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14. ABSTRACT A major gap in understanding of blast TBI is how external kinetic blast energy translates to pressure transients in the brain. This project used miniaturized pressure sensors engineered at the LLNL to measure immediate increases in intracranial pressure (ICP) combined with longer-term measurements of biological ICP. We found that the existing LLNL sensors were not capable of measuring pressure changes in a wet environment. We solved this problem by enclosing a reference volume over the sensor diaphragm which provided reliable measurements over a range of pressures. We found that the brain responded differently to sensors implanted for 14 days in the rats cranial vault at different locations and that epidural sites minimized brain cell death and glial scarring. Static and dynamic pressure tests of the modified sensors reliably measured pressure transients in a test chamber connected to the fluid percussion device. The modified sensors reliably detected pressure transient in the brain of rats subjected to fluid percussion TBI. Modifications to the circuitry of the sensors provided accurate and reliable measures of temperature within a physiological range. A limitation was revealed that the sensor could not detect small pressure changes associated with biological ICP and will require further engineering and fabrication.					
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INTRODUCTION:

The major objective of this research effort was to create new sensing technologies and perform preliminary studies prior to rapid transition to testing in blast TBI models. This seed project proposed to use miniaturized, state-of-the-art pressure/temperature sensors engineered at LLNL to measure the immediate increases in ICP combined with longer-term measurements of biological ICP and intracranial temperature. The experience gathered from this seed proposal provided valuable data on sensor placement, long-term brain tissue responses to implanted sensors, and sensor capability of dual measurement of biologic ICP and impact pressure transients that will be directly applicable to subsequent transition into blast TBI animal models.

BODY:

Task 1: To evaluate existing LLNL prototype micro pressure sensors in a rat impact TBI model

Task 1a: Perform impact pressure recording from sensors implanted in the brain of rats subjected to varying magnitudes of fluid percussion TBI

We performed initial static calibration curves for the existing LLNL sensors in both dry and wet environments.

Figure 1: Photograph of current LLNL microsensor. The sensor diaphragm is packaged with a connector lead and exterior protective coating.

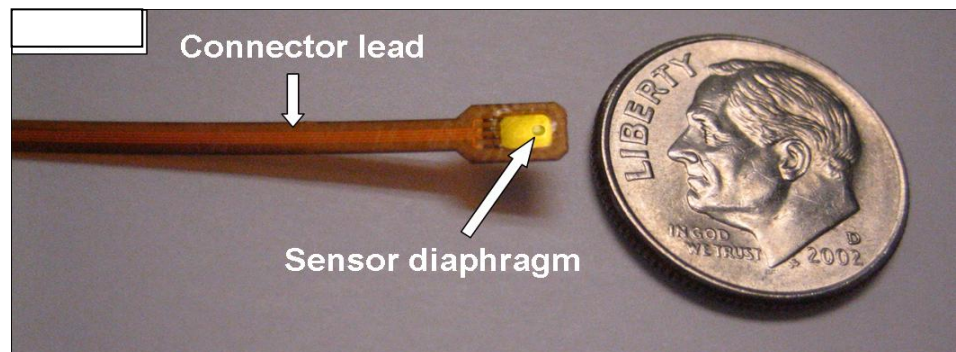


Figure 2. Dry static pressure calibration: Changes in sensor output voltage were recorded over a range of pressures applied to the sensors. Note that the sensors were unresponsive to pressures under 20 PSI. Between 20 and 50 PSI both sensors produced a linear response to increasing pressure.

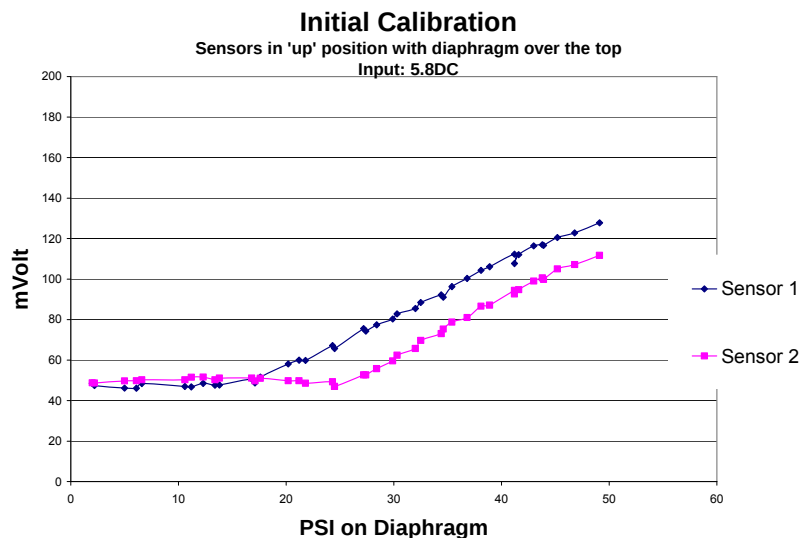
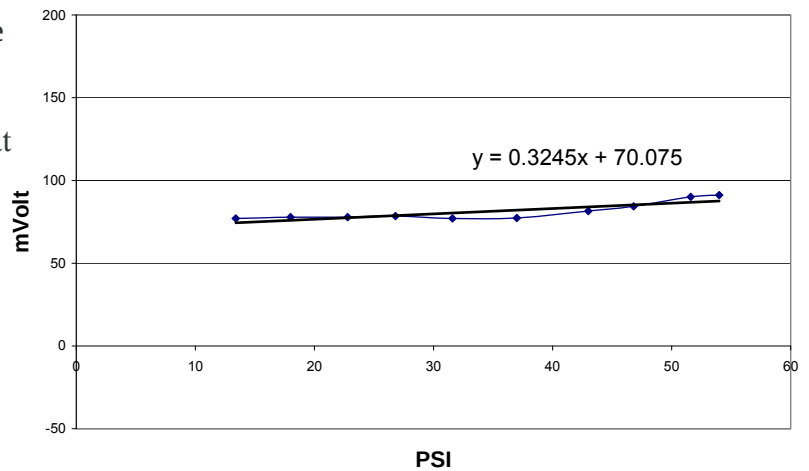
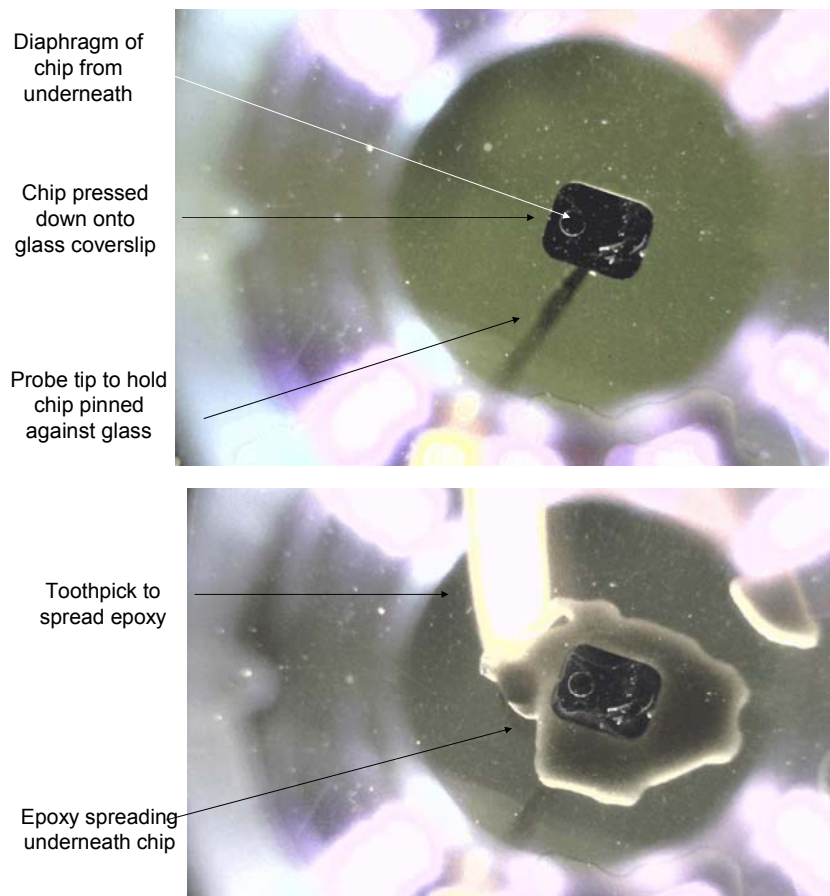


Figure 3. Wet condition static pressure calibration: Changes in sensor output voltage were recorded over a range of pressures applied to the sensors. Note that this sensor was unresponsive to changes in applied pressures. Furthermore, we found that now testing this sensor in a dry environment, it was clear that this sensor was irrevocably damaged from the fluid leakage. Sensor redesign was necessary to solve this problem.



The problems associated with the lack of response of the existing LLNL sensors in a wet environment posed a significant problem. We found that the existing LLNL pressure sensors were limited in their ability to detect pressure transients in a wet environment. We determined that a sealed reference volume over the sensor diaphragm would be required in order to reliably detect pressures in a wet environment across a range of impact and blast TBI pressures. After considerable experimentation with a variety of backing materials and epoxy methodologies, we were able to successfully overcome this limitation.

Figure 4. We successfully enclosed a reference volume for on the the pressure sensor, enabling the contact pressure sensors to be placed in a fluidic environment and detect a change in pressure. The epoxy application process procedure is shown for enclosing an extremely thin layer of glass over the sensor diaphragm, creating a closed and sealed reference volume. All three views are taken from beneath the setup looking upward, through the transparent glass coverslip onto the backside of the chip. The top picture shows the setup of the procedure before epoxy is applied. The middle picture shows the epoxy spreading across the backside of the chip, as an advancing front of epoxy can be



seen. The lower picture shows the chip after the epoxy has finished spreading, contacting the entire backside of the chip but not the diaphragm. During the curing process the liquid epoxy is heated to ensuring a strong bond and a hermetic seal. The excess glass coverslip is later precisely trimmed away with a special dicing saw.

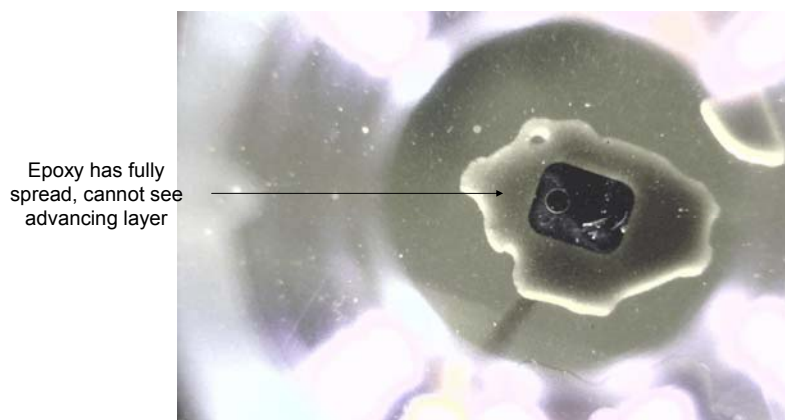


Figure 5. A fluidic test chamber was built to test and characterize the device. A pressure chamber was designed and fabricated to both create an electrical connection to the chip and allow connection to the fluid percussion instrument, enabling us to measure the dynamic characteristics of the sensor.

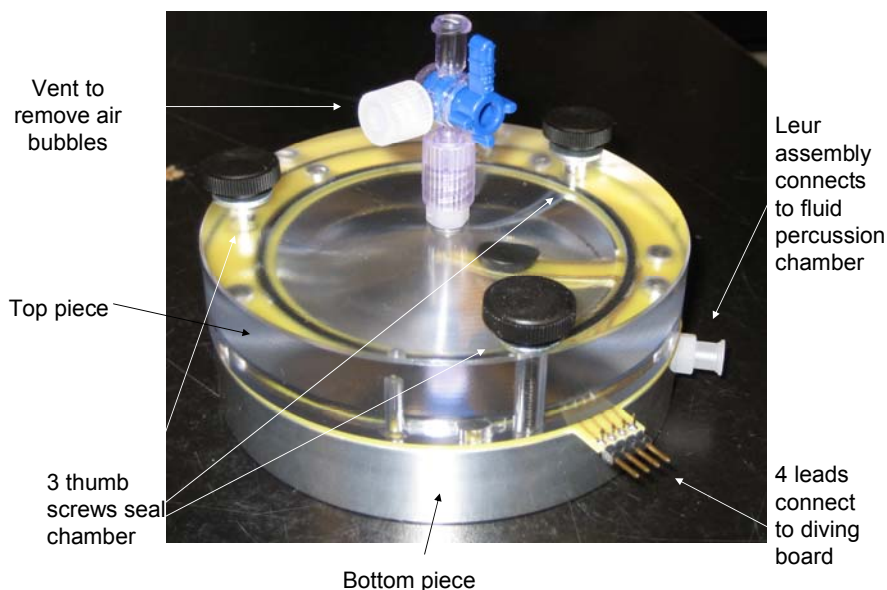
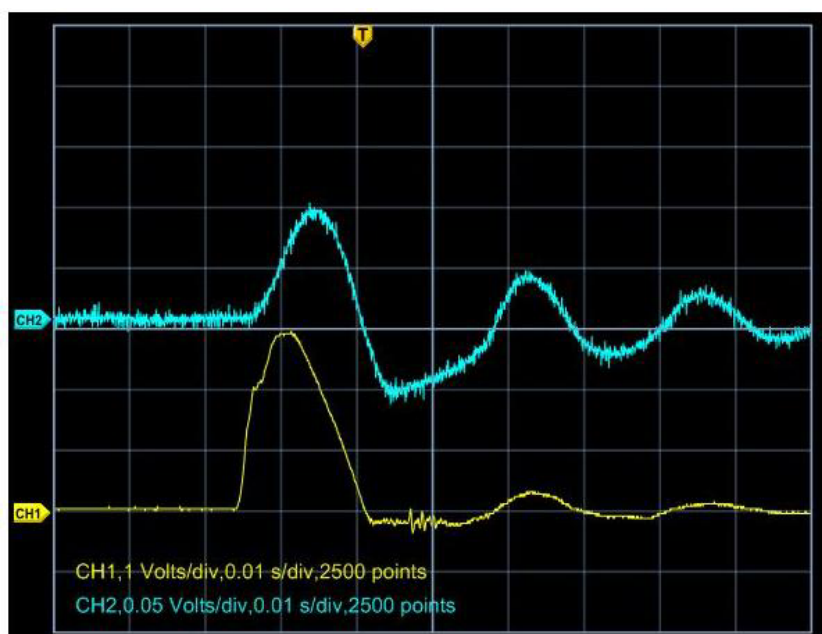


Figure 6. This figure shows the dynamic pressure tracing of a sensor with an enclosed reference volume. The test chamber (figure 9) with sensor chip was connected to the fluid percussion device through the Luer fitting. The chamber was subjected to a fluid percussion impact. The screenshot shows the LLNL sensor signal in the blue upper trace and the standard fluid percussion pressure transducer signal in the yellow, lower trace. Each division on the X-axis is 5 msec. Note the high correspondence of the LLNL sensor to the FP transducer. Also note the amplified secondary waveforms. We discovered a trapped bubble in the test chamber that caused the rebounding secondary pressure changes. Not only did the sensor respond but it was undamaged from repeated tests indicating a functional seal.



Task 1b Evaluate brain responses (e.g. cell death, glial scarring) to sensors implanted in the brain for up to two weeks

We performed evaluation of brain responses to sensors implanted for 14 days in four different intracranial locations.

Figure 7. We implanted sensors in different locations within the rat skull/brain to determine brain tissue reactions to the implants. The sensors remained implanted for 14 days. The gross pathology of the brain shows that implant configuration 1 resulted in the greatest gross infarction on the surface of the cortex while implant configurations 3 and 4 showed essentially no gross pathology.

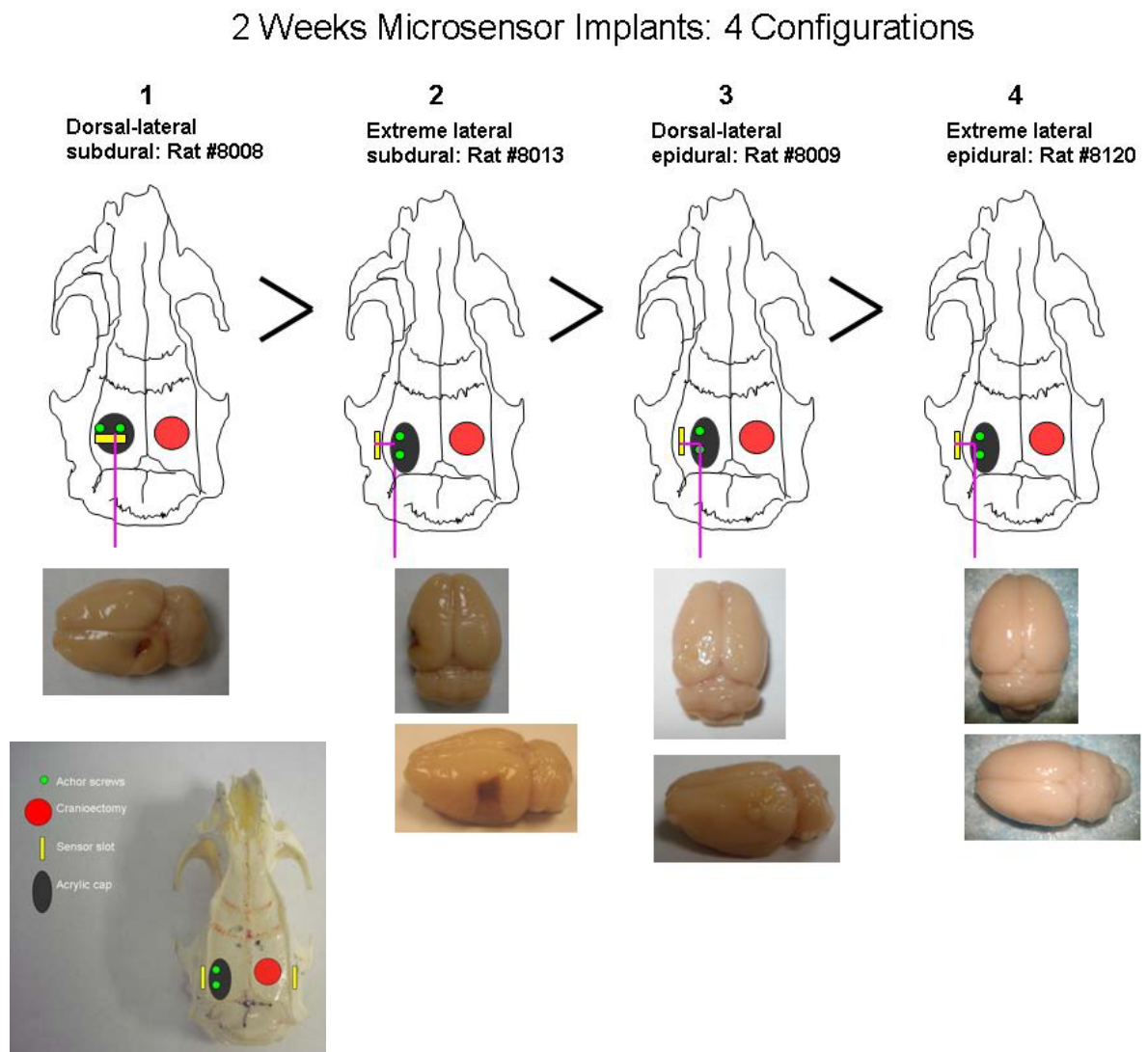


Figure 8. Histology was performed to examine areas of brain tissue infarct in response to sensor placement in each of the four implant configurations. The sensors remained implanted for 14 days. The tissue was then sectioned and stained with Cresyl-violet. In configurations 1 and 2, histological stains showed infarction (2X objective, black arrows) localized to the implant site. For configuration 3, there was less tissue damage and with configuration 4 there was minimal evidence of cortical damage with cresyl violet staining.

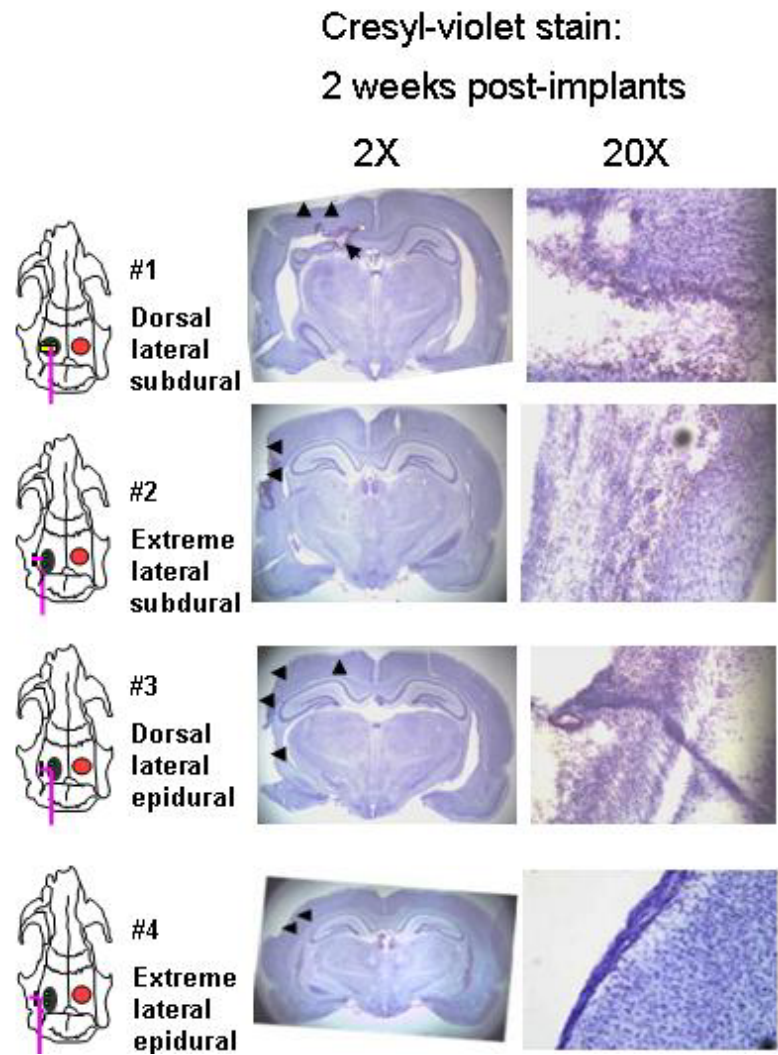


Figure 9. Histology was performed to examine areas of microglia reaction using a microglia –specific antibody (anti Iba-1) as an indicator of inflammatory responses to sensor placement in each of the implant sites. Configurations 1 and 2 showed the greatest inflammatory response (20X objective) localized to the implant site.. Configuration 3 had minimal infiltration of activated microglia.

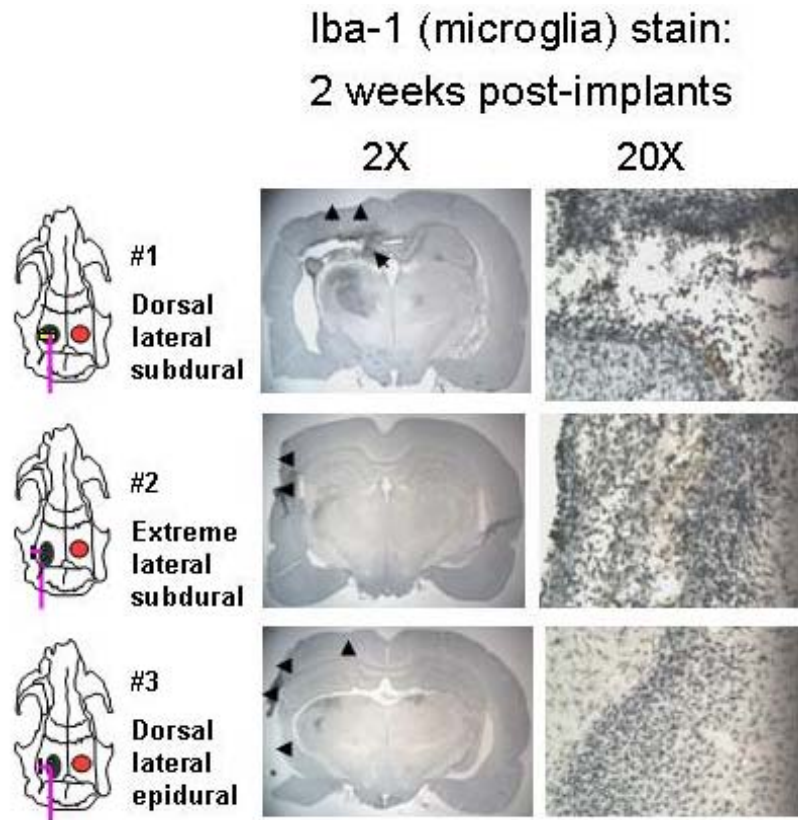
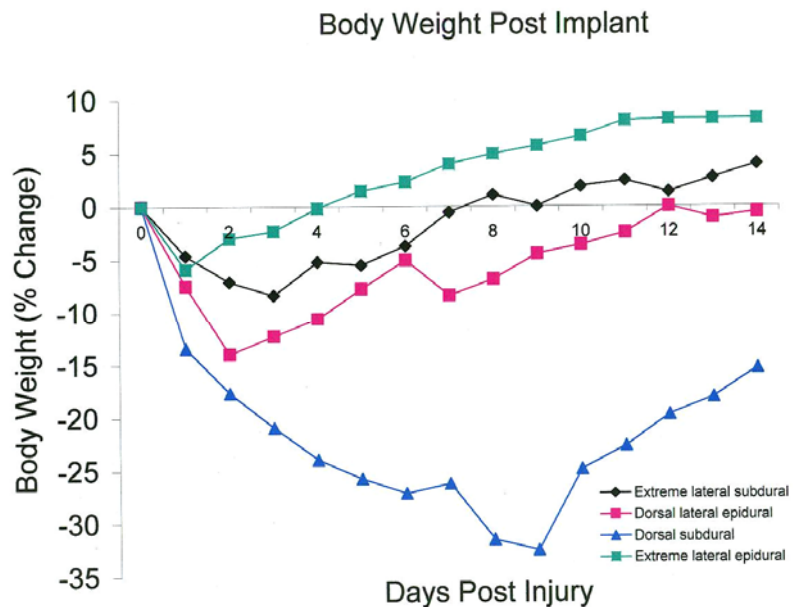


Figure 10. Body weight was used as an indicator of general health of the rat. The different sensor implantation configurations produced very different body weight responses over the 2-week period. The extreme lateral epidural implanted animals (Configuration 4) showed the greatest recovery in body weight (green line).



Task 2: To evaluate newly developed multi-modality LLNL micro sensors in a rat impact TBI model:

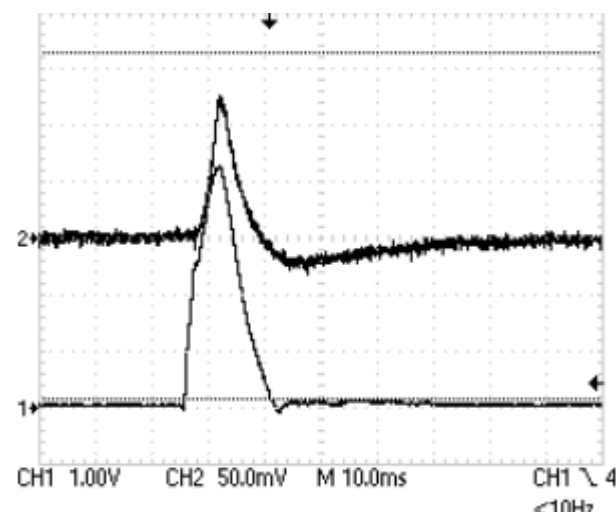
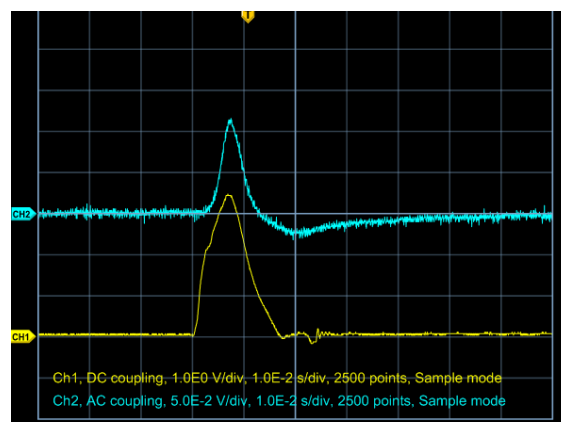
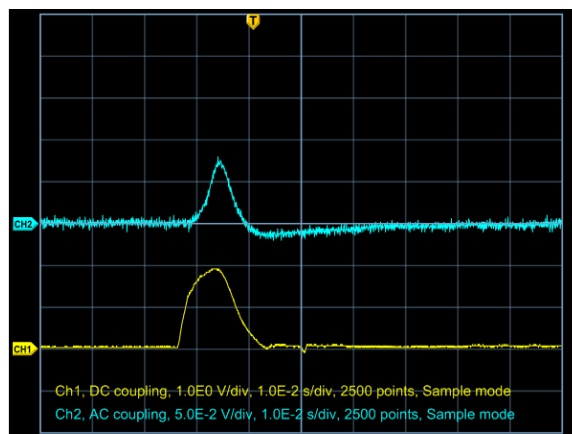
Task 2a: Perform impact pressure recording from multiple sensors implanted in various intracranial:

We implanted the modified sensors with the enclosed reference volume into the brain of rats and subjected them to varying magnitudes of fluid percussion TBI.

Figure 11. The three screenshots below show the LLNL sensor's signals plotted simultaneously with the fluid percussion reference pressure transducer signal following mild (upper screenshot), moderate (center screenshot), or severe (lower screenshot) fluid percussion TBI in the rat. The LLNL sensor was placed within the rat's skull in a lateral epidural position.

While it appears that the fluid percussion reference sensor has a greater sensitivity to pressure than the LLNL sensor, this difference is actually due to the different voltage output characteristics of the fluid percussion pressure transducer and the LLNL sensor. There is also some force reduction as the dynamic pressure wave travels through the Luer fitting into the rat's cranial vault. Overall, these data demonstrate that dynamic measurements with the LLNL sensor can be performed with a high level of precision and that the modified LLNL sensor readings corresponds to the upstream fluid

percussion reference pressure transducer. It is also noteworthy that the LLNL sensor's peak signal occurs slightly after that of the fluid percussion reference transducer peak signal. This is due to the LLNL sensor being located "downstream" of the reference sensor, as the dynamic pressure wave will reach the reference sensor before it reaches the LLNL sensor.



Task 2b: Perform extended biological ICP recording from sensors implanted in the brain of rats subjected to varying magnitudes of fluid percussion TBI:

We encountered a limitation of the existing LLNL sensors in that they were not sensitive enough to detect the relatively small pressure changes (10-40 mm Hg or less than 1 psi) associated with biological ICP from brain swelling. Even with the incorporation of the reference volume over the sensing diaphragm, static pressure testing was not able to reliably detect pressure changes in the brain swelling range. As detailed below our collaborating engineers determined that a thinner diaphragm could solve this problem.

Figure 12. Engineering calculations were performed to predict how a change in thickness of the LLNL sensor diaphragm could increase the sensitivity to low pressures encountered with changes in biological ICP (less than 1 psi).

Calculating the voltage output for an applied uniform pressure

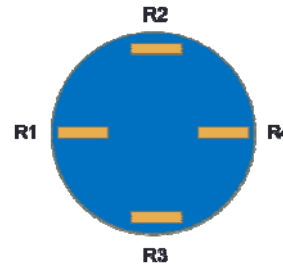
$$V_{out} = V_{in} \frac{2 * (\alpha_1 + \alpha_2)}{1 + \alpha_1 - \alpha_2}$$

$$R1 = R4 = R0 * (1 + \alpha_1)$$

$$R2 = R3 = R0 * (1 - \alpha_2)$$

$$\alpha_1 = \sigma_r * (\pi_l + \nu * \pi_t)$$

$$\alpha_2 = -\sigma_r * (\pi_t + \nu * \pi_l)$$



Equations from MAE 229
MEMS Design



α_1 and α_2 correspond to the change in resistance divided by the nominal resistance of the resistor. π_l and π_t correspond to the longitudinal and transverse piezoresistive coefficients of boron doped silicon. ν is the poisson's ratio.

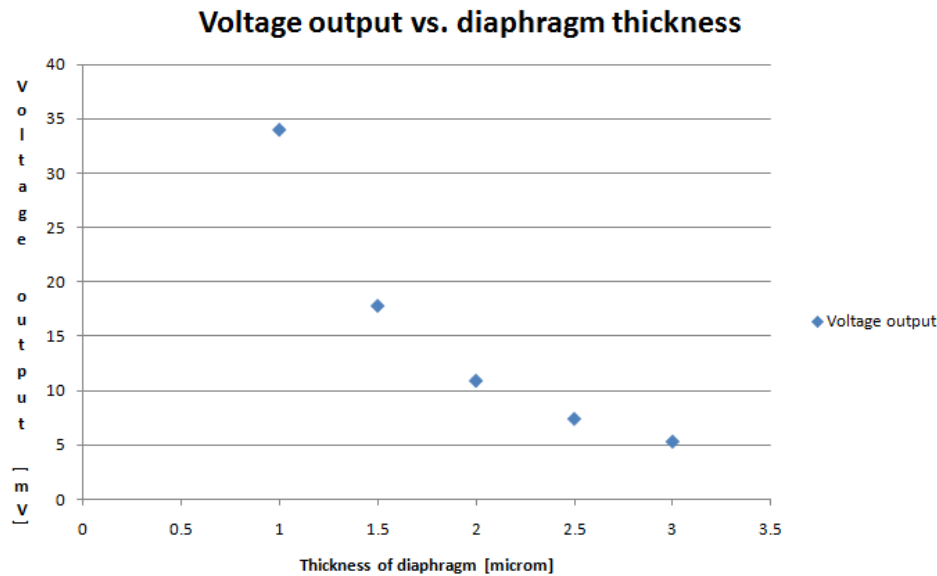
Thus, the larger the radius and the thinner the diaphragm, the larger the radial stress and the larger the voltage output to an applied pressure. This is plotted in the graph below:

Calculation of σ_r

- From Timoshenko, Theory of Plates and Shells:
- This is valid only at the outer edge of the plate, and for small deformations
- σ_r = radial stress
- P = uniformly applied pressure
- r = radius of the plate
- t = thickness of the plate

$$\sigma_r = \frac{3}{4} * \frac{P * r^2}{t^2}$$

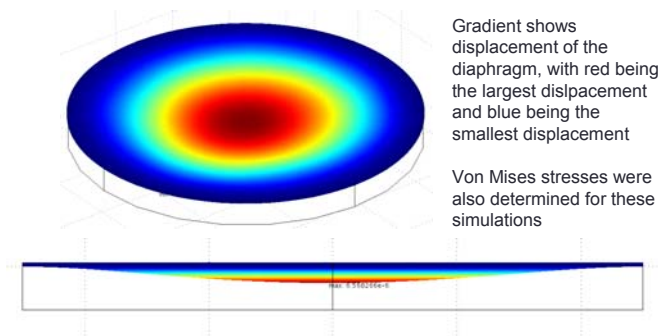




The plotted points were derived from the following parameters: a 500 micrometer diameter diaphragm, 1 mmHg applied, 5V as the input, and $\pi l = 71.8e-11$, $\pi t = -66.3e-11$. Thus, it appears that we would want to select a diaphragm with a thickness of 1 micrometer and a diameter of 500 micrometers. However, one of the consequences of thinning the diaphragm is that it is more likely to burst when exposed to the large 50 psi pulse it will experience during an actual blast.

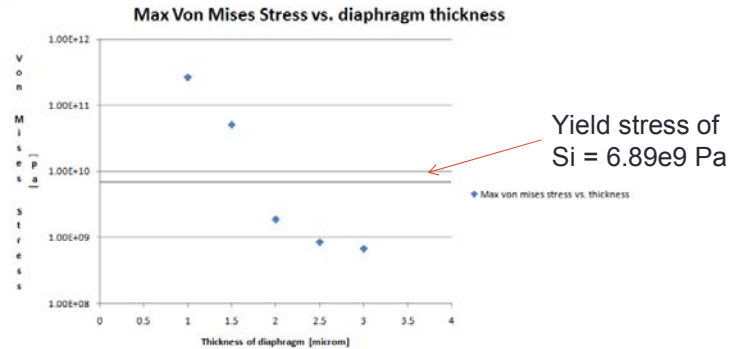
The Von Mises Stress for an applied load of 50 psi was determined using COMSOL Multiphysics, a finite element modeling program. The picture below shows a simulation of the diaphragm bending for a 3 micrometer thick diaphragm. The rainbow gradient shows the deflection of the diaphragm, with red being the largest deflection and blue being the smallest.

COMSOL, 3 micrometer thickness simulation



The Von Mises Stresses were determined for a number of diaphragm thicknesses, and are plotted below:

Summary of COMSOL Results



- Even though 1 and 1.5 micrometer thicknesses yield the best voltage output for 1mmHg applied, they will yield under an applied load of 50 psi
- 2, 2.5, and 3 micrometers will not fail under a load of 50 psi



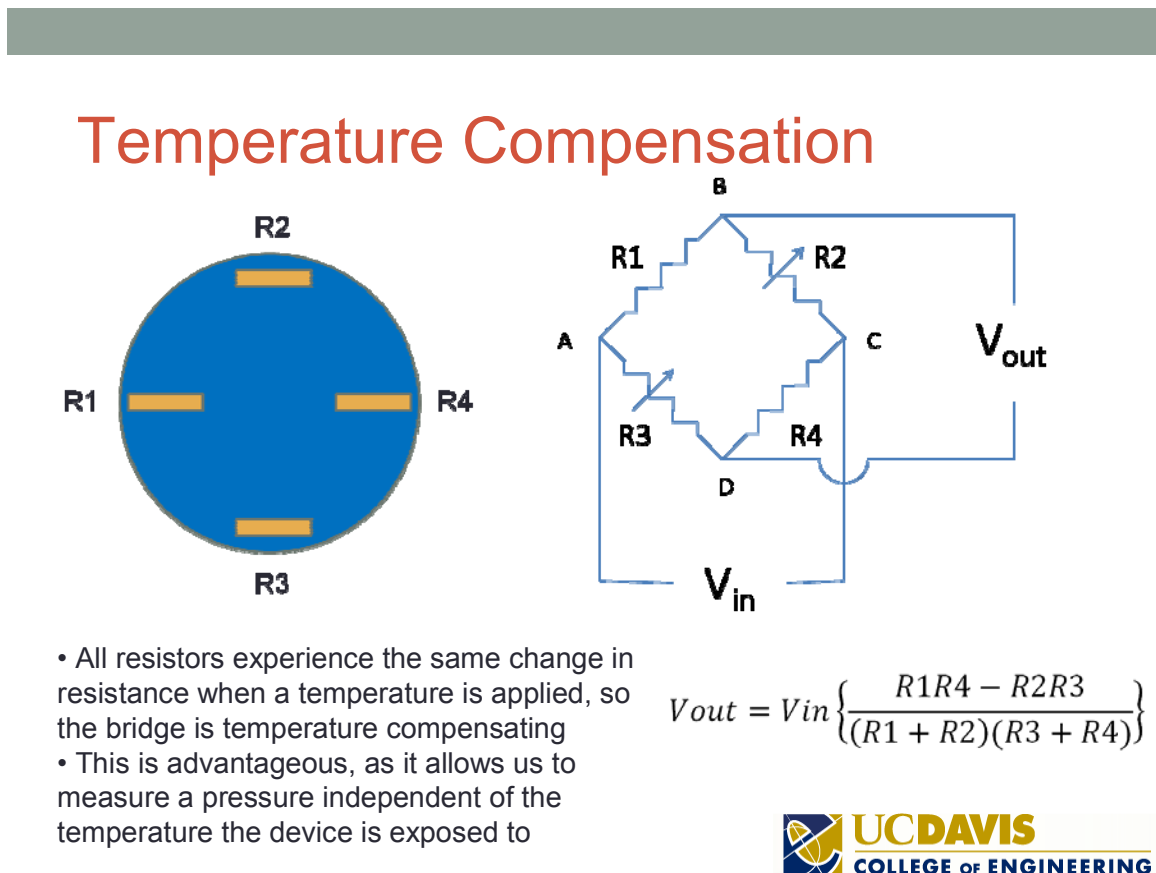
The black horizontal line plotted in the panel above shows the yield stress of silicon single crystal. Because the Von Mises Stress of the 1 and 1.5 micrometer thick diaphragms exceeds the yield stress, these diaphragms would permanently deform and possibly burst when exposed to a blast of 50 psi. Thus, dimensions of 500 micrometer diameter and 2 micrometer thickness seem to be optimum in surviving the 50 psi blast without incurring damage and still being capable of measuring a pressure of 1 mmHg with acceptable accuracy. These dimensions yield a signal to noise ratio of 7 for a 1 mmHg load, and a safety factor of 3.7 during the 50 psi blast. However, in order to create a sensor with these dimensions, we would need to perform a re-fabrication of the sensor which could not be accomplished in the FY-2010-2011 budget due to financial and time constraints.

Task 2c. Perform extended temperature recording from sensors implanted in the brain of rats subjected to varying magnitudes of fluid percussion TBI:

We took advantage of a design in the LLNL sensors that corrected pressure measurements for changes in sensor temperature. As detailed below, we were able to alter the wiring circuitry to now precisely measure temperature. We performed temperature-current calibrations of the modified sensors and were able to reliably measure changes in temperature within a physiological (range (34 to 45 degrees C) within an accuracy of 0.2 degrees C. We can now confidently measure intracranial temperature from the same sensors that measure intracranial pressure. This will be extremely useful in chemical blast TBI in which the animal will be exposed to a high temperature blast.

Figure 13. Engineering calculations for measurement of temperature with the LLNL pressure sensor.

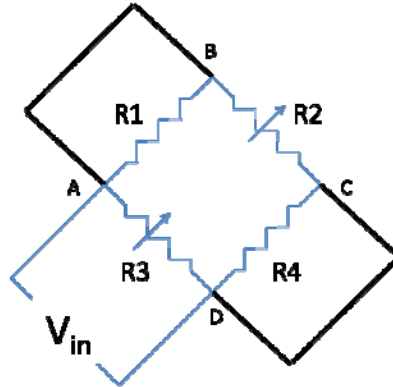
Design and experiment modifications were performed that lead to the ability to measure temperature. It is often desirable when making pressure measurements to be able to isolate the voltage increase due to pressure change from the voltage increase due to temperature change. This is accomplished using temperature compensation, as shown in the picture below:



The voltage output from the Wheatstone bridge is due to a pressure increase only, as temperature change will cancel each other out, as the numerator should remain zero unless a pressure is applied. This is advantageous for pressure measurements but not for temperature measurements. Temperature measurements can be made by shorting across R1 and R4, and measuring the resistance change of R2 and R3, which are now in parallel. This is shown in the figure below:

Goal 1: Temperature sensing

- This is advantageous for measuring pressure independent of temperature, but is not useful for measuring temperature
- To measure temperature, we must modify the setup to no longer be temperature compensating
- This is accomplished by shorting across R1 and R4



The bridge and subsequent resistance change are given as follows:

Equivalent Temperature sensing circuit

- The wheatstone bridge can be redrawn as shown below
- We can apply an input voltage and measure the current change across the resistors

$$R_{eq} = \frac{R2R3}{R2 + R3}$$

$$R = \frac{(R2 + \Delta R)(R3 + \Delta R)}{R2 + R3 + 2\Delta R}$$

$$R = \frac{R2R3 + \Delta R(R2 + R3) + \Delta R^2}{R2 + R3 + 2\Delta R}$$

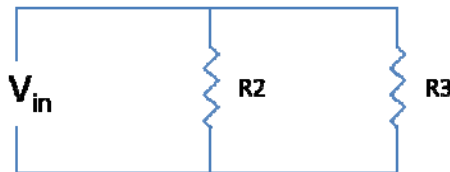
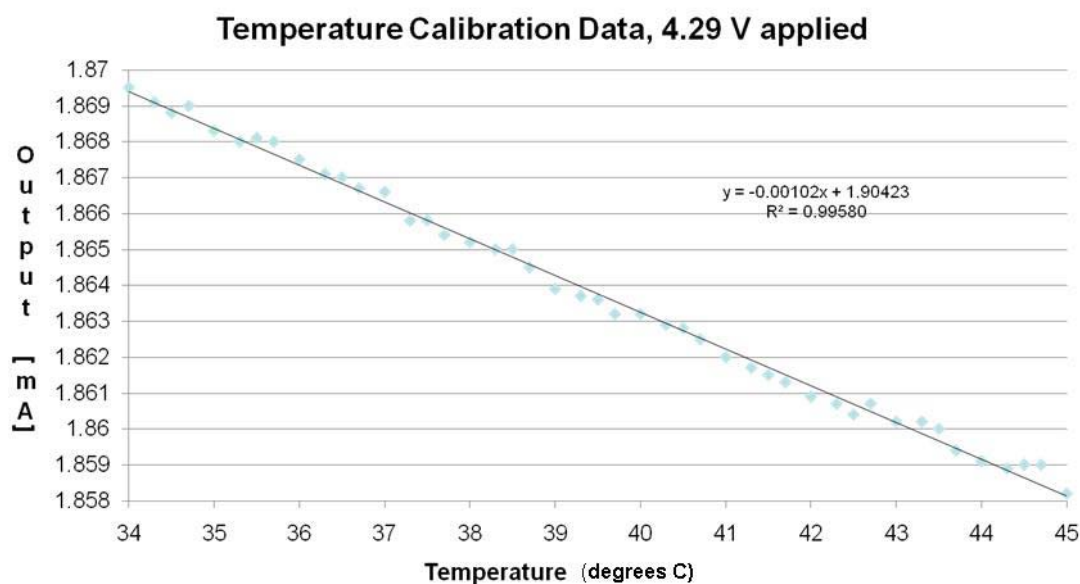


Figure 14. We have incorporated these changes and have successfully measured temperature with the rewiring of the circuitry described above. Below is a temperature calibration curve for the modified LLNL sensor. Note the linear correspondence between temperature and output amperage. There is a high degree of correlation ($R > 0.99$) which should produce a highly reliable measurement of brain temperature using the modified circuitry.



Temperature Measurements



KEY RESEARCH ACCOMPLISHMENTS:

Task 1: To evaluate existing LLNL prototype micro pressure sensors in a rat impact TBI model.

- 1) Static calibration of the original LLNL sensor in a dry environment demonstrated the capability of reliably detecting pressures from 20-50 psi (refer to Figure 2 above).
- 2) Static calibration of the original LLNL sensor in a wet environment was unable to reliably detect pressure changes in the range of 20-50 psi. Thus, engineering modifications to original LLNL sensor would be necessary in order to make pressure recording in the brain of rats subjected fluid percussion TBI (Figure 3).
- 3) We implanted the LLNL pressure sensors in the rat cranial vault in four different orientations. We found that the extreme lateral epidural placement produced minimal cell death and glial scarring to the brain upon histological evaluation at 14 days after surgical implantation (Figures 7, 8, 9, 10).

Task 2: To evaluate newly developed multi-modality LLNL micro sensors in a rat impact TBI model

- 4) We determined that creating a closed reference volume over the sensor diaphragm would increase sensitivity and ensure reliable performance in a wet, brain tissue environment.
- 5) We successfully modified the existing LLNL MEMS pressure sensor to add a sealed reference volume over the sensor diaphragm (Figure 4).
- 6) We designed and fabricated a special test chamber that connects to the fluid percussion device to perform dynamic calibrations of the MEMS pressure sensors (Figure 5).
- 7) We performed static and dynamic pressure tests of the modified sensors with reference volume and were able to reliably measure pressure transients in a test chamber connected to the fluid percussion device. The modified sensor is now reliable in a wet environment (Figure 6).
- 8) Static pressure calibration tests determined that the modified LLNL MEMS pressure sensor did not have the sensitivity to detect the small of the pressure associated with biological ICP (less than 1 psi).
- 9) Pressure measurements were successfully made from LLNL modified sensors implanted in the brain of rats subjected to fluid percussion TBI. The new sensors reliably detected pressures from a range of injuries (1.25 – 2.75 ATMs) (Figure 11).
- 10) Engineering calculations were performed for modifying the existing MEMS pressure sensors by reducing the thickness of the sensing diaphragm. This change should increase sensitivity to lower pressures characteristic of biological ICP associated with brain swelling and edema while retaining capabilities of accurately detecting high pressures associated with impact or blast TBI (Figure 12).
- 11) Engineering calculations were performed for modifying the existing MEMS sensors to incorporate temperature sensing capabilities (Figure 13).
- 12) Temperature calibration curves were successfully conducted ensuring that the modified LLNL MEMS sensor could detect small changes (0.2 degrees C) in temperature within the biological range of 34-45 degrees C (Figure 14).

REPORTABLE OUTCOMES:

Lyeth B., Bonner D., Van K., Gurkoff G., Kotovsky J. “Development of a Thin Film MEMS Sensor for Detection of Pressure Fluctuations in TBI” poster presentation, ATACCC-2011, Ft. Lauderdale, FL

CONCLUSION:

The purpose of this project was to modify existing micro-electro-mechanical systems (MEMS) pressure sensors engineered and fabricated by LLNL to measure pressure transients in the brains of rats subjected to fluid percussion impact TBI. The long range goal is to use the modified sensors to characterize the pressure transients in the brain of animals subjected to blast TBI. The existing LLNL sensors were found to have limitations that prevented measurement of pressure in a wet environment such as a living brain. We engineered modifications that resulted in making sensitive and accurate pressure measurements in the brain of rats subjected to fluid percussion TBI. Intracranial pressure measurements in rats from the modified sensors directly corresponded to the extracranial pressure measurements recorded by the standard pressure transducer at the outlet of the fluid percussion device. Further engineering modifications allowed for precise and reliable measurements of temperature with the modified sensors. A shortcoming of the modified sensors was the inability to measure very low pressures associated with biological ICP from brain edema (less than 1 psi). Engineering calculations indicate that a thinner sensor diaphragm will make such small pressure measurements feasible without compromising high pressure measurements associated with blast TBI. The third generation sensors are planned to be designed and fabricated for the option year of this project.

“So What Section”: What is the value of the scientific knowledge of this sensor project? These extremely small, implantable sensors will provide a unique opportunity to collect pressure and temperature measurements within the brain of an animal subjected to blast TBI. Little is known about how external pressure variations from blast translate into pressure changes within the brain. Only a limited number of studies (Bauman, et al., 2009; Chavko, et al., 2007) have examined rapid pressure changes in the brain from exposure to blast. Data from our sensors will also be extremely useful for characterizing animal blast TBI models. For example, how does the orientation of an animal in a blast tube or in a chemical blast situation influence the pressure transient within the brain? How do pressure transients within the brain relate to brain pathology? Another important aspect of these sensors is the ability to measure long-term biological ICP associated with brain edema and swelling. These indwelling sensors can provide a comprehensive time course of the brain pressure response to TBI. Finally, the temperature measurements from the modified sensors will be valuable for determine the effects of high temperature chemical blast explosions to brain function. Past research has documented that raising the brain temperature by as little as 2-3 degrees C can result in significant worsening of outcome after TBI. Laboratory and clinical studies have demonstrated that elevated brain temperature following TBI is associated with increased pathology and worsened outcome (Clifton, et al., 1991; Sacho and Childs, 2008). Inflammatory cytokines (e.g., IL-1beta and TNF-alpha) which are associated with pyrexia (Dunn, 2006) are significantly elevated in brain following TBI (Bartfai, et al., 2007) and may contribute to elevated brain temperature. Furthermore, warfighters in the Mideast War Theater are exposed to environmental conditions (desert heat in full battle gear) that may influence regional brain temperature. Virtually nothing is known about regional changes in brain temperature following blast TBI. Development and testing of multifunctional sensors with temperature sensing capabilities will be highly valuable for determining heat transfer characteristics to the brain in future experiments of blast TBI. Does the brief high external temperature from an explosive blast raise brain temperature? Do perturbations in the brain from blast cause biological reactions that result in higher brain temperature? Such questions can be readily addressed using the sensors under investigation in this project.

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