Mechanisms of Brain Injury: Effect of different loading rates on mechanical, electrical, and chemical responses in cells and tissues

S&T Campaign: Sciences for Lethality & Protection
Battlefield Injury Mechanisms

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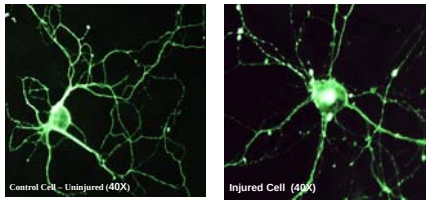
Research Objective

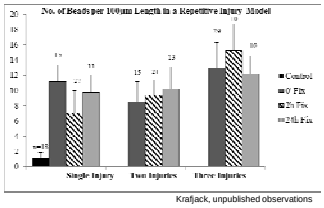
Test the hypothesis that loading rate affects the **M**echanical/**E**lectrical/**C**hemical response of brain (cells and tissue) at different length scales

1. **Develop** methods to create high rate loading at different length scales
2. **Evaluate** the MEC response and mechanisms after high-rate loading
3. **Formulate** cellular injury criteria from MEC thresholds

Mechanical & Morphological Response



Incidence Of Axonal Swelling Increases With Injury, Further Increasing With Repetitive Injuries And Time After Injury



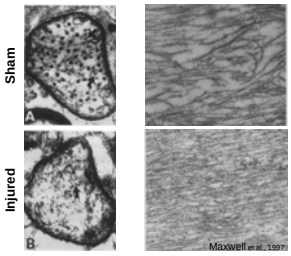
Krajack, unpublished observations

Chemical Response

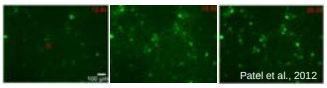
Impaired Axonal Transport

Mechanisms of Impaired Axonal Transport (Microtubule disruption)

Mechanisms of structural damage to the axon (Neurofilament Compaction)

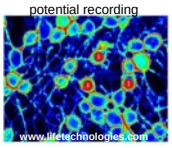


Time-lapse Ca^{++} Imaging

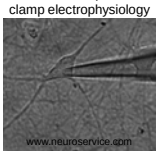


Electrical Response

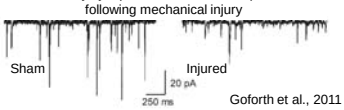
Live cell membrane potential recording



Whole cell patch clamp electrophysiology



Excitatory synaptic transmission is depressed following mechanical injury



Goforth et al., 2011

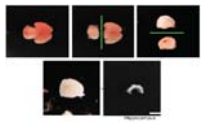
Challenges

- Novel in situ experimental methods are needed to understand the effects of different loading rates and stress-states on cells.
  - Mechanical/electrical/chemical response of cells is not fully understood.
  - MEC coupling is not understood.
- New mathematical models needed to relate MEC response to different rates of loading.
- Stress measuring methods do not exist.
- Visualizing cells in real time during injury.
- Response of cell and tissues to coupling of pressure and strain is not understood. New experimental methods are needed to understand the pressure-strain coupling.

ARL Facilities and Capabilities Available to Support Collaborative Research

- We are developing in situ experimental methods to monitor the **Mechanical** response of **cells** and **tissues** during and following various loading paradigms.
- Establishing techniques to measure the **Electrical** response from the cellular to network level following mechanical loading.
- Institute methodologies to evaluate **Chemical** response following mechanical loading.

E18 Rat



Microdissection of Hippocampus

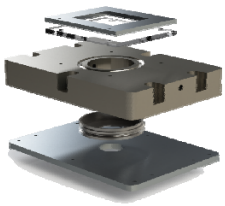
Cultured 11 DIV on Silastic Membranes

Cell Injury Controller II

Confocal Microscopy

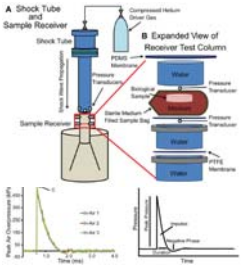
Flex Cell Injury Device

Biaxial Stretching Device



Live Cell Imaging

Blast Tube for Cell Cultures



Complementary Expertise/ Facilities/ Capabilities Sought in Collaboration

- Modeling uncoupled and coupled MEC responses to rate dependent mechanical loading.
- Cell culturing methods.
- Novel staining methods to quantitatively evaluate cell and tissue response.
- Stress measuring methods at cellular scale.
- Micro-electrode arrays embedded in flexible substrates.
- Behavioral studies to correlate with measured MEC responses.

[1] A.M. DiLeonardi, J.W. Huh, R. Raghupathi. Impaired axonal transport and neurofilament compaction occur in separate populations of injured axons following diffuse brain injury in the immature rat. *Brain Research*, 1262:174-82, 2009.
[2] A.M. DiLeonardi, J.W. Huh, R. Raghupathi. Differential effects of FK506 on structural and functional axonal deficits after diffuse brain injury. *J Neuropathol Exp Neurol.* 71(11):959-72, 2012.
[3] B. Sanborn, T. Weerasooriya. Quantifying Damage at Multiple Loading Rates to Kevlar KM2 Fibers Due to Weaving, Finishing, and Pre-Twist. *International Journal of Impact Engineering*, 71:50-59, 2014.
[4] B. Sanborn, A.M. DiLeonardi, T. Weerasooriya. Tensile Properties of Dyneema SK76 Single Fibers at Multiple Loading Rates Using a Direct Gripping Method. *Journal of Dynamic Behavior of Materials*, In Review.
[5] T.P. Patel, S.V. Ventre, D.F. Meaney. Dynamic changes in neural circuit topology following mild mechanical injury in vitro. *Annals of Biomedical Engineering*. 1:23-36, 2012.

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