's brain;

Figure 6 is a graph showing signal power strength measured at several DBS leads in different patients against distance of the electrodes from a stereotactic target;

Figure 7 is an illustration of Figure 6 for an individual patient;

Figure 8 illustrates mathematically fitting of data obtained from several patients; and

Figure 9 is a plot showing a reconstruction of DBS leads in 3D stereotactic space, relative to an intended target.

Detailed description of embodiments of the invention

Referring to Figure 3, there is shown a system 100 operable for applying deep brain stimulation (DBS) to a patient and for use in determining the suitability of a target for deep brain stimulation (DBS) and/or the suitability of the implanted position of a DBS lead. In the embodiment shown, the system comprises two DBS leads 102, 104. The DBS leads 102, 104 are implantable into a patient's brain in accordance with conventional techniques (or other techniques yet to be developed). It will be appreciated that it is not necessary to have two DBS leads – sometimes a single lead can be used for unilateral stimulation; other times multiple leads are used e.g. for treating pain or epilepsy.

Each lead comprises a plurality of electrodes 106, 108. In the embodiment of Figure 3, each lead 102, 104 has eight segmented electrodes 106, 108 respectively, but it will be appreciated that any number of electrodes, or ring electrodes, can be provided.

Each electrode 106, 108 is electrically connected to an implantable pulse generator 110. This is preferably achieved via one or more wires 112, provided internally of the leads 106, 108. The wires run inside the leads 102, 104 to connect to each electrode 106, 108. The pulse generator 110 is typically implanted in a person's body e.g. in their chest, but this need not be the case e.g. during testing of the system. The pulse generator is operable to provide electrical stimulation pulses with parameters (e.g. duration, amplitude, frequency) that can be set dependent upon requirements.

The pulse generator 110 can communicate with a remote control module 112, which is not implanted in the patient's body. A suitable communication link may be radio, but other means of wireless communication are also envisaged. The remote control module 112 can be operated to control the pulses provided by the pulse generator 110 and/or to change the programming of the pulse generator 110. Once programmed, the communications link between the control module 112 and the pulse generator 110 is terminated, and the pulse generator will provide pulsed stimulation at a preset intensity, for a preset duration and/or at preset intervals.

Programming is conventionally achieved by manually screening each electrode to determine the benefit to the patient and avoid side-effects that occur at various

electrical stimulation parameters. Then, a determination is made of an electrode or a montage of electrodes to be used to optimise the benefit.

The implanted leads 102, 104 can also be used to record electrophysiological signals. Different signals can in principle be used, originating from different areas of the brain and from varying distances from the implantation site. Conveniently, the electrodes 106, 108 can detect/record local field potentials (LFPs). Alternatively, additional specialised non-circumferential detectors can be provided on the DBS lead e.g. at the tip of the DBS lead 102, 104.

"Listening" to an electrophysiological signal is equivalent to listening to a small number of neurons in the local vicinity in the brain. An LFP is an electrophysiological signal generated by the summed electric current from neuronal assemblies in the brain. Voltage is produced across the local extracellular space by action potentials and graded potentials in neurons in the area, and varies as a result of synaptic activity. "Potential" refers to electrical potential, or voltage, and this can be recorded with the electrodes 106, 108 of the DBS leads 102, 104 when implanted into a patient. LFPs are therefore closely related to the activity of individual neurons. As such, LFPs are useful parameters to record and analyse. Other useful neurophysiological signals, for example seizure activity, can also be detected through DBS leads. When DBS is applied to a patient's brain, it modulates pathological oscillations in the electrophysiological signals.

In Figure 3, the DBS leads 102, 104 are segmented electrodes 106, 108 arranged in a band b around the circumference of the lead 102, 104. This lead 102, 104 has two bands of electrodes and two circumferential or ring electrodes, but it will be appreciated that aspects and embodiments of the invention can utilise a variety of different leads with electrodes varying in number and arrangement. There is therefore a plurality of electrodes. LFPs detected by two, three, four or more electrodes may be used, and three or four may be preferable. In an embodiment the plurality of electrodes 106, 108 may be located in the same band b i.e. in the same transverse plane t relative to the longitudinal direction l of the electrode 102, 104. In another embodiment the plurality of electrodes 106, 108 may be located in different bands b i.e. in different transverse planes t relative to the longitudinal direction l of the electrode 102, 104. Alternatively, a plurality (e.g. 3, 4 or more) ring electrodes may be used. An LFP in the beta oscillation range can therefore be detected at the electrodes 106 or 108 on a DBS lead 102 or 104, respectively.

Referring to Figure 4, a DBS lead 102,104 is implanted into a patient's brain. The target co-ordinates "X" for insertion are selected using imaging guidance as discussed above. The coordinates of where the lead 102,104 is inserted is calculated. Here, the distance "D" of electrodes 106, 108, or an electrode montage (midpoint co-ordinates between a pair of electrodes), from an intended stereotactic target "X" is calculated. If the characteristic physiological signal of the target structure (the target nucleus in Figure 4), e.g. Beta oscillations of Parkinson's Disease, is strongest at the stereotactic target, the electrodes 106, 108 that are closest to the desired target (X) should show the strongest LFP signal (with the highest value or amplitude). This is illustrated in Figures 5a and 5b. In Figure 5a, the stereotactic target coincides with or is very close to the actual physiological target. As such, the middle two electrodes are the closest and register a high or higher signal than the outer two electrodes, which are further away, and register a low or lower signal.

The applicant has found a way of determining if the stereotactic target selected on imaging, X(F), is significantly different to a true physiological target X(T), e.g. as is the case in Figure 5(b). In Figure 5(b), the leads closest to the target record a lower signal and those further away record a higher signal. This occurs because the signal is originating from the true physiological target X(T) that is higher than what the surgeon targeted (in this example). The distance (D) (or optionally of a mathematical transform thereof) between (i) electrode positions or electrode montage positions on a DBS lead 102, 104 and (ii) an intended (image-based) target, against the strength of beta oscillatory signal (or optionally of a mathematical transform thereof), from each respective electrode/electrode montage can be plotted. Where an electrode 106, 108 was not implanted well (i.e. the true physiological target X(T) was too far away from the stereotactic target selected on imaging X(F)) and needed to be replaced, the slope of the graph was positive. That is, the signal strength appeared to increase with increasing distance from the source of the LFP signals, which cannot be the case as signal strength attenuates with distance. In tests, it was also found that replacing the electrode and making another implantation at the same target gave the same result (see Figure 7). I.e. the data were not indicative of a faulty lead or electrode, but rather when an electrode was inappropriately implanted the (nonsensical) results were indicative of the same. Conversely, where an electrode 106, 108 was well implanted (i.e. the true physiological target X(T) was at or near the stereotactic target selected on imaging X(F)), the slope of the graph was negative. That is, the signal strength appeared to decrease with increasing distance from the source, as would be expected.

A false target $X(F)$ may arise for a number of reasons. For example - because the atlas used in the original scanning was not appropriate for the current patient (it is only based on a small number of cadavers). Another reason is because of an error in surgical targeting. A further reason is because of an error in the CT to MR scan fusion.

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An embodiment thus involves one or more of the following steps:

- Selecting an intended target for stimulation X , at a particular location
- Calculating coordinates of where a DBS lead is inserted
- Calculating the distance D between the location of X and the implantation
10 coordinates
- Determining a value e.g. signal strength or power of an LFP signal at electrodes of the DBS lead
- Determining/fitting a mathematical function to the power values
- Determining whether the signal strength appears to decrease or increase with
15 increasing distance from the source
- On the basis of that determination, determining whether the DBS lead is well implanted

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As such, these calculations/determinations, and optionally plotting the data, enables a determination of whether there is a significant discrepancy between the selected target (based on imaging) and the optimal physiological target. The result can be calculated mathematically and/or illustrated graphically as discussed above to warn the physician when a target selected based on imaging may not be the optimum target. Specifically, the signal from an electrode is plotted against the distance of that electrode to the intended target (or a mathematical transform of the same), and while ignoring the order of the electrodes.

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Figure 6 is a graph showing signal power strength measured at several DBS leads (in different patients, each line representing one implant in one person) intraoperatively (anonymised actual data) against distance of the electrodes from a stereotactic target. This demonstrates that the slope is an effective way of screening for implants where the stereotactic target chosen is not the true physiological target. Figure 7 illustrates this for one individual, where one lead (that with the negative slope) is well placed. Here, the visually chosen stereotactic target is the true physiological target. Two attempts at implanting the target in the other hemisphere for the same patient is shown in grey and orange. On both attempts, the target selected using visual targeting was

not the true physiological target, and this resulted in side effects despite the lead being placed close to the intended target. These show with positive slopes.

As such, where the fit gives a negative slope, this is because the power signal decays with distance from the physiological target, as discussed above. This is indicative that the lead is implanted in a good position where the true physiological target $X(T)$ is at or near the stereotactic target selected on imaging $X(F)$. Where the fit gives a positive slope, that would seem to imply a power signal that increases with distance from the physiological target, which cannot be the case. That, as discussed above, is indicative that the lead is not inserted in the optimal position. This corresponds to the situation in Figure 5(b) where the stereotactic target $X(F)$ differs significantly from the true physiological target $X(T)$. It stands to reason that if the distance or the signal is expressed as the inverse value (example $1/\text{Distance to } X$), the slopes are inverted also (as shown in figure 8b) and discussed further below).

Figure 8(a) shows a plot of signal power (x axis) against implantation distance (y axis). The trend shown suggests a negative slope, which represents the standard or expected behaviour. Figure 8(c) shows the same data, but where the logarithm of the signal power is instead plotted on the y-axis, again against distance on the x-axis. The trend is more clearly a negative slope. I.e. taking the logarithm of the data has improved the fit to the data. Figure 8(b) shows a different fit – signal power on the y-axis against $1/(\text{distance } D)^2$ on the x-axis. Here a positive slope is seen – it is flipped compared with that of figure 8(a) or 8(c).

As exemplified by Figures 8(a)-(c), performing a mathematical transformation on the data, e.g. taking the natural log of the physiological signal may help provide a clearer indication of the quality of the location of an implant. A steeply declining slope, or one where the line fit to the data is best after taking the natural log of the signal, inspires confidence that the lead 102, 104 is headed towards the intended target or that it has passed through it. A more linear relationship between distance to target and signal could imply that the lead is passing close to but not through the target. It could also imply (in a larger target) that most electrodes 106, 108 are within the intended target. In most instances, only some of the many electrodes 106, 108 on a DBS lead 102, 104 are within the target, as the span of electrodes 106, 108 is designed to exceed the size of the target (providing some forgiveness in depth of placement of the DBS lead). This is illustrated in Figure 8.

Figure 9 is a plot showing a reconstruction of DBS leads in 3D stereotactic space, relative to an intended target X. The power of the LFP signal at each bipolar electrode montage (the signal between a pair of electrodes) on the lead is indicated by a colour code, with that labelled "HIGH" representing the highest signal recorded. The other two points are weaker signals. The Figure on the left shows that the highest LFP is recorded at an electrode closest to the intended target X, and therefore the intended target is the true physiological target. The Figure on the right is actual data illustrating the depictions in schematic Figure 5b and the real data ("REAL") in Figure 7. The highest LFP signal is recorded in an electrode further away from the intended target X. Therefore, the true physiological target lies above the intended stereotactic target in this example with real data. The "spot" closest to the physiological target represents the best position for DBS lead insertion.

Aspects and embodiments of the invention thus enable a physician to assess whether a DBS target location, as calculated from CT/MRI imaging and possible reference to a stereotactic atlas, is actually suitable for DBS, or whether another position would be better. The approximate position of the true target can be estimated from figures 6, 7 and 9 if the geometry and spacing of the electrodes 106, 108 on a specific DBS lead 102, 104 is known. Aspects and embodiments of the present invention further allow for an easy assessment to be made as to whether or not a better physiological target is available – without the need for blind revision surgery or invasive electrophysiology at the time of surgery

In addition, tracking the calculated results (slope, line fitting (linear, $\ln(\text{Signal})$, or $1/D$), curve fitting) over multiple implants can also help monitor errors in stereotactic targeting systems (e.g. a stereotactic frame error or a systematic CT-MRI image fusion error). Tracking over time may also provide an indication that an electrode is moving over time ("electrode migration").

Furthermore, the intercept of the line of best fit on the axis representing signal strength provides an estimate for the power of the signal at the target X. This can be utilized to judge the adequacy of an implant and also to model the signal field.

Although the appended claims are directed to particular combinations of features, it should be understood that the scope of the disclosure of the present invention also includes any novel feature or any novel combination of features disclosed herein either

explicitly or implicitly or any generalisation thereof, whether or not it relates to the same invention as presently claimed in any claim and whether or not it mitigates any or all of the same technical problems as does the present invention.

- 5 Features which are described in the context of separate embodiments may also be provided in combination in a single embodiment. Conversely, various features which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination.
- 10 For the sake of completeness it is also stated that the term "comprising" does not exclude other elements or steps, the term "a" or "an" does not exclude a plurality, and any reference signs in the claims shall not be construed as limiting the scope of the claims.

Claims

1. A method of checking the location of implantation of a deep brain stimulation (DBS) lead comprising a plurality of electrodes, the method comprising:
 - 5 deriving a value representative of an electrophysiological signal obtained from two or more of the electrodes;
 - comparing the derived values against the distance of the electrode from an intended stereotactic target location;
 - calculating a mathematical function representative of how the signal varies with
10 distance; and
 - on the basis of the calculated mathematical function, determining the proximity of an implanted DBS lead to a target implantation position.
2. The method of claim 1, further comprising calculating position coordinates of
15 where the DBS lead is implanted in a patient's brain.
3. The method of claim 1, further comprising calculating the distance between the implanted DBS lead and the intended target.
- 20 4. The method of any preceding claim, wherein calculating the mathematical function comprises fitting the derived values against distance and, optionally, using a mathematical transformation on the derived values such as taking a natural logarithm.
5. The method of claim 4, wherein calculating the mathematical function
25 comprises fitting the derived values against distance using a straight line fit or a curve.
6. The method of claim 5, further comprising determining whether the value representative of the electrophysiological signal decreases or increases with increasing distance from the intended stereotactic target location from the mathematical function.
30
7. The method of claim 6, wherein the mathematical function is a mathematical transformation on the derived values and has a positive or a negative value.
8. The method of claim 6 or 7, further comprising determining, when there is a
35 positive correlation between the derived values and the distance, that this indicates that the DBS lead is not implanted at an optimal position; and where there is a negative

correlation between the derived values and the distance, this indicates the DBS lead is implanted at a correct and/or optimal location.

5 9. The method of any of claims 6 to 8, further comprising comparing the correlation between the derived values and the distance, for a particular electrode or DBS lead, over time and determining whether the DBS lead is still implanted at a correct or optimal position.

10 10. The method of any preceding claim, wherein comparing the derived values and the distance comprises plotting the derived values against distance on a graph.

15 11. The method of any preceding claim, wherein detecting an electrophysical signal comprises detecting a local field potential (LFP) in the beta oscillation range (approximately 12-28Hz) emitted by the subthalamic nucleus (STN) of a person's brain.

12. The method of claim 11, wherein deriving the values representative of the LFP signal comprises deriving the signal strength or power.

20 13. The method of any preceding claim, further comprising displaying or outputting one or more of the derived values, distance or fit, or parameters relating thereto.

14. A system for checking the location of implantation of a deep brain stimulation (DBS) lead comprising a plurality of electrodes, the system comprising:

25 a deep brain stimulation (DBS) lead comprising a plurality of electrodes, the electrodes being operational to emit a stimulation pulse and/or to detect an electrophysiological signal;

a pulse generator operational to command one or more of the electrodes to emit a stimulation pulse and/or to detect an electrophysiological signal;

30 a remote control module operational to program the pulse generator to command one or more of the electrodes; and

software configured to run at the remote control module or other processor to perform the method of any of claims 1 to 13.

35 15. The system of claim 14, wherein the DBS lead is of circular cross section and the electrodes are distributed around the circumference thereof in a pattern and/or in bands.

16. The system of claim 14 or 15, wherein the pulse generator and remote control module are configured for wireless communication and, optionally or preferably, by radio.

5

17. The system of any of claims 14 to 16, wherein the electrodes are configured to detect local field potentials (LFPs) and, optionally or preferably, wherein the electrodes are configured to detect local field potentials (LFPs) in the beta oscillation range (approximately 12-28Hz) emitted by the subthalamic nucleus (STN) of a person's brain.

10

18. A method of performing deep brain stimulation (DBS), the method comprising:
inserting a DBS lead into a brain or using a DBS lead inserted into a brain, the DBS lead comprising a plurality of electrodes;
coupling the DBS lead to a remote control module;
15 performing the method of any of claims 1 to 13; and
using the control module to generate electrical stimulation signals at one or more of the electrodes.

15

19. A computer program configured to, when executed on a computing device, cause the computing device to perform the method according to any of claims 1 to 10.

20

20. A system substantially as hereinbefore described with reference to Figure 3 of the accompanying drawings.

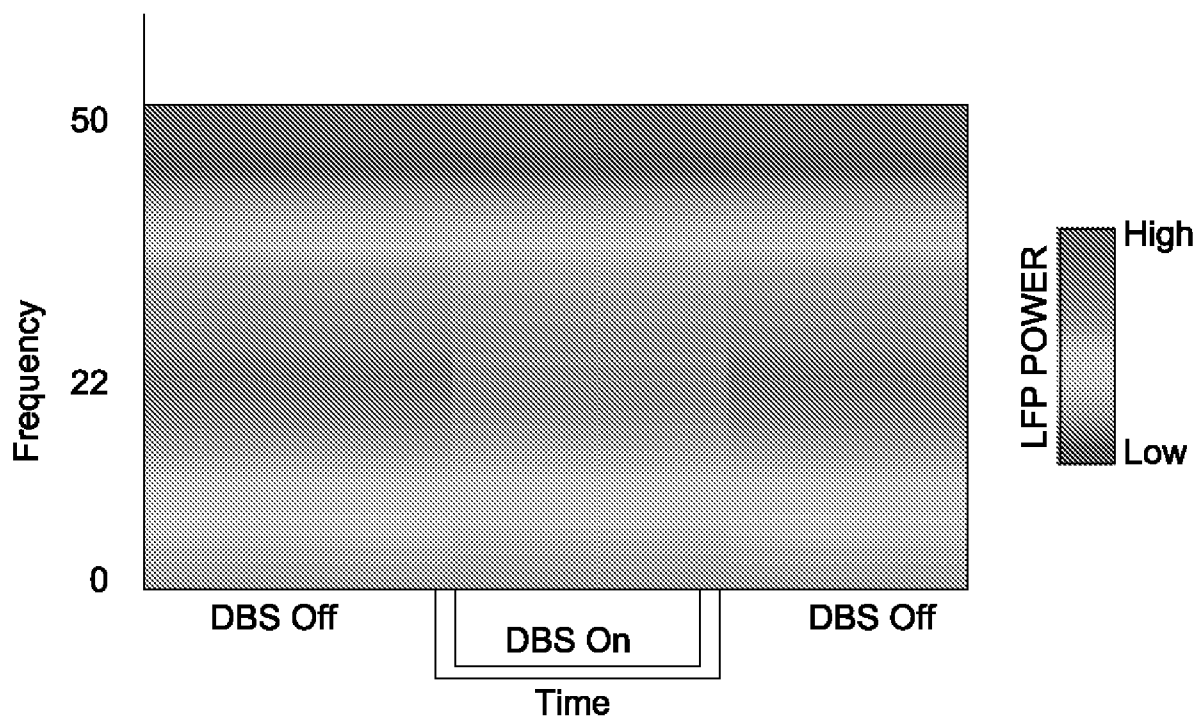


Fig. 1

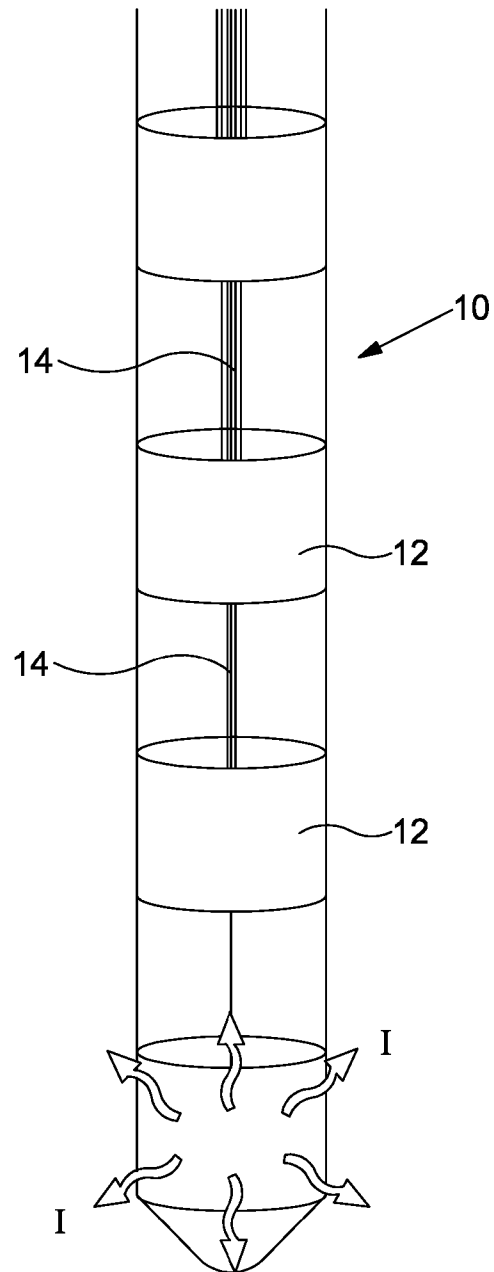


Fig. 2

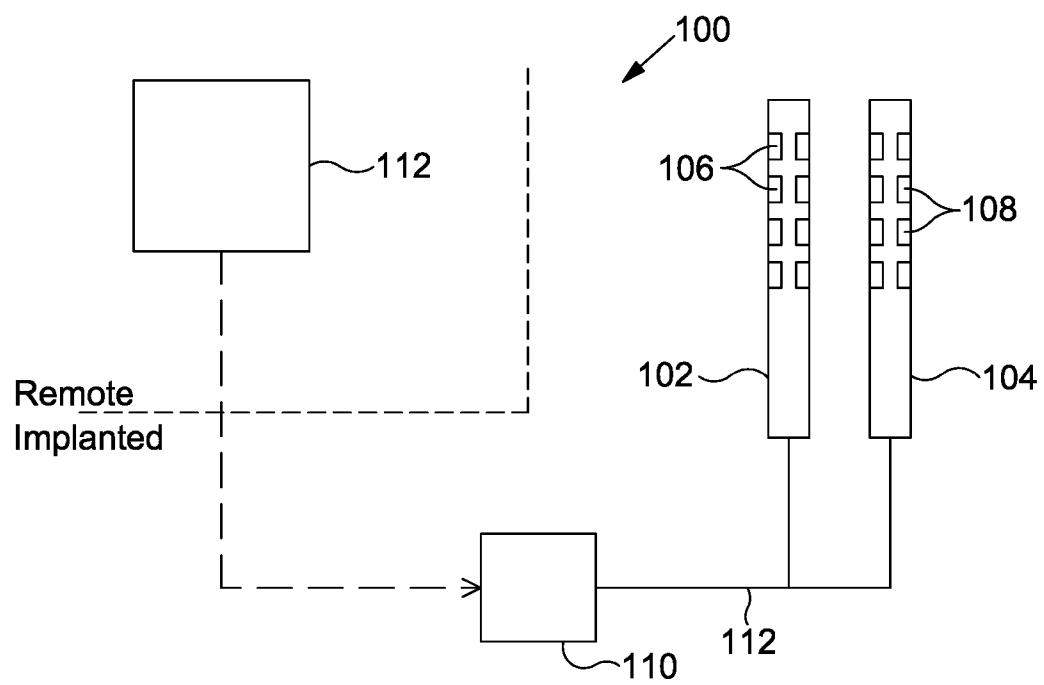


Fig. 3

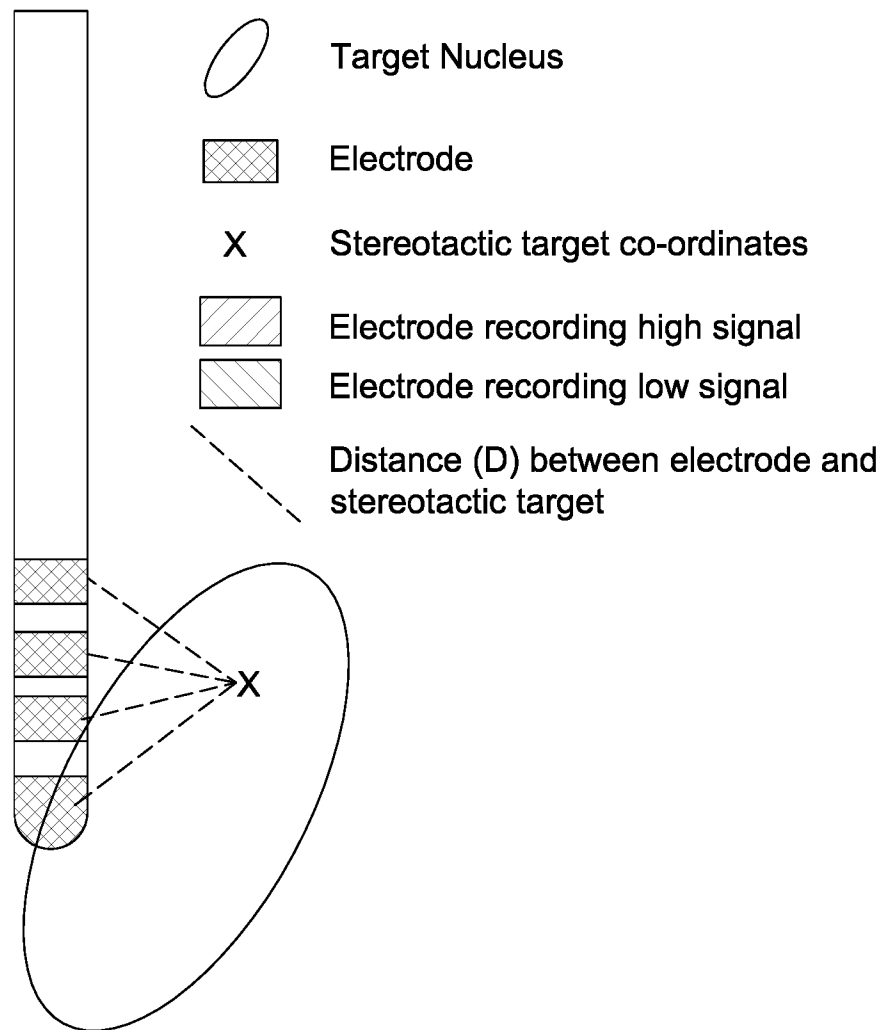


Fig. 4

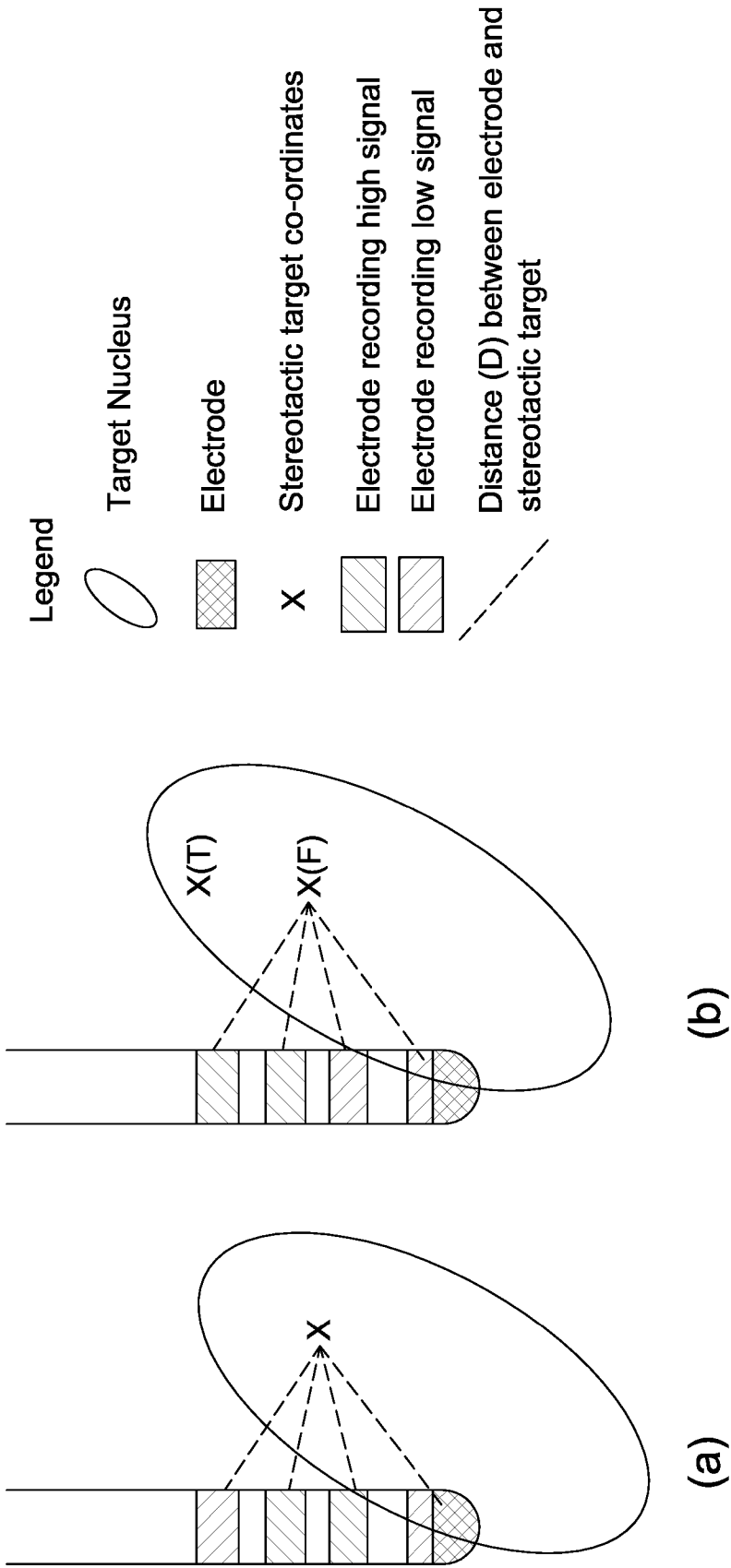


Fig. 5

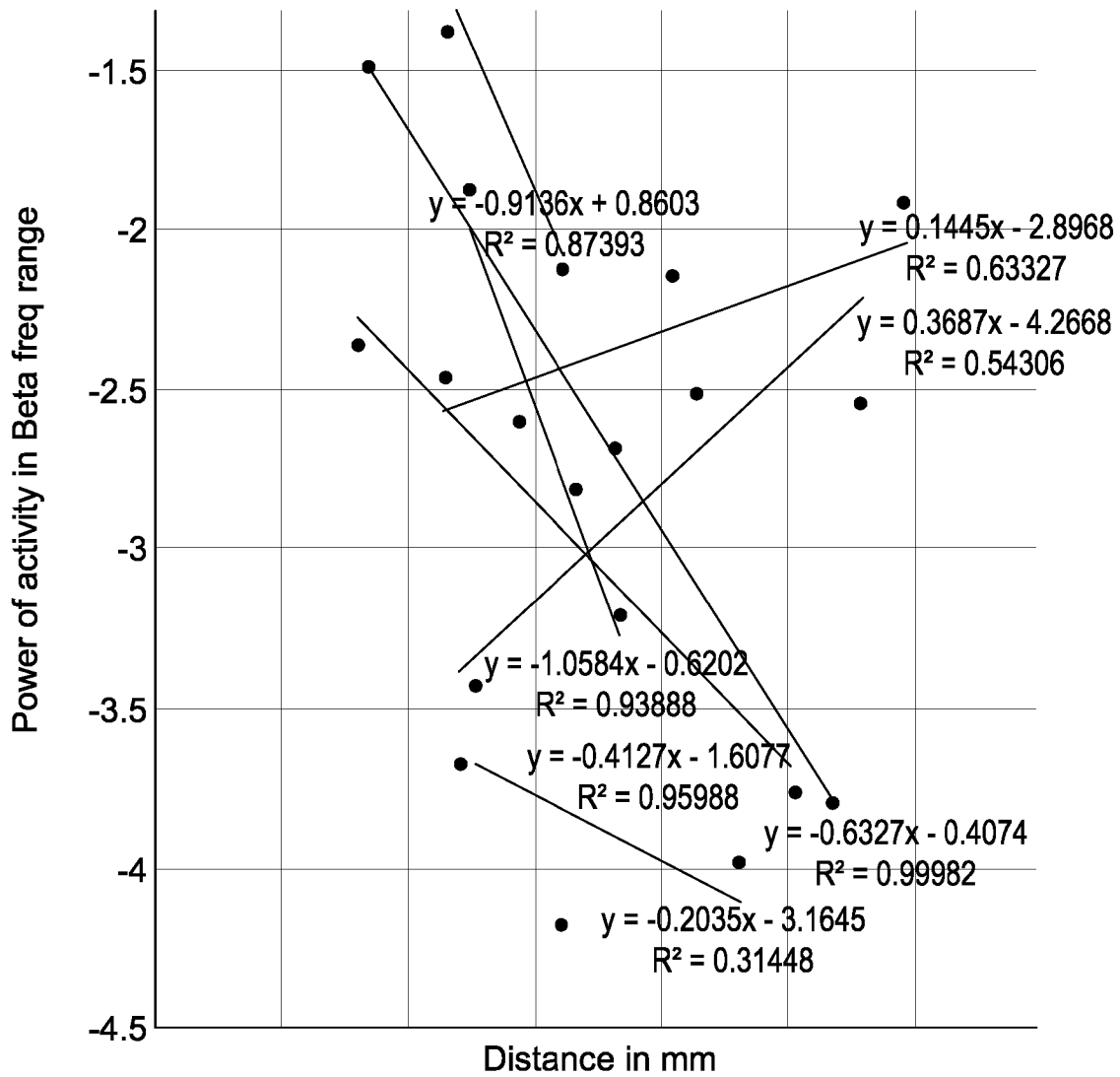


Fig. 6

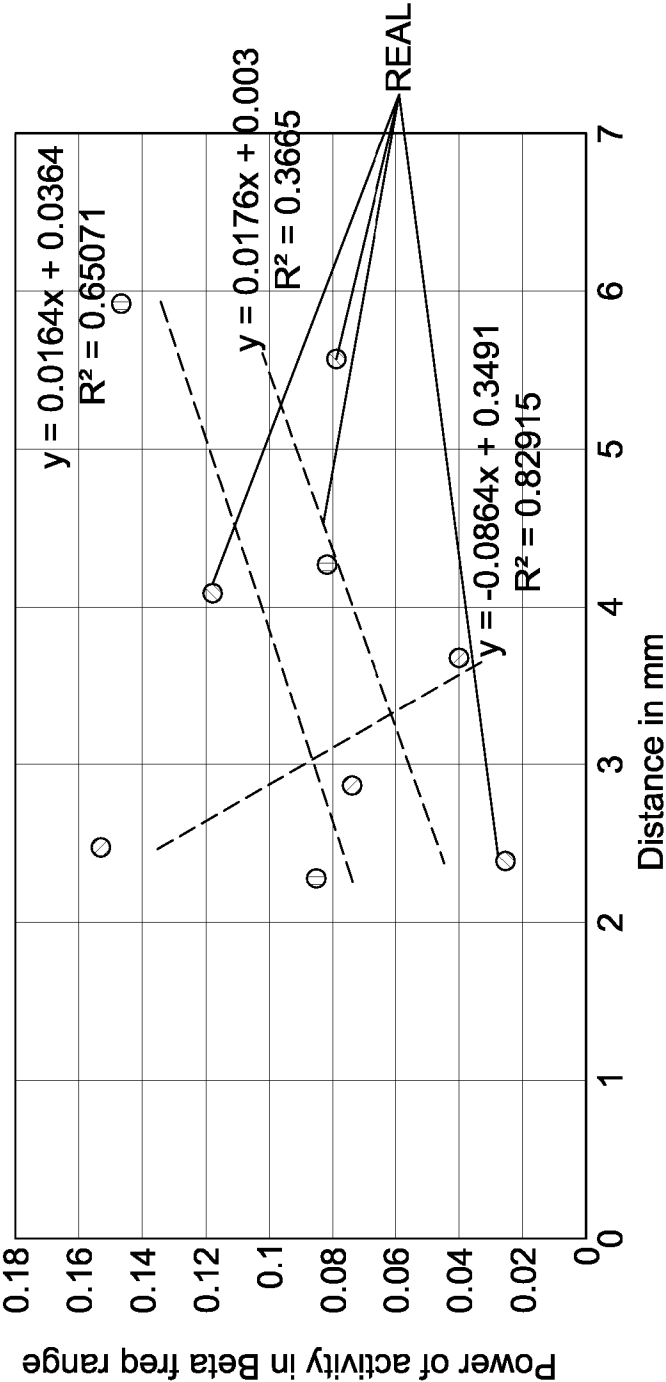


Fig. 7

Sample Size	12
Simple Linear Regression	
R-Squared	0.484
Line of Best Fit	$D = (-8.92 \times B) + 4.20$

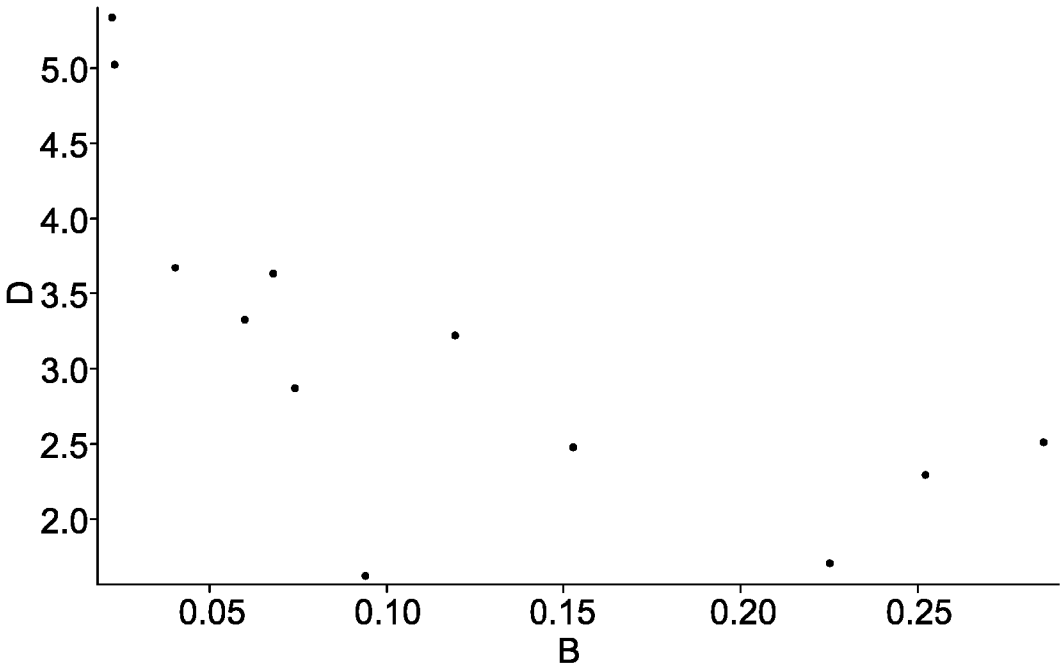


Fig. 8a

Sample Size	12
Simple Linear Regression	
R-Squared	0.272
Line of Best Fit	$a = (0.425 \times 1/Dsq) + 0.0555$

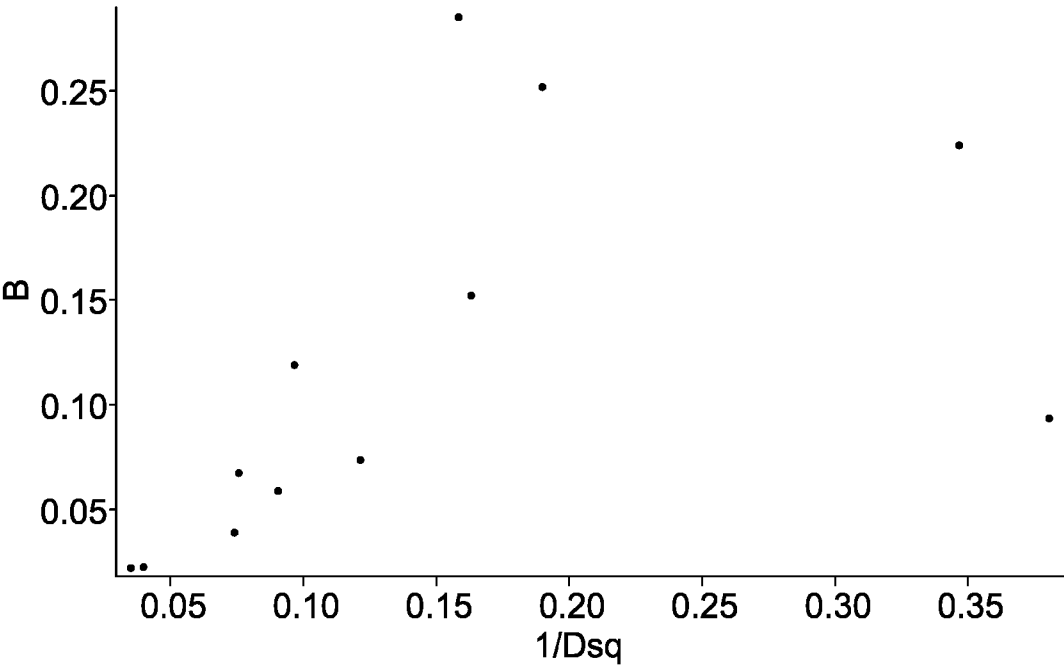


Fig. 8b

Sample Size	12
Simple Linear Regression	
R-Squared	0.732
Line of Best Fit	$LNB = (-0.636 \times D) - 0.449$

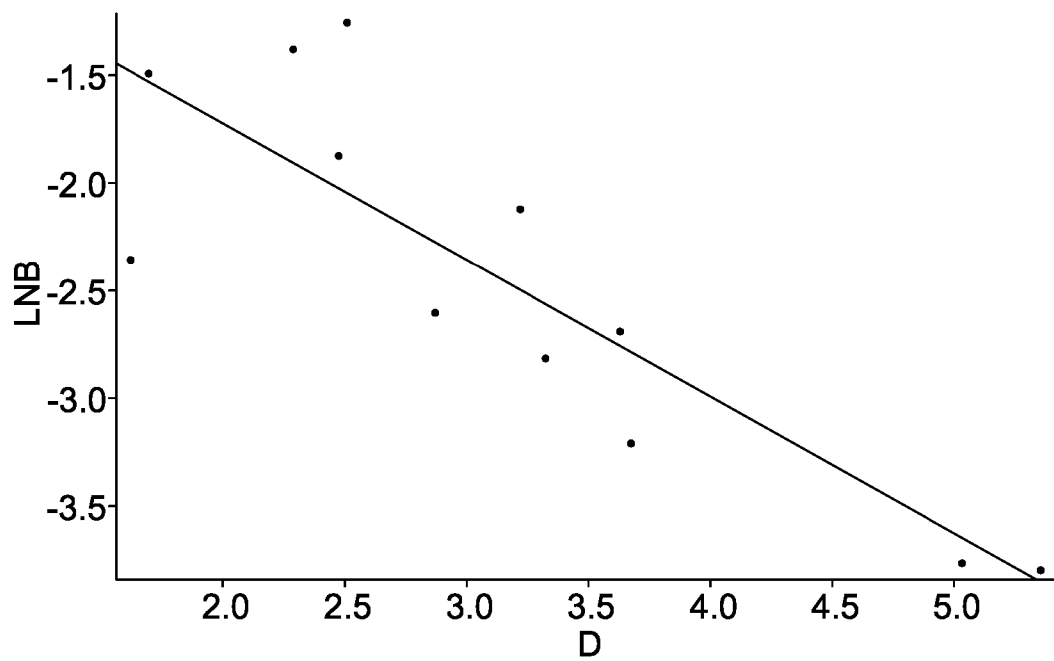


Fig. 8c

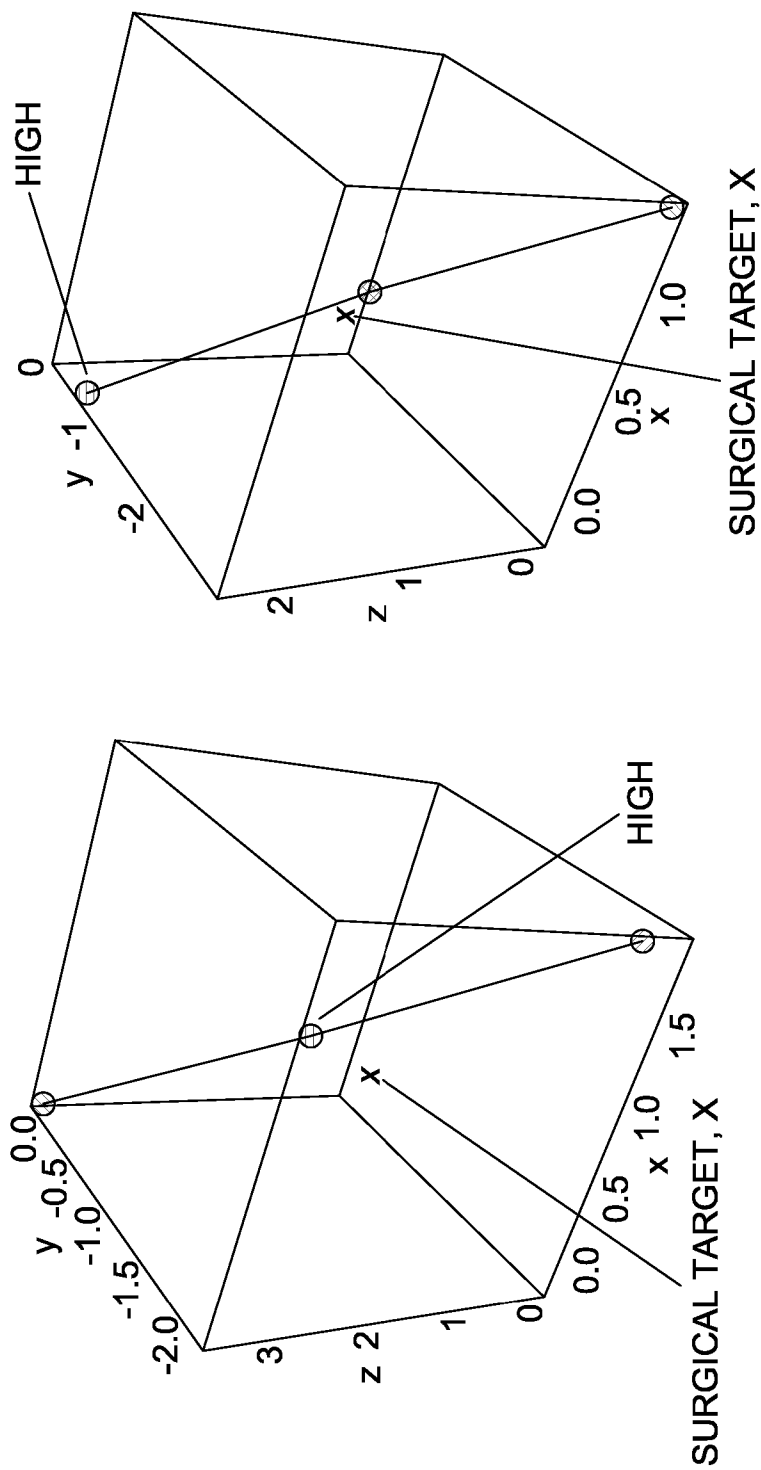


Fig. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/052418

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61B5/00 A61N1/05 A61N1/36 A61N1/08
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)

A61B A61N

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 2016/051812 A1 (MONTGOMERY JR ERWIN B [US] ET AL) 25 February 2016 (2016-02-25) paragraphs [0009] - [0013], [0049] - [0051], [0108] - [0110]; figures 6-11 -----	1-17
A	WO 2012/145244 A1 (MEDTRONIC INC [US]; NELSON DWIGHT E [US]; AGARWAL RAHUL [US]; JENSEN S) 26 October 2012 (2012-10-26) page 6, line 26 - page 37, line 26 -----	1-17
A	WO 2008/072125 A1 (KONINKL PHILIPS ELECTRONICS NV [NL]; PHILIPS CORP [US]; DECRE MICHEL M) 19 June 2008 (2008-06-19) page 8, line 1 - page 14, line 5 -----	1-17
A	US 2015/258339 A1 (BURCHIEL KIM [US] ET AL) 17 September 2015 (2015-09-17) paragraph [0026] - paragraph [0091] -----	1-17



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

9 November 2017

Date of mailing of the international search report

20/11/2017

Name and mailing address of the ISA/

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Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2017/052418

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. ☒ Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(vi) PCT - Program for computers.
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy. Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery. Rule 6.2(a) PCT - References to other parts of the application.
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

Information on patent family members

International application No

PCT/GB2017/052418

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		US 2017209687 A1 27-07-2017	
		WO 2015138290 A1 17-09-2015	
