

Fiber Optic Neural Prosthesis

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- **S.Park**, Y.-K Song, J. Aceros, M. Yin, D. Borton, A. V. Nurmikko, "Development of optically communicated intracortical neural recording system with fiber optics" In *Annual Meeting of Society of Neuroscience (SfN)*, 2011
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- **S. Park**, Y-K. Song, D. A. Borton, W. R. Patterson, M. Yin, J. Aceros, and A. V. Nurmikko, "An implantable intracortical neural recording microsystem with all-optical means for both transcutaneous telemetry and power delivery," In *Annual meeting Biomedical Medical Engineering Society*, 2010.
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- **S. Park**, D. W. Kim and H. C. Kim, "Development of human-computer interface device using electrooculogram for the amyotrophic lateral sclerosis (ALS) patient," In *the 3rd IEEE European Medical and Biological Engineering Conference*, 2005.

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- H-J. Kong, **S. Park**, T. Lee, J. Y. Lee, H. C. Kim and S-J. Oh, "Novel natural fill telemetric pressure flow study of discomfort and bladder outlet obstruction," *The Journal of Urology*, 182(2):601-606, 2009

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CHAPTER 1.

Introduction

It pays to keep an open mind, but not so open your brains fall out.

- Carl Sagan

1.1 Envisioning Future Technology

It is very intriguing to think what future we might have, and sometimes we are given chances to peek at how others imagine it by watching movies. Interestingly, there are many movies describing future in a dystopian way and among such movies, the movie named *Surrogate(2009)* gives an peculiar perspective on the future. In that movie, every person uses one's *surrogate*, a perfect young and charming looking body to live daily life, while one's actual body sits back and rests on a recliner in a secret place. Everyone is *connected* with a cable to a computer by plugging it to an *outlet* on the body, and transferring one's emotion, volition of movement, and all sorts of one's own will to the surrogate. This is surely a very naive way one can think, that we will be able to interpret the whole brain as we wanted, but the movie still has a point.

If we can access several parts of the brain simultaneously and extract those

signals to control a robot for any particular need, how much information can we take out of the brain? We can get a hint from several papers that have been published in the last decade. On early days of open-loop based experiments performed in 2000s, the 3-dimensional arm trajectories from offline cortical data from trained primates [15] was showing that the range from 150 to 600 cells or more being necessary, based on Taylor et al.'s calculation [16]. With a closed-loop real time data processing, the necessary neurons required to build desired trajectory is lower. We can partially estimate it based on L.Hochberg et al.'s papers, which they published in 2006 and 2012 respectively [17, 18]. In those papers, Hochberg and other colleagues showed the clinical application from their continuous ongoing project named Braingate. They could extract neural signals from a 100 channel microelectrode array (MEA) which was implanted in the brain of the human subjects, who were suffering from tetraplegia due to an accident or a neurological disease. Then they decoded the signal and applied it to control a simple computer interface for the first time [17].

However, even in a closed-loop system, many more neurons will be needed to predict intended movement accurately enough to make this technology practical. From the latest version of the project, they were able to build the motion trajectory of a robot arm, control the reach and the grasp from the attained neural signals from the subjects. They used two robot arms, one of which had 15 active degree of freedom (DoF) combined into a single DoF (hand open/-close), and the other had six DoF in the arm and four DoF in the hand. While more technical details can be found in their paper, the result shows that the subject who couldn't control her body under the neck nor speak, was able to drink coffee by controlling the robot arm by bringing a coffee cup close

to her mouth with a success rate of 62%, only by the neural signal from her motor cortex [18]. Although this is truly a great breakthrough in neuroscience research, it should be also noted that the robot arm had its own automated mechanism to prevent the erroneous control and the automated grasp control worked when its hand hit an object. Thus we cannot conclude that only 100 channels of MEA can provide enough data to control one arm fully as natural movement does. In fact, the degree of freedom that one arm has is more than 6, since fingers have their own DoF too. Therefore we can assume that several hundreds channels might be required to control upper limbs and lower limbs together for articulated movements.

This approximation immediately brings the question of data delivery. If we are able to collect neural signals from the brain as much as we want (so that we can control our own *surrogate* someday), how can we deliver such an enormous amount of information outside of the brain? Obviously it cannot be the metal wire based connection, which will increase the diameter and the mass of the wire bundle significantly even with the current smallest diameter wire (1 mil, 25 μm); For example, if 5 100-channel arrays are implanted for more dexterous control of both arms (This is rough estimation derived from [18, 19], based on neurons used in grasp actions in human and primate respectively) the total diameter of wire bundle would be 12.5mm already, let alone the crosstalk problem.

From their recent paper, Gao et al. compared their amplifier chip design for signals acquired from an MEA, to other groups' amplifiers for data delivery of 100 channels (96 channels for [5]'s design). The data rate of full frequency was around 30Mbps, with a 10 bit resolution of analog to digital conversion, and

the sampling rate of 31.25kSa/s per channel [5]. Thus if we assume extracting 500 channels of the neural data from the brain to control a robot for example, the required data bandwidth will be 500-600Mbps range (Consider Nyquist theorem that the data bandwidth should be twice of the data rate to avoid data aliasing). For further application which might require more scaled data, we will need to find the right method which has wider bandwidth for data delivery.

The most available option out of current technologies is optical communication for such big data delivery. Today, optical telecommunication is the dominant technology for data/information transmission owing to its wide bandwidth, low attenuation and low crosstalk regardless of the length of its path [20]. Thus an optical system is suitable for efficient, reliable and high-speed delivery of large amounts of data. Considering the bandwidth of current fiber optic communication systems has reached 100Gb/sec per channel already in 2006 [21], applications requiring fast transmission and processing of big data sets can benefit from optical systems. Therefore, multichannel neural recording system described above will certainly be the perfect example application which can benefit from optical methods for data communication.

My thesis work aims at building a prototype of fiber optic neural prosthesis, by adopting optical means to deliver neural data, and solving the engineering challenges while building such a system.

1.2 Background

1.2.1 Neural prostheses and brain machine interface

Achievements in neuroscience, engineering technology and computer science over the last two decades allowed neural prostheses to be prosperous and benefit many disabled people. There are many different types of neural prostheses including cochlear implant, artificial retina and deep brain stimulator (DBS) that are currently approved by the Food Drug Administration (FDA) and used for clinical use. Among these neural prostheses, there are brain computer interfaces (BCIs) which recently got attention for patients suffering from paralysis. BCIs collect neural signals from the paralyzed individuals with a specific type of sensor and bypass those signals to a computer system, to control external assistive technology such as a robot arm.

Paralysis can originate from various causes resulting in disability of one's volitional movement. Spinal cord injury (SCI) is one of the most common injuries that leads to partial or total loss of ability of movement by disabling descending motor pathway. Other degenerative disorders such as amyotrophic lateral sclerosis (ALS), which leads to loss of motor neurons, or muscular dystrophy, which leads to the muscle weakness and loss of muscle tissue, are the cause of paralysis as well [22]. There are many other disorders that result in paralysis, including the worst case of "*Locked-in syndrome*", but since the motor control area on the cerebral cortex is known to be maintained even after years of paralysis from the magnetic resonance imaging (MRI) research as shown in Figure 1.1 [3], researchers have tried to capture the neural signals

from the motor area of disabled patients and interpret them for bypassing signals to external decoding processor.

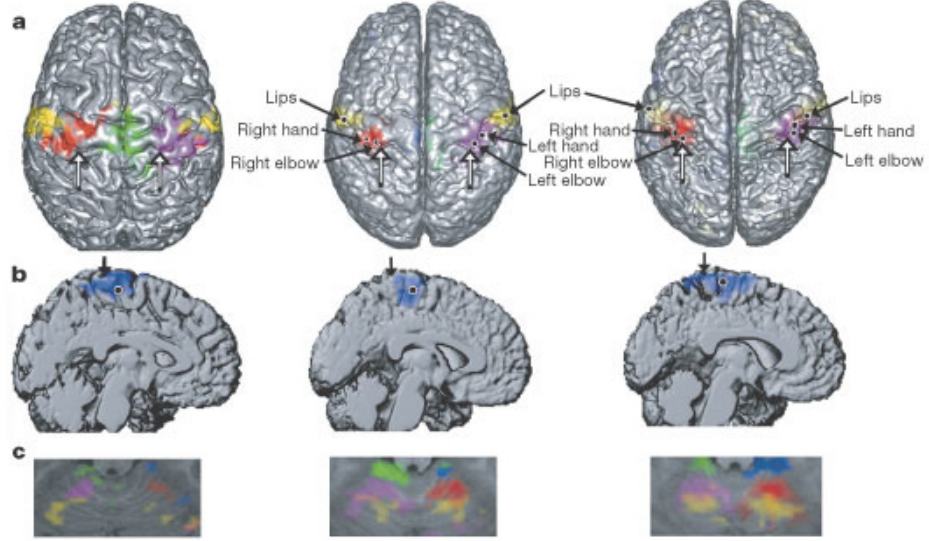


Figure 1.1: MRI based images from a paralyzed individual(left), paralyzed group (middle) and control group (right) showing the cortical activation associated with attempted and executed movements, courtesy of Shoham et al. [3]

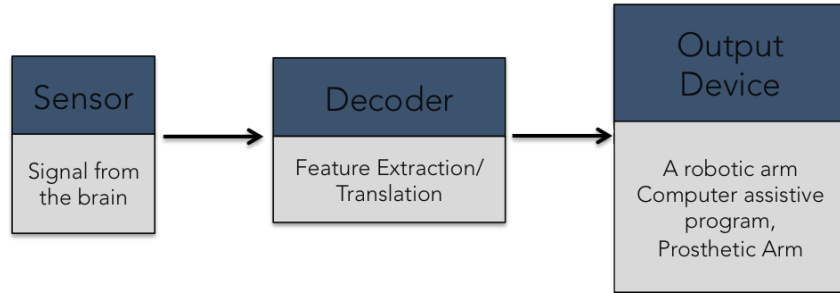


Figure 1.2: Design of BCI system

The basic design of a BCI can be described as in Figure 1.2 regardless of the type of sensor adopted to the system. For paralyzed patients or any possible BCI users, the BCI system requires input signals collected from the brain using a sensor or sensors. Depending on where the sensors are located

(Figure 1.3), acquirable signals vary. Through the decoding algorithm including feature extraction of the acquired signals, output action can be delivered to control the computer assistive programs, a physical robot arm, or a prosthetic arm of the patients. Regarding sensor modalities, primary methods are based on intracortical sensors, epidural/subdural sensors or non-invasive sensors that are collecting μV level extracellular signals generated from cortical layers. Novel methods are developed fairly recently, based on magnetic [23] or electromagnetic (fMRI) signals [24, 25], but these are not yet practical enough to be used in BCI application.

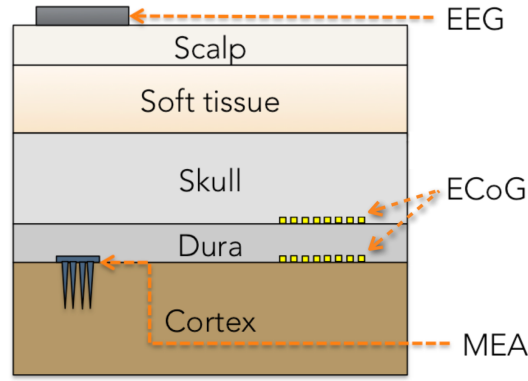


Figure 1.3: Sensor types in relation to the implantation sites

1. Intracortical sensors

For intracortical sensors, there are many different types of sensors that have been actively used in electrophysiology laboratories including various types of microelectrode array (hereinafter MEA), micro-wire, single electrode. Intracortical sensors have high spatial resolution ($100\mu\text{m}$) as well as high temporal resolution (50-100Hz), thus can provide the highest level of control in BCI applications [4].

The idea of recording neural signals with an MEA from a motor cortex

and processing these signals real time was successfully demonstrated in able-bodied primates, where the MEA implanted subjects could accomplish the goal directed tasks with visual feedback from different groups first in 2002 [16, 26]. (Note that the real-time “open-loop” decoding was preceded with a microwire recording setup shown in 2000 [15].) Along with advances in decoding algorithms and supporting technologies since then, the BCI system based on MEA could be applied to human subjects for clinical application [17, 18].

2. EEG

Another approach that has been developed in BCI, in parallel with the MEA based research was using field potentials (FPs), based on electroencephalogram (EEG). EEG is a non-invasive method of collecting neural signals evoked after the subject’s attention stimulus, by placing electrodes on the scalp. In a typical EEG application, the subject can select either letters, numbers, or other visual stimuli that rapidly appears on the screen, or other 2D cursor control to communicate with external world, by using the FPs collected by EEG electrodes [27, 28].

3. ECoG

Electrocorticogram (ECoG) is a recording modality that is located in between the MEA type sensor and the EEG sensors. The ECoG electrodes are placed on or under the dura, record field potentials like EEG, but have better spatial resolution (on the order of mm [29]) than that of EEG. The current application of the ECoG is exclusively targeted for

epilepsy patients. But since electrodes of ECoG are suitable for chronic implant and give less damage than penetrating MEA, possibilities for BCI application are widely open.

1.2.2 Neural signals

Neural signals collected from the sensors described above are all different from each other. The difference of the spatial resolution of signals for each sensor type can be compared in Figure 1.4. Depending on how far the electrodes are located from the signal source, the focus of recording and strategy to decoding process vary.

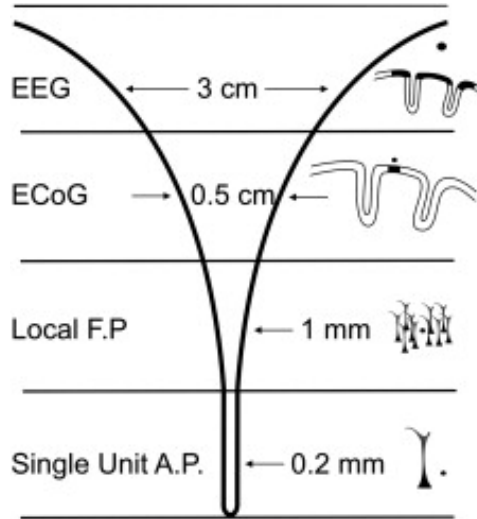


Figure 1.4: Comparison of spatial resolution of different modalities, courtesy of Schwartz et al. [4]

1. Single units

The intracortical sensors such as MEA or microwire generally measure the extracellular activities of a single neural unit. Especially since the pyramidal cells in layer V of the motor cortex have large cell bodies

(>100 μm) and generate large electrical potentials, the layer V is the ideal target layer for extracellular recording [4]. The amplitude of the single unit spike is from several hundreds microvolts up to millivolts and the frequency of the signal ranges from 300 Hz to 10 kHz [30].

2. Local Field Potential (LFP)

The signals from the same type of electrode, which is used for recording single units, also carry the information of lower-frequency (<250Hz) of summed neural activities of peri-electrode region. This is called local field potential (LFP), and is believed to be much less affected by geometry than single unit recording [4]. LFP shares the similar frequency bands with FPs collected by EEGs. Rickert et al. used LFP temporal tuning while primates were performing center out task [31], and Kennedy et al. demonstrated that a tetraplegic human could use a BCI by LFP amplitude based control [32], but it has not been thoroughly studied yet whether LFP based BCI application can perform as good as the single unit based BCIs. However, since LFPs can be attained simultaneously with single unit activities, we may expand the information used for BCIs by decoding both LFPs and single unit signals.

3. Field Potentials(FPs) attained from EEG

FPs can be attained by EEG. The location of EEG recording happens at 2-3cm away from the cortex, thus the electrodes of EEG cannot measure single unit activity of several microvolts potential, which will be picovolts (pV) range on the scalp. However, EEG can measure synchronous ac-

tivity generated by neurons. It has been estimated that 6cm^2 of cortical tissue should be synchronized to be on the order of a few microvolts so that it can be detectable on the scalp by the EEG [33, 34]. FPs used in EEG can be categorized into two groups: (1) rhythmic signals (2) Event related potentials (ERPs) [22]. The temporal resolution of the ERP signals is very low ($<1\text{Hz}$). For example, evoked activity used for BCI control such as P300 has inherent 300ms delay between the stimulus and the EEG activity [4].

Rhythmic signals include mu (8-12Hz from a specific origins, others are called alpha wave) wave and beta (12-20Hz or higher) wave. In sensorimotor cortex, these signals are used for BCI controls [35]. Higher gamma band signals (30Hz to 100Hz) are used recently only in intracranial recordings, since they are mostly filtered out in EEGs [22]. Mu and beta oscillations are thought to be suppressed during the movement, and active at the stage of planning the movement [36]. On the contrary, gamma oscillations are often assumed to be localized to the cortex, and cortical networks can generate their own gamma oscillations [37]. This suggests that they might carry specific forms of information that is different from lower band informations [38].

1.3 Related Works

The main component of BCIs is the neural recording system. While many neuroscientific research has accomplished on decoding the neural signals, the main focus of the research was not acquiring such signals effectively. Many

approaches for MEA based chronic multichannel recording involve a passively connected array with a percutaneous connection to the external amplifiers and processors that are still bulky in size [17, 18, 39, 40].

Thus, the integration of a neural recording system onto an implantable platform is highly desirable for future portable and wearable prosthetics, including on-board telemetry to transmit power and signals. Implantable cortical neural recording systems present challenges including the development and integration of ultra-low power microelectronics onto the system, and high-efficient transmission of power and data. Finally for future human application, biocompatible packaging is crucial, in conjunction with surgical and other clinical considerations. This is still a big and ongoing challenge for engineers in this area.

However, a comprehensive discussion of the many different types of neural recording system with different sensors described in the previous section is not possible nor the goal in this thesis. Hence we will limit our focus to brief discussion of current recording system mostly based on the MEA, since our system is built on the MEA based structure.

One of such example neural systems is the Hermes series developed by researchers in Stanford university. Through a series of published papers, Hermes series has shown the chronic recording results tested in primates and possibilities of using the system for the future human application [5, 11, 41]. Figure 1.5 shows the cross-sectional view of the Hermes system, where they connected a passive intracortical MEA percutaneously, then added stacks of PCBs and a radio frequency (RF) antenna with batteries. Their most recent microchip design was integrated with a preamplifier and an analog to digital converter

(ADC). The preamplifier power consumption was $2.2 \mu V_{rms}$ per channel, and full 10kHz data bandwidth with a 10 bit ADC with 31.25kSa/s (kilosamples per second). With 96 broadband channels, the total power consumption was about 30mW [5]. The frequency for RF transmission was not specified in Gao et al.'s paper, but could be found in Hermes D system, which was 3.9GHz [11].

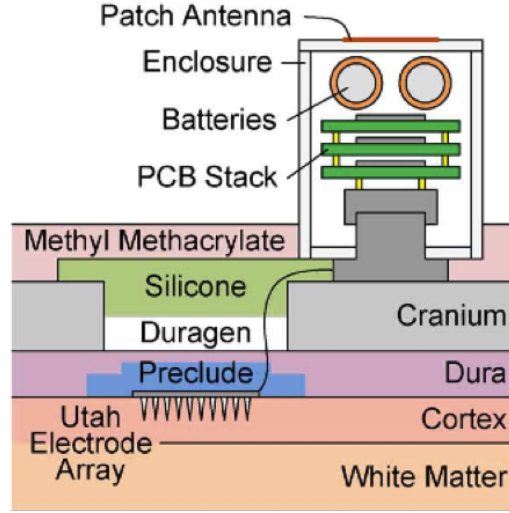


Figure 1.5: Cross section of head mounted Hermes E system, courtesy of Gao et al. [5]

Another group in Utah university, Harrison et al. has presented a micro-electronic chip (named INI) that contains a preamplifier, a voltage-regulator, an ADC, and an RF transmitter [10, 42]. They used a 10 bit ADC at the sampling rate of 15.7kSa/s and recorded 100 channels with 902-928MHz transmitter. The total power consumption was 8mW only for the microchip, with only 1 full channel transmission and spike thresholding for rest of the channels. The in vivo results were obtained from the cat's brain by connecting the INI chip with the passive array that was already implanted in vivo [10].

Including these devices, many neural recording devices from other groups

mostly use wireless communications for power and/or data transmission. However, there isn't any neural recording system currently designed or tested for fully implantable use: Mostly head-mountable setup tested in small animal models except Hermes series in primates [43, 44, 45]. Since implantable system requires entire hermetic sealing of the system, it will take more time for these system to have the full implantable setup.

While MEA based active neural recording technology has not achieved chronic level of full device implantation yet except the works in our lab in primates and pigs [46, 47, 48], another type of neural recording system that is worth to be noted is the wireless ECoG system. Charvet et al. developed a 64 channel wireless ECoG system named WIMAGINE for clinical applications and recently published their preliminary results in [6]. The system has ECoG sensors and supporting active microelectronics to be implantable intracranially and is capable of recording neural signals of 0.5Hz to 300Hz with less than $0.7\mu V_{rms}$ noise. It is powered by a inductively coupled coil with the modulation frequency of 13.56MHz, communicates wirelessly at 402-405 MHz [6]. They did not achieve in vivo validation of this system in chronic environment yet, but the system is still noteworthy and is expected to serve the role as advanced BCI system for human in future. Figure 1.6 shows their packaged ECoG system.

So far, neural recording systems with an MEA or an ECoG from other groups' recent works were presented. Most of the neural recording systems introduced here selected the wireless communication methods, and to our knowledge, there isn't any device using optical means in BCIs yet. One of the most similar application in neural prosthesis that adopts optical means can be found in retinal prosthesis, where photodiodes were used to power and

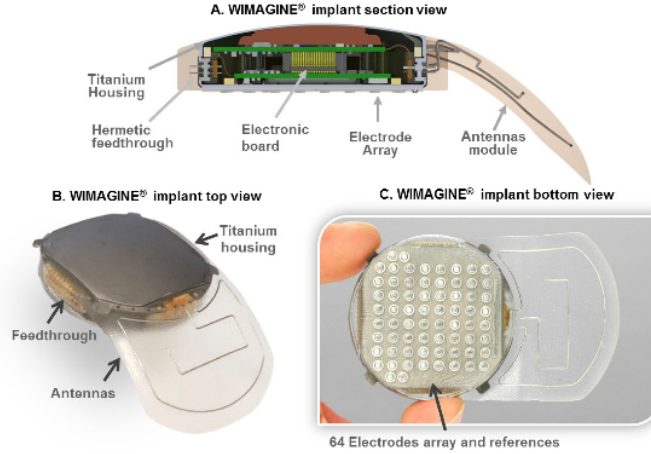


Figure 1.6: WIMAGINE implant packaging, courtesy of Charvet et al. [6]

sense the external stimuli from the incident infrared (IR) light shining through the natural window, the retina [49]. However, this concept is not applicable for our recording system since we need more power to run all the complicated microelectronics. We used optically well aligned fiber optics for our system to provide higher power and through the next chapters, we will discuss how we achieve building such neural recording system.

1.4 Project Aims

1.4.1 Final aim in a greater context

As discussed earlier, neural prosthesis eventually means the technology that can substitute the modality of lost functions of a disabled person resulted from an injury or a disease. To realize such a goal, motor prosthesis requires a neural recording system to collect neural data from motor cortical areas. The final aim of this project will be building a clinical applicable and implantable neural recording system based on fiber optics. If the concept can be fully realized, the

neural recording system will be implanted in multiple sites of the brain, record and send the neural data to the decoder. The decoder can be located in more spacious part of the body, such as abdomen, where the surgical accessibility is much easier than the brain region. Real time decoding of collected neural data can be then applied to the functional electrical system (FES), which is used to stimulate the muscles of the limbs for prosthetic use. If all of this modulation can be done optically, the system can form a fully “closed loop” system, which is an ultimate and ideal goal of motor prosthesis.

1.4.2 Preliminary aim and introduction to the work presented in this thesis

To realize the final aim of fiber optic neural prosthesis, validations in engineering aspects as well as clinical aspects need to be preceded. For clinical application of the neural recording system, even without other considerations in a closed loop system, we still need to solve many unknown problems including the safety and the chronic performance.

As a starting point, this thesis work aims at developing a chronic *in vivo* neural recording system based on a laboratory animal model. This is not only due to the time and expense the project will require to make a transition from bench top level completion to clinical applicable neural prosthesis, but also we can effectively show the concept of the device from the animal recording in more achievable way. Through the following five chapters, this thesis will focus on showing:

1. the development of highly efficient optical components to make fiber optic based neural recording system(*Chapter 2*)

2. the implementation of the total neural recording system based on an ultra-low power amplifier bonded onto a microelectrode array (*Chapter 3*)
3. the application of the technology to an appropriate animal model to study behavior related neural data (*Chapter 5*) with carefully designed surgery procedures (*Chapter 4*)
4. the analysis of the behavior related neural data (*Chapter 6*)

The main components of this thesis begins in Chapter 2 where the design of optical components will be discussed in consideration of optimization and fulfillment of several issues when building a neural recording system. This includes high conversion and transmission efficiency of the optical signals, and the design of a small sized optical components that can be fit onto the recording system for small animal models. Chapter 2 has three sections discussing three topics of 1) a power supplying system for the neural recording device, 2) a micro-chip laser to deliver the digitized neural data, 3) optical fibers as the pathways of delivering the power and the data.

Chapter 3 begins discussion of the fully implantable neural recording system based on the optical components addressed in Chapter 2. To enable the fully implantable system, we propose the separated front-end and the back-end system to have an efficient design to implant it in an animal model. Fabrication procedure of making the system is described orderly in this chapter. Then we discuss the fully implantable system that can be implanted in a rat model. The problems when the device was applied to the small animal model and practical modification of the fabrication processes are discussed during implementing the total system in Chapter 4, where the concept and implementation

of the two component system are also addressed.

Chapter 5 discusses the training setup for rat and the external device setup for recording the training behavior. The trained rats were doing the lever pressing task while freely moving. Based on the data acquired from the setup and the device described throughout these work, Chapter 6 coalesces the neural data that shows the neural population dynamics in a relation to the behaviors. Conclusion presents a brief discussion of the thesis work and suggests the contribution and the future directions of this research.

CHAPTER 2.

Optical Components for Neural Recording Device

The main idea of this work is developing a fiber optic based neural recording system. To build such a system, the first and foremost thing to consider is how to build optical components in the system. There are three major components referred to as 'optical components' in a fiber optic neural recording system. The first component is a power source that converts supplied optical power to electrical power, to operate electronics in the neural recording system. Since the component requires two conversions (from electrical to optical then optical to electrical), this might not seem to be a necessary component. Conventionally, other implantable systems use radio frequency (RF) by inductive coupling or batteries to power the system. However, considering its insusceptibility to electromagnetic noise, and sub-millimeter scale form factor (which will be described in the following sections), our optically powered system is a favorable option even with a drawback of two time conversion. The power converter that transforms optical power to electrical power is generally called as a photovoltaic device (hereinafter called PV), and since our lab has had

fabrication experiences in optoelectronic components including PV cells, we could fabricate our own high-efficiency PV device in a clean room facility at Brown University.

The second component is an optical data transmitter that changes electrical signal to optical signal (in Sec. 2.2). In the fiber optic based system, neural data needs to be delivered through an optical path from the system to an external decoder (that is, through an 'efferent' fiber). This means the data should be converted to an optical signal too. Thus an active light source such as a laser or a light emitting diode (LED) will be a good candidate for an optical data transmitter. We applied a micro-scale chip laser that can be mountable on a board and can be coupled to an optical fiber, which gives higher throughput than an LED when coupled with a fiber.

The final component as well as the main idea of this system is an optical fiber. The main role of the optical fiber is to deliver power and data for in vivo application. With these three main optical components, several design considerations of how we planned to make a neural recording device, and why we selected such design to solve our problem will be discussed in this chapter.

2.1 Photovoltaic Power Converter For Powering The System

2.1.1 Background

PV devices are devices that can convert optical energy to electrical energy. This is a type of PN junction diodes that supply voltage which can be specified

by the different band gap energy of differentially doped material. Theoretical details of such devices can be found in many textbooks on optoelectronics [50, 51], here only the brief overview of the p-i-n PV device will be discussed. A p-i-n PV is basically a PNdiode that has an additional intrinsic layer between the n and p layer. When the terminals of this PN junction diode are connected together, i.e. "shorted", and the junction is illuminated by the incident light, electron-hole pairs are generated due to the energy of photons from incident light. By the electric field, holes are collected by the p region and the electrons are collected to the n region. This flow of electron-hole pairs results in a photocurrent (or short circuit current) I_{SC} , which is proportional to the light intensity and to the cell area, as shown in Figure 2.1. When the junction terminals are reversely biased, this photocurrent flows the reverse direction from (+) to (-), which means a negative current to the bias. Thus the total product I_{total} can be expressed as follows:

$$I_{total} = I_{sc} - I_s(\exp(eV/kT) - 1)$$

where I_s is the saturation current, k is the Boltzmann constant, and T is the temperature in °K.

Negative current flow, thus the negative power $I \times V$ means the photocurrent can generate power in the opposite direction to a reversely biased device. Thus if a PV device is connected to a load without any external power source, it can supply the power to the load when illuminated. In our neural recording system, the load is an assembly of active electronic components. These components have functions such as amplification of sub mV level neural signal, conversion of analog signal to digital signal, digitization of serial data stream and transmission of neural data to external decoder. Various functions from

active electronics require some amount of constant power consumption. Figure 2.2 shows what components there are in our neural recording system and how much power each component consumes.

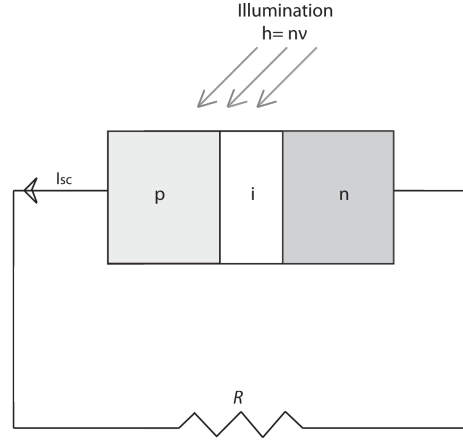


Figure 2.1: Photocurrent generated by light illumination

As seen in the Figure 2.2, PV cells should be able to supply more than 15mW constantly in a stable way in order to satisfy the power requirement of the whole system. This is the first thing to consider when designing a PV cell. Another thing to consider along with the first goal is how to make this conversion to be efficient enough to supply 15mW power to the system with less power. One might think if the optical power pumped from the external source can be limitless in principle, it doesn't need to be highly efficient at all. However, considering the optical energy which isn't successfully converted to electrical power will generate heat, and the heating is another crucial problem when designing an implantable device, it is obvious that higher conversion efficiency is better for the system.

The last thing to take into account is the operating voltage of the electronics used in the neural recording system. Most of the electronics in our system

run at 2.7V-3.3V range. Thus the third goal is that making the PV cell to supply the minimum operating voltage to the microelectronics; since the PV cell cannot supply higher voltage than an open circuit voltage V_{oc} which is decided by the material's band gap energy, it is important to design a PV cell that can supply more than 2.7V constantly. Most single materials used in solar cells or photovoltaic devices have V_{oc} less than 3V, (e.g. 1.11eV for Si, 1.43eV for GaAs [51]), it is another issue we need to consider whether we use serially connected single PV cells or select other ways to make the voltage to be in 3V range. In the next section, we will describe the approach we chose.

Components	Consumption	Unit
ADC(AD7495)	4.5	mW
Preamplifier (I-Pearl)	52	uW
Amplifier overall	1.3	mW
Controller	5	mW
VCSEL	2	mW
Total	13.8	mW

Figure 2.2: Total power consumed by the neural recording system

2.1.2 GaAs- AlGaAs heterostructure

When selecting a material for photovoltaic devices, GaAs is the preferred material among many candidates as it has advantages over other III-V compounds or Silicon owing to its direct band gap, high electron mobilities, high output voltage and its mature manufacturing technology [52]. However, since most

electrical systems require more than 3V (or 5V), around the 1.4V V_{oc} that a single GaAs cell has is not compatible to operate electronics. One way to solve this problem is to connect the single GaAs cells in series. In some applications and one of our former graduate students' work, the monolithic PV cell connected in series were fabricated to have the appropriate operating voltage range [52, 53].

However, it is known that multi-junction (tandem) PV cells have better performance for achieving higher efficiencies than the single cells in series [7, 54, 55]. The original tandem cell structure can be found from high-efficiency solar cells in some literature where the top cell material is lattice-matched to the base substrate [7]. In the same paper, it is shown that carefully designed multi-junction tandem solar cells had better conversion efficiencies as in Figure 2.12.

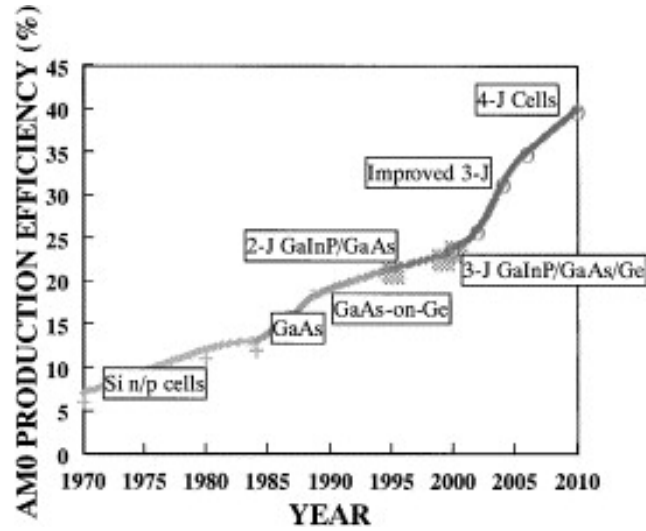


Figure 2.3: Chronological improvements achieved in multi-junction solar cell research in conversion efficiencies.[7]

For this reason, our former colleagues designed 3 tandem p-i-n layers of GaAs- AlGaAs substrate in 2005 [8]. Regarding the selection of the com-

pounds, there had been many studies of multi-junction PV cells based on different materials of AlGaAs or InGaP with GaAs substrate. But a recent paper shows that AlGaAs/GaAs and AlGaAs/AlGaAs designs seem to have advantages over GaAs/GaAs and the AlGaAs/InGaP designs [56].

Unlike other applications where PV cells use ambient light (such as solar cell), here we use the monochromatic light as a light source. To our knowledge, there hasn't been any attempt to use monochromatic light to power the system in vivo. The advantage of utilizing monochromatic light is that a PV cell specified to a monochromatic light can have much higher conversion efficiency than using ambient light. Monochromatic light can be focused onto the optical window, and the thickness and the composition of substrate layer can be optimized to a given wavelength. Our multi-junction tandem structure with two tunnel junctions between them was carefully designed for the IR light of 850nm wavelength to maximize the conversion efficiency. To do so, the optimized design to utilize 850nm wavelength needed to generate electron-hole pairs in the intrinsic GaAs layer, but not other layers in the device. Based on Adachi's paper [57], we can calculate the composition of the layer for the desirable wavelength of 850nm. First of all, the intrinsic layer is GaAs, of which band gap energy is 1.424eV. According to this band gap energy, the GaAs layer absorbs photons of 870nm and below. The band gap energy of $Al_{0.2}Ga_{0.8}As$ is 1.6734eV. This value is derived from the following equation [57].

$$1.424 + 1.247x \quad (0 < x < 0.45), \text{ for band gap energy of } Al_xGa_{1-x}$$

The wavelength corresponding to the band gap energy of 1.6734eV is 740nm; Thus the wavelength between 740nm to 870nm will generate effective electron-hole pairs in intrinsic layers. Another optimization required is the thickness

of each layer. In a simple way, the tandem cell acts as connecting three batteries in series. Thus the total current is limited by the component with the lowest current. To effectively transmit the light to the 3rd (the bottom) layer, the thicknesses of all layers were designed accordingly. Figure 2.4 shows the cross-sectional layering schematic for the designed tandem cell structure. It consists of 15 p-i-n structure layers on the GaAs substrate. With a careful consideration to match the target wavelength and its absorption, our lab designed the structure and the wafers were grown by IQE Inc. (Wales, UK) by metal organic vapor phase epitaxy (MOVPE). One of the applications utilized this PV device was a functional electrical stimulator (FES) tested acutely in a frog's sciatic nerve [8]. The device efficiency was around 40% at 40mW, with a $300\mu\text{m}$ diameter optical window to the incident light. However, in [8], the PV device wasn't considered to be used in any awake animal model. Thus in this thesis work, we showed the design of PV cells and the validation of the performance in *in vivo* application.

2.1.3 Device fabrication

The PV device was fabricated on the 15 tandem layer microcrystal heterostructure as described above. Figure 2.5 shows 5 different photomasks designed with AutoCAD for PV cells. Each PV device had a circular optical window in each square with a ring-type ($20\mu\text{m}$) ohmic contact. Three different sizes of PV cells were designed for different applications. The largest ones were $800\mu\text{m}$ by $800\mu\text{m}$ with a diameter of $600\mu\text{m}$ optical window. Others were $550\mu\text{m}$ by $550\mu\text{m}$ with a $400\mu\text{m}$ optical window and $300\mu\text{m}$ by $300\mu\text{m}$ device with a $200\mu\text{m}$ optical windows respectively. From one set of mask, 246 PV cells could

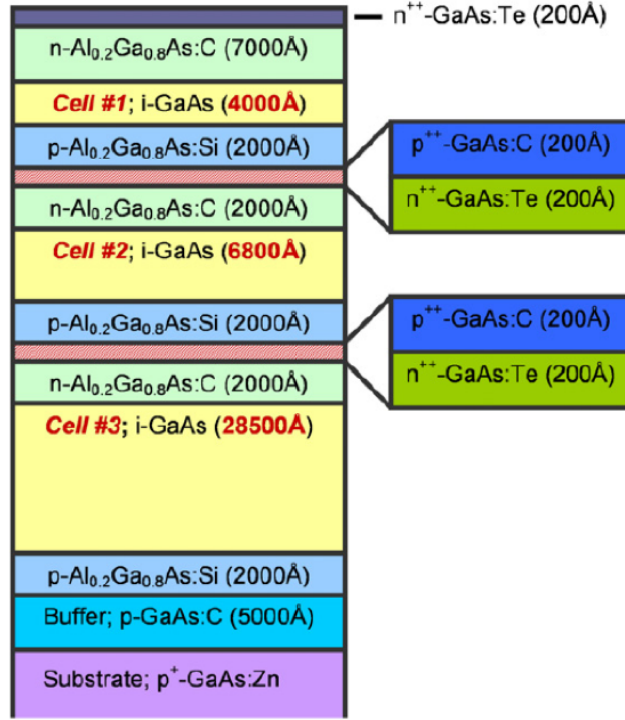


Figure 2.4: Layer composition of designed multi-junction heterostructure for our PV cells, published in [8]

be made in three different sizes. When the sample is prepared, either dielectric layer of SiO_2 or Si_3N_4 can be deposited by Plasma Enhanced Chemical Vapor Deposition (PECVD). The details and the principles of fabrication process described here including PECVD, etc. are explained well in [58] for further information. For our PV cell, we deposited SiO_2 onto the prepared substrate, based on the previous recipe without anti-reflection (AR) coating.

For deposition of SiO_2 , the setting used in the PECVD system (Plasma-Therm 790 series) was as follows:

- The temperature: 340°C (However, the actual temperature goes up to about 320°C at maximum)
- The chamber pressure: 900mTorr

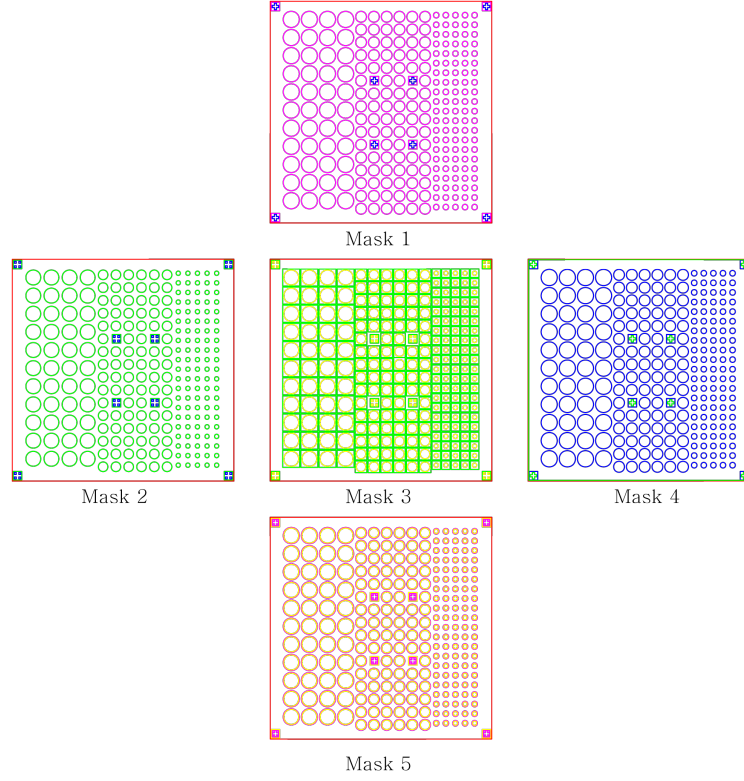


Figure 2.5: Photomasks for PV cell design

- The flow rate of N_2O : 150sccm
- The flow rate of SiH_4 : 50sccm
- The DC power for the chamber: 17Watts

Under these conditions, 3 samples were placed in the chamber each run. The deposition thickness for each sample slightly differed from one another because the placement of the samples in the chamber causes differences in the thickness, which also could be observed by the color of the deposition layer. Thus the ellipsometer was used to measure each sample's thickness and the deposition rate precisely. The ideal deposition rate (from the sample placed in the middle of the chamber) was $\sim 300\text{\AA}$. To achieve the desired thickness,

total deposition time of PECVD was 12 minutes.

After SiO₂ deposition, the ring contact area was opened for an ohmic (metal) contact. Mask 5 in Figure 2.5 was used for this structure. The SiO₂ dielectric layer needed to be etched to have the ohmic contact, so photolithography had to be preceded. Usually photolithography process consists of 3 steps. 1) Application of the photoresist (PR) solution 2) Exposure to the UV light 3) Development of the light-exposed PR on the sample.

On cleaned samples, the adhesion promotor (hexamethyldisilazane, HMDS) was spin-coated, then the positive PR (S1818) was spin-coated, both under 5000rpm for 30 seconds. The PR coated samples were baked on a hot plate for 2-3 minutes at 90°C. After aligning a mask and a sample on the stage of the UV aligner, the 365nm (i-line lithography) wavelength of UV was exposed to the sample for 54 seconds. Optimized developing time for the sample was about 1 minute in the solution of the ratio of MF312:DI water to be 1:1. The SiO₂ layer was then opened by wet etching using Buffered Hydrofluoric acid (BHF) to DI Water of 1:1 ratio, by soaking the sample fully into the BHF. The etching rate was about 60Å/sec. After opening the SiO₂ layer, n side (top) metal contact was made by electron beam deposition process with an electron beam (e-beam) evaporator.

Metal composition for n metal deposition was based on the paper([59]), which compared the resistance of Ni/Ge/Au on n-GaAs to that of Pd/Ge/Au. It was found that the resistance of both were similar, with a better surface morphology on the latter. Originally Ni/Ge/Au contact to n type GaAs was a popular metal composition because it has a very low contact resistance ($\sim 10^{-6} \Omega \cdot cm^2$). However, the surface morphology was very poor between Au

and Ge, and it required very high temperature sintering process (above 700°C) to smoothen the surface. To improve resistance of the Pd/Ge contact layer comparable to that of Ni/Ge/Au contact, Pd/Ge layer with Au was deposited on n-GaAs. When there are only Ge and Au, the interface between Ge/Au can cause a problem of 'rough' surface due to the alloy they make. However if Pd is deposited together with Ge/Au, it is not the case since Pd and Ge form Germanides at very low temperature, and no more Ge is left to alloy with Au. Therefore, in Chen's experiment where the contact resistances of Pd (300Å)/Ge(400Å)/Au(2000Å) and Ni(300Å)/Ge(400Å)/Au(3400Å) were compared, the average resistances for both were in the same range. (In the range of $10^{-6} \Omega \cdot cm^2$) under the same annealing process on the same doped material (n^+ GaAs).

Based on Chen et al's paper, we chose to use Pd/Ge/Au composition for n metal contact. As long as Pd is thicker than Ge, all Ge will be consumed to form Palladium Germanides and the thickness of each only changes the proportion of the Pd and Ge in Germanides as described above [59], thus we didn't precisely control the thickness of each metal. The thickness of the metal deposition was set to be 300Å for Pd, 400Å for Ge, and 1000 Å for Au. The deposition was done with the e-beam evaporator, with the vacuum level of 10^{-6} Torr. After metal deposition, lift-off process was followed to remove the photoresist. Unnecessary metals were lifted off by ultrasonic cleaning for 30 seconds. Annealing the sample at 420 °C of 2 minutes was followed to reduce the contact resistance while Pd/Ge were forming ohmic contact. After depositing of n metal contact on the ring shape opening, mask 3 was used to make a schottky contact (Ti/Au) which facilitates wire bonding to the n metal

contact. Photolithography, developing, and wet etching were followed as the previous metal deposition. The thickness of Ti was $500\text{\AA}$ and Au was $1800\text{\AA}$. The lapping process was followed before the p-metal contact deposition. The reason for lapping was to facilitate the device separation by making the whole sample thinner. The original thickness of the wafer was $600\mu\text{m}$, but the source sample was polished down to $200\mu\text{m}$.

The polishing and other remaining processes were as follows: • First, the source wafer was attached temporarily onto the polishing block by crystal bond (heating was required).

- Second, the sample was lapped on the polishing plate made of Quartz in presence of Alumina powder and DI water.
- The lapping process went on with the various the grain size of the Alumina powder, starting from $10\mu\text{m}$, then gradually to the smaller one, such as $5\mu\text{m}$, $1\mu\text{m}$, then $0.05\mu\text{m}$.
- The polished source was then chemo-mechanically polished again with diluted Clorox (bleaching agent), on a polishing cloth.
- To remove the native Oxide, the face of the source of the n-type metal deposition was protected with the PR, then was rinsed with the solution of HCl:DI water 1:1 before placed in the chamber of the e-beam evaporator.
- The cleaned sample was then mounted in the e-beam chamber, and the p-type metal deposition was followed with Ti/Au ($500\text{\AA}$, $1000\text{\AA}$ respectively).
- Annealing process was followed to reduce the contact resistance at 420°C for 1 minute under N_2 atmosphere.

After all processes were done, the sample was cleaned. From each sample,

photovoltaic power supplies (PPS) used for our neural recording system were separated one by one using a fine diamond tip scribe. The sample was placed onto the stage held with vacuum, and the scribe was mounted on the X-Y-Z stage under a microscope for accurate separation of each cell. For our neural recording system, the largest device of $800\mu\text{m} \times 800\mu\text{m}$ was used. The photographic image and illustration of sample devices are shown in Figure 2.6.

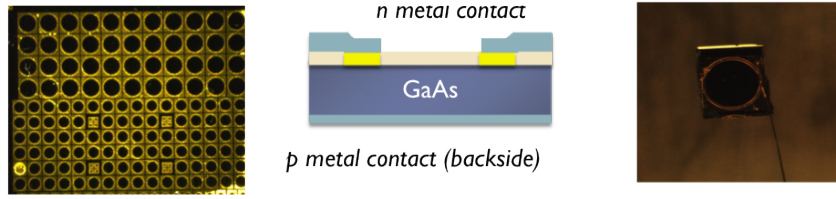


Figure 2.6: PV devices before separation, illustration of side view, and top view of each PPS

2.1.4 Device performance

Each separated device (PPS) was tested its performance by using HP parameter analyzer (HP4145B). 3D microstage was used to manipulate optical fiber's fine coupling to the aperture of the PV cell, with delivering collimated 850nm infrared (IR) laser. (Laser from MicroLaser Systems, output range was $850 \pm 5\text{nm}$. More details on the laser source were described in Chapter 5.) The device was mounted vertically on a small test board and wire bonded to the pad. While two probes were measuring n metal contact and p metal contact, IR light illuminated the sample PPS through the fiber, which temporarily in contact with the surface of the PPS. Figure 2.7 shows the I-V curve of the PPS under 0mW to 40mW illumination.

However, since the PV cell was a tandem structure, the lowest I_{SC} of one

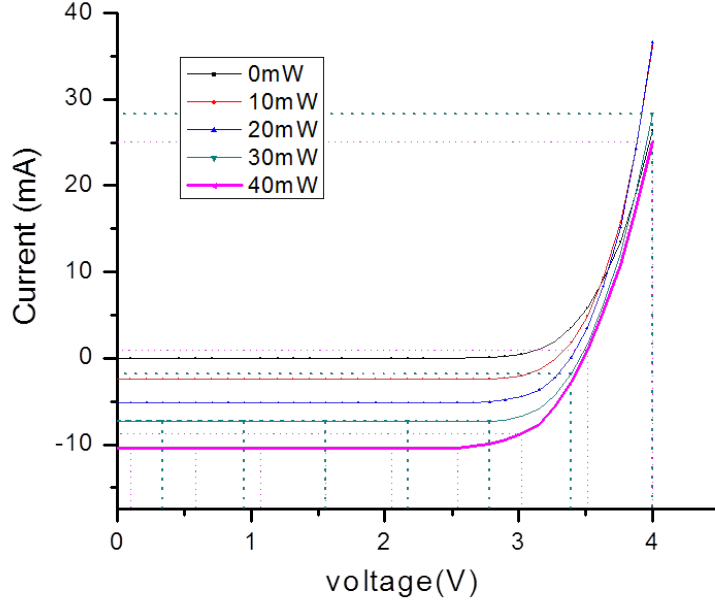


Figure 2.7: I-V plot of the PV sample under various illumination

layer would limit the whole I_{SC} . The illumination direction was from the top to the bottom layer, thus the aperture of the optical window had to be matched with the diameter of illuminated area and the distance had to be optimized for the light to reach the bottom. The ideal distance from the end face of illumination source to the surface of the PPS was acquired by plotting I-V curve during active alignment. From Figure 2.8, 1mm distance was found to be the optimal distance at 30-40mW illumination.

After finding the ideal distance, we coupled a 1mm long ‘optical spacer’, which was made by cleaving another glass optical fiber of $600\mu\text{m}$ diameter, to the PPS. Figure 2.9 shows the I-V curve with an optical spacer located between the PPS and the optical fiber under various illumination condition. After confirming better performance, we coupled the fiber to the PPS and the optical spacer assembly by active alignment. After optical components

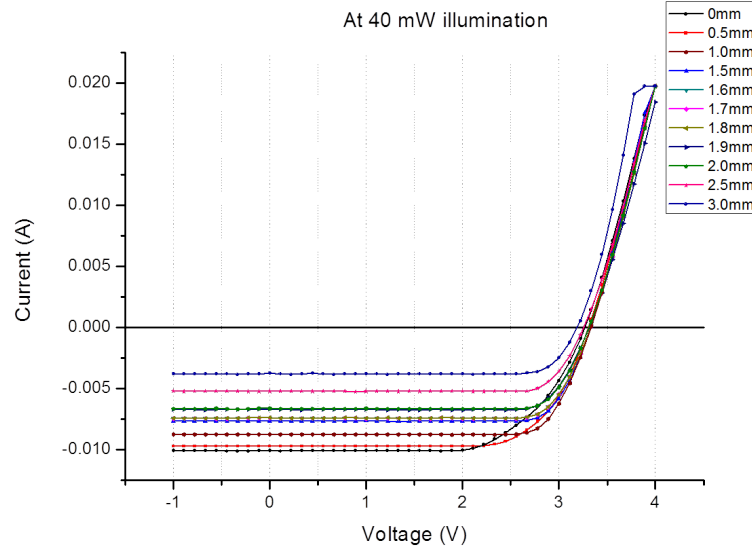


Figure 2.8: I-V plot of the PV with different distances from the illumination source to the surface under 40mW illumination

were aligned, fixation of components was done by applying a transparent UV curable epoxy (Norland, NOA81) on the coupling surfaces of the components.

From here, we could achieve the stable PPS with the operating voltage of 2.8-3.0V and the conversion efficiency of over 60%: The PPS can provide enough power to our neural recording system with external 30 mW source including possible coupling losses between connections.

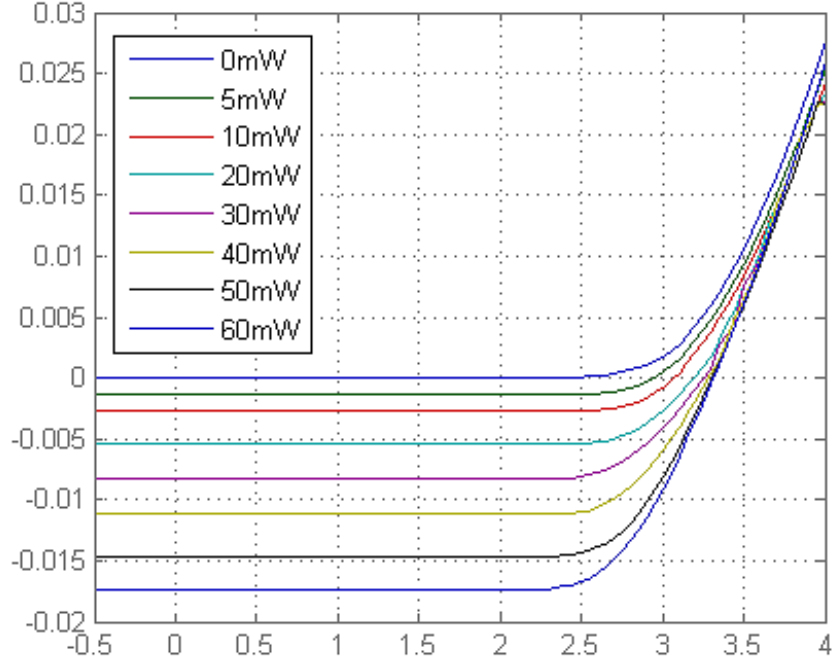


Figure 2.9: I-V plot of a fiber-coupled PPS under various illumination

2.2 Infrared Vertical Cavity Surface Emitting Laser for Data Transmission

2.2.1 Background

The development and prosperity of optoelectronic devices for data transmission in current communication systems largely owed to the wide data bandwidth that optoelectronics can have, along with the development of fiber optics of low attenuation and low crosstalk compared to conventional metal wire system. Among many optoelectronic sources for the data transmission, vertical cavity surface emitting laser (VCSEL) is currently widely used in gigabit Ethernet and fiber communication channels. Since its direction of the illumination is

perpendicular to the surface unlike edge-emitting lasers, fabrication of scalable 2D array is possible yet with a small form-factor and a low driving current of each VCSEL. The idea of VCSEL was first invented in 1977 by K.Iga [60], and after the first lasing operation with low threshold current was performed in 1989 [61], VCSEL research has been accelerated. The highest modulation speed for VCSEL reached at 56.1Gb/s as of 2013 [62], which gives more than enough room for neural data transmission when applied to neural prosthetics. Assuming the highest data bandwidth of current technology is available by a high-speed VCSEL as shown in [62], simple calculation with a 12 bit data/channel with the sampling rate of each channel with 40ksps, almost 50k channels of neural data can be delivered, which gives a much higher throughput than required for future BCIs.

In our wireless neural recording system (called as a brain implantable chip, BIC) described in [46] and elsewhere, we utilized a VCSEL as a data transmitter for its advantage over edge-emitting lasers or Fabry-Perot lasers to make fabrication process easier with confined dimension requirements for implantable system. In our fiber optic based neural recording system, an unpackaged VCSEL of 850nm wavelength was selected ULM Photonics Inc. (Germany, model no: ULM850-10-TN-N0101U) for coupling and other fabrication process issues. The dimension of a bare chip was $250\mu\text{m} \times 250\mu\text{m} \times 150\mu\text{m}$ (W $\times$ L $\times$ H). Specification of the device is shown in Table 2.1.

2.2.2 VCSEL and optical assembly

A VCSEL used in the our neural recording system is modulated by a digital controller chip, with a modulation frequency of 13.56 MHz. Figure 2.10 shows

Parameters	Units	MIN	TYP	MAX	Test Conditions
Wavelengths	nm	840	850	860	$I_{OP} = 6 \text{ mA}$
Threshold Current	mA	0.4	0.5	0.8	$T_{Chip} = 25 \text{ }^{\circ}\text{C}$
Threshold Voltage	V	1.4		1.8	
Slope Efficiency	W/A	0.3	0.4	0.5	$T_{Chip} = 25 \text{ }^{\circ}\text{C}$
Laser Forward Current	mA	3.0	3.7	4.5	$P_{opt} = 1.2\text{mW}$, $T_{chip} = 25 \text{ }^{\circ}\text{C}$
Thermal Resistance	K/mW		2.0		
3dB Modulation Bandwidth	GHz	7.5			$P_{opt} = 1.2 \text{ mW}$

Table 2.1: Electro-optical Characteristics of VCSEL (ULM 850-10-TN-N01010U), from [1]

the internal analog circuitry of a digital controller chip. (For the details of a ASIC controller chip will be discussed in Chapter 5) The controller chip has an internal TTL input converted from the digitized data, sends the signal to the biased VCSEL, enables the driving current up to have 3mW output at maximum.

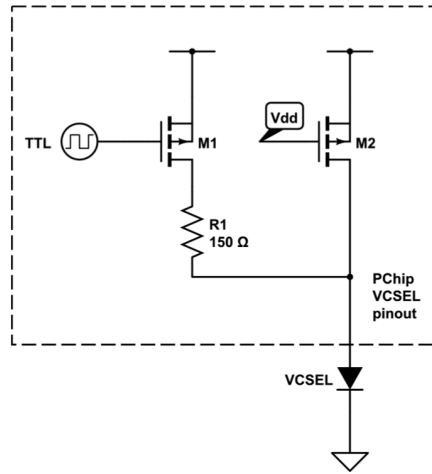


Figure 2.10: VCSEL driving circuit in a digital controller chip

The typical output of the VCSEL is $\sim 1.2\text{mW}$. In our system, VCSEL is coupled to an optical fiber, so the modulated signal from a VCSEL should be collimated before entering the optical fiber.

The VCSEL alignment to couple the fiber took a significant amount of time while making each device. It requires high efficiency coupling from a VCSEL to an optical link so that the neural data can be delivered to an external photodiode without any loss. Although pigtailed VCSELs of high coupling efficiency were commercially available, it was not the option for our system, because one requirement to make neural recording system is a small form factor that a commercial pigtailed VCSEL cannot meet. To couple a VCSEL to an optical fiber with having a high coupling efficiency, micro graded index (GRIN) lens was used based on the literatures [63].

For our VCSEL, among commercially available GRIN lenses, a micro-GRIN rod lens of 0.5mm diameter, 0.25mm pitch, with a 90% clear aperture and an NA of 0.55 (from Edmund Optics, NJ) was chosen. The end surface of the lens was broadband anti-reflection (BBAR) coated with 0mm working distance, of which reflection rate is less than 0.5% from 780nm to 840nm range. Coupling with a GRIN lens leads to a Gaussian-like beam shape that can be focused into the multimode core of the optical fiber with higher coupling efficiency. The VCSEL and the GRIN lens were passively aligned, then actively aligned with the fiber by adjusting x-y-z direction with a micro-manipulator. We could get the power of up to 1mW (hence the coupling efficiency was about 80%) from a GRIN lens and a VCSEL assembly whereas without a GRIN lens, the optical power was 200-300 μ W (with a coupling efficiency of about 16-25%). With the GRIN lens, it was also less sensitive to the displacement of the VCSEL during alignment.

Since making high efficiency optical assemblies were time consuming, PPS and VCSEL and GRIN lens assemblies were modularized, so those modules

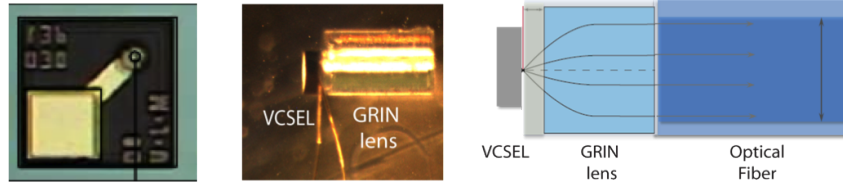


Figure 2.11: A VCSEL with a GRIN lens assembly

can be 'recycled' from one system to another. By making 'recyclable' optical assemblies, the whole fabrication process could be expedited. An optical assembly was built on a specially designed Alumina pad ($0.25'' \times 0.25''$) where two gold traces were printed. The optical components (either PPS or VCSEL with GRIN lens) were mounted vertically and fixed with thermally conductive epoxy (Epotek, H-70E), then actively aligned by monitoring the power from other end of the fiber with an optical power meter. Between the interface of each optical component, UV curable optical adhesive (Norland, NOA81) was applied. After the whole process was finished, another run of H-70E was applied to cover the whole assembly for mechanical strength. Figure 2.11 shows a VCSEL and an optical assembly fabricated before alignment.

2.3 Optical Fibers

2.3.1 Background

An optical fiber is a waveguide, which transmits light from one end to the other end by total internal reflection. Thus, optical fiber based communication permits data transmission over long distances at higher bandwidth with less attenuation than metal wires. It also doesn't have any crosstalk between

two closely located fibers, and is immune to electromagnetic interference. Some properties of optical fibers as described above make the optical fibers a good candidate for data delivery. However, to use optical fibers for in vivo application, it is important to know if the material of the optical fiber is biocompatible, and if the fiber is robust enough against any possible mechanical stress during the surgical procedure and after implantation. Material of optical fibers used in neural recording systems should be selected based on the following specific requirements.

The first requirement we considered was the mechanical strength of an optical fiber. The physical stress of neural recording system in the animal model especially comes from the mechanical deformation when the fiber is twisted or bent. This can happen either during the surgery or after device implantation when the animal is moving, since in our scheme, the connection to the external devices is percutaneous. To prevent cracking or damage to the fiber, we chose plastic optical fiber (POF) which is flexible compared to silica fibers.

Another important requirement was biocompatibility. Material wise, silica fibers and plastic optical fibers are both known to be biocompatible. However, to our knowledge, optical fibers have never been implanted in any human body for medical purposes. Clinical applications of optical fibers in human are mainly limited to optical sensors (or transducers) or imaging tools used in vivo acutely with protecting jackets. This means further research should be continued for medical application of fiber optic based implantable devices for human use. Chronic or acute implantations of optical fibers are routinely performed in optogenetic research in animal models. Unlike other optogenetic studies where

only a guiding canula is implanted chronically and an optical fiber is implanted acutely on every recording session, Sparta et al. [64] reported implantation of optical fibers in a mammalian brain for 2-6 weeks. Results from this study show reduced tissue damage was observed with chronic optical fiber implantation compared to conventional method. However, more chronic implantation research should be followed including performance characterization.

2.3.2 Coupling to optical components

Considering the requirements for animal experiments as discussed in the previous section, we purchased medical grade plastic optical fibers (POFs) from Chromis Fiberoptics for powering the neural recording system. The POF was a graded index perfluorinated optical fiber with a core diameter of $250\pm 10\mu\text{m}$ and a cladding diameter of approximately $490\pm 10\mu\text{m}$. The numerical aperture of the fiber was 0.18 and the bend radius was 10mm. For data delivery, larger core($400\mu\text{m}$) with similar cladding($500\mu\text{m}$) optical fibers (Paradigm Optics, WA) were used to match the dimension of GRIN lens. The selected optical fibers were both biocompatible and sterilizable [65], and were qualified for 1-2 months in *in vivo* studies.

The plastic optical fiber was cut with a POF cutter block and a extra sharp razor blade (Industrial Fiber Optics, AZ) then polished with $5\mu\text{m}$, $1\mu\text{m}$ and $0.3\mu\text{m}$ Aluminum Oxide lapping sheets (Thorlabs Inc.) on a polishing plate. For the fully implantable neural recording system, we used connectorized fibers with LC connectors by Chromis Optics. For the two-component neural recording system, the distal ends of fibers were connectorized with $500\mu\text{m}$ ceramic LC ferrules (Kientec systems, FL) prior to the assembly for generating

the optical input and output ports so that the two fiber optic cables for power and data could be easily plugged in/out through LC connector sleeves during animal experiments. The coupling efficiencies for both fiber connectors were measured as $>90\%$, and they successfully recorded neural data in freely moving animals. (See Chapter 5.)

2.4 Discussion and Conclusion

In this chapter, essential components to build fiber optic neural recording system were discussed. Three optical components were adopted to power the system and to transmit the data. The first component was PPS, which had a similar concept as of a solar cell, but only for monochromatic IR light. With a multi-tandem cell structure, we could achieve high efficiency PV cells to supply power to the neural recording system. It is important to note that the device can have even higher efficiency when it needs to be used in a more power-constraint system by adding AR coating. The theoretical maximum efficiency of PV cell for monochromatic light source can be estimated by assuming that the whole photons are absorbed and have higher energy than the band gap energy, and there aren't any recombination losses or other losses. The maximum efficiency in a single PV cell was once calculated by R.Pena et al. in [9]. In the case of GaAs and 850nm wavelength, the efficiency between $0.1\text{W}/\text{cm}^2$ and $1\text{W}/\text{cm}^2$ region was 75-80%.

Therefore, it seems that there is still a room for improving efficiency of our PV cell by AR coating. To estimate the reflection loss that happens in our current PV cells, the simplified reflectance estimation can be calculated from

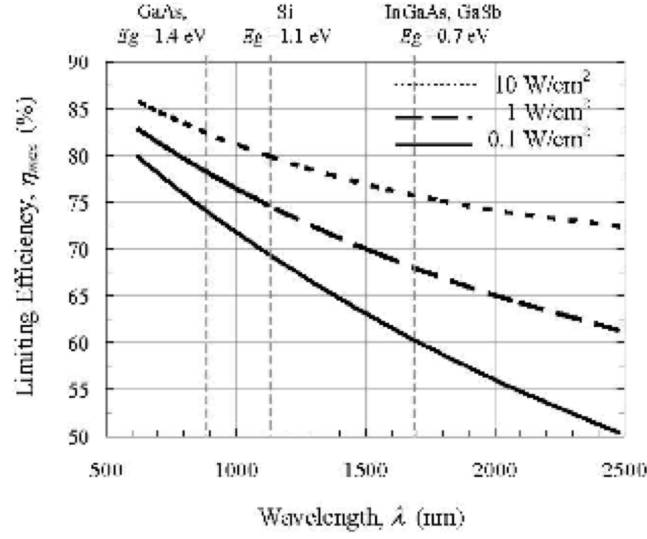


Figure 2.12: Theoretical maximum efficiency as a function of wavelength λ , from [9]

the following equation.

$$R = \left(\frac{n_{air} - n_{GaAs}}{n_{air} + n_{GaAs}} \right)^2$$

Using the refractive index of GaAs at 850nm found from [66], which is 3.662, and the refractive index of SiO₂ of 1.53739 [67] (based on [68]), the simple reflectance of the light from air to SiO₂ then GaAs is 0.1594, that is 16%. The combined reflectance ($2R/(1+R)$) is about 28%. Thus if AR coating is used we can get even higher efficiency the PV cell. Currently many researchers work on making highly effective AR coating, but one of the simplest AR coating would be using destructive interference. To have destructive interference, the refractive index of the coating material should be close to the square root of the two indexes of media interfaces with the coating material ($\sqrt{n_1 n_2}$). One such material known used in GaAs AR coating is Si₃N₄ [69]. Especially Si₃N₄ can function as a dielectric layer when it is used for AR coating. The simplified calculation for the optimal deposition thickness of Si₃N₄ for single AR coating

is from:

$$\delta_{Si_3N_4} = \frac{\lambda}{4n_{Si_3N_4}}(2k + 1), \text{ where } k = 0, 1, 2, \dots$$

λ is the wavelength of the incident light, and $n_{Si_3N_4}$ is the index of Si_3N_4 . The index of Si_3N_4 at 850nm is 2.1575[70], so the ideal thickness would be 2955Å. For future application in more power-constraint system, this simple AR coating would be the first step to improve the conversion efficiency. In our case where the power was supplied from the external device and the system was not power-starving, the conversion efficiency over 60% was still a good starting point for the fiber optic based neural recording system. The only concern would be the heat generation caused from the delivered optical power that was not converted to the electrical power, however, it didn't increase the ambient temperature of the board significantly, which was estimated to be in <2°C range.

In-house built PV cells with a custom built optical assemblies of commercially available VCSELs and optical fibers were all considered to meet the requirements for chronic in vivo application. Therefore, the fabrication of optical components for the neural recording system was time-consuming and requires precision. At first, every optical component was built on each neural recording system at the beginning of the whole process. This enabled checking and debugging the functionality of each component at every step of fabrication. However, it also had a drawback of wasting resources, because any failure during other fabrication processes after mounting optical assemblies made the working optical assemblies useless. By modularizing these optical components

separately as discussed in Sec. 2.2, the fabrication process became easier and the assemblies became reusable.

Most of this chapter focused on device fabrication on the bench top level. In the following chapters, we will discuss on building the whole system based on the optical assembly modules and the transition of the system from bench top to *in vivo* experiments.

CHAPTER 3.

Integrating Neural Recording Device with Micro-electronic Components

3.1 Brain Implantable Chip (BIC)

Early progress has been reported in the first steps along the development path towards the goal of fully implantable neural interface microsystems. We introduced some of other group's work in Chapter 1. Here, we will briefly present our works named brain implantable chip (BIC), which has been undergoing since 2005, with different versions of power and data delivery.

The BIC represents an integrated micro-electronic system that can record and transmit neural data to the external decoder. We have been developing a custom preamplifier chip that can be assembled onto an MEA, and a custom digital controller chip to control ADC and data transmission. Earlier versions of this work were published in [71], where the first version of preamplifier was described. This first version of amplifier had 10Hz to 7.3kHz bandwidth, with $9\mu V_{rms}$ noise level, and the power consumption of the total 16 channel amplification was 1.3mW. Up to this point, the multichannel MEA assembled with

the preamplifier was tested only *in vitro* without having the full functions of a neural recording system. Fully integrated microcircuits on the flexible substrate was first published in [46], where chronic *in vivo* recording was partially successful with the percutaneous connection. Fully implantable version was tested in a primate [72] and pigs [47]. The basic structure of the BIC system shares the common features as shown in Figure 3.1, that the active electronics are apart from the brain, to reduce any brain change due to the thermal generation from the electronics. These basic features were applied to the design of the fiber optic based system, which will be discussed in Sec. 3.2 more in detail.

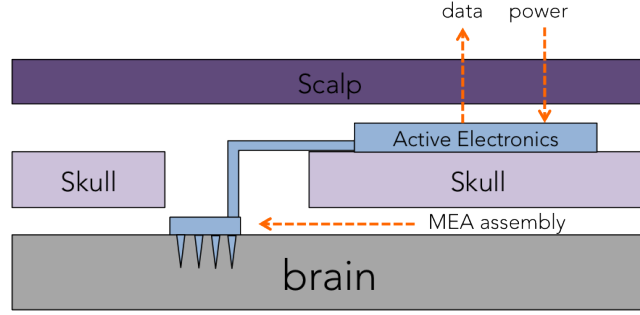


Figure 3.1: A device distribution overview of an implantable BIC system

3.2 Overall Structure of the Fiber Optic Neural Recording System

Figure 3.2 shows the overall design of the fiber optic neural recording system. It consists of two parts; the *front-end* and the *back-end*. The front-end acquires analog neural signals using the 16 channel microelectrode array, and transmits these signals to the back-end. The back-end generates digitized data of the

neural signals acquired from the front-end, and delivers the data to the external system via optical fibers using a laser (VCSEL) (see Sec. 2.2). The back-end also receives the modulated optical power from an external source through the optical fibers and converts it to the DC power and the clock for the entire system. Depending on the size of what animal model we select, this design has two different variations: the physically separated dual board system as in Sec. 4.2.2 for small animal models such as rat and the monolithic dual board system as described in Sec. 3.3.2 for larger animal models such as pigs or primates.

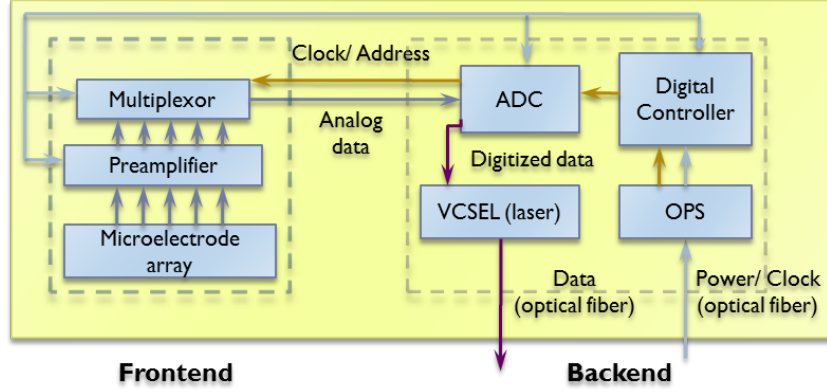


Figure 3.2: Block diagram of the fiber optic neural recording system

3.2.1 The front-end components

The front-end comprises of three main components: a microelectrode array (MEA), a preamplifier combined with a multiplexer. MEA acquires analog neural signals through each of the 16 channels of electrodes and each channel is connected to the metal pads on the bottom side of the array substrate, providing electrical contact. The low power preamplifier has the same number

and the spacing as the bonding pads of the MEA. The metal pads of the MEA and the preamplifier are bonded together by the “flip-chip bonding” process, which is described in the next section (Sec. 3.3.1). The preamplifier amplifies the signals picked up by the MEA, and multiplexes N -channels to $\log_2 N$ lines of addressing. These multiplexed and amplified analog neural signals are then delivered to the back-end.

System	Hermes C + INI	Hermes D	BIC
Connectivity	Wireless	Wireless	Wireless
Channels	1 full BW + 20 TC *	32 full BW	16 full BW
Transmission	900 MHz/FSK	3.9 GHz/FSK	13.56 MHz
Sampling	16 kSps	30 kSps	40 kSps
Resolution	10 bits	12 bits	12 bits
Data Rate	346 kbit/s	24 Mbit/s	15.36 Mbit/s
Power	63 mW	142 mW	15 mW
Enclosure	38 x 38 x 51 mm ²	38 x 38 x 51 mm ²	

Figure 3.3: Comparison of different MEA-based neural recording systems: INI [10], Hermes D [11]), and BIC [12].

The total power consumption of BIC is only 23.8% and 10.6% of that of the other MEA-based devices, INI based [10] and Hermes D [11] as in Table 3.3, these low power characteristics mainly comes from the use of optical method for data communication. The Hermes C+INI and Hermes D systems adopted RF modules with high RF ranges for wide-bandwidth data communication, which consumes more power. In case of the BIC, however, we were able to achieve data communication at a similar or wider bandwidth with only 15mW by the use of the optical fibers.

The preamplifier chip as well as the digital controller chip in the back-end are custom-designed application specific integrated circuits (ASICs). The

main work of design was done by F.Laiwalla and W.Patterson [8, 71] with undergraduate students in Brown, then with M. Yin [45, 48, 73]. The design of the preamplifier can be found from a series of other publications as well ([46, 71, 72, 74, 75]).

Preamplifier chips used in this work were all designed in 2008, and fabricated from 0.5-micron process through the Metal Oxide Semiconductor Implementation Service (MOSIS, CA). Most of the chips were from the batches of the 2009 and 2010 MOSIS run, except the first dozen of the earlier version of preamplifier designated as “M4B”: The details of older version can be found from [46, 47], and the later version designed in 2008, named as “Little Pearl”, described in [73]. As in Figure 3.4a, the amplifier has 16 bonding pads of 400 μm pitch to match the MEA bonding pads, and the noise level is $8.5\mu V_{rms}$ with 200x gain. The frequency bandwidth covers from 0.1Hz to 7.8 kHz, which can be used to amplify both local field potentials and spiking of neural activity.

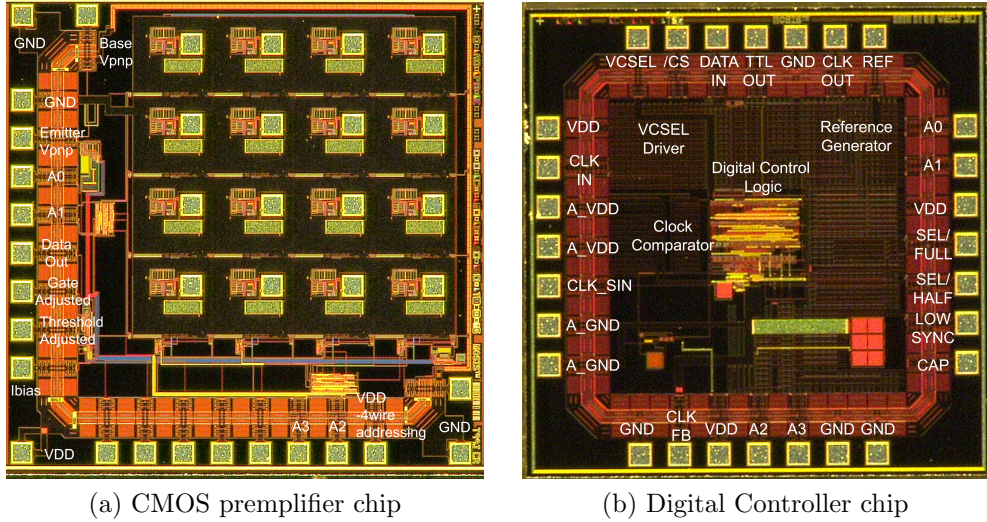


Figure 3.4: Images of ASICs

3.2.2 The Back-end Components

The back-end has a pair of optical fibers as an interface to external devices, one for digital data communication (via VCSEL) and another one to provide the power and the clock for the entire system. The back-end is comprised of four components: a PPS assembly, a digital controller, a low-power analog-to-digital converter (ADC), and a VCSEL assembly.

As described in Sec. 2.1, optical signal arrives at the PPS and passes the LC filter that separates the power and the clock signal. Fig. 3.5 shows this LC circuit, which consists of two surface mountable (SMD 0402) $350\text{ }\mu\text{H}$ inductors and capacitors.

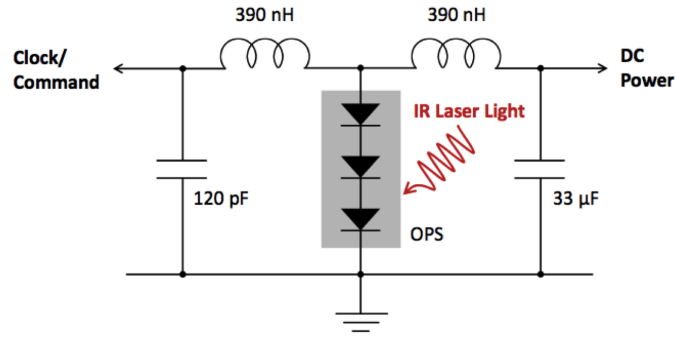


Figure 3.5: The LC circuit to separate the DC power and the 13.56 MHz clock signal from modulated optical signal

The filtered signal then goes into the digital controller chip, called *Pchip* (Fig. 3.4b), where the clock signal is extracted to transistor-transistor logic (TTL) clock signal by the comparator. The use of modulated power that conveys external clock source has two major benefits. First, this scheme requires much lower power compared to the on-board crystal oscillator. Second, the external decoder that receives optical data, does not need to extract the clock

signal to synchronize it with decoder’s own clock because the data is already phase-locked with the original clock of the processor. For these reasons, the current of the external laser source that feeds PPS is modulated by 13.56MHz square wave at 40% mean current.

The signal that goes through the bypass capacitor powers DC to the system, whereas the clock signal extracted from the signal feeds the clock to the digital controller. The digital controller was also designed by W.Patterson with undergraduate students. It enables analog-digital conversion by $\overline{CS}$ and reads digitized signals from ADC. The ADC module that we use is AD7495 (Analog Devices, MA). It has up to 1MSa/s throughput rate and 12 bit resolution.

Our current system uses the sampling rate of 40kSa/s for each channel with 16 channel sampling. However, ADC can be changed appropriately if, for example, faster sampling rate is required. Because the digital controller receives 2.5V as a reference voltage, the minimal amplitude resolution (1 LSB (Least Significant Bit)) is thus $2.5/4096 = 0.61\text{mV}$. Considering the preamplifier gain of 200x, $3\mu\text{V}$ resolution is fine enough to record neural signals. When ADC digitizes analog neural signal data from the front-end, the digital controller generates TTL output and modulates the VCSEL as explained in Sec.2.2.

3.2.3 External electronics for the neural recording system

Although the implantable neural recording device can be implemented on a single substrate, external electronics are still required in order to handle data and power simultaneously. The core component is a laser diode. We use the MicroLaser Systems 852nm diode laser, which was collimated and has an

FC connection for fiber coupling (MicroLaser Systems; Model SRT-F850S-60). The output intensity of the laser can be adjusted from the laser driver and a thermo-electric cooler (TEC) is connected to the laser. The output is 850 ± 5 nm, near infrared, with a spectral width <1 nm and a power stability $<1\%$ ([76]). The laser output can be modulated with the external clock that ranges from 50 kHz to 30 MHz. The clock is provided from the Common Platform System (CPS), which is in-house built electronics to control the inputs and outputs from/ to the neural recording system. It has the RF current driver for other types of BIC systems that utilize inductive coupling, a sinusoidal clock generator as outputs, and inputs for a photo-diode receiver, and a photoreceiver for a direct fiber input. More details about CPS including other functions is described in Sec.5.3.1.

3.3 Fabrication and Integration Of The Micro-electronics

3.3.1 Integration of microelectrode array (MEA) and preamplifier chip

One type of MEA is first developed by researchers in Utah university in 1992 ([77]). After successful recordings in several cats chronically (from 2 to 13 months [78]), Utah MEAs became one of the common tools to record extracellular neural activities in the brain. Utah MEAs are silicon based arrays with a three dimensional structure. After several steps of fabrication, a typical MEA has 10 by 10 square electrode needles of a length of $1000\mu\text{m}$ or $1500\mu\text{m}$, and

with a dimension of 4.2mm by 4.2mm. The pitch between each electrode is $400\mu\text{m}$. Insulation of each electrodes is provided by glass (EG 2790 from Ferro Corp., Cleveland, OH) and then by biocompatible polymer Parylene-C [79]. The backside of MEA has electrical contact by metal deposition of Pt/TiW/Pt with each layer thickness of 240/480/620 nm respectively, and the tip is metalized with Ti/Pt/Ir by 50/240/100 nm respectively and etched by reactive ion etching (RIE) after Parylene-C deposition [80]. Each electrode performs as one isolated channel when recording neural signal but it does not necessarily mean that each channel can only record one neuron per channel. In our system, a 100-channel MEA is diced to 16 (4 by 4) channel array. All these processes are done by Blackrock Microsystems (UT, USA) Inc.

As for the chip-to-chip integration of the microelectronic IC with each MEA, we designed a preamplifier chip described elsewhere, with the same spacing ($400\mu\text{m}$) as that of bonding pads of an MEA. Bonding of each pad of the preamplifier to its corresponding pad on the electrode was performed with the low stress flip-chip bonding technique using a conventional flip chip bonder (model M9, RD Automation, Inc.) with silver-based electrically conductive epoxy. The dimension of each contact pad was $80\mu\text{m}$ by $80\mu\text{m}$ and the length of each electrode needle was 1mm or 1.5mm. The array was housed with the glass holder to protect the tips of the MEA during the handling and flip-chip bonding process as shown in Figure 3.6.

The glass holder was made by dicing a glass substrate of 2mm with the same pitch as the MEA (by J. Lee, a research associate in the lab). The array was mounted onto a glass holder of which grooves were painted slightly with a photoresist (PR) solution that served as an adhesive. Then the assembly was

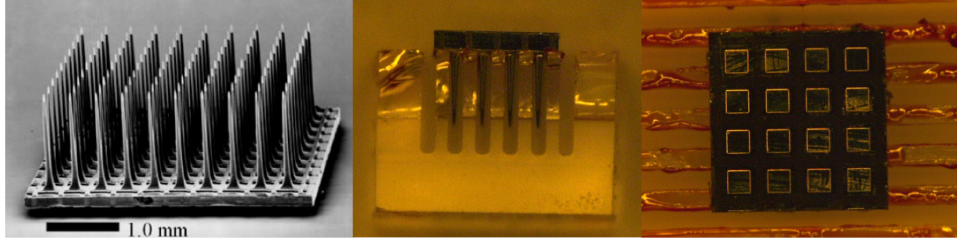


Figure 3.6: 100 channel Utah Microelectrode array and a 16 channel array with a glass holder

cured with 90°C on a hot plate for 2-3 minutes, so that the PR became viscous and the array and the glass holder can be bonded temporarily during the flip-chip bonding process. After scraping the residue of Oxide on the bonding pads of the MEA by a tweezer, the bonding pads and the preamplifier chip were single wire-bonded. This is a trick to break the innate Oxide that might have been deposited before the fabrication process. After making dots of short gold wires of $20\mu\text{m}$ thickness by wire-bonding on each pad, silver epoxy (E4110-PFC, Epotek, MA) bump was added on each pad before the flip-chip bonding.

When preparation of the chip and the MEA were ready and the calibration procedure of the flip-chip bonder was performed, the chip and the amplifier were placed in the flip-chip bonder. The array assembly was located on the upper plate and the preamplifier was located on the bottom plate and both were held with vacuum. The alignment of two components was guided by an optical alignment system in the flip-chip bonder, within a micrometer scale. After alignment is confirmed by monitoring it on the screen connected to the flip-chip bonder, the bottom plate was brought up slowly to the upper plate by the pneumatic controller until two plates met and the bonding pressure read 0.15kg. If all epoxy bumps were kept the same height, ideally slight gap around $10\text{-}20\mu\text{m}$ should be left between two components with the designated pressure.

The quality of bonding can be checked under the microscope after finishing the process, as can be seen in Figure 3.7. Finally, the plates were heated up to 90 degrees for 1 hour to cure the epoxy in between the two components then left overnight after heating off to cure thoroughly without any mechanical disturbance. After the curing was completed the assembly with the holder was soaked in Acetone so that the array assembly can be separated from the holder safely. The assembly was cleaned with regular Acetone-IPA-DI water afterwards.

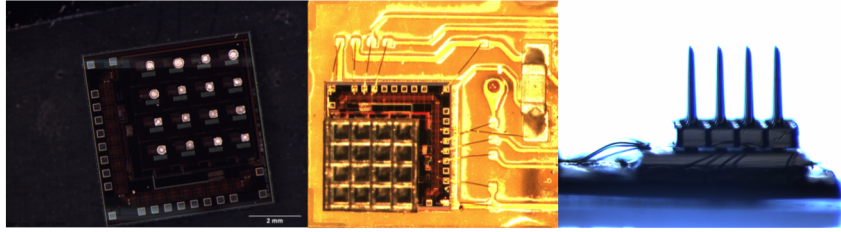


Figure 3.7: Images of a preamplifier chip with epoxy bumps and a flip-chipped assembly from top and side view

There had been a few modifications made from the conventional fabrication process described in [71] to improve the consistency, quality, and process efficiency. The first modification was the housing that has been made with small plates of GaAs. Housing was used to protect the tips of the MEA, and the conventional process started from building side walls first, then adding the top cover as shown in Figure 3.8. Building this array housing required a lot of effort under the microscope since the GaAs plates should be attached on the same level for each sidewall within the $20\mu\text{m}$ tolerance. The failure of matching the level resulted in low quality of flip-chip bonding.

Second was the control of the silver epoxy. We had been using silver conductive epoxy, which had a viscosity value of 3,000-4,000cPs (item number:

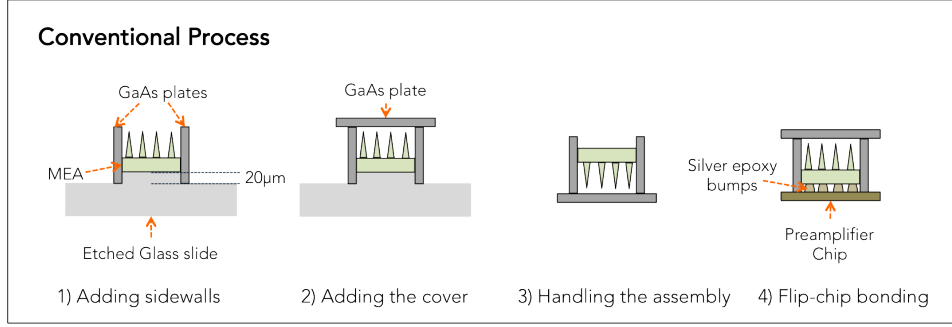


Figure 3.8: Conventional process of building a housing for MEA

H20E-PFC, Epotek, MA), and a pneumatic fluid dispenser to control the epoxy outflow while putting bumps on the bonding pads of the amplifier chip. Compared to the current epoxy with viscosity of 50,000-60,000cPs, the previous one was much less viscous. Sometimes this led to an inconsistent bump size because the surface tension of the conventional epoxy bumps was much lower, yielding uneven spreads around the metal pads and inconsistency on the height of each bump. Third issue was the existence of the Oxide layer. In fabrication foundry, the bonding pads might have undergone deposition of Alumina oxide during the chip fabrication process. The partial Oxide layer on the metal pad is not electrically conductive and may affect the contact quality. These issues could lead to contact problems during the flip-chip bonding process, by having some channels were not in contact and/or some channels were shorted together. Furthermore, the actual impedance value of each electrode in the array is not identical to the nominal value. Originally, the impedance of Ir tips are expected in the range of 70 to 200k Ω [80]. We measured the actual impedance values of each electrode using 5 arrays of 100 channels and found that actual impedance values varied from 100k Ω to 600k Ω , as in Figure 3.9. In Figure 3.9, each electrode was denoted as #1, #2, ... with a length of either

1mm or 1.5mm, and we can observe the standard deviation of each electrode varies a lot. This could be problematic when recording neural signals, because the impedance determines the capability to record small amplitude signals.

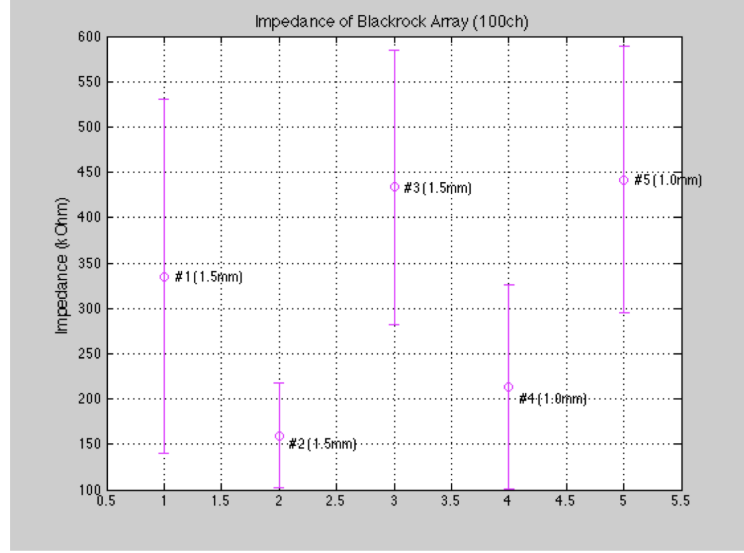


Figure 3.9: Impedance variation within different MEAs

The issue of contact quality, together with the variability of the impedance of electrodes, becomes significant when the number of available recording channels are 16 at maximum. The fabrication process with such uncertainties may affect the sensitivity of detecting neural signals of an MEA when it is implanted in animals. Note that due to the flip-chip bonding process, the impedance of the array through the preamplifier cannot be measured directly. The quality of the signal could be observed only after the device was fully encapsulated and measured with pseudo-spike signals in saline.

To verify the effectiveness of the new fabrication process compared to the conventional method, we made two devices with each process and placed them in the saline bath to record pseudo-spikes. The signals were applied through a Pt wire from a function generator, amplitude of $700\mu V_{pp}$ (see Chapter 4

for more details about pseudo-spike signals) We measured the signals of each device fabricated with conventional/new process, and compared the quality of acquired signals. In Figure 3.10 and 3.11, the two different results were shown. The device made with the conventional method (Figure 3.10), three channels out of a total of 15 working channels had full x200 gain with high signal to noise ratio (SNR), (noise level of $<20\mu V_{pp}$), four channels had less gain (x50 x100) with high noise level ($50\mu V_{pp}$ to $300\mu V_{pp}$), and all the other channels were noisy and unable to record the pseudo-spikes. In contrast, the device made with the new process (Figure 3.11) showed obvious improvement in the acquired signal quality. That is, 11 channels had full x200 gain with low noise ($<20\mu V_{pp}$), and three channels were fair (x130~150) but had lower noise level ($<100\mu V_{pp}$) than the conventional method.

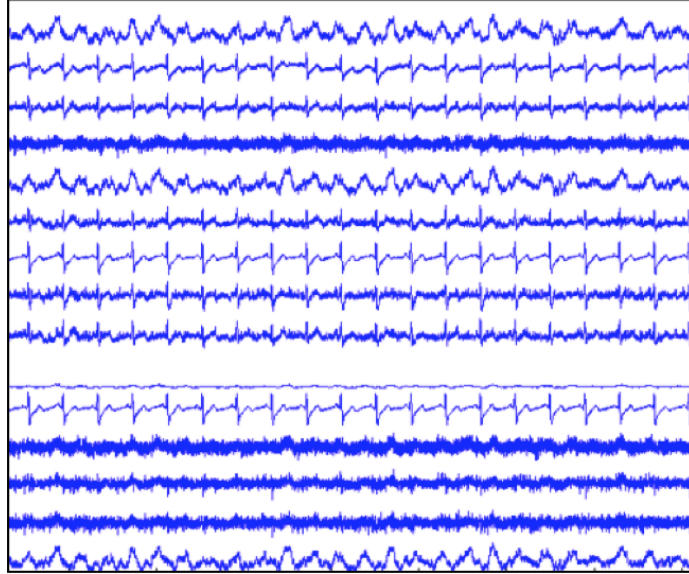


Figure 3.10: Pseudo-spike data recorded in saline with an MEA and a preamp assembly made by the conventional fabrication process

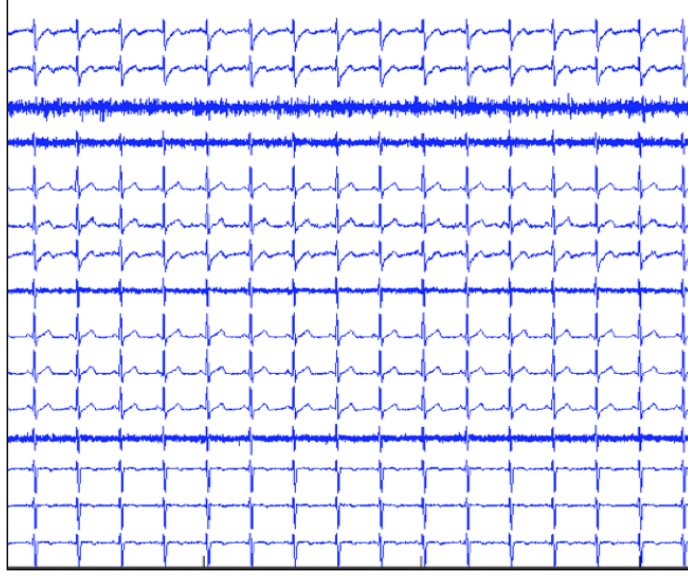


Figure 3.11: Pseudo-spike data recorded in saline with an MEA and preamp assembly made by the new fabrication process

3.3.2 Integration of microelectronics and flexible substrate towards optical brain implantable chip

With the array assembly described in the previous section, fiber optic neural recording system was designed to be fully implantable at first. We call this system the Optical Brain Implantable Chip (OBIC) and its basic design is similar to the BIC discussed in Sec.3.1. We planned to use a flexible substrate for the system, because the surgery procedure can benefit from such substrates for various animal models, including non-human primates, pigs, or even smaller animal model. This is due to our system's special features, which is the separation of the front-end and the back-end, as seen in Figure 3.1.

In our system, we selected Kapton[®] as the material for flexible substrates. Kapton[®] is Dupont.Inc's specific type of Polyimide film. It is known for its excellent chemical resistance, since there isn't any known organic solvent for

the film. It also doesn't melt or burn as it has the highest UL-94 flammability rating. The outstanding properties of Kapton[®] allows us to use it at both high and low temperature extremes where other organic polymeric materials would not be functional. More details of the physical and thermal properties of Kapton can be found in Dupont's website.[\[81\]](#)

These properties of Kapton as well as its biocompatibility matches well for being an implantable and flexible substrate. Since the first animal model we selected was a rat, the dimension and the geometry of the substrate were confined to a certain size. The accessible area of the skull of rat was less than 3cm×2cm (L×W) at most and it was too small for our previous BIC system to fit in, which was developed for primates. The solution was to place the back-end under the skin of the back and leave the "tether" – the connections between the back-end and the front-end – under the neck. However, the physical separation of the front-end and the back-end would introduce a mechanical stress because a rat actively moves its neck while freely moving, the tether had to be stretchable to relieve the stress induced by such movements. Considering these design requirements, we made dummy substrates with different geometries for a stress-strain test, using the same thickness of Kapton[®] substrate with a metalized layer of 100μm. [Figure 3.12](#) shows the idea how the test works. By displacing the dummy front-end and the dummy back-end slowly on two dimensional space, we could measure what design had better resilience of enduring mechanical stress. Based on the result shown in [Table 3.1](#), we decided the geometry of the tether for OBIC system. After the substrate outline was decided, electrical layout design was done with PADS (Mentor Graphics, USA) layout tool.

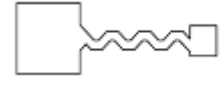
Tether Shape	Extension Length (mm)
	12.54
	12.76
	12.89
	14.76

Table 3.1: Maximum Extension Length with Different Shapes of Tether

The substrates of the selected design were manufactured by Microconnex (WA, USA). The substrates were $27\mu\text{m}$ per layer thick Kapton film with metalization of traces and pads of $100\mu\text{m}$ copper. With bare Kapton substrates, the front-end and the back-end of each substrate were bonded by a backing material named Cirlex[®]. Cirlex[®] is another type of Polyimide film, and with a thickness of $150\mu\text{m}$ bonded onto a Kapton substrate, it functions as a supporting material for a “thin” Kapton substrate when components were mounted and wire-bonded onto the substrate.

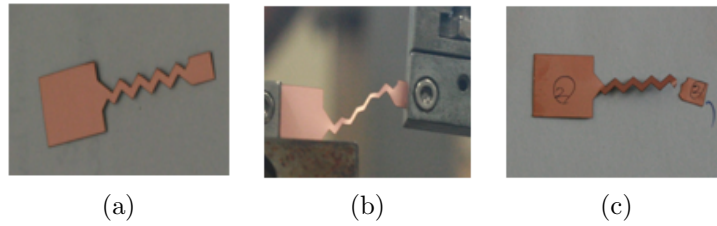


Figure 3.12: Various shapes of Kapton substrates were tested the stress-strain ration before the tether breaks

With a bonding agent film with thickness of $25\mu\text{m}$ (R/flex JADE A series,

Rogers Corp., AZ), which was made of crystal epoxy adhesive, the substrate and the backing material were bonded with a lamination process of 270°C before populating components. After cleaning by soaking the substrates into a cleaning solution in an ultrasonicator, optical component modules were mounted on the back-end. Other microelectronics and passive components were populated on the back-end and front-end of the substrate using Epotek's silver conductive epoxy (H20E-PFC) with an accurate fluid control system (Nordson EFD, RI). Components with bonded with Epoxy were cured on a hot plate at 90°C. After the back-end population was done, the front-end was populated by the same process. The micro-controller and a preamplifier ASICs were wire bonded using wedge bonder (Westbond Inc., CA) with 0.25mm Au wire. The bonding parameters were optimized based on the pull-test designed for our device. For the model type of Model 747677E wire bonder, the first and the second bonding power were all 300 (a.u., arbitrary unit), with 30 msec for each bonding.

3.3.3 Soft Packaging with PDMS for Implantable Use

The packaging for implantable devices is not a trivial issue if the device is planned to be used in clinical application. It still needs rigorous long-term studies to follow, but from various literature in surgical implants, in vivo microfluidic devices and many other in vivo environment [82, 83, 84] Polydimethylsiloxane (PDMS) has been already known for its biocompatibility and being an FDA approved material. Our approach to the implantable device was PDMS based soft packaging described elsewhere. The idea was to use half open molding to encapsulate the system. The mold was first designed using Solid-

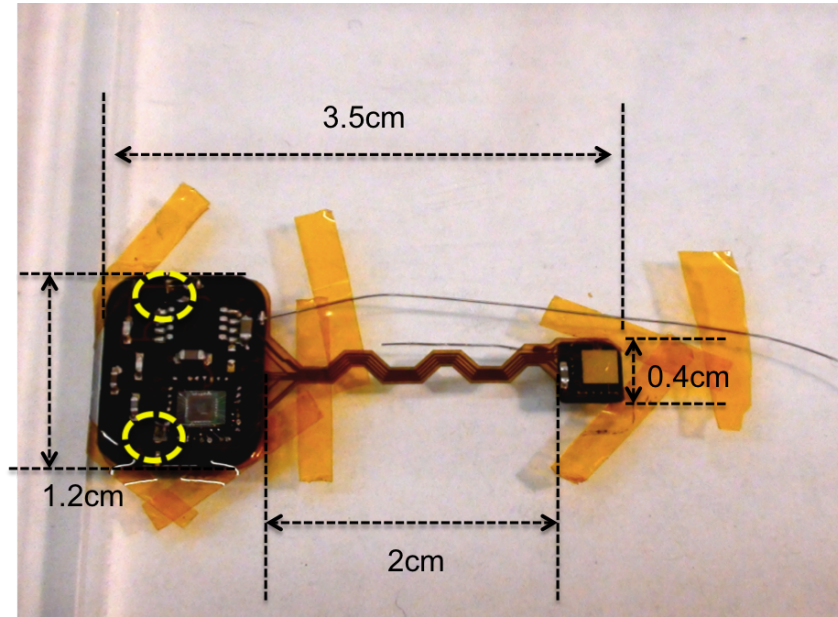


Figure 3.13: First version of implantable OBIC with the populated back-end

Works, then the CAD image (Figure 3.14) was sent to the machine shop to machine the mold made out of an Aluminum block. The wells of the mold were then polished delicately to have a smooth surface. As seen in the Figure 3.14, the mold is not for cast-molding, but has an open face so that PDMS can be carefully applied under accurate control and other consecutive processes can be monitored as well. Two holes located in each well of the mold were for the vacuum chucks. After installing Butyl O-ring in two vacuum chucks, the substrate was located in the wells held by a vacuum pump. The thickness of the mold was 7.36mm when PDMS was applied and fully filled the mold.

Throughout the trial, there were several points to keep high-quality of dense, fine PDMS packaging. First, the surface of the device should be clean enough so that the interface of the device and the PDMS doesn't leave any gap for air bubbles or possible weak point that might lead to ionic leakage from/to the device when implanted in vivo. In order to keep the clean surface of the

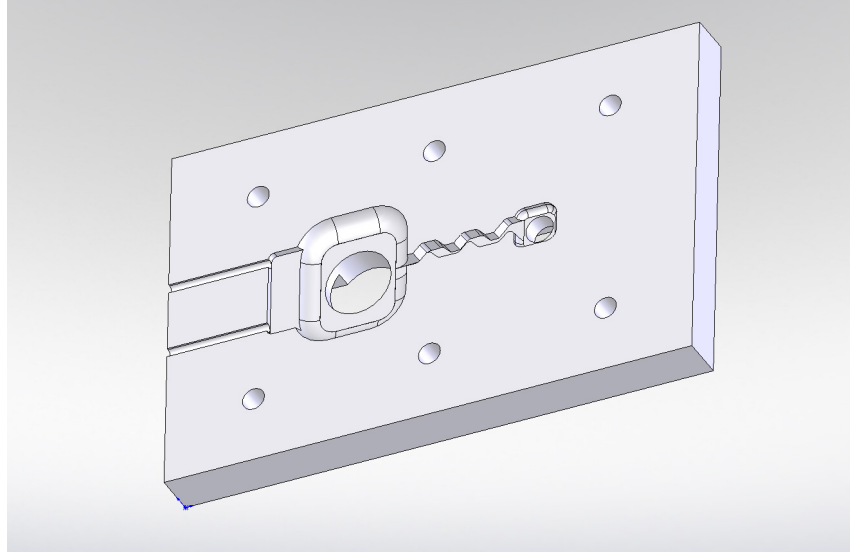


Figure 3.14: Encapsulation mold

devices, we prepared and performed all the processes in a semi-clean room environment. In addition to that, the cleaning process was intervened every step of the fabrication process. The main cleaning solution was MS-722 (Miller-Stevenson, CT), which contains Hydrofluoroether (HFE) and is compatible to most plastics and electronic components and can remove oil residue, dust and particulates. The device was soaked in the MS-722 first, then in deionized water (DI water), and finally in Isopropyl alcohol (IPA). Between each step, the device was blow-dried with Nitrogen gas. After cleaning, the device was baked on a hot plate at 90°C for 10 minutes to dry possible solution residue. Cleaning process was done right before PDMS application on the device.

Second important point to keep the quality of PDMS is the curing condition, especially the temperature for the curing; in several papers, it is shown that the mechanical properties of PDMS change depending on the curing temperature even with the same type of PDMS [85, 86]. The temperature determines the polymerization process of PDMS, which occurs slowly at lower

temperature but is accelerated at higher temperature. At higher temperature, the cross-linking density is increased but the degree of polymerization is decreased [2]. The cross-linking density affects the compression modulus, which is beyond the scope of this work, and the degree of polymerization affects tensile strength, tear strength, and other physical properties. Table 3.2 shows the relationship between the curing temperature and physical properties of PDMS (Sylgard184, Dow Corning) [2].

Curing temperature	Shrinkage	Tensile Strength	Tear Strength
(°C)	(%)	(MPa)	(N/mm)
23	0.7	6.1	17.7
40	0.7	6.2	15.4
50	1.2	5.7	14.8
60	1.8	5.4	13.7
80	4.9	5.2	12.8

Table 3.2: Relationship between the curing temperature and the physical properties of PDMS samples: modified from Ye’s [2] paper

Although the use of the PDMS curing and the type of the PDMS were different from ours, our observation was that the comprehensive performance of PDMS was improved when the curing temperature was lower, because the solidifying phase slowed down. This is an important point to be noted, because in our case the solidifying phase also led to the observable quality, i.e., the amount of air bubbles. Because the general procedure we had in the lab did not guarantee perfectly vacuumed PDMS while filling the open-face mold, there were always slight chances of air trapped in PDMS between the substrate and the components.

To resolve this problem, the curing temperature for our device was set to 65°C and the device with PDMS packaging was cured overnight. The temper-

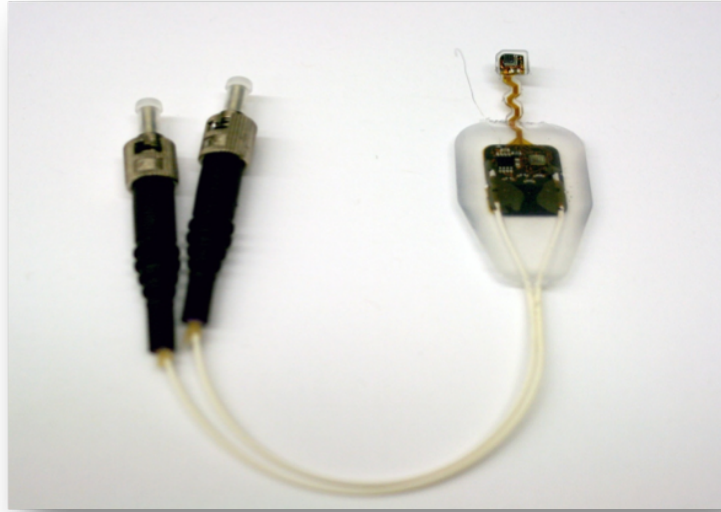


Figure 3.15: Fully encapsulated neural recording device

ature was found from many trials and errors with the encapsulation test unit (ETU) substrate from 40°C to 90°C, by checking PDMS quality thoroughly under a microscope. Figure 3.16 shows the closeup images of the successful PDMS packaging.

Once the device packaging was finished, there was no quantitative data available on the physical properties of this packaging, but we have been researching a long-term study to show the leakage current using the ETU test system in saline tubes. The related study can be found in [87].

3.4 Discussions and Conclusion

This chapter discusses on the components of the fiber optic neural recording system, consideration of the design selection, and fabrication processes. Soft packaging techniques for implantable use were also discussed. With the mod-

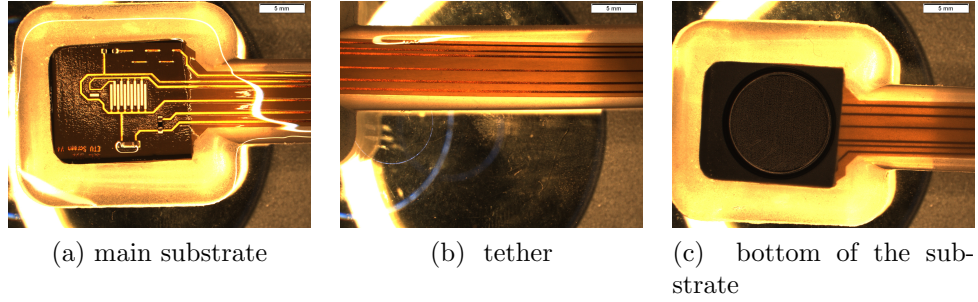


Figure 3.16: Example microscopic images of successful PDMS packaging of ETU

ularized optical components discussed in the previous chapter, we successfully designed and implemented our idea of building a fully implantable OBIC.

The fabrication processes had similarities originally to the conventional BIC process except the optical components, but there were modifications in the process because certain issues were appeared in the conventional fabrication process. One of the major issues was that the variation of impedance across the electrodes was not ignorable after flip-chip bonding. For 16 channel electrodes, malfunctions of some channels could be critical for being used in a chronic implant, especially some uncertainties were added when fabricated with the conventional flip-chip bonding process. By reducing such uncertainties, we were able to obtain very high yield from the flip-chip bonding process and recording system with enhanced performance.

Since the goal of the first version of neural recording system was to make it fully implantable, most part of this work focused on the chronic PDMS-based packaging. We used the ETU to test optimization of curing PDMS, and successfully applied it to the fully implantable OBIC. While our work was translated from the bench top level to a real animal model, we encountered several challenges. The bench top level test, along with the acute recording *in*

vivo showed that the system was capable of recording neural signals. However, the chronic recording in small animal model was not successful due to several factors of the limitation of fully implantable OBICs.

In next chapter, the limitation of the full implantable OBIC and the two component recording system for small animal model will be discussed.

CHAPTER 4.

Surgical Consideration And Implantation

Plans For Small Animal Model

4.1 Animal Model Selection

The ultimate goal for the original fiber-optic neural recording system suggested here was a fully implantable device with percutaneous outlets for two fiber optic connections. However, the animal model for the device should be at least the size of a rabbit (possibly heavier than 1-2kg) considering the size of the device, which was originally designed to be fully implantable. Our lab has previous experience in non-human primates and pigs with wireless neural recording devices [47, 73], thus these two animal models seem to be good candidates.

However, in cases using pigs or monkeys, the time and cost required for training was longer and the cost of performing the surgeries is higher than small animal models. Thus, laboratory rats were selected for device implantation.

The rats were easier to train in a simple motor task and allowed behavior analysis in correlation with neural ensemble activity.

We implanted the fiber optic neural recording devices in the rats ($n = 12$) acutely or chronically, and recorded the neural data. The animal model is not, however, limited to the laboratory rat and it will be another future direction that can happen to implant suggested recording devices in a larger animal model. Implantation in primates is also a required step to the fully implantable devices for future clinical application.

4.2 Surgical Consideration and Implantation Plans

4.2.1 Implantation of OBIC

The fiber optic neural recording system in Chapter 3 focuses mainly on the fully implantable version of the OBIC in device for chronic in vivo recording. The device shown in Figure 3.15 is the first version used in the rats. To implant the whole OBIC system in the body, the front-end array was implanted after the craniotomy and the durotomy, then fixed with the dental acrylic. After two connectors were fixed in a cone structure on the head by the dental acrylic, the back-end and the optical fibers were implanted under the back skin between the shoulder blades. After placing the back-end inside, the skin was sutured. Images from the surgery show this procedure in Figure 4.1). For this implantation, the device was enclosed in an antiseptic pack, sealed and sterilized with Ethylene Oxide gas prior to the surgery, then was opened right

before the surgery.



Figure 4.1: Surgical process of the OBIC system

The basic details of surgical procedure will be described later in this chapter, but the reason for the brief procedure of OBIC implantation here is to point out the problematic damage that appeared after the surgery. Since the suture was on the back and the optical fibers were wound inside under the skin, the OBIC implanted rat scratched the back during the recovery procedure and resulting in the opening of the suture as well as the damaging of the optical fiber. The damaged device didn't carry any optical data output, thus the rat was sacrificed and the device was explanted. Close observation under the microscope didn't reveal any obvious damage but there was a possible damage of optical fiber by deformation marked with red circles (Figure 4.2). However, on the fibers side, it was clearer that a slight fracture could be observed on the efferent optical fiber as shown in Figure 4.3, which might have caused the functional failure.

Since the mechanical strength of the fibers had a problem at the introducing point of the board, some changes were made to support the optical fibers. However, minor modifications of OBIC maintained the problems on the optical fibers when fully implanted in rats. This made us to change the whole design of the neural recording system accordingly to dedicate to a small animal.

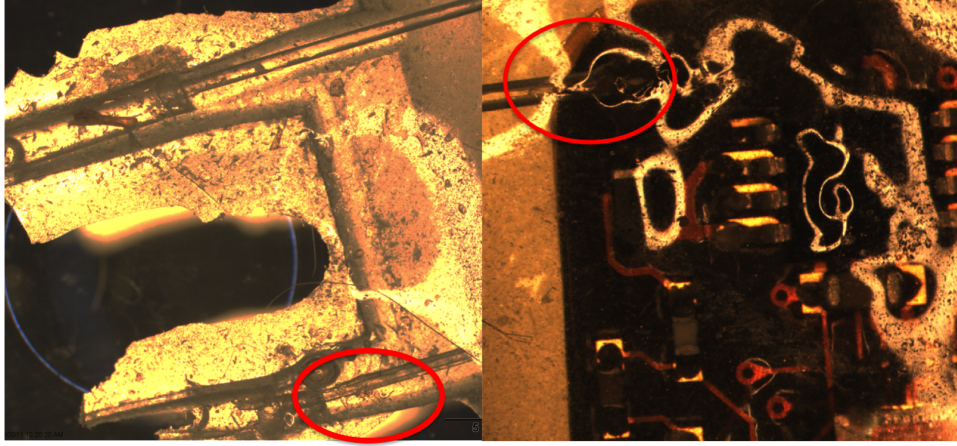


Figure 4.2: Explanted OBIC of possible damages marked with red circles

4.2.2 Configuration of the device for chronic recording

To facilitate the procedure for device implantation in rats, the dimension of the device got smaller, the back-end and the front-end were separated. Since the device could be too big for the animal to be fully implanted, only the front-end was designed to be implanted. Figure 4.4 shows the optimized device to the size of the rat model with the separated back-end and the front-end.

For the separated back-end and the front-end, the fabrication process was slightly changed. After mounting the electronic components, a wired ($\sim 1\text{cm}$ long) 9-pin micro-connector (Omnetics Co., MN) was soldered on the front-end as an interface to the back-end (Figure 4.4a). On the connector, 4 pins were used for address multiplexing, 1 for data, 2 for bias voltage for ASICs (VDD), and 2 for ground (GND) and a reference wire. All were miniaturized according to the size of the rat. The dimensions of each component are listed in Table 4.1.

Only the front-end was packaged with PDMS (NuSil R-2188) after being covered with the underfill epoxy (Hysol E-30CL, Loctite), since only the

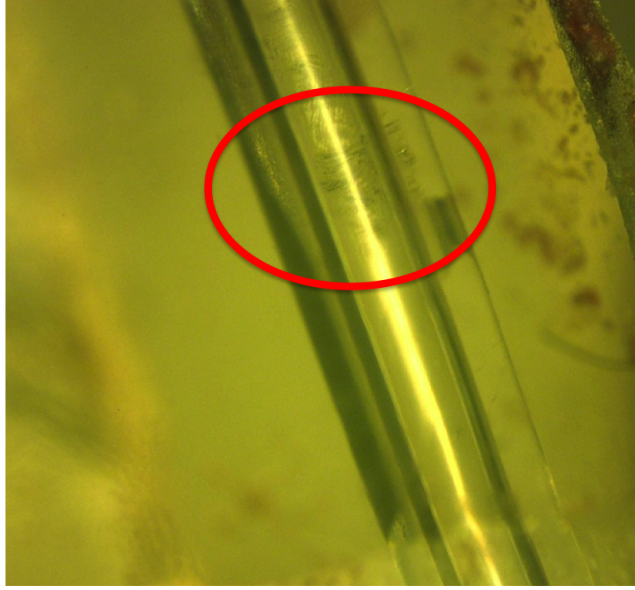


Figure 4.3: A close up image showing a slight fracture on an optical fiber

Component	dimensions(W×L)
Front-end	8.4mm×7.3mm
Back-end	20.8mm×7.3mm
Connector	7.4mm×4.3mm
LC-ferrule	6.4mm×1.249mm(length,diameter)

Table 4.1: Dimensions of miniaturized two component neural recording system

front-end was implanted. The back-end has the same electronics and the optical assemblies of a PPS and a VCSEL built on a smaller printed circuit board (PCB). The distal ends of fibers of the optical assemblies were connectorized with LC ferrules (Kientec systems, FL) with inner diameters of $500\mu\text{m}$. Fibers were connectorized because handling of the device becomes much easier during the fabrication process. Fiber optic cables were connected later during the recording session with the connector sleeves. As the final process step, the back-end was covered with Hysol over the electronics and thermally conductive epoxy (H70, Epotek) over the optical assemblies, for heat dissipation

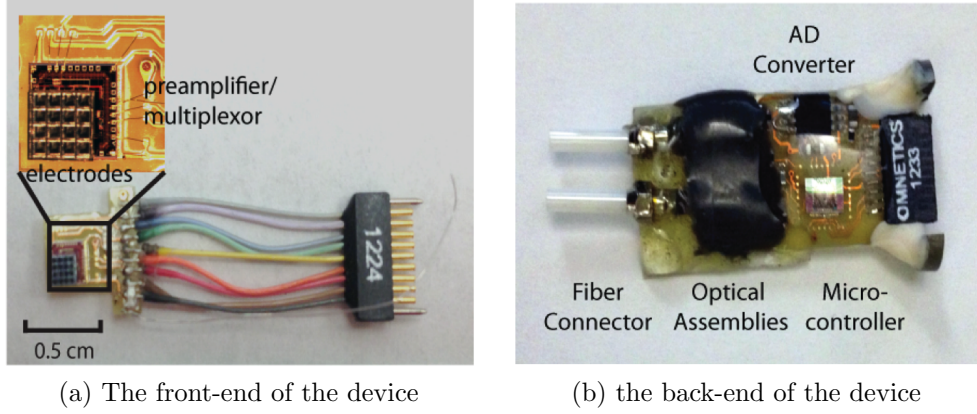


Figure 4.4: Newly designed two-component neural recording system, published in [13]

and mechanical strength [13]. Figure 4.4b shows the back-end after covered with epoxy. The back-end was not packaged with PDMS, since it stayed outside of the body and was plugged to the implanted front-end only during the recording.

4.2.3 Target area for recording and surgical plan

The neural data we were interested in was from the motor area. The behavioral task that the rats were trained required the rats to use their front limbs, thus the target region for array implantation was the forelimb area of the motor cortex, based on the mapping from electrical stimulation from Fonoff et al. [14]. The array size was $1.6\text{mm} \times 1.6\text{mm}$, and the craniotomy was planned to have the center of the array sit on the point of 2.5mm lateral and 1mm anterior from Bregma. Figure 4.5 shows where the array (the size of the array relative to the brain map is shaded with orange color) sits on the brain. Vertically, the cortex has laminar structure of 6 layers. Out of 6 layers, layer V contains large

pyramidal neurons and is known to be the main pathway of voluntary motor control. Parikh et al. studied the spiking activities in the rat motor cortex to characterize laminar differences [88]. Results from the histology analysis and the electrophysiology of this study showed the layer IV/V is known to contains more movement related and directional information. Layer V is usually located from $800\mu\text{m}$ to $1300\mu\text{m}$ below the surface, and for that reason, our vertical target area was layer V.

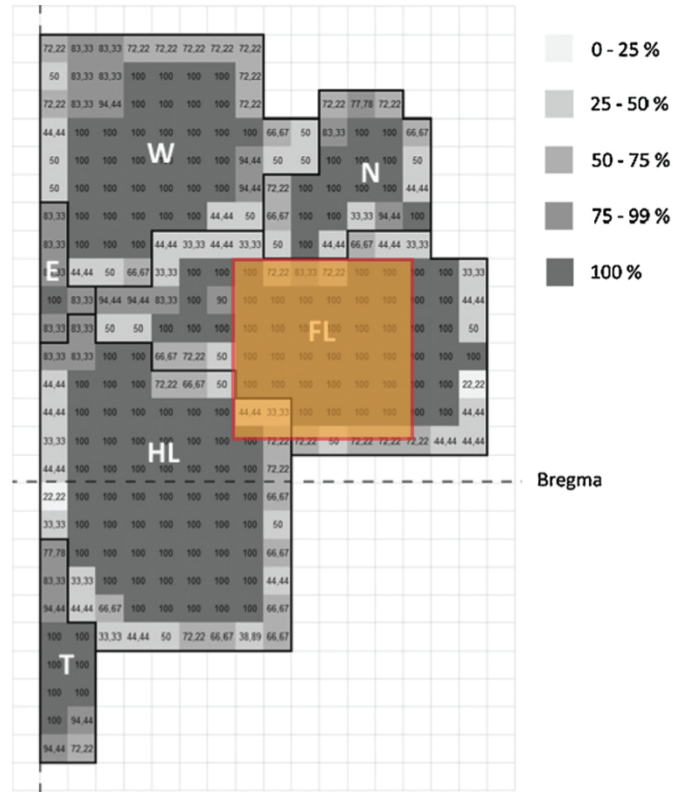


Figure 4.5: Target area of the front-end implantation (Image modified from Fonoff's paper[14])

In order to implant the front-end in the motor cortex of a rat, the skull and the dura needed to be opened before the implantation. Since the array was bonded with a preamplifier, which added the height, around the array was

gradually higher than the substrate as can be seen in Figure 4.6. The goal of the surgery was to make the dura opening as small as possible, but the skull opening where the board was placed, to be thin enough so that the insertion of the electrode tips into the cortex was guaranteed and stayed chronically after the recovery of the brain. We measured the skull for target area and marked the planned craniotomy and thinned the area before drilling the skull.

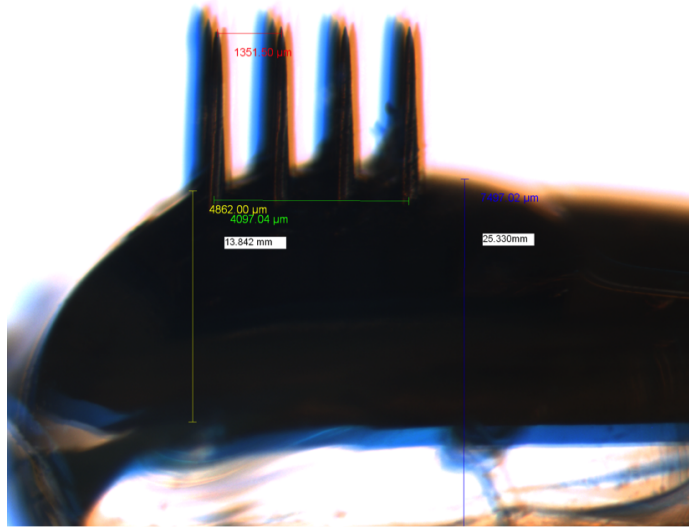


Figure 4.6: Sideview of the electrode array, after encapsulated with PDMS

4.2.4 Surgical procedure of implantation

All surgical procedures were followed under the animal protocol of Brown Institutional Animal Care and Use Committee (IACUC). The rats were kept under anesthesia (2% Isoflurane) throughout the surgery. A large incision was made along the midline to expose the skull over both cortical hemispheres. Either on the right or left hemisphere, the skull was thinned as the size of the front-end (8mm×7mm) so that when the front-end unit was lowered to the thinned skull (Figure4.7a), its MEA portion would target the forelimb/hind

limb area of the motor cortex. (On which hemisphere the array was going to be implanted was based on the observations of each rat during the training. More detail on this will be described in Chapter 5.) After thinning the skull, 4-5 skull screw holes were drilled (Figure 4.7b) and screws were installed (Figure 4.7c) around the thinned area. These screws were installed onto the skull to support the bone cement, because the bone cement (C&B-Metabond) covered the skull and fixed the device in position after the MEA was implanted. Since the bone cement was not able to be attached to the skull directly, screws became posts on which bone-cement could attach. After screws were tightly installed onto the skull, a craniotomy (2mm×2mm) was made on the forelimb and a part of the hind limb area (center at 2.5mm lateral and 1mm anterior from Bregma), then a durotomy followed (Figure 4.7d). On this targeted area, two large blood vessels lie on the cortex. Thus the durotomy had to be performed very slowly and with caution: We pinched the dura carefully with a sharp tweezer and poked it with a 32gauge needle. Once the dura was opened with a hole, the opening area could be slowly extended by enlarging the hole with the sharp tweezer.

After opening the dura, the front-end (of which back surface is attached to a wooden holder with PDMS (Quick-Cast, WPI) for better manipulation during the surgery) was mounted on the post of the micro-manipulator and lowered (Figure 4.8) until the MEA penetrated 1.2mm down in the brain. The insertion depth was measured from the point where the electrodes first touched the cortical surface. Figure 4.9 shows the consecutive images of the moment when the electrodes contact the surface, being aligned to avoid the large blood vessels. After the insertion, quick curable PDMS (Quick-Cast,

WPI) was applied around the edges of the board to cover the exposed cortex (which has a green color on the front-end in Figure 4.8). Then bone-cement (C&B-METABOND) was applied over the skull for securing the array and the connector. Once the array was fixed in place, the wooden holder was cut. At this point, a reference wire was separately inserted to the brain by drilling an extra burr-hole through the skull. Dental acrylic was applied several times afterwards to mount a cylindrical holder onto the rats head to protect the connector from environment. Figure 4.10 shows this procedure.

After the surgery, Buprenorphine was given to the rat as analgesic. Then the rat was brought back to the temporary cage with a heating pad under it and observed until it woke up from anesthesia. The rat was returned back to the colony when it was able to drink water and eat pellets.

4.3 Explantation and Histology

After chronic recording from 2 weeks to 6 weeks of each rat, the rats were perfused and the device was explanted. The point of explantation was decided when the recording didn't seem to have any noticeable neural spikes after spike sorting or the device failed to transmit the optical data. Post-mortem analysis was followed to find the recording failure, or different performance between each device.

After regular perfusion, the skull and the brain of a rat were taken out with the device. The device was explanted by carefully drilling the dental acrylic around the cylindrical holder. Figure 4.11 shows one of the explanted devices with the skull separated from the brain, where the fibrous tissue was grown

around the device. From observation of explanted devices ($n=12$), all MEAs were encapsulated with fibrous tissues. It seems the neural signals began to be lost when the encapsulation process of the device started with the “biofilm”, and the time of formation seemed to be different from one to another. A good device ($n=1$) stayed in the brain and could record the neural signal more than 30 days, although the number of channels decreased and the signal amplitude was lower, few others could record the signal up to more than 10 days ($n=4$). In a severe case, the devices ($n=2$) were completely enclosed with the regrown tissue, and the bone grew under the array, completely expelling the array from the brain. This happened within the 2 weeks of implantation to one of these devices. All these issues seemed to be related to the level of sterilization and how well the interface between the exposed brain and the device was sealed by the quick curable PDMS, which was applied after implantation to secure the brain without the dura. One of the devices had infection developed from the connector all the way down to the brain, due to the sealant did not completely cover the brain. It seemed that the recording lost spikes gradually when this encapsulation process was started. In some brains where the dura were grown back, the cortex didn’t show any evidence of implanted electrode. For some other brains where the infection happened, the indentation of the brain could be observed (Figure 4.13).

4.3.1 Observation of explanted devices

After explantation, devices were diagnosed after cleaning. Each explanted device was first cleaned by being soaked in diluted Chlorohexidine, then DI water, and finally with IPA then blow-dried with N_2 . On the device side, only one de-

vice failed during the implantation after changing the design to two-component system. By failure here it means the device was not transmitting any optical output after being powered on. The possible reason for the failure seemed to be the PDMS packaging, where infiltration of vapor might have shorted the inputs of the amplifier together during the implantation. Every device was soaked in the saline again and recorded pseudo-spikes for the diagnosis, and this particular failed device functioned only after fully dried. However, for other devices all functioned well (n=11) during the implantation and still had the similar performance after removing the tissue encapsulation. Except for damaged tips during the explantation, recording from the saline test showed the performance was comparable to the performance before the implantation. Figure 4.12a and 4.12b show the similar performances in terms of SNR except that the 4.12b has lost some channels.

4.3.2 Sterilization Of the device

The materials used in making fiber-optic neural recording system were all sterilizable with Ethylene Oxide (EtO). For fully implantable OBIC systems, devices were sterilized with EtO. However, a rat does not need highly aseptic environment. Thus we used a UV sterilizer for the front-end and the sealant PDMS sterilization for more than 10 minutes before the surgery. Surgery tools, gauze, cotton tips and drapes used in the surgery were all autoclaved through the Brown Animal Care Facility (ACF). Other minor surgical materials were sterilized by a hot glass bead sterilizer, and 75% Ethanol. The speed of the tissue growth might be dependent on the level of sterilization, however, no thorough study was done regarding this issue.

4.3.3 Histology

After perfusion, the brain was fixed by immersing the brain in 8% Paraformaldehyde. 24 hours before the brain slicing, the brain was taken out and soaked in 30% Sucrose in 0.1M Phosphate Buffered (PB) solution. For our analysis, the brains were sliced with 60/*um* thickness in coronal direction. The brain slices were placed on the glass slide, and stained with DAPI (4',6-Diamidino-2-Phenylindole, Dihydrochloride), and observed with a fluorescence microscope. Figure 4.14 shows one of the images from the DAPI labeled brain slice. The 400 μm indentation indicates the electrode penetration to the cortex in the given brain slice, however, recovery of brain tissue resulted in shorter traces of penetration than expected electrode length. Since the explantation performed after 2-3 months of implantation for most of the rats we implanted and this caused indentation of the brains, the best image we could get from the brains was Figure 4.14. The biological reaction between the brain and the array interface was not thoroughly studied in this thesis.



(a) Skull thinning



(b) Craniotomy and making screw holes



(c) Installing screws



(d) Durotomy

Figure 4.7: Surgical procedure

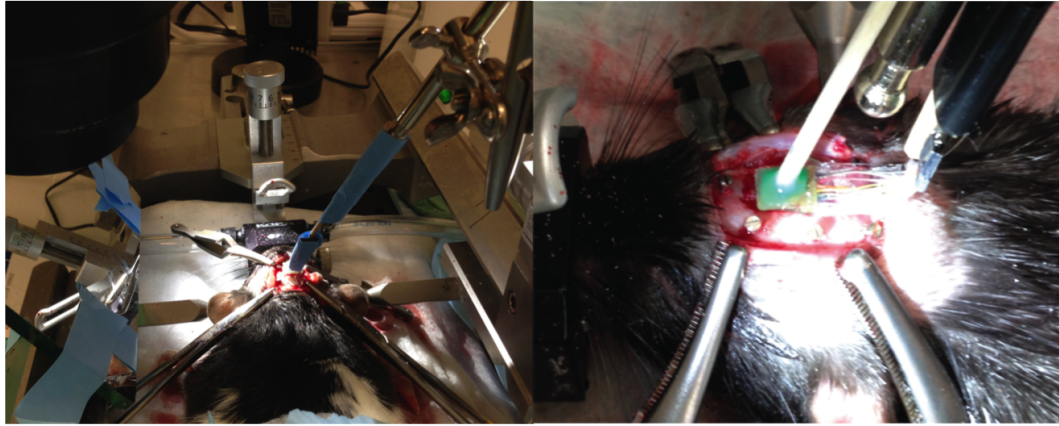


Figure 4.8: Implanting the front-end after durotomy, image taken from above

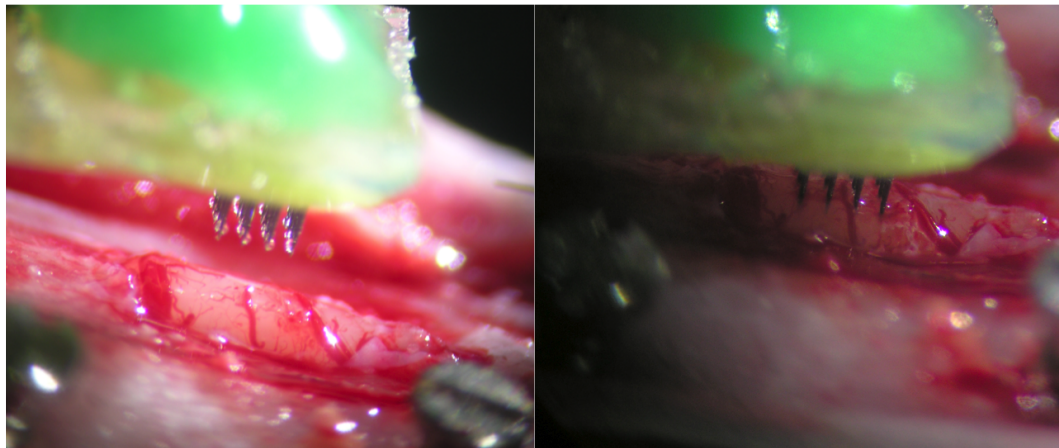


Figure 4.9: Closeup images of the moment when the MEA contact on the brain surface



Figure 4.10: Images of applying bone cement to fix the front-end onto the skull and the illustration of the syringe fixture

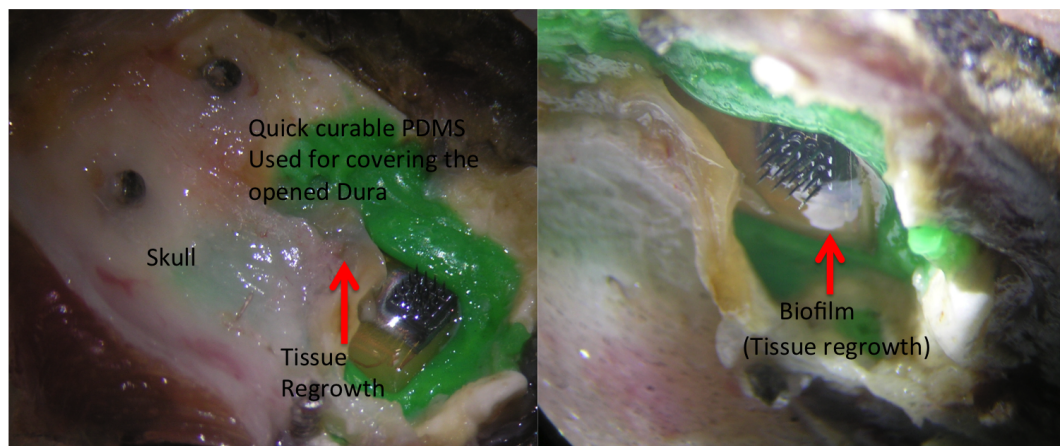
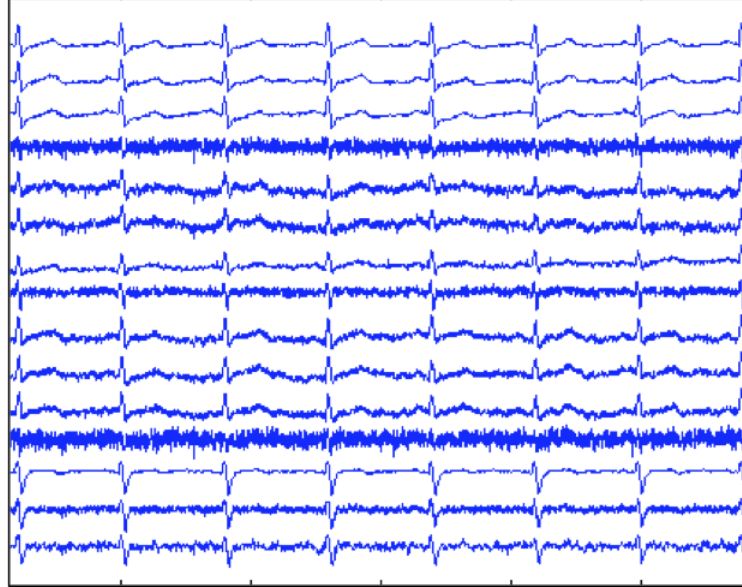
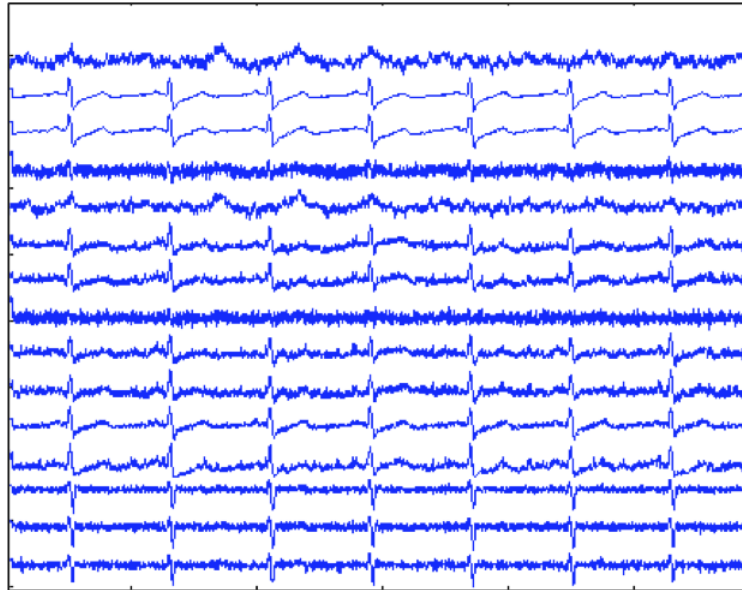


Figure 4.11: The explanted device with the skull and screws attached



(a) Example of pseudo-spike recording before implantation



(b) Example of pseudo-spike recording after explantation

Figure 4.12: Pseudo-spike Recordings from the same device immersed in saline

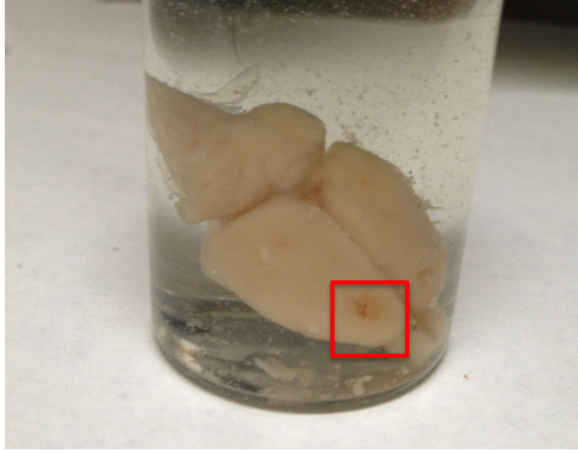


Figure 4.13: Explanted brain showing the indentation on the implanted site

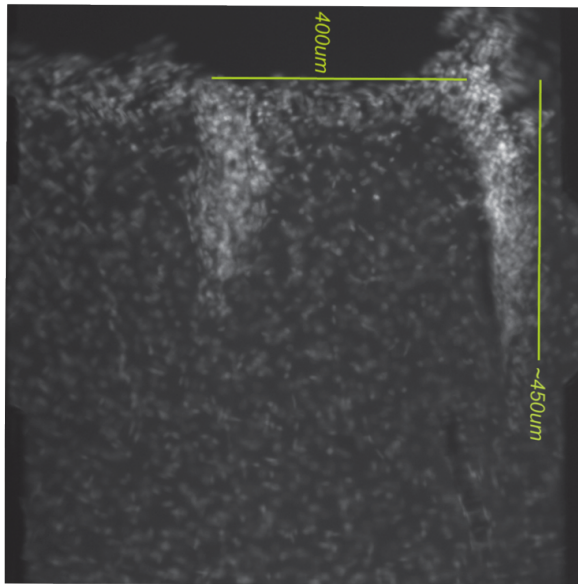


Figure 4.14: Histological evidence of cortical penetration of electrodes

CHAPTER 5.

Data Recording in Trained Animals

5.1 Background

5.1.1 Long-Evans rat and operant conditioning

After selecting animal model to be laboratory rats, we had to select the strain of rats we wanted to work with. Since the effects of the treatments can be different according to the strain, it is important to know unique characteristics of each strain. We chose Long-Evans (pigmented) rats to record neural data with behavioral tasks. There are several popular strains of the rats for lab use including Long Evans. For example, another popular strain is Sprague-Dawley (albino) rats, but the purpose for these two strains are usually different. Long-Evans rats' visual acuity far exceeds that of the albino rats [89]. Partly because of that, Long-Evans rats are used in more skillful motor tasks whereas Sprague-Dawley rats are studied for motor impairments in neurological disorder. Whishaw et al. has compared motor task performance directly between these two strains in [90]. In their study, the single reach for reaching pellets doesn't show big difference between Long-Evans and Sprague-Dawley. How-

ever, movements of the Sprague-Dawley rats were slower than those of the Long-Evans rats in general. Their conclusion is not different from the general idea of the purpose of using each strain, that Long-Evans rats are widely used for the studies of the neural and kinematic investigation of skilled movements, whereas Sprague-Dawley rats are more widely used for modeling neurological disorders [90].

One of the tasks that can show purposeful motor behaviors of Long-Evans rats is operant conditioning task. The neural data we're interested in was motor cortical activity. In order to record motor cortical activity from an awake rat, there are many ways to analyze it in a relation to a rat's repetitive behaviors such as grooming or random behaviors during freely moving. However, we wanted to design a task that a subject performs in more goal-directed way, and requires both learning and planning. In an operant task of gaining reward, the subject is motivated to perform desirable actions in a specific way so it can achieve reward.

According to [89], A standard operant chamber contains:

- The operandum, on which an animal act on or respond to
- Reinforcers, stimuli that increase the likelihood of responding
- Discriminative stimuli, that can control the animal's response

The Skinner's box is the most famous test chamber for operant conditioning developed by B.F. Skinner in 1930s [91]. A typical type of Skinner's box has two retractable levers. Depending on a rat's response in the chamber, the food reward is provided. In the next section, more details of our training task and the chamber design will be introduced based on the Skinner's box.

5.2 Designing Lever Pressing Task

5.2.1 Lever pressing task for motor cortical activity

Lever pressing task is a very common task used for laboratory rat training. The basic design of our training setup was based on the Skinner's box; a rat was trained to press the lever when the corresponding light above the lever was turned on. There were two levers on left and right side of the chamber. If the rat succeeded in pressing the lever above a certain threshold, the food dispenser dispensed a pellet to the food receptacle with a sound. Thus the operanda in this case were two levers, the reinforcer was the food as reward, and the discriminative stimuli was the lights located above the lever. Depending on the turn-on time of the visual stimuli (the lights above the lever), one can change the training routine, so that a rat can learn the lever pressing in conjunction with a memory task. Our goal of having lever pressing task was to have a discrete and definable series of movements during the neural recording, so we didn't include any memory relevant task.

Figure [5.1](#) shows the simplified illustration of the chamber. Note that the food dispenser is located at the opposite side of the levers in this figure. This arrangement is based on the training results from the rats trained in the previous chamber, where all the levers and the food dispenser were on the same side. When a rat was over-trained, it stayed in front of the food dispenser and only pressed each lever with each forelimb without moving. This was not the action we intended to train, so the arrangement has been changed in a way that the rat has to actively move from one side to the other to get reward.

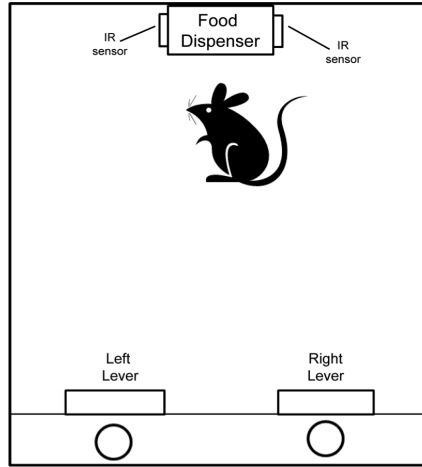


Figure 5.1: Illustration of the chamber design

5.2.2 Chamber design for training

According to the task designed in the previous section, a custom chamber was built. Usually more behavioral research-oriented labs have a sound proof independent chamber to train several rats at the same time. However, we didn't need to have a bigger chamber system with additional cost, the whole chamber was designed for our own purpose. Components including a chamber light (ENV-215M), control lights (ENV-221M), retractable levers (ENV-112), food dispenser (ENV-203-190), pellet receptacle (ENV-200R7M), infrared sensor (ENV-303HDA) and the sound generator (ENV-230) were all purchased from Med Associates (MA,USA). A PCI card and a controller board for reading inputs and writing outputs of each component were also purchased from the same supplier. Since all the components had the standardized width, the chamber was designed to have Aluminum rails so that the components could be slipped on front and the back wall. The transparent side walls were made of Plexiglass. The total size of the chamber was $27\text{cm} \times 30\text{cm} \times 26\text{cm}$ ($W \times L \times D$).

Figure 5.2 is the image of the chamber taken from the top view.

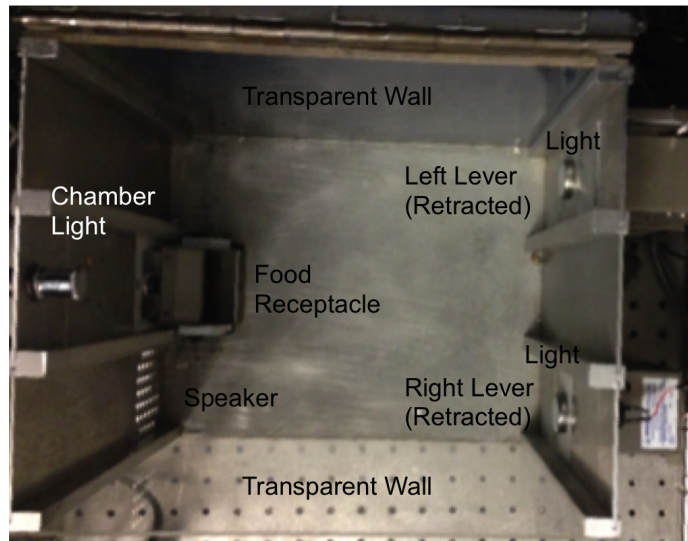


Figure 5.2: The training chamber seen from the top

5.2.3 Designing an automated training program for lever pressing

The training program was coded with C++. Originally Med Associates provided the library (704IO.dll) and two functions:

```
short ret = short PortRead(short rack, short port, short offset);  
void PortWrite(short rack, short port, short offset, short value);
```

Where the port could be set as either input or output and each component could be controlled according to the value and the offset.

However, the function didn't work with the provided library, because it lacked the link of the function directly connected to the library. As of 2011, the Med-associates didn't provide the solution (in consulting with the customer service), because most of their customers usually bought the whole package

including the built in software. Thus I added the following code, where the functions for writing on the port/ read from the port could be overrode to open and load the library. For other additional application to read/write functions to the controller by using the 704IO.dll library, this code (extracted only the essential parts) will be useful for coding other types of training programs.

```
/*-----  
added in smp704control.h file  
-----*/  
  
typedef short (WINAPI * _PortRead)(short rack, short port, short  
    offset);  
  
typedef void (WINAPI * _PortWrite)(short rack, short port, short  
    offset, short value);  
  
class smp704Control {  
protected:  
    HWND MainWnd;  
    HINSTANCE hGetProcIDDLL;  
    _PortRead PortRead;  
    _PortWrite PortWrite;  
public:  
    smp704Control();  
    ~smp704Control();  
  
    // initialization - load dll  
    bool LoadDLL(void);
```

```

// Set main window
void SetMainWindow(HWND mainWnd) {
    MainWnd = mainWnd;
}

// Wrapper for PortRead() and PortWrite()
short smPortRead(short rack, short port, short offset);
void smPortWrite(short rack, short port, short offset, short
    value);

    short Current_Value;

// Print log to GUI
void Log(const std::string & message);
// Print log to file
void PrintLog(const std::string & log);
};

/*-----
added in smp704control.cpp file
-----*/

bool smp704Control::LoadDLL(void)
{
    // get handle to dll
    hGetProcIDDLL = LoadLibrary("C:\\Program Files\\MED
        Associates\\MED IO\\704IO.dll");
    if (hGetProcIDDLL == 0) {
        std::cout << "failed to load 704IO.dll, error code: " <<
            GetLastError() << std::endl;
    }
}

```



```

        return false;
    }

    // get function pointer
    PortRead = (_PortRead) GetProcAddress(HMODULE (hGetProcIDDLL),
        "PortRead");
    if (!PortRead) {
        std::cout << "Failed to get function pointer: PortRead()" <<
            std::endl;
        FreeLibrary(hGetProcIDDLL);
        return false;
    }

    PortWrite = (_PortWrite) GetProcAddress(HMODULE (hGetProcIDDLL),
        "PortWrite");
    if (!PortWrite) {
        std::cout << "Failed to get function pointer: PortWrite()" <<
            std::endl;
        FreeLibrary(hGetProcIDDLL);
        return false;
    }

    std::cout << "Successfully loaded function pointers." <<
        std::endl;
    return true;
}

short smp704Control::smPortRead(short rack, short port, short offset)
{
    if (PortRead==0) return 0;

```

```

    short ret = PortRead(rack, port, offset);

    std::stringstream s;

    s << "PortRead(" << rack << ", " << port << ", " << offset << ")
        = " << ret;

    Log(s.str());

    return ret;
}

```

```

void smp704Control::smPortWrite(short rack, short port, short
    offset, short value)
{
    if (!PortWrite) return;

    PortWrite(rack, port, offset, value);

    std::stringstream s;

    s << "PortWrite(" << rack << ", " << port << ", " << offset <<
        ", " << value << ")";

    Log(s.str());
}

```

Whenever the function is called, the log is shown as in Figure 5.3. Thus the trainer who executes this program can easily check the input and the output of the controller. Once the port is opened and the program starts, a state flow machine in a While loop, monitoring the input and the output with every 50msec interrupt. States are divided largely into task →waiting→reward. Whenever a trained rat succeeds in pressing a lever, the rat gets the food with the presence of a beep sound. When the rat is retrieving food from a food

dispenser, the IR sensor can detect whether the rat pokes its nose into the dispenser and successfully collects the food. If the rat successfully follows this process, the trial is counted as one successful trial. In automated mode, the program runs until either the rat finishes 50 trials or the session runs for an hour (whichever comes earlier).

Usually a well-trained rat could finish one session of 50 trials within no longer than 20 minutes. The average was 15 minutes for trained rats. Everyday, the rat had to finish 3 training sessions before the surgery, and the training log file, which contained timestamps of the rat's behavior in CPU time was saved as .txt format.

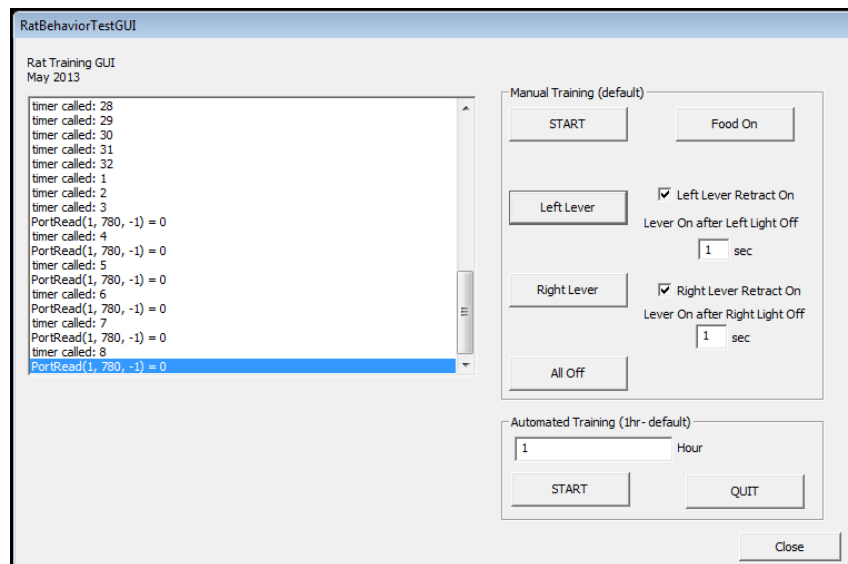


Figure 5.3: Automated training program made with C++/MFC

5.2.4 Handling and training a rat

All animal experiments were performed with Long Evans rats (Charles River, MA) older than 6 weeks (350- 500g). For chronic recordings the animals were

food-restricted by limiting daily food intake to 10-12g of pellets to keep the weight of the animal to be 80% to the average of the same age rats, following the guideline of IACUC. After 3 days from the food restriction started, a trained rat was moved from the colony to the setup back and forth everyday in a disposable paper cup then in a black box. The training was based on the procedure described in [92], with several changes according to our own purposes.

On the first day, the rat was left in the chamber for an hour to get accustomed to a new environment, and to find 10 food pellets (45mg per each pellet, chocolate flavor, from TestDiet Inc.) left in the food receptacle. At this point, the levers were retracted. From the second day, the chamber light was on to indicate the start of each session. On the same day, food pellets were dispensed one at a time in the pellet receptacle with the presence of a simple beep sound (10Hz, duration of 0.5 seconds) whenever the rat approached near the food receptacle. The chamber light was turned off after the rat succeeded in finding and eating the pellets in the receptacle more than 20 times. After that, one of the lever with the light above the lever was on. At this time, whenever the rat approached near the lever, the pellet was dispensed with the sound and the chamber light was turned on and the lever wasn't retracted back. If the rat began to have an idea that approaching the area near the lever could somehow "produce" the pellet, a water droplet with the powdered pellet was put on the lever. When the rat was in its "searching" mode to find the "secret" of getting pellets, it sometimes accidentally pressed the lever to climb the wall. Right after the rat was pressing the lever, the pellet linked with the sound was dispensed to the receptacle. From the repetitive confirmation after

several trials and errors, gradually the rat came to have an idea of pressing the lever. After one lever pressing was done, the rat could be quickly trained to press the other lever by the same process described above.

Each rat had different learning speed in training. Usually, the younger rats (right after 5-6 weeks) tended to learn the mechanism of the task and reward faster than the older rats (9 weeks or more), but the learning speed also varied a lot even among younger rats. The fastest learning was less than a day for the young and active one, which kept searching everywhere when placed in the chamber. For some rats, it took a week or longer to get an idea of lever pressing. It seems the activeness and appetite of the rat motivate to learn the task; the slow learners were less active and tended to stay in one position once they were accustomed to the chamber. However, once any rat completely learned the task (on the average of 3 days) after several sessions everyday for a week, they could finish the one session less than 20 minutes even they didn't do the training everyday afterwards. Another thing to be noted was that each rat has the preference on using either right front limb or left front limb regardless of the lever locations. These characteristics of each rat were recorded during the training, and we used this information to decide which hemisphere the device should be implanted.

Every rats was also handled for 2-3 minutes for 5 days then were fed chocolate coated sunflower seeds, a different type of reward from the task reward, after the training before the surgery. This helped us to plug in the back-end to the implanted front-end on the rat easily after the surgery while they were awake and placed in the chamber.

During the recovery of 2-3 days after the surgery, the rat was brought back

to the recording setup, and was observed the health condition. The recording session was continued while the rat was placed in the chamber, but no task was assigned, only the rewards were provided. The back-end and the holder were fixed with a paper tape temporarily by winding the tape loosely. Most of the rats could resume the task again on the third day after recovering from the surgery.

5.3 Data Synchronization

5.3.1 Common platform system (CPS) and computer interface

Figure 5.4 shows the diagram of the whole system to record the neural data and transmit those to the computer. To enable this, a controller system named common platform system (CPS) was built by W.Patterson and M.Yin in our BIC team. It has many inputs and outputs, for all versions of neural recording system that our lab developed, including radio frequency (RF) based BIC, tethered system (being fed the clock and the power through wires), and the fiber optic system. Here we'll only focus the inputs and outputs of CPS for the fiber optic system.

One of the outputs from CPS is the clock signal for RF/fiber optic system. It is generated as a TTL (0-3.3V) pulse of 13.56MHz. The clock signal is fed into the current source for the laser driver (more details about the laser driver, check Chapter 3) and generates a modulated IR signal. The data inputs received from a photodiode detector are collected into a field programmable

gate array (FPGA) on the CPS. On FPGA stage, data is firstly checked if it has a header called 'synch' (synchronization signal that tells the data reader of the beginning of 16 channel data), then sent to the output buffer. There are several data interface that CPS supports for the communication with the computer. a) the National Instruments data acquisition interface (NI-PCI6533, National Instruments, TX), b) a high-speed USB 2.0 interface in connection with Cypress EZ-USB microcontroller (Cypress, CA), c) a custom Cerebus digital to analog converter for use with the standard Blackrock Microsystems data acquisition system and d) a 1Gbps Ethernet interface (ZestET1, OrangeTree, UK). For our fiber optic system, the high-speed USB2.0 interface was used to collect the 16 channel data. However, for synchronization with other devices, the 16 channel data is bypassed to the 'Orange Tree' board too, which generates 20 channels by adding 4 additional channels for external triggering information then collected with Ethernet connection.

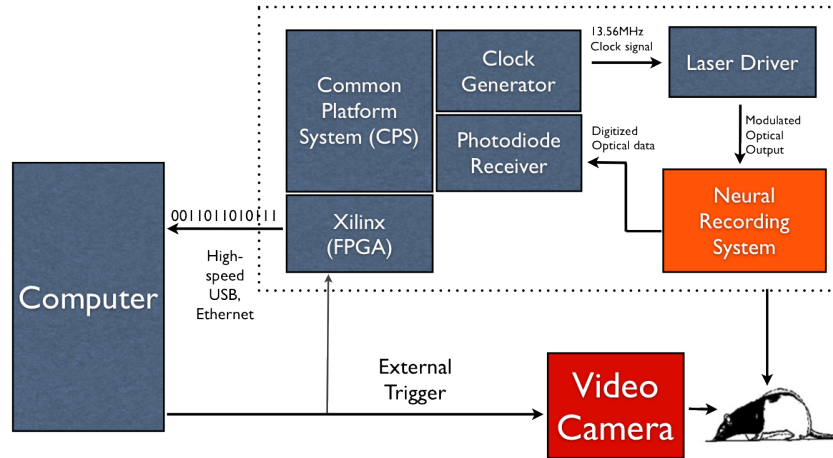


Figure 5.4: The whole diagram of recording system and computer interface

5.3.2 External triggering for video camera and neural data

A video camera or other types of recording device is necessary for behavioral study. Besides, other inputs might be necessary for more thorough behavioral analysis as well. In this sense, the neural data should be synchronized with all other types of inputs used for behavioral analysis, although the sampling rates of all devices are different. The simplest way to solve the timing issue is to add more channels onto the neural recording input so that we don't need to care about the differences in sampling rates throughout many other devices. This was a reasonable solution for us because the device that had the highest sampling rate was the neural recording system, which was 13.56MHz. Other devices such as a video camera, the sampling rate was usually 20fps-30fps. For the lever pressing chamber, the minimum timing resolution was 50msec (Thus the sampling rate was 20Hz at maximum). The video camera we chose was Firefly (Point Grey, Canada) which had a CMOS sensor and could communicate to the computer through the USB2.0. The camera had a port for external triggering. The whole recording setup is shown in Figure 5.5, and the camera can be seen in the inset picture. With the National Instrument's data acquisition system (DAQmx) and a Labview program, I built the camera control program that could be turned on with the 50msec pulse triggering. The generated signal was also sent from NI's interface (BNC-2120) to one of the inputs to the Orange Tree board, so that it could be combined with 16 channel data received from the neural recording system. Thus as long as the neural recording system started before the pulse generator, it could record the

turn on time of the pulse generator (thus the video camera) as one of the four additional channels. Through this way, the video camera recording and neural data could be synchronized easily.

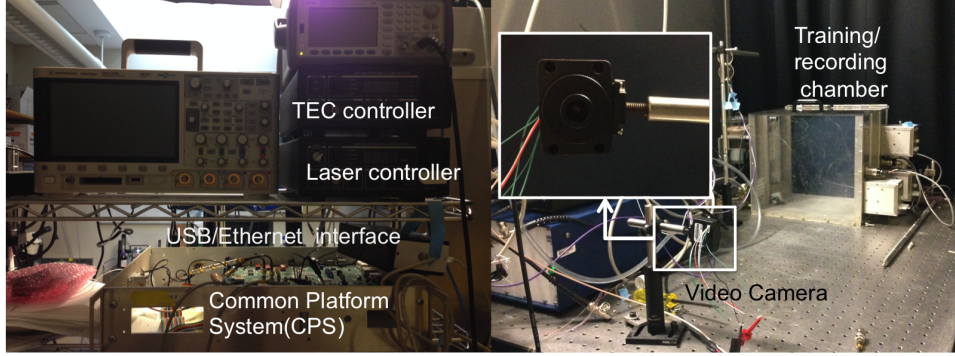


Figure 5.5: Recording setups including the CPS, training chambers and the video camera

5.3.3 Categorizing behavior with a visual cue

When the recording session was started, the rat started the behavioral task. The movie recorded the session from the side through the transparent acrylic window of the chamber and saved it as .avi file (the image on the right from Figure 5.5). Each recording session was about 10 minutes long, and 2 sessions were recorded per day up to 30 days after the surgery. Since the timestamps for the lever pressing, or collecting foods were saved separately and not synchronized with the video nor the neural data, we did the manual categorization by watching the video and analyzing it frame by frame. We categorized the video and extracted the timestamps when the rat was either 1) pressing the left lever 2) pressing the right lever or 3) collecting the food.

The starting point of each behavior might be subjective, thus we set the criteria to get the right timestamps amongst the consecutive frames of similar

behaviors. For 1) or 2), the starting point of the lever pressing was defined as the time stamp of the first frame out of consecutive frames that shows the rat was touching the lever. For food collection, among the frames when the rat was inserting its head into the food magazine, the frame right before the chamber light turned off was selected.

This was reasonable selection of timing for defining each behavior because in the case of lever pressing, the moment of the rat touching the lever was rather obvious point. However in the case of food collection, since the camera view was blocked by the side wall of the food receptacle, it was not obvious when the rat was actually collecting the pellets in the dispenser. One objective point was when the chamber light turned off. Because the automated training program commands to turn off the chamber light whenever the IR sensor was interrupted, which meant the rat pokes its head into the receptacle (this spend one cycle of a loop in the program), the estimated timing of food collection through many trials could be objective.

Using these criteria described above, the timestamps from the whole video were extracted. For example, during the behavior categorization, the point of the lever pressing from Figure 5.6, the point of the food collection from Figure 5.7 were marked with red rectangles. The extracted timestamps were from the video log file, which could be used in data analysis with the neural data in synchrony to the movie. The maximum innate tolerance of the timing of the video was <50msec since the frame rate of the movie was 20Hz. Thus the time window of interest expanded to ± 2 seconds for the peri-event histogram analyzed in Chapter 6.

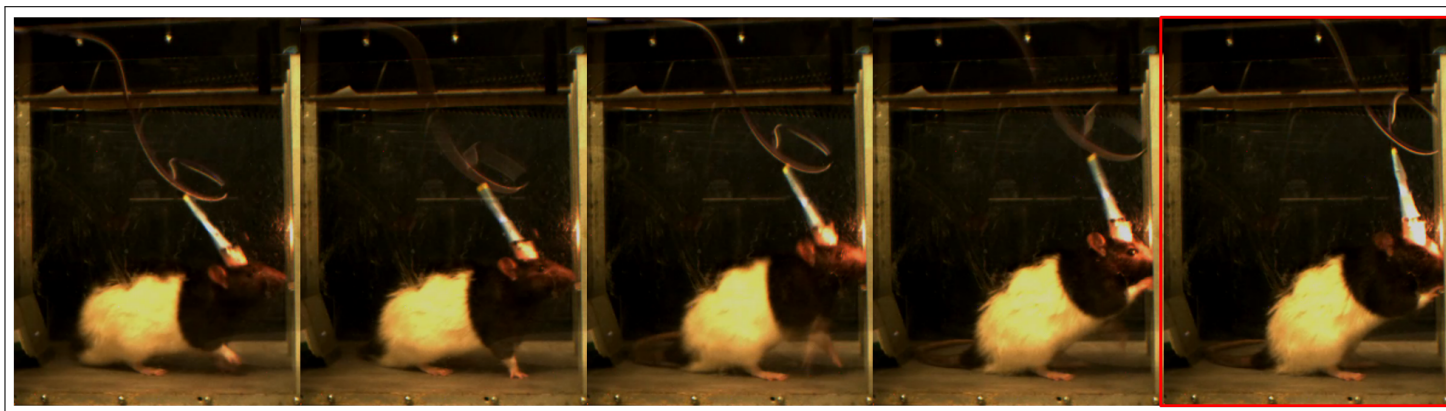


Figure 5.6: Consecutive frames of lever pressing



Figure 5.7: Consecutive frames of food collection

5.3.4 Dealing a huge amount of data: Data conversion in MATLAB

The original data format, .snifr, developed in our lab for the Embedded System for Prosthetic Application (ESPA) project, saves the minimal raw signal of 2 byte hex data. This is the most efficient way when archiving the neural data to keep it as the smallest file size, which usually has more than several millions of the data points. However, to process the data to be readable and treatable in more intuitive way, data conversion of .snifr file format was required. To convert the .snifr data to be loadable in MATLAB and other neural signal processing program, one should 1) change the .snifr data into data file format which is readable from MATLAB, 2) find Channel 1 (Synch channel) and align it from channel 1 to channel 16 then 3) remove any data loss which doesn't have full 16 channel data, 4) convert the hex type data to decimal or binary data. At this first stage of conversion, the .snifr file is changed to .dat file. I made two versions of MATLAB functions to load the .snifr data and converted it to .dat file of decimal data for both 16 channels (only the neural data) and 20 channels (the neural data with external triggering information).

```
function [index,data] =read_snifr2(filename, range)
```

In this function, 'index' returned as every point of time stamps except the possible data with missing synchs. 'data' returned as the whole data without any missing synchs in it. The function can also run without any input arguments, so that it can convert the whole .snifr file to the .dat file, or convert only certain range of the whole data.

However, when converting the .snifr file of 10 minute long data, which has usually around 1Gb file size, the MATLAB cannot handle the whole data at the same time with the memories of regular lab computer (which is usually 4GB to 8GB). The MATLAB runs on the Java Virtual Machine (JVM) that enables cross-platform functionality of MATLAB (between Windows, Mac OS X, Linux, etc.), but has a trade off between the performance vs. platform independence.

Hence to compensate the low performance, MATLAB provides MEX files([93]) to deal with a huge amount of data, by computing time-consuming MATLAB functions by calling sub-routines of C, or C++, which is more a platform specific language thus has higher performance (quick computation speed). With the same types of computation, the regular MATLAB based function took more than 30 minutes to handle the 10 minute long data, but the MEX function which did the same task, took only about 3 minutes to convert the same length data, significantly outperforming the Java based MATLAB function. Thus the data converting functions were all made using MEX. Once the data was converted to .dat file (decimal), it was changed into binary format to be imported in signal processing program like Offline Sorter (Plexon).

CHAPTER 6.

Neural Data Analysis from Chronic Recording

6.1 Neural Signal Analysis

6.1.1 Spike detection

In extracellular recording, noise from the various sources is inevitable. Various sources can be from the ambient environment of the recording setup, the hardware including preamplifier, multiple neurons in the brain combined with local field potentials (LFPs) [94]. The amplitude of extracellular action potentials is much lower than that of intracellular recording, ranging from several tens of microvolts up to millivolts and the shapes are variable because of the cell geometry, density of individual ion channels and the position of the electrodes with respect to active cell membranes [95]. For this reason, noise reduction in spike detection is an indispensable step to start with in case when the SNR is low and the spikes are hardly detectable.

It is widely believed that the spikes carry the major neural information

of the nervous system and most researchers agree that information is largely carried by spike rate (number of spikes in a specific time window) [22]. Thus spike detection is the first mandatory step in multiple neuronal data analysis, where the accuracy of the result affects all subsequent analyses [96]. There are numerous methods that can detect the spikes manually or automatically and supervised or unsupervised including power detection [97, 98], discrete wavelet method [99], match filtering [97], and continuous wavelet method [94].

However, deeper investigation on spike sorting methods is out of the range of this thesis work. Recorded signals that had high SNR could show spikes clearly compared to the baseline, thus we used the window thresholding method. Window thresholding is the conventional and common manual spike detection method, that detects the signals passing a certain amplitude. We first filtered the raw data which was recorded almost full bandwidth (0.3kHz to 7.8kHz) by using a bandpass filter of 300Hz to 10kHz, which filtered out LFP band signals (0Hz-300Hz). After the data was filtered, we applied the thresholding window of $\pm 3\sigma$ of the corresponding channel. All this work including multiple spike sorting, we used Offline Sorter (Plexon Inc.,TX), by importing the filtered data converted to the binary files. The sampling rate of each channel was set to 35.313kHz, and the custom MATLAB code was used for filtering and converting data as discussed in Chapter 5. After the spike sorting, outliers which had much higher amplitude than the average (which might be related to the external or bursting noise) or spikes that had too short interspike interval (ISI) were removed by visual supervision.

6.1.2 Local field potential (LFP)

LFPs of the neural data is another interesting part in neural data analysis. LFP is a sum of hundreds of neurons around the electrode tips, comprises usually within the frequency band of lower (0-20Hz) and higher (30-100Hz). It is not well known what LFPs do in relation to spiking activities in general, but several studies indicate that decoded data from LFP has additional meaningful information to single neuronal activity [100], and since LFPs degrade less than the spike signals over time, the information can be helpful to increase the lifetime of the implanted devices [101]. Besides, LFPs are largely from synaptic activity whereas spikes (action potentials) are generally from pyramidal cells [102], they can represent the inputs and local processing whereas spikes represent the outputs [103].

Some motor area recording, several results were reported that alpha (8-12Hz), beta (15-30Hz) field frequency region is usually prominent prior to a movement, and suppressed at the movement onset [104]. It is thought that a decrease at certain frequency band is caused from a decrease in synchrony of the underlying neural population. Likewise, an increase in power will be an increase in synchrony [101]. Thus the spectrogram of LFP in each channel can reveal such change in each local field chronologically, and the spatiotemporal array map of LFPs through all channel can reveal the propagation of information.

We used the multi-taper spectral analysis from Chronux toolbox made for MATLAB. Chronux toolbox is the open-source MATLAB library for analysis of neural data. The manual of Chronux can be found at [105], and the

materials are downloadable at [Chronux website](#). Multi-taper spectral analysis in Chronux toolbox has been well described in [106, 107], which describes applying a Fourier transform to the tapered time series signal. The tapering function used here is called Slepian function, where the time length T and the frequency bandwidth W make K ($= 2TW-1$) tapers for spectral estimation [102]. More details can be found in [107].

6.2 Acute Recording and Chronic Recording in Untrained Animal

Before chronic implantation, the fiber optic neural recording system needed to show its functionality by recording the real signals in vivo. Therefore, a device was first implanted in one of the untrained rat's brain. The acute recording was performed using both the OBIC system and the two-component system, as well as for the chronic recording, but in this section, only the result from two-component system will be discussed. (For the result of acute recording with OBIC, check [12].) The device was tested on bench-top first, and soaked in a saline bath while recording pseudo-spike signals for 24 hours as described in the previous section.

All the surgical procedures were the same as described in 4, except the skull was not covered by quick curable PDMS for acute recording. The recording was performed intraoperatively during the rat was under anesthesia.

Since the target region for recording was motor cortex, Ketamine and Xylazine mix solution was used, because it was not desirable that the neural activities in the motor area were completely shut down due to any anesthetic

effect. Ketamine is known for two opposing effects on the somatosensory system: (1) a complete suppression of all somatosensory responsiveness, including suppression of active limb movement and (2) a tonic excitation of a subgroup of cortical neurones depending on dosage level of Ketamine/Xylazine [108]. By controlling the level of the Ketamine/Xylazine mix, evoked potential and single neuron activity in the cortical system can be enhanced [108, 109].

The mix preparation was followed under Brown IACUC's protocol, where the rat was at first anesthetized with light Isoflurane ($\sim 1.5\%$) that was eventually turned off after Ketamine/Xylazine anesthesia. Ketamine and Xylazine mix was followed with a dose of Ketamine: 100 mg/kg, Xylazine: 10 mg/kg respectively. By using a manipulator on a stereotaxic instruments (Kopf, Germany), the front-end was lowered down for every $100\mu\text{m}$ after the tips of the array were first touched the target region and recorded the data for one minute. Figure 6.1 shows an example recording from several different depths while lowering the array down. Note that the signals from different depths don't indicate the recordings were from the same neuron.

From the acute recording, we could confirm that the device was compatible to other commercialized devices in recording neural spikes, although we were not able to record simultaneously and compared the data with any conventional MEA on the other hemisphere of the brain, due to the rat's unexpected death during the recording session. The possible reason for the death was the dosage of the Ketamine/Xylazine mix, which might have been higher than the regular dosage at certain point after the third injection.

The tested device was cleaned after the acute recording by soaking it in a solution of 4% Chlorohexidine soap overnight. It was cleaned with DI water

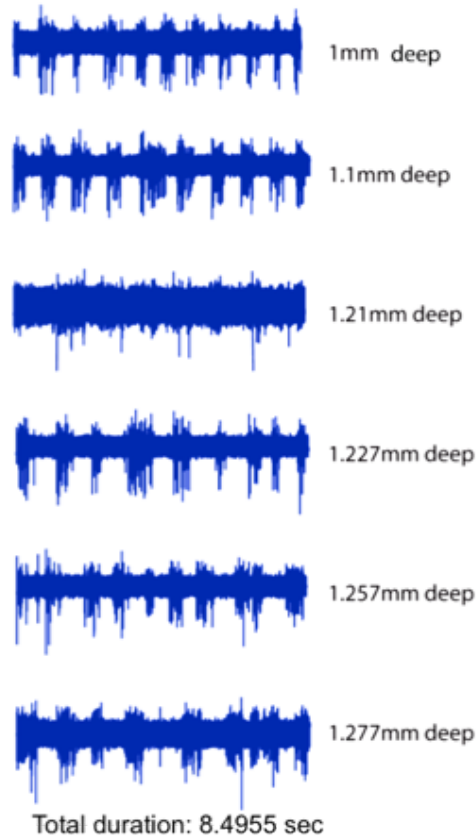


Figure 6.1: Acute recording from different depth in the motor cortical region and IPA with N₂ air blower) and sterilized again under the UV lamp for the next implantation.

After checking the performance of the device in acute recording, we implanted several devices to the untrained rats for the chronic recording. The goal for chronic recording without trained rats were to check overall surgical procedure we planned in Chapter 4, as well as the chronic recording performance of the device.

Several animals (n=3) were doing freely behavior while neural data was recorded without any task. During the first 10 minutes of each session, the animal was kept under anesthesia (2% isoflurane) and then woke up for the

rest of the session. The neural data was collected throughout the duration of the recording sessions, therefore it contained corresponding activities from anesthetized and awake states. The animals active behaviors during awake state consisted of walking, grooming, foraging pellets and exploration.

As an example Figure 6.2 shows recordings obtained during one of the sessions (6th day after surgery). The implanted device had spiking activity in 9 out of 16 channels on that day. Figure 6.2.(b) shows multichannel spike recordings obtained under Isoflurane anesthesia, at three selected electrode locations indicated by blue squares in Figure 6.2(a). For each electrode, most of the spikes originated from a single unit as shown by overlaid spikes in Figure 6.2.(c). Once the animal recovered from anesthesia and started behaving freely, recordings at the same electrodes showed obvious clear increase in spiking activity (Figure 6.2.(d), black traces). The plots of spike rasters (Figure 6.2.(d), red bars) obtained by thresholding the spiking data at 3.5 standard deviations above baseline showed that the spiking rate was continuously changing during awake state. Even though we did not aim to characterize or monitor the animals behavior in detail (beyond awake vs. anesthetized) in these device assessment recordings, visual inspection of behavior indicated that increases in spiking activity corresponded to active behavior of the animal which was not surprising for the neurons in motor cortex. This result was published in [13].

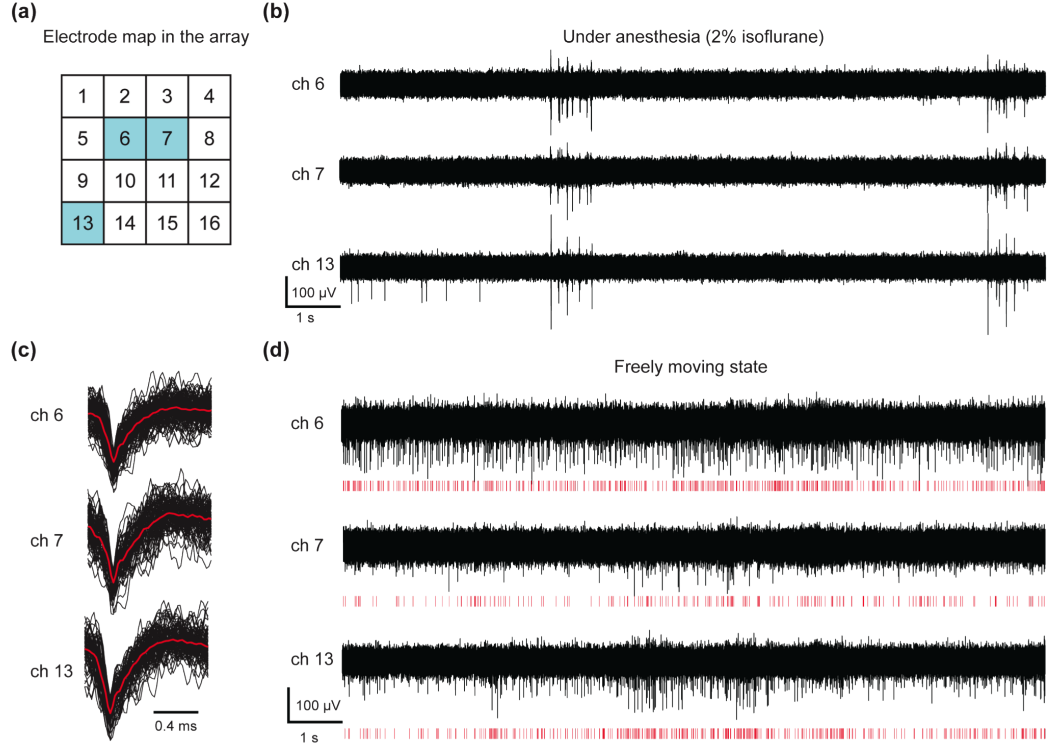


Figure 6.2: Example recordings from a chronically implanted device from 6th day after implant. Published in [13]

6.3 Chronic Recording Analysis in Trained Animal: Status Classification for Different Behaviors

6.3.1 Behavioral analysis and neural population activity

After testing implantation procedure and recording untrained rats' neural data acutely and chronically, we implanted the devices to the trained rats. With the filtered data from 300Hz to 10kHz, spike detection method was 3σ thresholding as discussed in Sec.6.1.1. Each channel went through the T-distribution E-M

(Excitation-Maximization) method that Offline Sorter provides, for multiple neuronal spike sorting in each channel. One thing to note is that even if the waveforms of some sorted neurons from the different channel might share the same features, geometrical distance of the array (which is $400\mu\text{m}$ from one channel to another) excludes the possibility that those signals were from the same neuron. The timestamps of sorted spikes were exported to the neural signal analysis program called NeuroExplorer4 (Nex Technologies, AL) and several features were analyzed in conjunction with the behavioral data.

The first feature we wanted to know was if there's any changes in neuronal population dynamics near the time around the event onset (Peri-event firing rate/ peri-event histogram). We checked the cross correlation between each event (left/right lever pressing, food collection) and extracted only highly correlated channels in ± 5 seconds near the event onset. This is based on the assumption that if a neuron didn't show any change in cross correlation at a given peri-event time range, it did not contribute to the event. Figure 6.3 and Figure 6.4 show peri-event histograms and rasters of extracted neurons that are highly correlated to the events. Red lines in the figures indicate the event onset time. For spatial analysis, the MEA map is shown in Figure 6.3. Since the bonding pads of the address line of a preamplifier chip had changed from the old M4B and the new l-Pearl, some of the channel numbers were flipped. (More information on the preamplifiers is described in Chapter 3.)

From these figures, we could confirm that there were neural population activities related to the behaviors. However, since the animal was not restrained its head and the events of movement were not explicitly defined, we extracted dynamic neurons corresponding to the behavior and analyzed them further in

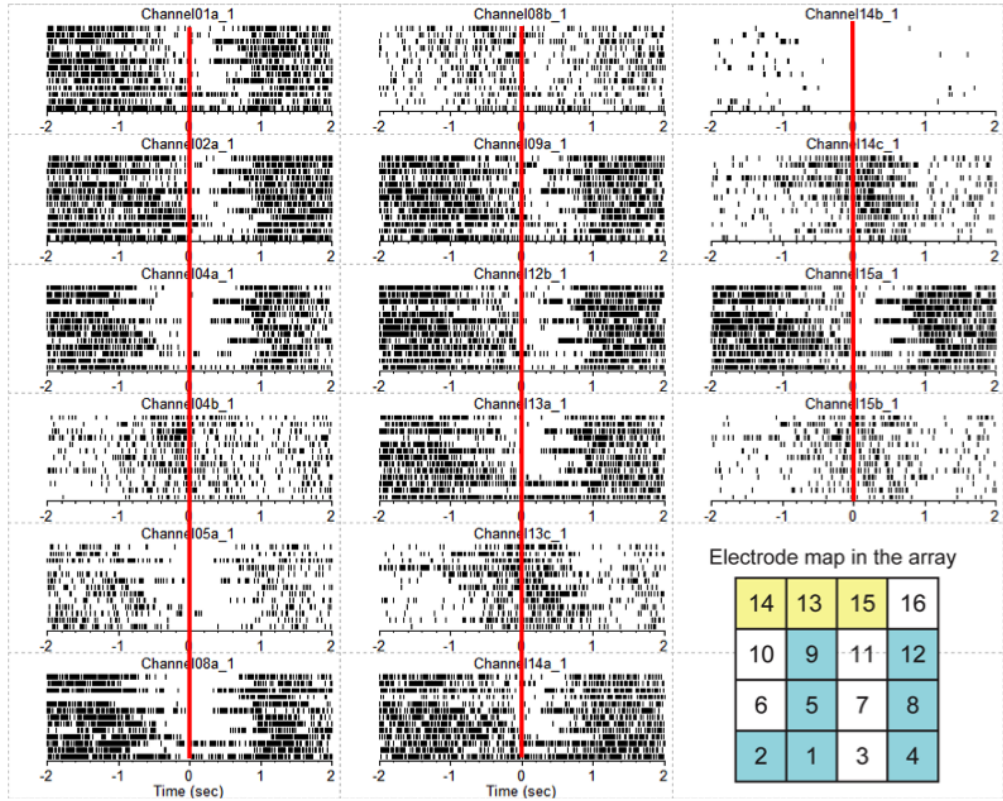


Figure 6.3: An example of Peri-event rasters of lever pressing and food collection on a specific day with a channel map of an array

the following section.

6.3.2 Principle component analysis in freely moving animal

The purpose of BCI devices is to decode neural signals recorded from motor cortical region of paralyzed patients and directly control their muscles, or artificial devices like computer interface or robotic arms [110]. Neural data analysis of the small animal model is yet far from achieving the goal, but it is still worthwhile to reconstruct the neural activities in phase space of freely behaving animal to study the population dynamics of motor cortex. Although

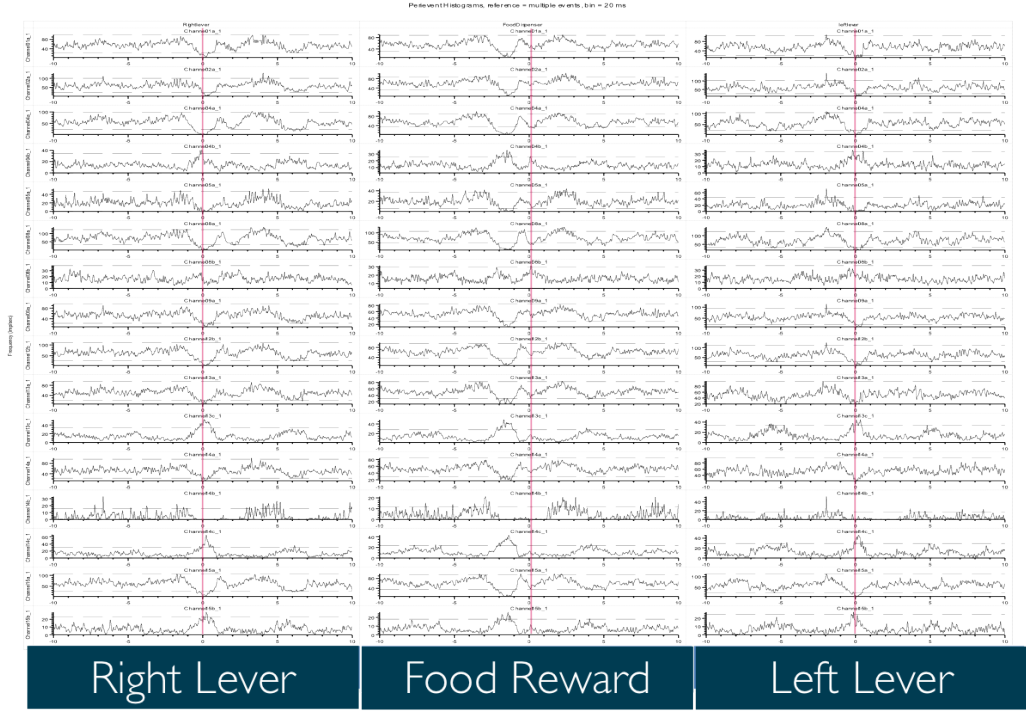


Figure 6.4: An example of Peri-event histograms of lever pressing and food collection on a specific day

a certain movement may not be perfectly repeated across trials, [111, 112, 113] it is a great interest for neuroscientific researchers that if a trained movement can convey any common spatiotemporal information of motor control process (in here "a sequence of lever pressing task"), which includes unexpected variations from each trial. In other words, does the neural trajectory evolve from any arbitrary to a stable neural state over the trials?

In Churchland's and Yu's papers [114, 115, 116], it was noted that neural responses might be the result from "internal processing" rather than external stimuli driven, as it was described earlier from Horwitz and Newsome's study on perceptual decision-making study [117]. The activity of each neuron tends to vary even though the external experimental setup kept constant [116].

To analyze recorded data from a MEA, it is desirable to reduce the dimensionality to analyze “neural trajectories” of the recording. The original dimensionality means one neuron per one dimension, and for multi-channel recording (number of neurons can easily go up to 100 or more) this high dimensionality makes it challenging problem to access the information directly from the data. Therefore, the high-dimensional neural data needs to be collapsed to a low-dimensional data, and the ‘neural trajectory’ from this data can be a summary of the data [114]. It represents high dimensional neural activity in a compact way along the time, and visualizes neural dynamics under different external conditions [116]. It is especially successful way to decode the time-evolving neural dynamics of multi-unit activities (MUAs).

We used our data to build the neural trajectory of the whole recording session, different from Yu et al.’s method [116]. Because rat behaviors were not strictly restrained during the task, and each single trial varies a lot in detail.

We first reduced the dimensionality of the neural data by smoothing the firing rates of 10msec bin width with a Gaussian kernel as shown in Figure 6.5 then we applied principle component analysis (PCA) to the smoothed data.

From the PC1 and PC2, we could reconstruct the neural trajectories on each day’s trial. We could observe that between the defined events (either “food collection” or “lever pressing”), the trajectory converges into two different regions. Figure 6.6 and 6.7 show the neural trajectories on a specific day (day26) of a rat (Spio4) at the moment of lever pressing and food collecting, respectively.

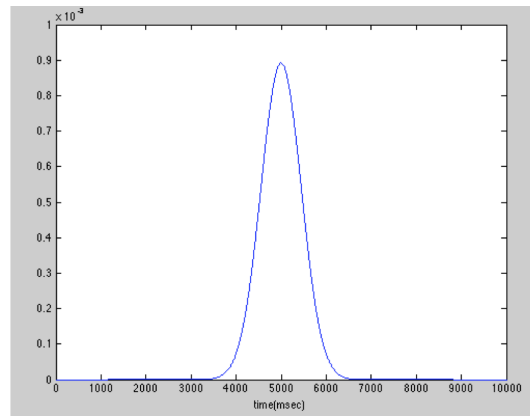


Figure 6.5: A Gaussian kernel used for smoothing, with full-width half maximum (FWHM) is 10msec

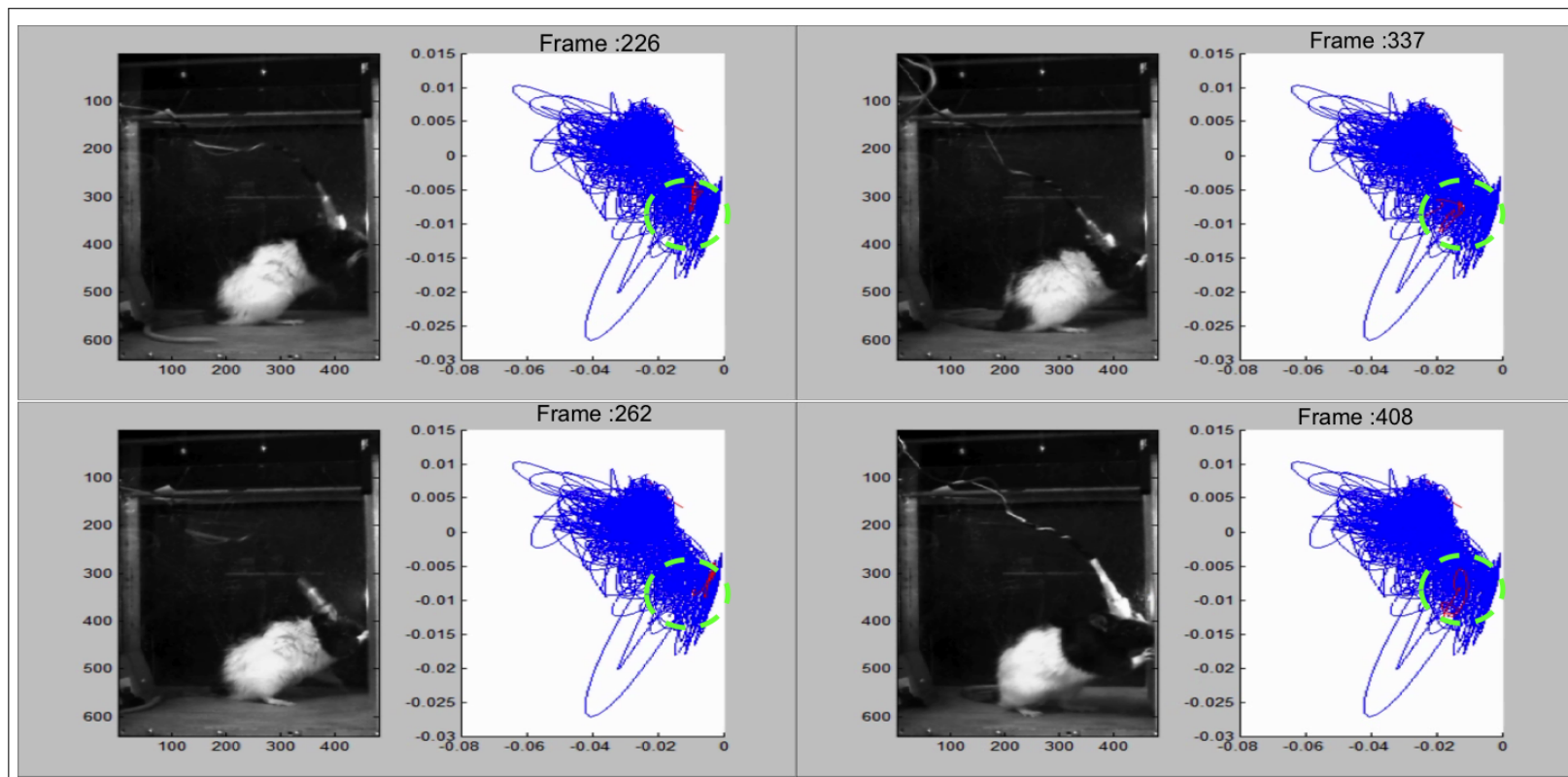


Figure 6.6: Neural trajectories during the lever pressing behavior: red trace denotes the current temporal state on each trajectory

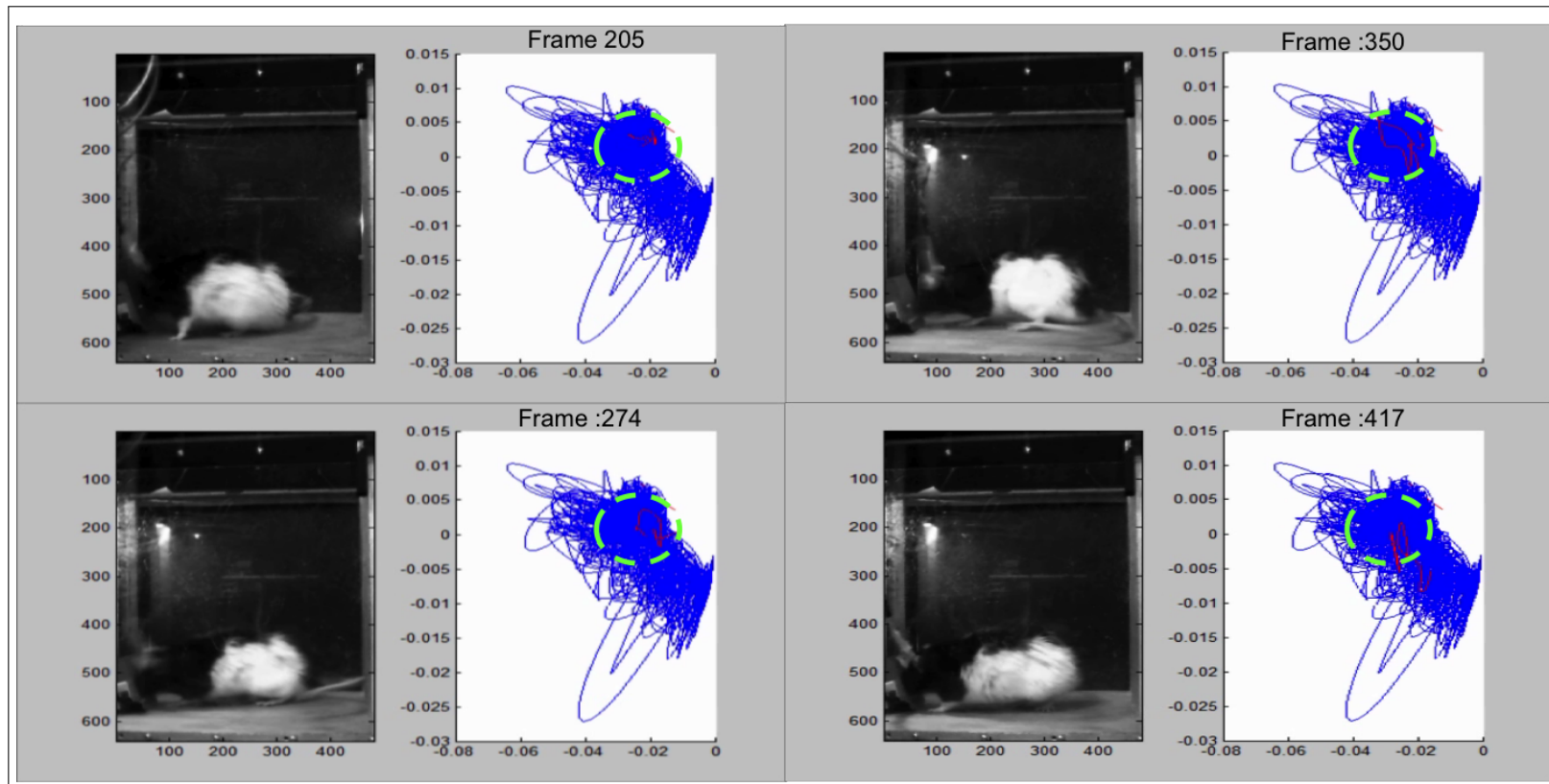
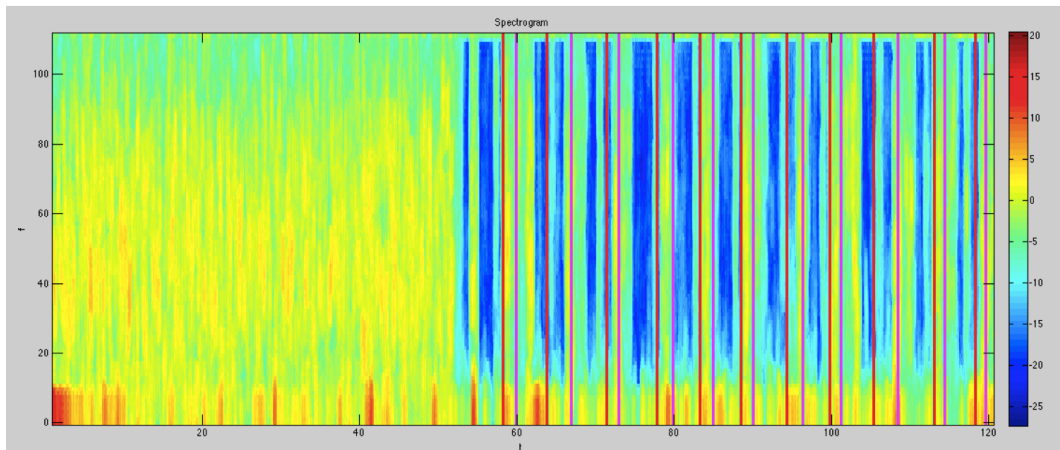


Figure 6.7: Neural trajectories during the food collection behavior: red trace denotes the current temporal state on each trajectory

6.3.3 LFP analysis in freely moving animal

As described in the previous section, LFP contains information that neural spikes might not have. Especially the Beta oscillations are of great concern in motor cortex during motor preparation. Since beta oscillations are believed to be the activity of multiple synchronous postsynaptic potentials around the electrodes [118], the temporal and spatiotemporal activities in LFPs might reveal some information in neural coding. Temporal dynamics of the LFP can be visualized by the spectrogram. The LFP spectrogram is shown in Figure 6.8, which contains several trials of rat's task. In this figure, we can observe there were more synchronous activities in beta oscillation prior to every single trial of lever pressing. Figure 6.9 shows each trial's LFPs from another channel more specifically. The data was filtered with 10Hz to 45Hz (Beta band), where the synchrony of neural activities could be observed prior to lever pressing (white line) and food collection (blue line), and suppressed during the event onset.



Red : Pressing the lever(right/left)
Magenta: Food collection

Figure 6.8: Chronological spectrogram of a rat, channel no.2, at day26

However, what causes the difference of the latency as well as the magnitude of this synchrony for each lever pressing is not clear. This may suggest that the synchrony in beta oscillation vary even though the external experimental setup kept constant as Yu et al. pointed out for single neural activities [116], or the external stimuli themselves vary. Thus it requires a better controlled behavioral setup to analyze temporal aspects of LFPs through the whole recording session. Another thing to be noted is that the power increase in the beta band prior to the rat's food collection was not as strong as that of lever pressing. This might indicate that the planned activity (lever pressing) causes stronger neuronal synchrony than a spontaneous reaction to the reward (food collection). These observations are worth to be followed by more carefully designed recording setup. For example, it will be clearer when the recording can be performed in head-restrained rats.

For the spatiotemporal beta band information how it propagates over the whole array during each event of either lever pressing or food collection, Figure 6.10 and Figure 6.11 show it for each event respectively. Each 4×4 array map was containing frequency and temporal information relative to other array. However, we couldn't find any notable common pattern between the different trials.

Another interesting region in LFPs is gamma band. The spectrogram of Figure 6.8 also shows the strong suppression in gamma band (higher frequency, 30-90Hz), but not consistent with the event onset. While gamma oscillation can give additional information to the local neural activities, gamma band suppression shown in our recording does not indicate that this is related to the gamma oscillations. In our case, it may need to be seen as the results in change

in gamma band in relation to the increase/ decrease of spiking activities, which can be phase locked to the gamma band [119].

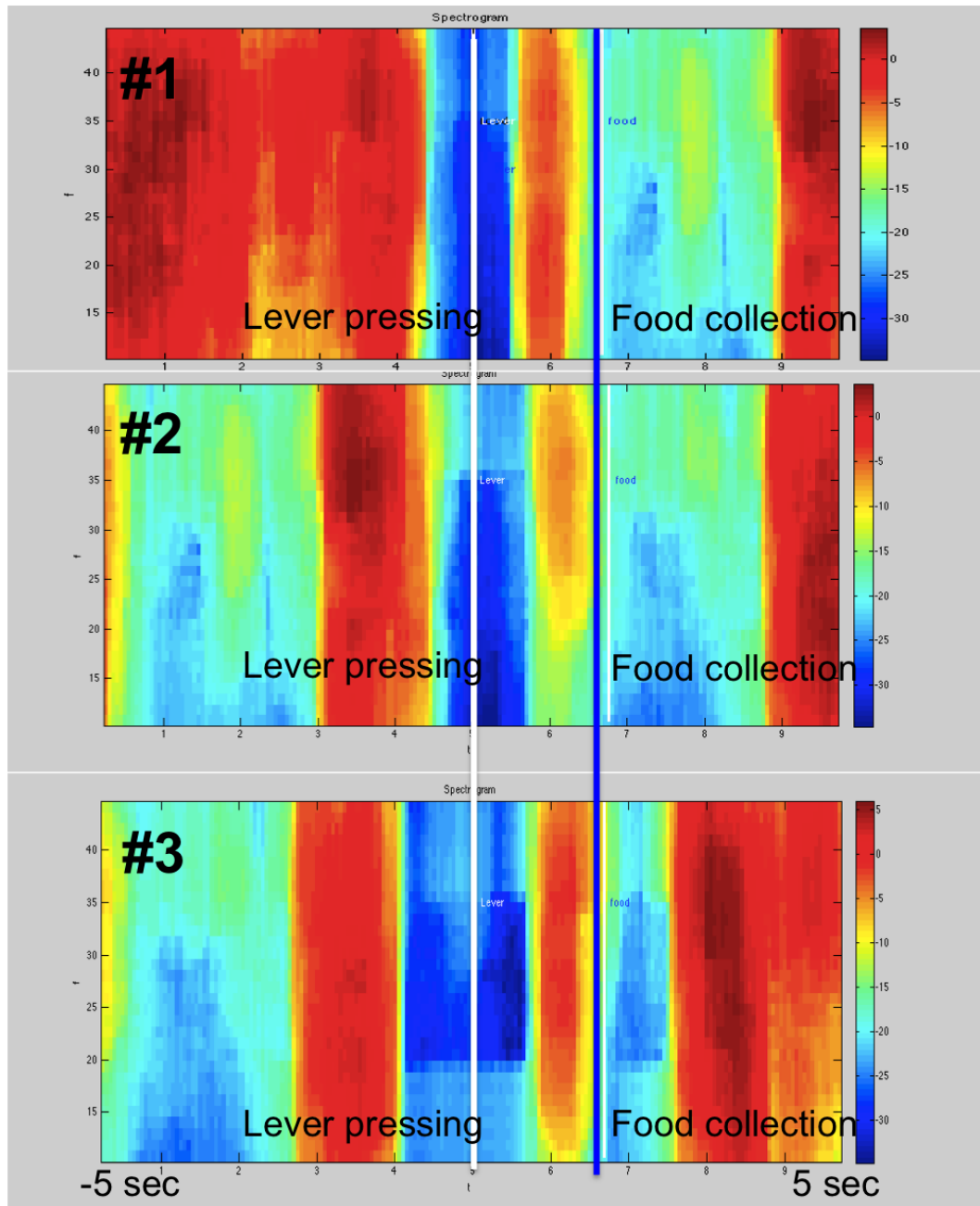


Figure 6.9: An example of beta band spectrograms of independent trials consist of lever pressing and food collection: time duration of ± 5 seconds before and after the lever pressing was plotted

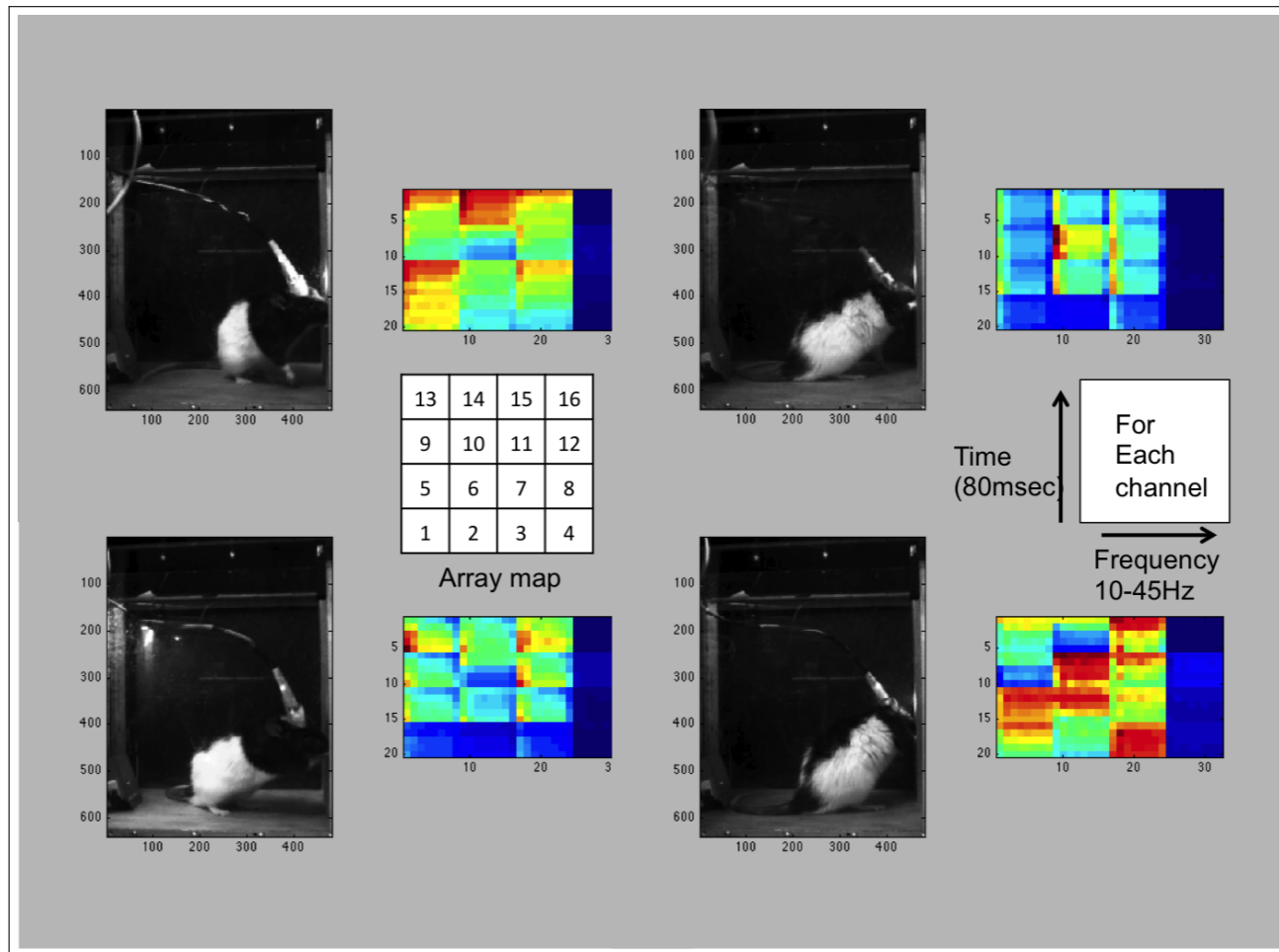


Figure 6.10: Spatiotemporal array map of LFP power spectrum analysis during lever pressing

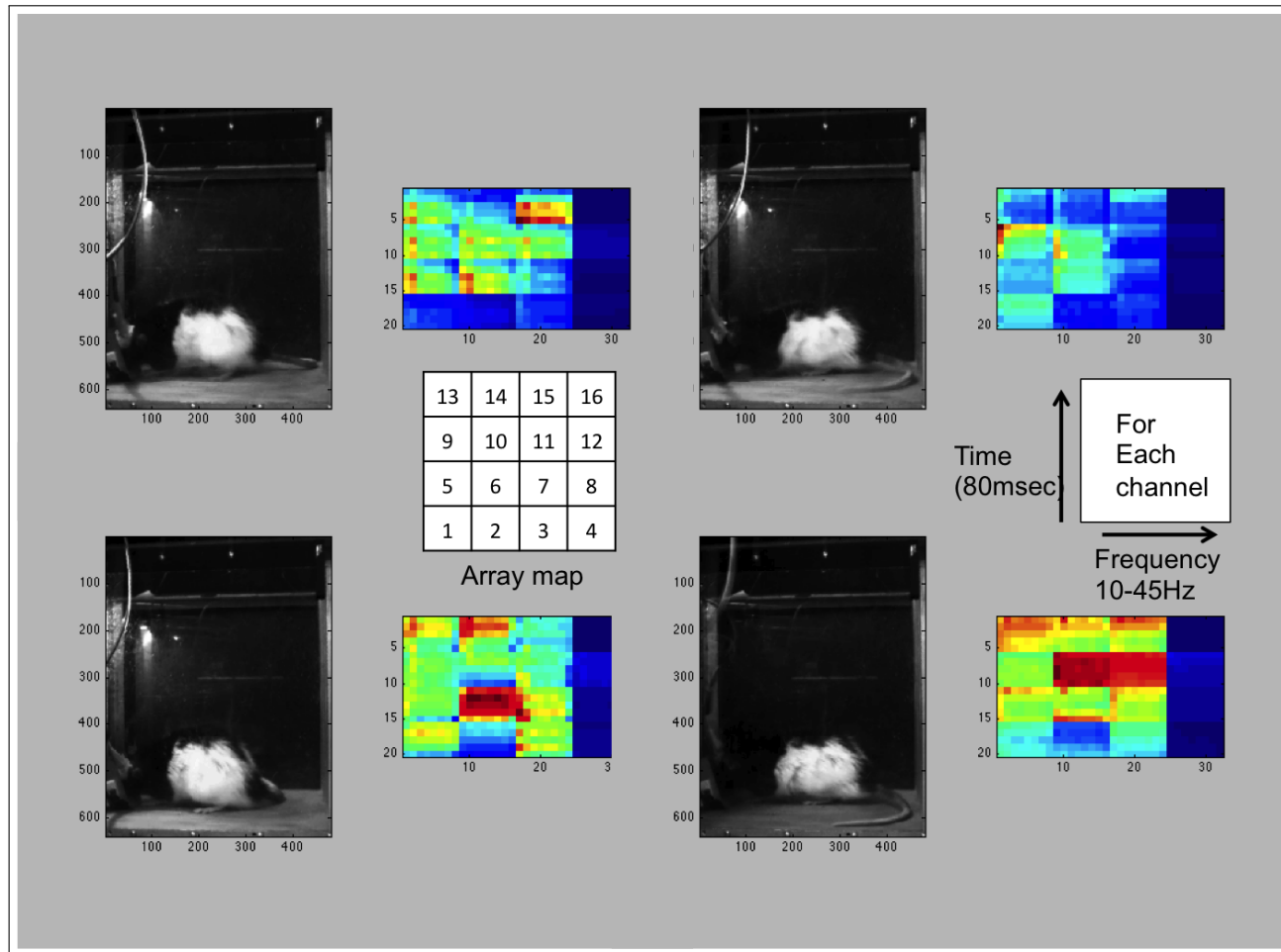


Figure 6.11: Spatiotemporal array map of LFP power spectrum analysis during food collection

6.4 Discussions and Conclusion

Through this chapter, we showed the data recorded with our fiber optic recording system in rat chronically. The device was first tested acutely, showing the functionality of the system. After acute recording, we implanted the system in untrained rats chronically. There were not many behavioral aspects we could get from the data, but it clearly demonstrated that the device was also capable in chronic recording, by showing the differences in sleep and awake state in rats. The next step was implanting the device in freely moving trained rats. On device wise, it was robust enough to use fiber optic system to record the neural data of freely moving animals for two 10 minute sessions everyday for a month for each animal.

The neural data we could obtained from the trained rats showed the neural population dynamics in several defined movements (“food collection” or “lever pressing”) while freely moving. It seemed the food collection and lever pressing had different population dynamics, but not noticeable difference between the left lever pressing and the right lever pressing. However, the data was not quantifiable since the rat was freely moving, and even though the behaviors were manually categorized with the same criteria (as described in Chapter 5), it was impossible to extract obvious changes of neural activities correlated to the behaviors, from pressing the lever to collecting the food. Thus we built the neural trajectory out of the neuronal firing rates to summarize higher neural activities in the phase plane. As can be seen in Figure 6.6 and 6.7, we could categorize two different behavior states.

This left us, however, necessity of designing more well defined task for

training, possibly in the head fixed setup; because the rats were not restrained in their movements, the trajectory was observed to be noisy and contained many other movements in it. It also might have affected temporal information in LFPs. We could observe the relative increase of the power in beta band prior to the movements, but the change was not precisely phase locked with the events.

With complementing the behavior set up in various animal models, the neural data collected with our system in conjunction with LFPs will indicate that decoded information can be applied to a simple form of neural prosthetics. For example, the behavioral tasks in rats can be combined with a possible closed loop system; We can study the neural trajectory if it converges into a more confined region in phase space, by feeding the neural population inputs back into the training system in real time. We can also think of controlling the rat to get more rewards whenever the firing rates hit a certain threshold, or build a minimized FES with our PPS and fiber optics such as demonstrated in [8] for a simple neuroprosthetics. While many open questions remain in neuroscientific research, with optical means, our device presented here will enable us to explore potential research area in a simpler way.

CHAPTER 7.

Conclusions of This Work and Envisioning Broader Application

In this thesis, we have suggested a novel concept of fiber optic neural prostheses, and presented the development and use of such system. To implement the feasible fiber optic neural recording system for *in vivo* use, first, we discussed the basic optical components adopted to this system. Adopting optical components was the main idea of our neural recording device, by which we can transmit power and data to/from the system. To develop this idea, the design and fabrication of the optical components for power and data delivery were discussed in Chapter 2. These optical components include a photovoltaic power supply (PPS of >60% efficiency with 2.8~3.0V supply voltage, dimension of $800\mu\text{m}\times 800\mu\text{m}$) fabricated in our lab, and a low power VCSEL (852nm, of 1.2mW output) with plastic optical fibers ($250\mu\text{m}$ or $490\mu\text{m}$ / $500\mu\text{m}$ inner/outer diameter respectively). Adopted optical components were compatible enough to power the neural recording system which consumed about 15mW, and deliver the data to the external device with high conversion and coupling efficiency. We also discussed about the considerations on other factors when integrating these components onto a small size neural recording system.

We then presented the design of a whole neural recording system with the optical components. The first suggested system aimed at fully implantable application with minimal percutaneous connection. This includes some of the application-specific integrated circuit (ASIC) chips we have designed and used in our lab, flexible Polyimide substrate, and polymeric packaging for optimal implantation. Our system has 16 channel multi-electrode array (MEA), bonded onto a custom low-power preamplifier chip ($7.3 \mu V_{rms}$, with $51 \mu W$ per channel), and a custom digital controller chip with other microelectronics to transmit the digitized data stream in an optical form. With the system, neural signals from 0.1Hz to 7.8kHz can be detected and recorded. We discussed how to optimize the fabrication process to reduce the noise level by changing the process at every step of fabrication. The packaging and the design of the substrate were also considered to be optimized so that the system can be used *in vivo* chronically.

After building the fully implantable recording system, we tested system on bench top, then by acute recording and finally by chronic recording. Device wise, the packaging and other issues related to the chronic implantation were taken care of. However, since we used the rat animal model and the dimension of the device was too big for the small animal model, the device should be implanted under the back when implanted in a rat. This caused the system failure due to the mechanical damage that the rat has made by reaching its back and scratching it with its hind limbs. Thus the small animal model was not good enough to validate the device in terms of the dimension, different from pig or monkey model where the whole system can stay on the skull.

Nevertheless, the use of rat was necessary in our system so that we could

train the rats and record freely moving behaviors in a relatively short term. The selection of small animal model could also expedite the process for device verification and validation. Thus a miniaturized, two-component neural recording system was presented for small animal model. The basic structure remained the same, but the separable front-end and the back-end made it much easier to be implanted in rats. We tested the two-component system in 1 untrained rat for acute recording, 3 untrained rats and 7 trained rats for chronic recording for 2 weeks to 4 weeks.

Along with the two-component neural recording system, we presented other behavioral setup , rat training, and surgical plans to collect long term behavioral neural data from rats. Plans and designs for device application to a real animal model required many unexpected modifications. In Chapter 4 and 5, trials and errors during the implantation and recording were discussed. We also described the design consideration of other external devices and software for recording rat's freely moving behavior in synchrony.

In the final chapter, we discussed how to analyze the neural data. We have tested our device in a chronic environment and could get neural data from the trained rats. But in regards to the contents of the data, it was extremely concerning what information we could extract out of collected data. One way was to observe neuronal population dynamics in relation to the categorized behaviors. However, this was not able to show the multifaceted behavior characteristics in freely moving behaviors. Thus we applied the principle component analysis (PCA) based neural trajectory which highlighted the different states for different behaviors. Along with the local field potential (LFP) analysis, this could provide useful information about the motor cortical activities of the

freely moving behaviors, and opened the possibility on the movement based application.

Leaving open possibilities on neuroscientific interpretation on the neural data, we could successfully deliver a new type of neural prosthesis. I believe the work presented in this thesis will become a stepping stone of building a high bandwidth, less susceptible to electro-magnetic noise and power-efficient neural prosthesis. The development of fiber-optic based neural recording system itself opens a possibility of a new area in neuroengineering: the powerful scalability. With optical means, the neural recording system can be extended up to several hundreds of channels for other larger animal models and possibly further application in clinical research. Furthermore, Combining to an optical fiber based functional electrical stimulation(FES), part of which was described in [8], the recording system will become an attractive option of an in vivo closed-loop system and shed light on clinical BCI application as well as basic neuroscience research.

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