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Abstract

In this paper numerous alternative treatments in addition to pharmacological therapy are proposed for their use in epileptic patients. Epileptic animal models can play a crucial role in the performance evaluation of new therapeutic techniques. The objective of this research is to first develop various epileptic rat models; second, develop a portable wireless closed-loop seizure controller including on-line seizure detection and real-time electrical stimulation for seizure elimination; and third, apply the developed seizure controller to the animal models to perform on-line seizure elimination. The closed-loop seizure controller was applied to three Long-Evans rats with spontaneous spike–wave discharges (non-convulsive) and three Long-Evans rats with epileptiform activities induced by pentylenetetrazol (PTZ) injection (convulsive) for evaluation. The seizure detection accuracy is greater than 92% (up to 99%), and averaged seizure detection latency is less than 0.6 s for both spontaneous non-convulsive and PTZ-induced convulsive seizures. The average false stimulation rate is 3.1%. Near 30% of PTZ-induced convulsive seizures need more than two times of 0.5 s electrical stimulation for suppression and 90% of the non-convulsive seizures can be suppressed by only one 0.5 s electrical stimulation.

1. Introduction

Epilepsy is one of the most common neurological disorders, with a worldwide prevalence of approximately 1%. Additionally, up to 5% of people may have at least one seizure in their lives [1]. Epilepsy is characterized by a sudden and recurrent malfunction of the brain. Due to sudden occurrence of epileptic seizures, daily activities are impaired and become dangerous for patients [2]. 25% of epilepsy patients cannot be treated sufficiently by any available therapy [3, 4]. Recently, alternative techniques, such as vagus nerve stimulation [5] or deep brain stimulation [6], have been proposed. Because intermittent stimulation may tend to decrease in efficacy over time due to neuron acclimation [7, 8], a closed-loop device is more likely to achieve seizure control than an open-loop seizure controller [4, 9–12]. NeuroPace Inc. [13] has developed an implantable responsive neurostimulation (RNS)

for the control of epilepsy in humans [14]. Clinical trials included a feasibility trial in 65 adults with epilepsy. 191 subjects were implanted with the RNS system at 31 sites [14, 15] and it was reported that over 50% of the subjects that completed the Open Label had a 50% or greater reduction in seizure [15].

The objective of this research was developing a closed-loop seizure controller and applying the controller to various epileptic rat models for seizure elimination. First, Long-Evans rats with spontaneous spike and wave discharges (SWDs) [16, 17] and pentylenetetrazol (PTZ)-induced convulsive seizures [18, 19] were developed. Some studies have discussed the association between SWDs of Long-Evans rats and typical absence seizures of humans [16, 17, 20–22]. Then, a portable wireless closed-loop seizure controller that can be mounted on the head of a rat was developed [23]. It integrated the on-line seizure detection module and an electrical stimulator, that can
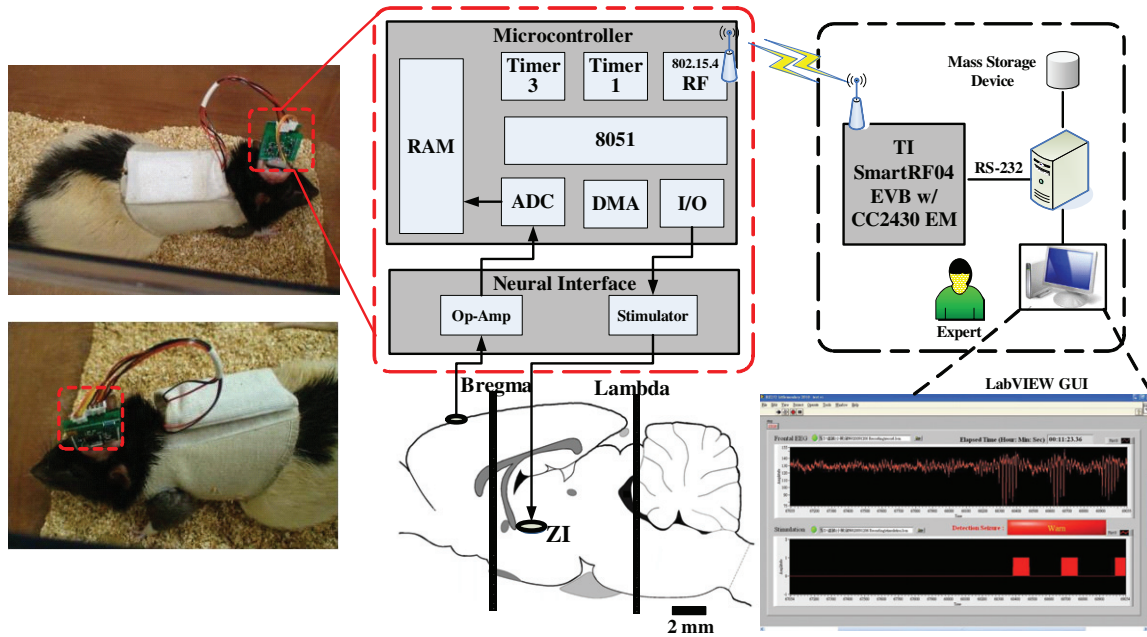
Figure 1. Functional block diagram of the developed closed-loop seizure controller.

provide a constant stimulation pulse train, when a seizure was detected.

For a closed-loop seizure controller, a seizure detection method that can monitor continuous EEG signals is essential [24–30]. The line length approach [25], data range autocorrelation combined with spike frequency [26], the wavelet FIR filter [27] and the Davies–Bouldin (DB) index [28] have been developed for continuous EEG analysis. For real-time operation and hardware implementation, a real-time adaptive Wiener algorithm has been implemented on the digital signal processor [29] and an event-based seizure detection algorithm along with a low-power digital circuit implementation has also been developed [30]. In this study, a seizure detection method that can be executed on an embedded platform in real time to monitor continuous EEG signals was also developed.

The developed seizure controller was applied to the animal models to perform on-line seizure elimination. The seizure detection accuracy, false stimulation rate and the seizure detection latency were analyzed for performance evaluation. The effectiveness of utilizing electrical stimulation to eliminate non-convulsive and convulsive seizures was also compared. Finally, fluctuations of brain tissue impedance caused by the responsive electrical stimulation for seizure suppression were discussed.

2. Animal models

Two epileptic rat models were developed in this study. One is Long-Evans rats with spontaneous non-convulsive SWDs. The other is PTZ-induced seizures. A proconvulsant PTZ (20 mg kg^{-1}, i.p.) was injected into Long-Evans rats to provoke convulsive SWDs. In general, all rats displayed intensive head nodding and facial twitching behavior accompanied by SWDs for 2 h after PTZ injection. According

Table 1. Dimension and weight of the seizure controller.

	Neural interface board	MCU board
Dimension (mm × mm × mm)	37 × 26 × 6	27 × 24 × 6
Weight (g)	2.19	2.25

to Racine's standard five-stage scale [31] for seizure stages, PTZ has induced a lot of stage 2 convulsive seizures. In our experience, ~90% of Long-Evans rats showed spontaneous SWDs. Only Long-Evans rats with spontaneous SWDs were used here. Screw electrodes were bilaterally implanted over the area of the frontal barrel cortex (anterior 2.0 mm, lateral 2.0 mm with regard to the bregma). A 4-microwire bundle, made of Teflon-insulated stainless steel microwires (#7079, A-M Systems), was used to stimulate the right-side zona incerta (ZI) (posterior 4.0, lateral 2.5 and depth 6.7–7.2 mm). A ground electrode was implanted 2 mm caudal to the lambda.

3. Closed-loop seizure controller

A portable seizure controller that consists of a neural interface and an embedded platform as shown in figure 1 was developed. The neural interface has an EEG amplifier for data acquisition and a stimulator to provide responsive electrical stimulation. Several tasks are implemented on the embedded platform including analog-to-digital conversion of EEG signals, execution of seizure detection algorithm, generation of pulse trains to stimulator and wireless transmission of EEG data to the host for monitoring and recording. Table 1 summarizes the weight and dimension of the seizure controller.

3.1. EEG acquisition

Spontaneous brain activities of the rat's frontal cortex are amplified thousand-fold and filtered in the range of 0.32–80 Hz. The sensing module was implemented by two operational amplifiers (AD8538, Analog Devices, Inc.). The amplified EEG is positive-biased to the input voltage range of an analog-to-digital converter (ADC) of the Texas Instrument (TI) CC2430 chip. The resolution of the ADC was configured to 10 bits and the sampling rate was 200 Hz.

3.2. Seizure detection

The seizure detection method was implemented on the 8051 microcontroller unit (MCU) that was embedded on the TI CC 2430 chip to perform real-time operation. After every 32 samples are buffered, these data and the previous 32 buffered data are integrated as a 64-point vector for analysis. The seizure detector reports a result for every 0.16 s (32 sampling cycles), and the MCU has to execute the seizure detection method in 0.16 s.

   Approximate entropy (ApEn) [32] with $N = 64$ and 64-point fast Fourier transform (FFT) was applied to the EEG data. The parameter setting for ApEn is $m = 1$, $N = 64$ and $r = 5$. The FFT is accomplished by applying the radix-4 architecture, since it is a feasible one to be implemented on a MCU. In the training phase, the continuous EEG signals were reviewed by an expert and a corresponding time course index was generated. Seizure events are labeled 1, whereas others are labeled 0.

   To extract spectral features that are highly correlated to the SWD, the Person correlation coefficients between the index time course and the concurrent EEG powers of various frequency bands were calculated. Frequency bands corresponding to the top two correlation coefficients were extracted as the spectral features. In total, three features including one entropy value and the powers of two selected frequency bands were used for classification. The linear least squares (LLS) [33] was utilized to classify if the buffered EEG segment belongs to a seizure event or not. Because the output of the LLS classifier is the weighted sum of the input features (three features in this study), it is suitable to be implemented on processors without high computing power for on-line processing.

   An adaptive thresholding mechanism based on the delta power of EEG was utilized to reduce the false detection rate during grooming and the wake–sleep states in rats. The slow-wave-sleep (SWS) EEG of rats has a high-amplitude oscillation within the delta frequency range (0.5–4 Hz) and high energy in the low frequency band also appears in grooming. If the averaged power level of the frequency band during the delta band was higher than a predefined constant value, the threshold of the LLS was switched to a higher value to reduce the false detection rate. To reduce the influence of EEG fluctuations, the temporal constraint is also used to make a final decision. If three consecutive segments were classified as seizure, the seizure detector will report that a seizure occurred and the electrical stimulator will be turned on. Due to this constraint, the detector has 0.5 s latency (0.16×3 frames = 0.48 s).

3.3. Electrical stimulation

A boost regulator (LM2735, National Semiconductor) is used to elevate the power supply from 3.7 to 20 V. A transistor 2N3904 and an optocoupler 4N35 are utilized to produce a constant current stimulation passing through two ZI microwires. When a seizure event is detected by the classifier, the MCU starts a timer to generate 800 Hz, 40% duty cycle digital pulses for 0.5 s from I/O port to the stimulator module. So the electrical stimulator produces an 800 Hz, 40% duty cycle and 30–40 μA constant stimulation pulse train sustained for 0.5 s in ZI to stop spontaneous or induced SWDs.

4. Experimental design

The experiments contain the training phase to determine the parameters for the seizure detector and the testing phase to evaluate the effects of applying the closed-loop seizure control on epileptic rat models. Figure 2 shows the developed experimental procedure and this procedure was applied to three Long-Evans rats with spontaneous SWDs and three Long-Evans rats with proconvulsant PTZ injection.

4.1. Training phase

In the training phase, the electrical stimulator was turned off and the seizure detection program was not executed. The seizure controller performed as a purely wireless EEG acquisition system. For each Long-Evans rat with spontaneous SWDs, the EEG data were continuously recorded for 5 h. For PTZ-induced seizures, each rat had two recording sessions at an interval of 3 days. For each session, the data were continuously recorded after PTZ injection and the duration is two and one-half hours. The total length of the EEG from a rat with proconvulsant PTZ injection was also 5 h. All of the recording processes were operated under light-on condition.

   The continuous EEG data were screened by an expert and the seizure onset time was defined as the onset of the epileptiform activity identified by the expert. A corresponding time course index was generated for each recording. Seizure events are labeled 1, whereas other EEG signals in various behavioral and physiological states such awake EEG, SWS and the grooming artifact are labeled 0. In the last step in the training phase, the EEG signals and the corresponding time course index are utilized to determine the system parameters as procedure mentioned in section 3.2. It is noted that for the training of LLS classifier, all SWD durations and the non-seizure segments with length equivalent to the SWDs were selected to avoid uneven numbers of data points for the LLS training. In the non-seizure segments, the ratios of data corresponding to WK, SWS and artifact are 1:1:1. The optimal parameters of the classifier were determined for each rat through an off-line process by the host computer.

4.2. Testing phase

In the testing phase, the parameters of the seizure detector that had been determined in the training phase were downloaded to
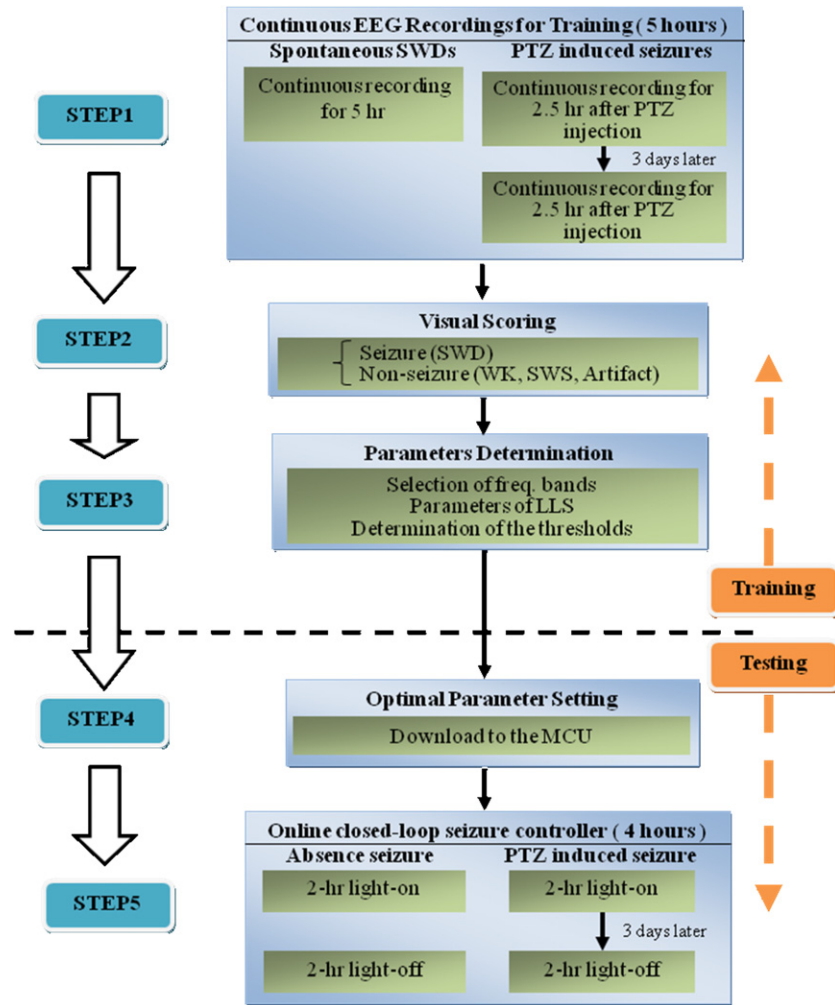
Figure 2. The experiments contain the training phase to determine the parameters for the seizure detector and the testing phase to evaluate the effects of applying the closed-loop seizure control on epileptic rat models.

the MCU and then the on-line closed-loop seizure controller was turned on. The seizure controller continuously executed for 4 h including a 2 h light-on period and a 2 h light-off period on each rat with spontaneous SWDs. For each rat with PTZ injection, the evaluation was separated into two 2 h sessions. One was under light-on condition and the other was under light-off condition. The interval between these two sessions was 3 days.

5. Results

5.1. Performance of seizure detection

Table 2 shows the observed SWD duration, and two selected frequency bands for each of the six rats in the training phase. The performance of the seizure controller was evaluated by three indices: accurate stimulation rate, false stimulation rate and detection delay time. Detection delay is defined as the time delay between the onset of an epileptiform activity scored by an expert and the time that the system turned on the

electrical stimulator. The accurate stimulation rate and the false stimulation rate were defined as

$$\text{Accurate stimulation rate} = \frac{\text{TP}}{\text{TP} + \text{FN}} 100\% \qquad (1)$$

$$\text{False stimulation rate} = \frac{\text{FP}}{\text{TP} + \text{FP}} 100\%, \qquad (2)$$

where TP is the true positive, the total number of correctly detected seizure events; FP is the false positive, the total number of non-seizure segments erroneously detected as seizure events; and FN is the false negative, the total number of misdetections of seizure events.

Table 3 summarizes the performance of the seizure controller operating on each rat. Calculating the accurate stimulation rate, false stimulation rate and the detection delay time by combining the 4 h data for each rat and averaging the results of the rats corresponding to the same model together, the average accurate stimulation rate, false stimulation rate and the average detection delay time were 95.6(2.5)%, 3.1(2.3)%, 0.56(0.03) s for rats with spontaneous SWDs (rats 1–3), respectively, and 97.9(1.5)%, 3.1(0.7)%, 0.49(0.03) s for PTZ-induced seizures (rats 4–6), respectively. The false stimulation

Table 2. The observed SWD duration and two selected frequency bands for each rat in the training phase. Subjects 1–3 are rats with spontaneous spike–wave discharges and subjects 4–6 are rats with PTZ injection.

Subjects	Total duration (h:m:s)	SWD duration (m:s)	SWD min (s)	SWD mean (s)	SWD max (s)	Band 1 (Hz)	Band 2 (Hz)
1 (Abs)	5:00:00	27:52	0.6	4.76	17.9	8–11	17–20
2 (Abs)	5:00:00	36:47	0.6	5.88	21.4	5–8	14–17
3 (Abs)	5:00:00	39:10	0.5	5.76	9.7	8–11	14–17
4 (PTZ)	5:00:00	27:35	0.7	2.92	16.1	8–11	14–17
5 (PTZ)	5:00:00	44:09	0.5	1.78	9.67	8–11	14–17
6 (PTZ)	5:00:00	41:21	0.5	2.32	9.7	8–11	18–21

Table 3. Accurate stimulation rate, number of false stimulations, and averaged seizure detection delay of the seizure controller operating on each of the six rats.

Subjects	Condition	State	No of SWD	Detected SWD	Accurate stimulation rate (%)	False stimulation	Detection delay (s)
1 (Abs)	Light-on	Awake	349	343	97.70	1	0.536
	(2 h)	Sleep	46	43		8	0.545
	Light-off	Awake	248	247	99.10	0	0.491
	(2 h)	Sleep	100	98		9	0.567
2 (Abs)	Light-on	Awake	250	230	92.00	0	0.547
	(2 h)	Sleep	4	2		0	0.599
	Light-off	Awake	246	235	95.20	4	0.54
	(2 h)	Sleep	26	24		2	0.556
3 (Abs)	Light-on	Awake	95	91	95.79	0	0.602
	(2 h)	Sleep	4	4		0	0.561
	Light-off	Awake	50	47	94.00	8	0.561
	(2 h)	Sleep	0	0	—	0	n/a
4 (PTZ)	Light-on	Awake	644	627	97.30	17	0.471
	(2 h)	Sleep	0	0	—	0	n/a
	Light-off	Awake	449	442	98.44	8	0.485
	(2 h)	Sleep	0	0	—	0	n/a
5 (PTZ)	Light-on	Awake	332	328	98.83	15	0.475
	(2 h)	Sleep	9	9		0	0.474
	Light-off	Awake	506	505	99.80	16	0.478
	(2 h)	Sleep	0	0	—	0	n/a
6 (PTZ)	Light-on	Awake	315	304	96.32	8	0.502
	(2 h)	Sleep	11	10		1	0.543
	Light-off	Awake	324	312	96.3	11	0.517
	(2 h)	Sleep	0	0	—	0	n/a

rate per hour and the seizure occurrence rate per hour are 2.66 (1.60), 118.16 (75.14) for rats with spontaneous SWDs and 6.33 (1.37), 215.83 (55.48) for PTZ-induced seizures (rats 4–6), respectively. Figure 3 shows the ROC curves of the models for rats 1 and 4, respectively. These results demonstrate that the proposed seizure detection method has good performance on the two epileptic animal models.

5.2. Seizure suppression by electrical stimulation

Termination of seizure events through responsive electrical stimulation of the ZI is presented in figure 4. Figure 4(a) shows some spontaneous SWDs that could be suppressed by single 0.5 s ZI stimulation. Figure 4(b) shows the spontaneous SWDs that required three 0.5 s ZI stimulations for suppression. Figure 4(c) shows the PTZ-induced seizures that could be suppressed by single 0.5 s ZI stimulation and figure 4(d) shows the PTZ-induced seizures that required two 0.5 s ZI stimulations for suppression.

The numbers of ZI electrical stimulations required to suppress the spontaneous SWD events and PTZ-induced seizures are analyzed in figure 5. As shown in figure 5(a), more than 90% of spontaneous SWDs could be suppressed by a single ZI stimulation. 60–70% of PTZ-induced seizures could be suppressed by a single ZI stimulation (figure 5(b)). On average, 20% of the PTZ-induced seizures could be suppressed by two times of ZI stimulation. These results demonstrate that the responsive electrical stimulation at ZI can successfully stop the seizures from the two developed epileptic animal models. More than 90% of the seizures can be suppressed by two 0.5 s ZI stimulations.

5.3. Analysis of brain tissue impedance

Figure 6 shows an example of impedance changes of a rat's brain tissue at ZI (rat 3) before and after using the developed electrical seizure controller. The impedance at hour −2 is
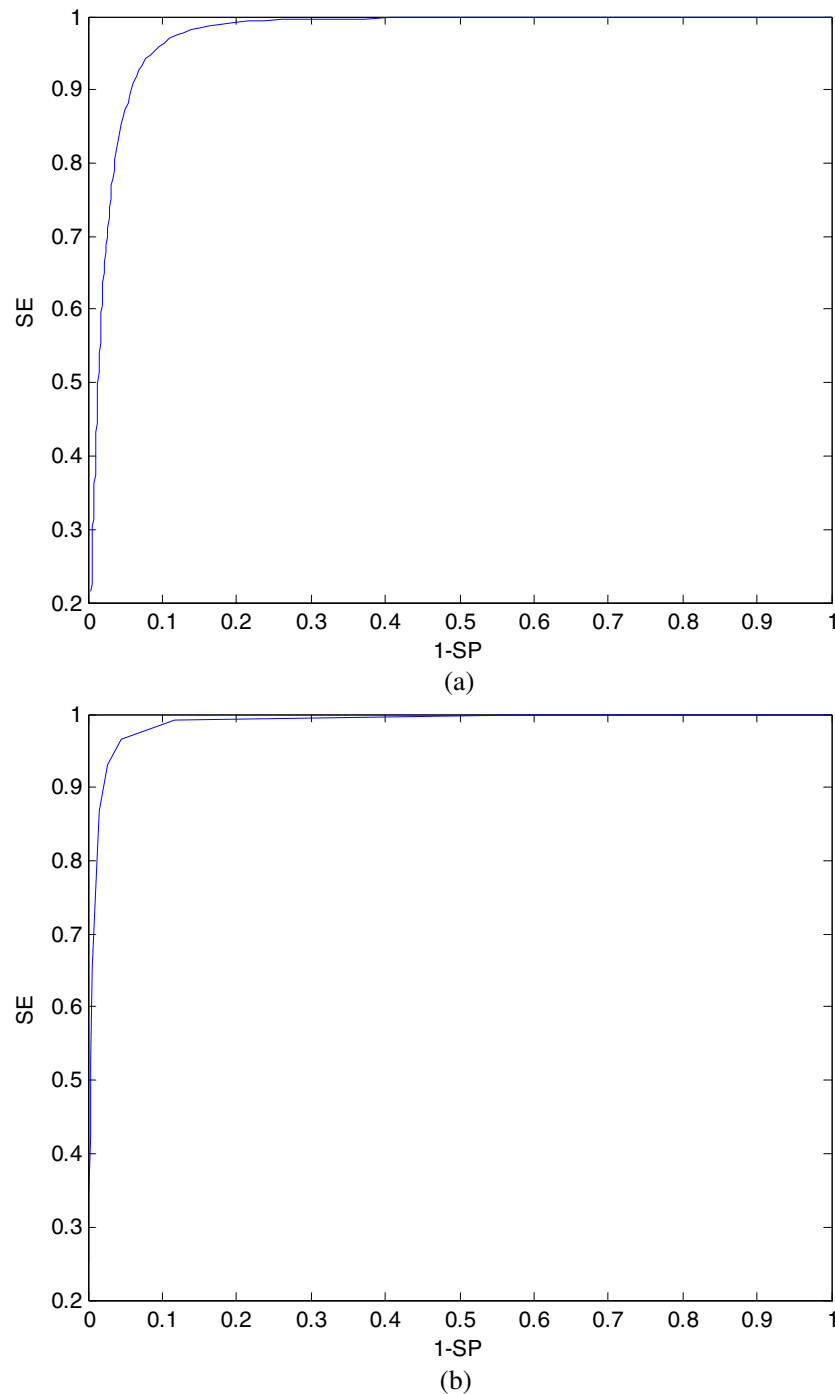
Figure 3. The ROC curves of the models for (a) rat 1 and (b) rat 4, respectively.

the baseline before seizure control and the seizure controller operated from -2 to 0 h. The constant current ($40\ \mu$A) stimulations were passed through a pair of ZI microwires (ZI 1 and 4). During the 2 h operation period, the seizure controller gave in total 104 times of electrical stimulation. The seizure controller was disabled from 0 to 12 h. The tissue impedance was measured by the Agilent 4294A impedance analyzer through the implanted ZI microwires. The result shows that the fluctuations of impedance were less than 20% for all of the wire pairs.

6. Discussion and conclusion

In this paper, a portable wireless closed-loop seizure controller including on-line seizure detection and real-time electrical stimulation was developed. It has been applied to six epileptic rats for seizure elimination. The seizure detection accuracy is greater than 92% (up to 99%), and seizure detection latency is less than 0.6 s for both spontaneous non-convulsive and PTZ-induced convulsive seizures. The average false stimulation rate is 3.1%. This system can also perform as a wireless
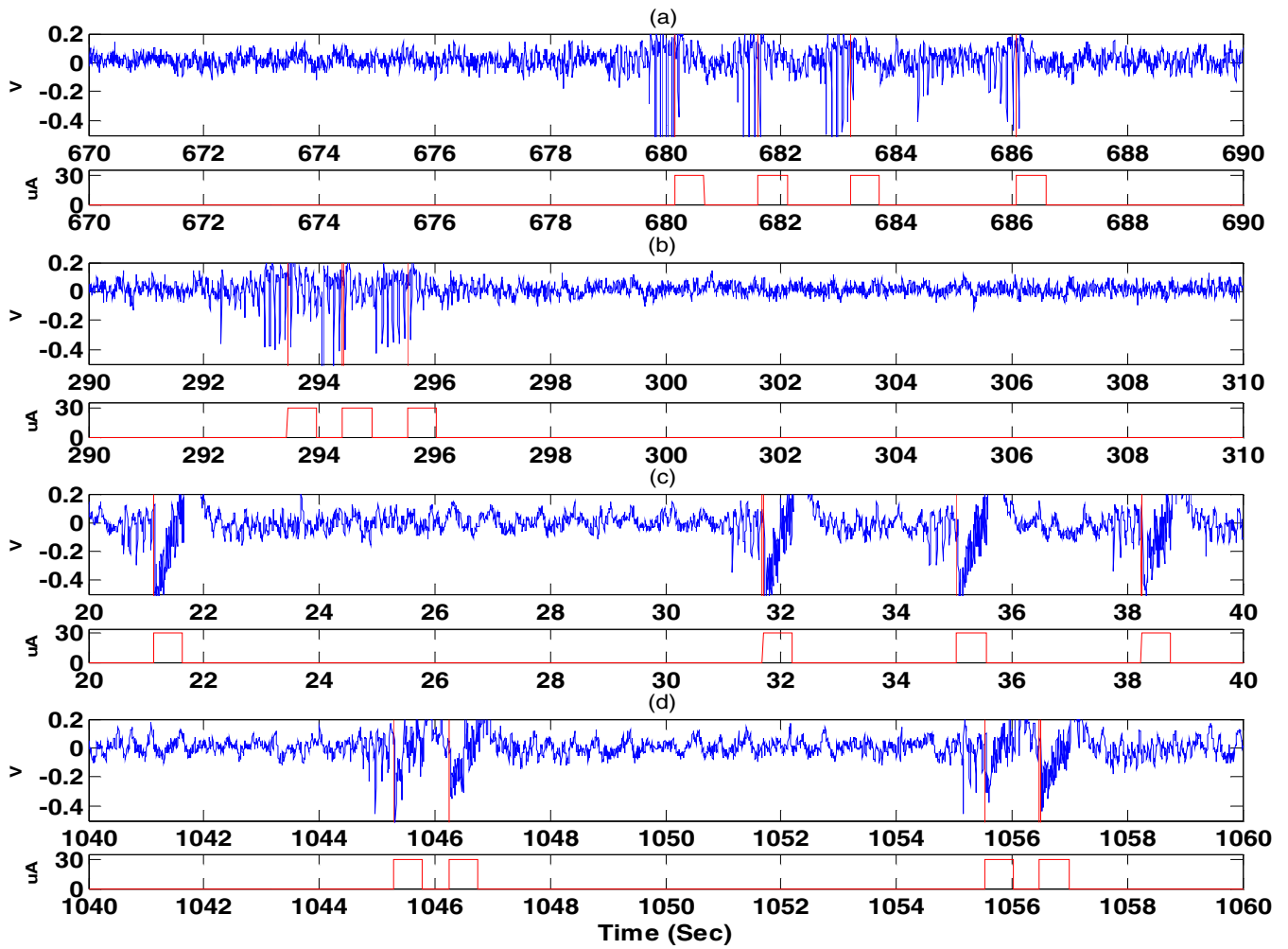
Figure 4. Termination of seizure events through electrical stimulation of the ZI. SWDs are stopped by single (a) or three (b) 0.5 s ZI stimulation. PTZ-induced seizures are stopped by single (c) or two (d) 0.5 s ZI stimulations. Data in (a) and (b) were recorded from rat 1. Data in (c) and (d) were recorded from rat 4. In each subplot, the upper panel shows EEG signals marked with ZI stimulation (red line), and the low panel shows 0.5 s ZI stimulation trains.
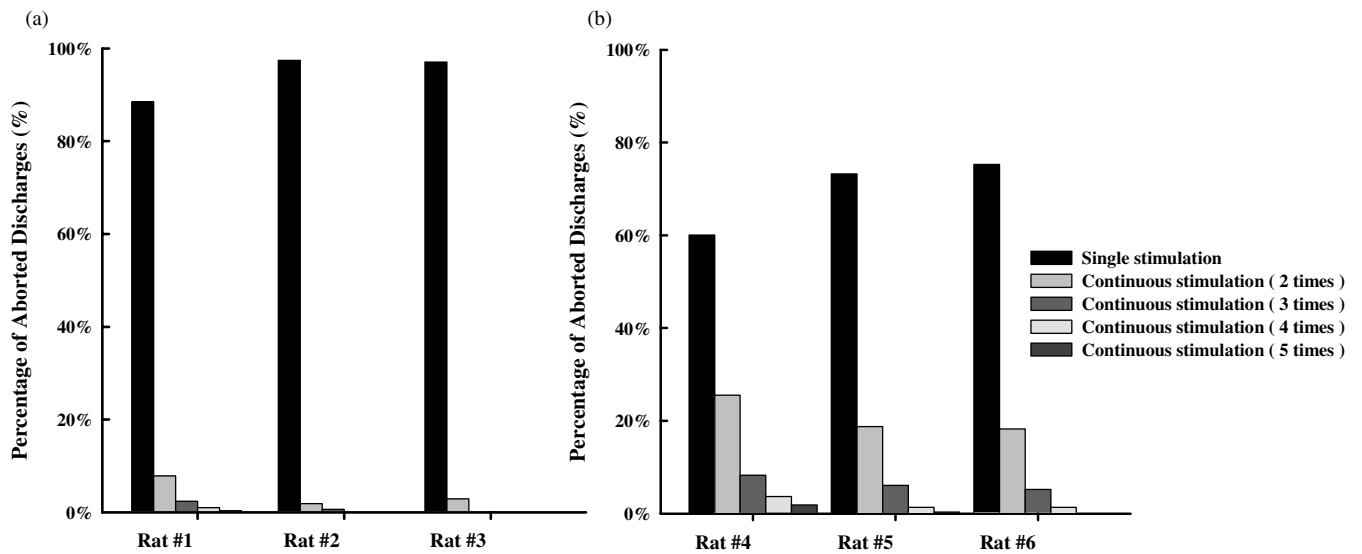

Figure 5. Analysis on the numbers of ZI electrical stimulations required to suppress (a) spontaneous SWDs and (b) PTZ-induced seizures.
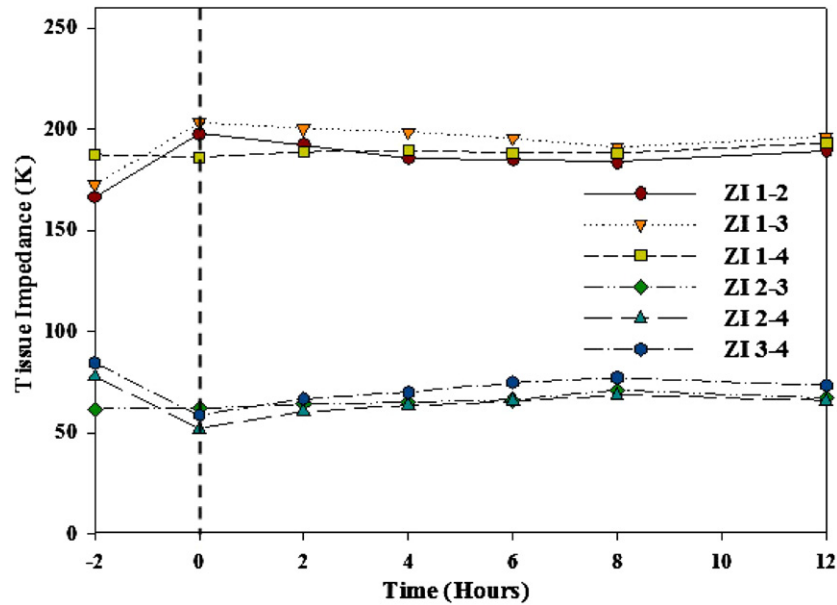
Figure 6. Changes of a rat's brain tissue impedance at ZI before and after seizure control (rat 3). The impedance at hour −2 is the baseline before seizure control and the seizure controller operated from −2 to 0 h. The seizure controller was disabled from 0 to 12 h.

Table 4. The weights of the three features in the trained LLS model corresponding to each of the six rats.

Features	1 (Abs) (%)	2 (Abs) (%)	3 (Abs) (%)	4 (PTZ) (%)	5 (PTZ) (%)	6 (PTZ) (%)
ApEn	80.63	38.89	44.74	63.92	25.49	55.88
Band 1	4.71	44.13	40.97	32.05	38.71	31.50
Band 2	14.6	16.97	14.29	4.03	35.80	12.62

on-line monitoring system when the electrical stimulator is disabled.

The current consumption of the microcontroller board (including amplifier) was 31.8 mA. The current consumption of the electrical stimulator was 21.6 mA, while the peak current was up to 23.8 mA during the stimulation. The voltage booster consumes most of the power to sustain constant current for immediate stimulation pulse generation. Table 4 shows the weights of the three features in the trained LLS model corresponding to each of the six rats. In general, combination of entropy and spectral powers is essential for the LLS model. For the computational cost of our proposed method, the ApEn requires 131 multiplications and 8450 additions; N-point FFT requires $\frac{3}{4}(N)\log 2N$ real multiplications and $2N \log 2N$ real additions by radix-4 architecture; LLS has only 3 multiplications and 3 additions. By utilizing 64-point radix-4 FFT and the shift operation for faster division/multiplication, the proposed method can be easily implemented on the 8051 MCU embedded in the TI CC 2430 chip for real-time operation.

The 800 Hz and 30–40 μA constant electrical stimulation at ZI could successfully suppress both convulsive and non-convulsive seizures in the developed animal models. It is also observed that near 30% of PTZ-induced convulsive seizures need more than two 0.5 s electrical stimulations for suppression and 90% of the non-convulsive seizures can be suppressed by only one 0.5 s electrical stimulation. In this study, the stimulation pattern was fixed. The programmable electrical

stimulator will be developed to search for more effective stimulation patterns for various epileptic models.

Instead of regular or random electrical stimulations, the proposed closed-loop seizure controller also provides the possibility of investigating the influence of the responsive seizure controller on the brain. The preliminary result shows that the fluctuations of brain tissue impedance were less than 20% after 104 stimulations in 2 h. The preliminary result only shows that short-term electrical stimulations did not seriously affect the brain tissue. Evaluation on viability of the system for long-term implantation and the long-term (weeks, months, etc) influence of the seizure controller on the brain of the epileptic rat is in experiments. The seizure controller will also be improved by reducing the weight and size and sustaining the operation period in the future.

Acknowledgments

Appendix

A.1. Animal preparation

Two epileptic rat models, Long-Evans rats with spontaneous non-convulsive SWDs and PTZ-induced convulsive seizures,

were developed. Animals were kept in a room with a 12:12 h light–dark cycle with food and water provided *ad libitum*. All surgical and experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee of National Cheng Kung University. Rats were anesthetized by sodium pentobarbital injection (50 mg kg^{-1}, i.p.). Subsequently, the rat was placed in a standard stereotaxic apparatus. Screw electrodes were bilaterally implanted over the area of the frontal barrel cortex (anterior 2.0 mm, lateral 2.0 mm with regard to the bregma). A 4-microwire bundle, made of Teflon-insulated stainless steel microwires (#7079, A-M Systems), was used to stimulate the right-side ZI (posterior 4.0, lateral 2.5 and depth 6.7–7.2 mm). A ground electrode was implanted 2 mm caudal to the lambda. Dental cement was applied to fasten the connection socket to the surface of the skull. Following suturing to complete the surgery, animals were given antibiotics and housed individually in cages for recovery.

A.2. Setup for on-line monitoring

A host computer is configured as a virtual instrument (VI) for remote real-time monitoring. It utilizes RS-232 to connect with a Texas Instrument SmartRF04 Evaluation Board that contains a CC2430 Evaluation Module to receive the spontaneous brain activities and the seizure detection sequence (0 or 1) transmitted from the TI CC2430 on the head of the animal. A graphic user interface (GUI) was also developed and operated on the host computer for data display/storage.

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