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(54) Title: METHOD AND SYSTEM FOR OPTIMISATION OF DBS PROGRAMMING

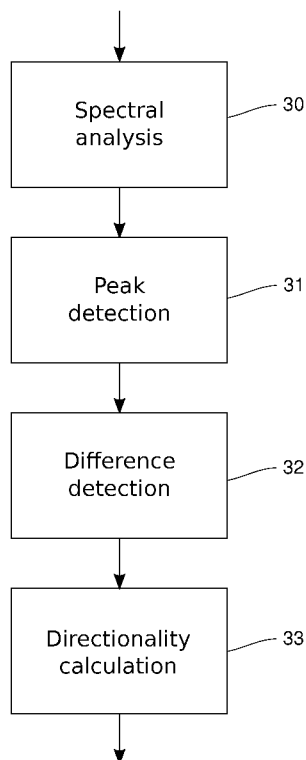


FIG. 5

(57) Abstract: A method and system are described for, based upon a plurality of previously-acquired directional LFP signals measured in a plurality of different directions at a directional sensor lead located in a predetermined region of a patient's brain, determining optimised patient-specific programming parameters for programming a directional stimulation lead with parameters for stimulating the said region. The method comprises a first step of determining, over at least one predetermined frequency range, a power-frequency variation curve of each of the directional LFP signals, a second step of identifying frequency peaks in the power-frequency variation curves, a third step of detecting one of the identified frequency peaks at which a maximum difference in signal power between the directional LFP signals occurs, and a fourth step of calculating a plurality of directional stimulation weighting factors on the basis of the relative signal powers of the directional LFP signals at the detected frequency peak.

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## Method and system for optimisation of DBS programming

### Field of the invention

The invention relates to the field of deep brain stimulation (DBS), which can be used for example to alleviate the symptoms of conditions such as Parkinson's Disease (PD). In particular, the invention relates to a method of determining optimised parameters for programming a stimulation regime for a directional deep brain stimulation electrode.

### Background of the invention

Deep brain stimulation (DBS) is a proven treatment option for patients with advanced Parkinson's disease (PD), and may consist of inserting DBS leads into target cerebral regions such as the subthalamic nucleus (STN), the globus pallidus internus (GPi) or the thalamus, such that electrical current can be applied to treat disease-specific motor symptoms in patients with PD. The spatial selectivity of DBS is of the utmost importance for the quality of the clinical result; firstly, spatial selectivity helps to ensure accurate targeting of the region for therapeutic stimulation. Secondly, it helps to avoid unwanted stimulation of neighbouring structures which could result in adverse effects. It is known to use a quadripolar DBS lead with four cylindrical electrodes, also referred to as contacts, arranged in successive axial sections along its length, ie four axial sections with one electrode per axial section. Such an electrode can be positioned using a known navigation technique; postoperatively, the four electrodes are tested manually by the operator to identify the electrodes which are best located in the target region. With a quadripolar electrode introduced into each of the target regions (eg right and left GPi, STN, thalamus) of both cerebral hemispheres, the procedure may typically be carried out as follows:

All the electrodes in both cerebral hemispheres are tested using different stimulation parameters, while the resulting clinical effects and side effects are assessed by interviewing the patient and by neurological examination. The patient is usually withdrawn from his/her medication before the procedure is carried out. There are four main variables that can be modified to configure the stimulation: a) the choice of active electrodes and their polarity, b) the stimulation amplitude (voltage or current), c) the frequency (Hz) and d) the pulse width (microseconds). The first electrode is selected and the stimulation amplitude (voltage or current) is slowly increased in 0.5 V (or 0.5 mA) steps, while the stimulation frequency and the pulse width remain fixed at 130 Hz and 60  $\mu$ sec respectively. After resting for 2 to 5 minutes at a certain parameter configuration, the effects and side effects are determined by asking the patient and by performing a neurological examination. The stepwise increase of the stimulation amplitude is continued until limiting side effects occur. The stimulation amplitude for the best clinical effect without manifestation of limiting side effects, ie submaximal stimulation, will be documented. The same testing has to be completed for the remaining contacts and then the whole contact-testing procedure is repeated for the contralateral hemisphere. At the end of such an extended clinical contact testing, the different contacts should effectively have been ranked according to clinical effects and according to the threshold, dependent on the stimulation parameters, above which side effects appear.

However, the above prior art manual method of contact testing has the disadvantage that it takes a long time to perform (3 to 5 hours per lead), and that this lengthy, time-consuming procedure typically needs to be repeated. The procedure thus requires the involvement of specially trained neurologists and/or highly skilled specialised nurses repeatedly, over extended periods of time. The lengthy procedure is also highly fatiguing for the patient, and the results are often suboptimal due to fatiguing of the patient and prolonged withdrawal of medications with long-lasting adverse effects. Furthermore, some of the clinical effects which could be used to inform the programming decisions may not develop during the period of clinical observation for the particular selection of stimulation parameters. Erroneous decisions may be made in the selection of stimulation parameters when relying on

short-term effects of stimulation only. Therefore, in many cases, stimulation effects must be reassessed again and again, often over longer periods of time, which may require inpatient admission for the subject.

As described above, therefore, the known method involves manually  
5 attempting to estimate the best configuration for symptom relief among the myriad possible different stimulation parameters. The patient's symptoms are alleviated by stimulation provided by a implanted pulse generator (IPG) and DBS electrode, programmed according to the estimation process described above. Further re-programming of the IPG may subsequently be required if the estimated parameters  
10 prove to be ineffective, and each re-programming necessitates a further clinical session for the patient.

The choice of the best-located stimulation contacts is a critical step for DBS programming in each individual patient. The manual screening procedure described above is very time-consuming for medical staff, fatiguing for the patient,  
15 and the results are often suboptimal. Consequently, this procedure must typically be repeated several times until a satisfactory parameter/contact configuration of stimulation has been identified. Unfortunately, in some patients an optimal stimulation programming is never attained, often due to lack of available expertise or time.

#### Prior art

20 It has been proposed to use a directional multi-electrode DBS lead to achieve directional stimulation. A directional multi-electrode lead is known from EP2626109, for example. A simple example is shown in figure 1, and will be used as an illustrative example in the following description of the invention. The lead shown in figure 1 has eight electrodes (contacts) arranged in four axial sections similar to the  
25 sections of the quadripolar lead described above. However, the second and third axial sections of the directional electrode each comprise three contacts  $3_1$ ,  $3_2$ ,  $3_3$  and  $4_1$ ,  $4_2$ ,  $4_3$ , formed as circumferential cylindrical surface segments, thereby allowing a different stimulation amplitude (voltage or current) to be programmed to each of three

different lateral directions for each of the two mult-contact sections. Such a directional lead permits the stimulation field to be shaped towards a desired direction within the target region, thereby allowing the DBS to be programmed with significantly greater stimulation accuracy to achieve the best clinical effect, while  
5 avoiding stimulating in directions which may induce unwanted stimulation-related side effects. However, the presence of eight stimulation contacts, with six of them stimulating in three different directions, means that the postoperative management of DBS patients, and the programming of the stimulation regime, are markedly more complicated than those of the quadripolar lead. The more electrodes on the lead, the  
10 more the manual testing of the contacts becomes time-consuming and the more the reliability of the procedure is adversely affected by patient fatigue. A lack of available expertise, infrastructure and time may be additional limiting factors impairing an appropriate manual contact testing of such a directional lead. As a consequence, the potential benefit of directional stimulation may not be fully exploited and its promise  
15 not fully realised.

A system and method are therefore needed for reducing the time taken to determine the programming parameters, and for improving their accuracy and reliability.

#### Brief description of the invention

20 The invention aims to overcome at least some of the above and other difficulties inherent in the prior art. In particular, the invention aims to provide a method as set out in claim 1, a system as set out in claim 12 and a computer-readable medium as set out in claim 15. Further variants of the apparatus and method of the invention are described in dependent claims 2 to 11, 13 and 14.

25 By systematically determining the directionality of the optimum stimulation parameters in dependence on directional local field potential (LFP) measurements, the programming parameter determining procedure can be performed a great deal

more quickly, accurately and reproducibly than was hitherto possible with contact testing carried out manually by a skilled operator.

#### Detailed description of the invention

The invention and its advantages will be explained in greater detail with  
5 reference to the accompanying drawings, in which:

Figure 1 shows a simplified schematic illustration of an example of a directional multi-contact DBS lead arrangement which may be used to provide LFP signal data to the method and system of the invention.

Figure 2 shows an example of frequency-power spectra of LFP signal data  
10 acquired from the lead of figure 1 for a particular DBS site of a particular patient.

Figures 3a and 3b show schematic graphical representations of DBS directional weightings which may be determined by the inventive method and system from the signal data of figure 2.

Figure 4 shows a simplified top-level abstraction of an example of a  
15 clinical procedure incorporating the method of the invention.

Figure 5 shows a more detailed view of the steps carried out in a method according to the invention.

Figure 6 shows in even greater detail the steps and substeps which may be carried out in a method according to the invention.

20 The drawings are intended merely as exemplary illustrations, for the purpose of understanding certain principles underlying the invention, and are not to be construed as limiting the scope of the invention. Where the same reference numerals are used in different drawings, these reference numerals are intended to refer to the same or corresponding features. However, the use of different reference

numerals should not necessarily be taken as an indication that the referenced features differ in any particular respect.

To identify the target cerebral structure for chronic stimulation, an intraoperative recording of the neuronal activity may be performed, for example using a directional multi-contact lead such as the one shown in figure 1. Such a recording may reveal evidence of exaggerated oscillatory synchronisation in the STN, GPi or thalamus, which may be detected in the local field potentials (LFP). Two broad types of oscillatory activity in patients with PD have been identified: beta band activity (13-30 Hz) and gamma band activity (65-80 Hz). The power of the beta band activity without medical treatment (ie levodopa) and the degree of suppression of this activity by levodopa and DBS correlate with clinical signs of Parkinsonism (bradykinesia and rigidity) and the degree of clinical improvement with treatment, respectively. Gamma band activity, by contrast, has been shown to increase during improvement of bradykinesia and rigidity. The method and system of the invention make use of the fact that LFP signals in specific frequency bands, especially the beta band activity, are linked to the motor signs and may be used as biomarkers to optimise deep brain stimulation. LFPs recorded from directional DBS leads are screened for individual direction and depth-specific differences in the power frequency spectrum in disease-related frequency bands (eg beta band). A specific algorithm is then used to process these signal data in order to output parameters for the optimum contact configuration for programming the subsequent DBS stimulation regime. The method and system of the invention may be employed for automatic programming of the IPG connected to a directional DBS lead. Alternatively, the method and system of the invention may be employed to provide optimised programming parameters to a clinician, thereby providing a supportive tool for the clinician for programming of the IPG for the directional DBS lead.

Figure 2 shows an example set of frequency-power spectra of LFP signal data acquired from the lead 1 of figure 1, for a particular DBS site of a particular patient. Curves 12, 13, 14, 15, 16, and 17 show the spectra of the LFP signal data acquired in the beta band from contacts 3<sub>1</sub>, 3<sub>2</sub>, 3<sub>3</sub>, 4<sub>1</sub>, 4<sub>2</sub> and 4<sub>3</sub> respectively. A local



peak 10 can be seen in the curve 14 for contact 4<sub>3</sub> at approximately 20 Hz. As will be described below, this peak 10 can be detected using an algorithm for detecting peaks in each spectral power curve and determining at which of the peaks the difference between the amplitudes (ie the spread of the amplitude values) among one set of directional contacts (ie 3<sub>1</sub>, 3<sub>2</sub> and 3<sub>3</sub> or 4<sub>1</sub>, 4<sub>2</sub> and 4<sub>3</sub>) are greatest. As will be described below, this maximum difference calculation may be based on normalized and/or baseline-corrected amplitude values of the frequency curves within a frequency window (referred to as the DIFR) at the peak under consideration. Signal differences and signal comparability can be improved by carrying out normalization and/or baseline correction steps in order to increase the signal-to-noise ratio. Normalization steps may include various spectral components, and may involve for example contrasting the the peak amplitude with the mean amplitude of the whole disease-related frequency band.

Note that the example given in this description assumes that the geometrical arrangement of the sensor lead contacts corresponds directly to that of the stimulation lead, however this need not necessarily be the case. Stimulation weightings may be mapped using appropriate transformation from the geometric configuration of the directional sensor(s) to the geometric configuration of the directional stimulation electrode(s).

Similarly, the method steps are described in the context of monopolar measurements (ie assessing each contact separately, with a common reference). In the monopolar method, power frequency curves are derived for each contact, and the magnitude of the disease-related spectral component is ranked for the contacts individually. However, it should be understood that the same techniques may be applied to more than single contact at once, in a bipolar or multipolar fashion, such that so-called "montages" or arrangements of multiple contacts may be assessed and ranked. Method steps applied to individual contacts in this description should be understood to encompass the application of the steps to montages of two or more contacts. Determining the magnitude of the disease-related spectral components in such a group-wise, combinatorial fashion greatly increases the number of possible

choices to be ranked, and improves the signal-to-noise ratio of the derived results (power frequency curves and detected peaks).

Figures 3a and 3b show how the spectral power curves of figure 2 may be used to derive directional weightings 6 and 7 for the stimulation amplitudes at contacts 3<sub>1</sub>, 3<sub>2</sub> and 3<sub>3</sub> (figure 3a) and contacts 4<sub>1</sub>, 4<sub>2</sub> and 4<sub>3</sub> (figure 3b). In figure 3a, the three electrodes 3<sub>1</sub>, 3<sub>2</sub> and 3<sub>3</sub> show almost zero directional weighting (8%, 9% and 8% respectively), whereas figure 3b shows that the three electrodes 4<sub>1</sub>, 4<sub>2</sub> and 4<sub>3</sub> are markedly weighted (16%, 23% and 35% respectively). In this example, the inventive method predicts that the DBS should be weighted in favour of the contact 4<sub>3</sub> in order to achieve optimum targeting of the structure to be stimulated. A manual contact testing was carried out blind on the patient whose LFP signals were recorded to generate the spectral curves of figure 2, and the manual contact testing produced the following recommended directional stimulation currents for each of the directional contacts of the DBS lead of figure 1 as follows:

15            3<sub>1</sub> : 4.0 mA  
              3<sub>2</sub> : 3.5 mA  
              3<sub>3</sub> : 3.0 mA  
              4<sub>1</sub> : 2.5 mA  
              4<sub>2</sub> : 2.5 mA  
20            4<sub>3</sub> : 2.0 mA

As can be seen from the above, the manual contact testing approach confirmed the prediction, made by the method of the invention, that contact 4<sub>3</sub> would provide the best result (lowest stimulation current for effective symptom relief). However, the manual contact testing took six hours of intensive, fatiguing clinical work, while the recommendation from the inventive method was delivered almost instantly.

Note that the graphical representation of figures 3a and 3b are examples of how the directional contact weighting may be presented graphically to a clinician so that he or she may adjust the DBS programming accordingly. Alternatively, the

calculated weightings may be used directly in an automated programming of the IPG and DBS electrode.

Figure 4 shows an overview of the context of the method and system of the invention in the overall DBS process. In step 20, directional LFP signals are  
5 acquired from directional sensing electrode 1, such as the lead shown in figure 1. The acquired signals are processed in step 21, using to a method according to the invention, to generate directionally optimised programming parameters which are then used in step 22 to program an IPG driving a directional DBS lead 8 (which may typically be the lead 1, ie the DBS lead serves as sensor and stimulation lead).

10 The LFP signal acquisition step 20 may comprise recording LFPs from the directional lead after its placement in the definitive position within the target structure (eg STN, GPi or thalamus). During the recording, the patient must be withdrawn from dopaminergic medication, the patient must be awake and in a resting position without any voluntary movement. Recording can be performed intraoperatively or  
15 postoperatively before the electrode is connected to the implantable pulse generator (IPG). Alternatively, LFPs can be recorded at any time point from the IPG itself, if the IPG is capable of LFP recording.

The method steps underlying step 21 of figure 4 are described below, with particular reference to figures 5 and 6. As described above, the method of the  
20 invention comprises the steps of

- spectral analysis 30 of the LFP signal data in order to generate spectral power curves for each directional electrode on the sensor lead 1;
- peak detection 31 to identify any local peaks in each of the spectral power curves;
- 25 - difference detection 32 for determining the peak at which there is the greatest difference in amplitude among the directional electrodes of a section of the lead; and

- directionality calculation 33, for deriving weightings for stimulation signals applied to each of the directional electrodes of the DBS lead 8.

Figure 6 shows an example flow diagram of a method according to the invention. In step 40, one or more suitable frequency bands are selected, according to current knowledge, for analysing the LFP signals associated with a particular disease. The frequency band(s) may advantageously comprise the beta frequency range (13-35 Hz). In principle, several frequency bands present in the LFP may be used as biomarkers (alone or in combination) to guide stimulation, however on the premise of an existing relationship to the disease. Such a relationship could be positive (associated with symptom alleviation) or negative (associated with symptom deterioration). In step 41, a suitable sampling frequency is determined for the subsequent spectral analysis, the sampling frequency being preferably at least twice the Nyquist limit for the LFP signal data. In step 42, the power-frequency-spectrum (spectral analysis with frequency decomposition) for each directional contact is calculated, at eg 1 Hz resolution. In step 43, local peaks in the power-frequency curves are identified. Within the disease-related frequency band, the frequency peak showing the largest differences among directional contacts is identified in step 44. In step 45, this peak frequency is transformed into a frequency range (DIFR) by adding and subtracting a predetermined spectral bandwidth, such as 3 Hz, to give a total width of 7Hz. The width of DIFR (eg peak frequency  $\pm$  3 Hz) can be set to maximize directional information between the contacts. The width of the DFIR may be predetermined, or it may be dynamically adapted, for example in dependence on a characteristic of the power-frequency curves. In step 46, the average amplitude for each directional contact over the DIFR is baseline corrected by subtracting 90% of the mean amplitude of the directional contact with the lowest amplitude in the DFIR. This step helps to reduce the effect of volume conduction and to improve the visualisation of the spectral differences between the contacts. The baseline corrected average amplitudes for each contact are then summed in step 47, and percentage distribution over the directional contacts is calculated to determine a directionality index (DI). The DI of each directional contact allows contacts to be ranked according to the likelihood that they will afford the best clinical response on stimulation, which is

defined as the lowest stimulation intensity required for sufficient clinical response. The percentage value itself does not indicate a percentage clinical response. Where two or more of the directional contacts in a particular lead section have similar DI values, they may be considered in combination for stimulation. The directionality index is superimposed graphically as a vector and as percentage value for each directional contact on a visual model illustrating the stimulation contacts and contact levels. This enables the clinician to immediately understand which section and which directional contact are likely to produce the best DBS results.

The parameters determined in the method described above may be exported (manually or automatically) into the IPG which drives the DBS stimulation device. The clinician should therefore start to deliver the stimulation on the contact with the highest directionality index, adjusting other stimulation parameters (current, frequency, pulse width etc) accordingly and, if necessary, move on to a different contact, or a different combination of contacts, suggested by the directionality index results if the stimulation effect is clinically not sufficient or if side effects occur. In IPGs with LFP recording capabilities and integrated analysis modules, the inventive method, and the system which embodies it could be fully integrated and automated as an internal feature of the IPG.

The method described above may preferably be implemented as instructions stored on non-transitory computer-readable media, and/or in a system comprising one or more specially configured or programmed electronic circuits.

## Claims

1. Computer-implemented method of, based upon a plurality of directional LFP signals measured in a plurality of different directions at a directional sensor (1) located in a predetermined region of a patient's brain, determining optimised patient-specific programming parameters (6, 7) for programming a directional multi-electrode stimulation lead (1, 8) with parameters for stimulating the said region, the method comprising:

a spectral analysis step (30) in which, over at least one predetermined frequency range, a power-frequency variation curve (12, 13, 14, 15, 16, 17) is determined for each of the directional LFP signals,

a peak identification step (31) in which at least one frequency peak (10) is identified in the power-frequency variation curves,

a difference detection step (32) of detecting one (10) of the at least one identified frequency peaks at which a maximum difference in signal power between the directional LFP signals occurs,

a directionality determining step (33) of calculating a plurality of directionally weighted stimulation indices (6, 7) for the directional stimulation lead on the basis of the relative signal powers of the directional LFP signals at the frequency of the detected frequency peak (10).

2. Method according to claim 1, wherein the said frequency range comprises the beta frequency range.

3. Method according to claim 1 or 2, wherein the spectral analysis step comprises determining power-frequency curves for a plurality of frequency ranges, the frequency ranges being usable alone or in combination to guide stimulation.

4. Method according to one of the preceding claims, wherein the directionality determining step (32, 33) comprises:

- selecting a directionality indicating frequency range, referred to hereafter as the DIFR, based on the detected frequency peak (10) and

5 - determining of a directionality index, referred to hereafter as DI, for each of a plurality of the electrodes of the directional stimulation lead (8) and/or for each of a plurality of montages of the electrodes of the directional stimulation lead (8).

5. Method according to claim 4, wherein the DIFR is a predetermined constant frequency range centered on the frequency of the detected frequency peak, 10 or wherein the width of the DIFR is selected in dependence on the frequency of the detected frequency peak.

6. Method according to claim 4 or claim 5, wherein the step of determining the directionality index comprises performing a normalization and/or a baseline correction of the average amplitude of each of the spectral power LFP curves (12, 13, 15 14, 15, 16, 17) in the DIFR.

7. Method according to claim 6, wherein the baseline correction comprises subtracting a predetermined proportion of the spectral mean amplitude from the amplitude of each of the curves.

8. Method according to claim 7, further comprising summing the average 20 amplitude of each curve over the DIFR to give a proportional distribution for each direction associated with said each curve.

9. System for determining optimised patient-specific programming parameters (6, 7) for programming a directional multi-electrode stimulation lead (8) with parameters for stimulating the said region, the system comprising:

25 means for receiving a plurality of previously-acquired directional LFP signals measured in a plurality of different directions at a directional sensor lead (1) located in a predetermined region of a patient's brain,

spectral analysis calculation means configured to determine, over at least one predetermined frequency range, a power-frequency variation curve (12, 13, 14, 15, 16, 17) for each of the directional LFP signals,

5 peak detection means (31) for identifying at least one frequency peak (10) in the power-frequency variation curves determined by the spectral analysis means,

difference detection means (32) configured for detecting one (10) of the at least one identified frequency peaks at which a maximum difference in signal power between the directional LFP signals occurs,

10 directionality determining means (33) for calculating a plurality of directionally weighted stimulation parameters (6, 7) for the directional stimulation lead (8) on the basis of the relative signal powers of the directional LFP signals at the frequency of the detected frequency peak (10).

15 10. System according to claim 9 wherein one or more of the spectral analysis calculation means, the peak detection means, the difference detection means and the directionality determining means are integrated into an implantable pulse generator device for driving the directional stimulation lead (8).

11. System according to claim 10, further comprising a sensor lead (1) for directional LFP recording.

20 12. System according to one of claims 9 to 11, further comprising the stimulation lead (8) for performing directional stimulation based on the directionally weighted stimulation parameters.

13. System according to claim 11 or 12, wherein the sensor lead (1) and the stimulation lead (8) are the same device.

25 14. System according to one of claims 9 to 13, further comprising a programmable implantable pulse generator device for driving the stimulation lead (8), wherein the programmable implantable pulse generator comprises means for acquiring or recording LFP signal data from the sensor lead (1).



15. Non-transitory computer-readable medium storing processor executable instructions on a computing device for carrying out the method of one of claims 1 to 8.

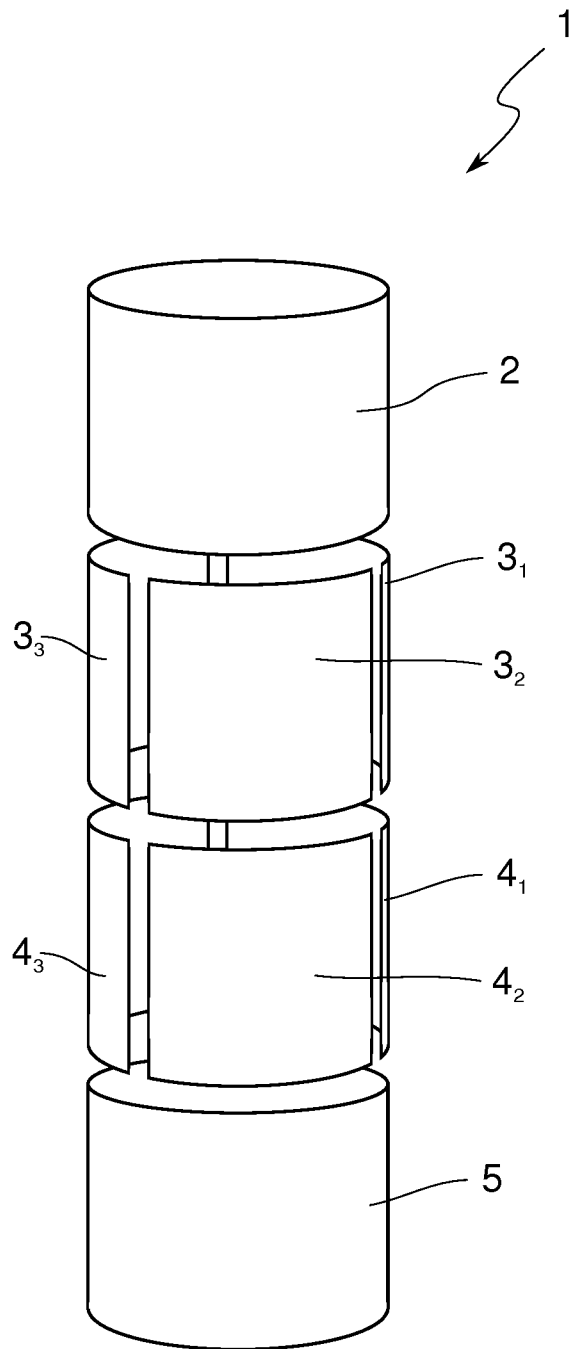


FIG. 1

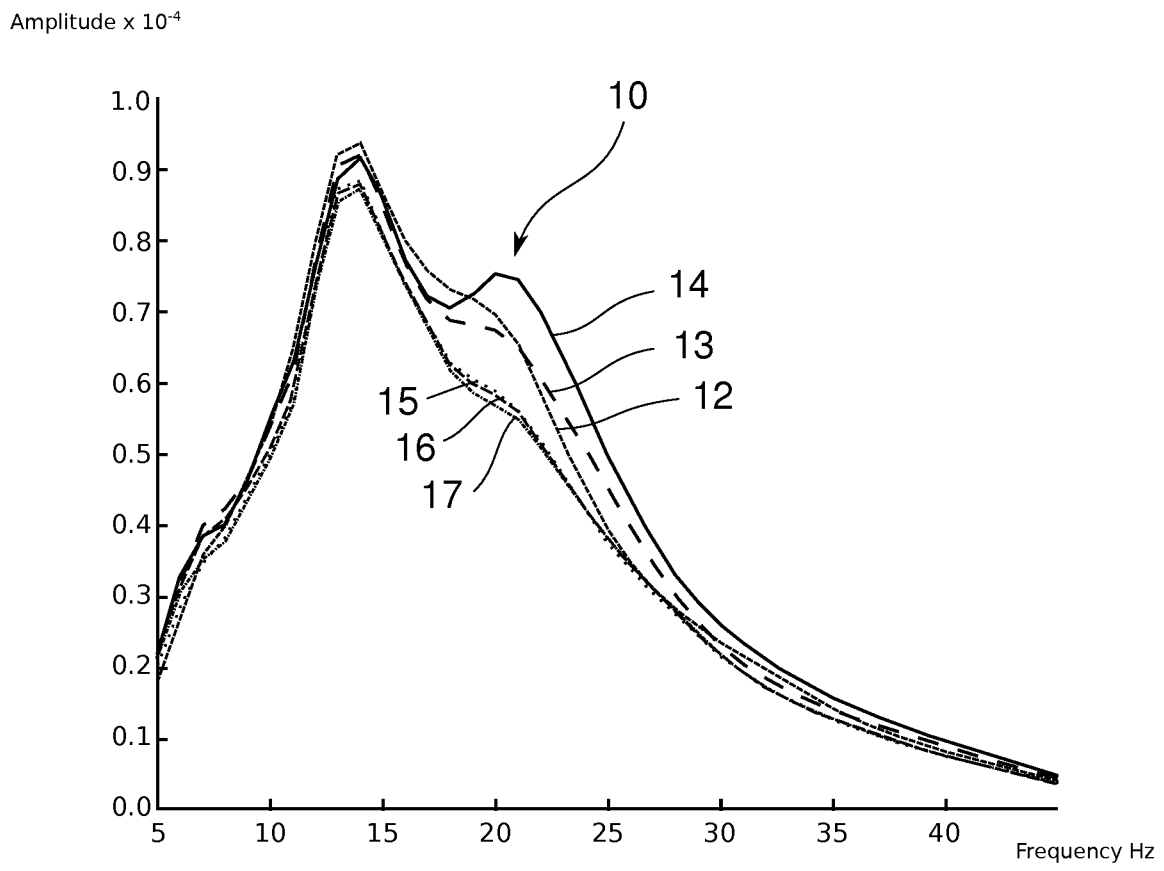


FIG. 2

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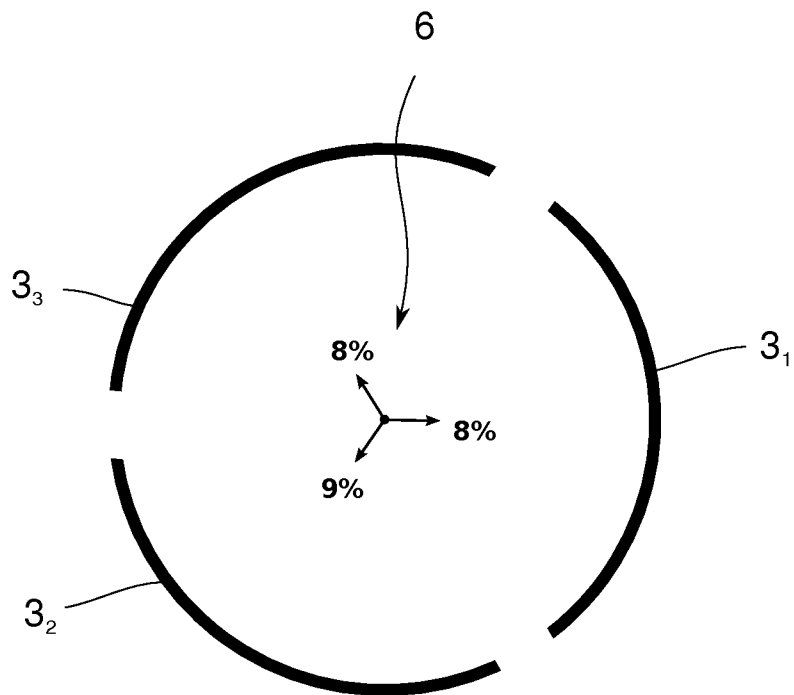


FIG. 3a

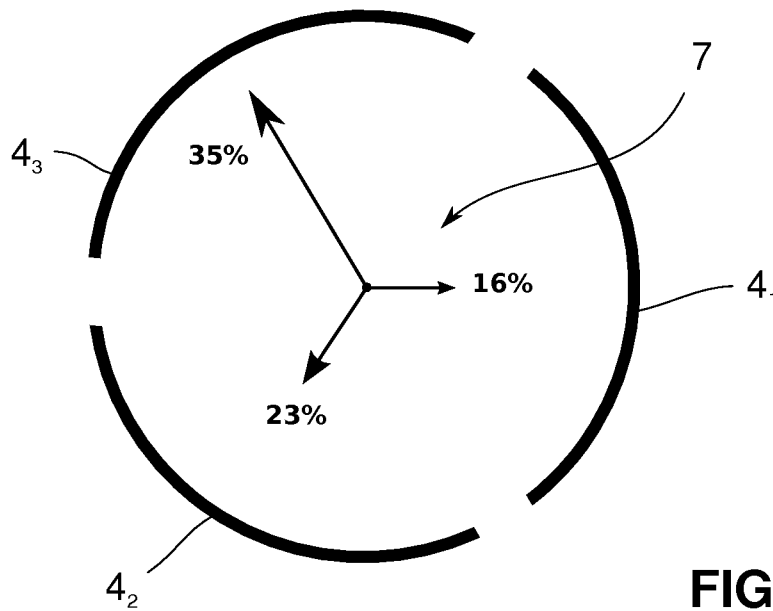


FIG. 3b

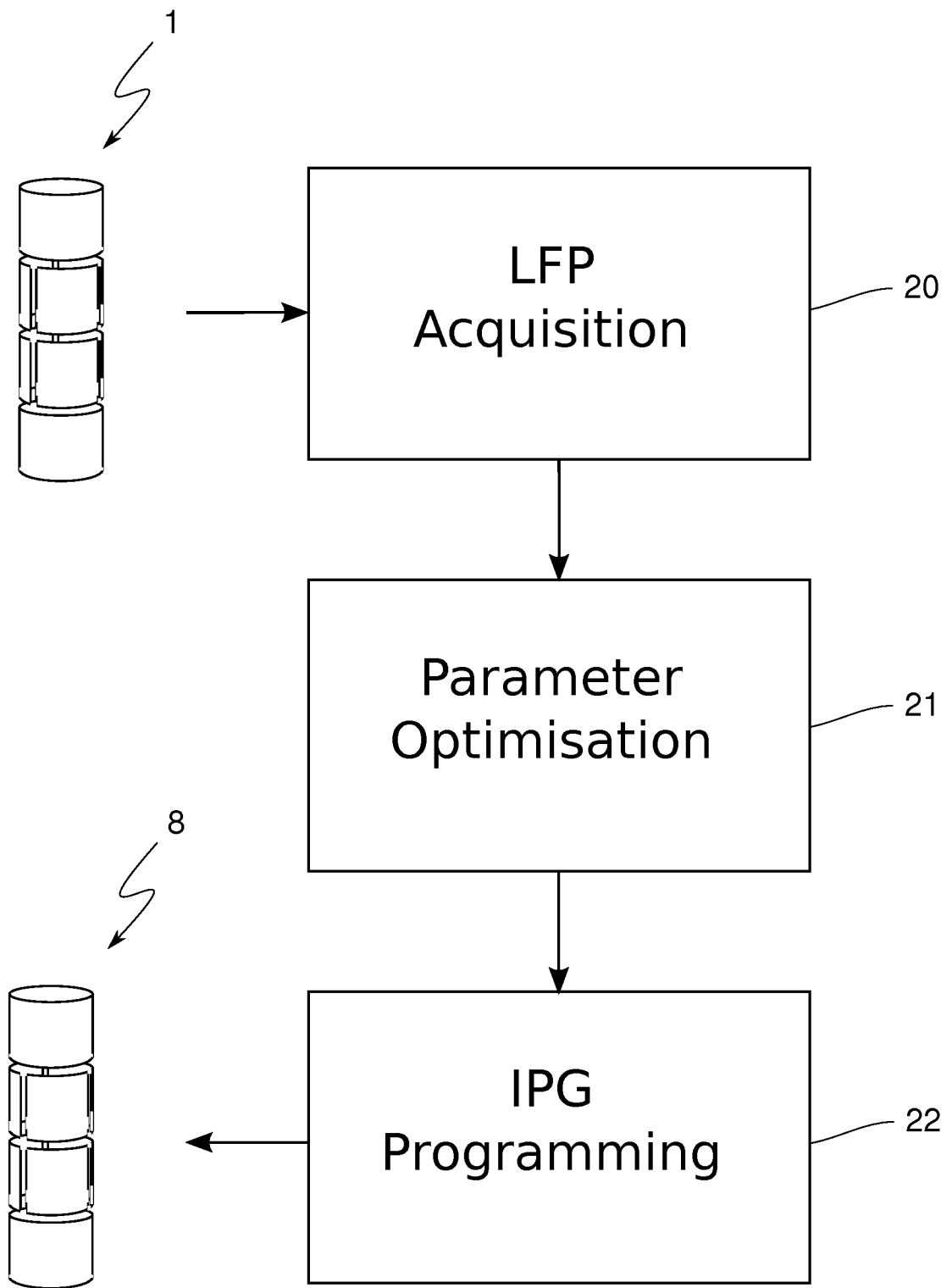


FIG. 4

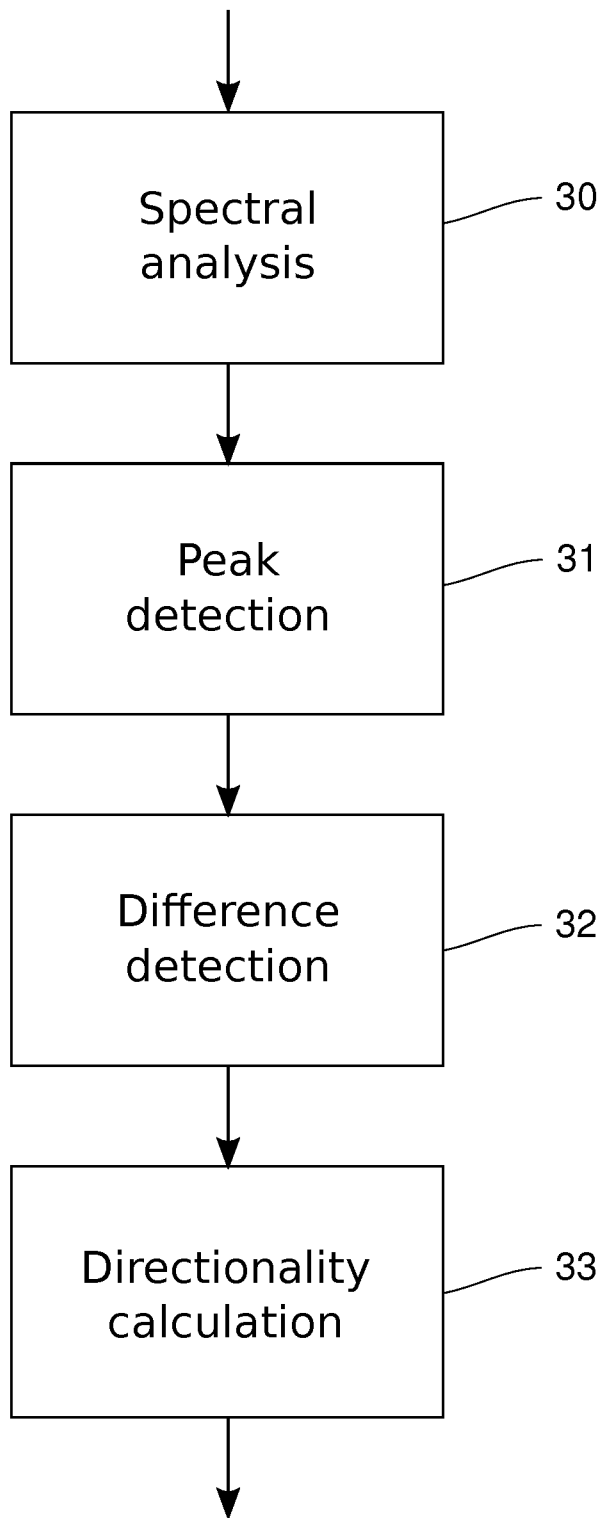


FIG. 5

6/6

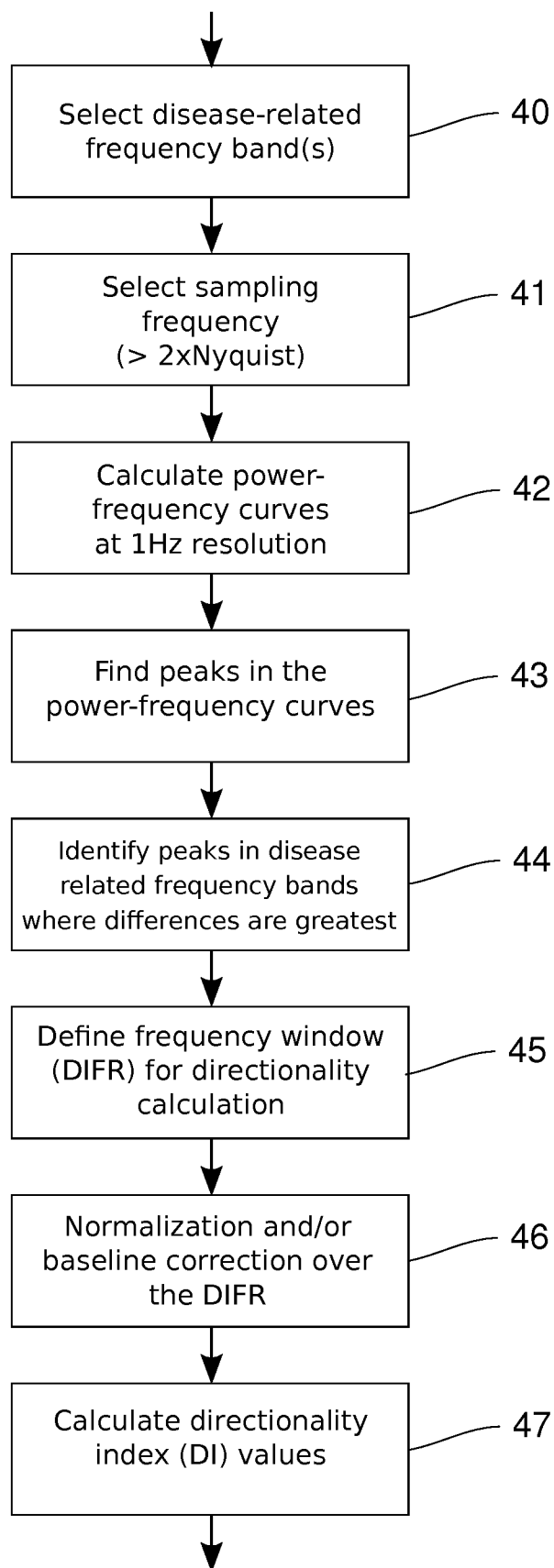


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2017/056184

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61B5/00 A61B5/048 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)  
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 2011/264165 A1 (MOLNAR GABRIELA C [US] ET AL) 27 October 2011 (2011-10-27) paragraphs [0055], [0061], [0078], [0109], [0114], [0119], [0158], [0160], [0203] - [0205], [0207], [0209], [0213] paragraphs [0222] - [0224], [0227] - [0232], [0235], [0241] - [0252], [0262], [0287] - [0311], [0349] - [0367] paragraphs [0384] - [0387]; claims; figures	1-15
X	US 2014/135870 A1 (CARLSON DAVID L [US] ET AL) 15 May 2014 (2014-05-15) paragraphs [0029] - [0040], [0042], [0045], [0051], [0079] - [0082], [0094] - [0109], [0112], [0116] - [0136], [0140] - [0144]; claims; figures	1-15
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Further documents are listed in the continuation of Box C.  See patent family annex.

\* Special categories of cited documents :

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Date of the actual completion of the international search 29 June 2017	Date of mailing of the international search report 06/07/2017
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Crisan, Carmen-Clara
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International application No

PCT/EP2017/056184

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