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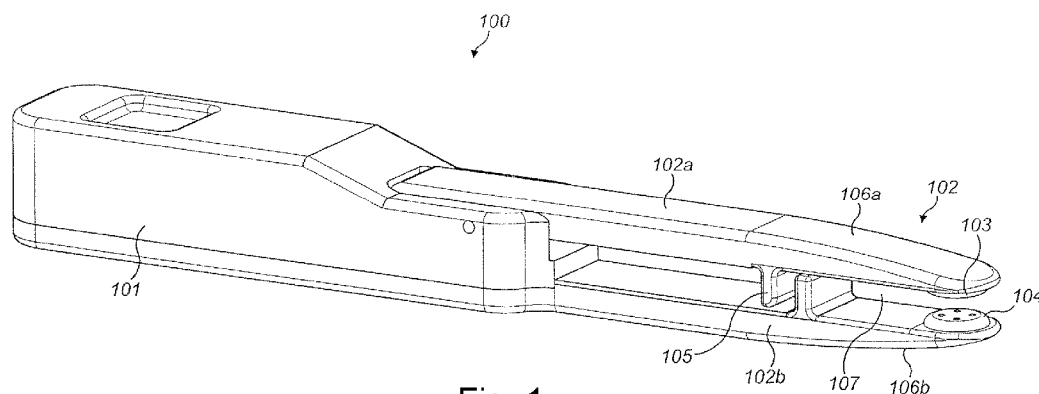


Fig. 1

(57) **Abstract:** An electrical impedance spectroscopy (EIS) system for the detection of tissue abnormalities of muscle, for example, because of neuromuscular disorders such as amyotrophic lateral sclerosis (ALS). In particular, a EIS probe is disclosed having a three dimensional array of electrodes separated from one another in the x, y and z coordinates by quantitative separation distances.

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Apparatus and Method for Evaluating Biological Tissue

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Field of invention

The present invention relates to apparatus and methods relating to the measuring of an
20 electrical parameter transmitted through human or animal body tissue and in particular,
although not exclusively, to method and apparatus for electrical impedance spectroscopy
(EIS).

Background art

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Neuromuscular diseases are a considerable source of mortality and morbidity. Their
diagnosis often relies on multiple investigations including blood tests, nerve conduction
studies and electromyography (EMG), imaging (e.g. MRI) and muscle biopsy. While each
of these tests have their own strengths, each has its own limitations. For example, the
30 muscle enzyme creatinine kinase can easily be detected in blood but is poorly predictive of
an underlying muscle disorder [Shaibani A, Jabari D, Jabbour M, Arif C, Lee M, Rahbar
MH. Diagnostic outcome of muscle biopsy. Muscle Nerve. 2015;51(5):662-8].

Taking motor neurone disease (MND) as an example of a severe neuromuscular disease requiring urgent research progress, there is no single diagnostic test and currently, the diagnosis is made clinically and, supported by multiple investigations, including nerve
5 conduction studies and EMG. EMG examination may proceed across each of the four craniospinal segments but there is evidence to suggest that this test works better in some segments than others. For example, examination of the bulbar segment (most usually of the tongue) has a lower sensitivity than other segments but a higher specificity, making the contribution of tongue EMG to diagnostic classification limited [Jenkins TM, Alix JJ,
10 Kandler RH, Shaw PJ, McDermott CJ. The role of cranial and thoracic EMG within diagnostic criteria for ALS. Muscle Nerve. 2016].

In addition, the development of effective biomarkers to track progression of MND and other neuromuscular disorders are of great interest as efforts to develop new therapies
15 continue. Recently, bioimpedance measurements have gained increasing interest as a biomarker of disease progression in amyotrophic lateral sclerosis (ALS) [Rutkove SB, Caress JB, Cartwright MS, Burns TM, Warder J, David WS, et al. Electrical impedance myography as a biomarker to assess ALS progression. Amyotroph Lateral Scler. 2012;13(5):439-45]; [Rutkove SB, Zhang H, Schoenfeld DA, Raynor EM, Shefner JM,
20 Cudkowicz ME, et al. Electrical impedance myography to assess outcome in amyotrophic lateral sclerosis clinical trials. Clin Neurophysiol. 2007;118(11):2413-8]; [Sanchez B, Rutkove SB. Electrical Impedance Myography and Its Applications in Neuromuscular Disorders. Neurotherapeutics. 2016]; [Benatar M, Boylan K, Jeromin A, Rutkove SB, Berry J, Atassi N, et al. ALS Biomarkers for Therapy Development: State of the Field &
25 Future Directions. Muscle Nerve. 2015] and [Rutkove SB, Kapur K, Zaidman CM, Wu JS, Pasternak A, Madabusi L, et al. Electrical impedance myography for assessment of Duchenne muscular dystrophy Ann Neurol 2017; 81(5): 622-632]. In this technique, alternating current (AC) of a given amplitude/frequency is applied and measurements of the electrical impedance are recorded. By applying AC over a range of frequencies,
30 information relating to both the electrical resistive and reactive properties of the tissue is obtained. The authors of these works utilised impedance measurements in limb muscles [Tarulli AW, Garmirian LP, Fogerson PM, Rutkove SB. Localized muscle impedance

abnormalities in amyotrophic lateral sclerosis. J Clin Neuromuscul Dis. 2009;10(3):90-6], and more recently, the tongue [McIllduff C, Yim S, Pacheck A, Geisbush T, T, Mijailovic A, Rutkove SB. An improved electrical impedance myography tongue array for use in clinical trials. Clin Neurophysiol. 2016;127(1):932-5] and [Shellikeri S, Yunusova Y, Green JR, Pattee GL, Berry JD, Rutkove SB, et al. Electrical impedance myography in the evaluation of the tongue musculature in amyotrophic lateral sclerosis. Muscle Nerve. 2015]. As muscles change during disease, for example, through atrophy, impedance parameters also change; i.e., the rise in resistance values is thought to occur due to muscle replacement by fat and connective tissue [Rutkove SB. Electrical impedance myography: Background, current state, and future directions. Muscle Nerve. 2009;40(6):936-46].

Previous work in both muscle [Rutkove SB, Caress JB, Cartwright MS, Burns TM, Warder J, David WS, et al. Electrical impedance myography correlates with standard measures of ALS severity. Muscle Nerve. 2014;49(3):441-3]; [Narayanaswami P, Spieker AJ, Mongiovi P, Keel JC, Muzin SC, Rutkove SB. Utilizing a handheld electrode array for localized muscle impedance measurements. Muscle Nerve. 2012;46(2):257-63] and [Schwartz DP, Dastgir J, Salman A, Lear B, Bonnemann CG, Lehky TJ. Electrical impedance myography discriminates congenital muscular dystrophy from controls. Muscle Nerve. 2016;53(3):402-6] and mucosal surface bioimpedance recording [e.g. Sun TP, Ching CT, Cheng CS, Huang SH, Chen YJ, Hsiao CS, Chang CH, Huang SY, Shieh HL, Liu WH, Liu CM, Chen CY. The use of bioimpedance in the detection/screening of tongue cancer. Cancer Epidemiol. 2010; 34(2):207-11] has utilised 2-dimensional planar electrode arrays. One potential limitation to this approach is that the injected current is dissipated through the tissue and extends along diffuse pathways of minimum resistance. Since impedance is affected by geometry, as well as underlying tissue characteristics, ($Z = G \cdot \rho_0$; where Z = impedance, G = geometric variables and ρ_0 = tissue variables) [Shiffman CA. Adverse effects of near current-electrode placement in non-invasive bioimpedance measurements. Physiol Meas. 2013;34(11):1513-29] changes in geometry, for example, due to muscle wasting, may lead to differing volumes of muscle being analysed. Furthermore, as biological tissue is rarely homogeneous the effect of geometric changes will be complex and difficult to define. In some muscles, for example the tongue,

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bioimpedance measurements are further complicated by the complex arrangement of muscle fibers which may run in multiple orientations.

Existing electrical impedance myography devices having a 2-dimensional array of electrodes are accordingly disadvantageous due to their generally limited reproducibility and sensitivity to change within the same subject over time (via different measurement sessions) and between different subjects (with measurements taken at the same time). Accordingly, what is required is apparatus and method for electrical impedance spectroscopy that addresses the above problems.

Summary of the Invention

It is an objective of the present invention to provide apparatus and method for measurement of an electrical parameter transmitted through human or animal body tissue that provides enhanced sensitivity, reproducibility and specificity over existing arrangements. It is a further specific objective to provide apparatus and method for electrical impedance spectroscopy (EIS) offering greater sensitivity for detection of pathology and a greater reliability of tissue status analysis.

The objectives are achieved via method and apparatus in which at least two sets of electrodes are provided and spatially separated by a quantitative separation distance so as to enable 3-dimensional tissue analysis. This 3-dimensional analysis is achieved via a 3-dimensional array of electrodes having at least a first set positioned approximately at a first plane and a second electrode set positioned approximately at a second plane with each plane separated by a quantitative separation distance to define a 3-dimensional electrode array. The quantitative separation distance between the electrode sets provides analysis of a fixed quantitative volume of tissue, between the opposed electrode sets.

The 3-dimensional array of electrodes is advantageous to create better defined current pathways through the tissue in contrast to existing 2-dimensional electrode arrangements. In particular, the inventors have identified that for such existing arrangements, the current pathway from a current source to a current sink is poorly defined as the current is not

confined to the shortest path between the electrodes and disperses outwardly into the tissue, having a 'rugby-ball' like profile. In general, it is not possible to predict or control the current path between two current injection electrodes; although approximations may be made assuming a homogeneous conductivity distribution [Kotre CJ. EIT image

5 reconstruction using sensitivity weighted filtered backprojection. *Physiol Meas* 1994; 15 Suppl 2a:A125-36]. Inspecting a planar arrangement of electrodes in an x - y plane, the bulk of the current will flow in this plane, with significant current only flowing in the z direction close to the electrodes. By injecting current through the tissue the current can be made to flow substantially in the z direction. The present system optionally based on a cubic or
10 rectangular cuboid arrangement of electrodes significantly improves the definition of the current pathways, allowing for a greater exploration of tissue/muscle integrity/anisotropy. This in combination with providing a quantitative tissue volume between the electrode sets significantly enhances the sensitivity and specificity of the present method and apparatus, giving greater reproducibility and accordingly a more sensitive and reliable tissue status
15 assessment.

In particular, the inventors provide apparatus and method utilising a 3-dimensional array of electrodes for analysis of a fixed volume of tissue via multi-frequency alternating current (AC) across multiple directions in both 2-dimensional and 3-dimensional electrode array
20 configurations depending upon the choice of active electrodes within the array. In particular, the inventors provide an electrical impedance system for tissue analysis that reduces sensitivity to geometry variations of the tissue which otherwise affect the resulting electrical signals and in particular mask variations in tissue properties resultant from pathological disruptions or other disease induced anomalies. The present system providing
25 a 3-dimensional tissue analysis via a x , y and z coordinate based electrode array has the potential to target identification of tissue abnormalities with regard to their position within the tissue under investigation and the extent of the abnormalities with regard to healthy tissue.

30 According to a first aspect of the present invention there is provided apparatus configured to provide measurement of tissue transfer impedance within human or animal body tissue, the apparatus comprising: a first electrode set comprising at least two electrodes arranged

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generally in a first x - y plane; a second electrode set comprising at least two electrodes arranged generally in a second x - y plane; wherein the second electrode set is separated from the first electrode set by a separation distance in a z direction to define a gap region between the first and second electrode sets to accommodate at least a portion of the human
5 or animal body tissue; a first electrical circuit including a first electrode of the first or second set as a current source and a second electrode of the first or second set as a current sink to enable the passing of current through the tissue; a second electrical circuit including a third and a fourth electrode of the first and second set different to the first and second electrodes to measure a signal corresponding to a voltage through the tissue between the
10 third and fourth electrodes sensitive to the current flow through the tissue between the first and second electrodes.

The second electrical circuit comprising two electrodes of the first, second or the first and second sets, is configured to provide a potential difference between the two respective
15 electrodes that are effective to act as sensing electrodes. The potential difference is accordingly sensitive to the interaction between the tissue and the flow of current created and maintained by the first electrical circuit (and the first and second electrodes). The signal that is identified as a result of the current and voltage at the two circuits may be considered to be the change in voltage resultant from the interaction between the tissue and
20 the current flowing between the first and second electrodes (current source and current sink). This signal may then be analysed to determine the electrical characteristics of the tissue and by analysing the electrical characteristics, it is possible to determine a status of the tissue and in particular muscle integrity and in particular anisotropy. The current may be an alternating current having a frequency in a range 50 Hz to 10 MHz, 50 Hz to 2000
25 kHz, 50 Hz to 1000 kHz or 50 Hz to 800 kHz.

The additional means to measure the electrical signal may comprise one or a plurality of electrical components including an amplifier such as a transimpedance amplifier, a pre-measurement drive equalisation device, a plurality of amplifiers, a calibration device, an
30 analytical electronics device configured to analyse the input current and resulting voltage. The present apparatus may comprise analogue signal processing components to detect and measure the electrical signal indicative of the integrity/anisotropy of the tissue.

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Preferably, the separation distance in the z direction between the first and second electrode sets is a known quantitative value. Additionally, and preferably a separation distance in the x-y plane between the electrodes of the first set and second sets are known quantitative values. The configuration of the present electrode arrangement is which the electrodes are separated from one another by known quantitative values provides a method and apparatus for the assessment of a defined volume of tissue (positioned between the array of electrodes). Accordingly, the present apparatus and method provide a calibrated means of electrical impedance spectroscopy that provides a tool for the repeatable and reliable determination of tissue characteristics independent of the device that is used for measurement and in particular the operator.

Preferably, a separation distance between any two of the electrodes of the first set and/or the second set in the x-y plane is less than the separation distance between the first and second electrode sets in the z direction.

Preferably, the first and/or second electrode sets each comprise at least four electrodes. Optionally, the first and/or second electrode sets each comprise four electrodes or 5, 6, 7, 8, 9 or 10 electrodes.

Preferably, each of the electrodes of the first and second sets are positioned in the respective x-y plane at vertices of an imaginary rectangle or square.

Optionally, the apparatus comprises means to fix and maintain the first and second electrode sets at the separation distance in the z direction. Preferably, the first electrode set is provided at a first member and the second electrode set is provided at a second member, at least end regions of the first and second members being spaced apart by the separation distance in the z direction to define opposed prongs.

Optionally, the apparatus comprises at least one removable sheath disposed over at least the end regions of the first and second members.

Optionally, the electrodes of the first and second sets are formed as separate metal nodes provided at the end regions of the first and second members. Optionally, the electrodes of the first and second sets may be printed onto at least respective regions of the removable sheath disposed at the respective first and second members. Optionally the electrodes are nodes of gold. Optionally the electrodes/nodes are printed onto the sheath.

Optionally, the first and second members are generally positionally fixed relative to one another such that the separation distance in the z direction between the first and second electrode sets is a fixed quantitative value. Optionally, the first and second members are cantilever mounted in opposed relationship and are capable of flexing, bending or deforming slightly to be brought towards one another slightly to reach a predefined quantitative separation distance in the z direction. Preferably, the inward movement of the members is arrested/stopped by at least one flange to set the predefined quantitative separation distance in the z direction.

Optionally, at least a distal end portion of at least one of the first and/or second members is positionally adjustable (e.g., by sliding, moving, bending, or otherwise deforming) to provide variation of the separation distance in the z direction to provide a plurality of different quantitative values for the separation distance in the z direction as required to accommodate different respective volumes of tissue.

Preferably, the apparatus comprises electronic components to provide and/or support current flow between the electrodes of the first and second electrode sets, the apparatus further comprising a housing to contain the electronic components.

According to a second aspect of the present invention there is provided a method of measuring tissue transfer impedance within human or animal tissue, the method comprising: providing a first electrode set comprising at least two electrodes arranged generally in a first x - y plane, providing a second electrode set comprising at least two electrodes arranged generally in a second x - y plane, wherein the second electrode set is separated from the first electrode set by a separation distance in a z direction to define a gap region between the first and second electrode sets to accommodate at least a portion of

the human or animal body tissue; passing current through the tissue using a first electrical circuit including a first electrode of the first or second set as a current source and a second electrode of the first or second set as the current sink; measuring a signal corresponding to a voltage through the tissue using a second electrical circuit including a third and fourth
5 electrode of the first and/or second set different to the first or second electrodes, the signal resulting from the current passing through the tissue via the first electrical circuit.

Preferably, the method comprises analysing the current between the first and second electrodes and the signal to determine an electrical transfer impedance of the tissue.

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Preferably, the method comprises analysing the electrical transfer impedance of the tissue to determine a status of the tissue.

Preferably, the electrical signal is a voltage resultant from passing the current through the
15 tissue between electrodes of the first and/or second electrode sets. Optionally, each of the first and second electrode sets comprise at least four electrodes.

Optionally, the step of passing the current through the tissue and measuring the electrical signal comprises using at least a first and second electrode of the first electrode set as a
20 respective current source and a current sink and using a first and second electrode of the second electrode set as respective sensing electrodes.

Optionally, the step of passing the current through the tissue and measuring the electrical signal comprises: using a first electrode of the first electrode set as a current source and a
25 first electrode of the second electrode set as a current sink; and using a respective second electrode of the first and second electrode sets as respective sensing electrodes.

Optionally, the step of passing current through the tissue and measuring the electrical signal comprises: using a first electrode of the first electrode set as a current source; using
30 a second electrode of the first electrode set as a current sink; and using at least a third and a fourth electrode of the first electrode set as respective sensing electrodes.

Optionally, the step of passing current through the tissue and measuring the electrical signal comprises: using a first electrode of the second electrode set as a current source; using a second electrode of the second electrode set as a current sink; and using at least a third and a fourth electrode of the second electrode set as respective sensing electrodes.

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Preferably, the step of passing the current through the tissue comprises applying current at a plurality of different frequencies and the step of measuring the electrical signal comprises measuring a plurality of electrical signals resultant from the passing of the current through the tissue at the plurality of different frequencies.

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Preferably, the step of passing the current through the tissue and measuring the electrical signal comprises: using an electrode of the first electrode set as the current source and an electrode of the second electrode set as the current sink; and using electrodes of the first and second electrode sets to measure the signal.

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Preferably, the step of passing current through the tissue and measuring the electrical signal comprises: using an electrode of the first electrode set as a current source; using an electrode of the first electrode set as a current sink; and using electrodes of the first electrode set to measure the signal.

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Optionally, the plurality of frequencies comprises frequencies in a range 50 Hz to 10 MHz, 50 Hz to 2000 kHz, 50Hz to 1000 kHz or 50 Hz to 800 kHz.

According to further aspects of the present invention there is provided a method of

25 detection of bulbar disease in ALS or other relevant motor system disorders. According to further aspects of the present invention there is provided a system for detection of abnormalities in ALS and in particular the detection of abnormalities in tongue tissue.

According to further aspects of the present invention there is provided a method, apparatus

30 and system of multi-frequency and multi-directional EIS.

Brief description of drawings

A specific implementation of the present invention will now be described, by way of example only, and with reference to the accompanying drawings in which:

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Figure 1 is a perspective view of an EIS probe according to a specific implementation having a pair of members (tongs) that mount respectively first and second sets of electrodes to define a 3-dimensional electrode array according to a specific implementation of the present invention;

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Figure 2 is a side view of the EIS probe of figure 1;

Figure 3 is a perspective view of the terminal end of the probe of figure 1 according to a magnified view;

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Figure 4 is a perspective illustrative view of the 3-dimensional electrode array having a first electrode set provided at a first tong (omitted for illustrative purposes) and a second electrode set provided at a second tong with the sets being separated in a z direction by a quantitative separation distance according to a specific implementation of the present

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invention;

Figure 5 is a perspective view of an EIS probe according to a further specific implementation adapted for limb-based 3D tissue transfer impedance measurement;

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Figure 6 is a further perspective view of the device of figure 5;

Figure 7 is a further perspective view of the device of figure 5;

Figure 8 is a side elevation view of the device of figure 5 is a closed or compressed configuration;

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Figure 9 is a side elevation view of the device of figure 5 in an open or extended/enlarged configuration;

Figure 10A is a first half of an electrical circuit to provide a current source as part of the
5 apparatus and method according to a specific implementation of the present invention;

Figure 10B is a second half of an electrical circuit to provide a current source as part of the apparatus and method according to a specific implementation of the present invention;

10 Figure 11 is an electrical circuit used for current generation according to one aspect of the present invention;

Figure 12 is an analogue signal processing circuit for signal detection and measurement;

15 Figure 13 is a graph of median resistivity versus frequency based on the real component of complex impedance results obtained by EIS investigations of a set of patients with ALS and volunteers using the probe of figure 1;

Figure 14 is a graph of median phase angle versus frequency based on real and imaginary
20 components of complex impedance results obtained by EIS investigations of a set of patients with ALS and volunteers using the probe of figure 1;

Figure 15 is a graph of median reactance versus frequency based on imaginary components of complex impedance results obtained by EIS investigations of a set of patients with ALS
25 and volunteers using the probe of figure 1;

Figure 16 is a graph of median magnitude versus frequency based on real and imaginary components of complex impedance results obtained by EIS investigations of a set of patients and volunteers using the probe of figure 1.

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Detailed description of preferred embodiment of the invention

Referring to figures 1 to 4, a handheld EIS probe 100 comprises a housing 101 from which extend, in a cantilever mounted arrangement, a pair of opposed members (or tongs) 102 that form a dual prong arrangement. In particular, a first elongate member 102a extends parallel and opposed to a second elongate member 102b. A distal end region 106a, 106b at each respective member 102a, 102b carries respective electrode mount discs 103, 104. The discs 103, 104 are positioned so as to be spaced apart in a z direction and are mounted on respective inward facing surfaces 102c of each member 102a, 102b. Each electrode disc 103, 104 comprises a generally circular planar face 103a, 104a with the planar faces 103a, 104a being aligned parallel with one another and separated by a quantitative separation distance D. Accordingly, a gap region 108 is defined between the opposed faces 103a, 104a which represents a distal end region of a general mouth or cavity 107 defined between the opposed members 102a, 102b.

A pair of flanges 105 project inwardly into and across the mouth 107 from each respective member 102a, 102b so as to overlap one another in the z direction. Each flange 105 does not extend the full separation distance between the respective surfaces 102c and carries at each respective end region, an electrical spring contact (not shown) that when contacted forms a circuit connection. Each cantilever mounted member 102a, 102b is configured with a degree of '*flex*' in the z direction so as to provide a degree of opening and closing of the mouth 107. Such an arrangement is beneficial to allow some '*play*' or adjustment of the quantitative separation distance D as the probe is manipulated to accommodate a predetermined/desired volume of body tissue into the mouth 107 and in particular into the region 108 between the opposed electrode discs 103, 104. Once the tissue is appropriately accommodated within the mouth 107 (and region 108) a user may then apply pressure onto external facing surfaces of each member 102a, 102b. The flanges 105 are then capable of abutting against the respective inward facing surface 102c so as to provide the desired and predefined quantitative separation distance D between the disc surfaces 103a, 104a.

As illustrated in figures 3 and 4, a first set of electrodes 111 are provided at first electrode disc 103 and a second set of electrodes 110 are provided at second electrode disc 104.

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Each electrode set 111, 110 comprises four respective electrodes positioned at the vertices of an imaginary square such that all the electrodes of each respective set are separated from one another by an equal separation distance in an x and y directions (within the z - y plane). According to the specific implementation, each of the electrodes comprises a small metal node coupled to support electronics (not shown) accommodated within housing 101. Such electronic components comprise known configurations as will be appreciated by those skilled in the art for delivering electrical signals such as current and measuring corresponding electrical signals (such as voltage) resulting from the electrical signals delivered. In particular, housing 101 may include one or a plurality of circuits including an amplifier for impedance measurement, a computer, processor or chip to perform calculations, data storage utilities, a battery, wired or wireless communication means, communication ports and the like as will be understood.

According to the specific implementation, the first electrode set 111 comprises four electrodes including a first electrode 111a, a second electrode 111b, a third electrode 111c and a fourth electrode 111d. Similarly, the second electrode set 110 comprises four electrodes including a first electrode 110a, a second electrode 110b, a third electrode 110c and a fourth electrode 110d. Each corresponding pair of opposed electrodes (e.g. 111a, 110a) is separated from one another by the same quantitative separation distance D in the z direction. Neighbouring electrodes in each respective set 111, 110 are separated from one another in the x direction by a separation distance E and in the y direction by a separation distance F . According to the specific implementation, separation distance E and F are equal and separation distance D is greater than each of the separation distances E and F .

The electronics are coupled to the respective electrode sets 111, 110 and in particular each electrode within each set 111, 110 such that current may be delivered to any one of the eight electrodes, current may be received at any one of the eight electrodes whilst an electrical signal or parameter may be sensed by any of the alternate electrodes within the first or second electrode sets 111, 110. That is, in normal use, selective electrodes of the 3-dimensional array include at least one electrode operating to deliver current (referred to herein as a '*current source*'), at least one electrode being configured to receive current (referred to herein as a '*current sink*') and at least two electrodes operating as sensing

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electrodes (referred to herein as '*potential sense*'). According to the specific implementation, the electrical signal that is sensed, as the current is transmitted through the body tissue (within region 108), is voltage. However, the present apparatus and method is not restricted to voltage sensing and/or voltage output with the present apparatus and method capable of outputting any one or a plurality of electrical parameters useful in the identification and assessment of body tissue including in particular pathological disruptions or tissue abnormalities within otherwise healthy tissue.

Table 1 below details various electrode configurations considered by the inventors as

beneficial for an EIS system to detect abnormalities in motor neurone disease (MND) and in particular for the detection of tongue abnormalities in ALS. In principal there are 70 possible combinations of electrodes that may be used; however, it is possible using circuit theory [Geselowitz DB. Introduction to "Some Laws Concerning the Distribution of Electric Currents in Volume Conductors with Applications to Experiments on Animal Electricity". Proceedings of the IEEE. 2004;92(5):864-7] to derive some sets from arithmetic combinations of other sets and only 20 are truly independent of each other.

Table 2 details an example of additional electrode configurations that if used, would allow the derivation of any of the possible 70 sets. Most of these arrangements have not been used as yet and optimisation of the exact measurement sets used is almost certainly

possible. Referring to figure 4 and table 1 below, the *z* direction may be labelled the *superior direction*, the *x* direction the *anterior direction* and the *y* direction the *lateral direction*. Table 1 identifies the current source, sink and sensing electrodes according to various different positional configurations for variation of the current pathways through the body tissue in which all electrodes of the 3-dimensional array are separated from one another by the respective quantitative separation distances D, E, F in the respective superior, anterior and lateral directions.

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Measurement set	Name	Current source	Current sink	Potential sense +	Potential sense -
Left posterior anterior	LEFT_POST_ANT	111a	111b	110a	110b
Left inferior superior	LEFT_INF-SUP	111b	110b	111a	110a
Right posterior anterior	RIGHT_POST-ANT	111d	111c	110d	110c
Right inferior superior	RIGHT_INF_SUP	111c	110c	111d	110d
Top posterior anterior	TOP_POST_ANT	111d	111c	111a	111b
Top medial lateral	TOP_MED_LAT	111b	111c	111a	111d
Bottom posterior anterior	BOT_POST_ANT	110d	110c	110a	110b
Bottom medial lateral	BOT_MED_LAT	110b	110c	110a	110d
Inferior anterior inferior anterior	INFANT_INFANT	111a	110b	111d	110c
Inferior anterior medial lateral	INFANT_MEDLAT	111a	111d	110b	110c
Superior anterior superior anterior	SUPANT_SUPANT	111b	110a	111c	110d
Superior anterior medial lateral	SUPANT_MEDLAT	110a	110d	111b	111c

Table 1. Electrode configurations suitable for EIS investigations using a tongue probe 100 according to figures 1 to 4.

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Additional measurement	Current source	Current sink	Potential sense +	Potential sense -
1	111c	110c	111b	110b
2	111d	110c	111c	110b
3	111d	110d	111a	110a
4	111c	110c	111a	110d
5	111c	110c	111a	110a
6	111c	110c	111b	110a
7	111d	110c	111a	110a
8	111a	110a	111c	110b
9	111b	110a	111c	110b

Table 2. Additional electrode configurations that could be used in EIS investigations using a tongue probe 100.

As will be noted, the twelve electrode configurations of table 1 include both 2-dimensional and 3-dimensional configurations, the latter being configurations not contained only within either the upper or lower electrode sets. Via the electronics within housing 101 all

5 electrodes within each of the first and second electrode sets 111, 110 may be activated differentially via a cross-point switch (not shown).

A further embodiment of the ESI probe 120 is illustrated in figures 5 to 9 with probe 120 specifically adapted for positioning adjacent a limb such as an arm of an individual so as to
10 provide a limb-based 3D impedance system. Device 120 comprises main body 122 having a display screen 124. Body 122 is divided into a first part 122a and a second part 122b as illustrated in figures 7 to 9. Each part 122a, 122b is mounted on a bridge member 126 such that the parts 122a, 122b may be opened and closed relative to one another for positioning around different size limb parts. In particular, part 122a is capable of sliding along bridge
15 member 126 so as to increase and decrease the separation distance of the 'jaw' defined by parts 122a, 122b. A locking and release actuator 123 (in the form of a rotatable screw is provided at first part 122a to positionally lock part 122a relative to part 122b (via bridge member 126). A strap 121 having an appropriate adjustment buckle extends between parts 122a, 122b for securing around limb 125.

20 Each part 122a, 122b comprises a corresponding electrode mount disc 103, 104 with each disc 103, 104 carrying a plurality of electrodes mounted on the opposed substantially circular planar faces 103a, 104a as described referring to the embodiment of figures 1 to 4. The construction, function, control and operation of the array of electrodes 110, 111 of the
25 embodiment of figures 5 to 9 may be as described for the embodiment of figures 1 to 4.

Adjustment screw 123 may be configured with a quantised adjustment configuration so as to set the predetermined separation distance between the respective and opposed discs 103, 104. Alternatively or in addition, the separation distance between the respective electrodes
30 at the discs 103, 104 in a z direction may be determined and/or identified via other electrical components such as distance sensing components as will be available in the art and as described referring to the embodiments of figures 1 to 4. However, the construction

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of the discs 103, 104 according to the further embodiment and hence the array of electrodes 110, 111 may differ from that of the embodiment of figures 5 to 9. In particular, the embodiment of figures 5 to 9 may comprise additional electrodes being configured for measurement of a larger volume of tissue between the first and second
5 electrode sets.

The device of figures 5 to 9 provides an adjustable probe having an adjustable separation distance in a z direction between electrodes (at the discs 103, 104). Display 124 may be configured to display an output signal indicative of the status of the tissue and/or to
10 indicate a readiness for measurement and progress through the measurements.

Electronic configuration

The present apparatus and method according to either embodiment of figures 1 to 4 and 5
15 to 9 provides a system to measure the tissue transfer impedance by injecting current through two electrodes within a first circuit whilst detecting the potential in the tissue via two different electrodes of a second circuit with the 'potential difference' electrodes acting as sensing electrodes and being different to the electrodes that provide the primary current flow. Preferably, the present system utilises alternating current applied over the frequency
20 range 67 Hz to 625 kHz in octave steps.

The present system may use two Howland current sources configured to provide a differential current source. The potential may be detected using a standard 3 op amp instrumental amplifier. Compensation for errors caused by band width limitation may be
25 corrected by storing locally, a calibration curve. Figures 10A and 10B are first and second parts of a current source circuit suitable for implementation within the present invention. U3 and U2 are DDS based devices and are programmed to generate a sine wave and a square wave respectively. The Sine wave is converted to a complementary sine wave by U1 to enable the two current sources, source and sink current. U3 and U2 are configured
30 to produce perfectly phase matched waveforms which are either in phase or shifted by 90°.

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Figure 11 is a circuit used for generation of current according to one aspect of the present invention. As illustrated in figure 11, complementary sine waves are fed to J12 and J13 and the amplifiers U701 and U704 are configured as Howland current sources. The current is fed to any pair of electrodes from the eight possible that are connected to J16 to J23 via the cross point switch U706. The electrodes used to sense potential is also selected by U706 and this signal is fed to the instrumentation amplifier made of the two halves of U705. The memory device U708 is used to hold calibration data for the front end circuit.

The signal detected via the third and fourth electrodes within the second electrical circuit may be measured using the analogue signal processing circuit detailed in figure 12. The circuit of figure 12 is based on the analogue switches U6B and U6C that are controlled by the DDS U2. U400 generates two outputs that are phase shifted by 180° and either one is selected by switches U6b and U6c. The switch control signal is in an exact phase relationship to the signal and hence only the in phase component is fed to the integration circuit of U10, C6, R6 and R405. After a defined integration period the output of the detector may be read into the controlling microcontroller through the analogue to digital converter U8. The integrator may be reset by closing the switch U6D, ready for the next measurement. By writing to the control registers of U2 it is possible to set the phase relationship between the sine signal and the demodulation square wave signal. The integration process may be repeated two times, firstly with the demodulation phase set to 0° and secondly at 90° phase shift. The measurements may be taken with the phase shift set to 0° corresponds to the real component of tissue impedance (its resistance) and when set to 90° to the imaginary component (its reactance). The process may be repeated for all the required frequencies to measure the full spectrum. Each spectrum may be measured for a minimum of eight times by the microcontroller in order that statistics may be determined for each measured spectrum.

An electrode interface may be used to connect the electrodes to the electronic system and include features such as constant force actuators to control the amount of force applied by the electrodes to the tissue. Further components may comprise multiplexes, cross-point switches, relays or other types of switching mechanisms configured to switch the connection between different electrodes and different components in the electronic systems

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as described including for example signal source channels, voltage sense channels and current sense channels. Each of the channels may be connected to suitable signal processors including or example a digital signal processor (DSP) that may be implemented with an FGGA for digital signal processing. Optionally, the DSP may interface with a computing device such as a PC, Notebook, Personal Digital Assistant, Smart Phone or other electronic device for algorithm execution. The connection between such peripheral devices may be implemented using wired or wireless connection such as WiFi, Bluetooth, Radio Frequency Connection.

10 Example 1

According to a specific implementation, each electrode within each of the first and second electrode sets 111, 110 is formed as a gold node at each surface 103a, 104a. Separation distance E and F may be 5 mm and separation distance D may be 7 mm when members 102a, 102b are compressed together (and flanges 105 abut surfaces 102c). According to the specific implementation, once members 102a, 102b are depressed, the spring contacts (not shown) provided at the respective end regions of flanges 105 and the adjacent region of surfaces 102c, make contact with one another to complete the electrical circuit and allow current to be delivered to a designated current source electrode.

20 Patient recruitment

In order to evaluate the present method and apparatus a test study was undertaken to identify the electrical signal differences between patients (with known ALS) and volunteers (with assumed healthy tissue). Bioimpedance was measured using the 3-dimensional electrode array of figure 4 including in particular consideration of the fixed electrode separation distances D, E and F. Such quantitative electrode separation distances provide identification and inclusion within the EIS system calculations of a quantitative fixed volume of tissue (present within region 108). This is beneficial to increase the sensitivity and specificity of the present apparatus and method which in turn means that the present system is less susceptible to arbitrary geometric variations between different

measurement sessions and/or between different subjects. A more sensitive and reliable system is therefore provided.

Multi-frequency and multi-directional EIS spectra were recorded for 22 patients with ALS and 19 healthy volunteers. An inclusion criteria was applied to the 22 patients involving diagnosis of ALS according to the Awaji-Shima criteria [de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008;119(3):497-503]. Evidence of lower motor neuron (LMN) involvement of the tongue by either clinical detection of bulbar symptoms by either an experienced clinician, or through EMG examination (using the Awaji-Shima criteria) was required.

Calibration and Measurements

Current with an intensity of 5 μ V was injected across 14 frequencies; starting at 76 Hz and then doubling at each step increase to a maximum of 625,000 Hz. Data were downloaded from the probe 100 to a standard laptop via Bluetooth. The probe was calibrated in a number of ways. Firstly, corrections were made to compensate for phase and gain errors introduced by various time constants. Spectra were measured across a precision 1 k Ω resistor. This curve was stored in the probe and all measurements calibrated against this. Secondly, the cell constant of the device was measured by placing the device in saline solutions ranging from 10 Ω m to 1 Ω m. The solutions were also measured using a Jenway 470 conductivity meter. The cell constant was also stored within the probe so that all recordings made by the probe 100 were reported in units of Ω m. Before and after use the probe was cleaned using the Tristel Wipes system.

Recording Procedure

Recordings were undertaken with the patient either sitting or lying in an upright position with the tongue resting in a neutral position in the mouth. Recordings were taken with the probe placed in the midline of the tongue. Data were also collected with placement on the left and right halves of the tongue (not shown). In patients able to protrude the tongue, these positions were repeated with the tongue protruded beyond the teeth. These latter

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recordings were to ascertain if there was any difference in the spectra between the intra- and extra-oral recording positions.

The output values for both the real and imaginary components at each discrete frequency and in each electrode configuration represent an average of eight measurements. The present apparatus was programmed to calculate the standard deviation of this average and to reject the value if it exceeded a pre-defined cut-off of 10% of the mean. The pseudocode for the measurement process is as follows:

```

10  While (not timedout)
    {
        Take measurement
        Store measurement
        If (n>=8){
15          Calculated measurement magnitude
          Calculate mean of measurement magnitudes
          Calculate stddev of measurement magnitudes
          If(stddev/mean<threshold){ //threshold = 0.1
              Finish(success)
20          }
          Remove oldest set
        }
    }
    Finish(Timeout)
25

```

At completion of the recording the real and imaginary components for each electrode configuration were visually inspected on custom written software. If data were rejected (as described above) then no spectra would be plotted for that electrode configuration. In some instances data with negative real part values or values of extremely high and constant resistance were obtained which passed the dispersion criteria; these likely reflect poor electrode contact. These were removed during data analysis as were other spurious data. If no usable data were evident during visual inspection, for example, due to patient

movement during recording, then the recording was re-attempted (providing the patient was happy to proceed).

Data acquisition and statistical analyses

5

Real and imaginary components of complex impedance were downloaded from the probe using Bluetooth to custom written software, saved (as XML files) and exported for further analysis. Real part (or resistivity, R , measured in ohms), imaginary part (or reactance, X , measured in ohms) were exported and phase angle ($\text{PhA} = \arctan2(X/R)$), and magnitude

10

($Z = \sqrt{R^2 + X^2}$) were calculated by additional custom software used to export the impedance parameters for further statistics and graphing of data in IBM SPSS statistics. Median and 95% confidence intervals were plotted.

Results

15

Median values for real and imaginary components, phase angle and magnitude are shown in figures 13 to 16 for the direction SUPANT_SUPANT detailed in table 1.

20

In particular, figure 13 is a graph of median resistivity versus frequency based on the real component of complex impedance results obtained by EIS investigations of a set of patients and volunteers using the probe of figure 1; Figure 14 is a graph of median phase angle versus frequency based on real and imaginary components of complex impedance results obtained by EIS investigations of a set of patients and volunteers using the probe of figure 1; Figure 15 is a graph of median reactance versus frequency based on the imaginary component of complex impedance results obtained by EIS investigations of a set of patients and volunteers using the probe of figure 1; and Figure 16 is a graph of median magnitude versus frequency based on real and imaginary components of complex impedance results obtained by EIS investigations of a set of patients and volunteers using the probe of figure 1.

25

These data represent the muscle bioimpedance recordings in which current has been provided and voltage sensed through a known quantitative volume of tissue in contrast to

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voltage sensed along the surface of muscle. The subtle differences in the data reveal underlying changes in muscle. The data can be combined with results from other electrode configurations (not shown) to further study changes in the tongue muscle of patients with ALS.

Claims

1. Apparatus configured to provide measurement of tissue transfer impedance within human or animal body tissue, the apparatus comprising:
 - 5 a first electrode set comprising at least two electrodes arranged generally in a first x - y plane;
 - a second electrode set comprising at least two electrodes arranged generally in a second x - y plane;
 - wherein the second electrode set is separated from the first electrode set by a
10 separation distance in a z direction to define a gap region between the first and second electrode sets to accommodate at least a portion of the human or animal body tissue;
 - a first electrical circuit including a first electrode of the first or second set as a current source and a second electrode of the first or second set as a current sink to enable the passing of current through the tissue;
 - 15 a second electrical circuit including a third and a fourth electrode of the first and/or second set different to the first and second electrodes to measure a signal corresponding to a voltage through the tissue between the third and fourth electrodes sensitive to the current flow through the tissue between the first and second electrodes.
- 20 2. The apparatus as claimed in claim 1 further comprising additional means to measure the electrical signal corresponding to the voltage between the third and fourth electrodes.
3. The apparatus as claimed in claims 1 or 2 wherein the separation distance in the z
25 direction between the first and second electrode sets is a known quantitative value.
4. The apparatus as claimed in claim 3 wherein a separation distance in the x - y plane between the electrodes of the first set and second sets are known quantitative values.
- 30 5. The apparatus as claimed in any preceding claim wherein a separation distance between any two of the electrodes of the first set and/or the second set in the x - y plane is

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less than the separation distance between the first and second electrode sets in the z-direction.

6. The apparatus as claimed in any preceding claim wherein the first and/or second
5 electrode sets each comprise at least four electrodes.

7. The apparatus as claimed in claim 6 wherein each of the electrodes of the first and second sets are positioned in the respective x-y plane at vertices of an imaginary rectangle or square.

10

8. The apparatus as claimed in any preceding claim further comprising means to fix and maintain the first and second electrode sets at a separation distance in the z direction.

9. The apparatus as claimed in any preceding claim wherein the first electrode set is
15 provided at a first member and the second electrode set is provided at a second member, at least end regions of the first and second members being spaced apart by the separation distance in the z direction to define opposed prongs.

10. The apparatus as claimed in claim 9 further comprising at least one removable
20 sheath disposed over at least the end regions of the first and second members.

11. The apparatus as claimed in claim 9 wherein the electrodes of the first and second sets are formed as separate metal nodes provided at the end regions of the first and second members.

25

12. The apparatus as claimed in claim 10 wherein the electrodes of the first and second sets are printed onto at least respective regions of the removable sheath disposed at the respective first and second members.

13. The apparatus as claimed in claims 9 or 10 wherein the first and second members are positionally fixed relative to one another such that the separation distance in the z direction between the first and second electrode sets is a fixed quantitative value.

30

14. The apparatus as claimed in claims 9 or 10 wherein at least one of the first and/or second member is positionally adjustable to provide variation of the separation distance in the z direction to provide a plurality of quantitative values of the separation distance in the
5 z direction.

15. The apparatus as claimed in any preceding claim further comprising electronic components to provide and/or support current flow between the electrodes of the first and second electrode sets, the apparatus further comprising a housing to contain the electronic
10 components.

16. A method of measuring tissue transfer impedance within human or animal tissue, the method comprising:

providing a first electrode set comprising at least two electrodes arranged
15 generally in a first *x-y* plane, providing a second electrode set comprising at least two electrodes arranged generally in a second *x-y* plane, wherein the second electrode set is separated from the first electrode set by a separation distance in a *z* direction to define a gap region between the first and second electrode sets to accommodate at least a portion of the human or animal body tissue;

20 passing current through the tissue using a first electrical circuit including a first electrode of the first or second set as a current source and a second electrode of the first or second set as the current sink;

measuring a signal corresponding to a voltage through the tissue using a second electrical circuit including a third and fourth electrode of the first and/or second set
25 different to the first or second electrodes, the signal resulting from the current passing through the tissue via the first electrical circuit.

17. The method as claimed in claim 16 further comprising analysing the current between the first and second electrodes and the signal to determine an electrical transfer
30 impedance of the tissue.

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18. The method as claimed in claim 17 further comprising analysing the electrical transfer impedance of the tissue to determine a status of the tissue.

19. The method as claimed in any one of claims 16 to 18 wherein each of the first and
5 second electrode sets comprise at least four electrodes.

20. The method as claimed in any one of claims 16 to 19 wherein the step of passing the current through the tissue and measuring the electrical signal comprises:

using an electrode of the first electrode set as the current source and an electrode
10 of the second electrode set as the current sink; and
using electrodes of the first and second electrode sets to measure the signal.

21. The method as claimed in any one of claims 16 to 19 wherein the step of passing current through the tissue and measuring the electrical signal comprises:

15 using an electrode of the first electrode set as a current source;
using an electrode of the first electrode set as a current sink; and
using electrodes of the first electrode set to measure the signal.

22. The method as claimed in any one of claims 20 to 21 wherein the step of passing
20 the current through the tissue comprises applying current at a plurality of different frequencies and the step of measuring the electrical signal comprises measuring a plurality of electrical signals resultant from the passing of the current through the tissue at the plurality of different frequencies.

25 23. The method as claimed in claim 22 wherein the plurality of frequencies comprises frequencies in a range 50 Hz to 10 MHz.

24. The method as claimed in claim 22 wherein the plurality frequencies comprise frequencies in the range 50 Hz to 2000 kHz, 50 Hz to 1000 kHz or 50 Hz to 800 kHz.

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25. The method as claimed in anyone of claims 16 to 24 wherein the separation distance in the z direction between the first and second electrode sets is a known quantitative value.

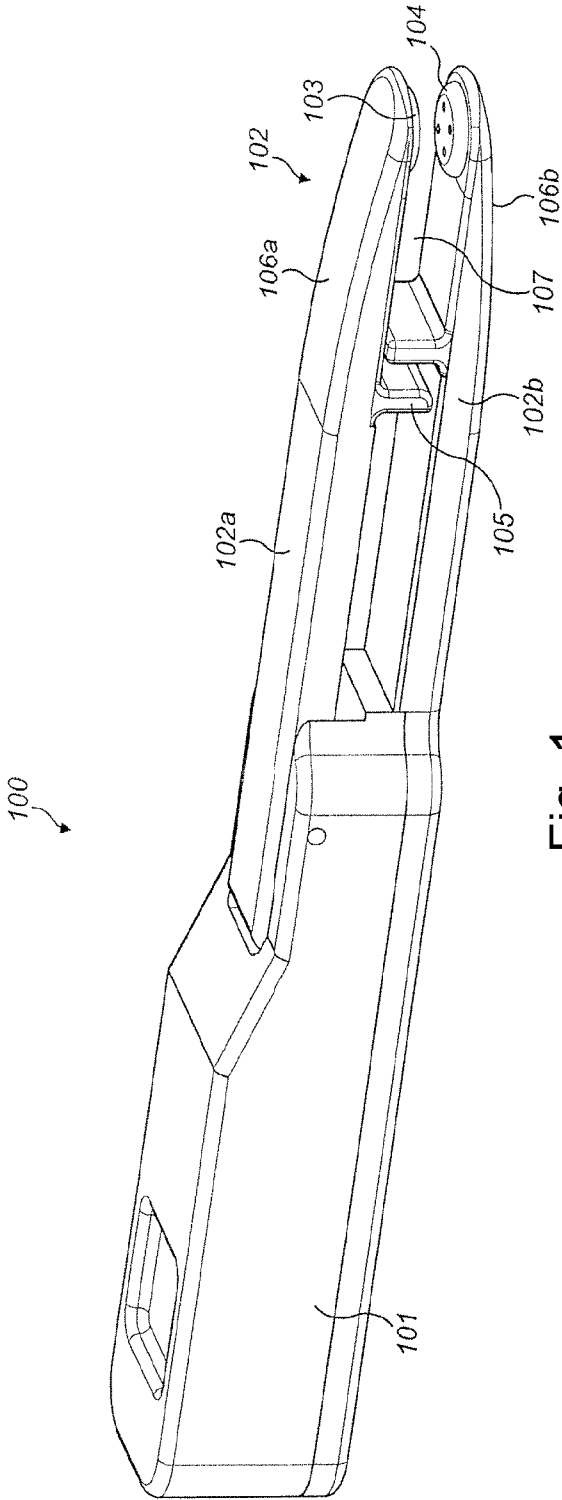


Fig. 1

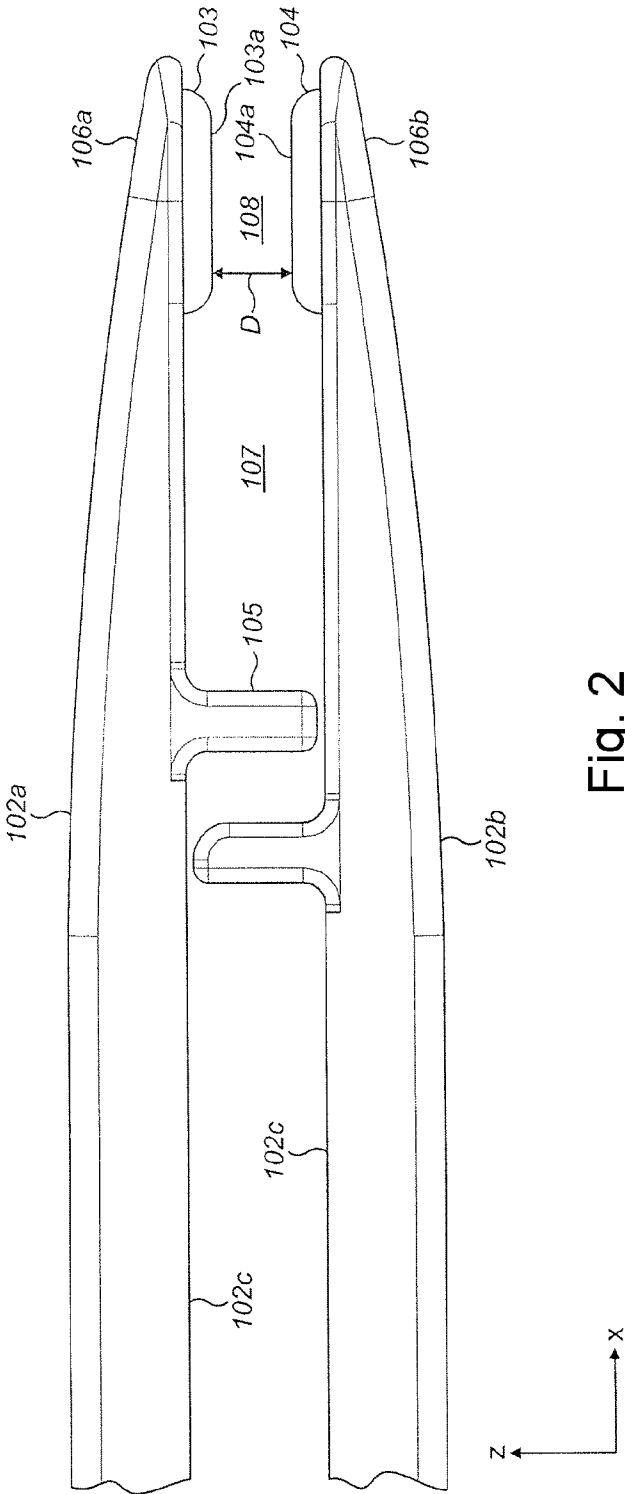


Fig. 2

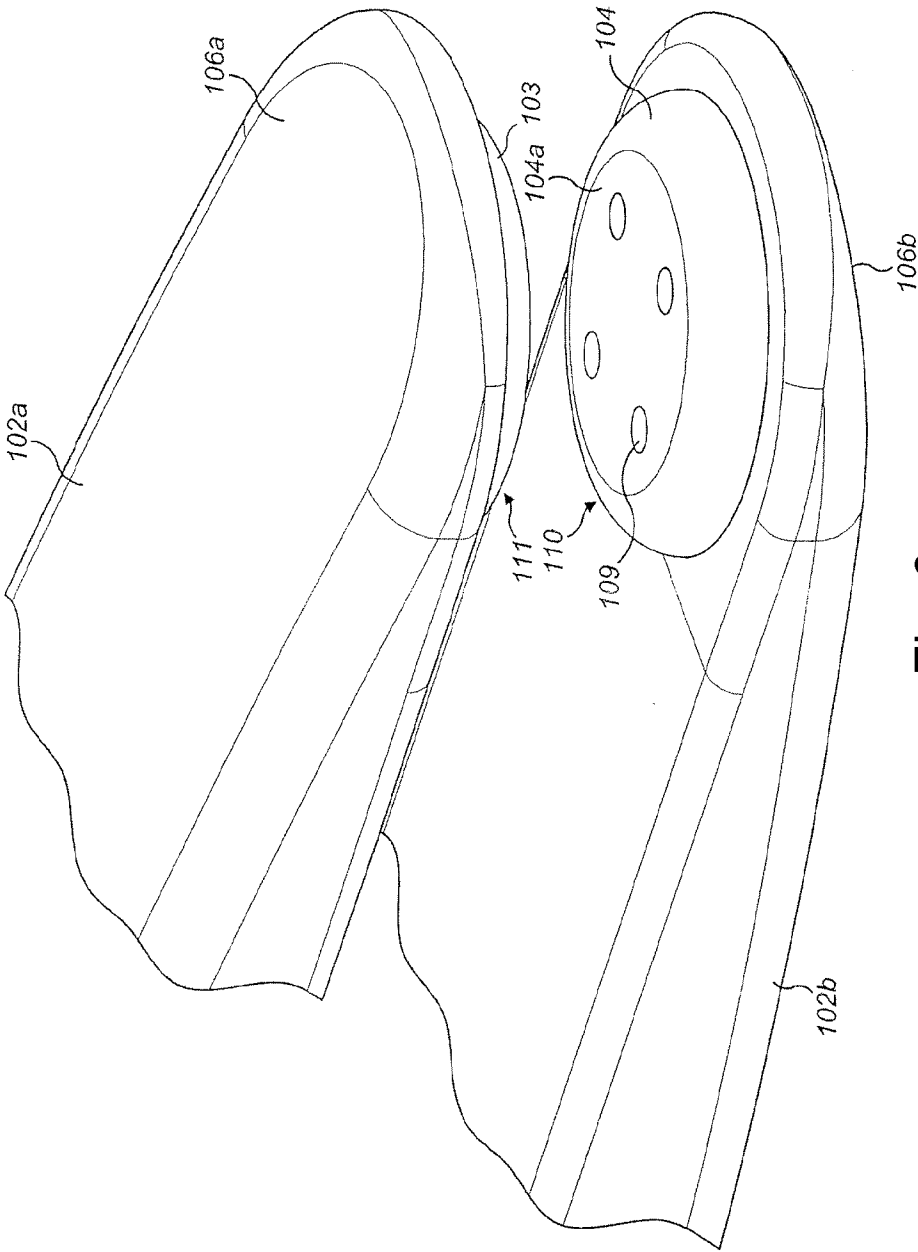


Fig. 3

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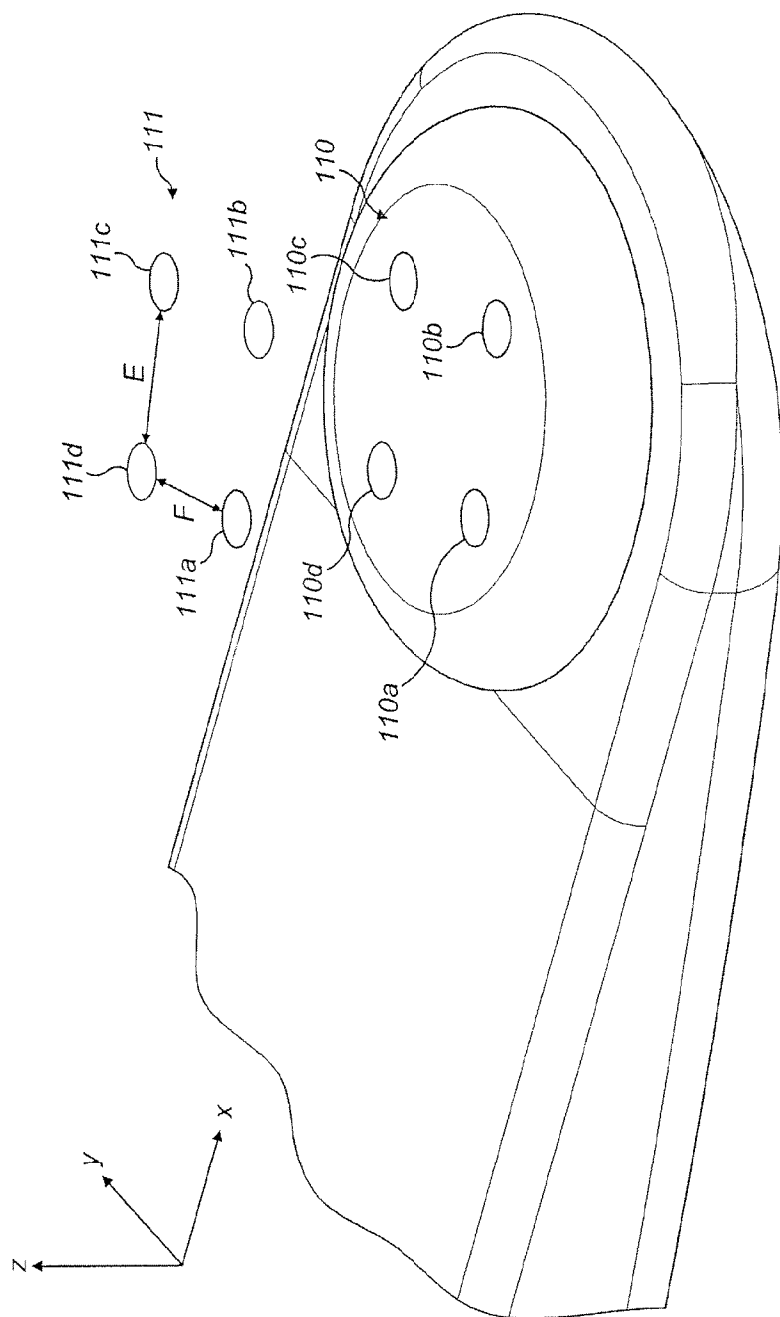


Fig. 4

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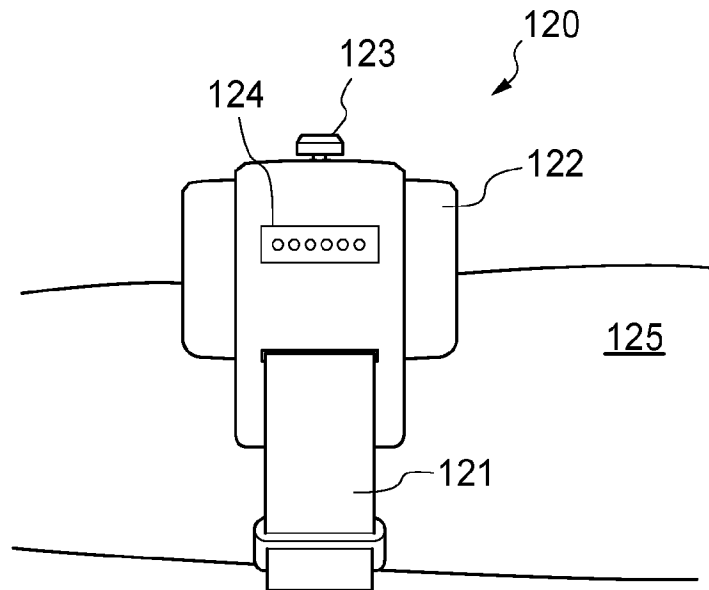


Fig. 5

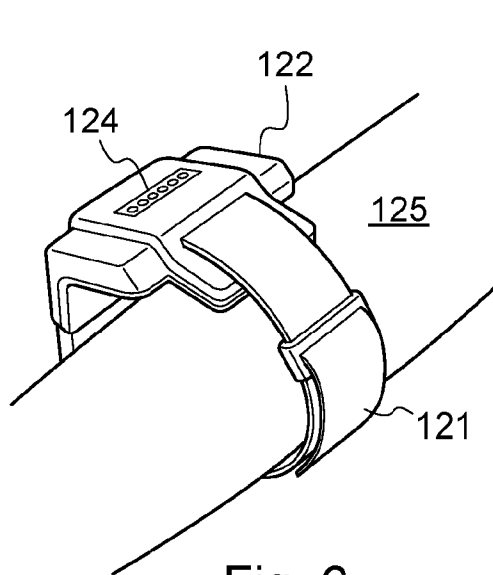


Fig. 6

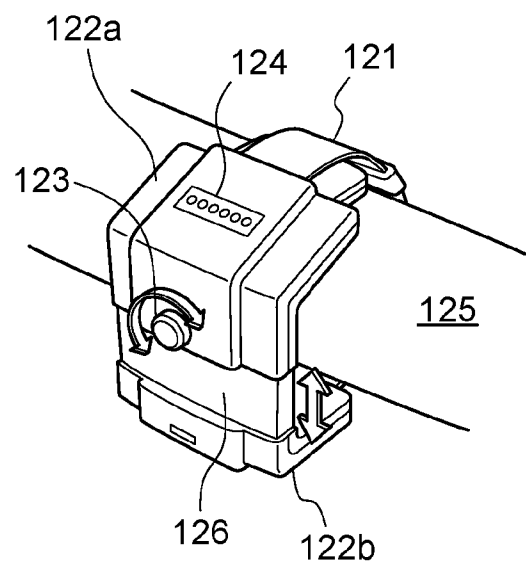


Fig. 7

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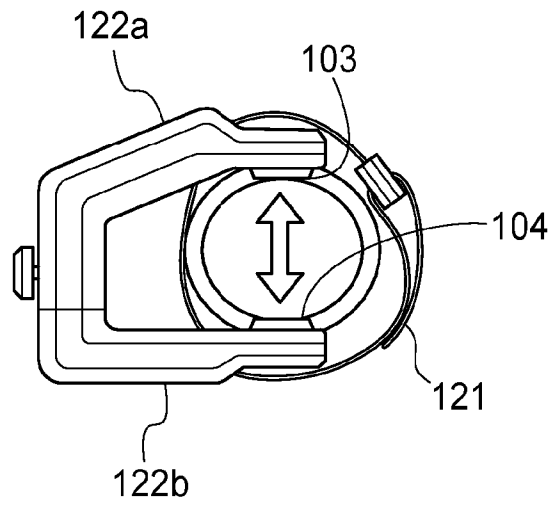


Fig. 8

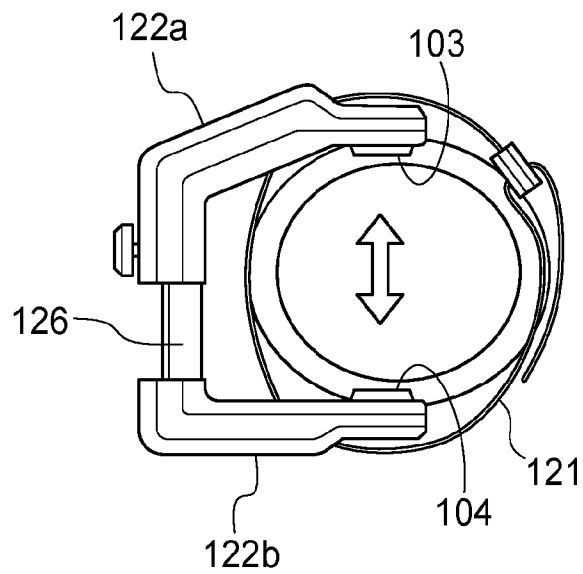


Fig. 9

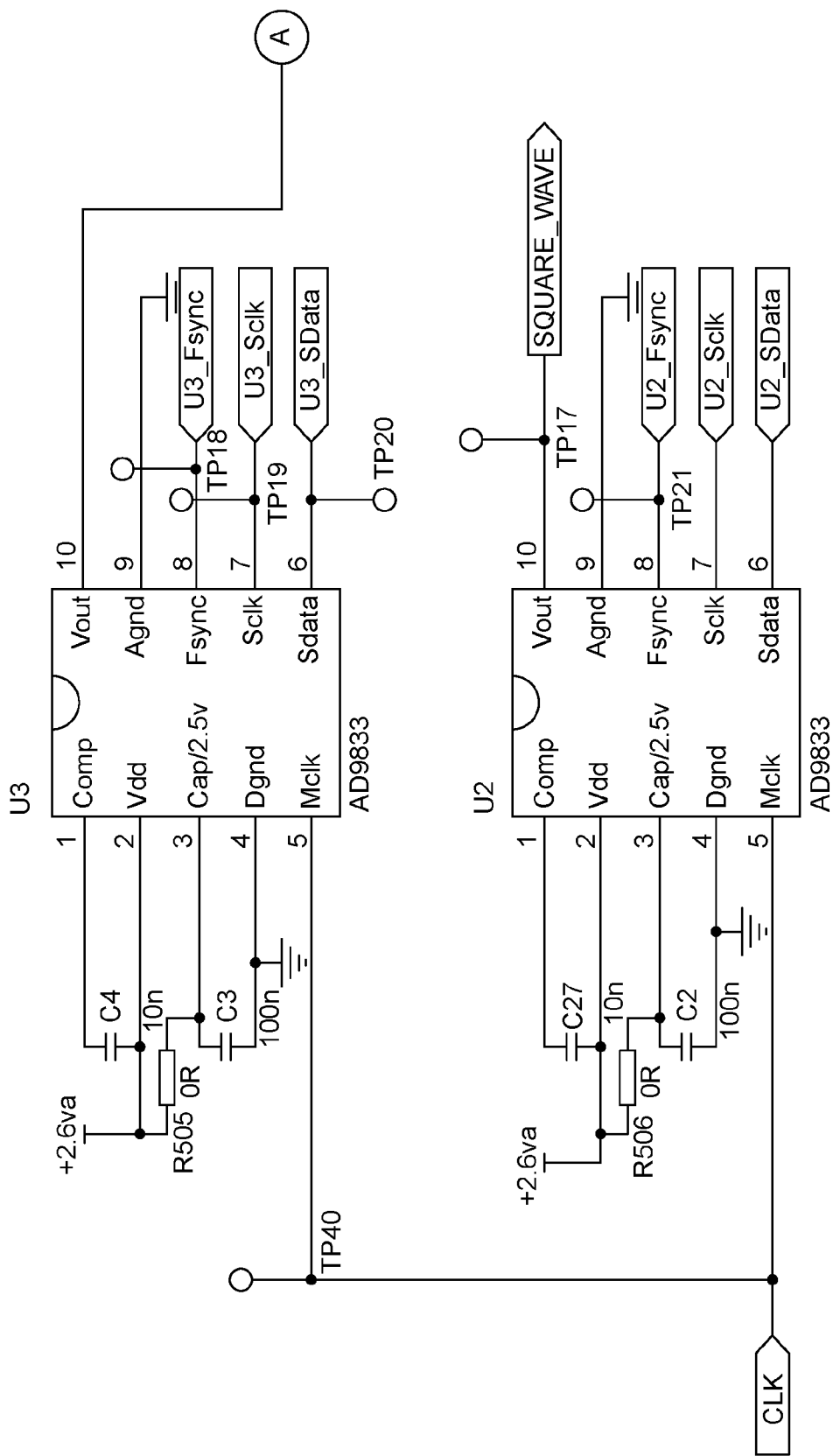


Fig. 10A

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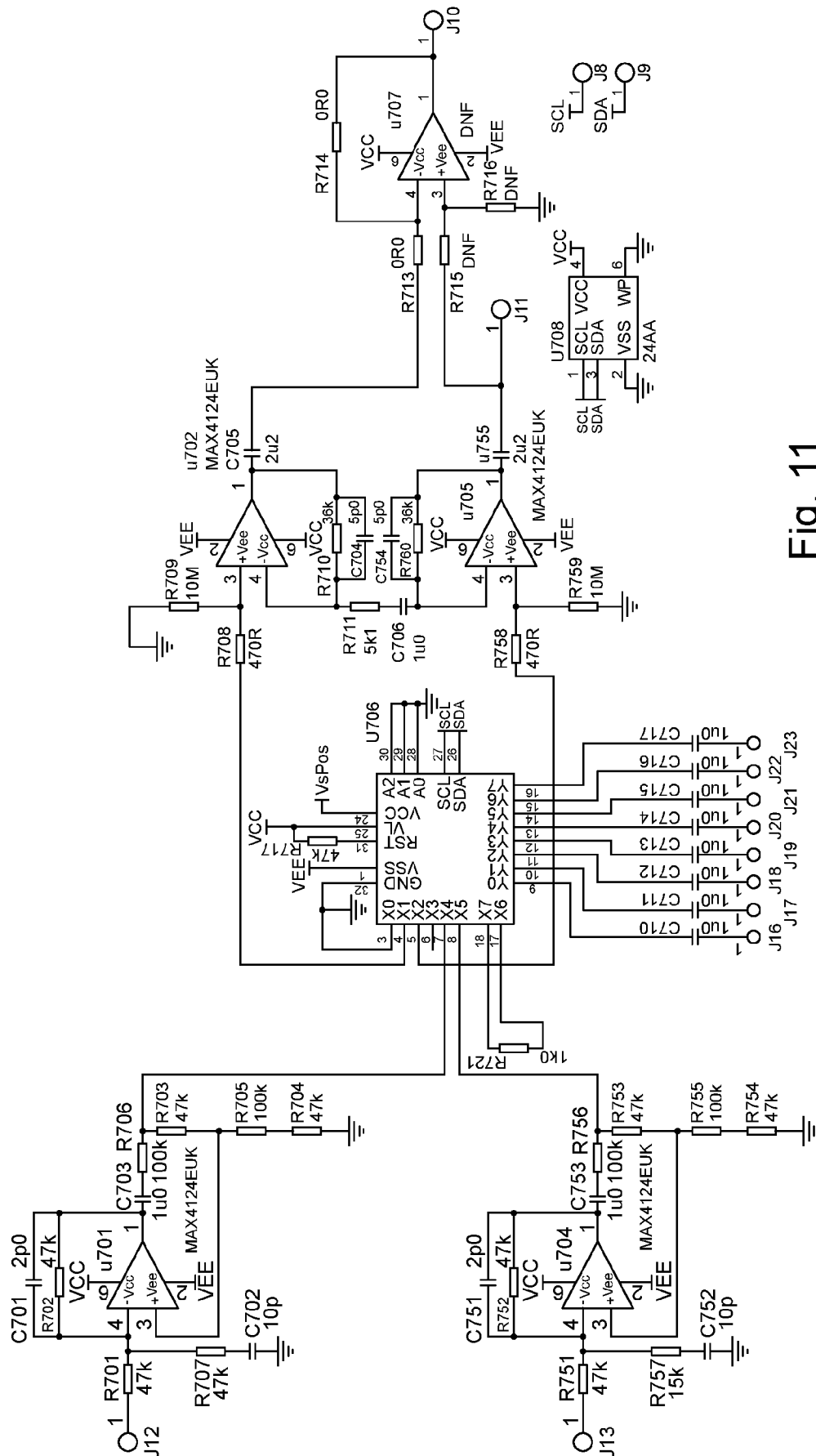


Fig. 11

11/14

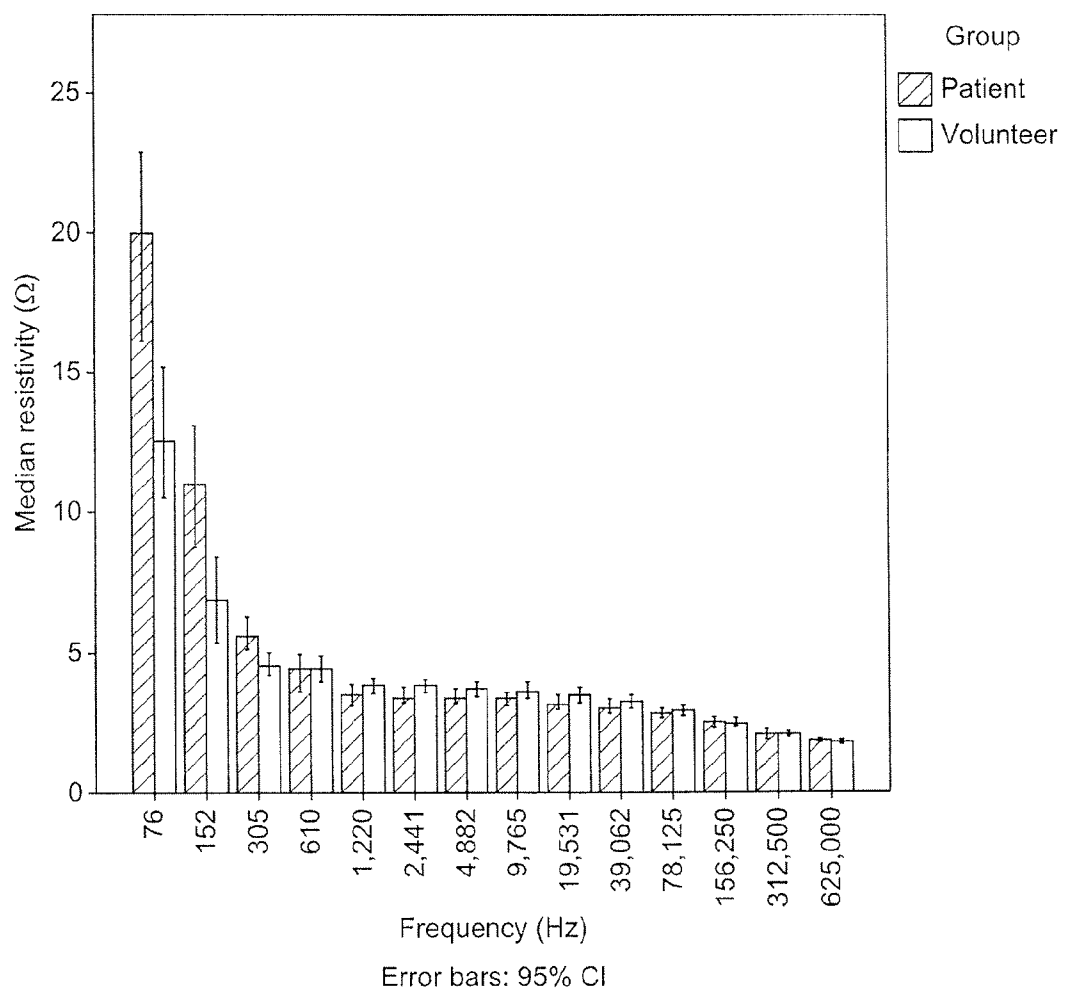


Fig. 13

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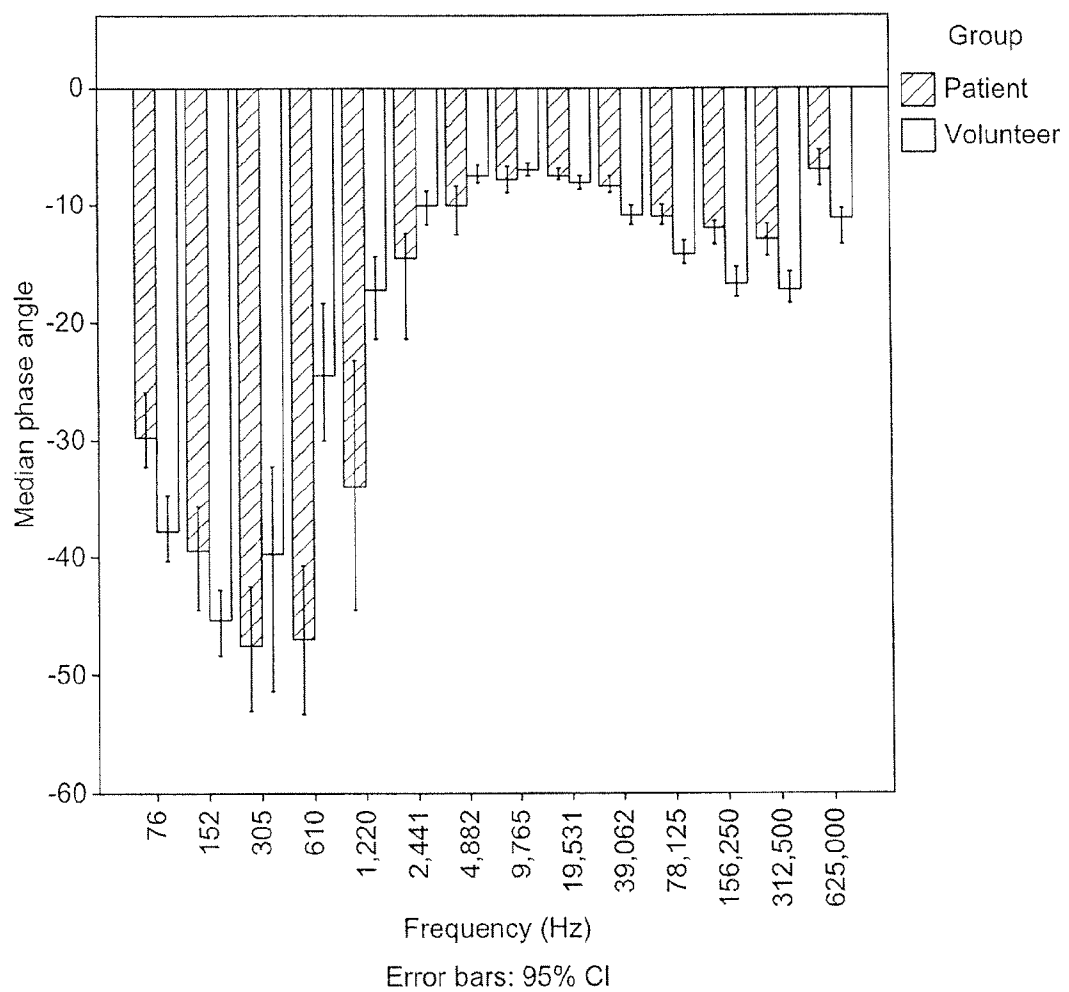


Fig. 14

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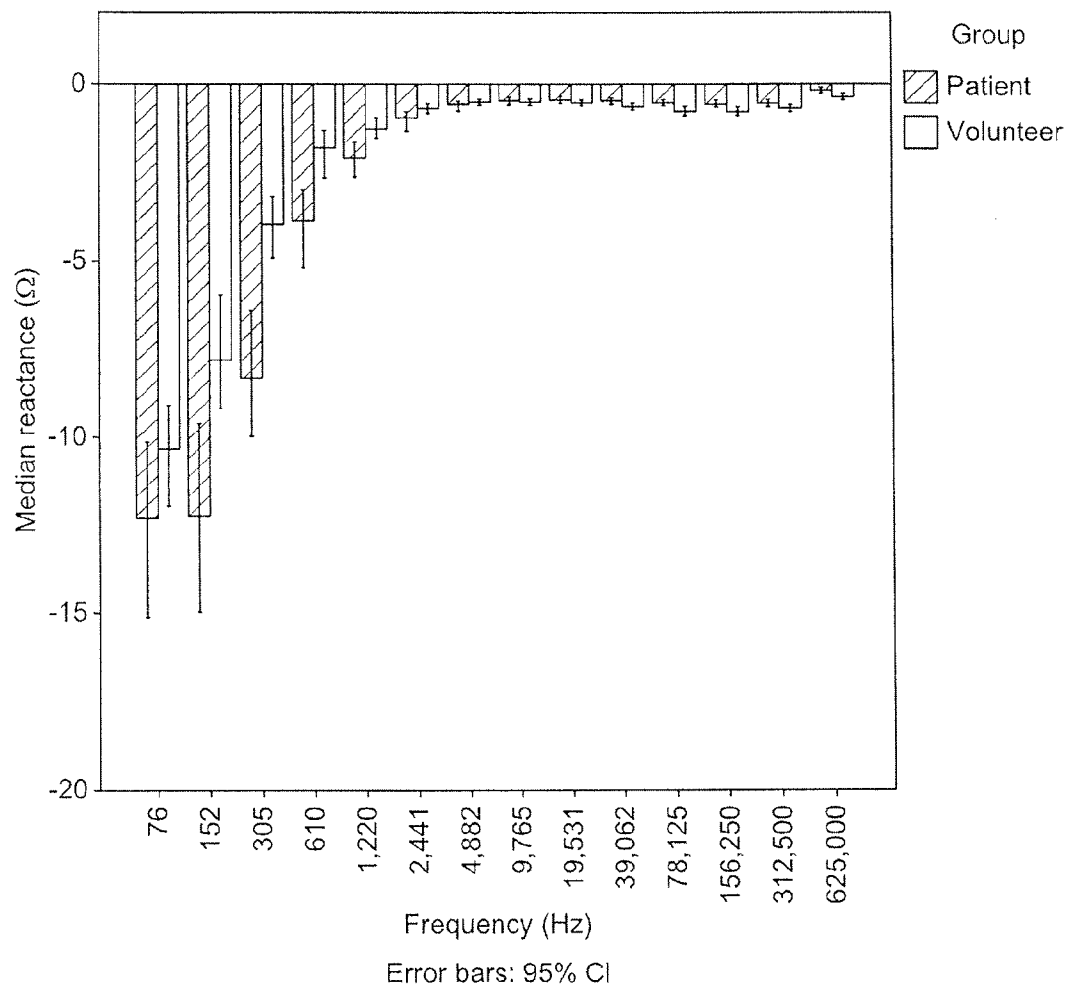


Fig. 15

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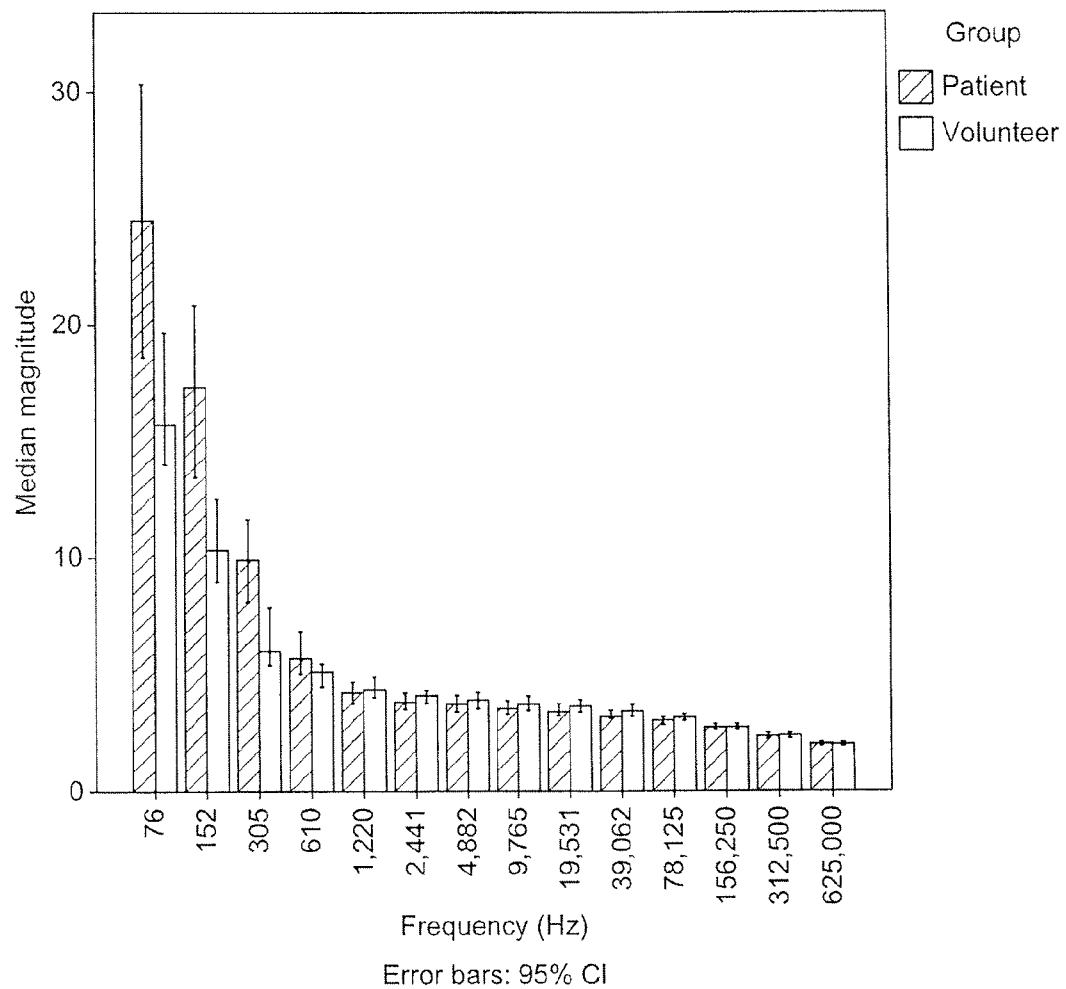


Fig. 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/051264

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/00 A61B5/053
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

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

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A	paragraphs [0025] - [0057]; figures 2, 6C, 7B	6,7
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A	paragraphs [0038] - [0063]; figures 1-4	6,7
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A	paragraphs [0046] - [0089]; figures 1-6B	7
X	WO 2009/067658 A2 (CANTOR DIVYA [US]) 28 May 2009 (2009-05-28)	1,2,5-24
A	paragraphs [0031] - [0042]; figures 3-6C	25
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Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

29 June 2018

Date of mailing of the international search report

09/07/2018

Name and mailing address of the ISA/

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Authorized officer

Dydenko, Igor

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/051264

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 2006/116599 A1 (DAVIS GRANT E [US]) 1 June 2006 (2006-06-01) paragraphs [0033] - [0042]; figure 1 -----	21
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