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Final Report on LDRD Project 130784 Functional Brain Imaging by Tunable Multi-Spectral Event-Related Optical Signal (EROS)

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Abstract

Functional brain imaging is of great interest for understanding correlations between specific cognitive processes and underlying neural activity. This understanding can provide the foundation for developing enhanced human-machine interfaces, decision aides, and enhanced cognition at the physiological level. The functional near infrared spectroscopy (fNIRS) based event-related optical signal (EROS) technique can provide direct, high-fidelity measures of temporal and spatial characteristics of neural networks underlying cognitive behavior. However, current EROS systems are hampered by poor signal-to-noise-ratio (SNR) and depth of measure, limiting areas of the brain and associated cognitive processes that can be investigated. We propose to investigate a flexible, tunable, multi-spectral fNIRS EROS system which will provide up to 10x greater SNR as well as improved spatial and temporal resolution through significant improvements in electronics, optoelectronics and optics, as well as contribute to the physiological foundation of higher-order cognitive processes and provide the technical foundation for miniaturized portable neuroimaging systems.

ACKNOWLEDGMENTS

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NOMENCLATURE

fNIRS	functional near infrared spectroscopy
EROS	event-related optical signal
SNR	signal to noise ratio

1. INTRODUCTION

1.1. Project Overview

Functional brain imaging is of great interest for understanding correlations between specific cognitive processes and underlying neural activity. This understanding can provide the foundation for developing enhanced human-machine interfaces, decision aides, and can even provide mechanisms for enhancing cognition at the physiological level. Furthermore, successful miniaturization of these devices can provide dismounted applications for war fighters and can provide small footprint, noninvasive methods for real-time monitoring of decision making in a wide variety of applications from scientists to analysts to decision makers.

The functional near infrared spectroscopy (fNIRS) based event-related optical signal (EROS) technique pioneered by Professors Gratton and Fabiani at UIUC is particularly promising as it provides direct, high-fidelity measures of temporal and spatial characteristics of neural networks underlying cognitive behavior, something not offered by other neuroimaging techniques such as EEG and fMRI. However, current EROS systems are hampered by relatively poor signal-to-noise-ratio (SNR) and depth of measure, limiting areas of the brain and associated cognitive processes that can be investigated.

We propose to develop a flexible, tunable, multi-spectral EROS system which will provide up to 10x greater SNR as well as improved spatial and temporal resolution through significant improvements in electronics, optoelectronics and optics. Our team is uniquely qualified to develop this enabling technology with expertise in optoelectronics and optical signal processing as well as cognitive science and functional brain imaging. Critical strategic partnerships and collaborative teaming will be conducted with the EROS pioneers, Gratton and Fabiani at UIUC, as well as UNM, NMSU and the MIND Research Network. We believe that this work will result in a number of peer-reviewed publications in the physiological foundation of higher-order cognitive processes as well as provide the technical foundation for miniaturized portable neuroimaging systems; an invaluable capability for numerous military and HSD applications.

1.2 Technical Approach

The current commercial EROS system used by Gratton and Fabiani is limited in wavelength (690, 830nm), modulation frequency (110, 300MHz) and uses low optical power. A UIUC study showed that higher wavelength and frequency resulted in a 65% increase in SNR compared with the lower parameter case [1]. We propose to fully investigate and optimize EROS system parameters in order to achieve an order-of-magnitude improvement in SNR, improved temporal and spatial resolution and increased depth-of-measure.

A flexible EROS system, shown in Fig. 1, will first be developed which will be capable of multi-spectral, tunable light sources from 650-1550 nm, modulation frequencies exceeding 1GHz, and interchangeable optics, photodetectors, electronics and signal processing algorithms in order to fully understand and optimize EROS measurements. EROS measurements will be taken in active brain areas to investigate our exploratory hypotheses for improvement in the following main areas:

Optical power: We will increase the optical power up to but not exceeding the Class I Laser limits defined by the FDA which should result in ~ 10 x power increases and ~3-6x SNR increase, depending on the level of associated scattering noise and filtering used. Increased power should also allow for increased source-detector spacing and therefore depth-of-measure.

Wavelength: A broader wavelength range (650-1550nm) will be investigated. Higher penetration depths in non-living brain samples [2] at longer wavelengths up to 1100nm (highest wavelength tested) have been observed although there will be a tradeoff with increasing absorption in water. Also, the optical scattering coefficients measured from 600-1000nm exhibit 40% more relative reduction over this span in areas with bone, a noise source for EROS from the skull, than body areas with no bone [3]. Corresponding EROS improvements of ~20% SNR at 1000nm are estimated compared to 830nm and should increase to ~60% at 1550nm assuming extrapolated trends. Furthermore, different areas of the brain show different absorption and scattering characteristics which indicates that EROS measurements may also show wavelength dependence depending on the part of the brain [2]. A comprehensive study of wavelength dependence of EROS signals for different areas of the brain will be conducted which is a new, publishable, potentially high-impact area. Multispectral approaches may then be used to increase spatial resolution in localizing parts of the brain and increase SNR by an estimated 20-200% in high-signal, low-noise wavelength regimes, depending on the nature of the spectral signatures discovered.

Modulation frequency: Increasing modulation frequency is expected to proportionally increase the temporal resolution although there is also some increase in noise as well. We expect a 1-3 times improvement in temporal resolution at 1GHz compared to 300MHz modulation frequency currently used. Higher frequencies which may further improve temporal resolution will also be investigated.

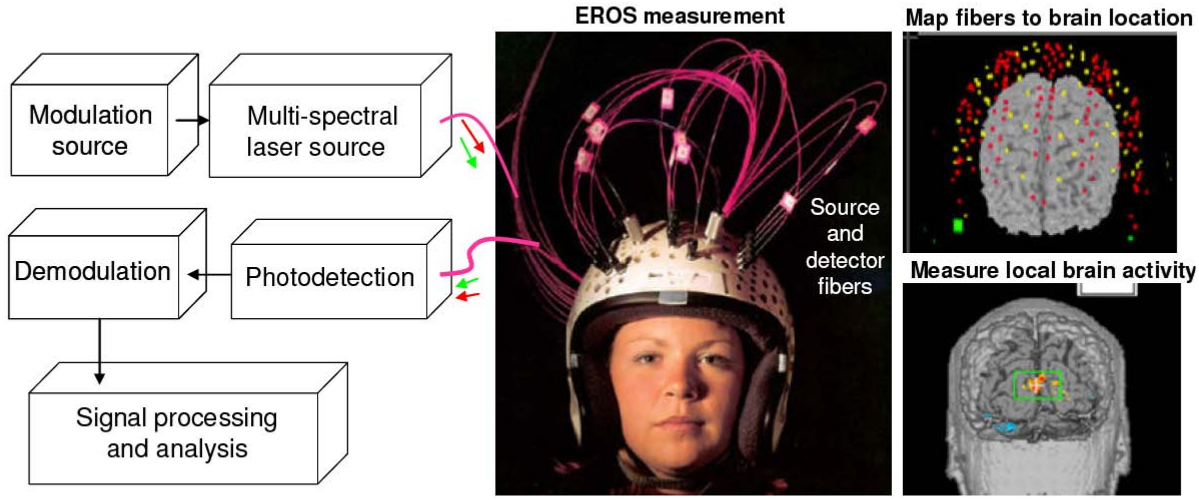

Figure 1. Proposed EROS system for functional brain imaging incorporating improvements in laser source wavelengths, modulation, optics and detection. *(Pictures from Gratton & Fabiani, UIUC)*

One important issue is that our proposed EROS system must and will fully comply with safety regulations for testing on human subjects, particularly with regard to laser exposure as defined by FDA regulations. We will work closely with the Human Subjects Board (HSB) at Sandia to ensure that all safety requirements are met. We have had initial meetings with Terry Reser, head of the HSB and our department's laser safety officer to address any immediate red flags, and none have been identified currently.

To date, the cognitive studies conducted with the current EROS system have only begun to scratch the surface of investigating spatiotemporal characteristics of higher-order cognitive function [4, 5]. If the proposed EROS system produces the expected improvements in SNR, temporal and spatial resolution and depth-of-measure, we will be able to study the spatiotemporal characteristics of several higher-order cognitive processes including analogy-making, novice-expert differences in complex tasks, and decision-making under uncertainty with much higher fidelity than previously possible. These collaborative studies will be conducted at UNM, the MIND Institute and UIUC.

In addition to developing an enabling technology for fundamental cognitive science research, the proposed work will also develop strategies for miniaturized EROS systems which could be used in the field for military or HSD applications. This work will provide the technical foundation for these types of portable systems for future development.

2. RESULTS

Previous accomplishments:

- Established working collaboration with Professor Gabriele Gratton and Monica Fabiani of the Cognitive Neuroscience Lab at the Beckman Institute at the University of Illinois at Urbana-Champaign (UIUC). This includes a visit to their lab in October 2008 including kickoff meeting and project review, observed EROS measurement setup and data collection on subject for different project, reviewed theoretical work and concluded that new flexible EROS model should be developed and validated with milk tank data.

- EROS model development in MATLAB and then FORTRAN incorporates the following: (1) Finite-element Cartesian mesh voxels with variable refractive index and scattering and absorption coefficients, (2) Monte-Carlo photon migration model after L.V. Wang [1] and (3) time-dependent photon tracking for an input pulse response. The flow diagram for the photon migration model is shown in Fig. 2.

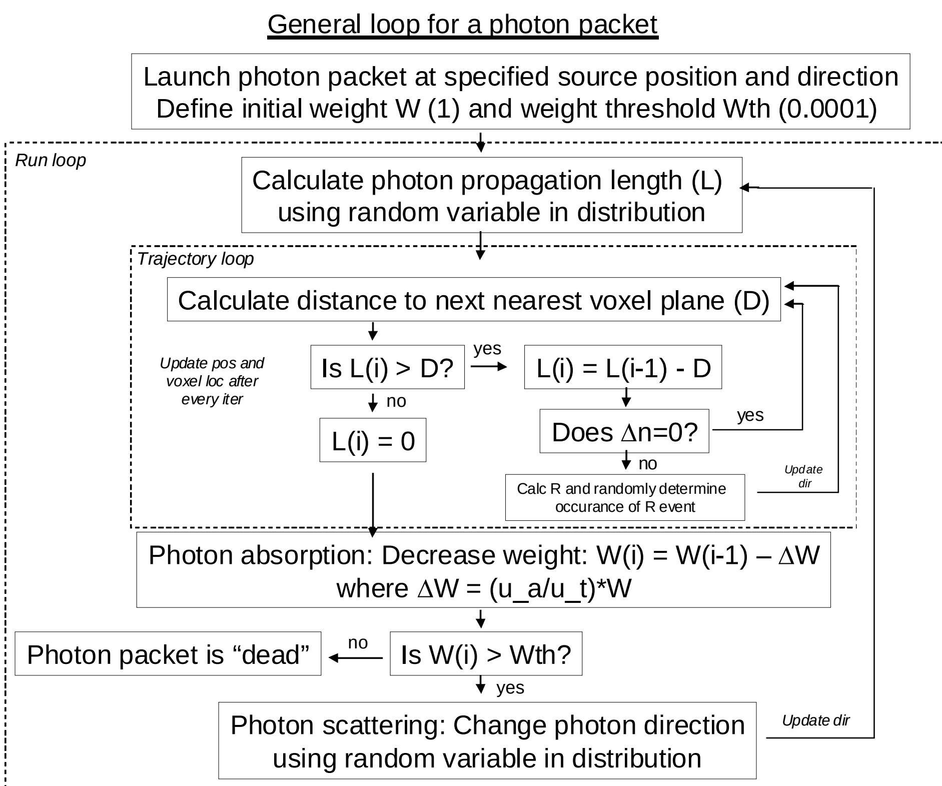

Figure 2 Flow diagram for photon migration model

- Model validation was performed by comparing with analytical results. Validation was also performed by comparing with experimental data in a milk tank experiment performed by UIUC shown in Fig. 3 where skim milk is used to simulate the scattering in biological media and differences in modulated light transmission are measured as a function of varying the position of a highly absorbing phantom in the milk tank.

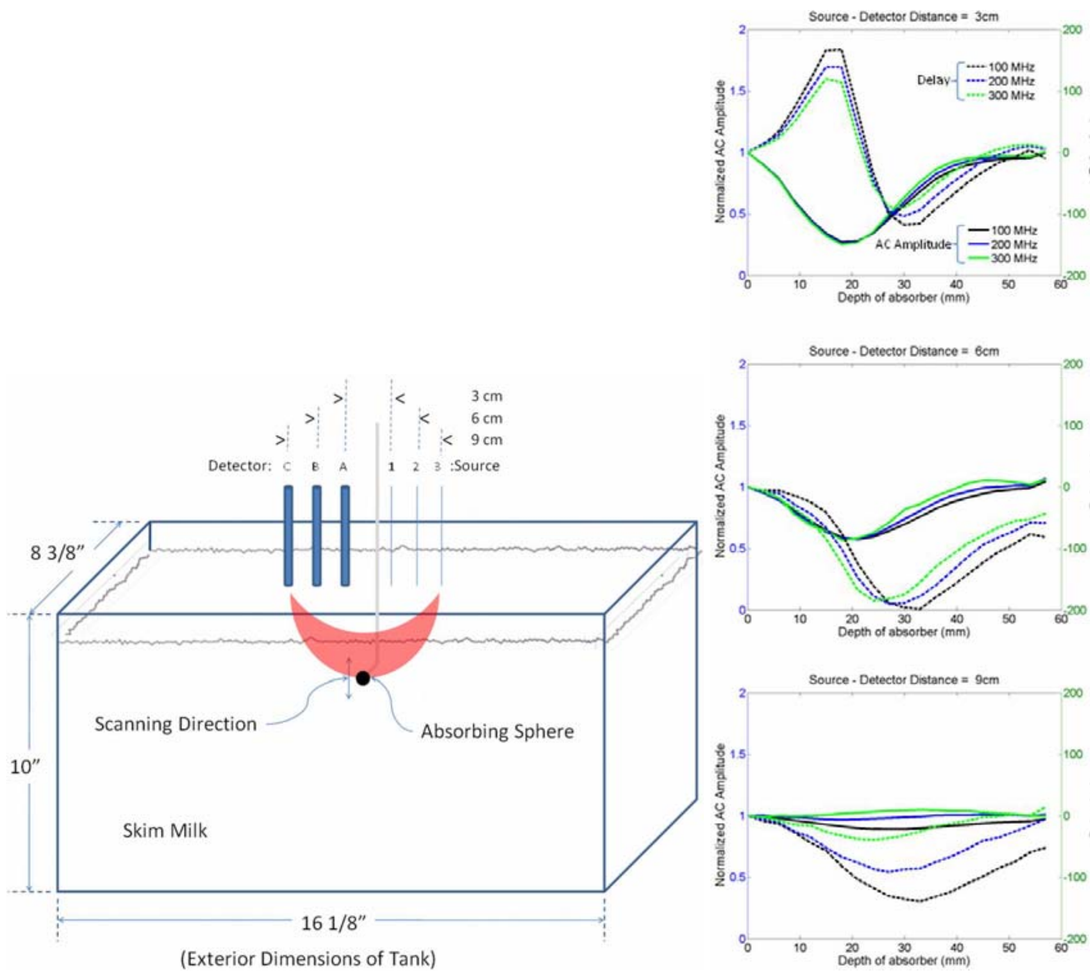

Figure 3. Schematic of milk tank experiment and detected AC amplitude and phase delay of a modulated NIR signal at the detector for source-detector distances of 3, 6 and 9 cm

Simulation results approximate this experiment by considering the impulse response under similar conditions which also show absorption and phase delay dependent on the position of the object, summarized in Fig. 4. A poster at the Human Brain Mapping Meeting in San Francisco, CA in June 2009 based on these experimental and theoretical milk tank results has been presented [6].

In summary, a flexible, time-dependent EROS model has been developed which will help guide future experimental explorations with relevant physics.

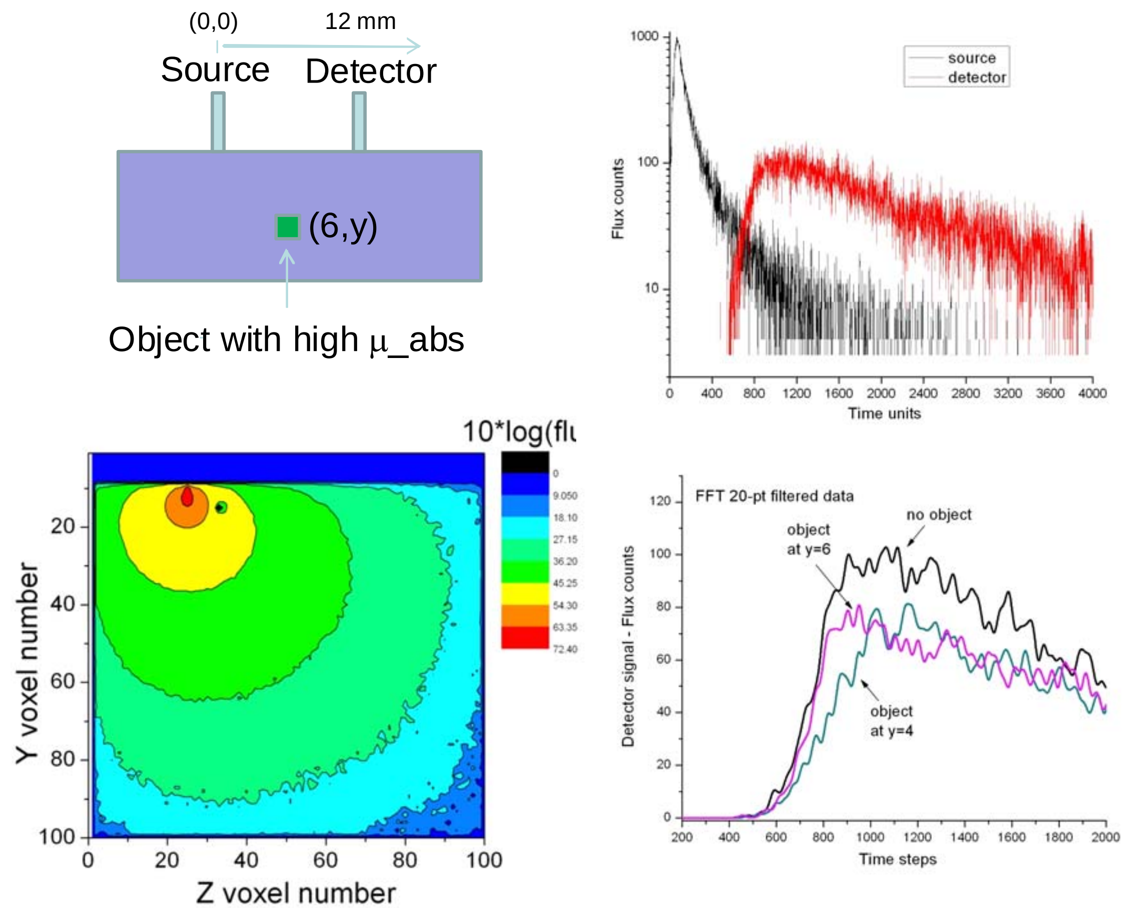

Figure 4. Simulation space, flux distribution, flux time signal at source and detector and detected flux signals for different object positions.

3. PROPOSED FUTURE DIRECTIONS

We propose a two-pronged approach for the future. We will work on further improvement in SNR by utilizing a differential sensing approach with multiple detectors for improved noise rejection, enhanced localization of active brain area and differential comparison of the signal from adjacent fibers.

Additionally we will focus on understanding the phenomena underlying optical changes in the neurons when they are activated, since improved insight into the underlying physical phenomena governing EROS behavior will help to optimize the measurement techniques. Optical response of activated rat neurons on a chip will be valuated using two-fiber scattering experiments and interferometry. These experiments will allow examination of EROS phenomena without interference of other activity in the brain and clarify dynamics and magnitude of the optical response of the activated neurons, which can be fed into the model to improve the fidelity of the simulation.

3.1 SNR Improvement

This year we intend to take a two pronged approach to the problem. First, we will continue to develop measurement techniques to improve the signal-to-noise ratio (SNR) using milk tank setup. This may include differential measurement techniques with multiple detectors for

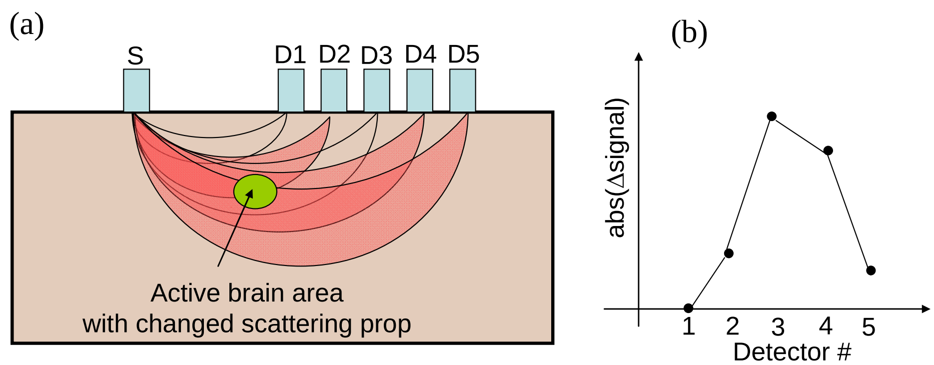

Figure 5 a) schematic of a differential measurement b) expected differential signal

improved SNR through noise rejection, enhanced localization of active brain area using multiple detectors and differentially comparison of the signal from adjacent fibers as shown in Fig. 5.

3.2 Understanding Underlying Phenomena

Additionally we will focus on understanding the phenomena underlying optical changes in the neurons when they are activated, since improved insight into the underlying physical phenomena governing EROS behavior, will help to optimize the measurement techniques. We will leverage an existing LDRD program (117841) which is targeting growth of primary rat neurons on glass substrates. The in vitro primary culture preparation will provide simplified and well-controlled environmental conditions, a key requirement for understanding the etiology of the scattering phenomena from active neural tissue. Neuron optical response can be examined without

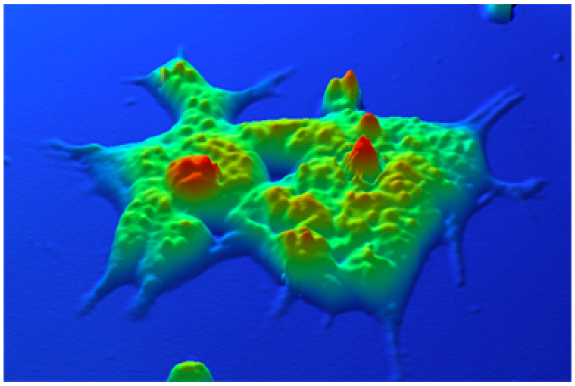

Figure 6 Interferometric image of human hct116 colon carcinoma cells (courtesy of VEECO)

interference of other phenomena in the brain, such as hemodynamic response which otherwise can swamp the EROS signal. Optical testing of neurons on the chip will include a measurement of optical scatter using a two fiber setup similar to the one in Fig. 3. Periodic neuron excitation will enable lock-in detection, thus improving the noise floor. We will also use stroboscopic optical interferometry (already in place) to examine optical response of a single neuron. Recent experiments in live cell interferometry [7] have revealed details of dynamics of optical change in the stimulated cell (see Fig. 6). These experiments will clarify dynamics and magnitude of the optical response of the activated neurons, which can be fed into the model to improve the fidelity of the simulation. Separate milk tank experiments will elucidate the behavior of the surrounding scattering medium. Finally, results of these experiments and models will be applied to more biologically-relevant models such as intact brain slices and live animals (UIUC collaboration).

3.3 Leading Edge Nature of Work

This work represents the first attempt to integrate experimental measurements of optical activity of activated neurons into a Monte Carlo model of the scattering media. Quantitative measurement of optical changes in neurons upon stimulation will also help resolve the question of whether these changes are mainly absorptive or scattering in nature, providing a valuable feedback for the model.

Characterization of optical response as a function of neural electrical activity in an isolated, on-chip system will allow isolation and observation of the relevant phenomena and distinguished them from other, interfering activity in the brain. Differential measurement schemes are also expected to contribute in isolating the relevant signal. Despite increasing activity in this field, EROS technique remains controversial [8] and these experiments will contribute to understanding the underlying, fundamental phenomena, as well as serve as a guide in measurement system optimization.

3.4 Technical Risk and Likelihood of Success

A number of technical risks and mitigation strategies have been identified as follows:

1. Limited improvement demonstrated with differential techniques
    a. Vary the number of detectors, optical power and detector spacing
    b. Consider alternative modulation methods and time gated detection
2. Optical response of neurons too small too measure
    a. Lock-in detection to improve noise floor
    b. Improved optical measurement collection (integrated waveguides instead of fibers)
    c. Collaborate with VEECO to improve signal collection (have an ongoing relationship)

While some technical risk does exist, we believe it can be mitigated with the suitable strategies.

4. CONCLUSIONS

Given the abbreviated (1year) duration of the program, substantial progress in understanding EROS was made. Recommendations for the follow on targeted better understanding of processes in neural tissue that contribute to the EROS signal, specifically:

– Determine nature, magnitude and dynamics of the optical change in activated neurons
– Contribute to the field – publications for Sandia, recognition in the community
– Experiment based models will drive system optimization for improved EROS detection

Another desired outcome of the follow on program includes a microsystem based platform for study of neural processes will take advantage of capabilities unique to Sandia and attract recognition, collaboration and funding.

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