Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Towards Real-Time In-Implant Epileptic Seizure Prediction

Joseph N. Y. Aziz, Rafal Karakiewicz, Roman Genov, Berj L. Bardakjian, Miron Derchansky and Peter L. Carlen

***Abstract*— We present an architecture of an epileptic seizure prediction system suitable for an implantable implementation. The microsystem comprises a neural interface, a spectral analysis processor and an artificial neural network (ANN). The neural interface and the spectral analysis processor have been prototyped in a 0.35 μm CMOS technology with experimental results are presented. The wavelet-based artificial neural network predicts the onsets of seizure up to two minutes before their occurrence in an in-vitro epilepsy model using a mouse hippocampal brain slice with recurrent spontaneous seizures.**

I. INTRODUCTION

Approximately 40 million people worldwide are epileptic. Epilepsy is the third most common neurological disorder following stroke and Alzheimer's disease, but it imposes higher costs on society than stroke. Present day therapy to control epilepsy includes several strategies, most of limited benefit.

Pharmacotherapy involves the long-term use of systemically administered drugs, which are often toxic because of their side effects on other organs or the brain. Surgery, which involves the excision of a relatively large amount of brain tissue, raises concerns about neurological disability caused by the removal of either normal or functionally necessary tissue. There is also the real but small risk associated with any invasive neurosurgical operation.

Approximately 60 percent of epileptic patients suffer partial seizures, 30 percent of which are intractable and do not respond to medication. A significant percentage of these patients are not suitable for surgical therapy. For such patients brain stimulation is presently done via implanted electrodes or via peripheral nerve stimulation.

Continuous vagal nerve stimulation is relatively ineffective, with only five percent of treated patients rendered seizure free [1]. Deep brain stimulation of the thalamus and white matter are also being investigated [2], [3]. An alternative, potentially more effective method for treating intractable epilepsy is direct electrical stimulation of the epileptogenic zone (focus), a concept only in its preliminary stages of development. The antiepileptic effect of continuous or intermittent electrical stimulation in-vitro has been demonstrated previously in pharmacologically modified brain slices [4], [5], [6], [7]. In addition several studies have shown some partial success in reducing afterdischarges and seizures in human patients and rats by continuous open-loop electrical stimulation [8], [9]. These results were not sufficiently compelling to warrant their use in patients with intractable epilepsy.

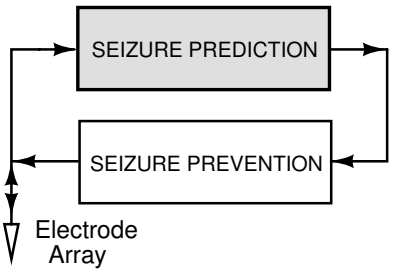


Fig. 1. The block diagram of the implantable medical device for autonomous seizure prediction and prevention. The device is implemented as a dynamical control loop that consists of feedforward and feedback pathways to predict and prevent intractable seizures respectively.

The methods discussed above use protocols that are empirical at best, and have no direct relationship to the underlying neuronal dysfunctional activity (*e.g.*, continuous stimulation), because there is no dynamic feedback to regulate the stimulation. None of these therapies considers the nonlinear dynamics of dysfunctional brain activity or utilizes an automated therapeutic feedback approach. Previous studies have reported algorithms which detect impending seizures from the electroencephalogram (EEG) and electrocorticogram (ECoG) recordings retrospectively [10], [11], [12]. In this paper, we present an overview of an envisioned implantable technology that will adaptively learn the abnormal brain electrical activity of seizures. Such technology is an important contribution towards a seizure prevention therapy schematically shown in Figure 1, which is an alternative treatment for patients with drug resistant epilepsy.

II. SEIZURE PREDICTION ALGORITHM

The evolution of a seizure (ictus in Latin) involves a preictal (*i.e.*, prior to seizure) transitional state that dynamically differs from the interictal (*i.e.*, between seizures) and ictal (*i.e.*, during a seizure) states [13]. It had been observed that the frequency content of neuronal electrical activity changes significantly during the progression of a seizure-like event.

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Canadian Institutes of Health Research and Krembil Neuroscience Center.

J. N. Y. Aziz, R. Karakiewicz and R. Genov are with the Department of Electrical and Computer Engineering at the University of Toronto, Toronto, ON M5S 3G4, Canada (email: roman@eecg.utoronto.ca)

B. L. Bardakjian is cross-appointed to the Department of Electrical and Computer Engineering and the Institute for Biomaterials and Biomedical Engineering at the University of Toronto, Toronto, ON M5S 3G4, Canada (email: berj@cbl.utoronto.ca)

M. Derchansky and P. L. Carlen are with Krembil Neuroscience Center at Toronto Western Hospital and the Departments of Physiology and Medicine at the University of Toronto, Toronto, ON M5T 2S8, Canada (email: carlen@uhnres.utoronto.ca)

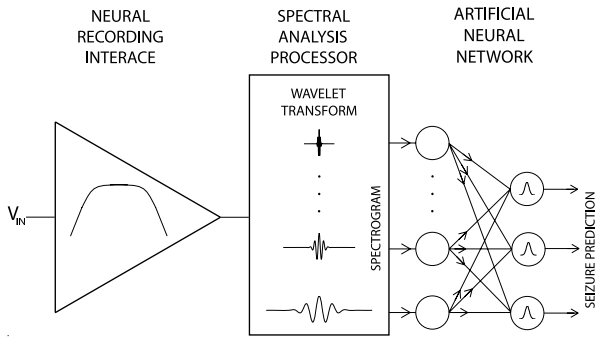


Fig. 2. Architecture of the feedforward seizure prediction path of the envisioned brain implant for seizure prevention.

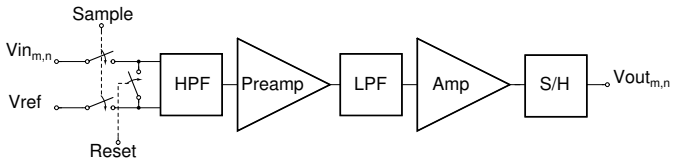


Fig. 3. Architecture of one channel of the integrated neural interface.

Time-frequency information of this activity can be used to classify different states of a seizure event.

The implication of this distinction in the states is that there is a possibility for seizure prediction, intervention, and prevention. The control of dynamic systems to keep them away from the stable manifold, once they are firmly established, is a laborious and challenging task. Consequently, the ultimate prerequisite for any control algorithm is the ability to predict the onset of undesirable dynamics prospectively, not retrospectively. Hence, the real-time prediction of state transitions becomes the key to a successful control strategy.

Figure 2 outlines the components of the epileptic seizure prediction system. The neural signal is acquired from the brain and introduced to a spectral analysis processor. The processor performs wavelet decomposition which allows the signal energy to be separated into independent frequency bands. The wavelet transform information is conveyed into the ANN for extracting signal energy standard deviations [14]. When processed, the relative energy contributions of these bands correspond to the probability of a seizure state (interictal, preictal or ictal). Thus, the ANN generates an estimate of an upcoming seizure-like event onset time.

III. Seizure Prediction Microsystem

A. Neural Recording Interface

Most of the frequency content of extracellular action potentials in the brain is concentrated between 0.1 Hz and 1 kHz. Signal amplitudes range from 50 μV to 500 μV, with 100 μV being a typical average value. For low-noise distributed neural potential field recording, a multi-channel integrated neural interface has been designed and prototyped. Multi-channel signal acquisition may allow to improve seizure prediction accuracy through spatial information

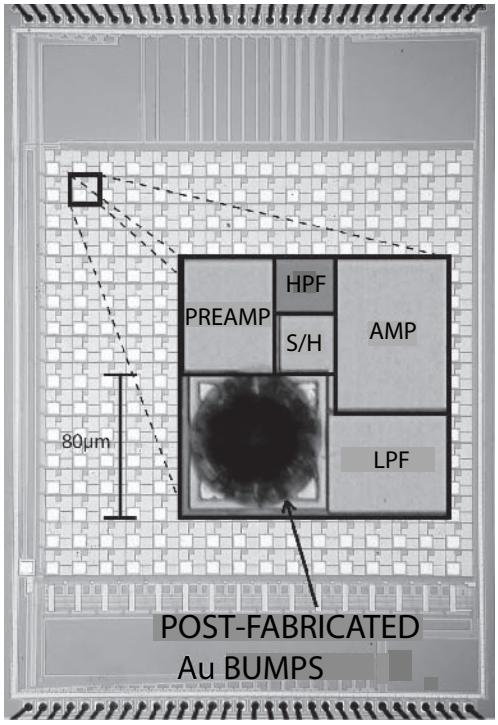


Fig. 4. Micrograph of the 256-channel integrated neural interface. The 3×4.5 mm^2 die was fabricated in a 0.35 μm CMOS technology. Electrode pitch is 170 μm.

processing. The neural interface acquires voltages on 256 independent channels simultaneously. The signal acquisition circuits are organized in a 16×16 array.

Each channel in the array contains a high-pass filter (HPF), a low-pass filter (LPF) and two amplification stages, as shown in Figure 3. Each channel also contains a sample-and-hold cell as necessary for truly simultaneous multi-channel recording. Array readout is implemented in a serial fashion as controlled by row and column address decoders. Off-chip double sampling is performed during calibration in order to remove DC offsets. Each channel is connected to on-chip differential recording electrodes. One reference electrode is shared by all channels.

The 256-channel integrated neural interface and signal processor was fabricated on a $3\text{mm} \times 4.5\text{mm}$ die in a $0.35\ \mu m$ double-poly CMOS technology. The die micrograph is shown in Figure 4. The golden bumps were post-fabricated on the surface of the die to contact directly with non-passivated aluminum pads. Each bump is 100 μm high.

The golden bumps serve as an intermediate step for attachment to an array of commercially available platinum electrodes. Figure 5 shows an overview of the electrode array. The assembly and attachment process is commonly known as flip-chip assembly. Each electrode shank is coated with Parylene-C and only a 50 μm tip is exposed.

B. Wavelet Transform Processor

The wavelet-based ANN (WANN) seizure prediction algorithm described in [14] requires extensive computing resources in order to operate in real time with a high

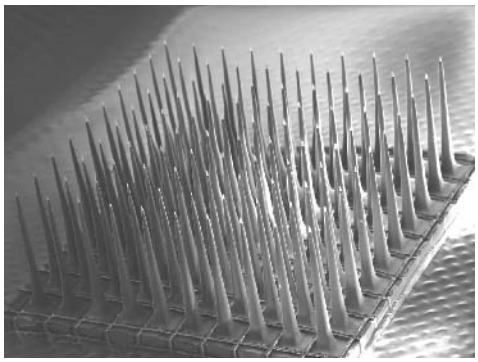


Fig. 5. Cyberkinetics platinum microelectrode array. Each electrode shank is coated with Parylene-C exposing only 50 μm tip.

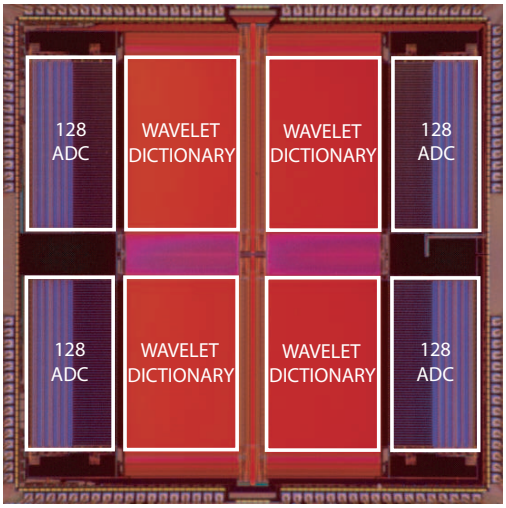


Fig. 6. Micrograph of the wavelet spectral analysis processor. The die measures 4mm $\times$ 4mm. A spectrogram of a neural recording is computed in real time using a Morlet wavelet dictionary stored in the on-chip DRAM memory. This is the most computationally intensive step in the seizure prediction algorithm.

detection rate. This computational throughput is beyond the capabilities of a desktop computer with a Pentium processor, particularly when more than one recording channel is used. The main computational burden, by far, is performing wavelet decomposition of the neural recording signal, which is necessary to train and run the artificial neural network as shown in Figure 1.

The wavelet spectral analysis processor shown in Figure 6 is a densely integrated, massively parallel energy efficient mixed-signal VLSI processor [15], [16]. It delivers over 175 billion binary operations per second for every milliwatt of power. Implemented in a 0.35 μm CMOS integration technology, the processor yields 1.8 billion operations per second [17]. Such computational efficiency and integration density are several orders of magnitude higher than those available from existing digital processors. This represents an energy-efficient and cost-effective solution for implementations of very computationally intensive learning algorithms, such as epileptic seizure prediction algorithms in real time, particularly on an implantable platform.

Morlet wavelet templates are stored in the on-chip DRAM-based analog array in a row-parallel fashion. Input data is presented serially into the input shift register. For every shift a 512-sample window of the input is correlated with all wavelet templates stored in the on-chip memory in analog domain. Correlation is performed in parallel on the entire array. The computed inner products are quantized by four banks of 128 analog-to-digital converters each.

C. Artificial Neural Network

Our prediction scheme combines wavelet transform computation and an ANN, and can successfully anticipate an in-vitro low-magnesium model of a seizure in mouse hippocampus slices in a timely manner [18], [19]. The wavelet transform quantifies the energy of each frequency band in the recorded signal emphasizing frequency information over absolute values. A recurrent neural network with radial-basis function nonlinearities is trained to deduct an impending seizure based on the wavelet-transformed inputs. The network classifies the underlying dynamics of spontaneous in-vitro events into interictal, preictal, and ictal activities, and predicts the onset of a seizure, as illustrated in Figure 2. Integrated implementation of the ANN does not require significant additional area or power resources.

IV. Experimental Results

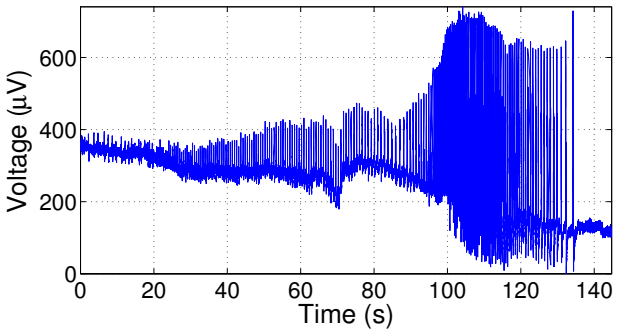
The functionality of the neural recording interface and wavelet spectral analysis processor has been validated in real-time seizure monitoring and spectral analysis experiments. A single recording cell has been connected to two external tungsten electrodes. The output of the channel was quantized off-chip and fed to the wavelet spectral analysis processor off line.

Figure 7(a) shows a seizure recorded in-vitro from an intact mouse hippocampus [20]. Figure 7(b) depicts the time-frequency map computed by the wavelet spectral analysis processor. To implement the envisioned seizure-predicting microsystem shown in Figure 1, the time-frequency map will be selectively sampled and fed to the ANN classifying brain-activity states in real time.

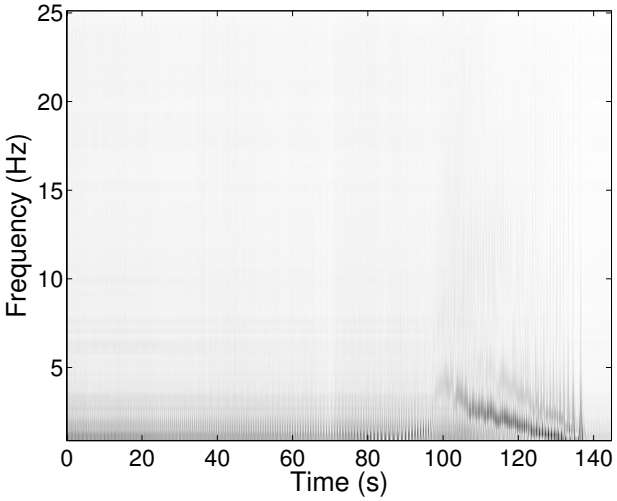
Figure 8 shows the result of an ANN system utilizing wavelet entropy and standard deviation as preprocessed inputs. Onsets of seizure events can be predicted up to two minutes before state transitions. The ANN was trained and run on data collected using bench-top instrumentation equipment.

V. Conclusions

We present a neural recording and spectral analysis integrated microsystem, an instrumentational and computational core of an envisioned miniature brain implant for automated epileptic seizure prediction. The two blocks have been prototyped and experimentally validated in real-time in-vitro epileptic seizure monitoring and spectral analysis, as necessary for an implantable implementation. An ANN was trained on wavelet transformed brain activity recordings to predict seizures in a timely manner.



(a)



(b)

Fig. 7. Seizure monitoring and spectral analysis experimental results: *(a)*, recording of an epileptic seizure in an intact hippocampus of a mouse performed on one channel of the integrated neural interface; *(b)*, a time-frequency map (spectrogram) computed on the wavelet spectral analysis processor.

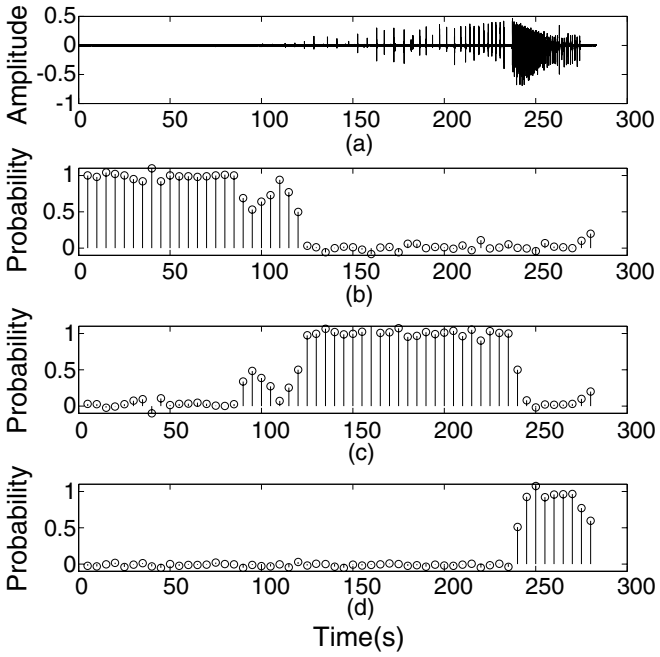


Fig. 8. *(a)*, A sample seizure recording. Posterior probabilities for the respective system states are shown at the corresponding times: *(b)*, interictal; *(c)*, preictal; *(d)*, ictal [19].

REFERENCES

[1] E. Ben-Menachem, "Vagus-nerve stimulation for the treatment of epilepsy," *The Lancet Neurology*, vol. 1, no. 8, pp. 477–482, November 2002.

[2] M. Hodaie, R. Wennberg, J. Dostrovsky, and A. Lozano, "Chronic anterior thalamus stimulation for intractable epilepsy," *Epilepsia*, vol. 43, no. 6, pp. 603–608, June 2002.

[3] A. A. Cohen-Gadol, M. R. Stoffman, and D. D. Spencer, "Emerging surgical and radiotherapeutic techniques for treating epilepsy," *Current Opinion in Neurology*, vol. 16, no. 2, pp. 213–219, April 2003.

[4] R. S. Ghai, M. Bikson, and D. M. Durand, "Effects of applied electric fields on low-calcium epileptiform activity in the ca1 region of rat hippocampal slices," *Journal of Neurophysiology*, vol. 84, no. 1, pp. 274–280, July 2000.

[5] B. J. Gluckman, H. Nguyen, S. L. Weinstein, and S. J. Schiff, "Adaptive electric field control of epileptic seizures," *The Journal of Neuroscience*, vol. 21, no. 2, pp. 590–600, January 2001.

[6] H. Khosravani, P. L. Carlen, and J. L. P. Velazquez, "The control of seizure-like activity in the rat hippocampal slice," *Biophysical Journal*, vol. 84, no. 1, pp. 687–695, January 2003.

[7] J. Lian, *et al.*, "Local suppression of epileptiform activity by electrical stimulation in rat hippocampus in vitro," *The Journal of Physiology*, vol. 547, no. 2, pp. 427–434, March 2003.

[8] A. L. Velasco, *et al.*, "Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: Preliminary report," *Archives of Medical Research*, vol. 31, no. 3, pp. 316–328, May 2000.

[9] N. Akamatsu, *et al.*, "Decreased susceptibility to pentylenetetrazol-induced seizures after low-frequency transcranial magnetic stimulation in rats," *Neuroscience Letters*, vol. 310, no. 2, pp. 153–156, September 2001.

[10] M. L. V. Quyen, *et al.*, "Anticipation of epileptic seizures from standard eeg recordings," *The Lancet*, vol. 357, no. 9251, pp. 183–188, January 2001.

[11] B. Litt, *et al.*, "Epileptic seizures may begin hours in advance of clinical onset: A report of five patients," *Neuron*, vol. 30, no. 1, pp. 51–64, April 2001.

[12] V. Navarro, *et al.*, "Seizure anticipation in human neocortical partial epilepsy," *Brain*, vol. 125, no. 3, pp. 640–655, March 2002.

[13] L. Iasemidis and J. Sackellares, "Chaos theory and epilepsy," pp. 118–126, 1996.

[14] A. Chiu, *et al.*, "Prediction of seizure onset in an in vitro hippocampal slice model of epilepsy using gaussian-based and wavelet-based artificial neural networks," *Ann Biomed Eng*, vol. 33, no. 6, pp. 798–810, June 2005.

[15] R. Genov and G. Cauwenberghs, "Kerneltron: Support vector 'machine' in silicon," *IEEE Trans. Neural Networks*, vol. 14, no. 5, pp. 1424–1434, 2002.

[16] ——, "Charge-mode parallel architecture for matrix-vector multiplication," *IEEE Trans. on Circuits and Systems II: Analog and Digital Signal Processing*, vol. 48, no. 10, pp. 930–936, 2001.

[17] R. Karakiewicz, R. Genov, A. Abbas, and G. Cauwenberghs, "175 GMACS/mW charge-mode adiabatic mixed-signal array processor," in *Proc. IEEE Symposium on VLSI Circuits*, 2006.

[18] A. Chiu and B. Bardakjian, "Control of state transitions in an in silico model of epilepsy using small perturbations," *IEEE Transactions on Biomedical Engineering*, vol. 51, no. 10, pp. 1856–1859, October 2004.

[19] A. Chiu, *et al.*, "Prediction of seizure onset in an in-vitro hippocampal slice model of epilepsy using gaussian-based and wavelet-based artificial neural networks," *Annals of Biomedical Engineering*, vol. 33, no. 6, pp. 798–810, June 2005.

[20] M. Derchansky, *et al.*, "Model of frequent, recurrent, and spontaneous seizures in the intact mouse hippocampus," *Hippocampus*, vol. 14, no. 8, pp. 935–947, April 2004.