

Wireless, Broadband, and Implantable Neuroprostheses

David Allenson Borton
B.S. Biomedical Engineering - 2006
Washington University in St. Louis

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David A. Borton

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Biology and Medicine and the School of Engineering as satisfying the dissertation requirement
for the degree of Doctor of Philosophy

Date _____
Dr. Arto V. Nurmikko, Advisor

Recommended to the Graduate Council

Date _____
Dr. John P. Donoghue, Reader

Date _____
Dr. Eric M. Darling, Reader

Date _____
Dr. Anubhav Tripathi, Reader

Date _____
Dr. Timothy Denison, Reader

Approved by the Graduate Council

Date _____
Dr. Peter M. Weber, Dean of the Graduate School

David Borton

CV

Positions and Honors

Positions and Employment

- | | |
|-----------|--|
| 2004 | Electrophysiology Research Assistant – Steven Mennerick, PhD. - WUSTL
Dynamics of the GABA-B receptor in Xenopus Oocyte |
| 2004-2005 | Computational Neuroscience R.A. – Todd Braver, PhD. – WUSTL
Role of the prefrontal cortex in maintenance of attention |
| 2005-2006 | fMRI Signal Analyst – Larry Snyder, M.D. PhD. - WUSTL
Connectivity of non-human primate frontal eye field to other cortical areas |

Other Experience and Professional Memberships

- | | |
|-------|---|
| 2006- | Student Member, Society for Neuroscience |
| 2006- | Graduate Student Member, IEEE |
| 2009- | Graduate Student Member, IEEE Engineering in Medicine and Biology Society |
| 2009- | Graduate Student Member, IEEE Biomedical Engineering Society |
| 2009- | Peer Reviewer, IEEE Engineering in Medicine and Biology Society |
| 2011 | Peer Reviewer: International Society for Circuits and Systems |

Honors

- | | |
|------|--|
| 2006 | S.W. Marston Scholarship |
| 2007 | Dana / Mahoney Fellowship |
| 2008 | Brain Science Program Reisman Fellowship |
| 2009 | Brain Science Program Reisman Fellowship |

Selected Publications

Most relevant to the current application

1. Borton, D., Yin, M., Aceros, J., Agha, N., Minxha, J., Komar, J., Patterson, W., Bull, C., & Nurmikko, A. (2011). Developing implantable neuroprosthetics: A new model in pig. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference* (Vol. 2011, pp. 3024-30). doi:10.1109/IEMBS.2011.6090828
2. Aceros, J., Yin, M., Borton, D. A., Patterson, W. R., & Nurmikko, A. V. (2011). A 32-channel fully implantable wireless neurosensor for simultaneous recording from two cortical regions. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 2011*, 2300-6. doi:10.1109/IEMBS.2011.6090579
3. Nurmikko, Arto V, Donoghue, J. P., Hochberg, L. R., Patterson, W. R., Song, Y.-K., Bull, C. W., Borton, D. A., Laiwalla, F., Park, S., Ming, Y., & Aceros, J. (2010). Listening to Brain Microcircuits for Interfacing With External World-Progress in Wireless Implantable Microelectronic Neuroengineering Devices. *Proceedings of the IEEE. Institute of Electrical and Electronics Engineers*, 98(3), 375-388. doi:10.1109/JPROC.2009.2038949
4. Borton, D A, Song, Y. K., Patterson, W. R., Bull, C. W., Park, S., Laiwalla, F., Donoghue, J. P., & Nurmikko, A. V. (2009). Implantable wireless cortical recording device for primates. *World Congress on Medical Physics and Biomedical Engineering, September 7-12, 2009, Munich, Germany*, 588-591.
5. Borton, David A, Song, Y.-K., Patterson, W. R., Bull, C. W., Park, S., Laiwalla, F., Donoghue, J. P., & Nurmikko, A. V. (2009). Wireless, high-bandwidth recordings from non-human primate motor cortex using a scalable 16-Ch implantable microsystem. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and*

- Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 2009, 5531-4. doi:10.1109/IEMBS.2009.5333189*
6. Song, Y-K, Borton, D. A., Park, S., Patterson, W. R., Bull, C. W., Laiwalla, F., Mislow, J., Simeral, J. D., Donoghue, J. P., & Nurmikko, A. V. (2009). Active microelectronic neurosensor arrays for implantable brain communication interfaces. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society, 17*(4), 339-45. doi:10.1109/TNSRE.2009.2024310
 7. Patterson, William R, Bull, C. W., Borton, D. A., Nurmikko, A. V., Simeral, J. D., & Donoghue, J. P. (2008). A neural interface microsystem with all optical telemetry for brain implantable neuroengineering application. *2008 Conference on Lasers and Electro-Optics* (pp. 1-2). IEEE. doi:10.1109/CLEO.2008.4551410
 8. Song, Y. K., Borton, D. A., Park, S., Patterson, W. R., Bull, C. W., Mislow, J., Simeral, J., Donoghue, J. P., & Nurmikko, A. V. (2008). Microelectronic neurosensor arrays: Towards implantable brain communication interfaces. *Electron Devices Meeting, 2008. IEDM 2008. IEEE International* (pp. 1-4). doi:10.1109/TNSRE.2009.2029493
 9. Song, Yoon-Kyu, Patterson, W. R., Bull, C. W., Borton, D. A., Li, Y., Nurmikko, A. V., Simeral, J. D., & Donoghue, J. P. (2007). A brain implantable microsystem with hybrid RF/IR telemetry for advanced neuroengineering applications. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference, 2007*, 445-448. doi:10.1109/IEMBS.2007.4352319

Additional recent publications of importance to the field (in chronological order)

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2. Wang J, Borton DA, Zhang J, Van Wagenen R, Burwell RD, Connors B, Nurmikko A. “Integrated optoelectronics for neural stimulation and recording in freely moving animals,” in *Lasers and Electro-Optics (CLEO) and Quantum Electronics and Laser Science Conference (QELS), 2010 Conference on*, 2010, pp. 1-2.
3. Wang J, Borton DA, Zhang J, Burwell RD, Nurmikko AV. A neurophotonic device for stimulation and recording of neural microcircuits. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference [Internet]. 2010 Jan [cited 2012 Jan 14];2010:2935–8.

Conference presentations

1. Society for Neuroscience **poster** presentation (2006-2011)
2. Engineering in Medicine and Biology **poster** presentation (2009-2011)
3. Engineering in Medicine and Biology **oral** presentation (2009)
4. Biomedical Engineering Society **oral** presentation (2011)

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Preface

The human brain is a magical device. There is no need to compare transistor counts, bandwidth, or power consumption – the brain simply outperforms any computational unit on the planet. It listens, it sees, it tastes, feels and it smells, parallelizing all this input to produce something completely new: a thought. For most of us, this thought is then translated from ionic currents in a neuron into calcium release in a muscle, causing contraction, or more simply, an action. It is the ability to make this transformation that can be lost when a person suffers from any number of diseases or insults to the body. One particularly palpable example of this loss is that of spinal cord injury. In this condition, the culmination of input and experience into a thought in the brain is unable to bridge the physical gap in the peripheral nervous system where the injury occurred. In extreme cases, when this gap is nearer the brain stem, it can render a person completely unable to communicate with or control any part of the world around them – they are “locked-in.”

The birth of the Neuroprosthetics field came from the idea that we could “unlock” this state by building devices to interface with the brain and understand its code; sensing the individual thoughts and translating them into efferent actions by a bridge of physical components. While our understanding of the organization of the brain, including those cortical areas engaged in creating volitional behavior, has advanced dramatically in recent years, there have been few attempts at building a system to enable people who are severely paralyzed to regain the ability to communicate and control their environment (I think some would disagree). One major barrier to success is due to the immense complexity of the task of reconnecting the brain’s action centers to the outside world. Not only must one have a solid understanding of motor command function of the cortex and the underlying neural communication codes contained its signals, but if we are going to engineer a device to establish and sustain a long-lasting interface with this biological system that allows us to read out those signals, we must also tackle immense engineering challenges: the interactions between native and foreign materials, constraints and limitations in

size and shape, as well as ease of surgical implantation must be considered on the same level of importance as engineering challenges such as amplifier performance, ADC bit depth, heat generation, and telemetry. Any realistic device must be able to reliably detect and transmit signals from inside the body to the outside, ideally out of view, across many decades, and most paramount it must be safe to the user.

This project focuses on our advances across many disciplines in order to achieve the goal of a fully implantable, low power, broadband, and wireless neural recording platform for use in persons with the inability to translate thoughts into actions. We focus not on one aspect of device research, such as microelectronic advances or biostability and biocompatibility, but on the macrocosm and how each facet influences each other.

The introductory chapter highlights the clinical and scientific importance of investigating and advancing neural control and provides an outline of the progression in modern device development. The second chapter describes the panoply of advances we have made in supporting technology and measurement systems for implantable neural sensors. In addition, a new animal model for implantable device development and the modified surgical procedures for its use are explained. Chapter three details the design and development of an externally powered, fully implantable, wireless, broadband neural sensor. The foundations of this device sparked the genesis of an internally powered microsystem, described in chapter four, planned for immediate clinical use with persons suffering central nervous system insult. These devices inspired the creation of an embedded neural signal processing system, the foundation of which is detailed in chapter five. Results from all sections have been condensed into chapter six along with discussion on the relevance of this thesis' findings in a greater context, scientific, and social. An adjacent, but related, project where light is used to stimulate neural circuitry using novel viral injection techniques in non-human primates is discussed as an appendix to this thesis, chapter seven.

A statement on ethics

Scientific research that involves animals in any form is extremely challenging. We are challenged to provide these animals with outstanding care while they participate in our studies, we are challenged to design experiments with the upmost care in order to avoid unnecessary use of animals, and we are challenged create an environment for the animals that will allow a level of comfort. All work in this thesis was reviewed and supported by the Brown University Animal Care and Use Committee, a group consisting of researchers across disciplines, university officials, and community members. This work was completed under protocol #0911091.

A few words on terminology in the field of neuroprosthetics, contextualizing this work

There is some terminology that pervades the field of neuroprosthetics that are poorly defined and overused. Thus, we would like to assert our understanding of a few of these terms most commonly misused and comment on their appropriate use in scientific research. For brevity, we will focus on the title of this thesis, “Wireless, broadband, and implantable neuroprostheses.” First, the term “wireless.” When the end goal is to have a system devoid of wires, one must develop a method to both power *and* transmit data to and from the device without physical connection. We see all too often groups refer to a device as “wireless” that accommodate *either* non-wired power (e.g. inductive coupling, photovoltaics, etc.) *or* telecommunication (e.g. UWB, FSK RF, IR, etc.) while leaving the other connected via cables. It is imperative that researchers develop these transcutaneous electromagnetic energy transmission schemes. However, for a *device* to be *wireless*, it must contain both in and out telemetry. In this thesis, our devices implement transcutaneous power delivery *and* transcutaneous data telemetry, thus can bear the name “wireless.”

A second term that should be clarified is “broadband.” In this thesis, and in most of the device development fields, the term refers to the width of frequency spectrum contained in the data collected. In neural systems, action potentials represent the highest frequency) changes worth

recording and transmitting for analysis. Thus, most devices implement amplifiers with high cutoff frequencies on the order of 10kHz, just beyond the end of the spectral content in an action potential. It follows that a sampling rate of 20kHz on each input is required to “catch” the frequency characteristics up to 10kHz (Nyquist). Returning to the term under discussion, “broadband” in neural data claims that *all* of the neural content is being recorded for analysis, essentially 0 – 10kHz. This puts a large demand on the data telemetry modality, which, generally leads to researchers compressing the data on the device itself before transmission. However, compression inherently results in loss of information. We should say that when you know what you are looking for in the data, such as the case in telephone communication, compression is extremely effective. However, there is continued debate on what are the “important signals” of the brain, and thus neuroscientists prefer to analyze *broadband* (uncompressed) neural data. Our devices transmit broadband data.

Lastly, we would like to comment on the use of the word “implantable.” There are two working definitions in the literature as it relates to biomedical devices: 1) a device that has been designed to withstand the rigors (mechanical, biological, electrical and otherwise) of the body and has been verified through in vivo studies, and 2) a device that may have the potential of being used in such settings but the researchers have not investigated this further. In this thesis, we presented two devices that are implantable by design and thus adhere to the first definition, as they have been implanted successfully in animal models.

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CHAPTER 1: Introduction

“Out of the cradle [and] onto dry land... here it is standing... atoms with consciousness... matter with curiosity.

I... a universe of atoms... an atom in the universe.”

- Richard P. Feynman, The Value of Science

1.1 Introspection and how technology drives our understanding of the brain

Much like how small discoveries on the fundamentals of basic physics enabled quantum leaps in our understanding of the universe, developments of new biomedical technologies unveil new challenges as well as opportunities for innovation in medical care. Before 1932 and Dr. Albert Hyman’s description of the artificial pacemaker, people with severe bradycardia and heart

block were given news that their heart may fail, and that their lifespan was limited. Now, millions of people across the world are alive and healthy with an implanted biomedical device pacing their heart. Before the development of the cochlear implant in 1978, 230,000 people with damaged cochlear hair cells had severe hearing impairment. Now, ever-advancing biomedical implants help those persons re-experience sound. These advances not only addressed a clear clinical need, but they made a leap in our understanding of how to interface technology with the human body. We are now on the brink of making such technological discoveries related to the brain-body interface.

Descartes posed the age-old question of consciousness: "*But what then am I? A thing that thinks. What is that? A thing that doubts, understands, affirms, denies, wills, refuses, and that also imagines and senses.*" Neuroscientists have for centuries attempted to address Descartes' view of consciousness, on the way discovering much about the physiology of brain function. For example the application of Magnetic Resonance Imaging (MRI) in 1973 to the brain by Lauterbur and Mansfield was a transformative technology, enabling diagnosis of the previously invisible illnesses and exquisite structural mapping of the brain while at the same time peering into the inner circuitry of the mind.

However, the function of the most fundamental unit of computation in the brain, the neuron, is still incompletely understood, especially its rich spectrally diverse nature. A new frontier in brain science resides in the ability to interface directly with individual neurons and populations of neurons, in a continuous manner. If there were a device to measure and transmit neuronal activity, and if our interpretation of the neural code were sound, clinical neuroscience would take another transformative leap. Persons with various plegias, or even those "locked-in", could potentially regain the ability to interact with the environment. The development of such a device is the goal of many contemporary researchers across the globe, and furthering this goal is the subject of this thesis.

1.2 Background

1.2.1 Size, power, and bandwidth of the human brain

The human brain is, in many ways, not terribly dissimilar to the human experience. Imagine, briefly, a world of averages. The average person living in an average town will maintain on average 150 meaningful relationships (Dunbar, 1992; Hernando, Villuendas, Vesperinas, Abad, & Plastino, 2009). These relationships, constructed over time from the currently 4,000,000,000 co-inhabitants, help the person accomplish tasks in his immediate neighborhood, town, and the world, but also define who he is. People communicate through these relationships in both digital and analog fashions (e.g. asking a question versus holding a conversation) and how well they communicate absolutely determines not only their ability to achieve common goals, but also the effectiveness of their relationships in the future. For the purpose of analogy, imagine you are a cell in the human brain, a neuron. You've spent your whole life growing up there and have made a few friendly relationships along the way, called synapses. The average neuron in the brain maintains roughly 7,000 synapses (Drachman, 2005; Williams & Herrup, 1988) and rests among roughly 100,000,000,000 co-inhabitants (Drachman, 2005). Neurons communicate with each other over synaptic links, which helps them accomplish tasks not only in their immediate cortical neighborhoods, but also across vast peripheral landscapes to control, for example, the movement of a pinky toe. A neuron communicates through both digital and analog (e.g. action potential versus lower frequency oscillations) and, in a sense, the effectiveness of communication determines the synaptic strength, or inter-neuronal relationships in the future. The dynamics of the 1.3 liters of semi-transparent neuronal goo consisting of 10^{15} interconnections equate, in this analogy, to the dynamics of the earth and all of its inhabitants. How do we observe these dynamics? How much can we expect to "hear?" How does one person or one neuron affect the neighborhood, town, or global drift? The answers to these questions, when asked about humanity

viewed from space are incredibly challenging. They are no less so when we consider the neuroengineer asking these questions about the brain and the neurons therein.

To give a rough perspective on power consumption, the human brain, a highly distributed, parallel, and hierarchal biological computer, is composed of about 10^{11} neural cells, which for computational purposes one can equate to “transistors.” Details of the local micro circuitry vary widely from region to region of the brain, but one universal feature of this 3-dimensional “ultra-very-large-scale-integration” design is the large number of interconnects between individual neurons (as mentioned near 7,000). This rich circuitry enables approximately 10^{15} interconnections, each plastic in nature, to operate a uniquely complex “software,” or neural code. Arithmetically, this is equivalent to well over petaflop computational rates even though the speed of individual communication is on the order of 10^{-3} seconds, or kHz. Perhaps most impressive is all of this computation is accomplished with total power consumption of roughly 20% of the body’s resting energy consumption (2400 kcal , $2400 \text{ kcal}/24 \text{ hr} = 100 \text{ kcal/hr} = 27.8 \text{ cal/s} = 116.38 \text{ J/s} = 116 \text{ W}$) or 23.3 W , on the order of a laptop computer (Mahesri & Vardhan, 2005). Power estimations of the human brain were made via surrogate measurements of deoxygenation in the BOLD signal from fMRI data, which in turn represent metabolism (i.e. energy consumption).

Not only does the brain operate “efficiently” (perhaps debatable), but it also transmits an astonishing amount of data between these thousands of synapses. While individual “point-to-point” communication occurs on the millisecond time scale, many other more slowly changing signals, superimposed across vast regions of neural tissue, also contain useful information. One can ask whether having 1000, 10000, 100000, and so on, neurons may improve decoding (or coding) performance up to 0.8, 0.9, or 1.0. Until we develop the ability to actually record from an order of magnitude more neurons (and eventually all the 100 billion neurons) in the brain, we may ask if there are simpler surrogates that meaningfully convey a partial summary of the spiking activity of all these neurons.

Field potentials (local field potentials, LFPs) may be one such candidate. They represent the spatial average of the electrical potentials generated by a large population of neurons. The subthreshold (analog, transmembrane currents) and suprathreshold (discrete spikes) electrical activity of a large population of neurons generates current sinks and sources at different points in cortex and subsequent potential changes near the electrode (Mitzdorf, 1985) As Gyorgy Buzsaki (Buzsáki & Draguhn, 2004) put it:

“Clocks tick, bridges and skyscrapers vibrate, neuronal networks oscillate.”

Described below are a number of frequency bands ranging from so-called “slow potentials” in the 1 to 100Hz range to the “fast potentials” above 100Hz. These signals are used in both basic neuroscience and state-of-the-art neuroprosthetics as control signals and neural correlates of peripheral movement and each may be useful for control signals. Thus, neural interface systems at least for the foreseeable future need to consider a broad band of signal sources that may be useful to extract command signals. Why do these various dynamic potentials emerge? The generators of these non-spike fields are transmembrane currents. Transmembrane currents are the result of modulation in endogenous neurotransmitter concentration (glutamate, dopamine, serotonin, etc.) at the synapses, which modify the amount of current flowing across the membrane and thus the surrounding electric field. These changes can be recorded extracellularly and, following the superposition principle, are summed across many neurons. This sum is referred to as the field potential. Some of these field potentials are oscillatory in nature, which may emerge either from the neural circuit itself or the biophysics of membranes (Buzsaki, 2006). Importantly, some of these field potentials may be symptoms of a broader computational system, while others may be the actual computations themselves. (Bullock, 1997). Later we will introduce the tools used to access these signals, and finally, their use in modern neuroscience.

Alpha band (7 – 12Hz)

Alpha rhythms are oscillations ~ in the 7-12 Hz range and thought to be generated by thalamocortical connections, originally discovered by Hans Berger in 1928 over the occipital cortex where they predominate. The mechanism for the generation of alpha oscillations has been extensively studied (György Buzsáki & Draguhn, 2004; Nicolelis, Baccala, Lin, & Chapin, 1995; Penttonen & Buzsáki, 2006) and can be summarized as “a physiological reflection of the unperturbed state of first-order thalamic nuclei and their primary sensory and motor cortical partners” (Buzsaki). While Nicolelis et al. originally hypothesized that these alpha oscillations originate in the cortex; other work has proposed the thalamus as the originator of these rhythms (P. Andersen & Andersen, 1968). In addition, alpha oscillations over the motor cortex are called *mu* rhythm and may in fact be of different origin than the alpha oscillations.

Beta band (15 – 30Hz)

Beta rhythms are described as 15-30 Hz oscillations seen in motor cortical areas. Their power is associated with preparatory activity, but not with the actual movement as they are suppressed during movement. The source of the beta rhythm is unknown, but may lie in the neurons that synchronously fire during the preparatory phase of movement in the motor cortex (Donoghue, Sanes, Hatsopoulos, & Gaál, 1998). Another hypothesis is that these rhythms reflect subthreshold synaptic input to the primary motor cortex (MI) from delay-period cells in premotor or prefrontal cortices, which then shut off during the movement itself (Fuster & Alexander, 1971; Weinrich & Wise, 1982).

Gamma band (30 – 100Hz)

Gamma rhythms can be intrinsic or evoked (by external stimuli) oscillations seen in the brain sometimes as a peak, but at other times as a broad increase in power in the 30-100Hz, even up to 250Hz (Fukuda, Nishida, Juhász, Muzik, Sood, Chugani, & Asano, 2008), which has also been directly or indirectly related to increases in local spiking activity (Rasch, Gretton,

Murayama, Maass, & Logothetis, 2008). There is some confusion in the labeling of the gamma range from 30-50 Hz, which is sometimes called beta, and sometimes gamma. For example, Fetz and colleagues report a 20-40 Hz range as gamma (Fetz, Chen, Murthy, & Matsumura, 2000), while Kristeva and colleagues refer to the 30-45 Hz range as gamma (Patino, Omlor, Chakarov, Hepp-Reymond, & Kristeva, 2008). Gamma signals are often simply noted as an increase in power across a broad band, with little evidence for it being “oscillatory” in nature.

Multiunit activity (>300Hz)

At frequencies greater 300Hz, but lower than 1kHz, one can measure multiunit activity (MUA) (Buchwald & Grover, 1970) from the electrical signal recorded from the brain using small tipped microelectrodes. Small electrode tips are required to allow isolation of local signals from strong, distant signals. This signal is generally thought to represent an average of the spiking activity in the surrounding volume without being affected disproportionately by the nearest, largest amplitude neuron. This is distinct from unsorted spikes, which are also sometimes referred to as multiunit activity (we will refer to this as multiple single units or MSUs), in which spikes are actively isolated from the signal. While it is unclear exactly what distance is “sensed,” depending on the electrode properties, the MUA is thought to represent a weighted sum of the extracellular action potentials of neurons within a sphere of about 200–300 μm radius, with the electrode tip at its center. “All in all, MUA most probably represents the average spiking of small neural populations around the electrode, and LFPs represent the weighted averages of dendrosomatic postsynaptic signals reflecting input activity (afferent or local)” (Logothetis, 2002).

Single-Unit spiking activity

At frequencies of about 1-3 kHz, one encounters the action potential (or spike), which is the fundamental output of a neuron. Neurons constantly maintain a voltage potential between the intracellular and extracellular space, separated by an impermeable membrane. This membrane

(shown below in Figure 1-1) is sprinkled with transmembrane proteins, some of which selectively allow ions to pass. These proteins are called ion channel proteins and ionic pumps. Ion pumps actively use adenosine triphosphate (ATP) to “push” ions against their concentration gradient and thus build the voltage and concentration potential from the intracellular to extracellular space. The most basic form of an ion pump is the Na^+/K^+ -ATPase, which move sodium out of the cell and potassium in, both against their gradients. At rest, a neuron maintains an internal potential of nearly -70mV with a high intracellular concentration of K^+ and high extracellular concentration of Na^+ . Initiation and propagation of information begins at the synapse (synaptic cleft) where neurotransmitters, such as glutamate, raise the membrane voltage in that region until a critical threshold voltage is reached. This value is generally around -55mV , however it is highly dependent on the distribution of voltage-gated ion channels. Since the ion channels are voltage-gated (meaning they open at a particular voltage, allowing ionic current to flow) and different ion channels (that is, channels selective for different ionic species) have varying voltage-regulated dynamics, the actual voltage change across the membrane during the “action potential” is characterized by several linear and non-linear components. It suffices to say, from the perspective of an extracellular recording electrode, the voltage sensed appears much like a singular event (positive deflection as sodium rushes in, negative as potassium rushes out to balance), hence the term “spike” for an action potential. As a discrete event, with a well-described underlying mechanism and correlate (Hodgkin & Huxley, 1952), it has attracted considerable study to understand function of neurons. The modern history of recording action potentials begins with Lord Edgar Adrian who used valves, developed during World War I, to amplify, and a capillary electrometer, to record, the millivolt scale neuronal potentials (Adrian, 1954). His work elucidated certain basic features of the action potential, such as its all-or-none property, a firing rate code, and the adaptation and refractoriness of responses. Adrian studied the properties of spiking in many diverse neural systems (although, mostly in the periphery) and related them to behavioral observations, thus founding the field of modern day behavioral neurophysiology with

the idea that information is encoded in spiking activity. In, “The history of electrophysiology has been decided by the history of electrical recording instruments,” Lord E.D. Adrian (who won the Nobel Prize in Medicine in 1932 for his discoveries regarding the function of neurons) was the first to record describe single action potentials and introduce the study of spike based coding.

Following Adrian’s work, Alan Lloyd Hodgkin and Andrew Huxley, biophysicists and physiologists described the initiation and propagation of the cellular action potential as a function of ionic conductance. Equation 1-1 describes the time-dependent membrane voltage ($\dot{V}_m$) as a sum of the individual ion channel (i) currents (I_i) over the capacitance of the membrane (C_m). Hodgkin and Huxley further described the current of each ion channel as containing both a linear and nonlinear (voltage-dependent) conductance (g_i), Equation 1-2. These components are shown in graphic form to illustrate the corollary in circuit form Figure 1-1.

$$\dot{V}_m = -\frac{1}{C_m} \left(\sum_i I_i \right) \quad \text{Equation 1-1: Neural membrane voltage}$$

$$I_i(V_m, t) = (V_m - E_i)g_i \quad \text{Equation 1-2: Voltage-dependent current}$$

A rearranged version of Equation 1-2 is known as the Cable Equation and is both time and length dependent where a neuron is modeled as a leaky cable with conductance of each ion channel (specifically, Na^+ , K^+ , and Cl^-).

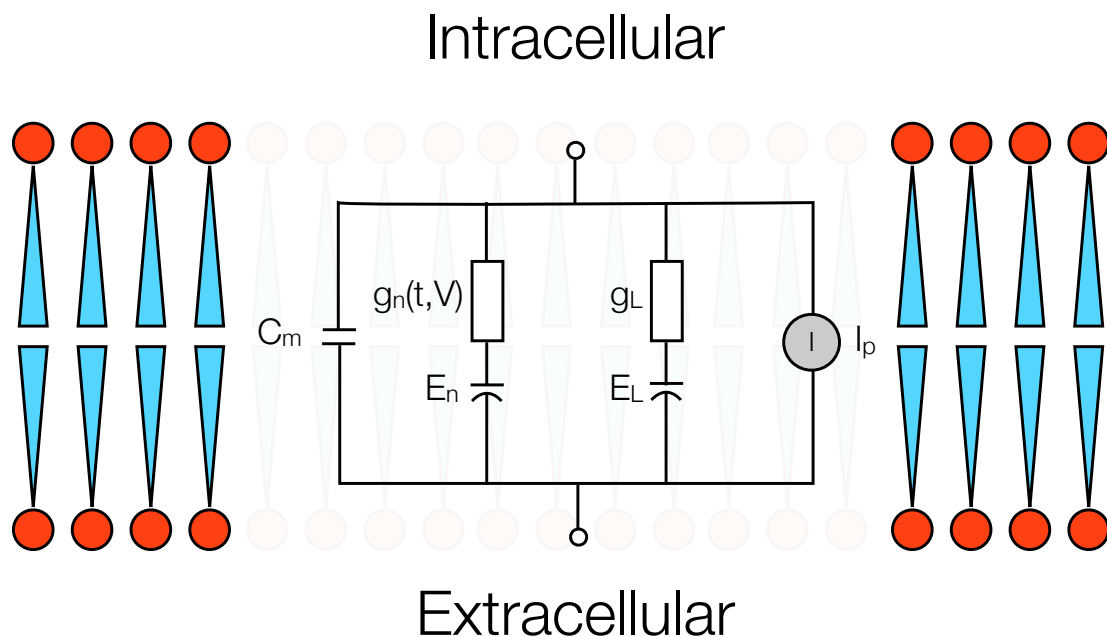


Figure 1-1: A representation of membrane potential in circuit form. C_m is the membrane capacitance, E_n and g_n represent the non-linear (voltage and time dependent) reverse potential and conductance of the membrane (respectively), and E_L and g_L are the linear components. Lastly, I_p is the ionic flow (current) produced by active ion pumps on the cell membrane. Membranes of most cells are made of a bi-lipid shell. Here, red circles represent hydrophobic, fatty chains of the membrane proteins while the blue triangles represent the hydrophilic chains. The circuit diagram represents a basic model for the dynamical characteristics (voltage-dependent) of the voltage across the bi-lipid membrane.

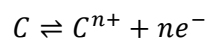
Hodgkin and Huxley's work won them the Nobel Prize of Medicine in 1963 and paved way for the juxtaposition of passive circuit elements to the biological cell. The cable equation has recently been extended to account for active intracellular components effecting membrane capacitance (Poznanski, 2010), which may add even further subcellular dynamics to the initial and maintenance of the action potential. Single unit activity has later been used to make fundamental conclusions about the function of neurons in the greater network. Tuning characteristics of

neuronal firing rate were discovered in the visual cortex (Hubel & Wiesel, 1959) and later the motor cortex (Amirikian, Georgopoulos, & Georgopoulos, 2000; Georgopoulos, Kalaska, Caminiti, & Massey, 1982) providing the foundation of modern neuroscience.

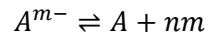
1.2.2 Listening to the Brain

Advances in understanding the brain and its constituent units could not have been done without coincident advances in technology to probe the nervous system. There are multiple electrical and chemical neural signal modalities that convey useful information about the nervous system. These signal modalities span many temporal and spatial scales, illustrated in Figure 1-3. As described above, these signals contain unique information about neural processing. Unfortunately, no single signal recording modality can “listen” across this extremely wide spatial and temporal scale. Several neural interfaces, or probes, have been developed over the last century and are used today to understand the brain. These are discussed below. Generally, the mechanism of electric conductivity in the body involves ions as charge carriers. Thus, detecting bioelectric signals involves interacting with these ionic charge carriers and transducing ionic currents into electric currents required by wires and electronic instrumentation. Electrodes that consist of electrical conductors in contact with the aqueous ionic solutions carry out this transducing function. The interaction between electrons in the electrodes and ions in the body can greatly affect the performance of these sensors. Thus, specific considerations must be made in their application (Plonsey & Barr, 2000).

At the interface between an electrode and an ionic solution redox (oxidation-reduction), reactions need to occur for a charge to be transferred between the electrode and the solution. These reactions can be represented in general by the following equations:



Equation 1-3: Forward ionization



Equation 1-4: Reverse ionization

where n is the valence number of the cation material C , and m is the valence of the anion material, A . For most electrode systems, the cations in solution and the metal of the electrodes are the same, so the atoms C are oxidized when they give up electrons and go into solution as positively charged ions.

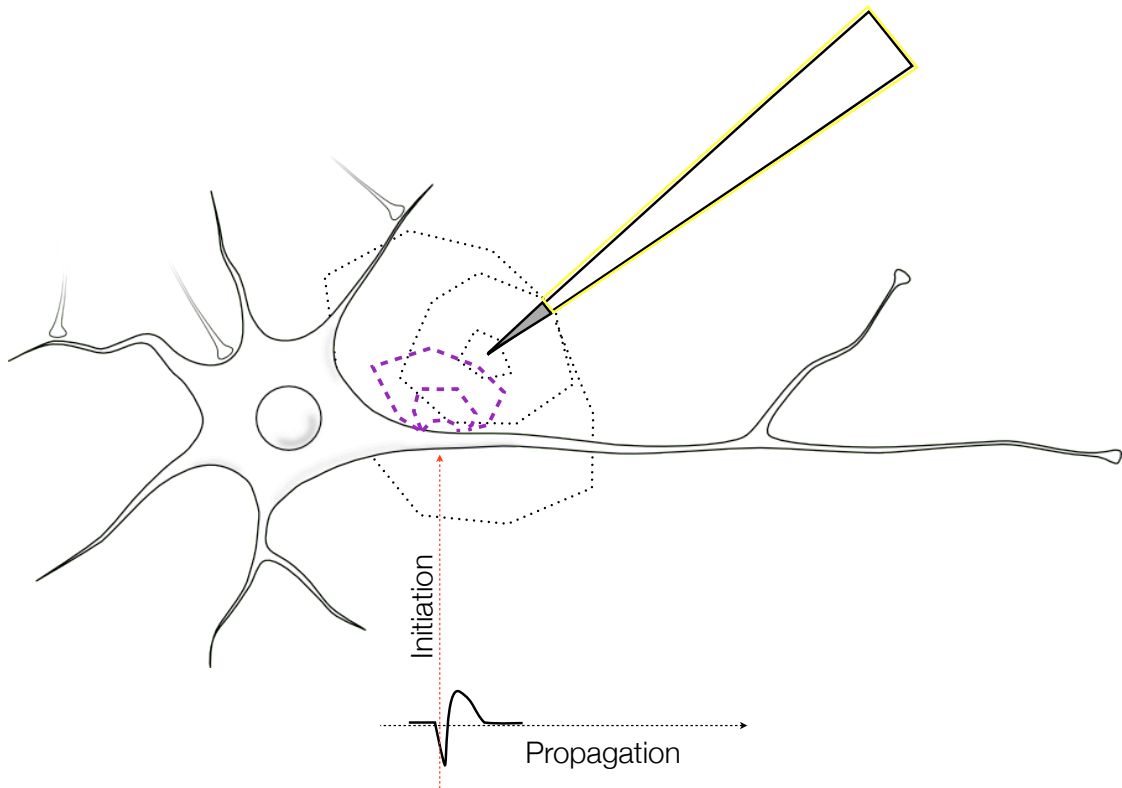


Figure 1-2: Simplified illustration of action potential initiation, field production, and propagation along the neuronal axon. Extracellular recordings from a single electrode sense the changes in the electric field near the neuron. The field sensed depends on both the field produced by the action potential across the membrane (purple-dotted) as well as the receptive field of the electrode (gray-dotted). The field produced by the neuron is highly dependent on the geometry of the axon, while the receptive field of the electrode is dependent on the exposed (conductive) tip volume and geometry. The effective combined field is an unresolved problem and under study by others (Gold, Henze, Koch, & Buzsáki, 2006; McIntyre & Grill, 2001).

These ions are reduced when the process occurs in the reverse direction. For best operation of the electrodes, these two reactions should be reversible, that is, it should be just as easy for them to occur in one direction as the other. In this way, the equation is never biased to build up charge and, eventually, degrade the cation or anion. The interaction between a metal in contact with a solution of its ions produces a local change in the concentration of the ions in solution near the metal surface, leading in turn to a potential difference between the electrolyte and the metal: the half-cell potential.

When no electric current flows between an electrode and the solution of its ions, the electrical potential observed by the electrode will be the half-cell potential. However, when a current is present, these potentials will be altered. The current changes discussed in this thesis will be neural in nature, caused by the release and uptake of ions from and into the intracellular space of the neuron. It should be noted here that there is some recent evidence that glial cells may play a significant role in regulation of neuronal firing patterns (Fields & Stevens-Graham, 2002). Electrodes made from noble metals such as platinum are often highly polarizable, that is, a charge distribution different from that of the bulk electrolytic solution is found in the solution close to the electrode surface. If the electrode moves with respect to the electrolytic solution, the charge distribution in the solution adjacent to the electrode surface will change, and this will induce a voltage change in the electrode that will appear as motion artifact in the measurement. Thus, for most biomedical measurements, non-polarizable electrodes are preferred to those that are polarizable. However, there is also a tradeoff of impedance with geometric surface area (GSA), described by Cogan, et al. (Cogan, 2008). As electrolyte interacting electrode surface area decreases, the effective impedance will rise. This rise in impedance in turn yield an increase in the thermal noise seen on the electrode, described by the Johnson-Nyquist equation:

$$v_n = \sqrt{4k_B T R \Delta f}$$

Equation 1-5: Johnson noise

where k_B , the Boltzmann constant (1.380×10^{-23} J/K), T the temperature (K), R the series resistance (or here the impedance), and Δf the bandwidth of the signal describe the effect of the thermal agitation of particles inside the electrical conductor (electrode) on the observed voltage. The highest amplitude effect on the electric potential observed by the electrode, however, is dominated by the ionic exchange between the intra- and extracellular space of the neuron. For detailed analysis and simulations, we refer the reader to Gold et al. (Gold et al., 2006). We discuss below the current materials and tools used to access these voltage changes of the neuron.

Electroencephalogram

The silver–silver chloride electrode is one that has characteristics similar to a perfectly non-polarizable electrode and is practical for use in many biomedical applications. However, due to impedance limitations when fabricate on the scale of neurons ($10\text{-}100\mu\text{m}$), this material is used primarily for large electrode applications. The electroencephalogram (EEG) consists of biopotentials that can be measured non-invasively on the scalp using surface electrodes. Silver/silver chloride electrodes (Ag/AgCl) are the most widely used electrodes in conventional biosignal recording setups. EEG recordings rely on the electrochemical redox reaction of silver with chloride that occurs at the scalp area where the signal is being acquired (as described above). These electrodes are the “gold standard” for EEG signal monitoring as they are non-polarizable, present outstanding reliability and show low and almost frequency-independent skin contact impedance values (few $\text{k}\Omega/\text{cm}^2$) in the frequency range of interest for conventional EEG signal acquisition ($1 - 50\text{Hz}$). These electrodes were first used by Hans Berger in 1929 to make paradigm shifting recordings of the brain (Berger, 1929). Large scalp electrodes are able to span the $1 - 50\text{Hz}$ frequency range, however they do so with very little spatial accuracy (poor resolution, $\sigma(\text{cm})$). In addition, although the electrodes themselves are non-polarizable, muscle movement anywhere on the scalp produces large biopotentials confounding the neural signal of interest.

Electrocorticography

The spatial limitation of scalp electrodes and the relative sensitivity to artifacts led to the development of an implantable electrode technology. In essence, numerous scalp electrodes are embedded in biocompatible polymers (silicone) and are implanted beneath the skull, either supra- or sub-durally. The signal recorded is referred to as electrocorticographic activity (or ECoG). Recorded from the cortical surface, ECoG has higher spatial resolution than EEG (i.e., millimeters versus centimeters), broader bandwidth (i.e., 0–200 Hz versus 0–50 Hz), higher amplitude (i.e., 50–100 μ V maximum versus 10–20 μ V), and far less vulnerability to artifacts such as EMG (Freeman, Holmes, Burke, & Vanhatalo, 2003). Generally, anywhere from 10 to 50 electrodes are embedded into a grid and laid across the cortical surface in order to gain broad electrical sampling coverage. The increase in spatial resolution and reduction of artifact make ECoG a suitable technology for investigation of neural activity and even clinical application. In fact, ECoG is currently used for localization of intractable epileptic foci for possible later surgical resection (Rosenow, 2001) and early use in control of prostheses (P. Afshar, Moran, Rouse, Wei, & Denison, 2011; Leuthardt, Schalk, Wolpaw, Ojemann, & Moran, 2004; D W Moran & Schwartz, 1999; Thongpang, Richner, Brodnick, Schendel, Kim, Wilson, Hippensteel, Krugner-Higby, Moran, Ahmed, Neimann, Sillay, & Williams, 2011).

Functional Magnetic Resonance Imaging

. While this thesis will does not provide technology for sensing magnetic resonance differences in tissue, the metabolic correlate that fMRI is imaging could be sensed more locally by implantable technologies. In addition, it is important for the reader to have a working understanding of all signals currently available for monitoring of neural activity so one can appreciate the uniqueness of our developed technologies.

It has been suggested that coherent, spontaneous blood-oxygen-level-dependent (BOLD) fluctuations of the brain reflect consciously directed mental activity. Alternatively, coherent

BOLD fluctuations may persist in the absence of normal perception and behavior, reflecting a more fundamental or intrinsic property of functional brain organization (Vincent, Patel, Fox, Snyder, Baker, Van Essen, Zempel, Snyder, Corbetta, & Raichle, 2007). The change in the magnetic resonance (MR) signal from neuronal activity is called the hemodynamic response (HDR). It lags the neuronal events triggering it by roughly 1 to 2 seconds, the time it takes for the vascular system to respond to the brain's need for glucose. From this point the signal typically rises to a peak at about 5 seconds after the stimulus. As activity stops, the BOLD signal falls below the original level, the baseline, a phenomenon called “the undershoot.” While the traditional approach to studying brain function is to measure direct voltage changes of neural tissue, fMRI can use the BOLD signal to observe surrogate changes in metabolic rate. Most of the brain’s energy consumption is devoted to ongoing metabolic activity not clearly associated with any particular stimulus or behavior, thus another interesting use of fMRI is aimed at understanding this ongoing activity and shown that fluctuations of the BOLD signal occur continuously, reflecting functional connectivity between distant locations of the brain (Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001).

Single wire microelectrodes

In order to probe voltage changes in close proximity to a single neuron, sensor size must be reduced to a point where it can be introduced into the tissue without significant damage, disrupting the natural behavior of the cell. As mentioned above, when the GSA of an electrode is sufficiently reduced, its impedance will rise to a point where the volume of tissue being sensed essentially reduces to zero (or so close to the electrode tip that no distant changes in field are heard). To obtain ideal extracellular recordings, the electrode will be placed directly adjacent (or even touching – see McIlwain & Creutzfeldt, 1967, a former Brown professor) a neuronal process. Thus, materials must be chosen that have either large effective surface area (porous or otherwise) or low material impedance values. Typical materials used for fabrication of single

microelectrodes are tungsten, platinum/iridium, stainless steel, and pure iridium. Sputtered iridium-oxide has recently been developed (Cogan, 2008) as a technique to increase the porosity of the coating material. Companies around the world machine the materials to form a conical tip with highly controlled conductive exposure down to a single μm . Electrode shanks are insulated in polymers, such as Parylene -C or a nylon to maintain impedance levels between 100kOhm to about 2MOhm. Indeed, many others are used, including glass, to avoid capacitive loss due to properties of dielectric.

Another technique to record from a single cell (and even a small set of ion channels on the membrane of the cell) is patch clamping. Patch clamp recording allows measuring current flowing from a single or a few ion channels (or the whole cell) by creating a sealed area on the surface of a cell membrane and the tip of a glass micropipette. This technique may be less invasive than intracellular recording (debatable, as a hole in the cell could rupture and dialyzes it), but has also a negative impact on the cell since a part of the cellular membrane is destroyed after removing the seal. However, both intracellular microelectrodes and patch clamping have limited potential for chronic and implantable technologies. Indeed, they do not allow simultaneous recordings from several individual cells, and they are not suitable for long-term studies or chronic settings, but they are useful for in-vitro measurements involving cells grown in dishes.

Single microelectrodes, since their introduction a century ago by Ida Hyde, have been used to unravel the mysteries of neuron function. However, a single electrode can only “listen,” depending on its impedance and orientation relative to the cell, to around $30\text{-}50\mu\text{m}$ in radius (Gold et al., 2006). The electric field drops as $\propto \frac{1}{r^2}$, which already informs us that we need to place our electrodes as close as possible to the cell. While single electrode recordings are extremely useful in fundamental neuroscience, studied here in the motor cortex (Evarts, 1968; LaMotte & Mountcastle, 1975; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975), it

was shown later (A. P. Georgopoulos et al., 1982) that while a single unit does contain information about a peripheral motor movement, this information becomes more informative when taken in context of other single cells. Thus, a population of neurons together contain correlated information toward motor control, thus leading to the development of microelectrode arrays (Maynard, Nordhausen, & Normann, 1997).

The microelectrode array

Microelectrode arrays composed of bundles of wires or so-called “microwire arrays” (Humphrey, 1970; Humphrey, Schmidt, & Thompson, 1970; Schmidt, Bak, & McIntosh, 1976) have been now largely replaced by “monolithic” arrays for work in primates (monkeys, and now in first human trials). Of these, we mention the Si-based arrays where lithographic and electrochemical techniques are combined to fabricate tapered micro scale beds of needles (Jones, Campbell, & Normann, 1992; C. Nordhausen, Maynard, & Normann, 1996; R.A. Normann, 1990). For example, in the so-called “Utah” microelectrode array, Pt or Pt/Ir coats each approximately pyramidal-shaped 1–2 mm long electrode, with its p-Si shank insulated by biocompatible Parylene-C, at its tip. The heavily doped Si provides a low-loss conducting path onto the planar support substrate wherefrom a wirebonded bundle (for a 100-element electrode array, 100 nylon-insulated 1 mil Au wires) transports the recorded neural signals through the skull and the skin to exterior electronics. Operationally, specialized neurosurgical techniques are employed to access cortical areas of interest with the arrays inserted to the brain typically using calibrated pneumatic single-tap impactors (R A Normann, Rousche, & Horch, 1994). The fabrication of this type of intracortical microelectrode structure has now been advanced to wafer scale processing so that the physical length of the microelectrodes can, in concept, be graded in a controlled fashion. The recording performance of these arrays depends on many factors, including a given surgical preparation and approach, making quantitative comparison of performance

between geometrically different MEA types ambiguous (however, currently, longitudinal studies are being compiled by J. Barrese, N. Rao, D. Borton, and others).

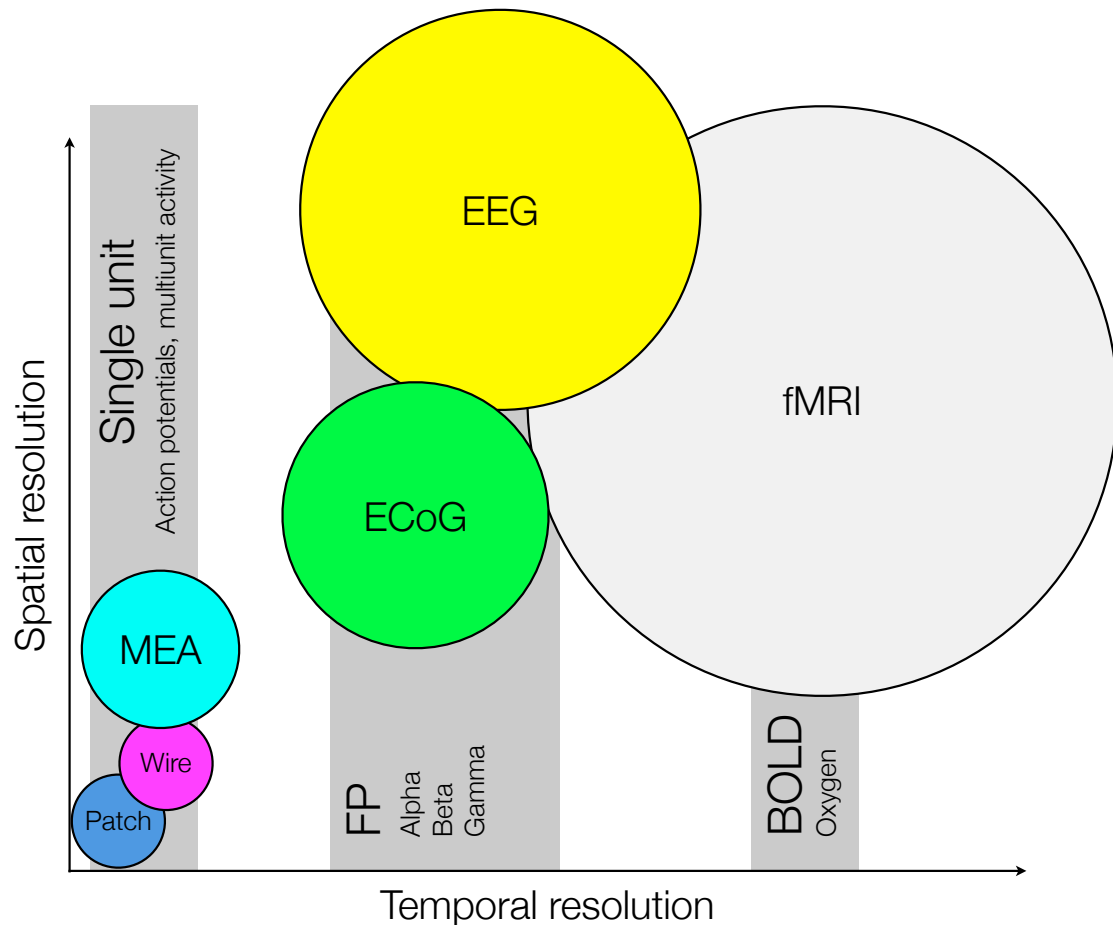


Figure 1-3: Relative spatial and temporal scales of neuronal signal recording modalities. There is a fundamental tradeoff between temporal and spatial scale. The size of each circle loosely represents the relative physical size of the neural sensor itself.

It should be noted that other approaches are used in practice to produce microelectrode arrays. Investigators at the University of Michigan using photolithography have etched multiple recordings sites along the depth a silicon shank (Csicsvari, Henze, Jamieson, Harris, Sirota, Barthó, Wise, & Buzsáki, 2003; Hoogerwerf & Wise, 1994; D. R. Kipke, Shain, Buzsáki, Fetz, Henderson, Hetke, & Schalk, 2008; D. Kipke, Williams, Hetke, Henderson, & Garell, 2011;

Yoon, Hwang, Shin, Park, Oh, Jung, Shin, & Kim, 2000). Multiple shanks are arranged in an array to achieve a three dimensional network of recordings sites whose relative coordinates remain unchanged during implantation.

An advantage of building recording sites in silicon is that amplifiers can be integrated into the same substrate; eliminating connectors between the electrodes and the amplifier improves reliability and signal quality. After years of being limited to acute recordings, Michigan electrodes were recently demonstrated for chronic recordings; signals were recorded up to 382 days post implantation (D. R. Kipke et al., 2008). However, it must be noted that the planar geometry of these electrode shanks introduces concern for safety in long-term, mobile patient implantation. While a single case of long-term implantation has been shown for the “Michigan” style microelectrode array, it is common that conical shank electrodes found in the “Utah” style microelectrode array record well for much greater lengths of time (Simeral, Kim, Black, Donoghue, & Hochberg, 2011; F Wood, Black, Vargas-Irwin, & Fellows, 2004) in humans and non-human primates.

1.2.3 A neural interface, beyond the sensor

Thus far, we have described the information rich electrical signals produced by the brain and the numerous methods used to probe these signals. However, in order to transform this voltage information into useful signals for the complex data analysis required for understanding cognition this data must be amplified, digitized, and transferred for consumption by a computer. This section will discuss the unsung heroes of modern neuroscience: the active components of a neuroprosthetic device.

Extracellular electrodes generate weak analog signals that need to be amplified, filtered and digitized to be transferrable to the world of computing for further processing and storage. Such functions are conducted in dedicated circuits often referred to as the analog front-end. The low-noise amplifier (LNA) is the main building block of such front-ends. Also referred to as a

neural amplifier in the field of neuroprosthesis, the LNA must amplify and filter the neural waveforms in order to remove any DC offset seen across a pair of differential electrodes. For most applications, a differential pair of electrodes consists of the sensing probe (located near a neuron) and a low-impedance reference electrode placed a significant distance away from the recording site and resting at a more global potential. The amplifier must provide sufficient gain, appropriate bandwidth, high signal-to-noise ratio (SNR), excellent linearity, and high common mode and power supply rejection ratios (CMRR and PSRR), in order to provide the required signal quality. In the case of a multi-channel interface, one such sensory circuit is needed for each electrode. Therefore, a neural amplifier must present low-power and small size, and be scalable to multiple parallel channels. Furthermore, it is essential to optimize the design for very low-power operation through a dedicated circuit design optimized for the signals of interest (low-frequency, high, or broadband).

To this end, numerous groups over the last 20 years have been designing analog integrated circuits (ICs), constantly building on each other to optimize performance for their unique application. The most common amplifiers used for neural signal acquisition are operation transconductance amplifiers, or OTA. In addition, some designs are employing active approaches like Chopper stabilization to attenuate $1/f$ noise (Denison, Consoer, Santa, Avestruz, Cooley, & Kelly, 2007; Denison, Santa, Jensen, Carlson, Molnar, & Avestruz, 2008), which is dominant in the low-frequency range (between 0.001Hz and a few hundred Hz) for CMOS integrated devices. This stabilizer can bring noise levels in those frequency bands down to $1.5\mu V_{\text{rms}}$, an impressive feat. Different bandwidth settings can be obtained by 1) tuning resistive values in a filter, 2) selecting different capacitors values from an array, or 3) changing the operating points of a circuit. Since bandwidth requirements greatly affect the design constraints of an amplifier circuitry, all permutations will not be reviewed. Instead, the focus will be on the amplifier designs that meet the needs of modern neuroscience and clinical needs: a bandwidth of 0.1Hz – 20kHz. This frequency range is wide enough to collect both low-frequency potentials as well as multi-

and single unit activity; and is referred to as a “full bandwidth” signal. Multielectrode array recordings will also be discussed.

Once a signal has been amplified on a single channel, it must be multiplexed with other amplified channels and digitized for later transmission. A widespread approach consists in sharing a fast digitizer between the multiple sensory channels. The sensory channels are directed toward the analog-to-digital-converter (ADC) employing time-division multiplexing (TDM) in the analog domain. The challenge with such an approach is how to minimize power consumption from the ADC and from the several unity-gain buffers needed to drive the ADC at a high rate as well as and isolate channels from each other. Moreover, the analog multiplexer must be designed carefully in order to avoid excessive crosstalk.

Both amplifiers and analog-to-digital converters are active electronics, meaning they require a constant supply of power to operate. A widely used mechanism for power transfer in implantable devices is radio frequency inductive coupling. In such a scheme, the power link is typically operated at lower carrier frequency (at a few megahertz) to limit absorption in biological tissues, while maximizing power transfer efficiency, whereas the uplink and downlink are pushed at higher frequencies to increase the data rate, while minimizing crosstalk and interference. In accordance with such a design philosophy, there is a high interest in low-power transmitters that stream data in the far field for enabling short-range monitoring at high data rate. In these schemes, the data uplink is operated at much higher frequencies than the power carrier center frequency. Several neural recording devices employing RF transmitters have been developed with components off-the-shelf (COTS) (Miranda, Gilja, Chestek, Shenoy, & Meng, 2010). For instance, HermesD is a COTS-based battery-powered neural recording system that allows the transmission of 32 broadband channels of neural data using frequency-shift keying (FSK) modulation, with an adjustable carrier frequency between 3.7 to 4.1 GHz. In (Rizk, Obeid, Callender, & Wolf, 2007), a COTS transmitter is transferring 96 channels of neural data from a single chip neural recording microsystem over a range of 2 m, using amplitude-shift-keying

(ASK) modulation. But, despite the high data rate achieved, the significant power consumption of these COTS transmitters (>100 mW) prevents their utilization in fully implantable or battery-less systems. A recent review of the state-of-the-art wireless neural interfaces developed on the benchtop can be found in **Table 1-1**.

This brings us to a critical boundary in neuroprosthetic research: the skin. While many researchers (including those discussed above) build impressive analog and digital circuitry for acquiring and processing neural data, few (very few) bring those technological advancements across this skin boundary and test them in vivo. This is a focus of our research and this thesis. It is absolutely necessary that devices created for neural rehabilitation and neuromotor prosthetic control be tested, evaluated, and used in the proper environmental context. This is a major challenge not only in neurotechnology, but all biomedical device research: moving from a device to a medical device.

Group	RTI _{rms}	Bits	S/s	# Ch	Data rate	Power	Amp	Area mm ²	Tx Modality
(Chae, Yang, Yuce, Hoang, & Liu, 2009)	4.9μV	6-9	2ksps	128	90 Mbps	6mW	OTA	8.8 x 7.2	UWB (RF)
An impressive low-power chip combining amplification, digitization, and data / power telemetry with massive data rate									
(R R Harrison, Kier, Chestek, Gilja, Nuyujukian, Ryu, Greger, Solzbacher, & Shenoy, 2009)	5.0μV	10	15ksps	100	345 kbps	10mW	OTA	5.4 x 4.7	902 & 928 FSK
Low-power integrated system including amplification, digitization, and power / data telemetry									
(Miranda et al., 2010)	5.0μV	12	30ksps	32	24 Mbps	142mW	OTA	38 x 38	3.7 & 4.1GHz FSK
A long range, high power implementation using the IN13 amplifier (Harrison 2009) and custom FSK RF telemetry									
(Yin & Ghovanloo, 2008)	7.3μV	8	20ksps	15	2.56 Mbps	4.8mW	OTA	3 x 3	75MHz PWM
An integrated ASIC with amplification, digitization and power / data telemetry using analog-to-time (ATC) conversion									
(Szuts, Fadeyev, Kachiguine, & Sher, 2011)	3.64μV	Analog	20ksps	64	10Mbps	345mW	Neuroplat	50 x 40	2.38GHz
A high power-consumption, but long-range (60m) digitization and transmission system with commercial preamplifier									
(Perelman & Ginosar, 2007)	3μV	10	40ksps	12	10.5Mbps	n. r. (high)	n. r.	3.7 x 3.9	Wire
High power-consumption microsystem with amplification, digitization and a wire (tethered) connection									
(A.M. Sodagar, Wise, & Najafi, 2009)	8μV	8	7.8ksps	64	2Mbps	14.4mW	n. r.	14.4 x 15.5	70 – 200MHz OOK
A dual-unit system with front-end (cortical) amplification and back-end (cranial) digitization and data telemetry									
(Rizk et al., 2007)	n. r.	12	31ksps	96	1Mbps	100mW	DHSM	50 x 40	916.5 MHz ASK
A large system with spike detection and unique automatic bit selection in the ADC and amplitude shift key telemetry									

Table 1-1: A review of recent neural interfaces designed explicitly for action potential detection and relatively high-bandwidth data transfer. Some values were not reported in the referenced texts. In general, most groups have taken a monolithic (single-chip) approach to neural signal acquisition and transfer.

1.2.4 What can the brain tell us that we don't already know?

Within the past decade, experiments on nonhuman primates have become progressively more sophisticated in enabling recording from brain microcircuits by intracortical MEAs with sufficient fidelity to enlighten our understanding of the neural code. For example, chronically implanted arrays yield signals from regions of the brain that can now be directly related, translated, and decoded into intended hand movements (Serruya, Hatsopoulos, Paninski, Fellows, & Donoghue, 2002; Taylor, Tillery, & Schwartz, 2002; C. E. Vargas-Irwin, Shakhnarovich, Yadollahpour, Mislow, Black, & Donoghue, 2010; Velliste, Perel, Spalding, Whitford, & Schwartz, 2008; P Yadollahpour, Shakhnarovich, & Vargas-Irwin, 2009) enabling long term (> 1 year) exploration of motor cortex in task performing monkeys. Within the primary motor cortex (MI), the location of the prime source for command output to the arm is known with an approximate spatial map in humans (Penfield & Boldrey, 1937) and non-human primates (Travis, 1955; Woolsey, Settlage, Meyer, Sencer, Pinto, & Travis, 1952). Command planning and spatial transformations have been indicated in what are referred to as the premotor areas, ventral and dorsal as well as pre- and post-arcuate areas (Gentilucci, Scandolara, Pigarev, & Rizzolatti, 1983; Schell & Strick, 1984). With recent development of decoding techniques towards real-time algorithms, based on probabilistic analysis (A. Afshar, Santhanam, Yu, Ryu, Sahani, & Shenoy, 2011; Churchland et al., 2010; Frank Wood, Black, Vargas-Irwin, & Fellows, 2004; Yu, Cunningham, Santhanam, Ryu, Shenoy, & Sahani, 2009), good correlation has been achieved for the arm movement of a monkey between the signals recorded directly from the brain and the physical action by the animal in 3-dimensions. The inputs for decoding movement kinematics are correlations in the rates of spiking activity across a microelectrode array, in conjunction with tracking the motion of the arm of the monkey, e.g., using a joystick or finger touch to move a cursor on computer screen. As a recent example, the neural commands thus decoded have enabled a monkey to operate both real and virtual robotic arms (Velliste et al., 2008). Taylor et al., have also exploited neural plasticity to bring a virtual 3-dimensional cursor under brain control (Taylor

et al., 2002). Their “co-adaptive” control algorithm requires no a priori knowledge about tuning properties of individual motor cells. This is an appealing feature for locked-in patients who have no means of training a control algorithm to relate neural activations with desired movements. The Taylor/Schwartz system used only 18 cells per animal subject, and was able to direct the virtual cursor to one of eight different targets. Vargas-Irwin et al. have used between seven and 30 (up to 120, though performance increase appears to level off around 30) motor cortex neurons in a macaque to achieve real time two-dimensional closed loop cursor control (C. E. Vargas-Irwin et al., 2010) in primates and begun to describe the critical direct information transfer between premotor and motor cortices (Bansal & Vargas-Irwin, 2011). These early intracortical brain-machine interface investigations are supported by electrocorticography motor area recordings by Moran et al. (P. Afshar, Moran, et al., 2011; D W Moran & Schwartz, 1999; Thongpang et al., 2011; W. Wang, Chan, Heldman, & Moran, 2010). All studies indicate that improving BMI performance in the future will hinge on the ability to increase the number of simultaneously recorded channels. One critical remaining challenge is to understand how well we can align the information gained from studying the non-human primate cortex to the human brain.

This challenge has been recently addressed by pioneering work from Kennedy (Kennedy, Bakay, Moore, Adams, & Goldwaithe, 2000) using cone electrodes to record from two neurons of a locked-in individual, Leuthardt et al. using ECoG grids to control joystick movements (Leuthardt et al., 2004), and Hochberg et al. (Leigh R Hochberg, Serruya, Friebs, Mukand, Saleh, Caplan, Branner, Chen, Penn, & Donoghue, 2006) using microelectrode array technology (NeuroPort) to record from hundreds of neurons. The BrainGate2 studies (Hochberg et al.) have demonstrated impressive point-and-click control, as well as basic control of a simulated arm (Chadwick, Blana, Simeral, Lambrecht, Kim, Cornwell, Taylor, Hochberg, Donoghue, & Kirsch, 2011; J. M. Lambrecht, Pulliam, & Kirsch, 2011).

Perhaps the most major limitation to current technologies employed by the neuroscientific community is their employment of a percutaneous connection. In the case of the

NeuroPort, this connector encases the one hundred gold wires (which in turn attached to the microelectrode array and, effectively, the neurons), interfacing the MEA with external electronics. Presently, the external electronics are composed of two standard PCs and a rack-mounted amplifier – obviously unable to be implanted. The driving long-term goal behind these works has been to develop a neurotechnology that might significantly restore or replace lost functions in neurologically or physically impaired humans. However, while this is also one of the major challenges behind this thesis, a precursor is developing appropriate microelectronic technology to enable implantable processing.

1.3 Challenges facing medical device technology development

Neuromotor disease and insults negatively affect the lives of millions of people worldwide. In some cases, such as in locked-in syndrome, the completely functional central nervous system is disconnected from the completely functional body. The birth of the neuroprosthetics field came from the idea that we could “unlock” this state by building devices to bridge this nervous system gap, detecting individual thoughts and translating them into efferent actions. While our understanding of the organization of the brain, particularly the shallow cortical layers, has advanced dramatically in recent years, there have been few attempts at building a complete system to enable people in such states to regain the ability to communicate and control their environment. Likely, this is due to the complexity of the task. Not only must one understand the function of the cortex and the underlying neural communication codes, but also one must engineer devices to interface with the biological system. And, the body must be viewed from a holistic perspective: the interactions between native and foreign materials, constraints and limitations in size and shape, as well as ease of surgical implantation must be considered on the same level of importance as engineering challenges such as amplifier performance, ADC bit depth, heat generation, and telemetry.

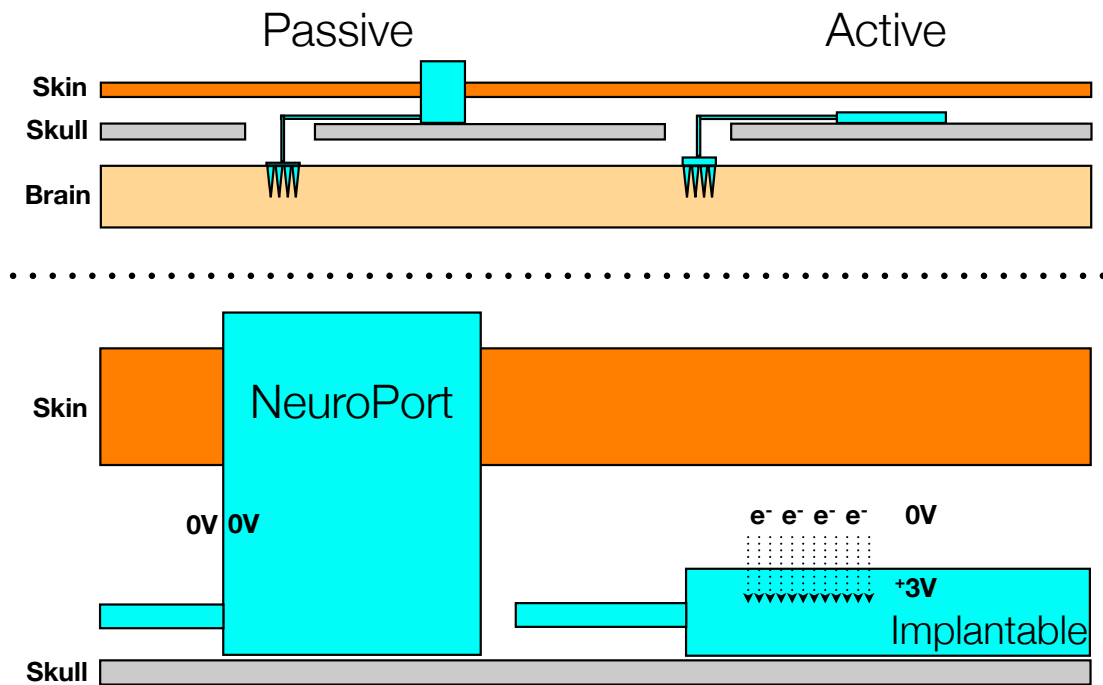


Figure 1-4: A device distribution overview (top) and detail of packing challenge (bottom) differences in passive versus active (constant electric field bearing) systems. e^- represent electrons, or more accurately any charged particle (ions) being driven by the electric field. The constant power necessary to support the microelectronics makes the neural interface *active*. The constant electric field generated drives charged molecules and ions into the packaging material and significantly increases the probability of transport across the barrier.

The ultimate goal in neural prosthetics as well as fundamental brain science in primates envisions a fully implanted wireless system for future high-performance chronic brain-body communication interfaces. As of today, a singular human clinical trial, led by the BrainGate group using an FDA-certified (NeuroPort) percutaneous intracortical microelectrode array recording platform, has been conducted (Leigh R Hochberg, Serruya, et al., 2006). To move beyond this, we need truly body embedded brain-interfaced microsystems where any number of neural sensor arrays plus all the active microelectronic circuits are sealed within the nonhuman primate's or human's ultimate protective envelope, the skin. The neural signals are broadcast only transcutaneously i.e., without any skin-penetrating (percutaneous) wires or feedthrough connectors, whatsoever. A fully implantable, wireless system presents formidable biomedical

engineering device challenges. Its benefits include elimination of the infection risk which is inherently present with any percutaneous connections, reduction in the mechanical vulnerability of the skull-mounted modules to accidental impact (e.g., moving animal or epileptic patient), and a host of clinical and health care benefits that are especially applicable to human subjects and patients (Badran, Arya, Bunstone, & Mackinnon, 2009; Griffith & Humphrey, 2006). Fully implantable neural microsystems could also offer access to several distinct brain locations for capturing neural signals from interacting sites in the cortex involved in coordinated cortical activity, integrating sensing, planning and action. However, even fully implantable systems, e.g. deep brain stimulation, can show long-term complications from gliosis (Griffith & Humphrey, 2006).

As mentioned earlier, one of the greatest challenges is transitioning a benchtop device into a medical device. Figure 1-4 depicts both the current NeuroPort pedestal-based neural recording platform and the hypothetical fully implantable microsystem. In that image the second greatest challenge is revealed: packaging an active device to maintain patient safety and system functionality. The topic of charge transport through various insulating materials is addressed briefly in this thesis, however more rigorous work will need to (and is being) done before a truly chronic device can be envisioned (see **Chapter 2**). The United States Food and Drug Administration (FDA) regulates all devices that fall under this broad definition of a “medical device”:

“... an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.” (FDA, 2010)

In other words, essentially every aspect of a device must be treated as a “medical device”: from sensor (*implanted device*) to external electronics (*accessories of a device*) to the software running on a remote PC or tablet (*component intended for diagnosis*). In order to deliver our platform to help individuals with paralysis from any number of insults or diseases, we must present safety, efficacy, and utility data to the FDA in such a way that they approve the implantable device, its supporting external electronics, and software. This is both a challenge and an opportunity to focus our efforts on making well-controlled and well-designed platforms, even in a research setting.

1.4 Introduction to the work presented in this thesis

Throughout the next five chapters (and published literature referenced), this thesis will address the progress made toward the following overarching areas of human neuromotor prosthetic and implantable technology research:

1. removing the percutaneous wire connection of current NeuroPort technology through the development of implantable, wireless neural sensors;
2. developing low-power ASIC elements to amplify and digitize broadband neural data (**Chapter 3 and 4**);
3. developing (**Chapter 2**) and leveraging (**Chapter 3 and 4**) an animal model appropriate for translation of device surgical and histological analysis to humans;
4. applying this technology to restore or replace lost functions in neurologically or physically impaired humans (**Chapter 4**);
5. making multisite, high-density, and broadband neural population recordings (**Chapter 3**);
6. developing wearable signal processing packages (**Chapter 5**).

The thesis begins in Chapter 2 with an in-depth look into the supporting technology advancements we have made, enabling neural interface devices to be powered and monitored for safety, implanted with high fidelity, and packaged for extended lifetime in saline environments. These topics are considered in three subsections of Chapter 2, a) Hardware and software for

acquiring and processing neural and diagnostic data, b) Development of surgical techniques and tools for neural prosthetic device development, and c) Protecting biologics and electronics by polymeric, metallic, and ceramic separation. Each of these topics is critical to a devices success.

Chapter 3 begins discussion of the significant device advancements that have made, specifically the creation of the (at the time of writing) first fully implantable, wireless, broadband neural recording microsystem. This device embraces all of the ideal characteristics of a chronic neural interface detailed throughout the introduction, including extremely low power consumption, small device profile for simple implantation, and high bandwidth data telemetry. To achieve this, many peripheral developments were made including an ultra-low power amplifier design suitable for flip-chip attachment to microelectrode arrays, substrate component partitioning to minimize heat generation, optoelectronic integration for data telemetry, and many more. The achievements made in this chapter have been published in several peer-reviewed forums. It is expected that the device will be translatable to a medical device through the FDA, and this pathway will be pursued in the near future. In vivo evaluation of the device described in Chapter 3 utilized animal models and monitoring electronics developed in Chapter 2.

Leveraging the success of this device in animal trials, and with the desire to explore the use of these technologies in epilepsy research, a very similar device was devised with three key distinctive properties. First, a medical grade battery was incorporated into the system to allow long-term, freely moving recordings necessary for the study of epilepsy. Second, the system was packaged with medical-grade II titanium for absolute hermeticity and patient safety. Lastly, the device utilized a high-frequency (OOK) RF data telemetry. All of these changes were made to address the need for a neurology patient to be completely mobile while under neurological evaluation for epileptic foci resection (Awad, Rosenfeld, Ahl, Hahn, & Lüders, 1991; Krings, Chiappa, Cuffin, Buchbinder, & Cosgrove, 1998). Currently, this device is under preclinical evaluation. However, during evaluation in non-human primates, various brain states of anesthesia

and sleep were explored, the preliminary results of which constitute unique recordings of sufficient interest to be included in this thesis.

Any recording device is only as useful as the interpretation of the data it produces. Decoding and control algorithms are not discussed in detail in this thesis, but a few that are used are discussed in Chapter 5. More importantly, this chapter introduces the wearable signal-processing platform developed for real-time decoding and prosthetic control. An effort that was started many years ago to bring algorithms currently run on PCs (as described above in the BrainGate trials and others) onto embedded processors, not unlike modern cell phones and mobile computers, has been advanced to a physical device, called the BrainPhone. This is a central member of a broader neural-interface-to-prosthetic-control picture, linking the data source (brain) to effector (e.g. prosthetic limb) for people with tetra- or paraplegia.

Finally, Chapter 6 coalesces the advancements made throughout these works in a “results” chapter, focusing on unique data collected and discussing its importance to the field of neuroprosthetics. Chapter 7 will give a brief overarching discussion and conclusion to this thesis and describe the all-important future directions of this research. The role each chapter plays in this thesis is visualized in Figure 1-5.

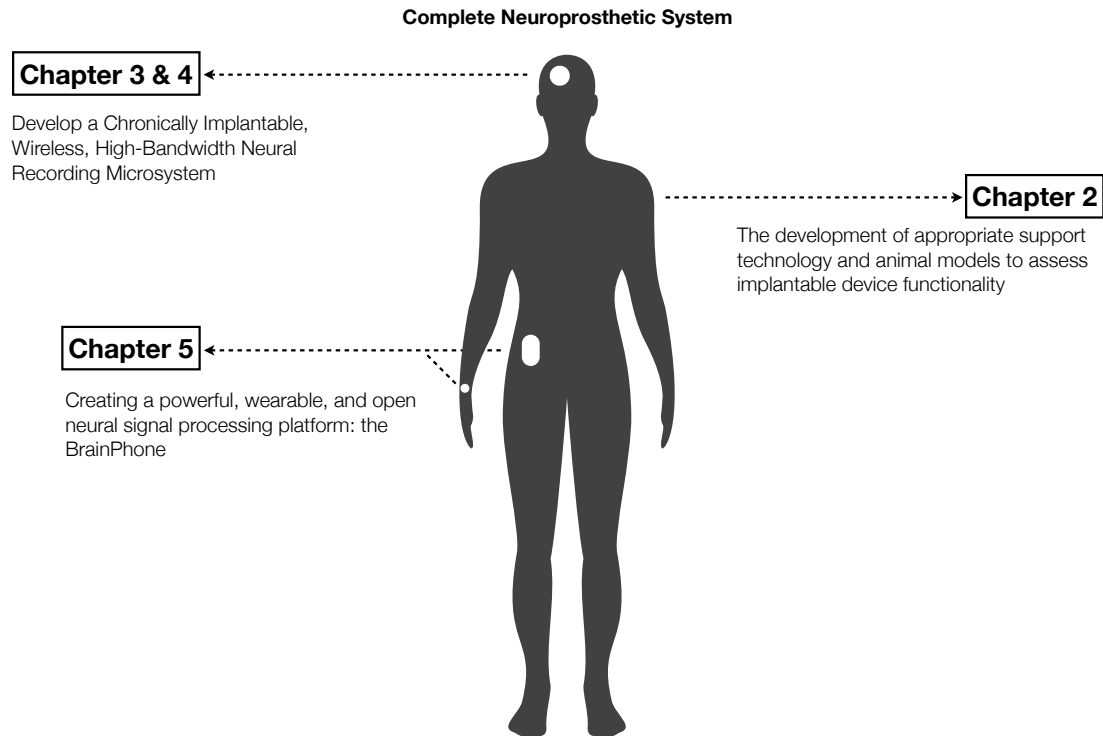


Figure 1-5: Complete neuroprosthetic system requires integration of the wireless, broadband, neural interface (Chapter 3 and 4) appropriate support technologies (Chapter 2) and finally a unified processor to translate and use the data for prosthetic control (Chapter 5). These three aspects bind this thesis into a cohesive product for persons with nervous system trauma.

1.5 Author's contributions to a large and complex team project

The research project discussed in this thesis required a cross-disciplinary group of capable researchers to complete. The work, involving an entirely new biomedical engineering implant device, required a seamless and combined effort of a cross-disciplinary team (about ten scientists), but specifically the neuroengineering team that I will mention below. The purpose of this section is to define what my role was as the lead graduate student investigator. While I worked very closely, by design, with everyone who worked on this project; we all contributed ideas and hands to each other's work. Below, I dissect my role by employing the structure of this thesis to describe in each chapter, starting with Chapter 2, who designed and completed each task and designate to some level of my contribution.

For notation, I refer to the Nurmikko Lab Neuroengineering Laboratory (NEL) as work done by the group. While I am an active member of this team, I will use the term NEL for work completed mostly by others or when it is impossible to distinguish the individual from the team.

Chapter 2: The development of appropriate support technology and animal models to assess implantable device functionality

Hardware and software for acquiring and processing neural and diagnostic data

The Common Platform System (CPS) was a piece of hardware created by the NEL. I discussed in detail the board design with members of the team and the NEL did the board schematics and layout. The original RF/IR receiver was designed by the NEL, I simply gave constant feedback through testing and evaluation. The firmware of the CPLD on the CPS was originally written by NEL and edited later by me (even later by other members of the NEL). The CPS was controlled by software, which I wrote in C++, and firmware written in C by NEL members. This software managed power levels on the implanted microsystem. Custom neural visualization software (RTVT) was invented completely by me to enable our microsystems to be used in neuroscientific experiments and enable live diagnostics. Several server applications needed to be written to both collect data from the ETS and display data from encapsulation / packaging studies, both of which were pieces of software I crafted. Lastly, this section discusses several data processing techniques, none of which I claim to be the inventor of, instead these are regularly used and published techniques (see text for references). However, I did write the very specific implementation of these algorithms for use in this research project.

Development of surgical techniques and tools for neural prosthetic device development

I designed all subprojects under this section with input from Dr. Moses Goddard (MG), members of the NEL, Dr. James Harper (VMD), and Dr. John Mislow (deceased). The use of swine for our task was wholly my innovation and the development of an IACUC-approved protocol was something I took the leadership on. Design input for the custom stereotactic frame

was conceived by me and then collaboratively made with the industrial design firm Kineteks (Warwick, RI). Members of the NEL substantially supported me to perform numerous surgeries necessary to validate the swine model and collect device data.

Protecting biologics and electronics by polymeric, metallic, and ceramic separation

The NEL and I completed initial evaluation of ionic leakage across PDMS with simplified coupons in a test rig designed by the NEL. I performed the experiments and analyzed the collected data, a launching pad for subsequent NEL team discussions designing the encapsulation test system (ETS, later described in this thesis) for long-term packaging evaluation. Once designed, the ETS and its many parts were compiled by the NEL and me. I completed all data collection from this system and analyzed it for use in guiding device packaging methods. The system is currently maintained by the NEL.

Chapter 3: Integrating state-of-the-art microelectronics with the nervous system: externally powered microsystems

Fabrication methods of the externally powered microsystem

The NEL designed integration procedures of the amplifier and the microelectrode array (published elsewhere). Through my detailed microelectronic integrated circuit analysis and members of the NEL we found faults in this integration method and later implemented changes to the integration process alleviating that issue. I innovated the choice of Kapton substrates, which also required a rigid backing to be applied to the microsystem substrate for fabrication (originally alumina, was changed to single-crystal sapphire). System fabrication was completed initially by members of the NEL and myself (I would prepare the substrates and populate boards with components, other members would integrate the ICs and wirebond them) and later taken over by NEL members completely in conjunction with an external integration company CV Inc. The microengineering-intense “packaging” (dielectric insulation) process of the neural implants and the associated protocol was adapted from work by a colleague (David Edell) by the NEL which I

transitioned and subsequently completed all packaging of externally powered microsystems in this project. The analysis of packaging methods was a first-year project of mine, guided by my advisor.

Substrate design considerations and development

This was mostly determined through NEL meetings and outside input from surgeons and physicians. I played a leadership role in soliciting that input and the final decision of geometry. The unique combination of optical and RF telemetry was a NEL decision. Analysis of ideal relative placement of the telemetry components was done by the NEL with my active participation.

Radio frequency inductive coupling for system power and clock

NEL.

Heat diffusion models

A result of heat observations on the internally powered microsystem during testing and operation (observed by NEL), I took on the thermal modeling of the device. I designed a COMSOL heat diffusion model based on well-defined principles and parameters from the literature of bioheat transfer to quantify our heat generation. I compared this model to data collected by NEL members of the system in air and tissue for accuracy and validity. In addition, I used a high-sensitivity infrared camera to analyze the per-component heat generation dynamics and overall distribution on the microsystems – a method translated from ultra low power integrated circuit evaluation.

Infrared vertical cavity surface emitting laser for wireless data transmission

The use of optical telemetry was a NEL design and implementation. To quantify the transmittance of 852nm VCSEL light in vivo, I invented an “optical forceps” combining a VCSEL and photodiode on opposite ends of the forceps clamp. This allowed for quick, in vivo (during implant surgery) determination of expected IR transmission through the animals skin.

Neural signal amplification: the design of “M4B” and “Pearl” Microelectronics Chips

The design specs were decided as a group (NEL), the layout was completed by a few members of the NEL team, and fabrication was completed through a MOSIS process in California.

Other microelectronic components used in the externally powered microsystem

Most remaining components were off the shelf and their integration to the system was trivial and required (i.e. rectifier, passive components, ADC, etc.). NEL.

Packaging of the EPM using polymeric compounds

The fabrication of a reliable electrically insulating protective envelope to the wireless implantable microsystems was one key subject. I invented and designed a packaging protocol with input from members of the NEL to standardize the process and achieve consistent results. I was also the person responsible for applying this packaging to every system before implantation (as above).

The first use of swine in chronic neurosensor evaluation in vivo

As stated above, I designed this animal model and the experiments to use them in device evaluation. Members of the NEL were instrumental in helping implant the devices and record from the subjects over extended periods of time.

Wireless recording in non-human primates

I led the project component in transitioning the wireless implantable microsystems to non-human primates. I trained two non-human primates on a center-out task, well-defined in the literature, to explore tuning characteristics of the neurons under study once the devices were implanted. This was wholly my work and constituted a significant amount of new knowledge and time. I performed the implantation of our (NEL) devices (six) into these animals with the help of neurosurgeons and physicians. In addition, I completed all data analysis and presentation of the data for review and publication.

General recording procedure for externally powered implantable microsystem

While I guided the development of this protocol, it was with heavy input from all members of the NEL.

Chapter 4: Integrating state-of-the-art microelectronics with the nervous system: internally powered microsystem

Brown NeuroCard description, images and historical significance

The components of the BNC were completely the collaborative effort of the NEL, just as the externally powered wireless implantable microsystem.. However, I conceived and presented the concept of a BNC to the group and then pursued the creation of the device for component validation and evaluation. Many members of the NEL later worked to implement the system, layout, fabrication, etc.

The internally powered microsystem

Because the internally powered microsystem was so heavily based on the advancements made in the externally powered microsystem, and because the team worked so tightly together, this is truly a NEL product as is stated in the patent claims. I took the leadership and implanted the system in swine and non-human primates and made countless recordings, supported by other members of the NEL. I also created and implemented the finite element heat generation and RF telemetry models in COMSOL for comparison to experimental results.

Chapter 5: Creating a powerful, wearable, and open neural signal processing platform: the BrainPhone (ESPA)

A look at the building blocks of the ESPA framework

The foundational work of the ESPA project was initiated and heavily guided by me. Key design concepts were mine. As the lead for this subproject, I held meetings with members of the neuroscience program and other members of the NEL and we jointly came up with a design suitable for all our needs. This framework has been slightly modified over the last several years, mostly by members of the NEL, to address growing demands of the framework.

A device implementation of ESPA: the BrainPhone

Few members of the NEL worked to identify candidate components for the first implementation of the BrainPhone and at this stage I played an advisory role. Currently, this system is being developed further by a subgroup of the NEL, formed and based on my initial work many years ago.

The creation of an HTTPS accessible database for neural data storage and mining

This was a part of the original designs in the ESPA framework, but has been implemented by a team effort of the NEL.

Preliminary tests of the Phase I BrainPhone

Initial benchtop evaluation and validation experiments were run by members of the NEL while I performed initial in vivo validation experiments in non-human primates.

Appendix: Optogenetics

For the optogenetics work, my focus was on the non-primate virus injection design and subsequent recording / stimulation sessions. This type of injection / recording had never been performed before in the context of optogenetics and we needed high precision injection and recording techniques. I developed a cannulated screw system that would allow multiple penetrations to the cortex in the identical location. This was fabricated by Kineteks and used by myself and the rest of the NEL team in numerous operations, and ultimately in the successful stimulation / recording sessions described in the chapter. I note that some of the techniques have been shared with other (neuroscience) laboratories at Brown.

On the use of “we” throughout this thesis

The nature of cross disciplinary projects with grand goals, such as the development of wireless implantable neural interface microsystems, is that they involve many people. This is a fundamental requirement for success when pioneering (in this instance a new biomedical engineering field), but using the proper pronoun for each context throughout a thesis as wide-

ranging as this would be both disjointed and confusing. In addition, as I mention above, the work by all of our teams is highly collaborative. Thus, for fluency and consistency, I have chosen to use the pronoun “we” when referring to all work completed either by myself, the NEL, or associated members of the Brown community, unless otherwise specified.

CHAPTER 2: The development of appropriate support technology and animal models to assess implantable device functionality

2.1 *Introduction*

When creating a device, one must visualize the challenge from a systems-level; a neural interface device alone is certainly unable to perform the desired operation of sensing neural activity and translating it into useful control signals. One must define methods for surgical implantation of the device to gracefully integrate it with the nervous system. The system needs power to be transferred to it, and thus needs external components to facilitate that power transfer and, in addition, retrieve the all-important data for further processing. Lastly, an electronically

active device must be protected from the environment to function properly, but also must maintain biocompatibility. These topics will be the subject of this chapter, focusing on the supporting systems for an implantable neural interface.

This chapter is broken up into three major subsections. In section 2.2: Hardware and software for acquiring and processing neural and diagnostic data we discuss the methodology used for data collection. The neural interfaces created through this thesis are novel and thus do not have support hardware readily available from a commercial vendor to accomplish tasks such as data processing and storage. Thus, we developed a host of in-house hardware and software elements allowing us to inspect and process wirelessly collected neural data. Section 2.3: Development of surgical techniques and tools for neural prosthetic device development we detail our design and fabrication of unique surgical support equipment enabling well-controlled implantation of the neural interfaces into both large and small animals. While neural interface device implantation in non-human primates has become somewhat commonplace, monkey is not always the most compatible animal model. In this section, we discuss the relevance of a new animal model, swine, for neural interface development and research, as well as the supporting surgical equipment we designed specifically for this purpose. The last section, 2.4: Protecting biologics and electronics by polymeric, metallic, and ceramic separation describes an understudied, yet critical topic for implantable electronics. Not only must an implant function in (relatively) non-conductive air on the benchtop, but also all of the integrated circuits must perform their operations without failure immersed in the highly conductive and corrosive environment of the body (Foster, Schepps, Stoy, & Schwan, 1979; S. Gabriel, Lau, & Gabriel, 1996). This last section attempts to highlight the underlying physical (electromechanical) properties of insulating materials and how these materials interact with biological tissues.

2.2 Hardware and software for acquiring and processing neural and diagnostic data

Introduction

The neural interfaces we will describe in later chapters can be simplified by imagining a box, where on one side, N-parallel channels of analog voltage are entering the box (input) and on the other side, a single stream of digital data is being transferred out (output). In addition, there is a dotted line pointing towards the box representing the wireless power supply (Figure 2-1). For now, this detail will suffice.

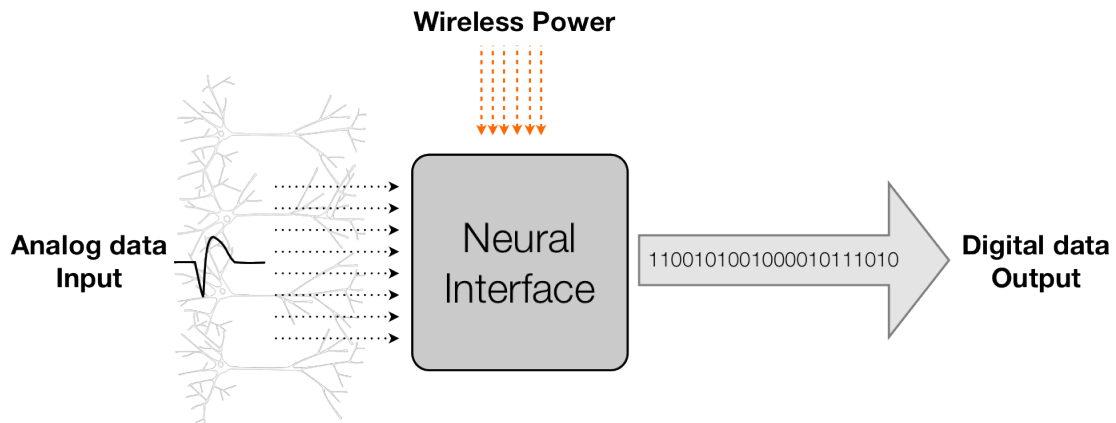


Figure 2-1: Simplified representation of the neural interface inputs and outputs. Parallel analog voltage information is sensed and converted into a serial stream of digital data.

The question becomes, how do we receive the digital data from the neural interface and translate it back into a voltage representing that on the microelectrode tip, and how do we safely deliver power to such a system? As discussed above, there are no commercial off the shelf (COTS) recording systems available for a novel microelectronic neural interface like that developed through this thesis. Several commercial data acquisition platforms do exist and are commonly used by electrophysiologists today (for example, Blackrock Microsystems' Cerebus platform, Plexons' Omniplex platform, and the Tucker Davis System 3). In addition to hardware incompatibilities, the data format for most recording systems are proprietary and thus inherently

inflexible to our needs. Thus, we designed a custom electronics package to give us the flexibility to work with various data types and control several modalities of power delivery to the microsystems. This system developed is called the Common Platform System (CPS).

2.2.2 Common Platform System (CPS) and Controller

Inputs and outputs

The CPS has many inputs and outputs. Power output options include radio frequency (RF) current driver for inductive coupling, an infrared (IR) laser for light delivery to a fiber optic cable coupled to an implant (devices powered by light alone), and a direct line output to drive the system. While both the RF and IR power delivery options coincidentally deliver a clock signal to the implant along with the power, the CPS includes a separate clock output line for the direct line power pathway. Available data input methods to the CPS are a direct TTL (0 - 3.3V) line, and a line from IR receiver (photodiode with amplifier) collecting modulated infrared light output from the neural interface device. A separate RF receiver unit was made, as a component to the Subacute Brown NeuroCard (see *Integrating state-of-the-art microelectronics with the nervous system: the Subacute Brown NeuroCard* for more information), to receive high-frequency FSK modulated data at 3.2-3.8GHz. All data inputs are then fed into a single field programmable gate array (FPGA) running a custom data-packaging program. This firmware program has two objectives: a) decide if the data synchronization signal is present in the incoming data, and if so, b) send the data to an output buffer to be passed on to one of the many data output options on the CPS.

The CPS implements the following physical data interfaces: a) the National Instruments parallel data acquisition board (NI-PCI6533, National Instruments, TX); b) a high-speed USB 2.0 interface based on the Cypress EZ-USB library, enabling throughput near 100Mbps; c) a custom Cerebus (Blackrock Microsystems, UT) digital to analog converter for use with the standard Blackrock Microsystems (BRM) neural signal processor data acquisition system (the BRM

system is currently used by our colleagues and collaborators in the neuroscience department locally at Brown as well as several other universities around the country); and d) a 1Gbps Ethernet interface (ZestET1 board with the GigEx chip from OrangeTree – see *Creating a powerful, wearable, and open standard neural signal processing platform: the BrainPhone*) for distribution of the data onto a network at truly impressive data rates.

Next, we will describe the radio frequency power monitoring components of the CPS. It is imperative to maintain tight control over forward power levels not to inadvertently damage living biological tissues.

RF power monitoring

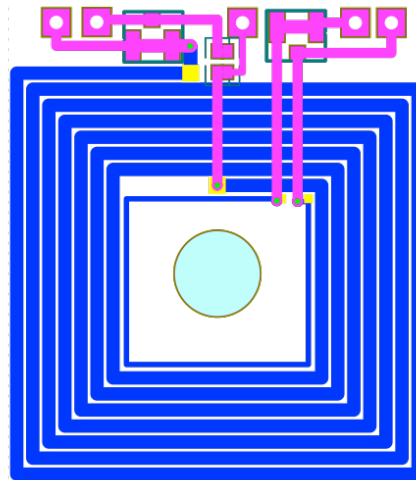


Figure 2-2: Pattern of primary and flux coils printed on the PCB for power delivery to the externally powered microsystem. Printed circuit board coils are very efficient because spacing can be well maintained, however the number of turns is limited.

The common platform hardware includes a board whose dedicated functionality is to monitor and deliver radio frequency energy for inductively coupled powering schemes. This power delivery pathway must be monitored, as the electromagnetic radiation not transferred to the microsystem will most likely be transferred to biological tissue and will in turn result in heat generation (think microwave oven). The RF monitoring board measures three variables: the forward voltage

delivered to the primary coil (7 turns printed on PCB), the reverse (reflected) voltage along that same path, and the flux voltage (measured from a single turn coil placed in the center of the primary coil). A diagram of the setup can be seen in Figure 2-2. The forward and reverse voltages were calibrated by placing the primary coil in free-space (i.e. with no secondary) and recording the difference between the forward and reverse voltages. Ideally, these would be equivalent measurements. The flux voltage measurements were calibrated by placing a bare microsystem substrate (printed with a secondary coil and capacitors to match the frequency) at a given distance from the primary coil with a known load. Thus, for a given forward voltage, a microsystem power draw could be expected and calculated. The flux coil measured the returned flux emitted from the secondary coil. Calibration values were recorded with the known- microsystem load and used as an offset during normal microsystem operation.

Digital to Analog Converter

As mentioned above, the common platform system has a dedicated output for providing data formatted for a Cerebus (BRM, Utah) Neural Signal Processor (NSP). This data path was developed to allow us to accelerate our development since the software for data collection and processing was already created, tested, and sold as commercial software called Cerebus Central (BRM, Utah). This added box was placed in the data stream between the CPS and the NSP. The NSP requires serial analog voltages as input. Since our microsystems (see *Chapter 3 and Chapter 4*) inherently output digital signals, and thus sends digital signals to the CPS, we collaborated with Blackrock Microsystems (then, Cyberkinetics) to co-develop a digital-to-analog converter (DAC). Data was transferred from the CPS (digital) into the DAC to become analog, then into the standard NSP (amplifier) input and through the standard Cerebus data path.

At first pass, this DAC seems unnecessary: why go from digital, back to analog, to finally return to digital in the end? However, the ubiquity of the Cerebus in neuroscience as a neural recording tool made it absolutely critical to a) format our output to be compatible with such a

system, and b) compare our in-house recording platform to the performance measures of the Cerebus platform. The addition of the DAC injected a small ($\sim 5\mu\text{Vp-p}$) repeating noise at the sampling rate to the test signals, but this did not distort the neural signals beyond recognition. In fact, this system was used successfully with a colleague (Sunmee Park) to record acutely through a completely optical (power and data) microsystem. Her microsystem begins to approach the fully implanted network of devices as schematized in Figure 1-5.

RJ45 Pin #	Wire Color	Signal Name
1	White / Green	CLK+
2	Green	CLK-
3	White / Orange	GND
4	Blue	SYNCH+
5	White / Blue	SYNCH-
6	Orange	+3.3V
7	White / Brown	DATA+
8	Brown	DATA-

Table 2-1: Pin designations for the DAC interconnect box fabricated by Blackrock Microsystems.

The CPS has many externally controlled settings (data source choice, forward RF power level, etc.) that must be managed by a remote PC. We thus created a small library of custom C++ code leveraging existing cross-platform user interface libraries (Qt 4.7.6 open source, Nokia). A human interface device (HID) profile was created for the CPS to communicate with the PC over standard HID USB (much like a computer mouse or keyboard). Since the data rate necessary for the control signals was not high, σ (kbps), we could use this USB descriptor (as opposed to the incoming neural data from the microsystem, which may run as high as 50-100Mbps). The custom control software, called CPS Controller, also recorded statistics on the performance of the microsystem such as net power delivered over time, or photodiode voltage on the input to the

CPS over time. These values, along with others, were stored in a local SQL-lite database created by the program for later reference (for complete description and general documentation on CPS Controller, please see - http://constellation.brown.edu/index.php/CPS_Control_Software - this contains links to both implementation and interface information).

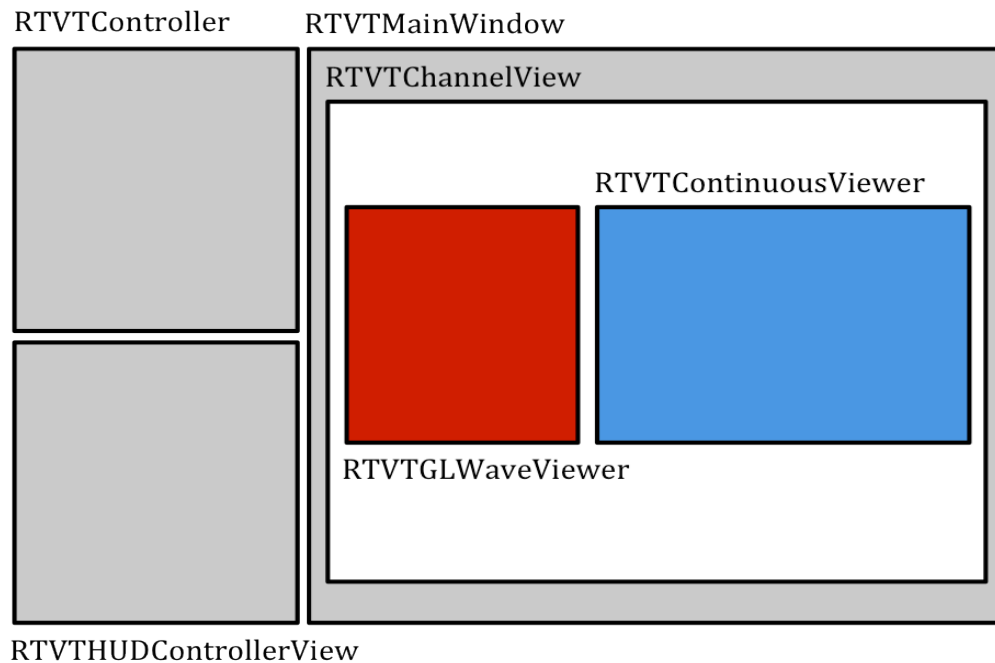


Figure 2-3: Layout of RTVT display. Class names are above / below each block. Shown later during operation and here schematically, the RTVTMainWindow is showing 100 RTVTChannelViews with only the RTVTGLOWaveViewer display object in the container class. Here we show how two different visualizer plugins can be displayed within one RTVTChannelView.

In brief, the user selects a number of virtual instruments to analyze the microsystem (i.e. power meter, LED, text field, etc.) and a data source (i.e. flux voltage, net power calculation, USB connection status, etc.). This collection of instruments makes up a “configuration,” which is later saved to an XML on disk and can be reused each time the program is instantiated (see Figure 2-3). Many configurations may exist at one time, and the appropriate one chosen since we develop systems with myriad powering and data telemetry schemes (power over IR, wire, or RF

and data collection over IR, wire, or RF). Instruments may also be saved as XML files and loaded at runtime, allowing them to be adjusted without requiring a CPS to be connected.

CPS Controller can be run on any Intel-based PC running UNIX, Windows, or Mac OS X. A fork (or branch, depending on the version control implemented for each program) of the source code were made for each platform and compiled to binaries that are also directly available from the Constellation server (see – *Content management systems for patient and subject data organization: Constellation*). The GUI application can be seen in operation with an externally powered neural interface in Figure 2-4.

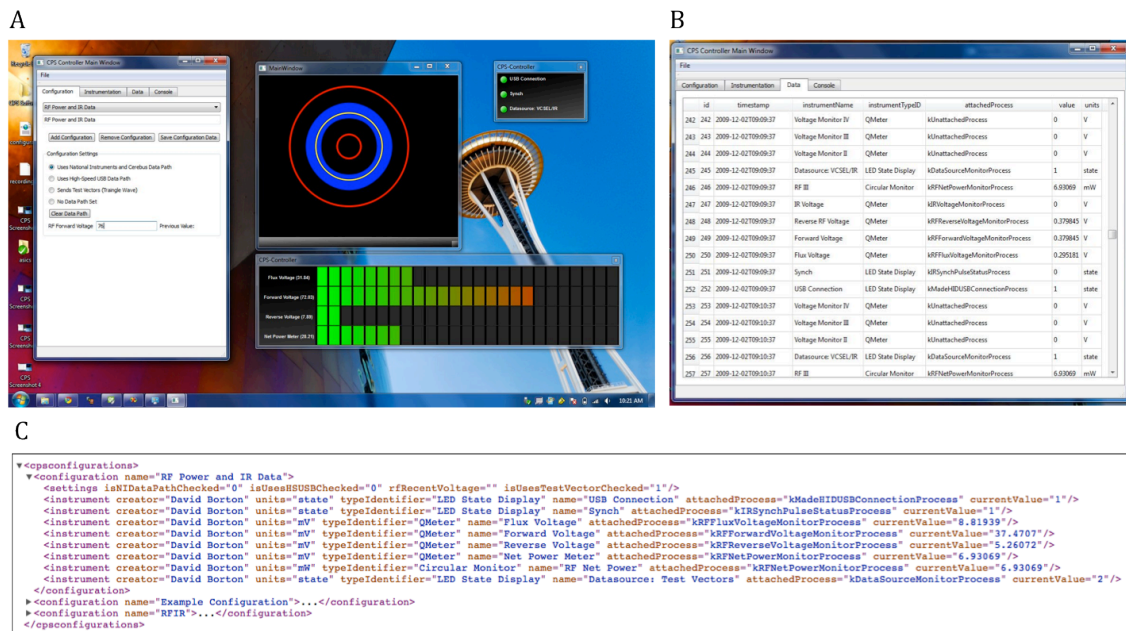


Figure 2-4: CPS Controller – Instrumentation widgets (A), data logging (B), and XML configurations file (C). The software gives the user active evaluation of system performance and logs the information for later analysis.

In the next section we will discuss visualization software for neural data. Thus far, all data visualization was diagnostic in nature for electronics, displaying information from the CPS.

The following software was specifically designed for neural data display for diagnosis of biological activity.

2.2.3 Real-time Visualization Toolkit (RTVT)

Introduction

It is always helpful to visualize data and neural data is no exception. Many illustrations of this can be found in fields ranging from information genetics to economics to distribution of taste buds (see *informationisbeautiful.com* for some interesting examples). For neural data, visualization generally takes the form of overlaid spike waveforms, histograms, or a subsampled continuous data stream. While there are several solutions commercially available for real-time neural data acquisition and display (Cerebus Central, Plexon, Tucker Davis, Trellis, etc.), they are all proprietary, expensive, and non-customizable, at least for our use. Thus, as was the case for neural interface data acquisition hardware, to meet our needs we developed a custom neural data visualization system.

Methods

We built a program based on C++/MFC software originally proposed to visualize two independent channels of the data stream coming into the PC from an internal National Instruments DAQ board. This solution allowed us to check for aberrant signal (external noise sources) and save that data to disk, as well as replay data recorded on earlier dates. While this software was extremely useful for our earlier 16-channel microsystems, it was unable to handle the visualization of 32 or 100 channels of data from our more recent microsystems. Thus, we developed a new system from scratch using a high-speed USB 2.0 interface instead of the NI DAQ board. Lower-level drawing techniques, such as OpenGL for fast waveform display, were implemented to increase the speed and flexibility of the program. This new system was labeled the Real-Time Visualization Toolkit (RTVT) with the lofty goal of displaying, saving, and

filtering data in real time. The program was written in C++ with Qt as the cross-platform library abstraction so that it could be compiled on UNIX, Mac OS X, and Windows. There are several layers to the program: a) a subsystem that controls USB data transfer into local buffers for later manipulation as well as data writing to disk; b) a configuration layer where the user defines constants of the particular microsystem being used; and c) a visualization window. We will discuss each system briefly below.

Subsystem

The subsystem has three actions: 1) it pulls incoming data from a data source (USB, Ethernet, file, etc.) and places it into an appropriate buffer for processing; 2) it rearranges the serial stream of data into a set of parallel buffers, one for each channel, so that later processing can be done on a channel-by-channel basis; 3) it writes the serial stream of data from the data source to a file on disk in binary format for later consumption. These three functionalities are discussed below.

A custom USB 2.0 driver was written based on the EZ-USB (Cypress Semiconductor) library to allow the PC (32-bit and 64-bit systems) to communicate with the device. Cypress provides a library for interfacing with the device from a C++ program and we used those libraries in our implementation. The subsystem creates a thread (Thread 1) dedicated to USB-to-program buffer transfer, since this process cannot be slowed down or data may be lost. This thread simply waits a given amount of time, then transfers the data from the data source (here, USB) to the dedicated buffer in memory (called the back buffer) and appends it to a storage buffer for transport to disk by another thread, copies it to a working buffer for further processing, then waits until it is called again. The data source has been completely abstracted allowing future data transfer mechanisms (USB3.0, TCP/IP, etc.) to be dropped into place without significant refactoring of the code. The working buffer acts as the second buffer in a double-buffer scheme so that the back buffer can be written to while working buffer is read from. Another thread

(Thread 2) is created to parse the serial data in the working buffer into synchronously accessible channel buffers for later access by the visualization layer. Thread 2 simply waits until new data has arrived, then goes from beginning to end of the working buffer, appending the data into each channel buffer. Pointers are kept in memory to assure proper read-write locations. A third thread (Thread 3) is created to handle reading from the storage buffer and writing to disk independently of other processes. The entire data flow of the subsystem can be seen in Figure 2-5.

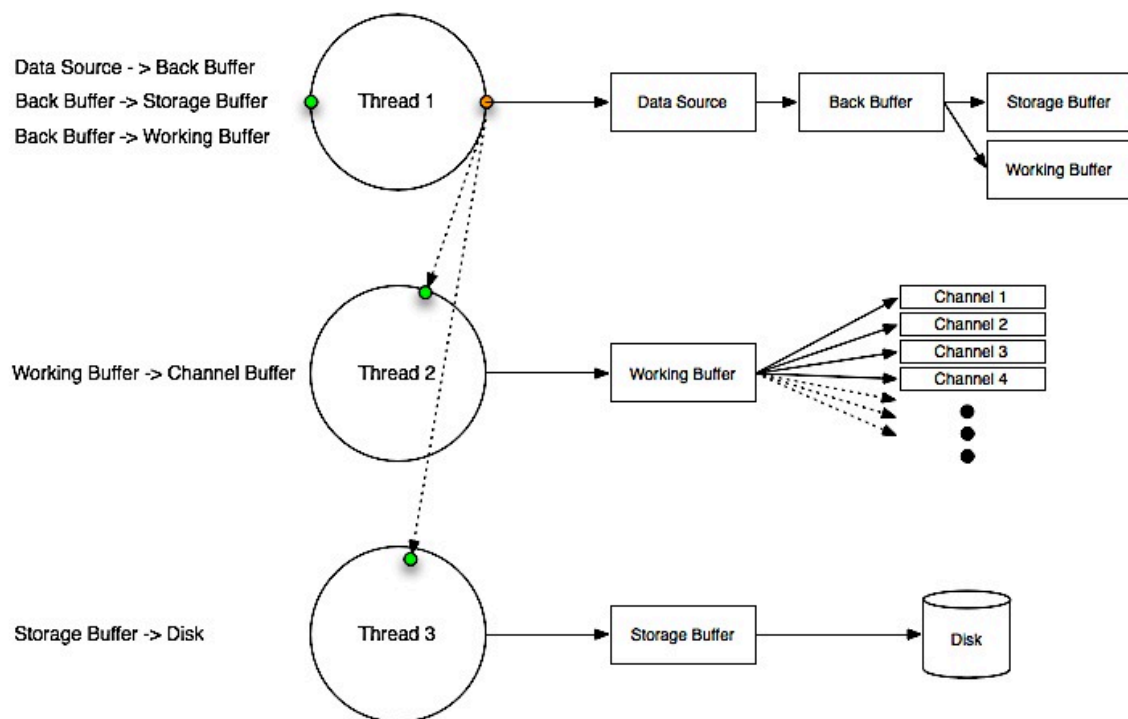


Figure 2-5: Subsystem and thread operation. Square objects represent buffers where data is either transferred into or out-of during the runtime of a singular thread. Threads (or system processes) are shown as circles and once a thread has completed an operation, it is terminated. A small circle on a thread represents a spawn of a new thread. Here, Thread 1 spawns processes Thread 2 and Thread 3 for parallel processing of data. Working and Back buffers are double-buffered (via pointers) to assure smooth operation.

Configuration

Configuration parameters, such as action potential threshold, number of channels to be displayed, and root directory for data storage are likely to change over the development cycle of a device, and certainly will change when developing myriad devices that will all need unique visualization settings. There are also configuration parameters that will not change very often; such as the subsystem parameters that are specific to the device we are testing (e.g. number of samples in a frame of data). In order to make switching back and forth between different configuration setups easier, a configuration file type was created. A configuration file is an XML document containing the configuration name, type, and then a long list of variables with associated values. XML is a key-value coded language – here a variable name is the key and the value the variable should take is the value paired with the key, hence key-value coding. This file is loaded at startup of the RTVT program and is used to initialize the subsystem. One main reason to use XML as the coding for the document is that the file can then be edited outside of the program by any number of text editors. This XML file follows the design pattern of the CPS Controller configuration file, as shown above in Figure 2-4.

Visualization

The primary objective in creating this software was to provide data visualization. We constructed the program to be modular, allowing new visualization methods to be implemented and “plugged-in” as they are designed. Any number of visualization objects can be placed within a ChannelViewer container class, which holds and controls access to the data buffer for the channel. When a view would like to use the data buffer to calculate or display, it must request a lock from the ChannelViewer – this way one can avoid multiple-thread access and read / write errors. Currently, we have implemented two visualization classes: 1) the WaveViewer class and, 2) the ContinuousViewer class. Both classes are optimized for OpenGL hardware accelerated graphics (> version 2.1), which takes some burden off of the CPU for drawing. Each visualization

object optionally can contain a method to draw a heads up display (HUD). This HUD is sent to the configuration block of the program and allows for user input into what is displayed in each visualization class, as well as the user-customizable parameters. For example, the WaveViewer class contains a description of the numerous thresholds that can be set to better extract action potentials from the neural data. This information is displayed and settable in the configuration HUD for the wave viewer (see Figure 2-6). All documentation, including implementation and interface information is available on the constellation.brown.edu content management system. It was a high priority that this program is open-source and free for other researchers to adapt to their needs. Documentation was automatically generated with DOXYGEN, as with the CPS Controller software.

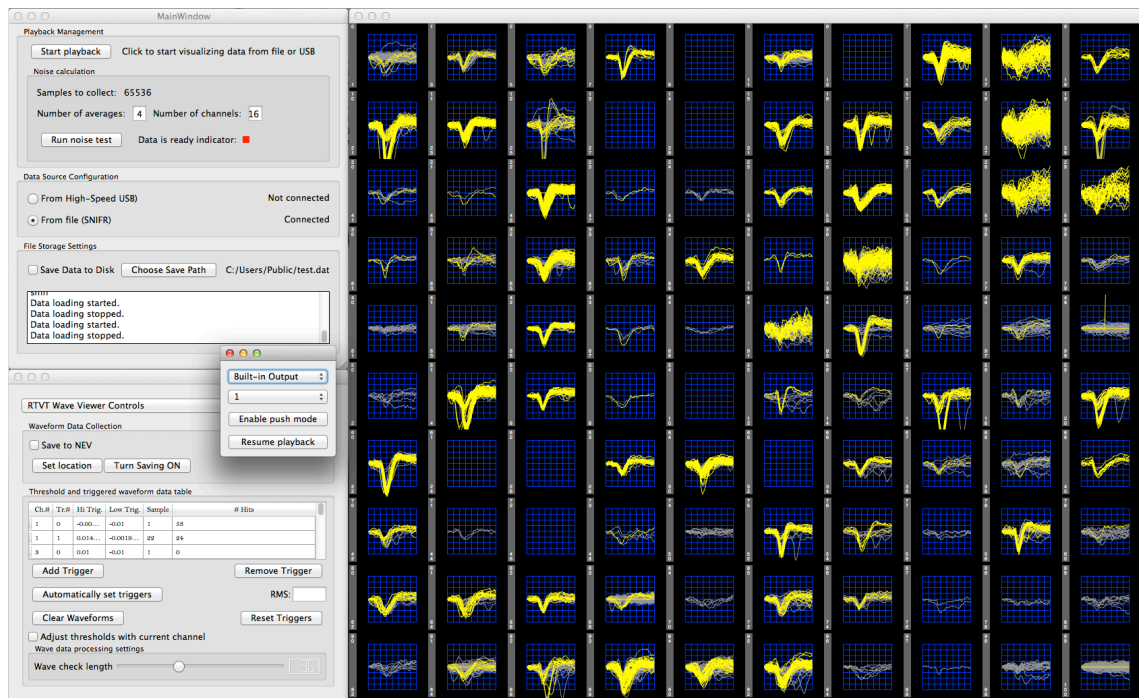


Figure 2-6: Snapshot of RTVT running 100 channels of data recorded from monkey JV using an SBNC implantable system. The RTVTController in the upper left handles data source control, data archival, and console output for diagnostics. The heads-up display (HUD) in the bottom left handles preferences settings from plugins. Here, we are viewing the RTVTGLWaveViewer plugin settings where threshold crossings can be set, along with waveform update speeds and output to NEV (neural event) files. The popup window is another plugin handling audio playback of the selected channel.

Use and limitations

While the RTVT application has allowed us to visualize, save, and analyze our collected data from many different microsystems (SBNC, BIC, OBIC, etc.) there are several limitations to the system. First, since the application is run within a non-real-time operating system (Windows, Linux, Mac OS X), there is no guarantee that events (like data transfer from USB) will occur at expected time steps. User inputs on many systems will interrupt and / or delay the operation of a particular application, thus adding increased uncertainty in timing (exact delays are impossible to quantify precisely due to operating system construction, but will be on the order of 2-30 ms). In addition, processing within each thread of the subsystem (described above) may be delayed variable amounts of time. To alleviate some of these issues, we have used realignment steps (wait for threads to finish before continuing). Unfortunately, these measures significantly slow down the operation of the application. This slow-down affects the ability of the application to perform all actions expected in a given time step. For example, if the user would like to display 100 channels of overlaid waveforms with the WaveViewer class, saving to disk can be slightly slowed down and cause data to be lost (or not saved). This tradeoff completely depends on the xPC being used for running the application; on a modern system there is no problem displaying and saving 100 channels of data (100 channels sampled at 20ksps with 16-bit sample size). However, if the user would like to display more channels or perform more complicated operations, s/he will without a doubt run into this timing issue and need to switch to a real-time system. We are developing the BrainPhone (see *Creating a powerful, wearable, and open neural signal processing platform: the BrainPhone* for more details) as an embedded piece of hardware to handle most of the more time-consuming tasks currently done on the PC, which, will eliminate many of the limitations mentioned above.

Another limitation is that an interface has not yet been created to allow separately compiled plugins to be added to the program at runtime. This would require minor modification

to the RTVT code base and will be completed at some point. For the time being, all plugins must be added to the main RTVT project and compiled together.

2.2.4 Encapsulation Test System (ETS) data acquisition, storage, and online display

We developed a data acquisition system specifically designed for collecting and storing encapsulation / packaging results for future analysis. This system included a custom printed circuit board for recording from up to ten systems, clock generation, an insulated bath containing oil for heat management, an electrometer (Keithly 6515 – fempto-ampere sensitivity) for precise current measurements, and an ohmmeter for resistance measurements between adjacent traces. This hardware we call the “frontend” of the DAQ system and discuss in detail in the “*Protecting biologics and electronics by polymeric, metallic, and ceramic separation*” section of this thesis. The current section will focus on the “backend” processing which consists of a custom C# program to monitor, control, and archive collected data (Blizzard), a MySQL database on a remote server for data archival (ETS_db), and an Adobe AIR cross-platform application for data visualization called DataPlotterWeb.

Blizzard

The encapsulation test system control software, Blizzard, was written in two distinct modules: 1) the hardware abstraction layer (HAL), and 2) the graphical user interface (GUI). The HAL handles communication with all external peripheral hardware components, i.e. the electrometer, ohmmeter, the custom PCB’s for encapsulation test unit control, and the voltage source. This layer is instantiated in the GUI and exposes several accessor methods to control the hardware configuration and to take measurements. The HAL was written in C# and the .NET frameworks provided by Microsoft (Redmond, WA) using several National Instruments (Austin, TX) libraries to communicate with the peripheral hardware. At startup, the GUI initializes all hardware connected to the HAL and connects to a remote database, the ETS_db (stored on the constellation server in MySQL), and downloads the most recent data locally for analysis by the

user. The main function of this GUI is to collect and archive measurements made on the encapsulation test units, as well as allow debugging of hardware being used to probe the encapsulation test units. Collection frequency is set in the preferences of the GUI. Once the program is set to run, it will collect measurements at a given frequency, store the data in a local database, and upload the new data to a server (constellation) for backup and remote viewing. On each upload cycle, the local and remote databases are compared against each other to identify differences. All differences are merged to assure both locations maintain all the data (in case one fails). In this mode, Blizzard can run autonomously.

Documentation for the Blizzard application, as well as a link to the database schema used for this project can be found on the constellation.brown.edu website.

DataPlotterWeb

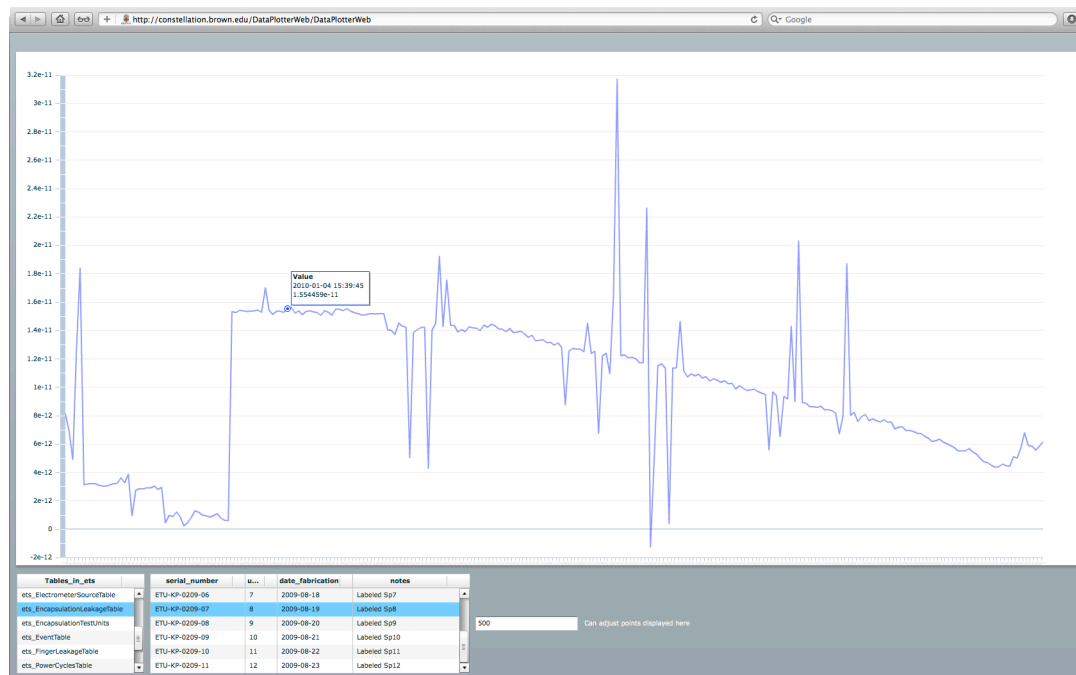


Figure 2-7: ETS data visualized live with DataPlotterWeb. Data is shown newest to oldest.

An immediate benefit of having data uploaded on each collection cycle (see above) is that data can be viewed “live” by any remote machine with access to the database. Generally, while databases are incredibly powerful for data storage, they are not visually intelligible. We created an Adobe Air program in the integrated developer environment (IDE) Flex Builder for visualization of the various measurements taken by the ETS. The benefit of using Adobe Air is that it is cross-platform and can also be viewed on the web through any web browser. This application consists of a large window displaying the entire data series of a selected table (or measurements from a particular piece of hardware). The displayed measurement can be selected in a table at the bottom of the page, which, is updated live from the database (see Figure 2-7).

2.2.5 Offline data processing techniques

In this dissertation, all analysis methods were conducted in MATLAB with a combination of custom and well-documented scripts. Since data was collected as raw binary files (SNIFR), the data was first de-serialized and placed in an $m \times n$ element matrix for processing. Next, depending on the type of information we were looking to extract, for example neuronal action potentials, the data was filtered, generally with a finite impulse response (FIR) band-pass filter from 500Hz to 5000Hz. Since we were looking for spikes, this filter generally reduced the low-frequency noise distracting our spike extractor. The data was then passed through a Multiscale Teager Energy Operator (MTEO), published in (Choi, Jung, & Kim, 2006), which extracts spikes based on large deviations from the standard deviation over a defined window, then finds the peak of the waveform from the modified energy operator, and finally extracts a 2ms window of data around the peak for display. Figure 2-8 shows a simple example of spike the spike extraction process. The MTEO spike extractor is described later in *Chapter 5: Creating a powerful, wearable, and open neural signal processing platform: the BrainPhone*. In order to differentiate multiple units on one channel, and if the recorded data was of sufficient length, we employed a density clustering algorithm developed in part by our colleague Carlos Vargas-Irwin

(Frank Wood, Black, et al., 2004), though this was rarely necessary for our needs. For all of our low frequency potential signal analysis, signals were band-pass filtered between 0.1Hz and 100Hz, generally with an FIR filter. The signals were then down sampled and power spectrum densities were taken within given bands (i.e. alpha, beta, gamma).

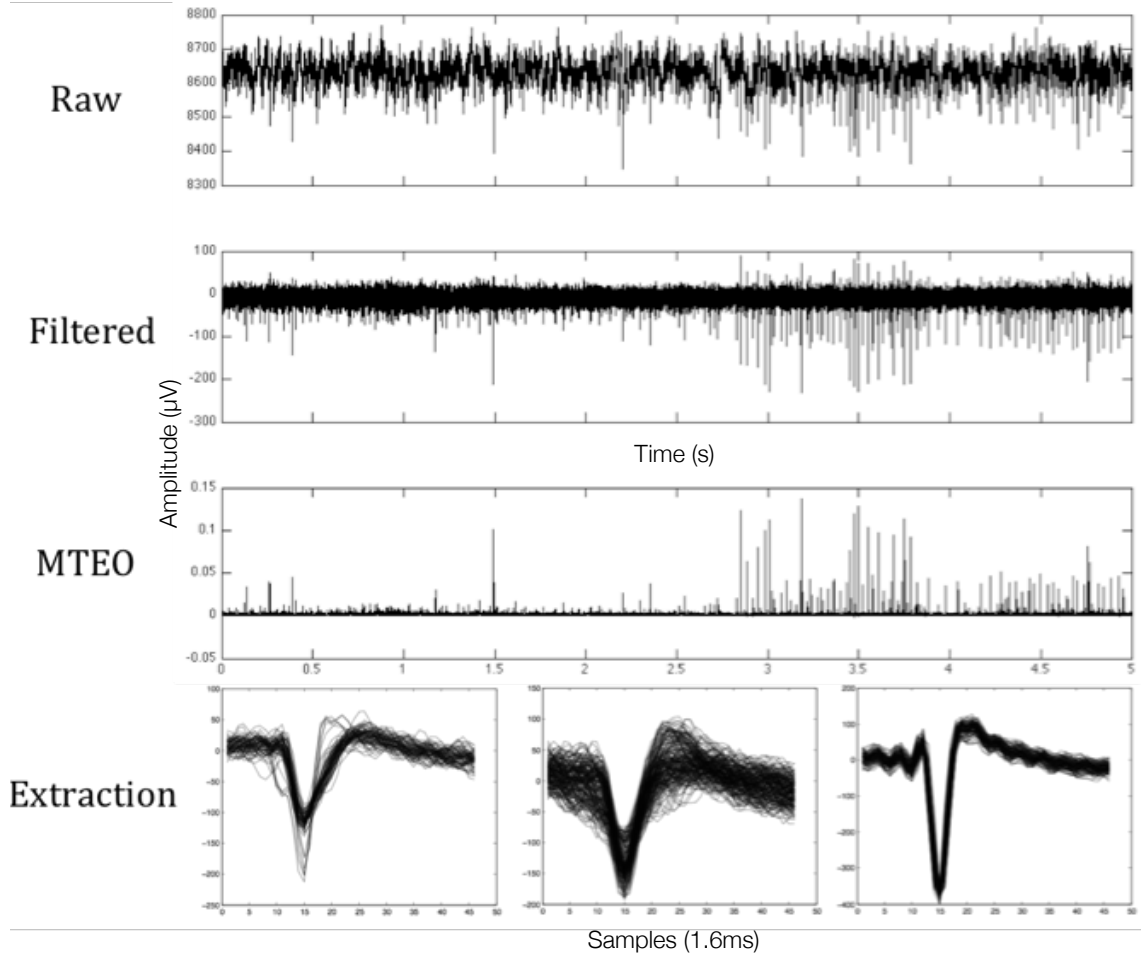


Figure 2-8: Spike extraction from raw data. Data is filtered with a simple bandpass filter from 300Hz – 5300Hz, then passed through the MTEO operation to find peaks in the filtered data. The peaks are thresholded at N-times the standard deviation of the noise.

For some of our more recent freely behaving non-human primate recording sessions, we decided to implement a single-trial based decoding scheme. Our colleagues at Stanford University and the University College London Krishna Shenoy, and Maneesh Sahani have

pioneered the use of state-space dynamical models, developed from applied mathematics techniques in neuroscience (A. Afshar, Santhanam, et al., 2011). The state-space idea, described thoroughly in (Ganguli, Bisley, Roitman, Shadlen, Goldberg, & Miller, 2008) proposes that highly heterogeneous and that the remarkably dynamical correspondence between single neurons and attention can be explained by a network model in which generically high-dimensional firing-rate vectors rapidly decay to a single mode, or “state.” The progression or transition of the population activity from one mode to another can be visualized as a state-space. Single-trial neural trajectory analysis, described below, defines this space in two dimensions of the decomposed firing rate across a neural population in motor cortex while Ganguli et al. focused on lateral intraparietal area (LIP).

The single-trial analysis method takes a windowed metric, here firing rate, within the last 100ms, across all input channels (here 100) and computes a reduced dimensional state of the network via eigenvalue decomposition. An analogous method is to use principal component analysis to find the greatest dimensions of variation and recast the measured value into that space. However, Byron Yu, et al. have shown that the Gaussian-process factor analysis method more realistically postulates the activity of a neuron (Yu et al., 2009) and will be used in later portions of this thesis for neural trajectory analysis.

2.2.6 Content management systems for patient and subject data organization: Constellation

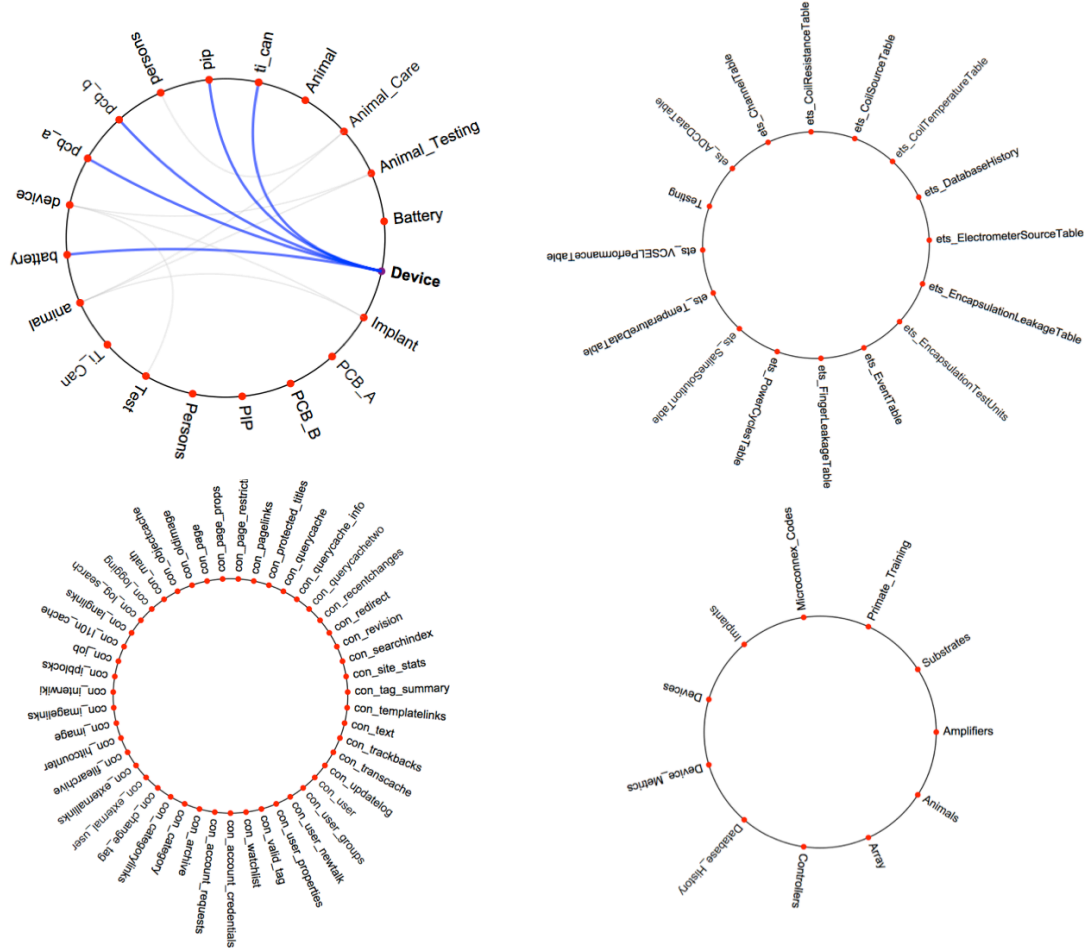


Figure 2-9: Schemas of four databases currently used in our laboratory and housed on the Constellation server. A schema is shown with relations shown in blue (A) of the SBNC device and recording database. This database was the first created and used for pre-clinical data collection. A-C show similar databases for the Encapsulation Test System, Constellation collaboration website, and the BIC projects respectively. All databases were implemented in MySQL and managed from a mix of custom software packages (Blizzard, Athena, and the Constellation Wiki) discussed in the text.

Much of the work described in this thesis was sponsored by the National Institute of Health through a Bioengineering Research Partnerships (BRP) grant. As part of this grant, we were tasked with creating a collaborative medium for all researchers on the award to share data and ideas relating to the project. To meet this goal, we created a web-based content management

system based on the well-established MediaWiki (Commons, n.d.) Library, the same engine on which Wikipedia is based. This system is a combination of databases and PHP (Personal Home Page, a hypertext preprocessor language highly utilized on the internet) scripts to enter and retrieve data. A diagram of some relevant database schemas is shown in Figure 2-9.

2.3 Development of surgical techniques and tools for neural prosthetic device development

2.3.1 Introduction

We read numerous articles in journals such as the Journal of Neural Engineering detailing incredibly impressive circuitry, and in some cases, systems for neural signal recording. However, the ratio of in vivo experiments to benchtop run experiments is astoundingly low. Across the field of neural device development and engineering a widely underestimated component is long-term viability in a biological environment. This includes issues such as surgical implantation and tissue response to foreign materials. How will we place the animal in stereotaxis? What is the risk-benefit tradeoff and how do we balance it? How big must the craniotomy be to accommodate the implant while not being a serious health risk to the patient? All of these questions are extremely important to answer on the quest to create a successful implantable device, and specifically here, a neural interface.

To answer these questions, we held discussions with local neurosurgeons Dr. Ming Cheng, Dr. John Mislow, and Dr. James Barrese, as well as with general surgeons Dr. Selim Suner and Dr. Moses Goddard. Their input has led to a refined implantation protocol that not only meets our research needs, but also will make the translation into a clinical human implantation protocol more straightforward when the device transitions into clinical trials. In this section, we will discuss several key projects that highlight the cooperation between surgeons and engineers in order to develop a consistent surgical procedure. These are a) an evaluation of pneumatic insertion parameters for the Brown made microsystems, b) the addition and development of a

porcine animal model for neuroprosthetic device testing and development, and c) the development of a large animal stereotactic frame enabling rapid device development.

2.3.2 The addition and development of a porcine model for neuroprosthetic device development

Modern medical device development has improved the lives of countless injured or diseased individuals. For example, more than 400,000 cardiac pacemakers are implanted every year in the U.S. (>4 million implanted in total) (Buch, Boyle, & Belott, 2011); over 200,000 total hip replacements trade titanium for bone, allowing people to walk and run again after traumatic limb injury. Developers of these devices (and myriad others) were confronted by challenges unable to be first addressed in humans directly. Instead, animal surrogates were used to validate the longevity, mechanical stability, biocompatibility, and ultimately efficacy of these devices. Without appropriate models it is unknown how long the translation process would have been from concept, to experimentation, and eventually, commercialization. Brain-machine interfaces (BMIs) are no different; they hold the potential to increase dramatically the quality of life for individuals suffering from brainstem stroke, advanced ALS, locked-in syndrome, and they face the same translational and development challenges.

For centuries, the preferred animal species for the field of neuroscience have been both rodents and primates (along with cats in the earlier experiments of Sherrington, but much less now). In rodents, neuroscientists gained incredible control over gene expression as early as 1974 (Jaenisch & Mintz, 1974), which led to fundamental breakthroughs in basic architecture and chemical signaling in cortical circuits. However, the morphology (lack of gyral patterns and size) of the rodent brain has prevented it from being a particularly good comparison to the human brain for many research directions. Non-human primates are regarded as the penultimate animal model for neuroscientific study and have been used extensively in the studies of higher cortical processing and neurological disease treatment. However, it is exactly their closeness to humans that can make working with monkeys ethically complicated and costly.

Indeed, there has been a critical need for a large animal model with complex sulcogyral topography and ethically more acceptable for study (the use of swine for consumption across a wide range of cultures around the world greatly reduces the societal concern for their use in research). Within other areas of research, such as toxicology (Svendsen, 2006), diabetes (Bjarkam, Cancian, Larsen, Rosendahl, Ettrup, Zeidler, Blankholm, Østergaard, Sunde, & Sørensen, 2004) and experimental surgery (Richer, Lacoste, Faure, Hauet, Ferrié, & Carretier, 1998), the use of swine has increased dramatically over recent decades. The emergence of pig experimental models reflects the considerable resemblance of the pig to the human neuroanatomy and physiology.

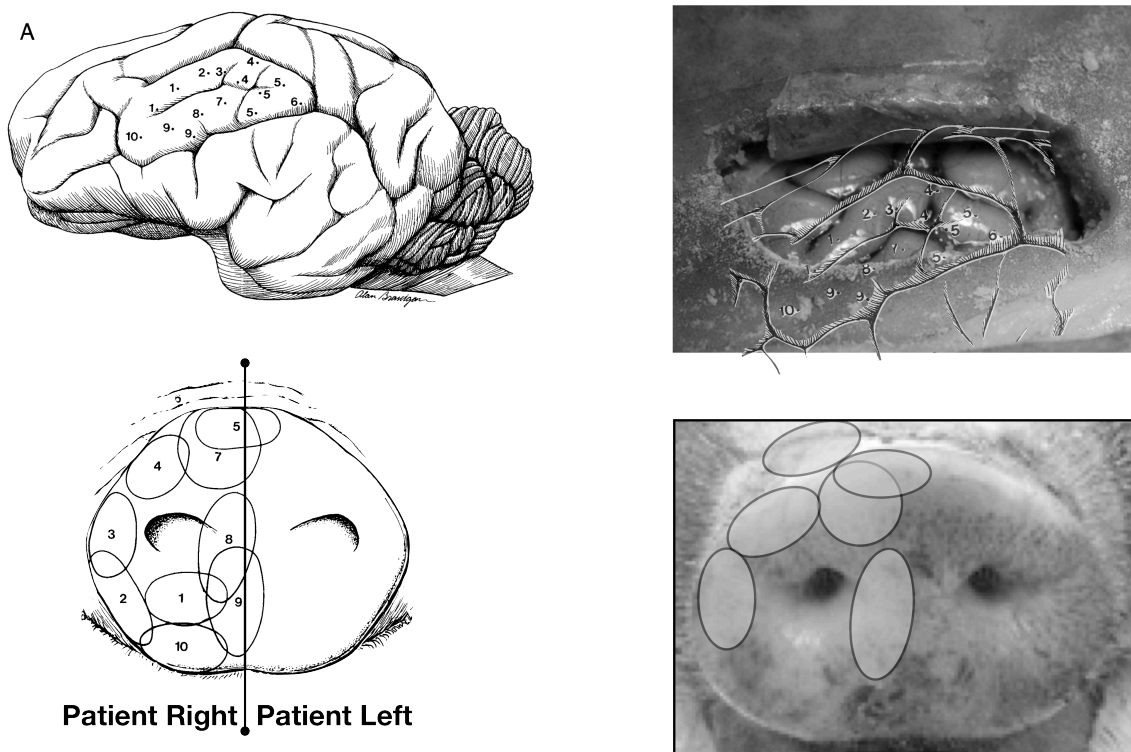


Figure 2-10: The upper rostrum area of the swine primary somatosensory cortex in diagrammatic form (left). Images show actual somatotopic areas in Yorkshire swine (right). Overlays are drawn to highlight sensory regions of the cortex that we were targeting for implantation. Image adapted from Lind, Moustgaard, Jelsing, & Vajta, 2007 and own art.

In addition, pig is widely available due to commercial production, leading to development of standardized laboratory pigs. These have considerable ethical and economic advantages over primates. An extensive evaluation of pigs in neuroscience was recently compiled (Lind et al., 2007) and provides an excellent comparison between commonly used species used in neuroscience. In addition, Figure 2-10 depicts the upper rostrum area of the primary somatosensory cortex in swine (Craner, 1991a, 1991b), an area we later used for our experimentation.

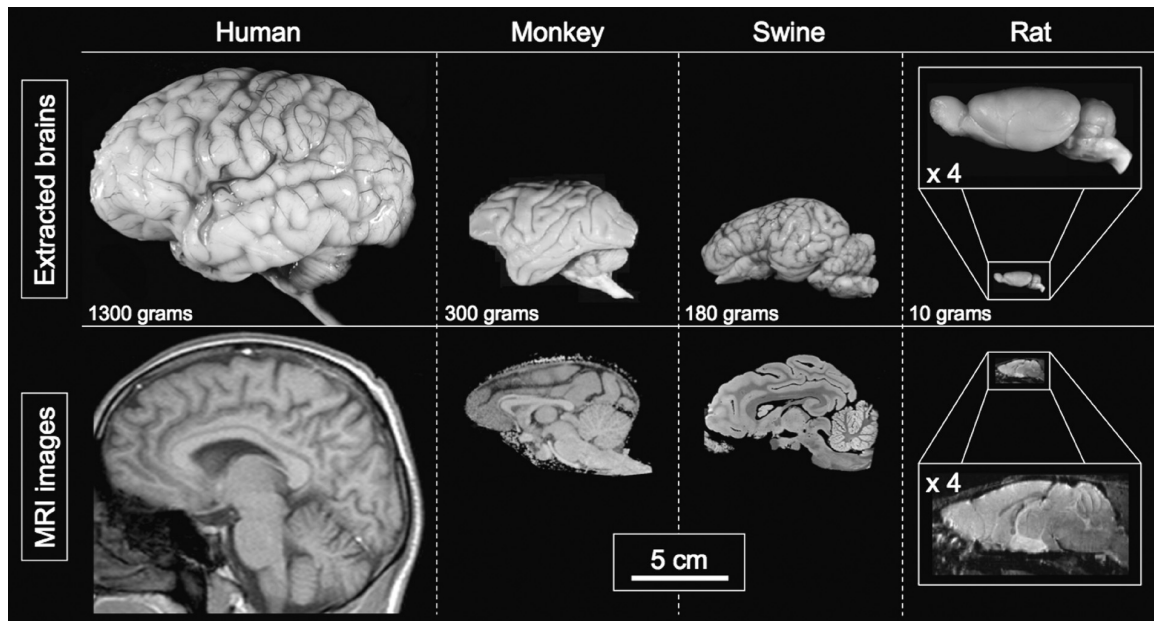


Figure 2-11: Brain size comparison between human, monkey, swine, and rat. It is notable that the size of the swine and monkey brain are very near each other. In addition, the swine, monkey and human brains are gyrencephalic unlike the rodent. Image from Sauleau, Lapouble, Val-Laillet, & Malbert, 2009.

Surgical procedures and considerations must be finessed for every device that comes in proximity to the human body in order to ensure maximal success of the implant. These considerations include: optimized thicknesses of packaging (electrical isolation) materials to achieve the “right” feel of the interconnect tether between the array and telemetric units on the

BIC system; choosing optimal fixation positions on the telemetric unit to maximize stability while reducing surgical complexity; and even defining incision patterns to minimize suture-line contact with the implant and, thus reducing irritation. Utilizing a swine model has allowed us to experiment with these factors, and has prepared us better for clinical trials when time comes. Rapid iterations of processes simply are not possible in the non-human primate model.

Long-term in vivo testing of the BIC microsystem has been done in body-temperature saline environments in the lab to evaluate leakage currents (ion transport) in and out of the packaged system, as well as in-plane across the substrate. While these tests are valuable, there are numerous potential problems on which this testing will not report. Mechanical stresses on the implant, relative motion of the skull from the brain/dura, and biocompatibility must be addressed in vivo. The swine model provides us with an animal we can experiment with in larger numbers than primates, and offers a cortical landscape that allows for comparisons with primates to be logically drawn.

Once we had established the pig as an appropriate model for this development work, the question arose as to which species would be most available, applicable, and affordable. For most medical research minipigs are used as they a) asymptote in weight at adulthood, and b) can be purchased from relatively genetically pure stock raised for research purposes – reducing unknowns between samples. However, a large frontal sinus pneumatizes the skull of many minipig species making the use of bony sutures unreliable for stereotaxic implantation as the distance between these and the brain structures may vary considerably between individuals (Bjarkam et al., 2004). In addition, in some species of minipig, the sinuses can be quite large, so large in fact that we would be forced to design our implantable devices for individual animals. Two possibilities of species arose: standard Yorkshire farm pigs, and Göttingen minipigs. The Yorkshire pigs are extremely accessible, inexpensive and have no extra sinuses in the cranium. However, the Yorkshire pigs have an incredibly fast growth rate, making experiments relatively

short-term. For device development, we only needed short-term experiments, on the order of months.

Limitations of the swine model - differences in monkey and human implantation

While the swine model has provided our group substantial evidence that our devices are safe, effective, and implantable, there are many questions that we cannot answer without animal models even more akin to human. For example, the skin thickness of a pig is far greater than a monkey or human. Trauma to the skin due to stretching from the implant may not be appropriately validated in the swine model. In addition, infrared data telemetry through the thick, non-pigmented skin of swine may not be representative of thin, human skin potentially with hair and pigmentation. A neuroscientist may look at the use of swine and wonder how cognitive findings may be applicable to primates. While there have been an increasing number of neuroscientific studies completed in swine, a well-established functional atlas of the swine brain is not currently available (though in progress (Félix, Léger, Albe-Fessard, Marcilloux, Rampin, Laplace, Duclos, Fort, Gougis, & Costa, 1999)). Thus, mapping any neurological findings from swine to primate cognition may be difficult at the present time.

Because we were able to increase our device implantation frequency, the swine model has also given us an opportunity to evaluate our external recording electronics. These devices include the RF power delivery and management boards necessary for safety monitoring during device operation - an integral part of the CPS. In addition, we have developed over the last year a unified development architecture for data processing, correlation decoding, and digital signal processing (see *Embedded System for Prosthetic Application*) which can be (and has been) built to an embedded system, taking advantage of modern microprocessors and vastly improving upon the speed of operation, modularity, and flexibility of current neural prosthetic systems in research. We are able to evaluate this device for recording from the BIC on swine.

2.3.3 Development of a large animal stereotactic frame

A brief history of stereotactic frames

Scientists and philosophers have for centuries been attempting to visualize and understand the architecture of the brain. Not surprisingly, there is much debate about the first approaches in reproducibly exposing neural targets during surgery or even autopsy. While there is much discourse about the history of neurosurgery, most agree that the apparatus constructed by Carl Dittmar in 1873 (Blomstedt, Olivecrona, Sailer, & Hariz, 2007), who constructed a frame for accessing the medulla oblongata, was the first scientific attempt to standardize how we access the brain. However, the first truly stereotactic frame (Cartesian coordinates) was made by Horsley and Clarke in 1908 and later adapted for human use by Mussen in 1918. While these apparatuses were mechanically robust and quite precise, they were not widely used. The emergence of modern human stereotaxis started with the frame designed by Spiegel in 1947 (Spiegel, Wycis, Marks, & Lee, 1947) for inserting a wire cannula into subcortical regions with minimal injury. Spiegel, in addition, defined the surgical plane of reference to be the line drawn between the inferior aspect of the orbit and the upper border of the external auditory meatus; two locations easily visible and accessible by a surgeon and fixed within an individual – this became known as the Frankfurt Plane after a committee of surgeons in Germany agreed on the landmarks. While the surgical procedures have changed a great deal since 1947, the basic principals of Spiegel's frame have not. One approach that has emerged, and that we employ in our design of a large animal stereotaxic frame, is using sharp pins to fixate the subject's cranium into the reference coordinate system.

A similar system was employed by Jens Sorensen et al (Nielsen, Sørensen, & Bjarkam, 2009) in their studies of Parkinson's disease through a Göttingen Minipig model. They implanted three fiducial markers into the cranium of the pig, placed the animal into an MRI (T2 weighted structural scan) scanner and made trajectories to sub-thalamic targets based on relative positions

of the fiducial and the target. While their frame did use pins for fixation, like the human frame, the head was placed very low in relation to the longitudinal bars, where all implantation equipment must be placed in our case. Thus, we needed to modify this frame to lift the cranium up and into a more accessible position for our equipment.

Our custom frame design

We engaged in what turned out to be an excellent collaboration with a local precision machining company, Kineteks (Warwick, RI), for the design and fabrication of custom stereotactic hardware. Their experience from having worked on sheep stereotactic instruments help immensely to accelerate the development process.

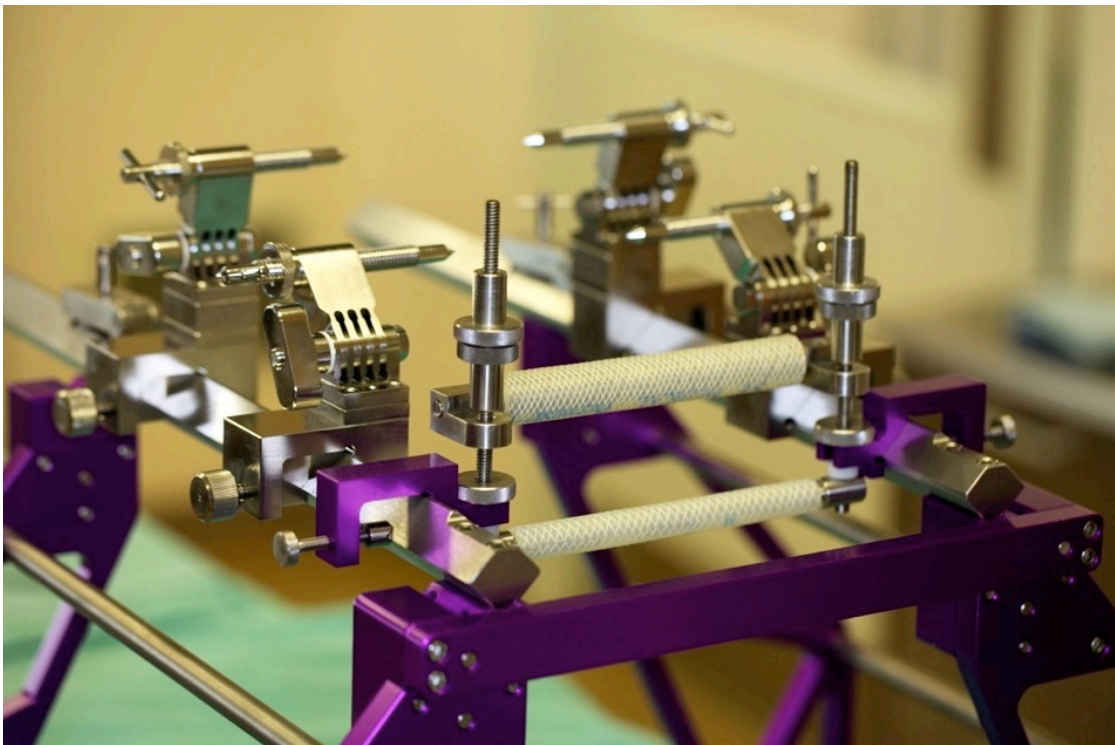


Figure 2-12: An image of the large animal stereotaxic frame developed in conjunction with surgeons and machinists at a local precision machine- shop. Longitudinal bars are standard Kopf dimensions with custom supports (purple) to accommodate animals as large as 35kg pigs. The frame base is attached to the patient table before placing the animal on the field, then the top of the frame is lowered and secured into place after anesthesia equipment and life-support are secured. While the image shows the muzzle clamp, this was not needed nor used in our experiments as the fixation pins proved to be extremely stable.

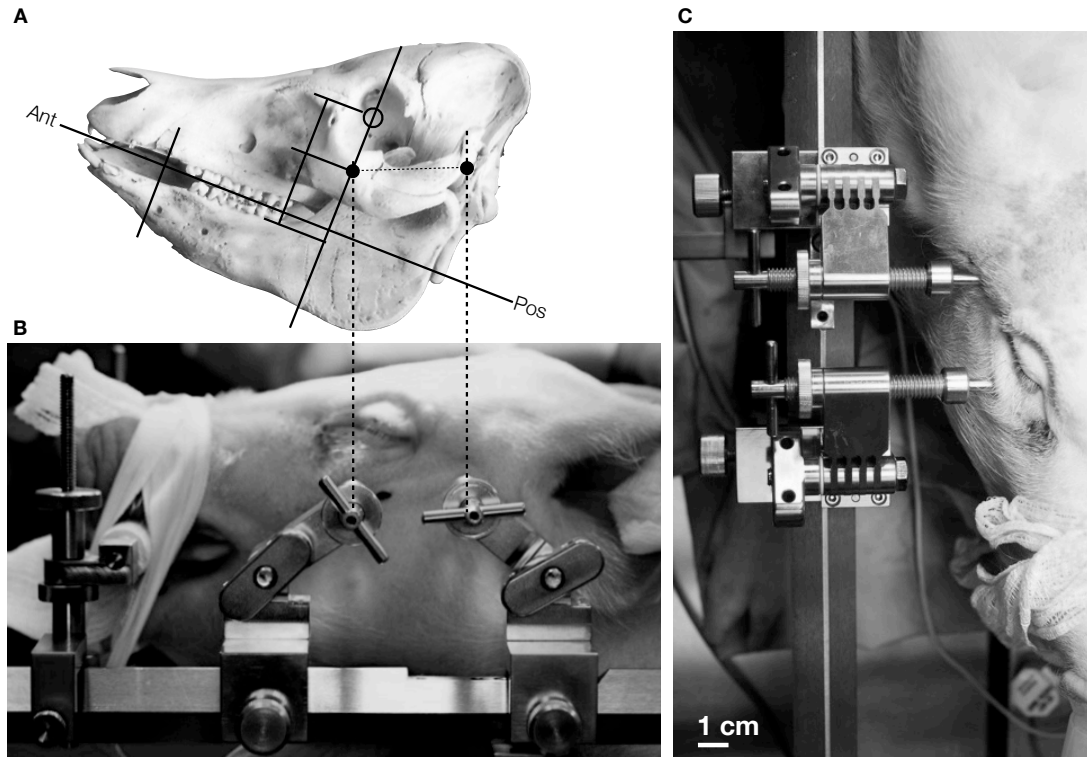


Figure 2-13: Placement of stainless steel pins for complete head fixation. The skull of a 30 kg Yorkshire pig was measured and analyzed to estimate placement of pins for stable fixation (a) relative to obvious features, such as the center of the pupil and the auditory meatus. The custom set of TiN- coated stainless steel commissioned by Kineteks LLC (Warwick, RI) were inserted into designated locations on both sides of the skull. Side view (b) and top view (c) give a sense of the stability achieved and specific locations chosen. Though not evaluated quantitatively, the stability of the four pins far surpassed that of the standard ear-bar plus nose clamp most often used.

Modeled after human neurosurgical frames, we developed a four-pin system wherein each individual stainless steel support pin attaches the standard Kopf longitudinal bars to secure the skull. The pin support system is made from 316-surgical steel and electroplated with TiN in order to reduce friction and extend the lifetime of the equipment while maintaining the ease of steam sterilization commonly used in hospitals and research facilities. A base unit supports the pins and attaches them to the longitudinal bars. During surgery, the pins themselves are twisted along their threads and advanced through the skin and into the zygoma on either side of the skull as well as along the zygomatic process of the temporal bone near the auditory meatus. The two pins in the zygoma support the majority of the weight of the head and neck while the two more

posterior fixation pins prevent rotation about the zygoma as seen in Figure 2-13. The tips of the pins have been made modular, as different geometries may be desired for various animal ages, species, etc. We have chosen a 5mm length tip with a 2mm base and a 5mm diameter shaft. The tip length was estimated from post-mortem pig skulls of similar aged pigs in order to not pierce completely through the bone, even when the entire pin is inserted; the angle of the taper was estimated from human neurosurgical fixation pins to reduce compression of the bone during insertion into the skull. However, it should be noted that bone density of pig and human skull are dissimilar, as are the compression tolerances.

The frame itself is made of titanium to maintain strength while at the same time being light enough for staff to handle and attach to the surgical table. The frame has also been made modular. The base of the frame attaches underneath the surgical table before the patient (pig) is placed on the table. Once the animal is in place and stable, the top of the frame can be dropped over the patient in place, simplifying the process of moving the patient from the prep room to the surgical field. The upper frame slots into and is secured to the base unit with four ¼ inch bolts. A snout clamp has been used in addition to the fixation pins to add support to the anterior portion of the head. This is not necessary and has generally only been used when the posterior fixation pins were unable to be used. The entire frame can be seen in Figure 2-12.

2.3.4 Evaluation of pneumatic insertion parameters in rodent and bovine

Several experiments were conducted in rodent and post-mortem bovine models in order to obtain optimal pneumatic insertion parameters for the microsystem. The integration of the MEA onto the amplifier ASIC meant that we had active electronics very near the brain and necessitated packaging to protect the body and electronics from each other. This extra bulk and material heterogeneity made us believe the insertion parameters may need to be adjusted for our particular case.

Methods

This series of insertion experiments were conducted with Dr. John Mislow (MGH neurosurgery) under approved Institutional Animal Care and Use Committee protocols (0911091). The subject was euthanized with 100% CO₂ before any experimentation was pursued. A roughly 1 inch incision was made with a #11 angular scalpel blade from just between the eyes (rostral to bregma - the sagittal suture separating the parietal from frontal plates) back to between the ears (caudal to Lambda, the fusion of the parietal and occipital plates of the cranium). Metzenbaum scissors were then used to both separate the fasciae planes as well as cut the skin away to produce two flaps over the temporal muscles of the rat, thus exposing completely the upper surface of the cranium. A curette was used to remove tissue coating on top of the skull to expose the cranium for drilling. Throughout the process, gauze was used to clean up the surgical sites and remove excess buildup. A Striker drill with a shaving bit was used to remove all but an eggshell layer of the skull over the left parietal plate. A roughly 0.5 cm diameter circular area was shaved down - this left enough area for our implant to be inserted and yet was minimized to reduce the amount of cranial pressure change when the dura was violated. Swelling of the brain can cause large area trauma and is a real issue when attempting intra-operative recording from cortex. The dura was not removed for this procedure as it was decided that rodent dura made a relatively realistic comparison to primate arachnoid - and since this methodology was developed as a model for primate cortical implantation, which is made through the arachnoid, the dura was left intact.

Supporting electronics were connected for single electrode recording, which included an x86 PC running LabView (National Instruments), a rack-mounted amplifier, and preamplifier stage. A Pt/Ir single wire (~300kOhm - Parylene C coated and tip exposed - Alpha Omega Inc.) was then placed in a stereotactic micromanipulator and lowered under a microscope to the surface of the motor cortex (A3; L2 from Bregma). The electrode was inserted with the

micromanipulator to a depth of 1 mm (varied from 0.8 mm to 2 mm). Recordings were made with an in-house LabView oscilloscope program sampling at 40kS/s for ten seconds.

When action potentials were clearly distinguished and recorded - measured at 110uV p-p - the electrode was removed with the micromanipulator. The cortical surface was then irrigated with large amounts of warm physiological saline aimed at keeping the cortical surface as fresh as possible. The neural interface (here, both the externally and internally powered microsystem have been implanted in pig) device was then positioned over the same cortical surface that the single electrode was placed. The array was centered on the same Loci (A3; L2, or 3mm anterior and 2mm lateral from the cranial plate fusion called bregma, in this example) and a pneumatic inserter with a 1 mm spacer (Blackrock Microsystems, UT) was positioned directly behind the microsystem. A pressure of 25 psi was used (raised from the 20 currently used in human implantation) for the insertion of the frontend system, pushing it into the cortex a distance dictated by the spacer (1 mm, in our case). The supporting electronics were then turned on and the neural interface was wirelessly powered and checked for normal operation and functionality.

After we were able to record neural data successfully, the device was carefully removed with forceps to reduce tissue damage. Again, the area was irrigated with large amounts of warm saline before the single electrode was replaced over the same area. The insertion point of the single electrode was purposefully moved adjacent to where an array electrode puncture was formed. In these experiments, one would ideally record from the same patch or cortex for both the array and single microelectrode. However, here the cortex was likely damaged in the exact area of the array implantation. Signals were again recorded with the single electrode recording system.

Results

We varied several parameters in the experiment: three anesthesia methods were used (Isoflurane, Ketamine, Propofol); two lengths of spacers (1mm and 1.5mm), two values of insertion pressure (25psi and 30psi), and three locations in the cortex were targeted.

The only combination that facilitated action potential recording from the electrode was induction through Ketamine with a 1.0 mm spacer inserted at less than 25 psi into the somatosensory cortex of the rodent. Under these conditions, we were able to record action potentials consistently around 140uV peak-peak on two channels of our array. Under Isoflurane and similar insertion parameters, we recorded less clear action potentials (lower p-p, within our noise envelope and thus difficult to detect with certainty). These data are shown in the results section of this thesis (Chapter 6). Detailed results from the bovine and rodent implantation tests are shown in Table 2-2 and Table 2-3 respectively. It was, at first, surprising that we did not consistently see neural activity in the implanted systems. We later hypothesized that the impact of the array into the cortex caused temporary deactivation. Since all of these implantation tests were acute experiments, we did not give the cortex time to recover. The primary objective of this study was to assure array penetration through the dura, which was validated at 25-30psi. In later rodent studies, we worked around the acute trauma of the pneumatic inserter by 1) opening the dura mater and simply lowering the array into place without the inserter (action potentials were obvious in nearly every case), or 2) moving to a chronic experiment where after inserting the array with the pneumatic inserter we could wait one day before recording from the device.

Location	Parameters		Observations	Follow-up experiments
	psi	mm		
Throughout the experiment saline was routinely washed over the exposed brain and dura mater to hydrate and maintain elastic properties. Towards the end of the experiment, the tissue did become dry and sticky (roughly 2 hours post dural excision).				
L Hemisphere, Frontal	20	1.5	Not clear, First insertion and still adjusting setup	Insertion of NeuroPort array on same bovine brain as BIC FE array to observe differences in insertion parameters under similar conditions (i.e. bovine cortex and supporting tissues). Could be done sans skull.
L Hemisphere, Frontal	20	1.5	Appears to have entered arachnoid - near flush with surface of cortex	
L Hemisphere, Frontal	20	1.5	Appears to have entered arachnoid - near flush with surface of cortex	
Upon investigation of the first three insertions, it appears that we were in fact not getting through the arachnoid, but instead the surface was dimpling around the electrodes, obscuring the view. Gentle retraction with forceps revealed the array still outside the arachnoid. We adjusted the insertion pressure to 30 psi to hopefully clear the membrane.				
L Hemisphere, Parietal	30	1.5	Much more clear that the electrodes have inserted into cortex	Insertion on rodent (rat) brain to calibrate depth for future acute in vivo experimentation
L Hemisphere, Parietal	30	1.5	Clear that the electrodes have inserted into cortex. Arachnoid began to dry after several saline washes - sticky	
L Hemisphere, Parietal	30	1.5	Clear that the electrodes have inserted into cortex	
After all insertions were completed we removed the arachnoid from the cortex to expose the naked cortex beneath. For implants done under 30 psi we were able to see clear electrode penetrations into the cortex. Though difficult to identify, we did not see any electrode penetrations under the arachnoid beneath the 20 psi implants.				
L Hemisphere, Parietal, sub-arachnoid space	Hand	Length of electrode	Electrodes, when placed directly on cortex, simply sink in without any applied force	--

Table 2-2: Bovine insertion tests with a pneumatic inserter. The pneumatization of the bovine skull made access incredibly difficult. In addition, the brain had been dead for several hours and thus did not maintain the biologic mechanical properties we had hoped to evaluate.

Insertion loci relative to Bregma	Parameters				Audible Neurons			Extracted Neurons		
	A	E	I	D	E	BIC	E	E	BIC	Electrode
Initial insertions were done in somatosensory cortex with less regard to targeted loci as we had expected large background activity. As this was found inconsistent, we proceeded to localize the insertions to the forelimb region of motor cortex and the barrel cell region of S1.										
Day 1: A2 L4 D1-2	Ket	W	30 psi / 1.5 mm	1-2 mm	Y	N	Y	Y	Y	Y
Day 1: A2 L4 D1-2	Ket	W	30 psi / 1.5 mm	1-2 mm	N	N	N	N	N	N
Day 1: A2 L4 D1-2	Ket	W	30 psi / 1.5 mm	1-2 mm	N	N	N	N	N	N
Day 2: A2 L4 D1-2	Ket	Pt/Ir	30 psi / 1.5 mm	1-2 mm	Y/N	N	N	Y	Y/N	N
Day 2: A2 L4 D1-2	Ket	W	30 psi / 1.5 mm		Y					
	Compared results with Post-Doc Kesuke from Professor Sheinberg's lab because we were not achieving consistent single electrode recordings									
Day 3: A2 L4 D1-2	Iso	W	30 psi / 1.0 mm	1 mm	N	N	N	N	N	N
Day 3: A2 L4 D1-2	Iso	Pt/Ir	30 psi / 1.0 mm	2 mm	Y	Y/N	N	Y	Y/N	Y
Day 3: A2 L4 D1-2	Iso	Pt/Ir	30 psi / 1.0 mm	1.5 mm	Y	N	Y	Y	Y/N	Y
Day 4: A2 L4 D1-2	Iso	Pt/Ir	30 psi / 1.0 mm	1.5 mm	Y	N	Y	Y	Y/N	Y
Day 4: A2 L4 D1-2	Iso	Pt/Ir	30 psi / 1.0 mm	1.5 mm	Y	N	Y	Y	Y/N	Y
Day 4: A2 L4 D1-2	Iso	Pt/Ir	30 psi / 1.0 mm	1.5 mm	Y	N	Y	Y	Y/N	Y
Day 5: A2 L3 D1	Pfl	Pt/Ir	30 psi / 1.0 mm	1.5 mm	Y	N	Y	Y	Y	Y
Day 6:	Device not functioning - new fabrication run									
Day 7: A3 L2 D1	Ket	Pt/Ir	25 psi / 1.0mm	1.0 mm	Y	Y	Y	Y	Y	Y
Notes: E = Single electrode; A = Anesthesia; I = inserter pressure; D = depth of electrodes in array; BIC = Brain Implantable Chip; W = Tungsten; Ir = Iridium Oxide tips ' Ket = Ketamine; Iso = Isoflurane; Pfl = Propofol; A2 = 2 mm anterior; L4 = 4 mm lateral; D1-2 = depth of 1-2 mm										

Table 2-3: Rodent pneumatic insertion results aimed to understand externally powered microsystem insertion parameters and how they differ from that of the original Blackrock microelectrode array.

2.3.5 Device sterilization with ethylene oxide gas

We faced many challenges developing implantable devices when compared to percutaneous ones. Certainly, as mentioned, new surgical procedures had to be developed to take into account the subcuticular, supra-cranial sections containing active electronics, facilitating energy transfer in and out of the body. We also had to re-evaluate the bioresponse to a foreign body in the context of a fully implantable microsystem. Certainly, one of the major reasons for developing a fully implantable system was to reduce the risk of infection imposed by an open connection through the skin. It may not be obvious that a percutaneous connection actually enables constant wound drainage, reducing the risk of serious adverse events. Certainly, a connector through the skin invites bacteria into the body, but any major bacterial buildup will be easily removed and cleaned. When the device is completely under the skin, any bacteria that were tracked into the body will enjoy a pocket of somewhat compromised tissue around the implant. As pressure builds from bacterial growth, it no longer is easily drained away from the microsystem. Thus, by removing a percutaneous connection, we have perhaps increased the risk of severe bacterial infection. Hopefully, as with any standard implant (Deep-Brain Stimulator, for example), we employ sterile technique during the surgical procedures to reduce the risk of infection.

To this end, we have performed sterilization analysis on our externally powered microsystem through a professional commercial partner, Nelson Laboratories. Our systems contain active electronics, and sometimes batteries, thus steam sterilization is not a viable option as it may damage these components. Instead, we perform Ethylene Oxide (EtO) gas sterilization to rid the implants of any living material. Ethylene Oxide sterilization is commonly used to sterilize medical and pharmaceutical products that cannot support conventional high temperature steam sterilization, such as devices that incorporate electronic components, plastic packaging or plastic containers.

EO is a tiny molecule in which two carbon and four hydrogen atoms are joined to one oxygen atom in a highly strained ring. Because of the chemical's very low boiling point (10.4°C), it becomes active at room temperature. In addition, it vaporizes and permeates rapidly through packaging, dissolving in substances like plastic and rubber to kill all organic life. EO readily kills all types of microorganisms under ordinary atmospheric conditions. It contains fragile molecular bonds, which allow it to quickly react with a wide variety of compounds. The resulting chemical reaction is called alkylation. In the Anderson EtO system employed at Brown University Animal Care Facilities, temperature is maintained between 20C and 23C over a period of 16 hours (8 hours of gassing, and 8 hours of outgassing). The relative humidity is near 20% (required between 15 and 90%). We sent our microsystem to be analyzed under these conditions for residual quantification and outgassing timeframe estimation.

Methods

Levels of ethylene oxide (EO) and ethylene chlorohydrin (ECH) trace residuals in the Brain Implantable Chip system (with Titanium pedestal) were determined by Nelson Labs in accordance with ISO 10993-7:1995 (R) 2001 requirements. The EO and ECH levels, after approximately two days of ambient aeration (degassing - ambient aeration is a worst-case scenario), were well within the acceptable limits for cumulative long-term in vivo medical devices (and in addition, below detectable limits). This supports the contention that implant assemblies may be EO sterilized and with the employment of appropriate outgassing time EO and ECH trace residuals will not pose a risk to patient safety and will likely not disturb the normal function of target tissue in close proximity to the implant. Requirements from FDA guidelines (FR 27482) are that:

1. The average daily dose of EO to the patient shall not exceed 0.1 mg/day. In addition, the maximum EO dose shall not exceed: 20 mg in the first 24 hours; 60 mg in the first 30 days; 2.5 g in a lifetime.

2. The average daily dose of ECH to patient shall not exceed 2 mg/ day. In addition, the maximum ECH dose shall not exceed: 12 mg in the first 24 hours; 60 mg in the first 30 days 50 g in a lifetime.

The objective of this study was to determine the necessary EO and ECH aeration (de-gassing) time for the Brain Implantable Chip that had previously been exposed to ethylene oxide gas sterilization at Nelson Labs approximating the cycle used by Brown University Animal Care Facilities.

Equipment and materials

Three fully fabricated and packaged externally powered microsystems were sent to the Nelson Laboratories. These systems were built on a Kapton (a DuPont polymer primarily composed of polyimide) substrate, a custom ASIC amplifier and multiplexer comprised of Si and metallic conducting traces (Cu and Au), a VCSEL made of GaAs, and several passive components made from ceramics and metals. The packaging of the systems was done with our standard NuSil 2188 Engineering Grade silicone potting elastomer. All systems contained a 4x4 element (16 electrode) silicon microelectrode array (MEA) from Blackrock Microsystems.

Results

After 2 weeks of testing at the Nelson Labs facilities, the residual EO and ECH measurements were returned to us in a lab report: *Laboratory number: 457196*

Procedure number: STP0016 REV 05. While measurements were taken out to two weeks post sterilization, the values were below detectable limits after 48 hours.

Summary of findings: Sterilization and Gas Residual Analysis

As stated by Nelson Laboratories, it is clear that less than observable amounts of residual EO, ECH, and EG remain after only 48 hours of outgas time. Applying these data to implant sterilization strategies, we can safely conclude that our implant will cause no harm to the animal

(or human) after 48 hours of outgassing. This, however, does not mean that recording quality will remain unaffected by the immeasurable amounts of the compounds left behind or by the humidity of the sterilization process. It is entirely possible that the neurons are more sensitive to residuals than our testing methods. To conclude this portion of the study on EtO sterilization effects on neural recording, a tissue culture study must be completed. Others (Ohnishi, Inoue, Yamamoto, Murai, Hori, Koga, Tanaka, & Akiyama, 1985) have shown deleterious effects of EtO on rodent cognition at high concentrations and over prolonged exposure (500ppm over 13 weeks). While in our work we do not study the effect of EtO on neural tissue directly, we do find that consistent and chronic neural recordings are achieved.

Metric	EO	ECH	EG
Average Daily Dose (<24 hrs; ppm)	<0.001	<0.001	--
Average Daily Dose (>24 hrs; ppm)	<0.001	<0.001	--
Residual Concentrations (>24 hrs; ppm)	<4.33	<4.33	<130

Table 2-4: EtO residuals from 0-48 hour after gas sterilization. It can be seen that our device releases all EtO residuals after <48 hours of outgassing. This gives us confidence that a) the device will have a below detectable content of potentially dangerous EtO residuals, and b) the system can be implanted < 48 hours after sterilization with EtO.

The data provided from Nelson Laboratories are valid only for the externally powered implantable microsystem, which has unique materials in comparison with the internally powered microsystem. Thus, these measurements must be retaken for all other devices that we currently are developing, i.e. the internally and the optically powered microsystems. In addition, if a device undergoes a change in design or component makeup, it may be necessary to conduct new

sterilization validation experiments in order to satisfy internal IACUC regulations as well as FDA requirements.

2.3.6 Final Implantation procedure in swine

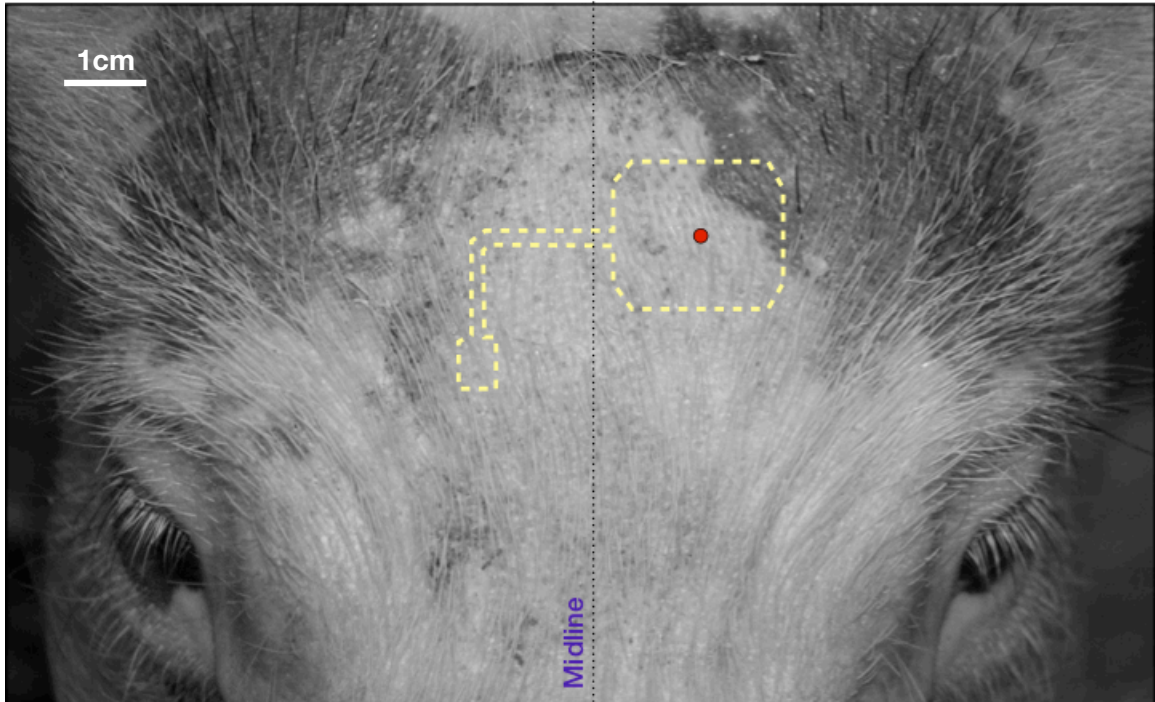


Figure 2-14: An image of pig P3 after 30 days of implantation. No signs of irritation or inflammation from device or implant-related tissue disruption. Recordings were made with a "wand," consisting of an RF coil (delivering power), and a photodiode (receiving data), gently placed on the skin surface. The figure impresses the importance and advantages of removing percutaneous connections from neural prosthetic devices in favor of less intrusive wireless telemetry

Taking all of the preliminary surgical, sterilization, and animal model design into consideration, we describe the complete device implantation procedure in swine.

An arched skin incision was made from the left posterior aspect of the head anteriorly returning to the right posterior aspect. This notably long incision was made to gain maximal access to craniotomy site (R parietal lobe) while at the same time moving the suture line away from the implant to reduce chances of irritation. Separation of the galea aponeurotica from the skull (and skin) was done in case a dural graft was needed to complete closure. A Stryker (USA)

cranitome was used to turn a 3cm x 1cm craniotomy above primary somatosensory cortex - specifically the area controlling the rostrum (Sauleau et al., 2009). After the durotomy was completed, the microsystem was positioned for insertion. Insertion was made through the arachnoid and pia mater by the commercially available pneumatic inserter (BRM, as used in the insertion study above) with a 1.5 mm spacer - the electrodes on this system have a 1.5 mm shank length. The craniotomy was then closed with the remaining bone flap and secured with medical-grade Ti mesh and screws (Stryker). This process has been used by numerous groups with high-percentages of success (Acharya, Tenore, Aggarwal, Etienne-Cummings, Schieber, & Thakor, 2008; Bansal & Vargas-Irwin, 2011; Miranda et al., 2010; Zerris, Donoghue, Hochberg, O'Rourke, & Chiocca, 2005).

One notable difference when implanting a completely wireless system is that the skin is completely sutured closed with no percutaneous connections (Figure 2-14) as are normally found when implanting microelectrode arrays or really any neural recording device currently fabricated by other groups. This poses some interesting questions and challenges that we had not, at least directly, anticipated. For example, should infection develop around or near a percutaneous (through skin) implant, exudate is freely able to exit the body and be cleaned by a caretaker. This is exactly the situation with the current NeuroPort neural interface, where a pedestal protrudes from the skin. While the pedestal may draw more harmful bacteria into the body, it also has a built-in mechanism for wound drainage. Switch now to the fully implantable scenario. A device will be completely protected by the skin from external bacteria; however, any infection that might occur around or on the implant will have no means of drainage. In this case, the infection may become acutely worse and require surgical intervention to add drainage, thus also introducing the potential for bacteria to the system. This is perhaps looking at the situation in a negative way. On the other hand, if an implantable device is done under aseptic conditions and has been proven sterilizable, it can be inferred that it will be significantly less of a risk to patient health than a percutaneous implant.

Focusing back to the current study, since swine use their foreheads as shovels, any protrusion of the implantation would not be tolerated from a simply physical perspective. This animal model pushes the limits of mechanical robustness compared to humans, for whom a neural prosthetic would be more accepted and likely treated with more care. Evaluating the device in swine gives us a “worst-case” scenario. The results thus far are very promising, showing that our fully implantable neural interfaces do sustain mechanical and biological stresses applied to them in swine.

In conclusion of this section, we point to Table 6-1 in Results, where the total number of days our neural interfaces have been implanted in swine and non-human primates. The numbers are impressive considering that we have only seen one adverse reaction to an implant (S2-ID#796).

2.4 Protecting biologics and electronics by polymeric, metallic, and ceramic separation

Introduction to the challenge

This section of the thesis serves as an introduction to the challenges that face biomedical device engineers regarding packaging. Generally, two topics must be considered: biocompatibility and hermeticity. The term “biocompatibility” can be further broken down into two processes: 1) the complex tissue reaction to a foreign material (or device), and 2) the package protecting against attack from a harsh ionic body environment. It is critical that implantable medical devices do not elicit any undesirable local or systemic effects in the human body. In addition, the package materials must protect from ionic flow. The term “hermeticity,” however, refers to the barrier that is made between the device and the body and is directly related to the second process definition of biocompatibility. An ideal hermetic seal stops ALL transport of gas, water, or ions. Unfortunately, such a material does not exist and all materials have a finite amount of permeability.

It must also be understood that the packaging challenge faced in implantable devices are not created equally. That is to say, *passive* devices face very different challenges than *active* devices. A passive device is defined as requiring no power to operate and thus, more importantly, does not maintain a static electric field between the inside of the device and the body. Examples of passive implants are the ECoG grids used clinically for localization of epileptic foci, and the NeuroPort 96 channel multielectrode array implanted in humans with tetraplegia. These devices transmit very small changes in voltage from the brain to electronics *outside* the body for signal amplification and digitization. An active device, such as the deep brain stimulator and the NeuroPace RNS, maintain power-consuming components inside the body, generally hermetically sealed in a titanium can. For all current *active* systems, the leads exiting the hermetic enclosure are passive as seen in Figure 1-4. The constant electric field inherent in active microsystems acts as a constant drive, pushing charged particles against the packaging material and drastically increasing the potential for charge transfer across the semi-impermeable barrier.

Electronic component failure caused by ionic or water permeation through the protective barrier is mainly due to shorting of two electrical contacts. As charged ions permeate the barrier, they build up on oppositely charged exposed contacts inside the implanted device. If enough ions accumulate, they will bridge two contacts points and cause a short, drawing large amounts of current, and making the system unable operate. Failure can also occur from water permeation. This mechanism may not be as clear since pure water is non-conductive and thus should not cause a short between two contacts. However, if pure water comes into contact with free electrons or protons, it will readily hydrolyze, splitting into two charge constituents, H^+ and OH^- . These, now ions, will migrate to oppositely charged surfaces and cause failure of the system over time, as discussed above. A simple schematic of this breakdown process is shown in Figure 2-15.

Not only do developers of implantable active devices face the challenges of electronic protection from the briny environment, they also face the geometrical and space constraints of the body. While we work to increase the compactness of the electronics, packaging often introduces

significant thickness to the overall device. This must be given serious consideration to avoid tissue necrosis (lack of blood supply, pressure, etc.).

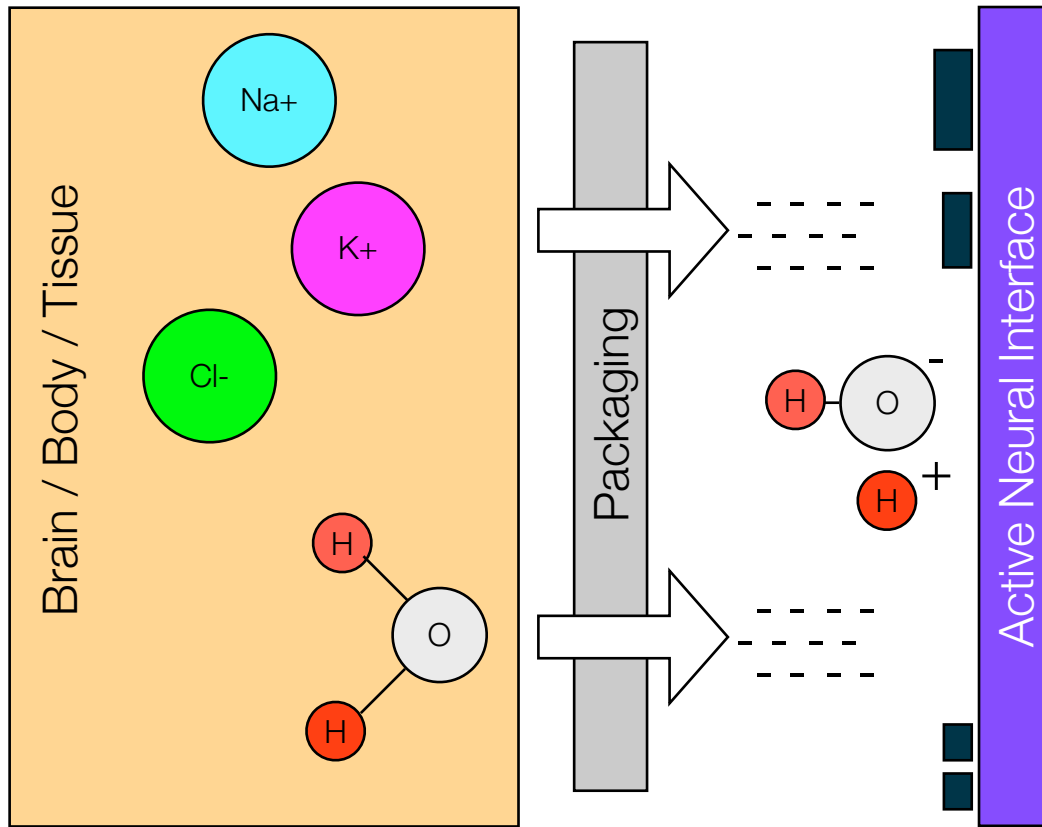


Figure 2-15: Simplified diagram of challenges facing active microelectronic packaging. For the case of polydimethylsiloxane (PDMS), it is generally thought that ions are too large to penetrate through the holes in the polymer interweaving. However, pure water (H_2O) is larger than the ions ($\text{Na}^+ = 0.95\text{\AA}$, $\text{Cl}^- = 1.8\text{\AA}$, $\text{H}_2\text{O} = 2.9\text{\AA}$) but is thought to pass through the polymeric barrier. Electric fields placed across the membrane drive the polar water molecule through the polymer, bending the O-H bonds to squeeze through.

2.4.2 History of insulators for implantable devices

Insulating biomaterials research has been underway for many decades to support technological innovations in implantable electronics such as the cardiac pacer, deep brain stimulators, and cochlear prostheses. Microelectronic components and integrated circuits have been used extensively in cardiac pacing and cochlear prosthesis implant systems. Both of these systems typically utilize large titanium or ceramic canisters for packaging the electronics, and

glass feedthroughs for interconnecting with stimulation leads and electrodes. The pace of development of these implantable devices has paralleled the pace of technological innovation. Development of the cardiac pacemaker is a very good example. The first recorded demonstration of electrical pacing of the heart occurred in 1872 using a system consisting of a 300V battery and hand held electrodes (Green, 1872). Following that important demonstration, it wasn't until endomyocardial electrodes, transistors, epoxy encapsulation, and high energy density batteries became available in the 1950s that the stage was set for development of the fully implantable cardiac pacemaker reported in (Elmqvist, 1978). In the 1970s, titanium casings replaced epoxy encapsulation, which allowed incorporation of integrated circuits based on silicon microelectronics technology. Lithium batteries (and even nuclear batteries (Parsonnet, Myers, Gilbert, & Zucker, 1975)), improved packaging, and improved lead technology resulted in complex pacemaker systems with implantable lifetimes of up to 15 years.

Today's pacemakers consist of lithium-ion batteries and electronics modules hermetically sealed within titanium canisters using glass insulated and sealed electrical feedthroughs. The size of the pacemaker is largely determined by the size of the battery and the titanium case, which are a few centimeters in diameter and a half-centimeter thick. Modern leads are typically multi-filament coils of a high nickel content stainless steel alloy (MP35N) insulated with silicone elastomer.

Throughout the history of the pacing industry, implantable materials considerations have dominated technological innovation. Silicone insulated leads have been very reliable and have been used for decades in cardiac pacing applications. Other lead insulation materials have been used to overcome the tendency of silicones to stick to tissue during insertion, and to reduce the diameter of the pacing lead (Doležel, Adamířová, Náprstek, & Vondráček, 1989). Polyurethanes used for this application were marketed in the 1970s. However, in several long-term clinical studies, polyurethane leads from several manufacturers tragically exhibited substantially higher failure rates than silicone leads. A possibly overlooked clue that may have alerted lead designers

to possible long-term instability issues with polyurethanes was the 1979 observation that both polyether and especially polyester urethanes were susceptible to hydrolytic degradation during relatively short-term water exposure.

The most important goal of the current work on insulating biomaterials is to identify possible failure modes for insulating biomaterials to avoid such clinical surprises. Many applications for implantable microelectronics and micro-machined (MEMS) devices are under development including biochemical sensors and drug delivery systems. Most of these applications require only subcutaneous implantation so the traditional titanium canister is the package of choice. Neuroprostheses, however, will require implantation of devices within the nervous system, and thus face significant challenges including the necessity for flexibility.

2.4.3 Rigid biomedical device packaging

Titanium

The natural selection of titanium for implantation is determined by a combination of favorable characteristics including immunity to corrosion, biocompatibility, strength, low tensile modulus and density and the capacity for joining with bone and other tissue - osseointegration. Many surface treatments have been developed to enhance both osseointegration and biocompatibility of metallic packaging and implants (e.g. hip and bone replacements) (Junker, Dimakis, Thoneick, & Jansen, 2009). The mechanical and physical properties of titanium alloys combine to provide implants, which are highly damage tolerant (R. Yang, Hao, & Li, 2007). However, the human anatomy naturally limits the shape and allowable volume of acceptable implants. Two further parameters define the usefulness of the implantable alloy, the notch sensitivity, or NS (the ratio of tensile strength in the notched versus un-notched condition), and the resistance to crack propagation, or fracture toughness (FT). Titanium scores well in both cases. Typical NS/FT ratios for titanium and its alloys are 1.4 - 1.7 (1.1 is a minimum for an acceptable implant material). Fracture toughness of all high strength implantable alloys is above

$50\text{MPa}\cdot\text{m}^{-1/2}$ with critical crack lengths well above the minimum for detection by standard methods of non-destructive testing.

These studies have proven titanium as an ideal metal for *biomechanical* implants. For our goal of creating implantable microelectronic interfaces, we must also consider the electrical insulation properties of potential packaging material. Electronics will not tolerate an ion-rich environment (e.g. saline, or cerebrospinal fluid – CSF). In addition to electronic failure, we must at all cost reduce the possibility that electronic failure causes harm to the animal or patient under study. A hermetic seal, define broadly as “air tight”, contemporarily consists of two metallic or ceramic pieces welded together enveloping the electronic payload. Metallic packaging generally consists of a biocompatible metal capsule that is either machined from a solid piece of metal or deeply drawn from a piece of sheet metal. Electrical signals enter and exit the package through hermetic feedthroughs. The feedthrough assembly often utilizes a ceramic or glass insulator to allow one or more conducting wires to exit the package without coming in contact with the package itself (Guangqiang & Zhou, 2010). This method has been successfully used for implantable pacemakers, cardiac defibrillators, implantable multichannel neuromuscular stimulators, deep brain stimulators, and cochlear implants. Metal-based packaging generally requires that a power-receiving coil or communication antenna be placed outside the package to avoid significant loss of power or radio frequency signals through the walls of the implanted device, thus requiring additional space within the body to accommodate the volume of the entire implant or an enormous hit in power-transfer efficiency.

Ceramics and glass

Ceramics and glass generally fall into the same category of encapsulant materials due to their shared need to be heated to great temperatures to turn into their liquid form. Most electronic biomedical implants cannot withstand these extremely high temperatures (depending on the constituents, 1000C° – 1230C°). However, ceramics and glass have near impermeable better

water barrier properties. These materials include films such as silicon nitride, silicon carbide, polycrystalline diamond, and metal thin films. Semiconductor materials like silicon, silicon dioxide, or silicon nitride are very popular because they are resistant to many corrosive environments. In order to package microelectronics with these materials, researchers can follow one of two pathways. First, a preformed ceramic / glass case is made under high temperature conditions. Following formation of the case, the sensitive components are placed inside. The case is then sealed with a weld joining the top and bottom case components. Alternatively, deposition tools like Chemical Vapor Deposition (CVD), or Plasma Enhanced Chemical Vapor Deposition (PECVD) are used to coat a thin conformal layer of ceramic or glass packaging on the microelectronic system. In a CVD system, the material (or precursors, e.g. silane for silicon) is heated at high temperature to form a gas in one chamber then moved into a cooler chamber where the gas is condensed onto the substrate (e.g. microsystem). Xiao, et al. have developed a promising coating based on crystalline diamond and have shown some evidence of stability and biocompatibility (Xiao, Wang, Liu, Carlisle, Mech, Greenberg, Guven, Freda, Humayun, Weiland, & Auciello, 2006). However, the fact that no commercially available neural implant uses an organic or an inorganic coating as a hermetic barrier suggests that this approach is still in the development stage.

2.4.4 Polymeric packaging

There are numerous organic polymeric materials that are used as encapsulants for electronics. These materials are divided into (1) thermosetting polymers, (2) thermoplastics, and (3) elastomers. For implantable medical device applications, only a few materials in the above three groups can be made ultrapure to serve as acceptable encapsulations for implants. Candidate materials include epoxies, silicones, polyurethanes, polyimides, silicone-polyimides, parylenes, polycyclic-olefins, silicon-carbons, and benzocyclo-butenes, as well as recently developed high-performance liquid crystal polymers (LCPs). Silicone rubber has been used as cable insulation

material, epoxies were used in part for electronic component encapsulation, and Parylene C is utilized as an insulation coating on electronics in implants in cats (Loeb, Bak, Salcman, & Schmidt, 1977; R.A. Normann, 1990; Yuen, Agnew, & Bullara, 1987) and more recently in humans (Leigh R Hochberg, Serruya, et al., 2006). The challenge of polymer encapsulations when applied to a long-term biomedical device primarily lies in their bio-stability within the body. Degradation of polymers includes hydrolytic, oxidative, and enzymatic mechanisms that deteriorate the chemical structure (Stieglitz, Schuettler, & Koch, 2005). Polymer encapsulation has been successfully used with relatively simple circuits using discrete, low-voltage components (Edell, 2004). However, it is extremely difficult to sufficiently control the adhesion to substrate, which depends strongly on substrate materials, humidity, and cleanliness. We will discuss later the mechanisms of failure in polymeric insulators, as these are used heavily in our research and the devices created in this thesis. The study of alkaline chains in the atomistic method allowed the use of macromolecular examination techniques. Alkaline polymers have been studied more in-depth than siloxane-based polymers, and it is a good starting place in beginning to understand the building blocks of charge transport in any insulating polymer.

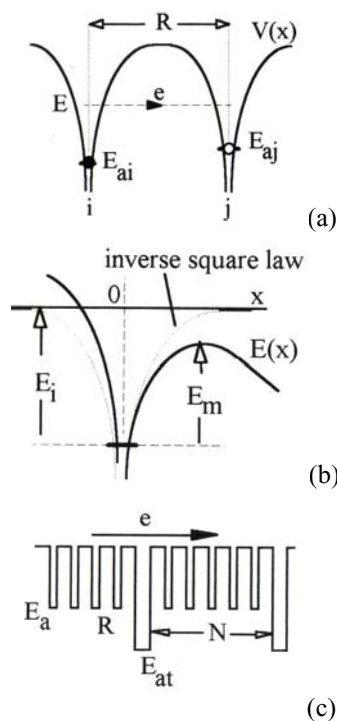


Figure 2-16: a) Resonant tunneling between neighboring states of the insulator. b) Under the Poole-Frenkel mechanism, energy state E_i is Coulombic in nature, decaying between the two states and modified by an electric field. c) Scheme for determination of charge mobility μ . μ is calculated by averaging the time spent in each state as the charged particle hops from one state to the next along the chain. This mechanism is generally referred to as electron or hole “tunneling.”

In the experiments of Teyssedre et al., molecular simulation was used to generate molecular conformations along the chains of atoms. A semi-complete model of charge transport must take into account defects in molecular weight distribution, free volume and vacuoles, conformations in the amorphous form, etc. Specialized techniques such as XPS (x-ray photoelectron spectroscopy) were used to visualize the conduction band. Various research groups have employed various techniques including bulk insulator resistivity monitors, Inter-digitated Electrode (IDE, not to be confused with Investigational Device Exemption, also used in this thesis) devices, four point resistance monitors, Young’s Modulus monitors, and surface bonding monitors to look at material characteristics. We note that as the chains become longer, the bands bend closer together. Conformational changes or variation along a polymer can introduce disorder

in the supra-molecular structure. Variation along the polymer is usually described as several members of the chain being of different orientation (R, S, etc.).

$$p_{ab} = v_{ab} e^{-(2\alpha_{ab}R)} e^{-(W_{ab}/kT)} \quad \text{Equation 2-1: (Lewis, 1990)}$$

$$v_{ab} = \frac{2.4 \times 10^{20}}{E_m} d^6 [(\lambda_a + \lambda_b)kT]^{1/2} \quad \text{Equation 2-2}$$

$$\alpha_{ab} = 0.49 E_m^{1/2} \quad \text{Equation 2-3}$$

$$W_{ab} = \frac{[\lambda_a + \lambda_b - (E_a - E_b)]^2}{4(\lambda_a + \lambda_b)} \quad \text{Equation 2-4}$$

$$E_m = \frac{(E_a \lambda_a + E_b \lambda_b)}{(\lambda_a + \lambda_b)} \quad \text{Equation 2-5}$$

Table 2-5: Formulation of rate of charge transfer, P_{ab} , that depends heavily on the wave function overlap, λ_a and λ_b (two neighboring states). d and R are in angstroms and energies $E_{a\&b}$ are in eV. This is very much a result of quantum mechanical analyses revealing the probability of charge transfer occurring between two distinct energy wells.

One problem with many of these band gap diagrams is that work functions (and indirectly, band gaps) are normally determined and estimated for materials on clean surfaces and under ultra-high vacuum conditions. The estimated work function values in polymer insulators are likely to be fairly different from the ideal measurements made, making the energy band gap slightly higher or lower than expected. Ionic species may also potentially exist in the polymer as a result of oxidation of the material, significantly altering the band gap. Another, more significant

possibility is that ions are formed by the dissociation of impurities under the influence of an externally applied electric field - Onsager mechanisms (Onsager, 1931; Teyssedre & Laurent, 2005). Yet another mechanism, though this seems unlikely considering our recent data, proposes an injection of charge from the electrodes into the bulk of the polymeric insulator. If this were the case, one would expect a consistent increase in the charge flux across the polydimethylsiloxane film as charges buildup in the material, which, again, we have not seen.

Since 1971, it has been known that polyimide is susceptible to hydrolysis (Dean, Jr., 2004; Edell, 2004). Polyimide also undergoes enhanced degradation in the presence of applied electrical potentials. Parylene-C has also been widely promoted as an insulating biomaterial. While effective for short-term encapsulation, Parylene-C undergoes hydrolysis with resultant craze cracking upon exposure to high-humidity. It may be that some materials are more rapidly degraded because they carry a greater percentage of chemical bonds favorable to degradation under the specific conditions. These materials may be useful in establishing activation energies for use with other materials that have not shown degradation thus far but are known to contain a smaller fraction of the suspected weak link. The hopping mechanism by which charges are thought to move from one available state in the insulator to another can be initiated by thermal excitation, by direct quantum mechanical tunneling, or by both.

With the density of potential trapping sites near $\frac{1}{10^{10}}$ per repeated unit of dimethylsiloxane being much lower than likely concentrations of impurities, only a fraction of the deep traps in the bulk insulator will be filled. This would infer that the current transfer is not impurity site limited, and that perhaps the measured current is due to slight imbalances of positively and negatively trapped charges (Lewis, 1990). The most complete expressions for charge transport dependencies on temperature, and material band overlap were described initially by (Lewis, 1990) and later by (Zakrevskii, Sudar, Zaopo, & Dubitsky, 2003).

Chemistry of polydimethylsiloxane

The low surface energy of polydimethylsiloxane (PDMS) is one of the main reasons for its usefulness in insulation applications. Having lower surface energy and being more hydrophobic than most other polymers, it can best resist the development of water films. Low surface energy is a direct manifestation of the low intermolecular forces between the outward pointing methyl groups of the PDMS. The Si-O-Si siloxane backbone of PDMS is highly polar and is somewhat shielded to the surrounding environment by the methyl groups. It is proposed that the hydrophobicity of the methyl groups on the surface and the close proximity of polymer linkage stop the movement of ionic charge through the PDMS membrane. The backbone, Si-O-Si bonds, is highly polarized with the Si being the positive charge sync and the oxygen being the negative charge sync. This hydrophilic backbone is likely what allows water (di-water) to flow somewhat easily through the polymer. The backbone of PDMS also forms $140^\circ - 180^\circ$ angles, providing the familiar silicone flexibility.

Conclusions of polymeric insulator research

As pointed out above, specific features of electron transport in the intermolecular space considered briefly here are likely the mechanisms of eventual charge movement through a polymer. Since the free path length of electrons in these polymers is short ($<1\text{nm}$ (Zakrevskii et al., 2003)), it is highly improbable that electronic breakdown occurs in them, i.e. the concept that at some critical field strength level, E_{cr} then for some field strength $E \geq E_{\text{cr}}$ the energy accumulated by an electron in the electric field during a unit time is higher than the energy lost by the electron due to scattering from phonons and defects during the same period of time, is likely not the initial cause of charge passage through a membrane. It appears important to emphasize that, as experimental evidence of others indicates (P E K Donaldson, 2003; Peter E. K. Donaldson, 1976; Edell, 2004; Von Hippel, 1937), the electrical breakdown of the polymer is not a critical event occurring. The electrical breakdown of polymers may instead be a kinetic process

that develops in time. It is characterized by the damage accumulation rate, i.e., relating to the lifetime of a polymer sample in the electric field. The breakdown itself (formation of a conducting channel) is perhaps instead a final stage of polymer degradation in the electric field. If electric breakdown is not the initial cause of initial failure, then it follows that the concept of a thermal breakdown is also inapplicable to the description of polymer degradation in the electric field because thermal breakdown is a critical event taking place at a definite current density (at the voltage at which the heat evolution rate exceeds the heat removal rate).

Another idea is that polymer breakdown is initiated by electromechanical means. This formulation relies on the idea that a narrow crack initially forms in an elastic material, followed by crack growth under the action mechanical stress when the energy released during the crack growth exceeds the energy required to form a new surface (Zeller & Schneider, 1984). While the conditions (e.g. energy) for propagation of cavities in the polymer placed in an electric field have been considered, discussion of how the initial “crack” or cavity are formed has not been rigorously discussed

It is currently believed that the initial “cracks,” or imperfections, in the polymeric barrier are caused most commonly by incomplete condensation of the polymer during formation. The existence of impurities, any appreciable level of humidity, and substrate preparation, in turn, cause the failure of complete condensation reaction. In our work, we take great care to clean all systems, perform all packaging in a cleanroom, and utilize long bake-out times for devices prior to polymer application. It is also important to understand what the relation is between the average electric-field intensity measured in experiments and the intensity of the actual electric field acting in a polymer insulator. To solve this problem, the formation of a space charge (SC) in a polymer should be considered. In spite of the fact that many research efforts have been devoted to studying the effect of the SC on the electrical breakdown of polymers, the problem still remains insufficiently clear. It can be supposed that the SC accumulation exerts a considerable influence on polymer aging because it determines the level of local electrical stresses.

2.4.5 Interesting intersection between hard and soft packaging

A group at Princeton, NJ has studied for several years the very interesting intersection of polymeric packaging with glass (Mandlik, Gartside, Han, Cheng, Wagner, Silvernail, Ma, Hack, & Brown, 2008). In their process, a PECVD system is used to create a thin layer from a mixture of hexamethyl disiloxane (HMDSO) and oxygen. This thin layer is essentially a SiO_2 – Silicone hybrid assembly where polymeric gaps are filled with SiO_2 . Because the polymeric sub-layers (SiO-CH_3 -) mechanically decouple the inorganic sub-layers (SiO_2) from each other, the cracks in the inorganic sub-layers are distributed randomly. This random distribution lengthens the permeation paths for water, ions, etc. and thus extends the lifetime of the packaged microelectronics. Originally developed for organic light emitting diode (OLED) packaging, this is a promising technology for implantable microelectronic packaging as well. We are currently exploring how to adapt this process to coat our implantable electronics.

2.5 Conclusion: where we stand with packaging for neural interfaces

In conclusion, our group has developed devices (described later) that belong to two different packaging “classes:” one focusing on absolutely minimized implant geometry and the other on very long-term, chronic implantation. After review of the current literature and preliminary experiments run in our lab, we have decided to package the first system with a polymeric silicone rubber to maximize flexibility while minimizing thickness and the second system with a hermetically sealed titanium case to ensure long-term robustness. It is clear we should not expect truly chronic stability with polymeric packaging because the mechanisms of failure are still sufficiently unclear. However, with diligent process control, we can expect to extend the lifetime of these polymeric barriers to reasonable lengths for short-term animal and, eventually, human use. In parallel, we have used rigid packaging methods to ensure chronic stability where geometric limitations are less stringent.

As we pursue translation of engineering and technological breakthroughs from the laboratory into the clinic, we must take every opportunity to prove functionality, reliability, and efficacy of the devices we produce. Supporting electronics to monitor function and securely store pertinent information are essential to these goals. Until recently, the utility of the domestic pig appears to have been neglected in providing a simple, flexible platform for testing these attributes. Here we have described the use of a novel stereotactic frame, and its use in neuroscience and neuroprosthetic device development using this relatively unexplored animal model. Stereotaxis and fixation was achievable with minimal effort and enabled implantation of a device under study in numerous animals. Lastly, we have introduced the central challenges in the field of microelectronic device packaging, out of which has come the current choices of polymeric and metallic packaging for the externally and internally powered microsystems, respectively.

CHAPTER 3: Integrating state-of-the-art microelectronics with the nervous system: externally powered microsystems

3.1 Introduction: Core foundations of all neural interfaces developed at Brown University

Building a neural interface is a complex challenge requiring skills from many scientific disciplines. We have spent our development energy creating instead of a singular device, a design that has become the foundation of, currently, four devices, with countless more to emerge as we continue our research. We began the process by assessing the constraints, or guidelines for an ideal microsystem: 1) full bandwidth on each recording channel (0.1Hz – 7.5kHz, requiring sampling rates >15ksps) to capture the complete informational richness of the electrical neuronal

communication landscape; 2) low-power operation ($<50\text{mW}$) to minimize complexity of power delivery and reduce heat generation; 3) wireless data telemetry to remove any potential infection route from percutaneous wire connections as well as enhance the independence and mobility of the subject; 4) bring amplifier and digitization logic onto the implanted system and as close to the signal source as possible to minimize data corruption from outside interference and simplify data transmission; and 5) separate the neural sensor from the majority of the electronics to focus heat-generating components into highly vascular and temperature tolerant tissue (e.g. skin versus cortex). These design choices are deceptively simple to make and lead to potentially very complicated solutions. However, by firmly adhering to these principles, we have been forced to innovate, which has given birth to the device implementations discussed in this thesis, and hopefully more in the future.

This chapter will discuss the critical components of the externally powered microsystem (EPM) including those for signal amplification, power over radio-frequency inductive coupling, data telemetry over infrared laser pulses, data digitization, and control logic. Each component has undergone a significant degree of development over the last five years and has been worked on by several individuals. We will discuss the current modality of each critical component being employed by the EPM. The following chapter (*Chapter 4*) will address the unique components of the internally powered microsystem (IPM), which, are not currently present in the EPM.

3.2 Introduction to the externally powered microsystem

Several groups worldwide are now working towards implantable wireless active microelectronic neural interfaces (D. Borton, Yin, Aceros, Agha, Minxha, Komar, Patterson, Bull, & Nurmikko, 2011; R.R. Harrison & Charles, 2003; Miranda et al., 2010; Mohseni, Najafi, Eliades, & Wang, 2005; Mojarradi, Binkley, Blalock, Andersen, Ulshoefer, Johnson, & Del Castillo, 2003; Rizk et al., 2007; Samsukha, Tabib-Azar, Harrison, & Chiel, 2004; Sanchez, Principe, Nishida, Bashirullah, & al, 2008; Amir M Sodagar, Wise, & Najafi, 2006; Y-K Song,

Borton, Park, Patterson, Bull, Laiwalla, Mislow, Simeral, Donoghue, & Nurmikko, 2009; Yin & Ghovanloo, 2008) with recent progress reflected by the sheer number of papers published in this topic and even special issues of journals (see *TNSRE 2009*). The concept of an implantable wireless platform, without any percutaneous skin-puncturing elements, demands the implementation of a heterogeneous, active microelectronics platform. At a minimum, the implanted “microsystem” requires in-situ integration of ultra-low-power microelectronic ASICs with the cortical microelectrode neural probes, and must provide broadband telemetry and a means to deliver power wirelessly to the active implanted components. In our laboratory, a 16-channel version of a fully implantable microsystem, whose design and performance is summarized in the following sections, has been implemented and tested on the bench top and used in animal tests. Our microsystem is a single-unit construct (Figure 3-1) where analog and digital chips are integrated onto a flexible substrate together with a low threshold, infrared semiconductor diode laser to transmit the digitized neural signals through the skin. Power and clocking are delivered to the system via inductive coupling (R.R. Harrison & Charles, 2003; Mohseni et al., 2005; Yoon-Kyu Song, Patterson, Bull, Borton, Li, Nurmikko, Simeral, & Donoghue, 2007; Zierhofer & Hochmair, 1990), but the system can also be configured to be powered optically using a high efficiency photovoltaic energy converter.

The initial use of a 16-electrode sensor as a development model of our system reduced its complexity, fragility and cost. This allowed us to test telemetry and power transfer, package design, and surgical adaptability more thoroughly and quickly. However, all aspects of the system have been designed to be scalable in two senses: first, the amplifiers and analog to digital converter (ADC) systems scale nearly linearly in power with increasing numbers of electrodes. We have already established that our inductive coupling loop is capable of supplying the additional power, and the preamplifiers (45 microwatt per electrode) are sufficiently low power that their thermal load on the cortex will still be acceptable. The infrared telemetry has so far demonstrated capacity for 32 channels in vivo and is scalable to 100 channels. The digital

processing is adaptable in its current form to any number of channels as long as the clock rate, limited by the telemetry channel, is sufficient to carry the data.

The second sense of scalability refers to the ability to place two or more separate cortical sensors in the cortex so that as more channels are available, they can be used to acquire data from different brain areas simultaneously. One example is to implant one array in the motor cortex and a second in the parietal cortex. This is possible because we separate the signal processing, power, and telemetry subsystems from the electrodes and their analog amplification and multiplexing. Channel addressing and ADC conversion have been designed to merge two sets of data into a single output stream at no increase in power, alteration in chip design, and no change in the number of wires to each array.

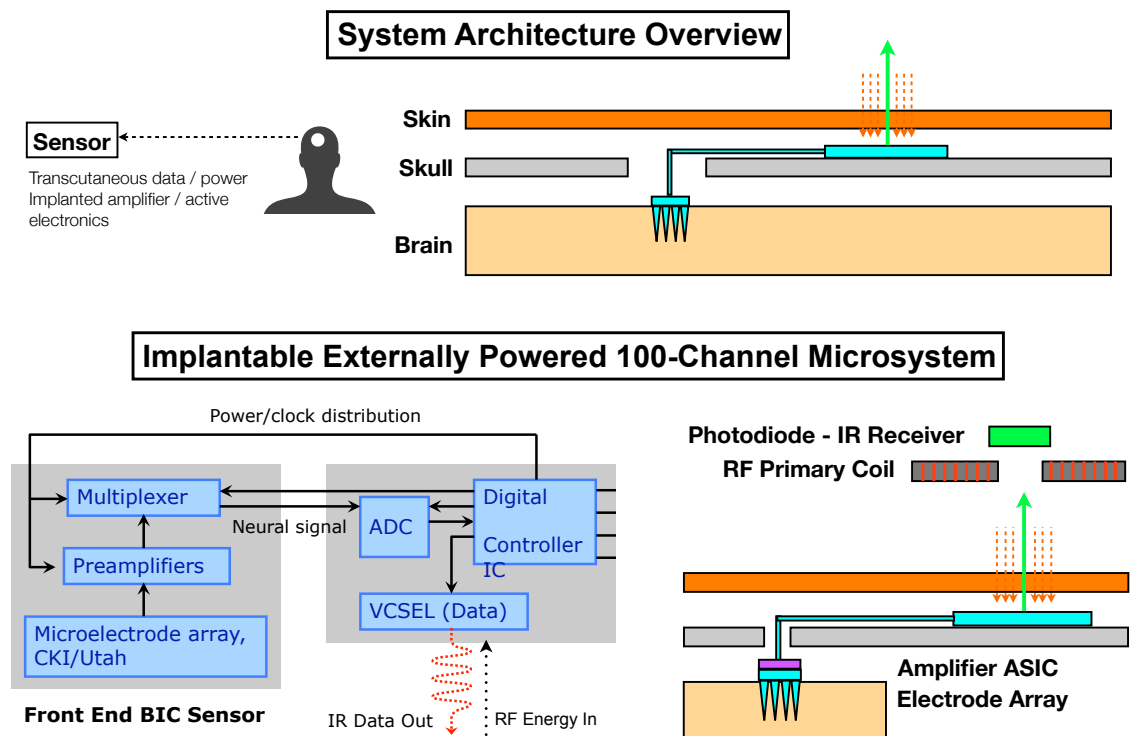


Figure 3-1: Wireless neural sensor architecture overview. The primary goal is to remove all percutaneous connections and replace them with means to wirelessly deliver power and data. The implantable externally powered microsystem (EPM) is shown both in diagrammatic form and in block form showing separation of active components in the system.

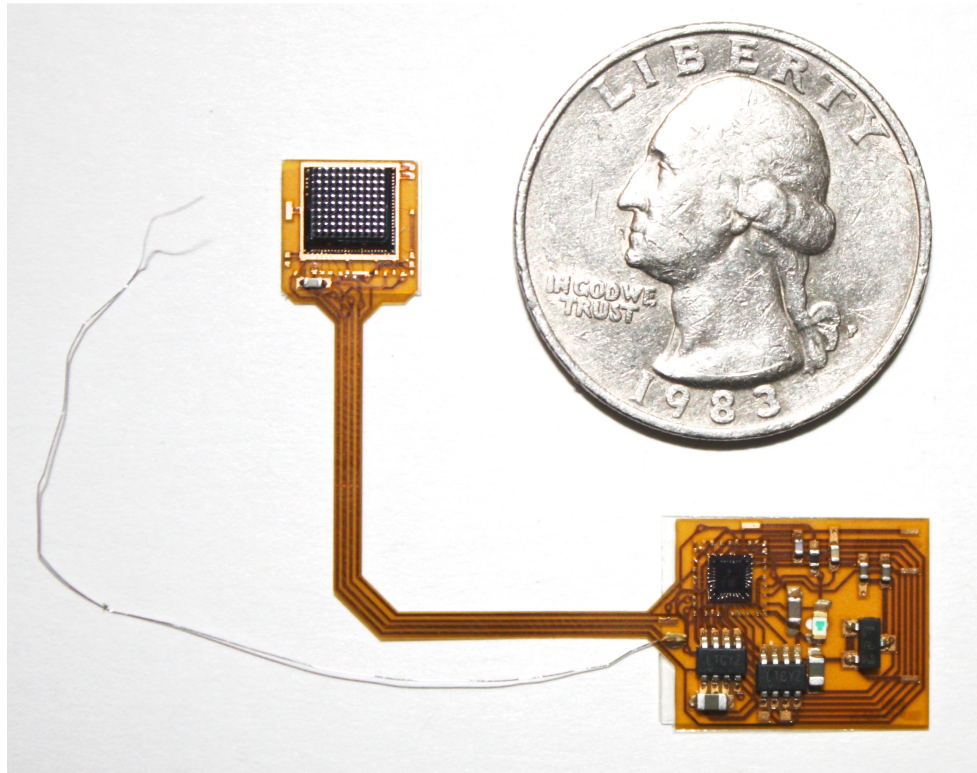


Figure 3-2: Anatomy of the implantable externally powered microsystem. A quarter is shown for size comparison. The neural sensor (left side of figure) is comprised of a microelectrode array (MEA) integrated with a custom amplification ASIC. This section of the system sits on the cortex (electrodes implanted into the cortex). The telemetric and digitization occurs on the larger of the two sections (right) which, rests on the cranium. On this unit, the secondary RF coil can be seen (printed on the substrate) along with the VCSEL (green dot in middle of system) for data transfer.

The rationale for our choice of the particular spatial distribution of the passive (cortical) neural sensor, the active signal acquisition electronics, the digital control components, and the telemetry and power elements, is based on a convergence of considerations of microelectronic device engineering, thermal loading, neurophysiology, anatomy, and surgical constraints. At one extreme of such possible layouts is a construct with all the microelectronic components physically integrated directly onto the multielectrode neural sensor. Such a monolithic “brain button” would be entirely located proximate to the brain, *i.e.*, below the skull. This is currently

being pursued elsewhere (Sohee Kim, Harrison, & Solzbacher, 2008). By contrast, our considerations have led to a “dual-panel” design with cortical and epicranial (subcutaneous) sections mounted on a common flexible polyimide substrate Kapton (DuPont, DE - fabricated by Microconnex, WA) as shown in Figure 3-2. Distributing the microelectronics payload in this manner can have several advantages for future human applications.

The cortical “front-end” panel consists of the electrode array flip-chip bonded (using an epoxy dot technique described elsewhere (W Patterson, Song, Bull, & Ozden, 2004)) to a monolithic low power CMOS IC with preamplifier array and analog multiplexer and a single bypass capacitor. Placing only the preamplifier-multiplexer chip directly onto the cortical microelectrode array ensures that we capture the full neural signals from the brain with minimal environmental interference while minimizing direct heating of the brain tissue. Our criterion for $\Delta T < 1\text{C}^\circ$ rise is near the typical thermal limit for medical implants (ISO 14708-1:2000 E standard requires that no outer surface of an implantable part of the active implantable medical device shall be greater than 2C° above the normal surrounding body temperature of 37C°).

A small flat ribbon cable, part of the common polymeric substrate, with seven embedded gold wires for signal and power connects the cortical panel to the epicranial “back-end” panel. That panel, placed between the skull and the skin, holds the A/D converter and a digital control ASIC as well as the power and data transmission components. Most of the system power dissipation occurs in these components. Their placement can enable improved heat dissipation by surgically arranging “arterial plumbing”, and allows ready access for infrared data detection and for RF inductive coupling. In addition, proper arrangement can isolate the neural sensor array (and amplifier ASIC) away from any magnetic forces that may be used to align the RF and telemetry units.

Figure 3-1 shows an electronic block diagram of the present 16-channel microsystem. Some of the key system requirements for the prototype units described below are: (i) mW level power consumption, (ii) ability to record both spikes and lower frequency field potentials, and

(iii) a safe packaging and encapsulation strategy for eventual long-term implantation in humans. A front photographic image of a prototype microsystem is shown, displaying components and interconnects wiring. The cortical front-end shown contains several discrete components which have now been integrated into the preamplifier chip. The “L” shape for this construct was based on its anatomy of a specific non-human primate. This was quantified by reconstructing the skull and the brain in a rapid-prototype plastic model from the monkey’s magnetic resonance imaging (MRI) scan and x-ray computed axial tomography (CAT) scan images. It should be noted that the specific substrate geometry is not difficult to adjust in order to fit a particular species of study. The surface-mount components on the epicranial section are fastened to their contacts with Ag epoxy (a process currently being migrated to solder reflow). The bare die of the digital controller IC is wire bonded to the gold bonding pads on the substrate. The conductive spiral on the back of the epicranial section is the RF coil used for inductive coupling. The largest components are the A/D converter (ADC) and the digital control application-specific integrated controller (ASIC). The ADC is an off-the-shelf, 12-bit, AD7594 (Analog Devices) packaged in a standard micro-SO8 package. The ADC operates at 34 to 40 ksps per channel depending on the way power is supplied. This choice of a high sampling rate preserves all the subtle features of the spike waveforms so that useful information enabling distinction between single and multiunit activity recorded at a single electrode is available from such data.

The ADC receives a clock and a start-of-conversion signal from the digital controller IC that also supplies the channel address to the amplifier circuit. The controller is a custom integrated circuit built in the AMI Semiconductor (currently ON Semiconductor, ID) 0.5-micron process through the Metal Oxide Semiconductor Implementation Service (MOSIS, CA) and has been described in more detail elsewhere (William R Patterson & Song, 2007). The controller has two other functions. First, it multiplexes the ADC data with a periodic synchronization code word that replaces the data from one channel. The external electronics that receive the neural data use this unique code word to find the beginning of the serial data stream and the first channel in the

frame lies immediately following the synchronization signal. Second, the controller converts the multiplexed data into the drive current for a low-current, high-efficiency, vertical-cavity surface-emitting laser (VCSEL) diode, which produces a peak optical output power of 2-6mW for the optical telemetry. The VCSEL occupies less than 1 mm² of substrate area. The controller derives its clock from either the RF inductive power loop or from modulation on the DC power source depending on the supply mode. The controller IC contains a comparator that regenerates the digital clock from a small sinusoidal signal separated from the appropriate source in the power module. Total system power consumption is approximately 12mW in the discussed 16-channel version including all parts of the implanted system. The 100-channel expansion consumes only 26mW with the addition of one ADC and the increase in amplifiers.

3.3 Fabrication methods of the externally powered microsystem

The fabrication of the system is divided in three sections: Section 3.3.1 focuses on integrating the front end amplifiers with the microelectrode array, Section 3.3.2 on backing and populating the flexible Kapton substrate and Section 3.3.3 on current methods for packaging the device for implantation.

3.3.1 Integrating the front end amplifiers with the microelectrode array

Integrating the intracortical microelectrode arrays to the front-end amplifier ASIC presents a significant challenge due to restrictions imposed by the amplifier and array design. Among these are pressure and temperature constraints on the amplifier connections to the array and on the metal electrode contacts at the base of the array. The preamplifiers have double polysilicon input capacitors buried underneath the input pads, the electrode arrays have Parylene insulation that has limited tolerance for high temperature, and the base of the array has only limited fracture strength (the breakdown values for each of the mentioned failure modes have not been sufficiently characterized to enable quantification of the limits). In addition, simultaneous

bonding of all 16-channel (and in other cases, 100 channels) was required. These constraints made assembly by soldering or ultrasonic bonding very difficult.

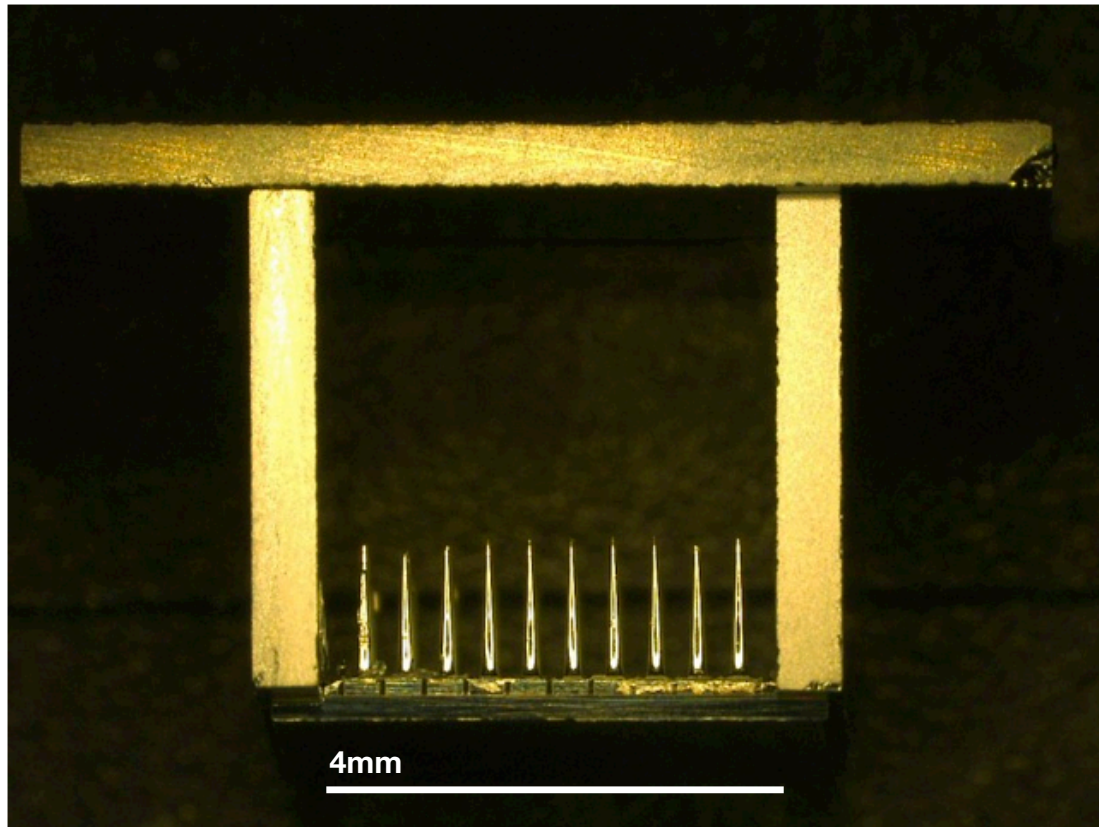


Figure 3-3: GaAs fixture developed for integration of the microelectrode array to the amplifier ASIC with matched input pad spacing. GaAs wafers are cleaved along lattice edge to provide extremely flat surfaces to mate with the MEA. The fixture is glued together temporarily with photoresist (cured by UV light) then later dissolved with acetone once integration is completed. The fixture is held by vacuum from the top (as shown) while it is brought above the amplifier ASIC. Once the bonding machine senses appropriate pressures, the system is cured at 90C for 4 hours.

A modified flip-chip process strategy was developed using thermally cured, electrically conductive, silver epoxy to avoid these issues (W Patterson et al., 2004). The two-part silver epoxy (Epotek Model H20E-PFC) was prepared and inserted into a needle and syringe for use with a pneumatic dispenser. Previously, a pin stamping (epoxy dot) technique was employed but this method is slow and presented reliability issues due to the applied pressure on the input pads

of the capacitors. A 32-gauge precision tip needle from Nordson EFD with an Ultra 2400 Series pneumatic dispenser from the same vendor allowed rapid and reliable dispensing of epoxy over the amplifier pads.

The 4×4 and 10×10 element intracortical microelectrode arrays were purchased from Blackrock Microsystems with electrode heights of 1.5 mm. They were assembled into a specialized holder (GaAs housing, see Figure 3-3) as previously described (W Patterson et al., 2004) and flip chip bonded together using an RD Automation Model M9A unit. They were cured for 1hr at 90°C in the machine and then for 3hrs at 90°C on a hotplate in room air. A former research associate and colleague, Yoon-Kyu Song, developed this process.

3.3.2 Rigid backing and population of the flexible substrate

Microconnex Inc. (Snoqualmie, WA) fabricated flexible Kapton substrates with embedded conductive traces for use as the substrate for our implantable devices. These substrates consisted of a dual layer flexible circuit with 18-25-18 Kapton, copper-ENEG metallization and had 27µm Kapton cover coats on both sides (as well as small hole for the IR laser transmission). Sapphire backing plates (254µm thick) were attached to the back-end and front-ends to provide a rigid support surface for supporting the device components and wire bonding without affecting the high flexibility provided by the tethering scheme. Sapphire was selected because it provides high mechanical strength as well as optical transparency to allow IR laser transmission through the device system. A 25µm thick type JADE-A Rogers Film was used as the bonding agent. The sapphire was attached using a fast lamination process at ~300psi, 190°C for 1hr. After bonding, the film was mechanically removed from the VCSEL hole area at the center of the back-end to avoid interference with the optical data transmission.

The passive and active device components were populated on the back-end and front-ends of the substrate using the same Silver epoxy used for the flip-chip process and the epoxy was cured on a hotplate at 90°C. The controller and amplifier ASICs were wire bonded to the

substrate using an ultrasonic wedge bonder with 1 mil Al-Si wire and finally two 5mil thick 90%Pt-10%Ir wires were attached with Silver epoxy to pads on the back-end. These wires are used as a common voltage reference electrode input to all the preamplifiers (preamplifiers share a common reference input).

3.3.3 Encapsulating the system using epoxy and PDMS

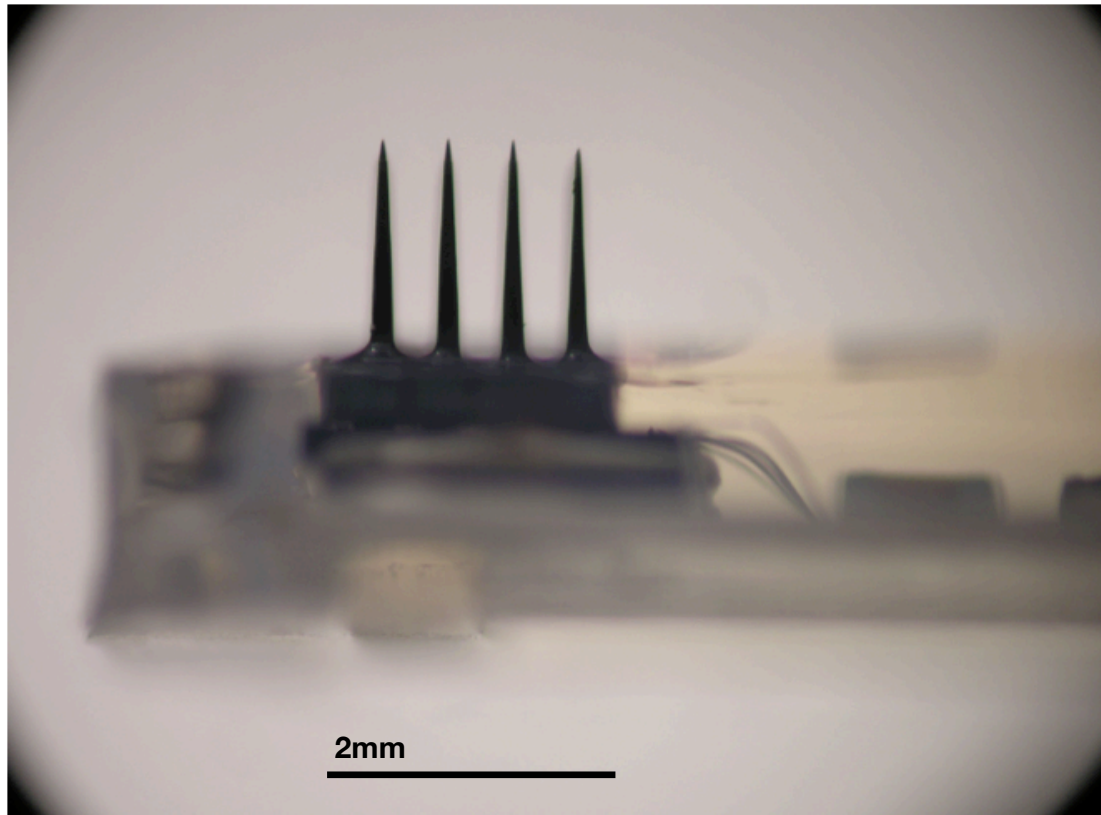


Figure 3-4: Encapsulation of the microelectrode array and amplifier ASIC on the externally powered neural interface. Note the PDMS (slightly opaque and blurred – out of depth of field - block coating the device) does not wick up the electrode shank and stops about 100 μ m above the base of the MEA. Wirebonds from the amplifier can be seen attaching to the substrate (address lines, power, ground, and reference).

Encapsulating the system for ensuring an impermeable barrier for the implant, allowing it to be isolated from body tissue (and vice versa, biocompatibility and biostability – see *Chapter 2*) is the last step in completing the full fabrication process flow. Medical devices aimed at long-

term functionality and reliability requires both mechanical robustness and ionic protection. While both are often addressed by using metal hermetic enclosures (laser-joined titanium or ceramics, such as are used in pacemakers, deep-brain stimulators, etc.), when a system must maintain flexibility along with the above-mentioned characteristics, polymeric or very thin crystalline insulators are required. Although visual prosthetics have been constructed using thin layer semi-crystalline encapsulants (S Kim, Bhandari, Klein, Negi, Rieth, Tathireddy, Toepper, Oppermann, & Solzbacher, 2009; J. D. Weiland & Humayun, 2008), here we use polymers (see detailed reasoning in *Chapter 2*). Systems are first cleaned in a series of ultrasonic baths for 3 minutes in each of MS-722 (Miller Stevenson, CT), then de-ionized H₂O, and finally isopropyl alcohol. Between each rinse, the systems are dried with a stream of N₂. The systems finally are dry-baked at 100 °C for 10 minutes to remove residual moisture from the substrate. Prior to silicone application, the surface is activated by application of a silicone primer (CF1-134). The entire microsystem is then potted in poly-dimethyl-siloxane (NuSil R-2188) for electrical isolation and mechanical flexibility. Careful control of silicone thickness must be maintained to assure flexibility in the tether and prevent buildup or wicking on the electrode array. For images of the structure after encapsulation, see (Y-K Song et al., 2009) and Figure 3-4.

The main functions of the encapsulation are to ensure a) that electrical leakage current to the adjacent tissue is minimized, and b) ionic leakage from the tissue to the electronic components is less than 10pA. For chronic implant applications, this presents a formidable challenge and has been studied to a degree (Peter E. K. Donaldson, 1976; Edell, 2004; Guangqiang & Zhou, 2010; Otsuka, Takeo, Ishida, Yamada, Kuroda, & Tachi, 1987; Wong, Fung, Tao, Lai, Tsang, Kong, Choy, Lee, & Lee, 2008). We view our initial approach, using polydimethylsiloxane (PDMS), specifically the NuSil R- 2188 formulation (NuSil, n.d.-a, n.d.-b), as a useful starting point for sub-chronic or short- term (1 to 3 months) in-vivo animal testing. In addition, we have designed and implemented an encapsulation test unit (ETU), which simulates

the topographical, thermal, and electrical stresses put on the encapsulant to test leakage current and component functionality over extended periods of soak time. This test system allows us to evaluate and characterize potential encapsulants under realistic conditions.

To evaluate the performance of our ‘soft’ encapsulation we have soak tested samples for six months in saline at $T = 52^{\circ}\text{C}$. The testing is done using a small test circuit board that is a simplified version of the complete, implantable neurosensor. The test structure enables continuous monitoring of the resistance between interdigitated conductors on the substrate surface as well as leakage current through the encapsulation material. The leakage currents are a proxy for the presence of ions that might have leaked through the encapsulation material. The test structure includes elements with all the same morphological characteristics that are encountered on the real devices and includes a working ADC. In spite of early successes, it is clear that chronic implants will require a more reliably impermeable barrier. We are presently exploring combinations of soft organic polymers with inorganic thin film multilayer barriers or heterogeneous mixtures, solid solutions of inorganic molecules in polymers. Candidate inorganic materials include SiC , SiO_x , or Si_3N_4 .

3.4 Substrate design considerations and development

Our implantable microsystem design is based on a dual panel concept, where, due to thermal and telemetric considerations, the physical layout of the implant separates the ultra-low power microelectrode/CMOS preamplifier assembly from the support components that provide the serial digital data stream for output. These consume considerably more power. Based on our thermal models, we have chosen a design pattern that limits the temperature rise at the cortex to less than 1°C (FDA stipulates that no implant surface can reach 2°C above body temperature) for a full 100 channel system. Many variations of the substrate’s geometry have been made, each possessing benefits for the surgical implantation and thermal separation. These can be seen in Figure 3-5, and they fall into three general categories: 1) the straight (or “dog bone”), 2) the “L”,

and 3) the “U.” All of the substrates we have designed follow our design principal of separating the heat-generating components of the active system from the cortex. This leads to a two-island construct: one holds the MEA-amplifier construct lies on the cortex while the other is significantly larger and rests on the skull, under the skin. We generally refer to the “cortical unit” as the neural signal frontend and the supracranial, subcuticular unit as the backend. More specifically, the frontend is a neural signal sensor unit and the backend is a “telemetric unit”. We will refer to these islands under both names throughout this thesis.

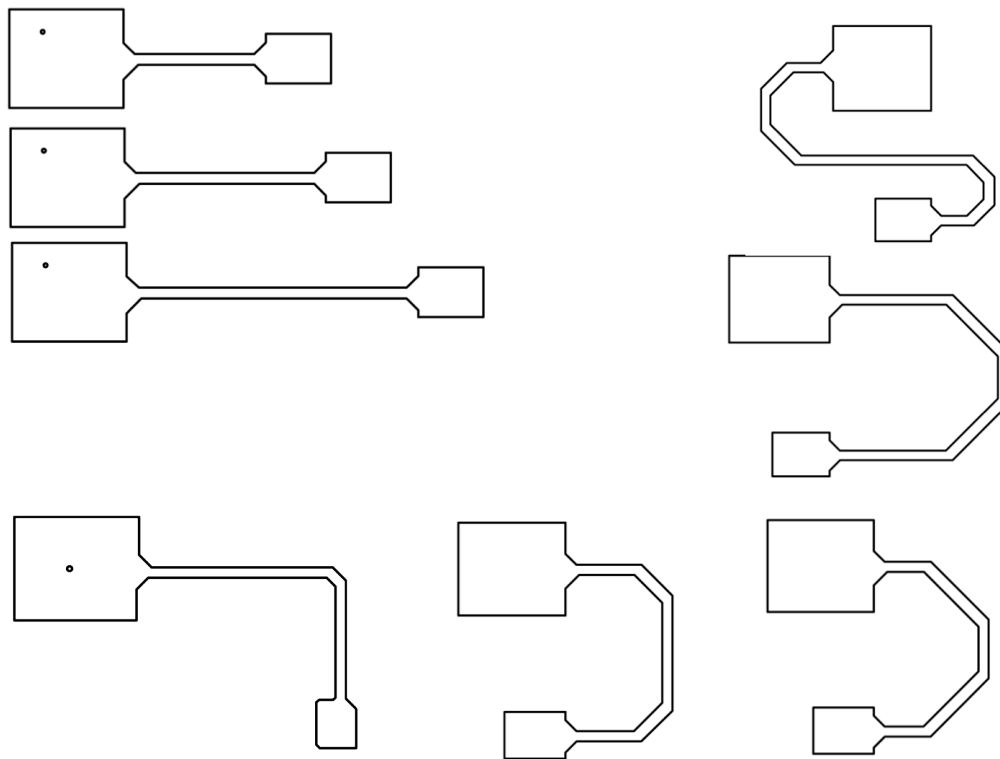


Figure 3-5: EPM substrates over three major revisions: “dog-bone” (top-left) was created to keep the telemetric unit on the same hemisphere as the neural sensor; “Big U” (right column) was created to potentially place the telemetric unit directly on top of or very near the craniotomy for the neural sensor, reducing the cranial area exposure; and “L” (lower-left) the current design that allows the telemetric unit to cross the midline.

The greatest incentive to moving from the “dog bone” design into the “L” or “U” design is to allow for crossing the midline of a rhesus macaque non-human primate. Crossing the midline

allowed us more flexibility in placement of the telemetric unit. The common substrate for the entire microsystem was originally a patterned liquid crystal polymer (LCP) which provides all the internal electrical interconnect wiring between discrete microelectronic chips. LCP is biocompatible, chemically inert, resistant to water absorption, and when metallized, is suitable for conventional printed circuit processing so as to minimize potential failures at soldered or wire-bonded connections and has been used in biomedical applications (Dean, Jr., 2004). However, after preliminary experimentation with this compatible substrate, we observed cracks in the metallization layers caused by bending of the substrate during manipulation upon implant (see Figure 3-6). While LCP is a flexible substrate, the adhesion of the metals to the substrate was poor. After much deliberation, we chose to use a $0.5\mu\text{m}$ Kapton (DuPont) polymeric base-layer substrate. This substrate has been successfully used in retinal implants and many other biomedical devices and shares many of the beneficial properties (inertness, biocompatibility, etc.) as LCP. In combination with a lamination layer of Kapton ($1\mu\text{m}$) on either side of the base layer we were able to achieve a mechanically and electrically robust substrate with insulated traces only exposed at contact pads. It should be noted that another approach might be to laminate an LCP-based substrate with another layer of LCP to reduce the possibility of delamination of the metallic traces. However, this process is difficult and was not pursued as a research topic in this thesis. In this application $0.5\mu\text{m}$ thick Kapton film is metallized with $12\mu\text{m}$ of Cu (1/3-ounce), $3\mu\text{m}$ of Ni, and $1.4\mu\text{m}$ of wire-bondable Au (fabrication by Microconnex, Snoqualmie WA, USA). This gives printed traces with a sheet resistivity of 2 milliohms per square. Those areas where components would be mounted were stiffened by bonding 250mm thick sapphire pads to the backside of the Kapton with heat / pressure curing epoxy film (Rogers R/Flex 7200 B 200). The design provides a flexible, integrated interconnect between the analog front end and the back end housing the ADC, command and control chip and optoelectronic modules through a set of eight “traces” on a 2 mm wide 2.5 cm long strip. This flexible interconnect allows easy placement of the electrode array and provides some relative motion between the array and support electronics when

implanted, mostly in the up/down direction (out-of-plane). It also insures that only the power of the CMOS analog chip is dissipated adjacent to the cortex while power for data conversion and transmission is dissipated between the skin and the skull where there is adequate vasculature and less sensitivity to temperature. Two of the seven traces provide power and ground, while four others select the electrode channel by addressing the on-chip multiplexer. The last trace returns the multiplexed analog data to the analog-to-digital converter. All traces except for the ground reference were 100um wide with a 200um center-to-center separation. The ground return trace was 150 um wide to reduce its resistance because any potential drop in this line from the DC supply current to the amplifiers is a direct offset to the data. The length of the tether is limited by the need to keep this offset to a negligible sub-millivolt level.

The power, data conversion and telemetry unit of the substrate (backend) was designed for flexible operation and ease of assembly. To aid in initial debugging, there are five extra solder pads on the side of the substrate that can implement a fully wired interface. Similarly, additional area was allowed for component and wire-bond placement. The inductor and capacitor network used to separate power and clock signals as discussed below is implemented in a mix of standard EIA 0603 and 0402 surface-mount RoHS-compliant components that are wired in place with conductive epoxy rather than Sn-Ag solder. This lowers the thermal stress seen by the electrode array and the substrate while avoiding the introduction of harmful elements, such as Pb.

As seen in Figure 3-7, the tether between the cortical unit and telemetric unit varies significantly from the behavior seen in the BRM NeuroPort wirebundle. While the BRM wirebundle is dominated by elastic deformation from the silicone rubber on each wire, our tethers show inelastic behavior. Because the cross-sectional area of our conductors (metallic traces) is much greater than the 1mil wire used in the BRM wirebundle, the inelastic deformation of the metal dominates the deformation of the entire tether. It is unclear at the moment whether this attribute is advantageous or not. We have successfully implanted these systems in numerous animals, so it is likely not a significant change.

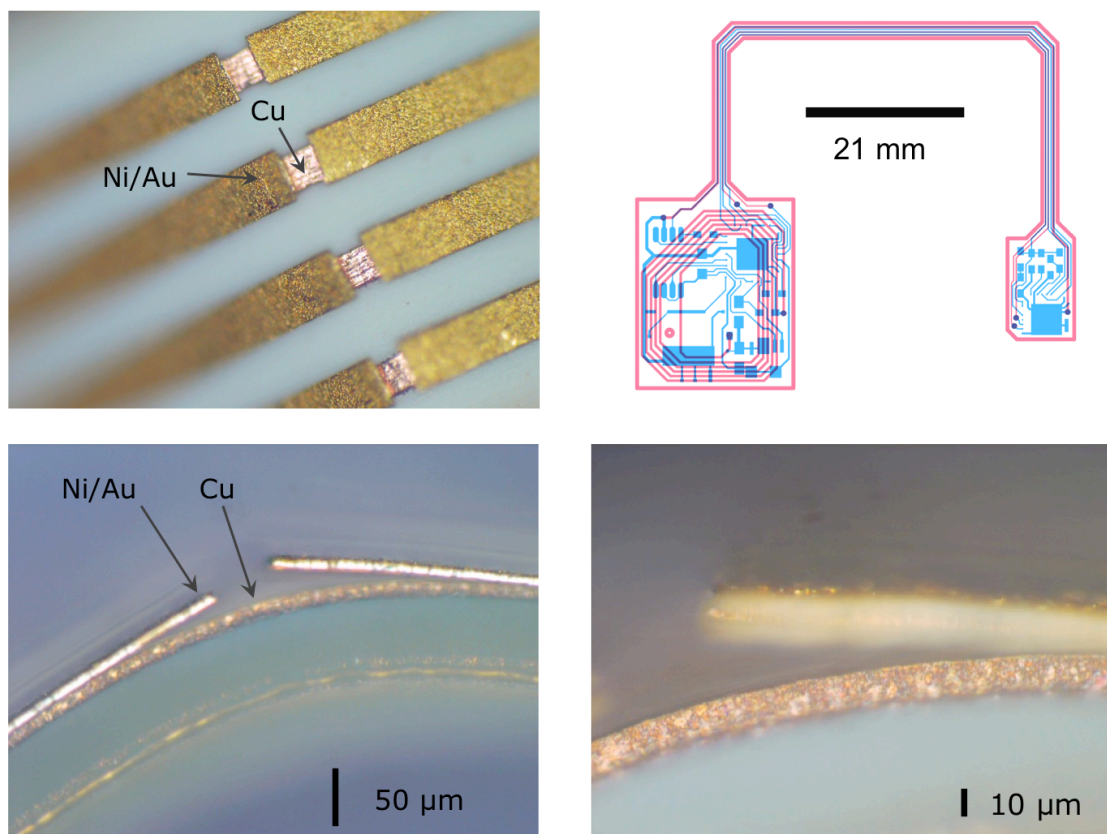


Figure 3-6: LCP substrate failure during bending. The “U” substrate was used for these tests, which showed delamination of the metallization from the LCP substrate during $>30^\circ$ bend over a 1cm bend radius. It can be seen that the Ni/Au layer fractured across the substrate. While the LCP itself is perfectly able to bend elastically, it was unclear to us if the metal adhesion to LCP was sufficient for our needs. Thus, we transitioned to a polyimide (Kapton) substrate with lamination to support the metallic traces.

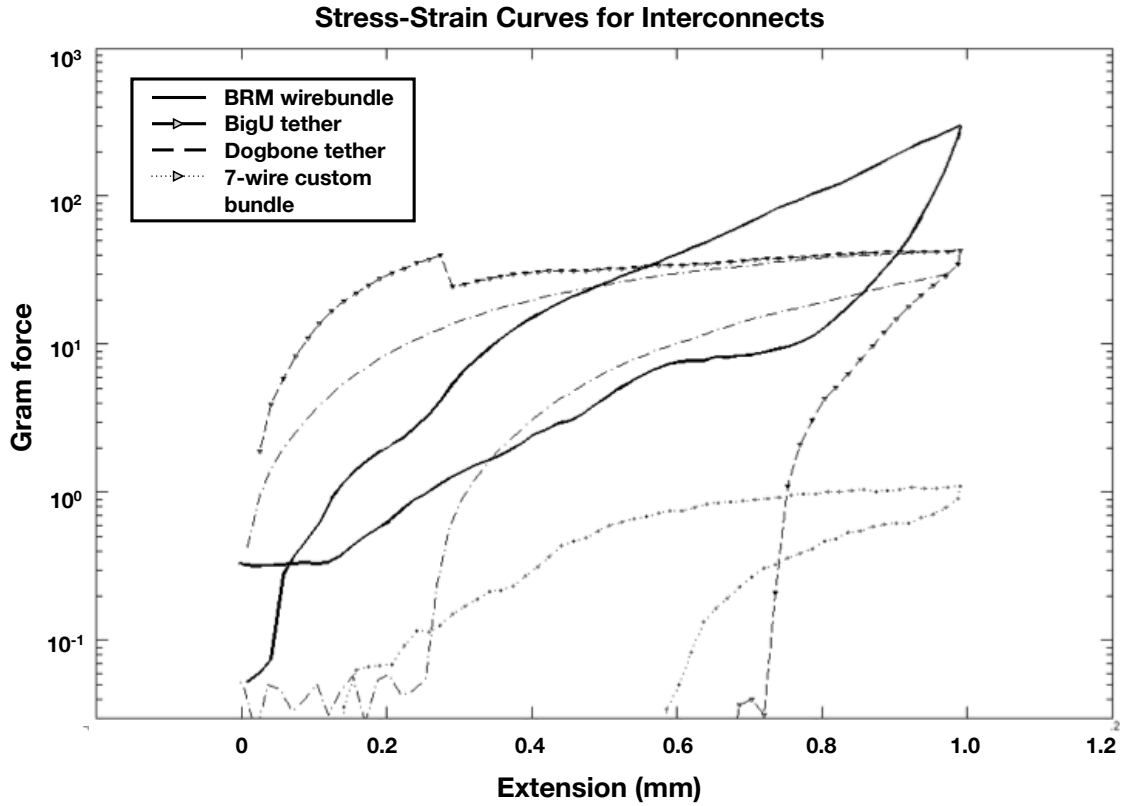


Figure 3-7: Stress-strain curves for a) standard Blackrock Microsystems NeuroPort wirebundle, b) “Big U” Kapton substrate, c) “Dog-bone” Kapton substrate, and d) a custom wirebundle with 7 gold wires. It is clear that the BRM wirebundle is undergoes purely elastic deformation during this test, while all of our systems shown a degree of inelastic deformation. Kapton-based systems were packaged in PDMS before testing.

3.5 Radio frequency inductive coupling for system power and clock

The externally powered microsystem shares a common power transmission scheme with many other devices we have developed: RF induction. In this scheme, a conducting coil (primary) is place outside the skin at a given distance from another conducting coil in the implant (secondary). The primary coil is driven by an alternating voltage at a given frequency (later extracted as the clock). In the case of the EPM, we drive the primary coil with a total output power of about 80mW at a frequency of 13.56MHz (yielding over 50ksp/s on each channel).

There are many factors that determine the transmitted power into the secondary coil and thus the microsystem, such as the distance between the coils and how well matched their impedances are in the LC circuit. We can match the impedances during fabrication of the devices, however once a system has been implanted, we must optimize the primary coil geometry to match the experimental situation. The most common variance between subjects is skin thickness, which affects the impedance seen by the transmitter and receiver (the two coils).

It is very important to optimize the power transfer between the primary and secondary coils in order to minimize heat generation and potential interference with the microsystem. Below we describe our methods for a) optimizing coil geometry to match the given biological constraints, and b) determining the amount of heat generation from the coils and the impact on tissue health.

3.5.1 Optimization of the mean radius of a primary coil outside the animal

Modeling of three-dimensional radio-frequency propagation and efficiency is extremely time-consuming and beyond the needs of this project. Instead, we wanted to understand the basic tradeoffs when designing the primary and receiving coil geometries for our particular situation, i.e. at a given distance of separation due to the skin. To solve this, we moved to a two-dimensional theoretical framework that has been well solved by others. Here, we will define the equations and variables that apply to our experimental setup. In addition, this model was used to evaluate the best design parameters for both the EPM microsystem and the IPM, as described later, contains a titanium case greatly affecting the RF inductive coupling performance. Thus, we needed to make several assumptions: a) titanium case and saline will not change the optimum mean radius by much; this is a huge assumption and is addressed later in *Chapter 4*; b) the geometry of each coil has been simplified to two single-turn coils; in reality, these consist of multi-stranded Litz wire and contain multiple turns each; c) we can apply the Biot-Savart approach to calculate the primary Φ_P and secondary Φ_S flux as a function of (b, a, h) where $b =$

mean radius of the secondary coil, a = mean radius of primary coil, h = separation of the coils along the z-axis, and d = diameter of the primary coil cross section (used to avoid a singularity in calculating the primary coil flux); and d) by maximizing $K = \frac{\Phi_s}{\Phi_p}$, the coefficient of coupling over a given (b, h, d) , we approach the ideal coil geometries for our experimental setup.

$$\vec{dB} = \mu_0 \frac{\vec{dl} \times (\vec{r} - \vec{a})}{|\vec{r} - \vec{a}|^{3/2}} \quad \begin{array}{l} \text{Equation 3-1:} \\ \text{Biot-Savart} \end{array}$$

Because we want the integrated flux in the plane of each coil, we are only interested in the z-component of the magnetic field, B_z at $z = 0$ and $z = h$. In addition, because of the circular symmetry of the problem, B_z does not depend on the polar angle but only on the radius away from the z-axis. We will evaluate B_z along only the x-axis for convenience. By geometry:

$$\vec{a} = a \cdot \cos(\varphi) \hat{i} + a \cdot \sin(\varphi) \hat{j} \quad \text{Equation 3-2}$$

$$\vec{r} = x \hat{i} + h \hat{k} \quad \text{Equation 3-3}$$

$$\vec{r} - \vec{a} = (x - a \cdot \cos(\varphi)) \hat{i} - a \cdot \sin(\varphi) \hat{j} + h \hat{k} \quad \text{Equation 3-4}$$

$$\vec{dl} = I (-\sin(\varphi) \hat{i} + \cos(\varphi) \hat{j}) \quad \text{Equation 3-5}$$

We then calculate the z-component of the magnetic field by integrating $\vec{dB}$ over the circumference of the primary coil:

This can be simplified by evaluating the determinant, which leads to Equation 3-7. It is convenient to cast this into a form in which the integral is dimensionless by removing a from the denominator and defining $x' = x / a$ and $h' = h / a$, which yields Equation 3-8.

We then integrate B_z over the areas of the primary and secondary coils. We are only interested in the ratio of those integrals because that is the magnetic coupling coefficient, K that we would like to optimize. In calculating the individual integrals, we can neglect any constant common to both fluxes, as they are equivalent.

$$\Phi_S \propto \int_0^{b/a} dx \int_0^{2\pi} d\varphi \frac{1 - x \cdot \cos(\varphi)}{\left| x^2 - 2x \cdot \cos(\varphi) + 1 + \left(\frac{h}{a}\right)^2 \right|^{3/2}} \quad \text{Equation 3-9}$$

$$B_z(a, x, h) = \oint \vec{B} \cdot \vec{k} d\varphi = \mu_0 I \oint d\varphi \frac{\begin{vmatrix} 0 & 0 & 1 \\ -\sin(\varphi) & \cos(\varphi) & 0 \\ (x - a \cdot \cos(\varphi)) & -a \sin(\varphi) & h \end{vmatrix}}{\left| (x - a \cdot \cos(\varphi))^2 + a^2 \sin^2(\varphi) + h^2 \right|^{3/2}} \quad \text{Equation 3-6}$$

$$B_z(a, x, h) = \mu_0 I \int d\varphi \frac{a - x \cos(\varphi)}{\left| (x - a \cos(\varphi))^2 + a^2 \sin^2(\varphi) + h^2 \right|^{3/2}} \quad \text{Equation 3-7}$$

$$B_z(a, x', h') = \frac{\mu_0 I}{a^2} \oint d\varphi \frac{1 - x' \cdot \cos(\varphi)}{\left| x'^2 - 2x' \cdot \cos(\varphi) + 1 + h'^2 \right|^{3/2}} \quad \text{Equation 3-8}$$

$$\Phi_P \propto \int_0^{1-\left(\frac{0.5d}{a}\right)} dx \int_0^{2\pi} d\varphi \frac{1}{|1 - x \cdot \cos(\varphi)|^{1/2}} \quad \text{Equation 3-10}$$

These two integrals, Φ_S , and Φ_P are easy to calculate in numerical solvers implemented in Mathematica (Wolfram). The magnetic coupling coefficient in terms of dimension ratios is

$$K\left(\frac{b}{a}, \frac{h}{a}, \frac{d}{a}\right) = \frac{\Phi_S}{\Phi_P} \quad \text{Equation 3-11}$$

And since we know b and h and can take a reasonable guess at d from the size of the cross section of the secondary coil, we can directly find the solutions to this model. The results are seen in Figure 3-8, which show that for the expected primary to secondary coil distance through skin of 10mm (5mm in non-human primate and 15mm in swine) we can expect optimal power transfer with a primary coil diameter of 32mm. The secondary coil diameter is fixed (implanted) and was input into the model as 9mm radius (18mm diameter).

3.6 Heat diffusion models

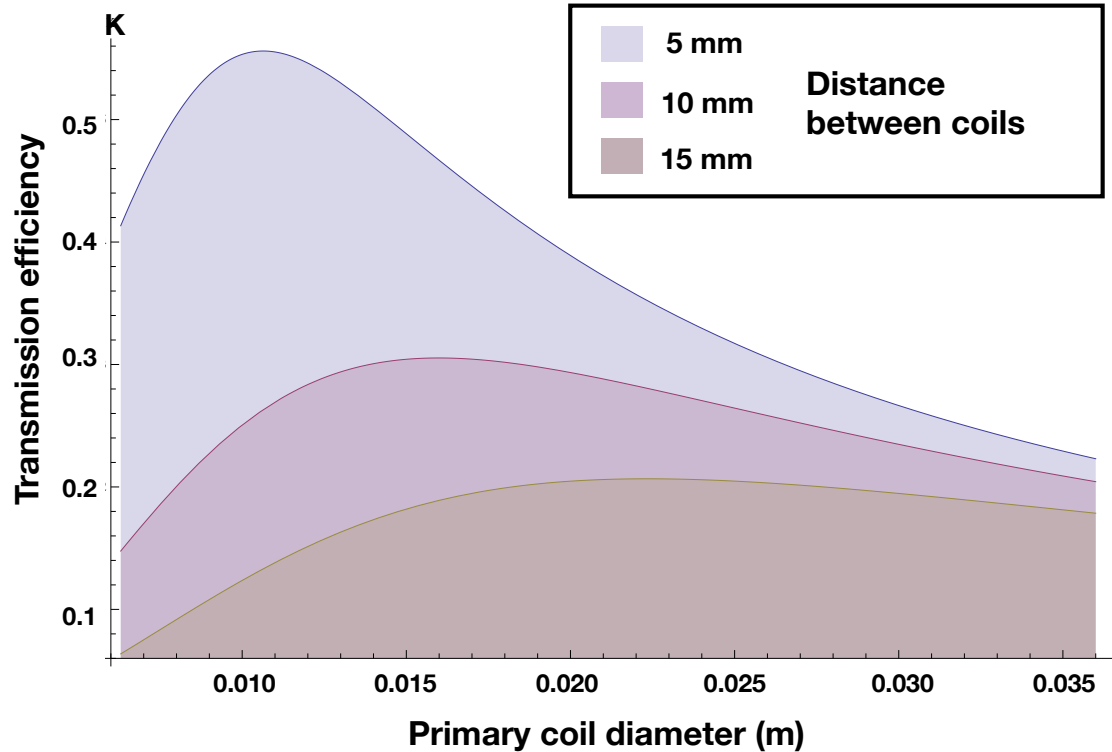


Figure 3-8: Coil diameter optimizations via numerical solving of the Biot-Savart formulation in Mathematica for inter-coil distances of 5mm, 10mm, and 5mm. It is shown that for our expected distance between primary and secondary coils (due to skin, about 10mm) we can optimize the transfer of power with a primary coil diameter of ~32mm (16mm radius).

As shown above, power transfer into the microsystem is not 100% efficient due to the thickness of the skin / tissue and the slight imperfections of the coils / matching networks. All power not transferred to the system will be either absorbed by the tissue and converted to heat, or reflected back to the primary coil. This heat generation needed to be both experimentally measured and computationally modeled in order to ensure we would not cause heat-related necrosis of the tissue. The exact temperature that necrosis will begin is complicated to state because it is a factor of time as well. However, the ISO 14708-1:2000 E standard states no outer surface of a device can rise more than 2C° above body temperature. We approached this issue

from two directions: 1) we experimentally recorded temperature increase of the system using an extremely sensitive (<20mK resolution) infrared camera (FLIR SC5000 series); and 2) we created a computational model of the system (i.e. tissue, bone, microsystem) and solved the bioheat equation in a finite element analysis software package (COMSOL).

3.6.2 Experimental infrared temperature analysis

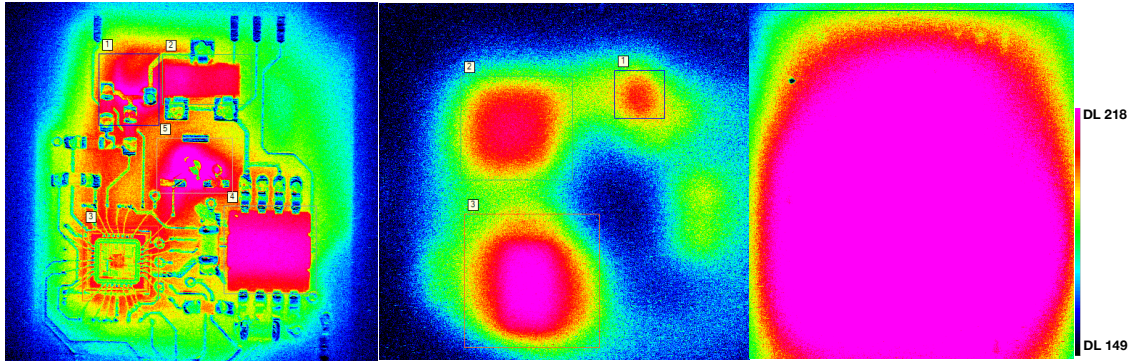


Figure 3-9: IR images from FLIR camera filtered from 2000nm – 5000nm. High infrared photon count (photon count, or digital level (shown on right as ranging from 149 – 215 a.u.), increases with intensity of pink) emitted from the materials of the externally powered microsystem during power-on over RF. (left) Unpackaged microsystem, (middle) PDMS packaged microsystem at startup, and (right) PDMS packaged microsystem at steady-state are shown in the images above.

Our externally powered microsystem was placed on a powering station setup underneath the FLIR infrared camera. The camera was connected to an x86 PC running the proprietary recording software from FLIR. While the microsystem was powered, photons of wavelength 3-5 μ m (the cutoff of the camera sensor, InSb, and its filters) were collected and counted to produce an image shown in Figure 3-9. Fundamentally, the intensity of the emitted energy from an object varies with temperature and radiation wavelength. If the object is colder than about 500°C, emitted radiation lies completely within IR wavelengths. In addition to emitting radiation, an object reacts to incident radiation from its surroundings by absorbing and reflecting a portion of it, or allowing some of it to pass through, as through a lens. From this physical principle, the Total Radiation Law is derived, which can be stated with the following formula:

$$W = \alpha W + \rho W + \tau W \quad \text{Equation 3-12}$$

where α , ρ , and τ are constants describing the object's incident energy absorption, reflection, and transmission respectively. For a pure blackbody (bb), Kirchhoff's law says that $\alpha(\lambda) = \varepsilon(\lambda)$, where $\varepsilon(\lambda)$ is the emission or emissivity of the material and the object is a perfect absorber and emitter. While our materials are not perfect emitters / absorbers, we can use the information to build an equation for emissivity of a so-called greybody:

$$\varepsilon = \frac{W_{obj}}{W_{bb}} \quad \text{Equation 3-13}$$

where W is the total energy emitted from the object and blackbody at a given temperature and, below, σ is the Stefan-Boltzmann constant ($5.67 \times 10^{-8} \frac{W}{m^2 K^4}$):

$$W = \sigma T^4 \left(\frac{W}{m^2} \right) \quad \text{Equation 3-14}$$

Emissivity values for materials can be referenced and these equations are built into the software package provided with the FLIR IR cameras. Since various materials have differing emissivity properties we cannot simply calculate temperature of the entire system from the average photon count. Using the software provided, we corrected the photon counts in each region of the image corresponding to the material in that region, in order to more precisely calculate temperature. When the packaged (PDMS) microsystem was imaged while under power, it was unnecessary to correct for emissivity as the bulk of the photon emission was from the PDMS surrounding the device. Thus, emissivity of PDMS could be applied to the entire image. The results of this experiment showed that temperature increase was highest near the ADC and the VCSEL, which, are the two most power-consuming components on the microsystem. Temperature increases were well below 1°C in ambient room temperature (24.5°C). The resultant

photon count maps can be seen in Figure 3-9 for both unpackaged and packed systems during turn-on and steady state operation.

3.6.3 Finite element analysis modeling

While experimental measurements give us insight into operation within one set of parameters, it often can be useful to build a model of the system in order to perturb or adjust variables and obtain expected or predicted changes. Here we have built a tissue model, based on the work by various researchers (Bazett & Love, 1948; Cooper & Trezek, 1971; Pennes, 1998; Popp, Li, Mei, Galle, & Neurohr, 1988; Wissler, 1985), that integrates our device into a modeled biological environment. This model approximates the bulk body tissue as a large cylinder and assumes that its boundary temperature remains at body temperature (37C°) during the entire simulation. This can be assumed to be a good estimation of the real case since the biological tissue that constitutes the skin, muscle, and bone is present radially from the implant. While in vivo, bone is generally below the implant (along with muscle) and skin is above the implant, the model, in this section, simply assumes a uniform tissue with perfusion rate and heat capacity / conductivity mentioned below, surrounding the implant and a small section of bone with different properties. The microsystem under test (here the externally powered microsystem; in the next chapter we ran the same simulation for the internally powered microsystem where power management is a much more serious issue) is located near the center of the cylinder (body tissue) and has the thermal properties appropriate of PDMS while the surrounding tissue has the thermal properties of dermis. The geometry also includes two large blood vessels, representing two vessels that may run through the dermis over the 2cm² surface area of the implant.

We begin by describing the generalized bioheat equation, which, in essence states that body tissue is perfused at a given rate, which adds a value to the general heat transfer equations. One assumption made is that the blood will always be at a fixed temperature because it travels through the body so quickly. This will effectively produce a very large heat sink, pulling away

heat generated at the implant. In addition, the body itself will produce heat through metabolism.

These sources can be formalized by:

$$\delta_{ts}\rho C \frac{\partial T}{\partial t} + \nabla \cdot (-k \nabla T) = \rho_b C_b \omega_b (T_b - T) + Q_{met} + Q_{ext} \quad \text{Equation 3-15}$$

With boundary conditions:

$$T = T_b \quad \text{Equation 3-16 tissue wall and blood vessel wall}$$

$$\mathbf{n} \cdot (k_1 \nabla T_1 - k_2 \nabla T_2) = 0 \quad \text{Equation 3-17 all other boundaries}$$

where δ_{ts} is a time-scaling coefficient; ρ is the tissue density (kg/m^3); C is the tissue's specific heat ($\text{J}/(\text{kg}\cdot\text{K})$); and k is its thermal conductivity ($\text{W}/(\text{m}\cdot\text{K})$). On the right side of the equality, ρ_b gives the blood's density (kg/m^3); C_b is the blood's specific heat ($\text{J}/(\text{kg}\cdot\text{K})$); ω_b is its perfusion rate ($1/\text{s}$); T_b is the arterial blood temperature ($^{\circ}\text{C}$); while Q_{met} and Q_{ext} are the heat sources from metabolism and spatial heating, respectively (W/m^3).

The intrinsic thermal properties of tissues depend strongly on their composition. Cooper and Trezek (Cooper & Trezek, 1971) recommend the following correlations for thermal conductivity of tissues that make up the dermis, which is where our heat generation is most likely to occur (i.e. largest power-consuming components are located there):

$$k = \rho \times 10^{-3} (0.628 f_{water} + 0.117 f_{proteins} + 0.231 f_{fats}) \frac{W}{m \cdot K} \quad \text{Equation 3-18}$$

$$c_p = 4,200 f_{water} + 1,090 f_{proteins} + 2,300 f_{fats} \frac{J}{kg \cdot K} \quad \text{Equation 3-19}$$

$$\rho = \frac{1}{\frac{f_{water}}{1,000} + \frac{f_{proteins}}{1,540} + \frac{f_{fats}}{815}} \frac{kg}{m^3} \quad \text{Equation 3-20}$$

where f_{water} , $f_{proteins}$, and f_{fats} are the mass fractions of water, proteins, and fats, respectively and $q_m^m = 170(2)^{\left[\frac{(T_o - T_t)}{10}\right]} \frac{W}{m^3}$. The steady-state solution with spatially and temporally constant parameters including the rate of heat generation with a fixed temperature on the skin T_{skin} is given by Equation 3-21:

$$T_i(x) = T_{skin} \exp \left[- \left(\frac{\omega_b \rho_b c_b}{k_t} \right)^{1/2} x \right] + \left(T_a + \frac{q_m^m}{\omega_b \rho_b c_b} \right) \left\{ 1 - \exp \left[- \left(\frac{\omega_b \rho_b c_b}{k_t} \right)^{1/2} x \right] \right\}$$

Equation 3-21 (above)

$$L_c = \left(\frac{k_t}{\omega_b \rho_b c_b} \right)^{1/2} \quad \text{Equation 3-22}$$

In addition, the temperature will decay over a characteristic length, L_c (Equation 3-22), giving us a sense of how far the heat will spread from the source given a set of skin perfusion and heat capacity parameters. While this can be solved for specific locations in the tissue, we decided to solve the problem in three-dimensions using finite element analysis (FEA). Representative three-dimensional geometries were created in COMSOL (Multiphysics Solver, Heat Transfer module). Boundary conditions, as described above, were used along with the generalized bioheat equation and heat transfer module (the heat transfer module appropriately handles transfer at the interface of materials). This method of heat transfer modeling through FEM has been used by others (Tungjitkusolmun, Staelin, Haemmerich, Tsai, Webster, Lee, Mahvi, & Vorperian, 2002).

Isosurface for 37.02 degrees Celsius at steady state

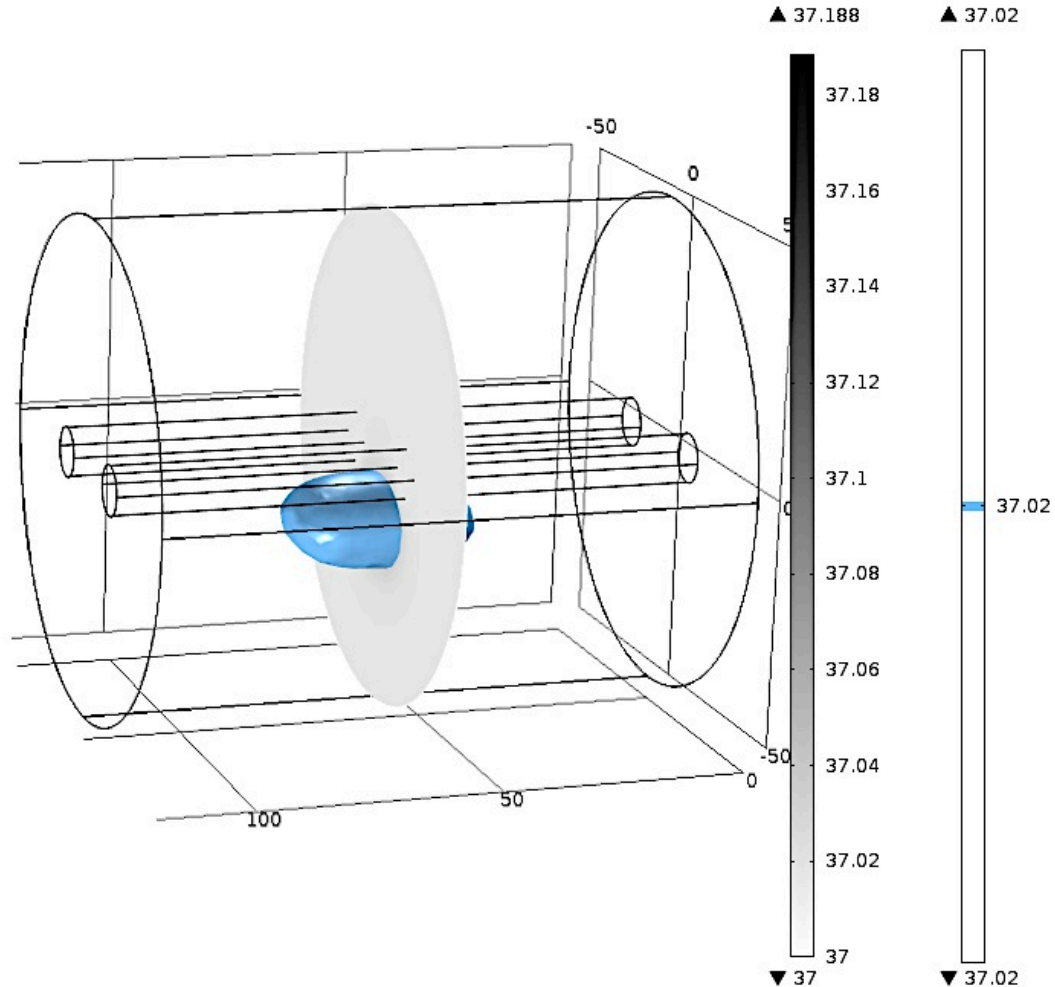


Figure 3-10 (left): 3D FEM model with isosurface of 37.02C° drawn in blue. All x-y-z dimensions are in mm. The two parallel cylinders model blood-carrying vessels. A larger cylinder represents the bulk tissue. A plane is drawn in the x-y dimensions showing very little dispersion of heat into the surrounding tissue. Tissue is modeled with parameters discussed below.

As can be seen in the results shown in Figure 3-10 and Figure 3-11, there is negligible heat rise in the tissues surrounding the EPM microsystem during charging and during normal operation. Total input power to the primary coil (and thus being delivered to the body) is about 80mW. The system requires roughly 25mW for proper operation, and as we calculated before, our transfer efficiency at the distance of between

5mm and 10mm is between 25-40%. Thus, we are in fact delivering enough power to turn the system on in this model. While much of the power is reflected back into the primary coil, some will become heat. But this finite element model solution shows that the amount of this heat will be very small, less than 0.02°C .

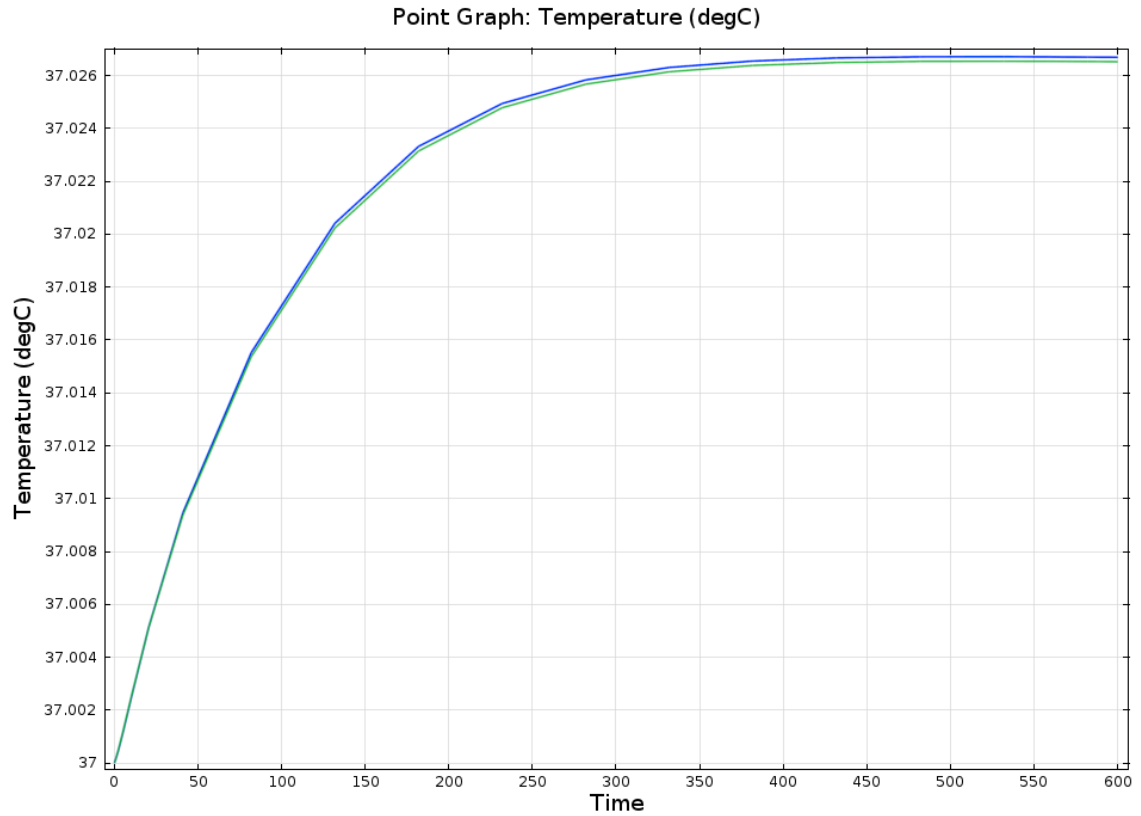


Figure 3-11 (right): Temperature plot of two points on the surface of the externally powered microsystem given over a period of 600 seconds (10 minutes). Steady state is reached at 450 seconds at a temperature of 37.02°C , a very safe level.

Parameter	Value	Description
rho_b	1000[kg/m ³]	Density of blood
c_b	4180[J/(kg*K)]	Heat capacity of blood
omega_b	6.4e-3[1/s]	Blood perfusion rate
T_b	37[degC]	Arterial blood temperature
T0	37[degC]	Initial and boundary temperature
k_d	0.512[W/(m*K)]	Thermal conductivity of dermis
rho_d	1060[kg/m ³]	Density of dermis
c_d	3600[J/(kg*K)]	Heat capacity of dermis
rho_b	1000[kg/m ³]	Density of blood

Table 3-1: List of parameters and values used in the COMSOL FEM model. Taken from models proposed in the Biomedical Engineering Handbook (Bronzino, 2000).

3.7 Infrared vertical cavity surface emitting laser for wireless data transmission

The concept of an optoelectronic data link enables considerable system flexibility for future neural prosthesis applications, including very large bandwidth capability and extremely low power consumption devices. It is what is used as the backbone for the Internet and lies across oceans and continents. The telecommunications industry adopted this method of communication for its robustness, cost-efficiency, and as mentioned its bandwidth. We needed something on a much smaller scale for our data telemetry, but nonetheless, bandwidth and power budget were extremely important. The first ideas of a vertical cavity surface emitting laser (VCSEL) came from the Tokyo Institute of Technology and the research of Kenichi Iga in the late 1970's, but the first device was not made until later (Kenichi. Iga, Koyama, & Kinoshita, 1988). In the late 1980's, optoelectronic researchers began creating semiconductor lasers operating at room temperature that could emit light up, out of a cavity, as opposed to along an in-plane edge by the use of distributed Bragg Reflectors (DBRs) to sandwich an active region, creating optical gain. The vertical emission from the cavity gave them their name (VCSEL). After more optimization,

the VCSEL became an ultralow threshold current, high efficiency, and very compact laser, which is now one of the most popular types of the semiconductor diode lasers for optical data communication applications today. The benefits of using this type of device for data telemetry are numerous, including a small form factor, high performance and reliability, and simple / scalable manufacturability (Jewell, Harbison, Scherer, Lee, & Florez, 1991). An excellent review of VCSEL fabrication and use in telecommunication can be found here (K. Iga, 2000)

We have thus employed an IR optical data link using a VCSEL emitting light at 852nm (a commercially available and mass produced version). We have used two devices in our work: one bare die VCSEL and another packaged. They are both an oxide confined VCSEL with a $12\mu\text{m}$ diameter circular aperture. The bare chip is manufactured by Emcore Corporation (Somerset, NJ) whereas the packaged VCSEL is manufactured by Optowell Ltd (Old Harlow, Essex). The dimensions of a bare die chip are $300\mu\text{m} \times 300\mu\text{m} \times 150\mu\text{m}$ (W×L×H). The device has typical electro-optical characteristics of 850nm wavelength, 1.8mA threshold current, and over 2.5Gbps maximum data rate. Sub-mA threshold, 10Gbps VCSELs are available in the high speed data communication module, but not commercially available in bare die form at the time of this work, nor are they needed since 10Gbps would equate to nearly 20,000 channels of neural data – far more than downstream processing can currently handle. The VCSEL output is controlled by the digital controller chip as described elsewhere, with 2.4mA and 0.4mA as high (logic level “1”) and low (logic level “0”) bias currents, respectively, at the data rate of 13.56 Mbps (with plans to increase). A typical output optical power at the high bias condition is 0.5mW, which is sufficient for establishing a robust optical data link, either via a silica optical fiber, or transcutaneously through skin with a thickness of a few millimeters (Figure 3-12).

There are many reasons why a VCSEL is a superior device for our specific case. First, the structure can be integrated in two-dimensional array configuration and easily fabricated in our university microelectronic fabrication center. Second, surface-normal emission is nearly identical

to the photo detector geometry giving easy alignment and packaging. Also, the circular and low divergence output beams eliminate the need for corrective optics on the emitter. Since we detect the emitted photons at a distance of nearly 10mm away from the source and after significant scattering, lenses have been used on the receiver to collect the light. Lastly, the VCSEL has lower temperature-sensitivity compared to edge-emitting laser diodes, so we can expect a well confined peak in the emitted spectrum. Extraction of the digitized infrared (850nm) neural signals from the microsystem is accomplished by collecting beam from the laser emerging directly through the skin, which is sufficiently transparent in the near infrared. This in turn is accomplished by placing a p-i-n photodiode (Hamamatsu) outside of the body and in the line of sight of the VCSEL.

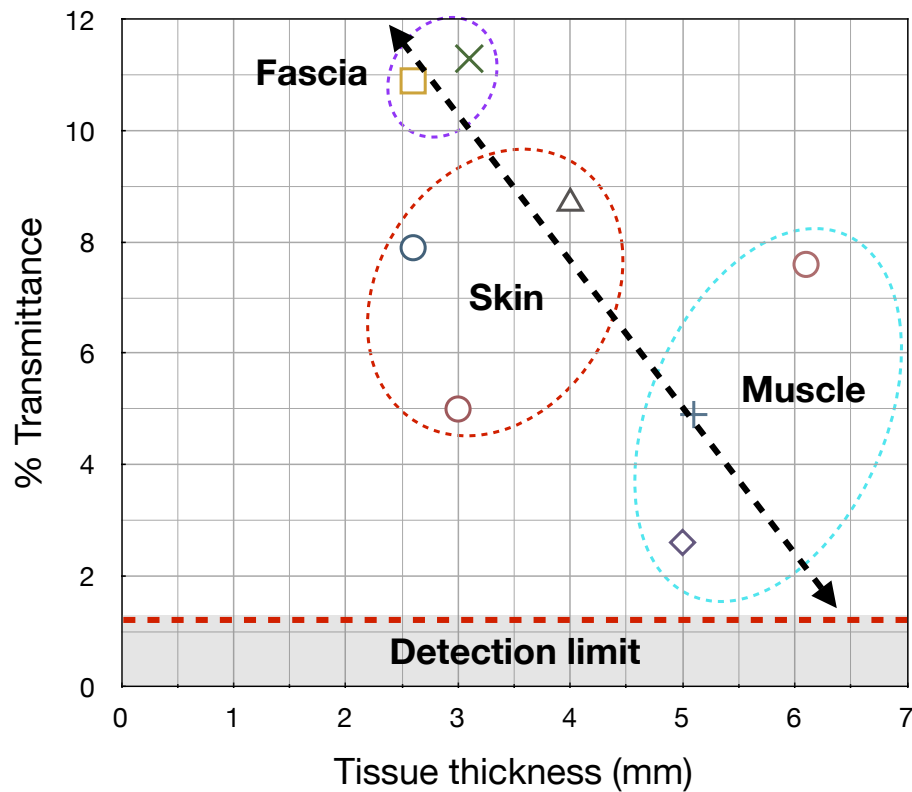


Figure 3-12: Transmission measurements of 852nm VCSEL mounted on forceps across from a si-photodiode. Measurements were taken from an anesthetized non-human primate during an implant surgery of a standard NeuroPort recording system. Skin transmittance, and varying thickness of muscle transmittance measurements were made with this system by clamping the tissue gently between the tip of the forceps. The black dotted-line shows the trend of more transmittance with thinner tissue.

3.8 Neural signal amplification: the design of M4B and Pearl

We have gone through several iterations of a neural signal amplifier, a project spearheaded by William Patterson in collaboration with several undergraduate and graduate students, including Dr. Ming Yin and Farah Laiwalla. We will only discuss briefly the designs, but instead focus on the performance of the various iterations of the amplifier ASIC and how they are applied to neural recording. All of these versions have been designed for “chip-to-chip” integration, which is the attachment of a silicon-based microelectrode array to an ultra low power, high performance CMOS amplifier IC chip on our front-end substrate (flip-chip). In our CMOS amplifier array design, each preamplifier possesses an input-bonding pad within its own area of the integrated circuit. The amplifier array pitch of $400\text{ }\mu\text{m}$ exactly matches that of the array of extracellular electrodes so that bonding each input pad to its corresponding electrode can be done by a low-stress bonding technique. Each amplifier also has a CMOS transmission gate switch attaching its output to a column line under control of a column select line.

Amplifier outputs are routed to the output buffer amplifier by row and column selection implemented with a digital row decoder and an analog column multiplexer also based on CMOS switches. Only a few wires are needed as the interface to the chip, including a few source select lines depending on the number of channels (e.g. 4 for 4×4 , and 8 for 10×10), output, power, and ground. Each version developed is described below:

- *M4 (Mouse version 4) 2004: A 4×4 prototype circuit was fabricated on a $2.2\text{ mm} \times 2.2\text{ mm}$ chip in the AMIS $1.5\text{ }\mu\text{m}$ standard 2M2P n-well CMOS process; its details can be found in (W Patterson et al., 2004).*
- *M4b (Mouse version 4, internally biased) 2005: 16-channel used in numerous publications (D. Borton et al., 2011; Y-K Song et al., 2009; Y. K. Song, Borton, Park, Patterson, Bull, Mislow, Simeral, Donoghue, & Nurmikko, 2008)*
- *MM7 2005: Slightly modified amplifier design to reduce low-frequency noise, however had an extremely long settling time (~hours) (unpublished)*

- *Pearl 2006: Fixed settling issue of MM7 (unpublished)*
- *Little Pearl 2008: moved Pearl to 0.5 μ m process (Aceros, Yin, Borton, Patterson, & Nurmikko, 2011)*
- *Big Pearl 2010: 100-channel version of Little Pearl (article in preparation)*
- *Big Pearl II 2011: introduced variable low-frequency cutoff (1-100Hz) and electrostatic discharge protection circuitry (article in preparation)*
- *Giant Pearl 2012: identical amplifier as Big Pearl II but introduced electrical stimulation circuitry, which also allows for spectral impedance measurements.*

Earlier data collected for this thesis was with the M4b amplifier, as opposed to the newer pearl series, and thus will be the primary topic of discussion. The M4b integrated preamplifier-multiplexer chip has some excess noise at low frequencies that limits its utility for local field potential (LFP) measurements. It exhibits an equivalent amplifier input noise of $7.3\mu\text{V}_{\text{RMS}}$ in a 50 Hz to 7.5KHz bandwidth. Typically, the 3dB design bandwidth for each amplifier is approximately 7.5KHz with a representative gain of 43dB. We have carefully analyzed the noise sources (William R Patterson & Song, 2007) and have developed a new design similar to that pioneered by Harrison and co-workers (R.R. Harrison & Charles, 2003) but have not yet used it in implantable units. These improved designs are implemented in the Big Pearl II amplifier with an anticipated equivalent noise voltage of $4.7\mu\text{V}_{\text{RMS}}$ and 45 dB of gain. (For design details see (William R Patterson & Song, 2007) and Yin, M. et al., ISSCC, in press) The power in both current and anticipated designs is about 45 - 50 μ W per channel depending on the exact power supply voltage. These performance values are viewed as acceptable for a practical chronic implant.

The design of a single low power preamplifier is shown in Figure 3-13. The preamplifier uses a capacitive-feedback, folded cascode operational transconductance amplifier (OTA) configuration with a source follower output buffer. The closed-loop gain of the OTA is set by the

ratio of the feedback voltage divider capacitors $C1$ and $C3$, which is $6.8\text{pF}/0.034\text{pF} = 200$.

Capacitor CL across the OTA output provides the dominant pole for the operational amplifier and sets the bandwidth of the circuit at 7.8 KHz.

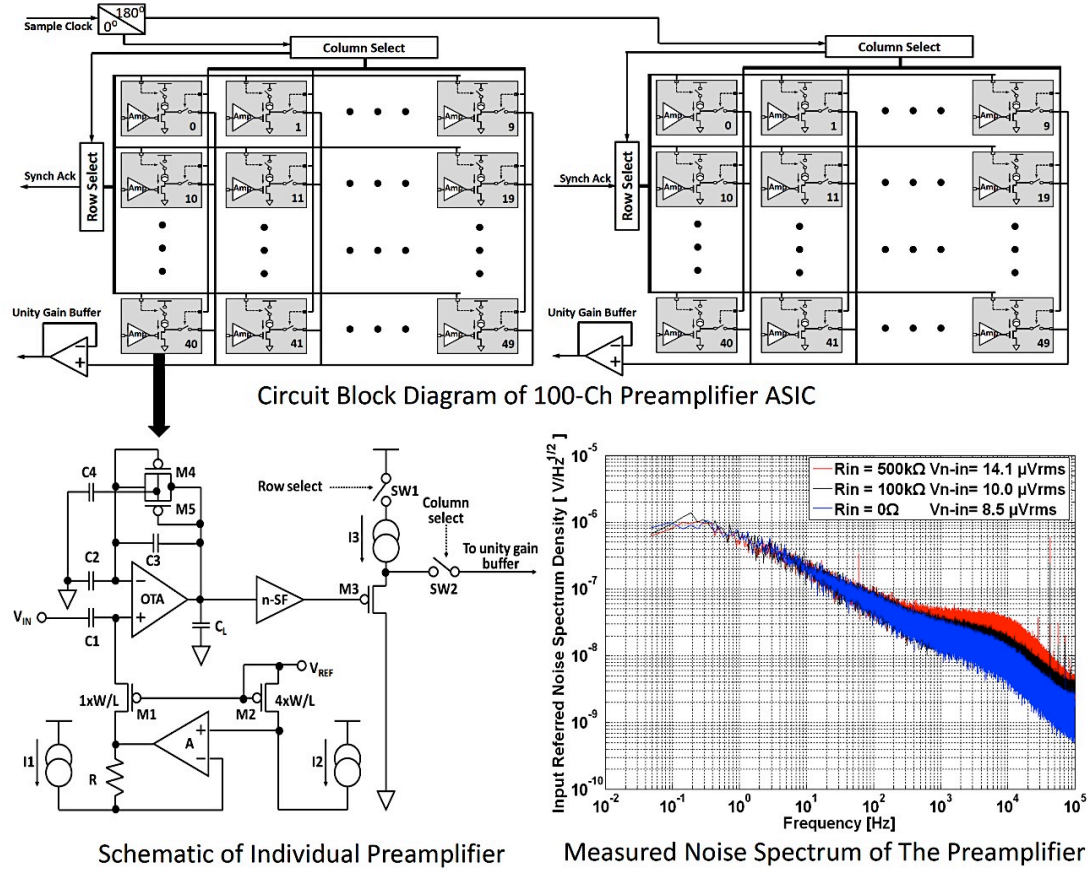


Figure 3-13: Schematic of individual preamplifier, its integration into an array, and noise performance spectrum with variable load input.

Any operational amplifier operating on a single power supply has to have its output offset to the center of its possible output voltage range. The diode-connected MOSFETs, $M4$ and $M5$, effectively bypass $C3$ at very low frequency so a DC bias at the non-inverting input of the OTA can suitably offset the OTA output. The required bias is applied through the pMOS pseudo-resistor, $M1$. The input capacitor $C1$ along with $M1$ forms an RC high-pass filter at $\frac{1}{2\pi} R_{M1} C_1$,

where R_{M1} is the equivalent resistance of the transistor $M1$. Other neural preamplifier designs (R.R. Harrison & Charles, 2003; Olsson, Gulari, & Wise, 2003; Wattanapanitch, Fee, & Sarpeshkar, 2007) use a diode-connected pMOS pseudo-resistor for this function. However, the problem with the diode connected scheme is that the high-pass frequency is very sensitive to process variation, especially to transistor threshold voltage variation. The biasing circuitry ($M2$, op-amp A , I_I , etc.) is shared by all the preamplifiers on the die and so constitutes minimal overhead.

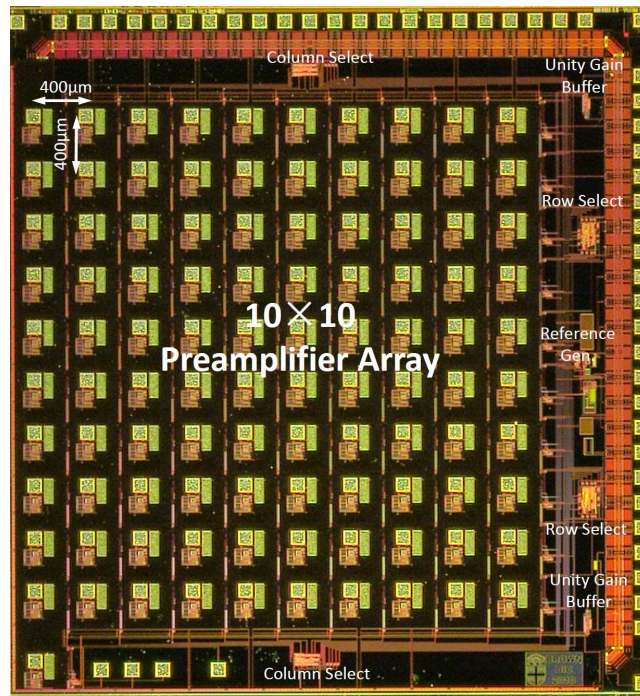


Figure 3-14: Microphotograph of the 100-channel amplifier and multiplexer ASIC, created by Ming Yin, and William Patterson, and manufactured through the MOSIS process. Input pads are on a 400μm center-to-center spacing for direct attachment to the microelectrode array via flip-chip bonding process.

The OTA is also designed in such a way that it achieves an optimal tradeoff between the noise and power dissipation. The input transistors are implemented using two large pMOS

transistors biased in sub threshold to minimize both flicker noise and thermal noise. Other critical transistors in the OTA are also properly sized and biased to reduce the total thermal noise of the preamplifier. The output of the OTA is buffered through an nMOS source follower followed by a pMOS source follower that can be turned on and off by the “Row Select” signals through the switch *SW1* line. These two source followers have higher output current than the OTA thus assuring adequate settling time for the ADC signals when driving the capacitance of the column lines and buffer amplifier input. The source followers also provide isolation from disturbances caused by charge injection generated by the transmission gate (*SW2*) that is tied to the column line and by charge-sharing with the capacitance of the column line. A micrograph of the 100-channel Big Pearl design can be seen in Figure 3-14.

Parameter	M4B	MM7	Pearl	Big Pearl	Big Pearl II
Number of channels	16	16	16	100	100
Noise (RTI*)	$7.7\mu\text{V}_{\text{RMS}}$	$4.8\mu\text{V}_{\text{RMS}}$	$8.5\mu\text{V}_{\text{RMS}}$	$8.5\mu\text{V}_{\text{RMS}}$	$3.6\mu\text{V}$
Gain	152	162	200	200	200
Power per amplifier	$52\mu\text{W}$	$52\mu\text{W}$	$51\mu\text{W}$	$51\mu\text{W}$	$51\mu\text{W}$
Total power @ 3V	1.4mW	1.5mW	1.5mW	6mW	6mW
High freq. cut-off	7.3kHz	7.3kHz	7.8kHz	7.8kHz	7.8kHz
Low freq. cut-off	4Hz	2.3Hz	0.1Hz	0.1Hz	0.01-100Hz

Table 3-2: Amplifier performance over five (5) generations / iterations of the custom ASIC *0.05 – 20kHz pass band, excluding thermal noise from the electrode (~3-6 μVRMS).

3.9 Other microelectronic components used in the externally powered microsystem

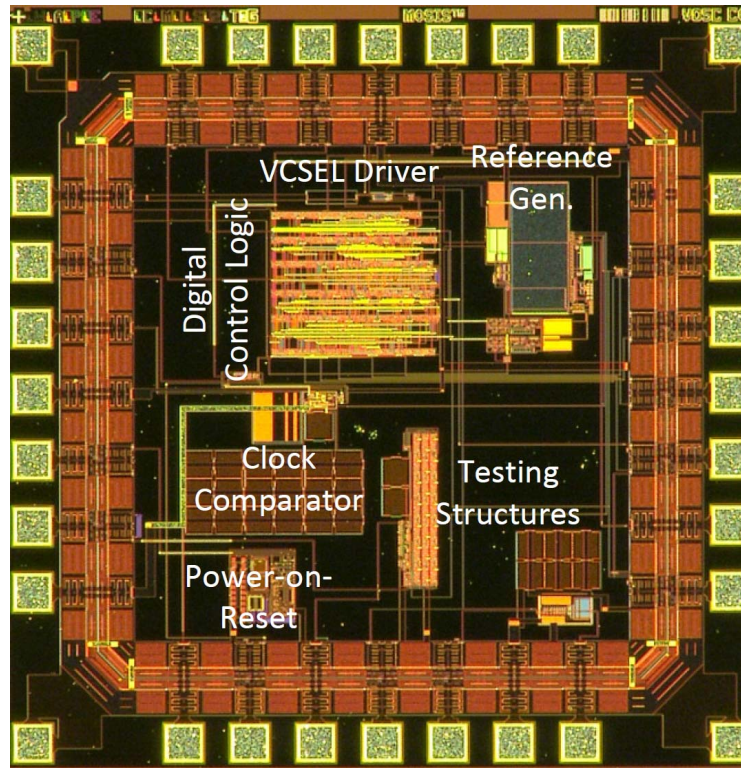


Figure 3-15: Microphotograph of the digital control ASIC fabricated in the AMI 0.5 μ m 2-poly 3-metal process through the MOSIS service.

The analog-to-digital converter chosen for the 16-channel test system is a very low power Analog Devices type AD7495BRM, a 12-bit successive-approximation-register (SAR) serial converter capable of 1Msps (Mega samples per second) conversion. Here it is used at 640 Ksps (Kilo samples per second) to give a per channel 40 Ksps conversion rate. The converter is in a 1 mm thick, conventional micro-SO8 package. The device requires only two control signals, one is a chip select that determines the beginning and end of conversion and the other is a simple clock. We use a 13.56 MHz clock and allow twenty-four clock cycles per conversion. The converter does not have an input buffer amplifier so it has a variable input capacitance. That capacitance is 6 pF during conversion and 20 pF during signal acquisition. This requires that the output buffer

amplifier in the amplifier integrated circuit be capable of adequate settling under the higher capacitance load and that it be stable with the lower load.

All digital control and multiplexing functions are incorporated into a single custom digital controller integrated circuit that directs the electronic traffic for the ADC and amplifier circuits. The controller chip performs four principal functions: first, it generates a full CMOS-level clock signal from a small sinusoidal signal separated from the output of the input power (here the “optical power supply”). Second, it uses a pseudorandom bit generator (PRBG) to create a periodic, 24-bit synchronization code and multiplexes that with the output of the ADC converter. This code is detected in the data to mark the beginning of each frame of data. Third, the controller ASIC provides current for the laser diode (VCSEL) that is used to transmit the digital data out of the body. The multiplexed digital signal is transmitted as infrared light directly through the skin. Finally, the controller contains a four-bit counter that supplies the address lines for channel selection in the analog multiplexer on the amplifier integrated circuit. The controller was designed using custom layout for the analog sections to generate clock and VCSEL drive using standard cells for the digital counters and control. The minimum clock rate of any flip-flop is 640 kHz, so simple dynamic flip-flops could be used to minimize power and area. The chip was fabricated in the AMI 0.5-micron process through MOSIS and is integrated onto the full microsystem. An image of the controller can be seen in Figure 3-15.

3.10 Packaging of the EPM using polymeric compounds

The EPM implantable microsystem must maintain a large degree of flexibility since the interconnecting tether between the array-bearing frontend of the system and the telemetric backend must traverse from the cortex, through the skull, up to the subcuticular space. This cannot be achieved with more traditional biomedical packaging materials (as discussed in *Chapter 2*) such as ceramics or metals due to their rigidity. Instead, we relied here on polymeric materials, specifically polydimethylsiloxane (PDMS) and Parylene-C: two very commonly used

medical-grade encapsulants. Unfortunately, not all siloxanes are created equally, and the choice of the optimal chemical configuration has been the subject of many commercial and institutional projects in-and-of itself. David Edell was sponsored by the NIH specifically to test various silicone formulations for biocompatibility, device protection, and longevity. We held discussions with Dr. Edell and as a result decided to use NuSil's formulation R-2188: one he found success with in his experiments. This particular formulation maintains minimal rigidity at the thickness we are applying; maintains adhesion to liquid crystal polymer and Kapton, two substrates we have explored, under accelerated conditions; has a long work time (nearly 4 hours), which was important to allow careful packaging around the microelectrode array; and finally performed well in Edell's bench top and in vivo (rabbit) experiments (Dean, Jr., 2004; Edell, 2004). In addition, this product is a research-grade version of a medical-grade polymer (MED-4211), which allowed us to test at a much lower cost (an order of magnitude). Generally, silicones are differentiated by their elongation, tensile strength, and dielectric strength. We also look at volume resistivity as a measure of how permeable the membrane may be to ionic diffusion. R-2188 has elongation of up to 625%, a tensile strength of 475psi, a dielectric strength of 450V/mil, and a volume resistivity of 1×10^{13} Ohm.

The efficacy of a packaging solution depends strongly on adhesion, which in turn depends on the substrates involved and the processing conditions applied. We have developed a cleaning process for our substrate and components that has led to satisfactory adhesion. Due to the importance of this process to the outcome of the device, it is listed here:

Process document for cleaning Kapton substrate with components

1. Preheat dry oven to 90C
2. Microsystems are removed from glass plate (used for fabrication, testing and transport) and placed on lintless cleanroom wipes
3. Microsystem is moved to glass dish containing MS-722 degreasing solution (oil removal)
4. Place glassware and system in ultrasonic cleaning system for 1 minute
5. Remove system from glassware with forceps and immediately blow-dry with N₂ (or other inert gas)
6. Place microsystem in glassware and immerse in Di-H₂O (ion removal)

7. Place glassware and system in ultrasonic cleaning system for 1 minute
8. Remove from glassware and blow-dry with N₂
9. Place microsystem in glassware and immerse in Isopropyl Alcohol (remaining H₂O removal)
10. Place glassware and system in ultrasonic cleaning system for 1 minute
11. Remove from glassware and blow-dry with N₂ - remove all traces of liquid
12. Carefully transport microsystem on lintless cleanroom wipes to the oven and bake (dry) for 15 minutes (dehydrate)

MS-722 (Miller-Stevenson) is a degreasing agent (hydrofluoroether – HFE) appropriate for cleaning electronic components indicated for removal of oils, corrosion, and particulates. In addition to the degreasing, we use deionized water ideally to remove all ions from the surface of the substrate and components. As mentioned earlier in *Chapter 2, packaging for implantable systems*, any void caused by dirt, or large amount of ionic concentration will be a potential and even likely failure point of the packaged system. Thus removal is necessary. Once systems are cleaned, we proceed with mold-based application of the encapsulant.

Our original molds were created out of machined Teflon to reduce adhesion of the PDMS to the mold itself as attempting to release a system from the mold forcefully can result in catastrophic damage. In addition, all of our molds are open-faced. This is required in order to protect the microelectrode array during the packaging process. While closed molds tend to have fewer air gaps and cure more uniformly, we must be able to visualize and protect the microelectrode array at all times. We hold the system in place with three vacuum holes: two on the telemetric unit and one on the cortical unit. These fixation points are necessary so that we can tilt the microsystem, in the mold, at various angles to aide the PDMS in wicking underneath all of the components (“underfill”). While Teflon is very ductile and difficult to machine in small features (thin features have a tendency to bend), because it is so soft it creates a very good seal to the microsystem at the vacuum holes. This solution worked well until the need for small features became overwhelming. We then switched to aluminum as the molding material, which is still easy to machine but maintains much greater strength at the thickness we were using. Once a system is cleaned and placed in a mold, it is ready for application of the encapsulant. Below is a

description of the process for application of either PDMS (NuSil R-2188), or the underfill compound Hysol (Loctite E-30CL):

Application of PDMS or Hysol (Loctite E-30CL)

1. Preheat oven to 65C
2. Degas encapsulant in syringe for 60 minutes (PDMS) or 10 minutes (Hysol) in the prince lab vacuum chamber
3. Clean mounting mold (Teflon / Aluminum) abrasively with lintless cleanroom wipes and isopropyl alcohol
4. Make sure screws are tight fixing the mold to the heater block
5. Coat mold in Teflon dry film to reduce chance of adhesion from the PDMS / Hysol to mold
6. Place system carefully into mold, vacuum should hold it in place
7. Begin underfilling the tether of the microsystem first – all application must be done with Engineering Fluid Dynamics pneumatic application system
8. Underfill the substrate (both frontend and backend) before any superficial is coated
9. Once the substrate is underfilled, slowly place PDMS / Hysol on the supracranial portion of the microsystem, under each wire bond and component until everything is under-filled
10. Place more PDMS / Hysol to cover each component completely, forming a protective shell
11. Slowly place PDMS / Hysol under the wire bonds of the cortical portion of the implant - be sure to cover the wire bond attachment locations on the amplifier and the capacitor on the frontend
12. Apply PDMS to the array only when all other locations are completed. Turn nitrogen gas on and adjust flow to stop PDMS from wicking up the electro shanks
13. Apply PDMS until it is flush with the surface of the mold
14. Turn on and ramp heat in mold with element @ 3C per minute until @ 90C
15. Place in oven for >4 hours @ 100C then let sit (generally 24 hours) @ room temperature (24-27C)

The end product of this packaging (seen in Figure 3-16) constitutes the final device to be implanted in the body. Because the materials are directly interacting with the tissue of the body, the vast majority of area is clearly coated in the applied PDMS. However, the microelectrode array protrudes through the encapsulant. Looking more closely at a single electrode (Figure 3-17), we can define the metallization, polymeric packaging, and supporting silicon. Parylene-C is used by Blackrock Microsystems during microelectrode array fabrication to obtain proper (200-800kOhm) impedances on the electrodes, leaving only a small length (20-50 μ m) of Pt/Ir metallization exposed. While we do not explicitly use this material for packaging, it is a part of the system as a whole and thus must be kept in mind as we discuss failure modes and fabrication issues.

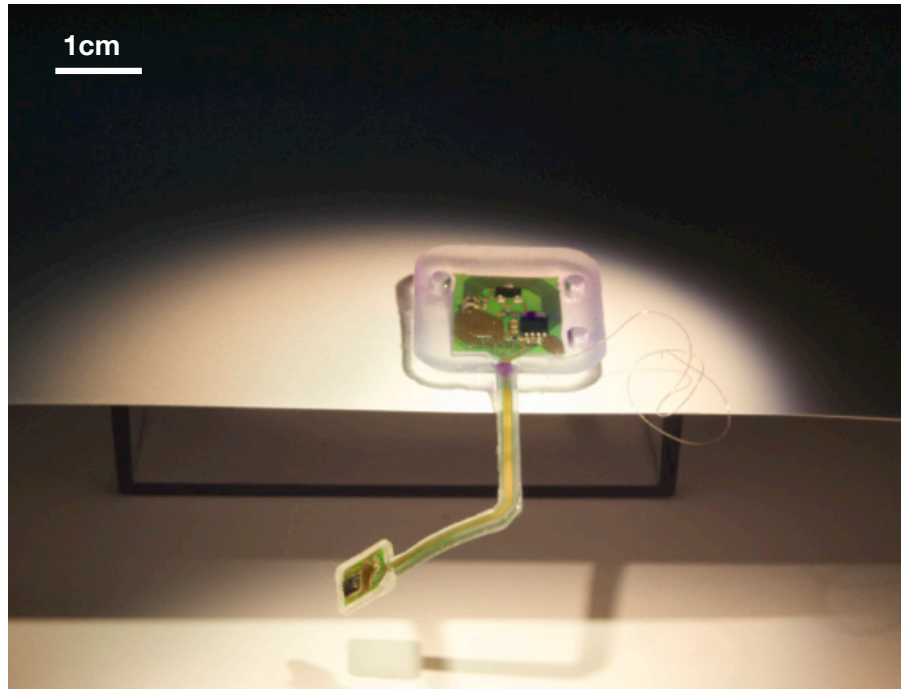


Figure 3-16: Final product after packaging with PDMS. This device is a 16-channel externally powered microsystem ready for sterilization and implant. Note the flexibility of the interconnection between the cortical and telemetric units.

3.11 The first use of swine in chronic neurosensor evaluation in vivo

We first described in *Chapter 2* the motivations behind developing a swine model for neuroprosthetic device evaluation. Here we detail the implementation of our first neurosensor implantation and use in Yorkshire pigs. This experiment was the genesis of an IEEE EMBC conference presentation and proceeding in 2011: *Developing Implantable Neuroprosthetics: a New Model in Pig*. Not only did this presentation introduce the pig into the panoply of animals used in neuroscientific research, but also provided a platform for accelerated device development, validation, and use in clinical trials.

All surgical procedures and experiments were conducted under approved protocols from the IACUC (0911091). Eight (8) Yorkshire pigs were purchased at weights varying from 30-50kg from Parsons & Sons (Hadley, MA). All animals were given one-week habituation before surgery or training was commenced. Seven (7) animals were implanted with identical 16-channel EPMs,

while one (1) was implanted with a 100-channel EPM. For all surgeries, pigs were induced with a Telazol/Xylazine IM injection, intubated, and maintained on Isoflurane/Oxygen for the duration of the surgery. Heart rate, blood pressure, and SPO₂ were measured and evaluated constantly throughout the surgery.

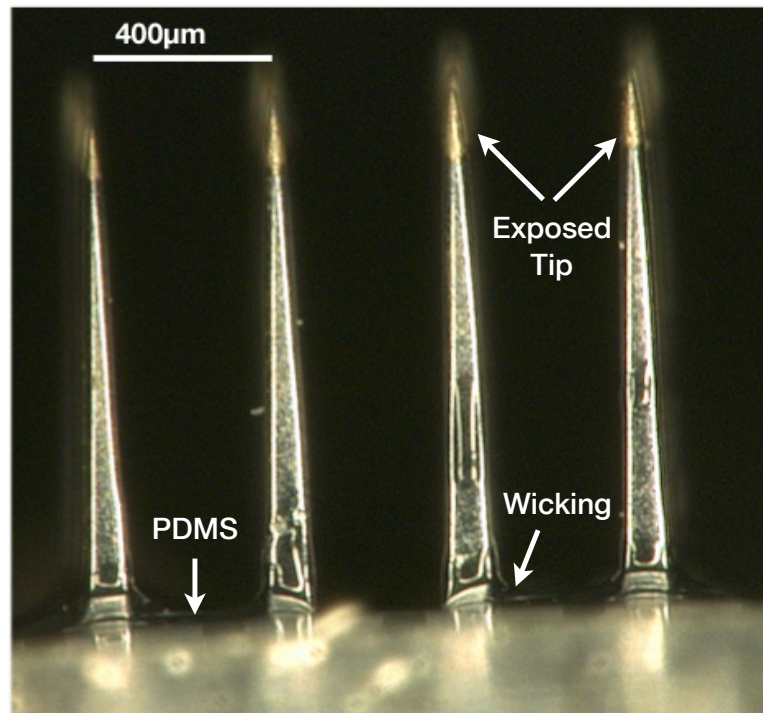


Figure 3-17: Packaged 4x4 MEA in PDMS. One can see the slight wicking of PDMS on the base of the electrodes, but more importantly, the insulating Parylene-C is plasma etched away at the tip to expose the Pt/Ir metallization. SEM images show Parylene C adhesion to the shank and exposure at the tip.

Once the animals were stable on the operating table, the stereotactic apparatus described in *Chapter 2* was used to secure the animal in place for surgery. An arched skin incision was made from the left posterior aspect of the head anteriorly returning to the right posterior aspect. This notably long incision was made to gain maximal access to craniotomy site (R parietal lobe) while at the same time moving the suture line away from the implant to reduce chances of irritation. Separation of the galea aponeurotica from the skull (and skin) was done in case a dural

graft was needed to complete closure. A Stryker (USA) craniotome was used to turn a 3cm x 1cm craniotomy above primary somatosensory cortex - specifically the area controlling the rostrum (Saikali, Meurice, Sauleau, & Eliat, 2010; Sauleau et al., 2009) (see Figure 3-18). After the durotomy was completed, the microsystem was positioned for insertion. Insertion was made through the arachnoid and pia mater by a commercially available pneumatic inserter (Blackrock Microsystems, UT) with a 1.5 mm spacer - the electrodes on this system have a 1.5 mm shank length.

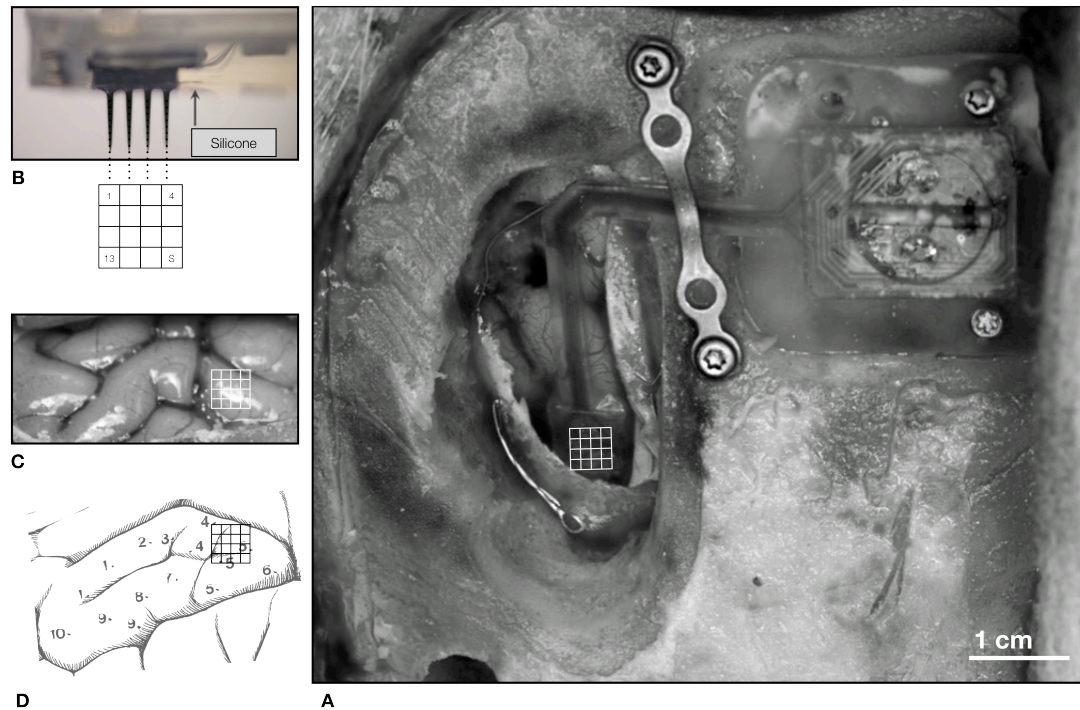


Figure 3-18: Surgical image of microsystem implantation in pig (a) where the telemetric unit is attached to the skull with two Ti screws, the interconnecting tether is protected by a titanium dog-bone and lies gently on the cortex running A-P. The array is shown inserted with a grid superimposed for reference to b-d: a diagram of electrode implantation location into the primary sensorimotor cortex. The 16 electrodes are about 1mm in height (after PDMS packaging) and thus were embedded that distance into cortex.

The craniotomy was then closed with the remaining bone flap and secured with medical-grade Ti mesh and screws (Stryker). This process has been used by numerous groups with high-

percentages of success (Acharya et al., 2008; Bansal & Vargas-Irwin, 2011; Miranda et al., 2010; Zerris et al., 2005). One notable difference when implanting a completely wireless system is that the skin is completely sutured closed with no percutaneous connections as are normally found when implanting microelectrode arrays or really any neural recording device. Since swine use their foreheads as shovels, any protrusion of the implantation would not be tolerated. This animal model pushes the limits of robustness compared to humans, for whom a neural prosthetic would be more amenable and likely treated with more care.

3.12 General recording procedure for externally powered implantable microsystem

Neural recordings from both swine and non-human primates have been conducted over the last several years with the externally powered implantable microsystem. As described earlier, this system requires both power and clock signals to be delivered over an RF inductive link. We developed an external box, containing the primary coil, flux coil, and an IR si-photodiode to both deliver and measure power, as well as receive the VCSEL output. The box is referred to as the RF-IR transceiver. The RF-IR transceiver can be seen in Figure 3-19 above a representative primate skull as arranged for non-human primate recordings. The primary coil is brought within 1-3mm of the skin above the externally powered microsystem (Figure 3-20 and Figure 3-19) and can be initially aligned by the power monitoring methods described in *Chapter 2*. Once the power monitor has guided initial approximate alignment, the RF-IR box must be further aligned to ensure that the light output from the VCSEL is directed into the photodiode. Generally, the 4-axis arm holding the RF-IR transceiver is adjustable enough to align the power and data elements. The arm is rigidly attached to the head fixation mechanism, so any movement of the animal during task execution will not be relative to the transceiver. In swine, we do not use head fixation mechanisms. Instead, train the animal to reduce its movement when we are petting it, or we mildly sedate the animal with Dexmedetomidine (intramuscularly) to reduce the movement. Either way, the RF-IR transceiver is then held over the implanted device by hand. Since swine are

used for device development, these short recordings are sufficient to gather functionality data and snippets of neural data. However, data collected in this method is insufficient for behavioral analysis.



Figure 3-19: RF-IR transceiver positioned above a representative primate skull. The box is held by a 4-axis adjustable arm (x-y-z-pivot) for fine placement over the implanted microsystem. The photodiode resides inside the aluminum case to protect it from RF “noise” coming from the primary coil powering the microsystem. Two SMA connectors can be seen, which, deliver forward power and sense flux voltage going to the implant and are used to monitor power consumption of the system and safety.

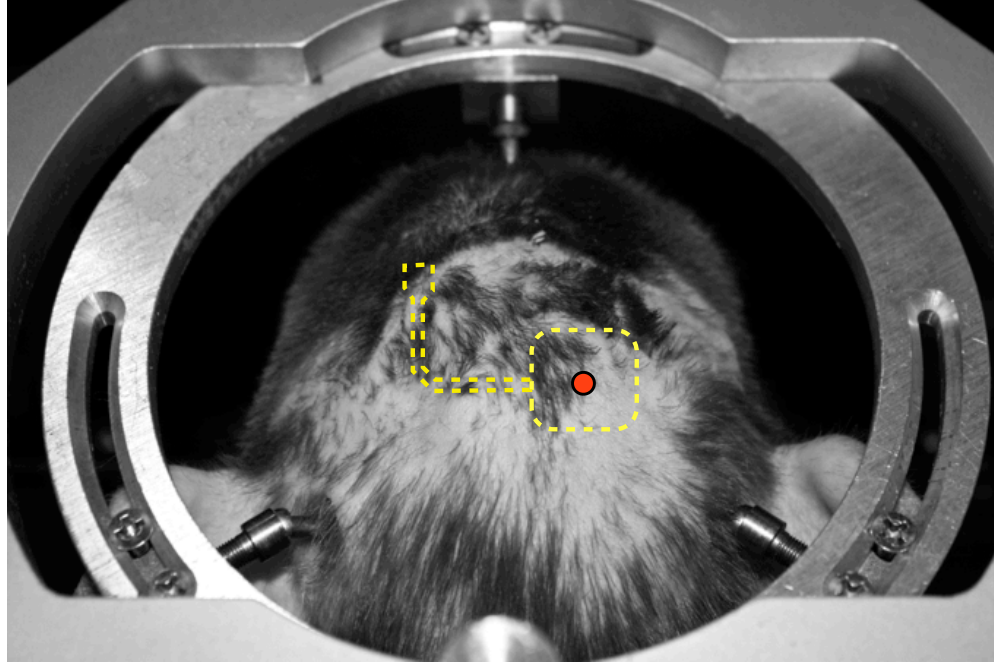


Figure 3-20: Top view of a non-human primate with halo showing the geometry of the externally powered microsystem having been designed for easy optical and RF access by the RF-IR transceiver. IR output location is shown in red.

3.13 Conclusion

It requires an interdisciplinary effort, and team to achieve what has been described in this chapter. We have presented our progress through several stages, from benchtop saline bath models to *in vivo* animal models, on a multi-tier process in the development of fully implantable, externally powered, cortical neural prostheses. The design choices made early in the development process were validated with finite element modeling, showing that heat generation of nearby tissue is negligible and well below FDA mandated standards. An ultra low-power operational trans-conductance amplifier ASIC was designed, and advanced over several generations, to effectively record from single neurons. In addition, we developed a digital controller to package the data from one analog-to-digital controller, inject a synchronization word, and drive a VCSEL for data transmission through the skin. We showed that non-human primate skin is sufficiently

transparent to infrared light at thicknesses exceeding 7mm. Lastly, we successfully implanted the externally powered microsystem in swine and monkey.

Our success in collecting neural data from these implanted systems further defines the utility of (swine) as test model for neurotechnology. More importantly, this work demonstrates the first fully implantable, wireless, and broadband neural recordings ever made in swine or non-human primates. For human subjects, this advance removes any percutaneous wire connection, reducing the possibility of infection by percutaneous defects. While this is in many ways simply a technological achievement, it opens the door to asking much more complex questions about fundamental brain science as the patient or subject can be interacting in a *natural* environment, not tethered to a rack of electronics. A limitation is that the externally powered microsystem necessitates the subject to be near the power source. Our next chapter will discuss a device based on the same microelectronic design foundations discussed here, but incorporating an internal power supply and long range data telemetry.

CHAPTER 4: Integrating state-of-the-art microelectronics with the nervous system: internally powered microsystem

4.1 Introduction

The development of an ultra-low power neural recording microsystem with integrated and active electronics for wireless data and telemetry is an extremely tall order. Added to that is the challenge to make a device that passes all FDA safety requirements. The externally powered microsystem, as described above, is one of our solutions. However, the EPM represents many significant deviations from what has currently been presented to the FDA, namely, soft-polymeric packaging of active electronics, and the placement of active electronics directly on the cortex (the integrated amplifier / MEA on the sensing unit). While we are confident that, ultimately, these

will be addressed in a pre-clinical study to validate safety and longevity, there is some further work necessary to shift the way active electronics in the body are viewed. Currently, there are only a handful of implantable devices with active electronics in them, and drastically fewer packaged in anything but hermetically sealed titanium cans. In addition, along with the many benefits of the EPM, there are many disadvantages. The most significant of those disadvantages is the inability of the system to run without constant external power.

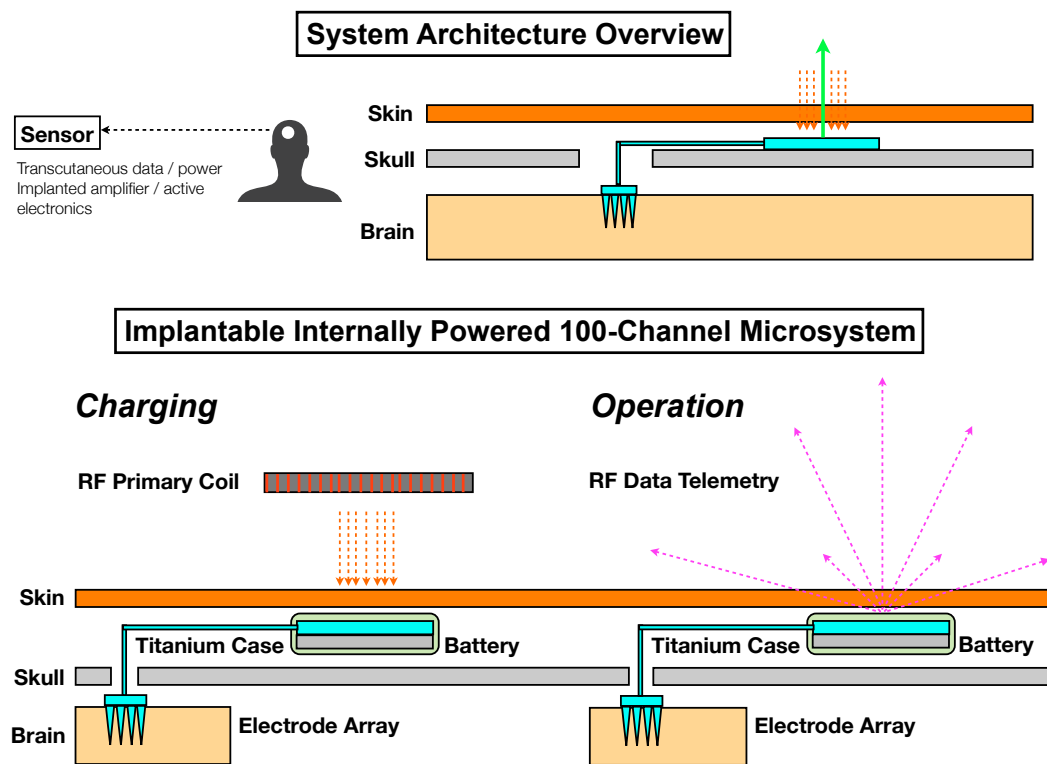


Figure 4-1: Architecture and design major design elements of the internally powered microsystem, IPM. Above, a general depiction of the goal: a subcutaneous with a cortically implanted unit. The IPM contains a battery and is charged with low-frequency radio frequency inductive coupling through a sapphire window embedded in the titanium case (bottom, left). Once charged, the system will broadcast broadband, digitized neural data over 3.2 - 3.8GHz carrier frequency (FSK modulated) over a distance of 3 meters and for 7 hours (full charge).

While the externally powered microsystem continues its path for validation, we developed a new device to address both the FDA challenges we face with implantable electronics, but also the ability to record without external power supplies. This device is termed the Internally Powered Microsystem, or IPM, and borrows heavily from the lessons learned from both the EPM and the Brown NeuroCard (BNC). The BNC is an external validation platform for neural recording electronics and data telemetry and was developed both for EPM and IPM component testing. Both the BNC and the IPM are described in detail in this chapter. The IPM is diagrammatically shown in Figure 4-1. These two devices were to act as transition points between currently implanted technologies and the EPM, as well as being effective devices to help diagnose various brain disorders under acute settings. The IPM device we developed was specifically designed to aid in the early diagnosis and detection of epileptic waveforms in persons with intractable epilepsy.

4.2 Brown NeuroCard description, images and historical significance

This section focuses on a parallel project that we started in order to both verify the “backend” electronics as well as the “frontend” amplifier. When we became close to beginning our in vivo studies, we realized the need for verification of our data acquisition electronics and wireless telemetry without introducing the complexity and potential confounds of surgical implantations. Considering that the array implantation introduces significant risk and variability between cases, we decided to develop a completely external device with identical electronics and the critical feature of being able to plug in to current NeuroPort pedestal assemblies. The clear advantage of this methodology was the immediate access to non-human primates in collaborators’ research labs with well-performing microelectrode arrays, completely removing the uncertainty of surgical implantation.

To this end, we developed what we referred to as the Brown NeuroCard (BNC), which includes the same electronics as the externally powered microsystem, including the custom

amplifier ASIC, controller, and infrared data telemetry but does not contain the microelectrode array. In collaboration with Blackrock Microsystems, we developed a mating connector for the NeuroPort system, allowing us immediately to leverage the current primates implanted with a NeuroPort system for data acquisition. We were able with this device to record from three different primates within a one-month period of time. In addition, this later served as a test platform for new amplifiers, allowing for direct comparison to the Blackrock neural signal processing system as well as our previous generation amplifiers. This initial concept can be seen in Figure 4-2.

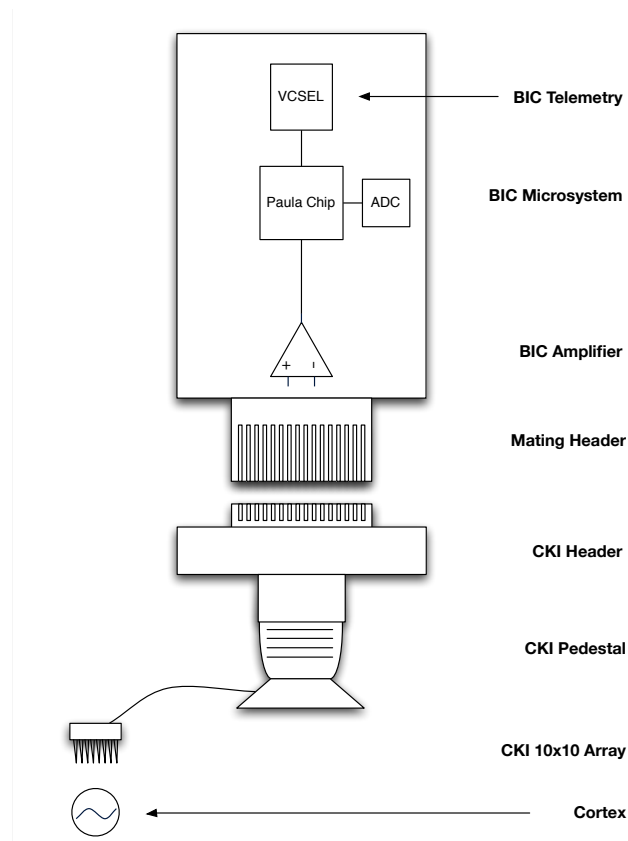


Figure 4-2: Initial design of the Brown NeuroCard (BNC). This was created as a verification platform for the amplification ASIC, as well as data telemetry. The substrate was FR-4, printed with nearly identical design as the BIC microsystem.

We began the design of the NeuroCard by taking the existing implantable microsystem and removing the silicon microelectrode array. At the time of development, we had created a 16-channel input amplifier, leaving 80 of the original 96 channels from the NeuroPort system unrecorded. Thus, we choose an arrangement of the mating connector to the NeuroPort pedestal to maximize the total channels to be recorded from (maximum 16 at once, however shifting the alignment enabled recording from >32 channels in total). The system contained an amplifier/multiplexer, microcontroller, ADC, passive components, the VCSEL for telemetry, and a Samtec connector all mounted on an FR-4 PCB. A complication to this exercise was the transformation of the of input channel numbers from the microelectrode array to the input channels of our amplifier. This was further complicated by the fact that the labeled “CKI Header” in Figure 4-2 separated the 96 channels from the SMA to 4 bays of 32 pins each (28 signal inputs, 3 ground lines, and 1 reference). Blackrock Microsystems provided us with the header-to-array mappings and another Brown lab (Donoghue, et.al) provided us with Cerebus channel designation to “CKI Header” mappings. Combining these (see Figure 4-3 and Figure 4-5) we were able to route the appropriate signal input into our amplifiers, the schematics of which are shown in Figure 4-4. To save space and remove the necessity for wire bonding to each input channel, the amplifier was flip-chip bonded to the PCB; this process also mimics that used in the fabrication of the externally powered microsystem.

Complete neural recording performance comparisons are discussed in *Chapter 6*. However, it is important to mention here that the success of the BNC at recording broadband neural data was a very clear validation of the EPM, and later IPM, architecture. In addition, we discovered several valuable and elucidating pieces of information through the process of fabricating and testing the BNC.

As mentioned above, the fabrication process requires a flip-chip of the amplifier array onto matched gold-pads on the PCB substrate. The electrical connection of this bond is made by silver particles in the conductive silver epoxy we dot onto the substrate before flipping the

amplifier onto it. While this is the same process as done on the EPM (flipped onto the MEA in that case), once the amplifier is attached to the BNC, we ideally have a very low impedance connection to the inputs of the amplifier, similar to a packaged chip for testing. Thus, one would expect similar performance of the amplifier. Surprisingly, this was not the case. In bench top testing, the amplifier produced aberrant noise spectra. The amplifier input pads were made of aluminum, which readily forms AlO_x . It appeared that the oxide developed thickly enough to cause capacitive-coupling of the input pads to the microelectrode array, where we had expected resistive-coupling. This coupling affected our low-frequency noise performance (summarized in Figure 6-9). To solve this problem, we made direct wedge bonds onto each input pad of the amplifier before flip-chip bonding onto the PCB. With this method, we achieved much nearer to ideal performance in the BNC. The implications of this finding on the EPM fabrication process were serious led us to re-plate each amplifier input pads with Au through an outside vendor (CVI, TX).

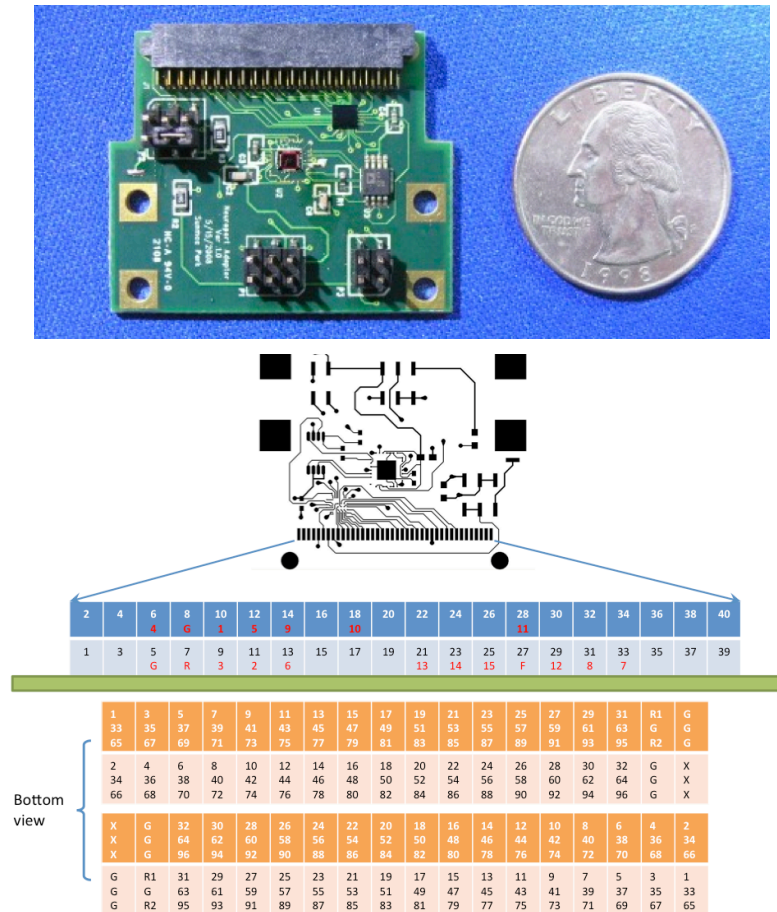


Figure 4-3: a) A populated Brown NeuroCard next to a US quarter for size comparison. The system was designed and fabricated in less that 2 months and produced a functional near-wireless recording system, b) a schematic of the BNC and the expanded channel mappings. Above the green line shows the Samtec connector on the BNC with numbers according to the BNC potential input channels to the amplifier. In red are the channels (in reference to Blackrock channels) recorded from when the connector is attached in this orientation.

When looking at the other side of this very important electrical connection we investigated the metallization on the microelectrode array, Pt/TiW/Pt. While epoxy bonding to this metallic stack should result in a solid bond, the solder process may cause metal migration and poor bond formation. Indeed we did see inconsistent connections between the amplifier and MEA after soldering them together. In addition, the solder process was difficult to integrate into the more general device fabrication process due to the heat required to reach eutectic points of the metals involved. Strangely, we still received poor SNR with an epoxy connection to the back of

the MEA (and Au plated amplifier input pads). We knew that wirebonds directly to the array effectively make connection (the NeuroPort device is just that) so we decided to try adding wirebonds to the array Pt/TiW/Pt contact pads. Surprisingly, this returned the noise levels to the expected values. It remains unclear why the silver epoxy itself does not make sufficient electrical connection to the MEA. It is clear, however that the wirebond is making very good connection to the underlying conductive layers in the MEA and eventually the Pt/Ir tip near a neuron.

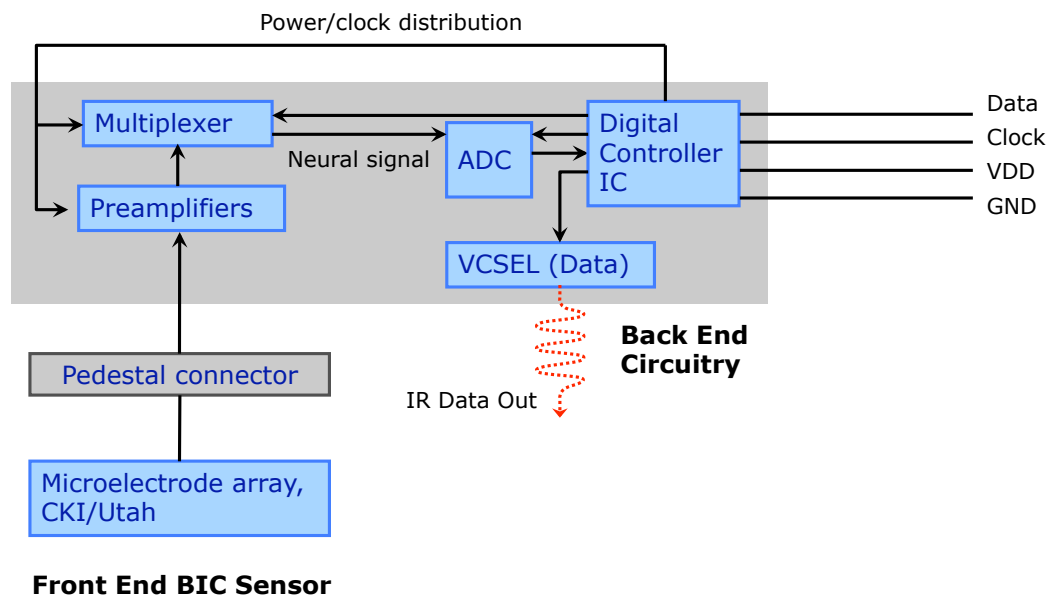


Figure 4-4: Schematic of Brown NeuroCard. Data out, clock, Vdd, and ground lines go to and from the Common Platform System (described in *Chapter 2*). Data is bifurcated to drive the VCSEL for validation of the laser data pathway. The later described Samtec connector sits between the “Pedestal Connector” and “Preamplifiers” in this diagram.

Regardless, the lessons learned from the BNC, the EPM, and the initial success of both led us to imagine a combination of the two device, sacrificing some size for the ability to record autonomously for an extended period of time. The internally powered microsystem is the product of that imagination

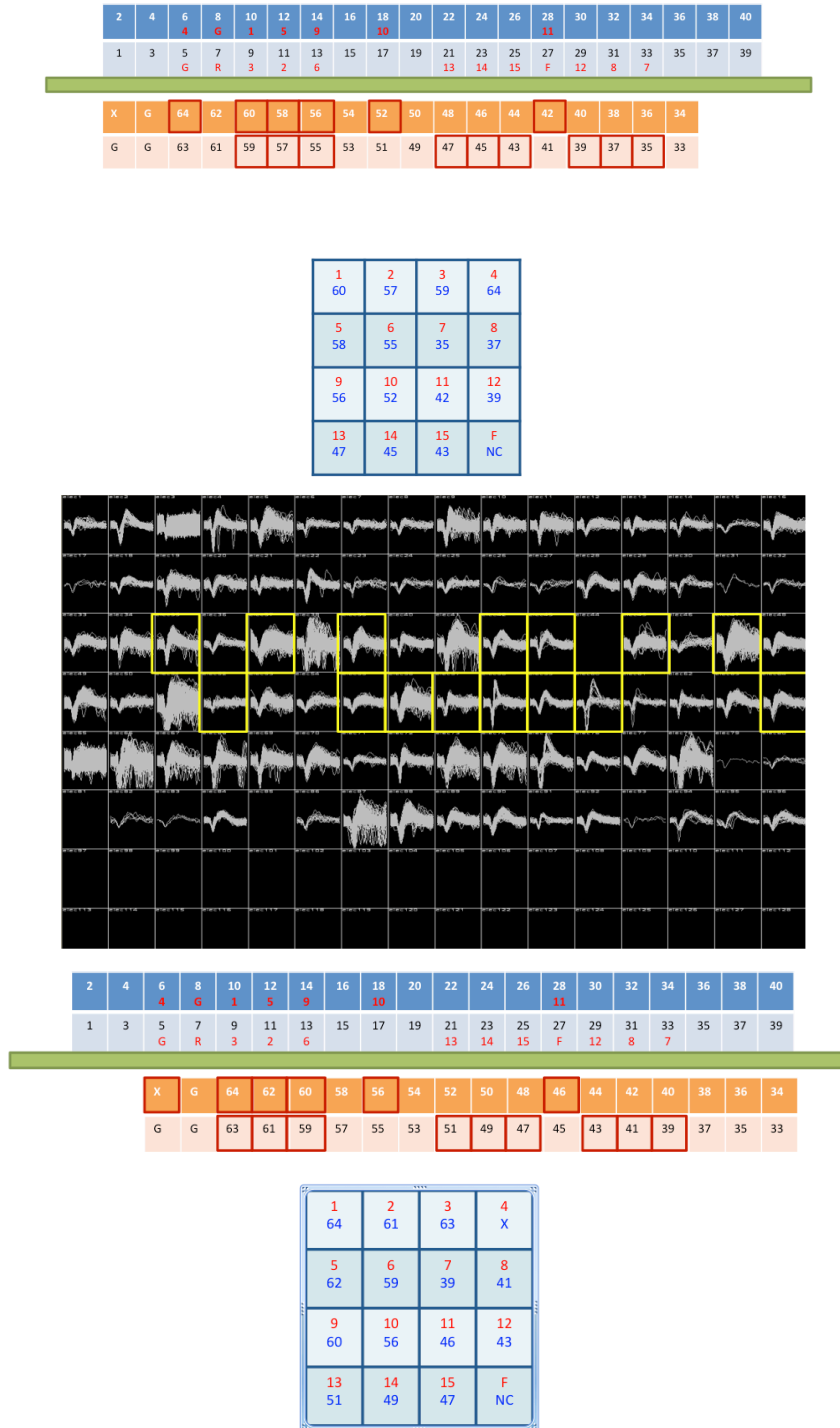


Figure 4-5: BNC recordings and physical connections for NeuroPort. a) The blue square grid is a representation of the amplifier input. Red numbers represent the input channel on the amplifier, whereas blue numbers are the corresponding channels in the NeuroPort. b) A screenshot from Cerebus Central, the recording software developed by Blackrock Microsystems, displaying yellow squares around channels used as input to the BNC in this connector orientation. c) A shifted orientation of the Samtec connector allows access to a completely different set of channels on the NeuroPort connector.

4.3 The Internally Powered Microsystem

Introduction

The internally powered microsystem (IPM) was developed with three overarching goals in mind: a) to aide in the diagnosis and potential early detection of epileptic activity in the human cortex, b) to enable longer range wireless recordings from freely-behaving non-human primates in natural environments, and c) to act as a stepping stone on the clinical approval pathway for implanted active neural sensors. These goals led to a number of design requirements and subsequent device modifications transforming the brain-implantable chip into an entirely novel neural sensing device aimed at near-term clinical use. Below we describe in more detail the driving motivations and the motivation-driven design changes to the externally powered microsystem leading to the internally powered microsystem.

4.3.2 Design motivation and resultant requirements

Epilepsy

Under a macroscopic lens, epilepsy is a considered brain disorder in which a person has repeated seizures over time. Seizures are defined as episodes of disturbed brain activity that cause changes in attention and behavior, often causing absence or convulsion. While epilepsy has been recognized since antiquity, the neuronal undercurrents are much less well understood. If we put on a mesoscopic lens, epileptic seizures are commonly considered to be the result of monolithic, hypersynchronous activity arising from an imbalance between excitation and inhibition in large populations of cortical neurons. The view of ictal, or during seizure, activity is highly simplified, and ignores a large degree of subtlety that may be present. This large population activity analysis is largely based on electroencephalogram (EEG) recordings, which reflect the averaged activity, or voltage changes, of millions of neurons recorded from on top of the scalp of an individual. Researchers have looked at the activity of smaller populations through electrocorticography

(ECoG, also referred to as intracortical EEG), which, places several (from 1 to 64) flat coin-shaped electrodes on the surface of the brain over an area of several centimeters. These recordings are much more specific, and have shown that pre-ictal states can have a great deal more heterogeneity than previously thought (Truccolo, Donoghue, Hochberg, Eskandar, Madsen, Anderson, Brown, Halgren, & Cash, 2011). How well these models capture mechanisms operating in human epilepsy remains an open question (Buckmaster, 2004; Jefferys, 2003). Very few human studies have gone beyond macroscopic scalp and mesoscopic intracranial EEG recordings to examine neuronal signals underlying seizures and thus, the behavior of single neurons in human epilepsy remains largely unknown. A deeper understanding of neuronal spiking during the different phases of seizure generation could have profound implications for seizure prediction and may provide the basis for new and more effective therapies for people with epilepsy.

Brain states and natural behavior

Recent behavioral neuroscience research on freely moving human/non-human primates and other animals has revealed great promise for next generation of Brain Machine Interfaces (BMIs) (L. Hochberg, Serruya, & Friebs, 2006; Sung-Phil Kim, Simeral, Hochberg, Donoghue, Friebs, & Black, 2007; Malik, Truccolo, Brown, & Hochberg, 2011; Velliste et al., 2008). This has created a considerable demand for microsystems that can simultaneously record neurophysiological signals from large numbers of single neurons across a wide range of spatial and temporal scales. Most modern recording systems require a wired percutaneous connection between the electrodes and external recording units. However, percutaneous connections restrict the subject's mobility, present a direct route from the skin to the brain for infection, and cause potential contamination of the signals due to external noise/interference. Hence, creating a wireless system that eliminates the need for percutaneous connection offers great advantages.

We have developed a fully implantable, hermetically sealed, wireless neural recording system. The system features 100 wideband (0.1Hz~7.8kHz) neural recording channels, a medical grade 200mAh rechargeable Li-ion battery charged by 2MHz inductive link, and both 3.2/3.8GHz FSK and 850nm IR for data telemetry. Shown in Figure 4-6 the system incorporates a 10×10 silicon-based intracortical microelectrode array (MEA) of the Utah type with 400μm electrode pitch (Blackrock Microsystems), a hermetically sealed titanium enclosure that houses the active electronics, and a 100-wire Au-wire bundle that connects the neural signals between the two. This section describes the specific clinical motivations for moving from a EPM-type device to the internally powered microsystem, the overall system architecture and circuit details of the implantable device, and initial bench top measurements of the entire device. Complete in vivo results are detailed in *Chapter 6*.

Stepping-stone for implanted active electronics in human patients

For decades we have been implanting active pacing electronics into the chest of patients with cardiac dysrhythmias. Pacers contain active electronics to both monitor and control cardiac contraction in patients with heart disease (Noble, 1984). Generally, a lead exits a titanium enclosure and penetrates the myocardium to deliver biphasic stimulation on command. Cardiac pacemakers have been reliably implanted since 1972 and have been helping people around the world continue to resume productive lives. Likewise, the deep-brain stimulator (DBS) functions in much the same way, pacing areas of the brain that exhibit aberrant activity (Eller, 2011; Morrell, 2011; Sohal & Sun, 2011; Stephen, Halpern, Barrios, Balmuri, Pisapia, Wolf, Kampman, Baltuch, Caplan, & Stein, 2012). In DBS device implantations, the titanium shell housing the active electronics is placed in the chest cavity in a similar way as the cardiac pacemaker.

We bring these examples to light simply to show what the FDA has seen through company submissions and is generally thought to be comfortable approving (from a schematic standpoint) for clinical use. When we look at a novel, modern device such as the EPM, we see a

challenge. The EPM incorporates active electronics onto the neurosensor (MEA), it is packaged in a polymeric wrapper (PDMS, Parylene C, etc.) as opposed to titanium, and finally the entire device is implanted within the head as opposed to the chest. It is generally thought that the closer to the brain parenchyma a foreign body is implanted, the more concern a physician and the FDA will have to use, or approve, the device. In addition, the potential failure modes associated with active electronics (power-to-ground shorts, material trace leaching, etc.) that are intracranial are all magnified.

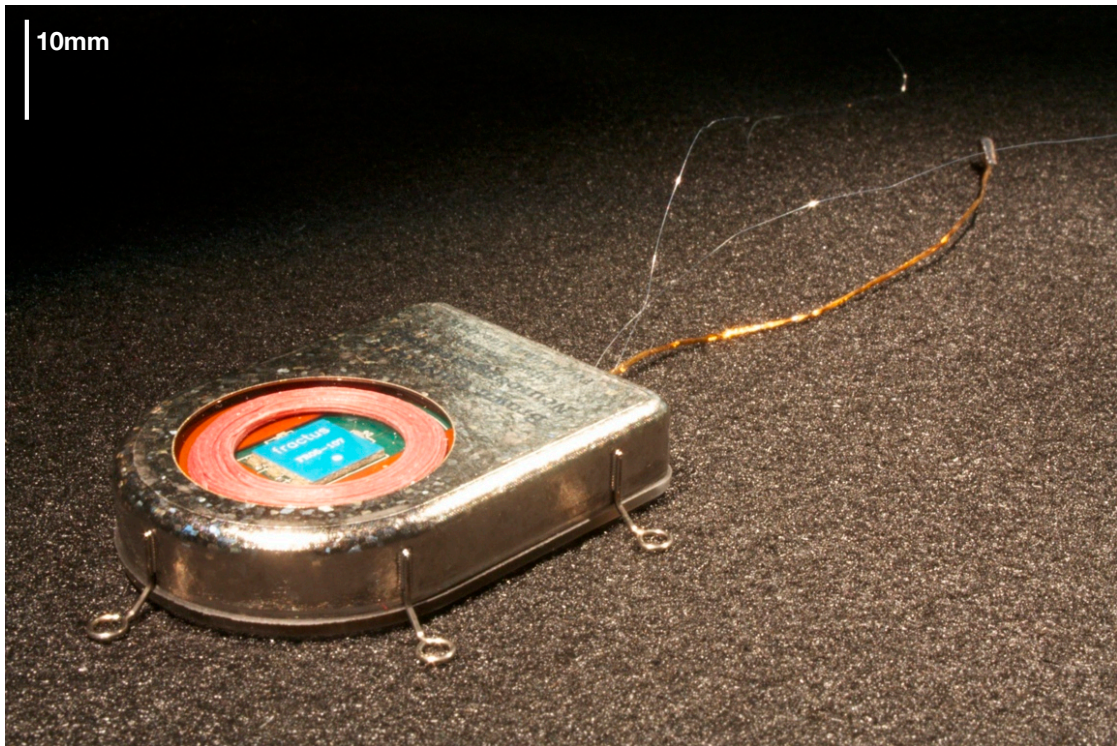


Figure 4-6: Completed internally powered microsystem before implantation. The secondary coil for inductive coupling can be seen inside the titanium case, as well as the Fractus UWB chip antennae used for data telemetry.

With this in mind, our FDA approval pathway, as well as our internal development pathway, views the internally powered microsystem (active electronics enclosed in a titanium shell, but still implanted in the head) as a stepping-stone to full EPM approval and validation. The

IPM moves the active electronics under the skin, and along with it adds a Li-ion rechargeable battery. While the battery may raise some concern, this has been done many times before (DBS, Pacemaker, and others) and we believe will not be a significant hurdle to approval of our device. If approved, the use of the IPM in human clinical trials paves the way for the next step in device integration realized in the EPM: amplifying and multiplexing the neural signal directly at the source, significantly reducing the number of wires needed to transmit the signals within the body, but also introducing active electronics on the cortex

4.3.3 IPM architecture and fabrication details

Overall System Block Diagram

Figure 4-1 shows the wireless neural recording device in diagrammatic form, while Figure 4-7 shows the system after completion of the manufacturing process. In this device, the neural 100-electrode sensor made by Blackrock (C. Nordhausen et al., 1996; R.A. Normann, 1990) is located at the distal end of a 100-wire Au-wire bundle. The proximal end of the wire bundle is connected to a hermetically sealed subcutaneous unit (akin to the telemetric unit of the EPM) that is implanted below the skin of the subject. The subcutaneous module hosts all active electronics within a hermetically sealed titanium enclosure. Welding of two sections, referred to as “top” and “bottom,” respectively, forms this enclosure. The “top” has a hermetically brazed single crystal sapphire window for electromagnetic transparency that facilitates (i) low loss wireless transmission of RF and/or IR neural data from the device and (ii) means for sending wireless power into the device via inductive coupling for recharging the embedded battery power supply. Certainly, the size of this window dramatically affects the efficiency of electromagnetic power transfer, either for power or data telemetry; this is discussed later. The bottom of the Ti-can contains an array of ceramic embedded Pt/Ir feedthrough pins laid out in a compact arrangement limited by current manufacturing techniques. To facilitate the electrical conduit from the individual wires of the Au-wire bundle to the feedthroughs, a parallel interface plate (PIP)

was developed and used to fan out the wires from the bundle onto the PIP. Individual Au-wires are wire bonded to specific PIP sites that connect to holes with commensurate specifications that allow alignment and insertion of the PIP onto the “bottom” section of the enclosure so as to provide the electrical contact to the feedthrough pins. The PIP is built on a flexible Kapton substrate overmolded by biocompatible silicone for protection of its internal wiring from ionically conducting body fluids.

The circuit block diagram of the active electronics including the rechargeable battery in Figure 4-7 shows three major blocks: the preamplifier board (PCB-A), the RF power/data board (PCB-B), and the Li-ion rechargeable battery.

Preamplifier Printed Circuit Board (PCB-A)

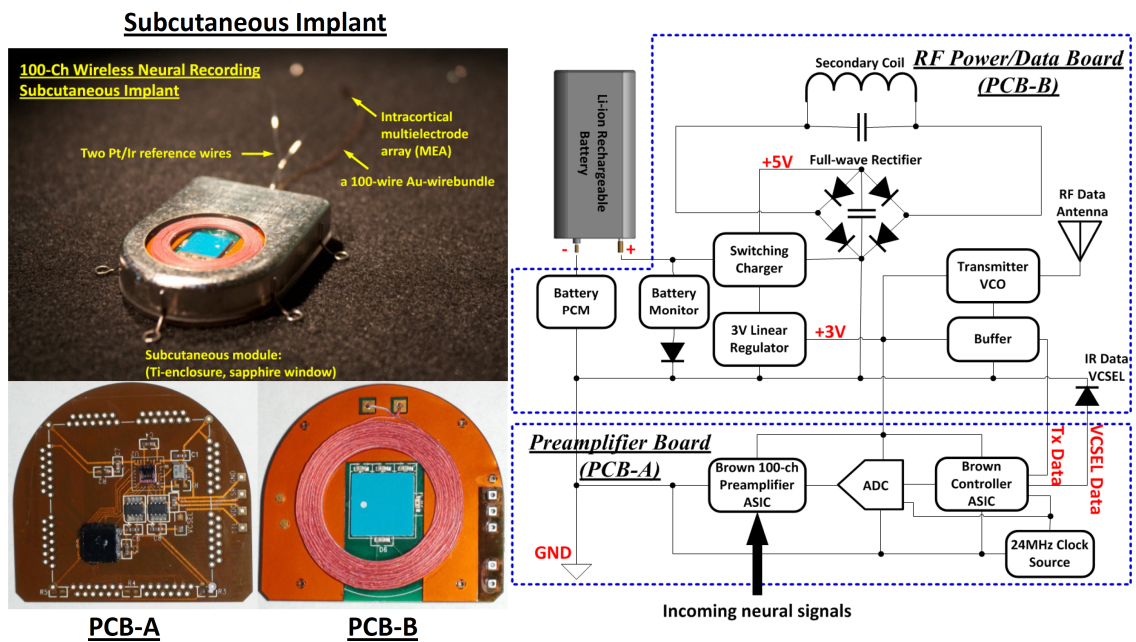


Figure 4-7: Internally powered microsystem completed (top-left), with internal PCBs shown (lower-left) along side the circuit block diagram (right).

PCB-A Figure 4-7 (bottom-left) integrates a 100-channel preamplifier ASIC, two SAR 12-bit ADCs, a controller ASIC, and a 24MHz clock source. The incoming neural signals on each

channel are conditioned and amplified by a low-noise low-power preamplifier implemented in the 100-channel preamplifier ASIC. Figure 3-13 shows the circuit block diagram of the 100-channel CMOS preamplifier ASIC (manufactured version shown in Figure 3-14). The preamplifier uses a capacitive-feedback, folded cascode operational transconductance amplifier (OTA) configuration with a source follower output buffer. It has a gain of 46dB and bandwidth of 0.1Hz to 7.8 kHz. For details of the preamplifier design, please refer to (Patterson III, Song, Bull, & Laiwalla, n.d.; W Patterson et al., 2004; William R Patterson & Song, 2007) and *Chapter 3* of this thesis. The 100 preamplifiers are divided into two groups of 50 preamplifiers each. The preamplifier outputs in both groups are multiplexed using the column/row select blocks running at a 1MHz clock generated from the main 24MHz clock source, which leads to a sampling rate of 20kSps/Ch. The two multiplexed analog neural signals are buffered with two unity gain buffers before they are fed into two commercial 12-bit SAR-ADCs (Analog Devices, LTC2366). Each ADC consumes 4.8mW from 3 V at 1MSps, requires a minimum of 14 clock periods for a single conversion cycle initiated by an active “LOW” chip select signal. In order to combine the two ADCs’ 12-bit effective data into a single serial bit data stream to drive the RF/IR transmitters, the multiplexing clocks for the two groups of preamplifiers as well as the ADCs’ chip select signals are shifted by 180 degrees from each other, therefore the 12 effective bits of each ADC data are aligned back to back without redundant bits. A controller ASIC manages the data flow between the preamplifier ASIC and the ADCs. It also packages the ADC data with a 24-bit synchronization pattern into a serial bit data stream that is fed into the PCB-B for wireless transmission.

Power/Data Printed Circuit Board (PCB-B)

PCB-B Figure 4-7 (bottom-left) shares the 3V VDD and GND with PCB-A. It also takes two formats of the 24Mbps serial bit data stream: 1) a TTL format that modulates a freely running commercial VCO, which outputs 5dBm 3.2/3.8GHz FSK power into a 1.5dBi UWB chip antenna for wireless data broadcasting (FR05-S1-P-0-107, Fractus), and 2) an open drain current source

that drives an 850nm VCSEL for IR data transfer. A wireless charger is also implemented on PCB-B with off-the-shelf components to charge a medical grade 200mAh Li-ion rechargeable battery (QL0200I-A, Quallion), which is able to operate the system for 7 hours after it is fully charged. A 210pF high Q SMD 0603 ceramic capacitor along with a secondary coil forms a LC-tank for the wireless charger to harvest the 2MHz RF energy from a 40 μ H external primary coil driven by a Class-AB power amplifier. The secondary coil is a 27-turn 27mm O.D. coil made from 46-AWG 40-strand Litz wire for minimum loss. It has an inductance value of 30 μ H with a Q of 75.4 at 2MHz. The received AC power is rectified by a full wave rectifier producing a 5V DC supply for a switching mode Li-ion battery charger chosen for its >85% efficiency over a wide range of supply voltage (4.35V~16V) and charging current (0.1A~2A). The charging current is programmed to be 0.1A (0.5C of the battery) taking 2hrs to fully charge the battery after it is being depleted. The wireless charger is equipped with three safety features: a self-timer that terminates the charging within 2.5hrs, a battery monitor that indicates the status of the battery, and a protection circuit module (PCM) that protects the battery from over-charging/discharging. A low-dropout regulator regulates the battery voltage and produces 3V supply for the rest of the system.

External Receiving Unit

External receivers were developed for receiving the RF or IR data. The radio frequency section of the receiving unit, which is documented here, was heavily influenced by the work of Miranda et al. (Miranda et al., 2010). The RF superheterodyne receiver shown in Figure 4-8 uses a 17dBi planar dual polarized antenna to reduce the movement sensitivity of the transmitter antenna. The incoming 3.2/3.8GHz FSK signal is first amplified by a 24dB LNA with NF of 0.9dB, and is down converted to 150/450MHz IF band by a 3.65GHz LO. The FSK-IF signal is amplitude-stabilized by an automatic-gain-control block and is then converted to OOK (On-Off-Keying)-IF signal by a 400MHz low pass filter. The OOK-IF is further down converted to the

baseband signal using a mixer and an 80MHz low pass filter. From the baseband signal, the digital data and clock are extracted using a data/clock recovery block. The recovered data is then forwarded to an FPGA and repackaged into 16-bit samples, which get buffered through an 8MB SDRAM and sent to a PC via USB 2.0 for further processing and visualization. The USB interface used here is identical to that described in *Chapter 3*, using the EZ-USB framework for high-speed data transfer.

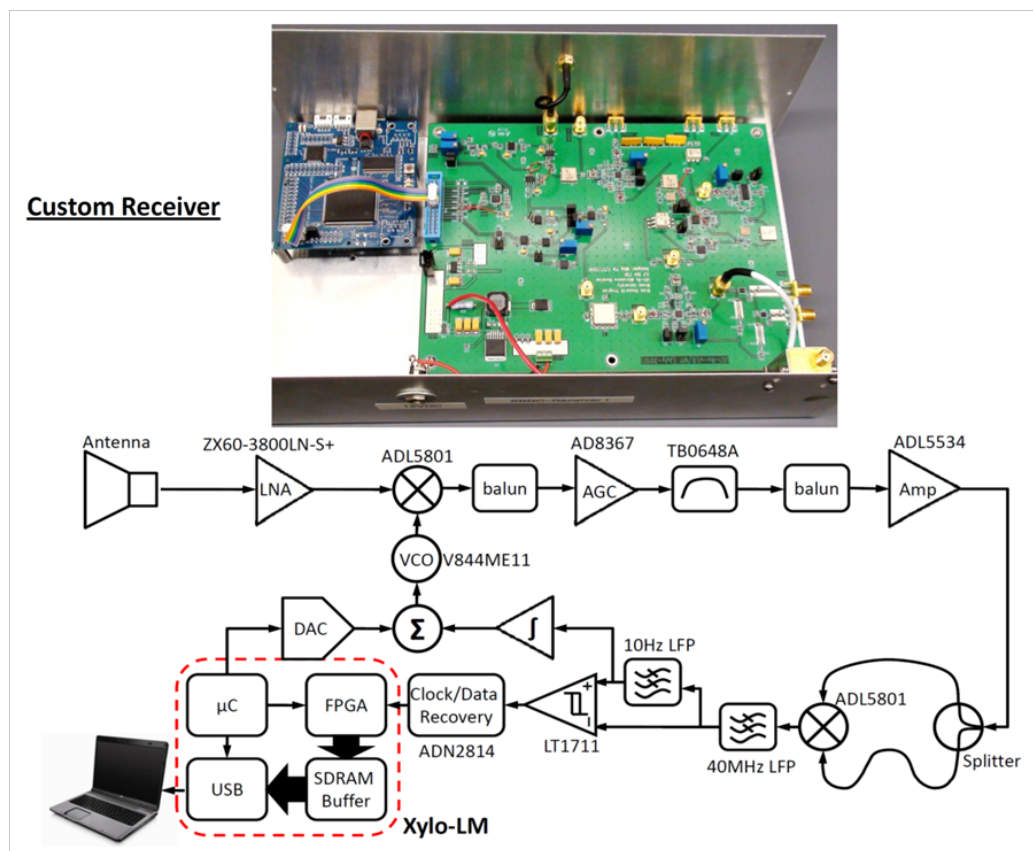


Figure 4-8: 3.2-3.8 GHz receiver and schematic, heavily based on the work by Henrique Miranda at Stanford University.

The receiving unit described above is currently implemented within a form acceptable for tabletop use ($\sim 5\text{cm} \times 40\text{cm} \times 10\text{cm}$) but not for wearable use. While we have focused our attention here on functionality, the receiver box will in the future be built into a wearable

package. This can be thought of as a “daughter card,” or auxiliary device, to the later discussed BrainPhone, described in detail in *Chapter 5*. The receiver will shortly become a wearable link between the neural sensor (EPM or IPM) and the wearable digital signal processing technology envisioned in *Chapter 5* for neural data extraction and execution.

Final assembly and bench top testing

The 100-Ch preamplifier and controller ASICs are fabricated in a $0.5\mu\text{m}$ 3M2P standard CMOS process and measure $5.2\times 4.9\text{mm}^2$ and $2\times 2\text{mm}^2$ respectively. The electronics on PCB-A and PCB-B along with the battery are encased into a $56\times 42\times 9\text{mm}^3$ Ti-enclosure with a 29.2mm diameter single crystal sapphire window on top for electromagnetic energy transfer. The secondary coil, chip antenna, IR VCSEL, and LED battery status indicators are placed directly below the sapphire window, achieves 32% inductive power efficiency at 5mm distance, <50% RF loss, and >95% IR transparency. Table 4-1 summarizes the remaining measured specifications of the system.

100-Ch Fully Implantable Wireless Neural Recording System Measured Performance	
Number of channel	100
Preamplifier gain, bandwidth, and input referred noise	200 (46dB), 0.1 Hz ~ 7.8 kHz, $8.5\mu V_{rms}$
Preamplifier input referred noise	$8.5\mu V_{rms}$ (0.1 Hz ~ 7.8 kHz)
Preamplifier ASIC size and power dissipation	$5.2 \times 4.9 \text{ mm}^2$, 6mW@3V
Controller ASIC size and power dissipation	$2 \times 2 \text{ mm}^2$, 10mW@3V (9mW for VCSEL driver)
System resolution and sampling rate	12 bits for all channels, 2 MSps (20 kSps/Ch)
RF FSK Tx frequency and power dissipation	3.2/3.8 GHz, 50mW
IR VCSEL wavelength and power dissipation	850nm, 9mW
Inductive power carrier and efficiency	2 MHz, 32%@5mm
RF receiver sensitivity	-60dBm
Battery	200mAh medical grade Li-ion rechargeable battery
Battery operational hours after fully charged	6.6hrs
Total power dissipation (when not charging)	30.2mA @3V
Titanium enclosure dimension	$56 \times 42 \times 9 \text{ mm}^3$
Total weight of the system	44.5g (7.4g for battery, 30.6g for the Ti-enclosure)

Table 4-1: Complete internally powered microsystem performance parameters. While many values, such as geometry and power consumption may not be ideal for implantation, the system as a whole represents the most advanced system integration for implantable neural prosthetics.

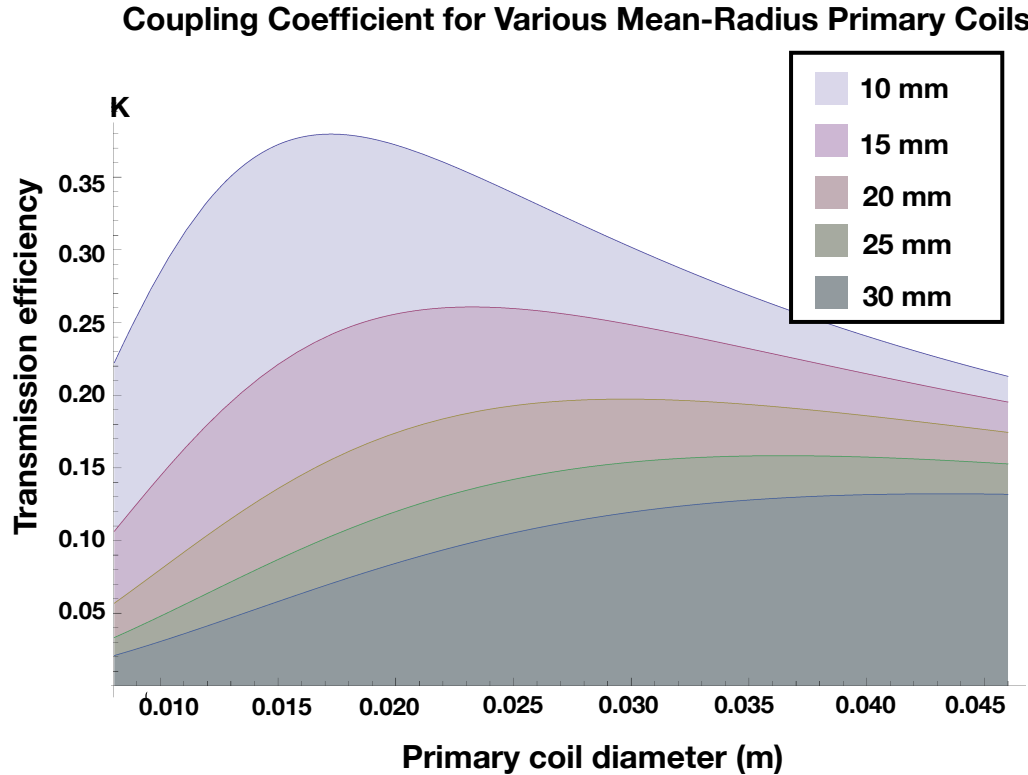


Figure 4-9: Coupling coefficients for various mean-radius primary coils, assuming fixed secondary coil.

Similar to the externally powered microsystem coil diameter optimizations that were completed, we likewise modeled the internally powered microsystem. The primary and secondary coils were modeled and we looked at optimal primary coil geometry given the fixed secondary coil. The secondary coil geometry was determined by the necessity to shrink the substrate as much as possible and limitations in the sapphire window diameter. Mathematica was used to solve the static electromagnetics described in *Chapter 3*, yielding the results in Figure 4-9. However, the assumptions made earlier for the EPM did not account the addition of a titanium (i.e. conductive) shell with a small electromagnetically transparent aperture for energy transfer. As alternating electromagnetic energy is incident upon a conductor, eddy currents will be induced by the changing magnetic field. Since these induced currents are of a small geometry and mostly confined to the surface of the conductor, there will be competing currents in opposite directions,

yielding an increase in effective resistance of the material. This is called the “skin effect” as it occurs on the “skin” of the bulk material. A material has a “skin depth,” which, is a frequency-dependent property defined as:

$$\delta = \sqrt{\frac{2\rho}{(2\pi f)(\mu_o\mu_r)}} \quad \text{Equation 4-1}$$

where δ = the skin depth in meters, μ_r = the relative permeability of the medium, ρ = the resistivity of the medium in $\Omega\cdot\text{m}$, also equal to the reciprocal of its conductivity, and f = the frequency of the alternating current in Hz. For Grade-2 Titanium, the material of our hermetic packaging, this equates to 0.257mm. The titanium shell thickness, governed by the braising and welding required to seal the device, is 1mm. Thus, significant “skin effect” was expected and observed. The skin depth for various grades of titanium can be seen in Figure 4-10. This added resistance to the forward electromagnetic energy is unfortunately immediately dissipated as heat and transferred to the surrounding tissue. While this remains to be optimized through modifications of the can geometry and its material constituents, we created a COMSOL model of the current device to estimate the temperature rise of the surrounding tissue given our expected (and measured) power transfer efficiency. This model used the same bioheat equations and assumptions as the previously defined model for the externally powered microsystem with some slight modifications. First, the solid model of the EPM was replaced with the CAD design model of the IPM designed in SolidWorks. Second, we ran two computational studies, one with the IPM surrounded by air to validate the in-air bench top heating measurements, and another with the IPM surrounded by human tissue, as was done before for the EPM. These two studies represent the experimental conditions we implemented in vivo: a) a fully implanted IPM in two pigs, and b) a semi-implanted, or partially exposed, internally powered microsystem in two non-human primates. A semi-exposed implant was necessary in several non-human primates due to the limitations of skull and surrounding tissue size. However, swine have a very thick cranium,

which, allowed full implantation and evaluation of the IPM. For the exposed implant, air was modeled as a continuous medium, with boundaries fixed at room temperature except where the air was in contact with the device or tissue. Along these boundaries, heat transfer was applied between the two materials. The IPM is shielded by titanium and sapphire (the electromagnetic window), two materials not used in the EPM. Titanium has thermal conductivity of 16.4 W/m-K, heat capacity of 0.523 J/g-°C, and density of 4.51 g/cc. Sapphire, used for the window, has thermal conductivity of 46.06 W/m-K, heat capacity of 0.799 J/g-°C, and density of 3.98 g/cc. These parameters were used for the COMSOL model, using the bioheat transfer equations outlined in *Chapter 3*.

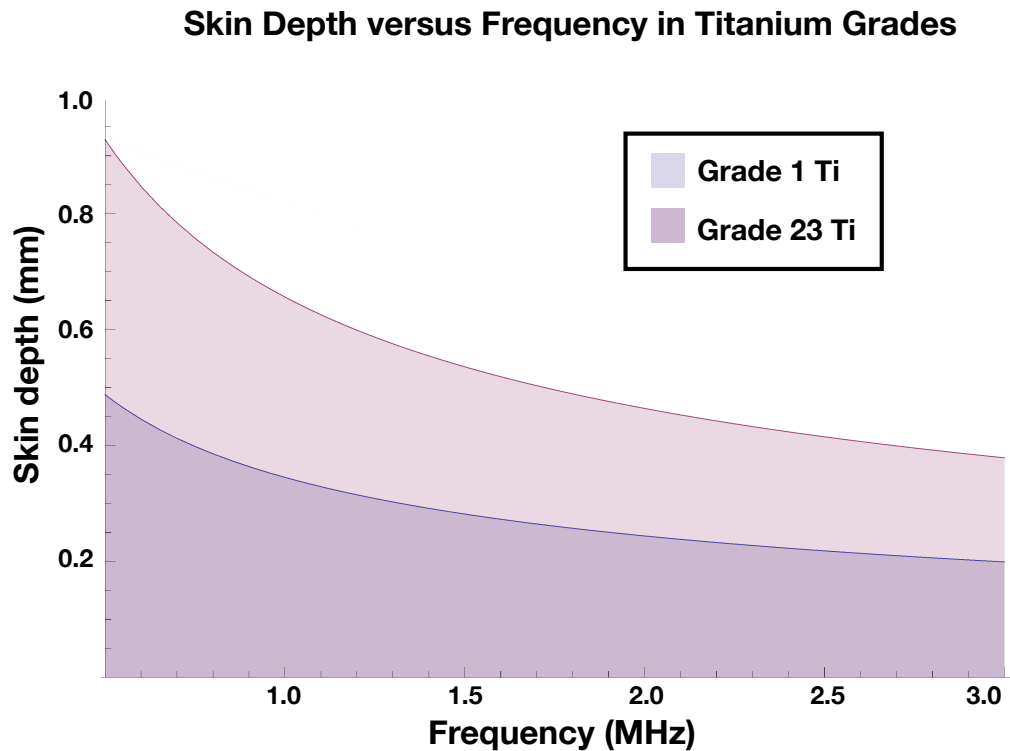


Figure 4-10: Skin depth varying with expected frequencies of use for RF inductive coupling. It is clear that titanium grade will have a large effect on heat generation.

The COMSOL model was calibrated against the experimental temperature recordings of the IPM in air (see Figure 4-12 – left, and Figure 4-11). We estimated that of the 2W of forward power being delivered to the IPM from the external charging system, about 1W was transferred to the titanium case. Of that 1W, 210mW are consumed by the microsystem during normal charging. This leaves 780mW being sunk to the case, and thus, to heat. In COMSOL, the case was defined as a heat generator with input of 780mW. While temperature increase of the IPM under constant-charging conditions just described is large ($\sim 20^{\circ}\text{C}$), it can be easily mitigated by active cooling. For implanted systems, this is accomplished by the natural vascularization of the skin. For all non-human primates in this study with exposed implants, we actively cooled the microsystem with wet gauze. Cold water applied periodically during charging to diffuse the heat generated by charging. This type of active cooling was less practical with an implanted system (in swine); however, it was also less needed as the body has internal mechanisms to cool the tissue, i.e. vessel dilation and tissue perfusion. The COMSOL model of the internally powered microsystem surrounded by skin and bone, as opposed to air, showed modest increases in temperature to the surrounding tissue. The spatial distribution of temperature can be seen in Figure 4-12, right side of figure. This rise in temperature is still unacceptable, as most biological living tissue will begin to become necrotic around 41°C (our models suggest that the tissue could be experiencing temperature near 42°C - see Figure 4-11). Thus, in our fully implanted experimental work with swine, we continued to provide the site with active cooling, as performed on the exposed implant, to keep the temperature as low as possible.

It is clear that one of the largest challenges we face with the IPM is reducing the temperature increase during charging, which is largely due to eddy currents in the titanium shell. One simple change we are implementing is drastically reducing the carrier frequency of the RF inductive link from 2MHz to 175kHz. This will increase the skin depth and thus effectively reduce the resistance seen from the titanium. In addition, while we are currently locked in to using titanium as the packaging material, we will increase the size of the sapphire window to its

practical limit (limited by welding and braising processes from the company we work with, the thickness of the titanium, and cost). These changes will be made in future versions of the device currently under development. However, for the data collected in this thesis, all devices necessitated active cooling and prudent charge durations to mitigate the tissue damage from heating.

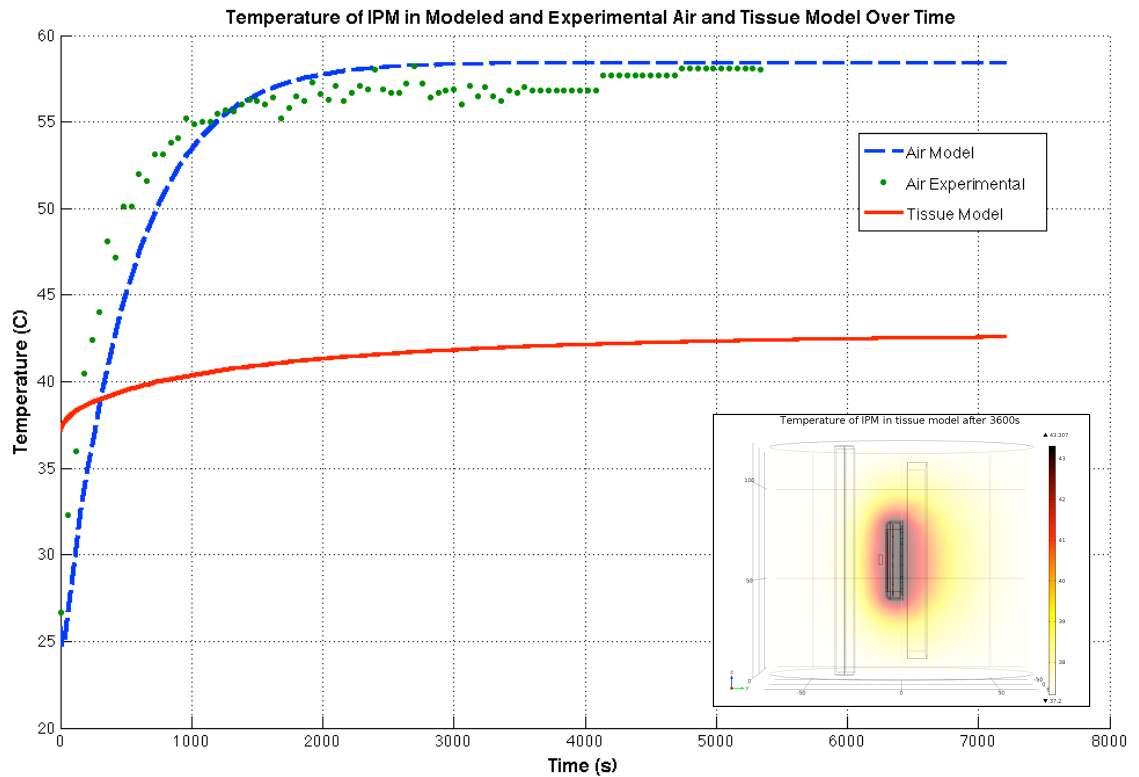


Figure 4-11: Temperature vs. time profile of the IPM during the charging process. The IPM was charged at a constant 40mA charging current (+33mA for the system itself to run), necessitating about 2W of forward power from the external charger. Experimental temperature measurements in air on benchtop (green, dotted), modeled air calculations (blue, dashed), and modeled calculations of the system in biological tissue (red, solid) are shown in the figure.

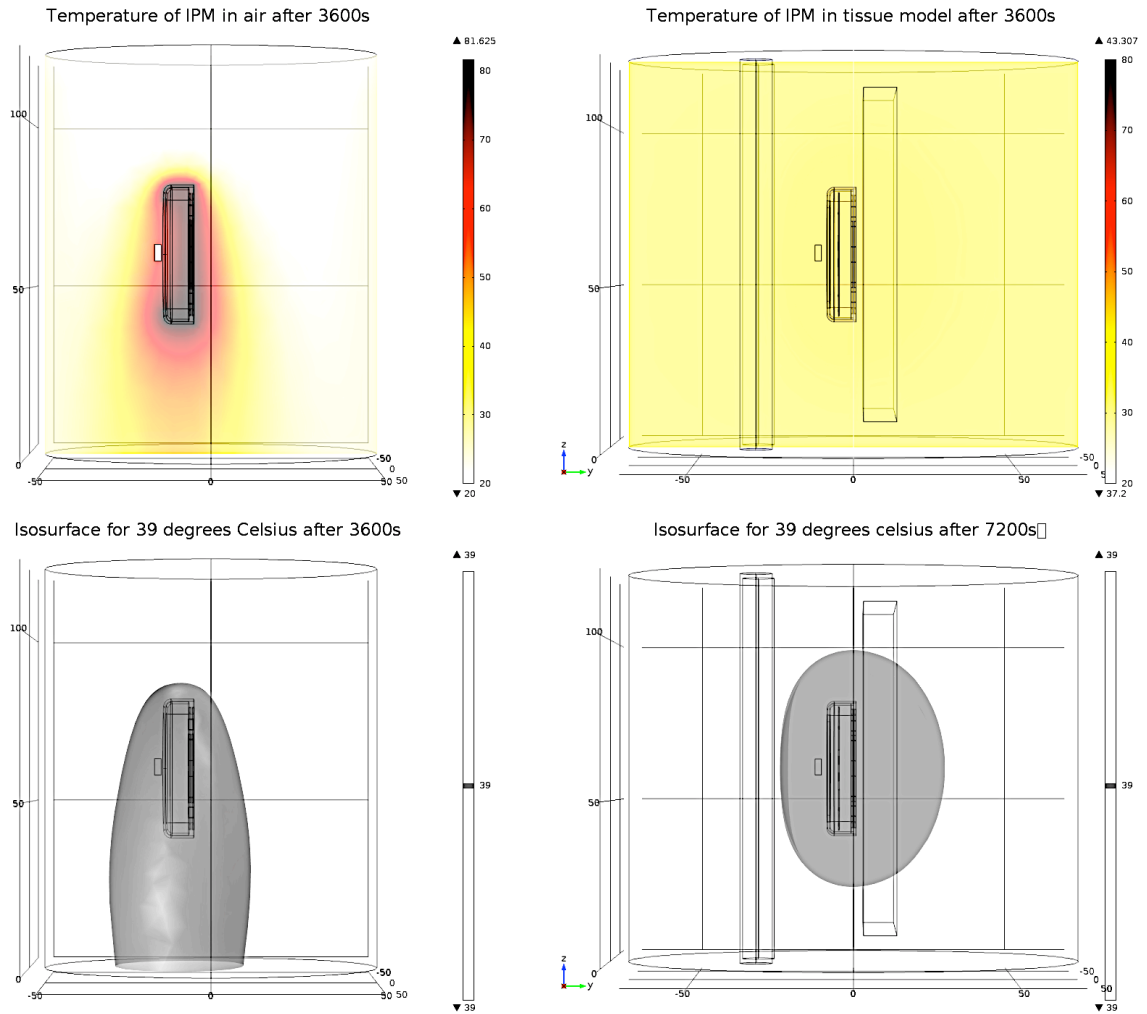


Figure 4-12: Modeled steady-state temperature profile of the IPM in air (top-left) and in biological tissue including models of bone, skin, and vessels (top-right). For clarity, an isosurface at 39°C (FDA regulated limitation for device temperature) is drawn in the lower half of the figure.

4.3.4 Custom case design for handling and sterilization

The IPM is an extremely complicated device to fabricate. Fabrication begins at Microconnex in Washington State, where the substrates are fabricated for the microelectrode array interconnection board. That board is then sent to Blackrock Microsystems in Utah to attach the microelectrode array and package the construct in their standard Parylene-C and PDMS process. Meanwhile, the internal PCBs are populated at CVI in Texas, including the flip-chip process of the amplifier ASIC onto the board. All boards are then returned to us at Brown in Rhode Island for testing and verification before being sent to Cirtec Medical in Massachusetts for final assembly and hermetic packaging.

While each company has its own packaging methods for shipment, it was apparent that we needed to build a case to protect the final device when it is assembled and returned to us for final validation and sterilization. We needed a case that was mechanically robust, would protect the microelectrode array from slight movements shipment or transport, was sterilizable, and very importantly was simple to open and close (the last hiccup a surgeon wants is a package that takes minutes to open). To develop this case, we worked again with Kineteks (Rhode Island). After many design meetings with surgeons, engineers, and designers, we came up with a construct that met all of our needs. The case is composed of statically dissipative carbon-doped PEEK. It has protective windows around the microelectrode array to allow for visual inspection yet protects it from objects falling into the space. The case is designed for ethylene oxide treatment, which is a gas that must reach all parts of the device. The design accordingly has minimized the area and number of contact points to the device. There is a simple latch mechanism to attach and detach the top plate of the case for removal of the device. Below each latch is a small cutout of the case to allow room for a surgeon's finger to pass and grab the top plate for ease of removal. Lastly, there are two large glass windows, one above the secondary coil to allow for visual inspection of the status LEDs on the IPM and electromagnetic access to the coil for charging, and the second above the microelectrode array to protect it from small falling objects, but allow for visible

inspection. The entire case can be immersed in saline for soak testing and will withstand accelerated lifetime temperatures of $\sim 57^{\circ}\text{C}$ (PEEK and glass are stable at high temperature and under 100% humidity), which we use for evaluating longevity of our implantable devices (Kurtz, 2011). Thus, each implantable device can be protected by the case while tested under accelerated conditions. The design model and final fabricated case can be seen in Figure 4-13. This case has currently been used to house, protect, and sterilize five internally powered microsystems for implantation in swine and non-human primates. There have been no electrostatic discharge damage to any of these five devices while in the cases and the cases have proven to be extremely helpful in safely testing the devices before and after implantation.

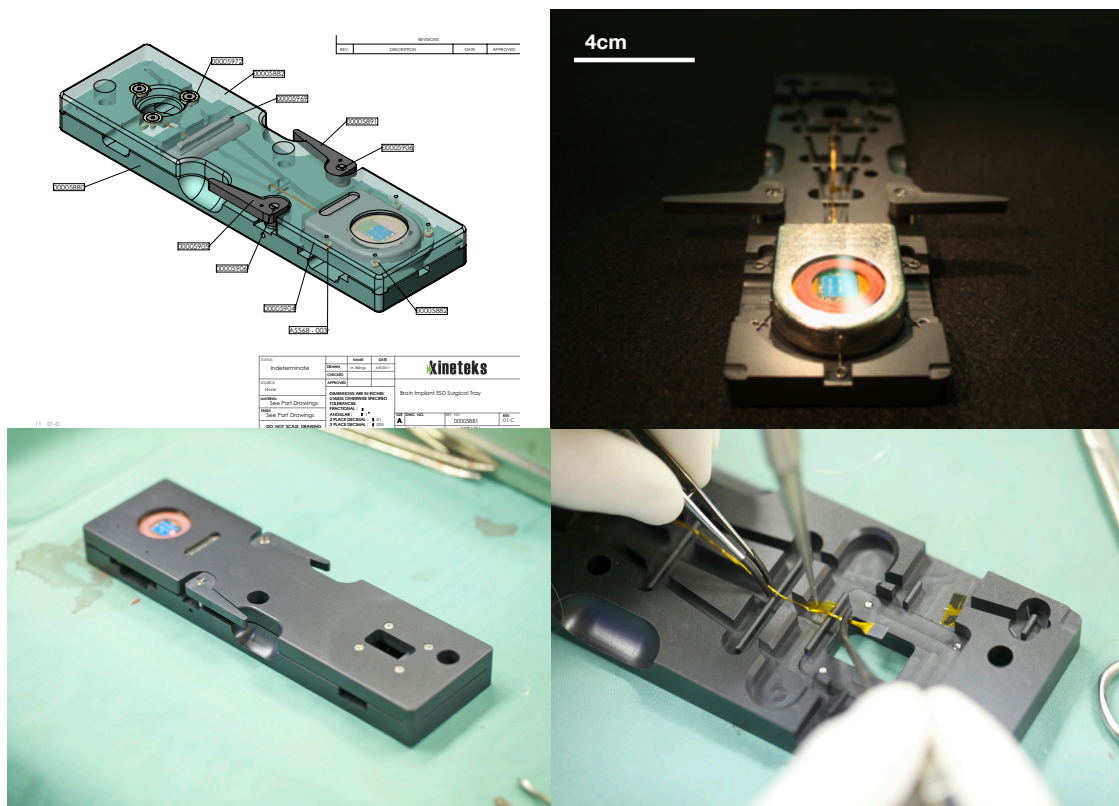


Figure 4-13: Custom sterilization and handling protective case made in collaboration with Kineteks. We used carbon-doped PEEK for electrostatic dissipative qualities as well as incredible strength.

4.3.5 The first broadband, fully implanted, wireless neural recordings from freely moving Yorkshire swine

The full functionality of the wireless neural recording system has been validated first on the bench and then in vivo in two adult awake Yorkshire pigs over a period of four months. During recording sessions, the systems were successfully recharged and powered up. Input channels showed consistent input referred noise level of $\sim 9\mu\text{V}_{\text{rms}}$ (about the expected values for the Big Pearl v1 amplifier ASIC). The internally powered microsystems in both animals recorded spiking and low frequency neural events. Animal S3 showed on average 50 out of 100 input channels with clear neural spiking activity with peak-to-peak amplitudes $\sim 120\sim 40\mu\text{V}_{\text{pp}}$. Animal S2 showed fewer (~ 10) channels with spiking activity. LFPs were also extracted from both animals as the data are increasingly used in neuroscientific research, specifically epilepsy detection. All neural data plots are shown in the results section of this thesis, *Chapter 6*. S2's implant was removed after 38 days due to a small infection likely caused by needle aspiration of a pocket of accumulated blood 15 days post-operatively. The device was fully functional on explant and allowed us to collect neural signals while the animal was euthanized for device explantation. This data is also shown in *Chapter 6*, and shows that the IPM may be used to distinguish brain states in animals; we are eager to explore the translation of such recording techniques to humans for disease diagnosis, as discussed previously, for epilepsy. S3's implant has been implanted, fully functional, and without notable body reaction for more than four months.

4.3.6 Broadband, wireless neural recordings from freely moving non-human primates

Two adult rhesus macaque non-human primates (JR, and JN) were implanted with an IPM in an identical process to the swine implantation, save a few changes due to the reduced size of the cranium. First, the bone-flap from the craniotomy was repositioned and secured back onto the cranium to protect the cortex from methyl methacrylate during the positioning process of the IPM. Second, the IPM remained exposed on the dorsal aspect, since the dermis could not be re-

approximated over the implant. Since non-human primates have significantly smaller skulls than humans as well as significantly thinner skin, we do not expect to leave the device exposed in the human implant condition, and in fact this would be unacceptable. Our neurosurgical colleagues strongly believe our device is subcutaneously implantable in human subjects. Methyl methacrylate was used to fill voids underneath the IPM from the extreme curvature of the skull to provide a flat solid platform for the device to rest on (similar to the shaving of the skull for the swine implant). Devices were tested in the operating room before and after implantation. While no (obvious) neural modulation could be seen immediately following device implantation, recordings of single unit activity we present in data collected just two hours post implantation as the animal was returned to its home cage for surgical recovery.

Both devices were implanted in the hand area of left primary motor cortex and have been fully functional for a combined total of over 180 days. These devices are each recording single unit activity on over 70 input channels; several inputs show multiple single unit activity. These numbers are comparable to anecdotally “good” implants of the standard Blackrock NeuroPort system in humans. For device charging, animals are sedated with a low dosage of Ketamine, removed from the cage and laid on a table for cleaning. The margins around the implant are cleaned once a week to maintain healthy tissue. A custom made acrylic (to reduce interference with the charging) “halo” attaches to the head-fixation posts on the monkey's head and allows for precise placement of the charging primary coil over the implanted unit. The IPM is generally charged at a current of 40mA (device-side) for 30 minutes, and then returned to its cage. Recordings are made while the animal is sedated with Ketamine, but also while waking up in the home cage. This transition of brain states, from sedated to awake, should be expressed in the data and we show some hints of that in the results of this thesis.

Implantation method adjustments for the IPM

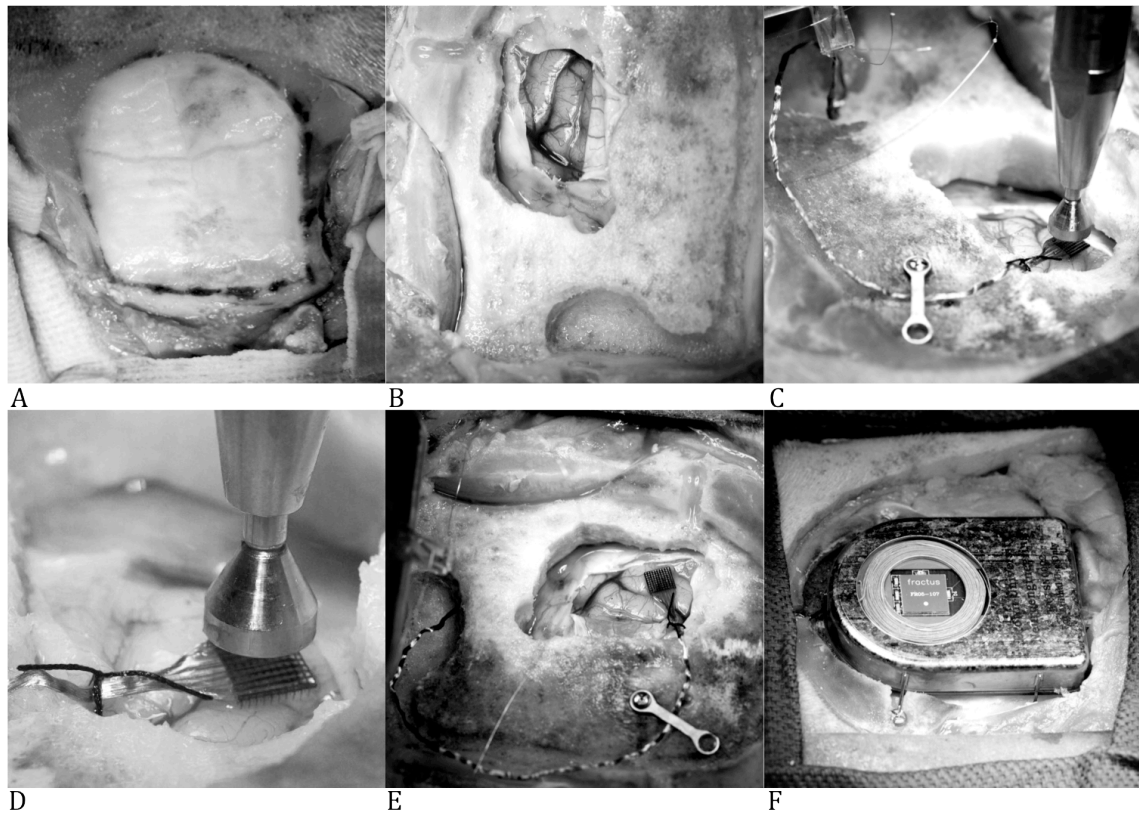


Figure 4-14: Internally powered microsystem implantation process in swine. A) Shave cranium to create a flat surface for the IPM to rest on when implanted. B) A top view of the cranium showing the craniotomy for array implantation and the durotomy above the primary somatosensory cortex. C) The array and wire bundle are placed and the pneumatic inserter is used to insert the electrode array through the pia mater and arachnoid and into the cortex (D). In (E) the array is inserted and the dura is being laid back on top and sutured closed. At this stage, reference wires are placed both on top of the dura and under the dura. The final step before closure of the skin is placing the titanium shell on top of the implantation site and securely fixing it in place with five titanium bone screws (Stryker).

One major challenge met in this experiment was showing that this system, as large as it is, could be chronically implanted under the skin. Our device implantation process in swine was modified from the EPM slightly to allow further refining of the cranium, making space for the titanium case housing the electronics in the IPM. The steps of this process can be seen in Figure 4-14. While the swine cranium is thick enough to allow this extent of cranioplasty, the non-

human primate skull is significantly thinner (5mm versus 15mm in swine). For non-human primates, as mentioned above, the system is left partially exposed and embedded in poly(methyl methacrylate) or PMMA, a biocompatible bone supplement used commonly in clinical craniomaxillofacial and orthopedic surgery.

4.4 Conclusion

In this chapter we have presented the implementation of a 100-ch fully implantable wireless neural recording system with inductive rechargeable battery and RF/IR data transfer for behavior neuroscientific research and brain disease treatment applications. This system leverages the microelectronic advancements described in detail in *Chapter 3* and builds on early successes of the Brown NeuroCard. The details of the internally powered microsystem architecture and circuit block diagram were presented and give a sense of the differences between the EPM and the IPM. Namely, the use of a rechargeable battery and long-range data telemetry in the IPM enable untethered neuroscience and long-term data collection. The full functionality of the device has been demonstrated via bench top measurements as well as in vivo experiments in two Yorkshire pigs and two rhesus macaque primates. Both neural spike and LFP signals were recorded from all animals in the study as devices were implanted for over 400 days and were fully functional during this time (Figure 6-12, Figure 6-16, and Figure 6-17). This represents a major milestone in both local (within Brown) implantable device development as well as more global potentials for advanced neuro-clinical care. Perhaps more importantly, we have fabricated and implanted the first highly sophisticated neural sensor with active electronics packaged in a human-compatible hermetic enclosure and shown efficacy as well as safety in four animals. This constitutes a significant step towards initiation of preclinical trials, which are planned for commencement shortly.

CHAPTER 5: Creating a powerful, wearable, and open neural signal processing platform: the BrainPhone

5.1 Introduction: The necessity for mobile computing to play an increasing role in patient care

Present neural data processing technology is impractical for daily patient use of a prosthetic. As an example, in the current BrainGate system (as in most all research neural signal acquisition systems), two desktop personal computers are used to process and store the neural data as well as to prepare signals for control of a prosthetic device (i.e. a cursor on a screen or a robotic arm). This significantly limits patient mobility and requires a technician for daily operation. In addition, nearly every other system that is employed in the clinic communicates on a different network, and requires a separate platform (PC or otherwise) to monitor and record the data. We see this as inefficient and impractical for long-term and mobile health care.

To address this issue, we assembled a team of neuroengineers, neuroscientists, and clinicians to develop an approach to data collection and processing that would advance our ability to deliver quality clinical care to persons with severe nervous system insult. The output of these initial meetings was a platform, the Embedded System for Prosthetic Application (ESPA), and a device, the BrainPhone, taking a modern hardware and systems approach for real-time signal processing and data collection. While this system was originally aimed at solving the intense processing demands of neural data collection and decoding, through the development process we came to realize that a more universal, or abstract, platform would allow data from all types of biosensors to be collected, processed, and distributed within one unified framework. The benefits of the latter approach are obvious within the context of a clinical care center where data must be integrated in order to deliver the most effective, and timely care. In addition, using one framework to collect many formats of patient-related data also simplifies outpatient care, though the use of our system in that context is outside of the scope of this thesis. The vision of the ESPA framework for clinical use can be seen in Figure 5-1, while a high-level block-diagram view of the data flow can be seen in Figure 5.

The goals of the ESPA project in regards to the deployment of wearable prosthetics are (i) to standardize the way we communicate with an effector, making it an open platform for prosthetic vendors to implement; (ii) to miniaturize all of the hardware and software necessary to perform such control tasks; (iii) to create of a common platform that allows for modularization in the design and utilization of the computational needs – promoting creation of an ecosystem for applications to access and harness the collected data to achieve specific research or clinical needs.

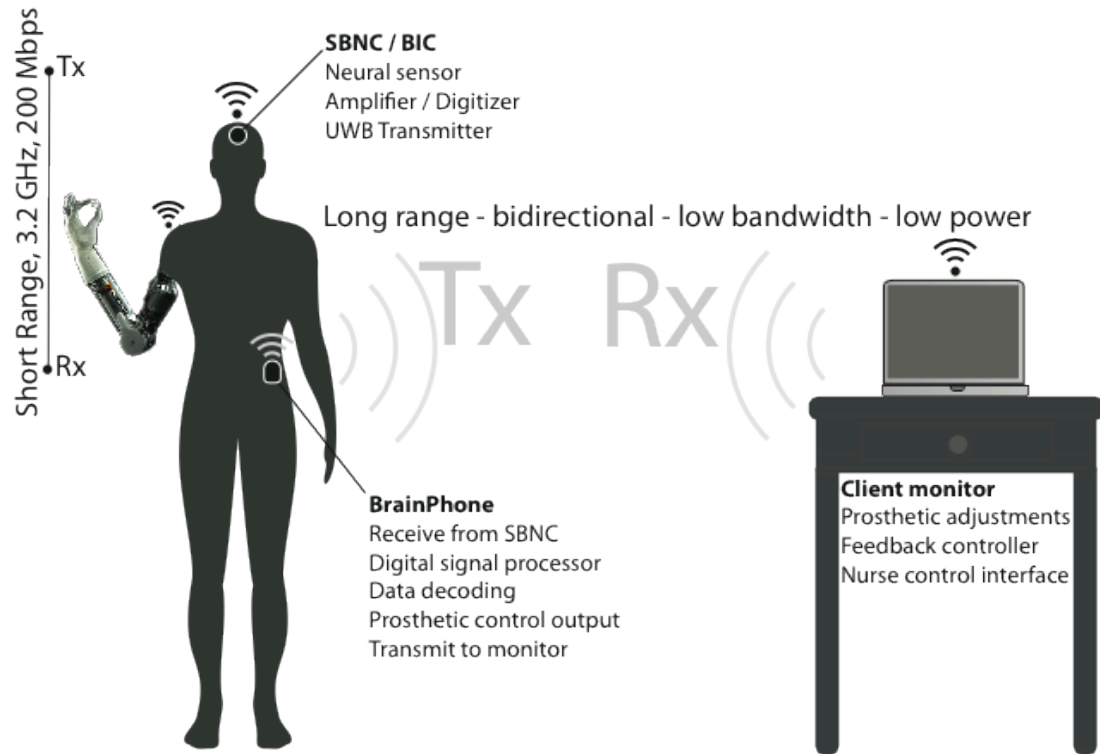


Figure 5-1: A vision of how the ESPA program can be implemented to receive data output from a neural interface, such as the EPM or IPM, process it, and output control signals to a prosthetic limb for an amputee. In the diagram, the SBNC/BIC designations are the IPM and EPM, respectively. The wearable BrainPhone can be seen at the waist of the human figure.

5.2 A look at the building blocks of the ESPA framework

5.2.1 Data flow

While the ESPA project's aim is directed more at a model than a device, we are still able to define hypotheses for expected outputs based on given inputs to the system. Generally, data processing of neural signals flows as follows: data is transmitted from a sensor (sensing); data is then processed by a digital signal processor (filtering); data is received by a computer (transferring); finally, data is compared with behavioral output (decoding) and the output is applied to an effector (control output). Whatever device is created to ESPA specification is meant to be a block that sits between the sensor and the effector, thus handling all filtering, data transferring, decoding, and ultimately providing effector-specific control output. Several

principles guide implementation of an ESPA system. Data preprocessing is common to all applications, whether for operating a computer cursor, a wheelchair, robotic arm, and others while the dynamics of each controller may be significantly divergent, i.e. when to provide feedback and where. The signals are first filtered and spike-like activity is tagged through thresholding and sorting. Lower bandwidth filtering will allow power spectral and other data to be computed from local field potentials (LFPs) and mid-band multi-unit activity. These additional signals are under investigation as part of other projects by our group and collaborators.

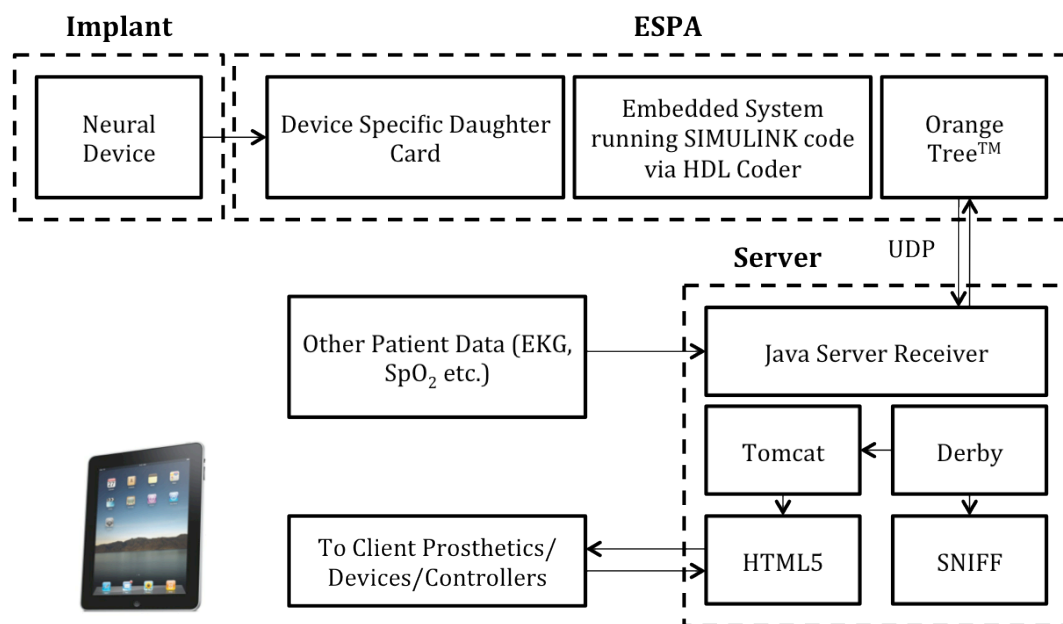


Figure 5: First generation implementation overview graphic of the embedded system for prosthetic application digital processing system. Data moves from the neural implant, such as the EPM or IPM described earlier, to the wearable device, label as ESPA above. After the data is processed for informational content, the data is passed over UDP to a backend server, labeled above as Server. Data can then be accesses by consumers, such as a clinicians tablet, a researchers PC, or other monitoring equipment.

The processed data and the raw data are then formatted and passed to control algorithms in a Standard Neural Interface File Format, SNIFF. SNIFF is a next-generation standard being developed at Brown for intercommunication between prosthetic devices and neural sensors;

SNIFR (Raw data) will allow for a much more efficient way of accessing neural data both during run-time by different components of the ESPA and off-line, while SNIFA (periodic and Asynchronous data) is much easier to access ad-hoc. The data can also be stored locally in the same SNIF format. We will discuss in further detail the database and access methods later in this chapter.

5.2.2 Filtering, decoding, and output of the system

The digital signal processing block of ESPA will carry out decoding processes that will include advances made by our colleagues in neuroscience (John Simeral, Wilson Trucculo, and others) in their work with tetraplegia human patients (Sung-Phil Kim, Simeral, Hochberg, Donoghue, & Black, 2008; Sung-Phil Kim et al., 2007; Sung-Phil Kim, Simeral, Hochberg, Donoghue, Friebs, & Black, 2011). ESPA performs filter building and adjustment, signal monitoring, and several related key housekeeping tasks in a second embedded processor. The microcontroller also sends commands to the computer and receives data on the state of the computer or effector. It uses this data along with information on the activity history of each neural channel as feedback to adjust the decoder. To the extent possible, communication to the assistive devices will be two-way wireless but clearly some devices may require cable connections. A large memory storage device (likely solid-state) under control of this housekeeping processor can store the neural data stream and device operation information locally for extended periods (up to 24 hours of raw data recording, ~256GB for a 24Mbit/s system data acquisition rate as currently used in the IPM, with the ability to stream out data via USB and TCP/IP to an external disk for longer recording times). As described above, the primary goal of the first implementation of an ESPA device is to make the user more mobile. In a similar way the goal of the first generation ESPA command-control-communication device is to extend that robust simplicity and portability to the prosthetic device interface. A block diagram of the first generation BrainPhone, implemented on an x86 laptop, can be seen in Figure 5-2.

5.3 A device implementation of ESPA: the BrainPhone

Our goal in designing and building this device is to close the electronic pathway from neural sensor (e.g. the Subacute Brown NeuroCard, the externally powered microsystem, and the internally powered microsystem) to the myriad human-controlled assistive technologies and clinical research goals (e.g. defining the focus of seizure onset in intractable epileptic patients) that such a system might play a significant role in controlling and data collection. By employing modern microsystem design paradigms, we can create a compact, externalized, and portable unit that receives wirelessly broadcasted data, performs the requisite neural signal filtering and decoding, and finally sends the all-important command and control signals to the patient's assistive technology (i.e. communication device, prosthetic limbs, etc.). This section will introduce the electronic configuration, the basic processor design, and most importantly, the computational model, currently built in SIMULINK (Mathworks). Using a combination of an FPGA (Field Programmable Gate Array) with other advanced, yet off-the-shelf microchip components gives us the unique combination of flexibility in data processing methodology and a low "cost" physical package; the combination allows both drastic reduction of power consumption and the ability to tailor the specific package for the specific patient. Description of the physical package and configuration is broken down into three phases to illustrate the pathway to the clinic-ready BrainPhone.

5.3.1 Phase I: The development of a self-contained real-time neural signal processing model on a standard PC

Digitized neural data is transmitted (wirelessly) to a PC running SIMULINK from existing neural recording devices (such as our in-house systems, and the commercial NeuroPort) over a UDP network. UDP is a powerful data transfer standard that supports throughputs approaching Gb/s and has been adopted throughout several industries. Since we build neural sensors with large bandwidths, we need to adopt a downstream pipeline that will be sufficient for

high-channel count (or multiple) devices. We use an OrangeTree™ UK network module (specifically, the ZestET1 card) to convert our neural sensors' serial datastream into a broadcast of UDP packets. The ZestET1 accepts serial input from the receiver. That is, data from the neural implant is currently transferred to the receiver, (e.g. BrainGate) through a percutaneous connection to a microelectrode array, or, as in our lab, through a wireless and transcutaneous link (e.g. EPM, or IPM), while also accepting other asynchronous event data, such as behavioral event timestamps or biological sensors such as temperature and intracranial pressure monitors.

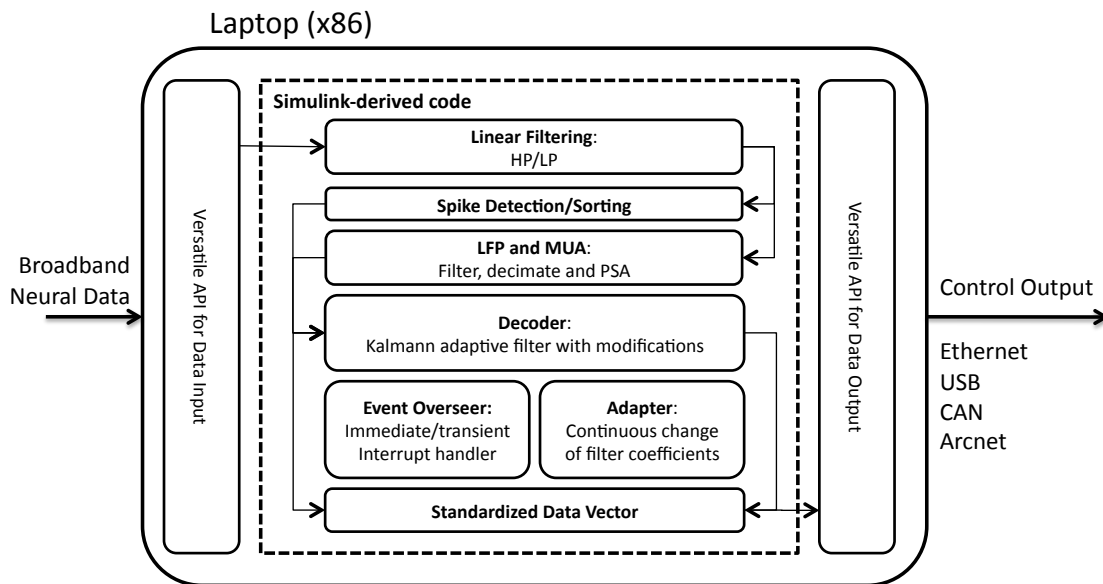


Figure 5-2: Block diagram of a x86-based laptop architecture running modular C-code blocks wrapped in Simulink s-functions to allow maximum portability both in parallel code development, data flow verification, and embedded system targeting. A versatile API would need to be created to interface with various prosthetics, beginning with point-and-click control, but expandable for any future control requirements. The Standardized Data Vector (SDV) will be the beginning of what will later mature into the Standard Neural Interface Format, allowing threads from anywhere in the system pull and access stored data

This system can sustain up to 200MBytes/s with latency of 6µsec, which translates into more than 4000 channels of broadband (.1Hz to 10kHz) neural data sampled at 20ksps, giving

plenty of room for the planned up-scaling and expansion of the IPM as well as including other multi-sensor systems into the datastream. Custom developed SIMULINK blocks, then filters, sorts and decodes the data in real-time on a powerful PC. Sorting and decoding methods used in this system are identical to those described earlier under data processing. However, the implementations used in the embedded system have been optimized for real-time operation and building to an FPGA, drastically reducing the size and increasing the speed.

5.3.2 Phase II: Building the model to an embedded system

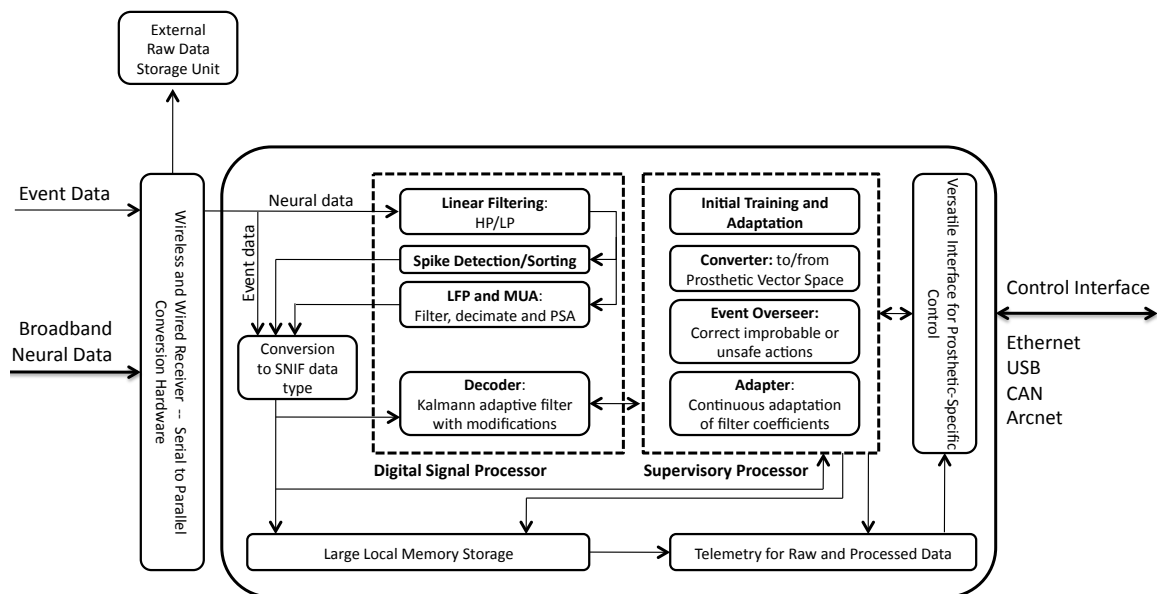


Figure 5-3: Data flow and detailed diagram of internal architecture of the Brain Phone hardware. Specifically, the digital signal processor handles the filtering, spike detection and sorting, slow potential changes, and decoding algorithms which the supervisory processor handles the oversight of the system. Data is converted into SNIF (Standard Neural Interface Format) files to allow ease of data flow and probing (sniffing) of data throughout the function of the system. Prosthetic-specific vector space conversion will be uploaded to the Versatile Interface for Prosthetic Control unit diagramed above.

While the previous phase has previously been completed, this and the following phase are an outline of what must be completed in order to make the device fall within geometric and clinical requirements. SIMULINK blocks will be built down to HDL (Hardware Description

Language) and deployed to an FPGA. Processed data from the FPGA will then be broadcast onto a UDP network through the use of the ZestET1 (as in Phase I). The bulk of the computational resources are based on the Spartan-6 FPGA (COTS) that have a speed of 140 GMACS (using symmetric FIR as benchmark). The benchmark to compare this basic embedded model with the traditional PC model will be one of speed of processing and power consumption. We strongly believe this will run much faster and with lower power consumption than standard PCs and is critical to building a wearable neural data processor.

Modules for filtering, spike detection, spike sorting, and arm velocity decoding as well as algorithms to generate control signals for a specific device (Dean Kamen / DARPA-funded DEKA prosthetic arm, Kinova commercial JACO arm, cursor control, and others) will be implemented in hardware. The entire data processing system, in addition to a basic wireless network infrastructure (for example, 802.11n) needed to control an arm will be implemented in hardware and assembled onto a PCB. As an example, in the case of the DEKA arm, a circuit to convert data packets containing control signals for transmission on a CAN-bus network (ISO standardized host-agnostic communication protocol originally developed for use in vehicles, now a standard in medical technology and used by DEKA) is required. This swappable circuit is what we refer to as a daughter-card to the BrainPhone. The entire system will be packaged into a wearable container, and will be tested as the data processing block for neural sensors already implanted in pig and NHP models. Finally, once bench top validations have been completed, the system will be used to record and process data in real-time from patients with epilepsy or other clinically appropriate patients. The use of the BrainPhone in this context completes the neural sensor-to-clinical patient pathway. A detailed view of the embedded processing occurring on the second phase BrainPhone can be seen in Figure 5-3.

5.3.3 Phase III: Packaging and external interfaces for clinical use

To begin translation of the ESPA BrainPhone into a hospital-ready device, the system must be packaged in such a way that is safe and convenient for use with a human patient. One major aspect is the use of battery technology for prolonged mobile operation – we aim for at least 8- hour capacity to coincide with clinical care-staff rotations. In addition, packaging must be easy to access and should be simple enough for the patient or nurse to change. We also will begin development on vendor-specific daughter-cards (described above as microelectronic circuits adding translation libraries to specific prosthetic interfaces), which attach physically to the wearable BrainPhone and will be constructed as a compact interface with a specific effector, such as a prosthetic arm. These cards would be responsible for both delivery and management of power as well as a data translation interface with the processing system. At this stage, the physical package of the BrainPhone consists of i) the main data processing board with FPGA and controller logic, ii) the daughter card for vendor-specific effector control, and iii) the exterior packaging with connectors to effector, a charging port, and access to battery for replacement. At this point, the hardware will be ready to start the validation process for human compatibility and safety.

5.4 The creation of an HTTPS accessible database for neural data storage and mining

While the BrainPhone handles data processing and prosthetic control, it also has the capability to buffer, packetize, and broadcast the neural and event data locally as well as remotely for later offline analysis using the wireless radio network. This data is collected by a “backend” system (server), which facilitates storage and access to the data and exists as a remotely located, secure, relational database. Data is streamed from the BrainPhone or other biosensor to the server over the UDP network. A protocol for quickly accessing this data is being developed by several students and will be made available to the prosthetics community when completed. This will allow other researchers to data mine securely and build data-enabled applications for

neuroscientific use, hopefully providing an ecosystem for the development of future device-specific control libraries and applications.

A diagram for the “backend” architecture is given here and is currently implemented on a single server PC and client tablet PC. The server runs an APACHE web server to handle HTTP requests from the client. A client is defined as any user (prosthetic device, researcher, clinician included) that requests non-real-time data (i.e. >100ms latency is acceptable). As a client makes a request, it is serviced by a JAVA server (TOMCAT) running behind APACHE to manage data extraction from the relational database and to render requests (a request is defined as a HTTPRequest, which has its own structure described in detail elsewhere) for display or otherwise. HTTP is a widely accepted standard for peer-to-peer communication and is supported by every PC / Tablet / Phone / etc. on the market today. We wanted to use this as our standard for communication in order to leverage the existing resources available for services like security, display, and transfer. Figure 5-1 shows how the backend server sits between the processed data coming from the BrainPhone (or other ESPA implementation) and the “consumers” or “clients” requesting data from the server.

In addition to high-speed neural data (~40MHz) and prosthetic control vectors (~50hz), patient data (~10hz) is available to care providers through HTML pages served over Secure HTTP from the “backend” server (available for consumption on any mobile device on the WPA2 secured wireless network). A care provider can access information regarding the status of an implant and the performance of the decoder, as well as update model parameters to perform fine adjustments to the decoding process. By interacting with the web interface, the care provider can send updated model parameters back into the “BrainPhone” through the backend over the UDP network. In addition to the data utilized for the neural-prosthetic system, the backend can be used as a "complete patient monitoring system", synchronizing data from other sources (e.g. EKG

machine, pulse oximeter, ICP monitor) with the time-stamped neural data to be stored in the database and accessed by the care provider over the same secure network system.

5.5 Preliminary tests of the Phase I BrainPhone

The phase I BrainPhone has been developed on a laptop PC running real-time SIMULINK models. This system was used to record and process raw data from an internally powered microsystem implanted in non-human primates. Data was collected over several weeks and an example of the processed data can be seen in Figure 5. It is difficult to appreciate the contribution of this system in the context of a paper. One should note that the processing here is occurring on a real-time system developed and designed to be embedded on a small, wearable device for truly untethered neuroscience and neuro-critical care. While this embedded, phase II device has not been created yet, our initial success makes us believe the transition will be relatively straightforward.

5.6 Conclusion

We have designed and begun to implement what we consider to be a forward thinking data processing cycle beginning with the generation of neural data and ending with intelligent outputs to control an effector. The first generation device accomplishing ESPA tasks such as data acquisition, signal filtering, linear regression of neural data against input control signals, and out prosthetic control vector generation, has been fabricated in the form of a x86 PC running SIMULINK. Our hope is that the open framework for prosthetic input/output control will encourage device developers to integrate libraries into the ESPA platform, expanding the horizons for patients with motor control damage. Finally, we have evaluated in preliminary study the data flow through the BrainPhone using the neural and event input from previously recorded data in non-human primates with the well-established NeuroPort recording platform.

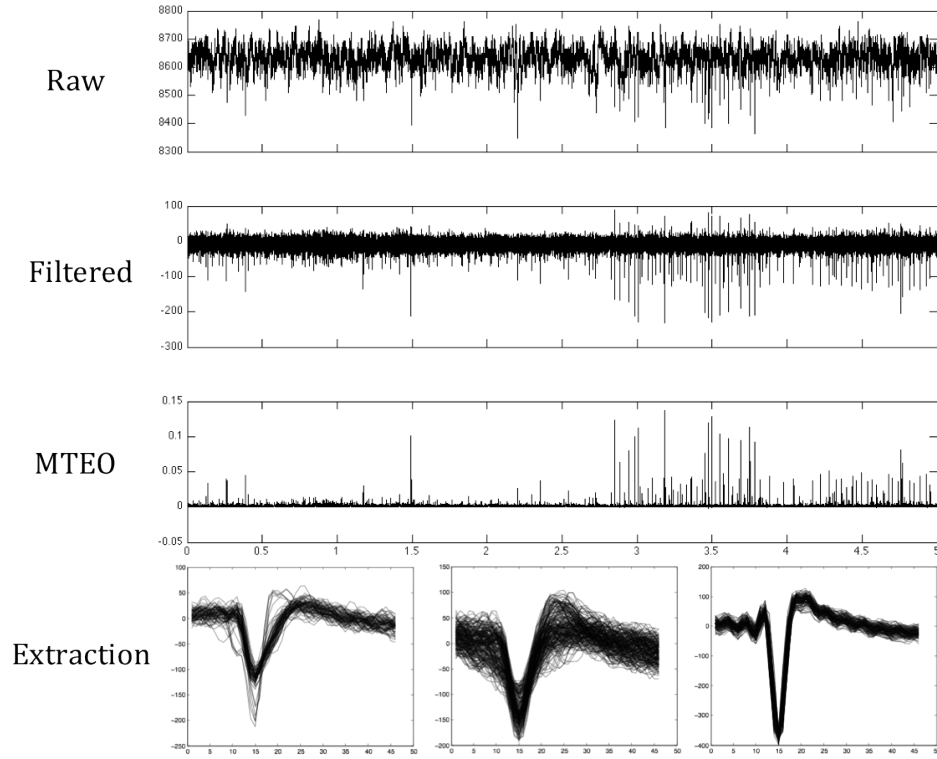


Figure 5: Data recorded from an IPM device implanted in non-human primate JR. Raw data (top) is filtered in real time with an FIR bandpass filter (second from top) then the multi-tail energy operator is applied to extract waveform peaks, and finally realigned (bottom).

CHAPTER 6: Results from implantable microsystems and discussion on their significance to future applications

6.1 Introduction

The previous chapters have described the advancements made in device engineering, design, and fabrication. This chapter focuses on the use of those devices for neuroscientific study. As we will show, our implantable neuroprostheses enable access to rich data in circumstances where a wired connection is unacceptable. These devices can be used for neuroscientific research as well as clinical diagnosis and even clinical care (e.g. neuromotor prostheses). Implications of the first fully implantable, wireless and broadband recordings in non-human primates are

discussed as they pave the way for neural recording of natural movements and potentially non-paraplegic outpatient use.

Each section of this chapter reports the significant results acquired during the respective study. All of the reported results build on the electronic and device development detailed in earlier chapters. Results from electrical diagnostics were reported in their individual chapter whereas below we report on the use of completed devices as tools for research.

6.2 Summary of advancements made in implantation and surgical design

(D. Borton et al., 2011)

Every biomedical device requires a unique combination of engineering and surgical prowess to be successfully used in vivo. We have consulted heavily with clinical surgeons to develop implantation protocols, including pre- and post-operative care to maximize the health of the subject, as well as the successful evaluation of our implantable microsystems. Skin incision patterns, craniotomy geometry, and dural closure methods have all been optimized to reduce irritation near the implant, tissue disruption, and pressure on cortical structures, respectively. We have optimized pneumatic insertion parameters through studies in rodents, bovine, swine, and non-human primates and the optimal insertion pressure is 25psi.

A new stereotactic frame was designed and fabricated to enable neuroprosthetic study in large farm animals, such as swine. We increased our in vivo device validation ability considerably by adding this animal model (and enabling frame) to this project. 11 pigs have been implanted with microsystems over the last two years alone (compared against 4 primates over 5 years). We hope the use of this animal is expanded to other universities and research groups – a topic discussed heavily in our recent publication (Y-K Song et al., 2009).

6.3 Recordings from the Brown NeuroCard with comparison to NeuroPort

(Y-K Song et al., 2009)

Implanting passive microelectrode arrays into nonhuman primates has become a relatively routine procedure. However, integrated constructs such as the one described here require a different set of surgical parameters to be “mastered” by neurosurgeons. One key issue is to ensure that microelectrodes reach their required target area and depth (the latter with sub-millimeter precision), while carrying the additional electronic payload and a mechanically distinct sensor-to-telemetric-unit interconnect. A practical approach to decouple the evaluation of microsystem electronic performance from surgical, anatomical and neurophysiological implant complications is to move the active electronics to an external platform and use input from existing implanted passive arrays. Such an approach has been adapted recently for neuroscientific studies in freely moving monkeys. We have pursued this strategy and developed a small printed circuit board (PCB) bearing all the active microelectronics. This PCB (3x3.7 cm) rigidly connects to a skull-mounted pedestal connector, and can be used in conjunction with standard passive implants in monkeys. The neural signals extracted from the board (by wire or wirelessly via IR) can then be directly compared in quality to those acquired from the same animal using a standard commercially available (rack-mounted) neural signal acquisition system. A snapshot of the multichannel recordings from a head restrained monkey is shown Figure 6-1. Comparison of the extracted spike waveforms acquired with the Brown NeuroCard to those collected with the commercial (and rack-mounted) Cerebus neural signal acquisition and processing system (NeuroPort), is shown in Figure 6 . Comparison of the signal-to-noise ratio of data acquired through the two systems shows similar performance. Figure 6-1 demonstrates the isolation of a single neural spike waveform with high temporal fidelity with either system. This in vivo monkey experiment validates our microsystem as a neural recording platform, since the completely implantable microsystem and NeuroCard test system are identical except for substrate materials.

NeuroPort vs. Brown NeuroCard (Abbott, M1)

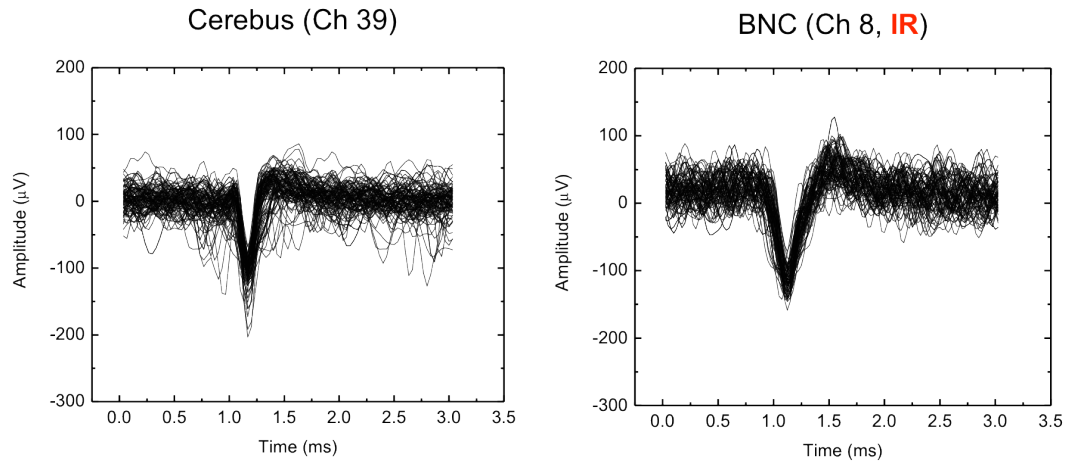


Figure 6-1: Neural recordings from monkey AB of the Brown NeuroCard and the Cerebus system. The Cerebus platform shows slightly lower noise values than the M4b ASIC on the BNC. Data was transmitted wirelessly in figure on right (IR).

NeuroPort vs. Brown NeuroCard (Costello, M1)

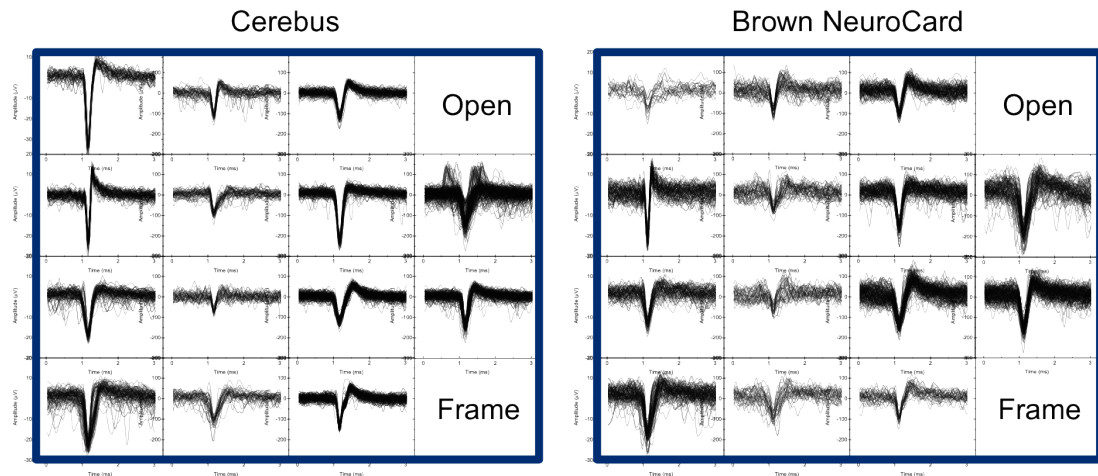


Figure 6: Neural recordings from monkey CS of the Brown NeuroCard and the Cerebus system. Implanted array and connectors are constant between data while (left) plots show data processed by the rack-mounted Cerebus amplifier and digital signal processors. The right plots show data collected by our custom M4b amplifier ASIC. All data was processed by the same offline spike extraction algorithms. Note, channel 1 (upper left) is a low firing rate neuron and did not fire during the BNC recordings (short duration).

6.4 Externally powered microsystem evaluated on benchtop and in primate

(D A Borton, Song, Patterson, Bull, Park, Laiwalla, Donoghue, & Nurmikko, 2009; David A Borton, Song, Patterson, Bull, Park, Laiwalla, Donoghue, & Nurmikko, 2009; William R Patterson, Bull, Borton, Nurmikko, Simeral, & Donoghue, 2008; Y. K. Song et al., 2008)

6.4.1 Component validation

We characterized the performance of a prototype 16-channel fully integrated system in benchtop tests (15 input channels and one channel overwritten with the synchronization signal in the controller). The unpopulated side of the substrate on the telemetric unit of the microsystem has an integrated six-turn metal strip spiral coil, with an outer diameter of 1cm, serving as an RF power receiver for inductive coupling. The RF frequency (the clock frequency) was 13.56 MHz, driven by a programmable RF signal generator through an external coil with dimensions matching the integrated coil. The multichannel amplifier outputs were multiplexed, digitized and converted into pulse code modulated (NRZ-PCM) infrared light pulses by the digital controller IC and VCSEL. Transcutaneously transmitted infrared (IR) pulses were received in free space by a silicon PIN photodiode (S6967, Hamamatsu Inc.), which converted the PCM light signal to a digital stream of electrical pulses for real-time reconstruction and storage. Signal acquisition and storage was done on an IBM-compatible PC through a custom digital interface board. The performance of one representative channel is shown in Figure 6-2a, where a bipolar transient voltage has been applied between a Ag/AgCl bath electrode and the reference electrode of a microsystem immersed in physiological saline. Clear bipolar spike waveforms are reconstructed from the PCM optical data stream. The waveforms acquired from the IR wireless system (Figure 6-2b) show identical gain to those from a wired system demonstrating the practical utility of the IR optical telemetry and RF inductive power delivery schemes.

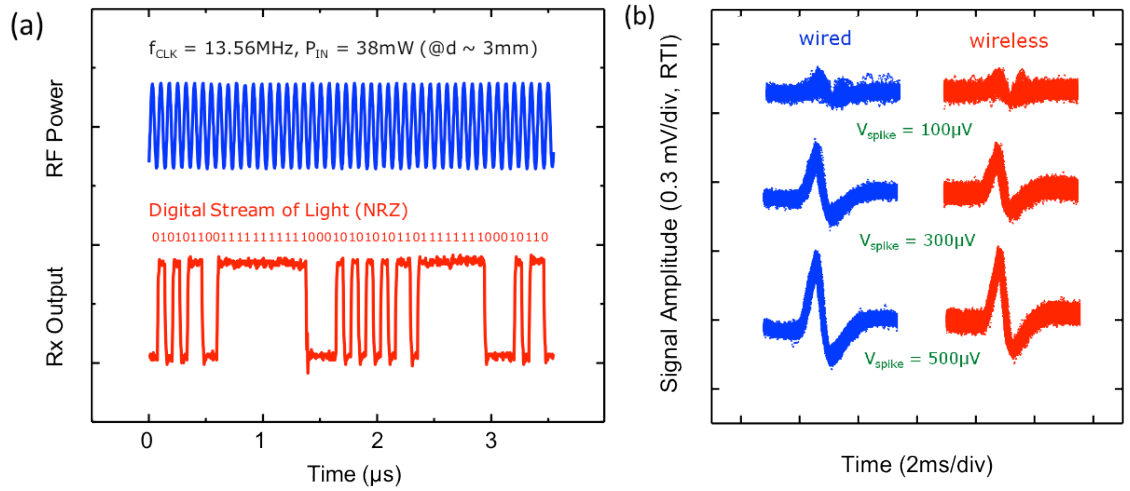


Figure 6-2: a) RF power sent into the extrinsically powered microsystem at a 13.56MHz clock rate (above) and optical data being received by the photodiode outside the system. For verification, electrical data output was recorded and processed in the same manner and from the same microsystem as the optical output (b). Data is identical, as expected.

We further validated the microsystem by running similar pseudospike measurements in acute rodent preparations. The experimental setup can be seen in Figure 6-5, where current injection was made through the reference wire implanted under the dura mater, far away from the MEA. The current ranged from $5\text{-}50\mu\text{A}$ and was injected in biphasic pulses to maintain charge balance. Pseudospike analysis is a simple measure of amplifier performance and can be taken, as shown, before, during, and after implantation of a device. Most devices have shown stable performance over time of implantation. When failure occurs, it general does so system wide, and not on particular input channels.

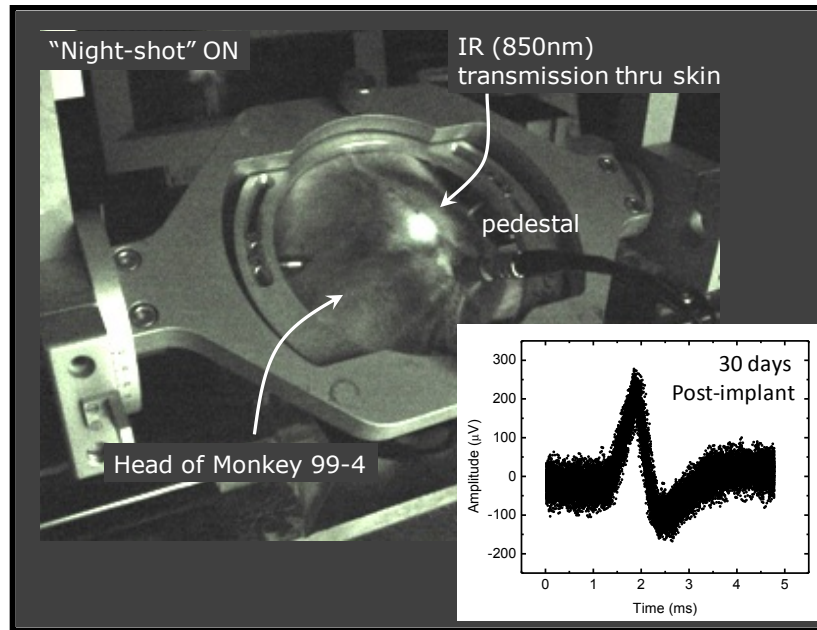


Figure 6-3: In vivo post-operative pseudospike injection during monkey training. This image was taken under “night shot” mode on the camera, filtering significant portion of non-IR light from view. VCSEL output can clearly be seen in the middle of the screen. Current was injected as described above and the resultant pseudospike data can be seen in the inset image 30 days post-implantation.

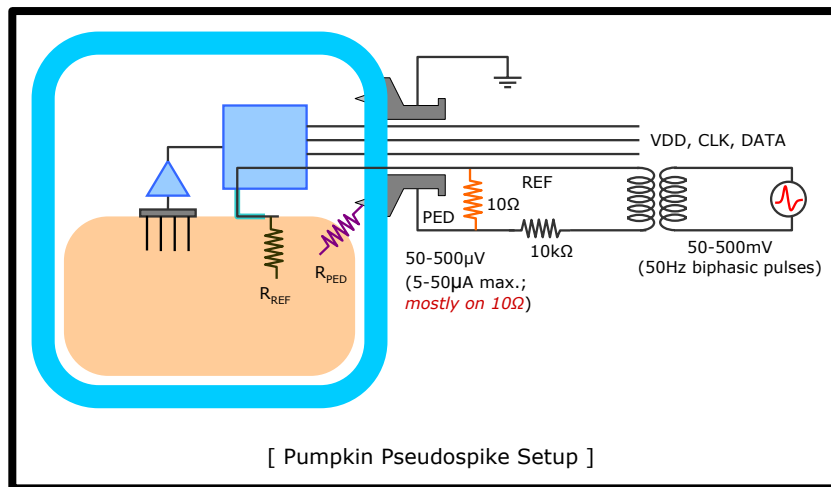


Figure 6-4: Pseudospike injection through reference wire into cortical tissue. Current returns through the amplifier inputs and is compared against output of the function generator. Blue represents the skin envelope and the tan color represents cortical tissue. An Agilent Arbitrary Waveform Generator was used with a 1000x attenuator to produce the $\sim 100\mu\text{V}$ signals needed.

Another important component to validate is the data telemetry. IR transparency of the skin is well known, but the detection limit of our system to collect consistent data was not known a priori. Thus, we made in vivo measurements of tissue transmittance in the IR wavelength (852nm). Transmittance is a percentage measurement of total power collected over total power output from the VCSEL. The “detection limit” is defined as the amount of transmittance needed to significantly differentiate binary 1’s from 0’s in the data stream. All measurements were made in non-human primate tissue during a implant surgery of a standard NeuroPort system. As it can be seen in Figure 6-5, the forceps-based measurement system was simple to use by clamping the tissue. All components were packaged in PDMS for electrical protection prior to use.

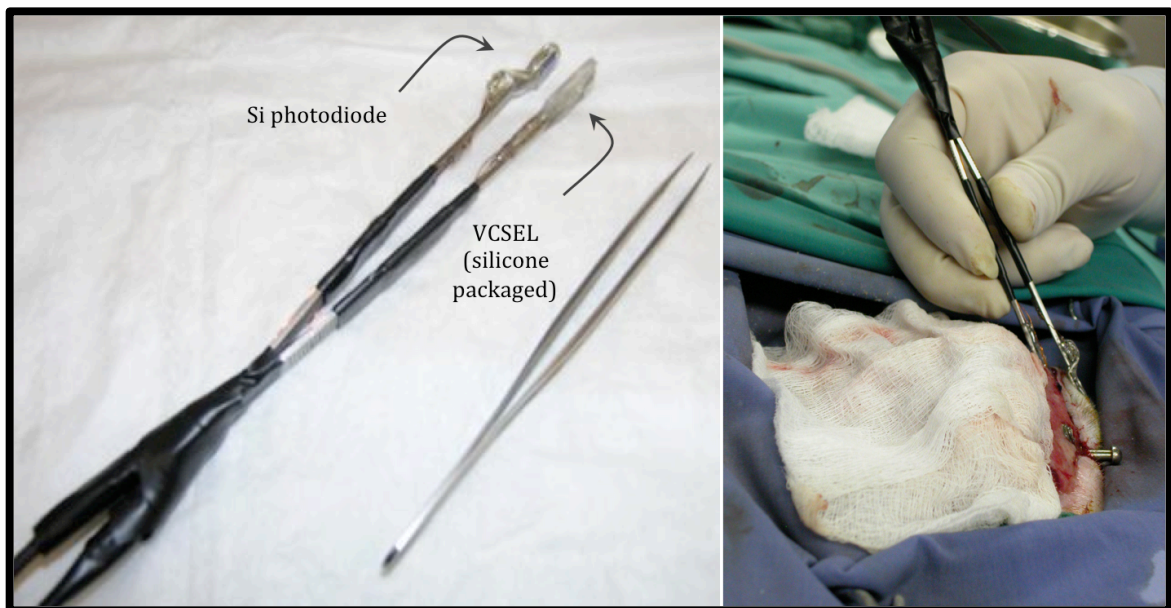


Figure 6-5: Forceps were outfitted with a VCSEL on one end and photodiode on the other to allow for easy, quick IR skin transmission measurements in a surgical setting. Measurements were taken from non-human primate dermis, muscle tissue, and fat tissue during an unrelated procedure.

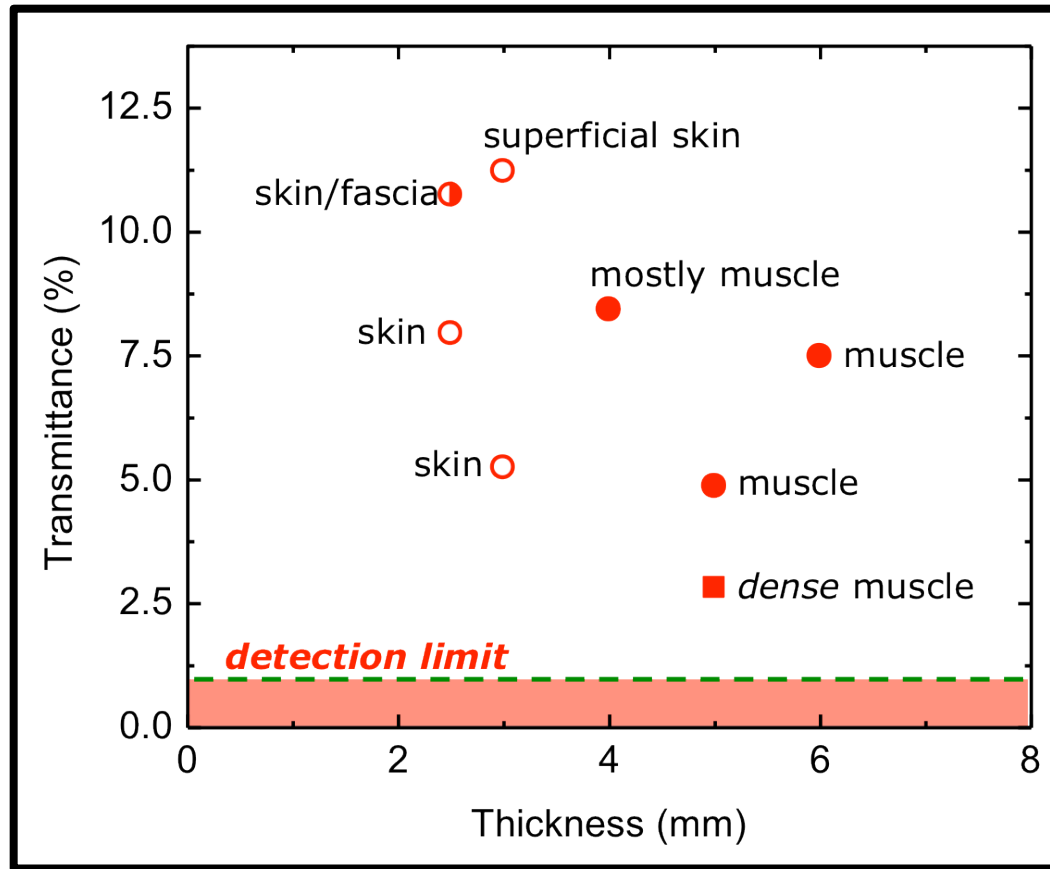


Figure 6-6: Results from applying the device shown in Figure 6-5 in vivo to measure IR transmittance. VCSEL transmission data from non-human primate in vivo experiments was collected through various tissue types.

6.4.2 Recording from a hybrid wired and wireless extrinsically powered microsystem in non-human primate

We implanted the hybrid (wired and wireless functionality) extrinsically powered microsystem into the right primary motor cortex of non-human primate SC. This device employed a percutaneous pedestal to safely deliver power and clock to the microsystem when operating in “wired” mode. Since only one wirebonding configuration could be made before packaging with PDMS (the choice of clock source was fixed), for wireless operation, the clock was delivered via a wire; however, power was still delivered wireless in this mode. The night vision camera shows the spot at which the IR laser beam exits through the skin. This implant also

includes an accompanying electrical feedthrough for in-situ comparison between the wireless (IR) and wired telemetry. The implant was placed in a monkey subchronically (for a period of ~30 days), and analyzed post-explant for functionality and performance. The top traces on Figure 6-7 show neural waveforms recorded on two channels of the microsystem. The extractability of these signals that verifies system functionality was maintained through the implantation process as well the handling during the actual implant surgery to record neural signals effectively. This durability is another initial indicator of the resilience of the packaging.

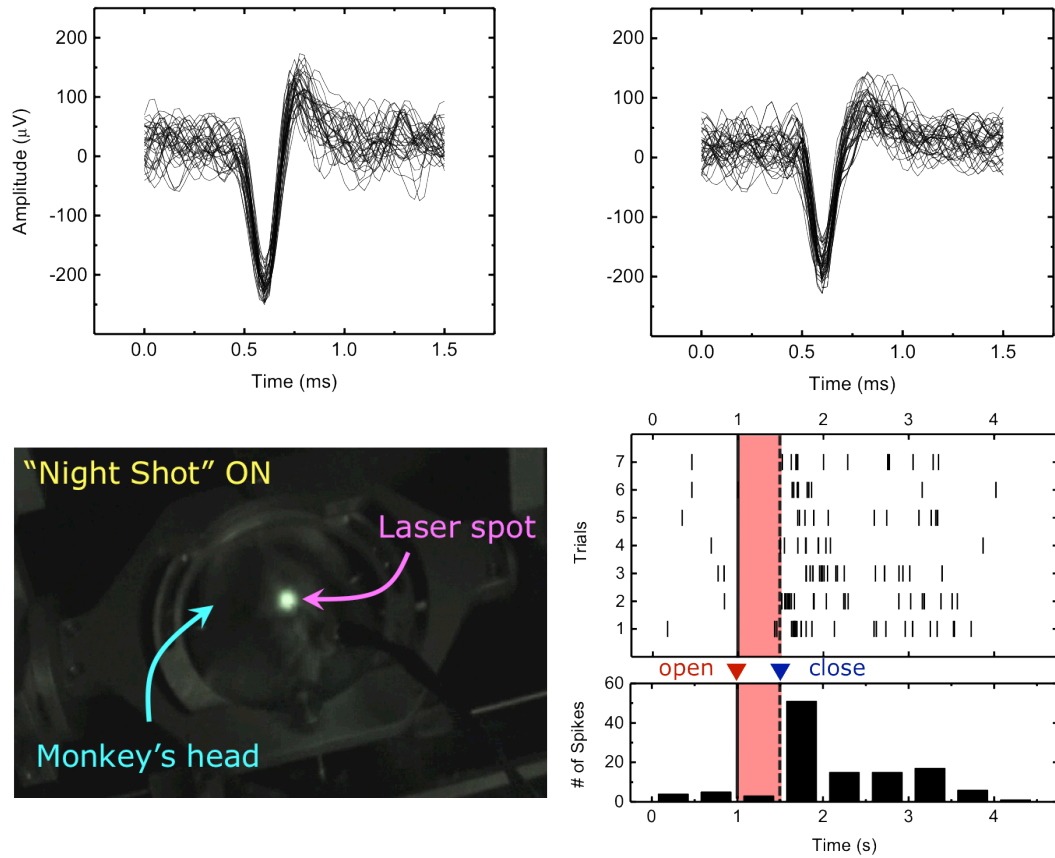


Figure 6-7: Wireless, fully implanted recordings from monkey LU. A) Monkey S, 7 days post implant 50 spikes superimposed Optical Data. B) Monkey S, 9 days post implant 50 spikes superimposed Electrical Data. C) “Night shot” image from camera showing primate SC with extrinsically powered implantable microsystem turned on and sending IR data out. D) Spike train data correlating hand aperture (open vs. closed) to neural signals.

The results in Figure 6-7 are significant for several reasons. First, it shows the first wirelessly transmitted action potentials recorded at full bandwidth from primate cortex of an implanted device (at the time). Second, the amplifier performance was proven sufficient to extract data from at least two channels in a 15-channel array. In addition, the infrared image showing the laser spot signifies that sufficient IR energy is transmitted from the microsystem through the skin of a primate (this was also shown in the experiments above). Lastly, the final image of Figure 6-7 shows correlation between left hand aperture and neural firing rate. This signifies that the microsystem can be used for neural decoding applications. The only setback of this experiment was that the microsystem was not technically wireless, even though it could be operated in a wireless mode; there was still a percutaneous connection for verifying data and power transmission. Our next experiments employed the first fully wireless implantable microsystem.

6.4.3 The first fully wireless externally powered microsystem implant and recordings

Leveraging on the success of our previous hybrid implantable system, we performed an implant in monkey LU with the first completely wireless microsystem. As described earlier, this implant is identical to the hybrid system with a different digital controller wirebonding pattern for clock to be extracted from the RF power input. The major significance of a fully implantable system can begin to be appreciated by looking at Figure 6-8. One should notice that the only protrusions from the skin are three standard head fixation posts of the animal. The system, only 2mm thick, is entirely below the skin with little to no disturbance of its natural shape as the system is incredibly thin, about 2mm thick. The implantation process is greatly simplified by removing percutaneous connections, which often require extra care during the operation to re-approximate the dermis. Recordings were made over a period of 30 days by bringing the wand close (~2mm) to the skin of the animal, immediately above the implant. Alignment of the VCSEL is much more difficult than alignment of the primary and secondary coils used for power telemetry. Thus, alignment of the coils (measured by power transfer efficiency) was used to find

the implant, and then fine adjustments were made to align the photodiode for maximized IR energy collection.

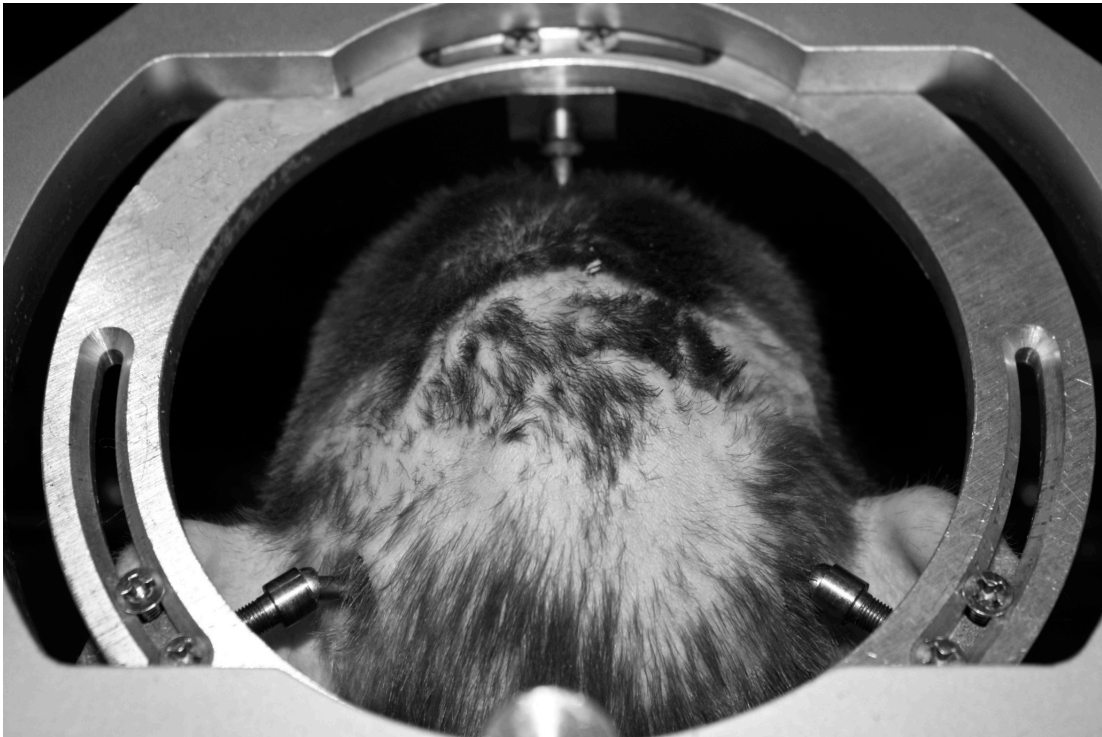


Figure 6-8: Monkey LU with a fully implanted extrinsically powered microsystem. No connection to the microsystem disturbs the protective skin barrier. In this image, the monkey is shown in head fixation while she performs a task on the computer screen in front. The microsystem is turned on and recorded from by the use of a “wand” that provides RF power at 13.56MHz and contains a light-pipe connected to a Si-photodiode for data collection. The wand is brought near the skin (about 2mm from surface). Generally, the monkey does not notice the presence of the wand.

While recordings were made for an extended period of time, few units could be isolated from the noise of the microsystem. A major contributor to the noise of this series of internally powered microsystems was identified in Chapter 4 as being the added resistive and capacitive load between the input of the amplifier and the metallization on the microelectrode array. This appeared to cause V_{pp} of nearly $110\mu V$, instead of the designed $\sim 50\mu V$. Below, in Figure 6-9, we show a series of bode plots accentuating the noise variability between systems, and even within one system. After further investigation on the topic, the source of the high levels of noise was identified poor connection between the amplifier and MEA, but only after the development of the

internally powered microsystem, which did not require direct integration of the amplifier to the back of the MEA. Instead, the system directly wirebonds the MEA to a PCB pad, likely breaking any built up oxide from the Ti/Pt inner layer (TiOx) on the array bonding sites. A comparison of the noise spectrum between systems with flip-chip integration (and the problematic intermetallic connection) is shown in Figure 6-9. Two EPM systems were re-evaluated for noise characteristics along with a recently implanted IPM. The major finding is an affirmation that noise levels across the spectrum are significantly higher in the EPM when compared to the IPM with the Big Pearl amplifier (Figure 6-9). As the parameter comparison table in Chapter 3 shows, the grounded input noise (RTI) values are similar between the M4b and Big Pearl amplifiers. Regardless, the significance of the fully implantable externally powered wireless microsystem being tested, successfully, in vivo still remains. The system was safely powered (measurements described and shown in Chapter 3), and data was extracted with consistency over infrared data telemetry. Well-behaving channels may have depended on the ‘fickle’ (i.e. variable strength, sometimes even disconnected) connection between the array and the amplifier, but over the numerous implantations performed, we did see single unit spiking activity. Our most successful EPM implantation was in a Yorkshire swine, P3. The implanted system exhibited spiking activity on five channels. These channels were consistently able to record action potentials over a period of >30 days. In fact, the study was only terminated because the bone growth of the pig has encased the implant, rendering the system unable to receive power. This data is shown in Figure 6-10.

While not described in this thesis, we have developed a “dual-frontend” microsystem, combining the data from two neural sensor units into one telemetric and power unit. Pre- and post-implantation images are shown in (Aceros et al., 2011) expressing the ability to perform dual implantations, side-by-side of the IPM. Two simultaneous implants have been used recently to explore coordinated activity between distant regions of cortex. Here, we implanted in the arm area of premotor dorsal and primary motor cortices. With data transfer pipelines of 1Gbps (VCSEL), there are few limitations to the number of neural sensor “front-ends” we can use. This

system has been described (Aceros et al., 2011) in rodents and is currently under development for pig and primate models.

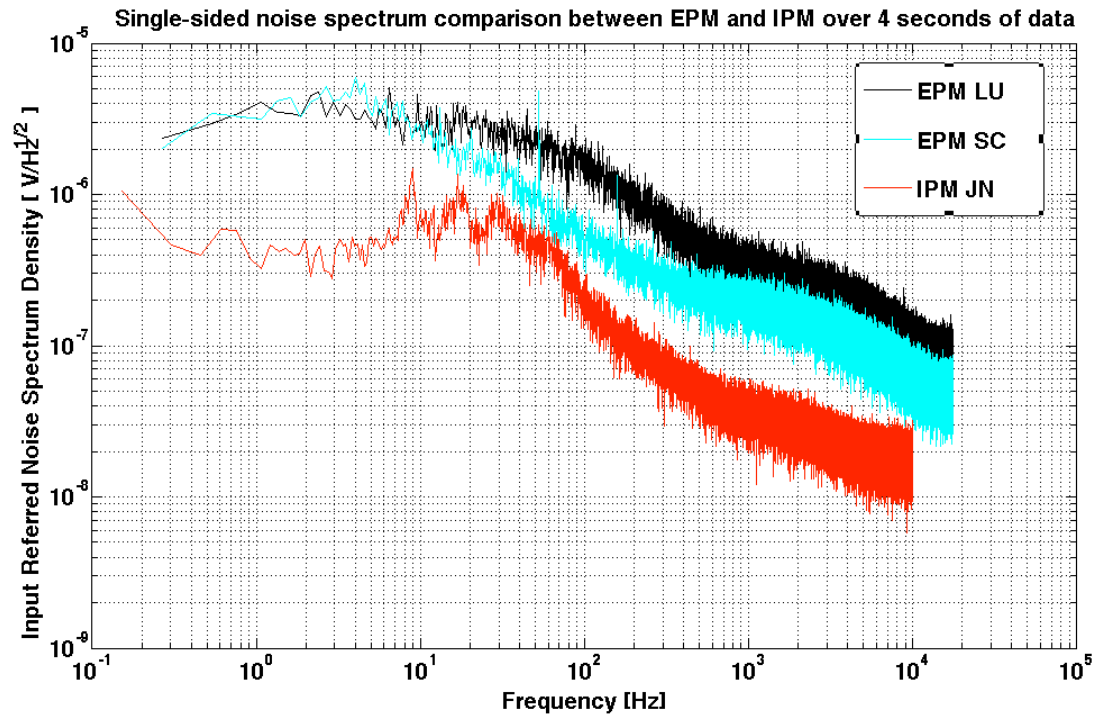


Figure 6-9: Single-sided noise spectrum comparisons between the externally powered microsystem implanted in two non-human primates and the internally powered microsystem implanted in non-human primate. The amplifiers, though slightly different on the three systems (EPMs use the M4b amplifier while the IPM uses the Big Pearl), the noise characteristics are very similar (see Chapter 3).

Biocompatibility of the EPM was evaluated by visual inspection and by no means represents how the device may react in all subjects. However, in 8 implantations in swine we saw no increase in infection rate and every explant showed healthy tissue around the implant. Generally, a thin fibrous film was present, encapsulating the device, as we would expect to be formed around a foreign material. It may help to investigate different potential coatings to apply for enhanced biostability, further reducing the reaction of the body.

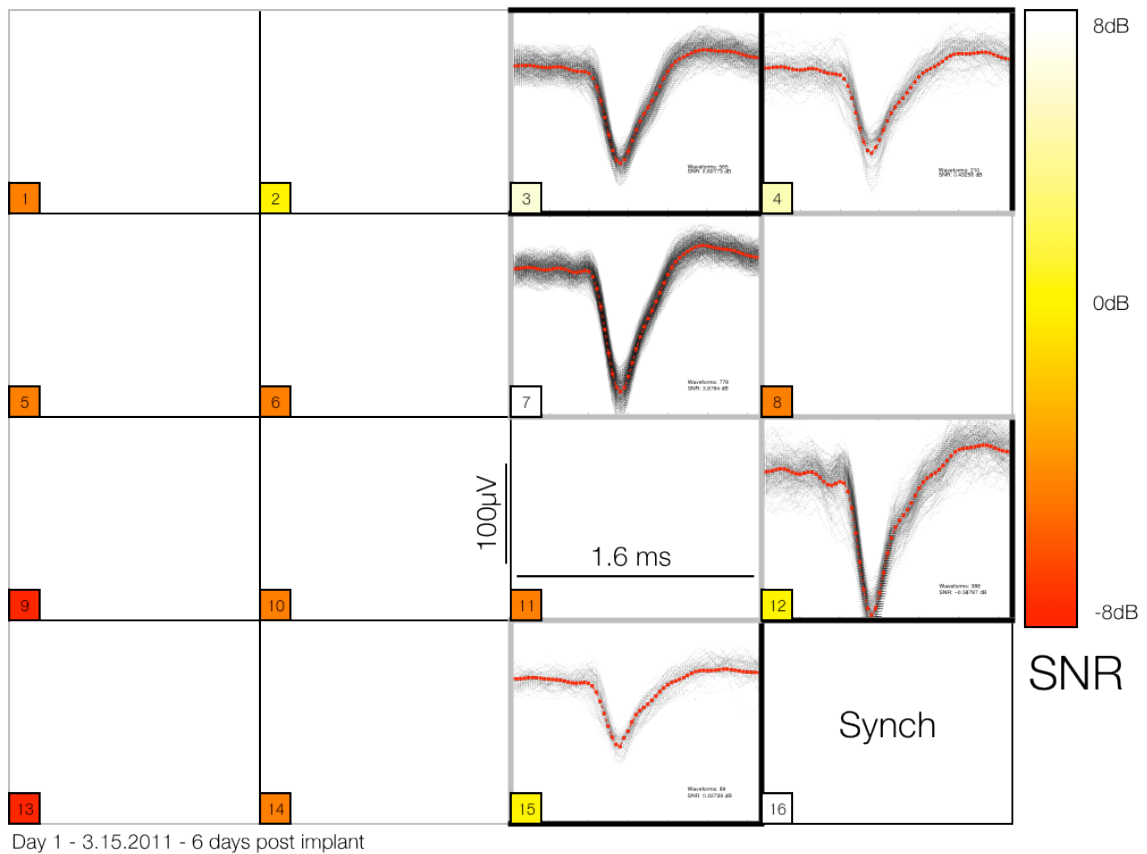


Figure 6-10: Recordings from pig P3 six days after implantation. These recordings were made completely wirelessly, as described in detail in Chapter 3. Signal to noise ratios were near 8dB on some channels. All channels not showing a spike exhibited high noise levels.

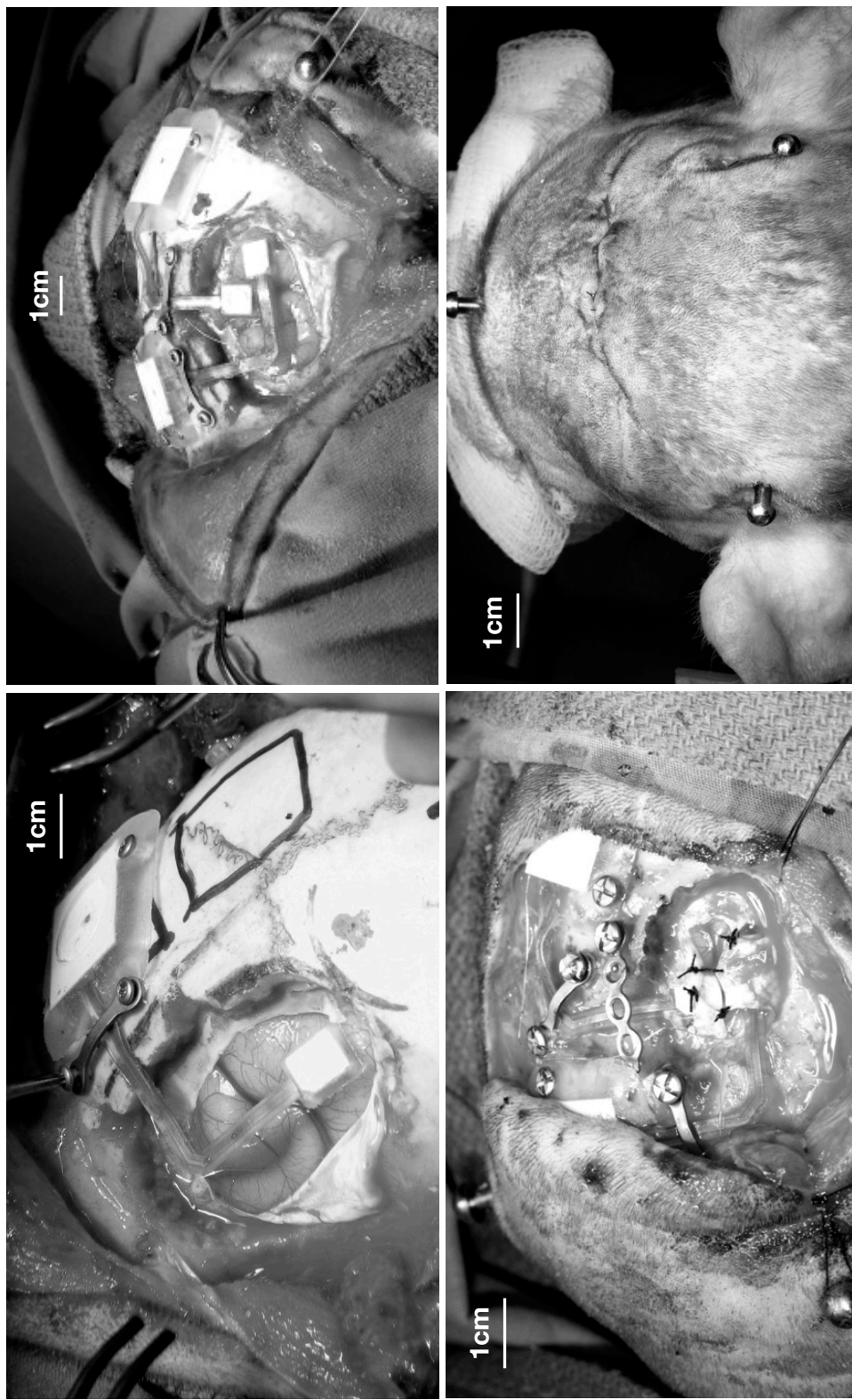


Figure 6-11: Implantation of four externally powered, wireless, neural interface microsystems in non-human primate. Dual implantations were performed successfully and post implantation (bottom-right), the subject can be sutured closed with no protrusions (here 3 titanium posts remain for head fixation).

6.5 Internally powered microsystem evaluated in vivo

(Borton, D. et al., Nature Neuroscience, in preparation; Yin, M., Borton, D. et al., ISSCC, in press)

The data presented in this section represents a culmination of lessons learned from the development of the EPM, collaboration with commercial partners, and innovative engineering from within our labs. Since the device designs are heavily based on the EPM, it was incredibly fulfilling to see the success of the IPM as homage to the EPM. The internally powered microsystem (described in Chapter 4) was targeted for monitoring brain activity of patients with intractable forms of epilepsy. However, progress towards that goal is described in this thesis and focuses on the validation of such devices in pig and non-human primate experimental models. We have previously detailed the microsystems themselves. This section will be focused further on the neural recordings made with the internally powered microsystem and some discussion on the connection both to epileptic research, as well as neuromotor prostheses.

6.5.1 Internally powered microsystem recordings in Yorkshire pig

The full functionality of the entire wireless neural recording system has been validated first on the bench and then in vivo in two adult awake Yorkshire pigs over a period of two months (the study was continued for one animal for over 7 months). During recording sessions, the systems were successfully recharged and powered up and channels show consistent input referred noise level of $\sim 9\mu V_{rms}$ (aligned with the expected values from simulation of the Big Pearl ASIC). The neural spikes extracted from 10 seconds sample of recorded data are shown in Figure 6-12. A majority of channels show clear neural spikes with amplitudes range from 60-160 μV_{pp} . LFPs were also extracted from the data as they are increasingly used in neuroscientific research. Figure 6-12 shows a detailed view of extracted spikes and LFPs on 4 channels (out of the 48 channels that carry clear neural spikes) from the same 10 seconds data.

Temperature increase has been observed and is due to charging (eddy currents in Ti-can) is obviously a major concern. We observed noticeable rises in skin temperature (qualitatively measured by touch) and applied active cooling for all animals. The FDA mandates that a device must meet the ISO 14708-1:2000 E standard requiring no outer surface of a device rise more than 2C° above body temperature (37C°). We have performed FEM modeling and in vivo measurements to characterize heat generation and optimizations have been implemented in the RF power link to reduce heating (see Chapter 4).

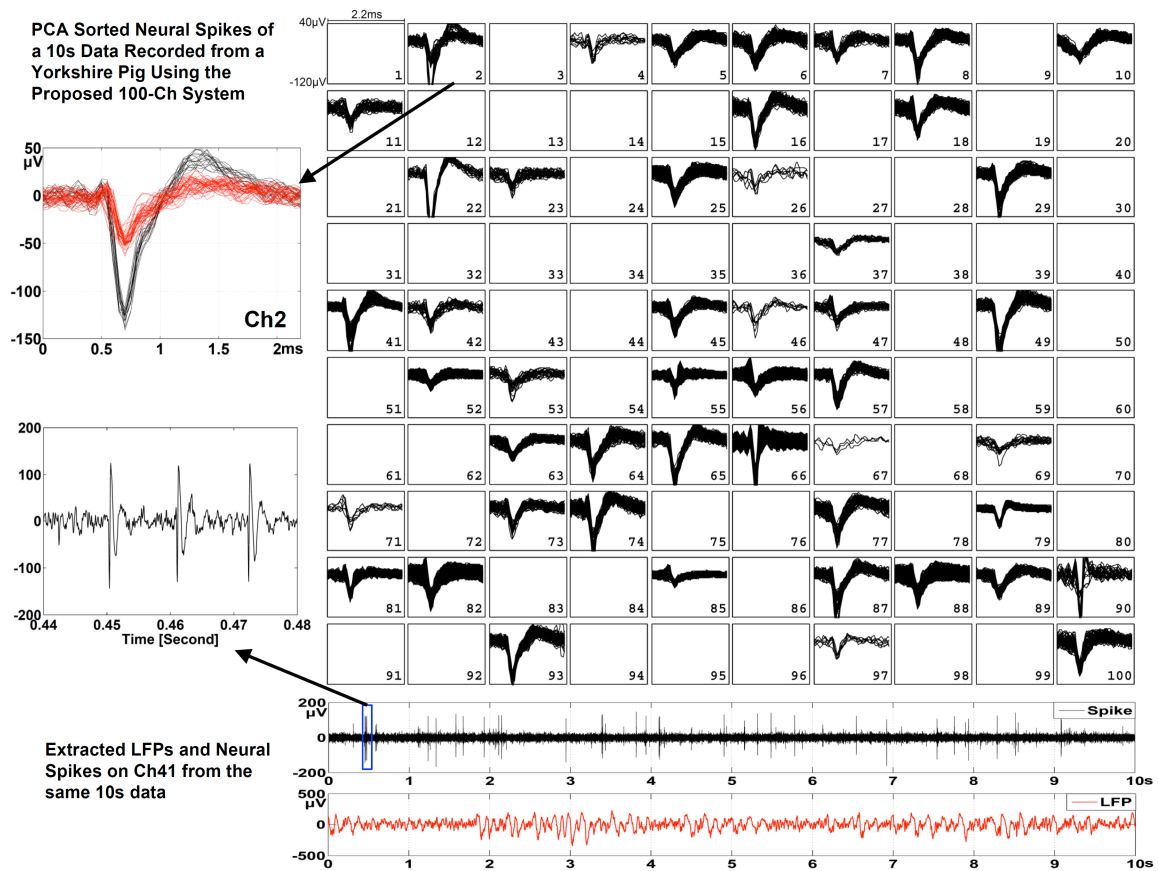


Figure 6-12: Neural recordings from awake Yorkshire pig using the 100-channel fully implanted wireless neural recording system. Recordings were made from a roughly 0.5m distance. Spiking activity can be seen on 44/100 channels, including multiple single unit activity and low frequency potential changes. Individual spiking neurons can be seen overlaid in the large window, which field potentials are shown in red on the bottom trace. Insets (left) show more detail of the individual waveforms and multiple units recorded from a single microelectrode.

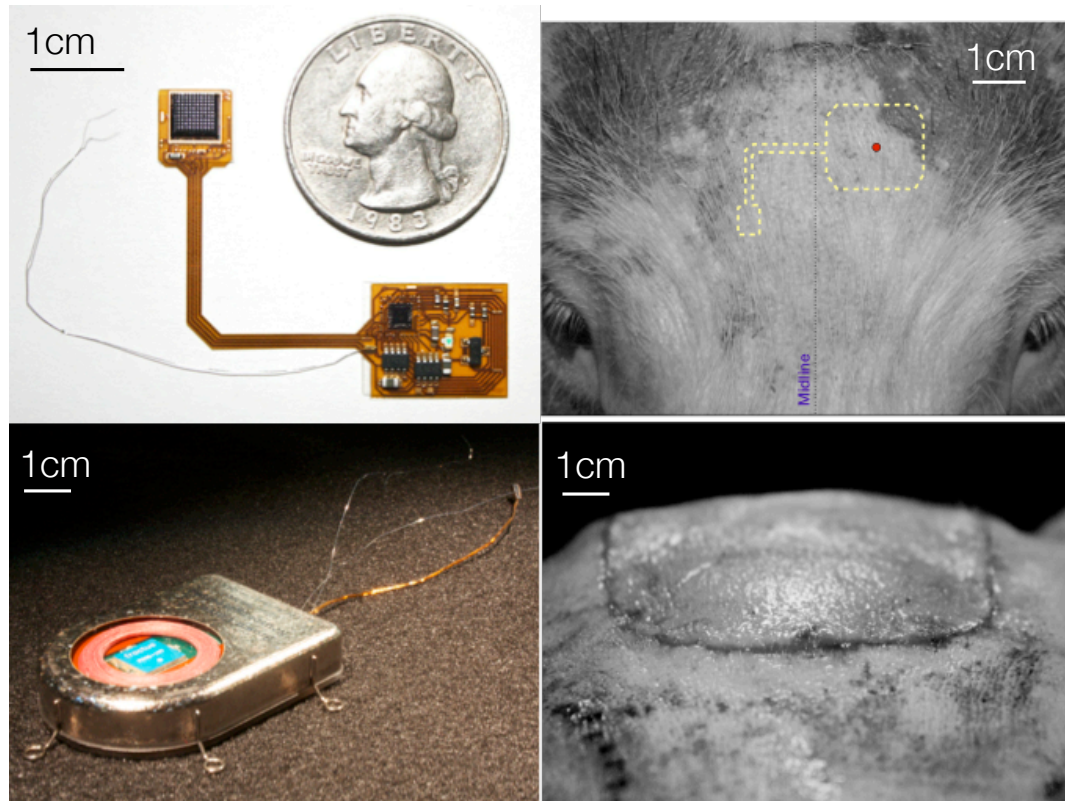


Figure 6-13: An externally powered (top-left) and internally powered (bottom-left) microsystem before implant into a swine (top-left) for long-term in vivo study. These devices share common electronic payload but have taken on significantly different form-factors to accommodate the internalized power supply and titanium packaging. The animals showed no signs of irritation or discomfort from either implant and were implanted for >5 months.

The first implanted pig, S2, developed a benign pocket of fluid likely due to surrounding tissue damage during the highly experimental surgery that required a large degree of cranioplasty. This procedure was much refined in the next case, S3, who has been implanted for over 7 months without adverse reaction. S2 was euthanized after 38 days. Euthanasia actually provided us with a unique opportunity to characterize the process of cortical network death. Thus, we made continuous cortical recordings before, during, and after injection of Beuthanasia-D (Figure 6-14). There was a clear drop in both spiking activity and low frequency power just 15 seconds after intravenous infusion of the agent. Frequency analysis of the noise was computed before and after injection showing a drastic reduction in overall power. While these are perhaps expected and

obvious statements, they allow us to differentiate what noise components are neural noise and what are not. Strangely, a neuron can be seen returning an active state after a period of quiescence (Figure 6-14-left), perhaps pointing to a more heterogeneous shutdown of the local cortical network. For reference, a swine with a completely implanted EPM (top) and IPM (bottom) are shown in Figure 6-13.

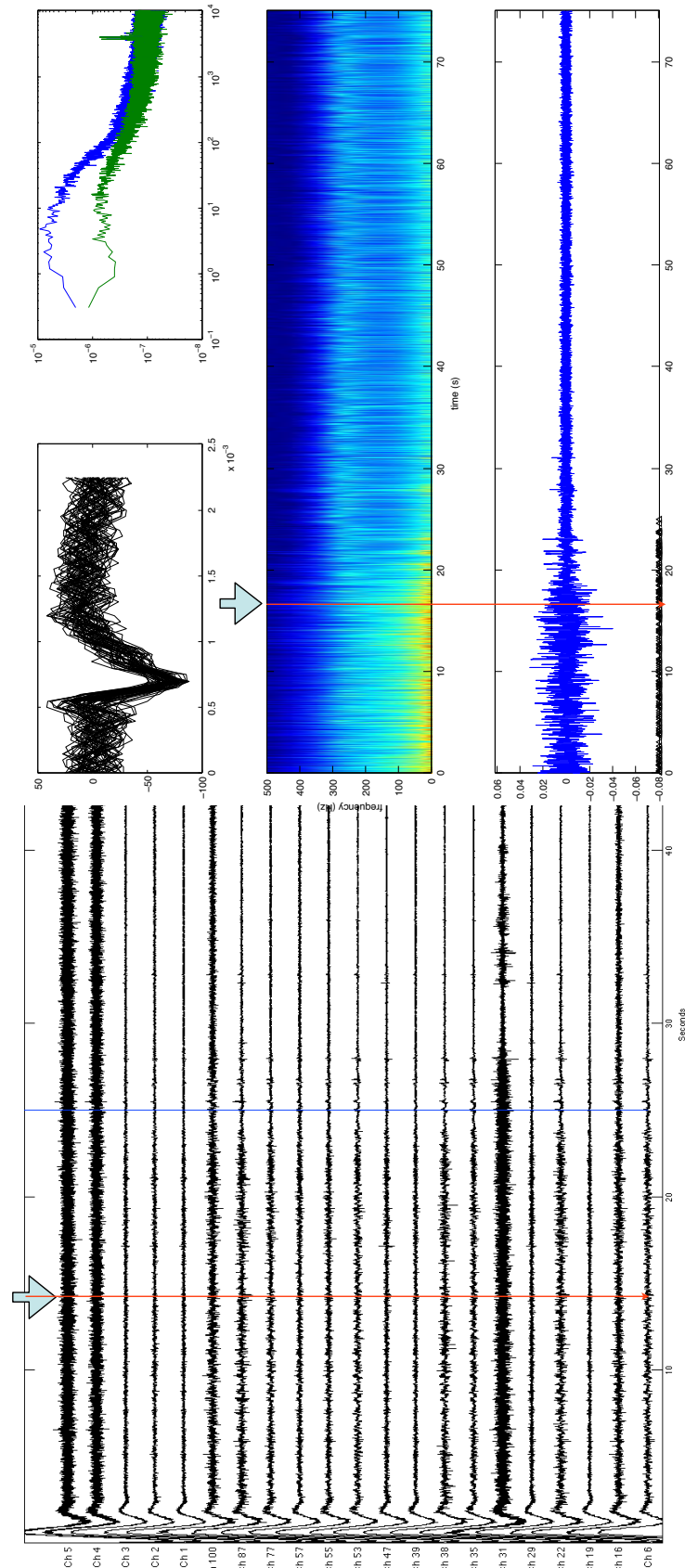


Figure 6-14: Cortical (primary somatosensory area, rostrum) recordings made during the euthanasia by intravenous injection of Beuthanasia-D. Heterogeneity can be seen in the neural activity (left), and even spurious activity of a singular neuron after a period of quiescence. Extracted spikes are shown (right-top) to indicate healthy neural activity before the injection. In addition, noise plots (blue) and after (green) also show obvious shutdown of the brain post-mortem. Spectrogram analysis shows a more gradual decrease in cortical activity, presumably as the network shuts down.

6.5.2 Internally powered microsystem recordings in non-human primates

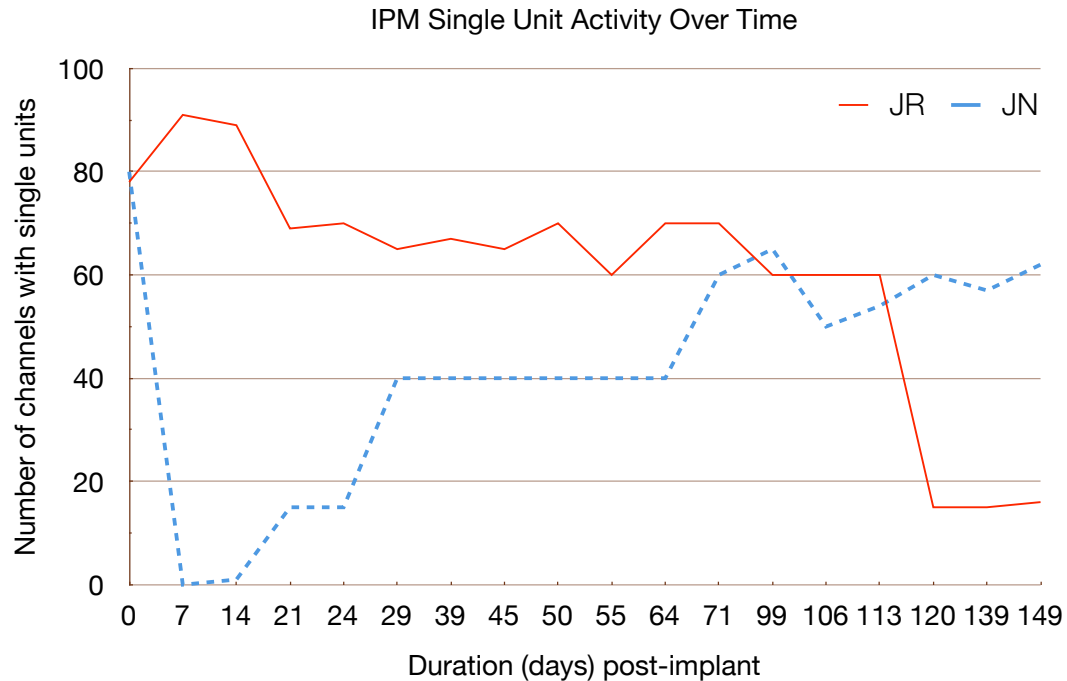


Figure 6-15: Single unit activity count (# of channels showing spiking activity, multiple single units on a single channel are not considered) over time. Monkey JR has shown significant drop over time, while the IPM implanted in JN has shown increase in single unit activity. Both systems record low frequency modulation, which may point to gliosis around the electrodes of monkey JR.

Figure 6-15 describes one of the capstone achievements of this project: a fully wireless, broadband neural recording platform implanted in non-human primates for extended, even chronic, duration and recording a significant amount of spiking activity, clearly translatable for neuroscientific use. It is interesting to note that the implant in monkey JN was able to record up to 80 single units the day of implantation. In fact, we were able to record during the surgery, which is extremely complicated with a tethered device. We note that during the implantation and immediately (<1hour) after, there were no discernable spiking units. However, between 2 and 3 hours post implantation we began to see reactivation of the cortex and a large number of spiking units. It is unknown why the unit count dropped in monkey JN over the days immediately

following the implantation. Our working hypothesis is that JN had a high-acceleration event (e.g. head impact onto the wall during recovery from surgery), which perhaps caused some local swelling and accumulation of micro/macro glial cells. The fact that after 2-3 weeks the recordings returned to normal is inline with this hypothesis as the immune system of the body concludes its response in roughly the same timeframe. Below are two figures showing average waveforms for every channel on both monkeys IPMs Figure 6-16 and Figure 6-17.

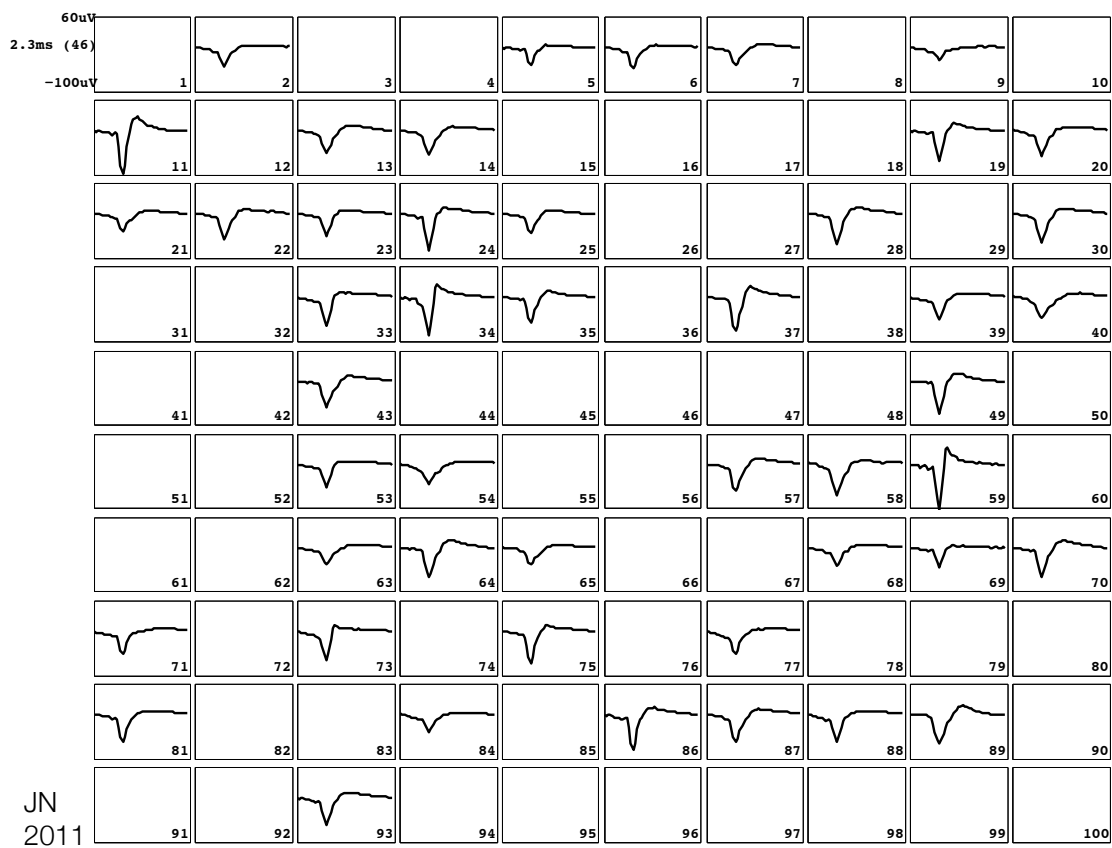


Figure 6-16: Average waveforms extracted from the broadband wirelessly transmitted data from the IPM in monkey JN. Each element of the grid represents recordings from one electrode and the representative average waveform extracted on that channel. 3.2 milliseconds of each waveform are shown.

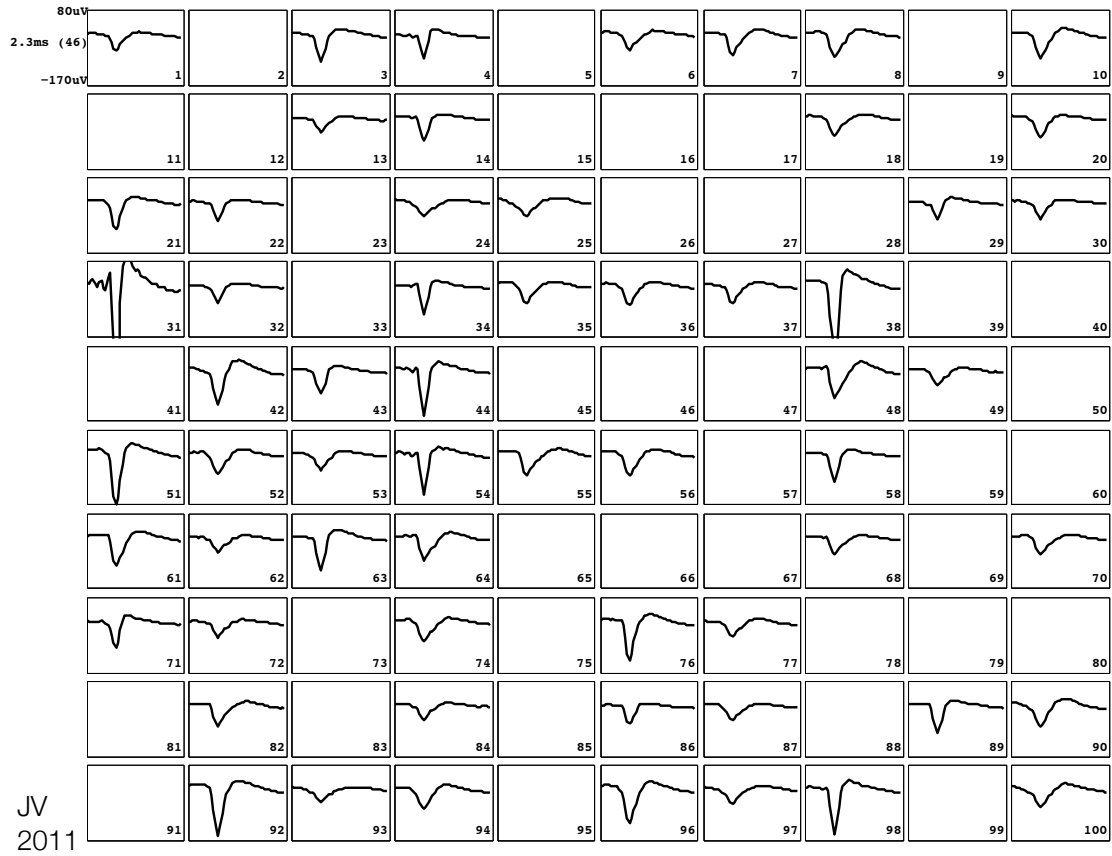


Figure 6-17: Average waveform extracted from the broadband wirelessly transmitted data from the IPM in monkey JR. This particular microsystem exhibits a very slow turn-on time for many of the amplifier on the amplifier / MUX ASIC. Often we must wait twenty minutes after charging the system to recover all channels.

6.5.3 Explorations with neural trajectories and discussion on the definition of dynamic brain states

Thus far we have limited our discussion and display of results to technical achievements: low-power, wireless microsystems were implanted and successfully transmitted broadband neural data to a receiver. We will now discuss the content of the transmitted data, techniques for interpretation, and some preliminary insights into the use of the IPM (or EPM) in detection of anesthetic states.

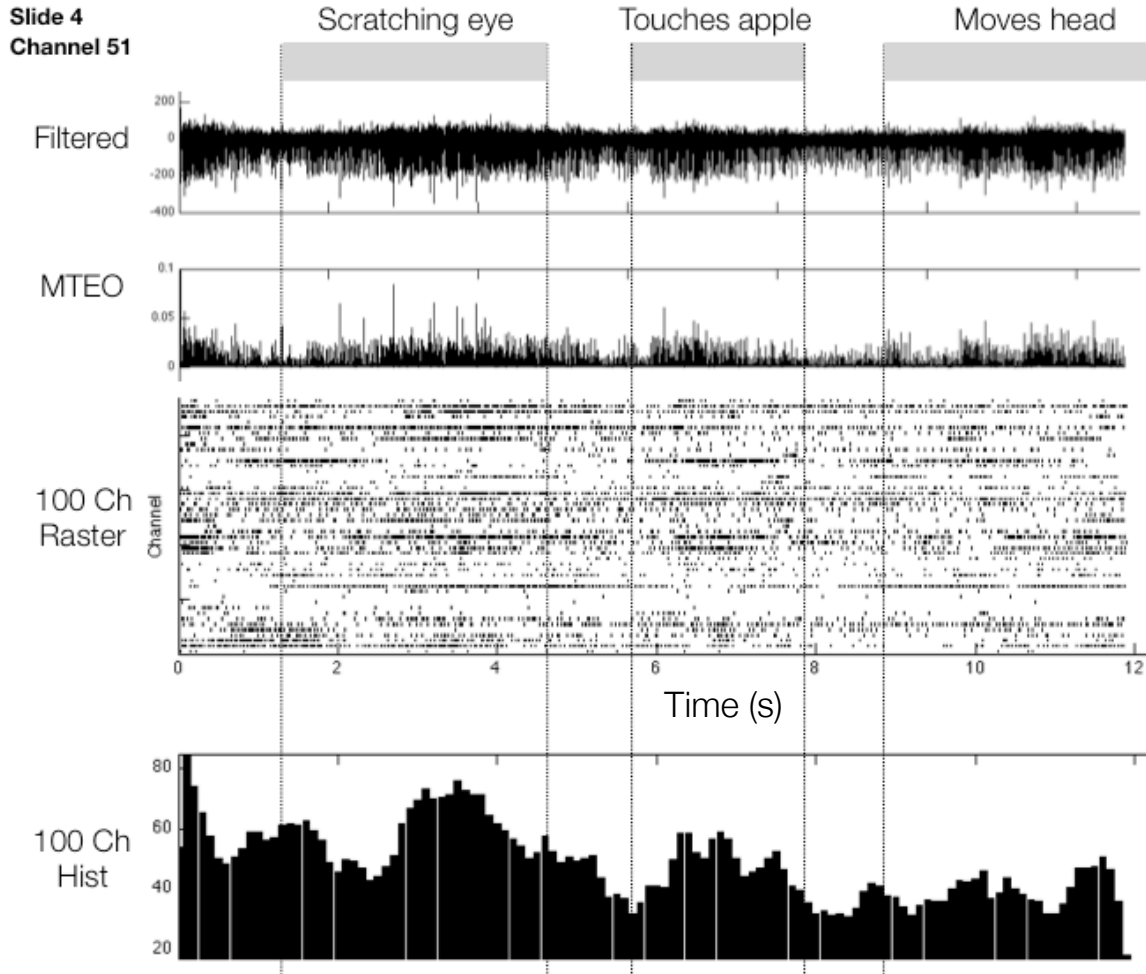


Figure 6-18: Spike filtered data (top) on a single channel of the IPM during freely moving events. Raster plots and histograms show population activity. The single unit activity shows clear correlation to movement of the arm during the events shaded above.

The IPM in both monkeys was implanted into the hand and arm areas of the primary motor cortex. Thus, we expect most of our data to be related to arm and hand movement. As shown in (A. Afshar, Santhanam, et al., 2011; Churchland et al., 2010; Santhanam, Yu, Gilja, Ryu, Afshar, Sahani, & Shenoy, 2009; Yu et al., 2009), we do see many individual units that are specifically turned to fire during motor command execution. The data presented in this figure was recorded not while the animal was performing a well-trained task, but rather while performing a completely natural behavior in its home cage. The untethered aspect of this recording system opens many avenues for research, including beginning to address the question of how well over-

trained behavior represents natural movement. Our monkeys have not been trained for a dexterous task and thus averaging over multiple iterations of repeated movements to observe true tuning curves of each neuron is out of the realm of possibility. Instead, we turned to a single trial-based analysis method. In this method, a high-dimensional space (100 individual input channels in our case) is reduced to 2 – 3 dimensions by feature extraction (common methods include the linear principal component analysis, but non-linear methods are also available). Beyond the benefit of visualizing the high-dimensional, noisy spiking data in a compact form, such methods can provide insight into the dynamics of circuitry underlying the neural activity. Eigen value decomposition is performed on the covariance matrix to find the directions that represent the data in the best mean square error sense. The Eigen vector associated with the largest Eigen value corresponds to the first principal component and so on. Another method of decomposition, unify the smoothing and dimensionality reduction into a common framework, has been described elsewhere (A. Afshar, Santhanam, et al., 2011; Churchland et al., 2010; Santhanam et al., 2009; Yu et al., 2009).

We employ it here to enable simple analysis of what is loosely called “brain state” while the monkey performs the very natural task of reaching for a piece of apple. The event was recorded and time-synched to the data with a video camera. When the first 2 or 3 dimensions are plotted with respect to time, the resultant plot is referred to as a “neural trajectory.” This trajectory is intended to define the path of brain state over time. In addition, one can expect, given the results from the aforementioned studies, that this path will contain clusters or stopping points, which can be used to separate one state from another. In Churchland’s work, they observe a consistent start and end state at distinct locations in the principal component 2-dimensional space over time. Our data, which is far less constrained than a monkey performing a repeated task in a chair, shows a similar trend seen in Figure 6-19. The trajectory, in the case of a monkey reaching for an apple and bringing it back to its mouth, is not a-priori known to begin and end at different

locations as we see in our data. In addition, it is encouraging that the path drawn by the evolution of brain state can allow visual separation of the task.

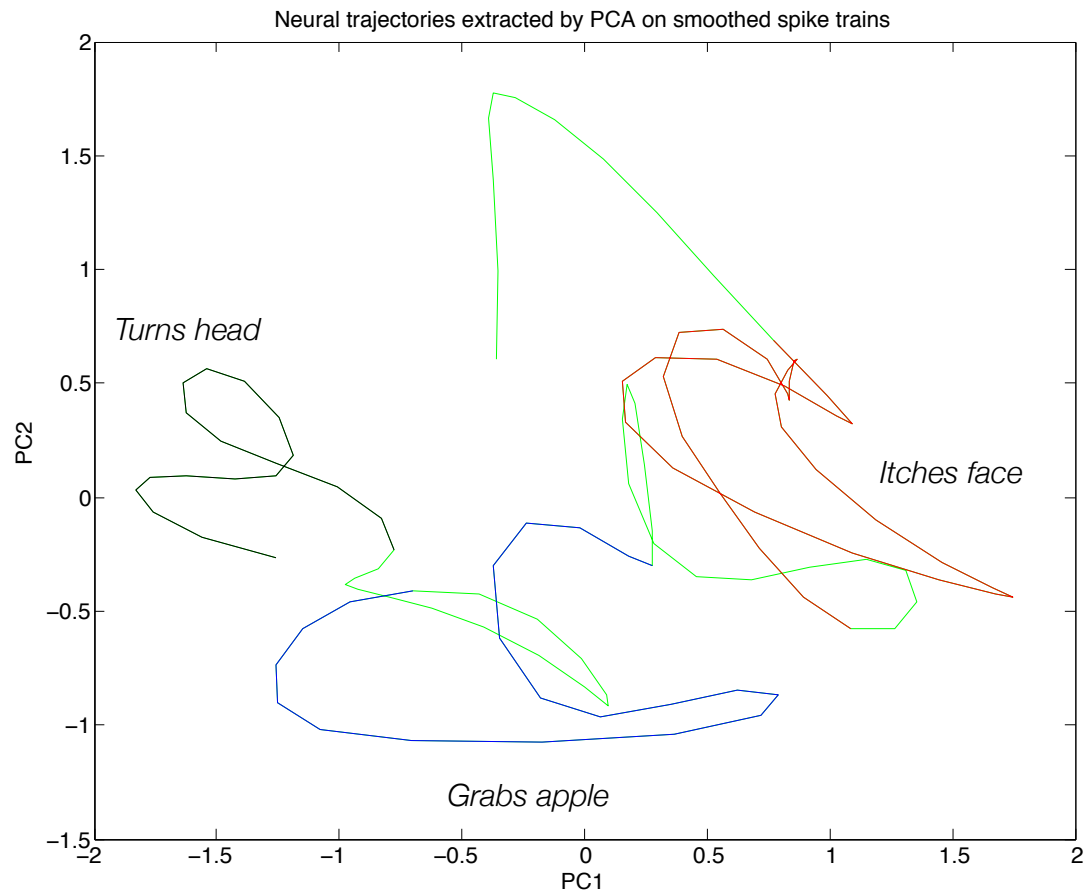


Figure 6-19: Neural trajectory of monkey JR turning his head (dark green), grabbing an apple (blue) and returning his hand to his face to both eat and itch his face (red). The first two principal components are plotted evolving over time.

One tantalizing question about brain state is its evolution during sleep. It has been shown that during sleep, rodents will replay events of their waking life, even task training is repeated during sleep (Drummond, 2000; Kissin, 2000). It is possible that with our current IPM technology we could record neural activity during the night. Metallic caging and antenna challenges have made that experiment out of reach, for the moment. Instead, we decided to explore another brain state that is not well understood, especially from the perspective of a single neuron or population

of neurons: anesthesia. EEG recordings are commonplace in the operating room and using the BIS index, an anesthesiologist can determine the depth of anesthesia a person is in (Drummond, 2000; Kissin, 2000). Indeed, EEG is a powerful tool for assessing the low frequency potentials of large areas in the brain. However, as we have learned from the study of nearly every aspect of brain function, a microscopic lens helps expose the subtlety of the system.

In brief, we report here on experiments conducted with two monkeys, JN and JR, under three forms of anesthesia commonly used in the human clinical operating room: isoflurane, propofol, and ketamine. Standard doses were used for non-human primates to attain complete anesthetic states. Broadband brain activity was recorded wirelessly with a internally powered microsystem, again demonstrating its utility. After the data was collected, it was processed in Matlab and custom UNIX shell scripts to explore the spectral content of the data. Average power was measured as a time-varying value in the Alpha, Beta, and Gamma bands for comparison to the standard measures of anesthetic depth. Here we show a representative example of such a dataset collected from JN during one such recording session Figure 6-20.

Several gems of information can be extracted from (Fowler, 2001). First, and this was quite striking, deep propofol anesthesia (0.8mg/kg/min (Fowler, 2001)) can completely depress motor cortex function Figure 6-22. As seen during the first 200 seconds of the data trace (and the previous 1200 seconds during the maintenance period, not shown), the motor cortex is quiet across all spectra, not unlike the post-mortem data collected from pig S2. Second, as presumably the propofol effect on positive GABA-ergic transmission decreases, we begin to see a low baseline firing rate return to the neuron, as well as an increase in the alpha (red) and beta (blue) power. The transition from no neural activity to some activity is global (i.e. across the MEA recording volume) and occurs over a period of 200-300 seconds and roughly 180 seconds after anesthetic intravenous delivery has stopped. Even more thought provoking is that the monkey shows no form of movement response to tactile stimulus, or even rotation of the endotracheal tube until 1300 seconds after infusion has stopped and well after neural activity has been

established, including very typical alpha rhythms seen on EEG. These results only lead to interesting question, for example, what is the cortical network doing during the electrically awake but no responsiveness time period? What cortical brain states correlate with depths of anesthesia? These questions are only posed here as a future application of the technology we have developed and described in this thesis. Lastly, on the question of anesthetic state detection, we have made some progress combining the concepts of neural trajectories to anesthetic state analysis. Below, we show a 3-dimensional construction of neural trajectory based on smoothed firing rates. The image was produced with data collected from monkey JR anesthetized with isoflurane (red) and during the latter minutes of the wakeful period (black) before returning to his home cage. We bring this figure the attention of the reader simply to show that anesthetic states appear to be linearly separable and thus easily classifiable. While much work remains to be completed to confirm these results, it is possible that with such data one could build a clinically useful “BIS”-type monitor based on much higher fidelity information such as single unit spiking rate. Other bands collected in this broadband dataset have not been evaluated for their role in brain state, but could easily be used as alternative dimensions of the neural trajectory and it is possible that analysis could lead to similar results.

Further, in Figure 6-23 we show direct comparison of the three anesthetic agents tested. One representative channel (channel 56) of the 200 electrodes across both implanted and tested non-human primates demonstrates incredible dynamics across the anesthetics states induced by the different agents. Characteristic burst-suppression is observed in the isoflurane data, along with heterogeneous and highly active neurons under ketamine. This figure alone contains incredible amount of information, and to process (and furthermore, interpret) it all will be future work for this research laboratory. Regardless, we believe this further expresses the utility of the IPM and EPM as clinically relevant biomedical devices, both for research and clinical use.

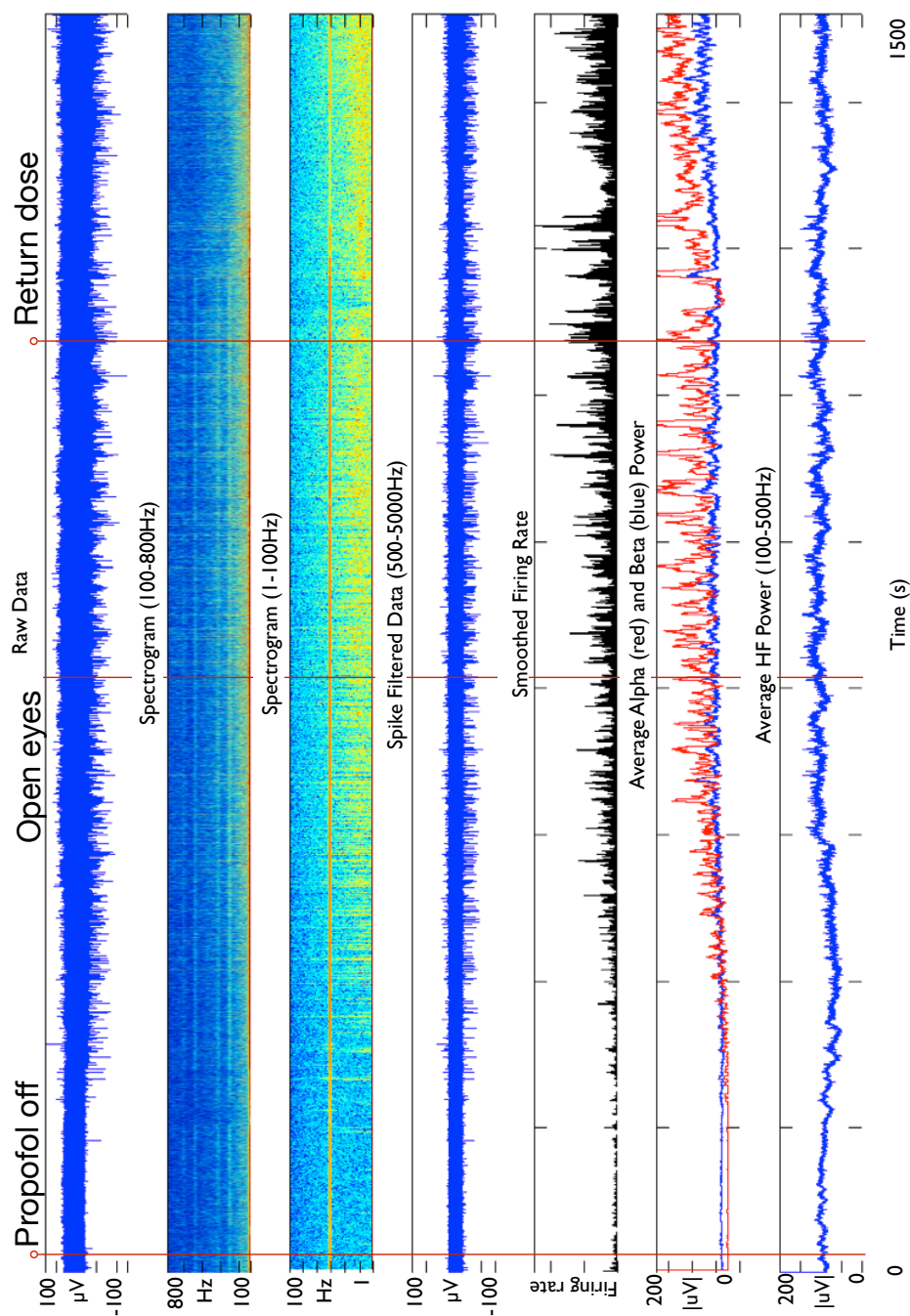


Figure 6-20: Wireless long time-course data from JN motor cortex during deep propofol anesthesia, wake up, and induction into ketamine for transportation. Clear transitions in brain state can be seen around 400 seconds after propofol is turned off and well before eyes open and the animal begins to respond to stimuli.

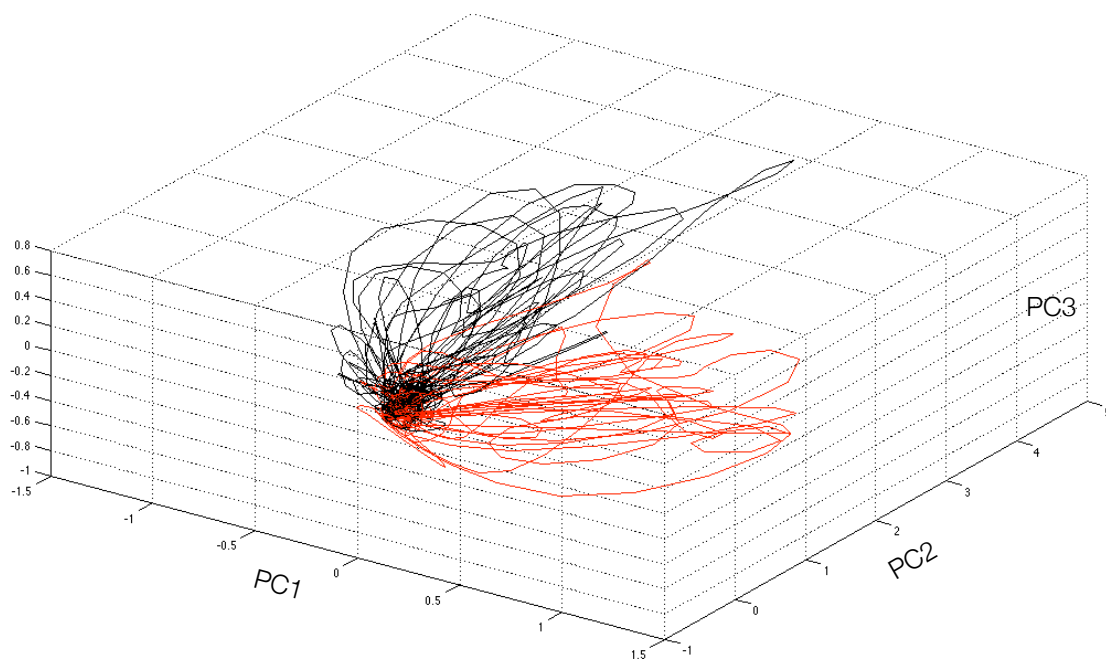


Figure 6-21: Principal components 1, 2, and 3 of the smoothed firing rate recorded across 40 channels of input in monkey JR. Isoflurane induced anesthetic state (red) can easily be distinguished from waking state (black). This is generally (in two dimensions) referred to as neural trajectories.

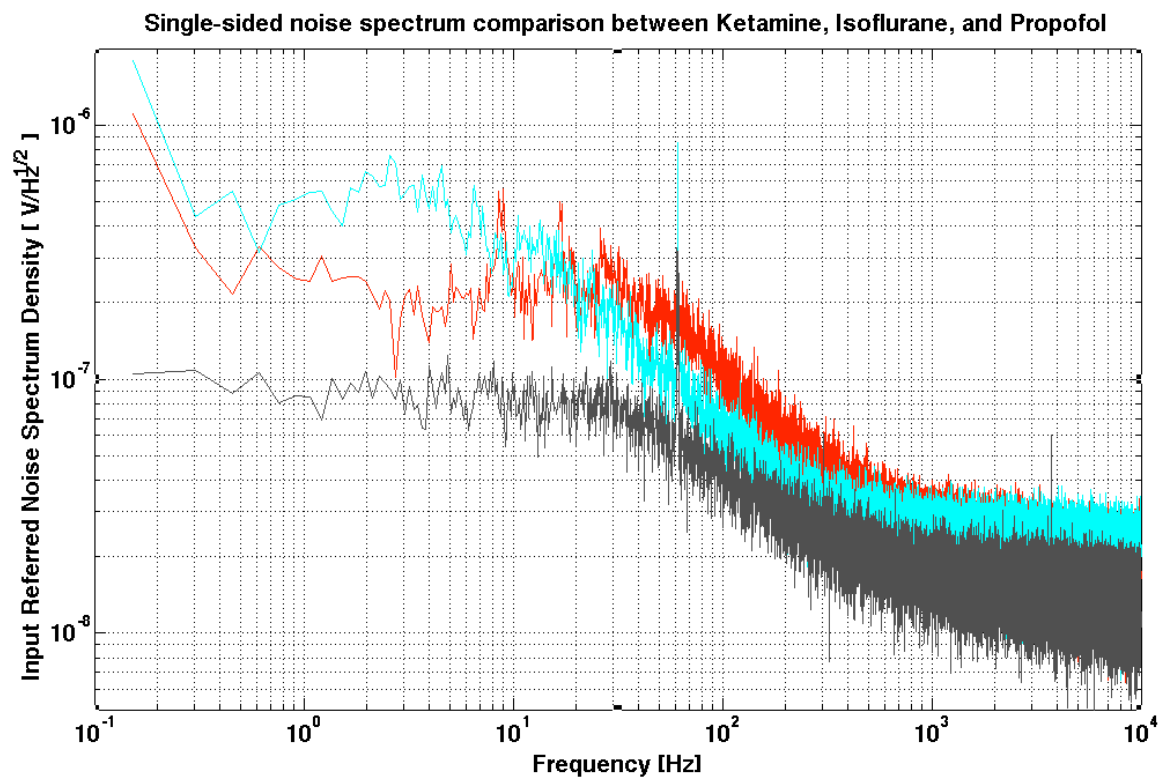


Figure 6-22: Single-sided noise spectrum of single recording channel (62) taken from monkey JN during three deep anesthetic states. Clear variation can be seen in brain activity between ketamine (red), isoflurane (light blue), and propofol (black). Propofol shows most significant quiescence. This difference is nearly a factor of 3, certainly enough to base classification.

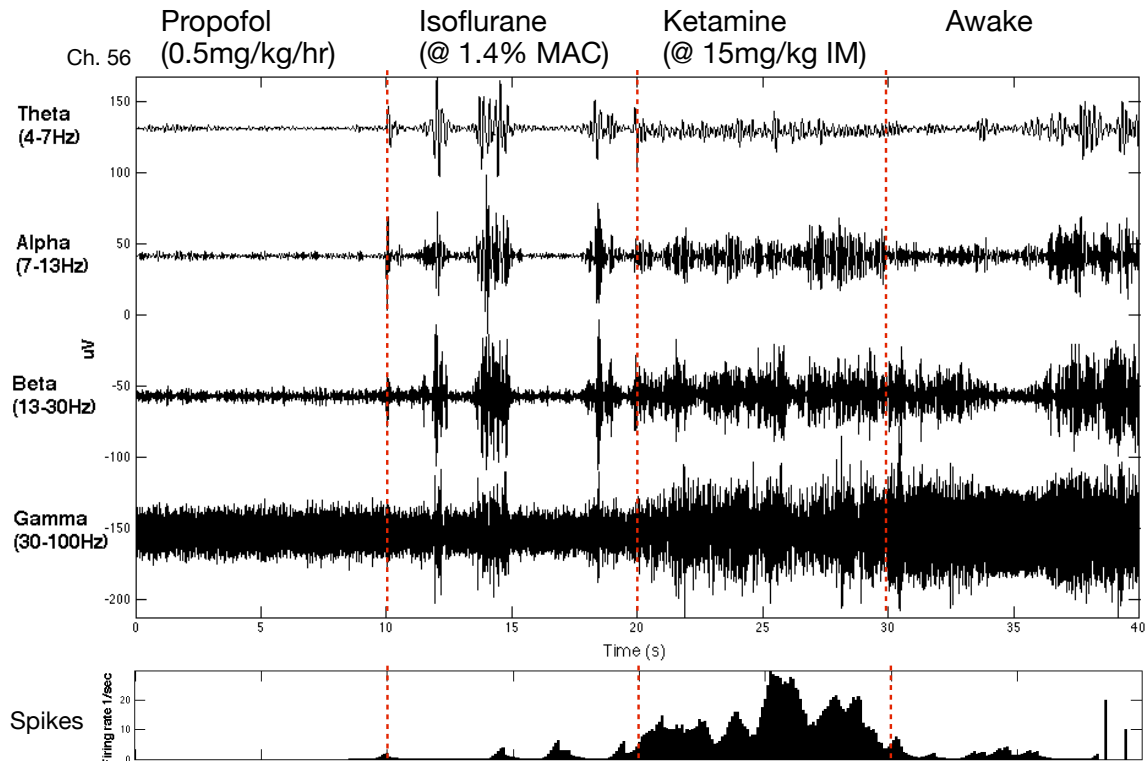


Figure 6-23: Wirelessly recorded broadband (field potential and spiking activity) neural activity from a representative channel (electrode 56 out of 100) during four distinct states including three states under surgical dosages of anesthetic agents. One should note the clear stereotypic differences between the agents, e.g. burst suppression of isoflurane and heterogeneous neural activity under ketamine. This is the first (that we are aware of) high channel count (100) broadband (0.1Hz – 7.8kHz) and wireless neural recordings made under anesthesia and may provide insight into the fundamental mechanisms of anesthetics on brain activity.

6.6 Longitudinal results from implantable microsystems in Yorkshire swine

A total of 11 broadband, wireless, and fully implantable microsystems (8 EPM and 3 IPM) have been implanted in swine for a combined total of > 600 days (See Table 6-1). During this time, we have had one device related health issue that required explantation.

6.7 Longitudinal results from implantable microsystems in rhesus macaque

A total of 7 broadband, wireless, and fully implantable microsystems (5 EPM and 2 IPM) have been implanted in 4 non-human primates (2 primates received 2 EPM devices each) for a

total of more than 900 implant days. There have been no serious device related health issues in these animals. See Table 6-1 for more detail.

Animal ID	Device implanted	Days implanted	% Channels with units	Location	Identifier
Swine					
778	EPM16	N/A	N/A	L-PSC-UR	JU
779	EPM16	25	0	L-PSC-UR	P2
780	EPM16	72	6	L-PSC-UR	P3
787	EPM16	65	2	L-PSC-UR	P4
791	EPM16	36	0	L-PSC	SU
792	EPM100	44	N/A	L-PSC-UR	A1
793	EPM16	149	0	L-PSC-UR	P5
788	EPM16	27	2	L-PSC-UR	FA
797	IPM100	N/A	N/A	L-PSC-UR	S1
796	IPM100	38	30	L-PSC-UR	S2
798	IPM100	>180	70	L-PSC-UR	S3
Non-Human Primate					
99-4	EPM16	14	0	R-MI	PU
B002	EPM16 (x2)	508	7	R-MI, R-PMd	SC
RQ6065	EPM16 (x2)	226	2	L-MI, L-PMd	LU
RQ6064	IPM100	>149	80	L-MI	JR
FA-01	IPM100	>114	60	L-MI	JN
Total device implants (pig)	11	Total days device implanted			>626
Total device implants (NHP)	7	Total days device implanted			>891
Total device Implants	18	Total days device implanted			>1522 days
		Total days device recording			>859

Table 6-1: Swine and non-human primate implantation history table. These data represent implantations of externally powered microsystems (IPM) and the internally powered microsystem (EPM) in both 16-channel and 100-channel configurations. Some animals (B002 and RQ6065) were implanted with two (2) systems each (x2). Channels (%) recording is defined as the ratio of total channels in system (16 or 100) to channels with data showing spiking activity (local field potentials were not evaluated in this analysis).

6.8 A comparison of optical and radio frequency data telemetry used in this work

We include this table to provide a concise comparison of optical and radio frequency data telemetry tradeoffs for neural prosthetics, given our recent in depth experience. This table should guide the reader towards the appropriate choice of telemetry for their unique application.

Feature	Infrared VCSEL	3.2 / 3.6 GHz FSK / OOK	Comments
Power consumption*	9 mW (avg.)	50 mW	An obvious power tradeoff strongly in favor of the optical communication
Practical transmission range**	2 cm	1 meter	Optical scattering from the skin greatly reduces optical collection distance while RF transmission is only slightly effected by the electromagnetic impedance variation of the skin. High-frequency RF transmitters require an oscillator (voltage-controlled and generally made into an integrated circuit) as well as an antenna. We use a UWB chip antenna consuming 1cm ² . In addition, a ground plane is necessary for generation of the EM waves. However, this is often necessary for the system regardless and may not consume additional PCB space.
Physical size (Tx)	Single chip (2mm ²)	VCO + antenna (variable size)	Optical receivers can be made exquisitely sensitive (APD, etc.) and optical noise is often easier to control than RF environmental noise. FSK / OOK RF receivers are difficult to build and require careful demodulation to achieve the best SNR.
Receiver complexity	Photodiode, amplifier	Amplifier, demodulator, (clock extraction)	The optical telecommunication industry focuses on high-bandwidth, low power, and long-term reliability. Mobile telecommunications has advanced significantly in recent years to optimize bandwidth / power tradeoffs and short-term reliability (i.e. modulation schemes to minimize BER within noisy environments).
Commercial use / support	Fiber optic telecom	Mobile / cellular telecom	

Table 6-2: Summary of optical and radio frequency communication tradeoffs as used in out externally powered microsystem and internally powered microsystem. *(@24 Mbps); **Transcutaneous range is determined from in vivo use of the telemetry modality in both swine and non-human primates.

6.9 Histology and post-mortem analysis

Post-mortem (both device and subject) analysis is essential to understand successes, as well as failures. Electrical diagnostics of the externally powered microsystem uncovered common trends in failure mode Figure 6-26. A faulty VCSEL connection method was found to be a culprit in these system failures, which led to the integration of a packaged laser diode (previously a bare

die was used). Poor packaging generally caused power and frontend failures. Poor packaging can be caused by several process missteps, specifically failures to clean microsystems thoroughly before packaging. We have developed a cleaning procedure that has led to the increase in well-packaged devices. EPMs that take advantage of these two advancements represent the 50->100 day section of the lifetime plot. Mechanical failures are rarely seen, but one such event did occur. During implantation, the telemetric unit of the EPM is secured to the skull by three titanium screws. In previous designs of the system, holes for these screws were made a priori during the packaging process. In one case, a surgeon tightened the screw at a slight angle, pressing down onto the hard backing (alumina). We have since switched backing material to single-crystal sapphire – a much more resistant material to cracking. Frontend failures are often difficult to diagnose. An expected failure (though rarely seen) is infiltration of saline / water along the seam of the microelectrodes as they exit the packaging. Water at this location may delaminate the PDMS and short the inputs of the amplifier together causing a high degree of cross-contamination of input signals. Instead, we have seen failure of frontend packaging on the bypass capacitor. This capacitor lies between power and ground and is thus an obvious place for charge to buildup. On one occasion, the packaging over that capacitor was thin enough to cause immediate failure after being turned on. Ionic buildup could be seen on the capacitor by the time of explantation two days later.

We have also completed histological analysis on one non-human primate explantation. The gross anatomy Figure 6-24, and subsequent staining for glial fibrillary acidic protein (GFAP) Figure 6-25 reveal changes in the neuronal organization. The macroscopic whole brain images (left) show an exceptionally large impression made from the frontend of an EPM. This impression was caused by downward pressure from the dura (on closure) and / or the skull upon reapproximation of the craniotomy. This degree of infiltration of the MEA into the cortex is not generally seen in standard MEA implantations. Our hypothesis is that this increased inward pressure is caused by the extra 2mm thickness added to the cortically implanted unit

accommodating the amplifier and silicone packaging. In subsequent animal implantations (swine and non-human primates) we have modified the surgical protocol to include a relaxed reattachment of the dura mater and 2mm shaving on the underside of the craniotomy before it is replaced. In 6 swine explanted since that time, we have not observed this degree of indentation into cortex. Another view, captured in slice form, can be seen in Figure 6-25 (bottom) also showing indentation of the interconnecting tether between the cortical and telemetric units.

GFAP-stained sections ((Griffith & Humphrey, 2006)) show modest build up around the microelectrode array. Similar results have been previously published (Griffith & Humphrey, 2006) and anecdotally reported by colleagues. The prepared slices do present definitive evidence that our MEAs did penetrate the cortex, which was an uncertainty when these devices were initially implanted.

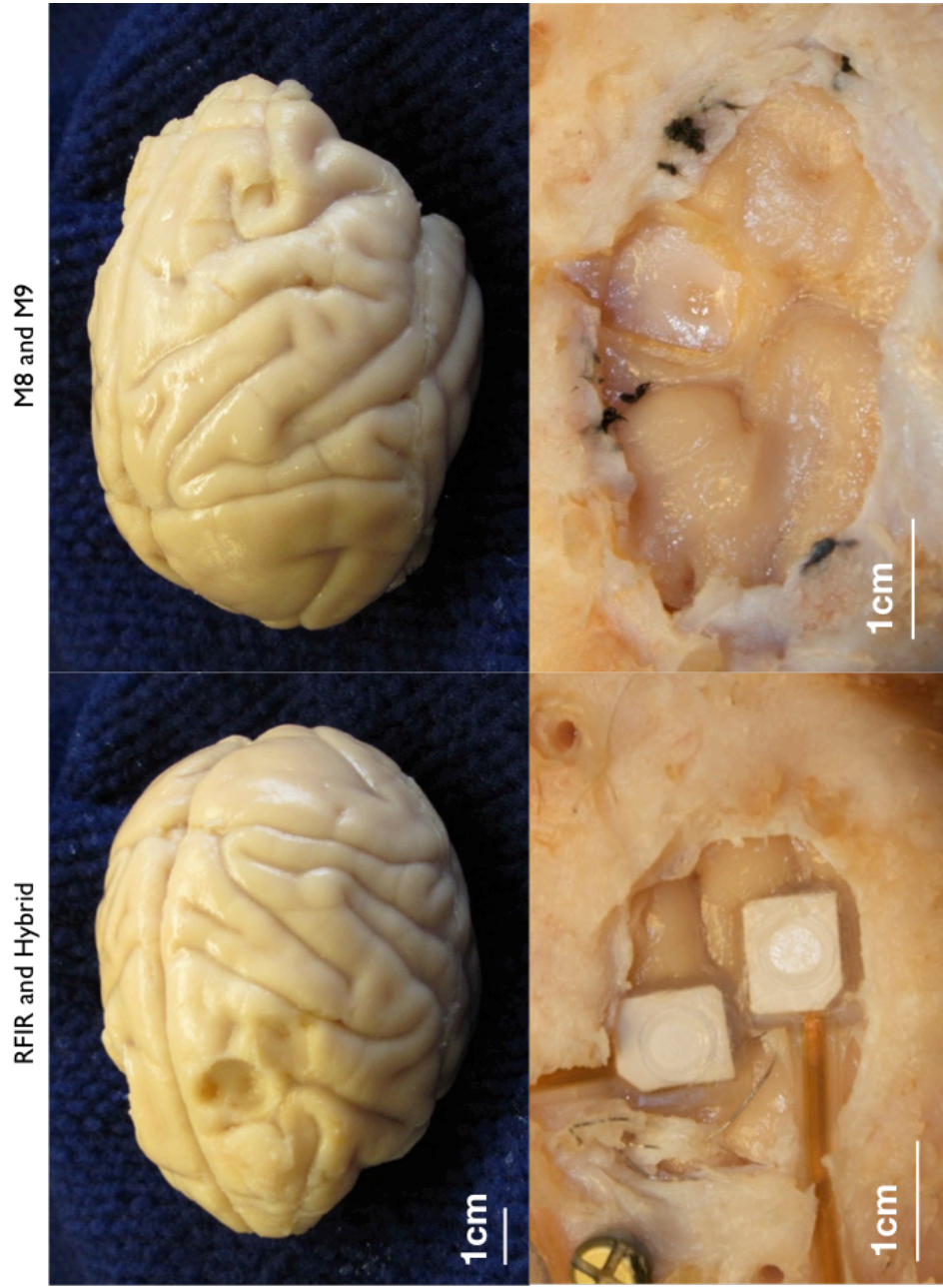


Figure 6-24: Extracted brain of monkey LU after 226 days of implantation. Whole brain (top) images show one location of gross indentation of one microsystem. No functional deficits were observed in this monkey prior to this finding. Frontend (below-left) images before explanation and after (right) show clear electrode tracks, affirming that the electrodes did piece the arachnoid and where thus very likely in cortical tissue. The next figure shows histological evidence confirming this assumption.

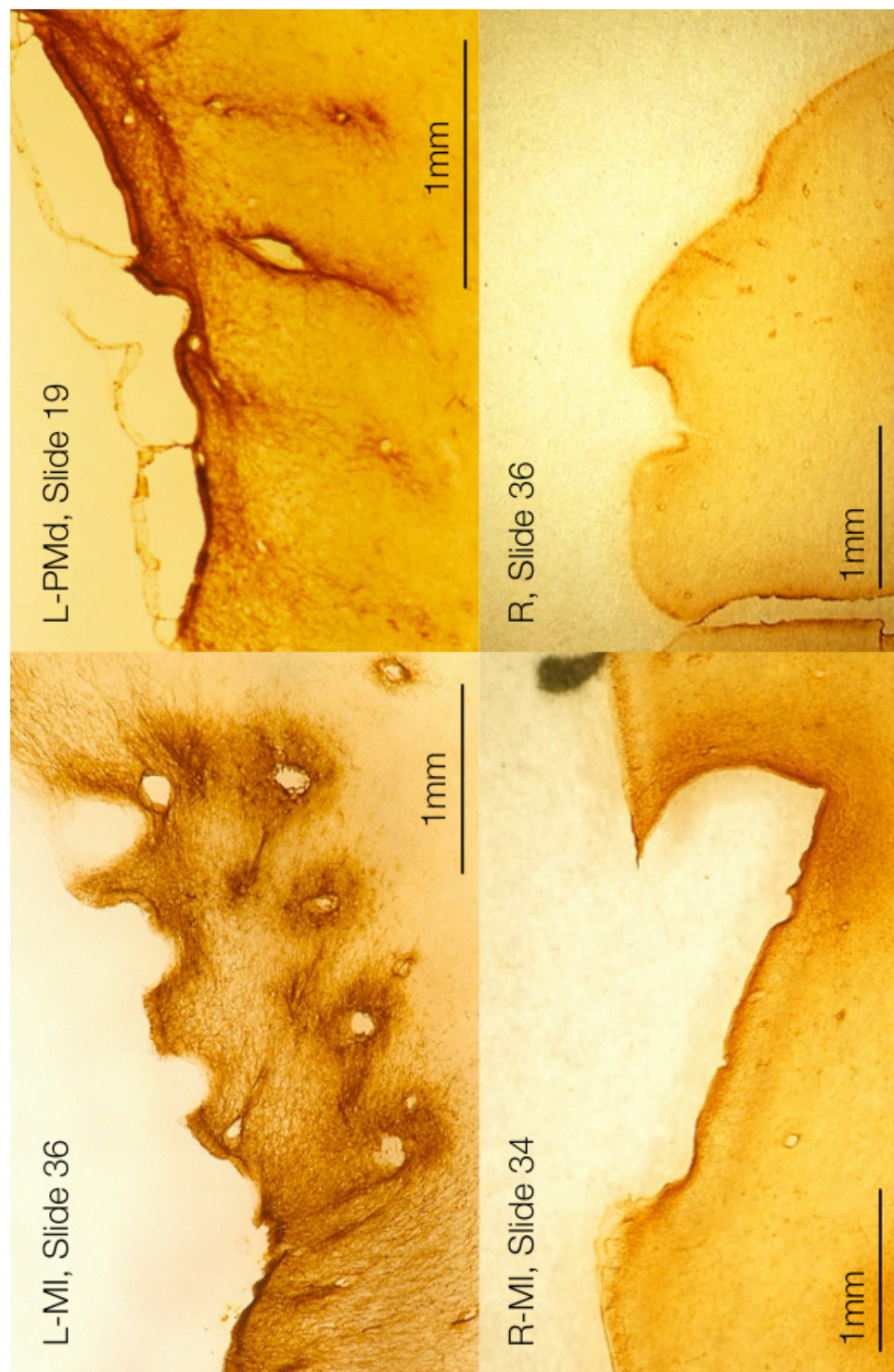


Figure 6-25: (top) Histological evidence of cortical penetration of the electrodes (4 x 4 element) in both MI and PMd regions. Minimal glial response is observed around the shank (top-left) and along the shank (top-right). Cortical depression was observed in two locations implying excessive inward pressure on two implantation sites (bottom-left, MI; and bottom-right). Left shows a cortical frontend impression and right shows interconnect impression.

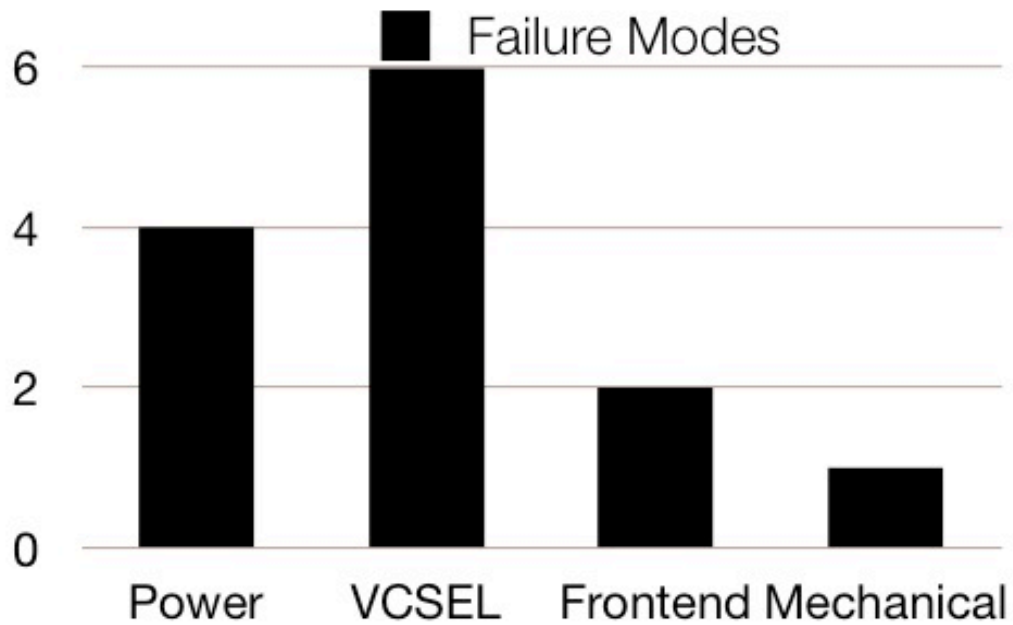
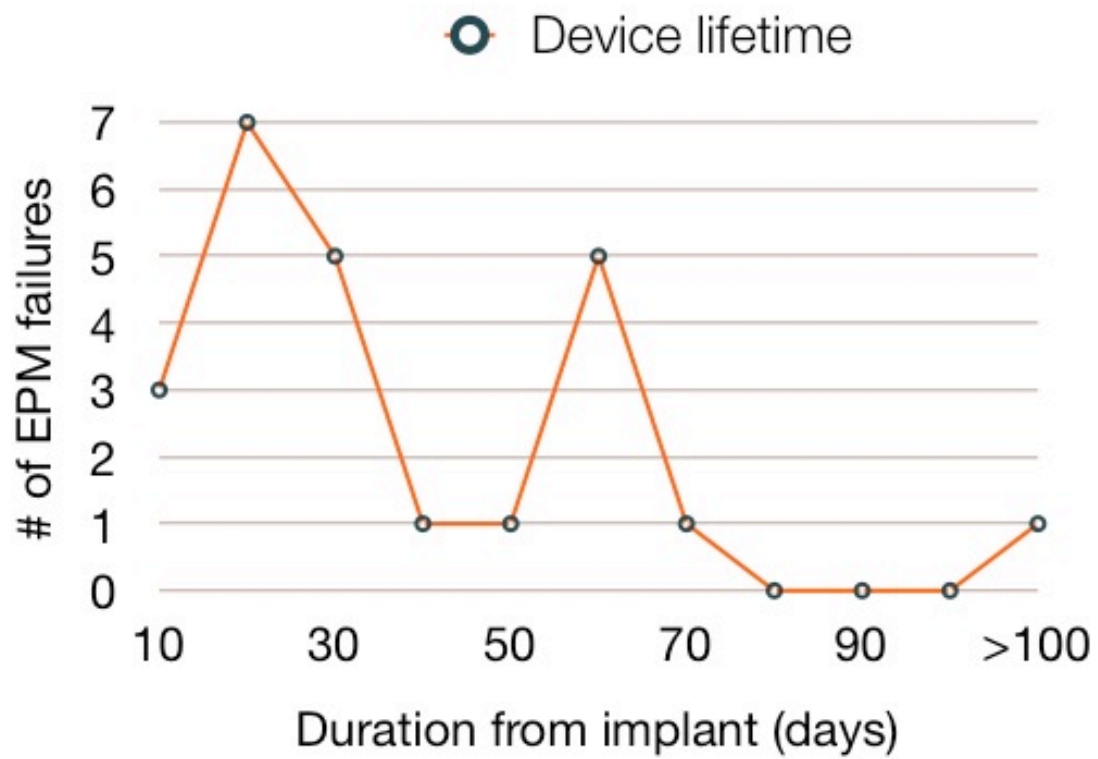


Figure 6-26: Distribution of the externally powered microsystem device lifetime (top) and device failure modes (bottom). All results are from in vivo testing in swine and non-human primates.

CHAPTER 7: Conclusions of this work and greater context

Conclusion of results and this thesis

We have presented the development and use of novel wireless, broadband, and implantable neuroprostheses in neuroscientific research. Two such systems were presented. First, we discussed the fabrication and design of an externally powered (RF inductive coupling at 13.56MHz), low profile (3mm), and polymeric-packaged (polydimethylsiloxane) 16-channel and 100-channel neural interface technology. This microsystem leverages an innovative low power (9mW) optoelectronic semiconductor laser (VCSEL, 852nm) for transcutaneous data telemetry. This externally powered microsystem (EPM) was shown to be safely powered (29mW for 100 channel microsystem) and to operate at temperatures well below FDA regulations ($<2\text{C}^{\circ}$). Further, the EPM was evaluated *in vivo* in a variety of animal models, beginning with rodent (for mechanical and insertion verification), then Yorkshire swine, and finally non-human primates.

Broadband neural data was collected from 11 animals (8 swine and 3 monkeys) totaling over 1200 implant days, representing a major milestone in neuroprosthetic device evolution: the first completely wireless, broadband, and fully implanted neural recordings made in primates.

We then presented our work on an implantable device incorporating an inductively charged (2MHz) lithium-ion battery and long-range (3 meters) RF data telemetry (3.2 – 3.8GHz, OOK) into a hermetically sealed titanium casing consuming only 90.6mW yielding over 6 hours of operation. This internally powered microsystem (IPM) was fully implanted into two swine, one for 30 days and the other for over 180 days. In both cases, the device was fully functional for the duration of implant time. The IPM was also successfully implanted (percutaneously due to geometric limitations of both the device and the species of non-human primates available) in two non-human primates. All implanted systems showed high single unit counts (>60%) throughout their use. Both systems described, leveraged a custom ultra low-power amplifier ASIC (6mW for 100-channel input, 3.6μ Vrms RTI noise) integrated with 510k-approved microelectrode neural sensor array, detecting signals from 0.1Hz to 7.8kHz (broadband).

The use of swine for device verification and validation enabled significantly accelerated device reiteration. To use swine for device implants in a neurosurgical context necessitated surgical tool innovation, specifically the development of a large animal stereotactic frame. We presented the design of such a tool and its use for surgeries on a relatively large number of animal subjects (8 EPM implants, and 3 IPM implants). This animal model was further described by our group in a peer-reviewed publication and will hopefully be used by other device developers for verification and validation experiments.

The development of such implantable, wirelessly transmitting microsystems enables study of a new area in neuroscientific research: *natural* behavior. Most neuroscientific research on the cortical dynamics of motor control relies on well-trained animals performing stereotyped tasks completely out of natural context. In addition, these approaches impose movement constraints on the subject that might prevent the investigation of natural grasp kinematics. There

has been very limited research on the cortical dynamics of natural movement primarily due to the technological limitations of the neural recording systems employed by the vast majority of neuroscientists. Jackson, Mavoori, & Fetz, in 2007, were able to record from a single neuron during various brain states (sleep, awake, trained-task vs. untrained). However, their study was significantly limited for two reasons: first, comparable untrained states are assumed from observation without direct measure, and second, they are only able to record from a single neuron. Our systems provide the potential for multineuronal, untethered recordings compatible with studying motor cortex dynamics during natural movements, even with the animal in its home cage.

Furthermore, the internally powered microsystem is soon to be used in early clinical trials as a tool for monitoring and locating foci of intractable epilepsy. Epilepsy is considered a brain disorder in which a person has repeated seizures over time. In turn, seizures are defined as episodes of disturbed brain activity that cause changes in attention and behavior, often causing absence or convulsion. While epilepsy has been recognized since antiquity, the neuronal undercurrents are much less well understood. This is the case for many brain states, including sleep, various forms of anesthesia, and even psychosis. Researchers have looked at the activity of smaller populations through electrocorticography (ECoG) or intracortical EEG. These recordings are much more specific than supracranial EEG, and have shown, in epilepsy, that pre-ictal states can have a great deal more heterogeneity than previously thought. Very few studies have gone beyond macroscopic scalp and mesoscopic intracranial EEG signals to examine neuronal spiking underlying these brain states and thus, the behavior of the single neuron or small population of neurons remains largely unknown during epilepsy. The IPM is a device uniquely positioned to aide such investigative studies.

We already are able to suggest from our initial findings that anesthetic states under various chemical agents (isoflurane, propofol, and ketamine) are in fact classifiable by observing a low dimensional representation of spiking rate. We believe we have also exposed hints that this

spiking activity may provide a more rich description of brain state under anesthesia than current methods (EEG, ECoG), and thus can potentially add to the understanding of anesthetic mechanisms and appropriate dosages in humans.

In parallel, a development effort was initiated to bring neural signal processing and decoding electronics onto a wearable platform. The foundational framework of this effort was designed by a diverse group of engineers, neuroscientists, and clinicians to address the needs of each group. Design specifications were presented leading to the first implementation of a portable, adjustable, and powerful neural signal processor. While the framework was demonstrated running on a laptop PC, all blocks were design to be compatible for later compilation into embedded hardware. In addition, data processing structures for neural decoding and cursor control from current human clinical trials (BrainGate2) were built into the platform. Finally, neural data was recorded from monkey JR from an internally powered microsystem and fed into the ESPA platform where it was processed, validating the system architecture. We envision such a platform playing a role in the larger clinical picture. While this system was originally aimed at solving the intense processing demands of neural data collection and decoding in a dynamical way, through the development process we have come to realize that a more universal, or abstracted, platform would allow data from all types of biosensors to be collected, processed, and distributed within one unified framework. The benefits of this approach are obvious within the context of a clinical care center where data must be *integrated* in order to deliver the most effective, personalized, and timely care. In addition, using one framework to collect many formats of patient-related data also simplifies outpatient care, though the use of our system in that context is outside of the scope of this project. The innovations we focused on were: a) to standardize the way we communicate with an effector, making it an open platform for prosthetic vendors to implement; b) to miniaturize all of the hardware and software necessary to perform such control tasks; c) to create a common platform that allows for modularization in the design and utilization of the computational needs – promoting creation of an ecosystem for

applications to access and harness the collected data to achieve specific research or clinical needs. For example, a deeper understanding of neuronal spiking (e.g, specific localization, timing, and so on) during the different phases of seizure generation could have profound implications for seizure prediction and may provide the basis for new and more effective therapies for people with epilepsy. Thus, a wearable, integrative, and portable signal processor such as the one described in this work could significantly improve the care we give patients.

In short, we return to the goals posed in the introduction of this thesis to reiterate the numerous challenges we met with enabling solutions:

1. removing the percutaneous wire connection of current NeuroPort technology through the development of implantable, wireless neural sensors;
2. developing low-power ASIC elements to amplify and digitize broadband neural data
3. developing and leveraging an animal model appropriate for translation of device surgical and histological analysis to humans;
4. applying this technology to restore or replace lost functions in neurologically or physically impaired humans
5. making multisite, high-density, and broadband neural population recordings
6. developing wearable signal processing packages

While these goals have been met, the devices and technologies presented in no way represent an optimal solution. Instead, they provide a stepping-stone (or a two) and a blueprint for future neuroprosthetic technologies to be built upon, improving our developments. Hopefully, in the end, one will find its way to helping humans with neurological disease and insult: the ultimate goal of this research, and researcher.

APPENDIX A: Advances in Optical Methods for Interrogating the Nervous System

“The phrase ‘electrical stimulation of the lateral hypothalamus’ is a shortened version of the statement that ‘there was a stimulating electrode in the lateral hypothalamus which affected an unknown number and unknown kinds of cells at unknown locations in the vicinity of the electrode’. The lateral hypothalamus is an area of brain and is not electrically excitable--only cells are. “

– J. Ranck, 1975

A.1 Introduction: Foundations of electrical neural stimulation and the need for alternative methods

For centuries, scientists have exploited the electrical nature of neural communication. We have learned to inject current through well-defined microelectrodes near a focus of interest in order to elicit a neural, or sometimes-behavioral response. While scientists have used this

technique to study connections and dependencies in the brain, physicians have used technology developed through commercial enterprises as a therapy for numerous diseased states. Deep-Brain Stimulators (DBS) are now widely used around the world in patients with Parkinson's Disease (PD), depression, Obsessive-Compulsive Disorder (OCD), and many others. This device is implanted into a malfunctioning region of the brain (i.e. sub-thalamic nucleus for PD patients) and is "paced" with high-frequency electrical pulses (pulse width ranging from 60-400 μ s, current intensities range from 1-5mA, and repetition rates are between 90Hz and 200Hz for effective therapeutic treatment (Joucla & Yvert, 2009)). While the technology has helped upwards of 100,000 people, the mechanism of action is still unclear. Numerous studies have been conducted, both analytically and experimentally (Ranck, 1975) developing our understanding of current flow from a stimulating electrode in the brain. While these studies do provide some insight into steering current to regions of interest, the sheer size of the electric field created by the electrodes and the complex, non-uniform geometric structure of cortical neurons (and their processes) makes focal stimulation incredibly complicated (Histed, Bonin, & Reid, 2009).

Targeted spatiotemporal access to neural populations at single neuron resolution is important to the study of neural circuits and cellular conditions, both for basic understanding of their functions as well as developing approaches to many classes of neuronal disorders. Modulating neural circuits by intracortical electrical stimulation is a well-established tool in electrophysiology and clinical neurosurgery, even if uncertainties are inherently present, given such non-selective activation of cells by the complex patterns of current flow (Nagel, Szellas, Huhn, Kateriya, Adeishvili, Berthold, Ollig, Hegemann, & Bamberg, 2003). In a broader context of the utility of external neuromodulation methods, systematic models of how activity in neural circuits occurs, whether normal or aberrant, are made complicated by the nonspecific nature associated with electrical, magnetic and pharmacological targeting. A new approach to neural modulation was recently developed with the discovery of a light-sensitive ion channel, Channelrhodopsin-2 (ChR2) (Schobert & Lanyi, 1982), followed by the discovery of an

optically activated chloride pump, Halorhodopsin (NpHR) (Chow, Han, Dobry, Qian, Chuong, Li, Henninger, Belfort, Lin, Monahan, & Boyden, 2010), and a proton pump, Archaeorhodopsin (Arch) (Boyden, Zhang, Bamberg, Nagel, & Deisseroth, 2005; Cruikshank, Urabe, Nurmikko, & Connors, 2010). Through the combination of genetic and optical methods these discoveries were rapidly advanced in mammalian animal models as fundamentally new methods for targeting neurons, now termed ‘optogenetics’.

Light-induced modulation enables both neuronal excitation and inhibition, each producing well-defined neuronal events with millisecond time resolution (Im, Cho, Wu, Wise, & Yoon, 2011; Jing Wang, Wagner, Borton, Zhang, Ozden, Burwell, Nurmikko, van Wagenen, Diester, & Deisseroth, 2011). There are many practical advantages of optical stimulation over electrical stimulation. For example, optical methods have minimal instrumental interference with simultaneous electrophysiological recording techniques (whereas equivalent stimulation via current inject will produce a “blind” period where the output from the stimulating electrode confounds the input of the recording electrode). Furthermore, the method is technically scalable for accessing potentially multiple target areas for controllable spatiotemporal modulation across the cortex and deeper brain structures (Jing Wang, Borton, Zhang, Burwell, & Nurmikko, 2010; Jing Wang et al., 2011). To advance such prospects, development of ‘dual-function’ chronically implanted devices for simultaneous light delivery and electrophysiological recording is needed. For localized light delivery, glass optical fibers have seen wide use in optogenetics to date, given their abundant commercial availability as flexible (though somewhat fragile) low-loss optical waveguides. In addition, an implanted optical fiber allows *in vivo* fluorescence detection in the intact brain for minimally invasive assessment of local opsin expression. So far, recording of optically evoked neural activity *in vivo* for rodent and non-human primate models has been mainly limited to the use of individual extracellular electrodes which are adhesively attached in parallel to the optical fiber. However, we have developed a coaxial, integrated optical stimulator

and electrophysiological recorder, termed 'optrode' (Jing Wang, Borton, et al., 2010; Jing Wang et al., 2011)

A.2 Fabrication of the optrode

The tapered optical fiber improved on design and fabrication, which, were recently reported as the single optrode [REF 20 from paper] for *in vitro* focal light delivery and extracellular (single neuron) electrical recording. This optrode, with or without the cladding metallic recording electrode layer exposed to brain tissue, was made specifically for chronic implantation in freely moving animals. The optrode elements were fabricated from a gold-coated step-index multimode optical fiber (50/125 μm core/cladding with a custom-designed gold buffer, Fiberguide Industries). Gold buffer on both ends was carefully removed by mechanical stripping. Fiber tips were cleaved and cleaned with acetone and methanol before processing. The tapered end was created by standard wet etching in aqueous hydrofluoric acid (HF, 49%) at room temperature (22–24 °C). Tip taper angle (6° – 30°) was controlled by the vertical pulling rate (0–20 $\mu\text{m min}^{-1}$). The tapered ends were shaped in such way in order to minimize the neuronal damage during insertion. The distal end was connected to a custom-designed connector (Multimode SMA905, Thorlabs) and mechanically polished using polishing films (grit sizes of 3 and 1 μm , Thorlabs). In those cases where the optrode was needed for electrophysiology as opposed to light delivery only, e.g. as a single self-standing device, the fiber was then rinsed in de-ionized water and loaded into a high vacuum thermal evaporator (Angstrom Engineering). A 25 nm thick titanium or chromium layer and 100 nm of gold film were sequentially deposited on the fiber. We found that the chromium layer enhances the adhesion between silica and gold film better than titanium. An electrical wire (magnet wire from Alpha Wire Company) was attached to the distal metalized part of the optrodes using silver epoxy (H20E, Epoxy Technology) and served as the conduit to external signal acquisition electronics. With the exception of the final 50–100 μm of the tapered tip, the metalized part of the fibers was insulated

using a UV-curable epoxy (Norland Optical Adhesive 81). Finally, the optrodes were encapsulated around the fiber connector by a heat shrink tube in order to prevent fracture and separation during possible bending.

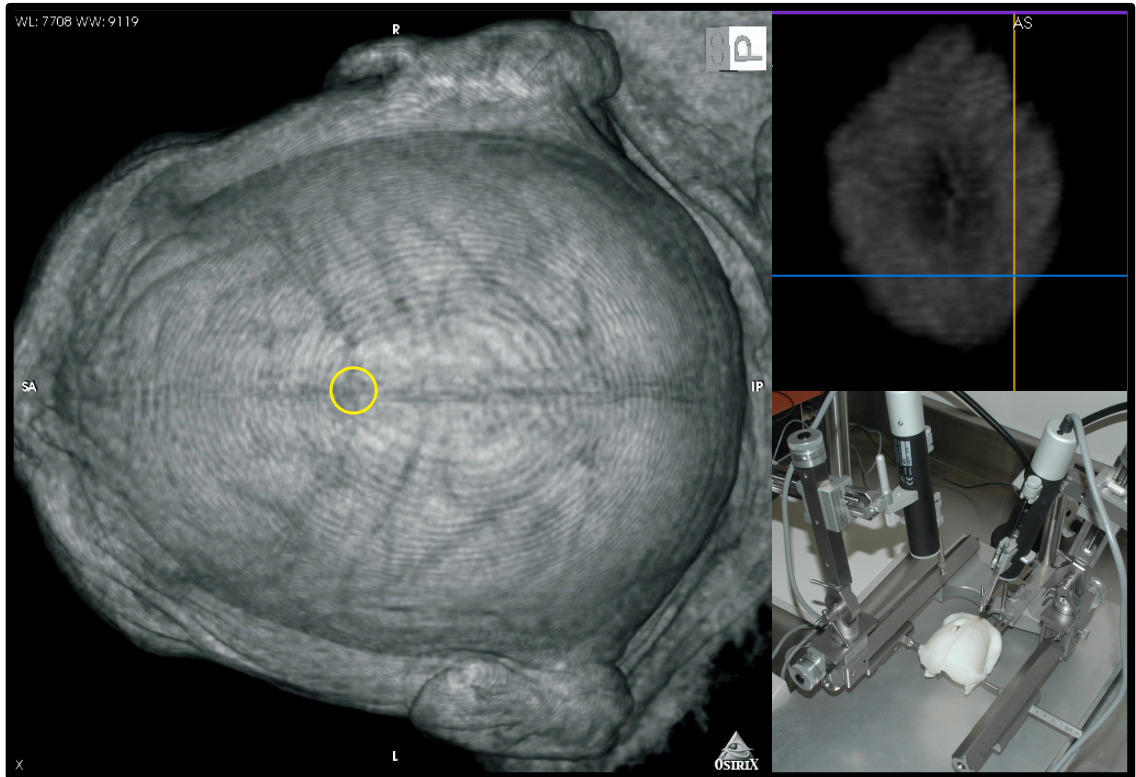


Figure A.2-1: MRI guided localization of cranial markers (bregma) and their relation to cortical locations for optogenetic construct delivery.

A.3 Development of novel viral delivery system for non-human primates

The targeting of deep or surface structures of the brain with millimeter precision is difficult. Generally, MRI-based guidance is performed by initially running a structural (T2-weighted) scan of the subject with fiducial markers in place for reference. With the help of computer modeling software, one can then define cortical targets by their position (3D) relative to the markers (Figure A.2-1). Another method, should markers be unavailable, is to use the naturally formed cranial sutures and their fusion points (Bregma, Lambda, etc.) as reference

locations. Regardless, once a target has been defined, the challenge of approach arises. How can we access that target? Can we do it repeatedly? In our case, we needed to deliver viral constructs to the arm area of primary motor cortex, premotor cortex, and somatosensory cortex. Once a structural correlation was found between target locations on the cortex and visible landmarks on the skull, we calculated trajectories for construct delivery. These trajectories were calculated in the BrainSight software (Rogue) and can be seen in Figure A.3-1. However, once injections are made, it is critical that at a later time, i.e. when making subsequent recording / stimulation measurements, that one is able to exactly return to the injection locations. Thus we designed a simple mechanism to allow consistent return to original injection sites.

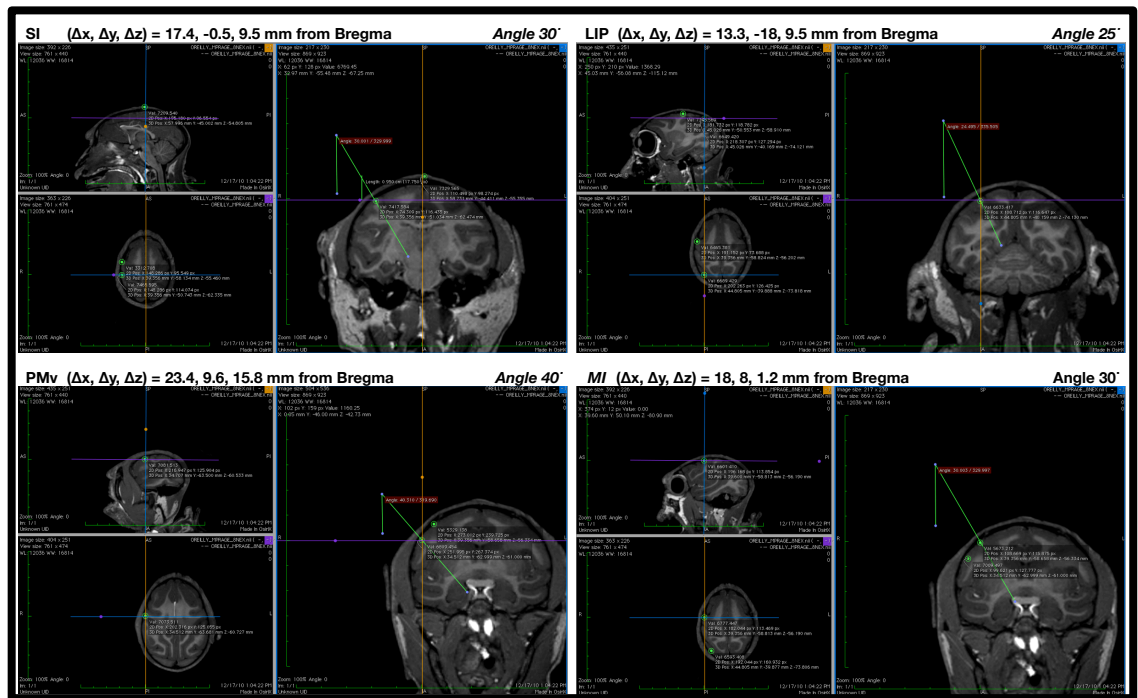


Figure A.3-1: Injection trajectories for PMd, PMv, SI, and primary motor cortex.

Standard titanium bone screws (Stryker) we cannulated (Kineteks) to a diameter of 300 μ m, enough for a stainless steel guide tube to be introduced. Target locations were marked on the skull and were subsequently drilled at the appropriate angle to reach the cortical target for

viral injection. Once drilled, a cannulated screw was inserted into the skull providing permanent access a well-defined location over long periods of time. The procedure was repeated at seven locations around the skull above target locations before viral injection. On each site a stainless steel guide tube was inserted into the cannulated screw followed by the injection needle into the guide tube. (Diester, Kaufman, Mogri, Pashaie, Goo, Yizhar, Ramakrishnan, Deisseroth, & Shenoy, 2011) depicts this process during an injection case in non-human primates.

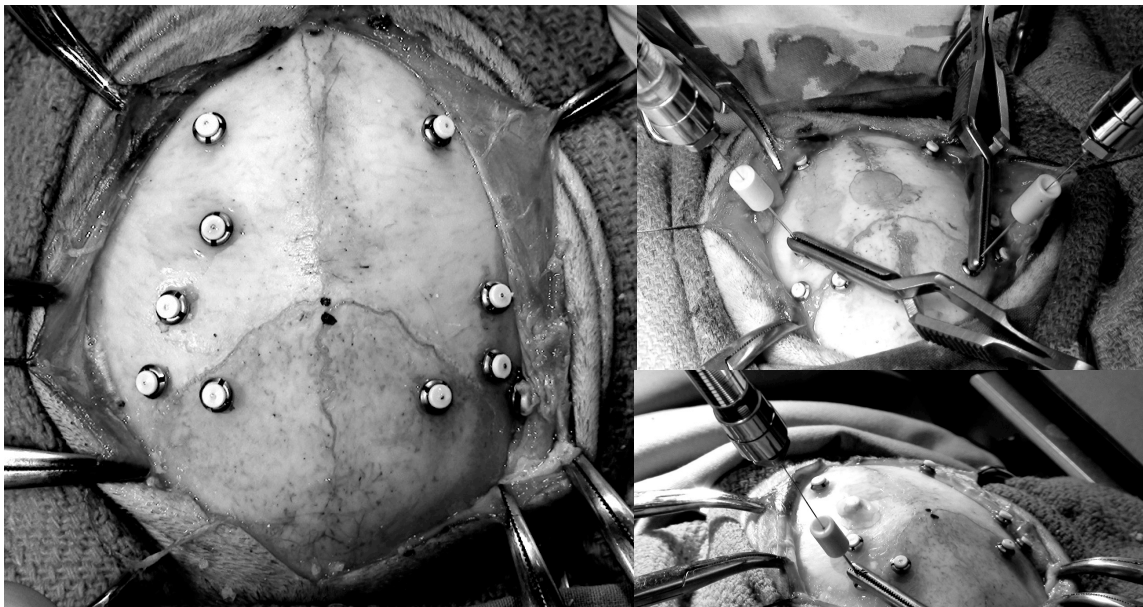


Figure A.3-2: (left) Cannulated screws implanted in the skull over the seven injection sites (nine screws were implanted, seven used). Guide tubes and Hamilton injection needles are shown on the right top and bottom figures.

The following constructs were used as they have been complementarily under study in non-human primates at Stanford University (Diester et al., 2011): AAV5-CaMKII-ChR2-EYFP, AAV5-hThy1-ChR2-EYFP, AAV5-hSyn-ChR2-EYFP, AAV5-hThy1-eNpHR2.0-EYFP. AAV5 (the adeno-associated virus type-5) is the viral package for all of these constructs. Each construct contains a different promoter (hThy1 = human thymine1 promoter; hSyn = human synapsin promoter; CaMKII = calcium/calmodulin-dependent kinase II promoter) with specificity to

different locations on the cell body, e.g. axonal membrane or synapse. A map of injection locations can be seen in Figure A.3-3. Cortical targets were chosen based on their role in motor planning (PMd, PMv), execution (MI), and visual-motor transformation (LIP).

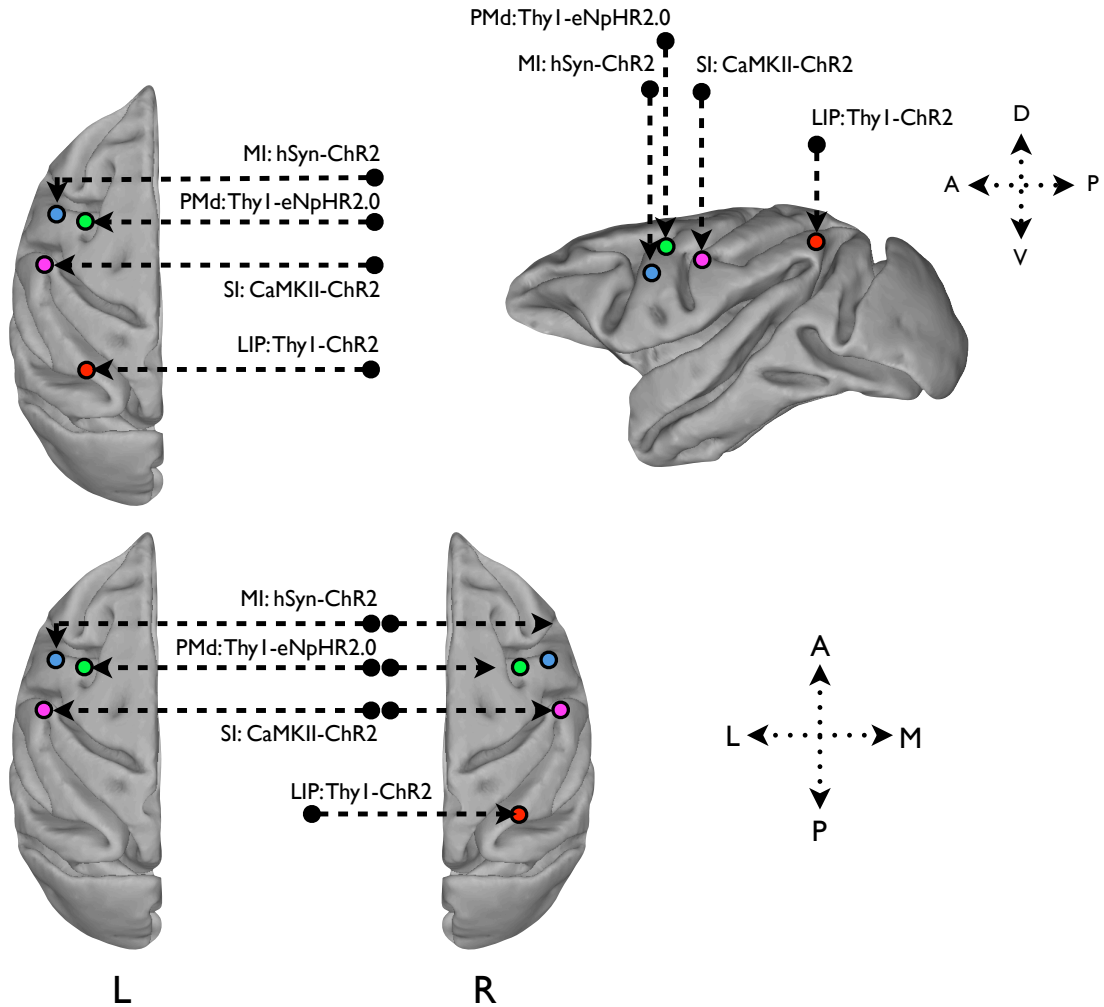


Figure A.3-3: Injection locations overlaid on the rhesus macaque MRI-base structural atlas with virus vectors noted. Injection locations were mirror on either hemisphere of the brain, except for the LIP site, which was not duplicated. *D* = dorsal, *V* = ventral, *A* = anterior, *P* = posterior, *L* = lateral, *M* = medial.

A.4 Acute neural activation through ChR2 in non-human primates with blue light

We waited three weeks to allow for transport of the viral payload to the cellular nucleus and for cellular mechanisms of protein production to have ample time for ChR2 production. Once

produced by the cell, its transport mechanisms migrate and embed the light-sensitive protein into the cell membrane. It has been shown that three weeks offers sufficient time for this process to occur in quantity to render the neuron “light-sensitive.” Once this time had passed, returned to each site individually with an “optrode” described above to evaluate the neural response to light stimulation in non-human primate cortex.

All sites, except for MI locations, showed healthy neural activity, evaluated by the ability to isolate and record from single units. However, only one site in this limited experiment showed light-induced changes in neural behavior. This site was on the lateral intraparietal (LIP) gyrus. At this location, we were able to activate neurons with high temporal accuracy via blue laser light impulses. The results are shown in (F. Zhang, Wang, Brauner, Liewald, Kay, Watzke, Wood, Bamberg, Nagel, Gottschalk, & Deisseroth, 2007).

It can clearly be seen that neuronal activity closely followed light stimulation. This work replicates that done at Stanford, and further builds the optogenetic knowledgebase, in particular the translation of techniques from rodent to non-human primate models. There is a general consensus that optical modulation of neurons in primates is more subtle than equivalent modulation in rodent models extensively discussed by Deisseroth et al. (Kells, Hadaczek, Yin, Bringas, Varenika, Forsayeth, & Bankiewicz, 2009). It has also been proposed that expression volumes may simply need to be increased to observe the same effect in primates as seen in rodents. Current practices inject about $1\mu\text{L}$ of virus into several cortical layers in columnar fashion. This in turn leads to expression of the membrane-bound light sensitive proteins within a 1mm^3 volume surrounding the injection site. Others (Kells et al., 2009) have begun to explore methods of global delivery of gene therapy, such as optogenetics. Methods employed to achieve global distribution include convection-enhanced delivery, a process wherein large ($100\mu\text{L}$) boluses of virus are injected at one time in an area with numerous projections throughout the brain, such as the thalamus. While initial studies have shown impressive expression, it remains to be seen if this expression enhancement in fact leads to light-modulation of the cells.

A.5 Histology

In order to evaluate expression in our experiment, the animal was euthanized and immediately perfused with 10% formalin to fix the tissue. The brain was removed from the cranium and sent to an outside vendor (Neuroscience Associates) for blocking and histology. There, the sections were stained for YFP (all viral constructs contained EYFP as the fluorescent marker) using an anti-GFP antibody. We did this antibody staining as opposed to directly looking at the fluorescence of the cells because antibody staining will maintain visibility indefinitely, while fluorescence will lose brightness quickly.

The GFP and YFP family of molecules were derived from jellyfish and there is not a mammal equivalent or 'close cousin.' Thus, there is nothing intrinsically in the non-human primate brain to which the antibody can bind. Since the antibody is polyclonal and is made against a number of epitopes on the YFP molecule, it is reasonable to believe that the anti-GFP would work with YFP - and it does (Figure A.5-3).

The antibody staining process is one of amplification. The presence of an antibody-antigen (YFP/GFP) complex is further increased by binding with secondary antibodies (against the IgG of the primary) and even further since the secondary has biotins attached which are attachment points for later avidin binding. The avidins are also complexed with horseradish peroxidase (HRP) and then 'enlarged' further by the fact that they cause polymerization of diaminobenzidine (DAB). The intensity of the YFP fluorescence can be influenced in a number of ways both chemically and by photo degradation. For the latter, prolonged exposure to ambient light of the certain wavelength spectra can reduce the emission or alter the molecule itself. Fluorescence microscope lights are very bright and can quickly cause degradation of the fluorescent protein.

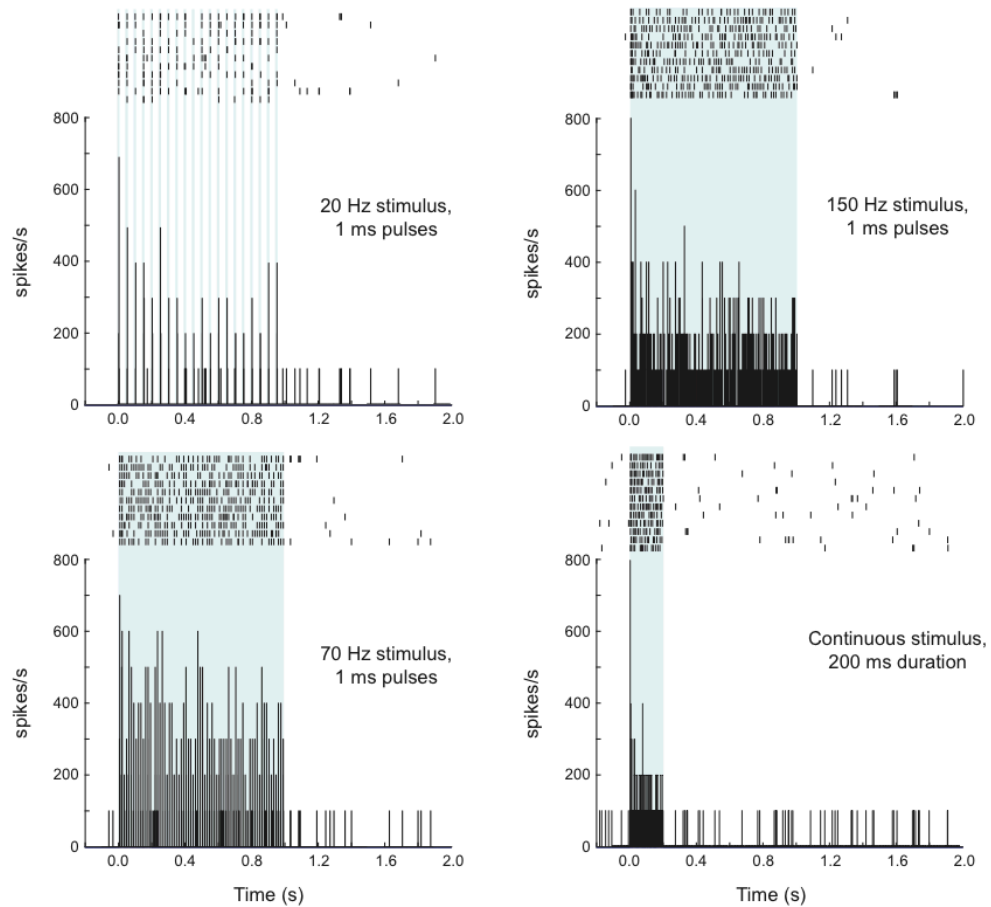


Figure A.5-1: Response of LIP neurons to pulsed and continuous blue laser light. This is one of the first recordings of light-sensitive neurons (through ChR2 transduction) in monkey cortex. This particular neuron was well time locked (<7ms) to the light pulses.

The remained of this section will be left to the reader at future time for interpretation.

Dark color indicates absorption (and existence) of the EYFP marker, and thus, expression of ChR2. Currently, all that can be surmised is that expression was seen in $>1\text{mm}^3$ volumes surrounding each injection site. In addition, projections from the motor cortex to the thalamus were transduced.

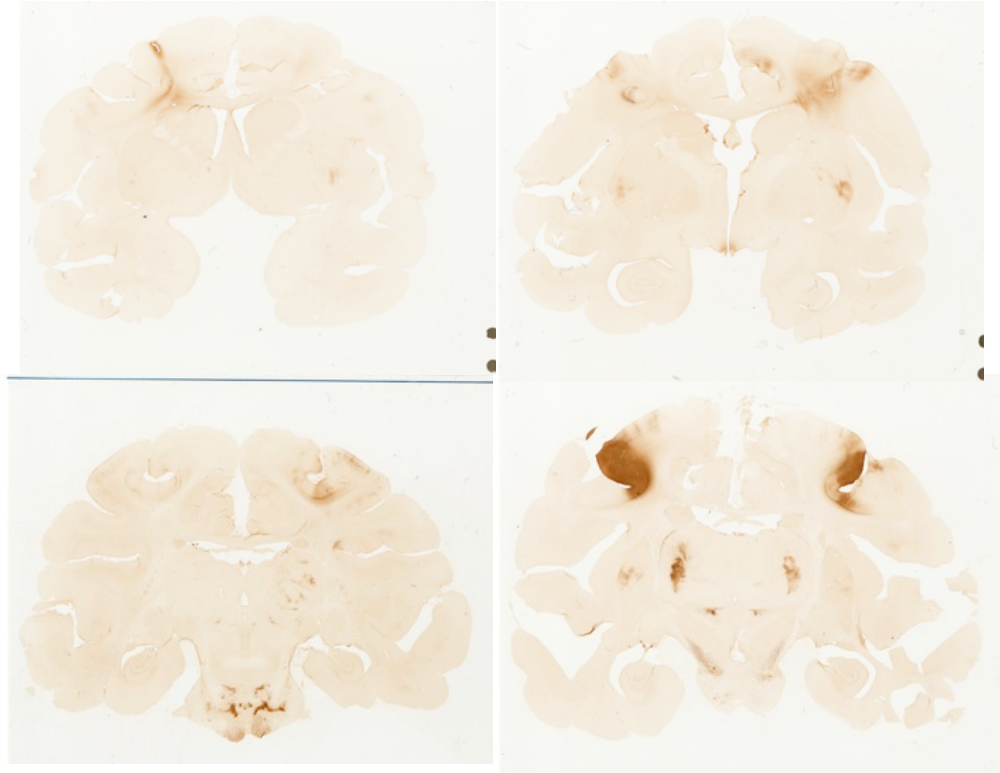


Figure A.5-2: Example histological slices showing expression in many areas of the brain, including the thalamus, axons in the pyramidal tract, and the putamen.

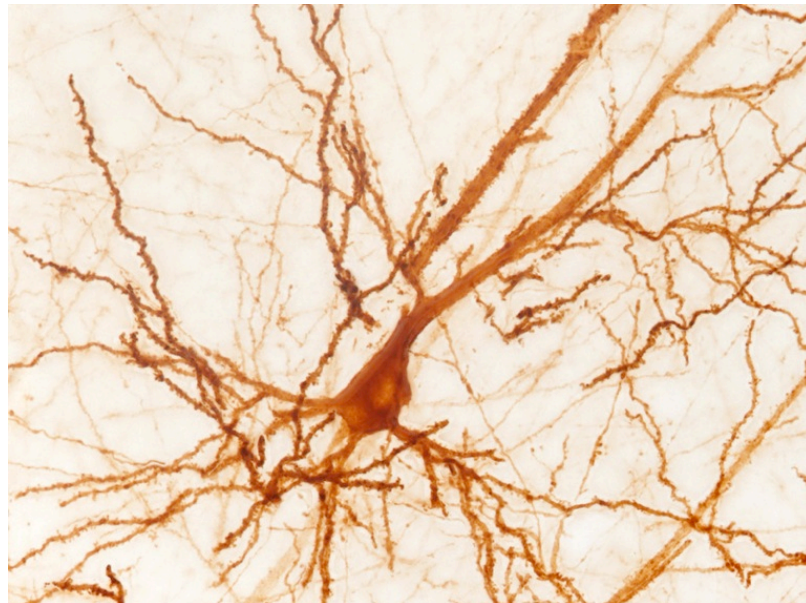


Figure A.5-3: Highly magnified image showing excellent binding of anti-GFP to the YFP protein present on the neurons - note the neuronal spines are visible.

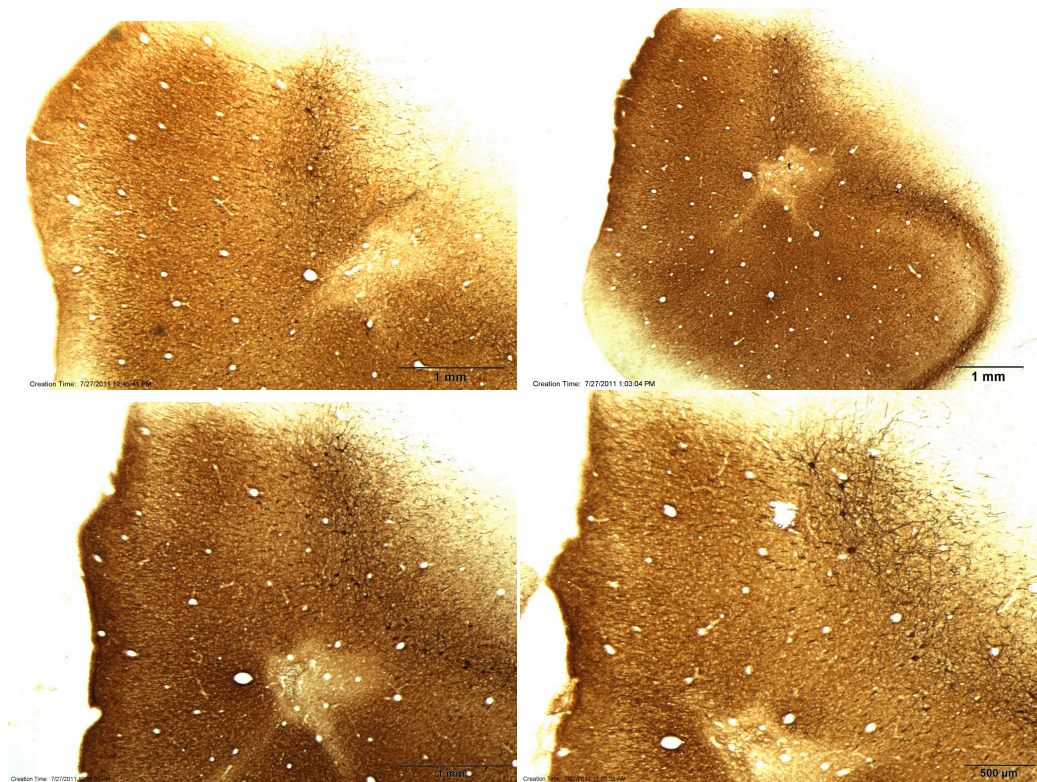


Figure A.5-4: Left primary motor cortex injection site. There appeared to be damaged tissue near this one injection location. Since no neurons could be isolated in this location, it is possible the area was damaged during the injection procedure.

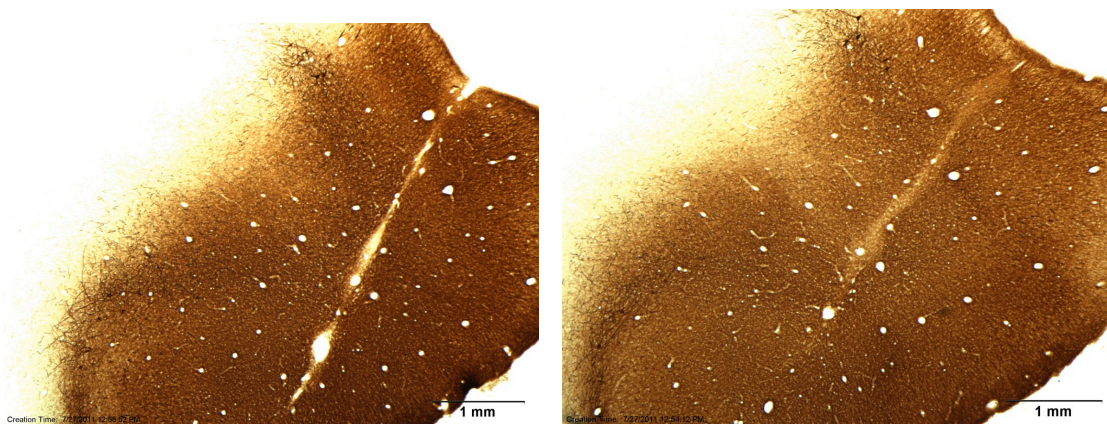


Figure A.5-5: Image of electrode, injection needle, or optrode tract and surrounding damaged tissue. It is unclear which instrument did the damage in this location, however extremely strong expression is still seen.

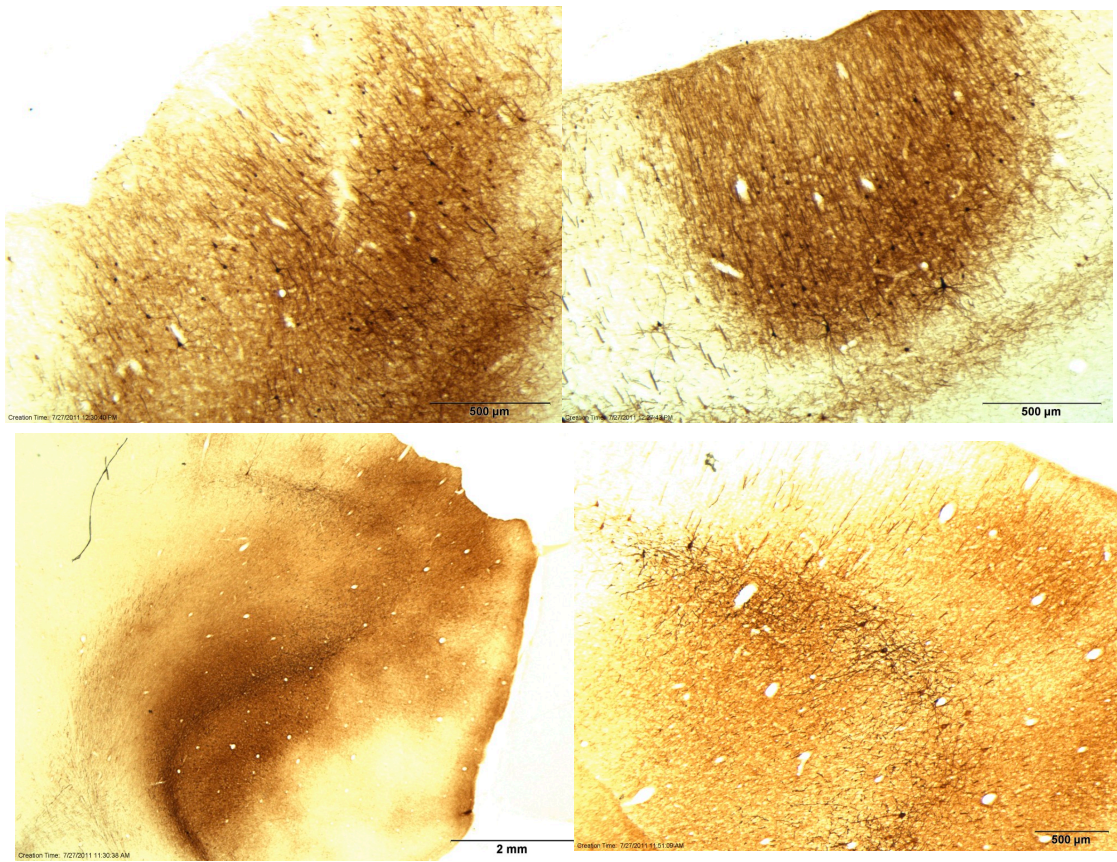


Figure A.5-6: Expression in LIP (top) where optical modulation of neurons reported above was recorded. The electrode tract can also be seen (top-left) and well defined ~1mm diameter of expression (top-right). Right PMd is shown in bottom figures – cell bodies can be seen at all locations.

Literature Cited

- Aceros, J., Yin, M., Borton, D. A., Patterson, W. R., & Nurmikko, A. V. (2011). A 32-channel fully implantable wireless neurosensor for simultaneous recording from two cortical regions. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 2011*, 2300-6. doi:10.1109/IEMBS.2011.6090579
- Acharya, S., Tenore, F., Aggarwal, V., Etienne-Cummings, R., Schieber, M. H., & Thakor, N. V. (2008). Decoding Individuated Finger Movements Using Volume-Constrained Neuronal Ensembles in the M1 Hand Area. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, 16(1), 15-23. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=4435078
- Adrian, E. D. (1954). The basis of sensation; some recent studies of olfaction. *British medical journal*, 1(4857), 287-90. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2093300&tool=pmcentrez&rendertype=abstract>
- Afshar, A., Santhanam, G., Yu, B. M., Ryu, S. I., Sahani, M., & Shenoy, K. V. (2011). Single-trial neural correlates of arm movement preparation. *Neuron*, 71(3), 555-64. doi:10.1016/j.neuron.2011.05.047
- Afshar, P., Moran, D., Rouse, A., Wei, X., & Denison, T. (2011). Validation of chronic implantable neural sensing technology using electrocorticographic (ECoG) based brain machine interfaces. *2011 5th*

- International IEEE/EMBS Conference on Neural Engineering* (pp. 704-707). IEEE.
doi:10.1109/NER.2011.5910645
- Amirikian, B., Georgopoulos, A. P., & Georgopoulos, A. P. (2000). Directional tuning profiles of motor cortical cells. *Neuroscience research*, 36(1), 73-9. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10678534>
- Andersen, P., & Andersen, S. (1968). *Physiological Basis of the Alpha Rhythm*. Appleton-Century Crofts.
- Awad, I. A., Rosenfeld, J., Ahl, J., Hahn, J. F., & Lüders, H. (1991). Intractable Epilepsy and Structural Lesions of the Brain: Mapping, Resection Strategies, and Seizure Outcome. *Epilepsia*, 32(2), 179-186. doi:10.1111/j.1528-1157.1991.tb05242.x
- Badran, K., Arya, A. K., Bunstone, D., & Mackinnon, N. (2009). Long-term complications of bone-anchored hearing aids: a 14-year experience. *The Journal of laryngology and otology*, 123(2), 170-6. doi:10.1017/S0022215108002521
- Bansal, A. K., & Vargas-Irwin, C. E. (2011). Relationships among low-frequency local field potentials, spiking activity, and 3-D reach and grasp kinematics in primary motor and ventral premotor cortices. *Journal of Neurophysiology*. Retrieved from <http://jn.physiology.org/content/early/2011/01/21/jn.00532.2010.abstract>
- Bazett, H. C., & Love, L. (1948). Temperature changes in blood flowing in arteries and veins in man. *Journal of applied physiology*, 1(1), 3-19. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18887571>
- Berger, H. (1929). Über das Elektrenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten*, 87(1), 527-570. doi:10.1007/BF01797193
- Bjarkam, C R, Cancian, G., Larsen, M., Rosendahl, F., Ettrup, K. S., Zeidler, D., Blankholm, A. D., Østergaard, L., Sunde, N., & Sørensen, J. C. (2004). A MRI-compatible stereotaxic localizer box enables high-precision stereotaxic procedures in pigs. *Journal of neuroscience methods*, 139(2), 293-8. doi:10.1016/j.jneumeth.2004.05.004
- Blomstedt, P., Olivecrona, M., Sailer, A., & Hariz, M. I. (2007). Dittmar and the history of stereotaxy; or rats, rabbits, and references. *Neurosurgery*, 60(1), 192-198. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17228269&retmode=ref&cmd=prlinks>
- Borton, D A, Song, Y. K., Patterson, W. R., Bull, C. W., Park, S., Laiwalla, F., Donoghue, J. P., & Nurmikko, A. V. (2009). Implantable wireless cortical recording device for primates. *World Congress on Medical Physics and Biomedical Engineering, September 7-12, 2009, Munich, Germany*, 588-591.
- Borton, D., Yin, M., Aceros, J., Agha, N., Minxha, J., Komar, J., Patterson, W., Bull, C., & Nurmikko, A. (2011). Developing implantable neuroprosthetics: A new model in pig. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference* (Vol. 2011, pp. 3024-30). doi:10.1109/IEMBS.2011.6090828
- Borton, David A, Song, Y.-K., Patterson, W. R., Bull, C. W., Park, S., Laiwalla, F., Donoghue, J. P., & Nurmikko, A. V. (2009). Wireless, high-bandwidth recordings from non-human primate motor cortex using a scalable 16-Ch implantable microsystem. *Conference proceedings : ... Annual International*

- Conference of the IEEE Engineering in Medicine and Biology Society. *IEEE Engineering in Medicine and Biology Society. Conference*, 2009, 5531-4. doi:10.1109/IEMBS.2009.5333189
- Boyden, E. S., Zhang, F., Bamberg, E., Nagel, G., & Deisseroth, K. (2005). Millisecond-timescale, genetically targeted optical control of neural activity. *Nature Neuroscience*, 8(9), 1263-1268.
- Buch, E., Boyle, N. G., & Belott, P. H. (2011). Pacemaker and defibrillator lead extraction. *Circulation*, 123(11), e378-80. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21422393&retmode=ref&cmd=prlinks>
- Buchwald, J. S., & Grover, F. S. (1970). Amplitudes of background fast activity characteristic of specific brain sites. *Journal of neurophysiology*, 33(1), 148-59. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/5411510>
- Buckmaster, P. S. (2004). Laboratory Animal Models of Temporal Lobe Epilepsy. *Comparative Medicine*, 54(5), 473-485.
- Bullock, T. (1997). Signals and signs in the nervous system: the dynamic anatomy of electrical activity is probably *Proceedings of the National Academy of Sciences*. Retrieved from <http://www.pnas.org/cgi/content/abstract/94/1/1>
- Buzsaki, G. (2006). *Rhythms of the Brain* (1st ed., p. 464). Oxford University Press.
- Buzsáki, György, & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science (New York, N.Y.)*, 304(5679), 1926-9. doi:10.1126/science.1099745
- Chadwick, E. K., Blana, D., Simeral, J. D., Lambrecht, J., Kim, S. P., Cornwell, A. S., Taylor, D. M., Hochberg, L. R., Donoghue, J. P., & Kirsch, R. F. (2011). Continuous neuronal ensemble control of simulated arm reaching by a human with tetraplegia. *Journal of neural engineering*, 8(3), 034003. doi:10.1088/1741-2560/8/3/034003
- Chae, M. S., Yang, Z., Yuce, M. R., Hoang, L., & Liu, W. (2009). A 128-channel 6 mW wireless neural recording IC with spike feature extraction and UWB transmitter. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 17(4), 312-21. doi:10.1109/TNSRE.2009.2021607
- Choi, J. H., Jung, H. K., & Kim, T. (2006). A new action potential detector using the MTEO and its effects on spike sorting systems at low signal-to-noise ratios. *IEEE transactions on bio-medical engineering*, 53(4), 738-746. doi:10.1109/TBME.2006.870239
- Chow, B. Y., Han, X., Dobry, A. S., Qian, X., Chuong, A. S., Li, M., Henninger, M. A., Belfort, G. M., Lin, Y., Monahan, P. E., & Boyden, E. S. (2010). High-performance genetically targetable optical neural silencing by light-driven proton pumps. *Nature*, 463(7277), 98-102. doi:10.1038/nature08652
- Churchland, M. M., Yu, B. M., Cunningham, J. P., Sugrue, L. P., Cohen, M. R., Corrado, G. S., Newsome, W. T., Clark, A. M., Hosseini, P., Scott, B. B., Bradley, D. C., Smith, M. a, Kohn, A., Movshon, J. A., Armstrong, K. M., Moore, T., Chang, S. W., Snyder, L. H., Lisberger, S. G., et al. (2010). Stimulus onset quenches neural variability: a widespread cortical phenomenon. *Nature neuroscience*, 13(3), 369-78. doi:10.1038/nn.2501
- Cogan, S. F. (2008). Neural stimulation and recording electrodes. *Annual Review of Biomedical Engineering*, 10(1), 275-309. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18429704>

- Commons, C. (n.d.). MediaWiki. Retrieved from <http://www.mediawiki.org/wiki/MediaWiki>
- Cooper, T. E., & Trezek, G. J. (1971). Correlation of thermal properties of some human tissue with water content. *Aerospace medicine*, 42(1), 24-7. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/5541087>
- Craner, S. (1991a). Somatosensory cortex of the neonatal pig: I. Topographic organization of the primary somatosensory cortex (SI). *The Journal of Comparative Neurology*. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1002/cne.903060103/abstract>
- Craner, S. (1991b). Somatosensory cortex of the neonatal pig: II. Topographic organization of the secondary somatosensory cortex (SII). *The Journal of Comparative ...*. Retrieved from <http://www3.interscience.wiley.com/journal/109691686/abstract>
- Cruikshank, S. J., Urabe, H., Nurmikko, A. V., & Connors, B. W. (2010). Pathway-specific feedforward circuits between thalamus and neocortex revealed by selective optical stimulation of axons. *Neuron*, 65(2), 230-45. doi:10.1016/j.neuron.2009.12.025
- Csicsvari, J., Henze, D. A., Jamieson, B., Harris, K. D., Sirota, A., Barthó, P., Wise, K. D., & Buzsáki, G. (2003). Massively parallel recording of unit and local field potentials with silicon-based electrodes. *Journal of neurophysiology*, 90(2), 1314-23. doi:10.1152/jn.00116.2003
- Dean, Jr., R. N. (2004). Novel biomedical implant interconnects utilizing micromachined LCP. *Proceedings of SPIE* (Vol. 5515, pp. 88-99). University of Michigan: SPIE. doi:10.1117/12.559831
- Denison, T., Consoer, K., Santa, W., Avestruz, A.-T., Cooley, J., & Kelly, A. (2007). A 2 μ W, 100 nV/rHz Chopper-Stabilized Instrumentation Amplifier for Chronic Measurement of Neural Field Potentials. *IEEE Journal of Solid-State Circuits*, 42(12), 2934-2945. doi:10.1109/JSSC.2007.908664
- Denison, T., Santa, W., Jensen, R., Carlson, D., Molnar, G., & Avestruz, A.-T. (2008). An 8 μ W Heterodyning Chopper Amplifier for Direct Extraction of 2 μ Vrms Neuronal Biomarkers. *2008 IEEE International Solid-State Circuits Conference - Digest of Technical Papers* (pp. 162-603). IEEE. doi:10.1109/ISSCC.2008.4523107
- Diester, I., Kaufman, M. T., Mogri, M., Pashaie, R., Goo, W., Yizhar, O., Ramakrishnan, C., Deisseroth, K., & Shenoy, K. V. (2011). An optogenetic toolbox designed for primates. *Nature Neuroscience*, 14(3), 387-397. Retrieved from [papers2://publication/doi/doi:10.1038/nn.2749](https://doi.org/10.1038/nn.2749)
- Doležel, B., Adamířová, L., Náprstek, Z., & Vondráček, P. (1989). In vivo degradation of polymers. *Biomaterials*, 10(2), 96-100. doi:10.1016/0142-9612(89)90039-2
- Donaldson, P E K. (2003). The essential role played by adhesion in the technology of neurological prostheses . Retrieved from [papers2://publication/uuid/255B7C4C-5901-4F21-9D7D-B68B1B566910](https://doi.org/10.1038/nn.2749)
- Donaldson, Peter E. K. (1976). The Encapsulation of Microelectronic Devices for Long-Term Surgical Implantation. *IEEE Transactions on Biomedical Engineering*, BME-23(4), 281-285. doi:10.1109/TBME.1976.324586
- Donoghue, J P, Sanes, J. N., Hatsopoulos, N. G., & Gaál, G. (1998). Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. *Journal of neurophysiology*, 79(1), 159-73. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9425187>

- Drachman, D. A. (2005). Do we have brain to spare? *Neurology*, 64(12), 2004-5. doi:10.1212/01.WNL.0000166914.38327.BB
- Drummond, J. C. (2000). Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. *Anesthesiology*, 93(3), 876-82. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10969323>
- Dunbar, R. I. M. (1992). Neocortex size as a constraint on group size in primates. *Journal of Human Evolution*, 22(6), 469-493. doi:10.1016/0047-2484(92)90081-J
- Edell, D. (2004). Insulating Biomaterials N01-NS-9-2323. *Insulating Biomaterials N01-NS-9-2323*. Retrieved from <papers2://publication/uuid/96D18FA7-3BE2-4370-80B5-A9AAF6370F22>
- Eller, T. (2011). Deep brain stimulation for Parkinson's disease, essential tremor, and dystonia. *Disease-a-month : DM*, 57(10), 638-46. doi:10.1016/j.disamonth.2011.09.002
- Elmqvist, R. (1978). Review of Early Pacemaker Development. *Pacing and Clinical Electrophysiology*, 1(4), 535-536. doi:10.1111/j.1540-8159.1978.tb03518.x
- Evarts, E. V. (1968). A technique for recording activity of subcortical neurons in moving animals. *Electroencephalography and Clinical Neurophysiology*, 24(1), 83-86. doi:10.1016/0013-4694(68)90070-9
- FDA. (2010). *Medical Device Classification - Is The Product A Medical Device?* Center for Devices and Radiological Health. Retrieved from <http://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/ucm051512.htm>
- Fetz, E E, Chen, D., Murthy, V. N., & Matsumura, M. (2000). Synaptic interactions mediating synchrony and oscillations in primate sensorimotor cortex. *Journal of physiology, Paris*, 94(5-6), 323-31. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11165903>
- Fields, R. D., & Stevens-Graham, B. (2002). New insights into neuron-glia communication. *Science (New York, N.Y.)*, 298(5593), 556-62. doi:10.1126/science.298.5593.556
- Foster, K. R., Schepps, J. L., Stoy, R. D., & Schwan, H. P. (1979). Dielectric properties of brain tissue between 0.01 and 10 GHz. *Physics in Medicine and Biology*, 24(6), 1177-1187. doi:10.1088/0031-9155/24/6/008
- Fowler, K. (2001). Anesthetic protocol: propofol use in Rhesus macaques (*Macaca mulatta*) during magnetic resonance imaging with stereotactic head frame application. *Brain Research Protocols*, 7(2), 87-93. doi:10.1016/S1385-299X(00)00051-9
- Freeman, W. J., Holmes, M. D., Burke, B. C., & Vanhatalo, S. (2003). Spatial spectra of scalp EEG and EMG from awake humans. *Clinical Neurophysiology*, 114(6), 1053-1068. doi:10.1016/S1388-2457(03)00045-2
- Fukuda, M., Nishida, M., Juhász, C., Muzik, O., Sood, S., Chugani, H. T., & Asano, E. (2008). Short-latency median-nerve somatosensory-evoked potentials and induced gamma-oscillations in humans. *Brain : a journal of neurology*, 131(Pt 7), 1793-805. doi:10.1093/brain/awn100
- Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science (New York, N.Y.)*, 173(3997), 652-4. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/4998337>

- Félix, B., Léger, M. E., Albe-Fessard, D., Marcilloux, J. C., Rampin, O., Laplace, J. P., Duclos, A., Fort, F., Gougis, S., & Costa, M. (1999). Stereotaxic atlas of the pig brain. *Brain research bulletin*, 49(1-2), 1-137. Retrieved from <http://rl3tp7zf5x.scholar.serialssolutions.com/?sid=google&auinit=B&aunit=B&aulast=Félix&atitle=Stereotaxic+atlas+of+the+pig+brain&title=Brain+research+bulletin&volume=49&issue=1-2&date=1999&spage=1&issn=0361-9230>
- Gabriel, S., Lau, R. W., & Gabriel, C. (1996). The dielectric properties of biological tissues: II. Measurements in the frequency range 10 Hz to 20 GHz. *Physics in Medicine and Biology*, 41(11), 2251-2269. doi:10.1088/0031-9155/41/11/002
- Ganguli, S., Bisley, J. W., Roitman, J. D., Shadlen, M. N., Goldberg, M. E., & Miller, K. D. (2008). One-dimensional dynamics of attention and decision making in LIP. *Neuron*, 58(1), 15-25. doi:10.1016/j.neuron.2008.01.038
- Gentilucci, M., Scandolara, C., Pigarev, I. N., & Rizzolatti, G. (1983). Visual responses in the postarcuate cortex (area 6) of the monkey that are independent of eye position. *Experimental Brain Research*, 50(2-3). doi:10.1007/BF00239214
- Georgopoulos, A. P., Kalaska, J. F., Caminiti, R., & Massey, J. T. (1982). On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 2(11), 1527-37. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7143039>
- Gold, C., Henze, D. a, Koch, C., & Buzsáki, G. (2006). On the origin of the extracellular action potential waveform: A modeling study. *Journal of neurophysiology*, 95(5), 3113-28. doi:10.1152/jn.00979.2005
- Green, T. (1872). On Death from Chloroform. *BMJ*, 2(623), 628-629. doi:10.1136/bmj.2.623.628
- Griffith, R. W., & Humphrey, D. R. (2006). Long-term gliosis around chronically implanted platinum electrodes in the Rhesus macaque motor cortex. *Neuroscience letters*, 406(1-2), 81-6. doi:10.1016/j.neulet.2006.07.018
- Guangqiang, J., & Zhou, D. (2010). *Implantable Neural Prostheses 2*. (D. Zhou & E. Greenbaum, Eds.). New York, NY: Springer New York. doi:10.1007/978-0-387-98120-8
- Harrison, R R, Kier, R. J., Chestek, C. A., Gilja, V., Nuyujukian, P., Ryu, S., Greger, B., Solzbacher, F., & Shenoy, K. V. (2009). Wireless Neural Recording With Single Low-Power Integrated Circuit. *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, 17(4), 322-329. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=5061585
- Harrison, R.R., & Charles, C. (2003). A low-power low-noise cmos for amplifier neural recording applications. *IEEE Journal of Solid-State Circuits*, 38(6), 958-965. doi:10.1109/JSSC.2003.811979
- Hernando, A., Villuendas, D., Vesperinas, C., Abad, M., & Plastino, A. (2009). Unravelling the size distribution of social groups with information theory on complex networks. Retrieved from <http://arxiv.org/abs/0905.3704>
- Histed, M. H., Bonin, V., & Reid, R. C. (2009). Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. *Neuron*, 63(4), 508-22. doi:10.1016/j.neuron.2009.07.016

- Hochberg, L., Serruya, M., & Friehs, G. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *NATURE-LONDON*. Retrieved from <http://www.niu.edu/user/tj0dgw1/pdf/tetraplegia2006.pdf>
- Hochberg, Leigh R., Serruya, M. D., Friehs, G. M., Mukand, J. A., Saleh, M., Caplan, A. H., Branner, A., Chen, D., Penn, R. D., & Donoghue, J. P. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*, 442(7099), 164-171. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=16838014&retmode=ref&cmd=prlinks>
- Hodgkin, A. L., & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *Bulletin of mathematical biology*, 52(1-2), 25-71; discussion 5-23. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/2185861>
- Hoogerwerf, A. C., & Wise, K. D. (1994). A three-dimensional microelectrode array for chronic neural recording. *IEEE transactions on bio-medical engineering*, 41(12), 1136-46. doi:10.1109/10.335862
- Hubel, D. H., & Wiesel, T. N. (1959). Receptive fields of single neurones in the cat's striate cortex. *The Journal of physiology*, 574. doi:10.1113/jphysiol.2009.174151
- Humphrey, D R. (1970). A chronically implantable multiple micro-electrode system with independent control of electrode positions. *Electroencephalography and clinical neurophysiology*, 29(6), 616-20. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/4098585>
- Humphrey, D R, Schmidt, E. M., & Thompson, W. D. (1970). Predicting measures of motor performance from multiple cortical spike trains. *Science (New York, N.Y.)*, 170(3959), 758-62. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/4991377>
- Iga, K. (2000). Surface-emitting laser-its birth and generation of new optoelectronics field. *IEEE Journal of Selected Topics in Quantum Electronics*, 6(6), 1201-1215. doi:10.1109/2944.902168
- Iga, Kenichi., Koyama, F., & Kinoshita, S. (1988). Surface emitting semiconductor lasers. *IEEE Journal of Quantum Electronics*, 24(9), 1845-1855. doi:10.1109/3.7126
- Im, M., Cho, I.-joo, Wu, F., Wise, K. D., & Yoon, E. (2011). Neural probes integrated with optical mixer/splitter waveguides and multiple stimulation sites. *2011 IEEE 24th International Conference on Micro Electro Mechanical Systems* (pp. 1051-1054). IEEE. doi:10.1109/MEMSYS.2011.5734609
- Jackson, A., Mavoori, J., & Fetzi, E. E. (2007). Correlations between the same motor cortex cells and arm muscles during a trained task, free behavior, and natural sleep in the macaque monkey. *Journal of neurophysiology*, 97(1), 360-74. doi:10.1152/jn.00710.2006
- Jaenisch, R., & Mintz, B. (1974). Simian Virus 40 DNA Sequences in DNA of Healthy Adult Mice Derived from Preimplantation Blastocysts Injected with Viral DNA. *Proceedings of the National Academy of Sciences of the United States of America*, 71(4), 1250. Retrieved from [/pmc/articles/PMC388203/?report=abstract](http://pmc/articles/PMC388203/?report=abstract)
- Jefferys, J. G. R. (2003). Models and mechanisms of experimental epilepsies. *Epilepsia*, 44 Suppl 1(1), 44-50. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/14641560>
- Jewell, J. L., Harbison, J. P., Scherer, A., Lee, Y. H., & Florez, L. T. (1991). Vertical-cavity surface-emitting lasers: Design, growth, fabrication, characterization. *IEEE Journal of Quantum Electronics*, 27(6), 1332-1346. doi:10.1109/3.89950

- Jones, K. E., Campbell, P. K., & Normann, R. A. (1992). A glass/silicon composite intracortical electrode array. *Annals of Biomedical Engineering*, 20(4), 423-437. doi:10.1007/BF02368134
- Joucla, S., & Yvert, B. (2009). Improved focalization of electrical microstimulation using microelectrode arrays: a modeling study. *PloS one*, 4(3), e4828. doi:10.1371/journal.pone.0004828
- Junker, R., Dimakis, A., Thoneick, M., & Jansen, J. A. (2009). Effects of implant surface coatings and composition on bone integration: a systematic review. *Clinical oral implants research*, 20 Suppl 4, 185-206. doi:10.1111/j.1600-0501.2009.01777.x
- Kells, A. P., Hadaczek, P., Yin, D., Bringas, J., Varenika, V., Forsayeth, J., & Bankiewicz, K. S. (2009). Efficient gene therapy-based method for the delivery of therapeutics to primate cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 106(7), 2407-11. doi:10.1073/pnas.0810682106
- Kennedy, P. R., Bakay, R. A. E., Moore, M. M., Adams, K., & Goldwaithe, J. (2000). Direct control of a computer from the human central nervous system. *IEEE Transactions on Rehabilitation Engineering*, 8(2), 198-202. doi:10.1109/86.847815
- Kim, S., Bhandari, R., Klein, M., Negi, S., Rieth, L., Tathireddy, P., Toepper, M., Oppermann, H., & Solzbacher, F. (2009). Integrated wireless neural interface based on the Utah electrode array. *Biomedical microdevices*, 11(2), 453-66. doi:10.1007/s10544-008-9251-y
- Kim, Sohee, Harrison, R., & Solzbacher, F. (2008). Influence of system integration and packaging for a wireless neural interface on its wireless powering performance. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 2008*, 3182-5. doi:10.1109/IEMBS.2008.4649880
- Kim, Sung-Phil, Simeral, J. D., Hochberg, L. R., Donoghue, J. P., & Black, M. J. (2008). Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *Journal of neural engineering*, 5(4), 455-76. doi:10.1088/1741-2560/5/4/010
- Kim, Sung-Phil, Simeral, J. D., Hochberg, L. R., Donoghue, J. P., Friehs, G. M., & Black, M. J. (2007). Multi-state decoding of point-and-click control signals from motor cortical activity in a human with tetraplegia. *2007 3rd International IEEE/EMBS Conference on Neural Engineering* (pp. 486-489). IEEE. doi:10.1109/CNE.2007.369715
- Kim, Sung-Phil, Simeral, J. D., Hochberg, L. R., Donoghue, J. P., Friehs, G. M., & Black, M. J. (2011). Point-and-click cursor control with an intracortical neural interface system by humans with tetraplegia. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 19(2), 193-203. doi:10.1109/TNSRE.2011.2107750
- Kipke, D. R., Shain, W., Buzsáki, G., Fetz, E., Henderson, J. M., Hetke, J. F., & Schalk, G. (2008). Advanced neurotechnologies for chronic neural interfaces: new horizons and clinical opportunities. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 28(46), 11830-8. doi:10.1523/JNEUROSCI.3879-08.2008
- Kipke, D., Williams, J., Hetke, J., Henderson, J., & Garell, C. (2011). Intracranial neural interface system. USPTO.

- Kissin, I. (2000). Depth of anesthesia and bispectral index monitoring. *Anesthesia and analgesia*, 90(5), 1114-7. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10781463>
- Krings, T., Chiappa, K. H., Cuffin, B. N., Buchbinder, B. R., & Cosgrove, G. R. (1998). Accuracy of electroencephalographic dipole localization of epileptiform activities associated with focal brain lesions. *Annals of neurology*, 44(1), 76-86. doi:10.1002/ana.410440114
- Kurtz, S. (2011). *PEEK Biomaterials Handbook* (p. 306). William Andrew.
- LaMotte, R. H., & Mountcastle, V. B. (1975). Capacities of humans and monkeys to discriminate vibratory stimuli of different frequency and amplitude: a correlation between neural events and psychological measurements. *Journal of neurophysiology*, 38(3), 539-59. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1127456>
- Lambrecht, J. M., Pulliam, C. L., & Kirsch, R. F. (2011). Virtual Reality Environment for Simulating Tasks With a Myoelectric Prosthesis: An Assessment and Training Tool. *JPO Journal of Prosthetics and Orthotics*, 23(2), 89-94. doi:10.1097/JPO.0b013e318217a30c
- Leuthardt, E. C., Schalk, G., Wolpaw, J. R., Ojemann, J. G., & Moran, D. W. (2004). A brain-computer interface using electrocorticographic signals in humans. *Journal of neural engineering*, 1(2), 63-71. doi:10.1088/1741-2560/1/2/001
- Lewis, T. J. (1990). Charge transport, charge injection and breakdown in polymeric insulators. *Journal of Physics D: Applied Physics*, 23(12), 1469-1478. doi:10.1088/0022-3727/23/12/001
- Lind, N., Moustgaard, A., Jelsing, J., & Vajta, G. (2007). The use of pigs in neuroscience: modeling brain disorders. *Neuroscience and Biobehavioral Reviews*. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/S014976340700019X>
- Loeb, G. E., Bak, M. J., Salcman, M., & Schmidt, E. M. (1977). Parylene as a chronically stable, reproducible microelectrode insulator. *IEEE transactions on bio-medical engineering*, 24(2), 121-8. doi:10.1109/TBME.1977.326115
- Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 357(1424), 1003-37. doi:10.1098/rstb.2002.1114
- Mahesri, A., & Vardhan, V. (2005). Power Consumption Breakdown on a Modern, 165-180. doi:10.1007/11574859_12
- Malik, W. Q., Truccolo, W., Brown, E. N., & Hochberg, L. R. (2011). Efficient decoding with steady-state Kalman filter in neural interface systems. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 19(1), 25-34. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21078582&retmode=ref&cmd=prlinks>
- Mandlik, P., Gartside, J., Han, L., Cheng, I.-C., Wagner, S., Silvernail, J. A., Ma, R.-Q., Hack, M., & Brown, J. J. (2008). A single-layer permeation barrier for organic light-emitting displays. *Applied Physics Letters*, 92(10), 103309. doi:10.1063/1.2890432

- Maynard, E. M., Nordhausen, C. T., & Normann, R. A. (1997). The Utah intracortical Electrode Array: a recording structure for potential brain-computer interfaces. *Electroencephalography and clinical neurophysiology*, 102(3), 228-39. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9129578>
- McIlwain, J., & Creutzfeldt, O. (1967). Microelectrode Study of Synaptic Excitation and Inhibition in the Lateral Geniculate Nucleus of the Cat. *Journal of neurophysiology*, 30(1), 1-21.
- McIntyre, C. C., & Grill, W. M. (2001). Finite Element Analysis of the Current-Density and Electric Field Generated by Metal Microelectrodes. *Annals of Biomedical Engineering*, 29(3), 227-235. doi:10.1114/1.1352640
- Miranda, H., Gilja, V., Chestek, C. A., Shenoy, K. V., & Meng, T. H. (2010). HermesD: A High-Rate Long-Range Wireless Transmission System for Simultaneous Multichannel Neural Recording Applications. *IEEE Transactions on Biomedical Circuits and Systems*, 4(3), 181-191. doi:10.1109/TBCAS.2010.2044573
- Mitzdorf, U. (1985). Current source-density method and application in cat cerebral cortex: investigation of evoked *Physiological reviews*. Retrieved from <http://physrev.physiology.org/cgi/content/citation/65/1/37>
- Mohseni, P., Najafi, K., Eliades, S. J., & Wang, X. (2005). Wireless multichannel biopotential recording using an integrated FM telemetry circuit. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 13(3), 263-71. doi:10.1109/TNSRE.2005.853625
- Mojarradi, M., Binkley, D., Blalock, B., Andersen, R., Ulshoefer, N., Johnson, T., & Del Castillo, L. (2003). A miniaturized neuroprosthesis suitable for implantation into the brain. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 11(1), 38-42. doi:10.1109/TNSRE.2003.810431
- Moran, D W, & Schwartz, A. B. (1999). Motor cortical representation of speed and direction during reaching. *Journal of neurophysiology*, 82(5), 2676-92. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10561437>
- Morrell, M. J. (2011). Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*, 77(13), 1295-1304. doi:10.1212/WNL.0b013e3182302056
- Mountcastle, V. B., Lynch, J. C., Georgopoulos, A., Sakata, H., & Acuna, C. (1975). Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *Journal of neurophysiology*, 38(4), 871-908. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/808592>
- Nagel, G., Szellas, T., Huhn, W., Kateriya, S., Adeishvili, N., Berthold, P., Ollig, D., Hegemann, P., & Bamberg, E. (2003). Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. *Proceedings of the National Academy of Sciences of the United States of America*, 100(24), 13940-5. doi:10.1073/pnas.1936192100
- Nicolelis, M. A., Baccala, L. A., Lin, R. C., & Chapin, J. K. (1995). Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system. *Science (New York, N.Y.)*, 268(5215), 1353-8. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7761855>

- Nielsen, M. S., Sørensen, J. C., & Bjarkam, C. R. (2009). The substantia nigra pars compacta of the Göttingen minipig: an anatomical and stereological study. *Brain structure & function*, 213(4-5), 481-8. doi:10.1007/s00429-009-0217-5
- Noble, D. (1984). The surprising heart: a review of recent progress in cardiac electrophysiology. *The Journal of physiology*, 353(5), 1-50. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1193291>
- Nordhausen, C., Maynard, E., & Normann, R. A. (1996). Single unit recording capabilities of a 100 microelectrode array. *Brain Research ...*, 726(1-2), 129-140. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/0006899396003216>
- Normann, R. A., Rousche, P. J., & Horch, K. W. (1994). Impact inserter mechanism for implantation of a biomedical device. US Patent Office. Retrieved from <http://www.google.com/patents?hl=en&lr=&vid=USPAT5361760&id=Fc0bAAAAEBAJ&oi=fnd&q=insertion+of+electrode+array+by+pneumatic&printsec=abstract>
- Normann, R. A. (1990). A penetrating, cortical electrode array: design considerations. *IEEE International Conference on Systems, Man, and Cybernetics Conference Proceedings* (pp. 918-920). IEEE. doi:10.1109/ICSMC.1990.142258
- NuSil. (n.d.-a). *R-2180 A Product Sheet*. Retrieved from http://www.nusil.com/products/engineering/electronics/general_purpose/conformal_coatings.aspx
- NuSil. (n.d.-b). *R-2180 B Product Sheet*. Retrieved from http://www.nusil.com/products/engineering/electronics/general_purpose/conformal_coatings.aspx
- Ohnishi, A., Inoue, N., Yamamoto, T., Murai, Y., Hori, H., Koga, M., Tanaka, I., & Akiyama, T. (1985). Ethylene oxide induces central-peripheral distal axonal degeneration of the lumbar primary neurones in rats. *Occupational and Environmental Medicine*, 42(6), 373-379. doi:10.1136/oem.42.6.373
- Olsson, R. H. I. I., Gulari, A. N., & Wise, K. D. (2003). A fully-integrated bandpass amplifier for extracellular neural recording. *First International IEEE EMBS Conference on Neural Engineering, 2003. Conference Proceedings*. (pp. 165-168). IEEE. doi:10.1109/CNE.2003.1196783
- Onsager, L. (1931). Reciprocal Relations in Irreversible Processes. I. *Physical Review*, 37(4), 405-426. doi:10.1103/PhysRev.37.405
- Otsuka, K., Takeo, Y., Ishida, H., Yamada, T., Kuroda, S., & Tachi, H. (1987). The Mechanisms That Provide Corrosion Protection for Silicone Gel Encapsulated Chips. *IEEE Transactions on Components, Hybrids, and Manufacturing Technology*, 12(4). Retrieved from <http://www.google.com/search?client=safari&rls=en-us&q=The+Mechanisms+That+Provide+Corrosion+Protection+for+Silicone+Gel+Encapsulated+Chips&ie=UTF-8&oe=UTF-8>
- Parsonnet, V., Myers, G. H., Gilbert, L., & Zucker, I. R. (1975). Clinical experience with nuclear pacemakers. *Surgery*, 78(6), 776-86. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/1188620>
- Patino, L., Omlor, W., Chakarov, V., Hepp-Reymond, M.-C., & Kristeva, R. (2008). Absence of gamma-range corticomuscular coherence during dynamic force in a deafferented patient. *Journal of neurophysiology*, 99(4), 1906-16. doi:10.1152/jn.00390.2007

- Patterson III, W., Song, Y.-K., Bull, C., & Laiwalla, F. (n.d.). 9 CMOS ICS FOR BRAIN IMPLANTABLE NEURAL RECORDING MICROSYSTEMS. *Springer*. Retrieved from <http://www.springerlink.com/index/w273082vq41r3173.pdf>
- Patterson, W, Song, Y.-K., Bull, C., & Ozden, I. (2004). A microelectrode/microelectronic hybrid device for brain implantable neuroprosthesis applications. *IEEE transactions on bio-medical engineering*. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=1337153
- Patterson, William R, & Song, Y.-K. (2007). Development of brain implantable microsystems. *CMOS Biotechnology* (pp. 259-292). Springer New York.
- Patterson, William R, Bull, C. W., Borton, D. A., Nurmikko, A. V., Simeral, J. D., & Donoghue, J. P. (2008). A neural interface microsystem with all optical telemetry for brain implantable neuroengineering application. *2008 Conference on Lasers and Electro-Optics* (pp. 1-2). IEEE. doi:10.1109/CLEO.2008.4551410
- Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, 60(4), 389-443. doi:10.1093/brain/60.4.389
- Pennes, H. H. (1998). Analysis of tissue and arterial blood temperatures in the resting human forearm. 1948. *Journal of applied physiology (Bethesda, Md. : 1985)*, 85(1), 5-34. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9714612>
- Penttonen, M., & Buzsáki, G. (2006). Natural logarithmic relationship between brain oscillators. *Thalamus and Related Systems*. Retrieved from http://journals.cambridge.org/abstract_S1472928803000074
- Perelman, Y., & Ginosar, R. (2007). An integrated system for multichannel neuronal recording with spike/LFP separation, integrated A/D conversion and threshold detection. *IEEE transactions on bio-medical engineering*, 54(1), 130-137. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=retrieve&dopt=abstract&list_uids=17260864
- Plonsey, R., & Barr, R. (2000). *Bioelectricity* (2nd ed.). New York: Springer.
- Popp, F. A., Li, K. H., Mei, W. P., Galle, M., & Neurohr, R. (1988). Physical aspects of biophotons. *Experientia*, 44(7), 576-85. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/3294033>
- Poznanski, R. R. (2010). Thermal noise due to surface-charge effects within the Debye layer of endogenous structures in dendrites. *Physical Review E*, 81(2). doi:10.1103/PhysRevE.81.021902
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, 98(2), 676-82. doi:10.1073/pnas.98.2.676
- Ranck, J. (1975). Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Research*, 98, 417-440.
- Rasch, M. J., Gretton, A., Murayama, Y., Maass, W., & Logothetis, N. K. (2008). Inferring spike trains from local field potentials. *Journal of neurophysiology*, 99(3), 1461-76. doi:10.1152/jn.00919.2007
- Richer, J. P., Lacoste, L., Faure, J. P., Hauet, T., Ferrié, J. C., & Carretier, M. (1998). Sacrococcygeal and transsacral epidural anesthesia in the laboratory pig: a model for experimental surgery. *Surgical and Radiologic Anatomy*, 20(6), 431-435. doi:10.1007/BF01653136

- Rizk, M., Obeid, I., Callender, S. H., & Wolf, P. D. (2007). A single-chip signal processing and telemetry engine for an implantable 96-channel neural data acquisition system. *Journal of neural engineering*, 4(3), 309-21. doi:10.1088/1741-2560/4/3/016
- Rosenow, F. (2001). Presurgical evaluation of epilepsy. *Brain*, 124(9), 1683-1700. doi:10.1093/brain/124.9.1683
- Saikali, S., Meurice, P., Sauleau, P., & Eliat, P. (2010). A three-dimensional digital segmented and deformable brain atlas of the domestic pig. *Journal of Neuroscience*. Retrieved from <http://linkinghub.elsevier.com/retrieve/pii/S0165027010004164>
- Samsukha, P., Tabib-Azar, M., Harrison, R., & Chiel, H. (2004). Wireless multi-channel sensor for neurodynamic studies. *Sensors*. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=1426320
- Sanchez, J., Principe, J., Nishida, T., Bashirullah, R., & al, et. (2008). Technology and Signal Processing for Brain-Machine Interfaces. *Signal Processing Magazine*. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=4408440
- Santhanam, G., Yu, B. M., Gilja, V., Ryu, S. I., Afshar, A., Sahani, M., & Shenoy, K. V. (2009). Factor-analysis methods for higher-performance neural prostheses. *Journal of neurophysiology*, 102(2), 1315-30. doi:10.1152/jn.00097.2009
- Sauleau, P., Lapouble, E., Val-Laillet, D., & Malbert, C. H. (2009). The pig model in brain imaging and neurosurgery. *Animal*, 3(08), 1138-1151. Retrieved from papers2://publication/uuid/505F32C7-1DAD-4F4D-9A10-27465F280534
- Schell, G. R., & Strick, P. L. (1984). The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 4(2), 539-60. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/6199485>
- Schmidt, E. M., Bak, M. J., & McIntosh, J. S. (1976). Long-term chronic recording from cortical neurons. *Experimental neurology*, 52(3), 496-506. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/821770>
- Schobert, B., & Lanyi, J. (1982). Halorhodopsin is a Light-driven Chloride Pump. *Journal of Biological Chemistry*, 257(17), 10306-10313.
- Serruya, M. D., Hatsopoulos, N. G., Paninski, L., Fellows, M. R., & Donoghue, J. P. (2002). Instant neural control of a movement signal. *Nature*, 416(6877), 141-2. doi:10.1038/416141a
- Simeral, J D, Kim, S.-P., Black, M. J., Donoghue, J. P., & Hochberg, L. R. (2011). Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array. *Journal of neural engineering*, 8(2), 025027. doi:10.1088/1741-2560/8/2/025027
- Sodagar, A.M., Wise, K. D., & Najafi, K. (2009). A Wireless Implantable Microsystem for Multichannel Neural Recording. *IEEE Transactions on Microwave Theory and Techniques*, 57(10), 2565-2573. doi:10.1109/TMTT.2009.2029957
- Sodagar, Amir M, Wise, K. D., & Najafi, K. (2006). A neural signal processor for an implantable multi-channel cortical recording microsystem. *Conference proceedings : ... Annual International*

- Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 1*, 5900-3. doi:10.1109/IEMBS.2006.259285
- Sohal, V. S., & Sun, F. T. (2011). Responsive neurostimulation suppresses synchronized cortical rhythms in patients with epilepsy. *Neurosurgery clinics of North America*, 22(4), 481-8, vi. doi:10.1016/j.nec.2011.07.007
- Song, Y. K., Borton, D. A., Park, S., Patterson, W. R., Bull, C. W., Mislow, J., Simeral, J., Donoghue, J. P., & Nurmikko, A. V. (2008). Microelectronic neurosensor arrays: Towards implantable brain communication interfaces. *Electron Devices Meeting, 2008. IEDM 2008. IEEE International* (pp. 1-4). doi:10.1109/TNSRE.2009.2029493
- Song, Y-K, Borton, D. A., Park, S., Patterson, W. R., Bull, C. W., Laiwalla, F., Mislow, J., Simeral, J. D., Donoghue, J. P., & Nurmikko, A. V. (2009). Active microelectronic neurosensor arrays for implantable brain communication interfaces. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society*, 17(4), 339-45. doi:10.1109/TNSRE.2009.2024310
- Song, Yoon-Kyu, Patterson, W. R., Bull, C. W., Borton, D. A., Li, Y., Nurmikko, A. V., Simeral, J. D., & Donoghue, J. P. (2007). A brain implantable microsystem with hybrid RF/IR telemetry for advanced neuroengineering applications. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference, 2007*, 445-448. doi:10.1109/IEMBS.2007.4352319
- Spiegel, E. A., Wycis, H. T., Marks, M., & Lee, A. J. (1947). Stereotaxic Apparatus for Operations on the Human Brain. *Science (New York, N.Y.)*, 106(2754), 349-50. doi:10.1126/science.106.2754.349
- Stephen, J. H., Halpern, C. H., Barrios, C. J., Balmuri, U., Pisapia, J. M., Wolf, J. A., Kampman, K. M., Baltuch, G. H., Caplan, A. L., & Stein, S. C. (2012). Deep brain stimulation compared with methadone maintenance for the treatment of heroin dependence: a threshold and cost-effectiveness analysis. *Addiction (Abingdon, England)*, 107(3), 624-34. doi:10.1111/j.1360-0443.2011.03656.x
- Stieglitz, T., Schuettler, M., & Koch, K. P. (2005). Implantable biomedical microsystems for neural prostheses. *IEEE engineering in medicine and biology magazine : the quarterly magazine of the Engineering in Medicine & Biology Society*, 24(5), 58-65. Retrieved from papers2://publication/uuid/F6A82856-9A0E-4073-8A32-CE0D5444F087
- Svendsen, O. (2006). The minipig in toxicology. *Experimental and toxicologic pathology : official journal of the Gesellschaft für Toxikologische Pathologie*, 57(5-6), 335-9. doi:10.1016/j.etp.2006.03.003
- Szuts, T., Fadeyev, V., Kachiguine, S., & Sher, A. (2011). A wireless multi-channel neural amplifier for freely moving animals. *Nature*. Retrieved from <http://www.nature.com/neuro/journal/vaop/ncurrent/full/nn.2730.html>
- Taylor, Dawn M, Tillery, S. I. H., & Schwartz, A. B. (2002). Direct cortical control of 3D neuroprosthetic devices. *Science (New York, N.Y.)*, 296(5574), 1829-32. doi:10.1126/science.1070291
- Teyssedre, G., & Laurent, C. (2005). Charge transport modeling in insulating polymers: from molecular to macroscopic scale. *Dielectrics and Electrical Insulation, IEEE Transactions on*, 12(5), 857-875. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=1522182
- Thongpang, S., Richner, T. J., Brodnick, S. K., Schendel, A., Kim, J., Wilson, J. A., Hippensteel, J., Krugner-Higby, L., Moran, D., Ahmed, A. S., Neimann, D., Sillay, K., & Williams, J. C. (2011). A

- micro-electrocorticography platform and deployment strategies for chronic BCI applications. *Clinical EEG and neuroscience : official journal of the EEG and Clinical Neuroscience Society (ENCS)*, 42(4), 259-65. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/22208124>
- Travis, A. M. (1955). Neurological deficiencies following supplementary motor area lesions in Macaca mulatta. *Brain : a journal of neurology*, 78(2), 174-98. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/13239907>
- Truccolo, W., Donoghue, J. A., Hochberg, L. R., Eskandar, E. N., Madsen, J. R., Anderson, W. S., Brown, E. N., Halgren, E., & Cash, S. S. (2011). Single-neuron dynamics in human focal epilepsy. *Nature neuroscience*, 14(5), 635-41. doi:10.1038/nn.2782
- Tungjitkusolmun, S., Staelin, S. T., Haemmerich, D., Tsai, J. Z., Webster, J. G., Lee, F. T., Mahvi, D. M., & Vorperian, V. R. (2002). Three-Dimensional finite-element analyses for radio-frequency hepatic tumor ablation. *IEEE transactions on bio-medical engineering*, 49(1), 3-9. doi:10.1109/10.972834
- Vargas-Irwin, Carlos E, Shakhnarovich, G., Yadollahpour, P., Mislow, J. M. K., Black, M. J., & Donoghue, J. P. (2010). Decoding complete reach and grasp actions from local primary motor cortex populations. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 30(29), 9659-69. doi:10.1523/JNEUROSCI.5443-09.2010
- Velliste, M., Perel, S., Spalding, M. C., Whitford, A. S., & Schwartz, A. B. (2008). Cortical control of a prosthetic arm for self-feeding. *Nature*, 453(7198), 1098-101. doi:10.1038/nature06996
- Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van Essen, D. C., Zempel, J. M., Snyder, L. H., Corbetta, M., & Raichle, M. E. (2007). Intrinsic functional architecture in the anesthetized monkey brain. *Nature*, 447(7140), 83-6. doi:10.1038/nature05758
- Von Hippel, A. (1937). Electric Breakdown of Solid and Liquid Insulators. *Journal of Applied Physics*, 8(12), 815. doi:10.1063/1.1710258
- Wang, Jing, Borton, D. A., Zhang, J., Burwell, R. D., & Nurmikko, A. V. (2010). A neurophotonic device for stimulation and recording of neural microcircuits. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 2010*, 2935-8. doi:10.1109/IEMBS.2010.5626296
- Wang, Jing, Wagner, F., Borton, D. A., Zhang, J., Ozden, I., Burwell, R. D., Nurmikko, A. V., van Wagenen, R., Diester, I., & Deisseroth, K. (2011). Integrated device for combined optical neuromodulation and electrical recording for chronic in vivo applications. *Journal of neural engineering*, 9(1), 016001. doi:10.1088/1741-2560/9/1/016001
- Wang, W., Chan, S. S., Heldman, D. A., & Moran, D. W. (2010). Motor cortical representation of hand translation and rotation during reaching. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 30(3), 958-62. doi:10.1523/JNEUROSCI.3742-09.2010
- Wattanapanitch, W., Fee, M., & Sarpeshkar, R. (2007). An Energy-Efficient Micropower Neural Recording Amplifier. *IEEE Transactions on Biomedical Circuits and Systems*, 1(2), 136-147. doi:10.1109/TBCAS.2007.907868
- Weiland, J. D., & Humayun, M. S. (2008). Visual Prosthesis. *Proceedings of the IEEE*, 96(7), 1076-1084. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=4539488

- Weinrich, M., & Wise, S. P. (1982). The premotor cortex of the monkey. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 2(9), 1329-45. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7119878>
- Williams, R. W., & Herrup, K. (1988). The control of neuron number. *Annual review of neuroscience*, 11, 423-53. doi:10.1146/annurev.ne.11.030188.002231
- Wissler, E. (1985). Mathematical simulation of human thermal behavior using whole body models. *Heat transfer in medicine and biology*.
- Wong, F. L., Fung, M. K., Tao, S. L., Lai, S. L., Tsang, W. M., Kong, K. H., Choy, W. M., Lee, C. S., & Lee, S. T. (2008). Long-lifetime thin-film encapsulated organic light-emitting diodes. *Journal Of Applied Physics*, 104(1), 14509. Retrieved from <http://scitation.aip.org/getabs/servlet/GetabsServlet?prog=normal&id=JAPIAU000104000001014509000001&idtype=cvips&gifs=yes>
- Wood, F, Black, M., Vargas-Irwin, C., & Fellows, M. (2004). On the variability of manual spike sorting. *IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING*. Retrieved from <http://jgaa.info/~black/Papers/woodTransBME04.pdf>
- Wood, Frank, Black, M., Vargas-Irwin, C., & Fellows, M. (2004). Scientific Commons: On the Variability of Manual Spike Sorting (2004), 2004 [Frank Wood Michael, Michael J. Black, Carlos Vargas-irwin, Matthew Fellows, John P. Donoghue]. Retrieved from <http://en.scientificcommons.org/43233190>
- Woolsey, C. N., Settlage, P. H., Meyer, D. R., Sencer, W., Pinto, T., & Travis, A. M. (1952). Patterns of localization in precentral and "supplementary" motor areas and their relation to the concept of a premotor area. *Research publications - Association for Research in Nervous and Mental Disease*, 30, 238-64. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12983675>
- Xiao, X., Wang, J., Liu, C., Carlisle, J. A., Mech, B., Greenberg, R., Guven, D., Freda, R., Humayun, M. S., Weiland, J., & Auciello, O. (2006). In vitro and in vivo evaluation of ultrananocrystalline diamond for coating of implantable retinal microchips. *Journal of biomedical materials research. Part B, Applied biomaterials*, 77(2), 273-81. doi:10.1002/jbm.b.30448
- Yadollahpour, P, Shakhnarovich, G., & Vargas-Irwin, C. (2009). Neurally Constrained Subspace Learning of Reach and Grasp. *Masters thesis*. Retrieved from <http://128.148.32.110/research/pubs/theses/masters/2009/payman.pdf>
- Yang, R., Hao, Y., & Li, S. (2007). Development and Application of Low-Modulus Biomedical Titanium Alloy Ti2448. *Trends in Materials Science*.
- Yin, M., & Ghovanloo, M. (2008). A clockless ultra low-noise low-power wireless implantable neural recording system. *Circuits and Systems*, 1756-1759. Retrieved from http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=4541778
- Yoon, T. H., Hwang, E. J., Shin, D. Y., Park, S. I., Oh, S. J., Jung, S. C., Shin, H. C., & Kim, S. J. (2000). A micromachined silicon depth probe for multichannel neural recording. *IEEE transactions on bio-medical engineering*, 47(8), 1082-7. doi:10.1109/10.855936
- Yu, B. M., Cunningham, J. P., Santhanam, G., Ryu, S. I., Shenoy, K. V., & Sahani, M. (2009). Gaussian-process factor analysis for low-dimensional single-trial analysis of neural population activity. *Journal of neurophysiology*, 102(1), 614-35. doi:10.1152/jn.90941.2008

- Yuen, T. G. H., Agnew, W. F., & Bullara, L. A. (1987). Tissue response to potential neuroprosthetic materials implanted subdurally. *Biomaterials*, 8(2), 138-141. doi:10.1016/0142-9612(87)90103-7
- Zakrevskii, V. A., Sudar, N. T., Zaopo, A., & Dubitsky, Y. A. (2003). Mechanism of electrical degradation and breakdown of insulating polymers. *Journal of Applied Physics*, 93(4), 2135. doi:10.1063/1.1531820
- Zeller, H. R., & Schneider, W. R. (1984). Electrofracture mechanics of dielectric aging. *Journal of Applied Physics*, 56(2), 455. doi:10.1063/1.333931
- Zeris, V. A., Donoghue, J. D., Hochberg, L. R., O'Rourke, D. K., & Chiocca, E. A. (2005). Braingate: Turning Thought into Action-First Experience with a Human Neuromotor Prosthesis: 885. *Neurosurgery*, 57(2), 425. Retrieved from http://journals.lww.com/neurosurgery/Fulltext/2005/08000/Braingate__Turning_Thought_into_Action_First.128.aspx
- Zhang, F., Wang, L.-P., Brauner, M., Liewald, J. F., Kay, K., Watzke, N., Wood, P. G., Bamberg, E., Nagel, G., Gottschalk, A., & Deisseroth, K. (2007). Multimodal fast optical interrogation of neural circuitry. *Nature*, 446(7136), 633-639. Retrieved from <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/efetch.fcgi?dbfrom=pubmed&id=17410168&retmode=ref&cmd=prlinks>
- Zierhofer, C. M., & Hochmair, E. S. (1990). High-efficiency coupling-insensitive transcutaneous power and data transmission via an inductive link. *IEEE transactions on bio-medical engineering*, 37(7), 716-22. doi:10.1109/10.55682