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Towards Integrated MEMS for Mechanical Studies of Embryonic and Adult Mammalian Brain

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We are currently pursuing two projects involving mechanical studies of mammalian brain that will ultimately use integrated MEMS microsystems. In the first project we intend to elucidate the role of mechanical tension in cerebral cortex development. The cerebral cortex is an integral part of the central nervous system (CNS) and comprises a diverse collection of neural structures, each with an intricate internal architecture. It is thought that mechanical tension is a major driving force for many aspects of CNS morphogenesis [1], but this possibility has been intractable experimentally using traditional approaches. We intend to quantify the relationship between tension and its effect on neurogenesis. In this study, 400μm-thick slices of embryonic mouse brain tissue are adhered to flexible PDMS membranes using fibrin gel. The tissue is held in a shallow well, and fluid access holes along the bottom of the well allow media and gas exchange on both sides of the tissue (Figure 1). Stretching the membranes produces tension in the tissue. To date we have achieved various levels of stretching, resulting in membrane strains ranging from 8% to 15%.

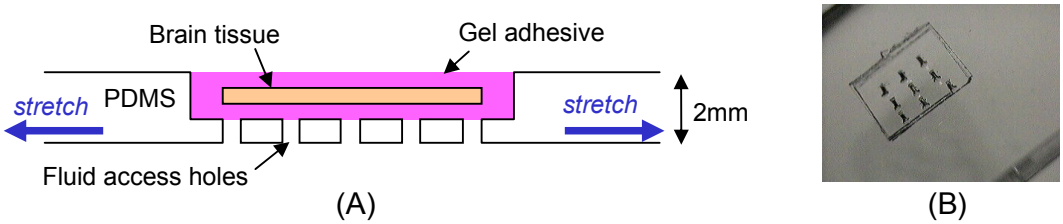

Figure 1. (A) Cross-section of membrane and tissue, (B) photo of a typical well (6mm^2, 400 – 700μm deep).

To date we have cultured embryonic mouse brain tissue (embryonic day 10.5) under tension for six days. The tissue exhibited extensive cell migration and spreading, which are normal and expected processes in living tissue. Subsequent Hoechst staining of the tissue showed intact nuclei, verifying tissue viability (Figure 2). We are currently designing a MEMS microsystem to deliver tensile forces to groups of neurons from embryonic cerebral cortex. The integrated system will use micromachined clamps to hold the membrane, while a microactuator will provide a quantified force to the membrane, and thus to the tissue.

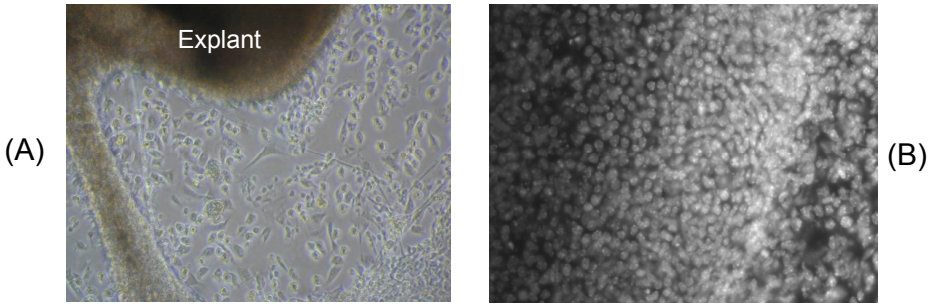

Figure 2. (A) Optical photography showing cell migration in stretched tissue after6 days in culture (100X). (B) Hoechst stain micrograph showing viable nuclei (400X).

The second project involves assessing the mechanical compliance of critical regions in the hippocampus of adult rat brain. Head injury affects over a million people each year in the United States and can lead to neurological disorders such as epilepsy. The hippocampus is the area of the brain responsible for memory and learning, and postmortem examinations of head-injured rats often reveal selective damage to this area. Within the hippocampus, certain regions are more susceptible to damage than others [2]. Protein expression studies suggest that cytoskeletal differences between the various hippocampal regions may influence mechanical integrity [3]. By measuring regional mechanical compliances directly, we intend to reveal the basis for this selective vulnerability.

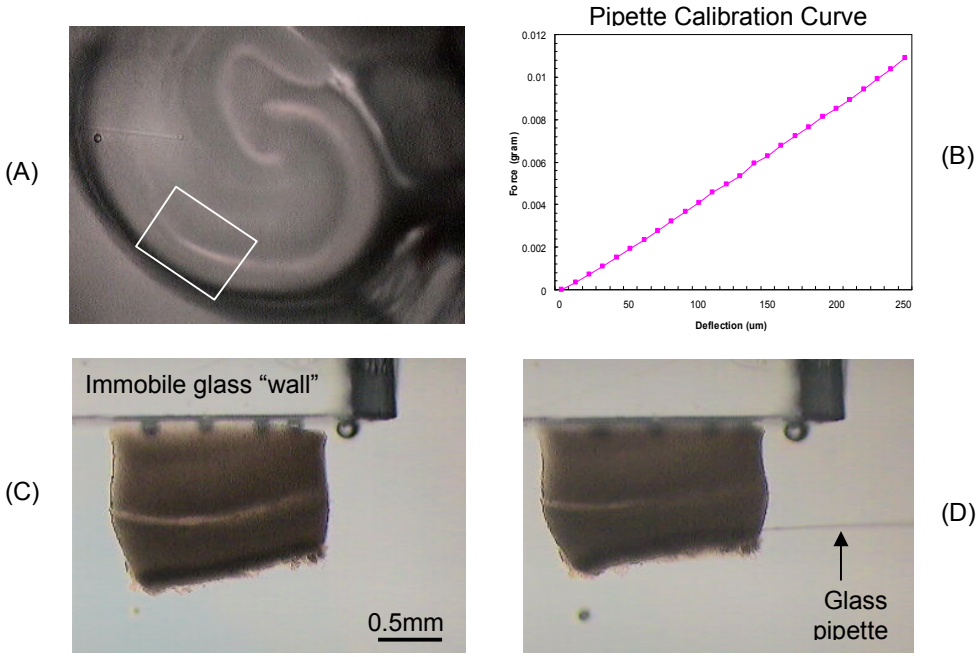

Figure 3. (A) 400µm-thick slice from adult rat hippocampus (40X magnified). (B) Typical calibration curve for the pipettes used. (C, D) Section highlighted in (A) as dissected and after deflection by a glass pipette.

The spring constant of 400µm-thick, millimeter-sized tissue samples dissected from adult rat hippocampus was initially measured using glass pipettes (Figure 3). A test chamber was constructed that consisted of a bath with a 0.5cm^2 piece of glass glued in the center. The glass served as a "wall," and the tissue was deflected against it. The bath was filled with artificial cerebrospinal fluid, and then the pipette (attached to a 3-axis micromanipulator) was brought in contact with the tissue. The spring constant of the pipette was separately calibrated using a high precision pan balance prior to the experiment. By visually measuring both the tissue and beam deflection, the spring constant of the tissue was derived. Preliminary results indicate the spring constant of the tissue ranges from 0.02 - 0.1 N/m depending on the location of the sample in the hippocampus and the extent of tissue deflection. We are currently designing a MEMS microsystem to measure the mechanical stiffness with greater precision and sensitivity. It will include polycrystalline silicon strain gauges, integrated signal processing electronics, and will be fabricated using standard processes.

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