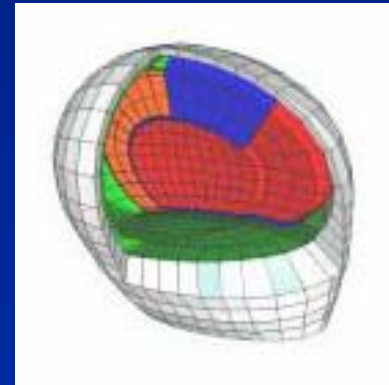
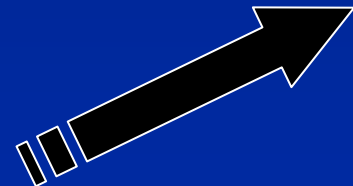
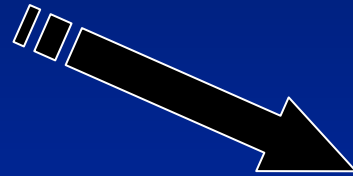
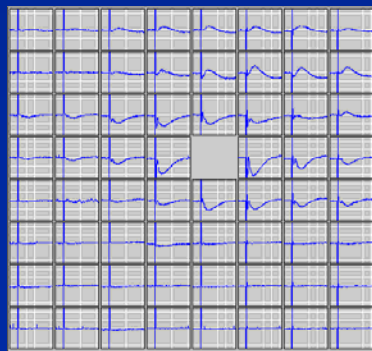




Quantitative Tolerance Criteria for SIMon: Cell Death and Dysfunction

Barclay Morrison III

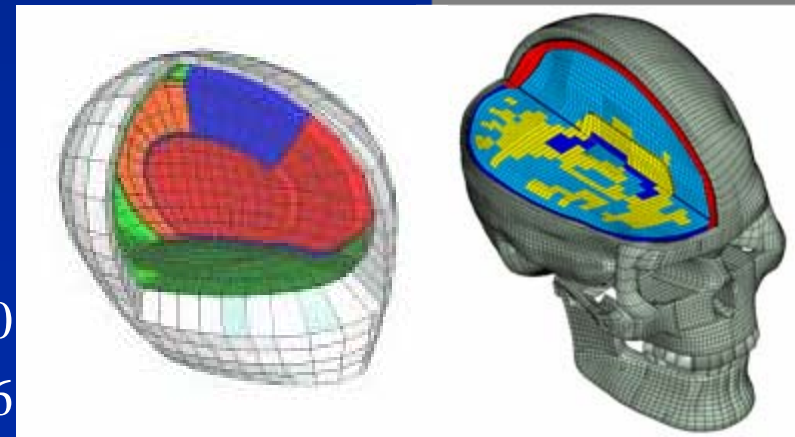
Columbia University



'Virtual' Crash-Test Evaluation



- Human body computational models:
 1. Computational methods (non-linear, large deformation)
 2. Geometry
 3. Interface conditions
 4. Material properties
 5. Compatible tolerance criteria
- Data will support SIMon's cumulative strain damage measure (CSDM)
 - Compatible with other FE models



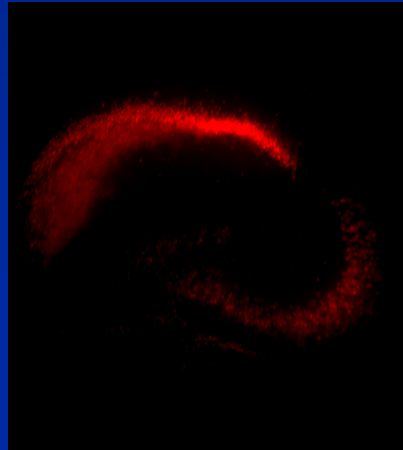
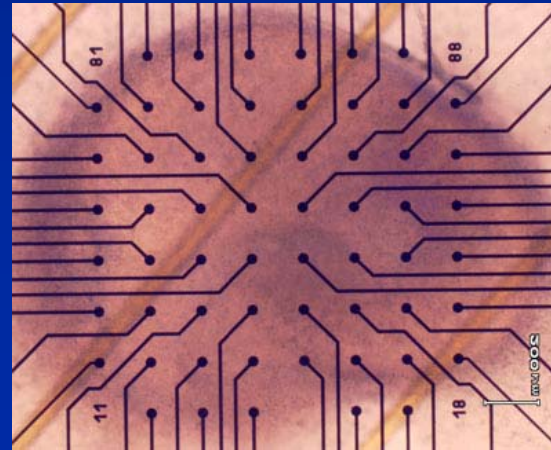
WSUBIM-2000

Zhang, J. Biomech. Eng. (2004), 226

Tissue Level Tolerance Criteria



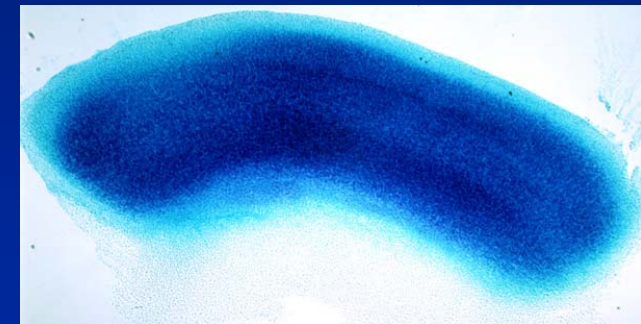
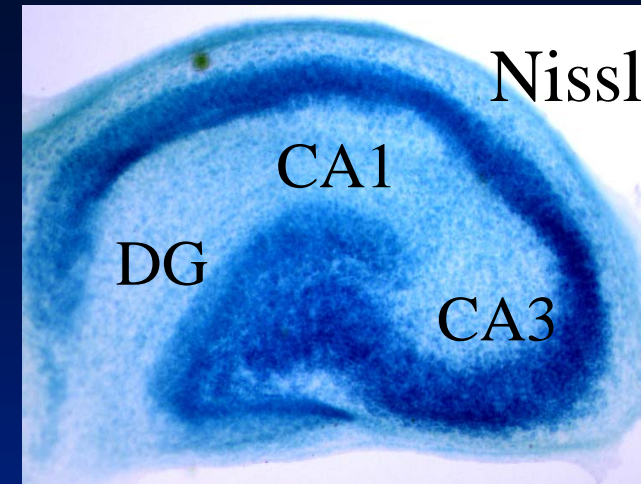
- Directly determine tolerance criteria to deformation
 - *In vitro* model
 - Easy access to the tissue
 - Precise control and verification of biomechanics
 - Cell damage and death
 - Propidium iodide staining
 - Hippocampus
 - Cortex
 - Neuronal function
 - Electrophysiology
 - Hippocampus



In Vitro Injury Model



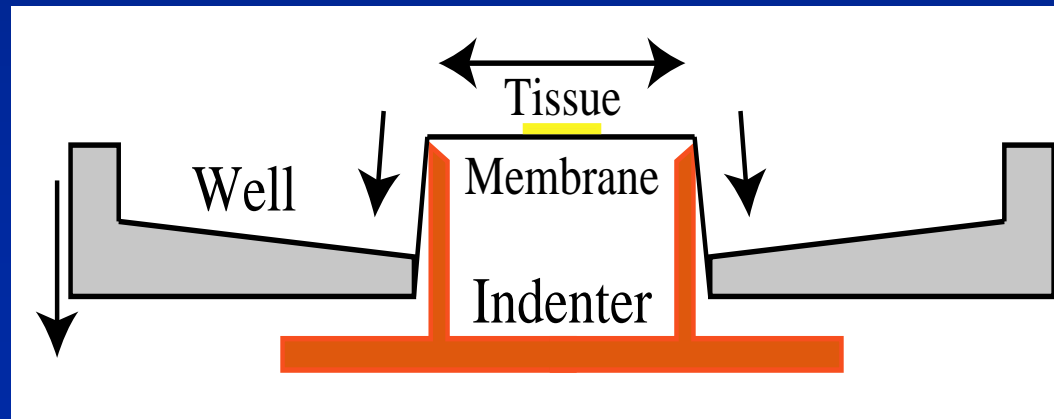
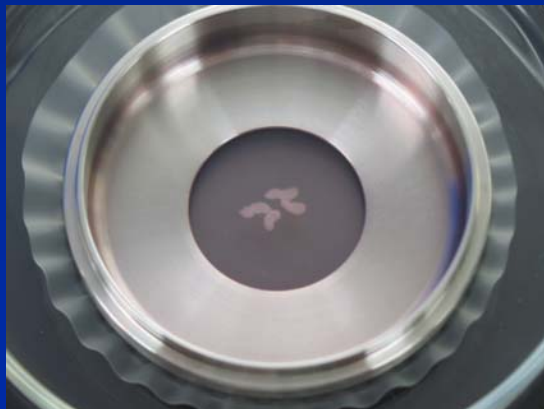
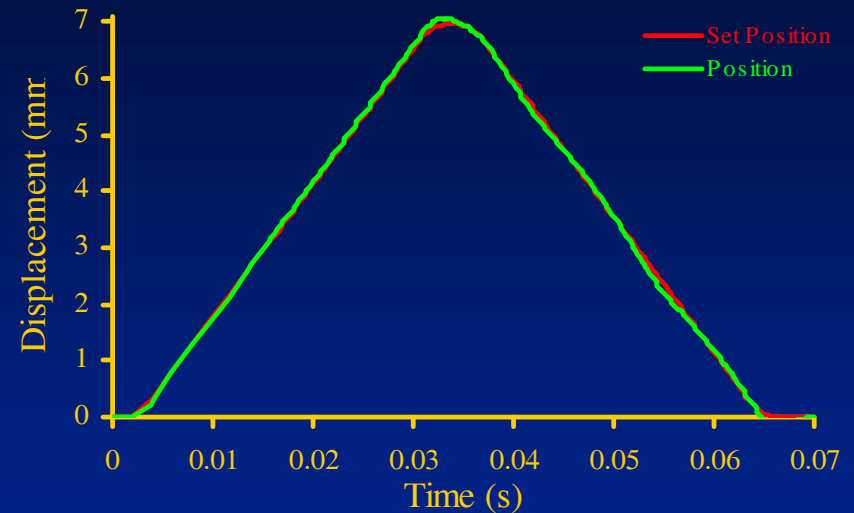
- 2 Components
 - Tissue culture model
 - Organotypic brain slice cultures
 - Maintain anatomical structures
 - Possible to quantify cortical, CA1, CA3, and DG cell death
 - Injury device
 - Precise control over biomechanics
 - Strain and strain rate
 - Sterile injury of the cultures
 - Measure cell death over time



In Vitro Model of TBI



- Precise control of
 - Injury biomechanics
 - Extracellular environment
- Increased access to tissue
 - Repeated measures

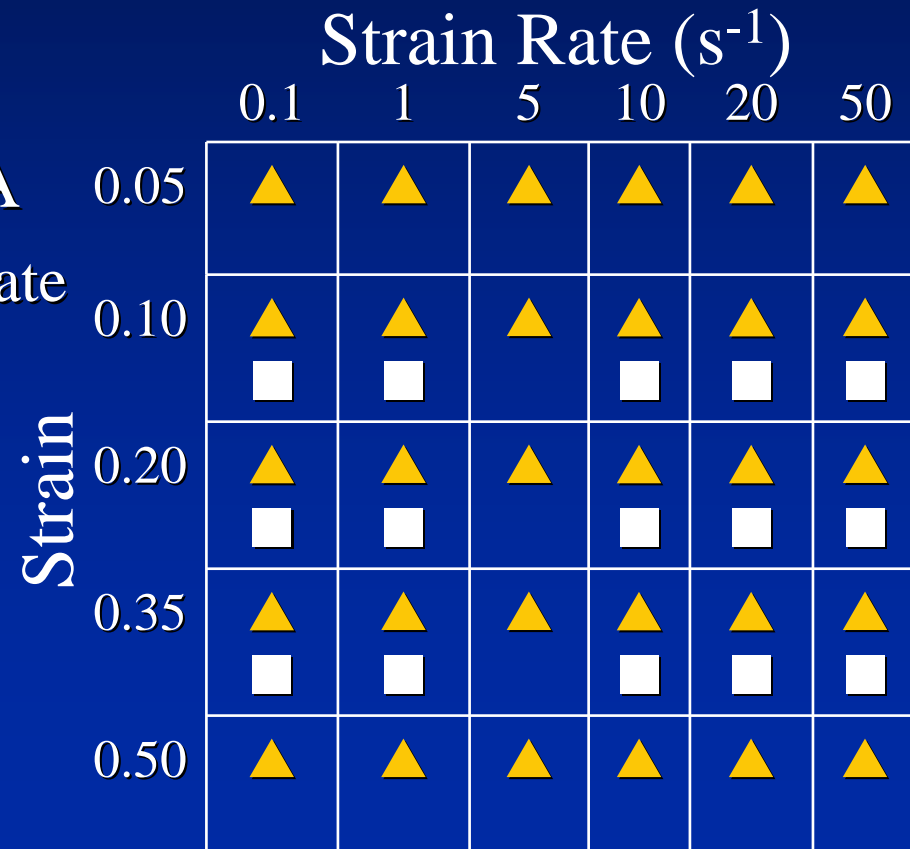


Tolerance Experimental Design



- Different combinations of strain and strain rate
- Measure region specific cell death/damage over time
- Determine tolerance criteria
 - Region specific tolerance
- Repeated measures ANOVA
 - Time X Region X Strain X Rate
- Predictive function

▲ = Hippocampus
■ = Cortex



Cell Death Tolerance Criteria

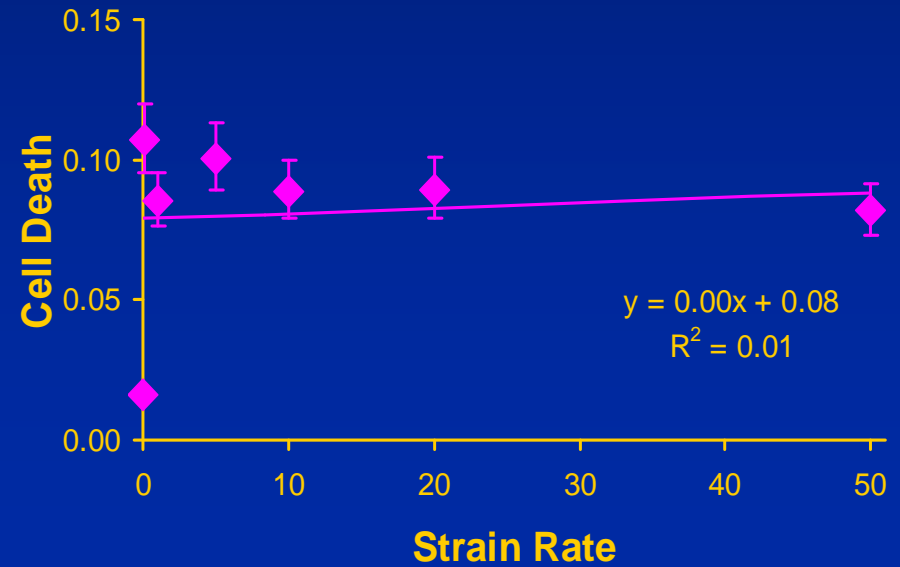
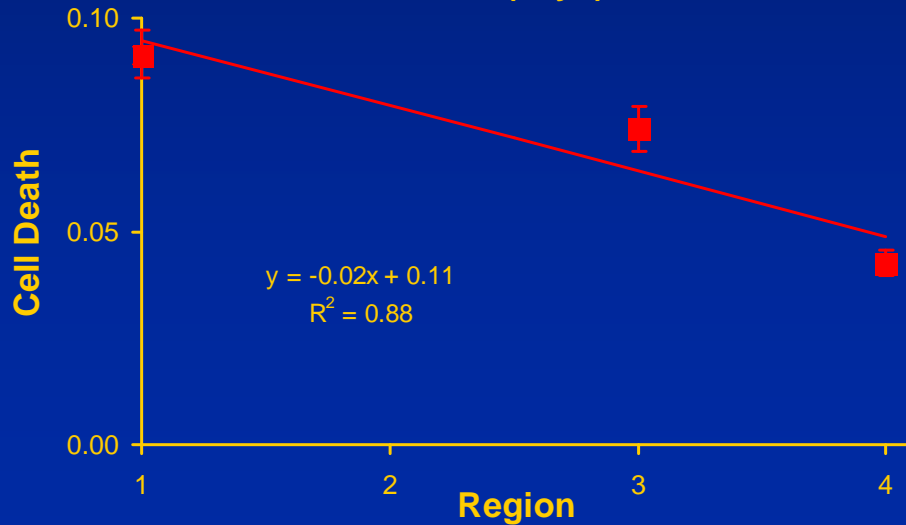
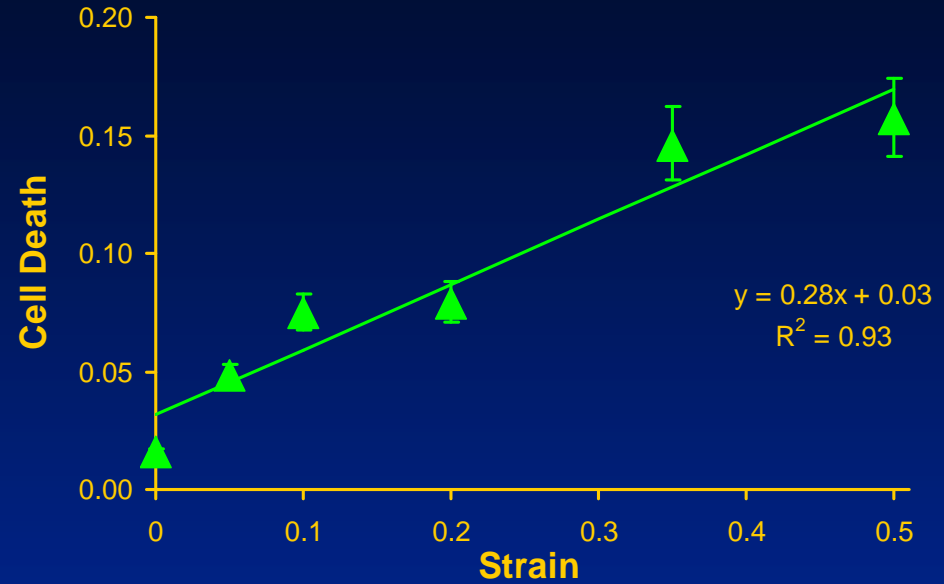
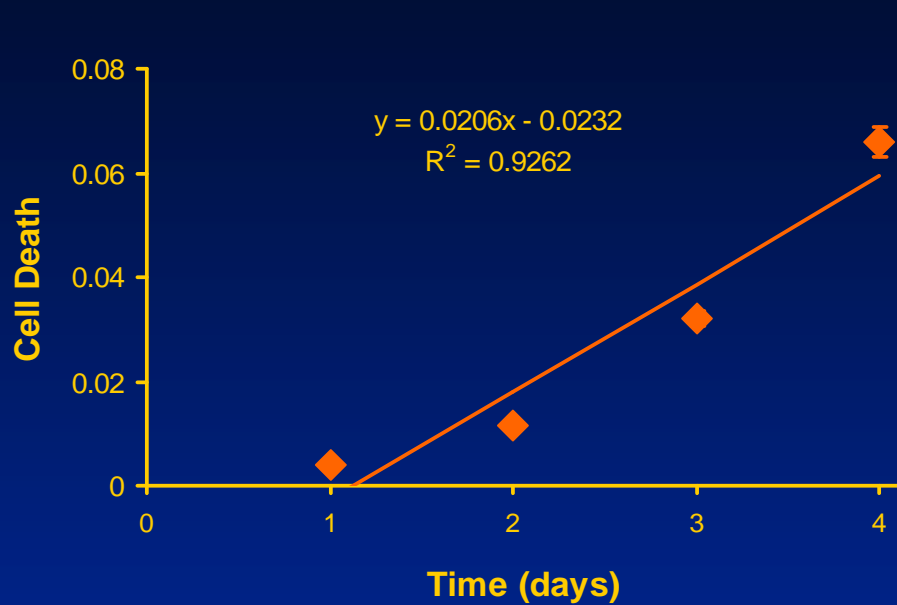


- Repeated measures ANOVA
 - Time dependent
 - Region dependent
 - Hippocampus vs. cortex
 - Even within the hippocampus
 - Strain dependent
 - Strain rate dependent
 - Only in the cortex

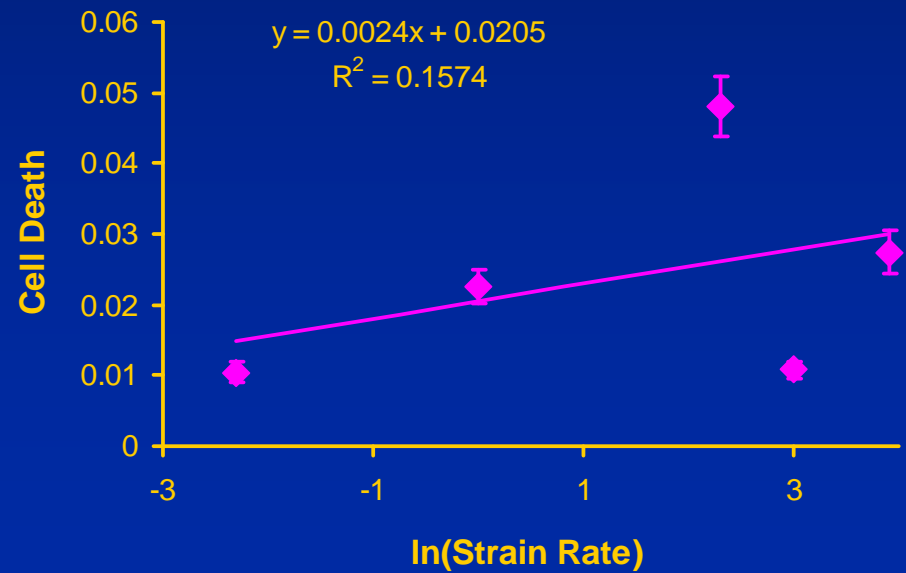
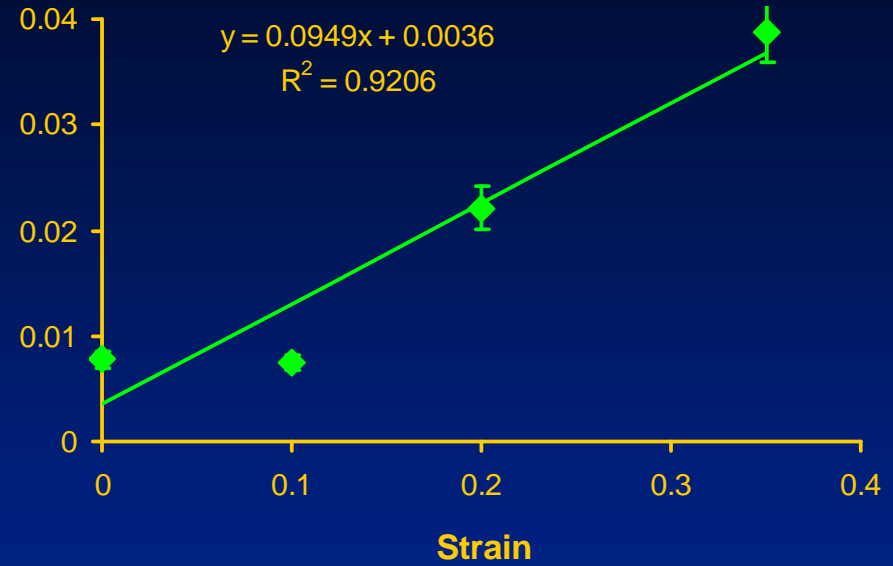
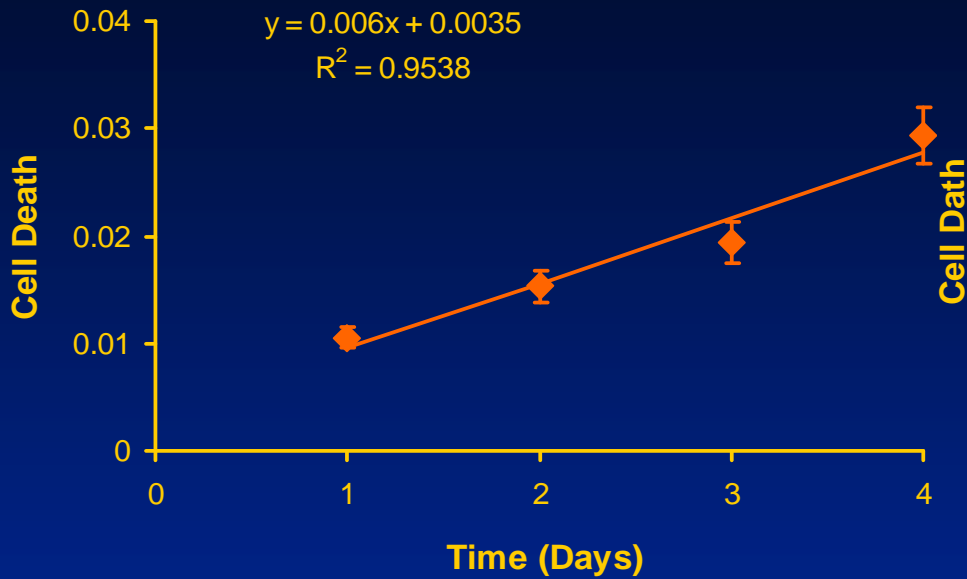
Cater, H. L., Sundstrom, L. E., and **Morrison III, B.**, J.Biomechanics 39: 2810-2818, 2006

Elkin, B. S. and **Morrison III, B.**, Stapp Car Crash Journal 51: 127-138, 2007

Hippocampus Cell Death Response



Cortex Cell Death Response



Cell Death Functions



$$\textit{CellDeath} = f(\textit{Strain}, \textit{Strain Rate}, \textit{Time})$$

$$\textit{CA1 \& CA3} = 0.0389 (\pm 0.0011) \bullet \textit{Strain}^{0.3663 (\pm 0.0029)} \bullet \textit{Time}^{2.0150 (\pm 0.0216)}$$

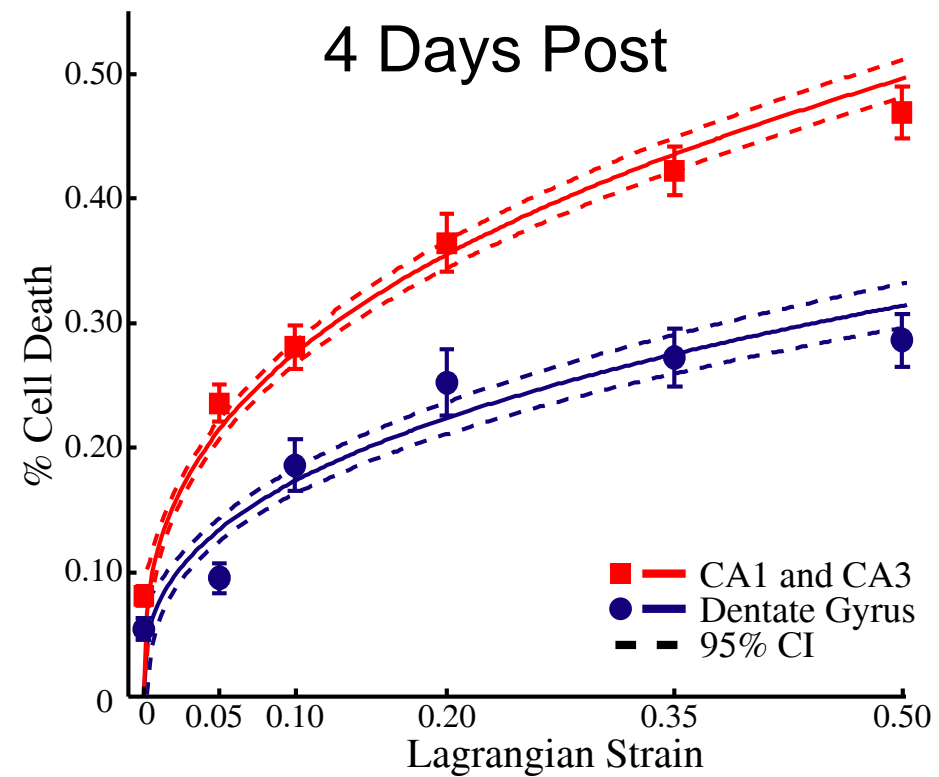
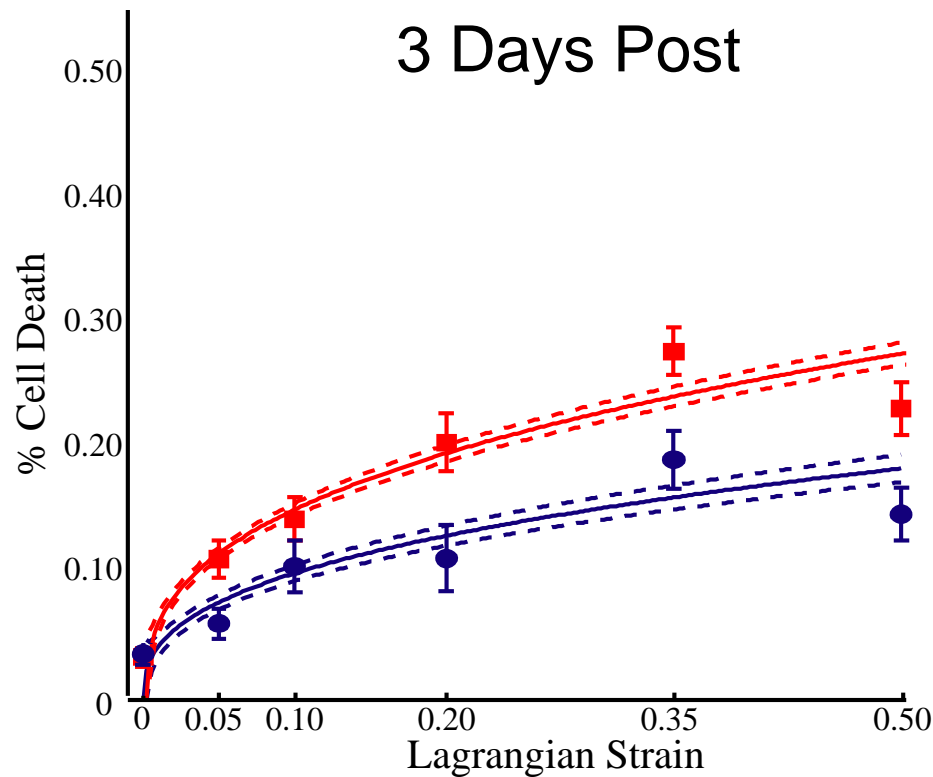
$$\textit{DG} = 0.0323 (\pm 0.0017) \bullet \textit{Strain}^{0.3721 (\pm 0.0056)} \bullet \textit{Time}^{1.8209 (\pm 0.0407)}$$

$$\textit{Cortex} = 0.094 (\pm 0.0021) \bullet \textit{Strain}^{1.5293 (\pm 0.0125)} \bullet \textit{Time}^{0.8337 (\pm 0.0120)} \bullet \textit{Rate}^{0.1175 (\pm 0.0029)}$$

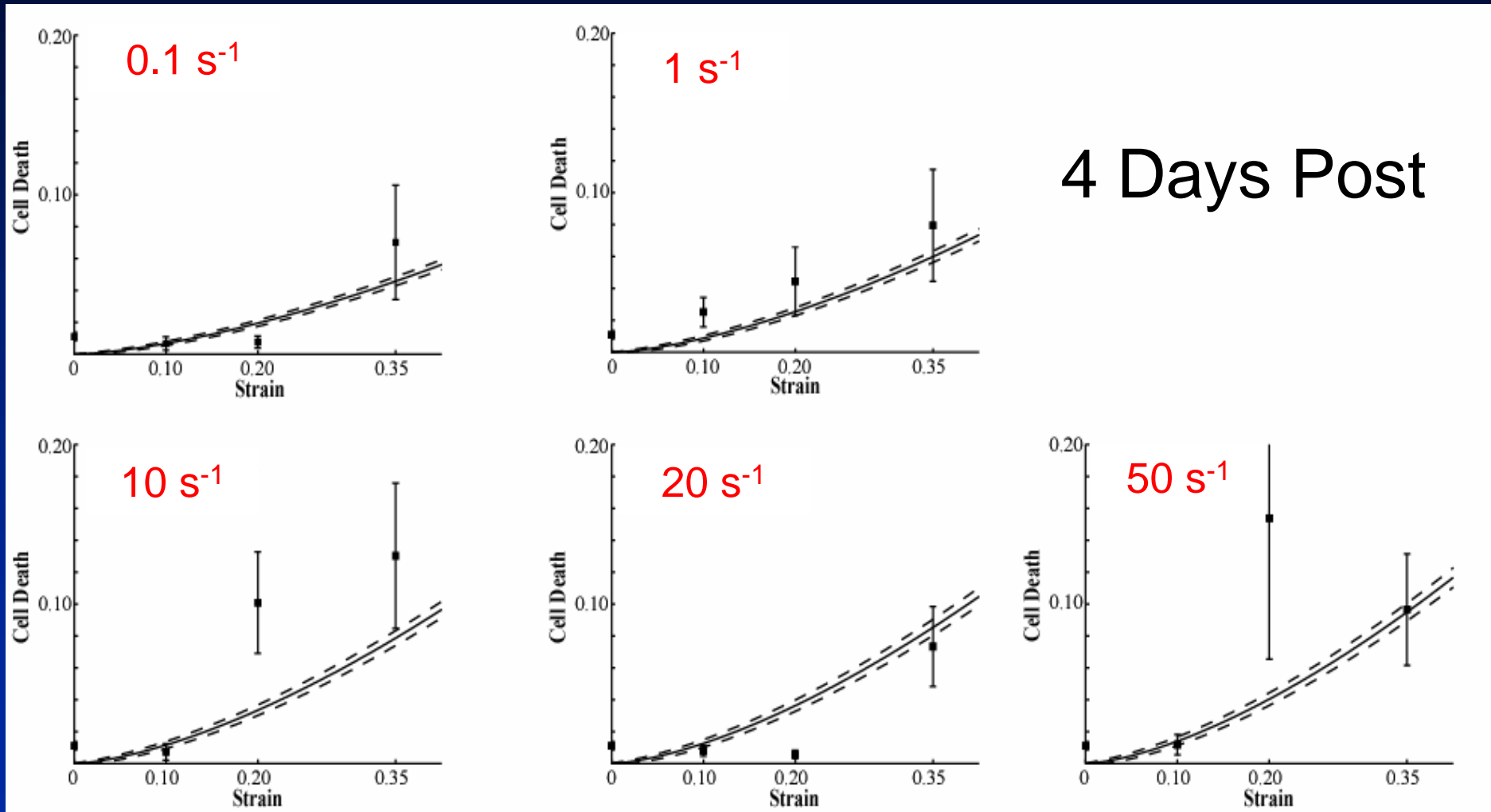
Hippocampus Cell Death



- FE tolerance criteria → cell death prediction
 - No strain rate dependence



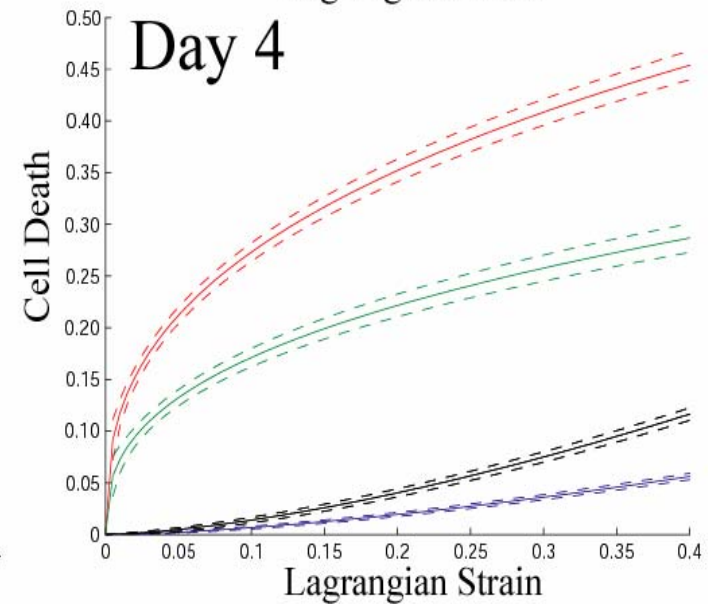
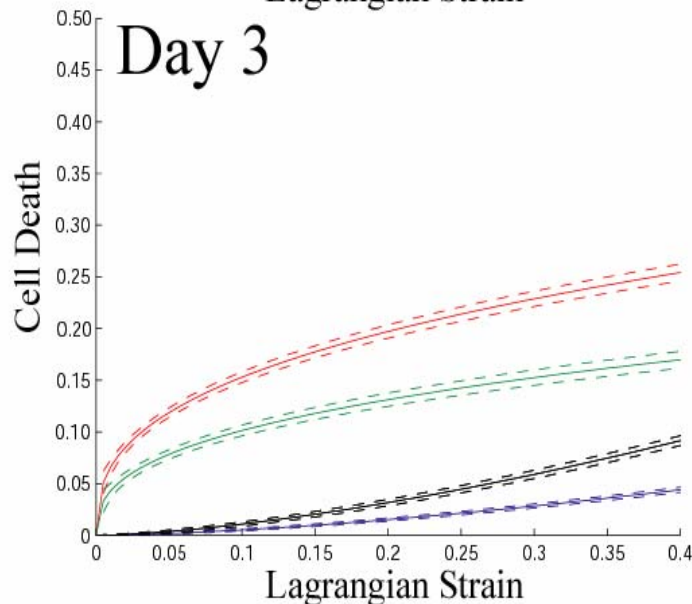
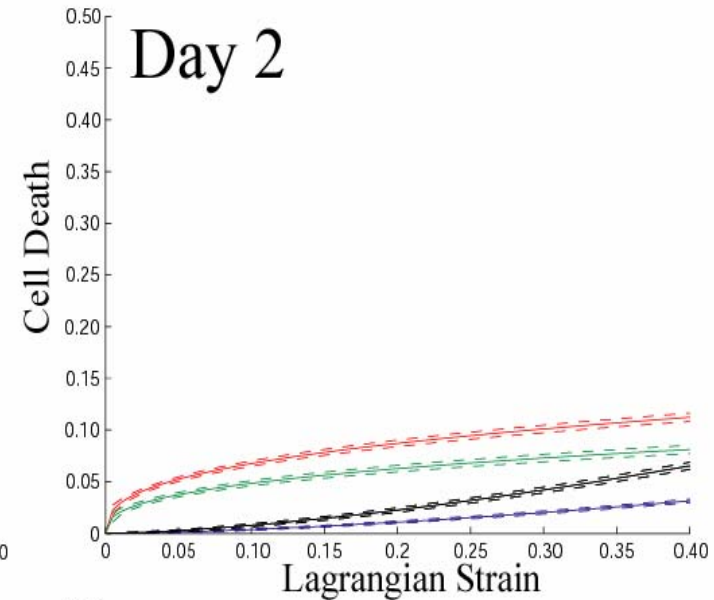
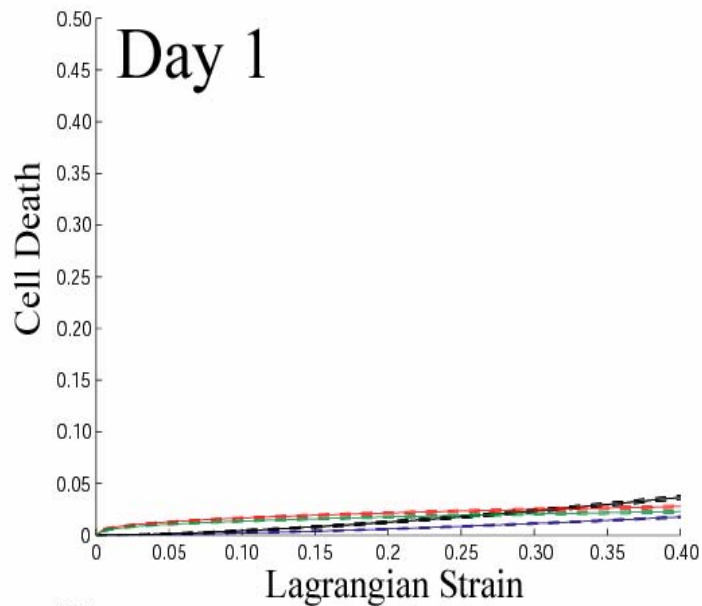
Cortex Cell Death



Tolerance Criteria



- *Hippocampal CA1 & CA3*
- *Hippocampal Dentate Gyrus*
- *Cortex at $50 s^{-1}$*
- *Cortex at $0.1 s^{-1}$*
- - - *95% confidence interval*



Cell Death Comparison



- Cortex is less vulnerable to injury
 - Max ~10% cell death at large strains and strain rates
 - Threshold between 0.10 and 0.20 strain
- Hippocampus death is not strain rate dependent
 - Cell death increases dramatically at days 3 and 4
- Regionally distinct response to deformation
 - FE models should include this heterogeneity
 - To provide accurate, regional predictions of cell death

Functional Tolerance Criteria



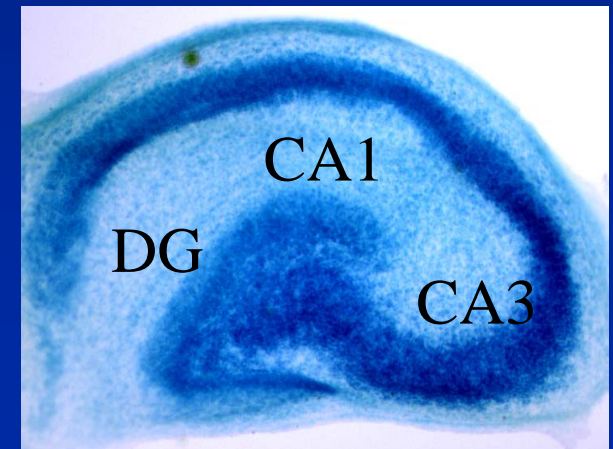
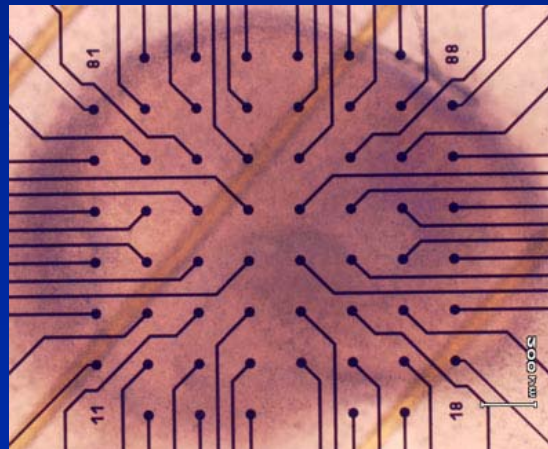
- Relationship between
 - Mechanical injury
 - Electrophysiological function
- Likely more sensitive than cell death
- May be more directly clinically relevant
 - i.e. being dazed, coma, learning impairment

Functional Tolerance Criteria



- *In vitro* TBI model
- Graded injury severity
- Stimulus / response curves
 - Stimulate either
 - Mossy fibers
 - CA3 Schaffer collaterals
 - Record
 - CA1C, D
 - CA3C, D
 - DG
 - Hilus

		Strain Rate	
		0.10	20
Strain	0.10		
	0.20		

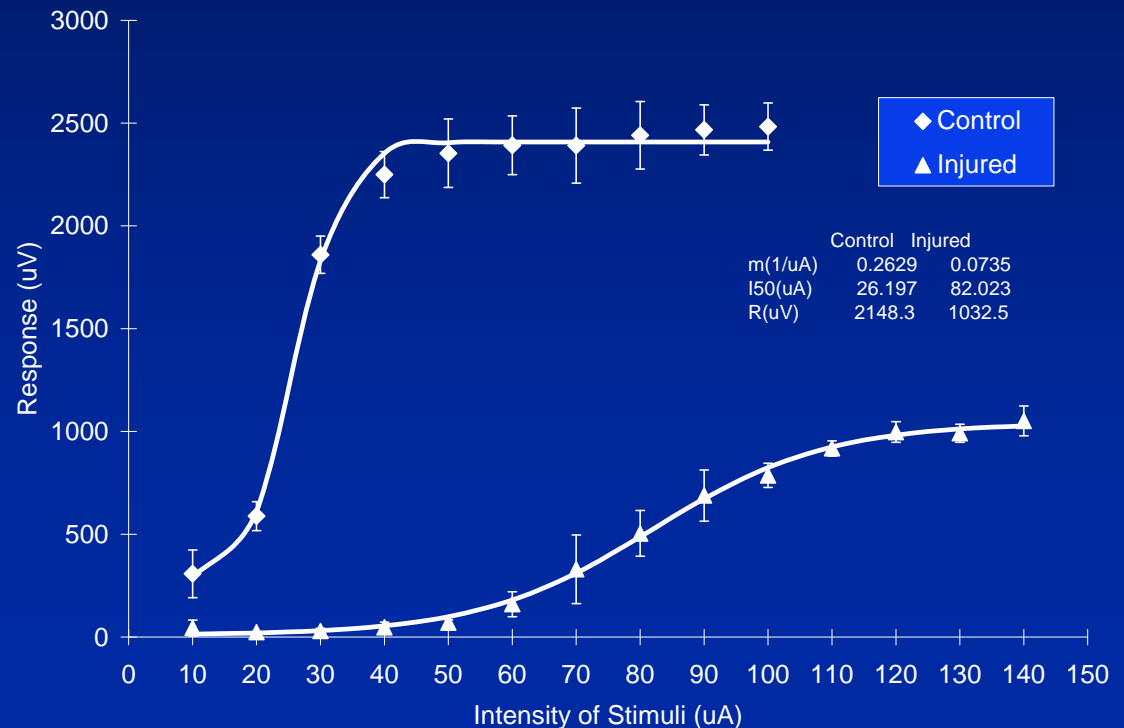


Functional Quantification



- Measure response amplitude
 - Region dependent manner
- Fit to a sigmoidal curve to compare parameters

$$R(S) = \frac{R_{\max}}{1 + e^{m \cdot (I_{50} - S)}}$$

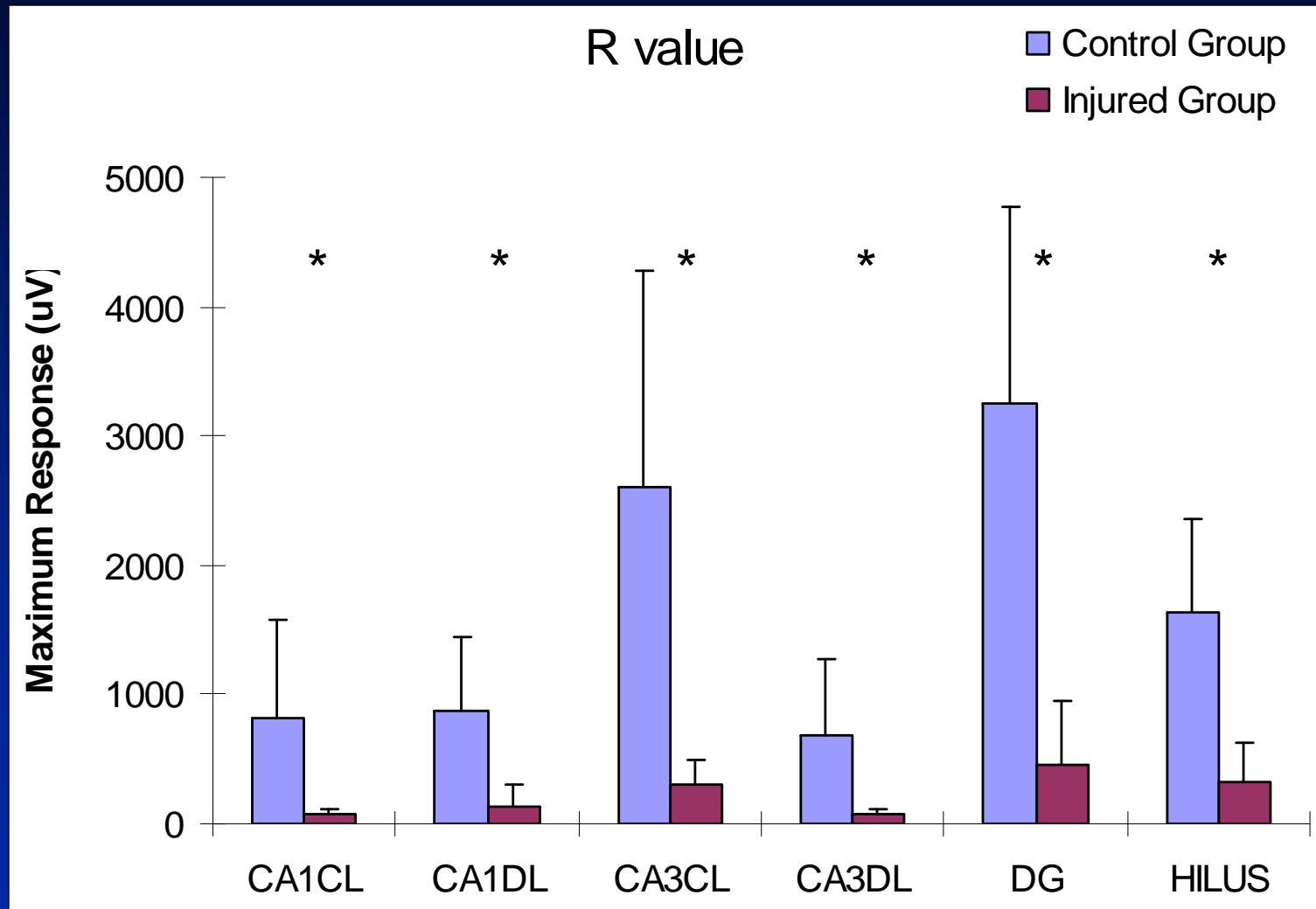


Experimental Design

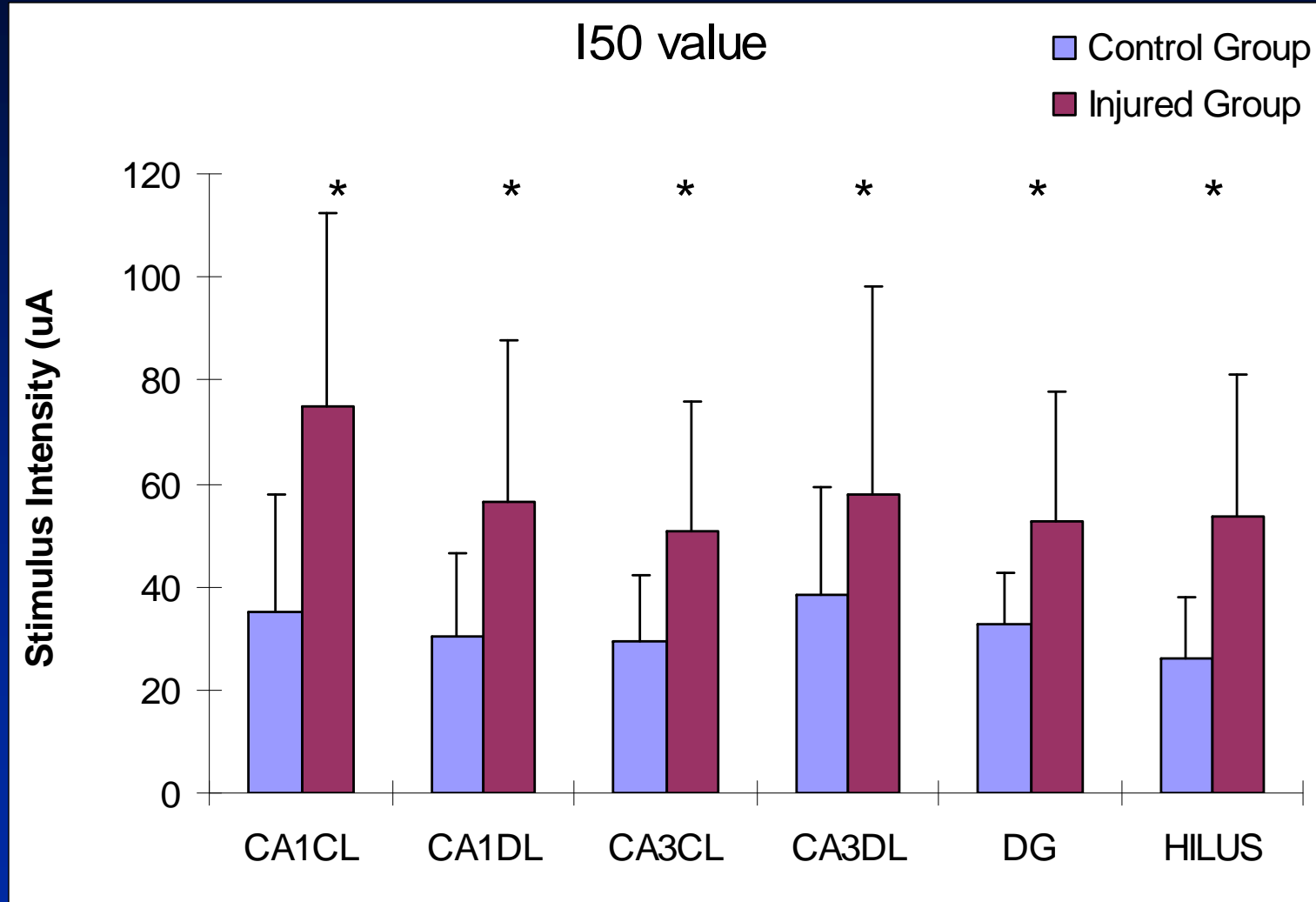


- Moderate to severe injury
 - $E = 0.20$; $E' = 20/s$
- S/R curves measured at 24h post-injury
 - 37°C , aCSF
- Fit data to sigmoid function
- MANOVA (m , R_{\max} , I_{50})
 - Region X Treatment
- Post-hoc tests to identify differences

Decreased R_{max}



Increased I_{50}



Discussion



- Response of controls is location dependent
 - Need to segregate by electrode location
- Early dysfunction after injury
 - At 24h dysfunction precedes cell death
 - Therapeutic window?
 - Tissue is less excitable
 - Requires greater stimulus for half maximal response
 - Tissue response is diminished
 - Maximum response is significantly attenuated

Moving Forward



- Effect of injury severity / biomechanics
 - Increasing groups for different injuries
- Time course of dysfunction
 - Does it simply precede cell death
- Functional tolerance of other regions
 - Cortical dysfunction without overt cell death
- Repetitive mild injury tolerance
- Therapeutic window & treatment studies
 - If cells are rescued, is function normal

Acknowledgements



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- Heather L. Cater

