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Epileptic Seizure Detection With the Local Field Potential of Anterior Thalamic of Rats Aiming at Real Time Application

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Abstract—**treating epilepsy with deep brain stimulation (DBS) is attracting more and more attention these years, especially the close loop method that gives stimuli when needed so that the implanted device will work longer. People have tried to detect seizure with electrocorticogram (ECoG), but the extra implants put more risks to it. We plan to detect seizure with local field potential (LFP) that recorded with depth electrodes of traditional DBS. To prove the validation of this method, we recorded local field potential (LFP) of anterior thalamic (ANT) of rats who have been induced to acute temporal lobe epilepsy (TLE) by kainic acid injected in hippocampus, and succeeded in detecting electrographic onset (EO) in these data. A variation of generic Osorio-Frei algorithm (GOFA) was used as the detection method with some adjustments which mainly focus on increasing calculation speed and decreasing number of total calculations to meet the future need of transplanting to battery powered embedded medical device.**

I. Introduction

THERE are about 50 million people in the world being suffered from epilepsy, one third of which are good candidate for a surgery including lesion excision, nuclei breakage and stimuli implantation.[1] Stimuli implantation includes vagus nerve stimulation (VNS) and DBS. Because of the possibility to damage normal nerve when undergo destructive surgery and the ineffectivity of VNS for about 1/3 patients who undergo this therapy, DBS seems to be a more promising therapy.[2] But up till now the dynamics of epilepsy is very unclear which makes it difficult to accurately determine where and when to stimulate. Present commercial products, both VNS and DBS, all use constant stimulation model no matter if seizure occurs[3], which causes curative effect decrease[4] unnecessary battery waste and more frequent battery change surgery which brings more sufferings and financial burden to the patients especially those in the third world. Although the dynamics of epilepsy is unclear, the electricity activities we can obtain now are enough to detect or even predict and then stop a seizure. Also referring to close loop method widely used in present cardiac pacemaker, close loop DBS for epilepsy is becoming a significant focus of recent research efforts. [1,3,5] Limited by the storage capacity and computing speed of present embedded technology, to develop a commercially feasible application of close loop DBS for epilepsy a reliable seizure detection algorithm with low time and space complexity is a must. Neuropace developed a close loop DBS system for epileptic seizure called RNS (responsive neurostimulation) [6], which is designed to detect electrographic patterns from intracranial electrodes and to deliver a short train of stimuli through the depth electrode whenever an epileptiform activity. The entire system is implanted in the skull. Simple algorithms are utilized including half-wave statistics, line-length characteristics and area characteristics of the ECoG signal. [6-8] Osorio and Frei developed a real-time seizure detection algorithm, generic Osorio-Frei Algorithm [9], and their group carried out a series of evaluation, improvement and clinical experiment using ECoG as the signal source to analysis.[5,10,11] But to record ECoG the surgery wound to the patient is very large, which significantly increases sufferings of patients and infection possibility. We would like to develop close loop DBS for epilepsy using the stimulation electrodes of traditional DBS electrodes as recording electrodes, in order to decrease system complexity, surgery difficulty and infection possibility. It has been reported that during seizure, LFP shows synchronized fluctuations as well as ECoG. [12] But whether LFP can be used for seizure detection has not been reported yet. In this issue we studied if it is feasible to detect EO of epileptic seizure with LFP of rats other than ECoG. We used a variation of the classic GOFA as the detection algorithm, and improved parts of it accordingly.

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II. Method

A. Experiment design

Temporal lobe epilepsy (TLE) is the most common epilepsy of all kinds, to cure which doctors put DBS electrodes in

ANT. To prove the feasibility of detecting epileptic seizure with LFP, we induced the rat to acute TLE model by injecting kainic acid (KA) in hippocampus, and then recorded and studied LFP from rats. Although drug was injected in hippocampus, we still don't know where the TLE starts. But to stimulate ANT has proved effective to reduce seizure frequency in rat. [13] Depth electrode for LFP recording was implanted in bilateral ANT same. The rat surgery was carried out in Beijing Neurosurgical Institute, Capital Medical University.

LFP signal is easier to record and has larger amplitude and less noise compared to EEG and ECoG because this signal is a general cumulation of all the nuclei neurons deep inside the brain around the electrode without faraway transmission or largely decreasing caused by meninge or skull. So a commercial bio-electricity amplifier which is commonly used for EEG recording in the hospital was used to record LFP signals and synchronical video. And then the data was offline analyzed on MATLAB using a variation of GOFA to detect EO. These are showed in the system scheme figure 1 by solid line. Then the detect result can be turned into a control signal for deep brain stimulator (DBS) to generate stimuli as the dotted line in figure 1.

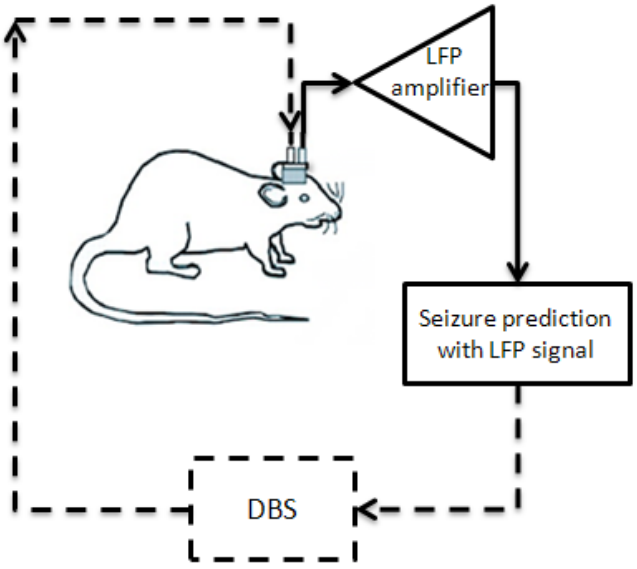

Figure 1 system scheme of close loop DBS for seizure detection and prevention

B. Material

Male wistar rats weighted 250 to 300 g were used in the experiments. The animals were housed in separate cages in a controlled environment with 12 hour light-dark cycle and the temperature set at 20℃. The animals had free access to food and water. To form the epileptic model kainic acid was injected to hippocampus of the rats. [14] The modeling was so valid that the rats showed typical symptoms of urgent epilepsy such as trembling, unreasoning falling and rigidity spasm and some of the behavioral onset were very violent. But without pulling out the wires for signal transferring, any violent behavioral onset will not disturb normal recording or causing big scale peak in the recorded signal.

All animal experiments were performed in Beijing Neurosurgical Institute, Capital Medical University, in accordance with the Guidance for Animal Experimentation of the Capital Medical University and Beijing, China guidelines for the care and use of laboratory animals.

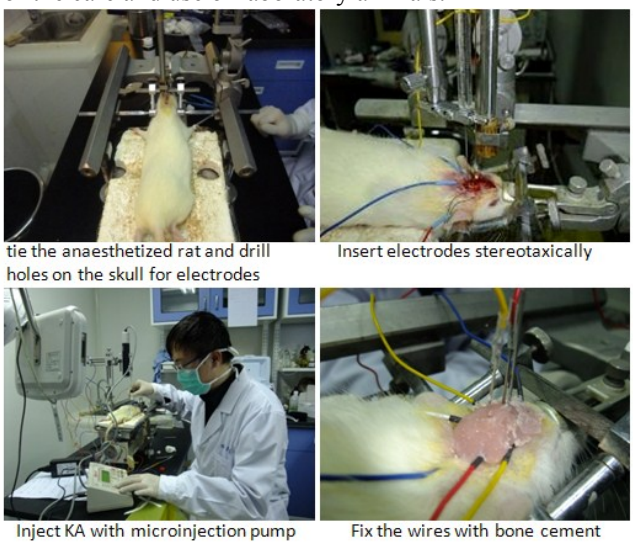

Figure 2 rat surgery procedures

C. Implantation experiment

The rat was anaesthetized with an intraperitoneal injection of pentobarbital at 40 mg/kg, the action time of which is about 4 hours. Then head of the rat was fixed to the stereotaxic frame (Model 1430, David Kopf Instruments, Tujunga, CA), and fore and hind feet were tied to stable position. We incised the scalp and drilled three holes through the skull in given positions for depth needle electrodes to go in. Parylene-coated stainless steel electrodes (model 017K025, Oxford Instruments Medical Systems, New York, U.S.A.; 400μm in diameter) with 0.5 to 1 mm exposed tip were implanted in bilateral ANT nuclei According to the Paxinos and Watson rat brain atlas [15]. The reference electrode was placed to a half- drilled a pit in the right frontal bone, so that disturb from brain or scalp will not couple in. And the ground electrode was placed in the midline anterior to the occipital suture. Micro injector was led to the left dorsal of hippocampus, and administered 0.2μl KA solution in 3 minutes time under the driving of a micro syringe pump (UMC4, World Precision, Instrument Inc., USA). After the injection the needle should be withdrawn 1mm and sustained for another 3 minutes before completely withdrawn in order to prevent KA solution from leaking into the surrounding irrelevance brain. The main procedures of the rat surgery are shown in figure 2.

D. Data acquisition

After the surgery the rats were kept in separate basin about 50cm in diameter. They were offered with moistened rat chow for one or two days after the surgery and then regular diet. Wires for recording signals were fixed to the skull with bone cement and extended to the amplifier with proper length for rat to move freely in the basin but unable to scratch the wires. LFP of ANT was recorded continuously for several

days with a 64-channel video EEG system (NicoletOne Sleep, Viasys Healthcare Inc., USA), and the rat behavior was monitored and recorded synchronously. Origin LFP signal was amplified by Nicolet C64 brain electricity amplifier and then analog-digital (A/D) converted to digital form which was recorded by the corresponding software. As the frequency of the valid composite of epileptic seizure is no more than 50Hz, we set the amplifier parameters as below: sampling rate 250Hz; resolution 0.5 microvolt; 50Hz notch. The data can be transformed to ".dat" format which can be read by MATLAB (Matworks Inc. USA).

E. Data analysis algorithm

A variation of the classic GOFA was used to detect EO, as will be described below. We modified the algorithm mainly for reducing calculation, storage space and power consumption without lowering performance which meets the need of integrating the technology on low power consume and dominant frequency embedded system. The algorithm is generally made up of three procedures as showed in figure 3: filter out the epilepsy related components from the unrelated parts; extract EO seizure features; turn the extracted feature into a control signal for DBS.

1. An order 22 DAUB4 level 3 wavelet-based FIR filter including was implemented to filter the epileptiform from the nonepileptiform. Pass band of the filter is 8Hz to 42Hz in which ordinary seizure occurs, and seizures outside this frequency range are unlikely to be detected because little weight was given to other frequency components. Other band pass filter can be used here as well, however we used this one the same as GOFA.
2. To feature the EO from the filtered data, firstly every filtered data with a subscript of k (k=O_{FG}, O_{FG}+1, O_{FG}+2,…) was squared, and then use the p-percentile data of an O_{FG} (the order of the foreground) order data before the *k-th* data to represent O_{FG}, as is known as order statistic filter, which ignore single spike or sudden burst very well comparing to moving average, so that these burst would not be classified as seizure. In GOFA p-percentile is 50% which is a median filter. Different percentile has different influence on specificity, sensitivity and detection speed.

$$FG_k = P_p(y_k^2, y_{k-1}^2, ...y_{k-O_{FG}+1}^2)$$

3. The p-percentile date of most recent O_{FG} data is then divided by background (BG) for normalization to get a dimensionless result r_k. BG is calculated by smoothing FG in a longer time scale using exponential forgetting. BG is calculated every s FG, and the next s-1 BGs are equal to this one.

$$BG_k = \begin{cases} (1-\lambda)median\{FG_k, FG_{k-s}, ..., FG_{k-(O_{BG}-1)s}\} + \lambda BG_{k-1} & k = ns \\ BG_{k-1} & (n-1)s < k < ns \end{cases}$$

$$r_k = \frac{FG_k}{BG_k}$$

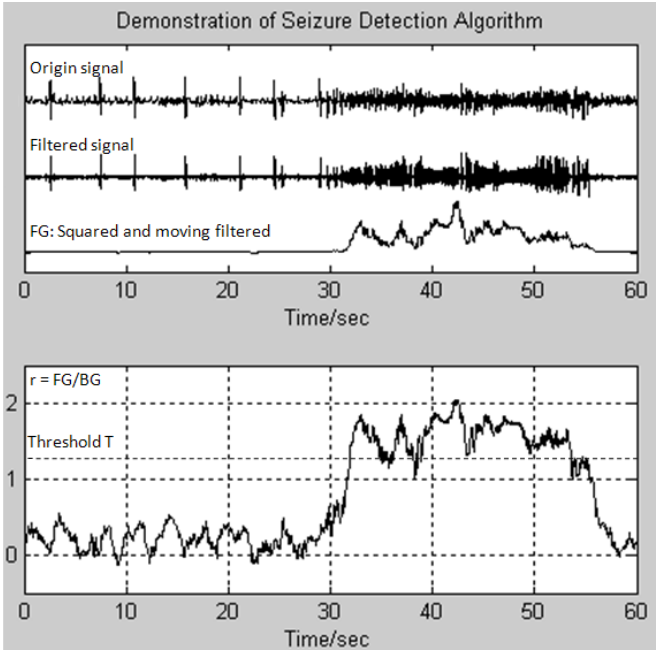

Figure 3 demonstration of seizure detection algorithm: the original signals are band pass filtered, squared and then moving median filtered to get the foreground. Smooth the foreground by using exponential forgetting to get background. r=FG/BG is used to detect seizures.

4. "r_k" rises rapidly when EO occurs, so that r alone when certain conditions be met can be used as a triggering signal to control DBS. To trigger up, r should be higher than a given threshold T for a duration D (T=22 and D=0.84 in GOFA [9]). And to trigger down, r should be lower than T for a longer duration D2. In clinic two seizures within a short period of time like 1 minute or 2 are considered to be one which is also more reliable in epilepsy prevention treatment to think this way.

III. RESULTS

Several parameters of GOFA were modified to reduce the number of calculations aiming at application on embedded system. The calculations lies mainly in band pass filtering, and FG calculation. For each sample which is 4 ms when sampling rate is 250Hz, filtering with an order 22 band pass filter and then squared consumes 22 multiplications, 21 additions and 1 square of float number, and calculating the FG need to efficiently sort O_{FG} float number, which needs squared O_{FG} times of compares and shifts at most in the first sequence of sorting, and at most $O_{FG}/2$ times of sorting when using insert sorting for all following data. For recent microcenter unit (MCU) with a dominant frequency of 5M, this will not be a difficult task to accomplish. However the possible application will probably implanted in human entirely and powered by battery, so without reducing performance any low power consumption design is welcomed.

To minimize the number of calculations we mainly changed two parameters. O_{FG} is 250 which equals to 1s of data at the sampling rate of 250Hz, half of O_{FG} used in GOFA. Shorter O_{FG} were used, but the algorithm became too sensitive, making it hard to determine EO seizure. On matlab

test, this did make the algorithm faster a lot. The forgetting factor λ is smaller than GOFA so that background is formed faster.

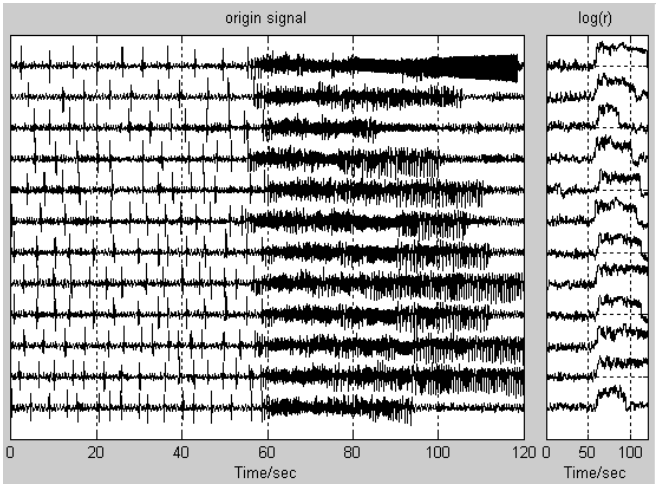

Figure 4 some other original data and their detection results

With these changes the modified GOFA still have good results. As in figure 3 the sudden nonepileptic bursts in origin and filtered data is well suppressed by median filter. But epileptiform seizure can be captured accurately by a sudden rise of "r_k". More successful seizure detections are showed in figure 4. 12 segments of 2min long ANT LFP data were analyzed, whose seizures occurs at about 60 second. Right side of figure 4 are "$\log(r_k)$" of the origin data in the left. Before EO there were many occasional spikes in origin data as could be seen more clearly in figure 3, but in synchronously recorded video no clinical onset (CO) occurred.

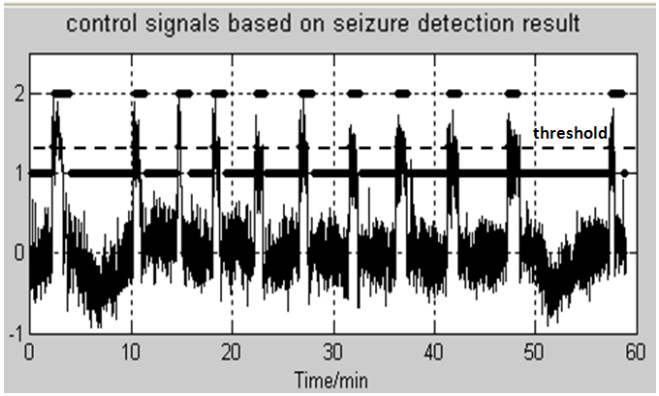

Figure 5 label the seizures whose "rk" overflows both amplitude threshold and time threshold

"r_k" alone can be turned into a control signal to trigger a treatment application. As in figure 5 using the perfect sensitivity and specificity detection parameter T=22, D=0.84s [9], a long sequence of LFP data can be labeled as epileptiform segments and nonepileptiform segments by the higher and lower thick lines above the signals. EO can be detected, and is also a prediction of CO as if there were a CO, it usually occurs some time after EO. EO labels can be used to trigger treatment automatically.

IV. Conclusion

It can be supposed that in a real time seizure detection and prevention active implantable medical device for epilepsy especially TLE: the depth electrodes like those in DBS system record ANT LFP, MCU calculates "r" with these data to decide if stimuli is needed, and finally electric stimuli is give when necessary. The main feature of this system is that the feedback source ANT LFP is directly recorded from the stimulation electrode. Some improvement on common DBS depth electrodes will make them suitable for LFP recording. This system scheme have obvious advantage comparing with ECoG based close loop DBS for epilepsy which needs to implant extra cortex electrodes: smaller surgery wound, low system complexity, which both reduce the risk of implants and surgery difficulty so that reducing infection possibility. We have proved the validation of detecting seizure with ANT LFP of rats, and modified parts of GOFA to meet the need of battery powered embedded system. Equally good results were obtained, while the speed is increase significantly.

References

[1] N.E. Bharucha NE, J. Sander, S.AlDeeb, A. Carpio, et al. The epidemiology of the epilepsies: Future directions, EPILEPSIA, vol. 38, May. 1997, pp. 614-618.

[2] A.V. Alexopoulos, P. Kotagal, T, Loddenkemper, et al. Long term result s with Vagus Nerve stimulation in children with pharmacoresistant epilepsy. Seizure, 2006, 15 (7):491～503.

[3] C.H. Halpern, U. Samadani, B. Litt. Deep Brain Stimulation for Epilepsy. Neurotherapeutics, 2008,5: 59-67.

[4] R.P. Lesser, S.H. Kim, L. Beyderman, et al. Brief bursts of pulse stimulation terminate after discharges caused by cortical stimulation. Neurology, 1999, 53(9): 2073-2081.

[5] N.C. Bhavaraju, M.G. Frei and I. Osorio, Analog seizure detection and performance evaluation IEEE Trans. Biomed. Eng. 2006, 53 238–245

[6] F.T. Sun, M.J. Morrell, R.E. Wharen. Responsive cortical stimulation for the treatment of epilepsy. Neurotherapeutics, 2008,5(1): 68-74.

[7] http://www.seizurestudy.com/

[8] http://www.neuropace.com/index.html

[9] I. Osorio, M.G. Frei, S.B. Wilkinson. Real-time automated detection and quantitative analysis of seizures and short-term prediction of clinical onset. Epilepsia 1998;39(6):615–27.

[10] S.M. Haas, M.G. Frei, and I. Osorio, Strategies for adapting automated seizure detection algorithms, Medical Engineering & Physics, vol. 29, Oct. 2007, pp. 895-909.

[11] I. Osorio, M.G. Frei, J. Giftakis J, T. Peters, et al. Performance Reassessment of a Real-time Seizure-detection Algorithm on Long ECoG Series, Epilepsia, 2002(43), 1522-1535

[12] B. Litt, R. Esteller, J. Echauz, et al. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. Neuron, 2001, 30(1): 51–64.

[13] M.A. Mirski, L.A. Rosell, J.B. Terry, R.S. Fisher. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Rev 1997;28:89 －100

[14] K. Yamamoto, T. Tanaka, Y. Yonemasu. Jacksonian seizure model induced by a kainic acid microinjection into unilateral sensori-motor cortex. Brain and nerve. 1995 May;47(5):477-83.

[15] G. Paxinos and C. Watson 2005 The Rat Brain in Stereotaxic Coordinates (New York: Elsevier Academic)