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LED-Based Optical Device for Chronic *In Vivo* Cerebral Blood Volume Measurement

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Abstract

We demonstrate a reflectivity-based cerebral blood volume sensor comprised of surface-mount light-emitting diodes on a flexible substrate with integrated photodetectors in a form factor suitable for direct brain contact and chronic implantation. This reflectivity monitor is able to measure blood flow through the change of the surface reflectivity and, through this mechanism, detect the cerebral-blood-volume changes associated with epileptic seizures with a signal-to-noise (SNR) response of 42 dB. The device is tested in an *in vivo* model confirming its compatibility and sensitivity. The data taken demonstrate that placing the sensor into direct brain contact improves the SNR by more than four orders of magnitude over current noncontact technologies.

Index Terms

Biomedical optical imaging; surface mounting; time–frequency analysis

I. Introduction

Epilepsy is a neurological condition characterized by recurring seizures in which clusters of neurons fire synchronously with no external stimulus. Approximately 1% of the human

population suffers from the condition; 20% of whose symptoms cannot be satisfactorily treated pharmaceutically [1]. This minority relies almost exclusively on invasive surgery [2]; an important part of which is the *in vivo* surface analysis of brain tissue using arrays of electrical probes to localize the focus of the seizures and direct surgical intervention [3].

There are several established approaches for mapping activity in the brain. The most established, which is electrophysiological recording from electrodes, does not have the temporal or spatial sampling necessary for the acute study of neuronal activity generation and spread due to volume conduction effects [4]. Other techniques, including functional magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography, do not have sufficient resolution to record brief paroxysmal events such as interictal spikes (the synchronous firing of neuron populations) [5].

Optical imaging using a charge-coupled device camera has been successfully used to measure short-duration events such as interictal, ictal, and secondary homotopic foci *in vivo* [3] as well as normal brain function [6]. A direct correlation between interictal spikes and neocortex tissue reflectivity due to cerebral blood-flow changes and the resulting change in hemoglobin oxygenation in response to increased neuronal activity has been demonstrated [7]. This method has high spatial and temporal resolution, and images can be generated at a high frame rate, making the process clinically valuable for tissue analysis prior to ictal onset zone and frequent interictal spike-zone removal [3]. The assembly used requires a significant amount of movement damping and can only be performed in a surgical environment, as the device must be externally mounted to the patient and the brain tissue must be exposed [8]. In optimal situations, the signal-to-noise ratio (SNR) is less than five [9].

Chronically implanted optical sensors for unmolested long-term epileptic studies have not yet been demonstrated. This technology would constitute a significant advance; Suh *et al.* have shown a correlation between interictal spikes and subsequent epileptic seizure with a temporal offset of approximately 1–2 s [3]. The presence of a quantifiable warning signal exterior to the neocortex provides an opportunity for real-time *in vivo* monitoring and detection for seizure management. [10]

In this paper, we demonstrate an integrated light-emitting diode (LED) and photodetector device applied to *in vivo* optical detection in a form factor suitable for chronic implantation and array development. This device is enabled by the miniaturization and high efficiency of LED technology and allows the development of a clinically applicable measurement system.

II. Approach

A small and scalable probe was designed, which measures reflected light with the precision necessary to distinguish between oxygenated and nonoxygenated brain tissue. Neural activity associated with seizures causes a 0.1%–5.0% reflectance change, depending on the intensity of the neural activity.

Commercially available surface-mount components were used to produce a thin form-factor element compatible with implantation for chronic measurement (< 1 mm thick). The LEDs and photodetectors are operated using a synchronous detection approach to improve the SNR and heterodyne the detected signal away from the frequency composition of physiological noise. The emitter–sensor-pair architecture can be scaled to multiple wavelengths and multiple sites using frequency domain or phase space encoding techniques.

A. Process Flow

The device was assembled using a flexible circuit board fabricated on polyethylene naphthalate [(PEN); Dupont/Teijin Q65A]. This substrate material demonstrates excellent transparency, reagent compatibility, flexibility, and tolerance of high processing temperatures (in excess of 200 °C in air) with minimal shrinkage or warpage. PEN can serve as an optically transparent replacement for polyimide in flexible circuit applications.

The process is shown in Fig. 1. The substrate is first solvent cleaned, and 10 nm of chrome and 80 nm of gold are thermally evaporated under vacuum. These metal films are patterned via contact photolithography, etched, and cleaned. Low-melting-point indium solder paste is dispensed on the bonding attachment pads, and the LED and photodetector are positioned on the paste. The assembly is reflowed on a hot plate at 170 °C for 15 s. The indium composite wets the chrome/gold intermetallic underlayer while alloying with the gold pads, preventing gold scavenging from the interconnect lines and also drawing the components into position via surface tension. The completed device is electrically contacted via an anisotropic conducting adhesive through a ribbon cable to a custom circuit board where the individual component connections are made using shielded coaxial connections.

For increased structural robustness and environmental encapsulation, the devices are first CVD coated with 200 nm of parylene-C, an optically transparent polymer used as a moisture barrier and electrical insulator. This is followed by a thin layer of a chemically activated epoxy adhesive. Once the adhesive is cured, the device is coated with a final 1- μ m-thick layer of parylene-C for biocompatibility and insulation against the saline environment of the brain. Fig. 2 shows a completed and encapsulated device.

The high efficiency and miniaturization of commercial surface-mount LEDs enable this application. The light emitter used for this paper (Kingbright; APHK1608VGC-Z) is a commercially available surface-mount LED, chosen for its small size (0.7-mm thickness, 1.6 $\times$ 0.8-mm length and width) and emission wavelength near an isosbestic point for hemoglobin and deoxyhemoglobin (535 nm), yielding a measure of total hemoglobin (Hbt) [9]. A surface-mount broad-spectrum phototransistor (Optek OP-500) was used. The use of a dual wavelength measurement would allow separate measurements of perfusion and oxygenation [5].

B. Measurement and Signal Analysis

Reflected light from the target as well as a waveguided baseline is incident on the photodetector. To improve the SNR, a synchronous detection approach is applied. The LED is driven directly with a function generator (Agilent 33220A) synchronized to a lock-in amplifier (Signal Recovery 7265) at 497 Hz, out of band and nonharmonic with traditional periodic noise sources (e.g., 60-Hz line hum), and above the frequencies of broadband animal metabolic activity (< 20 Hz). The photoresponse is conditioned through a current preamplifier (Stanford Research Systems SR570) which is then detected by the lock-in. Using synchronous detection and discarding the dc baseline which is structurally waveguided through the system, it is possible to measure reflectivity changes yielding reflected power changes less than 4 nW/cm². Owing to the high output intensity of the LEDs (0.5 cd), this can yield a measured reflectivity SNR of 42 dB for the brain surface measured during a seizure against the background noise of a surgical environment.

III. Results

Figs. 3 and 4 show the results obtained from two separate *in vivo* experiments performed at the Weill Cornell Medical College of the New York Presbyterian Hospital.

The device was placed on the intact dura above the rat neocortex, where the local field potential (LFP) was monitored via a contact electrode. Seizures were chemically induced by introducing 4-aminopyridine (4AP) to the neocortex, yielding polyspikes, and bicuculline methiodide (BMI), yielding interictal spikes. Synchronous data recording was performed, and the raw data are shown in Fig. 3(a). These neocortical surface-tissue reflectance changes follow seizure events. This reflectance change conforms to the expected 1–2-s delay for metabolic demand to respond with an increase in Hbt [3]. In the absence of a seizure, the reflectance approaches an asymptote corresponding to the equilibrium tissue blood volume.

Fig. 3 shows the small-signal sensing capabilities of the device; Fig. 3(a) shows polyspikes induced by 4AP treatment to the brain tissue to induce seizures, Fig. 3(b) shows the interictal response induced by BMI exposure, and Fig. 3(c) shows the device response during normal brain function. Some of the power in the small perturbations in the optical signal correspond to the heartbeat and respiration of the animal, as shown in Fig. 3(c).

Reflectivity deviation from the asymptote indicates a blood-flow modulating event, and the strength of the deviation is correlated to the departure distance. In order to quantify the response, a 4AP-induced polyspike data set in Fig. 4(a) was notch filtered to remove the reflectivity change attributable to the bandlimited animal heartbeat (3–8 Hz). The 3–8-Hz response and the notch-filtered response are shown in Fig. 4(b) and (c), respectively. The SNR for the device for seizure detection is 17 000 : 1 (42 dB), as measured by comparing the rms deviation of the unfiltered rms out-of-band signal noise to the total excursion seen during seizure, several orders of magnitude higher than external camera-based *in vivo* imaging technologies [9]. Because the sensor moves with the subject and is in direct contact with the brain, artifacts which limit the SNR with remote camera sensing are significantly reduced, and the larger sensor area and effective sampling window leads to greater photon capture. Processing of the signal to remove the heartbeat and respiration oscillations can lead to even greater sensitivity to seizure events.

IV. Conclusion

Miniature LEDs can enable reflectivity monitoring in a form factor suitable for biological application in both acute and chronic measurement scenarios. When mounted on a flex circuit and used with synchronous illumination and detection strategies, it is possible to measure real-time blood volume *in vivo* with enough SNR to reliably detect and classify seizure events. This system detects the blood-flow changes associated with epileptic seizures with performance exceeding that of other optical measurement strategies.

Further development of this sensor class will allow advance in detection technology and expansion into clinical applications. The use of dual-wavelength sensing will allow separate measurement and oxygenation, further improving the device utility. An arrayed device formatted into an implantable structure will allow the localization of seizure activity in chronically monitored individuals. This implantable architecture can also be applied to other chronic reflectivity- and fluorescence-monitoring applications where blood volume, oxygenation, or a fluorescent analyte are monitored.

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References

1. National institutes of health consensus development conference statement: Surgery for epilepsy. *Epilepsia*. 1990; vol. 31(no. 6):806.
2. Marks WJ, Garcia PA. Management of seizures and epilepsy. *Amer. Fam. Phys.* 1998 Apr; vol. 57(no. 7):1589–1600.
3. Suh M, Bahar S, Mehta A, Schwartz TH. Blood volume and hemoglobin oxygenation response following electrical stimulation of human cortex. *NeuroImage*. 2006; vol. 31(no. 1):66–75. [PubMed: 16480899]
4. Zhang Q, Liu Z, Carney PR, Yuan Z, Chen H, Roper SN, Jiang H. Non-invasive imaging of epileptic seizures in vivo using photoacoustic tomography. *Phys. Med. Biol.* 2008; vol. 53(no. 7): 1921–1932. [PubMed: 18364547]
5. Ma H, Geneslaw A, Zhao M, Suh M, Perry C, Schwartz TH. The importance of latency in the focality of perfusion and oxygenation changes associated with triggered after discharges in human cortex. *J. Cereb. Blood Flow Metab.* 2009; vol. 29(no. 5):1003–1014. [PubMed: 19293822]
6. Malonek D, Grinvald A. Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: Implications for functional brain mapping. *Science*. 1996; vol. 272(no. 5261):551–554. [PubMed: 8614805]
7. Bahar S, Suh M, Zhao M, Schwartz TH. Intrinsic optical signal imaging of neocortical seizures: The ‘epileptic dip’. *Neuroreport*. 2006; vol. 17(no. 5):499–503. [PubMed: 16543814]
8. Zepeda A, Arias C, Sengpiel F. Optical imaging of intrinsic signals: Recent developments in the methodology and its applications. *J. Neurosci. Methods*. 2004; vol. 136(no. 1):1–21. [PubMed: 15126041]
9. Sheth S, Nemoto M, Guiou M, Walker M, Pouratian N, Toga AW. Evaluation of coupling between optical intrinsic signals and neuronal activity in rat somatosensory cortex. *NeuroImage*. 2003 Jul; vol. 19(no. 3):884–894. [PubMed: 12880817]
10. Schwartz TH. Neurovascular coupling and epilepsy: Hemodynamic markers for localizing and predicting seizure onset. *Epilepsy Curr.* 2007; vol. 7(no. 4):91–94. [PubMed: 17694162]

Biographies

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Prof. Kymissis received the IEEE Electron Devices Society (EDS) Paul Rappaport Award in 2002 for his contributions to organic FET technology, the Shoulders–Grey–Spindt Medal at the 2002 IVMC for contributions to vacuum microelectronics, and the National Science Foundation CAREER Award in 2006. He currently serves on the Program Committees of the Materials Research Society, the International Society for Optical Engineers (SPIE), and several regional conferences. He is also the Chair of the IEEE EDS/Solid-State Circuits Society (SSCS) New York Section Chapter.

Fig. 1. Process flow for device integration. A polyethylene naphthalate substrate is used, and the optical components are attached to the gold/chrome interconnect using a low-melting-point indium-based solder paste. The integrated unit is encapsulated with parylene-C.

Fig. 2. Microscope image of completed sensor device. The top device is the LED, and the bottom device is the phototransistor. The finished package is $2\text{ mm} \times 2\text{ mm}$, and 0.8 mm thick, suitable for use in a rat model and thin enough for chronic implantation.

Fig. 3.

In vivo device results with both optical reflectivity and LFP electrode data. (a) shows polyspikes induced by 4AP treatment to the brain tissue. (b) shows the interictal response induced by BMI exposure. The figure shows interictal spikes caused by BMI; the optical reflectivity is scaled to eliminate the waveguided baseline. The numbers indicate the interictal spikes and the optical signal changes induced by each spike. Note that the optical signal is temporally delayed from the electrical signal. (c) shows the LFP and optical signal recorded from a normal cortex.

Fig. 4.

In vivo device results: (a) shows the raw reflectivity data measured using the miniature reflectivity monitor. The data in all three graphs are linear in power and have been normalized and scaled together. The SNR on this data, as measured by comparing the rms power of the in- and out-of-signal band response, is 42 dB. (b) shows the 3–8-Hz bandlimited signal, which is primarily the animal heartbeat, and (c) shows the data with the 3–8-Hz components notch filtered.