Design Considerations and Clinical Applications of Closed-Loop Neural Disorder Control SoCs

Chung-Yu Wu[1], Cheng-Hsiang Cheng[1], Yi-Huan Ou-Yang[1], Chiung-Chu Chen[2], Wei-Ming Chen[1], Ming-Dou Ker[1], Chen-Yi Lee[1], Sheng-Fu Liang[3], Fu-Zen Shaw[3]

[1] National Chiao Tung University, Hsinchu 300, Taiwan
[2] Chang Gung Memorial Hospital and University, Taoyuan 333, Taiwan
[3] National Cheng Kung University, Tainan 701, Taiwan

Abstract - This paper presents the closed-loop neural disorder control concept and some design considerations. Two architectures of closed-loop neuromodulation for Parkinson's disease and epileptic seizure are proposed. One is a closed-loop deep brain stimulator, which meets the IEC 60601-1 standard. The other one is an implantable SoC for epileptic seizure control, which is verified by animal experiment.

I Introduction

Parkinson's disease and epilepsy are common neurological disorders that affect the human nervous system. Parkinson's disease can be controlled by drugs as the main treatment. However, drug treatment has some side effects such as dyskinesia which influences the patient's quality of life. Commercial Deep Brain Stimulators (DBSs) are all of open-loop type. Once the device is turned on, stimulation is continuously performed. This leads to higher power dissipation and frequent battery replacement. Recent studies have suggested that open-loop DBS disrupt pathological neural synchrony which results in increased oscillatory activity throughout the cortico-basal ganglia network. Several researches has shown that closed-loop is a better way for Parkinson's disease therapy than open-loop [1]-[3]. Choosing an appropriate biomarker is critical for closed-loop system. Several clinical investigations have discovered the β-band (12-30Hz) of local field potential (LFP) detected in subthalamic nucleus (STN) is attenuated during and following STN-DBS [1], which suggests that DBS can suppress the pathological β-band activity. Given this behavior, the biomarker for the closed-loop DBS of Parkinson's disease can be chosen as the β-band activity in LFP.

On the other hand, for epilepsy, around 1% of the world population is affected. Epileptic seizures are caused by sudden excessive electrical discharges in a group of cortical neurons. Currently, numerous anti-epileptic drugs are available for seizure control. However, there are still nearly one-third of the patients remain either drug-resistant or develop limiting adverse effects. Recently, implantable devices with closed-loop electrical stimulation for epileptic seizure control have been presented as a potential and effective clinical treatment [4]-[5].

This paper presents two architectures of closed-loop neuromodulation SoCs for Parkinson's disease and epileptic seizure treatment. One is the closed-loop DBS system prototype used externally for Parkinson's patients with implanted DBS electrodes to test the closed-loop function and obtain parameters for implantable DBS devices before implant operation. The prototype includes a local field potential (LFP) signal acquisition unit, a processor in NI platform, a biphasic voltage stimulator, and a Graphical User Interface (GUI). The other is implantable SoC for epileptic seizure control, including a intracranial EEG (iEEG) acquisition unit, a bio-signal processor, an adaptive high-voltage-tolerant stimulator, a wireless power supply, and a medical radio-band transceiver.

This paper is organized as follows. Section II describes the system architectures and design considerations. System verification and experimental results are given in Section III. Future development is described in Section IV. Finally, Section V concludes this paper.

II. System Architectures and Design Considerations

A. Closed-Loop DBS System for Parkinson's disease

Fig. 1 shows the block diagram of closed-loop DBS system prototype used externally for Parkinson's patients. The system contains a LFP signal acquisition unit using TI ADS1299, a processor in NI platform with GUI, and a biphasic voltage stimulator using NI 9269. The LFP in STN is sensed and digitized by ADS1299. The digitized data are then processed by processor to calculate the β-band activity. Once the β-band power exceeds the preset threshold, the stimulator generates patient-specific 0.1−3V biphasic stimulation voltage waveforms. The whole system is integrated by using LABVIEW. The closed-loop DBS system meets the IEC 60601-1 for medical electrical equipment and provides for medical doctors to evaluate clinical responses during closed-loop stimulation.

The features of LFP acquisition unit includes:

1) Since the LFP signal is about 50−500μV, the low input-referred noise is required to reduce output noise from sources including power-line interference and electrically induced interference.
2) An ultra-low high-pass corner cutoff frequency should be designed to prevent saturation of the succeeding amplifier by electrode dc offset.

978-1-5090-1558-0/17/$31.00 ©2017 IEEE

3) Since the concurrent sensing and stimulation is essential, the high input common range and high CMRR of LFP signal acquisition unit is required. By choosing power supply of 5V for LFP signal acquisition system, it can sensing differential LFP with 3V stimulation common mode artifact.

According to [3], the β-band of LFP is an efficient bio-marker for Parkinson's disease. The β-band extraction and stimulation parameters control are implemented in NI platform. The β-band extraction is implemented by a decimation-in-frequency FFT algorithm to extract β-band power spectral density. On the other hand, the stimulation voltage, frequency, and threshold are adjustable through the GUI for patient-specific treatment.

The stimulator is implemented using NI 9269, which can generate positive and negative voltages for biphasic stimulation. The stimulation pulse width is fixed at 60μs, the stimulation voltage is adjustable 0.1-3V with 0.1V per step and the stimulation frequency is adjustable in 15-130Hz.

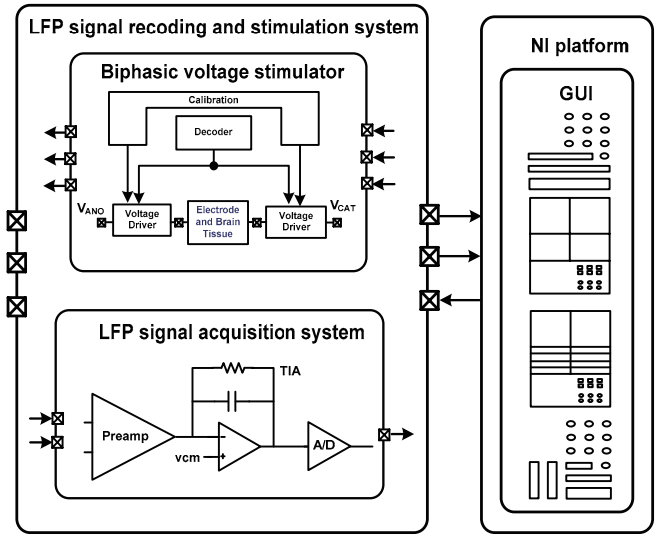

Fig. 1. Block diagram of the closed-loop DBS system prototype used externally for Parkinson's patients.

B. Closed-Loop Implantable SoC for Seizure Control

Fig. 2 shows the block diagram of the closed-loop implantable SoC for seizure control, where a 8-channel iEEG acquisition unit, a bio-signal processor (BSP), a adaptive high-voltage-tolerant stimulator, a wireless power supply, and a wireless transceiver are integrated [4]. The iEEG acquisition unit amplifies and digitizes the sensed iEEG signals. The digitized data are then processed by BSP for seizure detection. Once the seizure is detected, the stimulator generates a fixed 30μA biphasic stimulation current to suppress seizure onset.

The 8-channel neural-signal acquisition unit consists of 8 auto-reset capacitive-coupled instrumentation amplifiers (ARCCIA), band-pass filters, V-to-I programmable gain amplifiers, a multiplexer, a transimpedance amplifier (TIA), and a 10-bit DMSAR (Delta-Modulated Successive-Approximation-Register) ADC. Since the accumulated residue charges may saturate the neural-signal front-end amplifier. An auto-reset unit is required to provide fast discharge path to reset the amplifier to common mode voltage.

The bio-signal processor contains a feature extraction unit, a linear least square (LLS) classifier, and a seizure detector. The seizure features are extracted from power spectrum density in 4−64 Hz and entropy. The design considerations of bio-signal processor are listed as follows:

1) The latency should be less than 1s to prevent clinical seizure activity.
2) For effective stimulation, the detection accuracy should be larger than 90% by training patient specific detection parameters.

The adaptive high-voltage-tolerant stimulator with adaptive loading is implemented in a standard CMOS process. It consists of a high-voltage generator, a pair of current controllers and a pair of high-voltage-tolerant output drivers. The stimulator has been designed to deliver biphasic stimulus 30μA currents when seizure onset is detected. To adapt to a wide range of loading impedance between the electrode and the brain tissue, the high-voltage generator is designed to supply a variable supply voltage (up to 10V) for the output drivers.

Considering the implanted device, the wireless power and bilateral data telemetry is required to extend device lifetime and provide essential information for medical doctor. The inductive link power supply system is proposed to supply the power for the SoC at a carrier frequency of 13.56MHz. Due to high carrier frequency, the active rectifier with delay compensation is required to increase power transfer efficiency. To isolate the interference between power domains and satisfy different circuit requirements, three capacitor-free LDOs are integrated. For wireless data telemetry, OOK modulation scheme has been adopted for data transceiver to reduce power consumption. The OOK transceiver is designed for the FCC MedRadio Service band (401-406MHz). The implantable SoC receives detection parameters and transmits recorded iEEG to external control system for monitoring purpose.

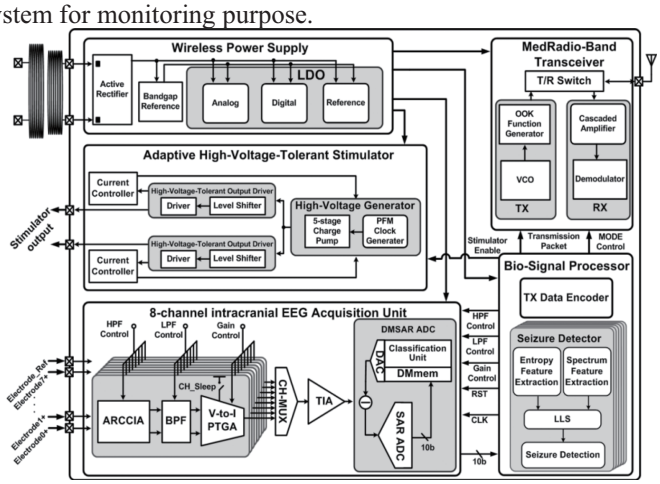

Fig. 2. Block diagram of the closed-loop implantable SoC for seizure control [4].

III. Experimental results

A. *Closed-Loop DBS System for Parkinson's disease*

Fig. 3 shows the measurement setup of the closed-loop DBS system. The LFP is generated by a LFP emulator. The recorded LFP is shown in the GUI whereas the biphasic voltage stimulation is shown in oscilloscope. The real-time adaptive closed-loop DBS is implemented in this system. The GUI performs the following functions:

1) Showing the recorded LFP and the calculated β-band power spectral density as shown in Fig. 4.
2) Enabling the programmable biphasic stimulation threshold, voltage, frequency to establish customized therapy for different patients as shown in Fig. 5.

Table I shows the performance summary of the built system prototype. This system must meet the IEC 60601-1 requirement before applied to clinical trial.

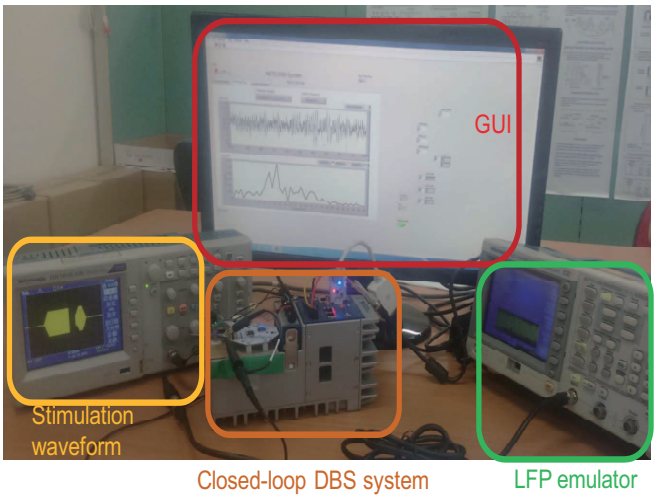

Fig. 3. Measurement setup of the proposed closed-loop DBS system.

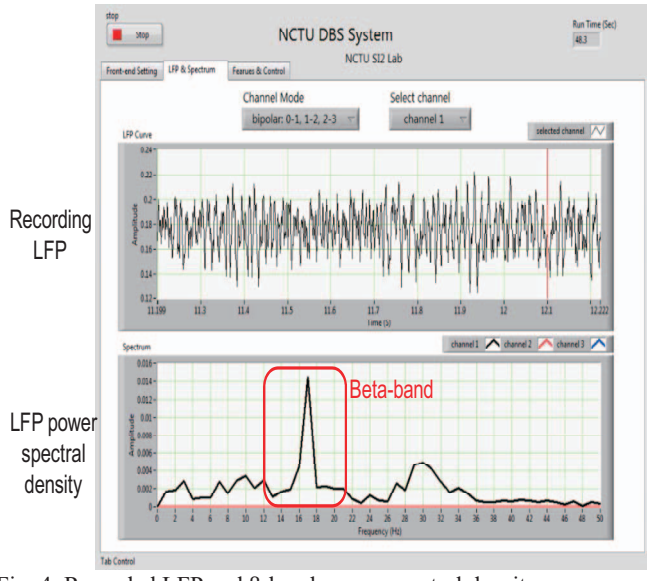

Fig. 4. Recorded LFP and β-band power spectral density.

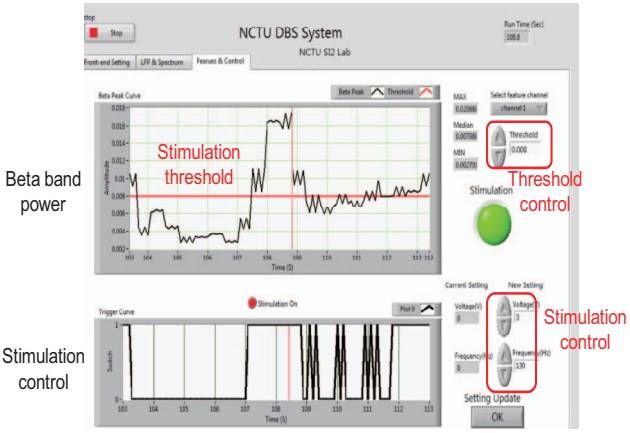

Fig. 5. β-band power spectral density and stimulation control panel.

TABLE I
Experimental results of closed-loop DBS system for Parkinson's disease

	Parameter	Experimental result
LFP signal acquisition unit	Input common range	5V
	Input referred noise	1μVpp
	CMRR	110dB
	ENOB	21.48
Stimulator	Stimulation pulse width	60μs
	Stimulation frequency	15−130Hz
	Stimulation voltage	0.1−3V

B. *Closed-Loop Implantable SoC for Seizure Control*

The functionality of the closed-loop seizure control SoC in 0.18μm CMOS technology is verified through the measurement on four adult Long-Evans rats with epilepsy. Fig. 6 shows the animal experiment results. The seizure onset is detected and suppressed within 0.8s. Table II shows the performance summary of the fabricated SoC.

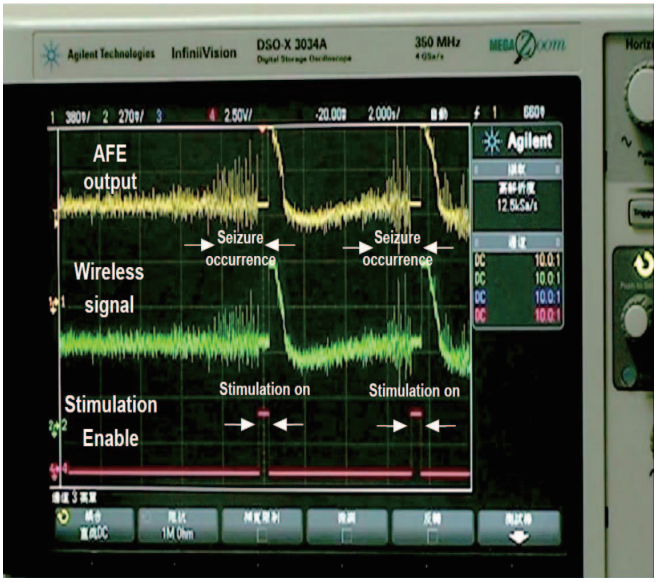

Fig. 6. Function validation of the closed-loop seizure control SoC on rats [4].

TABLE II
Experimental results of closed-loop SoC for seizure control

	Parameter	Experimental result
Signal acquisition unit	Input-referred noise	5.23μV_{rms}
	NEF	1.77
Bio-signal processor	Accuracy	92%
	Latency	0.8s
	BSP efficiency	77.91μJ/classification
Stimulator	Stimulation current	30μA
Wireless telemetry	Rectifier power transfer efficiency	84%
	Data rate	4M bps
	Power dissipation	2.8mW (standby)

IV. Future Development

After clinical trial and therapy validation, the closed-loop DBS system for Parkinson's disease will be implemented by CMOS SoC for low power and small device area. This system can also be developed into implantable devices as shown in Fig. 7 for more effective treatment of Parkinson's disease. However, the concurrent sensing and stimulation should be overcome in low supply voltage device. High-input-common-mode techniques in front-end amplifiers will be designed to eliminate stimulation artifacts in the next generation closed-loop DBS SoC. Moreover, integrating wireless power and data telemetry is required for implantable closed-loop DBS SoC.

In closed-loop seizure control SoC, up to 3mA electrical stimulation on cortical surface at seizure onset sites is required to control human epileptic seizures [6]. The future development of seizure control SoC will be developed to increase stimulus current. Channel number will also be increased to cover the human brain seizure onset sites. Moreover, to reduce implanted device area, only one pair of coil is adopted for wireless power and bilateral data telemetry and the power management with rechargeable battery should be integrated in the implantable device in future development.

V. Conclusion

This paper presents the design considerations and closed-loop solution to treat neurological disorders. A high integration and patient-specific closed-loop DBS system, which meets IEC 60601-1 standard is proposed in this paper. In the closed-loop seizure control SoC, verified by animal experiment is also presented in this paper. Future development on SoC solution enables the closed-loop neuromodulation a feasible therapeutic method to control neurological disorders.

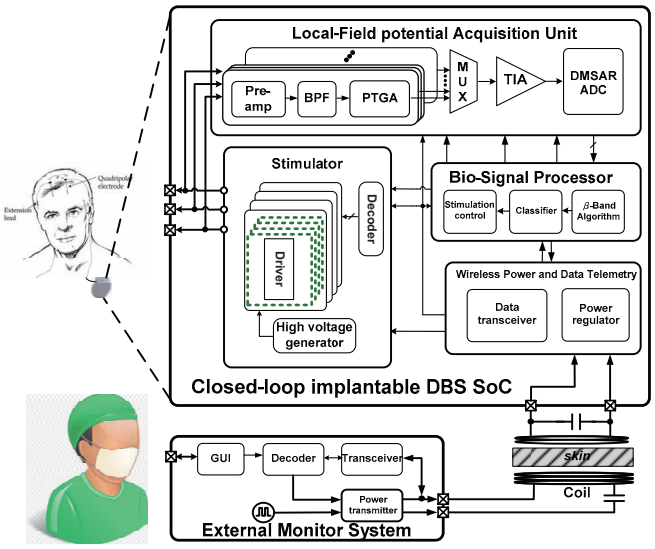

Fig. 7. Block diagram of closed-loop implantable DBS SoC with wireless telemetry.

Acknowledgements

The authors would like to thank Biomedical Electronics Translational Research Center, National Chiao Tung University for design environment support.

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