Interconnects and Packaging to Enable Autonomous Movable MEMS Microelectrodes to Record and Stimulate Neurons in Deep Brain Structures

by

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ABSTRACT

Long-term monitoring of deep brain structures using microelectrode implants is critical for the success of emerging clinical applications including cortical neural prostheses, deep brain stimulation and other neurobiology studies such as progression of disease states, learning and memory, brain mapping etc. However, current microelectrode technologies are not capable enough of reaching those clinical milestones given their inconsistency in performance and reliability in long-term studies. In all the aforementioned applications, it is important to understand the limitations & demands posed by technology as well as biological processes. Recent advances in implantable Micro Electro Mechanical Systems (MEMS) technology have tremendous potential and opens a plethora of opportunities for long term studies which were not possible before. The overall goal of the project is to develop large scale autonomous, movable, micro-scale interfaces which can seek and monitor/stimulate large ensembles of precisely targeted neurons and neuronal networks that can be applied for brain mapping in behaving animals. However, there are serious technical (fabrication) challenges related to packaging and interconnects, examples of which include: lack of current industry standards in chip-scale packaging techniques for silicon chips with movable microstructures, incompatible micro-bonding techniques to elongate current micro-electrode length to reach deep brain structures, inability to achieve hermetic isolation of implantable devices from biological tissue and fluids (i.e. cerebrospinal fluid (CSF), blood, etc.). The specific aims are to: 1) optimize & automate chip scale packaging of MEMS devices with unique requirements not amenable to conventional industry standards with respect to bonding, process temperature and pressure in order to achieve scalability 2) develop a novel micro-bonding technique to extend the length of current polysilicon micro-electrodes to reach and monitor deep brain structures 3) design & develop high throughput packaging mechanism for constructing a dense array of movable microelectrodes. Using a combination of unique micro-bonding technique which involves conductive thermosetting epoxy's with hermetically sealed support structures and a highly optimized, semi-automated, 90-minute flip-chip packaging process, I have now extended the repertoire of previously reported movable microelectrode arrays to bond conventional stainless steel and Pt/Ir microelectrode arrays of desired lengths to steerable polysilicon shafts. I tested

scalable prototypes in rigorous bench top tests including Impedance measurements, accelerated aging and non-destructive testing to assess electrical and mechanical stability of micro-bonds under long-term implantation. I propose a 3D printed packaging method allows a wide variety of electrode configurations to be realized such as a rectangular or circular array configuration or other arbitrary geometries optimal for specific regions of the brain with inter-electrode distance as low as 25 um with an unprecedented capability of seeking and recording/stimulating targeted single neurons in deep brain structures up to 10 mm deep (with 6 μm displacement resolution). The advantage of this computer controlled moveable deep brain electrodes facilitates potential capabilities of moving past glial sheath surrounding microelectrodes to restore neural connection, counter the variabilities in signal amplitudes, and enable simultaneous recording/stimulation at precisely targeted layers of brain.

I chose this project not because it was meaningful to me but shall be to people suffering from deadly neural disorders. I was a designer of blind aid device called Smart Cane which aids physically impaired users to navigate independently. Seeing them happy with my device and knowing more about brain disorder conditions while in the same field interested me to pursue Masters in Biomedical engineering focused towards neural & rehabilitation engineering. The work I did shall get this technology a step closer to diagnosing and treating people suffering from brain related disorders.

I also dedicate this work to my respectable mentor Dr. Jit Muthuswamy, my family and my friends who supported all the way through this process

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CHAPTER 1

INTRODUCTION

Long-term monitoring of deep brain structures using microelectrode implants is critical for the success of emerging clinical applications including cortical neural prostheses, deep brain stimulation and other neurobiology studies such as progression of disease states, learning and memory, brain mapping etc. [16] The implantable electrodes promise to restore lost brain controls and play a vital role in shaping the future of biomedical prosthetic devices such as Brain-Computer Interface (BCI) [18] [19], implants to restore visual and auditory functions, deep brain stimulation such as Parkinson's disease etc. In the aforementioned applications, implantable microelectrode technology is key to gain access to single neurons or a group of neurons in a given region of interest. Perhaps the single biggest factor that remains unsolved for decades is the unreliable brain tissue-microelectrode interface which hinders the progress of cortical and deep brain prosthetic implants.

I proposed a MEMS moveable polysilicon interface electrodes that can be extended with traditional stainless steel, platinum iridium electrodes, tungsten etcetera., using novel micro bonds to reach deep brain structures. The device will improve the reliability, fidelity and lifetime of neural interfaces with respect to recording, blocking and stimulation of neural signals. The thermo-electric actuators in the MEMS device [25] [27] designed to facilitate bidirectional movement of microelectrodes deep in the brain which enables long term monitoring of cortical and deep brain structures while maintaining the signal to noise ratio (SNR).

Lack of current industry capabilities in chip-scale packaging techniques for silicon chips with movable structures makes non-hermetic packaging of MEMS devices even cumbersome for reliable large scale packaging. To resolve the problem, indigenously developed novel chip scale packaging station was optimized and semi-automated to ease customizable packaging of MEMS devices. A new methodology of bonding was designed to reduce packaging times significantly and achieve scalability by controlling bonding, process temperature and pressure.

Another significant challenge is increasing the density of array of electrodes in a smaller region of interest with protective packaging and mounting techniques that can accommodate animal skull/skin growth, protective packaging [7] to prevent of inflow of brain fluids and prevent damage from mechanical impacts [30]. With the newly proposed packaging technique, a dense array of electrodes of desirable pattern which physically isolates the device from brain fluids and provide customizable mounting structures using advancements in 3D printing technology [6].

The goal is to make a reliable, high dense, high-throughput interface between deep brain structures and implantable electrodes can be realized by using MEMS movable microelectrode system with extended micro bonded conventional electrodes via a guided 3D printed package. At the system level, reliability studies on micro bonds, recommendations for packaging and assembly procedure are also incorporated in a top-down approach to achieve a reliable interface.

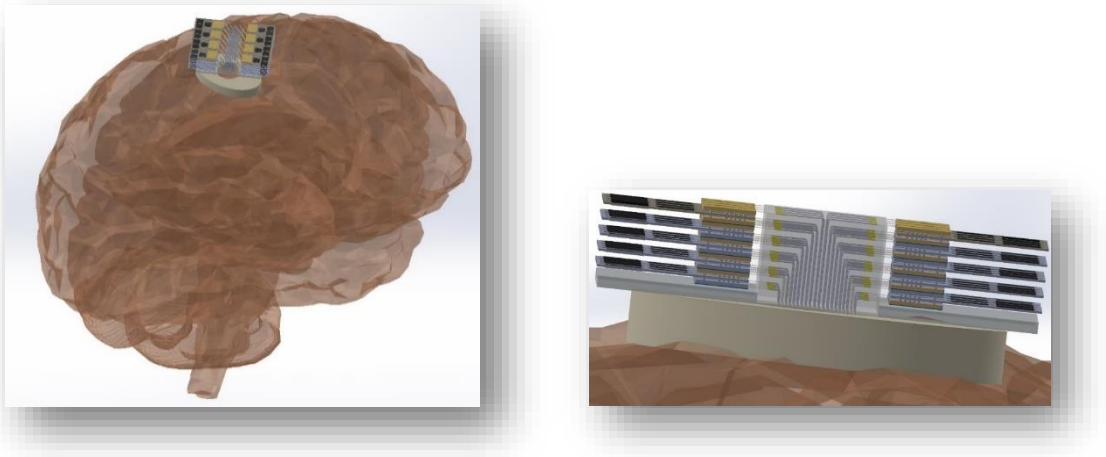


Fig 1. Array of Electrodes on Brain – Ultimate Goal of This Project

To evaluate the stated hypothesis, and address specific challenges described, the following aims are proposed.

Specific Aim 1:

Optimize and automate chip scale packaging of MEMS devices with unique requirements not amenable to conventional industry standards: a) determine optimum epoxy dispensing conditions to increase bond height ratio b) determine optimum bonding, process temperature and pressure to achieve scalability c) semi-automate the bonding process to avoid errors and quicken the process

Specific Aim 2:

Extend the length of MEMS moveable polysilicon electrodes using micro bonding technique to reach deep brain structures a) determine suitable bonding procedure b) determine assembly procedure to enable high scalable bonding c) analyze accelerated aging study

Specific Aim 3:

Design & develop high throughput packaging mechanism for constructing a dense array of movable microelectrodes a) design a physical model to isolate brain fluids from contacting packaged MEMS devices b) design a guided channel for electrode translation with customizable fabrication methodology to create dense array of electrodes in a given pattern c) determine assembly procedure for scalability up to 250 electrodes

Outline

The rest of the dissertation is organized as follows. Chapter 2 has the results of characterization of the improved methodology for flip chip interconnects and bonding procedure. Design of experiments were to done to find optimum flip chip parameters. Chapter 3 describes micro bonding techniques, results of accelerated aging study. Chapter 4 describes 3D printing concepts and designs, assembly procedure for high dense electrodes. Chapter 5 describes future work related activities followed by references and bio sketch and appendix.

CHAPTER 2

MODIFIED FLIPCHIP TECHNIQUE AND INTERCONNECTS FOR RELIABLE CHIP SCALE PACKAGING

Introduction

Packaging of Integrated circuits on silicon wafers are mostly done using a traditional wire bonding process. But wire bonding may not be a viable technique for MEMS packaging for the below listed reasons. a) bigger size compared to actual die b) no protection for active micro structures c) wire interconnects to die exposes MEMS active structures. Though several modalities of packaging have come up for Inertial measurement units (IMU) due to commercial applications like car, mobile phones, these encapsulation technique requires added microfabrication steps which increases the cost and complexity of fabrication process [1]

Fig 2. General Packaging Trends
http://www.memsjournal.com/2006/08/mems_packaging_.html

Emerging MEMS devices are in need of a device-specific packaging sooner than later. Injection molded process requires high capital investment and are only suited for high volume fabrication. QFN package is the widely used process in IC fabrication plants

Even though wafer level packaging is the most efficient way to move forward in the future, it still requires a lot of R&D to tune for device specific needs which requires a huge capital investment. On the other hand, flip chip packaging process [10] sounds like a high throughput, scalable, reliable process and MEMS packaging [15] becomes fairly easy and straightforward. I indigenously built flip chip packaging station which has two perpendicular arms to hold silicon

wafer and substrate using vacuum and two microscopes with prism mechanism for alignment at high accuracy and resolution. [8] [9]

Protecting the active structures in the MEMS device requires increased bond gap between silicone chip and substrates. To get the bumping bond heights to more than 1:1 ratio becomes a challenge. I propose here a modified bonding procedure over the existing DPAT. DPAT stands for **Dispense** the epoxy on to the bond pad using a needle, **Pull** the needle away from the bond pad, and let it **attach** using adhesion and surface tension characteristics. In the new methodology, **2(DP)-AT** which stands for Dispense, Pull, Dispense, Pull again and Attach. Once the epoxy is dispensed on to the pad, pull the needle away by ½ of the height of the bumps created, dispense the epoxy again at a controlled pressure for respective epoxy materials and let it attach. This technique creates on an average of 1:1.5 ratio of bond height.

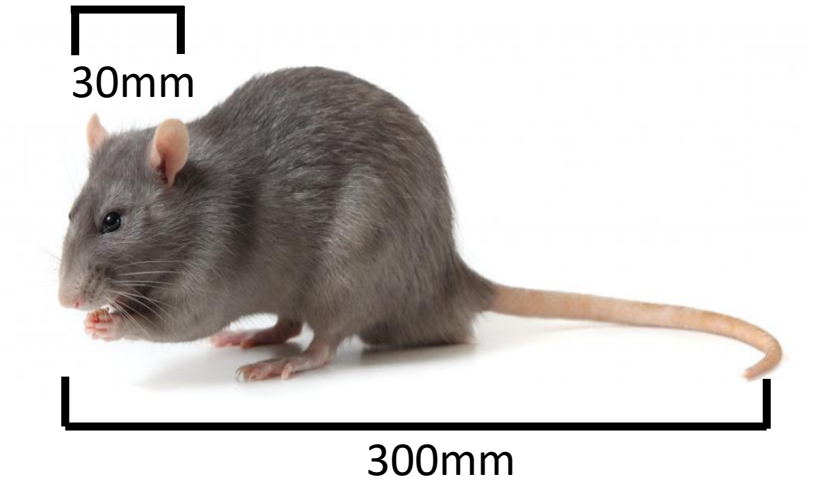


Fig 3. Rat Dimensions

The ultimate goal of this process is to fabricate a stack of devices that can be mounted on top of non-human primates. Several MEMS micro actuators have been designed and developed wide spread to suite different biological application (N. Jackson et al., 2010; Mukundan & Pruitt, 2009; Muthuswamy, Okandan, Jain, & Gilletti, 2005a, 2005b; Receveur, Lindemans, & de Rooij, 2007).

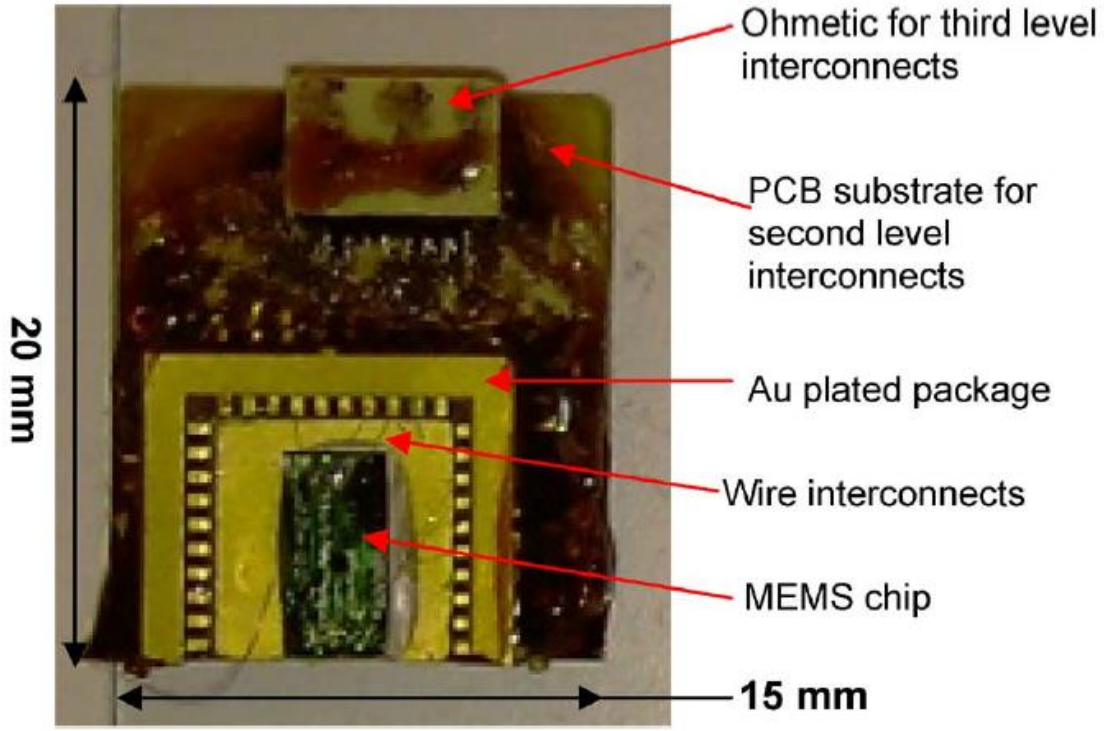


Fig 4. Wire Bonded Package

I propose here a methodology to scale the previously proposed devices (Jemmy sutanto et al 2012) in a smaller package using the optimized flip chip and bonding process. The output of the process will result in quicker fabrication times, more reliable, cost effective packaging process.

Methods

A. MEMS Testing samples

Three different types of MEMS testing samples was used in this study for optimizing the flip chip station and also for the development of interconnects. Those three include

1) Folded beam (chevron) type of actuator

2) Linear actuator

3) Linear actuator with a rotating gear

The Chevron actuator is the latest one with electrode dimensions as 50um in width and 4um in thickness. Most of these studies correlate to work done on this device by previous people [3] The die size is 2.8 mm x 6.3 mm and was fabricated using SUMMiT V process in Sandia National Laboratories, NM. This structure facilitates a moveable polysilicon electrode by means of thermal actuation with a stroke displacement of 5mm. A pulsed waveform was used to unlock and displace the electrodes in the device.

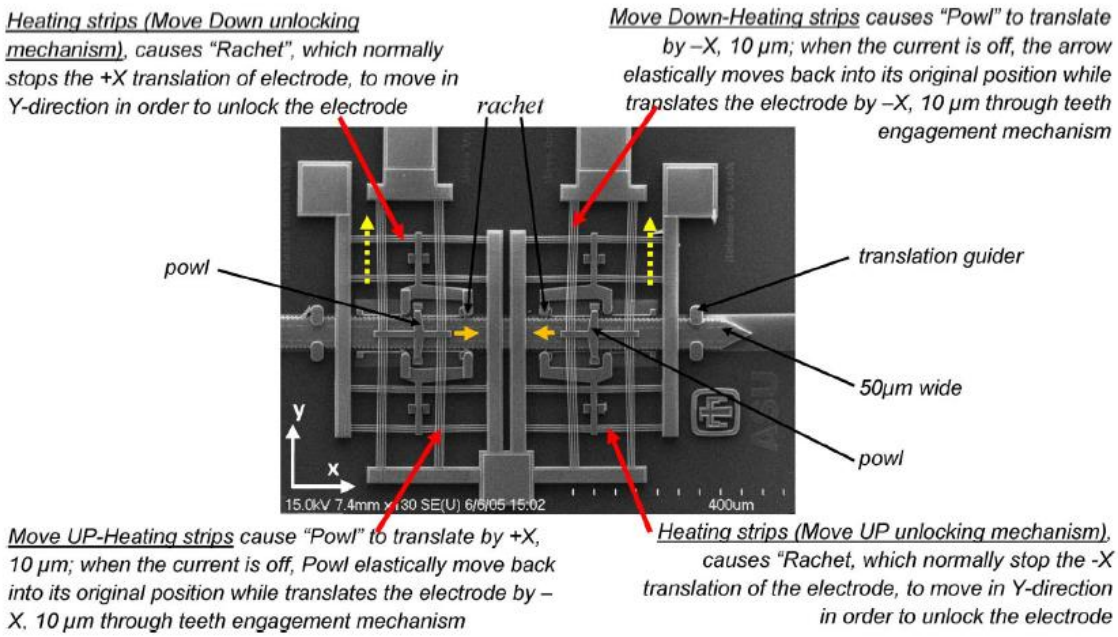


Fig 5 Electro-thermal actuators [3]

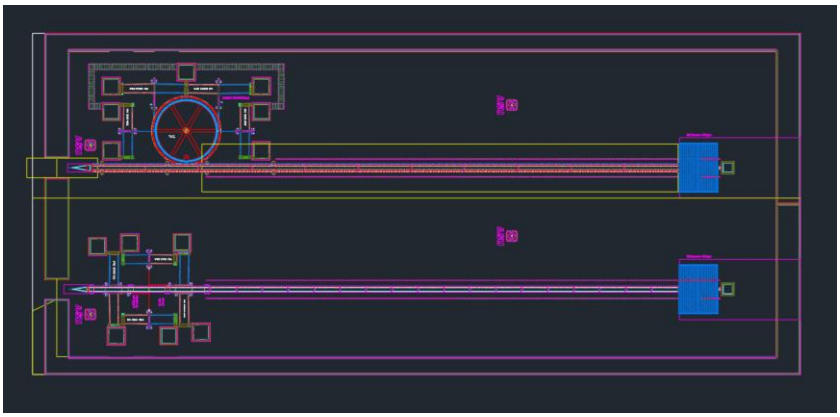


Fig 6 Layout of New Generation 2 Electrode Device (Gear + Linear)

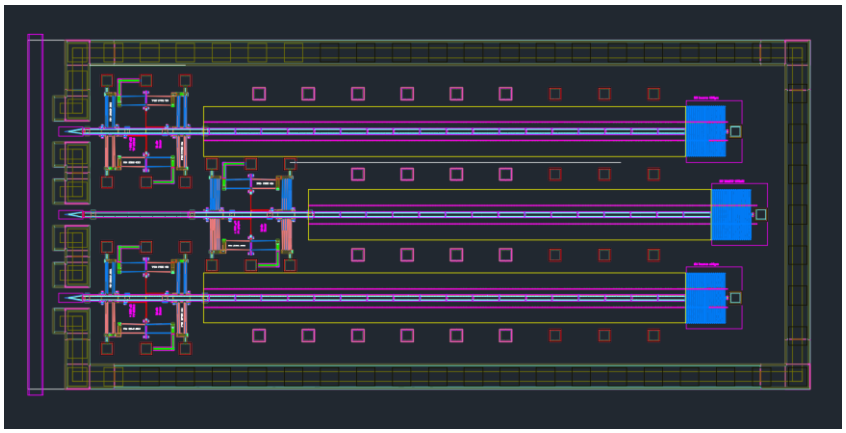
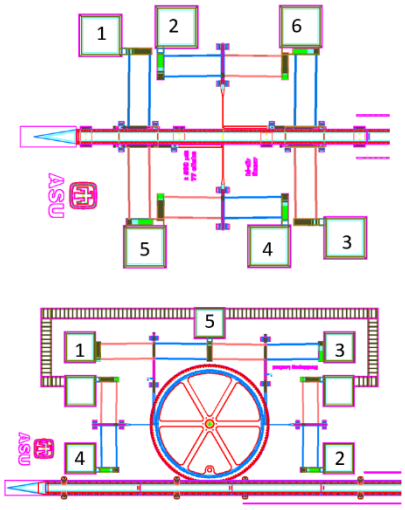


Fig 7 Layout of New Generation 3 Electrode Device (Linear)



1 – Forward drive actuator

2 – Disengage reverse drive actuator

3 – Reverse drive actuator

4 – Disengage forward drive actuator

5 and 6 – Ground

Fig 8 Detailed Pin Configurations

Recommended voltages for operation: Release-5.5 V; Forward-6.5 V; Reverse-7.5 V

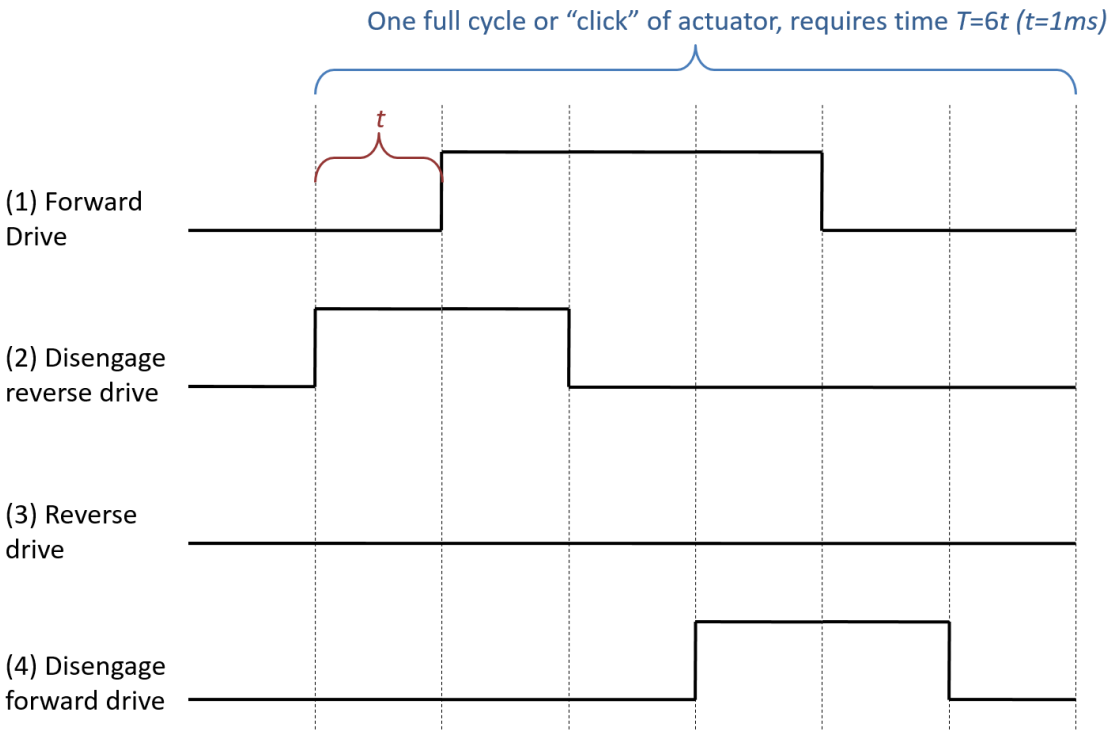


Fig 9 Recommended Forward Waveform

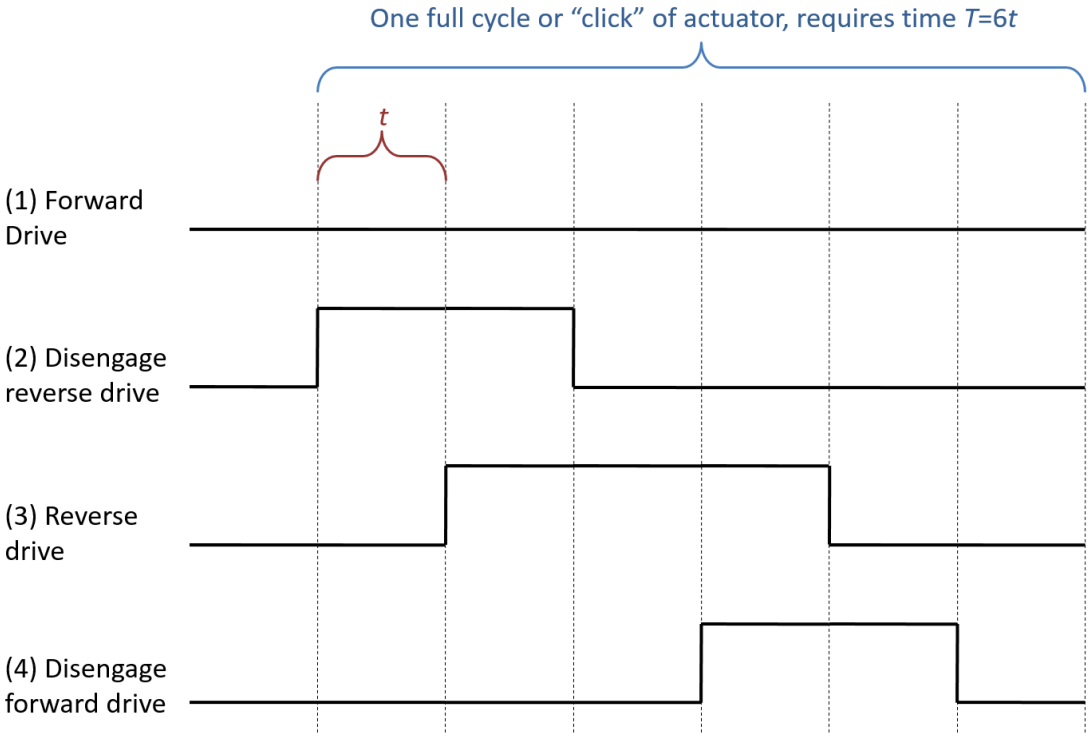


Fig 10 Recommended Reverse Waveform

B. Existing methodologies for interconnects

Several methodologies exist, among which the popular ones include (a) Thermo-sonic bonding which may interfere with highly sensitive MEMS micro sensors (b) Anisotropic conductive film (ACF) which particulates may contaminate the MEMS active area when it is applied to the die (c) Wire bonding which makes final product much bigger than the actual die (d) Through Silicon Via (TSV) which has lot of large scale fabrication problems. Most reported MEMS packaging steps via flip chip also require additional microfabrication steps (such as lithography) to develop its First level interconnects (FLIs), which electrically connects the die to the substrate. [3][1] Previous work in the lab had already demonstrated novel Ag micro bumps for FLI structures. It doesn't show any visible contamination of MEMS structures and functional impediment of MEMS operation, which did not require any extra microfabrication process. My work will involve using the aforementioned technique as the building platform for developing a unique, optimized and automated flip-chip-based approach for MEMS packaging which overcomes aforementioned problems.

C. Proposed bumping

Three techniques were proposed in the previous studies which includes

(1) Dip and attach technique (DAT)

(2) Dispense technique (DT)

(3) Dispense, pull and attach technique (DPAT)

All of the above techniques require three to several iterations for creating an aspect ratio of 1:0.8. The newly proposed technique will quicken the process by two steps to achieve more than 1:1 aspect ratio by a slight modification on DPAT called 2(DP)-AT. In the new methodology, **2(DP)-AT** which stands for Dispense, Pull, Dispense, Pull again and Attach. Once the epoxy is dispensed on to the pad, pull the needle away by ½ of the height of the bumps created, dispense the epoxy again at a controlled pressure for respective epoxy materials and let it attach. This technique creates on an average of 1:1.5 ratio of bond height.

For this process I chose a variety of needle tips, three different electrically conductive epoxy (EPO-TEK E3001, E3001-6, E3001-HV), and three different temperatures (25'C, 125'C, 150'C). These parameters were nailed down after a series of iterations and Design of experiments were performed to get the optimum conditions.

Dispensing Tips (Needle Size)	
BD PrecisionGlide Needle 25G x 7/8 in.	
BD PrecisionGlide Needle 25G x 1 in.	
BD PrecisionGlide Needle 21G x 1 in.	
BD PrecisionGlide Needle18G x 1/2 in.	
Nordson Precision Tips 30G x 1/2 in.	
Nordson Precision Tips 30G x 1/2 in. (45°)	
Nordson Precision Tips 30G x 1/2 in. (90°)	
Nordson Precision Tips 32G x 1/4 in.	

Tab 1. Needle Tips

The technique was automated to create bumps to avoid manual error. LabVIEW was used to control ThorLabs X-Y-Z and rotational motor settings based on the feed data from AUTOCAD for pin location values.

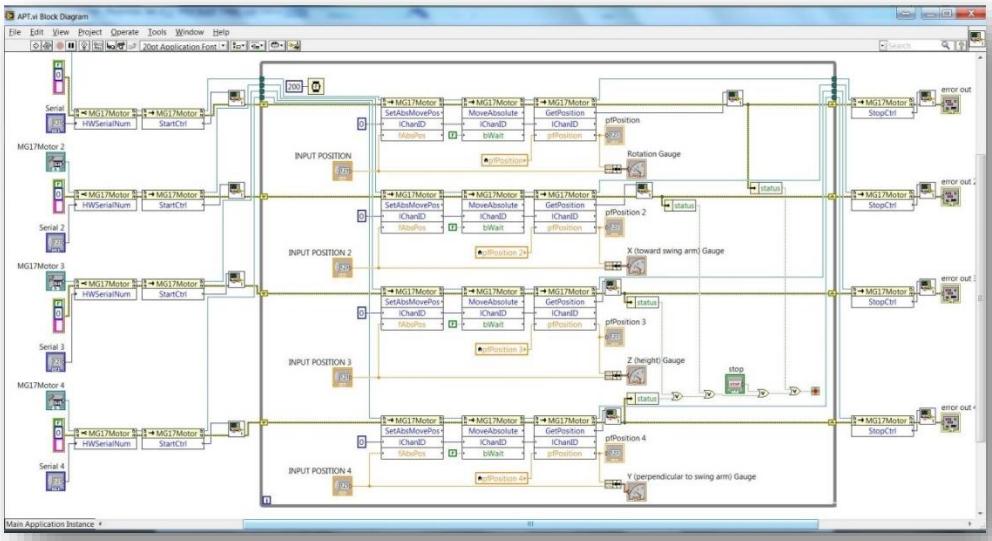


Fig 11. Back-End of LabVIEW Semi-Automation to Control ThorLabs Motor

Fig 12. Front-End of LabVIEW Semi-Automation to Control ThorLabs Motor

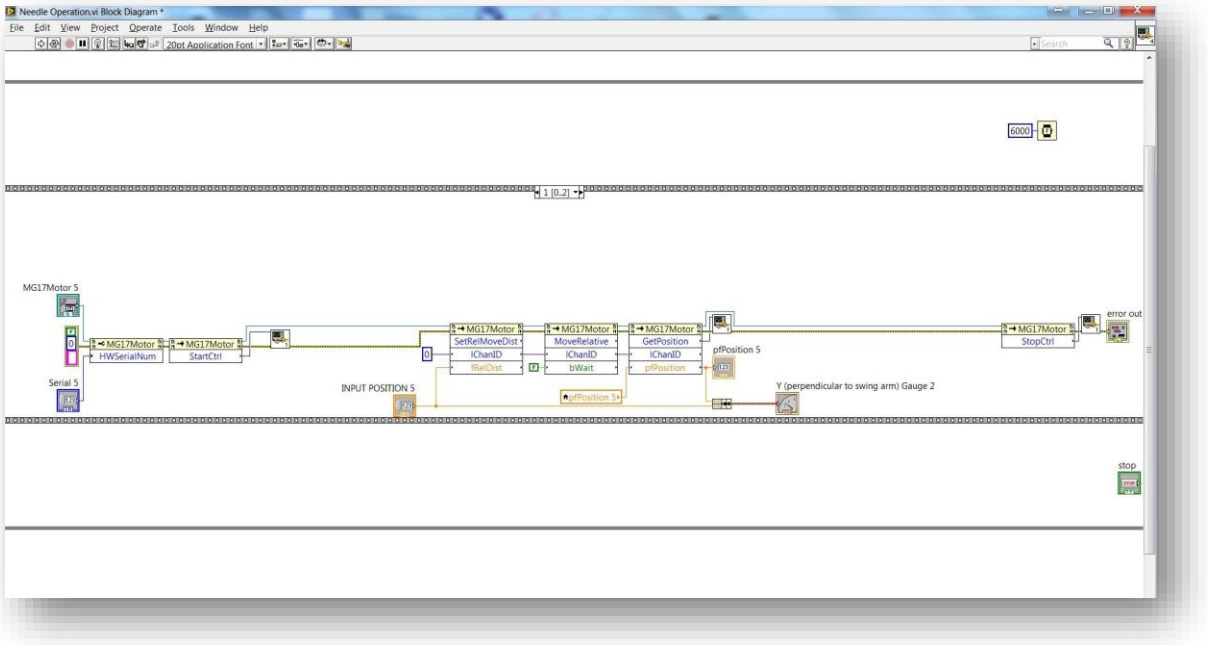


Fig 13. Back End of LabVIEW Semi-Automation to Control ThorLabs Motor – Repetitive Process

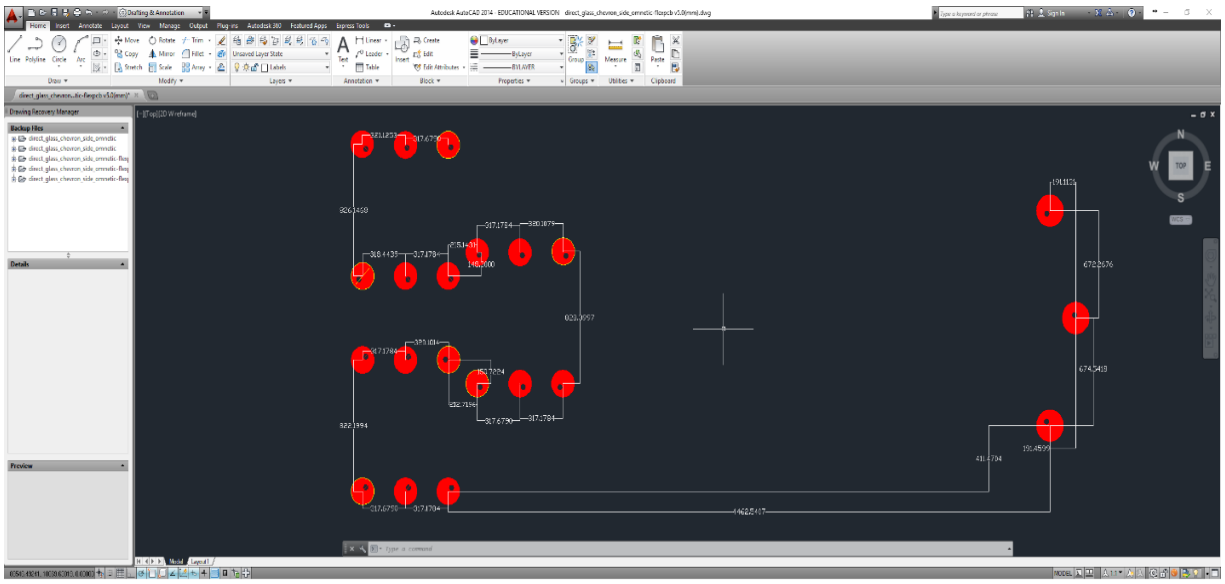


Fig 14. AUTOCAD Position Calibration

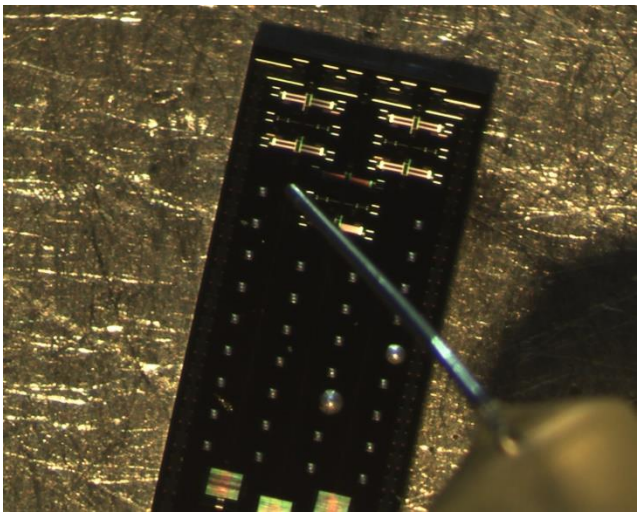


Fig 15. Epoxy dispensing setup

However, to modify and quicken the bumping process, few components were added to the existing station to get view of bonds from two angles.

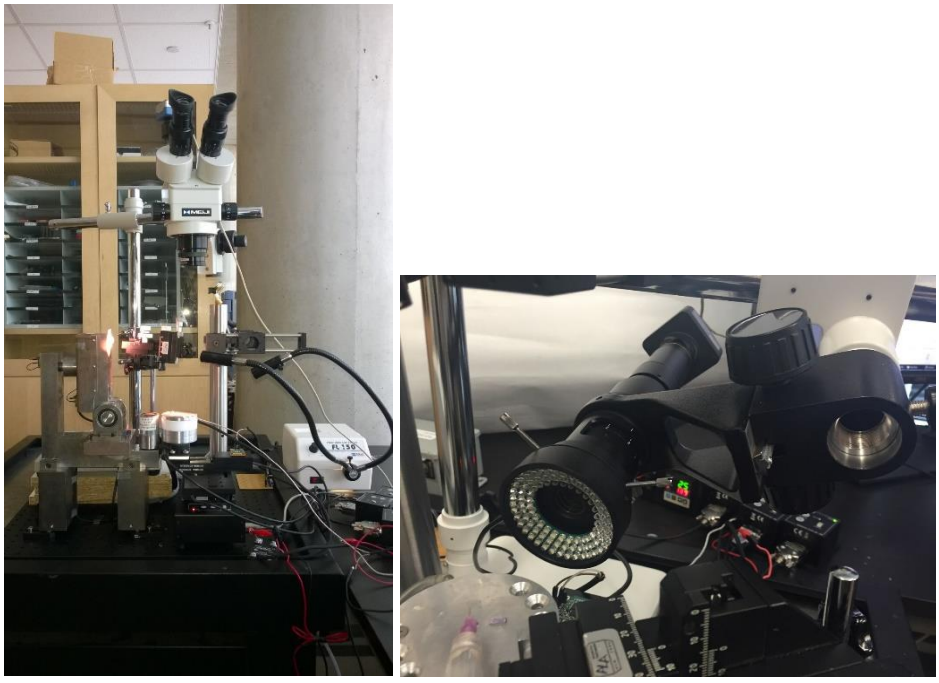


Fig 16. Flip Chip Station: Top & Side Microscope

D. New substrates

Glass substrates were used previously to flip chip. To create a stack of devices, thickness of the devices has to be thin. So I used flexible polyimide substrates instead of glass electrodes to reduce the substrate thickness to 100um.

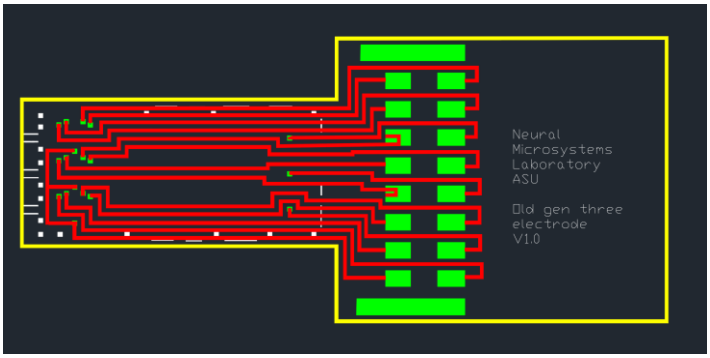


Fig 17. Three Electrode Old Gen Substrate (AUTOCAD DWG)

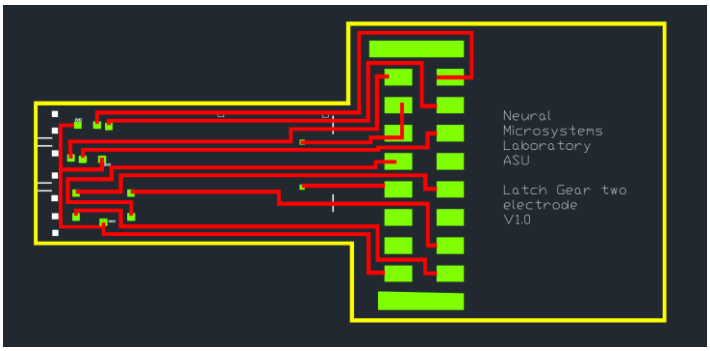


Fig 18. Two Electrode New Gen (Gear + Linear) Substrate (AUTOCAD DWG)

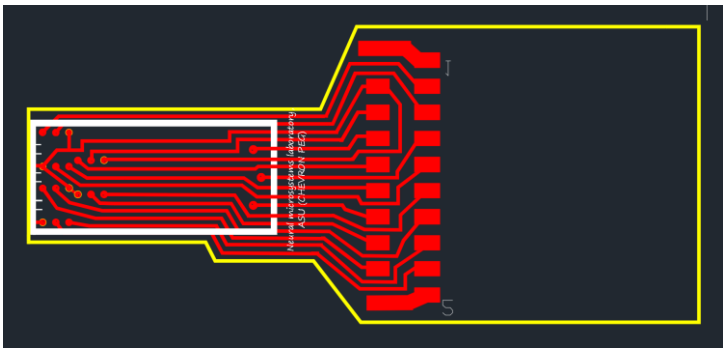


Fig 19. Three Electrode New Gen Substrate (AUTOCAD DWG)

All these substrates were fabricated by SF circuits, California. There are semi-transparent and is see-through. It can withstand up to 250’C and is gold plated on the pads.

E. Flip chip

The existing flip chip station [5] was restructured, improvised with

(a) New heater – 30W instead of 10 W to increase heating time

(b) PID temperature controller to automate heating

(c) Load cell accuracy was increased to measure in 1g resolution

(d) Accelerometers and gyroscopes to improve accuracy

(e) Prism holder

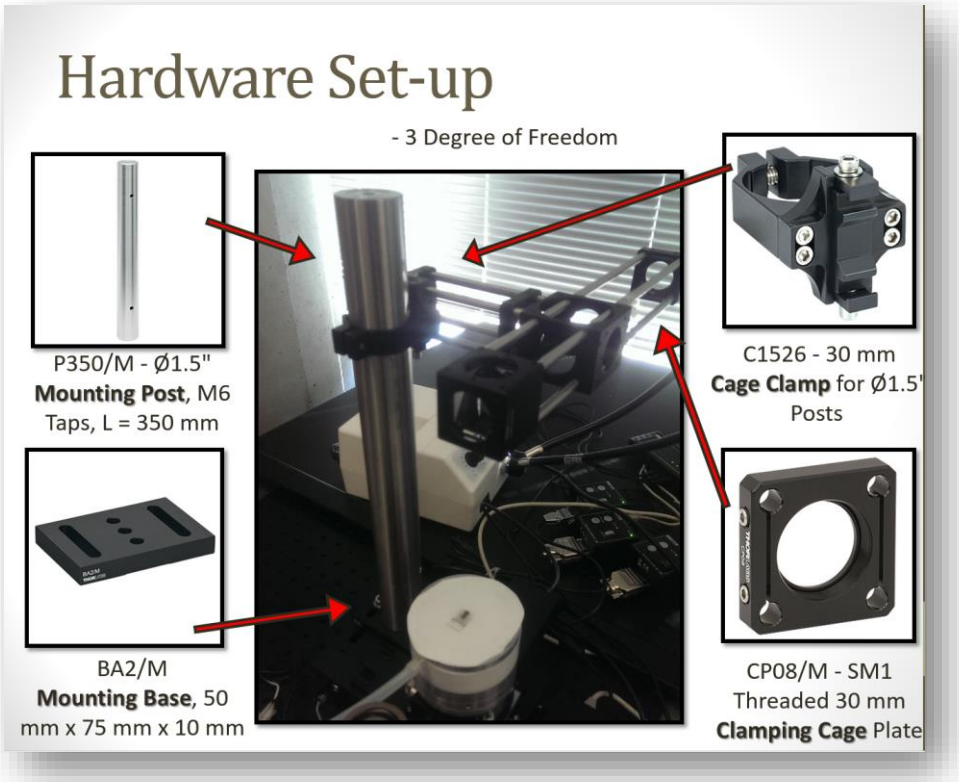


Fig 20. Flip-chip hardware set-up

(f) New valves for vacuum control at both arms

(g) New dispenser with optimum needle diameter of 125 microns

(h) Added cooler for quick curing

Upon improvement, a flip chip calibration procedure was put in place to maintain a constant resolution (Distance/pixel) for every bonding operation and I had an accuracy around 3.6 ±0.2 um. Check appendix for calibration and bonding procedure.

Results & discussions

A. Interconnects

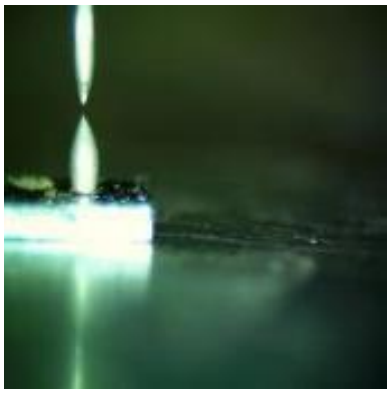


Fig 21. 25G x 1 inch Needle

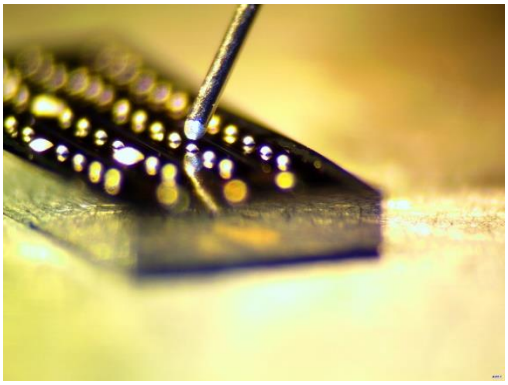


Fig 22. 32G x ¼ inch Needle

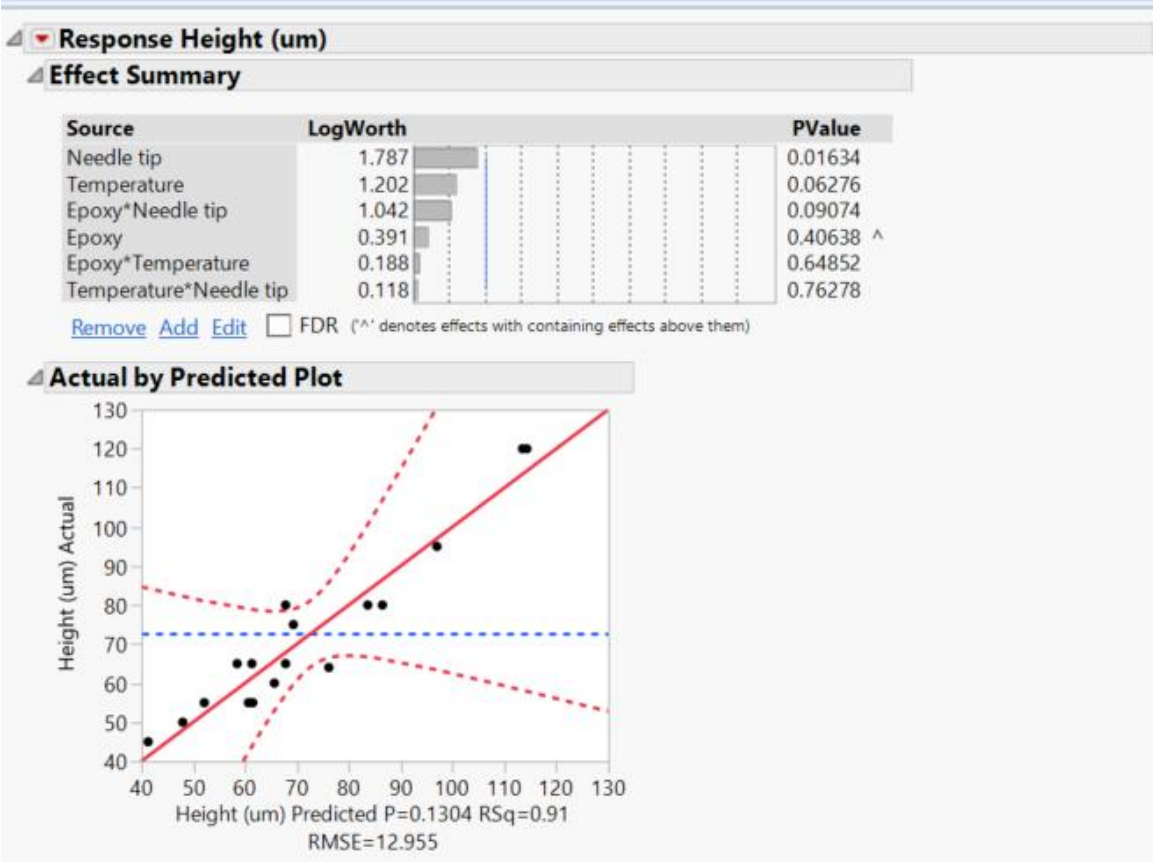


Fig 23. Curve Fitting using JMP tool

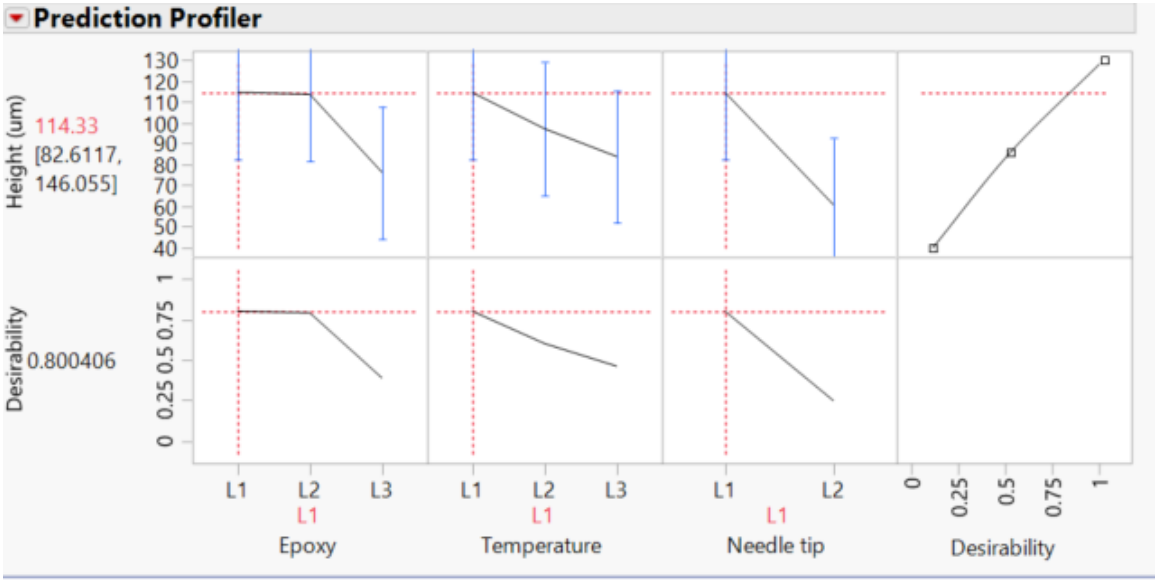


Fig 24. Prediction Profiler 1

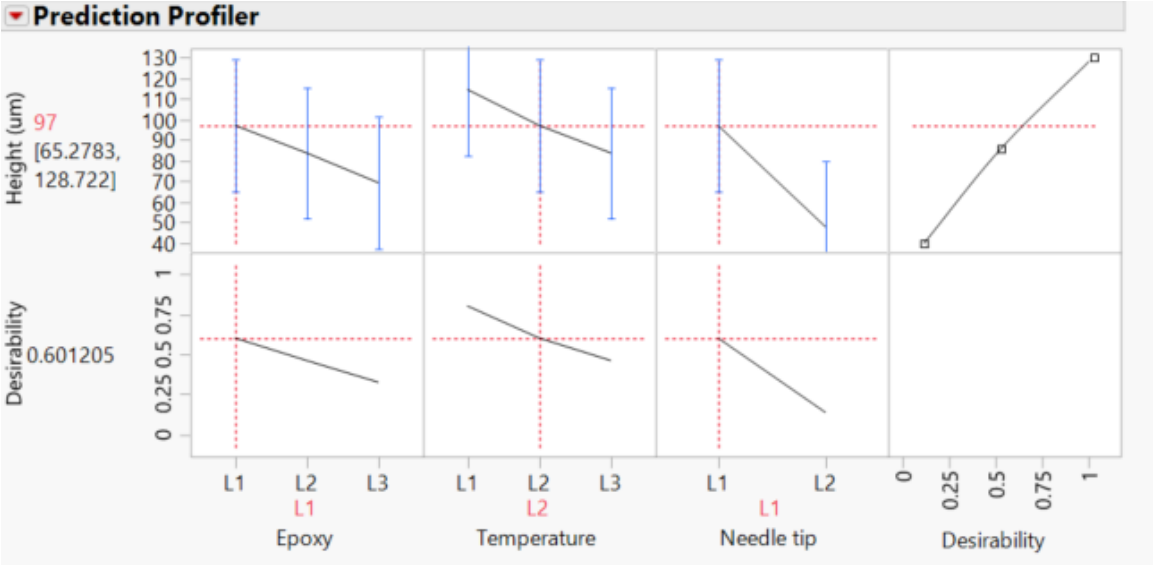


Fig 25. Prediction Profiler 2

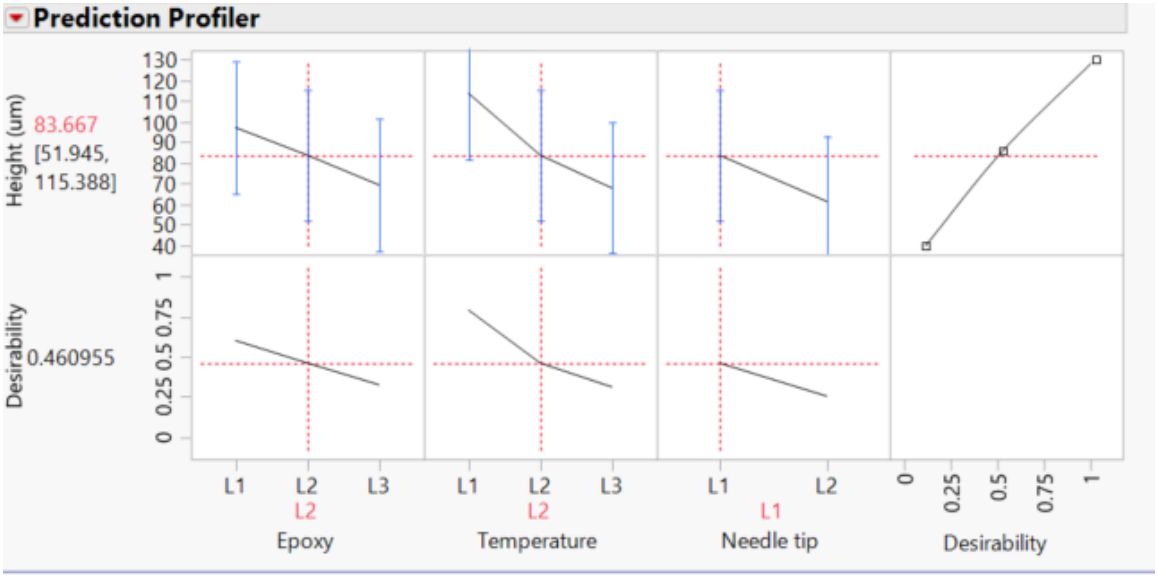


Fig 26. Prediction Profiler 3

With the obtained test results, I found an optimum setting for silver bump which is semi-automated, and can create a layer in less than 10 minutes. The heating time is reduced to less than 25 min. 32G needle was suitable for consistent results on an average produces more than 1:1 aspect ratio.

B. Flexible Substrate

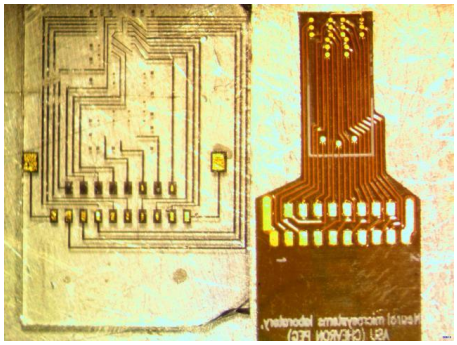


Fig. 27 Comparison Between Glass & Polyimide Flex Substrate

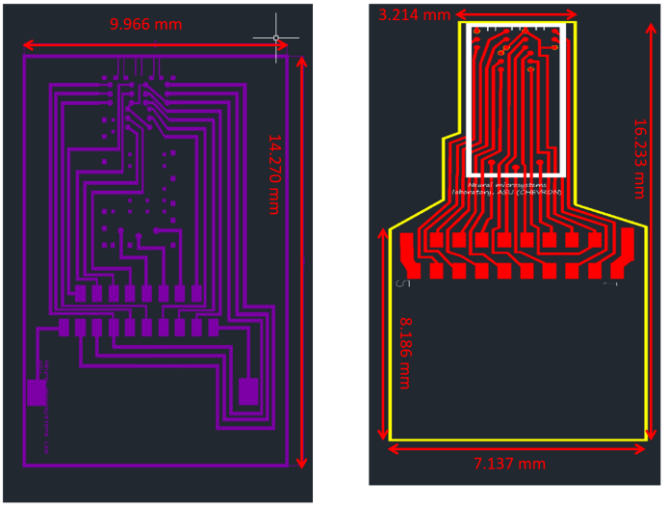


Fig 28. AUTOCAD Comparison

Size comparison:

Original Glass Substrate → 150.161 mm²

Flexible PCB → 89.869 mm²

Reduced area → 60.292 mm²; **40.15%**

CHAPTER 3

MICROBONDING TECHNIQUES TO EXTEND THE LENGTH OF TRADITIONAL POLYSILICON ELECTRODES TO REACH DEEP BRAIN STRUCTURES

Introduction

Bonding is a well-established field. Several technologies are there in place for structures of macro size but are limited when it comes to micro-bonding. Current techniques for microstructural bonding such as brazing, ultrasonic spot welding, soldering, Thermo-sonic, FIB material diffusion impose constraints such as high curing temperature, low throughput and scalability, stage preparation, low conductive property and material selectivity.

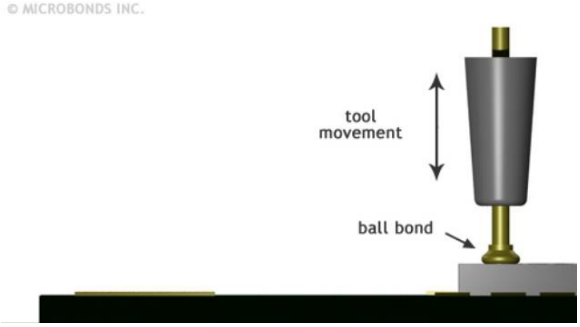


Fig 29. Thermo-Sonic Ball Bond
(http://www.microbonds.com/xwiretech/xwire_bkg.htm)

The above mentioned techniques are most suited for bonding a micro wire to a large substrate. And there are many such application where the aforementioned constraints are common. One such application with a constraint is bonding two micro-wires which should be conductive electrically and thermally. Few applications in the field of micro bonding were achieved by adhesives. [Micro-bonding was also achieved using tin-silver solder paste.

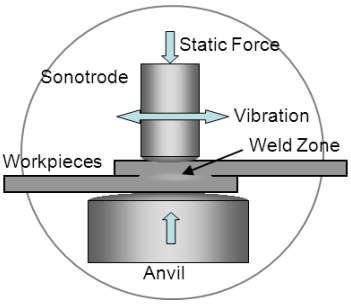


Fig 30. Ultrasonic Spot Welding
https://ewi.org/

Fig 31. Brazing
http://www.mechnol.com/

Over the past decades, electrically conductive epoxies have proven efficient, scalable and have rapidly expanded in microelectronics industry. [13] I designed a novel micro bonding technique using conductive epoxies with support structures and insulation layer to withstand corrosion and give structural conformity while being conductive. It was studied that tensile bond strength is inversely proportional to bonded surface area [12] [14] and that's primarily the reason behind proposed bond being less than 125um in diameter. This micro-bonding technique is used to bond a MEMS based moveable polysilicon microelectrode to traditional Platinum iridium, stainless steel and tungsten neural electrodes. The application of this technique was to increase the length of existing polysilicon electrode of 5 mm by external electrodes of 15-20 mm to reach deep brain structures up to 10 mm. The support structures were made out of polyimide to hold the epoxy in place while playing a major role in large scale bonding applications (e.g. all 250 electrodes at once). And the protective layer was non-conductive silicone to give hermetic sealing thereby avoiding reaction with other external fluids.

Though they are several methodologies to study the surface characteristics of brain, i.e. cortex layer like impedance tomography, sub-dural electrodes, EEG, ECoG etc, there are only a handful of tools to explore deep brain structures. Diseases like Parkinson's are treated by electrodes inserted deep into the brain and stimulating near basal ganglia. So this proposed technology can be used to bond and extend micro wires deep into the brain for electrical stimulation/recording/blocking. However, this technology can be extended to any application which requires bonds with/without electrical conductivity.

Methods

A. Existing methodologies and problems

Current techniques for microstructural bonding such as brazing, ultrasonic spot welding, soldering, FIB material diffusion bonding impose constraints such as high curing temperature, low throughput and scalability, stage preparation, low conductive property and material selectivity. My novel approach using a cost-effective commonly available thermosetting silver epoxy with the help of a coupling mechanism will deliver a robust, reliable and a scalable bonding technique for joining two micro-materials. A hollow cylindrical micro polyimide tube (100 μm inner diameter) acts as a lightweight coupling material. The polysilicon microelectrode and the extension needle (stainless steel, platinum/iridium, gold, nickel etc.) are inserted from each of the two sides of the polyimide tube filled with epoxy and cured.

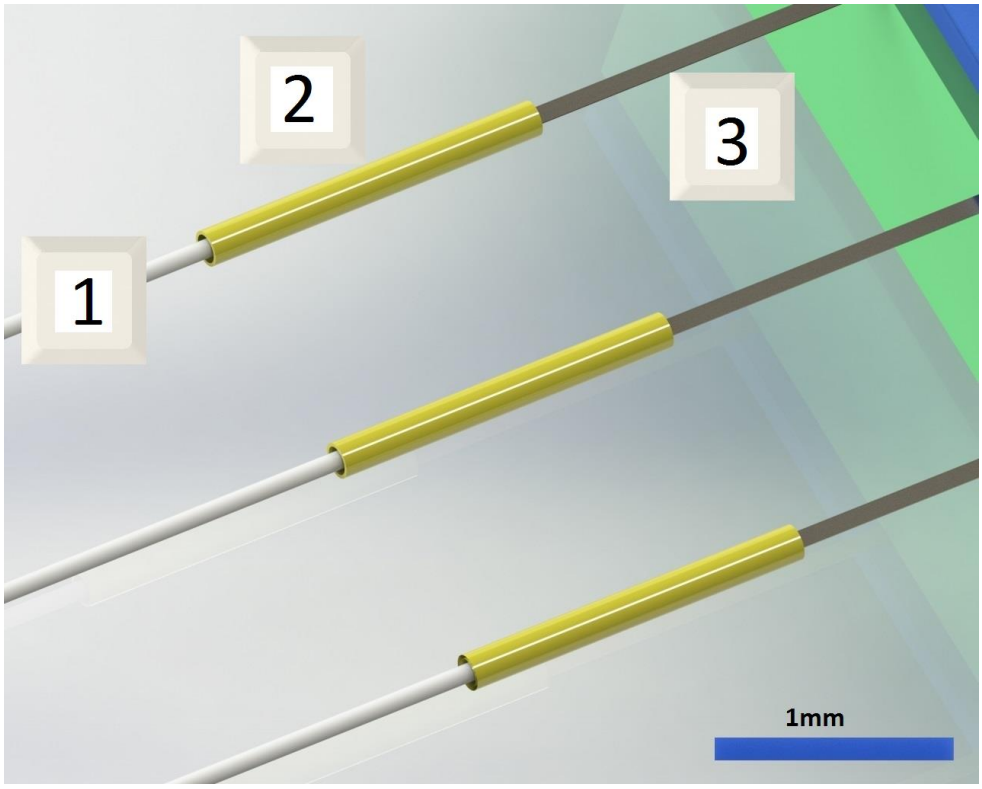


Fig 32. Micro-Bonding Structure

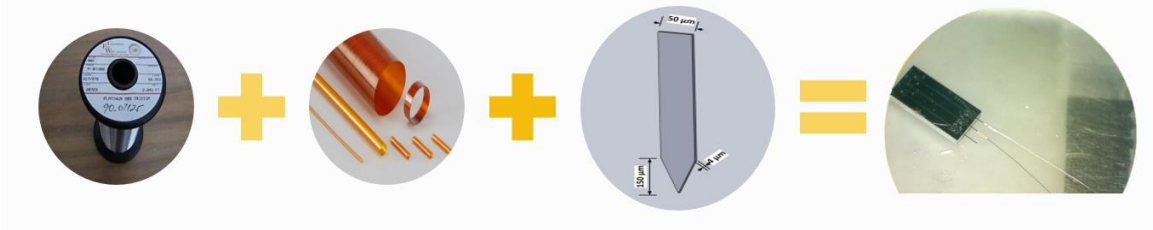


Fig. 33 SS/Pt-Ir/Tungsten + Polyimide + Epoxy + Polyimide = Strong Micro-Bond

1. Stainless steel / Platinum Iridium / Tungsten electrode
2. Polyimide support structure with epoxy inside and coated with biocompatible silicone
3. MEMS based moveable polysilicon electrode

B. Bonding procedure

The bond may be UV curable or one part or two or more-part cure that can be called a paste (silver/Nano particle paste) once prepared according to manufacturer specifications. After the paste is made, it has been gently inserted into a support structure wherein the support structure can be made of lightweight material with a hollow polygonal cylindrical structure decided by the nature of application. The support material is not limited to metals, non-metals and polymers. In my application, polyimide tubes of diameter 80um and length 1mm are used to hold the epoxy. The challenge comes when the paste has to be inserted across the length of the support structure uniformly. Care has to be taken that there is no bubble formation across the support structure. A micro-needle of desired micro bonding diameter has to take; in my application it is 30um since the polyimide support structure is 80um.

Step 1: Hold the micro-needle and support structure to an actuator for controlled movements and dip the micro-needle into the paste such that the paste sticks to the entire area of the micro-needle. Gently insert the needle with the paste into the support structure and rub it along the sides of the support structure. Continue this process once until the support structure is completely filled with the paste.

Step 2: Insert the two materials from the two sides of the support structure and possibly make a lap joint or other type of joints, which suits the application. Clean the excess epoxy, if any across the support structure using micro brushes or chemical process.

Step 3: Subject the bond to temperature, pressure, chemical or any UV process. The choice depends upon the curing time, physical and chemical properties of the material. Heat the bond to 302F for one hour and cure it in room temperature for one hour. Curing time can be reduced significantly depending upon the property of the paste, which includes viscosity, ratio of epoxy parts, temperature exposure, pressure and type of materials.

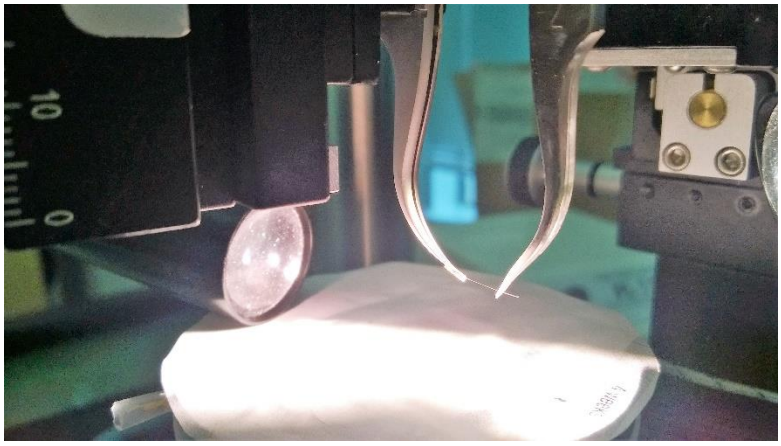


Fig 34. Polyimide, Epoxy & Stainless Steel Electrode

Result & Discussion

After a careful utilization of bonding procedure, these bonds were made and they were subjected to testing including

(a) electrical impedance

(b) tensile shear

(c) accelerated aging

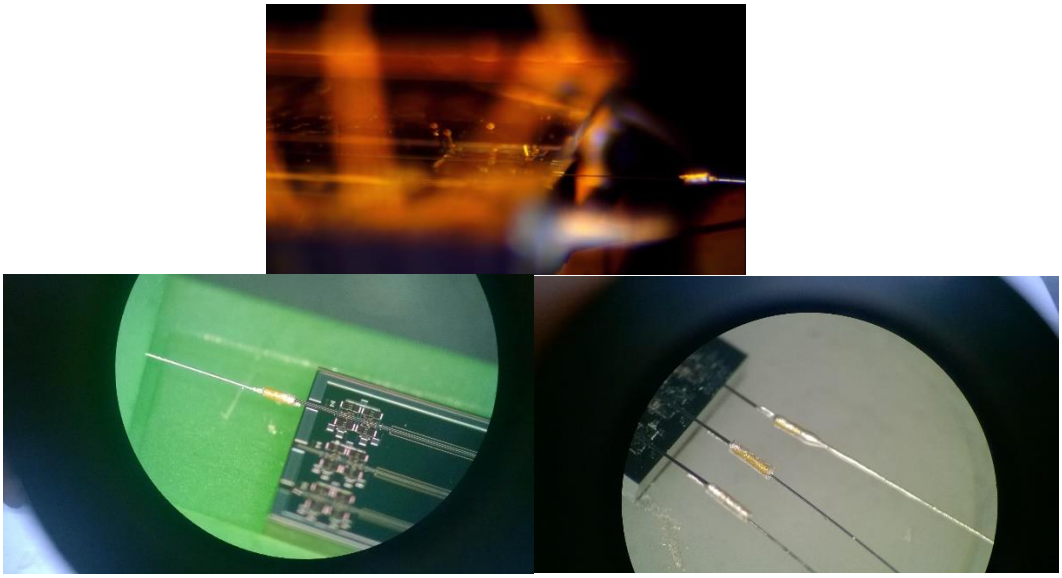


Fig 35. Stainless Steel Electrode Bonded with Polysilicon Electrodes

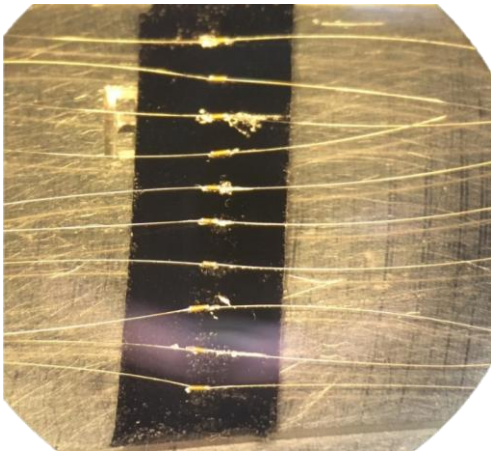


Fig 36. 10 bonds of SS-SS; 10 Bonds of SS-PI

w/o & w. Silicone Coated

(a) Electrical Impedance

The above bonds are subjected to electrical testing using CH instruments. They were given a constant voltage signal of 1V at a varying frequency from 0 – 10Khz and the impedance was studied.

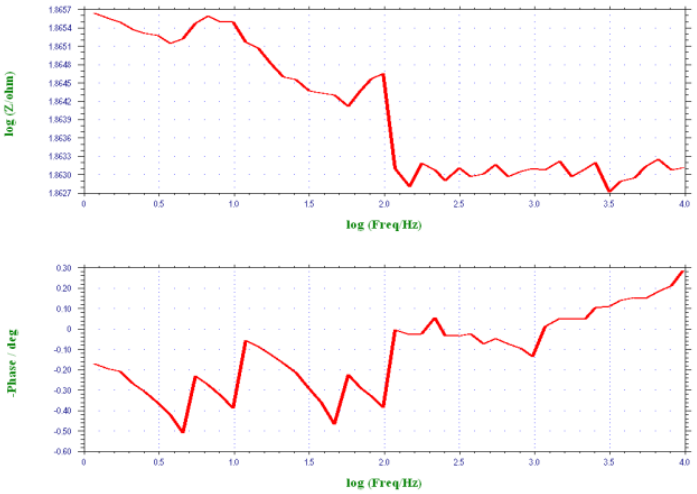


Fig 37. Impedance & Phase Study of SS-SS Bonds

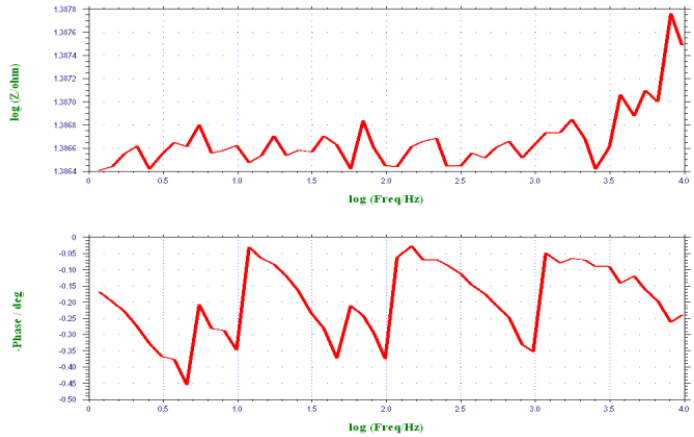


Fig 38. Impedance & Phase Study of SS-Pt/Ir Bonds

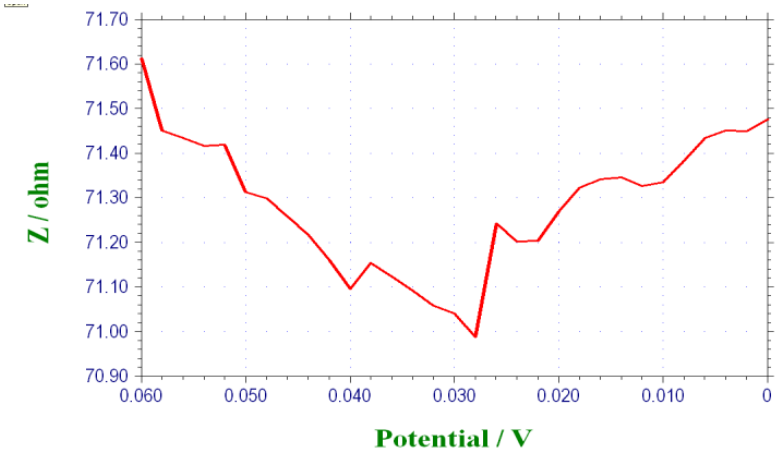


Fig 39. Impedance Potential (SS-SS)

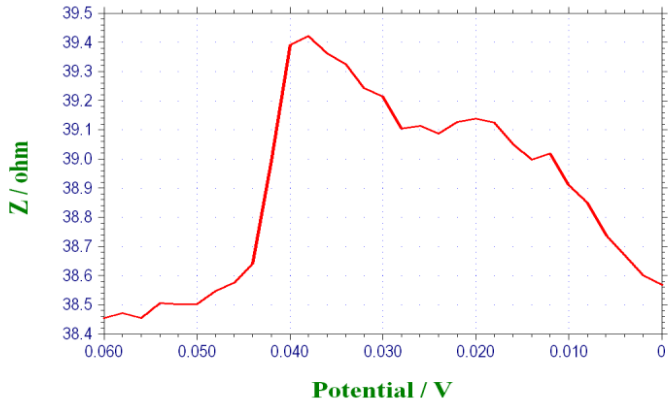


Fig 40. Impedance Potential (SS-PtIr)

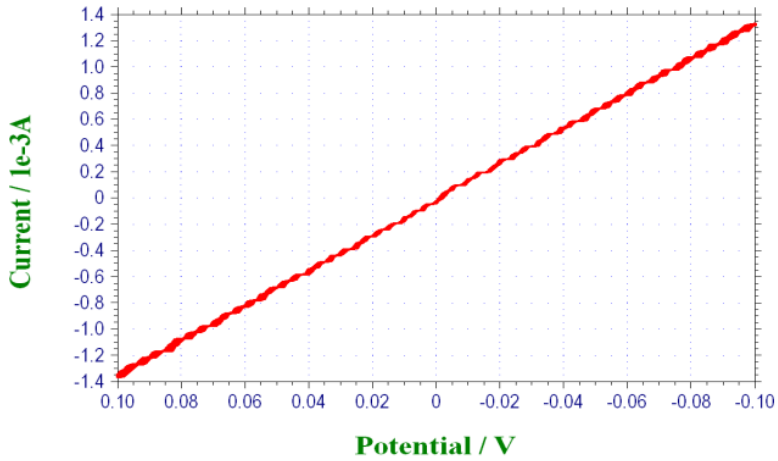


Fig 41. Cyclic voltammetry

The above tests describe that there is less capacitive component and more of a resistive component in the bond and it follows linear relationship. These data represent the average spectrum. The impedance of the stainless steel to stainless steel bond shows higher impedance than Stainless steel to Platinum Iridium bond.

C. Accelerated aging

Specimens of above tests were put in a salt solution to observe corrosion study, void formation, while interacting the with brain liquids. The salt solution with specimens were kept inside an incubator at 100’C for 30 days and they were periodically studied.

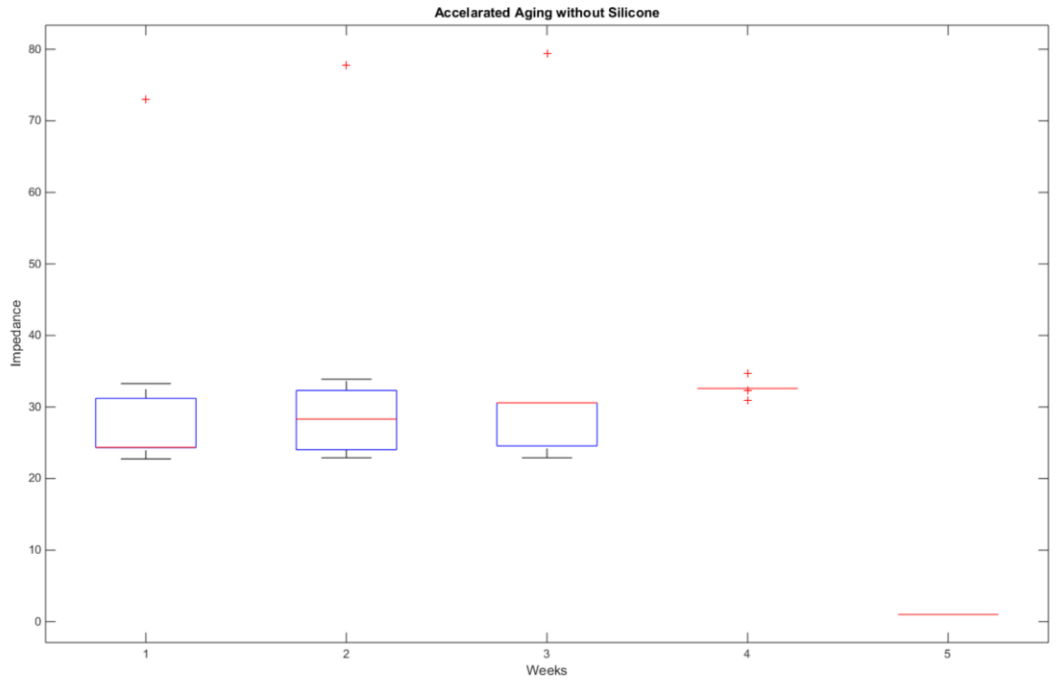


Fig 42. 20 bonds of Silicon Uncoated Bonds

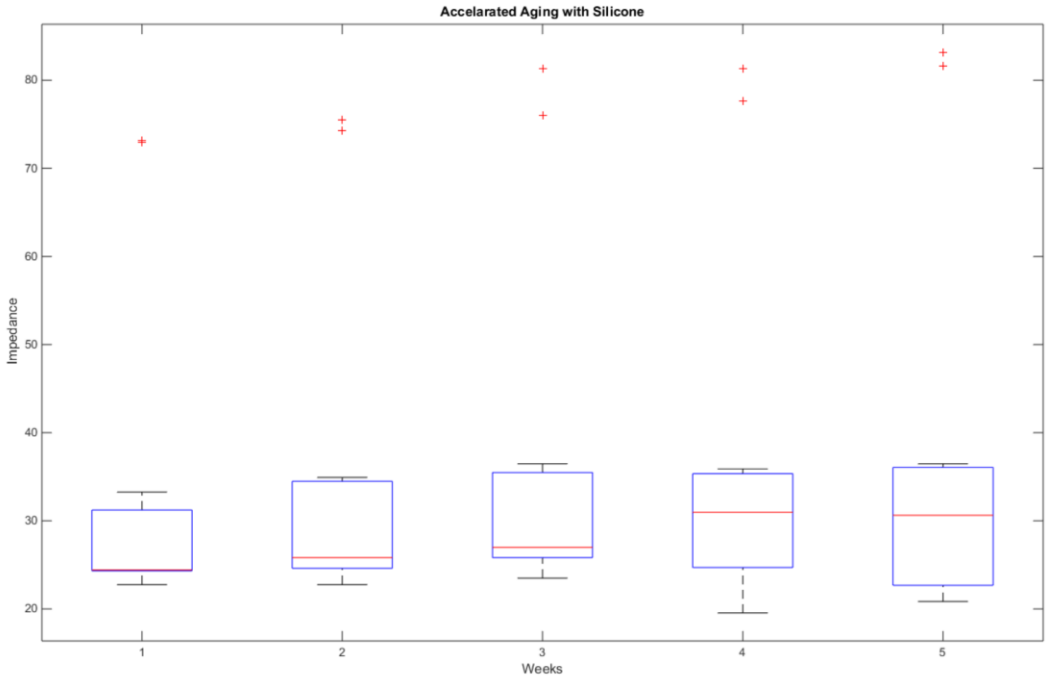


Fig 43. 20 Bonds of Silicon Coated Bonds

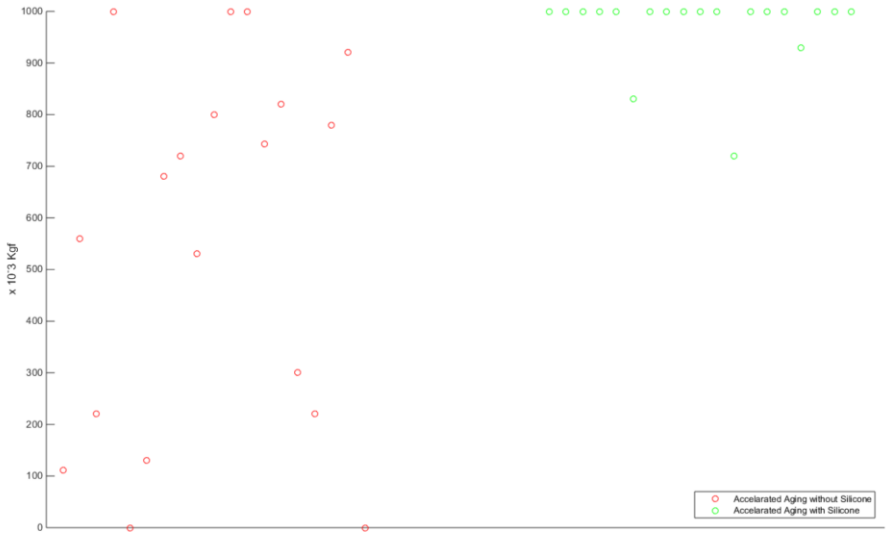


Fig 44. Accelerated Aging Test With and Without Silicone

D. In-vivo testing

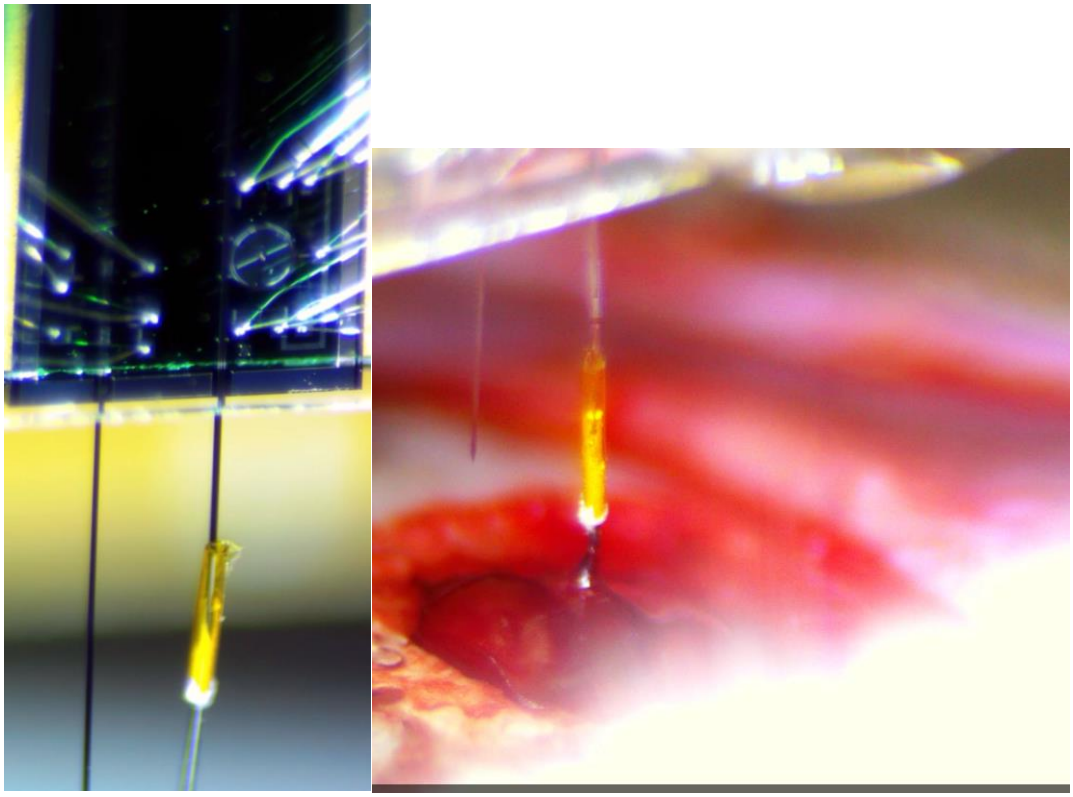


Fig 45. Rat Head

The electrodes were able to move in the brain past the weight of bonding. This proves that MEMS based actuators have enough force to push the electrode deep in to the brain without any bend. Also they electrode was able to move 1mm deep into the brain with a minute pulse worth of oscillation.

The application of the bond is not limited to medical, industrial, commercial and wafer fabrication applications. The microscale bonding technique withstands the stresses associated with microelectrode penetration and eventual steering in the brain. A scalable, microscale bonding technique has been demonstrated that enhances the ability of the autonomous, movable microelectrodes to sample neurons up to 10 mm deep in the brain while still allowing 5 mm of translational capability (with 6 μm displacement resolution) around the implantation site to search and seek neurons of interest. The reported bonding approach is critical to enable autonomous, movable microelectrode technology to sample ensembles of neurons in the deep brain structures. Coupled with micro actuators and robotic tracking algorithms that have already been built, the reported technique will now enable the realization of robotic microelectrode systems that will potentially track hundreds of single neurons in the superficial cortical and deep brain structures over long periods of time during behavior. The bonds can be optimized to result in faster curing time, robotics to do automated bonding, could be much more sleeker bond under controlled conditions.

CHAPTER 4

PACKAGING METHODOLOGY FOR ARRAY OF DEVICES

Introduction

The interface of the neural prosthesis is the micro-electrode either singular or in an array form. The brain consists of different layers and each layers corresponds to different processes and is still an unexplored and unpredictable system. Various methodologies and tools are used to understand the brain activity including FMRI imaging, opto-genetics, electrical stimulation/recording/blocking, optical stimulation etcetera. However most of these methodologies lack proper mounting mechanism. They are huge & bulky to fit on small animals, susceptible to body fluid ingress and cannot sustain long term studies due to performance issues. Many people have come up with their own ways of packaging their electrodes to be guided to reach brain structures.

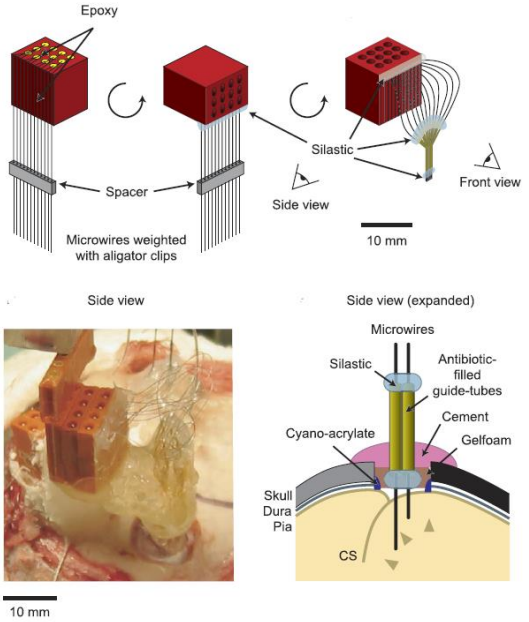


Fig 46 Microelectrode Array [17]

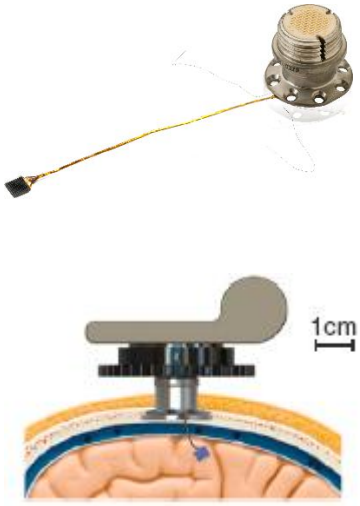
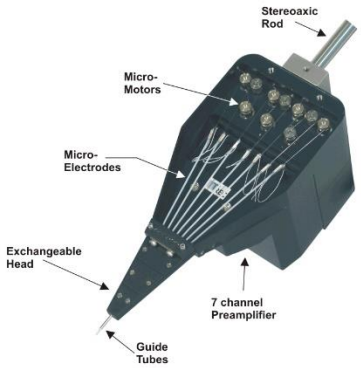


Fig 47. Black Rock Microelectrode Array http://www.blackrockmicro.com/ [26]

These electrodes have an inter-electrode distance more than 100-150um and the fabrication protocols to increase the density of electrode is not feasible and requires whole new

redesign. On top of all, these models are of standard dimensions to fit on animal heads and cannot be customized. It becomes too costly to fabricate given high capital investment.



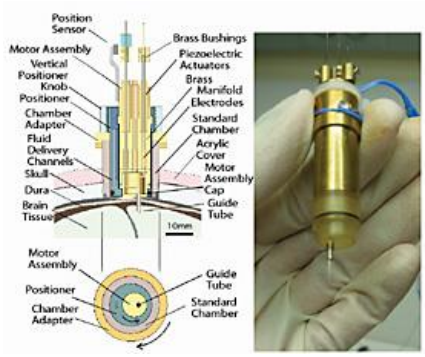
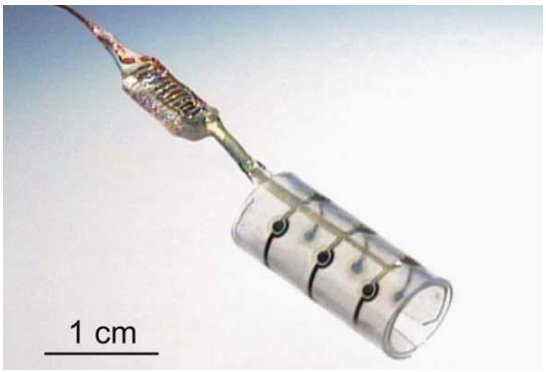


Fig 48 Thomas Recording
http://www.thomasrecording.com/

Fig 49. Burdick's Device
http://www.eas.caltech.edu/engenious/five/andersen

Similar problem exists with peripheral neural electrodes which do not target specific nerve fibers. They are generally made out of silicone based elastomer over stranded stainless steel leads [20] or platinum electrodes [21] [23]. They have sharp edges that evokes a foreign body response. These electrodes have high specificity which limits other clinical applications. Once implanted, there is no possibility of adjustments to correct signal problems. [22] The inner diameter of these electrodes can go only to 300um which limits itself to fairly big nerves in animals. [24]



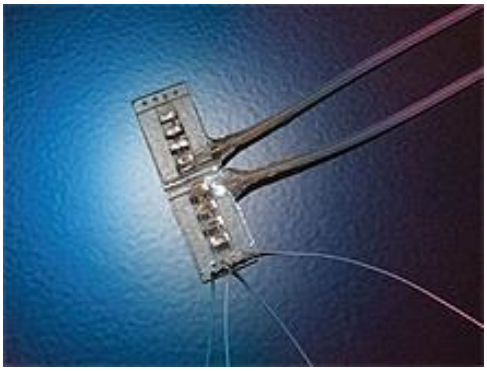


Fig 50. Nerve Cuff Electrode
(Case Western university)

Fig 51. APT Center
http://www.aptcenter.research.va.gov/

With the advancements in 3D printing, I propose here a highly customizable, light weight, small, and biocompatible packaging methodology. This methodology facilitates inter-electrode distance as low as 20 um and can also provide compartments or modules to add stack of MEMS moveable microelectrodes in the system [2] [25]. This makes it the only device to have a minimal inter-electrode distance with relatively high density of packaging.

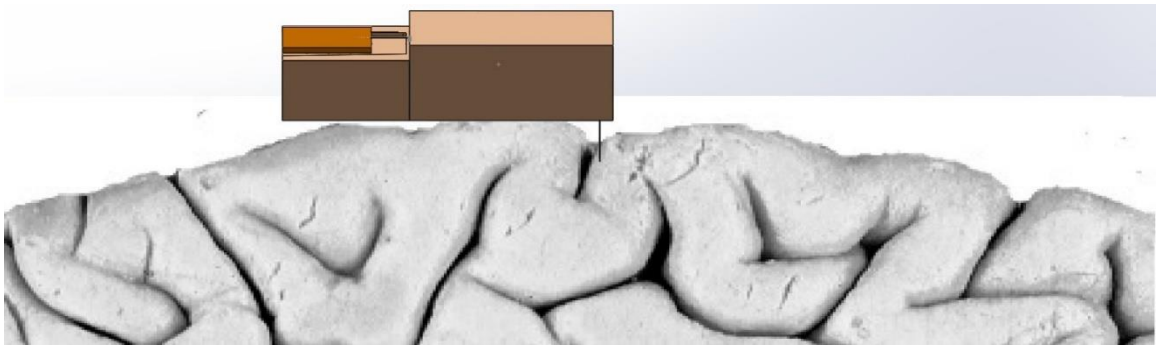


Fig 52. MEMS Packaged Device and its Illustration on Top of Brain

This can be further reduced in size as 3D printing technology gets more precise in future. The pattern of electrodes can be in any form to suit any area in brain be it circular, square or a polygon and at different depths of brain. A similar concept was implement for peripheral nervous system electrode where each nerve fiber can be specifically targeted. It is a conceptual CAD model and will be developed in the years to come.

Methods

SolidWorks was the software tool used to create these structures keeping well studied constraints. Those include

(a) Smaller size

(b) Light weight

(c) Guide for wires

(d) Easily mountable on head

(e) Scalability

(f) Quick assembly procedure

Results & Discussions

Several iterations have gone since the project has started.

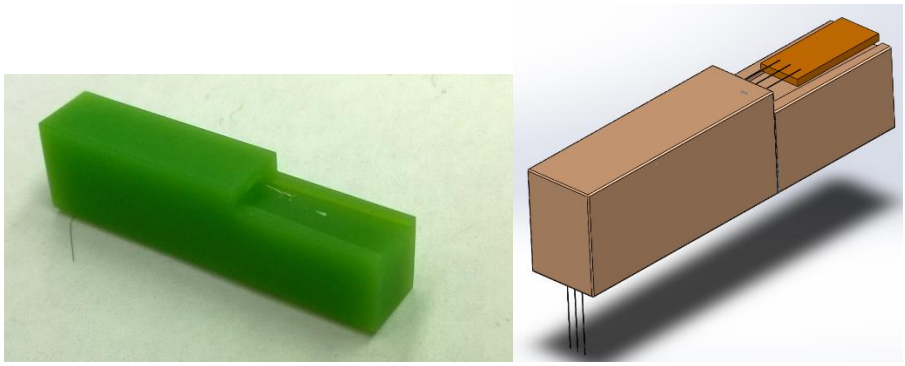


Fig 53. Version 1.0 MEMS model

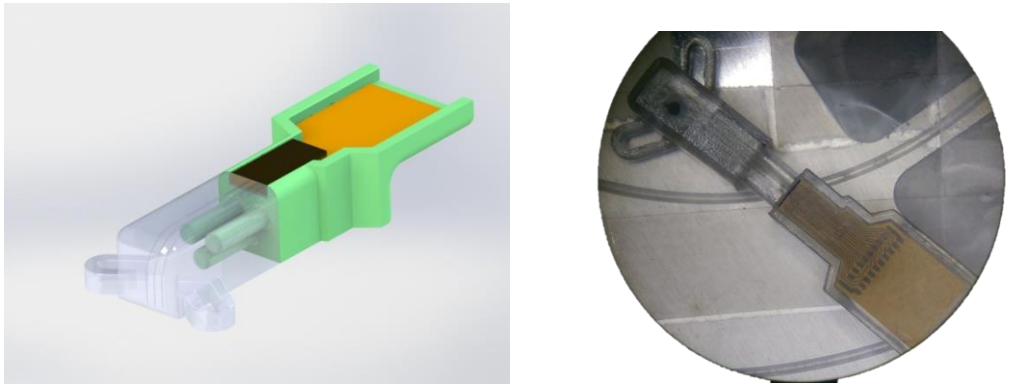


Fig 54 Version 2.0 – MEMS Module and Guide Isolated

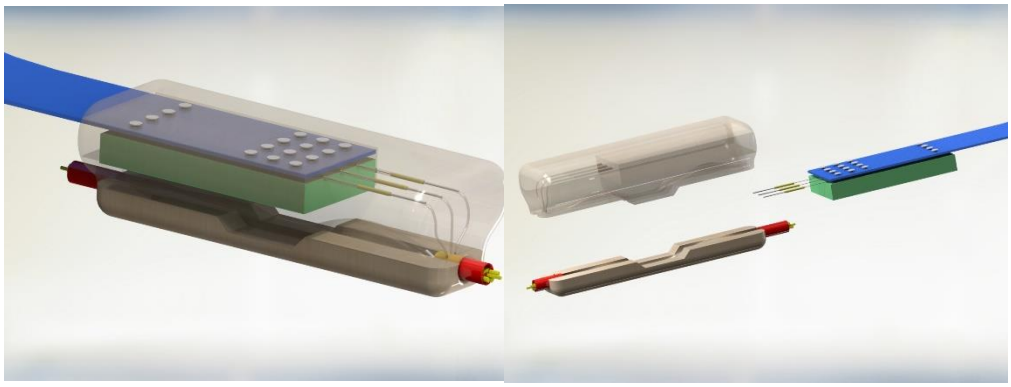


Fig 55 Peripheral Nervous System Module

A perforated 3-D printed plastic cuboid placed between the MEMS microelectrodes and the brain serves two functions – (1) as a guide for the array of microelectrodes and (2) a barrier against backflow of cerebro-spinal fluid (CSF) and skin exudates. Finally, the cuboid allows a series of electrodes to be projected in any pattern, be it circular, square, linear or rectangle by customizing the channel arrangement through a 3D printing process. The complete scalable prototype 3-channel system was tested in bench-top experiments and acute rodent experiments.

CHAPTER 5

FUTURE WORK

1. Flip chip can be optimized to yield faster turn-around time
2. Different epoxies can be tried and can also study various electrical & mechanical properties of micro-bonds
3. Optically clear flexible substrate for flip chip has to be designed, and can visually analyze the movement of electrodes under a microscope
4. Flip chip station heater has to be modified to prevent expansion
5. The micro bond can be even sleeker to prevent failure
6. In-vivo testing on live rats can be performed
7. More models can be printed to test the backflow of brain liquids

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APPENDIX A

PROGRAM FOR GENERATING CONTROL SIGNALS

```
#define FD 8   //Forward drive
#define DRD 9  // Disengage reverse drive
#define RD 10    // Reverse drive
#define DFD 11   // Disengage forward drive
int start = 0, temp = 0, count = 0, diff = 0;
int flag1 = 0, flag2 = 0, flag3 = 0, flag4 = 0;
int dummy = 0;
int c = 0, d = 0, e =0;;

void setup()
{
  Serial.begin(9600);
  pinMode(FD, OUTPUT);
  pinMode(DRD, OUTPUT);
  pinMode(RD, OUTPUT);
  pinMode(DFD, OUTPUT);

  start=millis();
  temp = start;
}

void loop()
{
  start=millis();
  diff = start - temp;

  //Reset the counter every one sec
//  if (start % 600 > 0 && start % 600 < 15)
```

```
//  temp = start;

  if (diff > 600)
  temp = start;

//  Serial.println(diff);
  while (Serial.available())
  {
     delay(10);
     if (Serial.available() >0)
     {
       e = Serial.read();
       temp = start;
       digitalWrite(FD, LOW);
       digitalWrite(DRD, LOW);
       digitalWrite(RD, LOW);
       digitalWrite(DFD, LOW);
       flag1 = 0;
       flag2 = 0;
       flag3 = 0;
       flag4 = 0;
       d = 0;
     }

  }

  if (e == 49)
  c = 49;
```

```
if (e == 50)
c = 50;

if (e == 51)
c = 51;

switch (c)
{
case 49:
// Forward motion
if (diff < 30)
flag2 = 1;
flag3 = 0;
if ((diff > 90) && (diff < 110))
flag1 = 1;
if ((diff > 190) && (diff < 210))
flag2 = 0;
if ((diff > 290) && (diff < 310))
flag4 = 1;
if ((diff > 390) && (diff < 410))
flag1 = 0;
if ((diff > 490) && (diff < 510))
{
  flag4 = 0;
  d = 1;
  Serial.println("Moved 6um forward..");
}
```

```
if (d == 1)
c = 0;
break;

case 50:
// Reverse motion
flag1 = 0;
if (diff < 30)
flag2 = 1;
if ((diff > 90) && (diff < 110))
flag3 = 1;
if ((diff > 190) && (diff < 210))
flag2 = 0;
if ((diff > 290) && (diff < 310))
flag4 = 1;
if ((diff > 390) && (diff < 410))
flag3 = 0;
if ((diff > 490) && (diff < 510))
{
  flag4 = 0;
  d = 1;
  Serial.println("Moved 6um reverse...");
}
if (d == 1)
c = 0;
break;

case 51:
```

```
  //Stop
  Serial.println("Movement halted!");
  digitalWrite(FD, LOW);
  digitalWrite(DRD, LOW);
  digitalWrite(RD, LOW); S
  digitalWrite(DFD, LOW);
  c = 0;
  break;
  }

  //Elecrtrode movement signal
  if (flag1 == 0)
  digitalWrite(FD, LOW);
  if (flag1 == 1)
  digitalWrite(FD, HIGH);
  if (flag2 == 0)
  digitalWrite(DRD, LOW);
  if (flag2 == 1)
  digitalWrite(DRD, HIGH);
  if (flag3 == 0)
  digitalWrite(RD, LOW);
  if (flag3 == 1)
  digitalWrite(RD, HIGH);
  if (flag4 == 0)
  digitalWrite(DFD, LOW);
  if (flag4 == 1)
  digitalWrite(DFD, HIGH);
}
```

APPENDIX B

FLIP CHIP CALIBRATION PROCEDURE

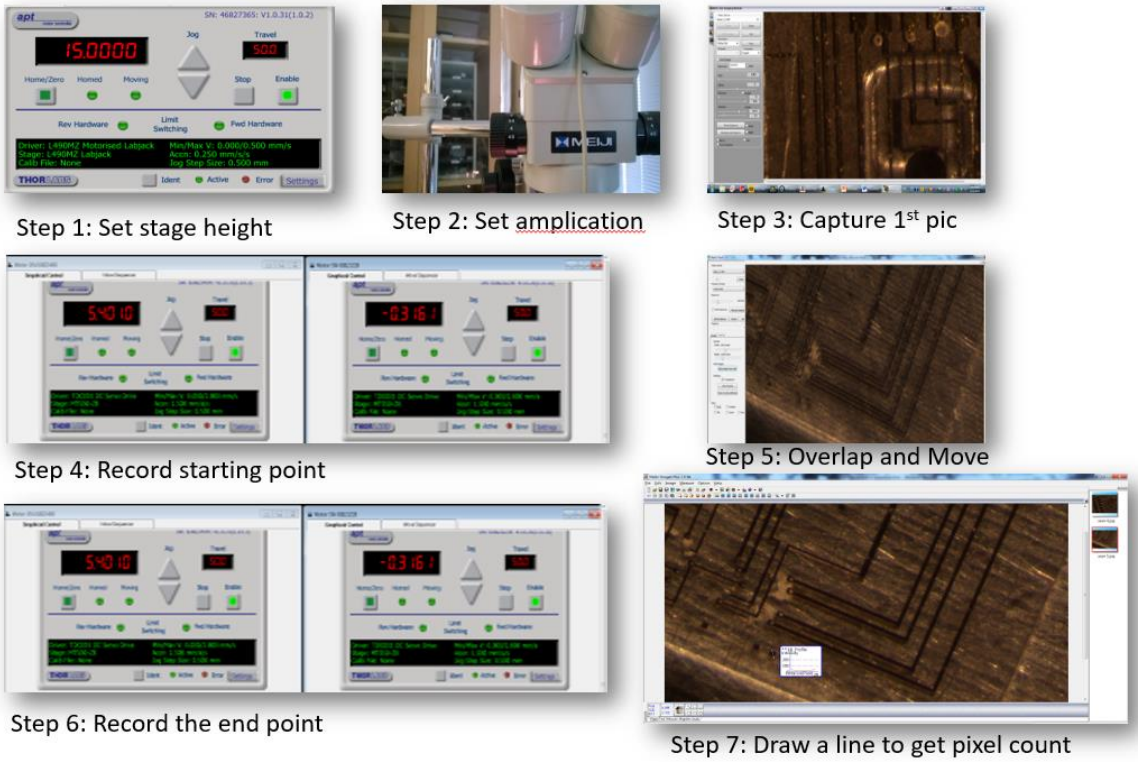


Fig 56. Calibration Procedure

Step 8. Euclidean distance/Pixel count = Length per pixel

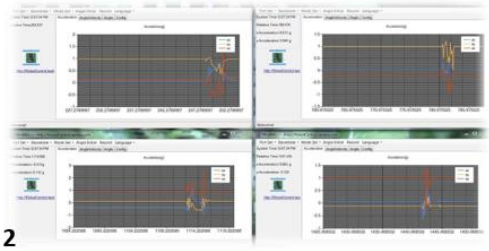
The expected resolution is around **3.6** ± 0.2 $^{\text{um}}/_{\text{pixel}}$

Attempt	X Start Point	X End Point	Y Start Point	Y End Point	Distance Square	Dist (um)	Pixel	Dist/Pix (um/pix)
7	3.467	3.831	-0.813	-0.251	0.449	669.804	180.00	3.72
8	3.467	5.382	-0.813	-0.590	3.716	1927.662	522.00	3.69
9	5.382	3.512	-0.591	-0.254	3.611	1900.232	543.00	3.50
10	5.382	6.091	-0.591	-0.133	0.712	843.517	230.00	3.67
11	6.633	6.417	-0.900	-0.316	0.388	622.665	178.00	3.50
12	4.829	5.401	-0.316	-0.316	0.327	571.880	166.00	3.45

Tab 3. Euclidean Distance Calculation

Detailed calibration procedure

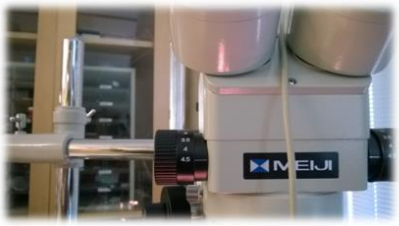
Step 1: Switch on the four accelerometers in the set-up.



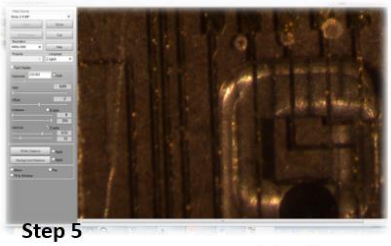
Step 2
Open MiniIMU, & look up the position value in the 4 programs

Step 3
Open APT user, choose the Z-motor value to 15mm (Serial no.: 46827365)

Step 4
Place the reference glass substrate on the top of Thorlab's stage.

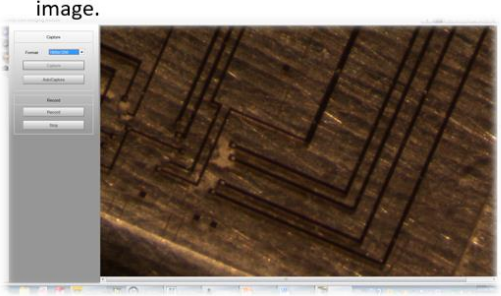


Adjust the zooming value to 4.5 in the MEIJI microscope. Make sure the camera is fixed tightly. Focus the microscope onto the glass substrate.

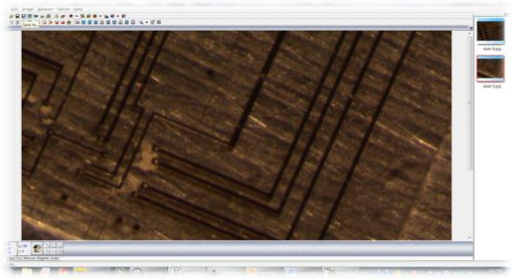


Step 5
Open Motic Image 2.0, click File -> Capture Window, ensure all the settings are entered properly as mentioned in the below image.

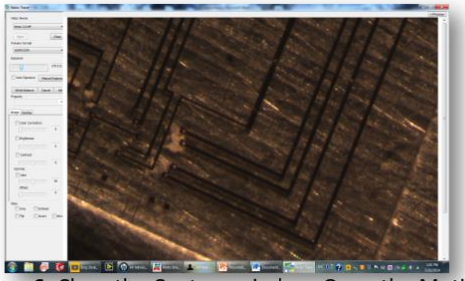
Move the glass substrate in such a manner that the microscope focuses the micro-points as shown below.



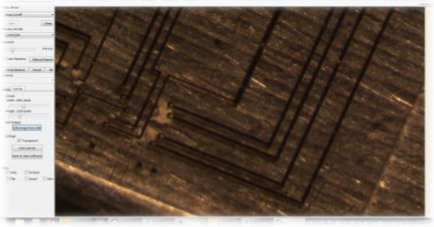
Take a picture by clicking the capture window.



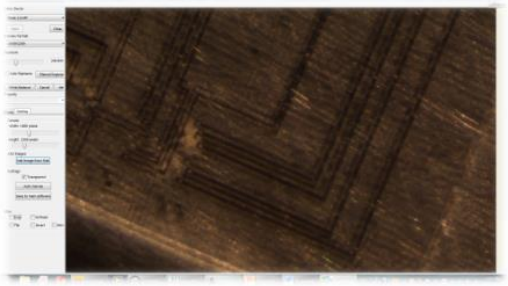
Go back to Motic Image Plus 2.0 window, save the picture in JPEG format as shown below



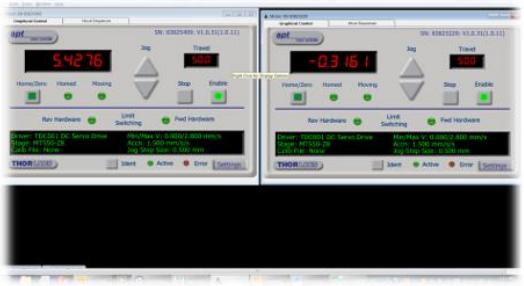
Step 6: Close the Capture window. Open the Motic Trace and ensure the settings as below



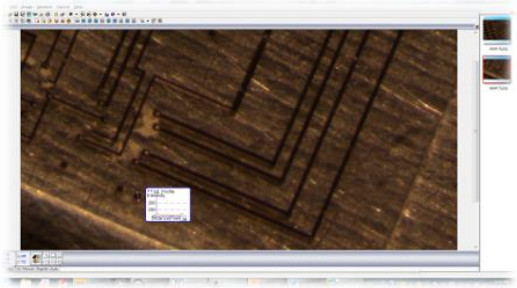
Click the overlay tab, Click 'Auto canvas'. Click 'Add Image from Disk', and choose the saved one. The opened image is over lapped on the live image.
Open the APT user and save the 'X' and 'Y value from the text box to an excel sheet.



Move the image through 'X' and 'Y' axis either using the manual motor control or APT user to overlay the image as below. (Two squares one on top of one other)



Step 7
Record the new 'X' and 'Y' value from the APT user window



Step 8
Open Motic Image Plus 2.0, Measure the pixel count between the two extreme ends of the square as show below
Swing Arm Coordinate

Fig 57. Detailed Calibration Procedure

Step 9

- Calculate the Euclidean distance. ((Old X – New X)^2 + (Old Y – New Y)^2)^(1/2)
- Euclidean distance /Pixel count = Length per pixel
- Ensure the value is around 3.6 ±0.2 um

APPENDIX C

FLIP CHIP BONDING PROCEDURE

Step 1:

Ensure that the whole set-up is in static state, i.e., Microscope, Swing Arm and THORLAB platform.

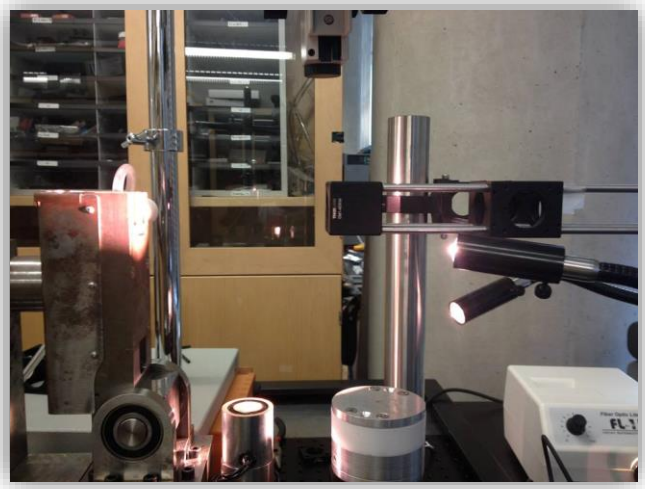


Fig 58 Flip Chip Station

Step 2:

Turn up the MEIJI High Intensity Illuminator. In the Motic Image Plus 2.0 -> Capture Window, change the focus to around 3.5 until the eight bonding bumps with at least one of the normal margins available in sight as image shown below.

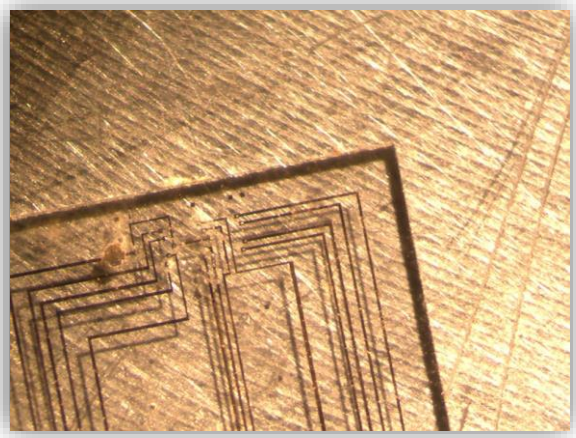


Fig 59. Glass PCB

Step 3:

Disable the vacuum. Place the swing arm on top of the substrate. Enable the vacuum with the substrate sucked tightly onto the swing arm.

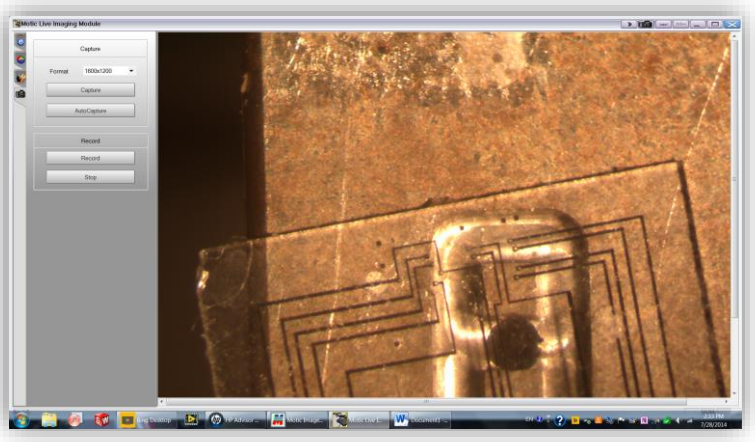


Fig 60. Vacuum Locked PCB

Step 4:

Close the Capture window. Open the Motic Trace and ensure the settings as below. Place the MEMS chip on the THORLAB platform in the middle of the microscope view.

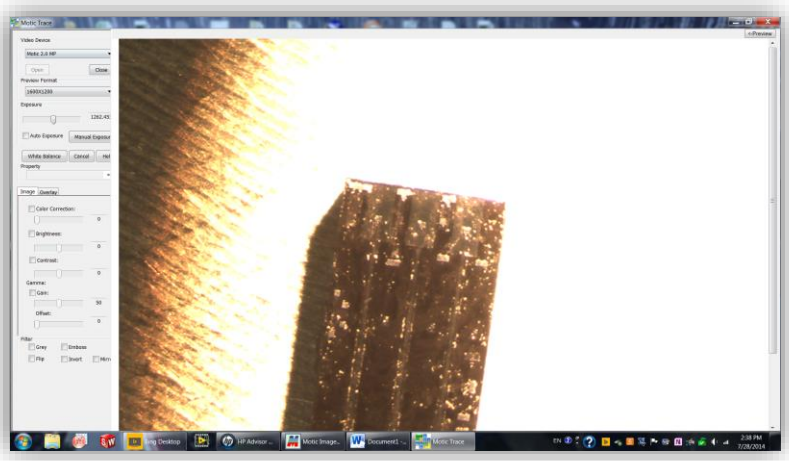


Fig 61. MEMS Chip Placement

Step 5:

Click the overlay tab, Click ‘Auto canvas’. Click ‘Add Image from Disk’, then load the images in such a sequence, the image from stage and the image on swing arm.

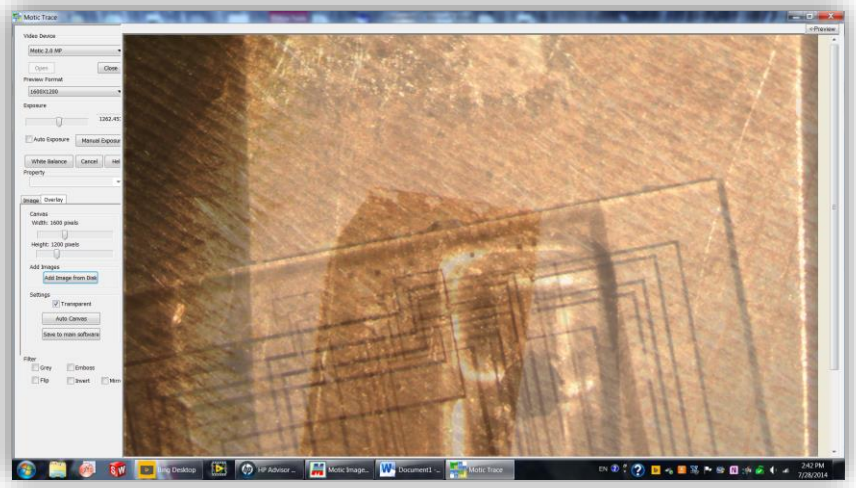


Fig 62. Overlay Match

Step 6:

Move the last loaded image and overlay the two loaded images by aligning the edges as shown in below image.

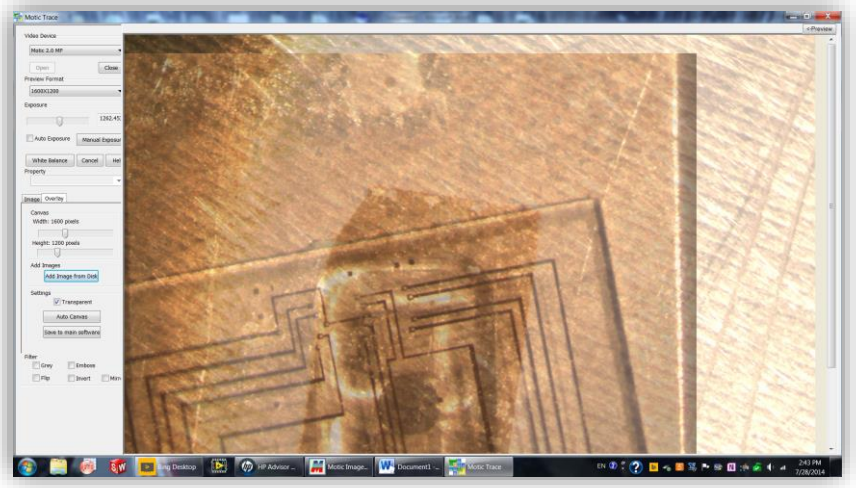


Fig 63. Side Loading of Two Images for Alignment Comparison

Step 7:

Move the image through ‘X’ and ‘Y’ axis either using the manual motor control or APT user to overlay the image as below. (Two pads one on top of one other).

Fig 64. Overlay Image

Step 8:

In the APT user, activate Z-axis motor to lower down the height. Close the swing arm, and activate electromagnet to make the entity tight.

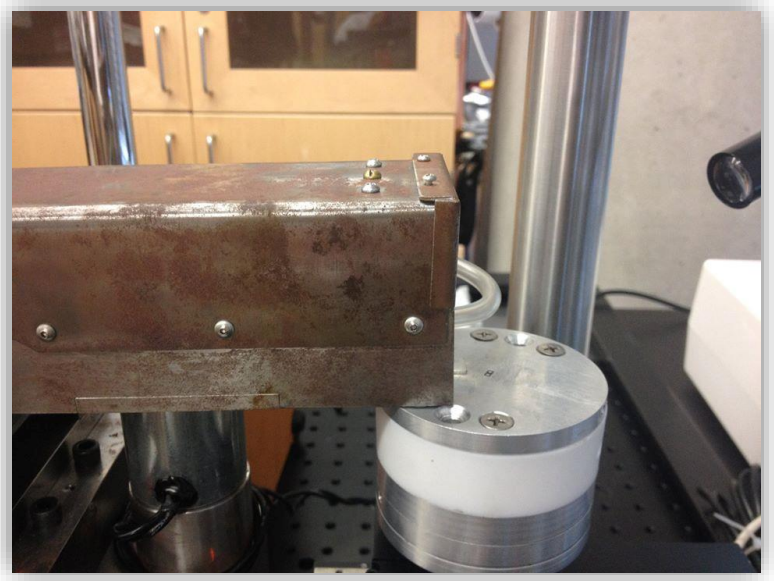


Fig 65. Flip Chipping Heated for 15 Min to 170’C

Step 9:

Turn on the TTM-J4 PID Temperature Control and the load cell. Set the temperature to 150 degree Celsius.

Step 10:

In the APT user, activate Z-axis motor to lift the THORLAB platform until the load cell gauge reaches 400 gram.

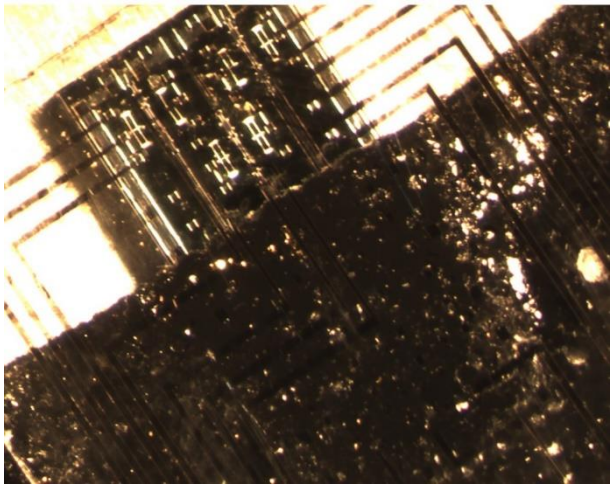


Fig 66. Flip Chipped Sample.

BIOGRAPHICAL SKETCH

Sivakumar Palaniswamy, M.S. BME | Sivakumar is a budding entrepreneur, an ideation expert, and has been a Research Aide at Neural Microsystems Laboratory, ASU, since 2013. His research focuses on developing brain tools using MEMS based moveable brain electrodes for deep brain study. Prior to joining ASU, he was an R&D engineer in the medical device design field in a leading Neonatal company in India. While at ASU, he co-founded a company called Neolight that uses light to treat Jaundice in newborn babies. He has taken projects from ground zero to production stage. His experience comes from his wide range of positions held as research engineer, design engineer and test engineer both in India & US. He holds two patents and won Edson, Bioaccel, Flinn foundation awards.