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An Embedded Deep Brain Stimulator for Biphasic Chronic Experiments in Freely Moving Rodents

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Abstract—This paper describes a Deep Brain Stimulation device, portable, for chronic experiments on rodents in the context of Parkinson’s disease. Our goal is to equip the animal with a device that mimics the human therapeutic conditions. It implies to respect a set of properties such as bilateral current-mode and charge-balanced stimulation, as well as programmability, low power consumption and re-usability to finally reach a suitable weight for long-term experiments. After the analysis of the solutions found in the literature, the full design of the device is explained. First, the stimulation front-end circuit driven by a processor unit, then the choice of supply sources which is a critical point for the weight and life-time of our system. Our low cost system has been realized using commercial discrete components and the overall power consumption was minimized. We achieved 6 days of maximal current stimulation with the chosen battery for a weight of 13.8g. Finally, the device was carried out *in vivo* on rats during a 3 weeks experiment as the used implantation technique allows battery changing. This experiment also permits to emphasize the mechanical aspects including the packaging and electrodes holding.

Index Terms—Biomedical engineering, Implants, Electrode driver, Deep Brain Stimulation, Low power.

I. ISSUES ON DEEP BRAIN STIMULATION DEVICES FOR EXPERIMENTATION ON ANIMAL MODELS

For over 20 years, effects of electrical stimulation of deep brain structures on motor symptoms of neuro-degenerative diseases have been of interest [1]–[4]. Deep brain stimulation (DBS) involves sending electrical pulses at a given frequency in specific nuclei of basal ganglia. For Parkinson’s disease, the first attempt of DBS treatment was applied in the Ventral Intermediate Nucleus [1], which stopped rest tremor but without beneficial effects on akinesia and rigidity. Henceforth, study on stimulation of other structures in animal models of the disease were conducted, showing that high frequency stimulation (HFS) of the subthalamic nucleus (STN) alleviated all the cardinal motor symptoms of Parkinson’s (PD) disease induced by MPTP in nonhuman primate model of the disease [5]. Based on this study, STN HFS was successfully applied to parkinsonian patients with advanced severe motor symptoms [2]. The electrodes of DBS, which are connected to a stimulator, are implanted chronically and continuous HFS of

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the STN induces dramatic improvement of the cardinal motor symptoms, such as tremor, akinesia and rigidity [6]. However, even if the beneficial effect of DBS on PD symptoms is well established, the underlying mechanism is still under debate [7]. This knowledge should lead to improve DBS therapy and devices, as well as the application of the approach to other neurological and psychiatric disorders.

Brain disorders can be modelled in laboratory animals, in order to develop pathophysiological states associated with behavioural outcomes. Animal models can be used to understand the functional mechanisms of DBS and also to develop new applications to brain diseases resistant to drug treatments. Nevertheless, except for non-human primates, the human DBS commercial implants cannot be used in rodents because of their large size. Thus, it is mandatory to develop specific embedded stimulators that mimic therapeutic action provided in human patients and adapted to small animals.

In the present paper we propose a new DBS dedicated stimulator, adapted for chronic experiments on rodent models and that mimics the conditions of DBS human therapy: bilateral, current-controlled biphasic stimulation. Besides this objective, the device to be designed should be highly configurable and tunable by the neurophysiologists for further analysis. In terms of embedded system design, the different materials composing the stimulator should be individually and globally optimized: electrodes for accurate STN targeting, adapted stimulation waveforms, stimulation circuitry for low power consumption and high battery capacity [8].

The rest of the paper is organized as follows. In section II, experimental constraints on the stimulator are summed up and existing setups for rodent DBS are compared. Thereafter, the complete system design is developed. The stimulation front-end circuit and its control and supply parts are described in section III. In Section IV, an important point is discussed: the minimization of the power consumption and the selection of the energy source adapted to the constraints of the chronic experiments. Our system has not only satisfactory electrical characteristics, but it has also been tested *in vivo*. Thus the mechanical aspects of the system, the packaging, the holding of the electrodes are detailed in section V, where results of implantation are also described. Finally, we discuss our results regarding the literature and conclude in section VI.

II. STATE OF THE ART OF EMBEDDED DBS STIMULATORS FOR RODENTS

Before reviewing and comparing the existing solutions, let us consider the important properties imposed to DBS devices,

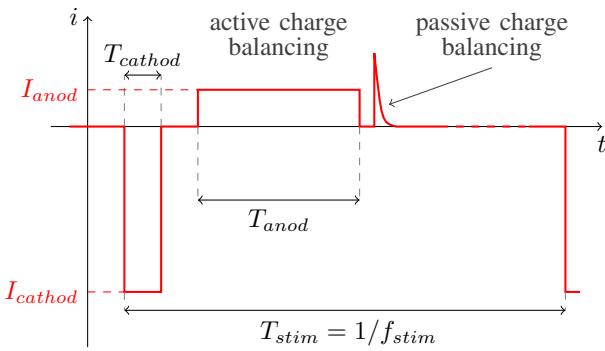


Fig. 1. Typical waveform of DBS current stimulation with active and/or passive charge balancing

according to the objectives previously announced: apply to the rodent the therapeutic conditions used for humans and be able to perform chronic stimulation on a freely moving animal.

A. Stimulator properties and corresponding design constraints

1) *Tissue safety*: Stimulation waveforms have to respect electro-neutrality of living tissue; therefore charge balanced stimulation protocols must be used [9]. Unbalanced waveforms for DBS can result in lesions around electrodes as related in [10]. As the electrical charge is the integral of current over time, DBS is often performed by constant current shaped pulses, with a total null area as detailed below.

Typical DBS current waveform is depicted in Fig. 1. A first negative current impulse, called cathodic pulse, is responsible for electrical stimulation of cells surrounding electrode contacts. Usually, the cathodic pulse duration T_{cathod} for DBS is set to $60\mu s$ [11], in the range of targeted cell chronaxy [12]; to reach therapeutic effect, the cathodic current I_{cathod} is increased until tremors stop. Pulse duration can ultimately be increased if more charges are needed to obtain the desired effect.

In order to have a charge-balanced waveform, two different techniques can be used or combined:

- Active charge compensation: a positive or anodic current pulse is delivered to the electrode. In order not to hyperpolarize neurons targeted by stimulation [9], the anodic current I_{anod} is lower than the cathodic current. Anodic time duration T_{anod} is then chosen to have a global charge over a stimulation period equal to zero and an interpulse delay is often added to prevent from cells hyperpolarization as explained in [9].
- Passive charge compensation: electrode is discharged through a resistor. This technique is the most efficient to ensure tissue safety, however the resulting current peak value is not under control and high current value can hyperpolarize targeted neurons [9].

Therefore, the design constraints related to tissue safety are to generate bidirectional currents under a wide range of voltage compliance, due to the variability and evolution of stimulated impedance

2) *Bilateral stimulation*: Chemical induced parkinsonism [13]–[16] can be either unilateral or bilateral. However, for DBS mechanism studies, behavioral evaluation has to be performed on groups of animals. In order not to induce dissymmetry in movement, bilateral Parkinsonism is used in majority of studies. This implies to implant two electrodes, one for each right and left subthalamic nucleus, and provide an adapted stimulation.

On rodents, the distance between the right and left subthalamic nuclei is relatively small ($5mm$ according to the rat brain atlas of *Paxinos and Watson, 1986*), and electrodes have to be implanted over a short operative time to limit the impact of anesthesia on the animal. A simple solution to face this problem is to design mechanically coupled electrodes. Hence, the stimulation can be made separately, with a two-channel system, or combined, with a one-channel system delivering twice the current needed on a single electrode.

The bilateral stimulation results then in design constraints on the electrodes and on the level of the delivered current. In this paper we discuss the required stimulation current as the sum of the currents for both hemispheres.

3) *Programmability*: The DBS waveform is periodic and its frequency f_{stim} is an important parameter. Frequencies less than $10Hz$ are known to increase motor symptoms of PD, whereas frequencies over $50Hz$ tend to decrease them; furthermore, the current threshold decreases as the frequency increases [11]. A generally accepted compromise to lower current levels is to set up stimulation frequency to $130Hz$, however this parameter can be changed if unsatisfactory physiological responses are observed. All stimulation parameters (frequency, amplitude and pulse duration, as shown in Fig. 1) should be tuned to obtain motor symptom reduction, as observed in a freely moving animals.

Moreover, these parameters can change after the implantation of electrodes and have then to be re-adjusted easily; some protocols even impose to stop stimulation, as for example MRI imaging. As we intend to address long-term stimulation, the design of the system must allow the easy tuning of the waveform parameters and the storage of a given experimental configuration.

4) *Freely moving animal*: This point is crucial in order to correctly evaluate therapeutic effect of DBS on rodent, especially complex motor activity and depression-like behavior [17].

Motor activity evaluation can be done using various tests. The most commonly used is the evaluation of locomotor activity in the open-field [18]–[20]. This test supposes an ease of access in the space; other motor tests have been developed to evaluate rigidity and catalepsy, which are two symptoms of PD, like for example the bar-test [21]. Parkinsonian non-motor disorders can also be quantified by the elevated plus maze [22], where the rodent has access to closed or open arms of the maze (anxiety-like behaviour), or sucrose preference [23], for which the animal is placed in the presence of two bottles to drink (depression-like behaviour). All these behavioural tests require the use of special equipments and the free motion of the animal in various areas without discomfort of being linked to an electrical device.

The resulting constraint for the stimulator is to be embedded on the rodents. As a consequence the volume and weight have to be managed. The volume is linked to the system placement in or on the body. The weight has to be bearable for the animal. We adopted an upper weight limit considering the physiology of the animal model: this limit corresponds to 5% of the average weight (around 400g) of a male *Sprague Dawley* rat, the commonly used specie for physiological experiments. The entire system (electronics, battery and cases) has to be less than 20g to limit impact on animal.

5) *Lifetime stimulation*: The embedded supply source has to provide enough energy for long term experimentation, either being changed or recharged. As a consequence, the overall power consumption has to be as small as possible without interfering with needs inherent with tissue safety. This condition has to be taken into account at all steps of stimulator design, from the front-end circuit topology to the global system powering strategy, including the choice of embedded battery.

6) *Re-usability and cost*: DBS studies on action mechanisms or side effect evaluations are based on chronic population experiments. The cost of the stimulation system has a big impact on the feasibility of experiments. The ideal stimulator for rodent experimental setup can be re-used for several experiments. In this case the battery has to be changed easily without excessive additional cost.

The need for cost effectiveness also has a repercussion on the adopted technology. Most of the available stimulators are designed on chips, although custom Application Specific Integrated Design solutions can be costly. All integrated solutions also have the drawback of being less flexible than the ones using off-the-shelf components, making them less adaptive for therapy enhancement studies. However the use of discrete electronics impact is not in favour of the system miniaturization.

B. Existing embedded stimulators for rodents

First used methods for electrical stimulation on freely moving rodents were based on rotating wire placed over animal's cage [18]. For the time of stimulation the animal had a wire plugged over their skull. However this solution limits the number of behavioral testing to an area defined by cable length; exploration of outlying area can induce tensions on animal skull where the electrode is fixed to the skull.

Several embedded DBS systems have already been designed for rodents, trying to satisfy previously reported constraints. We propose to review these solutions, focusing on one important criterion: the location of the circuit in rodent body.

Two studies [24,25] have reported systems with an electronic part implanted in the abdominal area of rodents, connected to an electrode implanted in the brain. The major advantage is that the animal can move easily after surgery. Nevertheless this choice presents major risks consecutive to surgery, like infections, especially in the abdomen region. It is then mandatory to use biocompatible materials.

In both studies, stimulation parameters are programmed using RF links; in [25], communication is done using Reed-switches and the RF emitter is a tubular device containing

the animal during the programming of stimulation. Of course, the animal movements are highly restricted and DBS action cannot be evaluated during programming. The battery is inside the animal body, implanted with the circuit, which requires additional surgery to change it, with additional infections risks. Moreover the use of RF link has a cost on global power consumption. In [24] no detail is given on tissue safety. Authors of [25] use charge balanced current waveforms. This first kind of DBS device is not adapted for experiments on rodents since it provides a high risk of side effects for a short time of action.

A second kind of embedded stimulators have been described in [16] and [26]. Both devices are wearable stimulators placed in vests. This solution solves two drawbacks of implanted devices: first, side effects of surgery are limited to electrode insertion and it is not necessary for electronics to be biocompatible as it is not in contact with tissues. Second, the battery is accessible on the back of the rodent and can be changed for long term experiments.

Nevertheless, such experiments are limited: animals also have to be placed in separated cages; even though, they can tear off their vest, and they risk severe brain damage if the electrodes are pulled out. The use of these wearable devices is in the end too risky for long term experimentation, even if both systems of [16] and [26] respect electrical conditions of tissues safety.

A third type of stimulators are detailed in [27] and [28]. These stimulators fixed to the skull with dental cement while electrodes are implanted into the brain. The risk of infection is limited compared to the first category of stimulators. Moreover, the risk of breaking the device is small if its volume and weight are limited. In [27] the battery cannot be changed due to the chosen packaging. In [28], the entire stimulator device can be separated from the head allowing a simple battery change and the use MRI apparatus during the experiment. Nevertheless authors of [28] did not consider the standards [9] for safe electrical stimulation.

In conclusion, the latter stimulator category seems to be the most suitable for long term experiments. All presented stimulators [16,24]–[28] were designed for unilateral stimulation, a setup only suitable for 6-OHDA-induced hemi-parkinsonism. As neurodegenerative diseases are bilateral, we have chosen to develop a system which allows bilateral implantation of electrodes in the STN of both cerebral hemispheres. For bilateral stimulation only one stimulation channel is needed but the maximum current has to be doubled.

Our system is the first DBS device developed for chronic long-term experiments on populations of rodents, respecting all safety procedures as summarized previously. Hereafter we describe in detail the circuit design, architecture and sizing, as well as considerations on power optimization, battery selection, and the specificities of the package attached to the implanted electrodes.

III. FRONT-END STIMULATION CIRCUIT

The front-end stimulation is the only part of the DBS device directly connected to electrodes. This circuit is in charge of

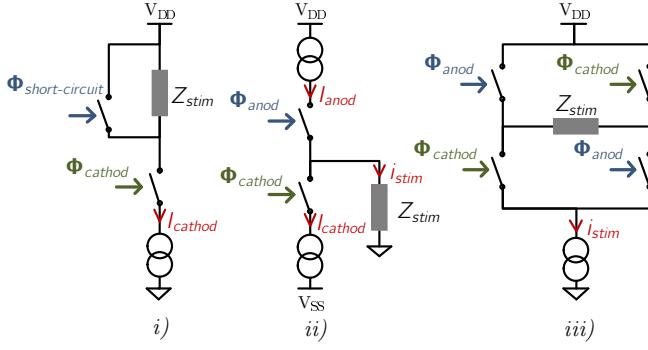


Fig. 2. Different circuits used for biphasic stimulation front-end. For structures *i*) and *iii*), the ground signal is the lowest potential of the supply source, for structure *ii*) the ground signal is the middle point of the symmetrical supply.

delivering the adequate current to the tissue. It may work under a high output voltage considering the impedance loading while respecting charge balancing.

A. Architectures for low-power electrical stimulation

The generic front-end for electrical stimulation consists of a current source connected to an electrode using a combination of switches. As a unique current source can only provide a monopolar current, different architectures combining switches and sources have been developed to allow the injection of positive or negative current and thus ensure charge balancing. Three structures, presented in Fig. 2, are basically used in stimulation circuits.

Structure *i*) in Fig. 2 [29]–[31] is based on one current source and two switches. This topology can only provide biphasic stimulus with passive charge balancing. Such circuits are suitable for embedded systems because of their asymmetric power supply and the simplicity of driving requirements. Nevertheless passive charge balancing is not suitable for DBS where huge amounts of charges are delivered to the tissue: the peak current reached when the electrode is in short-circuit is too high for therapeutic conditions.

Active charge balancing requires a second current source as described in [29,32]–[38] and illustrated in Fig. 2 *ii*). Anodic and cathodic currents are generated by separate sources and two switches control the timing of stimulation pulses. The electrode is referenced to ground signal, as a consequence, power supply must be symmetrical. This architecture requires a more complex powering circuitry, able to reach the high bipolar voltage needed to drive the electrode. As the resulting biasing power is approximately twice as high as for the previous topology, this architecture is not suitable for low power embedded systems. This topology is also not ideally performing in terms of charge balancing. The use of two sources at the highest and lowest potentials makes a mandatory use of respectively P and N transistors. Therefore the current sources are not perfectly paired and charges resulting from balancing errors can accumulate at the bio-electronic interface. If matching calibration techniques can be applied [39], a third switch is often added in that topology to provide passive discharge to solve such problems.

A third architecture is often used in stimulation systems [40]–[49], providing active charge balancing with one current source and four switches as shown in Fig. 2 *iii*). The current polarity through the electrode is changed, using switches organized in an H-bridge. The supply voltage is then asymmetric. The use of only one current source allows both a reduction of the global power consumption and simplifying the charge balancing. Passive charge balancing can also be performed by breaking the symmetry of switch command or by adding a fifth switch in parallel with the stimulated load. Nevertheless, due to the floating stimulation load, this structure cannot be used with multi-channel electrodes that have a common current return path as in [50] for example; in such a configuration, asynchronous stimulation of different channels can cause short-circuits between electrodes and possibly cause damage by involuntary charge injection in the tissue. In this case the Fig. 2 *ii*) is the only solution to provide biphasic current stimulation. As DBS uses a pair of electrodes with individual current return path for each cerebral hemisphere, the topology described in Fig. 2 *iii*) is the most suitable for chronic embedded DBS systems.

Whatever the adopted topology, there is a risk of involuntary charge accumulation in the tissue, due to small leakage currents. To prevent from such a situation, a DC blocking capacitor must be placed in series with the electrode. In Fig. 2, Z_{stim} is the combination of the electrode impedance and the DC blocking capacitor. The value of this additional capacitance is generally chosen so that the voltage drop is negligible compared to the voltage across the electrode in normal operation mode; nevertheless the global impedance Z_{stim} has to be taken into account when determining the maximum output voltage at the highest current values, to choose the appropriate voltage supply.

To realize our embedded DBS system, we chose the H-bridge topology presented in Fig. 2 *iii*). The system, described in Fig. 3, uses two levels of supply voltage. A low voltage supply V_{dd} , from the batteries, is connected to the current source and control circuits. The H-bridge is supplied with the high level voltage V_{HV} generated by a DC/DC converter.

V_{dd} is fixed by the choice of battery technology, and can vary due to the state of charge. In order to deliver a constant waveform over time, the stimulus generator uses a supply voltage independent current source. The schematic of this source is explained in section III-B. Additional circuits for timing control and voltage-level conversion are described in section III-C.

B. Supply-voltage-independent programmable current source

We designed a current source (see Fig. 3 and Table I for parts' references) that can be controlled using a variable resistance and switched ON and OFF to limit the impact of biasing on the power consumption. In order to limit the consumption and the area with discrete components, current sources topologies using operational amplifiers were excluded; the adopted current generator is mainly based on a single transistor $T2$. Transistors $T3$ and $T4$ are forming a current mirror to link the source output to the front-end stimulation.

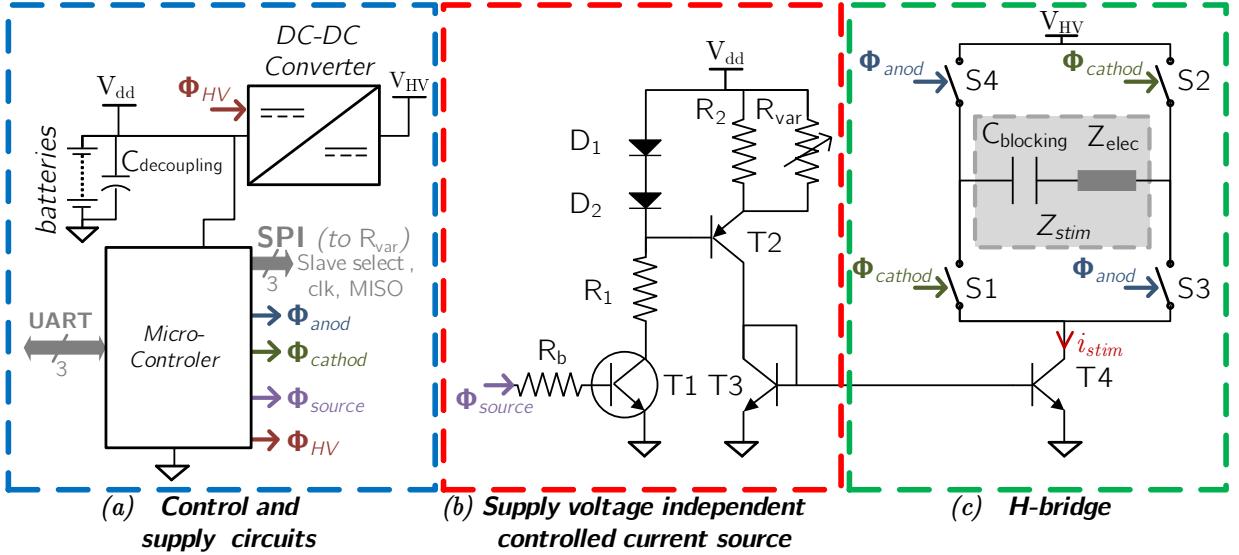


Fig. 3. Overall schematic of the developed DBS system. The circuit is divided in three parts. (c) The stimulation current (i_{stim}) is delivered to the load (Z_{stim}) composed of the electrode (Z_{elec}) and the blocking capacitor ($C_{blocking}$), by a H-bridge topology (green rectangle). (b) The current value is fixed by a supply voltage independent current source (red rectangle). (a) Supply circuits and a micro-controller (blue rectangle) drive blocks (c) and (b).

TABLE I
LIST OF ACTIVE COMPONENTS USED IN THE STIMULATOR

Part	Reference	Manufacturer
μ C	MC9S08SH8	Freescale
DC/DC Converter	LT3494	Linear Technology
D_1, D_2, T_1, R_1, R_2	PSSI2021-SAY	NXP
T_1	BC847-BW	Phillips
T_3, T_4	BCV61-C	Infineon
$S_1 - S_4$	MAX4623	MAXIM
R_{var}	MAX5484-ETE+	MAXIM

In order to reach accurate copying, T_3 and T_4 are matched transistors included in the BCV61C part. The current source is formed by the combination of D_1 , D_2 , T_2 , R_2 and R_{var} . To reach accurate values and reproducibility, D_1 , D_2 , T_2 and R_2 can be found in package using a PSSI2021SAY. Assuming that emitter and collector currents of T_2 are equal, the biasing current is:

$$i_{cT2} = \frac{2V_{D\ on} - V_{be\ on}}{R2//R_{var}} \quad (1)$$

where $V_{D\ on}$, $V_{be\ on}$ are voltages across the diodes and the BJT base-emitter junction. Both $V_{D\ on}$ and $V_{be\ on}$ can be considered as constant values if a sufficient biasing current is provided. If necessary, this condition can be reached by lowering the value of R_1 . Transistor T_1 is used as an ON/OFF switch, so that minimum voltage across R_1 is determined by:

$$V_{R1\ min} < V_{dd} - 2V_{D\ on} - V_{ce\ sat\ T1} \quad (2)$$

Contributions of R_2 and R_{var} can be separated. R_2 ensures a fixed minimum current (in our case $i_{R2} = 15\mu A$) and R_{var} , when decreasing, increases stimulation current. For R_{var} , we used a digitally programmable resistance (MAXIM MAX5484). The resistance variation is then linear, coded on a 10 bits value;

the expression of the global stimulation current is then:

$$i_{stim} = i_{R2} + \frac{(2V_{D\ on} - V_{be\ on})}{R_{min} + D \cdot R_q} \quad (3)$$

where D is the 10 bits value coding the resistance ($D \in [0, 1023]$), R_q is the quantum of resistance ($R_q = 50\Omega$) and R_{min} ($R_{min} = 110\Omega$) is the minimum resistance of R_{var} . From this equation, one can observe that the variation law of current is a hyperbolic function of R_{var} code as illustrated in the figure 4(a). Such variations have already been used for neural electrical stimulation [26] and seem adapted to DBS, where higher values of current are not often used unless there is electrode misplacement during surgery [11].

Power on the H-bridge depends directly on electrode impedance Z_{stim} and i_{stim} ; the power consumption of the programmable current source is approximated by:

$$P_{source} \approx V_{dd} \left(\frac{V_{dd} - 2V_{D\ on} - V_{ce\ sat\ T1}}{R1} + i_{stim} \right) \quad (4)$$

The first term is due to the current source biasing and can be reduced by increasing R_1 with respect to equation 2. The second term is directly linked to the required stimulation current. The supply voltage V_{dd} could be decreased, depending on the battery technology choice which will be detailed in section IV.

C. Control and supply circuits

The control circuit generates the switch commands for cathodic and anodic pulses Φ_{cathod} and Φ_{anod} by driving analog switches realized with a MAX4623, and sends the values of the required current levels through the command of the variable resistance using a Serial Peripheral Interface (SPI) link. This circuit also controls the current source bias voltage Φ_{source} and the command of the high-voltage power

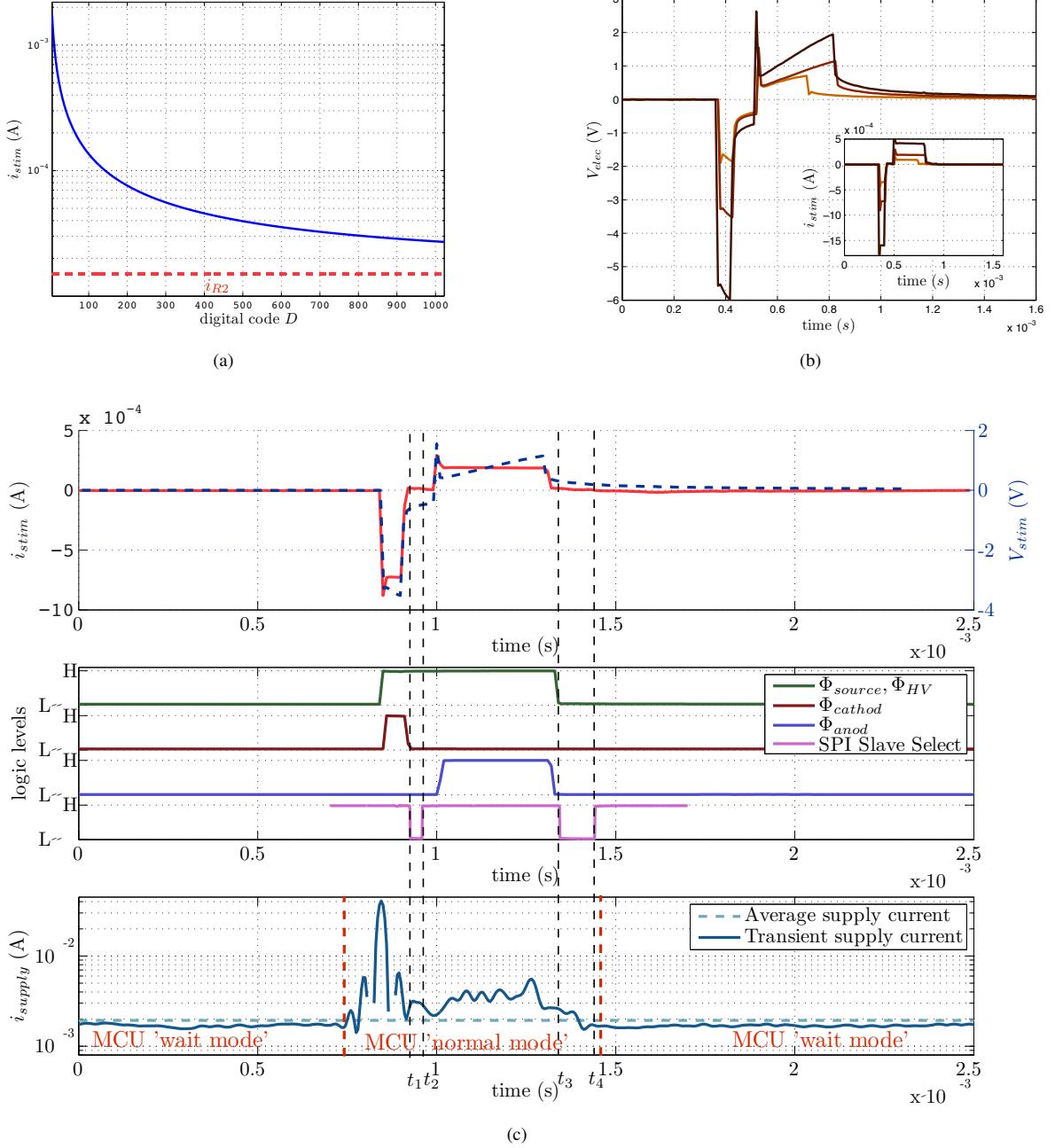


Fig. 4. (a) Graphical representation of the stimulation current i_{stim} as a function of the digital code of the variable resistance (b) Electrode response for biphasic stimulation of $I_{cathod} = 400, 800$ or $1600\mu A$ and $60\mu s$ pulse (c) Recorded chronogram of a typical stimulus ($60\mu s$ of $750\mu A$ cathodic current, charge balanced with a $250\mu A$ current pulse and $60\mu s$ of inter-pulse delay with a frequency of $130Hz$), corresponding logic commands and supply current. The average consumed current is reesented by a dashed line ($1.9mA$) for the used stimulation pattern

supply Φ_{HV} . A typical stimulation pattern is described in Fig. 4(c).

Parameters necessary to define a standard current stimulus as in Fig. 4(c) are: current sign and value, as well as timing of the cathodic and anodic phases.

Current sign management is done by generating cathodic and anodic signals in the right orders. The programming of a current value is performed with a *SPI* link, driving the variable resistance described in previous section (a 10 bits variable digital resistance with 1 code volatile memory register). As

currents are coded on 10-bits values, two bytes are sent by the *MCU* to generate each current value. However, for a given *SPI* baud-rate, this procedure is limited by the interval between two current pulses. In typical case, the inter-pulse timing, see Fig. 1, for *DBS* is $60\mu s$.

The most challenging section is the switching between cathodic and anodic values. Limiting the *SPI* baud-rate allows to minimize the *MCU* frequency, and thus the power as explained in the next section. The anodic code is stored in the resistance's non-volatile register when initializing a

new waveform, and is no longer transmitted; immediately after, the cathodic code is transmitted to the tap register to generate the first cathodic pulse. During the inter-pulse delay of each stimulation period, the non-volatile-register is copied in the resistance's tap register using a one byte communication (between markers t_1 and t_2 on Fig. 4(c)) to generate the anodic current. After the anodic phase, i.e. at the end of the stimulation waveform, the cathodic code is re-sent using two bytes to the tap register (between markers t_3 and t_4), configuring the current source for the next stimulation period. A timing difference ($t_2 - t_1 < t_4 - t_3$) can be observed on the logic output of the SPI Slave Select. With this strategy and a limited baud-rate of $147.5 \text{ kbit} \cdot \text{s}^{-1}$, the minimal inter-pulse delay is:

$$T_{\text{inter-pulse}} = \frac{N_{\text{bits}}}{BR} \geq \frac{8}{147.5 \cdot 10^3} = 54.24\mu\text{s} \quad (5)$$

With our current source and time resolution ($500\text{n}s$), charge balancing has a limited accuracy and a maximal equivalent DC current error measured at 520nA with a *picoammeter/voltage source Keithley 6487*. In order to decrease this unbalance, we implemented once every 256 periods (approximatively 2s) a passive discharge, by closing all switches and disabling the current source ($\Phi_{\text{anod}} = \Phi_{\text{cathod}} = '1'$, $\Phi_{\text{source}} = '0'$) ; the maximal error is then reduced to 72nA ; the additional DC blocking capacitor prevents from any residual charge on the tissue.

As illustrated in Fig. 3, the high voltage level necessary to provide current stimulation is generated from the embedded battery through a DC/DC switched mode power supply. The used topology is a Boost-Converter (*Linear Technology LT3494*) that levels up the voltage. The voltage across electrodes was measured for different levels of currents [51]. As voltage depends on both current value and pulse width, a measurement was conducted on saline solution with maximum values (i.e. 2mA and $500\mu\text{s}$) and the maximum measured voltage was near 8V , a set of electrode response voltages are presented in figure 4(b). The boost converter has to provide sufficient voltage for the electrode and for the voltage drop of DC blocking capacitor, switches and the current source. Moreover, the electrode impedance is known to increase after surgical implantation [52]. To ensure stimulation in any situation, a high voltage supply of 17.6V was used in the front end. This level can be adapted by changing external components of the used Boost-Converter.

IV. CONSIDERATIONS ON SYSTEM SUPPLYING

As often for embedded medical applications, the most challenging constraints for our chronic stimulator are the required power and energy. The power is imposed by the load, the system requirements and the circuit topology. We present in IV-A our strategy to minimize the power consumption. The energy challenge is related to the need for chronic stimulation, with minimal disturbance for the animal carrying the power source. In IV-B we will discuss the available battery technologies, and propose a suitable choice in our context.

A. Power management

In order to be integrated on animals skull, the volume and weight of the overall system have to be minimized. As the most prominent part of miniaturized systems are dedicated to power sources, the overall power of the system has to be optimized without influencing developed functionality. The power consumed by the system presented in Fig. 3 is given by:

$$P_{\text{stimulator}} = P_{\mu C} + P_{\text{source}} + P_{H-\text{bridge}} + P_{\text{boost}} \quad (6)$$

where $P_{\mu C}$ is the power of the MCU (Fig. 3 (a)), P_{source} is the power consumed by the controlled current source (Fig. 3 (a)), $P_{H-\text{bridge}}$ is the power consumed in the H-bridge (Fig. 3 (c)) and P_{boost} is the power consumed by the step-up DC/DC converter (Fig. 3 (a)).

We saw in a previous section that the current source power consumption can be reduced by limiting the diode current of $D1$, $D2$ (see Fig. 3). Moreover this current source can be turned off when not used by blocking transistor $T1$ (see Fig. 3). $P_{H-\text{bridge}}$ is approximated to the load power consumption as the switches equivalent resistance is negligible compared to the electrode impedance.

To evaluate and optimize the remaining terms, $P_{\mu C}$ and P_{boost} , we have to take into account both the mode of operation and the MCU frequency. Typical DBS stimulus waveform, as shown in Fig. 1, consists of short current pulses regarding the stimulation period. For example, consider a frequency of 130Hz , a cathodic pulse of $60\mu\text{s}$, an inter-pulse of $60\mu\text{s}$ and an anodic pulse of $600\mu\text{s}$ (ie. a cathodic current 10 times higher than the anodic current), the percentage of the period $1/f_{\text{stim}}$ during which no stimulation is applied to electrode is:

$$1 - f_{\text{stim}} \cdot (T_{\text{anodic}} + T_{\text{cathodic}} + T_{\text{inter-pulse}}) \approx 0.906 \quad (7)$$

This simple consideration implies that the stimulation hardware can be turned off most of the time (typically, more than 90% of time).

P_{boost} is inversely proportional to the efficiency of the Boost converter, and related to the output current. This current cannot be controlled since it is directly the stimulation current, but can be smoothed by adding decoupling capacitors of high values at the step-up output. Nevertheless, the boost circuit input power is also determined by its quiescent current. We choose a boost IC (*LT3494*) that can be turned in a shutdown mode, changing the quiescent current from $65\mu\text{A}$ to $1\mu\text{A}$. Φ_{HV} (see Fig. 3) controls the boost circuit commutation between the *active* and *power saving* mode, as illustrated in Fig. 4(c).

The most power consuming part of the system is the MCU. $P_{\mu C}$ can be separated in a static part and a frequency-dependent term:

$$P_{\mu C} = P_{\text{stat}} + P_{CPU} = P_{\text{stat}} + k \cdot f_{\text{clk}} V_{dd}^2 \quad (8)$$

where k is a constant in Farad, that depends on the processor technology and sizing. The static power of the MCU (*Freescale MC9S08SH8*) is determined by its operating mode. In '*normal*' mode, the static power is maximal and all peripherals are turned on. In '*Wait*' mode, the static power is

decreased and the *CPU* goes to a standby mode from which recovery is fast. One '*Stop*' mode can be used to limit even more power consumption but its recovery time is incompatible with the need for fast events described on Fig. 4(c). The clock frequency used for the *CPU* unit of the MCU has a proportional impact on power consumption. This power saving strategy has been applied on the developed system as shown in chronogram of Fig. 4(c).

The current source and step-up are turned on before cathodic command is applied to the H-bridge (see Fig. 4(c)). This activation corresponds to the first action of the MCU, changing from '*Wait*' to '*Normal*' mode. After the anodic pulse, the MCU is set under '*Wait*' mode again, just after shutting down the current source and the DC/DC converter. With this strategy, the supply current value is limited when no stimulation current is applied. Nevertheless f_{clk} has to be taken into account when the MCU is in *Normal* mode, ie when a stimulus is applied or when the stimulation system is receiving stimulation parameters. All these events are processed using hardware interrupts. The associated sub-routines have to be executed in time periods that are negligible compared to stimulation patterns, even configured for the shorter pulse duration ($60\mu s$). We chose $f_{clk} = 2MHz$, which is the lowest frequency ensuring the calculated SPI baud rate (see eq. 5); this value is much higher than traditionally adopted clock frequencies [24,25] (under the MHz), however, thanks to this power management strategy, the average current consumption is only $1.9mA$ (see Fig 4c), a level compatible with battery supplied systems. The resulting transient supply current was measured as presented in Fig. 4(c). The peak current around $40mA$ on a short period (less than $10\mu s$). The transient supply remains stable during the stimulation period except when the MCU is experiencing recovery time in the *Wait* mode.

B. Choice of supply sources

We expected to find a supply source able to deliver a current profile as in Fig. 4(c), and have the maximal energy with a system weight limit of $22.5g$ as specified in section II. As our current source is independent of the supply voltage, the low voltage supply V_{dd} can be chosen between $2.9V$ and $5.5V$.

Human oriented Implanted Medical Devices (*IMD*) batteries have been of interest since the first implantation of pacemakers about 50 years ago [53]. Supply sources occupy $25 - 60\%$ of their volume [54], and technology improvements have enhanced patient's quality of life, by limiting surgery. Different technologies are used for human oriented *IMD*, depending on the therapeutic target and associated power requirement [53]–[56], as summarized in Table II. Lithium technology is largely dominant for these applications. These technologies are potentially interesting for our stimulator; however, the weight of batteries used for human *IMD* largely exceeds $20g$. And regarding overall performances, weight and size reduction affects the total embedded energy but also reduces available power, as the surface of electrode plates is smaller.

We conducted a dedicated study to find the optimal power source, respecting our cost-effectiveness needs for chronic population implantation. In order to evaluate most adapted

TABLE II
TYPICAL BATTERY TECHNOLOGIES USED FOR DIFFERENT TYPES OF IMD CORRESPONDING TO DIFFERENT POWER REQUIREMENTS

Technology	Typical applications	Energy density (mWh/g)
Lithium Iodine (Li/I_2)	CP	210 – 270
Lithium-Manganese Dioxide (Li/MnO_2)	CP - Nstim - DDS	230 – 270
Lithium-Carbon Monofluoride (Li/CFx)	Nstim - CD	≈ 440
Lithium-Silver Vanadium Oxyde (Li/SVO)	CP - Nstim - CD	≈ 270
Lithium-Thionyl Chloride ($Li/SOCl_2$)	CD - DDS	≈ 500
Li-ion	Cochlear Implant (Secondary batteries)	$\sim 100 - \sim 350$
CP	: Cardiac Pacemaker	($30 - 1000\mu W$)
Nstim	: Neurostimulators	($30\mu W - 10mW$)
DDS	: Drug Delivery Systems	($100\mu W - 2mW$)
CD	: Cardiac Defibrillator	($30 - 100\mu W$)

technologies for this system, we compared commercially accessible batteries of less than $20g$. Based on available datasheets, maximal constant current was extracted and related to cell voltage to compute the available power; the energy was computed using the capacity and the cell voltage; both parameters can then be normalized with the weight of the element. Results are shown in terms of energy versus power and energy density versus power density (see Fig. 5). This study only takes into account the average nominal power as a first criterion. To support the peak power observed in Fig. 4(c), a secondary source acting like a decoupling capacitor will be chosen, as explained later in the section.

We observe from Fig. 5 that not only lithium batteries are potential candidates for our application. Zinc technologies, except for Zn/Ag_2O , tend to have available energy higher than lithium technologies. The *NiMH*, Zn/MnO_2 and *LiPo* batteries tend to deliver more power than other technologies. The analysis of the energy density versus power density in Fig. 5(b) results in three groups of candidates:

- The first one is composed of *NiMH*, Li/V_2O_5 , *LiPo* and Zn/Ag_2O . It is characterized by a reduced energy density compared to others technologies ($\leq 102mWh/g$). Such batteries cannot supply the stimulator more than approximately 16 hours per gram, whereas their power density could be adapted (except for Zn/Ag_2O).
- The second group is composed of Li/CFx and the majority of Li/MnO_2 batteries; these batteries show higher energy density but have a reduced power density that makes them not suitable for the application.
- The last group is composed of Zinc/Air, Li/FeS_2 and $Li/SOCl_2$ technologies. These technologies allow for long term stimulation, their minimal energy density is higher than $3.102mWh/g$ (corresponding in our case to approximately 48 hours of stimulation per gram), and

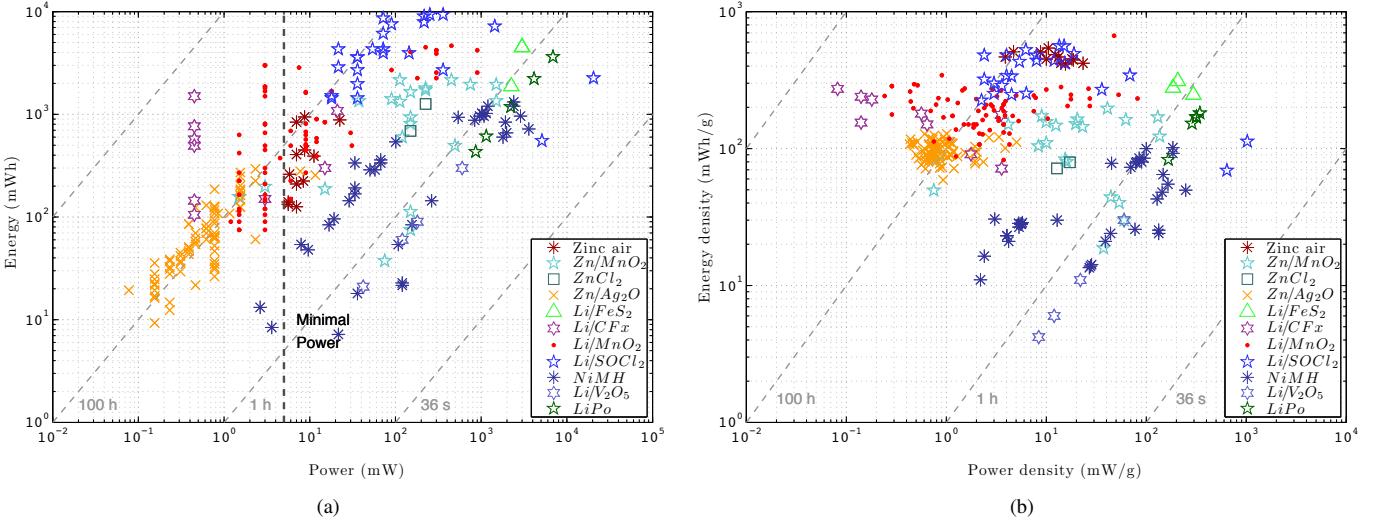


Fig. 5. Evaluation of small (commercially available less than 20g) batteries technologies: Zinc/Air, Zinc/Manganese dioxide (Zn/MnO_2), Zinc chloride ($ZnCl_2$), Zinc/Silver oxide (Zn/Ag_2O), Lithium/Iron disulfide (Li/FeS_2), Lithium/Polycarbon Monofluoride (Li/CFx), Lithium/Manganese dioxide (Li/MnO_2), Lithium/thionil chloride ($Li/SOCl_2$), Nickel Metal Hydride ($NiMH$), Lithium/Vanadium pentoxide (Li/V_2O_5), Lithium polymer ($LiPo$); (a) energy versus power (b) energy versus power density

have satisfying specific power. Only few models of small Li/FeS_2 are available, which are not adapted for our specific spacial design needed for skull implantation.

We conducted tests with both Zinc/Air and $Li/SOCl_2$ batteries. Nominal voltages are 3.6V for $Li/SOCl_2$ and 1.35V for Zinc/Air cells (1.6V in open circuit), so that three Zinc/Air cells in series are mandatory. Zinc/Air cells packaging (button package) makes them more suitable for the final version of the stimulator. We used *PowerOne zinc/air p675 Implant plus* batteries for both tests and animal implantation.

We now focus on the requirement for peak power supply. To prevent from unexpected reset of digital parts, a decoupling capacitor was used as a secondary source to supply the current peak observed in Fig. 4(c). Ceramic capacitors are simple and good candidates for such a task as their power density is much larger than conventional batteries, even if their energy density is reduced. Using a triangle approximation of the observed peak current, the minimal decoupling capacitance providing less than 100mV voltage drop for the supply profile can be determined by:

$$C_{decoupling} \geq \frac{Q}{\Delta V_{min}} \approx \frac{(I_{max} - I_{average}) \Delta t}{2 \Delta V_{min}} = 16\mu F \quad (9)$$

Ceramic capacitors with these values can be found in package as small as 0603 (1608 Metric), so that impact on the final design size is negligible.

V. IMPLANTATION ON RODENT SKULL AND EXPERIMENTAL RESULTS

A. Mechanical implantation

All components from schematics presented in Fig. 3, except electrodes and associated blocking capacitor, have been integrated on a 6 layers printed circuit board (length: 30mm,

height: 14mm) as presented in Fig. 6(c). As for external control, a reset switch serves the purpose of stopping the stimulation immediately and a three-wire RS-232 access for stimulation programming were used. MCU flashing can be performed via a dedicated on-board connector, allowing for stimulation program and user interface release without hardware replacement.

The circuit, batteries and electrodes were fixed on the skull using custom plastic packaging, designed using a 3D printer. The package is divided in two main parts:

- *The electrode container*: (Fig. 6(a)) this part, attached on the rodent's skull by surgery and fixed with dental cement, supports the electrodes for both left and right cerebral hemispheres, the blocking capacitor and an external connector (Fig. 6(b)). The plastic shape was designed as small as possible in order to limit the impact on animal behavior after surgery and acts as mechanical support for the second part's mounting
- *The stimulator container*: this part(Fig. 6(d)) is designed to fix the stimulation board and batteries on the skull. The top of the box includes a drilled column for the system to be screwed to the electrode container and to turn on the global system by contacting both poles of the electrical supply.

We fabricated the plastics shape with a *Makerbot Replicator 2* with *natural PLA (polylactic acid polymer)* material. The height of the global system when mounted on the animal is 24mm. The use of a two parts system allows for device retrieval, and facilitates MRI or other analysis when needed. It also allows stimulator re-use when the rodent is sacrificed.

A custom electrode system has been developed. This system permits a two side implantation in one surgery. The distance between the two electrodes is set according to the rat brain atlas of *Paxinos and Watson (1986)* and correspond to the distance between the two targeted STN. The electrodes support

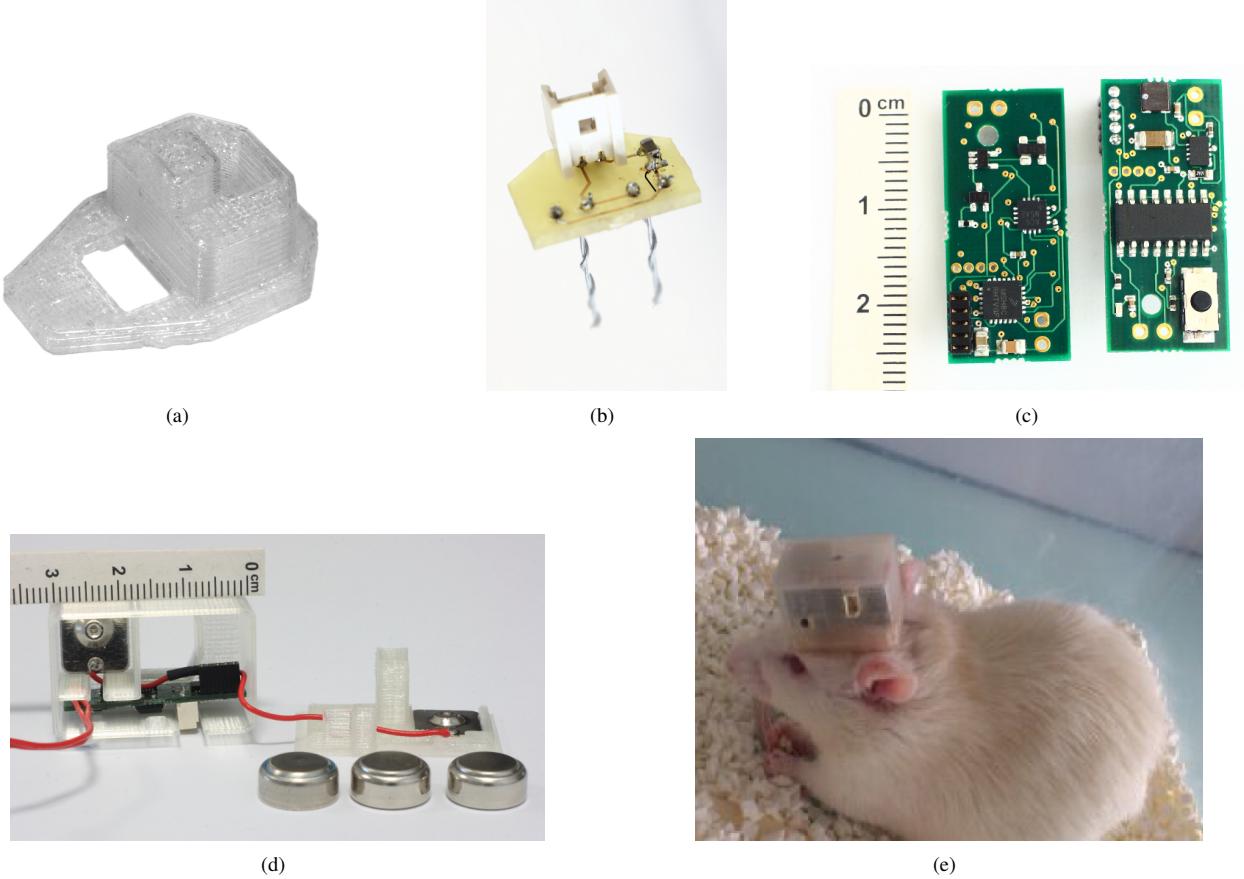


Fig. 6. Stimulator, circuit packaging and implantation on rodents' skull. (a) electrode container; this part is fixed with cement on the cranium of the rodent (b) custom electrodes for bilateral STN stimulation; both electrodes are in parallel and the support board includes the blocking capacitor (c) electrical stimulator board (d) assembled stimulator in container, shown with used Zinc/Air batteries, the top is then screwed on the electrode container after the surgery (e) stimulator chronically implanted on a rat; a three wire cable is connected to the device only for waveform programming, stimulation remains active during all experimentation phases.

board is shown in Fig. 6(b). A high value high voltage capacitor ($10\mu F$ under $25V$ MURATA 0603[1608Metric]) is embedded as close as possible to the electrodes to provide DC current blocking in any case and lessen the impact of passive components surface on stimulator main board.

The developed electrodes are needle-like two wire electrodes of twisted tungsten (built from *tungsten Wire .008 Bare, .0110 Coated, Phymep, France*). Electrode diameter has been chosen to be similar with a widely used electrode for monolateral electrical stimulation of *STN* structures on rodents [58]. A first pole is made by a wire section. For the second pole, the current return half-cell electrode was constructed by a $2mm$ long wrap of the second conductor. The distance between the two poles is $1mm$. Electrodes are associated in parallel (both cathodes are connected together, both current-return paths are connected together), and connected in series with the blocking capacitor.

The overall stimulator has a weight of $13.8g$, under the limit of $20g$ for the targeted rodent.

B. Surgery and experimental results

The stimulator was implanted and tested on an adult male Sprague–Dawley rat weighing $324g$. Surgical and experimental procedures were performed in accordance with European Communities Council Directive 2010/63/UE and National Institute of Health Guide for Care and Use of Laboratory Animals.

A first anaesthesia was induced using a mixture of *Xylazine* ($10mg/kg$) and *Ketamine* ($7.5mg/kg$). Custom concentric bipolar electrodes for both cerebral hemispheres were then implanted simultaneously in the *STN* under stereotaxic conditions according to the atlas of Paxinos and Watson (1986).

After this first implantation, the stimulation hardware was not directly screwed on the skull to limit postsurgical risks. Smoothed angles in the electrode support enhance the healing and thus limit animal awareness of additional material on the top of the head. We observed no skin reaction, infection or rejection phenomena against the *PLA* electrode container. The stimulator container was fixed on the animal eight days after the implantation of the stimulating electrodes, during a short and light anaesthesia induced using *isoflurane* (5% during 1 to 2 min) to prevent the rat sudden movement during the

placement.

Electrical parameters of chronic stimulation were chosen according to those used in the stimulated Parkinsonian patient showing reversal of motor deficits. The frequency was fixed to 130Hz and pulse width to $60\mu\text{s}$. The stimulation intensity was gradually increased (by steps of $50\mu\text{A}$) in order to determine the required level. Based on these tests, we used an intensity of $400\mu\text{A}$ per side, which was just below the threshold ($450\mu\text{A}$) inducing the manifestation of abnormal involuntary movements. The rat was then chronically stimulated for 3 weeks during which the animal presented normal behaviour without any visible discomfort.

VI. DISCUSSION AND CONCLUSION

Our objective was to develop a stimulator that allows safe chronic bilateral DBS in freely moving small rodents and reproduces the human therapeutic conditions. In section II, we exposed constraints that such devices have to satisfy during experiments on animal populations: tissue safety, bilateral stimulation, programmability, adaptation to freely moving animal, stimulation life time and reusability in a context of low cost devices. The design choices we made respect these specifications and our system was both electrically and *in vivo* characterized.

We discussed the performances of our stimulator in comparison with state-of-the-art systems for rodents, referenced in section II-B. In [24], the stimulator was only tested in saline solution and authors of [16] and [26] give no detailed information about *in vivo* experiments, so we examined only [25], [27] and [28] which results are shown in Table II. A first part sums up characteristics related to *in vivo* experimentation, whereas a second part synthesizes important electrical features. We note that none of these *in vivo* used devices are based on ASIC solution. Stimulators are presented in a chronological order. Most recent devices are fixed on the skull, which certainly provides greater ease of handling and reduces the risk of infection. Nevertheless the implantable device presented in [25] has electrical features compatible with required properties for DBS, in terms of current range and maximal voltage. In [27], stimulation is in voltage mode, and limited to small values that could be problematic when considering focal electrode with higher impedances. This is not compatible with our specification for current mode, ensuring a better control of injected charge. In [28], stimulation is in current mode but long term tissue safety is compromised by the absence of biphasic charge balancing.

The limited performance of our system in term of lifetime stimulation can be explained by the hardware capacity to generate a more complex waveform than in [28]. The digital part in our system is faster than [25,27], thus can reach better timing precision and accurate charge balancing. Moreover, the development of a two-piece mechanical packaging as in [28] allows for changing batteries without any additional surgery, so that the life time of the stimulation on one animal can be easily increased. Electrical stimulators in the litterature are often realized with ASICs, nevertheless all of chronic *in vivo* demonstrated devices use discrete components. This consideration can be explained by the need of cost-effectiveness,

TABLE III
STIMULATORS FOR RODENT COMPARISON

	[25]	[27]	[28]	This work
Biphasic	yes	yes	no	yes $(I_{error} \leq 72\text{nA})$
Bilateral	no	no	no	yes
Programmable	yes	yes	no	yes
Removable	no	no	yes	yes
Fixation	implanted	skull	skull	skull
$I_{min}(\mu\text{A})$	50	V.M.	50	26 $\approx 13\text{p.h.}$
$I_{max}(\mu\text{A})$	600	V.M.	120	2036 $\approx 1018\text{p.h.}$
resolution	12 steps	50 steps		10 bits non linear
$V_{max}(V)$	18	2.5	5	17
$f_{stim}(\text{Hz})$	131	2 – 250	130	10 – 300
time resolutionw		$30\mu\text{s}$		500ns
Lifetime (days)	21	90	7 (R.B.)	6 (R.B.)

V.M. : Voltage Mode
p.h. : per hemisphere
R.B. : removable batteries

related to long-term experimentation on animal populations. Finally, let us note that no figure of merit dedicated to *in vivo* electrical stimulation exists yet, which could quantify differences between existing alternatives, and help select optimal solutions for a given experimentation.

To summarize, we developed in this paper the design procedure of an embedded stimulator, from the front-end circuit, to the choice of battery and packaging. We detailed the qualitative specifications on such systems for experimentation on small animals and deduced descriptive and quantitative elements, so that this reasoning can be re-used for further development of new devices for chronic implanted stimulation.

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In parallel with his hospital activity as a Neurophysiologist performing the electrophysiological mapping during surgery, he was the head of a research group in the Inserm unit investigating the functional mechanisms of this approach in animal models. In 1998 he was appointed to Inserm position as a permanent position researcher. In 2001, he came back to Bordeaux as a PI in the CNRS unit of Professor Bernard Bioulac. In 2005 he was promoted to Research Director position. Since 2011, he is the leader of the Team "Monoamines, Deep Brain Stimulation & Parkinson's disease" in the Institute of Neurodegenerative diseases in Bordeaux University.

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