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Penetration force measurements in the central nervous system with silicon electrodes

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ABSTRACT

PENETRATION FORCE MEASUREMENTS IN THE CENTRAL NERVOUS SYSTEM WITH SILICON ELECTRODES

by
Ashwini Arun Nikam

One of the major challenges in neural engineering is the tissue damage that occurs during insertion of microelectrodes into the central nervous system. The damage occurs as a result of the dimpling effect that is due to the insertion force. A method which can reduce the penetration force can also reduce dimpling and the resulting tissue damage.

There are two objectives in this thesis. One is to measure the penetration force with Michigan electrodes, which are silicon based electrodes. The second is to reduce the penetration force by using mechanical vibrations.

First, the penetration force was measured in the rat brain. To measure the penetration force, the microelectrode was connected to a load transducer. Because dura is a tough membrane to penetrate, it is usually removed during surgery in experimental animals. The dura mater was not removed in these experiments in order to keep the intactness of the cortex. The microelectrode was pulsed at a rate of 5 Hz using a piezoelectric crystal and a pulse generator.

The results show that the vibration technique is successful in reducing the penetration force by 25%. In this study, we have concentrated only on reducing the penetration force in order to reduce dimpling. To our best knowledge no work has been yet reported on the use of vibrations for reducing electrode penetration force. Chronic experiments will have to be conducted to investigate if the vibrations alone cause any tissue damage.

PENETRATION FORCE MEASUREMENTS IN THE CENTRAL NERVOUS SYSTEM WITH SILICON ELECTRODES

by
Ashwini Arun Nikam

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PENETRATION FORCE MEASUREMENTS IN THE CENTRAL NERVOUS SYSTEM WITH SILICON ELECTRODES

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In the name of Sai, Most Gracious, Most Merciful

"Have faith and patience. Then I will be always with you wherever you are."
(Sai Baba's sayings)

To my parents, to my sister Prachi and to my brother Rhushikesh

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CHAPTER 1

INTRODUCTION

1.1 Objectives

The objective of this work is to measure the penetration force with Michigan microelectrodes and Utah 2D arrays on the rat brain. For large penetration forces, there is a corresponding rise in the dimpling effect that ultimately results in tissue damage [12]. To avoid this tissue damage, it is critical that the penetration force of the microelectrode be reduced. This constitutes the second objective of the thesis.

1.2 The Need for This Study

In the field of neural engineering, silicon electrodes have found many applications in experimental animals. Their ability to simultaneously record activity from many individual cells has been one of the best tools to understand how brain processes information to sense and control body functions [3]. Microelectrodes are primarily inserted into neural tissue for the purpose of stimulating and recording. The insertion of microelectrode into brain causes tissue damage. Leading hypotheses for the failure to record neural activity are encapsulation and loss of neurons due to insertion trauma and device presence [18]. Evidence also suggests that altered microenvironment at the interface may trigger neural death [18]. The insertion leads to tearing, cutting, stretching, compression of tissues as well as fluid displacement, vessel rupture, vessel dragging [31] Also, intracerebral bleeding and edema are some of the complications observed while inserting microelectrodes into the brain [8].

Dimpling of a brain surface is defined as the distance traveled by the microelectrode from the first contact to the point of penetration observed in the force - time graph [3]. Penetration force is defined as the first peak value observed in a force - time graph plotted using the data collected during the insertion process. Several studies have also focused on measurement of insertion force, brain tissue deformation and applied force to the cerebral probes as a result of insertion [17]. They have implemented different approaches towards reduction of insertion force on the pia mater. No other group has attempted to measure insertion force with the dura mater. Dura mater was always removed during experiment as it is tough to penetrate. But, removing dura makes the cortex vulnerable for mechanical damage. Also, some of the groups attempted to measure insertion force of microelectrode on extracted brain tissue. The brain starts changing its mechanical properties after it is explanted from the host, which can give inaccurate force measurement. To avoid this, insertion force is measured on a live animal in this thesis. It is also observed that the rise in dimpling is proportional to insertion force and hence tissue damage occurs [31]. In order to reduce tissue damage and penetration force, the method of mechanical vibration is tested in the experiments of this study.

There are four major chapters in this thesis. First chapter discusses the objectives of this work whereas the second chapter is about previous work done and their results. Third chapter describes the methods implemented and the experimental setup, developed in the thesis. Fourth chapter discusses the results collected using these methods and comparison of results with literature.

The future work will include the study of chronic effects of using mechanical vibrations during electrode insertion. Also, similar measurements should be repeated for other parts of the nervous system such as the spinal cord and other areas of the brain.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Microelectrodes are used for recording and stimulation application in neural engineering. It would be logical to state that sharpness of microelectrode tip is inversely proportional to penetration force required to insert the microelectrode into the tissue [31]. Thus, lesser penetration force would be required for a microelectrode having a sharp end to penetrate into the tissue. The latest research has measured insertion force and dimpling while inserting microelectrode into the nervous tissue [31]. The results so obtained have been very useful for researchers and has helped immensely to calculate microelectrode insertion force into the nervous tissue for experimental purposes. Without knowing microelectrode insertion force, if a researcher attempts to penetrate a microelectrode into the nervous tissue, then there is a major risk involved. The application of a higher insertion force than required, could lead to tissue damage. To avoid such complications, many researchers have performed experiments on rats to calculate insertion force and dimpling effect. It has also been observed that even with small amount of insertion force the tissue damage is still present and cannot be neglected [30]. Thus, the need to invent method to reduce insertion force and dimpling effect was taken into consideration. Some groups came forth with a theory of reducing penetration force by cleaning electrode tip properly and fabricating microelectrode with sharper edges, but these experiments were performed with the pia mater intact. The dura mater was surgically removed before all insertions.

Several groups attempted different methods and experimental designs to measure insertion force of different microelectrodes. One group used a vibratory actuator in kHz range to reduce the insertion force on explanted brain tissue [4]. Their results concluded that insertion force reduced by 70% with the application of vibratory actuator. Another group experimented on measuring insertion force on a live animal brain with different types of microelectrodes. This group did not test the effect of vibrations. Their results were used to measure mean insertion force, maximal compression force, minimal compression force, maximal tension force measured during the retraction phase. They compared force observed using other microelectrodes with a force measured with tungsten microelectrode.

In the thesis, it would be worthwhile to study membranes surrounding the brain so as to know their anatomical structure, density, hardness and other such parameters.

2.2 Brain Membranes

The brain and spinal cord are surrounded by three membranes in order to protect them from direct shocks and injuries. They are called as brain meninges. These three meninges are dura mater (outermost), arachnoid mater and pia mater (innermost and adherent to the brain).

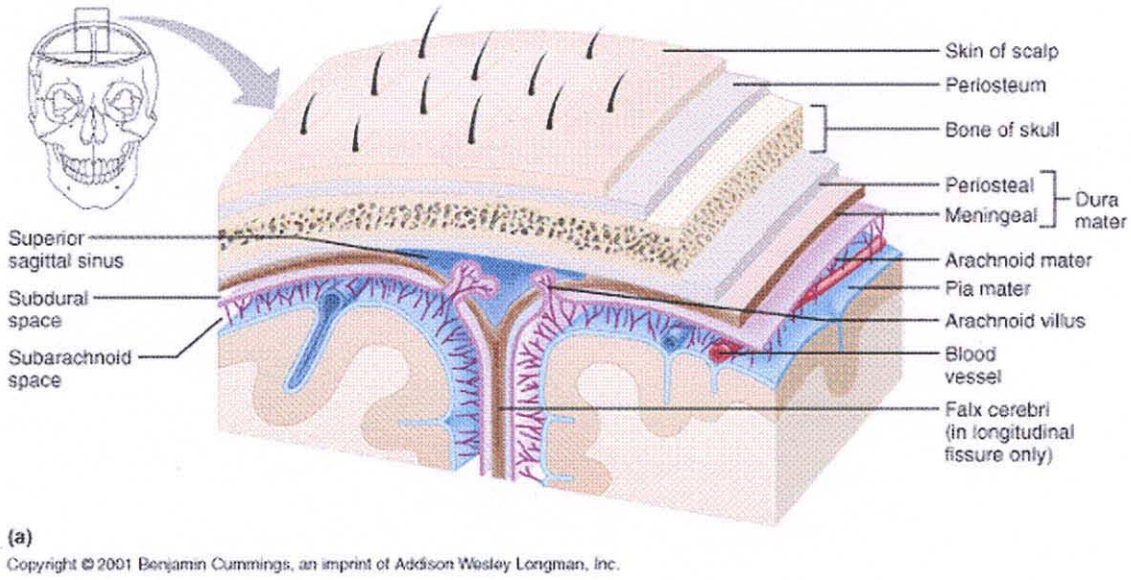

Figure 2.1 Meninges of the CNS [15].

2.2.1 Dura Mater

Dura mater is also called as meninx fibrosa or pachymeninx, and is toughest amongst the three brain meninges. This membrane is farthest from the brain cerebral cortex and spinal cord and closest to brain skull bone. Dura mater surrounds the brain and spinal cord. Being thick and tough, it not only provides protection to the brain but also supports large venous channels carrying blood from brain towards heart. Larger blood vessels present in the dura mater split into capillaries when they reach pia mater. Dura mater is composed of dense fibrous tissue. Its inner surface is covered by flattened cells which are similar to those present on the surfaces of pia mater and arachnoid. The space between dura mater and arachnoid mater is called as subdural cavity.

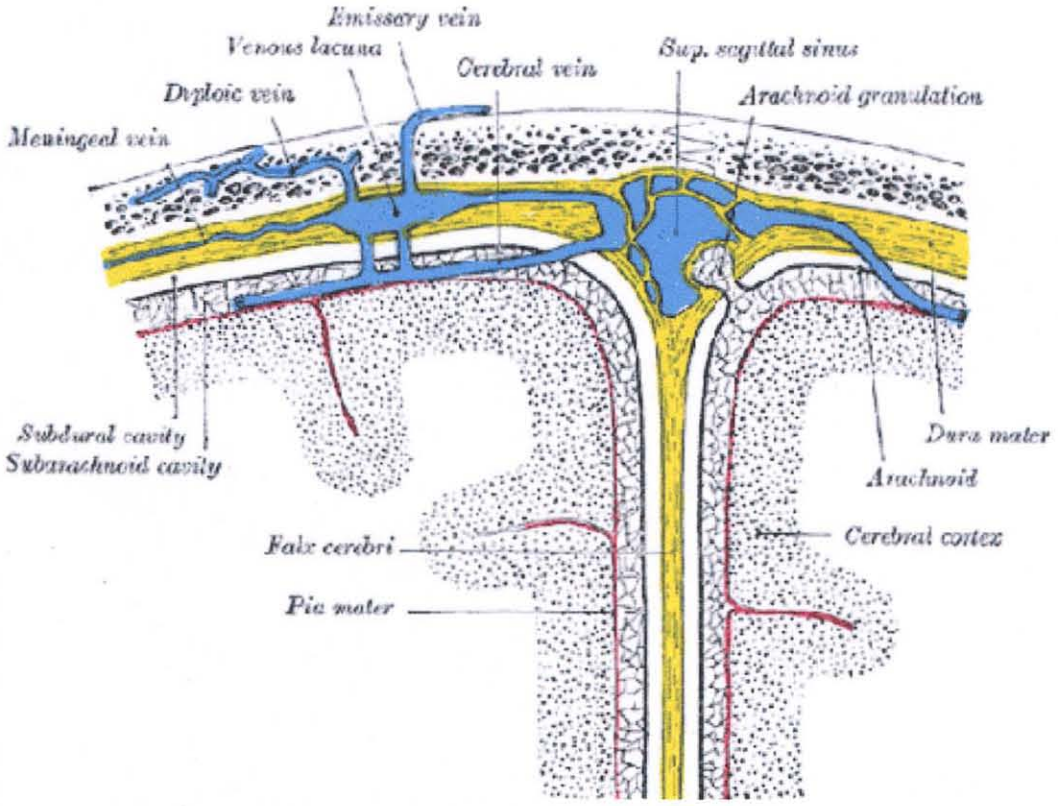

Figure 2.2 Detailed diagram of brain meninges [10].

2.2.2 Arachnoid Mater

Arachnoid mater is the middlemost layer amongst brain meninges which lies between dura mater and pia mater. Arachnoid mater is so named because of the web like composition of fibrous tissue present in it. Similar to subdural space, there is a space between arachnoid mater and pia mater known as subarachnoid space. This is the most protective membrane for brain and spinal cord as it acts like a cushion for them and absorbs mechanical shocks. It is covered by flat cells and it is impermeable to fluid. Arachnoid and pia mater are sometimes together called leptomeninges, which basically means thin as both of them and thinner as compared to dura mater. The subarachnoid space contains cerebrospinal fluid (CSF) which is produced in brain by modified

ependymal cells in the choroid plexus. About 500ml of CSF is produced in the brain everyday and about 150ml is present in subarachnoid space, excess is drained into the circulating blood. The cerebrospinal fluid acts as a greasing agent between the meninges and also provides distribution on neuro-endocrine factors which are responsible for releasing hormones into circulating blood in response to a neural stimulus.

2.2.3 Pia Mater

Pia mater is the innermost layer amongst brain meninges. Also it is the most delicate brain meninx. It is closely adhered to the brain and spinal cord. It is a very thin membrane composed of fibrous tissue covered on its outer surface by a sheet of flat cells thought to be impermeable to fluid. Pia mater contains blood vessels and blood capillaries which constantly provide nourishment to the brain. Pia mater follows gyri and sulci of the brain structures. But in a rat's brain there are no gyri and sulci. Detailed structure of brain is explained in Figure 2.3

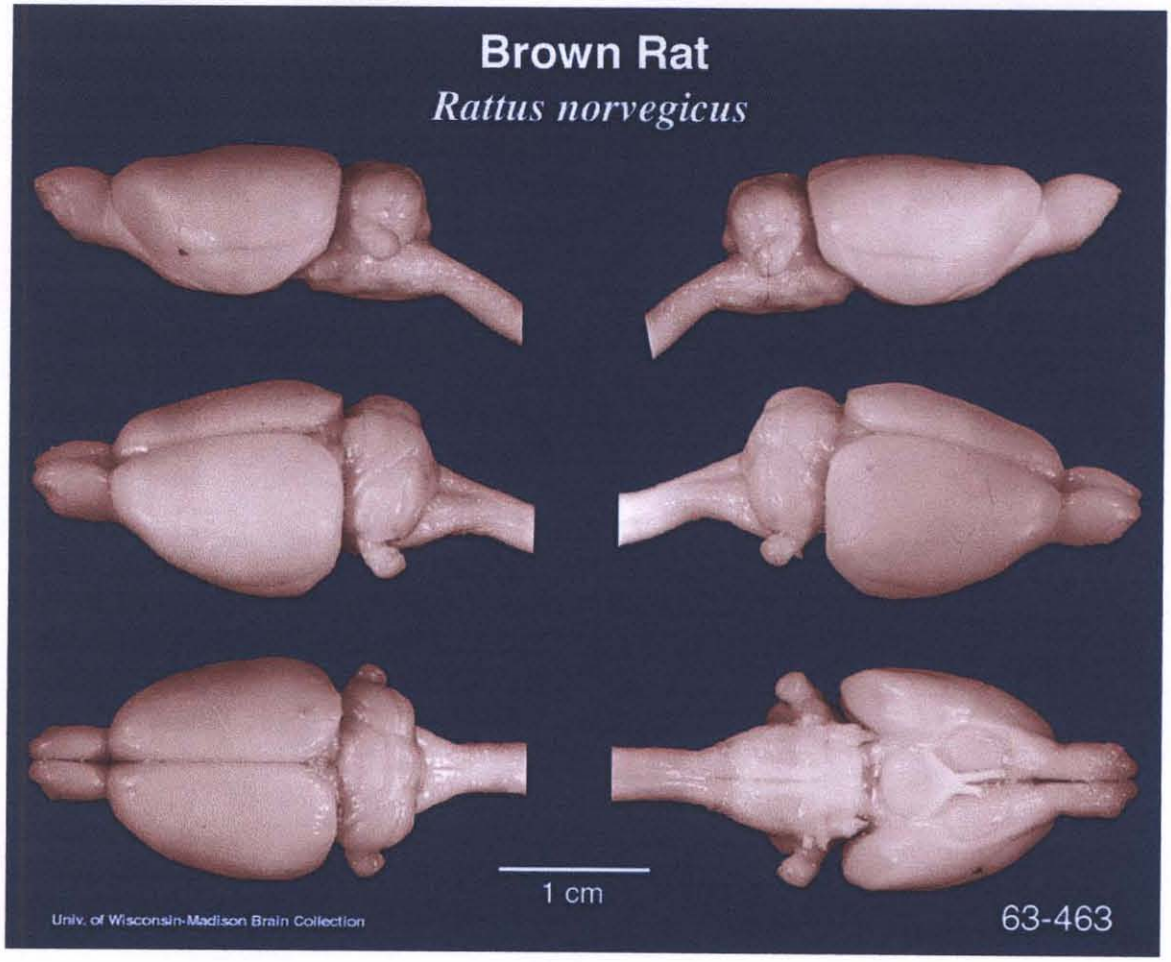

Figure 2.3 Images of rat brain [23].

2.3 Relevant Research

A usual method of measuring insertion force is to insert the microelectrode on an anaesthetized rat brain with manually controlled micromanipulator or with a motor driven micromanipulator. Different methods have been implemented to reduce the insertion force. Various kinds of electrodes are used; insertion force is measured with different opening angle and different shaft material [2]. From one study it can be seen that the insertion force changes with different types of electrodes. Table 2.1 shows the electrodes used to measure the insertion force.

Table 2.1 Data on the microelectrodes included in the study.*Tungsten Rod: A-M Systems, INC,**VSAMUEL, ACREO A/S Sweden, ***Caltech Microprobe. The Opening angle for T10 and T3 are estimated from pictures taken through microscope [2].

Electrode ID	Opening Angle	Material	Coating	Provider	Shaft size	Cross Sectional Area	Shaft Shape	Number of insertions
T10	10°	Tungsten	None	Tungsten rod**	Ø = 50 µm	1962 µm²	Round	20
T3	3°	Tungsten	None	Tungsten rod	Ø = 50 µm	1962 µm²	Round	34
A4	4°	Silicon	Silicon Nitride	VSAMUEL**	20 x 38 µm	950 µm²	Square	10
C12	12°	Silicon	Silicon Nitride	Caltech***	25 x 30 µm	750 µm²	Square	34
C8	8°	Silicon	Silicon Nitride	Caltech	25 x 30 µm	750 µm²	Square	4
C4	4°	Silicon	Silicon Nitride	Caltech	25 x 30µm	750 µm²	Square	64

A craniotomy was performed on a rat brain. A common set up was used for all experiments to measure the insertion force. The microelectrode was inserted at a speed of 2mm/s and penetration depth was kept at 2mm.

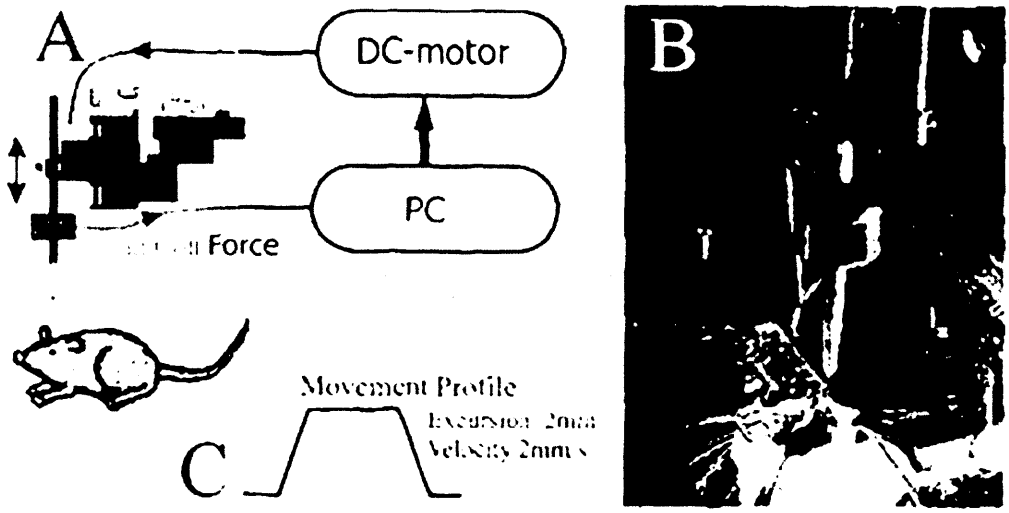

Figure 2.4 Experimental setup
A) Schematic drawing of the setup including the rat, a motor controlled micromanipulation and a PC, B) A picture of the experimental setup, and C) the movement profile used to advance and retract the microelectrodes into the cerebral cortex [2].

The measured insertion forces are as shown in Figure 2.5. A graph of measured force (mm) against time(s) is plotted. First peak was called penetration force. The black scale represents measurement of first microelectrode insertion and gray scale corresponds to second insertion reading into the brain. It can also be observed from the graph that force increases continuously until it reaches a maximum force point A which is the penetration force. The insertion force reduces abruptly as soon as the microelectrode penetrates into the brain. The maximal compression force measured during the first insertion was 0.87+/-0.14 mN. Although insertion force reduced rapidly after the termination of microelectrode movement in the brain, it never reached null point during the experiment. The insertion force attained a constant level after the movement of microelectrode was stopped.

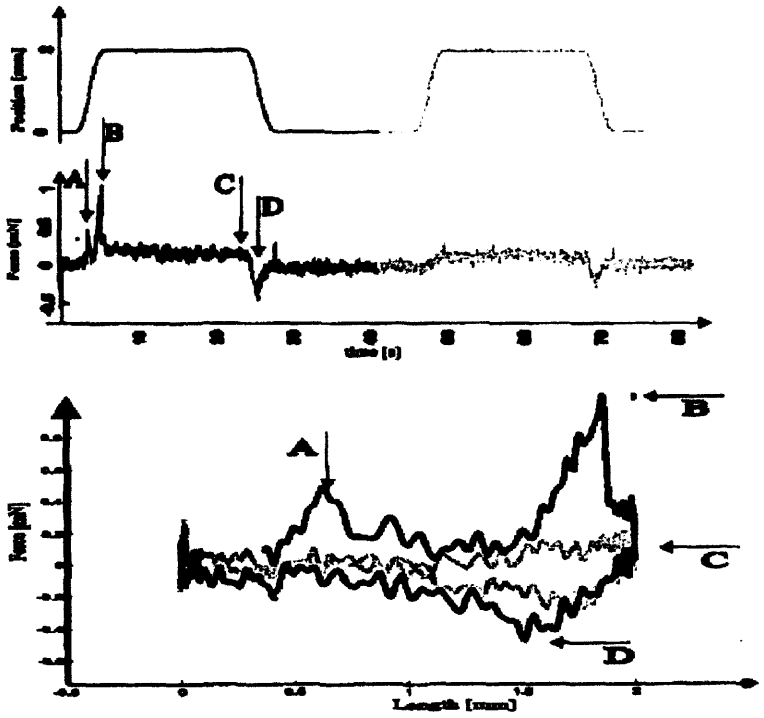

Figure 2.5 Top panel depicts the force and length measured during the insertion of a single tine VSAMUEL microelectrode (black trace-1st insertion; gray trace-2nd insertion).The bottom trace shows the stress/strain curves. A: Force at the point of penetration; B: Maximum compression force measured at any point during insertion; C: Minimal compression force measured while the needle was fully advanced (2mm); D: Maximal tension force measured during the retraction phase [2].

The electrode was inserted twice on the same position in order to measure penetration force of electrode during second insertion. The insertion force observed on first insertion was 0.62 ± 0.23mN and on second insertion was 0.15 ± 0.03mN.

In a study on measurement of insertion force and a use of chemical on pia mater to reduce the insertion force showed significant results [16]. Intracortical electrodes were used in order to puncture the pia mater. But, these electrodes can cause more dimpling and trauma [16]. Thus, interest was in the development of more flexible substrates in order to reduce the micromotion after implantation. But, such devices have difficulty penetrating the pia without buckling.

In paper [18], a technique for reducing the mechanical integrity of the pia's collagen network by treatment with collagenase is evaluated experimentally. Dura and pia mater are the main structural barriers for intracortical microelectrode insertion. Dura is thick and tough to penetrate, so it is surgically retracted from the brain to expose pia mater. Sprague-Dawley male rats were used for the acute experiment. The rats were anaesthetized with ketamine/xylazine/acetonin (50:5:1mg/kg) [18]. Simultaneous pulse rate and blood saturation is measured. The rats were placed in a stereotaxic frame and the cranial plates were exposed. Two craniotomies were performed on the rat for 2-4 mm holes on anterior and posterior of bregma. One site from anterior and one from posterior was selected for collagenase treatment. Twenty mg/ml collagenase mixture contains 0.36 mN $CaCl_2$ in 50 mM hepes buffer with equal amount of ky jelly [18]. The dura was pierced with 27g hypodermic needle and opened with micro-scissors to make more space for electrode array to penetrate. The electrodes were made from 50 μm tungsten microwire insulated with polyamide arranged in 2 X 4 array. The force was measured by a load cell attached to the electrode with the help of in-line amplifier. The whole system was calibrated to measure the change in force with respect to change in voltage.

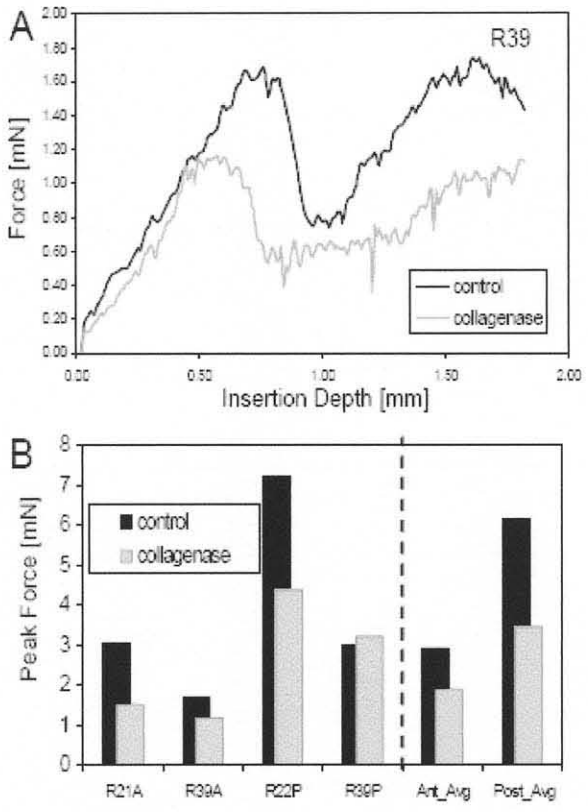

Figure 2.6 Representative force-distance curve for 2*4 array insertions in an acute animal. B: summary of peak insertion forces for acute experiments. "A" and "P" indicate anterior and posterior sites, respectively. Right of vertical dashed line is the averages for all anterior and posterior sites in the study [18].

From the Figure 2.6 it can be observed that the collagenase-treated sites have reduced penetration forces by 30 % on average. A brain phantom was constructed to measure the insertion force by the other group. Four different types of electrodes were used to measure penetration force for the brain cortex [17]. They have conducted many experiments to measure penetration force *in vivo* and *in vitro* conditions. To measure force *in vitro* the brain phantom was used. It was made up of agar gel with concentration of 0.6 % in DI water. It has an elastic modulus of 10Kpa which is compatible with the mechanical properties of white and grey matter of human brain. To model pia and dura mater 20 μm thick polyethylene foil with an elastic modulus of 100MPa was used, which

is analogous to the pia and dura mater of human brain. The two set ups were used to conduct the *in vivo* and *in vitro* experiments. The motor driven micromanipulator was used for brain phantom and *in vitro* tests. A piezoresistive force sensor was attached to the clamp of manipulator. A manually operated micromanipulator was used for the *in vivo* experiments. A force sensor with high sensitivity was used to measure the force as lower insertion forces were expected in this experiment. The picture of set up was as shown in Figure 2.7.

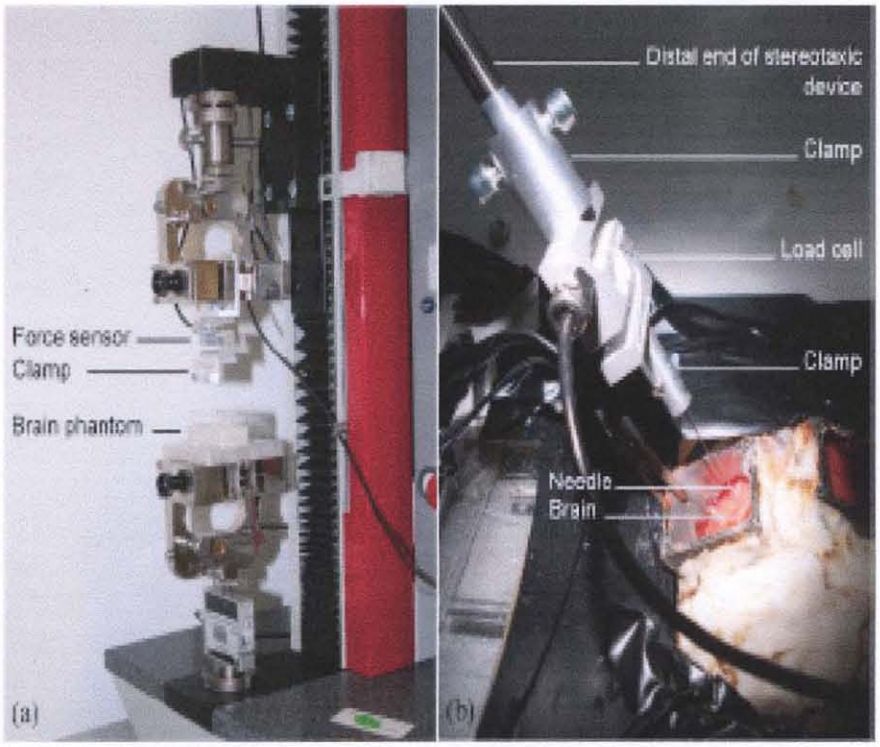

Figure 2.7 Test setup for insertion experiments (a) used for brain phantom and in vitro measurements (b) used for in vivo tests [17].

The four electrodes which used for this experiment were cerebral probes, silicon and glass probes, tungsten wire probes and polyimide probes. The shaft shapes of these electrodes were different from each other. Silicon probe had a rectangular shape, glass probe had triangular shape, tungsten wire was round shaped, and polyimide probes were

rectangular in shape. In Table 2.2 the thickness, width, length and tip angle for these electrodes are given. The set up was tested on brain phantom, *in vivo* and *in vitro*.

Table 2.2 Geometrical properties of applied cerebral probes [17].

Material	Thickness [µm]	Width [µm]	Length [mm]	Tip angle
Silicon	100	120	4 and 8	17
Glass	175	500	4 and 9	49.3
Polyimide	10	460	2	66
Tungsten	135	-	optional	15-20

In vivo measurements were carried on anaesthetized Long Evans rats and unanesthetized monkey. In order to minimize the animal experiments only silicon probes were used for this experiment. Silicon probes were sharp enough to penetrate through pia and dura both. The penetration force of a rat dura was 41 ±25.5 mN. *In vitro* tests were carried on cow and lamb brain stored in saline for 1-3 days or stored in plastic box immediately. They also showed almost the same results. All these electrodes were tested on brain phantom. A linear increase was observed when the electrode touched brain phantom. The rupture of the polyethylene foil was considered as penetration. The results are given in the Table 2.3.

Table 2.3 Insertion and retraction forces of cerebral probes and corresponding tissue dimpling [17].

Probe	Insertion force [mN]	Retraction force [mN]	Dimpling [mm]
Silicon			
Phantom	~3=8	-13=3.5	0.5=0.08
In vitro (pia)	33.8=20.2	-12=2.7	5.5=2.14
In vitro (pia)	47.5=25	-1	-
In vitro (dura)	41=25.5	-5=2	pia
Glass			
Phantom	33.6=2.6	-7=1.16	0.83=1.33
Polyimide			
Phantom	0.33=0.05	-0.22=0.08	0.51=0.165
In vitro (pia)	no penetration	-	-
Wire			
Phantom	13.5=1.3	-7=4.7	0.45=0.13
In vitro (pia)	14=10.4	-12=5.3	3.9=1.32

Glass electrodes were tested only on the brain phantom. Silicon probe was tested on all the three. Tungsten wire took less force than silicon probe to penetrate into the brain pia mater (*in vitro*). Largest dimpling was observed with the glass probe on the brain phantom, and the lowest was observed with tungsten wire with brain phantom. Polyimide electrode did not penetrate through pia in the *in vitro* experiment. Another paper discussed the *in vivo* implant mechanics of the flexible, silicon-based ACREO microelectrode arrays recently developed by the VSAMUEL consortium [3]. The objective of the work was to measure penetration force with ACREO electrodes. The group compared cleaned and uncleaned off-shelf electrodes in order to examine the effect of surface energy. The silicon-based arrays were manufactured at ACREO Ab, Kista, Sweden. So they are referred as ACREO electrodes. These ACREO silicon electrodes have an opening angle of 4 degrees and 1-8 shafts. The shaft shape was rectangular and was coated with silicon nitride. The results of these electrodes are compared with single-

shaft tungsten electrodes with an opening angle of 3 and 10 degrees. It is usually observed that the penetration force (insertion force) and dimpling increases with larger cross-sectional area and opening angle. It is logical to mention that the use of sharper electrode tip would reduce the required insertion force.

In paper [3], a different concept is put forth that before the insertion if electrode is treated with silane or piranha (chemicals used to reduce/increase the hydrophobic properties), then the insertion force decreases significantly. The careful cleaning of the electrode has been an important factor in order to count for the biocompatibility of an implanted biosensor. After cleaning the electrode, a change was observed not only in the foreign body reaction but also in the compression force. Various membranes of brain have varying degrees of hydrophobicity and the arachnoid surface is usually impermeable to hydrophilic substances. By changing the electrode material properties like hydrophilic or hydrophobic, the electrode insertion force changes with the insertion mechanics. The eight types of electrodes were used for this experiment. three tungsten and five ACREO electrodes with different opening angle and electrode type, number of shafts, different distances between shafts, shaft size at the tip, shaft shape, coating which can be seen from the Table 2.4

Table2.4 Specifications on the microelectrodes included in the study [3].

Electrode ID	Electrode Provider	Electrode Type	Number of shafts	Distance Between shafts [µm]	Opening angle [°]	Shaft size at tip [µm]	Shaft size at base [µm]	Shaft Shape	Coating	Material	Num Insertions
K1.1.4	*ACREO***	K1	1	-	4	25 x 38	25 x 200	Rectangular	Silicon Nitride (SN)	Silicon	5
K1.2.4	*ACREO***	K1	2	500	4	25 x 38	25 x 200	Rectangular	SN	Silicon	9
K1.3.4	*ACREO***	K1	3	500	4	25 x 38	25 x 200	Rectangular	SN	Silicon	10
K1.4.4	*ACREO***	K1	4	500	4	25 x 38	25 x 200	Rectangular	SN	Silicon	9
E5.8.4	*ACREO***	E5	8	200	4	25 x 38	25 x 200	Rectangular	SN	Silicon	11
M4.4.4	*ACREO***	M4	4	600	4	25 x 38	25 x 200	Rectangular	SN	Silicon	8
T1.1.3	Tungsten*	T1	1	-	4	Ø = 50	Ø = 50	Round	None	Tungsten	20
T1.1.10	Tungsten*	T1	1	-	10	Ø = 50	Ø = 50	Round	None	Tungsten	5
F1.1.10	Tungsten*	F1	1	-	10	Ø = 150	Ø = 150	Round	None	Tungsten	11

To manufacture the tungsten electrodes, commercially available round tungsten rods were cut into appropriate lengths and manually electro sharpened. To create a tip, one end of the rod was lowered into a 2N aqueous solution of KNO_3 and an AC current was passed through the solution to electrolytically oxidize and etch the tips of the wire. The opening angle was measured and it was cleaned carefully before implantation. They used single shaft silicon electrode (ACREO) with the cross sectional area of 25 X 38 µm at the electrode site, and the area expanded to 25 X 200 µm at the shaft base and with an opening angle of 4 degrees. Now to test the effect of using cleaned electrode on implant mechanics, electrodes were cleaned with piranha solution and hydrogen peroxide or the probes were silanized by brief exposure to dimethylsilane vapors. These are the standard methods to clean silicon based materials as it removes both organic and metal residues. All the electrodes were rinsed in de-ionized water before implantation. The set up for this experiment was as shown in Figure 2.6. The surgical procedure is same for all experiments. The electrode was attached to load cell (10 gms) and the load cell to the micromanipulator. The micromanipulator was placed just above the brain surface. The

electrode was advanced into the pia surface using a motor controlled micromanipulator. The microelectrodes were always inserted according to a ramp and hold profile. The collected data were then low pass filtered at 25 Hz.

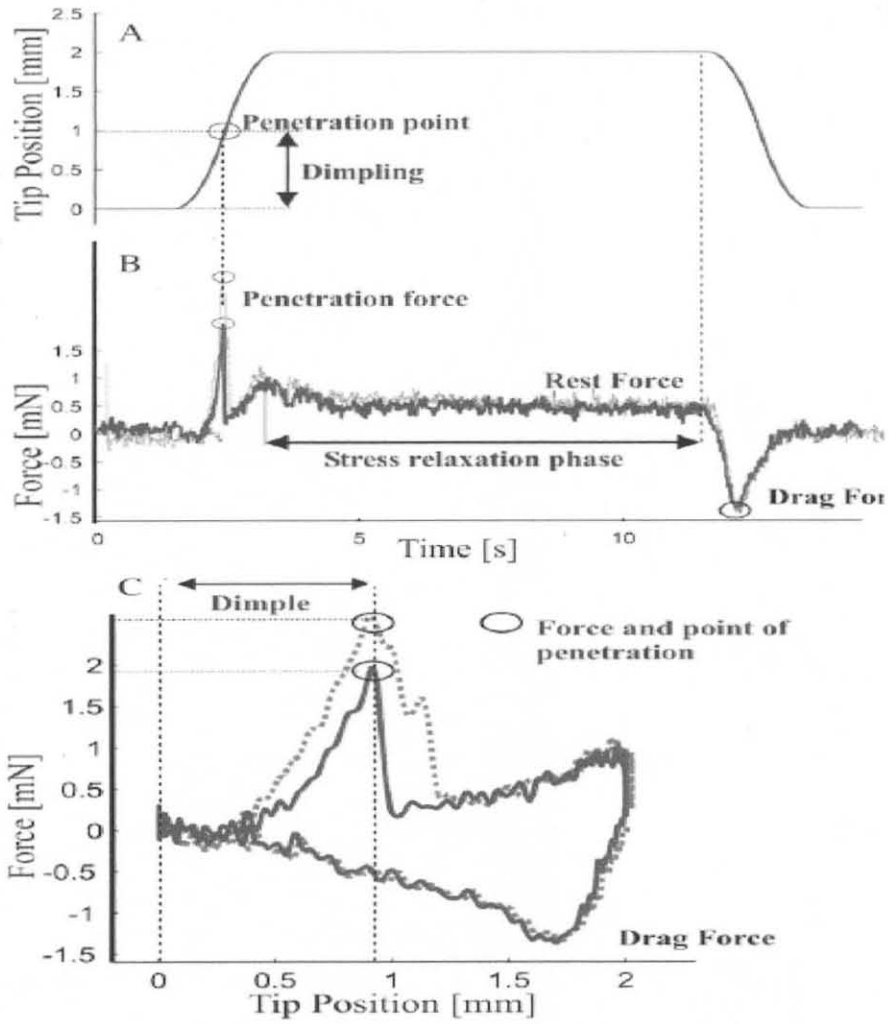

Figure 2.8 Typical Measurements taken during insertion of a single shaft silicon electrode into rat cerebral cortex. The dashed, light grey curves correspond to the first insertion-retraction phase, whereas the solid, dark grey curves represent the second insertion. (A) Position of the electrode while advancing it into the brain. At 0mm the electrode is at the surface of the brain and at 2mm the electrode is fully advanced into the brain.(B) force traces. The dura mater was removed prior to implantation, while the pia mater was left intact. The following points of the data were compared: penetration force, rest force, drag force and dimpling. (C) Length-force curves were plotted to better identify the penetration force, the penetration point, and the drag force [3].

This way the insertion force was measured and compared for both tungsten and ACREO electrodes. This group observed that the ACREO electrodes produced the smallest dimple and least penetration force. The highest penetration force among all the electrodes was observed with the 150μm diameter tungsten electrodes. Dimpling of the brain surface was defined as the distance traveled by the microelectrode from the beginning of the insertion to the point of penetration. The point of penetration was defined as the first peak in the force curve. A continuous increase was observed in the penetration force and dimpling until the force reached till the penetration force. These concepts are explained in detail in the Figure 2.8. As soon as the electrode touches the brain membrane there was a continuous increase in penetration force. The moment when electrode breaks and penetrates into the tissue, the insertion force starts decreasing. The force measured at this point was called as the penetration force. The results of the study are as shown in the Table2.5.

Table 2.5 Comparison of the measured penetration, maximum, rest, and drag forces and the dimple at the point of penetration for the different groups of electrodes studies. All data have been corrected for any force offset [3].

Electrode ID	1st insertion FORCE Mean ± std [mN]				2nd insertion FORCE mean ± std [mN]				1st insertion DIMPLE mean ± std [mm]	2nd insertion DIMPLE mean ± std [mm]
	Penetration	Max	Rest	Drag	Penetration	Max	Rest	Drag	At Penetration	At Penetration
K1.1.4	0.48±0.18	1.03±0.21	0.07±0.04	-0.49±0.06	0.10±0.04	0.29±0.02	0.07±0.02	-0.29±0.09	0.37±0.14	0.32±0.12
K1.2.4	0.86±0.36	1.08±0.19	0.22±0.05	-0.80±0.17	0.17±0.23	0.50±0.13	0.15±0.07	-0.59±0.13	0.40±0.13	0.46±0.18
K1.3.4	1.81±0.54	2.01±0.52	0.69±0.40	-1.30±0.32	0.53±0.46	1.16±0.62	0.51±0.42	-0.98±0.22	0.58±0.20	0.57±0.21
K1.4.4	0.83±0.37	1.82±0.44	0.60±0.26	-1.38±0.58	0.21±0.13	1.13±0.42	0.42±0.28	-1.15±0.49	0.37±0.14	0.33±0.12
E5.4.4	2.42±0.77	3.16±0.75	0.69±0.29	-2.06±0.58	0.23±0.15	0.96±0.34	0.48±0.31	-1.21±0.30	0.53±0.14	0.62±0.33
M4.4.4	2.04±0.77	3.79±1.23	1.42±0.51	-2.21±0.55	0.52±0.31	2.08±0.45	1.17±0.36	-1.87±0.56	0.54±0.18	0.64±0.23
T1.1.3	0.62±0.26	0.74±0.23	0.22±0.14	-0.56±0.20	0.16±0.12	0.44±0.20	0.15±0.11	-0.45±0.20	0.38±0.09	0.46±0.24
T1.1.10	0.85±0.33	0.99±0.31	0.28±0.07	-0.58±0.08	0.24±0.09	0.59±0.17	0.15±0.05	-0.46±0.19	0.58±0.20	0.56±0.25
F1.1.10	1.15±0.51	1.65±0.35	0.54±0.12	-0.89±0.11	0.10±0.05	0.66±0.18	0.28±0.10	-0.62±0.15	0.47±0.22	0.50±0.36
Mean std	**1.45±1.04**	**0.28±0.39**	**0.57±0.50**	**-1.15±0.70**	**0.28 ±0.39**	**0.91±0.61**	**0.40±0.43**	**-0.87±0.52**	**0.48 ±0.18**	**0.54±0.28**

The results show that the insertion force of the ACREO electrodes is less than the tungsten electrodes.

These groups have measured the penetration force with different electrodes and came up with the theory and results that the use of hydrophobic/hydrophilic chemicals before insertion reduces the penetration force. Also, use of collagenase acts to weaken the pia mater's internal network reduces the penetration force. These methods can reduce the penetration force when inserted on pia mater but they can not reduce it while the dura mater is not removed before the penetration. A method needs to be invented in order to reduce the penetration force without removing the dura mater, in order to keep the intactness of the brain. The methods are discussed in detail in chapter 3.

CHAPTER 3

METHODS

3.1 Microelectrode Description

3.1.1 Michigan Probe Electrodes

Michigan probe microelectrodes were used for measurements of the insertion force. The Probe is designed by university of Michigan and produced by NeuroNexus Technologies [11]. All probes are mounted and electrically connected to PC boards using ultrasonic bonding. Exposed connections were stabilized and insulated with silicone. The pins on the PC board mate directly to standard integrated circuit DIP sockets or Samtec connectors, permitting easy handling and connection. The probe is made of silicon substrate with silicon dioxide/nitride insulation. The electrode material is iridium. The probe dimensions are as follows: thickness -15 um;length -3mm, 5mm, 10mm; with an impedance 0.2-3 MOhm (connector -16ch: DIP, 32/64ch: Samtec MOLC-110-01-S-Q).

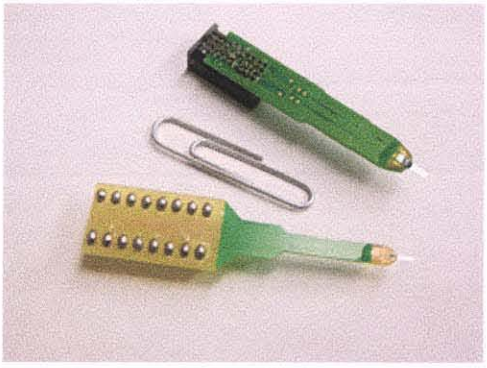

Figure 3.1 Michigan probe electrodes [11].

3.1.2 Utah Electrode 2D Array

The electrode arrays are known as "Utah array" as researchers at Utah University designed it and are made commercially available through Cyberkinetics Inc. [22]. Both the substrate and shank are made of silicon. Its diameter is 80μm at the base and the tip is

tapered, and thus it is a sharp electrode with platinum coating at the tip. Each electrode is electrically isolated from the neighboring electrodes with a moat of glass around the base. The shank length varies from 0.1 to 1.5 mm. The electrodes are 400μm spaced apart and project out of the plane of 0.2 mm thick silicon substrate. Each of the electrodes are connected to a very fine 0.06m long, 37 μm diameter, 20 % Ir-Pt wire is used as a reference wire. Lead wires are bonded to rear surface of the array and potted with silicon elastomer. The electrode used in the experiment was a 3 X 5 array, with only 10 of the shanks available.

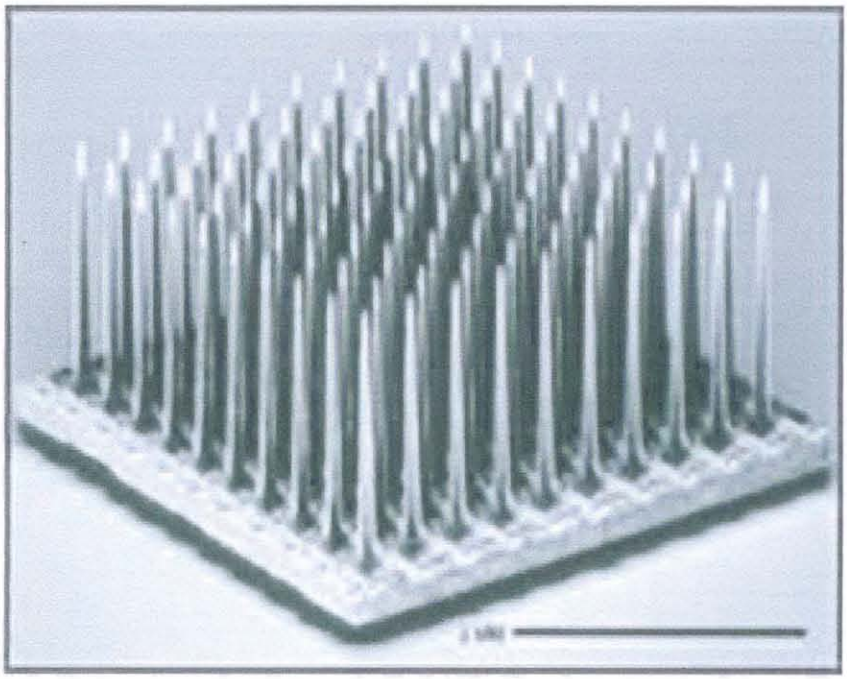

Figure 3.2 Microscopic picture of Utah 2D array [22].

3.2 Digital Eyepiece Camera

A digital camera shown in Figure 3.3 was used to observe and record microelectrode penetration into the brain on a computer. It was directly connected to the USB port of computer and fit in the eyepiece of microscope. The camera was easy to use and straight forward to install.

Figure 3.3 Digital eyepiece camera used in this experiment and referred as PC camera [12].

3.3 Force Transducer

This transducer (Grass technologies, Model FT03) is based on Wheatstone's bridge concept. Four strain gages are forming a bridge which measures the strain produced on a cantilever beam by force applied. The cantilever beam is sufficiently sensitive to measure the small forces observed in the project. The stability is also very high. Accuracy is ±1 %. The sensitivity of the sensor is 2.44mV/mN. The resolution is 1 parts in 25,000. Heavy integral clamping handle is made so as to bear large weights [13].

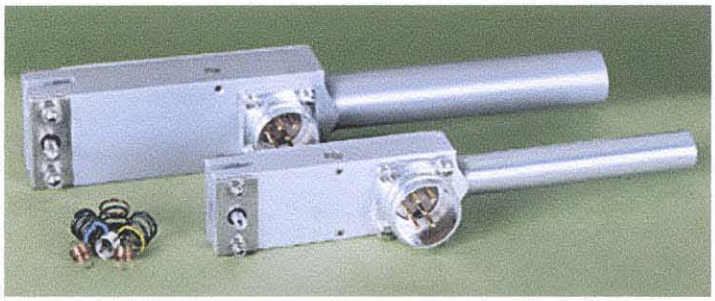

Figure 3.4 Force displacement transducer model FT 03 [13].

3.4 Piezoelectric Actuator

A piezoelectric actuator was used for these experiments. To generate mechanical vibration when applied a voltage pulse was applied, the actuator generated mechanical vibrations in the vertical direction. The piezoelectric actuator can be used for 0 Hz to 20 kHz range. It was pulsed at a rate of 5Hz and voltage of 150 V.

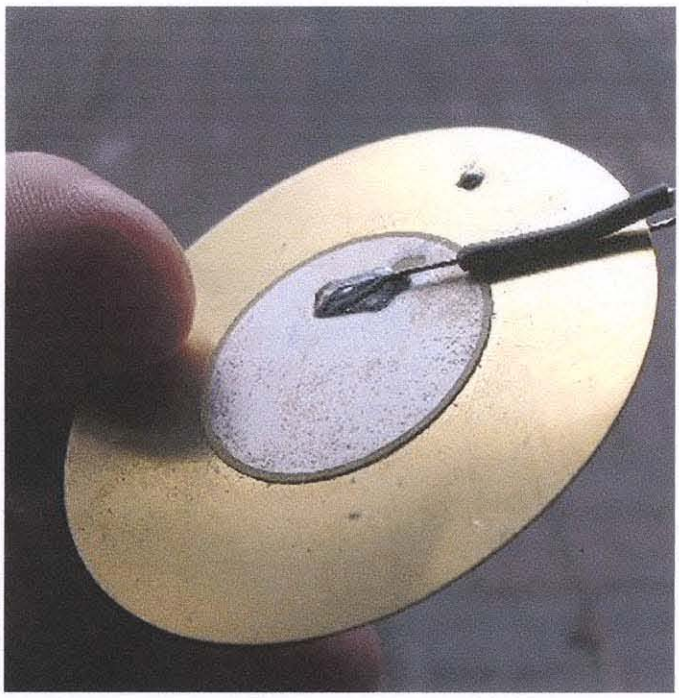

Figure 3.5 Piezoelectric actuator [14].

3.5 Micromanipulator

This micromanipulator is manufactured by World Precision Inc. The M325 three-axis fine-controlled manual micromanipulator has been built from precision micrometer actuated linear slides. Each slide is comprised of a micrometer head and a magnetic linear slide. The micromanipulator has been carefully designed to minimize wear in the moving components to achieve a long operational life without the necessity for frequent maintenance or adjustment.

Figure 3.6 Manual micromanipulator [38].

3.6 The Calibration Process

To calculate the penetration force the change in voltage was needed to measure. The transducer was connected to the computer with the data acquisition board. The transducer was calibrated with the weight of 2 gm. A 2 gm weight was hanged on the sensing end and change in voltage baseline was measured accordingly in LABVIEW

As, 1kg = > 9.8 N

$10g = 9.8 \times 10^{-2}$ N.....(Equation 1)

And after applying 10 g the voltage deflection was 0.024 V. Thus,

10 g = 0.024 V.

Putting equation (1) in the above expression, we get

$0.024\ V = 9.8^{*}\ 10^{-2}$ N

1 V = 408.3 mN

Sensitivity = 2.44mV/mN.

3.7 In Vitro Experimental Set Up

The set up shown in Figure 3.7was used earlier in this project. To measure the insertion force the microelectrode was placed at the piezoelectric crystal, whereas the piezoelectric crystal was connected to the micromanipulator. The piezoelectric crystal was connected to a stimulator to be operated at a certain frequency. The explanted brain tissue was placed on the load cell beam and the load cell was connected to the computer so as to check the changes in the force as the electrode was inserted into the brain tissue. The

insertion process was observed with a PC camera which was connected to the microscope and to the PC. The micromanipulator was operated manually.

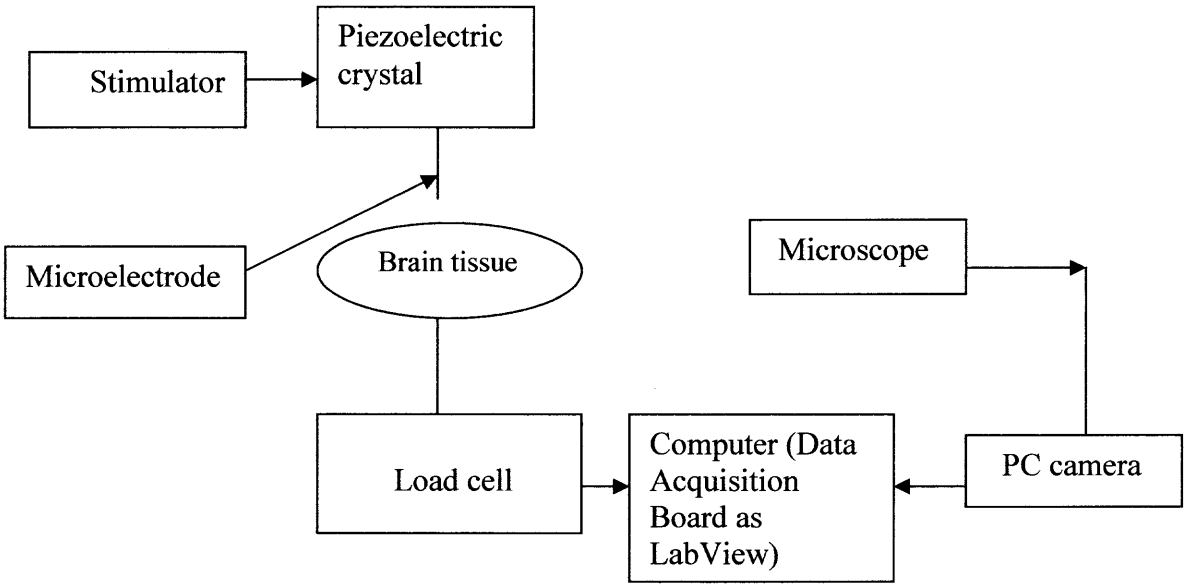

Figure 3.7 *In Vitro* experimental setup

The reason to change this set up was to measure the force on a live animal, and it wouldn't have been possible. The load cell beam was not strong enough to hold a 400gm rat. Also, the signal we were expecting was in 10 -20 gms so the weight of the live animal would have suppressed the signal. This set up would have worked if we used brain tissue. But as after removing the brain from the animal it starts changing its mechanical properties. The brain shows its actual mechanical properties when the blood vessels in the brain carry normal levels of blood pressure. After removing the brain from the body the blood vessels start collapsing and hence the mechanical properties of the brain are affected. The electrode was going through the brain membranes easily with no efforts. Taking out the brain with dura mater is challenging.

3.8 In Vivo Experimental Set Up

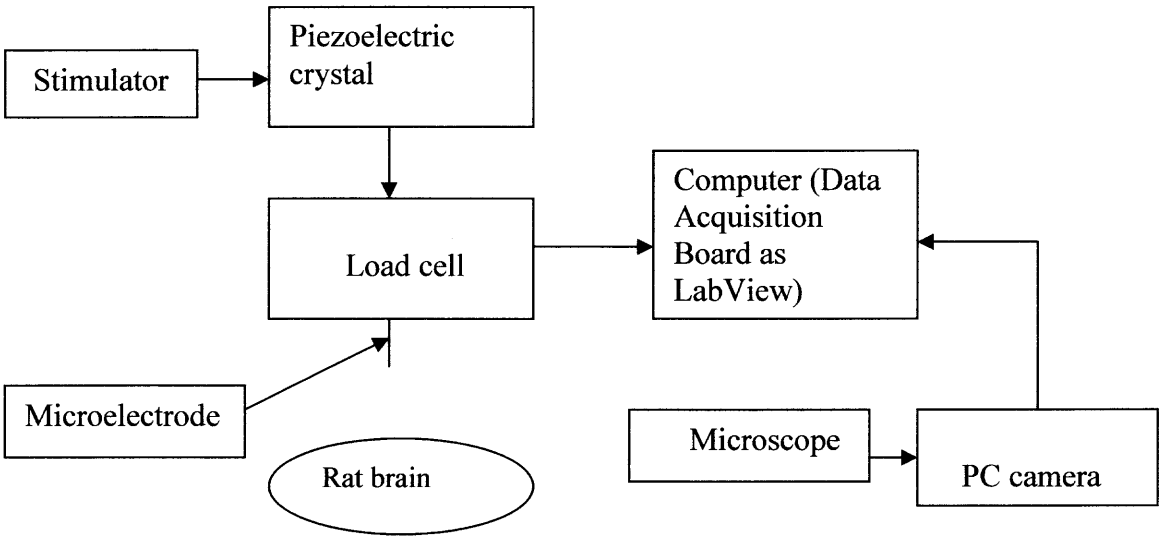

Figure 3.8 *In Vivo* experimental setup.

The set up shown in Figure 3.8 was the set up was decided to use to solve this problem. The fundamental difference is the use of live animal rather than explanted tissue. To measure the insertion force the microelectrode was mounted to the sensing beam of the load cell. At the top end of the sensing beam the piezoelectric crystal was glued with epoxy. The transducer was held by a micromanipulator that has a 3-axis movement capability. The piezoelectric crystal was driven by a pulse generator. The insertion process was observed with a PC camera which was mounted to the microscope. The micromanipulator was operated manually. Also, the electrode was attached at the load cell beam so the weight of the animal doesn't matter in the measurement of the insertion force. When the piezoelectric crystal was pulsed with a pulse generator before the whole set up with the table was unstable and produced a large amount of noise. To avoid this noise the assembly was mounted on a Plexiglas board firmly. The first trial was taken on

a fresh chicken nerve to check the set up was working properly instead of opening the animal directly. Dimpling and some amount of insertion force were observed. It was tried on a silicon piece as well but it was piercing through and easily.

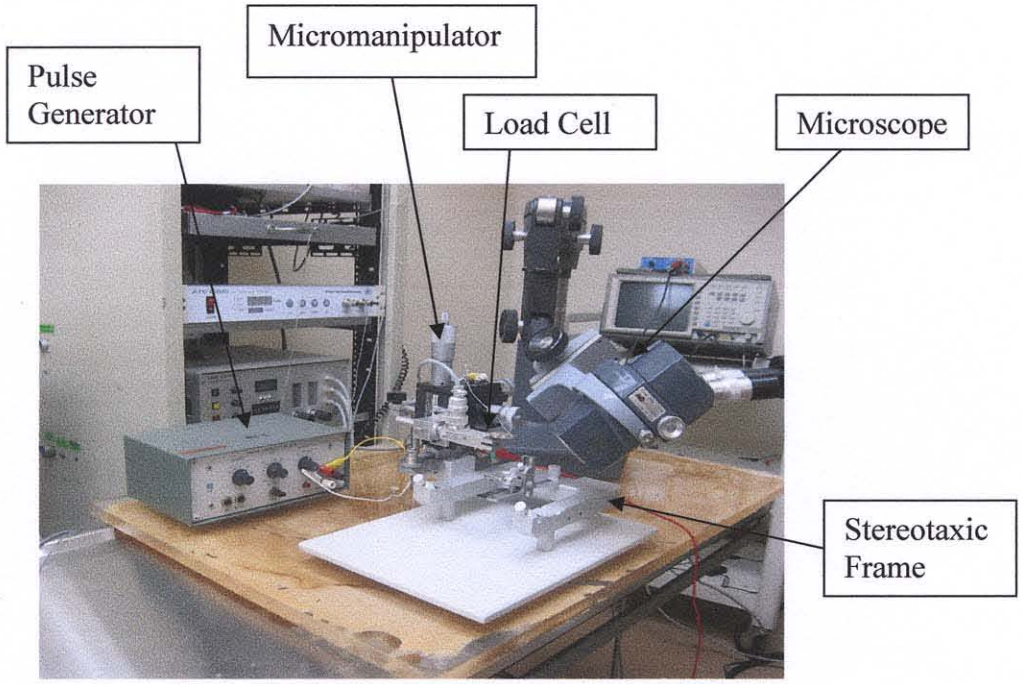

Figure 3.9 The set up used for the experiment.

The Sprague Dawley (approximately 350-400gms) rats were used for this experiment. All experimental procedures were approved by the Animal Use and Care Committee at Rutgers University. The rat was anaesthetized with the intraperitonial injection of 0.15ml of ketamine and 0.15ml of xylazine solution. To maintain the anesthesia after every 20 minutes 0.12ml of ketamine was given. To avoid the inflammation of the brain dexamethasone(2mg/kg) was injected once in the beginning of the experiment. The depth of anesthesia was assessed by continuously monitoring the paw pinch response and blood oxygen saturation. The rat's body temperature was maintained at 37 degree centigrade. The rat's head was placed in a stereotaxic frame using ear bars. An incision

was made down the midline of the cranium to expose the skull and the skin flaps were pulled back and taped to the side of stereotaxic frame to produce a watertight pool. A surgical operation was performed in the skull, to remove a bone flap, was removed in order to access the brain (craniotomy) [12]. The care was taken not to break the dura.

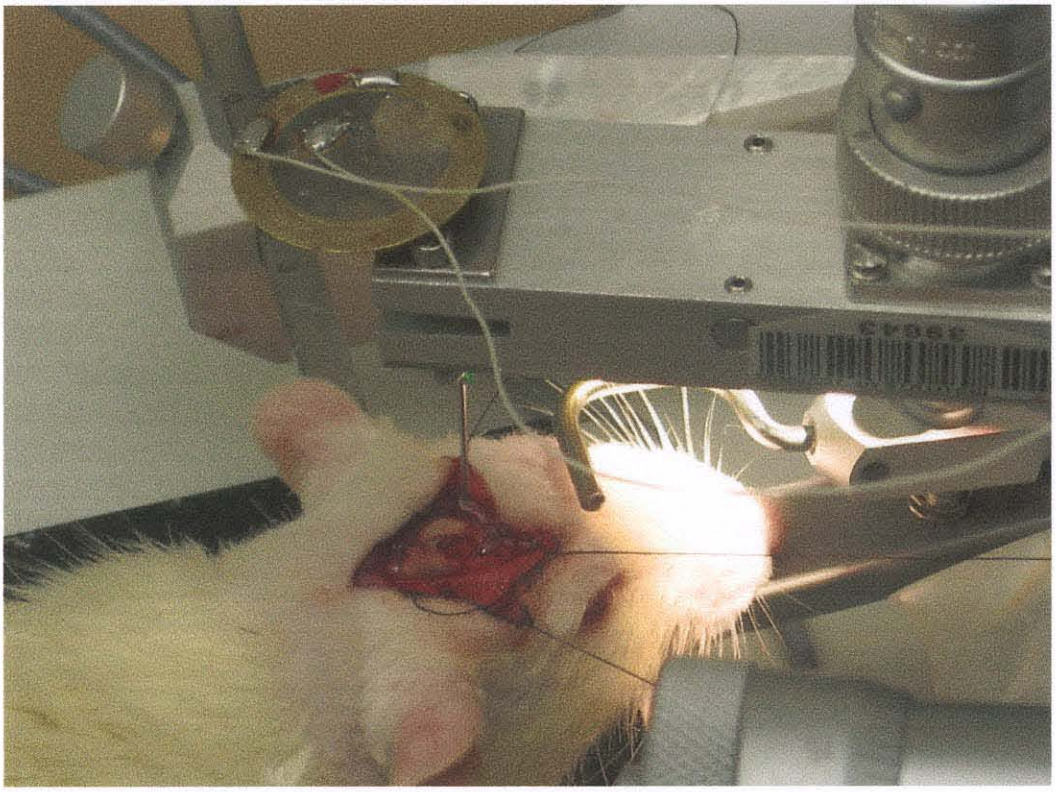

Figure 3.10 A close picture of the sensor, piezoelectric crystal, and microelectrode and rat brain during the experiment.

3.9 Experimental Procedure for Michigan Probe Electrode

Animal was kept on the Plexiglas board. The frontal and parietal lobes of the rat were exactly below the electrode. The microscope was adjusted to have a close view of the electrode penetrating into the brain. The PC camera was put into one of the eyepieces of the microscope to image the electrode movement on the computer. The electrode was advanced into the brain looking at the magnified image of brain and electrode on the

computer. Continuous acquisition to the spreadsheet LabView VI was used to measure the voltage from the force transducer. The voltage changes in milivolts as the electrode starts penetrating into the brain. The VI was stopped when the electrode penetrated into the brain. To measure the penetration force with vibration the piezoelectric crystal was pulsed at 5Hz. The vibrations generated by the piezoelectric crystal made the electrode shake in vertical direction. This way the data was collected with the vibration and without vibration. The recorded data was stored in a text file. This text file was loaded into MATLAB. The signal was then filtered with Butterworth low pass filter. The force signal was then plotted against time axes. The results are discussed in the next chapter.

3.10 Experimental Procedure for Utah 2D Array

The surgical procedure for measuring the penetration force of Utah array was the same for the Michigan Probe electrode. The Utah array was glued to the needle tip connected to the force displacement transducer instead of a Michigan probe electrode. The same experimental procedure was also similar. The array had 10 electrode shanks in 4*3 configuration (two shanks were broken off in the matrix).

3.11 The LabView Virtual Instrument

Continuous acquisition to spreadsheet file program, which comes with the LabView package, modified to suit our needs was used for acquiring the signals into the computer. A screen shot of the program is shown in the Figure 3.11. This virtual instrument

demonstrates a simple way to write voltage data continuously to text file readable by spreadsheet programs. Each row is a scan and each column is a channel. Columns are separated by commas and rows by an end-of-line character. This program uses the intermediate DAQ functions: AI confi, AI start, AI read and AI clear, and the file functions from the UTILITY palette. This example also uses error chaining and the general error handler 6.

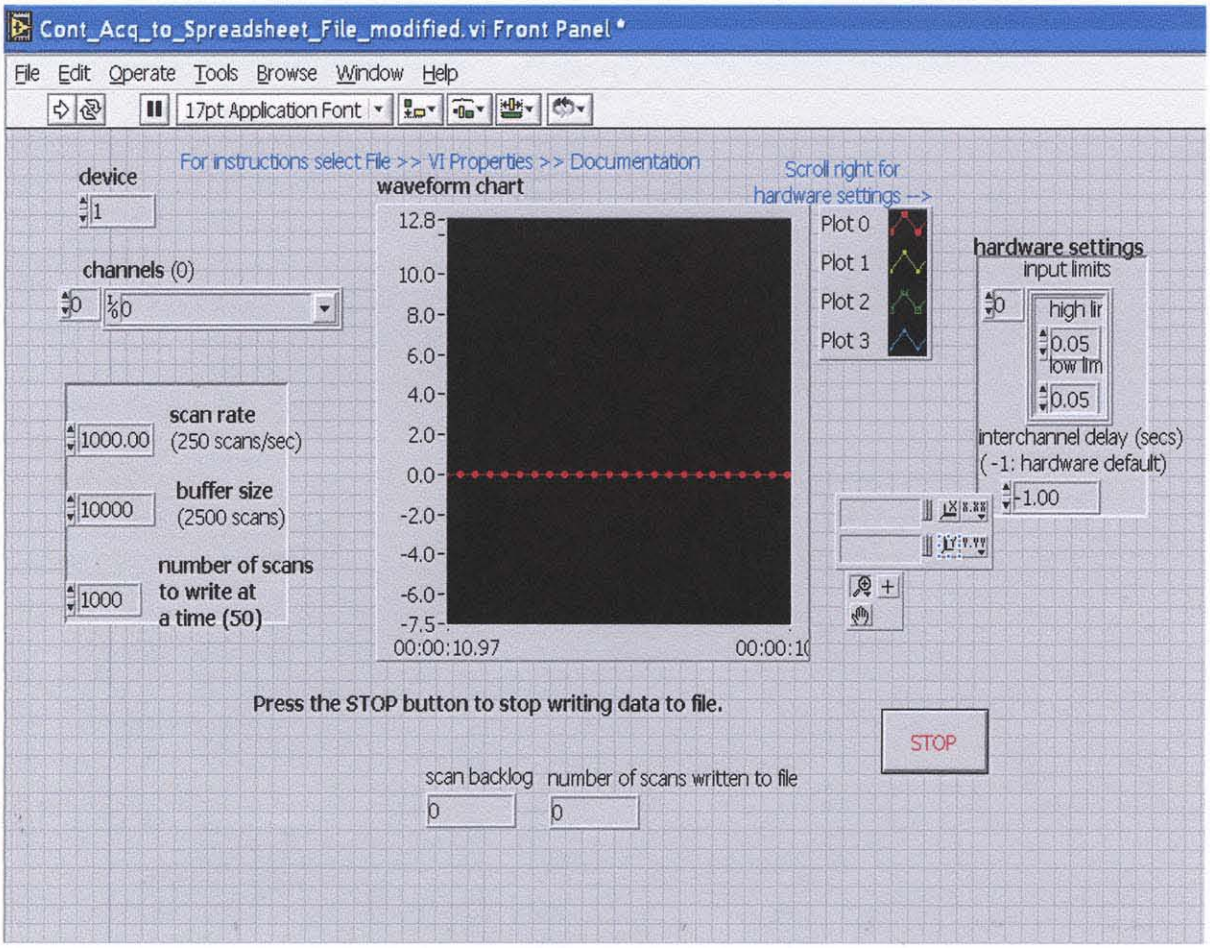

Figure 3.11 The screenshot of the VI used to measure data, with scan rate of 1 KHz.

CHAPTER 4

RESULTS

4.1 Calculation of Cut-off Frequency

The data was sampled at a rate of 1000 samples/second. Therefore, the sampling frequency was 1000Hz. Using Nyquist Theorem,

Maximum filtering frequency = (Sampling Frequency/2) = 500Hz.

The force signal was observed to reduce the noise when Low Pass filter was used.

The value entered into Matlab butter() command as cut-off frequency =15/500 is 0.03.

4.2 Results for Michigan probe electrode

Penetration force measurements were made based on the force. Twelve insertions were made on the brain to collect the data; out of which three were insertions with vibration and five of them were insertions without vibration. To calculate the peak penetration force, the baseline force was subtracted from the peak point. The same procedure was repeated for all the data. The mean of multiple trails were taken to calculate the average penetration force with vibration and without vibration. A sudden increase in the baseline was observed as soon as the electrode touches the brain surface (figure 4.1). The micromanipulator was operated manually and hence the force increases in steps. The increase stops for a second as the micromanipulator was rotated through one cycle and before the second cycle starts. The peak point where the force drops sharply is called the penetration point.

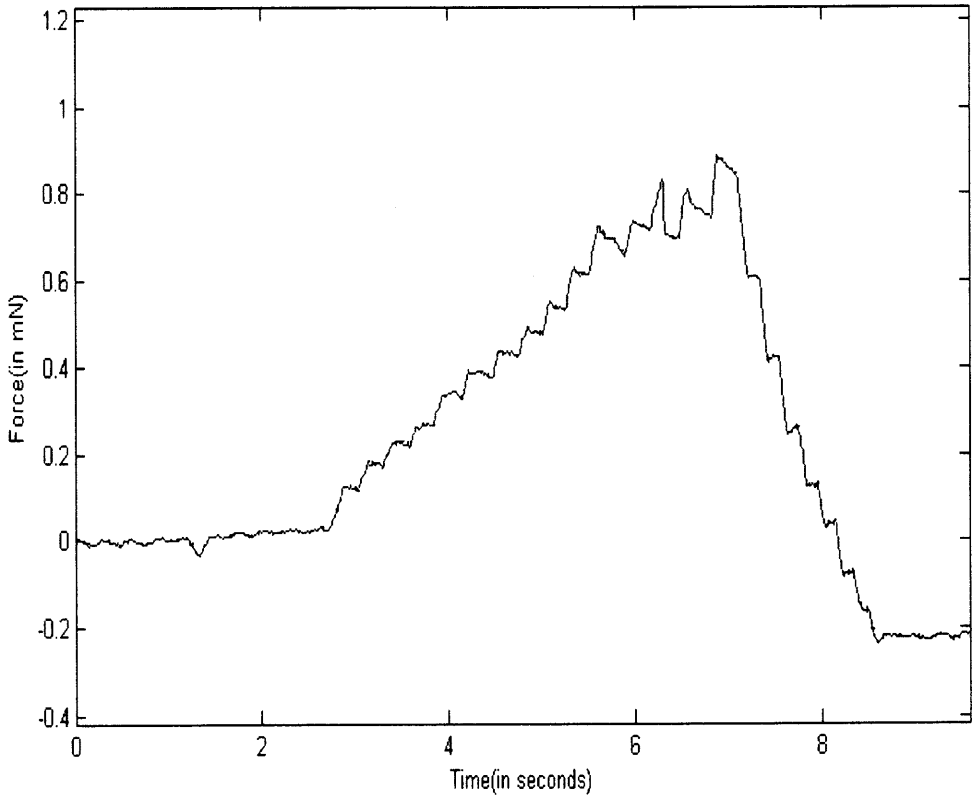

Figure 4.1 Graph of penetration force with no vibration with Michigan probe electrode.

Figure 4.1 shows the graph of the force as a function of time as the electrode was inserted into the brain. The penetration force for dura was 0.86mN for this trial, the mean force over the trail was 0.75mN. The force started decreasing immediately after the electrode penetrated into the dura mater. The penetration rate was very slow although the electrode was manually inserted into the dura mater.

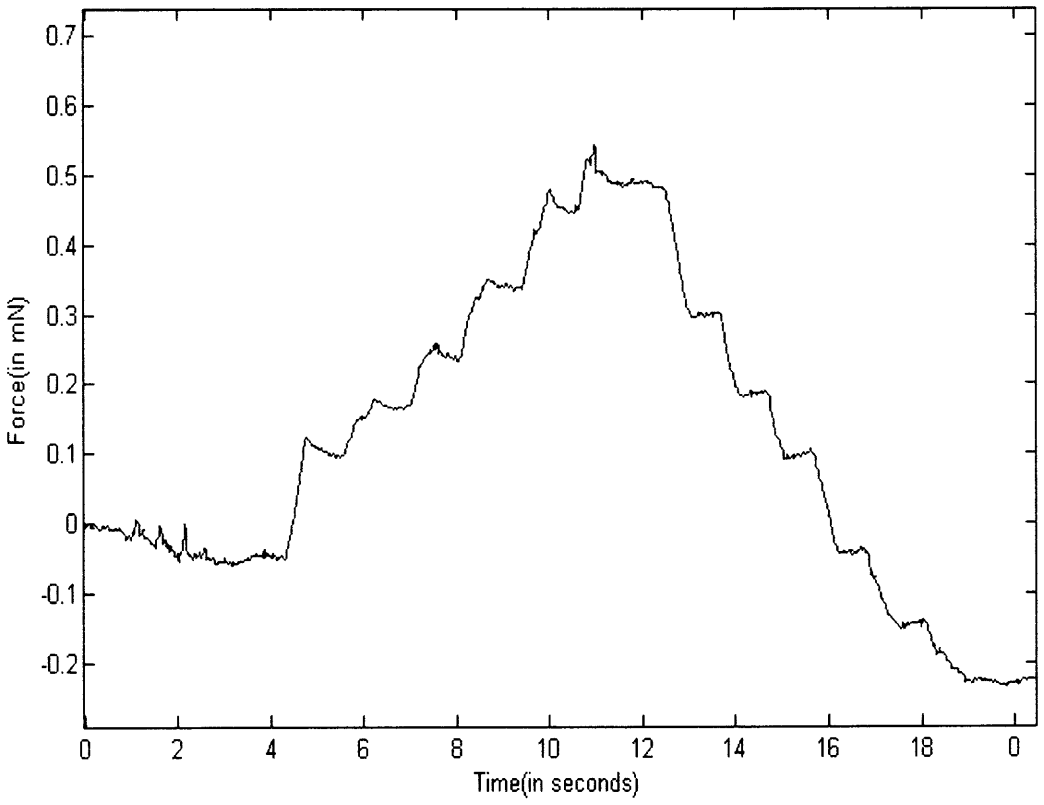

Figure 4.2 Graph of penetration force with vibration with Michigan probe electrode.

The graph shown in Figure 4.2 is the penetration force with mechanical vibrations. The plot is filtered with a low-pass FIR filter in Matlab to remove the force fluctuations due to vibration. The piezoelectric crystal is activated at a rate of 5 pulses per second. The penetration force with vibrations is 0.55 mN in this trial, the mean penetration force is 0.57mN over n trials.

Table 4.1 Comparison of the penetration forces with and without vibration with Michigan Probe Electrode.

PENETRATION FORCE OF MICHIGAN PROBE WITHOUT VIBRATION (mN)	PENETRATION FORCE OF MICHIGAN PROBE WITH VIBRATION(mN)
0.65	0.55
0.76	0.55
0.86	0.61
0.72	-
0.79	-
Mean ±std-- 0.75±0.078	Mean ±std-- 0.57 ± 0.034

In Table 4.1 the measurements are summarized. The data were collected with and without vibration. Three insertions were made with vibrations at 5 Hz and 5 insertions were with no vibration. The mean penetration force without vibration was 0.75±0.078 mN and the mean penetration force with vibration was 0.57 ± 0.034mN. The results show that the use of vibration reduced the penetration force to about 75% of the value without vibration.

4.3 Results for Utah 2D Electrode array

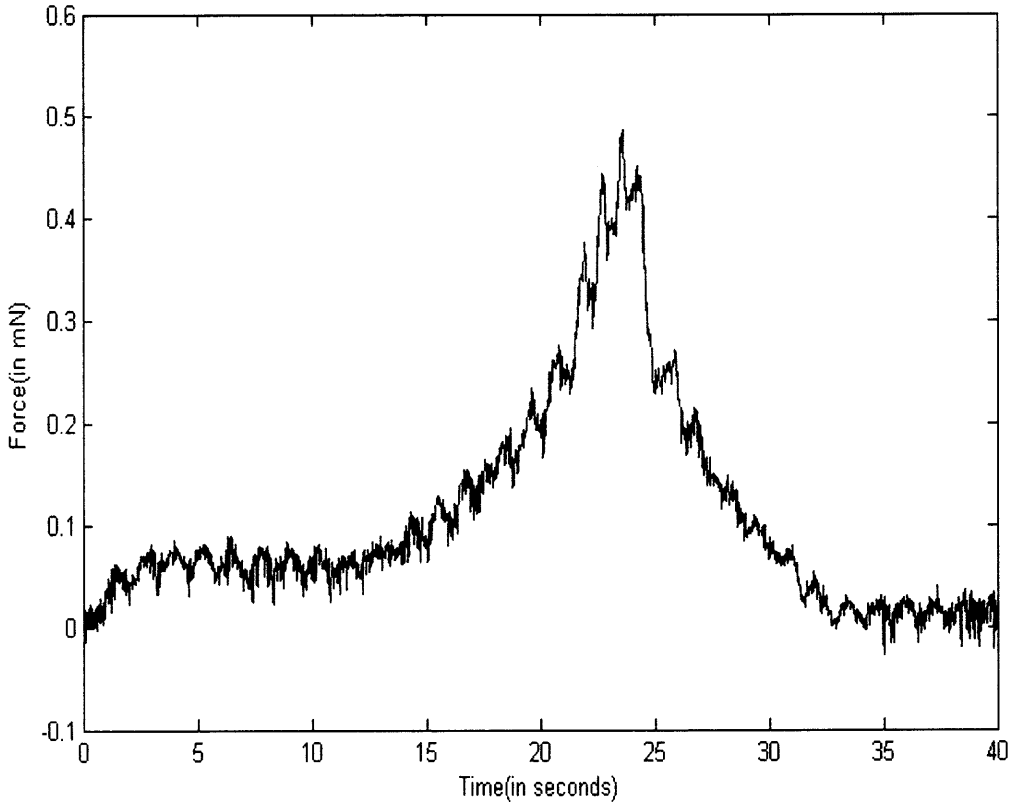

Figure 4.3 Graph of penetration force with no vibration with Utah 2D electrode.

Figure 4.3 is a graph of the penetration force measured with the Utah 2D array. There is a sudden increase in the baseline force. After the penetration, force decreased abruptly. The force value at the peak is 0.43 mN in this trail. The mean force is 0.31mN.

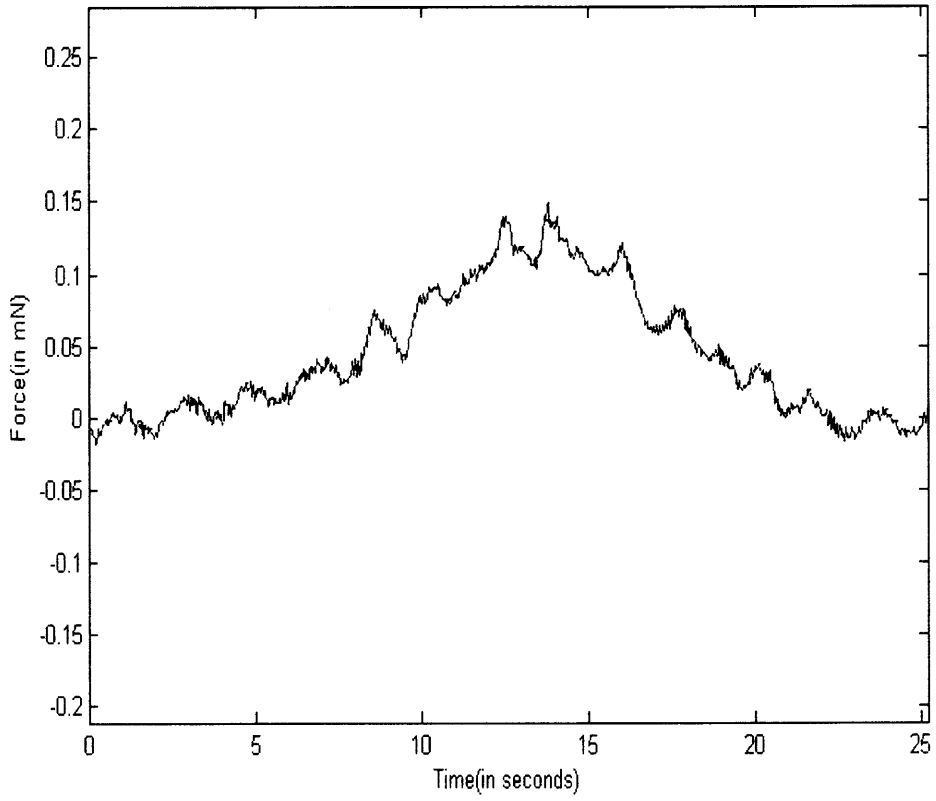

Figure 4.4 Graph of penetration force with vibration with Utah 2D electrode.

Figure 4.4 is a graph of penetration force measured with the Utah 2D array, when vibration was used. The signal is filtered in Matlab with a low-pass FIR filter to remove noise due to mechanical vibrations. The penetration force was reduced to 0.15 mN in this trial, the mean penetration force is 0.20mN.

Table 4.2 Comparison of the penetration forces with and without vibration for Utah 2D electrode.

PENETRATION FORCE OF UTAH 2D ARRAY WITHOUT VIBRATION (mN)	PENETRATION FORCE OF UTAH 2D ARRAY WITH VIBRATION(mN)
0.25	0.25
0.24	0.16
0.44	0.15
0.30	0.27
0.35	-
Mean ±std--- 0.31±0.082	Mean ±std--- 0.20±0.062

Table 4.2 is a comparison of the results of penetration forces measured with and without vibration for the Utah electrode array. The force has reduced to 64% with vibration technique. Penetration force depends on many things like opening angle, tip cross-sectional area, coating material and, shaft shape. The penetration force of the Michigan Probe single shaft electrode is almost double than the penetration force of the Utah 2D array. Also the penetration force with vibration for the Michigan probe is almost three times of the Utah electrode array. The coating material for the Michigan probe electrode is iridium and for Utah 2D array is platinum. The Utah array shaft tips are very sharp compared to Michigan probe shaft tip. The sharper the electrode, the smaller is the penetration force. To confirm that the results are not coming from the same mean a statistical analysis was performed on the force measurements. For Michigan probe electrode the test results rejected the hypothesis (P= 0.0086) which means that the

population means are not the same. For the Utah array the hypothesis results did not reject the hypothesis at the 5% significance level, but the P value was considerably small (P= 0.0661).

4.4 Discussion

In Table 4.3 the penetration force of Michigan probe electrode and Utah 2D array are compared with the penetration force of the various types of microelectrodes. Very few groups have measured the penetration force for the dura mater. All the papers have reported measurement of penetration force on pia mater; dura was surgically removed before insertion. The penetration force depends on many things such as opening angle, tip cross-sectional area, coating material and the shaft shape [21]. The mean penetration force for ACREO electrode, tungsten electrode, and Michigan Probe is 1.28mN, 2.62mN and 0.75mN respectively. From the Table 4.1, the Michigan probe electrode has a less penetration force with mechanical vibrations. The penetration force reduces by almost 25 % of the original value. From Table 4.2 the mean penetration force for Utah 2D array is 0.31mN. The mean penetration force with vibrations is 0.20mN. Penetration force for the Utah electrode has reduced by 35 %. The lowest measured penetration force is 0.31mN which with vibration can be lowered to 0.20mN.

Table 4.3 Comparison of the penetration forces from previous work done with penetration force measured with Michigan probe electrode and Utah 2D electrode

ELECTRODE PROVIDER	NUMBER OF SHAFTS	OPENING ANGLE (°)	SHAFT SHAPE	COATING MATERIAL	NUMBER OF INSERTIONS	PENETRATION FORCE (mN)	PENETRATION FORCE WITH VIBRATION (mN)
ACREO (pia)	1	4	RECTANGULAR	SILICON NITRIDE	5	0.48±0.18	-
ACREO (pia)	2	4	RECTANGULAR	SILICON NITRIDE	9	0.86±0.36	-
ACREO (pia)	3	4	RECTANGULAR	SILICON NITRIDE	10	0.81±0.54	-
ACREO (pia)	4	4	RECTANGULAR	SILICON NITRIDE	9	0.83±0.37	-
ACREO (pia)	8	4	RECTANGULAR	SILICON NITRIDE	11	2.42±0.77	-
ACREO (pia)	4	4	RECTANGULAR	SILICON NITRIDE	8	2.04±0.77	-
TUNGSTEN (pia)	1	4	ROUND	-	20	0.62±0.26	-
TUNGSTEN (pia)	1	10	ROUND	-	5	0.85±0.33	-
TUNGSTEN (pia)	1	10	ROUND	-	11	1.15±0.51	-
SILICON (dura)	1	17	-	-	1	41±25.5	-
GLASS (phantom)	1	49.5	-	-	1	33.6±2.6	-
TUNGSTEN (pia)	1	15-20	-	-	1	14±10.4	-
INTRACORTICAL ELECTRODES	8	-	ROUND	-	6	2.45±0.56	-
VSAMUEL (pia)	1	4	SQUARE	SILICON NITRIDE	10	0.62±0.23	
MICHIGEN PROBE(dura)	1	45	RECTANGULAR	IRIDIUM	11	0.75±0.078	0.57±0.0346
UTAH 2D ARRAY (dura)	10	-	ROUND	PLATINUM	10	0.31±0.082	0.20±0.06

CHAPTER 5

CONCLUSION

The Michigan probe and Utah array are frequently used for neural recording and stimulation. The penetration force for the Utah 2D array on the dura mater is the least compared to all the other electrodes tested and reported in the literature. The results have shown that vibrations have reduced the penetration force significantly. These results suggest that mechanical vibration of the microelectrode can be a useful technique to minimize the tissue damage during insertion of microelectrodes.

CHAPTER 6

FUTURE WORK

Several groups have reported about their results on insertion force for brain and peripheral nerve which was discussed in the previous chapters. In this thesis, the attempt was to reduce the insertion force by vibrating the microelectrode. There may be other ways to reduce the insertion force. Our technique was tested on an intact rat brain. The conditions of anesthesia and blood CO_2 might have affected our measurements of force. In the future, the parameters should also be monitored during testing.

No research work has been reported on a method to reduce the insertion force for the spinal cord. Future work can focus on reducing penetration force for the spinal cord as well as different parts of the brain cortex. Most importantly, the chronic effect of using mechanical vibrations during electrode insertion should be studied.

APPENDIX

THE MATLAB CODE USED FOR FILTERING THE SIGNAL

```
cd('C:\Documents and Settings\ASHWINI\Desktop\ashwini text')
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA6.txt');
A = outdata*0.4083;
plot (A)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA7.txt');
B = outdata*0.4083;
plot (B)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA8.txt');
C = outdata*0.4083;
plot (C)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA9.txt');
D = outdata*0.4083;
plot (D)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA10.txt');
E = outdata*0.4083;
plot (E)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA11.txt');
F = outdata*0.4083;
plot (F)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA12.txt');
G = outdata*0.4083;
plot (G)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA14.txt');
H = outdata*0.4083;
plot (H)
xlabel('Time(in seconds)');
```

```
ylabel('Force(in mN)');
[b,a]=butter(3,0.03)
outdata = filter (b,a,'DATA140.txt');
I = outdata*0.4083;
plot (I)
xlabel('Time(in seconds)');
ylabel('Force(in mN)');
```

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