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SaBer DBS: a fully programmable, rechargeable, bilateral, charge-balanced preclinical microstimulator for long-term neural stimulation

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Abstract

To effectively study the mechanisms by which deep brain stimulation (DBS) produces its therapeutic benefit and to evaluate new therapeutic indications, it is vital to administer DBS over an extended period of time in awake, freely behaving animals. To date multiple preclinical stimulators have been designed and described. However, these stimulators have failed to incorporate some of the design criteria necessary to provide a system analogous to those used clinically. Here we define these design criteria and propose an improved and complete preclinical DBS system. This system is fully programmable in frequency, pulse-width and current amplitude, has a rechargeable battery and delivers biphasic, charge-balanced output to two independent electrodes. The system has been optimized for either implantation or for use externally via attachment to rodent jackets.

Keywords

deep brain stimulation; programmable; rechargeable; chronic; bilateral; biphasic; charge-balanced

1. Introduction

Commercial neural stimulators that are designed for the clinic are effective for use in patients; however they are both much too large and prohibitively expensive for preclinical work. It is not uncommon for such work to be performed by tethering the animal via a cable and commutator to an external stimulation system. Such an approach is not without its difficulties. Long-term tethering is not desirable given that it involves the permanent

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attachment of the subject to the stimulation system which neither adequately reflects the clinical experience nor does it allow the subject complete freedom of movement. Furthermore the logistics of tethering many animals is again costly, both financially and in terms of housing space, thus reducing throughput in chronic DBS experiments. Drawing from our experience in performing small animal DBS we describe the development of a fully programmable and rechargeable stimulation device that should be effective in preclinical DBS research.

It is obvious that stimulation of different, specific brain structures will modulate neural activity within specific neural networks. It is perhaps less obvious, although well known, that this modulation will be dependent on the stimulation parameters and the duration of stimulation. The subthalamic nucleus (STN) remains the most commonly reported DBS target for Parkinson's disease with stimulation typically delivered with 60 μ s duration pulses at a frequency of 130Hz. The prevalence of these parameters within the clinical literature has seemingly translated into acceptance of them by preclinical device designers. This acceptance has guided the engineering leading to the development of a number of rodent stimulators with fixed frequencies and pulse-widths mirroring the idealized Parkinson's paradigm (Harnack et al., 2008; Liu et al., 2008; de Haas et al., 2012). However, the full breadth of both neuropsychiatric and non-neuropsychiatric disorders over which DBS might find application, remains unknown and will arguably remain unknown whilst preclinical research is limited to these fixed parameters.

To elucidate how to specifically and optimally modulate brain function in myriad conditions, and to optimize stimulation paradigms for specific disorders or pathways, requires an open and exploratory investigation of the full parameter space in order to evaluate the most efficacious approach using the many advantages of preclinical experimentation. New targets - and the parameters with which to stimulate them - can only be identified given the correct tools and these tools are discussed in detail herein.

2. Design considerations

A rodent stimulator should optimally perform the same functions as a clinical stimulator as accurately as possible. A deep brain stimulator is little more than a variable duty cycle square wave generator. However the parameter space is large including at least frequency, pulsewidth and current (or voltage) amplitude. These waveform parameters may then be applied in multiple electrode contact configurations (contact selection and polarity). While these parameters cover the scope of current DBS applications it is worth considering that this parameter space may be extended to include; the temporal pattern of stimulation (Cota et al., 2009; Quinkert et al., 2010; Medeiros et al., 2012), the duration for which it is delivered (Ewing and Grace, 2012) and the waveform shape.

2.1. Parameter space

2.1.1. Mode—Until recently human DBS was largely administered in constant voltage mode. Preclinical research is almost universally performed in constant current mode which is becoming more common in clinical applications with the introduction of the Eon™ Rechargeable IPG system (St Jude Medical) and the Activa SC™ (Medtronic) which is operable in both constant voltage and constant current mode. Constant current mode has the advantage of delivering the same stimulation amplitude independent of changes in stimulating electrode resistance, which may vary with alterations in the electrode or its microenvironment.

2.1.2. Frequency—Defined as the number of stimulation pulses per second. DBS is most commonly applied at what are termed “high” frequencies (>100Hz with 130Hz and 185Hz

being particularly prevalent in the STN literature). And, whilst some authors have suggested that low frequency DBS may be “deleterious” (Kupsch et al., 2003; Timmermann et al., 2004; Kuncel et al., 2007; Florin et al., 2008) it seems plausible to suggest that the frequency dependence of therapeutic effects will be target specific as evidenced by effective therapeutic 5–10Hz stimulation of the pedunculopontine tegmentum (Nandi et al., 2008).

2.1.3. Pulseswidth—Defined as the duration of a single pulse; 60–210 μ A are typical (Volkman et al., 2002). The pulseswidth is likely to play an important role in which neural elements are being affected by the stimulation with brief pulse durations favoring the activation of myelinated fibres rather than neural cell bodies (Ranck, 1975; Nowak and Bullier, 1998).

2.1.4. Amplitude—In constant voltage mode the amplitude refers to the magnitude of the potential difference driving the current; typically 0.1–10.5V (Volkman et al., 2002). In constant current mode the voltage is dynamically adjusted in response to changes in the load impedance. Thus the current delivered is maintained at the same amplitude throughout the stimulation pulse and for the duration of treatment regardless of changes in electrode/tissue impedance.

2.1.5. Waveform—Current therapeutic strategies employ square waveforms (either voltage or current). A monophasic wave is such that the waveform has either only positive or negative components. A biphasic waveform contains both positive and negative components. In clinical DBS these components are matched to ensure zero net current delivery per period since it has been shown that monophasic stimulation induces significant tissue damage (Piallat et al., 2009).

2.1.6. Summary - minimum design criteria—A rodent stimulation device needs to satisfy the following design specifications: (i) charge balanced, (ii) square wave generation with (iii) frequencies between 2 and 200Hz, (iv) pulseswidths between 60 and 200 μ s and (v) constant current amplitudes between 0 and 1mA (Fig. 1). In addition the device should be capable of bilateral stimulation (2 independent stimulation channels) and be remotely programmable and rechargeable for subcutaneous implantation.

3. Materials and Methods

The stimulation system comprises the device programmer and the device itself. It also includes the firmware which is permanently written into the memory of the onboard microprocessor which controls the stimulation parameters of the stimulation device.

3.1. Programmer

The programmer provides communication between any standard computer and the device via a USB serial communication interface designed around a USB UART interface (FT232R, Future Technology Devices International Ltd.). The programmer also acts as a battery recharger (Microchip - MCP73811) which is powered directly from the USB port of the computer. Recharging the battery takes approximately 30 minutes.

3.2. Device

3.2.1. Rechargeable battery—The device is designed to surmount a (nominally) 3.7V lithium-ion polymer (LiPo) rechargeable battery (Renata ICP521630PM). These batteries have a 250mAh capacity, a mass of 5.4g and measure 31.5 $\times$ 17 $\times$ 5.7mm which provides an approximate size for the PCB footprint.

LiPo batteries benefit from high energy density and high charge and discharge rates. They are shipped and stored in a state designed to better handle shelf life. This state involves being stored at approximately 50% capacity and includes an additional chemical stabilizer in the cells which is lost when the packs are cycled (discharged - recharged). New batteries must be “broken in” to first break down the stabilizer and then to achieve their full charge voltage of 4.2V. A LiPo battery must not be discharged below 2.6V. Discharging the battery beyond this point may irrevocably damage the cell which may not then be fully rechargeable.

3.2.2. Voltage regulation—Jitter on power supply lines can cause shifts in voltage levels, causing timing errors and a loss of timing accuracy. The voltage supply for the microprocessor must be well regulated. As such a 3.3V micropower voltage regulator (ON Semiconductor, MC78LC33NTRG) is used to regulate the supply to the microprocessor.

3.2.3. Charge pump—Tissue is capable of increasing its resistivity over 10 fold in response to electrical stimulation. To be certain of constant current delivery to the stimulated region it is necessary to provide sufficient voltage at the input to the current source that it will be capable of delivering current over a wide range of electrode/tissue impedances. To generate a large enough voltage from batteries small enough to be comfortably carried by/ implanted in a rat a charge pump (National Semiconductor, LM2704) is used to generate a larger voltage from the supply. The charge pump, by storing and accumulating charge, is capable of generating significantly larger output voltages than it receives on its input. The maximum output voltage of the LM2704 is 20V. Human devices tend to operate on a 0–12V power supply. However, the impedance of rodent electrodes tends to be higher owing in part to their significantly smaller contact area.

3.2.4. Current sources and charge-balancing—A current source supplies current to a load regardless of its resistance. The current sources are based on typical transistor current source designs where the reference current is set by applying a fixed voltage across a resistance set by the digital potentiometers (Fig. 3). The voltage reference is fixed by the constant voltage drop across a diode. The current sources are switched via a high speed N channel MOSFET transistor switch (NXP, 2N7002) driven by the output of the microprocessor. Charge balancing is achieved by capacitor coupling and shorting the electrodes (to ground) immediately following the stimulation pulse (Fig. 5).

3.2.5. Microprocessor—Stimulation parameters are controlled via an onboard microprocessor (Texas Instruments, MSP430). The microcontroller generates a square waveform with a frequency and pulsewidth defined by the user via a standard pulsewidth modulation (PWM) waveform generator. The 1MHz internal clock drives two counters one defining the frequency and the other the pulse-width. The microprocessor also controls the digital potentiometers (Analog Devices, AD5290) which set the stimulation current with the help of a soft SPI protocol. The frequency, pulse-width and current are set by the user via the programming hardware and software. In addition the microprocessor can be remotely switched on and off via a magnetically actuated reed switch (Coto Technology, RI-80S). The microprocessor switches the charge pump on and off to conserve power while in sleep mode. Lithium ion batteries must not be discharged below 2.6V since once discharged beyond this level the battery can not be safely recharged. Thus the microprocessor monitors the battery voltage every 2 seconds. At battery voltages below 3V the microprocessor sends a warning message to the terminal. At voltages below 2.6V the microprocessor shuts the device down to prevent damage to the battery.

3.3. Firmware/software

The firmware is written permanently into the memory of the microprocessor and includes all the instructions to program the stimulation parameters and the brownout code to shut down the device at low battery voltages. Thus the software for programming the device is local to the device and may be accessed using the programmer from any computer with a terminal program installed. The terminal program under Windows is Hyperterminal which needs to be configured to communicate with the serial port with a baud rate of 1200, one stop bit and no parity. A recommended terminal program is putty which is available for both Linux and Windows. Accessing the firmware occurs automatically when the device is connected to the programmer yielding the interface pictured in Fig. 2.

3.4. Operation

The device is recharged and programmed by tethering the animal via a commutator and cable to the programming and recharging unit. Programming takes seconds, recharging takes approximately 30 minutes. During this time the animal must remain attached to the system. Between recharging/reprogramming sessions the device will run freely for a time determined by the stimulation parameters (10 days using common settings, Fig. 6) and need not be connected to anything allowing the animal complete freedom of movement. The user can adjust stimulation parameters by first typing the first letter of the parameter (indicated by the parenthesis), enter and then the value followed by enter. The units in which the parameters should be entered are also given (frequency in Hz, pulsewidth (time on) in μ s and current in μ A).

3.5. Electrodes and lead system

The device is designed to be fully sealed and reusable. Devices are en-capsulated in silicon and sterilized by exposure to ethylene oxide gas.

However the electrodes and their connections need to be disposable. As such an inexpensive interconnect system has been designed to connect the device to the electrodes. This lead system contains six cables which connect to the device via an Omnetics nano single row connector. This connection is over-molded and sealed with silicon sealant to prevent leakage of body fluids into the connectors and to prevent disconnection of the interconnect lead from the device. The six 30AWG cables (one each for power, ground, send, receive and two stimulation outputs) run to a tiny PCB containing simply the externalized connector (Omnetics 5-pin micro latching circular) for programming and recharge and 4 wire wrap terminals, one each for each of the stimulation outputs and two for ground connections. The length of the interconnection can be varied to suit the implantation site (subcutaneous/intra-abdominal). This disposable head-stage also contains an LED which flashes when the microprocessor is sending warning messages alerting the operator to low battery voltages.

Custom made platinum electrodes (being commercialized by Gaeltec) are implanted in the stimulation target as demanded by the stimulation paradigm and the bare wire terminations wrapped to the appropriate post. The square wire-wrap posts cut slightly into the wire creating a contact-weld and a reliable solderless connection.

3.6. Surgical procedure

The specifics of anaesthesia and analgesia will vary across laboratories. In general, the optimal implantation procedure involves making a larger than normal incision in the scalp from between the eyes to 1cm posterior to the ears. Electrodes are implanted in the target and secured to stainless steel screws fixed in the skull using a thin layer of dental cement. Through this large scalp incision it is possible to tunnel the complete device back into a subcutaneous pocket. We have experienced fewer post-surgical complications when

tunneling the device down on one side of the animal rather than directly over the spine. Attempts to implant in the back, over the spine tends to lead to the abrasion of the overlying skin, lesions and finally device exposure. In our experience leaving the device freely floating on the animal's side provides the greatest longevity for subcutaneous implants. It is crucial to force any trapped air from the subcutaneous pocket before closing the incision. While the scalp incision we use is uncommonly large we have found it easier to implement and better tolerated by the animals than the alternative approach of using two separate incisions - one on the scalp and one on the animal's back/side - with subsequent tunneling of the connector between the two. Following implantation of the electrodes and the device the excess electrode wires are wrapped (3 turns) to the appropriate terminal on the connector and any excess wire and wrapping post is snipped away. The connector is then cemented in place taking care not to foul the latch and the incision sutured tightly around the implant.

4. Results

4.1. Impedance estimation

To estimate the expected impedance of rodent stimulation electrodes measurements were made from rats with platinum electrodes implanted in either the ventral striatum or the medial prefrontal cortex (diameter, $330\mu\text{m}$; tip exposure, $500\mu\text{m}$, Plastics 1). Impedance was measured between the deep brain electrode and a stainless steel reference screw implanted at lambda. The electrode/tissue impedance of the medial prefrontal cortex was $14\pm 2\text{k}\Omega$ and the ventral striatum $11\pm 2\text{k}\Omega$ (mean $\pm$ SEM, $n = 10$, impedance measured at 1kHz using the RHA2000-EVAL board, Intan Technologies, LLC). These results do not differ significantly.

Estimating an approximate electrode/tissue impedance of $12\text{k}\Omega$ it is clear that the voltage compliance of the device is capable of reliably stimulating the target over a broad range electrode/tissue impedances with stimulation currents up to 1mA (Fig. 4).

4.2. Bench top testing

The device delivers charge balanced neural stimulation pulses with user-defined frequency, pulsewidth, current and phase (Fig. 5) to two independent stimulation channels (the figure depicts one channel deliberately wired to deliver monophasic pulses to illustrate the effect of the charge balancing circuitry). In shutdown mode the device enters an ultra-low power mode consuming $1\mu\text{A}$. During active stimulation the power consumption is dependent on the set current and the duty cycle (Fig. 6).

4.3. in vivo testing

The device (Fig. 7) has been used by various groups piloting preproduction prototypes. The device has been used to generate low frequency stimulation in animal models of traumatic injury (Fig. 9), 5 days of continuous high frequency stimulation of the nucleus accumbens in naïve adult rats (Ewing and Grace, 2012) and 12 days of continuous high frequency stimulation in the medial prefrontal cortex, nucleus accumbens and medial thalamus in an animal model of schizophrenia (Universitätsklinik Carl Gustav Carus an der Technischen Universität Dresden). In a separate study the device was used to generate stimulation artifacts of different amplitudes to produce an in vivo data set with which to develop the necessary algorithms for accurate stimulation artifact removal for local field potential analysis. Stimulation was performed in the ventral hippocampus with LFP recordings made in multiple brain regions. Data shown depict the varying amplitudes of stimulation artifacts recorded in the core of the nucleus accumbens (frequency = 130Hz, pulse-width = $100\mu\text{s}$, amplitudes = 50, 100, $200\mu\text{A}$, Fig 8).

5. Discussion

Here we have presented the development of a preclinical neural stimulation devices which matches the performance of those used in the clinic (such as the Active SCTM (Medtronic) or the EonTM (St. Jude Medical, Table 1)), produced at a fraction of the cost and meeting all of the design criteria outlined above.

The device successfully delivers charge-balanced current pulses. Charge-balancing is necessary to insure zero net current delivery per period, a requirement that is generally accepted as necessary for the long-term safety of chronic stimulation. In our design charge balancing is achieved passively by monophasic capacitor-coupled pulsing (Cogan, 2008) of the electrodes avoiding the possible inaccuracies in charge balancing inherent in active charge-balancing schemes. The inclusion of the charge-balancing capacitor also blocks any net DC current flow providing an additional safety feature on the stimulator output (Sooksood, 2010). This charge-balanced output is available on two independent stimulation channels facilitating bilateral stimulation which is most common in clinical applications. The output is fully programmable in frequency over the full range of expected useful frequencies, from the low frequency stimulation ($\approx 2\text{Hz}$) applied in the stimulation of the radial nerve to the high frequency stimulation ($> 100\text{Hz}$) typically applied in therapeutic deep brain stimulation.

The duration of the stimulation pulse is known to potently influence which neural elements are affected and is programmable to cover the full range of the stimulation period (from $1\mu\text{s}$ to the period ($1/f$) of the stimulation) spanning the full range of typical therapeutic pulse-widths ($60\text{--}210\mu\text{s}$ (Volkmann et al., 2002)). The current amplitude is programmable over a wide range and is delivered with a high voltage compliance (20V) facilitating reliable stimulation over a broad range of electrode/tissue impedances (Fig. 4). The current output is constant ensuring consistent delivery of current regardless of changes in electrode/tissue impedance which may vary within and between pulses. In addition, this charge-balanced, fully programmable, bilateral stimulation output is remotely programmable without the need for any specialized software via connection to the device programmer by an externalised connector.

Experience from clinical research and our own experience (Ewing and Grace, 2012) highlights the need for chronic DBS studies to better understand the underlying mechanisms. As such, the device is fitted with a rechargeable battery which is automatically recharged whenever the animal is connected to the programmer, allowing stimulation up to the lifetime of the subject. In shutdown mode the device draws approximately $1\mu\text{A}$ providing an extremely long shelf-life for the device. In active mode the device draws approximately 1mA providing up to 10 days of continuous stimulation between battery recharging. In addition to programming the device, the firmware continuously monitors the battery voltage, alerting the user when recharge is required and shutting the device down to protect the battery if necessary. Finally, the device is fitted with a magnetic switch for remotely turning the device on and off without requiring connection of the device to the programming hardware. While some of these features have been previously described, this device represents a substantial improvement in preclinical stimulation design by incorporating all of these features in a single package small enough to be safely implanted in rats.

Platinum and platinum/iridium are impossible to solder requiring spot-welding to make a permanent connection between the electrodes and other system components (solder-pads/sprung connectors). To negate the problems associated with such connections we have designed an electrode system which connects to the device via simple wire-wrap techniques during implantation providing an extremely safe and reliable electrical connection.

5.1. Additional design criteria and current limitations

In addition to the design criteria detailed above there are further criteria that are of interest in the ongoing development of rodent neural stimulators.

5.1.1. Temporal pattern—Current therapeutic strategies employ no temporal patterning; i.e., stimulation pulses are delivered at evenly spaced intervals determined by the frequency. However there is evidence to suggest that the temporal pattern of the pulses may yield different effects; pulses with a pseudo-random interpulse interval achieve different results than evenly spaced pulses with the same mean frequency (Cota et al., 2009; Quinkert et al., 2010; Medeiros et al., 2012). The device described here is not yet capable of temporal patterning since it is designed to best mirror current clinical practice. However research in this area is of great interest and is likely to lead to new therapeutic indications. Temporal patterning forms part of the ongoing development of SaBer DBS.

5.1.2. Contact selection/separation—Human DBS electrodes typically contain 4 electrode contacts with each contact being individually programmable. Each electrode contact can be programmed as an anode or a cathode (for bipolar stimulation). For monopolar stimulation the electrode contacts can only be programmed as cathodes with the stimulator case acting as an anode (Volkman et al., 2002). Contacts are cylindrical with a length of 1.5mm separated by either 0.5mm or 1.5mm (Medtronic Model 3389 and Model 3387 respectively). Stimulation can be delivered between any selection of the contacts (bipolar stimulation (stimulation occurring between 2 (or more) contacts separated by a small (mm) distance)). The case of the device can be selected as an electrode contact, with the result that the electrode implanted in the brain would act as a monopolar stimulation electrode (Volkman et al., 2002). Case referencing forms part of the ongoing development of SaBer DBS.

6. Conclusion

In summary, despite several published methods describing deep brain stimulation devices for preclinical research (Winter et al., 1998; Millard and Shepherd, 2007; Harnack et al., 2008; Forni et al., 2012; de Haas et al., 2012) none of them meet the complete design criteria for a fully programmable (amplitude, frequency, pulse-width), charge balanced, chronic (> months stimulation), bilateral neural stimulator. To address this need SaBer DBS has been developed which functions similarly to devices currently in clinical use. SaBer DBS is in the process of being commercialized by Digitimer (with Gaeltec developing the electrodes and leads) to provide preclinical researchers with access to a rodent stimulator which matches the performance of clinical devices. Pre-production prototypes are being successfully implemented in collaborating laboratories employing multiple stimulation paradigms (University of Pittsburgh (high frequency (130Hz), adult rodent DBS), Universitätsklinikum Carl Gustav Carus TU Dresden (high frequency (130Hz), adolescent rodent DBS) and the University of Glasgow (low frequency (5Hz) spinal stimulation)).

Acknowledgments

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Highlights

- SaBer DBS, a preclinical stimulation device that functions similar to devices currently in clinical use, such as the Active SCTM (Medtronic) or the EonTM (St. Jude Medical) has been developed.
- The device is small enough for subcutaneous/intra-abdominal implantation in the rat or can be carried externally using rodent jackets.
- The device is rechargeable allowing stimulation up to the life expectancy of the subject.
- The device is fully programmable in frequency, pulse-width and current amplitude allowing the study of any common stimulation paradigm.
- Two independent outputs are charge-balanced ensuring zero net current delivery per period.

Figure 1.

Desired device output - an idealised DBS waveform. The shaded areas indicate regions of current flow. The large amplitude, short duration portions of the wave are those believed to impose significant effects on the stimulated neurons. The charge injected during this initial phase of the wave is balanced by low amplitude, long duration portions immediately following the initial pulse. This ensures zero net current delivery per cycle.

```

/dev/ttyUSB0 - PuTTY

SaBer: Vstim = 0V, Vmcu = 3286mV
f)frequency=150Hz,p)ulsewidth=50us,c)urrent=50uA,r)un,s)top OFF --> f = 100

SaBer: Vstim = 0V, Vmcu = 3286mV
f)frequency=100Hz,p)ulsewidth=50us,c)urrent=50uA,r)un,s)top OFF --> p = 200

SaBer: Vstim = 0V, Vmcu = 3286mV
f)frequency=100Hz,p)ulsewidth=200us,c)urrent=50uA,r)un,s)top OFF --> c = 150

SaBer: Vstim = 0V, Vmcu = 3286mV
f)frequency=100Hz,p)ulsewidth=200us,c)urrent=153uA,r)un,s)top OFF --> r

SaBer: Vstim = 21V, Vmcu = 3286mV
f)frequency=100Hz,p)ulsewidth=200us,c)urrent=153uA,r)un,s)top ON! -->

SaBer: Vstim = 21V, Vmcu < 2562mV
f)frequency=100Hz,p)ulsewidth=200us,c)urrent=153uA,r)un,s)top ON! -->
Low battery!
Battery voltage critically low.

Low battery!
Battery voltage critically low.

repeated seven more times

Low battery!
Battery voltage critically low.
Emergency shutdown.

```

Figure 2.

SaBer DBS user interface. Stimulation parameters are adjusted by first typing the first letter of the parameter (indicated by the parenthesis), enter and then the value followed by enter. ON!/OFF indicates whether the device is currently running or not. At voltages approaching 2.6V the firmware returns error messages to the computer before enforcing an emergency shutdown to save the battery.

Figure 3.

Circuit overview. The programmer connects to the computer via a standard USB cable and acts as a communication interface between the computer and the device. It also charges the rechargeable battery directly from the USB port. The microprocessor generates a square wave with a frequency and pulsewidth specified by the user which drives the MOSFET switches, switching the current sources on and off, charging the coupling capacitor during the “on” phase. The coupling capacitors store charge and discharge to ground during the “off” phase. The current sources have a 20V voltage compliance to react to a wide range of tissue impedances.

Maximum electrode/tissue impedance for different set currents at different voltage compliances

Figure 4.

The voltage compliance of the device is designed to deliver reliable current delivery over a broad range of electrode/tissue impedances. At set currents of up to 1mA the device is capable of stimulating loads of up to 20k Ω . At lower, and more typical stimulation currents (100–200 μ A) the device is capable of reliable stimulation of loads up to 100k Ω .

Figure 5.

(A) SaBer DBS delivers anodic pulses at user-defined frequencies, pulse-widths and current amplitudes. Parameters shown are highly typical in rodent stimulation; $F = 130\text{Hz}$, $PW = 100\mu\text{s}$, $I = 500\mu\text{A}$, $\text{load} = 33\text{k}\Omega$. Top trace of each subfigure depicts the charge balanced circuit output, bottom trace depicts the unbalanced output. (B) Grounding the electrodes between pulses removes noise and improves pulse shaping and pulse width accuracy. Parameters shown are $F = 130\text{Hz}$, $PW = 60\mu\text{s}$, $I = 500\mu\text{A}$, $\text{load} = 33\text{k}\Omega$ (C) Capacitive charge balancing produces a negative phase with an equal area to that in the positive phase. Exaggerated parameters have been selected to highlight the charge balancing. Parameters shown are $F = 130\text{Hz}$, $PW = 2000\mu\text{s}$, $I = 500\mu\text{A}$, $\text{load} = 33\text{k}\Omega$

Figure 6.

The device's current consumption is dependent on the set current and the duty cycle. At higher output currents and longer pulse-widths the device draws increasing current leading to a shorter battery life. At typical parameters seen to be effective in Parkinson's disease (130Hz, 60µs, 100µA) the duty cycle is 0.78% drawing approximately 1mA giving a battery life of 250 hours.

Figure 7.

(A) The device (not including the interconnect system) measures 33×20×8mm following the attachment of the battery and encapsulation in silicon. (B) Communication with the device, once implanted, is via a custom-made cable and commutator which mates with the interconnect system. (C) A custom-made platinum electrode is kept straight for accurate surgical targeting via a stainless-steel support. (D) A simple stainless steel screw electrode is used as the ground/reference for stimulation. (E) The interconnect system can be made to custom lengths for alternate implantation routes and includes square wire-wrap posts for electrode connection during surgery.

Figure 8.

The parameters of the stimulation delivered by SaBer DBS can be altered “on the fly” to study the effects of different stimulation protocols in any brain region/network. Data shown depict the varying amplitudes of stimulation artifacts in the LFP recorded from the nucleus accumbens during ventral hippocampus stimulation (frequency = 130Hz, pulse-width = 100µs, amplitudes = 50, 100, 200µA). Top: raw LFP traces. Bottom: Power spectra for each stimulation condition.

Figure 9.

Activity in the spinal cord evoked by electrical stimulation. The traces show cord dorsum potentials (CDPs) recorded from the surface of the cervical spinal cord. This represents neuronal activity induced in the spinal cord by impulses travelling along the radial nerve (A) or from the pyramids (B). (A) The traces show response to single stimuli of $20\mu\text{A}$ applied to the radial nerve with an increasing pulse width ($24\mu\text{s}$ to $200\mu\text{s}$). Lengthening the pulse width leads to recruitment of more afferent fibres and therefore CDPs of increasing amplitude. (B) Similar traces evoked by stimulation of the pyramids (activating the corticospinal pathway) using a fixed pulse width (0.2ms) but increasing stimulus intensities from $20\mu\text{A}$ to $500\mu\text{A}$. The increasing stimulus currents recruit progressively more corticospinal fibres and evoke CDPs of successively larger amplitude.

Table 1

A comparison of preclinical and clinical neural stimulators. - indicates that the parameter is unavailable.

Function	SaBer DBS	Medtronic Activa SC™	St. Jude Medical Eon™
Frequency	2–500Hz	3–185Hz	2–1200Hz
Pulsewidth	0–100% of period	60–450 μ s	50–500 μ s
Set current	13–1000 μ A	0–25.5mA	0–25.5mA
Set voltage	-	0–10.5V	-
Supply voltage	3.6V	3.2V	-
Battery capacity	250mAh	4.5Ah	-
Channels	2	2	16
Mass	11.5g	67g	-
Volume	33×20×8mm/4cc	65×49×15mm	42cc
Programming	Wired (tether)	Wireless	Wireless