Optimization of the production and insertion of 3-dimensional polyimide electrodes into rats

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Abstract:

Polyimide cortical implants are a recording platform created to reduce the impact of micromotion and minimize the immune response of the brain. Closely matching the stiffness of the brain is key to minimizing the immune response, and could extend the life of an intracortical implant.[1] A separate inserter was made and force measurements were taken on a model for the human cortex showing the forces exerted at faster speeds ($6mms^{-1} \pm 1$) were smaller in magnitude than slow ($0.4\ mms^{-1} \pm 0.1$) or medium ($3\ mms^{-1} \pm 0.5$) speeds. Measuring the adhesive forces between the electrode and 0.5% agar gel, wet glass, and wet steel showed the electrode had a greater tendency to stick to agar gel. To accommodate the neural growth factors, the polyimide electrodes must be "rolled" into a cylindrical structure. A system was developed that resulted in 15% of all electrodes being rolled in the correct shape.

Key Words: Polyimide, intracortical, 3-d electrode, inserter, neural growth factors

Introduction:

Non-invasive neuro-potential monitoring techniques such as electroencephalography (EEG) have been used to monitor neural activity on a broad scale, but are not able to record the action potentials of a single unit neuron. Intracortical implants monitor action potentials on a cellular basis by inserting a thin conductive microwire was into the brain and recording signals from individual neurons. Microwire can be made of tungsten or another metal with a high Young's Modulus, 400-410 GPa, giving the metal the appropriate strength to break through the brain tissue without buckling. However the number of functioning electrodes decreases over time as reported in an experiment by Nicolelis et al. where the number of functioning microwire electrodes implanted in 3 macaque monkeys decreased 40% in 18 months.[2]

Many neural prosthesis's would rely on the durability of life-long intracortical implant to replace vision or hearing loss. A neural prosthesis is a device that takes sensory information, and bypasses the sensory organs and nerves involved and delivers the information straight to the brain. Many sensory aids, like the cochlear implant, rely on some of the sensory machinery being intact, like the auditory nerve and cochlea. People with damaged inner ear organs would not qualify for a cochlear implant, and would need a lifelong neural prosthesis to restore their hearing.

One problem preventing current electrodes to be planted in the brain for amounts of time longer than 18 months is the immune response triggered when a foreign material is detected. When an object is forced through the brain severing and dragging blood vessels, severe pressure is exerted on the surrounding tissue causing damage and lowering recording quality.[3] Cortical implants only record the strongest signals once the swelling subsides, and then all channels slowly degrade over time. Previous electrode designs take advantage of the rigidity and high impedance of microwires of different materials without regard to their effect on the tissue. Two standard electrode designs that improve upon the primitive single tungsten wire insertion are the Utah Electrode Array and the Michigan electrode array.

Several factors of the foreign body response contribute to the loss of the electrical signal including glial scar formation, and activation of microglia and astrocytes. The glial scar is a formation of glial tissue and fibroblasts that surround the electrode insulating the electrode pad from any neural activity. The glial scar also inhibits neuronal expansion into the area where the electrode is positioned by encapsulating the electrode from the environment of the brain.[4] After the immediate implantation occurs, the glial cells in the surrounding area activate. Astrocytes in the activated form increase the production of inflammatory factors, extracellular matrix production, and migrate toward the site of insertion. Microglia secrete lytic enzymes in an attempt to degrade the electrode, but may be detrimental to neuron growth in the area due to the neurotoxic environment created. In total astrocyte and microglia cells account for anywhere from 35-75% of the cells in the brain whereas only 25% of brain cells are neurons.[5] Statistically inserting an electrode should yield usable signals, but the reaction of the brain makes long term measurements difficult to achieve with current technology. The initial inflammatory response of the brain tissue also creates what has been called a "kill zone" around the electrode where there is an extreme lack of neurons.[6]

To measure the speed or the forces exerted on the electrode during insertion, many experimental groups use a motor and complex setup to take measurements. In one experimental setup to measure various speeds of insertion, brain slices were used along with stepper motor to inject the electrode into the brain slice at a constant speed.[3] Implanting the electrode at very slow speeds was generally found to cause more tear of the tissue and greater damage, where fast implantations at around 200um s^{-1} caused less fluid displacement and blood vessel rupture. The sharper the tip of the needle used for insertion, the less damage is caused. However, blood vessel severing causes extreme increases in pressure and lower quality signals negating any efforts to reduce detrimental forces during implantation.[3] Another method of calculating the forces exerted during insertion involved a motor controlled micromanipulator connected to a computer that recorded the compression and tension forces.[7] The material used during testing was also an in vivo rat cerebral cortex.

Some proposed reasons for the immune response generated when inserting an electrode include the implant material, the implantation method, and the rigidity of the electrode itself. In an effort to combat the immune response the electrode that was created was made of polyimide, a flexible biocompatible polymer, and had a 3 dimensional enclosure filled with a neural growth factor. The polyimide coating is biocompatible which would decrease the effect of the glial scar. The neural growth factor injected into the center of the 3-dimensional structure is added in hope that neurons migrate towards the electrode instead of migrating away as other experiments have found.[4] The electrodes were created using a batch fabrication method, and then rolled over onto itself two and a half times using a series of hypodermic needles. The final dimension of the electrode at the recording sites was 190um wide with a diameter of 300um as shown in Figure 1.

Methods:

To develop an effective way to roll the tip of the polyimide electrode, several designs were tried until a final model was chosen and used. The basis of rolling electrodes includes two hypodermic needles, the larger needle having an inner diameter of 300um and the smaller needle having an outer

diameter of 150um. The end of each needle was cut along the length of the needle so that the tip of the electrode could be wedged in the small needle and then guided into the large needle which would be held in place as the small needle rotated to create a cylinder. The width of the electrode at the tip is 190um with a thickness of 10um. Handles were soldered to the ends of both needles to make gripping and rotating easier. Once the electrodes were rolled they were cured in an oven at a temperature of 300˚C.

An electrode was decided to be rolled successfully if it had been rolled two and a half times and had a diameter of 300um ±10. The correct size was determined by what pattern was needed for the vias and electrode pads to align on the inside of the newly created cylinder. Also the outcomes of the electrode rolling were separated into four categories: correctly rolled, spiraled, incompletely rolled, and broken. Spiraled simply means that while the electrode was being rolled, each loop did not land on top of the last loop, but to its side.

Two designs were made for rolling the electrodes, and tested with prototypes. The prototypes were made of steel cubes and cardboard. One design was chosen to be manufactured into plastic. Testing involved taking a polyimide electrode and rolling it while making observations to potential error in the rolling process as well as the time it took to complete rolling. The plastic stand made was used to roll 20 electrodes. A microscope was used to view the rolling process as the small needle was rotated. A wire was used as a clamp to close the large needle after the small needle was inserted for batch #3.

To determine the forces between the electrode and water, wet stainless steel, wet glass, and 0.5% agar gel, a digital scale was used with a micromanipulator. The electrode rested on the test substance so that ¾ of the shaft was in contact with the substance. A micromanipulator peeled the electrode off the test material while the scale took measurements every 0.2 seconds. For each material 10 trials were taken.

To construct the stainless steel inserter, a 23 gauge stainless steel hypodermic needle was sanded down until a half of the needle was left. A second needle was also sanded down, and added to the first needle so that a full hypodermic needle was formed, but had detachable halves. The glass inserter was made by sanding down a glass capillary tube until it had a 45 degree bevel angle. The capillary tube was then cut 4mm from the tip of the blade. A rubber hose was added to the outside along with four thin metal wires to act as handles. The electrode shaft is then put into the inserter so that the tip of the electrode is near the tip of the glass tube. After insertion the inserter is left in the dental acrylic apparatus.

The inserter models were tested each in agar gel, then used in a surgery. The goal of the inserter was to place the polyimide electrode 1.5-1.7mm into the brain and be removed leaving the electrode behind undisturbed. Another parameter for building the inserter was that it couldn't damage the brain due to any motion parallel to the surface of the brain that could tear the surrounding tissue. The two different materials considered for the design were glass and stainless steel. To test each design a prototype was made and was loaded with a polyimide electrode and inserted into 0.05% agar gel with

a micromanipulator. Success was measured based on whether the electrode was left behind at the correct depth.

To measure the forces the inserter would exert on the brain, a 23 gauge stainless steel needle and a glass capillary tube were tested separately by attaching each one to a micromanipulator. The diameter of the steel needle and glass capillary tube was and 650um and1.2mm respectively. The micromanipulator was used to insert the device into 0.05% agar gel 4mm deep without removal. The agar gel was placed on a scale that measured changes in weight every 0.2 seconds. The inserters were tested at 3 different speeds: fast ($6 mms^{-1} \pm 1$), medium ($3 mms^{-1} \pm 0.5$), and slow ($0.4 mms^{-1} \pm 0.1$). Exact speeds could not be calculated using force data so estimates were used.

For surgery, a glass inserter was used by hand and lowered into the brain. Using tweezers the glass tube was inserted as fast as was accurately possible and then removed to leave the electrode behind. The area was treated with standard surgical protocol, and the inserter left into the dental acrylic construction.

Results:

After creating several designs and simple prototypes, a plastic block was created to align the needles and hold them in place as shown in Figure 3. In total 20 electrodes were rolled using the plastic block, and 3 were rolled by hand. On average, rolling electrodes by hand took an hour, whereas rolling the electrodes using the plastic block took 20 minutes. According to the table in Figure 4, only 3 of 20 electrodes were rolled correctly, and 11 of 20 were spiraled.

For batch #3 the rolling method was improved upon by wrapping a small metal wire around the larger needle to keep it from bowing out at the ends. During batch #3 the average time taken to roll an electrode was reduced to 15 minutes, although the success rate did not change. Clamping down the large needle created completely rolled electrodes and it also increased the probability of breaking off the tips, or spiraling the electrode.

	Rolled Correctly	Spiraled	Broken	Incompletely Rolled
Hand rolled (3)	0	3	0	0
Batch #1 (3)	1	2	0	0
Batch #2 (6)	1	1	0	4
Batch #3 (7)	1	5	1	0
Total	3	11	1	4

Figure 4: electrode rolling results.

The force testing was carried out using the same sample of agar gel and the same person to ensure that all data collected would be consistent. The average maximum peaks, averages and standard deviations of maximum peaks were calculated for each set of 10 trials. The data from all four force tests are displayed in Figure 5. It appears that the adhesion forces between wet glass and the electrode and wet steel and the electrode are similar as seen with the average maximum peak values of 0.158mN and 0.159mN respectively. Also the forces between the polyimide electrode and the agar generated the largest peaks on average with 0.219mN with a standard deviation of 0.0654. When surgery was performed on a rat cortex, the electrode remained in the brain while the wet glass inserter was pulled away due to a great affinity for the brain over wet glass.

The data collected from the forces between water and the electrode were the most variable with the smallest magnitude. The average maximum peak height, being the peak before the sudden rise and plateau was 0.0433mN, which is roughly one quarter the magnitude of the force between the electrode and wet steel or glass. The cubic-like shape of the graph and positive values are due to the tendency of water to stick to the electrode, and then slide back onto the scale as the electrode is being lifted. Once the electrode broke free from the water, the last rise and plateau are formed as the rest of the mass of the water is returned to the original dish.

In the production of the inserter, the glass capillary tube and stainless steel needle halves were used and tested. The two steel halves were tested in a mock surgery using agar gel and a micromanipulator, and even though the needle size more closely fit the size of the electrode the halves would frequently collapse in on each other. Also due to the tendency of stainless steel to resist adhesives a more user friendly method using stainless steel was not considered. Instead the glass inserter was tested in agar gel and used to implant the electrode into a rat cortex as shown in Figure 5. The rat bled minimally, and the electrode was delivered with minimal visual damage.

The forces the stainless steel and glass capillary tube exert on the brain are very similar, as show in Figure 6. When the capillary tube was first inserted into the agar, an initial peak occurred, and then gradually subsided due to the viscoelastic behavior of agar gel. The first part of the peak shows consistent slopes for all trials, meaning the speed of insertion was generally uniform throughout the tests. However the peak height differs throughout the tests when the speed of insertion is changed. The average peak height for a fast trial was 7.37mN and for a medium trial it was 10.5mN for glass capillary tubes. Comparing the average max peak at medium speeds with stainless steel, 4.13mN, and glass capillary tubes, 9.60mN, the forces appear to be different due to the different surface area involved with each. However, calculating the average force of the stainless steel with the same surface area of the glass capillary tube produces a more comparable average peak size 7.63mN to the glass capillary tube force of 9.60nM.

Discussion and Conclusion:

Overall, the goal of the study was to find an efficient rolling mechanism, and develop an inserter to deliver the polyimide electrode. The final design of the inserter was validated by conducting force

tests to measure the optimal speed of insertion, and the forces in play between the polyimide electrode and the materials in its surrounding environment.

Due to the 15% success rate of the electrode, it is evident that rolling the electrode by hand or with a stand does not greatly improve efficiency. The possibility of a learning curve was considered, although success rates did not improve throughout the course of rolling the electrodes. The main reason the electrodes did not roll in a cylinder and instead rolled into a spiral was because of the horizontal motion of the small needle while rolling, and the movement involved in removing the needles from the stand. To eliminate this problem, the large needle should be eliminated, and instead a stainless steel block should be used with a hole with the same diameter as the inner diameter of the large needle. A slit would also be cut in the block to allow the electrode to slip through. With this system the small needle and electrode can be inserted into the steel block, rolled, and then cured with minimal handling.

In batch #3, clamping the large needles with a wire helped stabilize the system during rolling, although there was not an increase in the amount of successfully rolled electrodes. The spiraled electrodes could be fixed by forcing the spiral into a cylinder shape and curing the electrode again.

The force testing between the electrode and wet glass and agar gel verified offered a possible explanation for the successful implantation during the surgery. The electrode had a higher tendency of sticking to the agar gel than to the glass tube. However the graphs clearly indicate that the agar gel, and therefore the brain, is a viscoelastic material and movement within the tissue is prolonged after any applied force. Because of extra force readings on the graph the velocity of the insertion can't be directly calculated, although the basic trend is that as the velocity of insertion is increased the force decreases. The agar gel model does not account for blood vessels and the heterogeneous nature of the brain, even though the agar gel mimics brain tissue. Calculating the forces and the speed of insertion depends on whether large blood vessels can be avoided. Therefore, the damage caused by the inserters could not be measured in the agar gel model.

The results for the forces of insertion for stainless steel and glass show that any rigid material would exert the same forces on the brain. The brain tissue is much softer so glass and steel comparatively have the same hardness. From the standard deviation, 7.63mN and 9.60nM as calculated are similar enough by comparison to conclude that stainless steel and glass capillary tubes have the potential to produce the same magnitude of forces on the brain. Stainless steel is shown to exert less force per area than the glass capillary tube because the inner diameter of the test subject was not taken into account. Stainless steel needles have much thinner rims than the glass capillary tube. Stainless steel could be used as an insertion technique in the future depending on the resources available to manufacture a stainless steel device on such small scales. Using a glass capillary tube entailed the simplest construction process compared to steel, and a more advanced design for a glass inserter is show in Figure 6 with the connector included.

In conclusion, the force tests and electrode rolling methods were developed to construct polyimide electrodes and insert them into the brain. Although the electrode roller did not have a high

enough success rate, the current model will lay the ground work for a successful model in the future. With the data collected on adhesion forces, new electrode inserters can also be easily made and used to deliver a flexible polyimide electrode efficiently.

Figure captions:

Figure 1: An example of a rolled electrode rolled 2 and a half times with an inner diameter of 300um.

Figure 2: Experimental setup for measuring forces. The sample is attached to the micromanipulator and peeled away from the test substance on the weighing dish.

Figure 3: Final electrode rolling design. Each needle as well as the electrode shaft is about 1 cm long.

Figure 5: Graphs of the forces between the electrode and different substances. The average of the data points is displayed in red while individual trials are displayed in black.

a) Forces between wet stainless steel and electrode. The average peak, maximum peak, and minimum peak are -0.16mN, -0.25mN, and -0.074mN respectively. The standard deviation of the data is 0.057mN with 9 trials taken.

b) Forces between wet glass and electrode. The average peak, maximum peak, and minimum peak are -0.16mN, -0.34mN, and -0.053mN respectively. The standard deviation of the data is 0.076mN with 10 trials taken.

c) Forces between 0.05% agar gel and electrode. The average peak, maximum peak, and minimum peak are -0.22mN, -0.30mN, and -0.13mN respectively. The standard deviation of the data is 0.065mN with 10 trials taken.

d) Forces between water and electrode. The average peak, maximum peak, and minimum peak are -0.045mN, 0.053mN, and 0.034mN respectively. The standard deviation of the data is 0.006mN with 10 trials taken.

Figure 6: The inserter design that was used for surgery.

Figure 7: a) The average force of insertion for a 23 gauge stainless steel needle at medium speeds (3 $mms^{-1} \pm 0.5$). The maximum peak was 5.26mN, the minimum peak was 3.22mN and the average peak was 4.13nM. The standard deviation was 0.556mN for the data set of 10 trials. Measurements were taken in 0.2 second increments due to the limitation of the digital scale.

b) The average force of insertion for a glass capillary tube with a 1.2mm diameter at medium speeds (3 $mms^{-1} \pm 0.5$). The maximum peak was 11.7mN, the minimum peak was 7.71mN and the average peak was 10.5nM. The standard deviation was 1.40mN for the data set of 10 trials.

c) The average force of insertion for a glass capillary tube at fast speeds ($6mms^{-1} \pm 1$). The maximum peak was 8.62mN, the minimum peak was 6.07mN and the average peak was 7.37nM. The standard deviation was 0.969mN for the data set of 5 trials.

d) The force of insertion for a glass capillary tube at slow speeds (0.4 $mms^{-1} \pm 0.1$). The maximum peak was 23.6mN, the minimum peak was 8.62mN and the average peak was 14.8nM. The standard deviation was 5.80mN for the data set of 4 trials.

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