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**(54) APPARATUS FOR MEASUREMENT OF NEURAL RESPONSE**

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(56) References cited:  
**WO-A1-2004/021885 US-A- 5 758 651**  
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**US-B1- 6 473 649**

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- **RICHARD A. B.: 'An Electronic System for Extracellular Neural Stimulation and Recording' DISSERTATION, GEORGIA INSTITUTE OF TECHNOLOGY August 2007, XP055135370 Retrieved from the Internet: <URL:http://smartech.gatech.edu/handle/1853/16192> [retrieved on 2012-01-30]**

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## Description

### Technical Field

**[0001]** The present invention relates to measurement of a neural response to a stimulus, and in particular relates to measurement of a compound action potential by using one or more electrodes implanted proximal to the neural pathway.

### Background of the Invention

**[0002]** Neuromodulation is used to treat a variety of disorders including chronic pain, Parkinson's disease, and migraine. A neuromodulation system applies an electrical pulse to tissue in order to generate a therapeutic effect. When used to relieve chronic pain, the electrical pulse is applied to the dorsal column (DC) of the spinal cord or dorsal root ganglion (DRG). Such a system typically comprises an implanted electrical pulse generator, and a power source such as a battery that may be rechargeable by transcutaneous inductive transfer. An electrode array is connected to the pulse generator, and is positioned in the dorsal epidural space above the dorsal column. An electrical pulse applied to the dorsal column by an electrode causes the depolarisation of neurons, and generation of propagating action potentials. The fibres being stimulated in this way inhibit the transmission of pain from that segment in the spinal cord to the brain.

**[0003]** While the clinical effect of spinal cord stimulation (SCS) is well established, the precise mechanisms involved are poorly understood. The DC is the target of the electrical stimulation, as it contains the afferent A $\beta$  fibres of interest. A $\beta$  fibres mediate sensations of touch, vibration and pressure from the skin. The prevailing view is that SCS stimulates only a small number of A $\beta$  fibres in the DC. The pain relief mechanisms of SCS are thought to include evoked antidromic activity of A $\beta$  fibres having an inhibitory effect, and evoked orthodromic activity of A $\beta$  fibres playing a role in pain suppression. It is also thought that SCS recruits A $\beta$  nerve fibres primarily in the DC, with antidromic propagation of the evoked response from the DC into the dorsal horn thought to synapse to wide dynamic range neurons in an inhibitory manner.

**[0004]** Neuromodulation may also be used to stimulate efferent fibres, for example to induce motor functions. In general, the electrical stimulus generated in a neuromodulation system triggers a neural action potential which then has either an inhibitory or excitatory effect. Inhibitory effects can be used to modulate an undesired process such as the transmission of pain, or to cause a desired effect such as the contraction of a muscle.

**[0005]** The action potentials generated among a large number of fibres sum to form a compound action potential (CAP). The CAP is the sum of responses from a large number of single fibre action potentials. The CAP recorded is the result of a large number of different fibres de-

polarising. The propagation velocity is determined largely by the fibre diameter and for large myelinated fibres as found in the dorsal root entry zone (DREZ) and nearby dorsal column the velocity can be over 60 ms<sup>-1</sup>. The CAP generated from the firing of a group of similar fibres is measured as a positive peak potential P1, then a negative peak N1, followed by a second positive peak P2. This is caused by the region of activation passing the recording electrode as the action potentials propagate along the individual fibres.

**[0006]** To better understand the effects of neuromodulation and/or other neural stimuli, it is desirable to record a CAP resulting from the stimulus. However, this can be a difficult task as an observed CAP signal will typically have a maximum amplitude in the range of microvolts, whereas a stimulus applied to evoke the CAP is typically several volts. Electrode artefact usually results from the stimulus, and manifests as a decaying output of several millivolts throughout the time that the CAP occurs, presenting a significant obstacle to isolating the CAP of interest. Some neuromodulators use monophasic pulses and have capacitors to ensure there is no DC flow to the tissue. In such a design, current flows through the electrodes at all times, either stimulation current or equilibration current, hindering spinal cord potential (SCP) measurement attempts. Moreover, high-pass filter poles in measurement circuitry generate increased electrical artefact with mono-phasic pulses. The capacitor recovers charge at the highest rate immediately after the stimulus, undesirably causing greatest artefact at the same time that the evoked response occurs.

**[0007]** To resolve a 10uV SCP with 1uV resolution in the presence of an input 5V stimulus, for example, requires an amplifier with a dynamic range of 134dB, which is impractical in implant systems. As the neural response can be contemporaneous with the stimulus and/or the stimulus artefact, CAP measurements present a difficult challenge of amplifier design. In practice, many non-ideal aspects of a circuit lead to artefact, and as these mostly have a decaying exponential appearance that can be of positive or negative polarity, their identification and elimination can be laborious.

**[0008]** A number of approaches have been proposed for recording a CAP. King (US Patent No. 5,913,882) measures the spinal cord potential (SCP) using electrodes which are physically spaced apart from the stimulus site. To avoid amplifier saturation during the stimulus artefact period, recording starts at least 1 - 2.5 ms after the stimulus. At typical neural conduction velocities, this requires that the measurement electrodes be spaced around 10 cm or more away from the stimulus site, which is undesirable as the measurement then necessarily occurs in a different spinal segment and may be of reduced amplitude.

**[0009]** Nygard (US Patent No. 5,785,651) measures the evoked CAP upon an auditory nerve in the cochlea, and aims to deal with artefacts by a sequence which comprises: (1) equilibrating electrodes by short circuiting

stimulus electrodes and a sense electrode to each other; (2) applying a stimulus via the stimulus electrodes, with the sense electrode being open circuited from both the stimulus electrodes and from the measurement circuitry; (3) a delay, in which the stimulus electrodes are switched to open circuit and the sense electrode remains open circuited; and (4) measuring, by switching the sense electrode into the measurement circuitry. Nygard also teaches a method of nulling the amplifier following the stimulus. This sets a bias point for the amplifier during the period following stimulus, when the electrode is not in equilibrium. As the bias point is reset each cycle, it is susceptible to noise. The Nygard measurement amplifier is a differentiator during the nulling phase which makes it susceptible to pickup from noise and input transients when a non-ideal amplifier with finite gain and bandwidth is used for implementation.

**[0010]** Daly (US Patent Application No. 2007/0225767) utilizes a biphasic stimulus plus a third phase "compensatory" stimulus which is refined via feedback to counter stimulus artefact. As for Nygard, Daly's focus is the cochlea. Daly's measurement sequence comprises (1) a quiescent phase where stimulus and sense electrodes are switched to  $V_{dd}$ ; (2) applying the stimulus and then the compensatory phase, while the sense electrodes are open circuited from both the stimulus electrodes and from the measurement circuitry; (3) a load settling phase of about 1  $\mu$ s in which the stimulus electrodes and sense electrodes are shorted to  $V_{dd}$ ; and (4) measurement, with stimulus electrodes open circuited from  $V_{dd}$  and from the current source, and with sense electrodes switched to the measurement circuitry. However a 1  $\mu$ s load settling period is too short for equilibration of electrodes which typically have a time constant of around 100  $\mu$ s.

**[0011]** WO 2004/021885 discloses a method and device for measuring an evoked neural response comprising a sensor for obtaining a sensed signal representing the evoked neural response, a high gain amplifier having a signal input for receiving the sensed signal and having a reference input, and means for altering or setting a reference voltage at the reference input to prevent the amplifier saturating with variations of the sensed signal.

**[0012]** Further, connecting the sense electrodes to  $V_{dd}$  pushes charge onto the sense electrodes, exacerbating the very problem the circuit is designed to address.

**[0013]** Evoked responses are less difficult to detect when they appear later in time than the artifact, or when the signal-to-noise ratio is sufficiently high. The artifact is often restricted to a time of 1 - 2 ms after the stimulus and so, provided the neural response is detected after this time window, data can be obtained. This is the case in surgical monitoring where there are large distances between the stimulating and recording electrodes so that the propagation time from the stimulus site to the recording electrodes exceeds 2 ms. Because of the unique anatomy and tighter coupling in the cochlea, cochlear implants use small stimulation currents relative to the

tens of mA sometimes required for SCS, and thus measured signals in cochlear systems present a relatively lower artifact. However to characterize the responses from the dorsal columns, high stimulation currents and close proximity between electrodes are required, and therefore the measurement process must overcome artifact directly, in contrast to existing "surgical monitoring" techniques.

**[0014]** Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

**[0015]** Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

## Summary of the Invention

**[0016]** This disclosure provides a method for measuring a neural response to a stimulus, however, this and other methods disclosed herein do not form part of the invention.

**[0017]** According to a first aspect the present invention provides an implantable device for measuring a neural response to a stimulus, the device comprising:

- a plurality of electrodes including one or more nominal stimulus electrodes and one or more nominal sense electrodes;
- a stimulus source for providing a stimulus to be delivered from the one or more stimulus electrodes to neural tissue;
- measurement circuitry for amplifying a neural signal sensed at the one or more sense electrodes; and
- a control unit configured to control application of a stimulus to the neural tissue and measurement of an evoked neural response, the control unit configured to settle the measurement circuitry prior to a stimulus by connecting the or each sense electrode to the measurement circuitry to allow the measurement circuitry to settle towards a bio-electrically defined steady state, the control unit further configured to recover charge on the stimulus electrodes by short circuiting the stimulus electrodes to each other, the control unit further configured to cause the stimulus source to apply an electrical stimulus from the stimulus electrodes to neural tissue while keeping the or each sense electrode disconnected from the measurement circuitry, the control unit further configured to impose a delay during which the stimulus elec-

trodes are open circuited and the sense electrode is disconnected from the measurement circuitry and from the stimulus electrodes, and the control unit further configured to measure a neural response signal present at the sense electrode by connecting the or each sense electrode to the measurement circuitry after the delay.

**[0018]** It is to be understood herein that open circuiting of an electrode involves ensuring that the electrode is disconnected from other electrodes, the stimulus source, the measurement circuitry and from voltage rails. Ensuring that the sense electrode is disconnected from the stimulus electrodes during the delay period avoids charge transfer onto the sense electrode(s) and associated artefact. The present invention recognizes that connecting the sense electrodes to the stimulus electrodes during a post-stimulus delay period can undesirably give rise to such charge transfer and associated artefact, particularly if the delay is short relative to the time constant of the stimulus electrodes, the latter typically being around 100  $\mu$ s. The sense electrode is preferably open circuited during the post-stimulus delay so as to be disconnected from all other electrodes of the array, to prevent such charge transfer to the sense electrode from other non-stimulus electrodes. With particular regard to the case of spinal cord response measurement, the present invention recognizes that in the spinal cord, the stimulation electrodes may never reach equilibrium at the stimulation rates used for chronic pain, so that connecting them to the stimulating electrodes at any time would increase artefact. This lack of equilibrium is due to the nature of the Helmholtz layer which causes fractional pole variation in the electrode impedance with frequency, with time constants as long as tens of milliseconds.

**[0019]** The present invention recognizes that it is beneficial to provide for pre-stimulus settling of the measurement circuitry towards a bio-electrically defined steady state. This ensures that charge recovery occurs in the settling stage prior to the stimulus and not during or immediately after the stimulus and thus does not give rise to artefact during or immediately after the stimulus. Thus, the present invention captures the bio-electrically defined steady state as reference point voltage at the end of the measurement cycle, when the system is in its most stable state. The system then amplifies the difference between the captured voltage and the reference point voltage. Where repeated measurement cycles are undertaken, the present invention further permits the measurement amplifier to accumulate a bias point over multiple cycles rather than re-setting the bias point each cycle. The settle period is preferably sufficiently long to permit the electrodes and circuitry to reach an equilibrium, and for example the settle period may be around 1 ms or greater, as permitted by a stimulus rate. For example if therapeutic stimuli are applied to a dorsal column at about 100 Hz and do not give rise to a slow neural response, then after

the approximately 2 ms duration of an evoked fast response up to about 8 ms would be available for the settling period. However, this is generally longer than required and the settling period may be substantially less than 8 ms.

**[0020]** The delay may be in the range of substantially zero to 1 ms, and for example may be about 0.3 ms. Such embodiments permit onset of the neural response to be observed, this typically occurring about 0.3 ms after the stimulus for an electrode 3 cm away from the stimulus site. In embodiments in which an amplifier of the measurement circuitry has a very high dynamic range, and/or if using a measurement electrode closer to the stimulus electrode, the delay may be set to a smaller value for example in the range of 50 - 200  $\mu$ s. The delay is preferably set to a value which ensures the measurement amplifier is not saturated and therefore performs linearly at all times when connected without experiencing clipping, and for example a feedback loop may be implemented to determine a suitable delay which avoids amplifier saturation for a given stimulus.

**[0021]** In preferred embodiments of the invention, the signal from the or each sense electrode is passed to a sample-and-hold circuit at the input of a measurement amplifier. In such embodiments measurements of a single evoked response may be obtained from a plurality of sense electrodes, even if the measurement circuitry of each electrode is connected to the control unit only by a two wire bus or the like, as is commonly required in implanted electrode arrays.

**[0022]** Additionally or alternatively, a buffer or follower amplifier is preferably provided in some embodiments, between the sense electrode and the measurement amplifier. The buffer is preferably connected to the sense electrode without interposed switches, so that the high reverse impedance of the buffer effectively prevents switching transients from being conveyed to the sense electrode, thereby avoiding artefact which may arise upon the sense electrode if subjected to such transients. The buffer amplifier is also preferably configured to give current gain to drive a storage capacitor of a sample and hold circuit. A series capacitor may be interposed between the sense electrode and the buffer to avoid DC transfer with the tissue in the event where the amplifier malfunctions. This capacitor also allows the bias voltage of the amplifier to equilibrate as the electrode voltage can drift over time periods of several tens of seconds..

**[0023]** In preferred embodiments of the invention, the stimulus and sense electrodes are selected from an implanted electrode array. The electrode array may for example comprise a linear array of electrodes arranged in a single column along the array. Alternatively the electrode array may comprise a two dimensional array having two or more columns of electrodes arranged along the array. Preferably, each electrode of the electrode array is provided with an associated measurement amplifier, to avoid the need to switch the sense electrode(s) to a shared measurement amplifier, as such switching can

add to measurement artefact. Providing a dedicated measurement amplifier for each sense electrode is further advantageous in permitting recordings to be obtained from multiple sense electrodes simultaneously.

**[0024]** The measurement may be a single-ended measurement obtained by passing a signal from a single sense electrode to a single-ended amplifier. Alternatively, the measurement may be a differential measurement obtained by passing signals from two sense electrodes to a differential amplifier.

**[0025]** While recovering charge by short circuiting the stimulus electrodes together, it may in some embodiments be advantageous to disconnect the sense electrode from the measurement circuitry, for example by setting a sample-and-hold circuit to "hold".

**[0026]** Embodiments of the invention may prove beneficial in obtaining a CAP measurement which has lower dynamic range and simpler morphology as compared to systems more susceptible to artefact. Such embodiments of the present invention may thus reduce the dynamic range requirements of implanted amplifiers, and may avoid or reduce the complexity of signal processing systems for feature extraction, simplifying and miniaturizing an implanted integrated circuit. Such embodiments may thus be particularly applicable for an automated implanted evoked response feedback system for stimulus control. Thus, in a further aspect, the present invention provides a method for feedback control of a neural stimulus, the method comprising an implanted control unit obtaining a CAP measurement in accordance with the method of the first aspect, and the implanted control unit using the obtained CAP measurement to control the delivery of subsequent neural stimuli by the implant.

**[0027]** In some embodiments of the invention, an averaged CAP measurement may be obtained by (i) delivering a first biphasic stimulus which starts with a pulse of a first polarity and then delivers a pulse of a second polarity opposite to the first polarity, and obtaining a first measurement of a CAP evoked by the first stimulus; (ii) delivering a second biphasic stimulus which starts with a pulse of the second polarity and then delivers a pulse of the first polarity, and obtaining a second measurement of a CAP evoked by the second stimulus; and (iii) taking an average of the first measurement and the second measurement to obtain an averaged measurement. Such embodiments exploit the observation that artefact polarity usually reflects the stimulus polarity, whereas the CAP polarity is independent of the stimulus polarity and is instead determined by the anatomy and physiology of the spinal cord membrane, so that averaging the first and second measurements will tend to selectively cancel out artefact. Further noting that for some electrode polarity configurations, such as monopolar, an "anodic first" biphasic stimulus usually has a lower stimulus threshold for neural recruitment than a "cathodic first" biphasic stimulus, the averaged measurement may have a morphology of either (i) a typical CAP of half amplitude if only the anodic-first stimulus exceeds the stimulus threshold; (ii)

the average of two CAPs of different amplitude if both stimuli exceed the stimulus threshold but the cathodic first stimulus does not cause saturation recruitment; or (iii) a typical CAP if both stimuli exceed saturation recruitment. Some embodiments may therefore obtain a curve of the averaged measurement vs. stimulus amplitude in order to obtain information regarding the recruitment effected by each stimulus, and such information may be used for feedback control by the implant.

**[0028]** In some embodiments, the method may be applied contemporaneously with administration of a drug, in order to gauge efficacy of drug delivery. For example, the implant may comprise or be operatively connected to a drug reservoir and drug delivery pump, with the pump being controlled by feedback based on CAP measurements.

**[0029]** According to another aspect the present invention provides a computer program product as defined in claim 12. The present invention recognises that when considering spinal cord stimulation, obtaining information about the activity within the spinal segment where stimulation is occurring is highly desirable. Observing the activity and extent of propagation both above (rostrally of) and below (caudally of) the level of stimulation is also highly desirable. The present invention recognises that in order to record the evoked activity within the same spinal segment as the stimulus requires an evoked potential recording system which is capable of recording an SCP within approximately 3cm of its source, i.e. within approximately 0.3 ms of the stimulus, and further recognises that in order to record the evoked activity using the same electrode array as applied the stimulus requires an evoked potential recording system which is capable of recording an SCP within approximately 7 cm of its source, i.e. within approximately 0.7 ms of the stimulus.

**[0030]** In preferred embodiments the stimulus comprises a bi-phasic pulse, and the stimulus electrodes have no capacitors. In contrast to a monophasic pulse and capacitor arrangement, such embodiments permit the stimulus electrode current to be interrupted, or forced to zero, at those times where it would interfere with measurement. Omitting capacitors is also desirable in order to minimise the size of the implanted device.

#### Brief Description of the Drawings

**[0031]** An example of the invention will now be described with reference to the accompanying drawings, in which:

Figure 1 illustrates currents and voltages which can contribute to SCP measurements;  
 Figure 2 illustrates the circuitry of one embodiment of the present invention, throughout five phases of a measurement cycle;  
 Figure 3 illustrates idealised waveforms arising in the circuit of Figure 2 during each phase of the measurement cycle;

Figure 4 illustrates SCP measurements made using the embodiment of Figure 2;  
 Figure 5 illustrates the circuitry of an alternative embodiment of the invention implementing differential CAP measurements;  
 Figure 6 illustrates delayed activation of a measurement amplifier to avoid clipping;  
 Figure 7 illustrates an embodiment in which alternate phased stimuli are used to obtain an averaged CAP measurement;  
 Figure 8a illustrates the "anodic first" and "cathodic first" CAP responses induced by the method of Figure 7, while Figure 8b illustrates the averaged measurement obtained therefrom;  
 Figure 9 illustrates the CAP response to anodic-first and cathodic-first stimuli, respectively, with increasing stimulus amplitude;  
 Figure 10 illustrates the nature of differential CAP measurements in the spinal cord;  
 Figure 11 illustrates a model of a metal electrode in a conductive solution;  
 Figure 12 illustrates segmented electrodes which may be used to reduce artefact without sacrificing noise, impedance or current carrying capacity;  
 Figures 13a and 13b illustrate the effect of epidural administration of Lignocaine on suppression of the spinal evoked responses; and  
 Figure 14a is a plot showing the artefact arising when electrode shorting is performed, and Figure 14b is a plot showing the artefact arising when the sense electrode is disconnected from the measurement circuitry and from the stimulus electrodes after the stimulus.

#### Description of the Preferred Embodiments

**[0032]** Figure 1 shows the currents and voltages that contribute to SCP measurements. These signals include the stimulus current 102 applied by two stimulus electrodes, which is a charge-balanced biphasic pulse to provide low artefact. Alternative embodiments may instead use three electrodes to apply a tripolar charge balanced stimulus. In the case of spinal cord stimulation, the stimulus currents 102 used to provide paraesthesia and pain relief typically consist of pulses in the range of 3-30 mA amplitude, with pulse width typically in the range of 100-400  $\mu$ s, or alternatively may be paraesthesia-free such as neuro or escalator style stimuli. The stimuli can comprise monophasic or biphasic pulses.

**[0033]** The stimulus 102 induces a voltage on adjacent electrodes, referred to as stimulus crosstalk 104. Where the stimuli 102 are SCP stimuli they typically induce a voltage 104 in the range of about 1-5 V on a SCP sense electrode.

**[0034]** The stimulus 102 also induces electrode artefact, which is a residual voltage on an electrode resulting from uneven charge distribution on its surface. The electrode artefact is indicated in the voltage waveform 104

after cessation of stimulus crosstalk. The stimulus 102 disturbs the galvanic interface between the sense electrode and the tissue, so that after stimulus crosstalk in voltage 104 concludes, a voltage known as the electrode artefact continues on the electrode, as indicated in waveform 104 in Figure 1. Electrode artefact is very difficult to measure, and depends on factors such as the stimulation pulse, the geometry of the electrodes and the bio-electrical nature of the tissue surrounding the electrodes. Electrode artefact can have a typical value of 500  $\mu$ V at a time 50  $\mu$ s after stimulation ceases. Electrode artefact is difficult to measure because it is indistinguishable from electrical artefact, the latter being caused by the amplifier's exposure to the high stimulation voltages. Further, the causes of electrical artefact can be subtle, and therefore hard to identify and eliminate.

**[0035]** An appropriate stimulus 102 will also induce nerves to fire, and thereby produces an evoked neural response 106. In the spinal cord, the neural response 106 has two major components: a fast response lasting ~2 ms and a slow response lasting ~15 ms. The slow response only appears at stimulation amplitudes which are larger than the minimum stimulus required to elicit a fast response. The amplitude of the evoked response seen by epidural electrodes is typically no more than hundreds of microvolts, but in some clinical situations can be only tens of microvolts.

**[0036]** In practical implementation a measurement amplifier used to measure the evoked response does not have infinite bandwidth, and will normally have infinite impulse response filter poles, and so the stimulus crosstalk 104 will produce an output 108 during the evoked response 106, this output being referred to as electrical artefact.

**[0037]** Electrical artefact can be in the hundreds of millivolts as compared to a SCP of interest in the tens of microvolts. Electrical artefact can however be reduced by suitable choice of a high-pass filter pole frequency.

**[0038]** The measurement amplifier output 110 will therefore contain the sum of these various contributions 102-108. Separating the evoked response of interest (106) from the artefacts 104 and 108 is a major technical challenge. For example, to resolve a 10  $\mu$ V SCP with 1  $\mu$ V resolution, and have at the input a 5V stimulus, requires an amplifier with a dynamic range of 134dB. As the response can overlap the stimulus this represents a difficult challenge of amplifier design.

**[0039]** Figures 2a - 2e are schematic diagrams of the five phases of operation of a sample and hold (S/H) measurement amplifier in accordance with one embodiment of the present invention. The stimulus and measurement circuitry 200 comprises a buffer amplifier 206 that is always connected to the sense electrode 202 such that there is no switch between the sense electrode 202 and the buffer amplifier 206. The output of the buffer amplifier 206 drives a sample and hold circuit 208, followed by a high gain amplifier 210 with unity gain at DC. The front-end amplifier 206 has sufficiently wide bandwidth

that it can follow the voltage induced on the sense electrodes 202 by the stimulus pulse, and settle before the SCP begins. A current source 212 can be selectively connected to stimulus electrodes 204 to deliver a stimulus. The stimulus electrodes 204 and sense electrode 202 are in the same electrode array of a single implanted device.

**[0040]** The stimulus and measurement circuitry 200 operates to obtain a SC measurement using five phases. The first phase shown in Figure 2a open circuits the stimulus electrodes 204 and connects the sense electrode 202 to the measurement amplifier 210 by setting the sample and hold circuit to "sample". The first phase shown in Figure 2a allows the amplifier chain 206, 210 to settle, with no disturbance from the stimulating electrodes 204.

**[0041]** In the second phase shown in Fig 2b, the stimulus electrodes 204 are short circuited to each other. This allows the stimulating electrodes 204 to recover charge, so as to avoid DC injection to the tissue as is required for electrical implants. During this phase, the sample-and-hold 208 is set to "hold" so that charge transfer on the stimulus electrodes 204 does not disrupt the measurement amplifier 210.

**[0042]** In the third phase shown in Figure 2c, the stimulation is applied. The stimulus electrodes 204 are switched to the current source 212, and the sample-and-hold 208 is set to "hold" so that the large stimulus crosstalk seen on electrode 202 is not presented to the measurement amplifier 210.

**[0043]** The fourth phase shown in Figure 2d provides for a post-stimulus delay. In this phase the stimulus electrodes 204 are open circuited, and the sample-and-hold remains in the "hold" position, to allow the electrodes 202, 204 settle towards equilibrium, as defined by bio-electrical conditions.

**[0044]** Finally, in the fifth phase shown in Figure 2e, the SCP present at sense electrode 202 is measured by switching the sample-hold 208 to "sample".

**[0045]** When performing repeated measurement cycles in this fashion, it is noted that the switch positions are the same in the phase 1 "settling" and the phase 5 "measuring" states. Thus, the state of phase 5 is maintained, by virtue of a subsequent phase 1, until the electrodes and circuitry are in equilibrium, even after the time that useful SCP data is no longer present or being captured. Such embodiments thus provide a greater length of the "settle" state.

**[0046]** Figure 3 shows idealised waveforms arising during the SCP measurement process of Figure 2. Figure 3 illustrates the current 302 of stimulus electrodes 204, and the output voltage 304 of amplifier 210, during each of the five phases of the measurement cycle. Importantly, it can be seen that phase 1 permits the amplifier bias point to settle to a steady state as defined by bio-electrical conditions at the sense electrode, while phases 2-4 do not disrupt the amplifier 210 bias point.

**[0047]** An advantage of this circuit is that in the phase 2 equilibration, the circuitry around amplifier 210 is a low-

pass filter, and is therefore relatively immune to noise and input transients. This also allows the amplifier 210 to accumulate its bias point over successive measurement cycles, as it does not need to be reset for each cycle. Moreover, because of the buffer 206 before the sample/hold 208, the input-referred effect (i.e. the effect upon sense electrode 202) of the charge injection into the sample/hold 208 is lower.

**[0048]** In the embodiment of Figure 2, the sense electrode 202 is never shorted to the stimulus electrodes 204, recognising that this creates dis-equilibrium in the sense electrodes and adds artefact, rather than having the effect of creating equilibrium as previously thought. In some embodiments, it may be possible to overlap the "settle" (equilibrate) phase of Figure 2a, and the "charge recovery" phase of Fig 2b, although it would be expected that the artefact would be higher, and the time taken to reach equilibrium longer.

**[0049]** Figure 4 is a plot of 22 separate measurements of ovine SCP made using the embodiment of Figure 2. The measurements were obtained sequentially for differing stimuli, the stimuli comprising biphasic current pulses of 40  $\mu$ s pulse width and a current amplitude which varied from 0-10 mA. The measurements were then plotted on a single chart to produce Figure 4. The recorded signals consist of the neural response and a small electrode artefact. The neural response is tri-phasic, consisting of a positive P1 peak followed by a negative N1 peak and then a secondary positive P2 peak. The neural response morphology in Figure 4 is characteristic of extracellular recordings of axonal compound action potentials. The first phase P1 is dominated by the capacitive current due to the initial membrane depolarization. Phase 2 is dominated by  $\text{Na}^+$  ion current and is negative due to the influx of  $\text{Na}^+$  ions during the neuronal membrane action potential. The third phase is positive due to the  $\text{K}^+$  ion conduction during repolarization.

**[0050]** The waveforms of Figure 4 have lower dynamic range and simpler morphology than measurements produced by previous approaches, due to the absence of stimulus crosstalk and reduced artefact. When wishing to provide a system built on an implanted integrated circuit, wide dynamic range amplifiers are difficult to design, as are signal processing systems for feature extraction. Beneficially, the nature of the measured waveforms shown in Figure 4 permits, for example, a circuit for extracting the peak-to-peak SCP amplitude to have fewer components than would be required to operate upon the waveform produced by previous approaches. Thus the techniques of the present invention for artefact reduction greatly assist in building a practical implanted, evoked response feedback system.

**[0051]** Moreover, it is notable that in this case of a 40  $\mu$ s pulse width the measurement system is settled and ready to record prior to onset of the evoked CAP. The sense electrode was less than 50mm from the stimulus electrode, and a post-stimulus delay of 50  $\mu$ s was observed before the measurement amplifier was switched

in to obtain the recordings shown in Figure 4. As can be seen in Figure 4 the largest peak to peak response was about 2.4 mV, significantly less than the voltage present when applying a 10 mA stimulus. Moreover, the epidural space is much smaller in sheep than in humans, and so the electrode is expected to be closer to the ovine neural tissue and the magnitude of the sensed tri-phasic potentials is correspondingly higher in the sheep than is expected for humans, emphasizing the difficulty of making such recordings.

**[0052]** Figure 5 illustrates the circuitry of an alternative embodiment of the invention in which a differential measurement amplifier is used, and charge recovery is via a voltage rail  $V_{dd}$ . As can be seen, in accordance with the present invention the measurement phases are carried out in a corresponding manner despite the use of different hardware.

**[0053]** In the embodiments of either figure 2 or figure 5, artefact can cause the high-gain measurement amplifier 210 to clip, and the amplifier can subsequently be slow to recover. However, in preferred embodiments the sample point, being the transition from the "stimulate" to "measure" phases, is delayed, allowing clipping to be avoided. Figure 6 illustrates the manner of determining a suitable delay 602, which is often in the range of 50-200  $\mu$ s, noting that the fast response typically concludes within about 2 ms. Such embodiments may permit use of a higher amplifier gain than would otherwise be the case. In particular, a variable delay and increased amplifier gain may be particularly apt in circumstances where high-gain is desired, and parts of the SCP of interest do not immediately follow the stimulation. Thus, delaying the start of measurement will avoid the side effects of clipping.

**[0054]** In another embodiment of the invention shown in figure 7, a method to eliminate artefact from an SCP measurement is to alternate the phase of stimulus waveforms and take an average of obtained measurements. This method is effective when the stimulus electrodes have different area. For example, in tripolar stimulation a central electrode is driven anodically in the first phase and consists of a single electrode of the array, whereas the electrode driven cathodically in the first phase consists of two electrodes of the array connected in parallel. The electrodes in parallel would usually be on either side of the other stimulating electrode. Similarly, if stimulation were between one electrode in the epidural space and one electrode elsewhere, such as being attached to an implant body, then a mode of stimulation referred to as "monopolar" stimulation is obtained.

**[0055]** Figure 7 shows the stimulus current for a positive "anodic-first" stimulus 702, and the stimulus current for a negative "cathodic first" stimulus 704. In this embodiment these are applied in succession with respective CAP measurements obtained after each stimulus. The respective measurement electrode voltages 706 and 708 arising from each such stimulus are also shown. It will be observed where indicated in waveforms 706, 708 that

the artefacts from each of the two stimuli are of substantially identical magnitude, but opposite sign. In most situations it will be found that the artefact polarity depends on the stimulus polarity. An example of this would be electrical artefact caused by the high-pass poles of the front-end amplifier 206. Clearly, either phase could be used for stimulating nervous tissue, though their effects will differ.

**[0056]** In contrast, the positive and negative phase stimuli 702, 704 produce SCPs of differing amplitudes, but approximately similar shape and importantly of similar polarity, as this is determined by the anatomy and physiology of the spinal cord nerve fibre membranes. Thus, when the voltages 706, 708 resulting from the positive and negative phase stimuli 702, 704 are recorded, and averaged, the opposite phase stimulation artefacts substantially cancel, leaving the SCP or a combination of the two SCPs 710. Note that in practical situations, the artefact can have much higher amplitude than the SCP, making it much harder to detect the SCP than is apparent from Fig 7.

**[0057]** The response of the spinal cord to these two polarities of stimulation are referred to as the "anodic" and "cathodic" SCP responses, as referred to the electrode considered to be that closest to the recording electrode. I.e. anodic tripolar stimulation makes the central stimulating electrode anodic in the first phase of stimulus. Usually cathodic stimulation has a lower threshold for neural activation than is the case for anodic stimulation. Nevertheless, the SCP polarity is independent of whether the stimulus is anodic 702 or cathodic 704.

**[0058]** Figure 8a illustrates spinal cord measurements obtained in response to anodic and cathodic monophasic stimulations, respectively, the stimuli being of equal amplitude. Note that the measurement obtained in response to the anodic stimulation lacks the characteristic P1-N1-P2 form, indicating that the anodic stimulation did not evoke a neural response in this case. In contrast, the measurement obtained in response to the cathodic stimulus exhibits a significant evoked neural response.

**[0059]** Figure 8b shows an average of the two responses in Fig. 10a. As can be seen, while the characteristic form of the SCP has been altered, the artefact is essentially removed as stimuli of opposite polarity and equal amplitude produce artefact of opposite polarity and equal amplitude, which cancel when averaged.

**[0060]** This embodiment of the invention further recognises that the averaged waveform of Figure 8b can be used to obtain a range of information despite the atypical SCP form. In this regard, Figure 9 illustrates SCP growth curves against stimulus amplitude, for both anodic and cathodic monophasic stimuli. Figure 9 also shows the growth behaviour of the average SCP against stimulus amplitude. It can be seen from Fig 9 that the threshold of the average response is identical to the threshold of the more sensitive response for cathodic stimulation.

**[0061]** When the stimulus amplitude is in the range 902 such that only the cathodic stimulus produces an SCP,

then the averaged SCP waveform would have a normal SCP morphology but would be half the amplitude compared to a true cathodic SCP due to the averaging. In the region 904 where both the anodic and cathodic responses contribute to the averaged SCP, the resultant averaged SCP waveform will have morphology in between the two measurements. It would not directly represent an SCP, but rather the average of two different SCPs. Nevertheless, this waveform could still be valuable for example in implementing an automatic control loop for stimulation adjustment, as it gives a value proportional to neural recruitment.

**[0062]** It is further to be noted that the principle portrayed by Figure 9 applies in a similar manner to other stimulus polarities. For example, some embodiments may stimulate with a tripolar arrangement having a centre electrode operating as a cathode and having two edge electrodes, being those immediately to each side of the centre electrode, operating as anodes. This tripolar arrangement means that the recovery charge is shared between the two edge electrodes. For a biphasic tripolar stimulus the cathodic charge on the 2nd phase is shared between two electrodes and thus is half that on the first phase. Thus the principle shown in Figure 9 is true for tripolar stimulation, at least up to the point where the current is twice the threshold current at which point the edge electrodes' currents are each at the threshold and will thus start to generate action potentials.

**[0063]** Some embodiments of the invention, such as the embodiment of Figure 5, may use differential amplifiers so as to detect the voltage difference between two sense electrodes. Differential amplifiers simplify the task of separating electrode artefact. If they are connected to electrodes with similar area, and separated from the stimulation electrodes in a similar manner, then they receive similar levels of electrode artefact and this will be removed when their difference voltage is obtained. However, in such a system the voltage recorded by the amplifier is the difference between the voltages at two points along a bundle of neurons, and can thus be difficult to interpret. When making SCP measurements, it is preferable to use single-ended amplifiers as they more accurately measure the SCP, and they are more sensitive in measuring the SCP.

**[0064]** Differential amplifiers are often used because they provide a means to reduce electrode artefact, when other means have been insufficient. However, Figure 10 illustrates a problem of measuring SCPs with differential amplifiers. It shows a spinal cord potential. As this potential travels along the spine at a velocity, which can be as high as  $80 \text{ m} \cdot \text{s}^{-1}$ , it can also be considered as a spatial wave. Given that a peak-to-peak cycle of the fast response of an SCP typically lasts for 1 ms, the wave will travel 8 cm in this time. Using this  $1 \text{ ms} = 8 \text{ cm}$  scale, a 5cm electrode array is drawn alongside the SCP in Figure 10. Connected to this electrode array are two amplifiers configured to make differential SCP measurements from separate pairs of sense electrodes. As can be seen from

Figure 10, the difference between the voltages on the adjacent electrodes will be quite small and significantly smaller than the peak to peak amplitude of the SCP, and thus more susceptible to electrical noise generated by the amplifier. The output of the amplifier will approximate the differential of the SCP, and thus be harder to interpret than a simple measure of the SCP itself. If measuring evoked SCPs with a micro-package stimulator design, for example in a system using a two-wire bus, differential measurements between non-adjacent electrodes are not possible. Further, if wishing to measure the slow response of the SCP, which has a period of about 6 ms and correspondingly reduced signal gradients, differential measurements are even more difficult to effect. Thus it will be appreciated that single-ended measurements are preferable, as long as artefact can be kept at a sufficiently low level.

**[0065]** With the measurement sequence of the present invention, the artefact is reduced so that some embodiments may instead use a single-ended amplifier, even in situations where previously they would have suffered from too much electrode artefact. Moreover, trials to date show that recording can be initiated with an extremely short time interval from cessation of the stimulus, permitting the same electrode array to be used for recording and stimulation, and even permitting recordings to be made on the electrode immediately adjacent to the stimulus electrode in an electrode array with electrode spacings of less than 10 mm.

**[0066]** Single ended amplifiers have the further advantage that they consist of fewer capacitors and amplifier components than differential amplifiers, so will take up less space on a silicon chip, which is a significant benefit when intended for use in an implanted system with many electrodes and where the silicon area for each amplifier is limited.

**[0067]** Preferred embodiments of the invention may comprise a separate amplifier chain (e.g. 206, 208, 210, see Fig 2) for every electrode, organised in parallel manner, permitting simultaneous recording of a single CAP from multiple sense electrodes in parallel, and also eliminating the switching noise arising in systems which switch the sense electrode to a shared measurement amplifier.

**[0068]** Further embodiments of the invention may employ divisible electrodes, as discussed below with reference to Figures 11 and 12. When considering electrode artefact in particular, the sources of electrode artefact are relatively poorly understood. The surface of a metal electrode can be modelled as an RC network. For an accurate model, an infinite-phase element is required, but for the explanation of artefact a simple RC model will suffice, as shown in Figure 11a. A conductive solution can be modelled as a mesh of resistors. Where a conductive solution meets a piece of metal of finite dimensions, the metal provides an alternative conduction path to the solution. This charges the electrode-to-tissue capacitances at the "ends" of the electrodes, with opposite

polarities. The electrode does not acquire net charge, but it does cease to be in equilibrium. After the external current ceases, then the electrode will pass current through the solution as it re-equilibrates for a short time after the stimulus. This current will affect the potential of another electrode in the solution, and in the case of multi-electrode arrays a unique such current will arise at every electrode in response to local conditions experienced at that electrode. The cumulative impact of such re-equilibration currents is seen by a sense electrode as electrode artefact.

**[0069]** A similar effect happens when current flows between two electrodes, as shown in Figure 11b. During application of a stimulus, the current preferentially flows between the parts of the electrodes where they are closest. When the current is interrupted, the charge on the surface of the electrodes must re-equilibrate; this also leads to a residual current and contributes to electrode artefact seen by a sense electrode.

**[0070]** The model of Figure 11 predicts that using smaller electrodes will reduce artefact. However, smaller electrodes will have higher noise when used as measurement electrodes, and higher resistance and lower current carrying capacity when used as stimulus electrodes. Two means to reduce artefact without sacrificing noise, impedance or current carrying capacity are shown in Figures 12a and 12b. The electrode configuration of Figure 12a reduces artefact induced in a single metallic electrode; the electrode is composed of two or more smaller electrodes that can be disconnected during a stimulation phase, and reconnected during a measurement phase. In the configuration of Figure 12b, an electrode is segmented, and individual current sources are provided for each segment. This forces the current in the segments to match, and so reduces artefact.

**[0071]** The evoked response telemetry of the present invention may in some embodiments be used to monitor the effect of a delivered compound. The administration of compounds (drugs or other chemical therapeutics) to effect a change in the nervous system is common for treatment of a wide number of diseases and disorders. Anaesthetics of various types are administered to the spinal cord for the relief of pain. Perhaps the most common form is administration of anaesthetics in the epidural space for pain relief during child birth.

**[0072]** In such embodiments, a catheter comprising a drug delivery tube may be fitted with electrode elements and configured to obtain neural response measurements in accordance with the present invention in order to monitor drug-induced effects on the neural response. Alternatively an electrode array may be temporarily or permanently implanted and used to apply neural stimuli and monitor the neural response. The neural response measurements may be obtained repeatedly during administration of the drug in order to directly measure the effect of the administered drug and control the dosage delivered.

**[0073]** Figures 15a and 15b illustrate the effect of ad-

ministration of anaesthetic to the spinal cord, with a neural response being present prior to administration and largely being absent subsequent to administration. As can be seen, there is a direct correlation between the measured evoked response and the dosage of the anaesthetic. A "partial block" may be effected by ceasing administration of the anaesthetic once the neural response amplitude reduces to a desired level. The technology described herein is suitable for full implantation within the body of a subject and as a result the evoked potential monitoring could be used in the administration of an active compound to produce a therapeutic benefit. The system could be integrated within an implantable pump to control the administration of the compound.

**[0074]** Figure 14 shows two plots which compare the artefact arising when electrode shorting is performed, to the artefact arising when the sense electrode is disconnected from the measurement circuitry and from the stimulus electrodes after the stimulus.

**[0075]** The plots of Figure 14 were obtained from an array placed in a saline bath, and were taken under the following conditions. A stimulation comprising a biphasic pulse of amplitude 10mA and duration 400  $\mu$ s was applied using a tripolar configuration, with electrodes E1 and E3 grounded and electrode E2 stimulating, at a stimulus rate of 40Hz. The artefact measurement of interest (1502, 1512) was obtained on electrode 4 for each plot. Measurements were also obtained on electrodes 5 to 7 using the method of the present invention in both plots, these measurements indicated collectively at 1504, 1512. The measurement parameters for each plot included recovering charge on the stimulus electrodes by short circuiting the stimulus electrodes to each other for 100  $\mu$ s before stimulation. As shown in Figure 14a, when the sense electrodes were shorted as taught by prior art methods, the artefact in the measurement 1502 was considerably larger than the artefact present in measurements 1504. In contrast, when the sense electrode E4 was disconnected from the measurement circuitry and from the stimulus electrodes after the stimulus, as taught by the present invention, the artefact in the measurement 1512 from electrode E4 was considerably reduced. The effect of this benefit in preferred embodiments is that an evoked response can be recorded in a single measurement with sufficient signal to noise ratio to permit analysis of the individual evoked response measurement. Moreover, such "single shot" measurements can in some embodiments be obtained in response to normal therapeutic stimuli. This avoids wasting battery power to deliver a train of high power stimuli having parameters which are well outside normal therapeutic settings and thus not of therapeutic benefit, to enable an averaged response to be extracted over a large number of measurements, as is required in systems having poor artefact performance.

**[0076]** It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the scope of the inven-

tion as defined by the appended claims. For example in the measurements stages of charge recovery (Figure 2b), stimulate (Figure 2c) and delay (Figure 2d), the sense electrodes are described as being disconnected from the sense circuitry. In the embodiment of Figure 2 this is effected by setting the sample and hold 208 to "hold", and it is noted that in alternative embodiments the sample and hold 208 may be positioned elsewhere in the measurement chain. Such embodiments are all to be understood to be within the scope of the phrase "disconnecting the sense electrode from the measurement circuitry" or similar as used herein. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

### Claims

1. An implantable device for measuring a neural response to a stimulus, the device comprising:
  - a plurality of electrodes including one or more nominal stimulus electrodes and one or more nominal sense electrodes;
  - a stimulus source for providing a stimulus to be delivered from the one or more stimulus electrodes to neural tissue;
  - measurement circuitry for amplifying a neural signal sensed at the one or more sense electrodes; and a control unit configured to control application of a stimulus to the neural tissue and measurement of an evoked neural response, the control unit further configured to recover charge on the stimulus electrodes by short circuiting the stimulus electrodes to each other, the control unit further configured to cause the stimulus source to apply an electrical stimulus from the stimulus electrodes to neural tissue while keeping the or each sense electrode disconnected from the measurement circuitry, the control unit further configured to impose a delay during which the stimulus electrodes are open circuited and the sense electrode is disconnected from the measurement circuitry and from the stimulus electrodes, and the control unit further configured to measure a neural response signal present at the sense electrode by connecting the or each sense electrode to the measurement circuitry after the delay;
  - characterized in that** the control unit is further configured to settle the measurement circuitry prior to a stimulus by connecting the or each sense electrode to the measurement circuitry to allow the measurement circuitry to settle towards a bio-electrically defined steady state.
2. The device of claim 1, wherein the plurality of electrodes form an implantable electrode array.
3. The device of claim 2, wherein the electrode array comprises a linear array of electrodes arranged in a single column along the array, or comprises a two-dimensional array having two or more columns of electrodes arranged along the array.
4. The device of claim 2 or claim 3, wherein the sense electrodes are configured to be open circuited during the post-stimulus delay so as to be disconnected from all other electrodes of the array, to prevent charge transfer to the sense electrode from other non-stimulus electrodes.
5. The device of any one of claims 1 to 4, adapted to undertake repeated measurement cycles, and comprising a measurement amplifier adapted to allow for accumulation of a bio-electrically defined steady state bias point over multiple cycles without re-setting the bias point each cycle.
6. The device of any one of claims 1 to 5, wherein a feedback loop is implemented to determine a suitable minimum delay which avoids amplifier saturation for a given stimulus.
7. The device of any one of claims 5 to 6, wherein a buffer or follower amplifier is provided between the sense electrode and the measurement amplifier, so that the high reverse impedance of the buffer effectively prevents switching transients from being conveyed to the sense electrode, thereby avoiding artefact which may arise upon the sense electrode if subjected to such transients.
8. The device of any one of claims 5 to 7 comprising a buffer amplifier configured to give current gain to drive a storage capacitor of a sample and hold circuit at the input of the measurement amplifier.
9. The device of any one of claims 1 to 8, wherein each electrode is provided with an associated measurement amplifier, configured so as to avoid the need to switch the sense electrode(s) to a shared measurement amplifier.
10. The device of any one of claims 1 to 9, wherein the implant comprises or is configured to operatively connect to a drug reservoir and drug delivery pump, with the pump being controllable by feedback based on CAP measurements.
11. The implantable device of any one of claims 1 to 10 wherein the control unit is configured to obtain a CAP measurement and to use the obtained CAP measurement to control the delivery of subsequent neural stimuli by the implantable device.
12. A computer program product comprising computer

program code configured to cause the implantable device of claim 1 to execute a procedure for measuring a neural response stimulus, wherein the procedure comprising:

settling measurement circuitry prior to a stimulus, by connecting a sense electrode to the measurement circuitry to allow the measurement circuitry to settle towards a bio-electrically defined steady state; recovering charge on stimulus electrodes by short circuiting the stimulus electrodes to each other;  
 applying an electrical stimulus from the stimulus electrodes to neural tissue, while keeping the sense electrode disconnected from the measurement circuitry; imposing a delay during which the stimulus electrodes are open circuited and the sense electrode is disconnected from the measurement circuitry and from the stimulus electrodes; and  
 after the delay, measuring a neural response signal present at the sense electrode by connecting the sense electrode to the measurement circuitry.

13. The computer program product of claim 12, wherein the procedure further comprises obtaining an averaged CAP measurement by (i) delivering a first stimulus of a first polarity, and obtaining a first measurement of a CAP evoked by the first stimulus; (ii) delivering a second stimulus of a second polarity opposite to the first polarity, and obtaining a second measurement of a CAP evoked by the second stimulus; and (iii) taking an average of the first measurement and the second measurement to obtain an averaged measurement.
14. The computer program product of claim 13, wherein the procedure further comprises obtaining a curve of the averaged measurement vs stimulus amplitude in order to obtain information regarding recruitment affected by each stimulus.
15. The computer program product of claim 14, wherein the recruitment information is used for feedback control by the implantable device.

#### Patentansprüche

1. Implantierbare Einrichtung zum Messen einer neuralen Antwort auf einen Reiz, wobei die Einrichtung umfasst:
- mehrere Elektroden, die eine oder mehrere nominelle Reizelektroden und eine oder mehrere nominelle Erfassungselektroden umfassen;  
 eine Reizquelle zum Bereitstellen eines Reizes,

der von der einen oder den mehreren Reizelektroden Nervengewebe zugeführt werden soll;  
 eine Messschaltungsanordnung zum Verstärken eines neuralen Signals, das an der einen oder den mehreren Erfassungselektroden erfasst wird; und

eine Steuereinheit, die konfiguriert ist, das Anlegen eines Reizes an das Nervengewebe und die Messung einer evozierten neuralen Antwort zu steuern, wobei die Steuereinheit ferner konfiguriert ist, Ladung auf den Reizelektroden durch Kurzschließen der Reizelektroden miteinander zurückzugewinnen, die Steuereinheit ferner konfiguriert ist, zu bewirken, dass die Reizquelle einen elektrischen Reiz von den Reizelektroden an Nervengewebe anlegt, während die oder jede Erfassungselektrode von der Messschaltungsanordnung getrennt gehalten wird, die Steuereinheit ferner konfiguriert ist, eine Verzögerung festzulegen, während der die Reizelektroden in einem offenen Stromkreis angeordnet sind und die Erfassungselektrode von der Messschaltungsanordnung und von den Reizelektroden getrennt ist, und die Steuereinheit ferner konfiguriert ist, ein neurales Antwortsignal, das an der Erfassungselektrode anliegt, durch Verbinden der oder jeder Erfassungselektrode mit der Messschaltungsanordnung nach der Verzögerung zu messen;

**dadurch gekennzeichnet, dass** die Steuereinheit ferner konfiguriert ist, die Messschaltungsanordnung vor einem Reiz durch Verbinden der oder jeder Erfassungselektrode mit der Messschaltungsanordnung auszugleichen, um der Messschaltungsanordnung zu ermöglichen, einen bioelektrisch definierten stationären Zustand zu kommen.

2. Einrichtung nach Anspruch 1, wobei die mehreren Elektroden ein implantierbares Elektrodenarray bilden.
3. Einrichtung nach Anspruch 2, wobei das Elektrodenarray ein geradliniges Array von Elektroden, die in einer einzelnen Kolonne entlang des Arrays angeordnet sind, umfasst oder ein zweidimensionales Array, das zwei oder mehr Kolonnen von Elektroden, die entlang des Arrays angeordnet sind, umfasst.
4. Einrichtung nach Anspruch 2 oder Anspruch 3, wobei die Erfassungselektroden konfiguriert sind, während der Verzögerung nach dem Reiz in einem offenen Stromkreis angeordnet zu sein, derart, dass sie von allen weiteren Elektroden des Arrays getrennt sind, um eine Ladungsübertragung von weiteren Nicht-Reizelektroden zu der Reizelektrode zu verhindern.

5. Einrichtung nach einem der Ansprüche 1 bis 4, die ausgelegt ist, wiederholte Messzyklen durchzuführen, und einen Messverstärker umfasst, der ausgelegt ist, eine Akkumulation eines bioelektrisch definierten stationären Arbeitspunktes über mehrere Zyklen ohne Neueinstellung des Arbeitspunktes in jedem Zyklus zu ermöglichen. 5
6. Einrichtung nach einem der Ansprüche 1 bis 5, wobei eine Rückkopplungsschleife implementiert ist, um eine geeignete Minimalverzögerung zu bestimmen, die eine Verstärkersättigung für einen gegebenen Reiz verhindert. 10
7. Einrichtung nach einem der Ansprüche 5 bis 6, wobei ein Puffer oder ein Folgerverstärker zwischen der Erfassungselektrode und dem Messverstärker vorgesehen ist, derart, dass die hohe Umkehrimpedanz des Puffers wirksam verhindert, dass Umschalttransienten zu der Erfassungselektrode übertragen werden, wodurch ein Artefakt vermieden wird, das an der Erfassungselektrode auftreten kann, wenn sie derartigen Transienten ausgesetzt ist. 15  
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8. Einrichtung nach einem der Ansprüche 5 bis 7, die einen Pufferverstärker umfasst, der konfiguriert ist, eine Stromverstärkung zu bieten, um einen Speicherkondensator einer Abtast- und Halteschaltung am Eingang des Messverstärkers anzusteuern. 25  
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9. Einrichtung nach einem der Ansprüche 1 bis 8, wobei jede Elektrode mit einem zugeordneten Messverstärker versehen ist, der konfiguriert ist, die Notwendigkeit zu vermeiden, die Erfassungselektrode(n) zu einem gemeinsam verwendeten Messverstärker umzuschalten. 35
10. Einrichtung nach einem der Ansprüche 1 bis 9, wobei das Implantat einen Arzneimittelbehälter und eine Arzneimittelverabreichungspumpe umfasst oder konfiguriert ist, sich betriebstechnisch damit zu verbinden, wobei die Pumpe durch eine Rückmeldung auf der Grundlage von CAP-Messwerten steuerbar ist. 40  
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11. Implantierbare Einrichtung nach einem der Ansprüche 1 bis 10, wobei die Steuereinheit konfiguriert ist, einen CAP-Messwert zu erhalten und den erhaltenen CAP-Messwert zu verwenden, um die Übermittlung nachfolgender neuraler Reize durch die implantierbare Einrichtung zu steuern. 50
12. Computerprogrammprodukt, das Computerprogrammcode enthält, der konfiguriert ist, die implantierbare Einrichtung nach Anspruch 1 zu veranlassen, ein Verfahren zum Messen eines neuralen Antwortreizes auszuführen, wobei das Verfahren umfasst:
- Ausgleichen einer Messschaltungsanordnung vor einem Reiz durch Verbinden einer Erfassungselektrode mit der Messschaltungsanordnung, um der Messschaltungsanordnung zu ermöglichen, in einen bioelektrisch definierten stationären Zustand zu kommen; Zurückgewinnen von Ladung an Reizelektroden durch Kurzschließen der Reizelektroden miteinander; Anlegen eines elektrischen Reizes von den Reizelektroden an Nervengewebe, während die Erfassungselektrode von der Messschaltungsanordnung getrennt gehalten wird; Festlegen einer Verzögerung, während der die Reizelektroden in einem offenen Stromkreis angeordnet sind und die Erfassungselektrode von der Messschaltungsanordnung und von den Reizelektroden getrennt ist; und nach der Verzögerung, Messen eines neuralen Antwortsignals, das an der Erfassungselektrode anliegt, durch Verbinden der Erfassungselektrode mit der Messschaltungsanordnung.
13. Computerprogrammprodukt nach Anspruch 12, wobei das Verfahren ferner das Erhalten eines gemittelten CAP-Messwertes durch Folgendes umfasst:
- (i) Übermitteln eines ersten Reizes mit einer ersten Polarität und Erhalten eines ersten Messwertes eines CAP, das durch den ersten Reiz hervorgerufen wurde;
- (ii) Übermitteln eines zweiten Reizes mit einer zweiten Polarität, die der ersten Polarität entgegengesetzt ist, und Erhalten eines zweiten Messwertes eines CAP, das durch den zweiten Reiz hervorgerufen wurde; und (iii) Bilden eines Mittelwertes des ersten Messwertes und des zweiten Messwertes, um einen gemittelten Messwert zu erhalten.
14. Computerprogrammprodukt nach Anspruch 13, wobei das Verfahren ferner das Erhalten einer Kurve der gemittelten Messwerte über der Reizamplitude umfasst, um Informationen hinsichtlich eines Recruitment, das von jedem Reiz beeinflusst wird, zu erhalten.
15. Computerprogrammprodukt nach Anspruch 14, wobei die Recruitment-Informationen für eine Rückkopplungssteuerung durch die implantierbare Einrichtung verwendet werden.

### Revendications

1. Appareil implantable de mesure d'une réponse neuronale à une stimulation, le dispositif comprenant :

- une pluralité d'électrodes incluant une ou plusieurs électrodes(s) de stimulation nominale et une ou plusieurs électrode(s) de sens nominal, une source de stimulation pour fournir une stimulation à délivrer par l'une ou plusieurs électrodes de stimulation à un tissu neuronal et un circuit de mesure pour amplifier un signal neuronal détecté à l'une ou plusieurs des électrodes de sens et
- une unité de contrôle configurée pour contrôler l'application d'une stimulation au tissu neuronal et la mesure d'une réponse neuronale évoquée, l'unité de contrôle étant configurée, en outre, pour récupérer la charge sur les électrodes de stimulation en court-circuitant les électrodes de stimulation, l'unité de contrôle étant configurée, en outre, pour amener la source de stimulation à appliquer une stimulation électrique par les électrodes de stimulation au tissu neuronal, tout en maintenant l'électrode de sens ou chaque électrode de sens débranchée du circuit de mesure, l'unité de contrôle étant, en outre, configurée pour appliquer un retard au cours duquel les électrodes de stimulation sont en circuit ouvert, et l'électrode de sens est débranchée du circuit de mesure et des électrodes de stimulation, et l'unité de contrôle étant, en outre, configurée pour mesurer un signal de réponse neuronale présent à l'électrode de sens en raccordant l'électrode de sens ou chaque électrode de sens au circuit de mesure après le retard,
- caractérisé en ce que** l'unité de contrôle est configurée, en outre, pour régler le circuit de mesure avant une stimulation en raccordant l'électrode de sens ou chaque électrode de sens au circuit de mesure pour permettre de régler le circuit de mesure dans un état stable défini bio-électriquement.
2. Appareil de la revendication 1, dans lequel la pluralité d'électrodes forme un réseau d'électrodes implantable.
  3. Appareil de la revendication 2, dans lequel le réseau d'électrodes comprend un réseau linéaire d'électrodes disposé en une colonne unique le long du réseau, ou comprend un réseau bidimensionnel ayant deux colonnes d'électrodes ou plus disposées le long du réseau.
  4. Appareil de la revendication 2 ou de la revendication 3, dans lequel les électrodes de sens sont configurées pour être en circuit ouvert pendant le retard de post-stimulation, de manière à être débranchées de toutes les autres électrodes du réseau, pour éviter le transfert de charge vers l'électrode de sens à partir d'autres électrodes de non stimulation.
  5. Appareil de l'une quelconque des revendications 1 à 4, conçu pour effectuer des cycles de mesure répétés et comprenant un amplificateur de mesure conçu pour permettre l'accumulation d'un point de polarisation d'état stable défini bio-électriquement sur plusieurs cycles sans régler de nouveau le point de polarisation à chaque cycle.
  6. Appareil de l'une quelconque des revendications 1 à 5, dans lequel une boucle de rétroaction est mise en oeuvre pour déterminer un retard minimum approprié qui évite la saturation de l'amplificateur pour une stimulation donnée.
  7. Appareil de l'une quelconque des revendications 5 à 6, dans lequel un amplificateur séparateur ou suiveur est prévu entre l'électrode de sens et l'amplificateur de mesure, de sorte que l'impédance inverse élevée du séparateur évite effectivement l'acheminement des transitoires de commutation vers l'électrode de sens, évitant, de ce fait, l'artefact pouvant apparaître sur l'électrode de sens si elle est soumise à ces transitoires.
  8. Appareil de l'une quelconque des revendications 5 à 7, comprenant un amplificateur séparateur configuré pour donner un gain de courant pour commander un condensateur de stockage d'un circuit échantillonneur-bloqueur à l'entrée de l'amplificateur de mesure.
  9. Appareil de l'une quelconque des revendications 1 à 8, dans lequel chaque électrode est équipée d'un amplificateur de mesure associé, configuré de manière à éviter le besoin de commuter l' (les) électrode(s) de sens à un amplificateur de mesure partagé.
  10. Appareil de l'une quelconque des revendications 1 à 9, dans lequel l'implant comprend ou est configuré pour se raccorder en fonctionnement à un réservoir de médicament et à une pompe d'administration de médicament, la pompe pouvant être commandée par rétroaction sur la base de mesures CAP (port d'accès au cathéter) .
  11. Appareil implantable de l'une quelconque des revendications 1 à 10, dans lequel l'unité de contrôle est configurée pour obtenir une mesure CAP et pour utiliser la mesure CAP obtenue pour commander la délivrance de stimulations neuronales ultérieures par l'appareil implantable.
  12. Programme informatique comprenant un code de programme informatique configuré pour amener l'appareil implantable de la revendication 1 à exécuter une procédure pour mesurer une stimulation de réponse neuronale, dans lequel la procédure comprend :

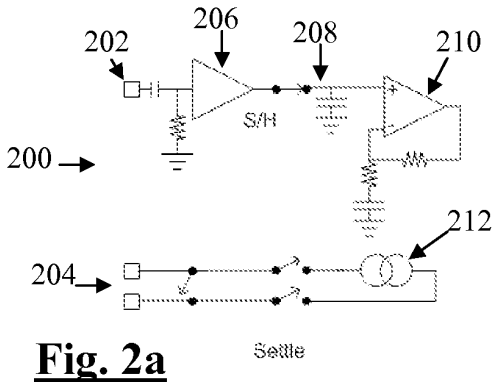
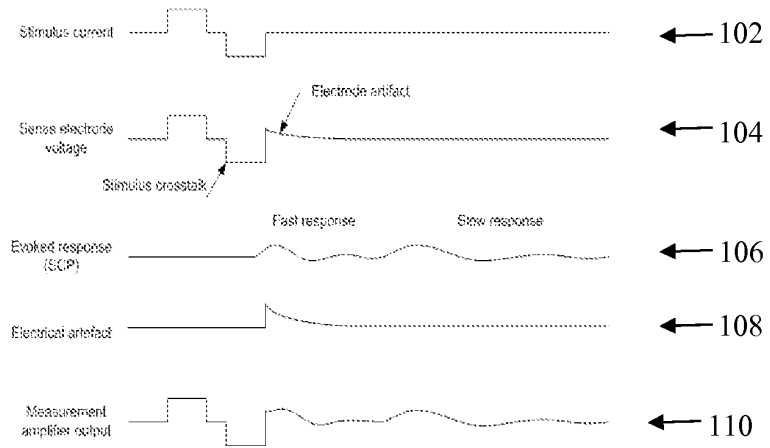
le réglage d'un circuit de mesure avant une stimulation, en raccordant une électrode de sens au circuit de mesure pour permettre de régler le circuit de mesure dans un état stable défini bio-électriquement, 5  
 la récupération de la charge sur les électrodes de stimulation en court-circuitant les électrodes de stimulation, 10  
 l'application d'une stimulation électrique par les électrodes de stimulation au tissu neuronal, tout en maintenant l'électrode de sens débranchée du circuit de mesure, 15  
 l'application d'un retard au cours duquel les électrodes de stimulation sont en circuit ouvert, et l'électrode de sens est débranchée du circuit de mesure et des électrodes de stimulation et après le délai, la mesure d'un signal de réponse neuronale présent à l'électrode de sens, en raccordant l'électrode de sens au circuit de mesure. 20

13. Programme informatique de la revendication 12, dans lequel la procédure comprend, en outre, l'obtention d'une mesure CAP moyennée en (i) délivrant une première stimulation d'une première polarité, et en obtenant une première mesure d'un CAP, évoquée par la première stimulation, (ii) délivrant une seconde stimulation d'une seconde polarité opposée à la première polarité, et en obtenant une seconde mesure d'un CAP, évoquée par la seconde stimulation, et (iii) en réalisant une moyenne de la première mesure et de la seconde mesure pour obtenir une mesure moyennée. 25 30
14. Programme informatique de la revendication 13, dans lequel la procédure comprend, en outre, l'obtention d'une courbe de la mesure moyennée par rapport à l'amplitude de la stimulation afin d'obtenir des informations relatives à la sélection affectée par chaque stimulation. 35 40
15. Programme informatique de la revendication 14, dans lequel les informations de sélection sont utilisées pour la commande par rétroaction, par l'appareil implantable. 45

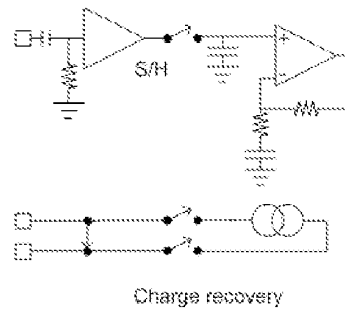
50

55

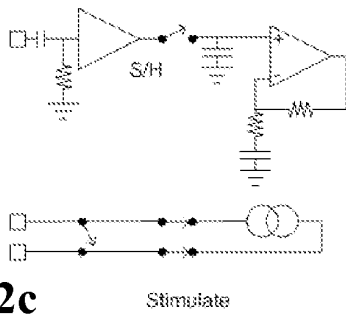
**Figure 1**



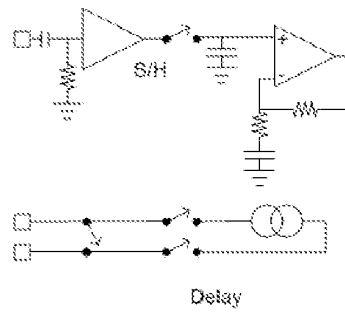
**Fig. 2a**



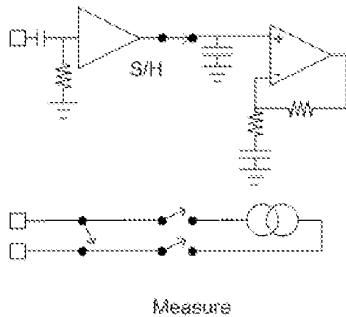
**Fig. 2b**



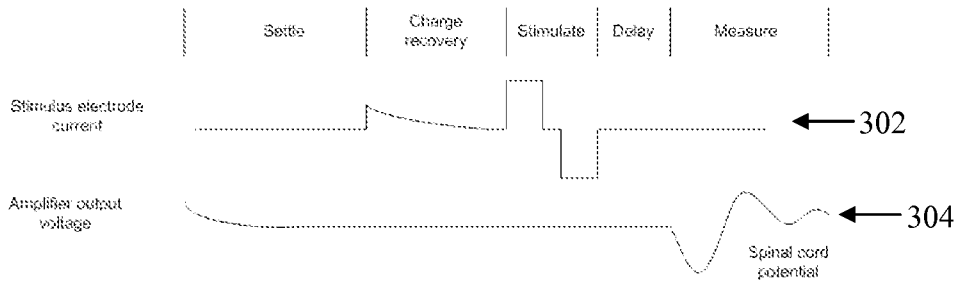
**Fig. 2c**



**Fig. 2d**

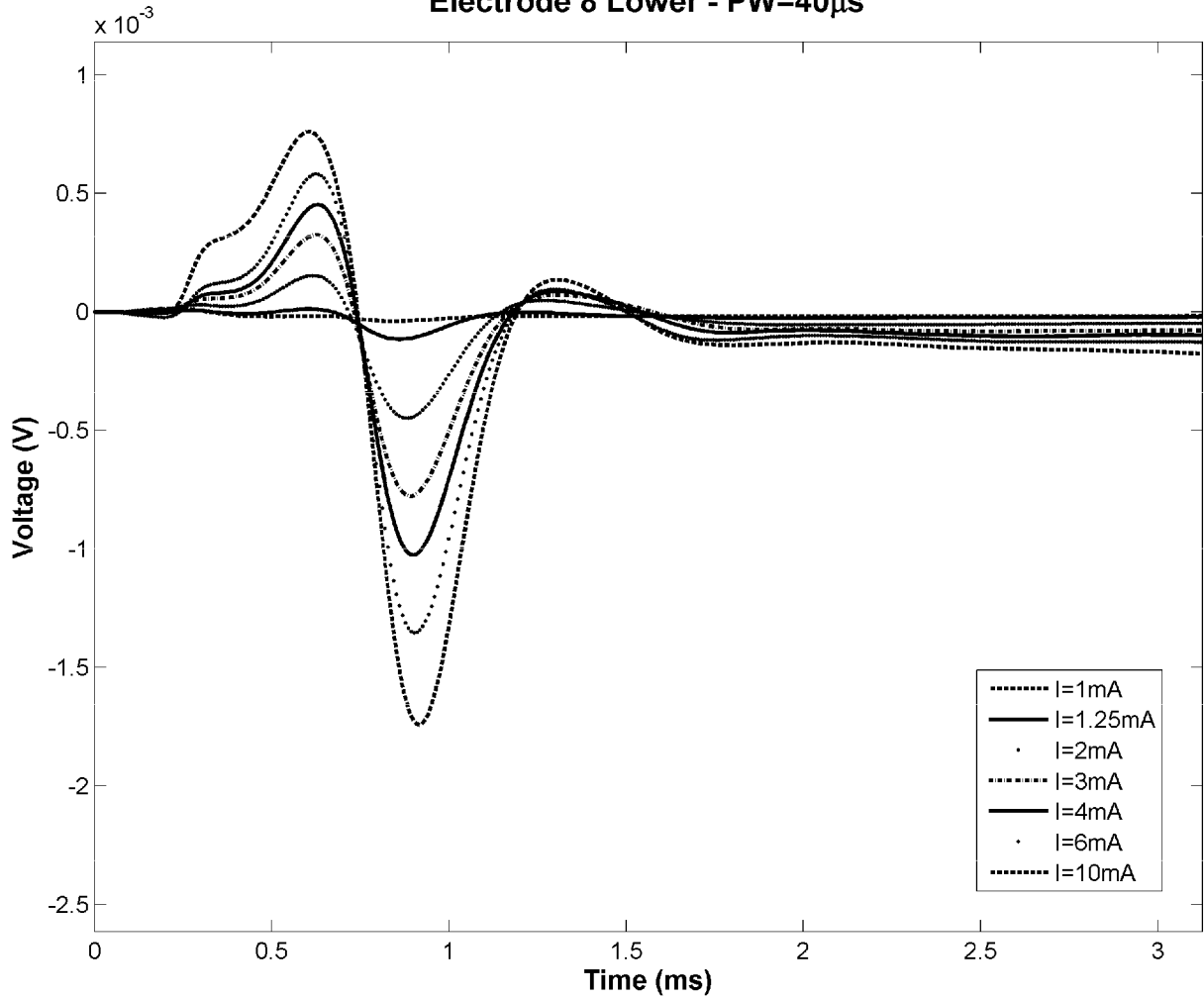


**Fig. 2e**

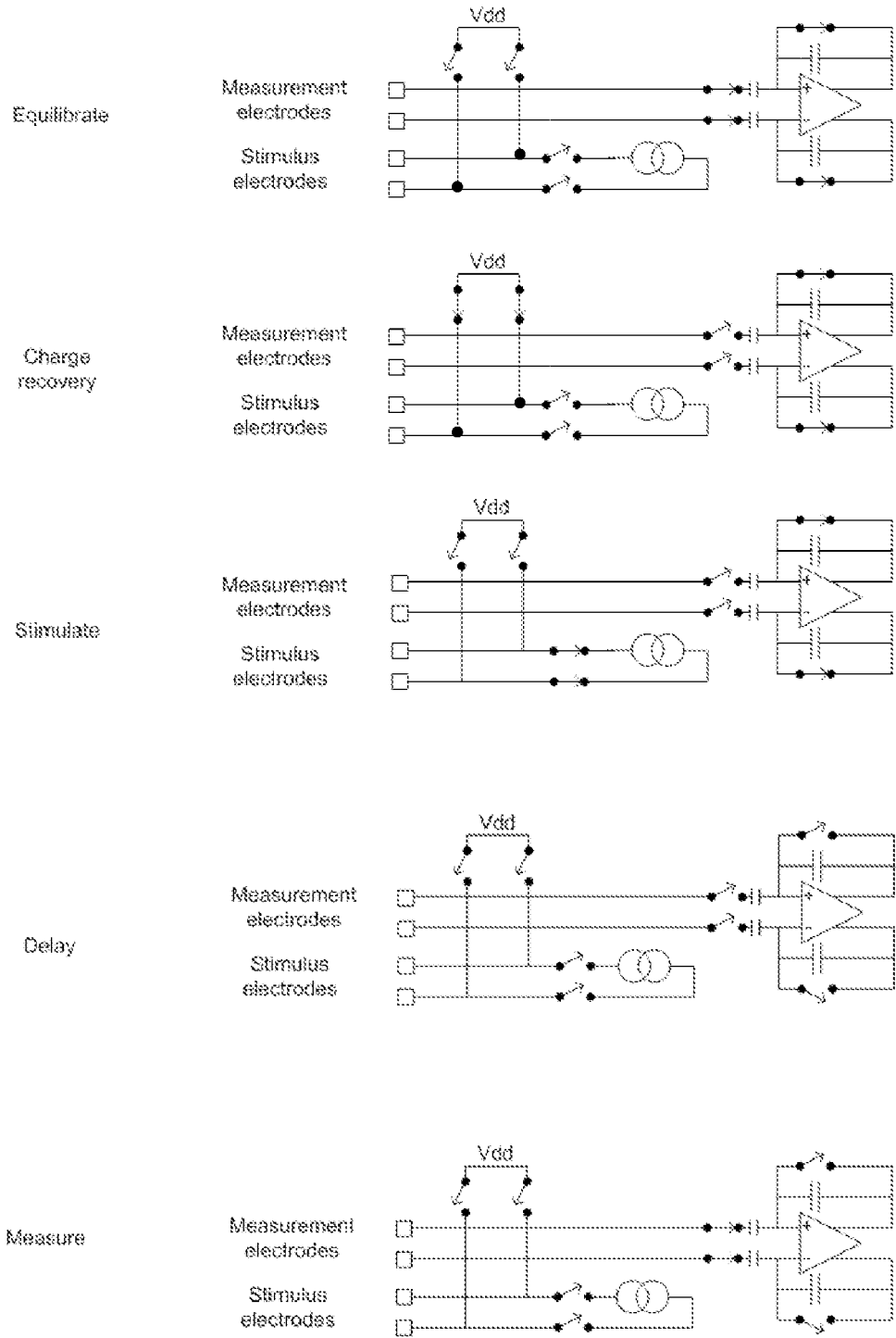


**Figure 3**

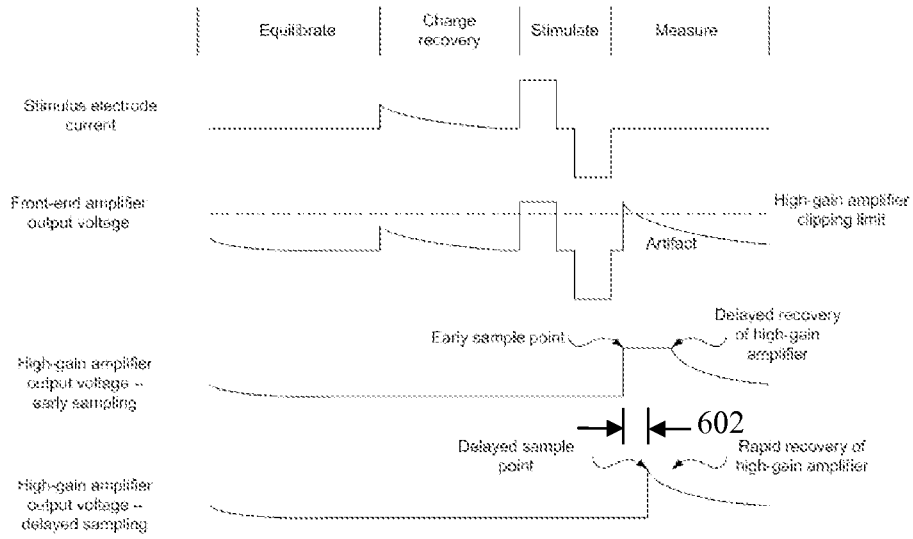
**EXP4-1 - Monophasic Stimulation - Sheep SCP Recording  
Electrode 8 Lower - PW=40 $\mu$ s**



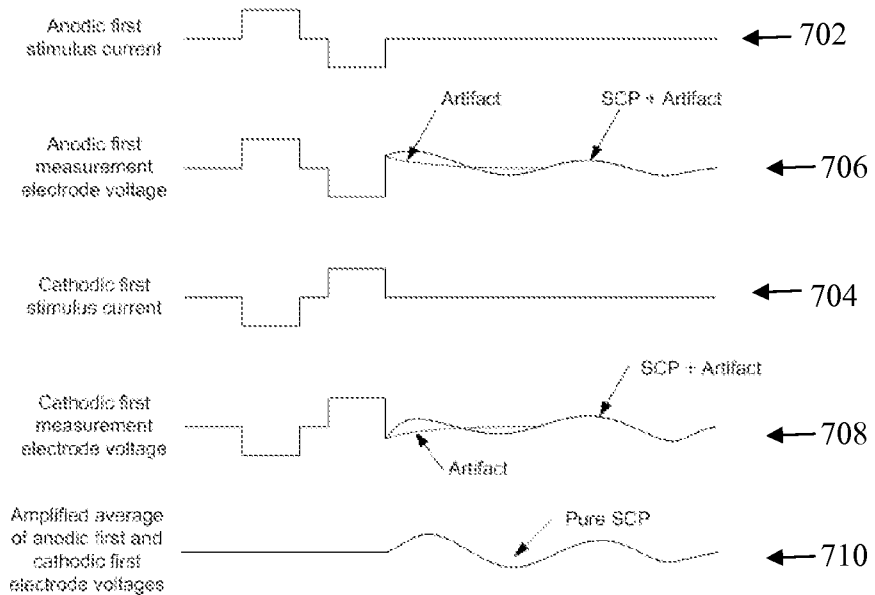
**Figure 4**



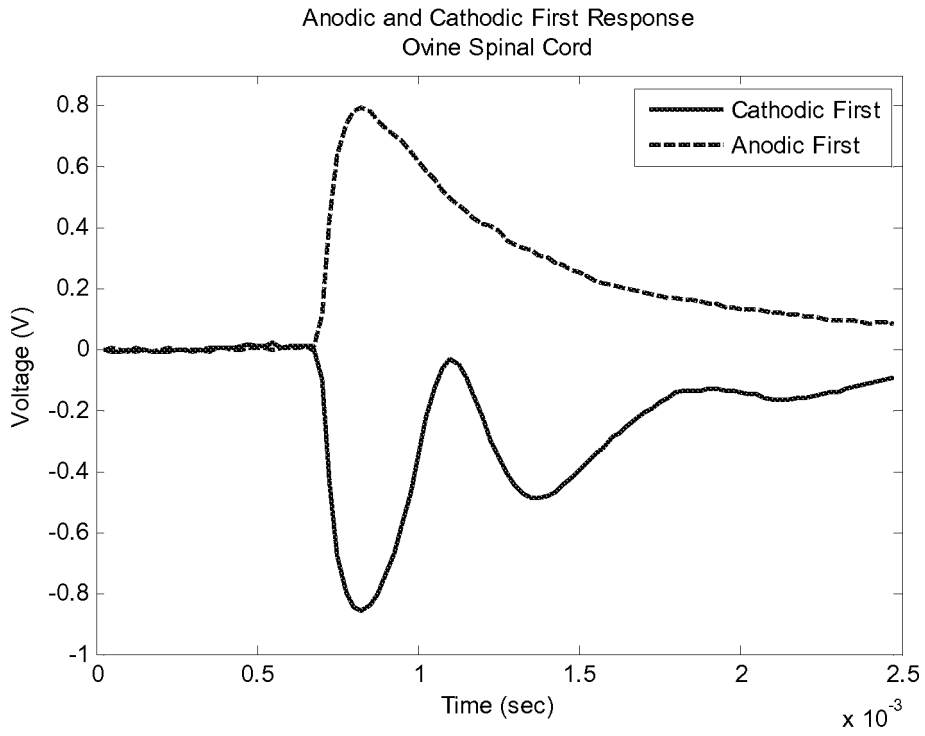
**Figure 5**



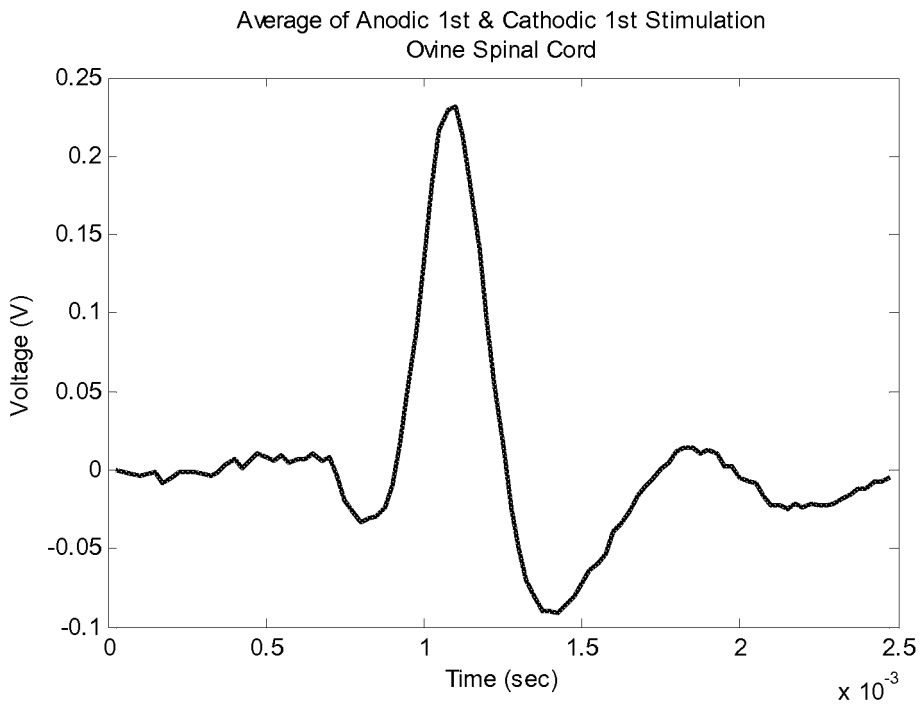
**Figure 6**



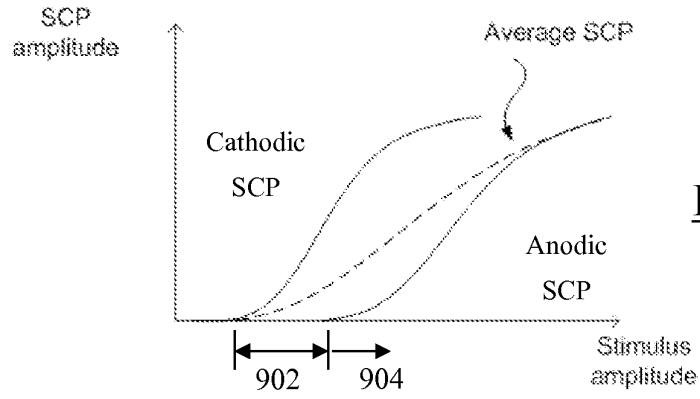
**Figure 7**



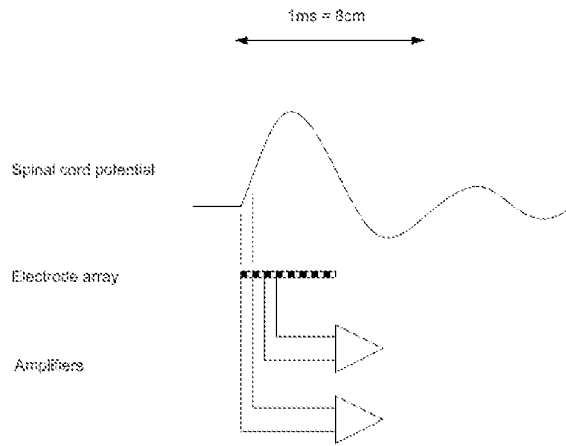
**Figure 8a**



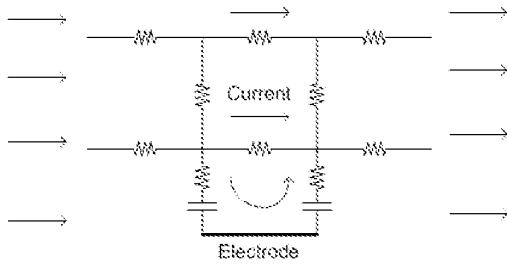
**Figure 8b**



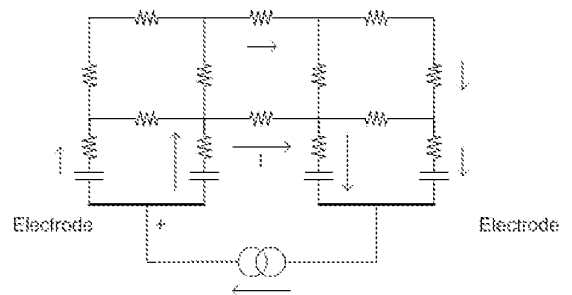
**Figure 9**



**Figure 10**



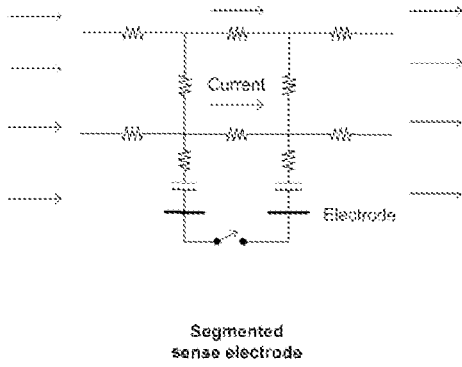
**Metal electrode  
in uniform field**



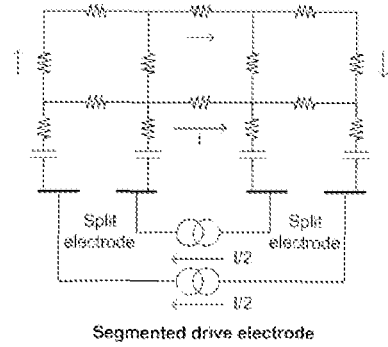
**Flow between metal  
electrodes in ionic solution**

**Figure 11a**

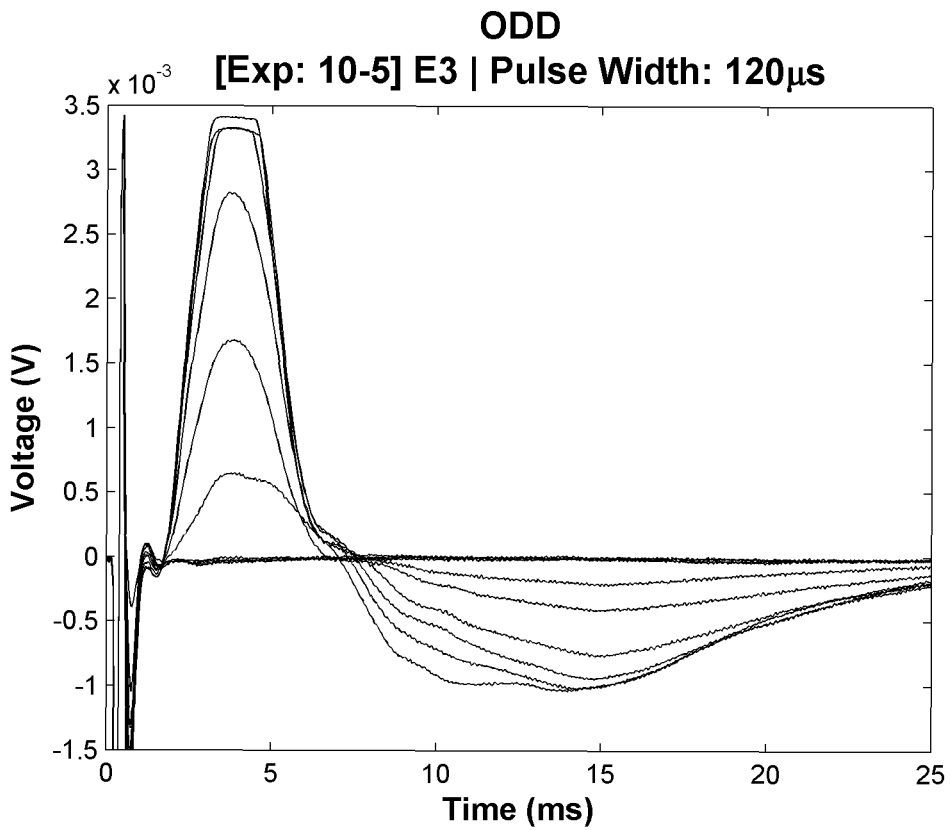
**Figure 11b**



**Figure 12a**

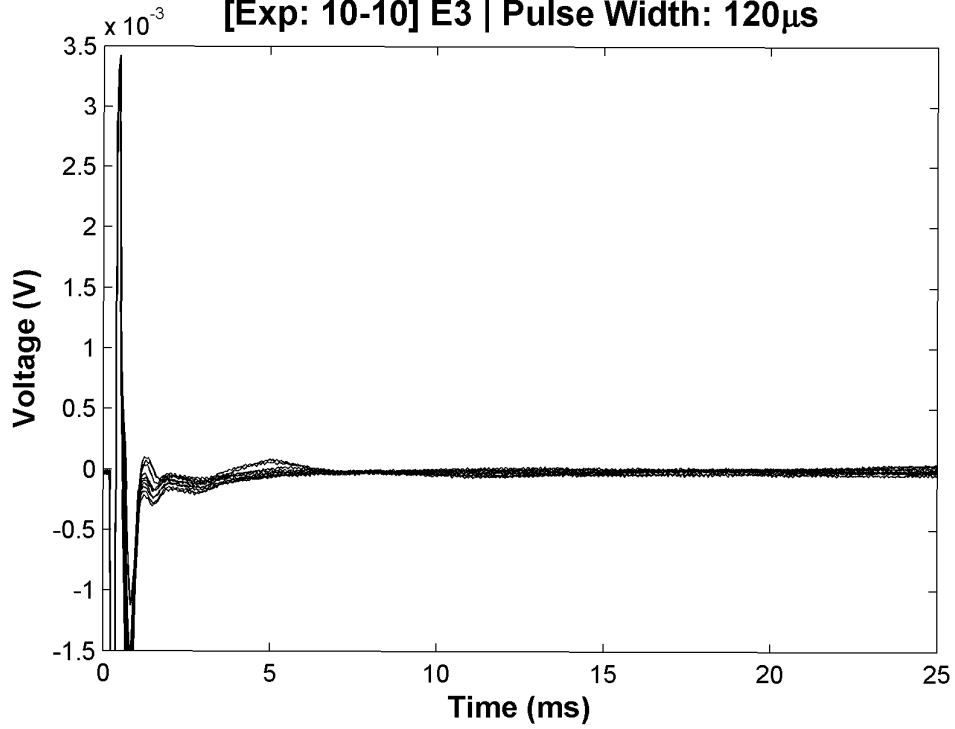


**Figure 12b**

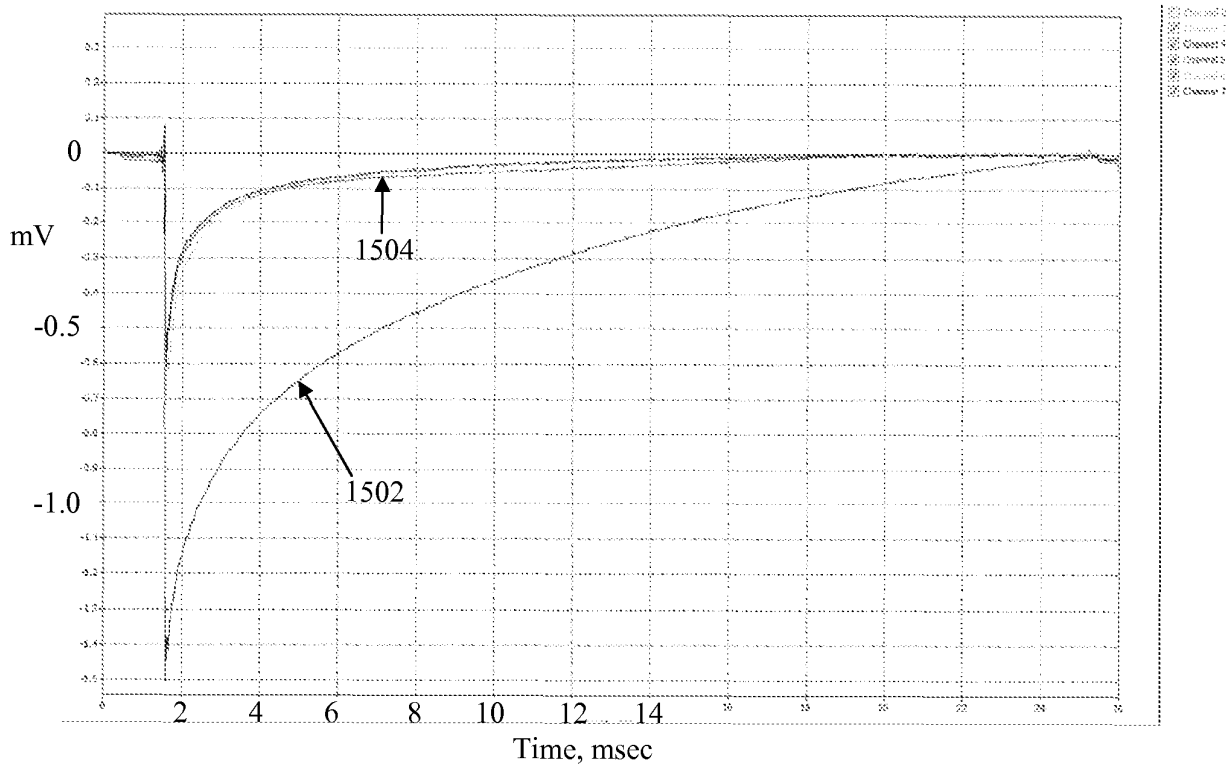


ODD

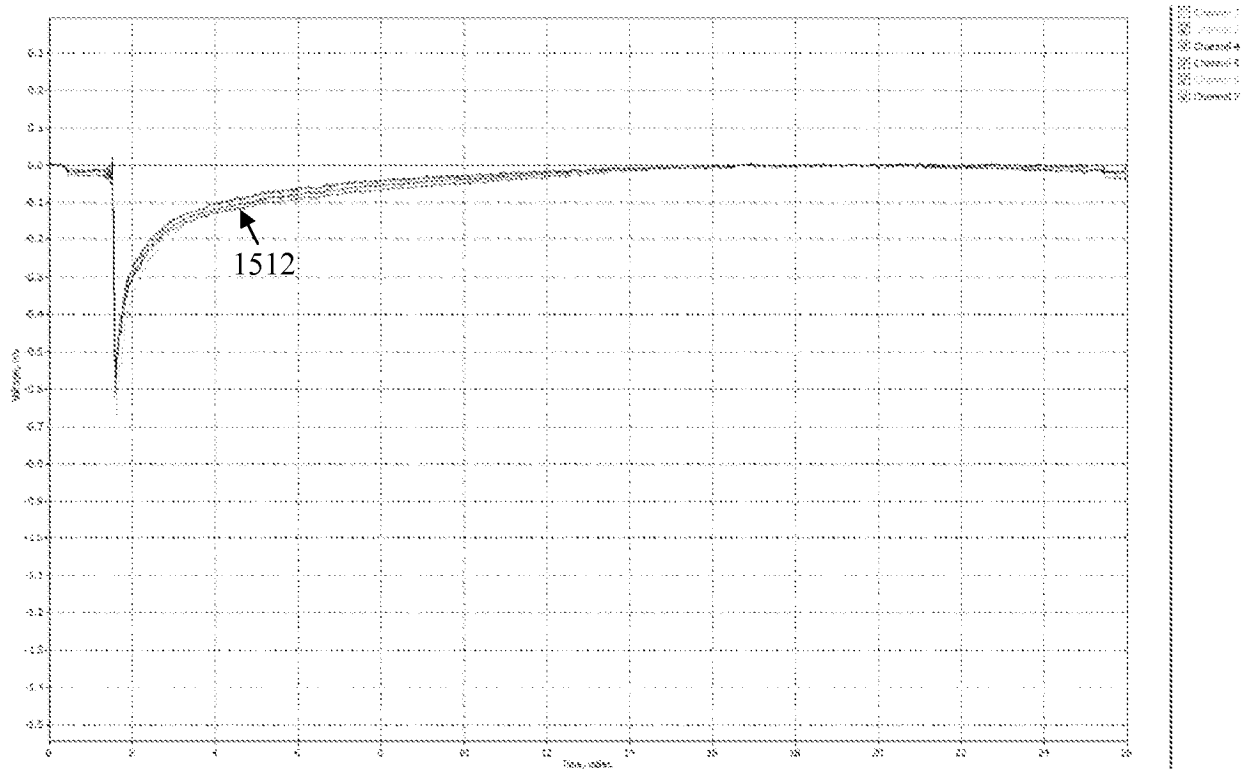
[Exp: 10-10] E3 | Pulse Width: 120 $\mu$ s



**Figure 13b**



**Figure 14a**



**Figure 14b**

**REFERENCES CITED IN THE DESCRIPTION**

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**Patent documents cited in the description**

- US 5913882 A [0008]
- US 5785651 A [0009]
- US 20070225767 A [0010]
- WO 2004021885 A [0011]

专利名称(译)	用于测量神经反应的方法和装置 - a		
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[标]申请(专利权)人(译)	萨鲁达医疗有限公司		
申请(专利权)人(译)	萨卢达MEDICAL PTY LIMITED		
当前申请(专利权)人(译)	萨卢达MEDICAL PTY LIMITED		
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发明人	PARKER, JOHN LOUIS SINGLE, PETER SCOTT VALLACK KARANTONIS, DEAN MICHAEL		
IPC分类号	A61N1/36 A61N1/05 A61B5/04 A61N1/372 A61B5/00		
CPC分类号	A61B5/04001 A61B5/7203 A61N1/36125 A61N1/36135 A61N1/36146 A61B5/4848 A61B5/6846 A61B5/7285 A61M5/1723 A61M2230/08 A61N1/36071		
优先权	2011901817 2011-05-13 AU		
其他公开文献	EP2707096A4 EP2707096B1		
外部链接	<a href="#">Espacenet</a>		

#### 摘要(译)

一种用于测量对刺激的神经反应的方法。通过将感测电极连接到测量电路以允许测量电路朝向生物电定义的稳态稳定，在刺激之前确定测量电路。通过使刺激电极彼此短路，在刺激电极上恢复电荷。然后从刺激电极向神经组织施加电刺激，同时保持感测电极与测量电路断开。在刺激之后，施加延迟，在此期间刺激电极开路并且感测电极与测量电路和刺激电极断开。在延迟之后，通过将感测电极连接到测量电路来测量存在于感测电极处的神经响应信号。