TOWARD ACCESSIBLE EVALUATION OF THE ELECTROPHYSIOLOGY OF HUMAN VISION

by

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Submitted to the Program in Media Arts and Sciences, School of Architecture and Planning, on May 9, 2014 in Partial Fulfillment of the Requirements for the Degree of Master of Science in Media Arts and Sciences

ABSTRACT

As photoreceptors in our retinas capture discrete photons, that energy is converted into an electrochemical signal which shoots back through the optic nerve and into our visual cortex. We can sample that signal as it’s transmitted, by delivering specific stimuli and recording the aggregate response of the photoreceptors, but systems which accomplish this in current practice are out of reach for most ophthalmic clinics and completely unavailable to consumers. With a reimagined signal capture system and an optimized system design, I demonstrate a robust method for capturing the electrical signals emitted from the retina. With the improved accessibility and decreased cost of this technology, there are immediate opportunities for improved ophthalmic care on a broad scale. But beyond the clinical implications, accessible electroretinography presents an unprecedented opportunity for individuals to characterize their specific experience of color, contrast, and movement, making way for a whole new paradigm of tailored display technologies.

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Toward Accessible Evaluation of the Electrophysiology of Human Vision
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"Anything worth doing is worth overdoing."

"If duct tape doesn’t work, you’re not using enough."

- Canham family motto(s)

The reason I wrote this thesis, and in fact the reason I came to graduate school, is part of a larger pursuit - the need I feel to build and create an ideal. This ideal is composed of an elegance and potent efficacy, an instantly obvious purpose and function and an irrefutable relevance. What my time at MIT has taught me is that clarity in design is born of clarity in need, a driving need to answer a question. Science, in all of its forms and facets, is born of needing to find the answer to a question, and the emergence of these ideals occurs when there is nothing else we can do but pursue that answer because, at the core of what we are and how we define our identity, we need to know. My greatest accomplishment will have been finding the truth in what it means to be a scientist, and therein finding purpose.

I feel incredibly lucky in my academic experience to have had the freedoms afforded me by MIT. I am eternally grateful to Professor Raskar who both allowed me the space and time I needed to answer my questions and created the structure within the Camera Culture group to support that. The Tata Center for Technology and Design, in its program of travel and collaboration in India has afforded me an invaluable perspective and humility.

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MICROELECTRIC WAVEFRONTS: AN IMAGE OF SEEING

There is something elusive and fascinating about vision. It is a seemingly infallible fact of our existence that we are bound to our own sight, incapable of ever knowing the experience of another individual. There is a dream of being able to record our vision - to capture our interactions with photons and from that reconstruct exactly what we have seen. There may even be a distant future in which we will record our vision throughout our lives and when we die, it can be downloaded in its entirety, an entry in the vast library of human experience and knowledge. I believe that furthering the reach and capacity of the field of visual electrophysiology is the foundation of such a future.

“Seeing” is mired in myriad, vastly variant processes. We are still generations away from truly understanding the mechanics of our visual cortex, or of the true distinction of where visual data stops and the perceptual fills in. Yet each of these linked processes which together create the emergent experience of vision leave an electrical signature as they fire in sequence. Visual electrophysiology is the science of recording those signatures, spanning the movements of the...
eyes, the electrical emissions of the stimulated retina, and the resultant activity in the visual cortex.

The human retina is composed of millions of small cells – such as photoreceptors – which create an electrochemical response as light arrives at the back of our eyes. They are the pixels which contribute to our entire field of view. As each of these cells activate, the energy they emit couples and accumulates, creating an aggregate, measurable response. The acquisition of this potential is the field of electroretinography (ERG).

Each individual has a unique distribution of rods and cones, and therefore a unique way of experiencing the same energy and spectrum of light. There are averages across populations: the majority of cones are centered within the fovea, or central vision, and there are approximate ratios between the types of cones which account for color vision - the short-, medium-, and long-wavelength cones (blue, green, and red respectively). But as studies have shown, these distributions vary widely among individuals, ranging from 1:1 L- to M-cones to 1:16. All of the technologies which are designed to excite our retinas, the lighting, the displays, are all designed with respect to a standard which only represents a single static average of how human beings experience color. Imagine if we had tools and technologies which actually reflected the incredible variability within our species.

There is an exciting opportunity to radically change the accessibility of knowledge, of our own awareness of how our physiology operates. So many of our biological processes are obfuscated, often by their scale, and even further distanced from the populace by the expensive and complex tools which can measure them. We have seen throughout history what beautiful, emergent discoveries can occur when a particularly powerful tool becomes democratized. There is no greater fuel to innovation than to enable anyone, regardless of education or age, the ability to interact, to manipulate, to play, and to discover.

Classic visual electrophysiology systems are like many medical devices — expensive and complex, delegated only to the realm of highly trained clinicians. But within the broader realm of health care, we are beginning to see just such a radical change in how people perceive their medical data. As consumer health technologies are growing in popularity and prominence, people are beginning to question the status quo – why does this information need to be so isolated and restricted?

If we could similarly democratize visual electrophysiology, the implications are staggering. To be able to know, across populations of millions, the variations in each person’s interaction with

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1 Hofer et al., “Organization of the Human Trichromatic Cone Mosaic.”
the wavelengths of light around us. Or to be able to map each person’s unique sensitivity to contrast. This information holds the potential to fundamentally change the way we not only perceive our own vision, but how the devices and tools we create interact with it.

1.1 IN THIS CENTURY, WHAT IS ITS RELEVANCE?

While some of the aforementioned aspirations may be distanced from us by decades, there is an immediate value to developing systems which make visual electrophysiology more accessible. This tool is in fact one of the only ways to objectively measure vision. Beyond verbal accounts of a patient’s quality of sight, electroretinography is a critical tool to inform clinicians of retinal function in an objective, quantifiable way. Variations in ERG signals can even indicate pathologies months or years before a patient may become aware that anything is wrong, or a change may manifest in a retinal image.

Diseases which affect the retina are clearly manifest in ERG recordings\(^2\). Diabetic retinopathy is one of the leading causes of blindness\(^3\), and the projected burden of this disease is climbing as rates of diabetes are increasing in both developed and developing economies\(^4\). In the case of diabetic retinopathy, when the pathology begins to manifest in the patient’s vision, that loss of sight is irreversible. Tools such as electroretinography, if readily available, can change a patient’s trajectory, saving their sight.

Beyond retinopathies: nyctalopia\(^5\) (night blindness) and photophobia\(^6\) (discomfort or pain to the eyes due to light exposure) are detectable using new visual electrophysiology techniques. Objective visual evaluation is also crucial in assessing vision in those who do not possess the ability to communicate their experience of it. Measuring visual acuity and development in children or individuals with disorders of speech could be greatly facilitated by robust visual electrophysiology tools.

1.1 BEYOND THE CLINIC

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\(^3\) Fong et al., “Retinopathy in Diabetes.”

\(^4\) King, Aubert, and Herman, “Global Burden of Diabetes, 1995-2025.”

\(^5\) Miyake et al., “Congenital Stationary Night Blindness with Negative Electroretinogram.”

\(^6\) Kooijman et al., “Prolonged Electro-Retinal Response Suppression (PERRS) in Patients with Stationary Subnormal Visual Acuity and Photophobia.”
The human retina is responsible for some surprisingly complex visual processing, before the signals even reach the brain. There are cells within our eyes which only respond to specific subsets of the visible spectrum - our photoreceptors. But they are not the only cells which generate a response to light. Our retinas generate signals at the onset of a bright stimulus, or the onset of a dark one, or at the movement of a stimulus from left to right, or right to left. Each of these processes generates an electrical signature, and each of the cells which generate them are delicately linked to the circulation and metabolism of the retina and each other. There is an incredible wealth of information in the electrical signals our eyes create, if we could only see it.

All changes within our bodies, no matter how slight, have a measurable impact. Some manifest so dramatically as to be called pathologies, but more still enact changes which simply vary by day, or time of year, or stage in life, but nonetheless alter the ways in which we interact with our world. The timescales of our experience of vision are inherently long, with changes almost imperceptible. But the limits of our cells and their pathways have tangible impacts on our experience. The tiredness we feel after staring at a screen for an entire day, or simply before we've had enough coffee, is an emergent effect of the delicate metabolism in our eyes. There has never before existed a system which can take a snapshot of this so easily as to allow us to be aware of it in our daily experience.

But if there did exist such a tool, we could know and understand the state of our eyes as they change, not only when it emerges as a headache. We could channel this information into our displays, adapting the hue, contrast, or other characteristics in real time to deliver an experience that is targeted to our eyes in their current state. As our eyes become saturated, our displays could be modulating their intensity to reverse that saturation, or even prevent it from occurring.

1.2 WHY CAN’T WE NOW?

It has been said that conducting visual electrophysiology tests suffers “death by a thousand cuts.” Practically, this means that there are many elements of a visual electrophysiology exam which must go right for the results to be usable, and often, many of them go wrong.

This phenomenon is in part due to the fact that most current systems still require a substantial working knowledge of the fundamental physics inherent in visual electrophysiology to know if the test is being conducted correctly. For example, the placement of the electrodes is at the discretion of the technician and can vary considerably from test to test. There are several key aspects of the orientation and overall state of the patient (grounding, fidgeting, eye dryness and blinking) which if not carefully accounted for can render the data unusable.
But why do these challenges persist? We are measuring an emergent property of a biological process, on a nanoscale, several layers of removal from what we can tangibly experience. And each individual is different. Systems to conduct visual electrophysiology have to date merely considered the essential science, but little has been done to reduce the inherent complexity, to create a system optimized for usability as well as accuracy.

Like other realms within healthcare, there is little impetus for the status quo to change. The reimbursement structures are defined, the regulatory hurdles are daunting, the people have already been trained and the systems are already in place. But if we look just slightly further into the potential future which we can create, we are left with no choice but to pursue and realize a better solution.

1.3 THE CONTRIBUTIONS OF THIS THESIS

Towards the fulfillment of the requirements for the degree of Masters of Science in the department of Media Arts and Sciences at the Massachusetts Institute of Technology, I have solely imagined and realized a system which accomplishes visual electrophysiology measurements in a wearable interface which is optimized for robustness and ease of use. I intend to prove that this technology accomplishes visual electrophysiology in a clinical context but also renders this tool relevant in the realm of consumer electronics.

As a component of this work, I will give an account of the methodology by which we established the viability of visual electrophysiology as a pursuit and how we have applied this methodology to many projects and collaborations within the Camera Culture Group at the MIT Media Lab and the Tata Center for Technology and Design.

I will then describe in detail the elements of this system and the ways in which they (a) target a specific physiology within the human retina, and (b) are optimized for integration into a system designed for ease of use and robustness.

The core of the results which I will put forth will demonstrate the essential clinical functionality of this system as well as functionality outside of clinical interest within the realm of potential consumer applications. I will then demonstrate the ease of use and robustness of the system through the results of a series of tests designed to assess these characteristics.

Finally I will, given the demonstrated efficacy of this paradigm, propose several theoretical systems which are enabled by the ease and robustness of this technology and have significant implications for how individuals not only understand their vision but integrate this knowledge into the existing technological systems which we interact with so closely in our day to day lives.
2 ORIGINS AND POTENTIALS

2.1 THE HUMAN EYE AND ITS INTERACTIONS WITH LIGHT

The eye is the camera of the human body. It is the first in a series of complex processes which lead to our experience of vision. The analogy to a camera is an effective one - after all, they both possess the same fundamental building blocks: an aperture or iris, a lens, and a sensor, the retina. However, the model of a camera barely begins to encompass the depth and complexity of the visual processes of which the human retina is capable. Beyond sensitivity to wavelength, there are structures within the retina which are uniquely tuned to sense contrast and directional movement, and are capable of modulating their sensitivity over 6 log units of luminance. But furthermore, each of these structures is delicately linked to the circulation and metabolism of the entire retina and in cases of disease their function is fundamentally altered.

We can watch the function of these structures with a different type of camera. Instead of measuring photons, we can measure the rays of electrons which are emitted as each cell within the retina is activated. The waves of electromagnetic potential that ripple through the tissue of the eye as the retina receives and processes photons are the signatures of these processes. By stimulating each process individually we can watch how that signature varies and in so doing gain a glimpse of how our eyes are changing over time and circumstance.

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Hoefflinger, “The Eye and High-Dynamic-Range Vision.”

Toward Accessible Evaluation of the Electrophysiology of Human Vision
Signal Pathways

The human retina is composed of three cellular layers, separated by two layers of synapses (see Figure 2). The path of communication, from the cells which receive the photon energy to those which relay that information to the brain, actually travels from the outermost layer, to the

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8 Kolb, “Functional Organization of the Retina.”

Toward Accessible Evaluation of the Electrophysiology of Human Vision
innermost, then out through the optic nerve. This communication channel, in the most general terms, is as follows:

0. When no stimulus is present, there is a steady state current called the “dark current” which flows through the membranes of the photoreceptor cells.

1. When a photon arrives at photoreceptor cell, this activates several signal transduction pathways which cause the ion channels in the cell walls of the photoreceptors to close, resulting in a hyperpolarization of the cell. In other words, the potential difference between the interior of the cell and the exterior becomes more negative.

2. Via the first layer of synapses (called the inner plexiform layer) this hyperpolarization triggers the intermediary neurons to either similarly hyperpolarize or depolarize (their potential becomes more positive). Some of these neurons, called amacrine cells, if excited by the neighboring hyperpolarization, create a transient response. Other amacrine cells are intrinsically sensitive to photons, and when excited create a sustained response.

3. Via the second layer of synapses (the outer plexiform layer), this combination of hyperpolarization and depolarization, either in transient time scales or sustained ones, reaches the ganglion cells. Up until this point in the communication pathway, the potentials have been graded, as opposed to the all-or-none action potentials which are the language of the ganglion cells. Ganglion cells respond to either neighboring potential changes or direct stimulation by photons according to their receptive field (more on that later).

Each layer of the retina can be activated by photons, though the majority of the polarization due to photon energy originates in the outermost layer with the photoreceptors.

Adaptation

Each of the cells which undergo a change in polarization across its membrane requires a certain amount of time to return to its natural state of polarization before it may be excited again. The visual pigment molecules (like rhodopsin in rod photoreceptors) are temporarily transformationally altered in the transduction of photon energy to electrochemical potential and must return to their steady state before the reaction can take place again. These are the mechanisms which underlie the property of adaptation. A dark-adapted test removes stimulus

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9 Dowling, “Retina.”

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and ensures that the cells within the retina are at full firing power at the onset of the flash. Specific tests can conversely saturate certain parts of the retina, effectively preventing them from contributing to the ERG waveform until they replenish their consumables and thus isolating the unsaturated retina. It is possible to isolate mechanisms with not only stimulus intensity but temporal frequency. The rod photoreceptors are not capable of contributing to the electroretinogram signal at higher frequencies\textsuperscript{10}, making it possible to isolate the cone photoreceptor response by supplying stimuli at higher frequencies (above 20-25 Hz).

\textit{The Eye Dipole}

![Diagram of the dipole created by the electrical activity of the human retina and the locations at which it is measured. Red colored arrows indicate electrical wave fronts which accumulate, while black colored arrows indicate those wave fronts which interfere and do not contribute to the overall waveform.}

The orientation and shape of these photoreceptors is what creates a dipole within the entire eye. Photoreceptors are cylindrical and tightly packed, especially within the center of the retina, or the fovea. As the electrochemical reactions take place in each photoreceptor, an electric field is created, emanating from the center of the cell. All components of this field which point outward

\textsuperscript{10} Padmos and Van Norren, “Cone Spectral Sensitivity and Chromatic Adaptation as Revealed by Human Flicker-Electroretinography.”

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from the sides of the cells will cancel with the field of the adjacent photoreceptor, but the components which are directed along the central axis of the cell and the eye will combine, resulting in a dipole effect within the entire eye. The aggregate electrochemical activity within the retina - each of the hyperpolarizations or depolarizations that occur throughout this pipeline, and the time at which they occur — affects the polarization of this dipole and creates the overall waveform of the ERG.

2.2 CURRENT STANDARDS

Visual electrophysiology as a clinical science is regulated and standardized by the International Society for Clinical Electrophysiology of Vision who publishes a series of standards for the most commonly performed visual electrophysiology exams\(^\text{11}\). Those exams are detailed as follows.

2.2.1 Flash

Full-field flash ERG is the most fundamental visual electrophysiological test. A full-field stimulus is traditionally delivered by a Ganzfeld dome, usually a white hemispherical dome with an integrated chin rest where the patient stabilizes their head such that the surface of the dome occupies their entire field of vision. The stimulus and background illumination are then directed at the dome to create the effect of a full-field stimulus. Other methods of delivering full-field stimulus include Maxwellian view systems which use an optical system to create a full-field stimulus in a smaller interface with more adaptability. Within flash ERG, there are a multitude of tests which vary the intensity, duration, repetition, and wavelength of the stimulus and background illumination, as well as the level of adaptation of the individual, each calibrated to test a specific aspect of retinal function.

The current ISCEV standard highlights five responses of interest elicited by a flash ERG:

1. rods, targeted by dark adaptation followed by a weak flash (0.01 cd s m\(^{-2}\));
2. cones, targeted by light adaptation followed by a strong flash (3.0 cd s m\(^{-2}\));
3. maximally combined response, targeted by dark adaptation followed by a strong flash (3.0 cd s m\(^{-2}\));

4. oscillatory potentials, targeted by dark adaptation followed by a strong flash (3.0 cd s m$^{-2}$) and isolated via digital filtering;

5. and 30-Hz flicker, targeted by light adaptation followed by a strong flicker (3.0 cd s m$^{-2}$) at 30 Hz.

![Image of standard full-field ERG recordings in a representative normal subject. Flash luminance is indicated adjacent to each response and onset is indicated by the dotted lines. Key features to note: the maximal response (bright flash with dark adaptation) has both a strong negative trough and positive peak, while the rod and cone responses do not possess the strong negative trough. The rod response occurs over longer time scales while the cone response is much quicker. Adapted from Jacobi.]

The majority of the clinical significance of a normal flash ERG is in the characteristics of the first two waves of the response: a- and b- wave. The origin of these components is as follows. The a-wave is a sharp negative trough quickly following the stimulus, largely attributed to the hyperpolarization of the cone photoreceptors (most visible in Figure 2, maximal response). Next follows the b-wave, a large peak attributed to the bipolar cells and other neurons within the retina. The a-wave amplitude is measured from the signal baseline to the minimal point of the wave, while the b-wave amplitude is measured from the trough of the a-wave to its peak. The implicit time of this wave is measured from the onset of the stimulus to the b-wave peak. Oscillatory potentials are found within the rising edge of the b-wave and are thought to represent some of the feedback mechanisms which take place between the layers of the retina.

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12 Jacobi, Miliczek, and Zrenner, “Experiences with the International Standard for Clinical Electroretinography.”
As mentioned previously, the primary pathologies which result in abnormal response to a standard flash ERG are ischemic retinopathies (i.e. diabetic retinopathy), retinitis pigmentosa, and nyctalopia or night blindness. These pathologies result in a degradation or malfunction of the photoreceptors or pigment epithelium, where much of the electrical potential from a flash stimulus is generated. The resultant abnormalities are detectable as changes in implicit time or amplitude in the a- or b-waves. Variations in oscillatory potentials, which are most susceptible to changes in circulation within the retina, are also highly indicative of retinal pathology, though are somewhat more difficult to reliably determine.

2.2.2 Pattern

The pattern ERG (pERG) is a temporally modulated contrast-reversal test which targets the function of the retinal ganglion cells whose dysfunction may not be reflected in the waveforms elicited in full-field flash ERG. A standard PERG stimulus consists of a checkerboard which alternates at a rate of approximately 2 Hz. This stimulus will elicit a "Transient ERG" waveform characterized by: a small trough at 35 ms from the point of pattern reversal, called N35, followed by a much larger peak, P50 at 45 - 60 ms from pattern reversal, and finally a small trough at 90 - 100 ms, N95. The most clinically relevant measurement is the amplitude of the P50 peak, which in normal subjects is between 2.0 and 4.0 microvolts.

Changes in this amplitude are early indications of an onset of glaucoma, permanent optic nerve damage caused by increased pressure in the eye. Measuring this pressure is the classic way to evaluate the progression of glaucoma but in early stages it is unclear if that pressure is in fact causing damage to the neurons. Pattern ERG is a direct measurement of the health of those cells, allowing clinicians to discern which patients should be recommended for preventative treatment and which need not be - preserving resources and preventing individuals from being needlessly exposed to unnecessary treatments.

2.2.3 Multifocal

The classic flash electroretinogram is an aggregate measurement - its spatial sensitivity is very low. Recently the first multifocal electroretinogram (mfERG) was demonstrated which successfully delivered a stimulus to a small, specific area of the retina and recorded the response. Modern mfERG exams target several regions simultaneously and rapidly switch...

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14 Bresnick et al., “Electroretinographic Oscillatory Potentials Predict Progression of Diabetic Retinopathy.”
15 Bach and Hoffman, “The Origin of the Pattern Electroretinogram.”
16 Bearse Jr and Sutter, “Imaging Localized Retinal Dysfunction with the Multifocal Electroretinogram.”
from one area subset to another. The integration of some signal processing then isolates the response of each individual region, generating a map of retina response.

![Figure 5](image)

**Figure 5. mtERG stimulus and results. Adapted from Hood17.**

The introduction of multifocal electroretinography and its ability to test specific regions of the retina had a dramatic effect on the use of electroretinography in ophthalmology. Multifocal ERG has become highly relevant in the monitoring of early onset diabetic retinopathy and macular degeneration18.

2.2.4 Recent Advances

Recently there has been some progress in the development of lower cost, simpler tools for visual electrophysiology. The most notable case is developed by LKC Technologies, who recently patented a system which utilizes one specific type of ERG test - 30 Hz flicker - to detect retinal ischemia, a result of diabetic retinopathy. The LKC system, called RETEval, utilizes only skin

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18 Hood et al., “The Multifocal Electroretinogram.”
electrodes which plug into a handheld device and performs a test in less than 5 minutes\textsuperscript{19}. RETEval has been priced around $5,000, which is substantially less than full ERG systems, which are usually based in a desk-top computer and cost on the order of $100,000 - $200,000. Other manufacturers of ERG systems include Diagnosys, LLC (Espion Visual Electrophysiology System), Electro-Diagnostic Imaging, Inc. (Veris Compact), and Metrovision (Vision Monitor Visual electrophysiology).

\section*{2.3 BEYOND STANDARD CLINICAL APPLICATIONS: POTENTIALS OF VISUAL ELECTROPHYSIOLOGY}

While the established and standardized visual electrophysiology exams have defined the field thus far, beyond these standard uses is a body of research which explores far more than the pathological characteristics of these waveforms. This work, generally encompassed by visual psychophysics, has utilized visual electrophysiology methods to elucidate some of the most fundamental mechanisms of how we experience color, contrast, and movement. It is within these studies where some of the most exciting potentials of an accessible way to perform visual electrophysiology emerge.

\subsection*{2.3.1 Color Experience}

Of all the photoreceptors in our eyes, roughly five percent are responsible for our experience of color\textsuperscript{20}. In our trichromatic vision system, short, medium, and long wavelength sensitive cones (S-, M-, and L-cones respectively) make up the dimensions of our biological representation of color. In digital color spaces, this translates to the RGB representation. But our eyes are not as uniformly organized as a Bayer mask on a CCD sensor - the cone mosaic is as unique to an individual as their fingerprint.

There are several methods of determining the distribution of the cone types within the retina. The first images ever captured of distinct cones distinguished by their spectral sensitivity were generated by Roorda and Williams at the University of Rochester in 1999\textsuperscript{21}, using adaptive optics and a technique called retinal densitometry. In this method, adaptive optics allowed the researchers to eliminate blur much like in telescopic systems pointed at distant galaxies. With the blur eliminated, they were able to capture images of discrete photoreceptors and distinguish them as they responded to retinal densitometry, in which the absorption of the pigment epithelium (where the photoreceptors are located) is measured given specific spectral stimulus.

\textsuperscript{19} Severns, “Device to Monitor Retinal Ischemia.”
\textsuperscript{20} Purves et al., “Anatomical Distribution of Rods and Cones.”
\textsuperscript{21} Roorda and Williams, “The Arrangement of the Three Cone Classes in the Living Human Eye.”
This method, while exact, relies on the significantly complex adaptive optics approach and is inaccessible on a large scale.

Some of the more accessible methods are far less direct. By measuring an individual’s ability to distinguish different colors, we can intuit a relative assessment of their sensitivity to different wavelengths. In psychophysics, this technique is called heterochromatic flicker photometry. Two lights are flickered at around 30Hz, a test light and a reference, while the luminosity of the test light is adjusted in steps until the subject reports that the flicker has disappeared\textsuperscript{22}. The disappearance of the flicker indicates that the two lights are at the same lumiance, or luminous intensity. When applied to generating L:M (long-wavelength sensitive to medium wavelength sensitive) ratios, the test light is set to a specific wavelength while the reference is achromatic. The technique is repeated for all wavelengths to yield a relative spectral sensitivity curve. To calculate the L:M cone contribution ratio this curve is fit with an equation of weighted sums of L- and M- cone absorption curves. However, the reliability of this method is limited by the fact that large changes in the L:M ratio, such as from 2:1 to 3:1, predicts only a small change in relative sensitivity, 0.05 log units, which is well within the usual measurement error of psychophysical flicker photometry\textsuperscript{23}.

The electrophysiological analog to this psychophysical method, however, is far more reliable than the reported results from naïve subjects. In electroretinogram flicker photometry, the test light is modulated until it produces the same amplitude electrical response as the reference light. This technique has been well documented by the Neitz group\textsuperscript{24} and produces fairly noise resistant readings very efficiently compared to the psychophysical alternative.

Implications of Variations in Ratios of Cone Photoreceptors

The cones are clustered in the fovea, or central vision, and their numbers diminish rapidly towards the periphery of the retina. The way that each cone photoreceptor cell responds to different wavelengths is well established\textsuperscript{25} - originating in the specific absorption spectra of the proteins within the cells and varies little from individual to individual\textsuperscript{26}. But as mentioned

\textsuperscript{22} Bone and Landrum, “Heterochromatic Flicker Photometry.”
\textsuperscript{23} Carroll et al., “Flicker-Photometric Electroretinogram Estimates of L.”
\textsuperscript{25} Merbs and Nathans, “Absorption Spectra of Human Cone Pigments.”
\textsuperscript{26} Smith and Pokorny, “Spectral Sensitivity of the Foveal Cone Photopigments between 400 and 500 Nm.”
previously, the ratios of different kinds of photoreceptors vary considerably amongst individuals. But what are the practical consequences of this?

![Normalized absorption spectra of the short, medium, and long wavelength cones and their corresponding opsins. Adapted from Gouras and Brainard et al., Functional Consequences of the Relative Numbers of L and M Cones.](image)

Figure 6. Normalized absorption spectra of the short, medium, and long wavelength cones and their corresponding opsins. Adapted from Gouras.

When we learn colors as children, we are taught associations. We learn to associate our experience of wavelength, color, with a qualitative classification and not a wave number. But our experience of color isn't limited to knowing what is red and what is blue. The aggregate effect of a scene, of all of its constituent elements of wavelength, contrast, and intensity, is the result of linkages and codependences as delicate and intricate as those which populate the systems and physiologies which allow us to perceive it. In the end, it's all physics, but what that practically means is that if we understand our unique sensitivities to wavelength, we also gain an understanding of energy and how it's absorbed.

The retina's role in our overall experience of vision may be a single part of an elaborate process, but it is inevitably the gateway. When Brainard et. al. set out to elucidate the role of the L/M ratio in vision, their ultimate conclusion was that this ratio was indeed responsible for much of the variation in individual photopic luminous efficiency, or how well our eyes transmit light.

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27 Gouras, “Color Vision.”
28 Brainard et al., “Functional Consequences of the Relative Numbers of L and M Cones.”

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to electrical signals, but that this variation was barely translated into any variations in our experiences of unique colors, like yellow. So while the retina may not be the deciding factor in our experience in distinct colors, it does give us a picture of the eye processes wavelengths relative to one other. Practically, what this phenomenon implies is not that we can find a true yellow, but that we can tailor a scene or display to an individual’s unique sensitivities to a broad spectrum of light, taking advantage of what they are most sensitive to.

**But What About The S-Cones?**

The short wavelength cones are the odd ball in the triad of color vision - they are both morphologically and functionally distinct from the L and M cones. Aside from a noticeable different spectral sensitivity, their densities are almost identical among individuals\(^{29}\) compared to the vast variability in L and M cone densities. Generally, S-cones are more sensitive, a sort of mediator between the opposing red-green mechanisms of the L and M cones and the achromatic rods. Clinically, S-cones are actually of significant interest\(^{30}\) - their electrophysiological signature is noticeably impacted by diabetes\(^{31}\), glaucoma\(^{32}\), and retinitis pigmentosa\(^{33}\). Protocols which isolate S-cones have been developed which select an adapting background which saturates both the rods and L and M cones before delivering the stimulus, and are thought elicit an almost pure S-cone response\(^{34}\).

2.3.2 Spatial and Temporal Contrast Sensitivity

Each rod and cone has a corresponding receptive field, a cone-shaped volume in physical space which describes all of the paths of light which will result in the activation of that photoreceptor. The receptive field of a ganglion cell, then, is the volume in space which corresponds to all of the combined receptive fields of the rods and cones which the ganglion cell is connected to via the intermediary neurons (horizontal, bipolar, and amacrine cells). A receptive field is most often represented by a cross section of this volume.

It is this way that the ganglion cells are receptive to contrast. There are many types of receptive fields for the many types of neurons which exist in our body, but within the ganglion cells of

\(^{29}\) Hofer et al., “Organization of the Human Trichromatic Cone Mosaic.”
\(^{30}\) Greenstein et al., “S (blue) Cone Pathway Vulnerability in Retinitis Pigmentosa, Diabetes and Glaucoma.”
\(^{31}\) Yamamoto et al., “Selective Reduction of the S Cone Electroretinogram in Diabetes.”; Mortlock et al., “Silent Substitution S-Cone Electroretinogram in Subjects with Diabetes Mellitus.”
\(^{33}\) Swanson, Birch, and Anderson, “S-Cone Function in Patients with Retinitis Pigmentosa.”
\(^{34}\) Chiti et al., “The S-Cone Electroretinogram.”
the retina, the most prominent types of fields include a center, surrounded by a concentric ring. Ganglion cells are characterized as either ON, OFF, or ON-OFF — they fire rapidly when there is stimulus present in the center of the receptive field and absent in the surround, or vice versa, or they fire as a transition is made from on to off or off to on.

![Receptive fields of ganglion cells](image)

**Figure 7.** Receptive fields of ganglion cells — shown are examples of ON-center and OFF-center cells, which either respond to a light center with dark surround or a dark center with light surround (respectively). Adapted from Kolb.

Some of the most interesting ganglion cells are directionally sensitive — they respond only to stimuli moving left to right, but not right to left. The variety of ganglion cell types is one of the indicators of the complex visual processing which occurs directly within the retina before signals even reach the brain.

Most assessment of our electrophysiological response to moving stimulus patterns is focused on the signals that result in the visual cortex, called visual evoked potentials. This is in part because the visual system “strongly adapts” to motion, meaning that the brain produces strong after-effects associated with certain types of moving stimuli. This results in more specific and sensitive responses in visual evoked potentials to different motion stimuli with different adapting conditions, and not nearly as sensitive or specific responses in pure electroretinograms. Again, understanding our experience of vision necessitates considering

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35 Kolb, “Functional Organization of the Retina.”
36 Bach and Ullrich, “Motion Adaptation Governs the Shape of Motion-Evoked Cortical Potentials.”
the entire pipeline, but the retina still plays an essential role in this processing and it's a role that we can measure quantitatively.

2.4 CURRENT CHALLENGES

The question becomes: why hasn’t visual electrophysiology evolved to activate these potentials?

There are several challenges inherent in the current standards for visual electrophysiological testing which are the primary barriers to wider adoption of this tool in clinical practice. Many of these challenges exist in either the calibration steps or the inherent diversity amongst patients, but they share the same theme - essentially, visual electrophysiology systems are still highly compartmentalized, with little innovation in streamlined or optimized design aimed specifically at reducing the complexity of the system and making the technology easy to use.

A classic system to perform electroretinogram measurements consists of three elements:

1. a stimulus delivery system, which traditionally incorporates a large dome for delivering a full field flash and may include a separate dome for delivering pattern or multifocal stimuli which utilizes a CRT or LCD display behind an optical system (usually a large Fresnel lens) to fill the visual field;

2. a signal amplifier, which may or may not be a standard third party electrophysiology amplifier unit which amplifies and filters the signals from the electrodes and transmits it to the processor;

3. and a signal processor and control unit, which in almost all cases is a standalone computer preloaded with software which includes all of the sensitive timing and synchronization control sequences to create the stimulus and accurately correlate the response received from the amplifier to it, as well as display and post-process the data.

Most standard flash ERG systems use xenon flash bulbs for their high intensity output and their ability to deliver sub-5 ms flashes of light. However, xenon bulbs degrade over time, which not only results in a decrease in maximum output, but also a fluctuation in output from flash to flash which varies within several percent of light output. Furthermore, the systems which exist to evaluate xenon flash intensity have an inherent uncertainty of around 10%. Without

38 Drasdo, “Vision Research.”
an accurately tuned stimulus, it is very difficult to say anything specific about the results of the test.

The ISCEV recommends calibrating electronics with maximum interval of one year\textsuperscript{40}, yet only offers a high level description of calibration protocols without a specific indication of the tools with which to perform a calibration (such as an appropriate signal generator to simulate the micro volt magnitude electroretinogram signals). The onus of effective calibration methods then lies on the technical knowledge of the individuals responsible for maintaining the equipment, which can vary considerably from urban tertiary care centers to small clinics.

Aside from the variations which can be attributed to changes in equipment state, there are many sources of variability in ERG recordings which can be attributed to how the test is administered. The position and quality of contact of the electrodes is a considerable contributor to this variation. The orientation of the patient during the test is just as crucial, as any movement during the test can cause spikes or saturation in the sensitive analog circuitry.

Even in cases of ideal equipment state and test administration, there are inherent variations in an electroretinogram signals which are entirely normal or non-pathological. The retina is intricately linked to the chemistry of the entire body, and will vary as that chemistry does - diurnally\textsuperscript{41} and with age\textsuperscript{42}.

Ultimately, whether the sources of error are in the equipment or the administration of the test, performing electroretinography with current systems still requires significant technical knowledge of the science behind the test to achieve actionable results. This can’t be expected to change without a significant evolution in the implementation of visual electrophysiology hardware.

2.5 IMPLICATIONS: VALUE TO STAKEHOLDERS

There are many groups or individuals who have a stake in the development of accessible visual electrophysiology systems. Within this cohort are many of the standard stakeholders in medical technology systems - the patients who experience the technology, the care givers who use it, and the administrators who procure it. In addition, in markets which can facilitate this

\textsuperscript{40} Brigell et al., “Guidelines for Calibration of Stimulus and Recording Parameters Used in Clinical Electrophysiology of Vision.”

\textsuperscript{41} Hankins, Jones, and Ruddock, “Diurnal Variation in the B-Wave Implicit Time of the Human Electroretinogram.”

\textsuperscript{42} Birch and Anderson, “Standardized Full-Field Electroretinography.”

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kind of application, there are consumer use cases which incorporate general users and non-medical distributors.

**Neuro-Ophthalmologists, Patients, and Care Systems**

A medical technology is designed with a dual user profile in mind, considering simultaneously the doctor and the patient, making those two groups the primary stakeholders. In addition to the doctor-patient interaction, another main consideration is how this technology will integrate into the system of care, which directly impacts both the design of the device and the system with which it is distributed.

The greatest potential benefit available to this collection of stakeholders would be a transformed care experience:

- ophthalmologists who previously could not afford the technology now can deliver that service to their patients;
- clinics which do not have the in-house expertise to administer the old technology can now provide the service via our simplified and streamlined user interface;
- patients now have a quicker, more comfortable care experience;
- an easier interface increases data quality, providing better information for clinicians and better diagnostic outcomes.

There are no major downsides which are experienced by the patient, but the clinician and care system have to weigh the benefits against the additional cost (albeit small) of funds and time to incorporate a new technology into their practice.

In the specific case of our direct collaborator, LV Prasad Eye Institute, this system of clinicians and eye care structures has the ability to directly inform and fund the development of this technology via the LVP-MITRA Innovation Center, recently inaugurated on October 25, 2013 in Hyderabad, India. The inauguration of this center was a direct result of our efforts with the Institute to conduct workshops promoting innovation in ophthalmology. This Center serves as a physical epicenter for the continued collaboration amongst the student participants in the workshops, the clinicians active in mentoring innovation and the researchers from MIT who are involved. LV Prasad Eye Institute’s large network of clinics provides an ideal structure already in place for prototype testing. Given the number of resources at the Institute’s disposal to be an active contributor in this development, its influence over the eventual end product which may result from this work is very high.
While the individual patients themselves do not possess any physical resources which directly influence the development, it is ultimately their experience of the technology, coupled with the clinicians experience, which is the greatest deciding factor in whether the technology is actually used and thus the greatest single consideration in its design. The patient’s greatest resource in influencing the solution is their opinion and their choice.

Open assessments still to be considered are the issues of where and when the technology will be deployed and manufactured. As those decisions are being finalized, I will consider the stakeholders within the supply chains and distribution mechanisms. This assessment, however, is beyond the scope of this thesis.

**The Indian Market**

There are several motivations for designing an accessible electroretinography technology for the Indian market. Frankly, the sheer population size and correspondingly large prevalence of eye disease are significant motivators in and of themselves. Furthermore, the limited eye care infrastructure in the majority of the country mean that there is proportionally more unmet need than in a more developed country. The higher prevalence of vitamin A deficiencies in India\(^{43}\) lead to a higher incidence of night blindness, a common symptom of the deficiency, further broadening the potential need for diagnostics which better enable clinicians to deliver care, especially in remote areas.

**Developed Markets**

Within developed markets, such as the one that surrounds us in Cambridge, the set of potential stakeholders is slightly different. The many high quality tertiary care centers within the greater Boston area have the funds and expertise to perform effective visual electrophysiology. A tool which is lower cost and easier to use has little added value, especially within the first few years of its life in the market as it is proving its efficacy. However, within this market, there exists the potential to engage an entirely different stakeholder group - consumers outside the patient-caregiver-administrator stakeholder triumvirate. An additional potential stakeholder is the consumer who is excited about the idea of a quantified self - of collecting information about their well-being to lead a more informed lifestyle. Accessible electrophysiology has many potential interesting consumer applications which are detailed in a later chapter.

In a consumer health model, the key stakeholders are:

1. The user. The primary influences on the development of the technology which consider the user manifest in ease of use, esthetics, cost, and outright functionality. The user affects these elements with their feelings from their impressions and experience using the technology and their perception of its value. With a primary goal of widespread adoption of the technology, the user's experience is the chief influence in the development of the device.

2. The retailer. In pursuing the goal of widespread adoption, designing with retailers and distributors in mind can be a significant facilitator. These stakeholders have the most influence in deciding whether or not to distribute the product. While this decision is also linked to the perceived consumer demand, it is also impacted by the ease of which the device may be procured and transported. Practically, this translates to the availability of the materials of which it is constructed, its size, cost, and many other physical features of the device which impact how it is displayed in storefronts or stored in the distribution chain. In the early development of the technology, this translates to impact on essential design decisions.
Over the course of the development of this technology, we were concurrently experimenting with some models of “accelerating innovation” in the context of our group at the Media Lab and the Tata Center for Technology and Design. What myself and my colleagues found over the course of these experiments is worth mentioning here, as it greatly impacted the time course of the development of not only my thesis work but now several other projects within our research group. There is a very exciting potential inherent in the formalization of these ideas and their application in many different fields and contexts.

3.1 IN THE FACE OF LIMITED RESOURCES AND TIME: DESIGNING IN CONTEXT

New technologies and materials which have huge implications in diagnosis and treatment of diseases have caused the fields of medicine and engineering to merge, creating new fields and a new generation of interdisciplinary researchers. This has also thrown into sharp relief the challenges of developing new technologies which must not only meet stringent standards for efficacy and safety, but also must be highly usable and economical. Many researchers have transitioned to this space because of the incredible opportunity it presents to create tools which have a direct impact in improving quality of life. Even more have recognized that the markets for medical devices have been slow moving and are ripe for disruption by well formulated innovation.

Yet there are significant hurdles to designing medical devices, chief among them (1) identifying opportunities for disruptive innovation and (2) incorporating design which is appropriate for the clinical context in which technologies will be integrated. Medical engineering innovation hubs like those in Boston and San Francisco have flourished in part due to the co-location of state of the art medical facilities and research institutions, but even when the barriers of distance are eliminated, identifying and executing projects still requires significant timelines. This is due in most part to the second hurdle mentioned above: care systems are incredibly complex and the knowledge of the inter-workings of this system and what information is needed to design a device do not often occur in the same person. Inadequate communication between developers of a technology and potential stakeholders results in poor design, inefficacy, and inevitable failure of the device in the market. Both great ideas and good design require a deep integration of these two elements of knowledge: of the care system and the prototyping/design process.
Like the migration to health, many researchers within engineering and science academia are beginning to recognize the opportunities present in focusing their research on applications in developing contexts. Many of the same principles which elongate timelines in designing medical technologies apply in this domain as well. Resource-constrained settings are like scaled care systems—they are characterized by the same complexities, amplified. Identifying projects which are both (1) feasible and (2) impactful in this domain is a non-trivial process and still today there are many wasted efforts in international development due to ineffective assessment of those two crucial elements. You can imagine, then, the complexities inherent in designing medical technology in developing contexts.

It is through conversations and meetings between two spheres of knowledge: technical design and clinical context by which we can assess for each idea its relevance, complexity, and resultant innovation potential. Yet most collaborations between these spheres of knowledge consist of isolated meetings, greatly spaced in time. What this method is effectively doing is only giving us a few snapshots, a few single data points of what is in reality a whole surface of potentials.

But if you could open an information super highway between these two spheres, you could rapidly fill in the rest of the data points to see the whole landscape.

3.2 METHODS OF ACCELERATION

Among the attempts to further eliminate the barriers to medical device design, hackathons (short, intensive rapid prototyping sessions) are increasingly used to foster development in this space. Yet the greatest outcome from this model is often awareness and connections, with the quality of prototypes notoriously low. Most hackathons are also isolated events, providing no structure for continued work or collaboration. Yet the model of focusing on a single pursuit for a short period of time still presents exciting potential for breakthroughs in the field of medical technology design.

In 2011, the Media Lab first hosted the Design Innovation Workshop in Pune, India, a four day event aimed at disseminating some of the design principles at the core of the guiding philosophies of the MIT Media Lab and to engage and inspire students from all fields in India to reinvent the future. This event was very successful at introducing a large number of students to the idea of “learning by doing,” and from this workshop and the three that have followed, several companies have been incorporated and several students have come to study at the Media Lab as a result. In 2013, at the third such event, myself and several researchers from our group taught several tracks of the workshop and became very acutely aware of the potential such a format possessed if applied to designing medical devices.
The following July, we held a new kind of workshop in Hyderabad, India in collaboration with the LV Prasad Eye Hospital, modeled after the Design & Innovation Workshops but focused on developing ophthalmic devices. The key distinction between our event and the previous events in this series was two-fold: firstly, we established a deep connection with a partner hospital who pledged several clinicians and researchers to attend the entire duration of the workshop; and secondly, we set out with a very high standard for prototype outcomes. Our goal, first and foremost, was to develop disruptive, viable technologies and all other details of the event were to facilitate that goal.

The method employed to achieve this goal was to bring together the two spheres of knowledge: technical design and clinical context, and with this duality of expertise at hand to create an environment in which a complete assessment of potential projects and design criteria can be conducted. The chief innovation in this model is to condense what would normally require several meetings or events separated by several weeks or months of time into an intensive, one-week period. Over 100 students from top Indian institutions attended the workshop and with the guidance of 10 MIT instructors and a host of clinical mentors, over 20 prototypes were developed to address some of the most critical needs of the ophthalmic care community, as identified at the start of the week. As a direct outcome of this event, LV Prasad committed to starting an innovation center on their campus to further support activities around developing technologies to improve eye care.

As a component of this July workshop, we also conducted a follow-up workshop, in October, in which we invited the most promising students to return and participate in the continuation of several projects. This follow-up event was intended to provide a structure to both reiterate some of the principles the students were first exposed to in July and to encourage them to continue this work in a tangible way. This event was wildly successful, in part because of its more manageable size and pre-selected attendees, but also because we were located directly on the LV Prasad campus, with direct access to supplies and guidance.

This dual event model - a broad event to generate exposure to a large set of both people and ideas followed by a focused event to cultivate the most promising of those two sets, was very successful for us. The community created by both events has only grown since the workshop, and the progress achieved at the second workshop was a significant contributor to several active research areas in our group at the Media Lab, including this thesis.

3.3 ELEMENTS OF A SUCCESSFUL WORKSHOP
Our immediate next steps were to integrate some of the lessons we learned in Hyderabad into the next event. The importance of eliminating barriers of distance was even further underscored in July, as the primary location of the event was distanced from the hospital (and essential supplies) by several hours of Indian city traffic. A summary of the essential elements of a successful workshop are as follows:

- **Critical location selection.** A successful workshop hinges greatly on the location and partner selected to host. This host most often has the following characteristics, more or less ordered by importance: convenient location, on-site lodging for students, adaptable, flexible, and dedicated local partner to facilitate these logistics, convenient prototyping space with nearby lunch and dinner amenities.

- **A dedicated logistics team,** separate from those responsible for content preparation and teaching. This logistics team should have dedicated subteams for: PR and web development, lodging and transportation, on-site materials procurement, and budget management and disbursement.

- **Pre-workshop project and instructor curation.** The broad outlines of the projects to be considered during the workshop should be outlined over the course of several meetings between stakeholders both in and out of context before the start of the workshop. Full articulation of the projects is not necessary, but some preliminary prototyping should occur before the workshop begins. Later stage implementation design can occur at the workshop itself. Similarly, the instructors should be intimately involved in this process.

### Table 1. Overview of example workshop schedule

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<th>Day 1</th>
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<tr>
<td>Inauguration</td>
<td>Design iteration</td>
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<td>Tour of relevant medical facilities</td>
<td>Design review</td>
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<td>Challenge explication</td>
<td>Implementation iteration</td>
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<td>Team formation</td>
<td>Implementation review</td>
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<td>Project area selection</td>
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<th>Day 3</th>
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<th>Day 6</th>
<th>Day 7</th>
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<tr>
<td>User testing and evaluation</td>
<td>Prototype showcase</td>
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<tr>
<td>Prototype development</td>
<td>Closing ceremony</td>
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and should be appropriately inculcated with the expected structure of the workshop and what will be made available.

- A dedicated admissions team who are responsible for evaluating applications to the workshop and communications to the applications and admitted students. A singular point of contact for the attendees is critical for creating a well-organized front for the workshop.

3.4 CASE: ELECTRORETINOGRAPHY

The concept of developing accessible electrophysiology tools first came to the attention of the group in the spring of 2013. At the first workshop conducted in July, we evaluated visual electrophysiology with our collaborators at LV Prasad as a viable arena to focus the efforts and resources of our research group. Our initial assessment identified this field as somewhat of a niche market - electroretinography is only essential in a small number of cases, but has interesting potential to provide actionable information in many clinical circumstances. It became clear that the chief barrier to more widespread use of the tool was the technological complexity and cost inherent in existing solutions.

I like to refer to such scenarios as "chicken and egg conundrums." Need drives simple solutions, yet conversely simple solutions can generate need. In many cases, there is a stall in innovation because there is no urgent need for simpler solutions, but if we change a status quo and interject a new type of technology design, this course can be altered.

We assembled a team of students in the July workshop to focus their efforts on affordable visual electrophysiology. Through this initial attempt we became acutely aware of the exact resources and expertise needed to develop a robust system with which to develop electrophysiology systems, let alone those focused on the signals associated with vision which are characteristically several orders of magnitude smaller than other electrophysiological signals. However, while our attempts to develop a functional visual electrophysiology system in July were unsuccessful, we did make the important realization that cost of components associated with such a system could be radically optimized. If we could indeed build a system optimized for complexity and cost, then we could not only dramatically disrupt the existing economy for visual electrophysiology but also generate new commercialization avenues which never before existed.

In October, we dedicated a team of 7 students to the development of this system. Our co-location with the LV Prasad Eye Institute was a huge facilitator in this event. They brought over a state of the art visual electrophysiology system for us to work with uninterrupted for the duration of the week. With this team of students skilled in building and debugging circuits, we were able to
sense ERG signals for the first time. It was just before this event that I chose to focus on this area for my thesis work. This initial development stage, of being able to focus solely on this work for 7 days with a team of students, was instrumental in the development of my own understanding of the field. I credit this experience with greatly accelerating my progress in this space. Two students in particular who have contributed greatly here are Vijay Sadashivaiah and Ayush Sagar, who have participated now in many workshops and are continuing work with the Camera Culture group and the LV Prasad Eye Hospital.

There has been some continued work in ERG at workshops following the event in October, though after that point I began to focus in Cambridge on the work that formed the bulk of this thesis. While the workshop experiences were very informative, all of the systems and data presented here are of my own design and generation.
4 DESIGN

In the pursuit of designing an accessible system to measure visual electrophysiology, I wanted to demonstrate a test that was at once attainable and relevant. Full field flash electroretinography has implications in many retinal ischemias and the architecture to implement a flash based test can be used to test many systems, providing information regarding night blindness, color blindness, and other pathologies. Beyond a full-field flash, the hardware to implement pattern or multifocal tests deviates significantly. It was by this reasoning that I chose to develop a system which implemented a full field flash test with the ability to perform light adapted, dark adapted, as well as color based tests.

In the process of building this system, I had several constant goals in mind. The first and foremost of these was to build a system which could successfully perform visual electrophysiology, as per the established standard. The second goal was to demonstrate in clear terms that this tool could be used easily, and without the barriers that plague existing systems. I wanted to eliminate the specific barriers which contribute most poignantly to the lack of use of this system. The identification of these barriers was conducted jointly with ophthalmologists and visual electrophysiology experts at the LV Prasad Eye Institute through the previously described workshop model. Chief among these was technical skill required to use the test, susceptibility to patient state, and total amount of patient discomfort. I wanted to create a device which exhibits the potential for this science to elucidate some truly fascinating elements of our own experience of vision. By achieving these goals concurrently, I aim to prove the relevance of visual electrophysiology beyond a clinical domain, and demonstrate the irrefutable potential of this tool to radically change the way we think about vision on a large scale.

To accomplish these goals, I set about the task of rethinking the way that this test is usually performed in a clinical context. There were two things which I wanted to change immediately - first, the test itself need not be tied to a whole machine which occupies an entire corner of a room. This is a characteristic, frankly, of many medical technologies. There simply doesn’t need to be an entire cart to accomplish this test. This goal was in some ways straightforward - there are obvious ways to minify a stimulator dome, and beyond that it is simply a matter of condensing many individual parts in to a clever interface. The second aspect which immediately caught my attention was that of the electrodes. The standard use of corneal electrodes requires numbing drops, administered before the test. Even with these drops the test was still almost impossible to administer in children. The idea of requiring contact with the eye, frankly, seemed medieval. My goal from the beginning was to create a system only reliant

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on skin electrodes. This puts me at somewhat of a disadvantage, as signal amplitudes via skin electrodes are typically a fraction (12%) of the amplitudes attainable from electrodes imbedded in contact lenses. The center of the cornea is in fact the best place to measure the signal, as it coincides with the axis of the dipole of the eye, but my evaluation is that the benefits of improved comfort and decreased complexity are too high to justify the use of corneal electrodes.

But beyond eliminating contact with the eye, the placement of these electrodes is where I identified a significant potential source of variability, a source of error which would in fact be amplified with the use of skin electrodes. In attempting to prove the utility and feasibility of electroretinography on a large scale, what I propose must in fact be more repeatable and robust than existing methods which are only used as often as a few times a year on the same person. I decided then to incorporate a way to position the electrodes in a consistent, repeatable way.

Beyond these significant aspects, a reduction in cost without a compromise on the quality and accuracy of the instrumentation was crucial. This could largely be achieved with the combination of the reduction in size and complexity of the entire system and the use of more readily available, lower cost components, such as high power LEDs in the stead of xenon bulbs.

The most important practical implication of these changes is the ultimate change in the experience of the user or patient. Fundamentally, this is what I set out to change most, and each choice in the design of the system was guided by the impact it would have on that experience.

4.1 GLASSES-MOUNTED INTERFACE

The design of my system is centered on a pair of glasses, or goggles. The electrode positioning and stimulus delivery are all combined in this interface, which is controlled by a laptop computer. The fundamental architecture of data transmission built into this system means that it can easily be directed instead toward a Bluetooth enabled smartphone, enabling a truly portable system. However, in the scope of this thesis I chose to instead focus on the non-trivialities of the integration of the hardware into this interface, and the design of the tests, leaving the implementation of data processing on a mobile phone (a fairly straightforward task given the low computational complexity) to future work.

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44 Esakowitz, Kriss, and Shawkat, “A Comparison of Flash Electroretinograms Recorded from Burian Allen, JET, C-Glide, Gold Foil, DTL and Skin Electrodes.”

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The placement of the electrodes required a delicate balance of robust, consistent positioning which can simultaneously adapt to the many different individual’s eyes. This all then should integrate seamlessly into the rest of the glasses mounted system. Eventually, the solution presented itself as I attempted to minimize the stimulation dome concurrently. Creating a full field stimulus requires a large dome only when the dome is far from the face. To that end, I designed a pair of small domes which encompass the eye and fit as a pair of swimming goggles. The stimulator is constructed of white plastic and illuminated from behind, creating a uniform, diffuse, and full-field stimulus. Upon the creation of this dome, it became obvious to use this system to position the electrodes as well. The goggles were outfitted with mounts into which the standard gold cast disc electrodes could be inserted, at the center of the bottom lid and at the outer canthus. A reference electrode mount was positioned over the bridge of the nose, in between the eyebrows.

In production level editions of this technology, it is of course feasible to implement this stimulator and electrode positioner with the electrodes built into the device. Some of my future work in this space will be the exploration of alternative electrode materials, including conductive rubbers with sufficiently small DC impedance, whose deformability will accomplish the same effect rendered by conductive gel, but are reusable and easily sterilized between users. This exploration, however, is outside the scope of this thesis.

The stimulator is then encompassed and positioned on the face by a case which holds the high power LEDs and driver (the LED mount). The case will deliver the stimulus to the stimulator one eye at a time. While the stimulator only fits onto the face in one orientation, the case which surrounds it is symmetrical along its axial plane, which means the stimulator may be flipped within the case and the goggles may then be replaced onto the face, with the LEDs now illuminating the other eye.
4.1.1 Fit Adjustment

There are several considerations for variations in facial shape and proportion which must be integrated into the design to ensure that the technology is adaptable to these variations. Chief among these is inter-pupillary distance. I have integrated this consideration into the prototype developed for this thesis because without it the device is almost unusable in anyone with an inter-pupillary distance significantly different from the one dimensioned into the part.

To account for variations in this dimension, there must be some freedom in the x-axis of the device\(^\text{45}\). To accomplish this, two design elements were integrated. First, the bridge which connects the two white stimulator domes is composed of a flexible rubber. This creates an effect similar to that of swimming goggles - the domes naturally fit into the eye sockets and the tension created by the pull enacted by the ear pieces or head strap forces the deformation of the bridge piece, thusly enacting the change in the distance between the two domes to account for the individual’s own inter-pupillary distance. The second element is the adjustment in the LED mount such that it can properly enclose the domes. This is accomplished in the bridge of the LED mount - herein the two separate pieces are joined by a socket, with one piece fitting into the other. When the apparatus is assembled and placed on the user’s face, the conformation of

\(^{45}\) The different axis in this system are defined as follows: the x-axis is the intersection of the sagittal and dorsal planes, the y-axis is the intersection of the dorsal and medial planes, and the z-axis is the intersection of the sagittal and medial planes. The origin is defined as the apex of the right cornea.
the dome to fit the user’s face will also translate to the expansion or contraction of the socket of the LED mount.

The variations in the y-axis dimensions of the eye sockets are generally speaking not significant enough to warrant building in an adjustment mechanism into the device. Practically, this means that those variations will most likely not lead to a poor connection at the electrodes which, aside from comfort, is the chief motivator for creating fit adjustment.

4.1.2 Delivering Stimuli Beyond The Accommodation Limit

There are some interesting implications of creating a full field stimulus without also providing a proper fixation point, as is the case in the method I have described. In traditional systems which utilize a Ganzfeld dome, the stimulus surface is within the range on which the human eye is capable of fixating, however, these systems are necessarily large in order to encompass the entire visual field.

\[ \text{Figure 10. (A) Illustration of the principles of the Maxwellian view method. (B) A more common, adaptable implementation of the Maxwellian view. Adapted from Westheimer}^{46}. \]

\[ \text{46 Westheimer, "The Maxwellian View."} \]

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Another method of delivering full-field stimuli is called a “Maxwellian view” system which is comprised of a system of lenses which when placed near to the eye will illuminate a large surface area of the retina. Maxwellian view systems are advantageous in that they allow the incorporation of beam splitters and other light modulation tools to rapidly switch between types of stimuli all the while in a small system. While the Maxwellian view system is also positioned close to the eye, in fact closer than we can focus, the optics of the system create a point (point T in Figure 10B), upon which the eye can fixate, or accommodate. There are no such optics in my proposed system and thus nothing which the eye can focus on.

Traditionally, fixation points are provided to reduce the amount of movement of the eye which could occur during the test and result in artifacts within the signal. However, some reduction in movement can also be achieved by doing exactly the opposite - by eliminating anything upon which to focus. In my experiments, I have found that when comparing tests (A) with stimuli delivered to a dome within my accommodation limit with no fixation point and tests (B) with stimuli delivered beyond my accommodation limit, that the eye is more likely to dart around for a fixation point within focusing range in the former case, but is in a more relaxed state in the latter. This appears to lead to a reduction in eye movements. Further investigation is required to formalize this theory, but within the scope of this thesis, formalizing a fixation strategy was not essential to obtaining meaningful results.

4.2 DIFFERENCE SIGNALING: THE BINOCULAR COUPLING ADVANTAGE

Given the disadvantages of using exclusively skin electrodes, I wanted to reexamine the way that the signals were captured to see if there were possible ways to improve signal quality in spite of the low expected amplitudes. In systems which use Ganzfeld domes (which are in fact the majority - Maxwellian view systems are most often reserved for experimental research), unless one eye is patched, both eyes receive the stimulus and only one eye is traditionally measured at a time. However there is an important characteristic of eye movements which can pose a significant advantage, a phenomenon called binocular coupling. The movements of our eyes are inherently coupled, such that guiding one eye will result in similar movements in the other. This characteristic has been used in the past to computationally control the rotation of an eye undergoing retinal imaging. In my case, this phenomenon creates the possibility of establishing a new dynamic baseline from which to measure electroretinography signals.

The greatest signal artifact associated with the use of skin electrodes for electroretinography are associated with eye movements. This is because of the fact that in this method, unlike with the

47 Lawson et al., “Computational Retinal Imaging via Binocular Coupling and Indirect Illumination.”
contact lens corneal electrode, when the eye moves it changes its orientation relative to the electrode. With the cornea like a positive terminal on a battery, the distance between the cornea and the point on the lower lid where the electrode is affixed is like a resistor and its impedance is proportional to the distance. As the eye moves and the impedance changes, the resultant artifacts are several orders of magnitude larger than the signals of interest. When measuring the electroretinogram from a single eye, even slight eye movements create large artifacts and blinks completely saturate the amplifiers, requiring several seconds for the circuitry to return to a steady state.

But when these signal artifacts occur, they occur in both eyes. If we measure the signals emitted from both eyes and examine the difference between them, we have effectively cancelled the contribution due to the eye movements.

It is possible to perform this difference signal processing entirely digitally, collecting two entirely separate electroretinograms from each eye concurrently and then taking the difference in post processing. This method remains sufficient as long as the analog circuitry does not saturate. Once the circuit saturates, it’s no longer possible to separate out the difference signal and that information is lost. In the analog filtering and amplification pipeline (described in more detail later in the implementation section), the potential for saturation occurs in the two stages which incorporate some gain - in the instrumentation amplifier at the input and the final gain stage before arriving at the analog to digital converter (ADC). It is possible to implement this difference signaling in analog circuitry before it even reaches the final gain stage. In this method the artifacts which are common to two eyes, and are responsible for saturating the amplifiers in the traditional system, are eliminated before the signal reaches the amplifier. To my knowledge this is the first description of this method.

The purpose of this thesis, to demonstrate the possibility of an optimized interface for visual electrophysiology, is served just as well by an implementation of the standard methodologies. For this reason I have implemented the standard single-eye measurement method for the capture of the results presented here. The implementation of the difference signaling technique will be part of future work.
5  METHODOLOGIES

What follows is a description of the methodologies implemented in the administration and evaluation of the full-field flash ERG.

5.1  FLASH ERG

A broad overview of the steps in administering the test follows.

Preparation

- The user is given a description of the test to inform them of what to expect. In clinical applications, a technician would deliver this orally; in consumer applications this information would be contained in an informational or instructional booklet.

- The specific test is selected from the software interface.

- The user is situated in a comfortable stance, either sitting upright in a comfortable chair or reclined against a high backed chair or headrest. This will minimize slight movements which can disrupt the sensitive circuitry during the test.

- The goggles are fitted to the user: the user puts on the pair of goggles and makes minor adjustments to ensure comfort and good contact of the electrodes.

- When the user is ready the test begins. In a clinical setting, a technician would initiate the test, either via the computer or phone interface or physical buttons on the device. In consumer settings, the user would press a physical button on the goggles which is easy to access, given the user’s vision is already obstructed by the goggles.

- A 30 second period of rest precedes all tests - this gives the user time to relax their muscles, take deep breaths, and blink as much as they want. Audio instruction will indicate the start of this period and its duration, guiding the user. During this period, there is no illumination within the goggles. Once this period is complete, the adaptation-flash-adaptation cycle begins for the specific test.

Baseline Testing: standardized full-field flash, maximal response (now known as dark-adapted 3.0)
This test is a standard, ground truth test which establishes a baseline for each individual. It is performed according to the standard for full-field electroretinography as established by the ISCEV.

- The user is adapted to darkness for 20 minutes, including the period of rest.
- After the adaptation period, a 5ms 3.0 cd s m\(^{-2}\) flash illuminates the field.
- This flash is repeated in 10s intervals until five usable responses are achieved. The software performs thresholding on the responses to assess whether they are free from significant artifacts, and then adjusts the number of remaining tests to perform accordingly. The maximum number of flashes the system will administer is twenty (20).

**Snapshot Testing: evaluation of current state**

This test is intended to provide a snapshot of the current adapted state of the retina as compared to the baseline established in the maximal response test.

- The user is adapted to darkness for 30 seconds in addition to the period of rest.
- After the adaptation period, a 5ms 3.0 cd s m\(^{-2}\) flash illuminates the field.
- The flash is repeated in 10s intervals until five usable responses are achieved with a maximum number of twenty (20) flashes.

### 5.1.1 Signal Processing

After the responses from each of the testing scenarios is collected, the following post-processing steps are performed to clean the data and calculate the metrics of interest. First the individual responses are aligned with respect to the onset of the stimulus and averaged. The next step is concerned with evaluating some essential metrics about the waveforms from the data. The metrics include:

- a-wave amplitude, measured from signal baseline to a-wave trough (aA);
- a-wave implicit time, measured from stimulus onset to a-wave trough (aI);
- b-wave amplitude, measured from signal baseline to b-wave peak (bA);
- and b-wave implicit time, measured from stimulus onset to b-wave peak (bI).
This averaged response is first detrended. The b-wave peak is defined as the local maximum in the window of 200 ms past the onset of the flash. The a-wave trough is defined as the local minimum between the b-wave peak and the onset of the stimulus. The waveform amplitude and implicit time are then defined as the difference between the b- and a-wave amplitudes and implicit times respectively.

\[
\text{Signal amplitude: } bA - aA, \\
\text{Signal implicit time: } bI - aI
\]

As a measure of signal quality, the signal to noise ratio (SNR) was calculated based on the resultant averaged signal. This was implemented using the MATLAB function `snr`, which calculates the SNR using the sampling frequency of the data and a default window.

5.2 EVALUATION

Beyond the bare efficacy of the system, I wanted to explore some concrete assessments which could support claims of ease of use. The robustness of the device boils down to its sensitivity (or lack thereof) to changes in everything except what it’s intended to measure. The most direct measure of this is repeatability, or the amount of variation in tests administered in the same individual. It is established and expected that electroretinogram waveforms cannot generally be compared from one testing center to another\textsuperscript{48} but instead each laboratory establishes its own set of normative values. Thus, my goal was not to compare my system directly with a gold standard, but to instead evaluate its consistency under different controlled conditions.

Both the snapshot and baseline tests were assessed for repeatability. The baseline test was performed three (n = 3) times in succession and the snapshot test was performed five (n = 5) times in succession, each on a single individual (AO). The coefficients of variation were calculated for the amplitude, implicit time, and SNR metrics of each test. As discussed previously, comparisons between individuals are not useful for determining robustness or consistency, as there is much expected variation amongst individuals. Future work will include the administration of the test in multiple individuals to assess the repeatability within each individual.

\textsuperscript{48} Jacobi, Miliczek, and Zrenner, “Experiences with the International Standard for Clinical Electroretinography.”
6 IMPLEMENTATION

As described earlier, there are broadly three elements to the implementation of a visual electrophysiology system: signal capture, stimulus delivery and timing and synchronization. The following sections describe the exact characteristics implemented in the device used to obtain the results.

![Image of the complete system](image.png)

*Figure 11. Image of the complete system. This implementation includes an elastic band which securely positions the glasses against the face. Not shown: USB cable to connect control circuitry to the laptop computer.*

6.1 SIGNAL CAPTURE

6.1.1 Electrodes

In this system, I used industry standard gold cast disc electrodes. Traditionally, the electrodes are filled with conductive gel, such as Ten20 neurodiagnostic electrode paste, and are taped to the skin. In the experiments I have conducted throughout the course of my thesis, I have used...
the same standard Ten20 conductive gel. However, in future work, I will implement a permanent conductive silicon rubber in the cup of the cast disc electrode which can easily be sterilized from individual to individual and no longer requires the use of a consumable, such as the gel.

The effective impedance of the electrodes, with conductive gel, averaged 18 Ohms and did not exceed 20 Ohms.

6.1.2 Circuitry

Electroretinogram signals are typically within a range of 100-200 microvolts peak to peak. To ensure adequate sensitivity to these signals, the circuitry was tunable to a resolution of around 252 nanovolts. This is accomplished via two separate gain stages in addition to filter stages to eliminate unwanted noise.

As is standard in electrophysiology systems, an instrumentation amplifier is used as the first stage to capture the minute differences between the positive electrode, placed closest to the center of the eye and the strongest point of the dipole along the optical axis, and the negative electrode, placed on the ipsilateral outer canthus near to the eye, where the response of the retina has minimal effect. The reference node of this amplifier connects the reference node of the entire circuitry to a point of average electrical activity on the body (in this implementation, in between the eye brows). This allows the filters to eliminate unwanted signal components with respect to the body’s baseline.

Figure 12. Circuit block diagram for standard ERG approach. The stages are as follows: A D620 instrumentation amplifier, 30 Hz Sallen Key Butterworth low pass filter, 0.3 Hz Sallen Key Butterworth high pass filter, non-inverting amplifier.

Figure 13. Circuit block diagram for difference signaling approach. The stages are as follows: A D620 instrumentation amplifier for right eye signals and A D620 instrumentation amplifier for left eye signals, A D620 instrumentation amplifier to combine left and right eye signals, 30 Hz Sallen Key Butterworth low pass filter, 0.3 Hz Sallen Key Butterworth high pass filter, non-inverting amplifier.
In the case of future implementations of difference signaling, the positive and negative points of each eye are sampled, while a single reference electrode is sampled from the forehead. Two separate instrumentation amplifier stages (Left and Right) accept the inputs from each eye. The gain of these two stages is coupled and modulated by a potentiometer. The output of the Left and Right instrumentation amplifiers is then funneled into a second instrumentation amplifier stage where the common mode between the two signals is rejected. This gain is also modulated by a potentiometer. Of the total gain affected in these first two stages, the majority comes from the second amplifier. At this point the difference signal then undergoes traditional filtering and amplification. When switching from testing the left or right eye, the signal need just be inverted in the post processing.

The ISCEV standards indicate the following three requirements for circuitry to sense ERG signals: (1) that the range of signals amplified should be within at least 0.3 and 300 Hz; (2) the input impedance of the amplifiers should be at least $10^6 \Omega$; and (3) that the amplifiers should be AC coupled.

In this filter circuit implementation, I selected two cascaded second-order Butterworth filters in the Sallen-Key topology. The two-pole filters provide $-12$dB attenuation in the stop band. The Sallen Key approach is essentially a passive filter stage coupled with a unity gain voltage follower, a simple yet effective topology with practically infinite input impedance in accordance with the Standard.

The first filter stage is a low pass filter with a cutoff of 30Hz. I selected a lower cutoff than the recommendations of the standard to accommodate the smaller subset of tests I intended to perform, and also to deliver better performance given the lower quality signals captured while using skin electrodes. Improving the usability by using skin electrodes as opposed to corneal electrodes also makes this system far more susceptible to noise due to the main lines alternating at 60Hz. By reducing the cutoff frequency to 30Hz, I reduced this effect while still ensuring that I am capable of effectively amplifying the signals of interest, given the clinically relevant tests I have chosen to perform. It is trivial to implement a separate circuit channel that may be selected to sense signals in higher frequency bands, such as the $> 100$ Hz oscillatory potentials which are highly susceptible to early diabetic retinopathy.

The second filter stage is a high pass filter with a cutoff of 0.3Hz as indicated by the Standard. This stage is exceptionally necessary, as there are several elements of the sensing system which contribute some DC offset which, if not eliminated, is also amplified in the final stage and shoots
the signal level way off the charts of the analog to digital converter. This also accomplishes the requirement of eliminating the DC bias and AC coupling the circuit.

After filtering out unwanted signals, an additional gain is added to the system via a non-inverting amplifier with programmable gain.

Total gain, $G$:

- $G_1 \times G_2 \times G_3$, for the difference signaling application
- $G_2 \times G_3$, for the singular signaling application

$G_1 = \frac{49,400}{R_{g1}} + 1$, $G_2 = \frac{49,400}{R_{g2}} + 1$, $G_3 = \frac{100,000}{R_2} + 1$

The gain for the instrumentation amplifier stage(s) are as indicated in the data sheet for the Analog Devices AD620 model used in this prototype\(^{49}\). The resistor values used in the capture of the data presented in this thesis are:

$R_{g2} = 2080 \Omega$, $R_2 = 128 \Omega$

$G = \left(\frac{49400}{2080} + 1\right) \times \left(\frac{100000}{128} + 1\right) = 19360.6875$

The output of the filter and amplification stages is fed into the analog to digital converter (ADC) module of an Arduino microcontroller. This is a 10-bit ADC and with a default reference of 5V, which according to the resistor values listed above means that the ADC can resolve changes in the signal as small as 252 nanovolts and measure a signal range of 258 µV. An Arduino was selected for its size, ease of use, low cost, and ease of procurement.

The entire circuit is unipolar, with the low voltage level at 0V and high voltage value at 5V. Both of these levels are provided by the power pins on the Arduino, which is the sole power source in the circuit. This in part reduces the chance that ground loops will occur between different power sources. A reference line at 2.5 V is injected into the system via a voltage divider between the 5V and 0V lines coupled with a voltage follower to provide a stable reference. All of the operational amplifiers which support the filters and amplifiers are powered by 0-5V while all the filters reference the 2.5V line. This implementation was chosen in part due to the fact that the Arduino ADC has a maximum range of 0V to 5V. The reference electrode connected the human body is then connected directly to the 2.5V reference, creating an output in which

\(^{49}\) “Low Cost Instrumentation Amplifier.”

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voltages over 2.5V correspond to positive signals, and voltages less than 2.5V correspond to negative signals.

6.1.3 Digital Acquisition

Any digital signal filtering required was performed on an Intel Core i5-2435M CPU at 2.40 GHz, in 64-bit MATLAB R2014a in Windows 8.1. To capture the output of the analog circuitry, the Arduino microcontroller was interfaced directly to the MATLAB environment via a virtual serial port and the MATLAB Instrument Control Toolbox. A call and response routine was executed to capture the data which involved the following high level steps:

1. The MATLAB script defines the sampling duration time.
2. A serial connection is established between the Arduino and the MATLAB environment.
3. The MATLAB script sends to the Arduino the sampling duration in milliseconds.
4. Upon receiving the number, the Arduino loops for the designated duration, each time polling the ADC for the output of the analog circuit and writing that value to the serial port.
5. The MATLAB script waits until the Arduino is finished sending samples, at which point it reads in the values.

Regardless of the value the buffer size is set to, it will max out at 25,000 bytes, but this does not effectively mean that the serial buffer is dropping bytes. A read call to the serial port will clear the buffer and the remaining samples waiting will fill it again. This process, of allowing the buffer to fill to 25,000 bytes and then emptying it, can be repeated indefinitely as far as I have been able to determine.

It is possible to choose a smaller buffer and pole the Arduino to fill that buffer repeatedly, to achieve a more continuous monitoring effect. However, the result is a noise in the signal which appears to be caused by an artifact of the sampling method: decay in the signal occurs at the beginning of each buffer before the signal starts to level out. This decay manifests as a jagged noise in the signal, with peaks at the beginning of each buffer.

For continuous monitoring, then, a single sample buffer is used, which prevents this decay from affecting the overall signal waveform, but results in a much slower sampling rate. It is possible...

50 Full code included in appendices.
that, since the Arduino is responsible for powering the entire analog circuitry, when the computational activity increases, as the Arduino begins sampling its ADC instead of mindlessly looping, that this causes some drop or fluctuation in the power line. Artifacts like these are some of the drawbacks of utilizing a system like the Arduino microcontroller. As for the ultimate impacts this effect may have on the utility of the captured signals, the evaluation of electroretinogram signals is ultimately relative: peak to peak voltage and timing. An effect such as a DC offset will ultimately have little effect on the accuracy of those assessments and any decay at the beginning of sampling can be avoided by rejecting a number of samples at the beginning of the buffer.

6.1.4 Calibration

To test the functionality of the system, several test signals were generated and then fed into the circuitry. There were several characteristics of the system which were important to evaluate: first, the efficacy of the filters at attenuating signals in the stop band; second, the accuracy of the amplifier given a known signal; and third, the effective sampling rate of the system.

Amplification and Filtering

For the first two tests, a test input was generated to feed into the analog circuitry. This input consisted of an audio tone, created in Audacity 2.0.3 and output via the Microsoft Realtek High Definition Audio sound card. To create a unipolar signal from the bipolar audio, this output from the computer was combined via a summing amplifier with a 2.5V reference. Once the signal was offset, it was then sent through a voltage divider which divided the voltage by a factor of 7937, with a resultant sinusoidal peak to peak voltage of 377 microvolts. Three frequencies were tested: 15Hz, 60Hz, and 1000Hz, to evaluate the efficacy of the filter stages. The analog circuitry showed expected amplification of the 15 Hz signal, approximately 60% attenuation of the amplified 60 Hz signal and a greater than 95% attenuation of the amplified 1000 Hz signal.

Sampling Rate

For the third test, the electrodes were affixed in their standard configuration. A single capture window was recorded while the test subject also held between the forefingers and thumbs of their right and left hand the positive and negative leads (respectively) of the audio output from the computer while a 2Hz tone was generated by Audacity. This waveform dominates all other signals and is clearly received by the analog circuitry at the eyes. As a capture window is received, the number of samples per period of the 2Hz tone waveform is calculated, indicating the effective sampling rate of the capture system.
This calibration step was performed successively to assess if there was any variation in the calculated sample rate. For the measured sampling rate of 6903 samples/second, the measured rate varied approximately +/- 2 samples. A possible cause of this variability is the resolution of the ADC as it discretizes the signal – the algorithm which measures the number of samples per 2Hz cycle searches in the waveform for a specific point which repeats, and then calculates the number of samples between those repeated points. I chose a low frequency waveform for calibration to achieve (1) enough samples per period to be within several factors of the Nyquist frequency and (2) enough periods per capture window to be able to perform several samples/period calculations to observe any variability of this value within a single capture window. Even though the ADC is heavily sampling the 2Hz waveform, as it is discretizing the signal it may not capture the exact same point in each period of the waveform. This is largely the cause of any variability in the estimation of the sampling rate.

In this document, when I discuss “sampling rate,” I am referring to the resultant rate, which is a function of how long it takes the Arduino to execute the commands necessary to sample and send the ADC readings, limited both by the actual sampling rate of the ADC and the baud rate of the serial communication. This resultant rate is thus obviously highly dependent on the architecture of the Arduino program. There are of course some issues with indirectly measuring the sampling rate, such a critical aspect of the system. I ultimately chose this method of calibration for two reasons. First, while the clock speed of the Arduino chip is known, the actual assembly executions which are derived from the high level programming language are somewhat obfuscated. So calculating the delay between calls to the ADC for its value is difficult. Secondly, I wanted to employ a method of calculating the sampling rate which did not in effect alter the sampling rate as it measured it. For example, it is possible for the Arduino chip to send a time stamp along with the ADC measurement via the serial port. However, aside from the time required to execute that function, this value is an unsigned long value – this added to the integer value from the ADC increases the number of total bytes transmitted per sample fivefold, obviously drastically altering the total number of samples it is possible to capture and send in a single time window. Ultimately, given the relatively small variation in the measured sampling rate in this method, I was satisfied with this evaluation and confident of its accuracy in the scope of the frequency characteristics of the signals of interest.

6.2 STIMULUS DELIVERY

The stimulus is delivered by a model YSH-FRGBB-IA high power InGaN RGB LED from Young Sun LED Technology CO. LTD. The three LED channels were driven by a constant current supply at 350 mA and their intensity was modulated by a pulse-width modulated signal from the Arduino then smoothed out to an analog voltage. The Standard defines a full-field flash as
having a duration no longer than 5 ms, a calibrated color temperature of 7000 K, a flash strength of 3.0 cd s m\(^{-2}\) (a measurement of time-integrated luminance) with a tolerance of ±10% (0.05 log unit).  

6.2.1 Field

The entire field of vision is stimulated. This is accomplished via the eye dome described previously. The uniformity of this field was calibrated with a combination of modulating the distance between the LED and the dome, and the dimensioned thickness of the plastic.

6.2.2 Intensity

The stimulus intensity was calibrated to 3.0 cd s m\(^{-2}\) in accordance with the Standard. A silicon photodiode sensitive to 350-1100 nm with a 10 ns rise and fall time and 13 mm\(^2\) area was used to measure the optical power over a given area emitted by the stimulus. This was then converted to photopic luminance units in accordance with the CIE standard observer and then integrated over time to arrive at time-integrated luminance.

Retinal Illuminance

While the intensity of the stimulus may be accurately calibrated in terms of its power, ultimately we are attempting to calibrate the amount of light reaching the retina. This is subject, primarily, to changes in pupil diameter. Retinal illuminance, measured in Trolands, converts standard illuminance into a measure of the amount of light reaching the retina as a function of the pupil diameter. The Standard does not specify the need to incorporate a calculation of retinal illuminance into the calibration of visual electrophysiology systems and in this prototype I have not implemented such a feature. However, for increased clinical relevance and specificity, monitoring pupil diameter via an IR camera system is a possible addition to the system. The incorporation of a camera can also be utilized to monitor gaze – this feature would make possible the integration of algorithms to (1) automatically reject data which is polluted by eye movements or (2) calculate the exact position of stimulus arriving at the fundus.

6.2.3 Wavelength

The spectrum emitted by the stimulus was calibrated with a Hamamatsu model C11351 Mini-spectrometer. From this the calibrated color temperature was calculated and set to 7000 K.

6.3 TIMING & SYNCHRONIZATION

To achieve accurate timing and synchronization of the capture and stimulus portions of the system, the digital control code implemented in MATLAB defined the millisecond duration of aspects of the test and the Arduino microcontroller implemented these durations. The implementation of this, in pseudo code, is as follows:

1. MATLAB sets the parameters for testing: the capture window duration, the onset time of the stimulus and the stimulus duration, in milliseconds.

2. The MATLAB code then transmits these parameters serially to the Arduino microcontroller.

3. Upon receipt of the parameters, the Arduino begins capture. The timing is executed by using the built-in function `millis` in the Arduino programming language, which counts the number of milliseconds since the program began, to decide how long to loop while sending ADC signals before turning on the stimulus, how long to loop while the stimulus is on, and how long to loop while the stimulus is off. This sequence is as follows:

   **PRE-STIMULUS WINDOW**
   a. the LEDs are set to their adapting state
   b. the timing variables for the pre-stimulus window are initialized
   c. the capture-and-send loop begins and loops until the window is completed

   **STIMULUS WINDOW**
   d. the LEDs are set to their stimulus state
   e. the timing variables for the stimulus duration are initialized
   f. the stimulus ping (a HIGH-LOW fluctuation in the data) is transmitted
   g. the capture-and-send loop begins and loops until the window is completed

   **POST-STIMULUS WINDOW**

---

52 Full code included in appendices.

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h. the LEDs are set to their adapting state
i. the stimulus ping is transmitted
j. the timing variables for the post-stimulus window are initialized
k. the capture-and-send loop begins and loops until the window is completed.

4. On the other side, the MATLAB code empties the serial buffer until there are no more remaining samples to be received and stores this data.

Pinpointing the exact onset and offset of the stimulus was also crucial. To accomplish this, the Arduino sends a characteristic ping over the serial connection before turning on the stimulus and after turning it off. This ping can then be removed from the data digitally in the MATLAB code and gives a very clear indication of the onset and offset of the stimulus.

**Drawbacks**

By far the most subtle and challenging aspect of a visual electrophysiology system is the timing. Without a robust system to establish the timing relationship between the stimulus and the measured response, the utility of the data is questionable. Establishing this timing relationship is challenging, but there is some saving grace in the fact that it is ultimately a relative measurement.

My method integrates the stimulus delivery and signal capture into a single controller. This provides the advantage of not requiring the synchronization of two separate controllers, each with their own timing system. However the key drawback with this method is that the implemented code is inherently sequential. What this practically means is that it can't do more than one thing at a time. To implement this method effectively, then, it is crucial to choose a code sequence which is consistent and organized.

There are three key opposing tasks which in an ideal world should happen simultaneously but in a sequential method needed to be managed:

1. measuring the signal,
2. turning on and off the LEDs, and
3. measuring time.

The most important characteristic of the system is the consistency with which the signal is sampled. To achieve this, the code must be designed such that the number of tasks which the
microcontroller must perform in between each call to the ADC must be as consistent as possible. The code I have written is optimized for this, with one key drawback – the stimulus ping. As I am sending the ping to indicate the exact onset and offset of the stimulus, I am losing the time it takes to do so, which corresponds to a few microseconds. Future work will focus on the development of a more robust and accurate sampling method.
7 RESULTS

7.1 FLASH ERG

7.1.1 Snapshot Test

Figure 14. Results of “Snapshot” test. Total number of averaged signals n = 5. Circuit resolution tuned to 252 nV. Stimulus onset, offset and duration shown in red, captured signal in blue. A- and b-wave peaks are indicated by red stars.

<table>
<thead>
<tr>
<th>Subject: AC</th>
<th>Amplitude (µV)</th>
<th>Implicit time (ms)</th>
<th>SNR (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29.71</td>
<td>18.69</td>
<td>12.33</td>
</tr>
</tbody>
</table>

Table 2. Metrics of snapshot test on subject AC.

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7.1.2 Baseline Test

Figure 15. Results of snapshot test. Total number of averaged signals $n = 5$. Circuit resolution tuned to $252 \, nV$. Stimulus onset, offset and duration shown in red, captured signal in blue. A-and b-wave peaks are indicated by red stars.

<table>
<thead>
<tr>
<th>Subject: AC</th>
<th>Amplitude (μV)</th>
<th>Implicit time (ms)</th>
<th>SNR (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>109.49</td>
<td>14.92</td>
<td>10.26</td>
</tr>
</tbody>
</table>

Table 3. Metrics of baseline test on subject AC.
7.2 ROBUSTNESS EVALUATION

7.2.1 Snapshot Test

Figure 16. Results of five (n = 5) successive administrations of the snapshot test on subject AC. Above each averaged result are the superimposed individual signals which contributed to the average (in black).
Table 4. Results of the key metrics for each snapshot test: amplitude, implicit time, and SNR. The coefficients of variation for each of these metrics across the five tests are shown in bold.

7.2.2 Baseline Test

Figure 17. Results of three (n = 3) successive administrations of the baseline test. Above each averaged result are the superimposed individual signals which contributed to the average (in black).
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<table>
<thead>
<tr>
<th>Test number</th>
<th>Amplitude (uV)</th>
<th>Implicit Time (ms)</th>
<th>SNR (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72.03</td>
<td>14.63</td>
<td>11.84</td>
</tr>
<tr>
<td>2</td>
<td>109.49</td>
<td>14.92</td>
<td>10.26</td>
</tr>
<tr>
<td>3</td>
<td>88.27</td>
<td>11.73</td>
<td>14.90</td>
</tr>
</tbody>
</table>

| Mean        | 89.93          | 13.76              | 12.33    |
| Coefficient of Variation | 0.21          | 0.13              | 0.19    |

*Table 5. Results of the key metrics for each baseline test: amplitude, implicit time, and SNR. The coefficients of variation for each of these metrics across the three tests are shown in bold.*
DISCUSSION

8.1 SIGNAL QUALITY

The calculated SNR of the majority of the signals is within a reasonable range (10-20 dB). There are a few outliers, but overall this performance is very promising given the susceptibility of this circuitry to mains and environmental noise. In the early stages of the development of this prototype, often it would only output a solid bar of mains noise, or would jump around as a result of moving the device. This data shown here is made more robust in part due to a few key features. Utilization of battery power to source the LEDs instead of an ACDC transformer connected to the mains made a significant difference. Furthermore, reducing the electrode lead length by mounting the circuit directly onto the elastic strap of the glasses greatly reduced the systems susceptibility to environmental noise. Longer leads are more likely to shift with any slight fidgeting and in general act as antennas.

Signal averaging proves to be (as expected) a very effective way of minimizing the contributions of random noise in the signals. As shown in the superimposed raw signals (in black in Figures 16 and 17), individual signals can contain significant noise. It is entirely likely that the noise would be further reduced by averaging more than five raw signals. The key tradeoff in this scenario is that averaging more signals requires more time. Longer tests are less convenient to the user and incorporate a greater chance that the user will shift or blink during the test administration.

8.2 SIGNAL FEATURES

The captured signals demonstrate the essential characteristics of full-field flash ERGs. The snapshot test is most akin to the cone response (light adapted, with a bright flash) while the baseline is an implementation of the combined rod-cone maximal response (dark-adapted, with a bright flash).\(^53\)

The snapshot tests demonstrate the characteristic absent a-wave of cone responses – as well as some more pronounced fluctuations on the ascent of the b-wave. Within the series of snapshot tests were some of the SNR outliers. This is somewhat expected – longer periods of adaptation

\(^53\) See Figure 4 for the characteristic waveforms for each of these tests.

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serve to stabilize the retina as well as the capture system, and without them the data is more susceptible to circumstantial noise.

The baseline tests exhibit the characteristic sharp a-wave trough of dark-adapted combined responses and larger amplitudes. The SNR of the baseline tests is also more consistent, which follows based on the reasoning described above.

8.3 SIGNAL REPEATABILITY

In assessing the repeatability of this system, it became apparent that some metrics are more robust than others. In both the baseline and snapshot tests, the most consistent metric was implicit time, with coefficients of variation (CoV) of 0.13 and 0.05 respectively. Though the baseline tests exhibit twice the variability in implicit time as the snapshot tests, this is likely entirely due to the difference in number of tests, n (three vs. five). I anticipate that increasing the number of baseline tests performed will further drop the CoV.

There was far more variability seen in the amplitudes, though that amount of variation was approximately the same for the baseline and snapshot tests (0.21 and 0.19 respectively). I would have guessed that there would in fact be far more variation in such a metric in the snapshot test, as the baseline test incorporates more protocol to stabilize the system. These equivalent variations could be explained by a number of factors. The time of day of each test may have played a roll – the subset of baseline tests were taken midday, while the snapshot tests were taken at night. Further sources of inter-session variability could include minute changes in posture, eye fatigue over time, or the presence of auditory distractions which may lead to involuntary eye movements.

The most disconcerting metric, in terms of its variability, is SNR. It is fairly consistent in the baseline test (CoV = 0.19), but is highly inconsistent in the snapshot test (0.70). It is possible that the method I have chosen for calculating the SNR, using the built in function in MATLAB, may not adequately capture the essence of the signal to noise ratio in this data. Visual inspection of snapshot tests two and five do not clearly demonstrate a significant variation in SNR, yet the calculated metric is an order of magnitude different (2.30 vs. 25.99 respectively). Further investigation of better methods of establishing signal quality may yield more consistency.

These measurements of variability may seem high – they indicate around 20% of variation within a data set – other measurements of variability within traditional ERG systems grant some perspective.
Figure 18. Box plots of key metrics: amplitude, implicit time, and SNR for baseline (n = 3) and snapshot (n = 5) tests. The central mark is the median, the boxes include the 25th and 75th percentiles, and the whiskers extend to the most extreme data points.

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In assessing the variability of a particular metric called the photopic negative response (PhNR), Mortlock et al found that coefficients of variation of A-wave and B-wave amplitudes using skin electrodes in 31 subjects were 0.44 and 0.29 respectively. What is even more comforting is the fact that their measurement of PhNR implicit time showed a similarly small CoV (0.06), which implies to an extent that there is less variability in the temporal characteristics of ERG signals, which my data also demonstrates. Jacobi et. al also demonstrate similar levels of variability in the photopic and scotopic ERG, further noting that the variability increases noticeably with stimulus intensity.

Given the scope of potential levels of variability, the preliminary results here are exciting. Not only does the system function in its most essential tasks but it does so consistently. By showing this, we have put forth the possibility of many unprecedented application for visual electrophysiology.

\[54\] Mortlock et al., “Inter-Subject, Inter-Ocular and Inter-Session Repeatability of the Photopic Negative Response of the Electroretinogram Recorded Using DTL and Skin Electrodes.”

\[55\] Jacobi, Miliczek, and Zrenner, “Experiences with the International Standard for Clinical Electroretinography.”

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AND BEYOND: POTENTIAL SYSTEMS AND APPLICATIONS

Given the consistency that can be achieved in such a preliminary prototype as the one I have presented here in this thesis, the possibilities of what can be accomplished after future work of optimization and improved design are of keen interest. What excites me most falls within the realm of characterizing our experience of color. The goal is not to identify true red – our identification of individual colors is as much a function of association and perception as wavelength. Instead, I am very interested to explore what impact modulating the relationships between the three color channels has on our experience of color temperature, hue, and contrast.

9.1 INDIVIDUAL PHOTOPIC LUMINOUS EFFICIENCY

The majority of variation in cone mosaics in the retina is within the L:M ratio (long-wavelength sensitive cones to medium wavelength sensitive cones), as the distributions of short-wavelength sensitive cones is almost identical across individuals. This test employs electroretinogram flicker photometry to estimate the L:M cone ratio as demonstrated in. For a full explanation of this method, see Appendix A. The tests are performed at 30 Hz to ensure the isolation of cone response. This test can yield each individuals photopic luminous efficiency - a measure of how well we convert light power into the signals which are transmitted to the brain. The CIE publishes a standard for this, which is an average across a population - but given the documented variability in L:M cone ratios, it follows that this variability will be translated to an individual’s photopic luminous efficiency. Furthermore, given the amount that an individual's own retina's metabolism changes and adapts to the environment, a snapshot of this can provide information on the state of that metabolism. This information can be utilized in a number of interesting ways.

9.1.1 Tailored Media

By measuring an individual’s sensitivity to different visual cues with ERG, we can create tailored media which activate the most sensitive parts of our unique experience of vision. Our displays

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56 Hofer et al., “Organization of the Human Trichromatic Cone Mosaic.”

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can be tailored not only to our baseline of luminous efficiency, but can also be updated with information from a snapshot test at different points throughout the day. Different displays can then be modulated depending on the task at hand (reading text, watching movies, etc.) given the current state of the retina. Further electroretinogram tests which evaluate sensitivity to contrast (such as the pattern ERG), can be implemented in future devices to add a further dimensionality to the assessment of retinal state.

**Gaming**

The human eye will exhibit different responses to flash stimulus after exposure to different amounts and types of ambient stimulus. In gaming, an attenuated response to a flash stimulus could indicate reduced visual sensitivity, providing feedback to the user that they should rest their eyes, or change their distance from the screen. More specific tests can lend further information as to a user’s current sensitivity to visual cues, such as chromatic and achromatic contrast. These specific tests can be designed based on the types of stimuli present in specific game environments, and optimized to test the types of responsivity that are crucial to a heightened response to the environment. Users can detect how their responsivity is changing over time and the displays can then modulate to activate that changing responsivity. Gamers can improve their response to the game environments or sustain their heightened response over longer periods of time than previously attainable.

**Remote piloting**

That same display modulation to individual responsivity can have interesting applications beyond gaming. In situations of prolonged exposure to, and interaction with, video such as remote piloting, there are significant advantages to modulating displays to accommodate to the visual systems adaptation or reduction in sensitivity to the visual input. One potential advantage that this method can provide is the extension of the amount of time an individual can effectively respond to the visual stimulus. This advantage can reduce the number of people required to administer remote piloting systems over long periods of time, greatly reducing the cost of such systems.
10 CONCLUSIONS

The electrophysiology of vision is at once an obscure and elusive thing, but its intrinsic linkage to our perception and experience is fascinating and possesses great potential. The mechanics of vision are as unique to an individual as their fingerprint but we have yet to tap into that knowledge. What has been obfuscated is increasingly coming to light, ushered by smaller, cheaper, easier tools and a growing sense of self in a greater populace.

What made electroretinography stand out and stick through the process of vetting via workshops and meetings was not just this sense of untapped wonder, but rather the fact that it has relevance that extends beyond the niche market it has occupied, and further still beyond a niche market of quantified self users or gamers. Visual electrophysiology remains the only objective measurement of visual function and unlocking this potential has staggering implications for eye care access globally.

By completely rethinking the way this information is tapped, I have presented here something which is just the beginning of a radical change in this field. Truly, if a single graduate student can alone design, build, and program a tool to conduct visual electrophysiology in a consistent, optimized way, then imagine what can come next.
REFERENCES


References


Figure 19. Schematic of system for signal capture and stimulus delivery (excluding LED module and driver).
Generated using Eagle 6.5.0.
Figure 20. PicoBuck LED Driver schematic of unit obtained from Sparkfun Electronics.

APPENDIX B: CODE

munsell.m : MATLAB code for the creation of the Figure 1.

% MUNSELL COLOR REPRESENTATION GENERATOR
% AMY CANHAM | APRIL 2014
%
% Creates six sided patches at different locations in the Munsell color
% space

% Set parameter limits
hMin = 0; hStep = 10; hMax = 360; % hue
sMin = 0.2; sStep = 0.05; sMax = 1; % saturation
vMin = 0.4; vStep = 0.05; vMax = 1; % value

% Generate complete vectors
hVec = hMin:hStep:(hMax-hStep);
sVec = sMin:sStep:(sMax-sStep);
vVec = vMin:vStep:(vMax-vStep);

% Initialize figure
figure(1); set(gcf,'Color',[1 1 1]); clf; hold on

% Define faces by their vertices
faces = [1 2 3 4; 3 4 8 7; 5 6 8 7; 1 2 6 5; 1 3 7 5; 2 4 8 6];

for v = vVec(1:2:end) % from the top to the bottom
    for s = sVec(1:2:floor(end/2)) % from the center outwards
        for h = hVec(1:2:end) % from 0 degrees, in a circle
            % VERTICES: Use the hsv values to define the cylindrical
            coordinates
                phi = [h       h+hStep h       h+hStep h       h+hStep h
                       h+hStep];
                rho = [s       s       s+sStep s+sStep s       s
                       s+sStep s+sStep];
                z   = [v       v       v       v       v+vStep v+vStep
                       v+vStep v+vStep];
            % Convert to polar coordinates
                x = rho.*cosd(phi);
                y = rho.*sind(phi);
            % Define the struct variable for the patch function
                block.Vertices = [x' y' z'];
                block.Faces = faces;
                myHSV = hsv2rgb([h/360 s v]);
                patch(block,'FaceColor',myHSV,'EdgeColor',hsv2rgb([h/360 1
                       v]),'MarkerFaceColor','none',...
                       'MarkerEdgeColor','none')
        end
    end

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%Randomize the blocks at the edges
dock = numel(hVec)/floor(numel(sVec)/2);
i = 0;
for s = sVec(floor(end/2):end)
i = i+1;
    for h = hVec(unique(randi(numel(hVec), [1 (randi(numel(hVec))-i*dock)]))
        phi = [h       h+hStep h       h+hStep h       h+hStep h
h+hStep];
        rho = [s       s       s+sStep s+sStep s       s
s+sStep s+sStep];
        z   = [v       v       v       v       v+vStep v+vStep
v+vStep v+vStep];
        x = rho.*cosd(phi);
        y = rho.*sind(phi);
        block.Vertices = [x' y' z'];
        block.Faces = faces;
        myHSV = hsv2rgb([h/360 s v]);
        patch(block, 'FaceColor', myHSV, 'EdgeColor', hsv2rgb([h/360 1
v]), 'MarkerFaceColor', 'none', 'MarkerEdgeColor', 'none')
    end
end
end

set(gca, 'View', [45 28])
axis equal
axis off

flashERG.m: MATLAB code to control the stimulus delivery and data capture

%% Corresponding Arduino Code
% // ERG STIMULATE AND CAPTURE CODE
% #define RED 11
% #define GREEN 9
% #define BLUE 10
%
% int rgbFLASH[3], rgbADAPT[3];
% int window, start, flash, i, raw;
% char window_lowByte, window_highByte, start_lowByte, start_highByte,
flash_lowByte, flash_highByte;
% unsigned long t0, t1;
%
% void setup() {
%   //initialize LED
%   analogWrite(REDFD, 0);
%   analogWrite(GREEND, 0);
%   analogWrite(BLUED, 0);
%   //initialize serial
%   Serial.begin(115200);
%   while (!Serial) {}}
%   //defaults
% rgbADAPT[0] = 0;
% rgbADAPT[1] = 0;
% rgbADAPT[2] = 0;
%
% rgbFLASH[0] = 127;
% rgbFLASH[1] = 127;
% rgbFLASH[2] = 127;
%
window = 20000;
% start = 5000;
flash = 100;
%
t0 = 0;
t1 = 0;
%
} 

% void loop() {
%   //If we've received a full instruction of 12 bytes
%   if (Serial.available() == 12) {
%     // Receive window time
%     window_lowByte = Serial.read();
%     window_highByte = Serial.read();
%     window = word(window_highByte,window_lowByte);
%     // Receive stimulus start time
%     start_lowByte = Serial.read();
%     start_highByte = Serial.read();
%     start = word(start_highByte,start_lowByte);
%     // Receive flash duration time
%     flash_lowByte = Serial.read();
%     flash_highByte = Serial.read();
%     flash = word(flash_highByte,flash_lowByte);
%     // Receive RGB values for adaption
%     rgbADAPT[0] = Serial.read();
%     rgbADAPT[1] = Serial.read();
%     rgbADAPT[2] = Serial.read();
%     // Receive RGB values for flash
%     rgbFLASH[0] = Serial.read();
%     rgbFLASH[1] = Serial.read();
%     rgbFLASH[2] = Serial.read();
%     // Start capture
%     // set LEDs to ADAPT until we reach start time
%     analogWrite(RED, rgbADAPT[0]);
%     analogWrite(GREEN, rgbADAPT[1]);
%     analogWrite(BLUE, rgbADAPT[2]);
%     t0 = millis();
%     t1 = 0;
%     while (t1<start) {

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Appendix B: Code

raw = analogRead(0);
Serial.write(lowByte(raw));
Serial.write(highByte(raw));
t1 = millis();
t1 = t1-t0;

// set LEDs to FLASH (approx 34 samples at Fs = 6.903 kHz)
Serial.write(lowByte(1024));
Serial.write(highByte(1024));
Serial.write(lowByte(0));
Serial.write(highByte(0));
analogWrite(RED, rgbFLASH[0]);
analogWrite(GREEN, rgbFLASH[1]);
analogWrite(BLUE, rgbFLASH[2]);
t0 = millis();
t1 = 0;
while (t1<flash) {
    raw = analogRead(0);
    Serial.write(lowByte(raw));
    Serial.write(highByte(raw));
t1 = millis();
t1 = t1-t0;
}

// set LEDs to ADAPT for remaining window time
Serial.write(lowByte(1024));
Serial.write(highByte(1024));
Serial.write(lowByte(0));
Serial.write(highByte(0));
analogWrite(RED, rgbADAPT[0]);
analogWrite(GREEN, rgbADAPT[1]);
analogWrite(BLUE, rgbADAPT[2]);
t0 = millis();
t1 = 0;
while (t1<window-(start+flash)) {
    raw = analogRead(0);
    Serial.write(lowByte(raw));
    Serial.write(highByte(raw));
t1 = millis();
t1 = t1-t0;
}
}
else {
analogWrite(RED, 0);
analogWrite(GREEN, 0);
analogWrite(BLUE, 0);
}

% Initialization
if exist('micro','var')
    instrreset
clear micro
clf
Appendix B: Code

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end

% Parameter Definition

%-----------------------------WINDOW-----------------------------
sampleSize = 2; % in bytes
window = 2000;
bufferSize = window*7;
nS_bin = dec2bin(window); % nSamples;
if numel(nS_bin)<16
    padding = repmat('0',1,16-numel(nS_bin));
    nS_bin = [padding nS_bin];
end
nS_lowbyte = nS_bin(9:16); nS_highbyte = nS_bin(1:8);
nS_lowbyte = uint8(bin2dec(nS_lowbyte)); nS_highbyte = uint8(bin2dec(nS_highbyte));

%-----------------------------SAMPLING RATE-----------------------------
Fs = 6903;

%-----------------------------START TIME-----------------------------
start_ms = window/2; % in ms
start = start_ms; % round((start_ms*10^-3)/(1/Fs)); % in samples
start_bin = dec2bin(start);
if numel(start_bin)<16
    padding = repmat('0',1,16-numel(start_bin));
    start_bin = [padding start_bin];
end
start_lowbyte = start_bin(9:16); start_highbyte = start_bin(1:8);
start_lowbyte = uint8(bin2dec(start_lowbyte)); start_highbyte = uint8(bin2dec(start_highbyte));

%-----------------------------FLASH DURATION-----------------------------
flash_ms = 5; % in ms
flash = flash_ms; % round((flash_ms*10^-3)/(1/Fs)); % in samples
flash_bin = dec2bin(flash);
if numel(flash_bin)<16
    padding = repmat('0',1,16-numel(flash_bin));
    flash_bin = [padding flash_bin];
end
flash_lowbyte = flash_bin(9:16); flash_highbyte = flash_bin(1:8);
flash_lowbyte = uint8(bin2dec(flash_lowbyte)); flash_highbyte = uint8(bin2dec(flash_highbyte));

%-----------------------------ADAPTATION RGB VALUES-----------------------------
rgbADAPT = [0 0 0];

%-----------------------------FLASH RGB VALUES-----------------------------
rgbFLASH = [127 127 127];

% Serial Port Setup
info = instrhwinfo('serial');
if ~isempty(info.AvailableSerialPorts)
if ~strcmp(info.AvailableSerialPorts{1},'COM1')
    port = info.AvailableSerialPorts{1};
elseif numel(info.AvailableSerialPorts) > 1
    port = info.AvailableSerialPorts{2};
else
    error('Error: no Arduino serial ports available')
end
else
    error('Error: no Arduino serial ports available')
end

micro = serial(port);
set(micro,'BaudRate',115200);
set(micro, 'InputBufferSize', 50000)
fopen(micro);
pause(2)

ha = actxserver('SAPI.SpVoice');

%% Capture
clc
res = input('New resistor values? (y/n): ','s');
if strcmp(res,'y')||strcmp(res,'Y')
    disp('Enter resistor values:')
    Rg = input('Rg: ');
    R2 = input('R2: ');
elseif ~exist('Rg','var') || ~exist('R2','var')
    Rg = 2080;
    R2 = 128;
end
disp(Rg)
disp(R2)

eye = input('Which eye? (l or r): ','s');

totalCollected = 0;
totalUsable = 0;

i = 0;
data = cell(1);

figure(1); set(gcf,'Color',[1 1 1]); hold on

which = input('Enter 1 for Snapshot, 2 for Baseline: ');
switch which
    case 1
        % ADAPTING
        invoke(ha,'speak','Beginning adaptation for thirty seconds');
pause(30)
    case 2
        % ADAPTING
        invoke(ha,'speak','Beginning adaptation for twenty minutes');
pause(5*60);
invoke(ha,'speak','15 minutes to go');
pause(5*60);
invoke(ha,'speak','10 minutes to go');
pause(5*60);
invoke(ha,'speak','5 minutes to go');
pause(5*60);
end

invoke(ha,'speak','Testing starting in 5');
invoke(ha,'speak','4');
invoke(ha,'speak','3');
invoke(ha,'speak','2');
invoke(ha,'speak','1');
while (totalUsable<5)&&(totalCollected<20)
tic
    if micro.BytesAvailable > 0
        dump = fread(micro, micro.BytesAvailable); % EMPTY BUFFER
        clear dump
    end

    beep
    fwrite(micro,nS_lowbyte); fwrite(micro,nS_highbyte);
    fwrite(micro,start_lowbyte); fwrite(micro,start_highbyte);
    fwrite(micro,flash_lowbyte); fwrite(micro,flash_highbyte);
    fwrite(micro,(rgbADAPT));
    fwrite(micro,(rgbFLASH));
end

done = 0;
newbuff = micro.BytesAvailable;
oldbuff = micro.BytesAvailable;
raw = [];
while done<10
    oldbuff = newbuff;
    newbuff = micro.BytesAvailable;
    if newbuff==oldbuff
        done = done+1;
        if newbuff == 50000
            raw = [raw;
            fread(micro,micro.BytesAvailable/2,'int16')];
        end
    else
        done = 0;
    end
    pause(0.05)
end
raw = [raw; fread(micro,micro.BytesAvailable/2,'int16')];
test = -(raw/1023*5)+5;
outOfRange = (sum(test>=5)-2) + (sum(test<=0)-2);
if ~outOfRange
    i = i+1;
data{i} = test;
totalUsable = totalUsable+1;
figure(1)
plot(data{i}+5*(i-1))
axis([1 numel(data{i}) 0 5*i])
disp([num2str(numel(data{i})) ' data points']);
end
totalCollected = totalCollected + 1;
beep
invoke(ha,'speak',[num2str(totalCollected) ' samples collected. ' num2str(totalUsable) ' are usable.']);
t = toc;
% Ensure that there is at least 10 seconds between flashes
if t<10
    pause(10-t)
end
fclose(micro);
invoke(ha,'speak','Testing complete');
delete(ha);
clear ha;

% Align data sets to stimulus onset
n = numel(data);

st_ind = find(data{1}>=5);
head = st_ind - 50; tail = length(data{i}) - st_ind - 50;

newdata = [];
for i = 1:n
    st = find(data{i}>=5); st = st(1);
    newdata = [newdata data{i}((st - head):(st + tail))];
end

disp([num2str(totalCollected) ' samples collected.']);

% Save data
saving = input('Save file? (y/n): ','s');
if strcmp(saving,'y')||strcmp(saving,'Y')
t = clock;
    filename = ['ERG_' num2str(t(1)) ' - ' num2str(t(2)) ' - ' num2str(t(3)) ' - ' ...
    num2str(t(4)) ' - ' num2str(t(5)) ' - ' num2str(round(t(6))) '.txt'];
    fid = fopen(filename,'w');
    fprintf(fid,'%c eye\n\nMaximal Response Window = %d ms, Start time = %d ms, Flash duration = %d ms\nRg = %d Ohm, R2 = %d ohm\n',...
    window,start,flash,Rg,R2);
    fprintf(fid,'RGB values for Adaptation: ');fprintf(fid,'%d,%d,%d\n',rgbADAPT);
    fprintf(fid,'RGB values for Flash: ');fprintf(fid,'%d,%d,%d\n',rgbFLASH);
Appendix B: Code

Toward Accessible Evaluation of the Electrophysiology of Human Vision

ident = input('Enter identifier string: ','s');
fprintf(fid,'%s
',ident);
fprintf(fid,'Tests collected: %d
',n);
formatstr = [];
for i = 1:n-1
    formatstr = [formatstr '%f, '];
end
formatstr = [formatstr '%f
'];
fprintf(fid,formatstr,newdata');
fclose(fid);
disp(filename)
else
disp('File not saved.')
end

analysis_baseline.m : MATLAB code for generating repeatability analysis of the baseline test

%%% Baseline Analysis
clear

set(0,'DefaultAxesFontName', 'Neuton')
set(0,'DefaultAxesFontSize', 18)
% get file names
files = dir;
dump = [];
for i = 1:length(files)
    if length(files(i).name)<3
        dump = [dump i];
    elseif ~strcmp(files(i).name(1:3),'ERG')
        dump = [dump i];
    end
end
files(dump) = [];

% get data
data(length(files)).samples = [];
stimulus = zeros(length(files),2);

subset = [2 7 8];
SNRs = zeros(size(subset));
As = zeros(size(subset));
ITs = zeros(size(subset));
for i = 1:length(subset)
    fid = fopen(files(subset(i)).name);
    line = [];
    header = [];
    % while we're still reading header lines...
while isempty(line)
    id = fgetl(fid);
    header = [header ', ', id];
    line = str2num(id);
end
%Now we're reading data - the number of elements is the number of
%samples taken
nSamples = numel(line);
formatstr = [repmat('%f, ',1,nSamples-1) '%f
'];
rest = fscanf(fid,formatstr,[nSamples,inf]);
%store 'em
data(i).samples = [line; rest'];
nPts = length(data(i).samples);

% Record location of stimulus
stimulus(i,:) = find(data(i).samples(:,1)>=5)';

% Eliminate stimulus indicators
pip = find(data(i).samples>=4.9)';
dip = find(data(i).samples<=0.1)';
data(i).samples([pip dip]) = [];
nPts = nPts - (numel(pip)+numel(dip))/nSamples;
data(i).samples = reshape(data(i).samples,nPts,nSamples);
data(i).avg = mean(data(i).samples,2);

% Plot
h = figure; clf;
set(h,'Color',[1 1 1]);
subplot(2,1,1)
axis off; hold on;
plot(data(i).samples,'k')
title(['Baseline Test ' num2str(i)])

% Analysis
G1 = 49400/2080 + 1;
G2 = 100000/128 + 1;
G = G1*G2;
Fs = 6903;
samples = detrend(data(i).avg)/G;
st = stimulus(i,1); dur = stimulus(i,2)-st;
t = ((1:length(samples))/Fs)';
%Find b-wave peak between stimulus and 50 mS (~345 samples)
new_window_ind = st:(st+1000);
dummy = samples(new_window_ind);
[bA, bIT_ind] = max(dummy);
bIT = t(bIT_ind)-t(st);
%Find a-wave trough between stimulus and b-wave peak
new_window_ind = st:bIT_ind;
dummy = samples(new_window_ind);
aA, aIT_ind] = min(dummy);
aIT = t(aIT_ind)-t(st);
As(i) = (bA-aA)*1e6;
ITs(i) = (bIT-aIT)*1e3;

%Calculate SNR
SNRs(i) = snr(samples,Fs);

%Plotting
subplot(2,1,2)
hold on
plot(t*1e3,samples*1e6,'b')
plot(t([aIT_ind bIT_ind])*1e3,[aA bA]*1e6,'r*')
plot(t([st st+dur st+dur])*1e3, [-2.5 2.5 2.5 -2.5]/G*1e6,'r')
xlabel('Time (ms)')
ylabel(sprintf('Normalized\nVoltage') ' ( \muV)')
axis([0 500 -100 100])
drawnow;

fclose(fid);

SNR_mean = mean(SNRs);
SNR_std = std(SNRs);
SNR_cov = SNR_std/SNR_mean;
A_mean = mean(As);
A_std = std(As);
A_cov = A_std/A_mean;
IT_mean = mean(ITs);
IT_std = std(ITs);
IT_cov = IT_std/IT_mean;

baseline_outs = [As' ITs' SNRs';A_mean IT_mean SNR_mean;A_cov IT_cov
SNR_cov]

analysis_snapshot.m: MATLAB code for generating repeatability analysis of the snapshot test

 analysis_snapshot.m : MATLAB code for generating repeatability analysis of the snapshot test

 clear
 set(0,'DefaultAxesFontSize',18)
 set(0,'DefaultAxesFontName','Neuton')

 % get file names
 files = dir;
dump = [];
for i = 1:length(files)
if length(files(i).name)<3
dump = [dump i];
elseif ~strcmp(files(i).name(1:3),'ERG')
dump = [dump i];
end

dump = files(dump); % get data

data(length(files)).samples = [];
stimulus = zeros(length(files),2);

subset = 1:length(files);
SNRs = zeros(size(subset));
As = zeros(size(subset));
ITs = zeros(size(subset));
for i = 1:length(subset)
    fid = fopen(files(subset(i)).name);
    line = [];
    header = [];
    % while we're still reading header lines...
    while isempty(line)
        id = fgetl(fid);
        header = [header '; ' id];
        line = str2num(id);
    end
    %Now we're reading data - the number of elements is the number of
    %samples taken
    nSamples = numel(line);
    formatstr = [repmat('%f, ',1,nSamples-1) '%f
'];
    rest = fscanf(fid,formatstr,[nSamples,inf]);
    %store 'em
    data(i).samples = [line; rest'];
    nPts = length(data(i).samples);

    % Record location of stimulus
    stimulus(i,:) = find(data(i).samples(:,1)>=5)';

    % Eliminate stimulus indicators
    pip = find(data(i).samples>=4.9)';
    dip = find(data(i).samples<=0.1)';
    data(i).samples([pip dip]) = [];
    nPts = nPts - (numel(pip)+numel(dip))/nSamples;
    data(i).samples = reshape(data(i).samples,nPts,nSamples);
    data(i).avg = mean(data(i).samples,2);
    st = stimulus(i,1); dur = stimulus(i,2)-st;

    % Plot
    h = figure; clf;
    set(h,'Color',[1 1 1]);
subplot(2,1,1)
axis off; hold on;
plot(data(i).samples(st-1200:st+2000,:), 'k')
title(['Snapshot Test ' num2str(i)])

% Analysis
G1 = 49400/2080 + 1;
G2 = 100000/128 + 1;
G = G1*G2;
Fs = 6903;
samples = detrend(data(i).avg(st-1200:st+2000))/G;
t = ((1:length(samples))/Fs)';
%Find b-wave peak between stimulus and 50 mS (~345 samples)
st = 1200;
new_window_ind = st:(st+1000);
dummy = samples(new_window_ind);
[bA, bIT_ind] = max(dummy);
bIT = t(bIT_ind)-t(st);
%Find a-wave trough between stimulus and b-wave peak
new_window_ind = st:bIT_ind;
dummy = samples(new_window_ind);
[aA, aIT_ind] = min(dummy);
aIT = t(aIT_ind)-t(st);
As(i) = (bA-aA)*1e6;
ITs(i) = (bIT-aIT)*1e3;

%Calculate SNR
SNRs(i) = snr(samples,Fs);

%Plotting
subplot(2,1,2)
hold on
plot(t*1e3,samples*1e6, 'b')
plot(t([aIT_ind bIT_ind])*1e3,[aA bA]*1e6, 'r*')
plot(t([st st st+dur st+dur])*1e3, [-2.5 2.5 2.5 -2.5]/G*1e6, 'r')
xlabel('Time (ms)')
ylabel([sprintf('Normalized\nVoltage') ' ( \muV)'])
axis([0 500 -50 50])
drawnow;
fclose(fid);

SNR_mean = mean(SNRs);
SNR_std = std(SNRs);
SNR_cov = SNR_std/SNR_mean;
A_mean = mean(As);
A_std = std(As);
A_cov = A_std/A_mean;

IT_mean = mean(ITs);
IT_std = std(ITs);
IT_cov = IT_std/IT_mean;

snapshot_outs = [As' ITs' SNRs';A_mean IT_mean SNR_mean;A_cov IT_cov SNR_cov]