Pixel density and retinal response for series photodiode circuit arrays

Stephen Martin

Promising new research measuring the properties of series photodiode circuits has shown that they may be suitable for retinal prosthesis [1]. Photodiode arrays, in order to be effective in this capacity, must be pulsed with infrared light ($\sim$900nm) at a much higher intensity than ambient light. The light must be infrared for this particular application because light in the visible spectrum may damage existing photoreceptors in the retina at the high intensities required to stimulate the needed currents.

Although research on this has been promising, what is not as well understood is how the brain will process signals from this source with differing pixel densities. This is an important topic, especially with regard to the prospect of retinal prosthesis: if the density of pixels is too low, vision will be blurry, and the cost of a prosthesis will not be worth the benefit to vision. On the other hand, the technical challenges involved in making a pixel density that is unnecessarily high will make the cost of the device rise dramatically. As a step to address this, I propose to study the effect that pixel density of series photodiode circuits has on the response signals of the retina.

This study will have two major stages: first, we will make measurements of the response signals of a rabbit's retina. This can be done by submerging the retina in a saline solution against a bed of planar electrodes. Research has already been done in this fashion, in which a retina was flashed with 60μm pixels from a monitor [2]. We, however, will obtain an array of series photodiode circuits as closely packed as possible (currently, there are some devices with sensor spacing as small as 25μm [3]), place it over the retina (which is, in turn, over the bed of electrodes) and pulse it with an pixellated infrared light. From this, we can analyze response signals from the tissue. Very precise measurements will need to be taken to establish what the noise from the photodiodes themselves will be, but once known, we can subtract off this background and analyze the response alone. This experiment will be repeated for differing effective photodiode densities (by selectively switching off circuits) in order to test the effect that pixel density has on the response signal. As a control, we will also repeat this test without the photodiode array, and with the pulsed light source in the visible spectrum (in order to establish what signal we are hoping the photodiode array will mimic).

In the second stage of research, we will use the data obtained during the above experiments to attempt to construct a phenomenological model of how pixel density in photodiode circuit arrays affects retinal response. This will require collaboration with specialists in the cellular structure of the retina. In addition, we hope to then use this phenomenology to simulate and model in detail how these devices stimulate retinal activity, which would then provide clues as to how pixel density would affect overall angular resolution in a retinal prosthesis of this type.

The research group at UC Santa Cruz led by Alexander Sher has already developed much of the technology and expertise required to execute this project. Should this research succeed, it will give developers of information needed to effectively manufacture retinal prostheses. The proposed timeline for this project is as follows:

Weeks 1-2: Obtain materials, develop experimental procedure in detail
Weeks 3-6: Construct pixel displays and photodiode array (if not already available).
Weeks 7-8: Initial calibration and performance tests of instruments
Weeks 9-10: Run control tests without retina sample (background calculation)
Weeks 11-13: Run control tests with RGB pixels, retinal samples and without photodiode array
Weeks 14-17: Run tests with IR pixels, photodiode array and retinal samples. Initial evaluation of effectiveness of background reduction techniques.
Weeks 18-20: Analyze data
Weeks 21-23: Collaborate with specialists to develop phenomenology supported by theory and evidence
Weeks 24-28: Further organize and analyze data, and compose report of our findings.

Many of the instruments needed for this study are available (i.e. the experimental setup with the planar electrode array), but some will have to be assembled or purchased (such as pixel screens). The software needed for data analysis is also readily available. With these costs in mind, I am requesting $50,000 for materials, samples, and salary.

[1] Loudin, J. D., Cogan, S. F., Mathieson, K., Sher, A., Palanker, D. V. Photodiode Circuits for Retinal Prostheses. *IEEE Transactions on Biomedical Circuits and Systems* **5**, No. 5 468-480 (Oct. 2011)

[2] Sher, A. Exploring Neural Function, Structure, and Development. *PHYS 205 lecture series* (January 2013). http://physics.ucsc.edu/∼joel/Phys205/Jan28-Sher-Retina.pdf

[3] Mathieson, K et. al. Photovoltaic retinal prosthesis with high pixel density. *Nature Photonics* **6**, 391397 (2012).

Development of micro-needle electrode arrays for neural tissue analysis

Stephen Martin

One of the most daunting puzzles in biophysics is the study of the electrical signals exhibited by the nervous system. In addition to being extraordinarily complex, the components of this system (neurons) are also very small and densely packed—in brain tissue, a typical separation distance between neurons is $\sim 25\mu$m. One strategy taken to measure and analyze such systems is to externally observe neural tissue by placing an actively multiplexed array of closely spaced planar electrodes on its surface [1]. Although this technique has been successful, a concern still exists: tissue on the surface of a sample is damaged when preparing a sample for measurement. If this tissue is damaged, observing the surface of neural tissue will not be as reliable as observing its interior.

In an effort to address this problem, a promising new "Bed of Nails" type of electrode array has been developed in which 61 closely packed (60μm separation) electrode "micro-needles," arranged in a hexagonal pattern, are used rather than surface electrodes to penetrate tissue up to 250μm and take measurements from the sample's undamaged interior [2]. I propose to further study and adapt the fabrication process of these arrays in order to (1) increase the array size from 61 electrodes to $\sim$500 in order to make more robust measurements and (2) further reduce the electrode spacing from 60μm to $\sim 30\mu$m in order to improve spatial resolution.

This research will require significant modifications to the developmental process used in making the 61-electrode array. For example, the micro-needles manufactured previously have a base diameter of 25μm (any smaller may affect the impedance of the electrode, and the signals we wish to amplify are only $\sim$30-110μV). If we are to space these needles only 30μm apart, then this will not leave enough room for outgoing contacts to leave the array in the same plane as the needles, as was done before. If narrowing the base width of the needles is not possible, then we will devise a method of carefully introducing vias through the backside of the array. In addition, because the array will be so large and densely packed, we will develop a protocol for carefully etching the tips of the needles to prevent electrode-electrode interference.

Upon completion of this array, I will run comparison tests with previous arrays (both planar and micro-needle) to gauge the overall effectiveness of the new array design. This is typically done by bringing the array into contact with an acute slice of brain tissue in a saline solution. Because we will not be able to use the same slice of tissue for each detector, we will need to harvest several samples from rats that are similarly aged. From these samples, we will attempt to *locate* the neurons by the electrical signals they emit (using a spike-sorting regime based on a two-dimensional Gaussian distribution) to determine the advantage of making such a densely-packed array. A previous study found that decreasing the array spacing from 120μm to 60μm increased the ability to locate neurons by a factor

of 3.2 [2], so I am optimistic about our ability to improve spatial resolution. Any problems with the new device would likely stem from noise and electrode-electrode interactions, so the development process will need to be carefully regulated.

Should this array design prove more effective than previous designs, it may then be utilized in various neurological projects. For instance, as it stands, there is currently ongoing research on *in vivo* brain studies involving rats, both in the laboratory and in a natural setting (using wireless amplifiers) [3,4]. However, these are using planar electrode arrays, and may greatly benefit from a practical "Bed of Nails" design.

This project will a collaborative effort, with contributions from neuroscience, engineering, and physics. I have been drawn to the team led by Alexander Sher at UCSC, which has a broad base of both knowledge and perspective. With some exceptions (i.e. bulk materials), the instrumentation and materials readily available in this laboratory will help greatly with the time and cost requirements. The approximate timeline for this project is as follows:

Weeks 1-2: Collaboration and design of proposed electrode array.
Weeks 3-4: Acquire materials needed for fabrication; gain familiarity with instrumentation.
Weeks 5-12: Work in conjunction with Dr. Sher's research group to develop a functional "Bed of Needles" array.
Weeks 13-14: Initial calibration and testing of array.
Weeks 15-18: Conduct comparison tests on brain tissue to determine relative benefits of device.
Weeks 19-20: Perform data analysis of tests, and compose a report of our findings.

This gives a total proposed time span of 20 weeks. As much of the instrumentation and materials are already available, I anticipate that $30,000 will be sufficient for cost of materials, samples, and salary.

[1]Sher, A. Exploring Neural Function, Structure, and Development. *PHYS 205 lecture series* (January 2013). http://physics.ucsc.edu/∼joel/Phys205/Jan28-Sher-Retina.pdf

[2]Gunning, D.E., Beggs, J. M., Dabrowski, W., Hottowy, P., Kenney, C. J., Sher, A., Litke, A. M., and Mathieson, K. Dense arrays of micro-needles for recording and electrical stimulation of neural activity in acute brain slices. *J. Neural Eng.* **10**, 016007 (2013).

[3] Viventi, J. et. al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nat. Neurosci.* **14**, 15991605 (2011)

[4] Szuts, T. A. et. al. A wireless multi-channel neural amplifier for freely moving animals. *Nat. Neurosci.* **14**, 263-269 (2011)