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Micromechanical Modeling of Brain Injury from Blast-Induced Intracranial Cavitation

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Award Period (5/11/18 to 9/30/19)

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Computational & Cellular Biology of Blast (C2B2) And Combat Casualty Care (CCC) Program Review

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Micromechanical Modeling of Brain Injury from Blast-Induced Intracranial Cavitation

Description: Investigate mechanisms of cavitation-induced brain tissue damage on a microscale resulting from blast exposure to the Naval warfighter

Task 1 – Investigate blast and impact damage to vascular structures through blood-brain barrier (BBB) model and simulation

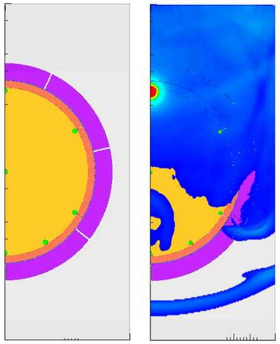
Task 2 – Verify simulations by comparison to experimental damage in cellular networks.

Task 3 – Investigate through simulations the efficacy of notional personal protective equipment (PPE), e.g. helmet to mitigate damage to vascular structures.

Naval Need:

- Blast exposure of naval warfighters may induce fluid cavitation within the brain potentially leading to TBI
- Investigating this phenomenon leads to an understanding of the injury mechanisms & provides tools to investigate injury mitigation strategies with advanced personal armor

Cavitation bubble collapse within the blood-brain-barrier structure – Pressure plot



FY18 Accomplishments:

- Presented at the American Society of Mechanical Engineers (ASME) International Mechanic Engineering Congress & Exposition (IMECE), November 6, 2017, Tampa, FL. Haniff S, Taylor I Blast-induced cavitation leading to damage of the blood-brain barrier. (IMECE2017-72677)
- Completed SNL-UNMHSC SAND Report SAND2018-7333
- C2B2 Project Funding Received April 2018
- Continued microscale investigation of cavitation-induced damage to blood-brain barrier structures (Task 1)
- Performed single element testing of Tillotson EOS (Task 2)

Impact: We provide an understanding of the mechanisms of brain injury resulting from blast exposure

Predicted blast-induced fluid cavitation leads to damage of fine structures in BBB

Dr. Chad Hovey, PI; Sandia National Laboratories

Abstract C2B2

- We will continue our investigation of cavitation bubble damage to vascular structures comprising the blood-brain barrier. We will complete our investigation into the effects of cavitation bubble collapse, which generates localized pressure pulse wavelets and microjetting that cause damage to endothelial layers and the sensitive tissues comprising the inter-endothelial tight junctions. This work will include studying the effects of bubble size, location, and number, in the presence of compressive waves of various magnitudes and loading directions. We will attempt to validate this work through a collaboration with the researchers at Brown University who are currently studying cavitation bubble damage in cellular networks within a laboratory environment.

OBJECTIVE

- **Navy warfighters may have blast exposure, thought to cause TBI by way of cavitation. Our objective is to understand the cavitation injury mechanisms.**

- **We hypothesize that cavitation bubble collapse, leading to micro-jetting, is the mechanism of injury at the micro- and nanometer length scales.**

- **Impact: Our work offers a framework to understand how micro- and nanoscale structures are damaged.**

- **Orig./Excit.: Super sagittal sinus (mm), Axon fiber bundle (um), and BBB (bubble diameter 600 nm).**

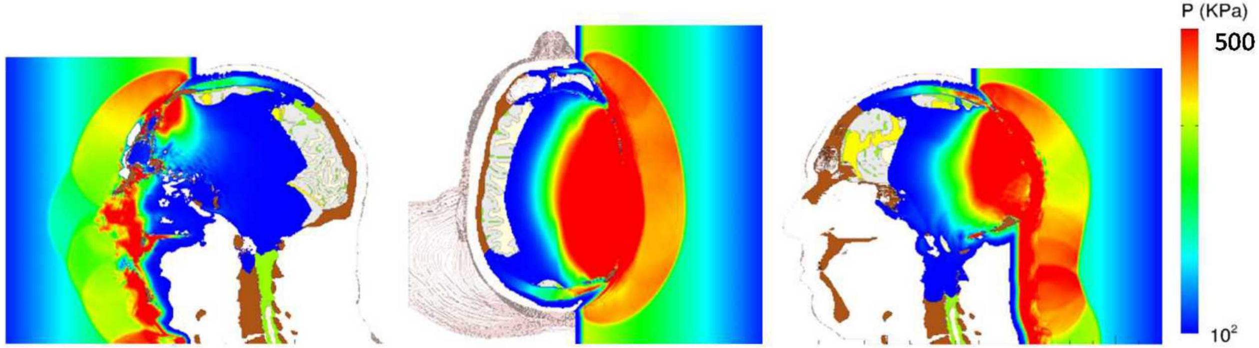
TECHNICAL APPROACH

- **Baseline: Full-scale cadaver head model ("Bob") blast simulations have informed inputs for milli-, micro- and nanoscale models.**
- **Continued investigation on damage to vascular structures comprising the blood-brain barrier (BBB) caused by bubble collapse.**
- **Results parameter space:**
  - **Damage as a function of bubble diameter, location, and density**
- **Risk:**
  - **Lack of experimental data for model verification.**

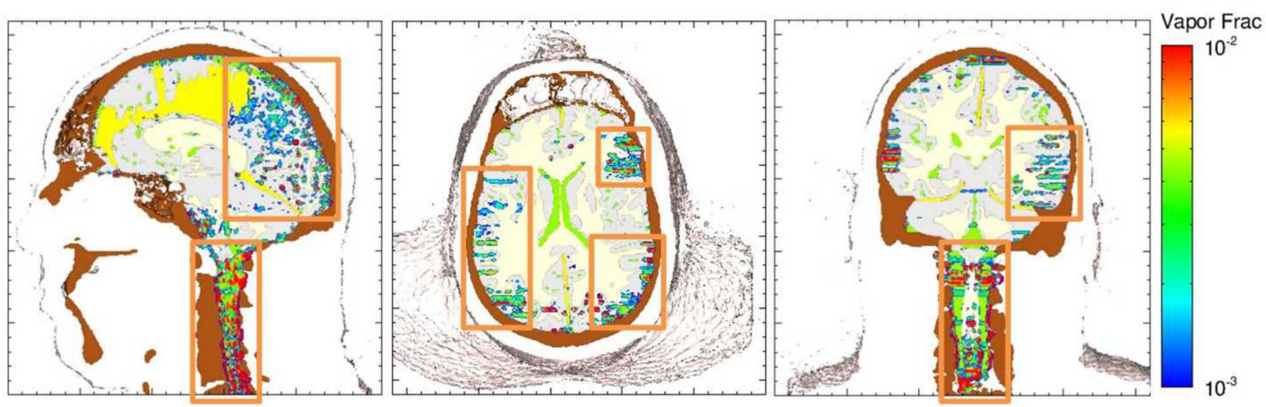
Microscale Modeling & Simulation

Macroscale Blast Simulations predict regions of intracranial fluid cavitation

Intracranial Pressure from 260 kPa Blast



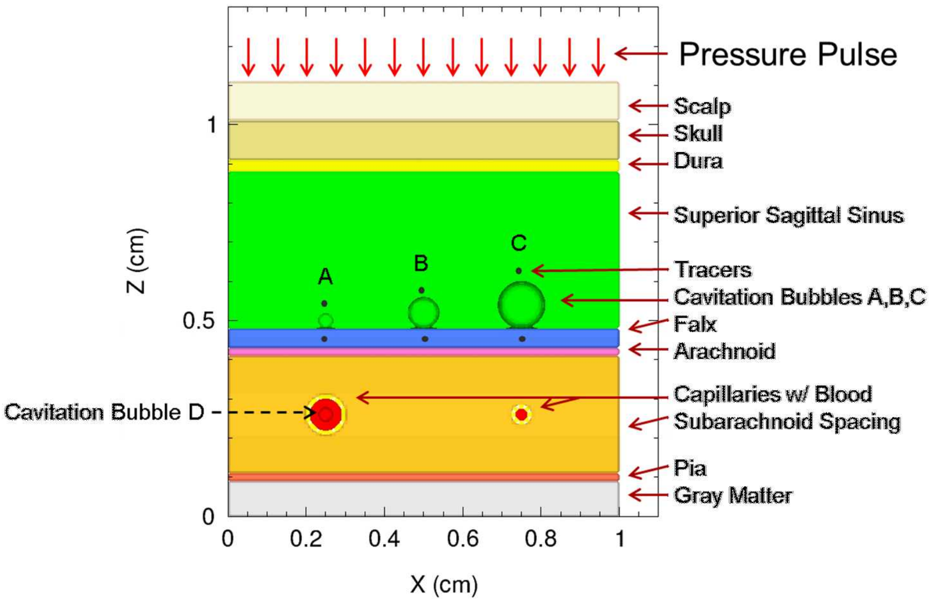
Cavitation Vapor Volume Fraction



Cavitation predicted in white matter regions of the corpus callosum, cerebellum and brain stem → Suggested regions for microscale modeling

Past Microscale Models

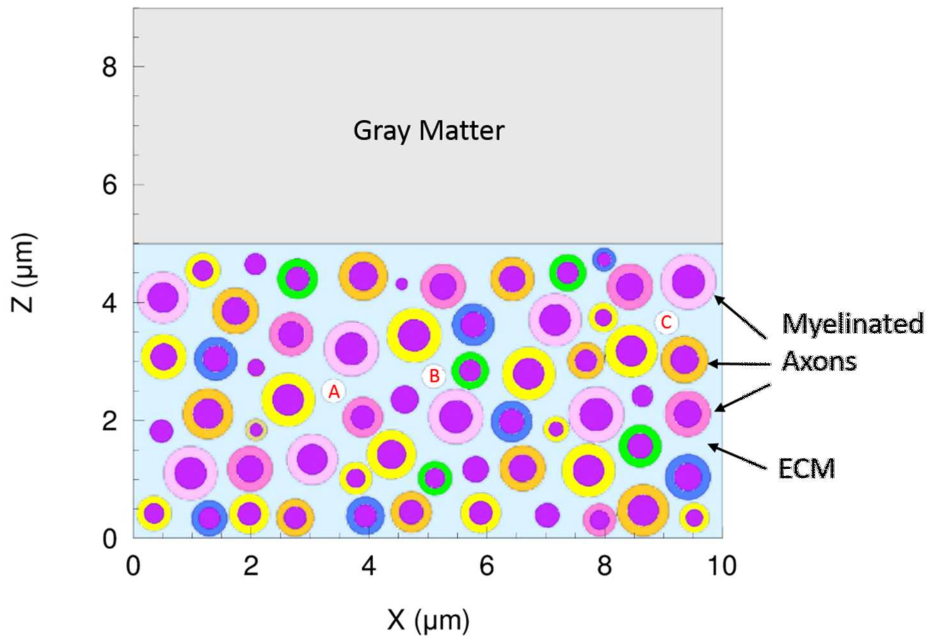
Superior Sagittal Sinus



1 cm x 0.5 cm x 1.25 cm

Bubble Diameter:
A: 0.4 mm
B: 0.8 mm
C: 1.2 mm
D: 0.4 mm

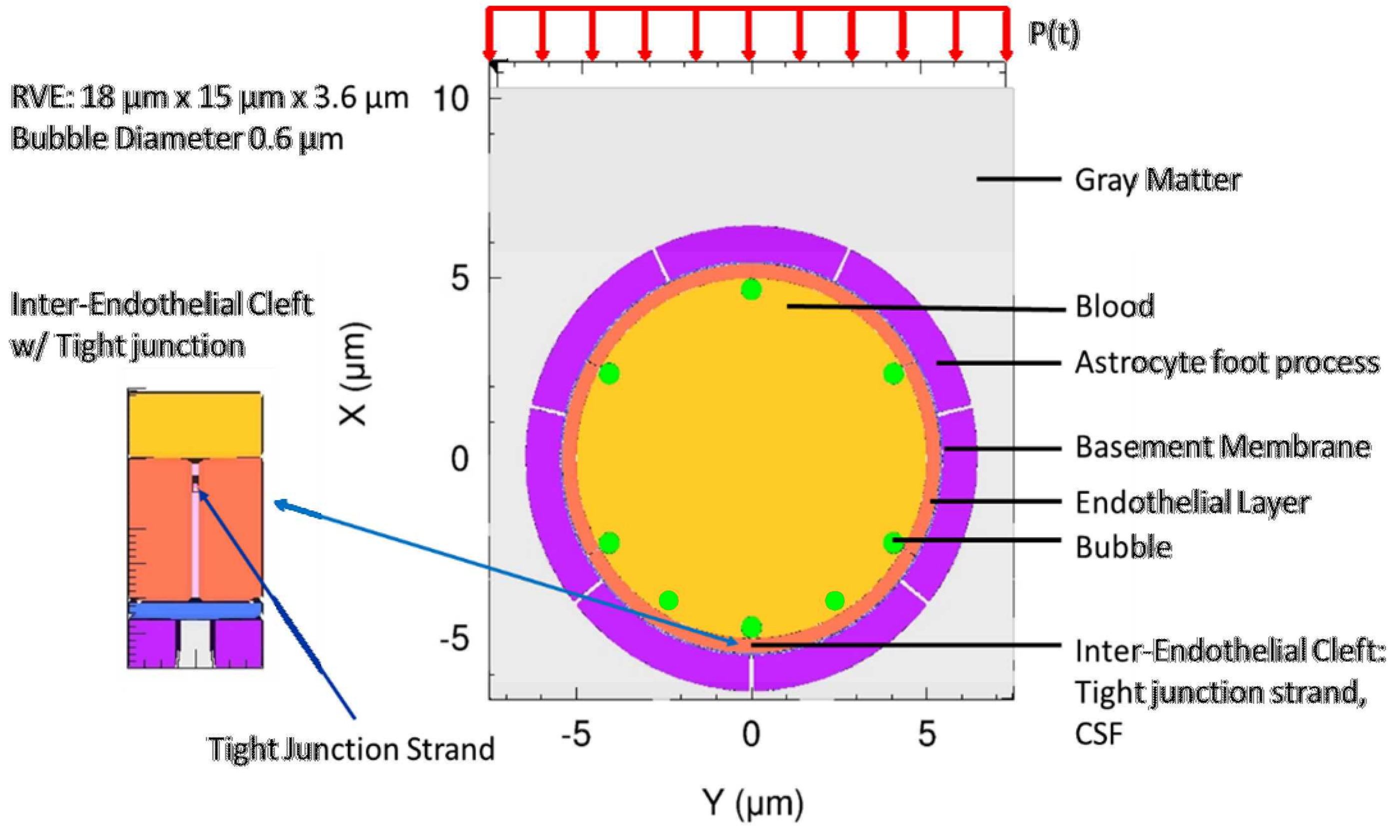
Axonal Fiber Bundles



10 µm x 10 µm x 9 µm

Bubble Diameter of 0.6 µm

Microscale Model of the Blood-Brain Barrier (BBB)

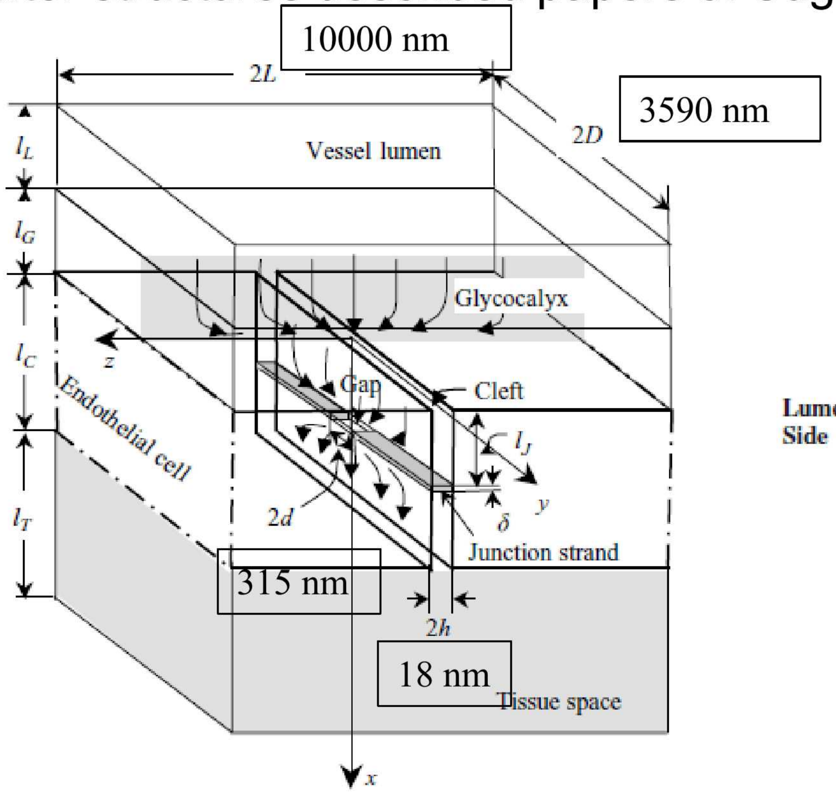


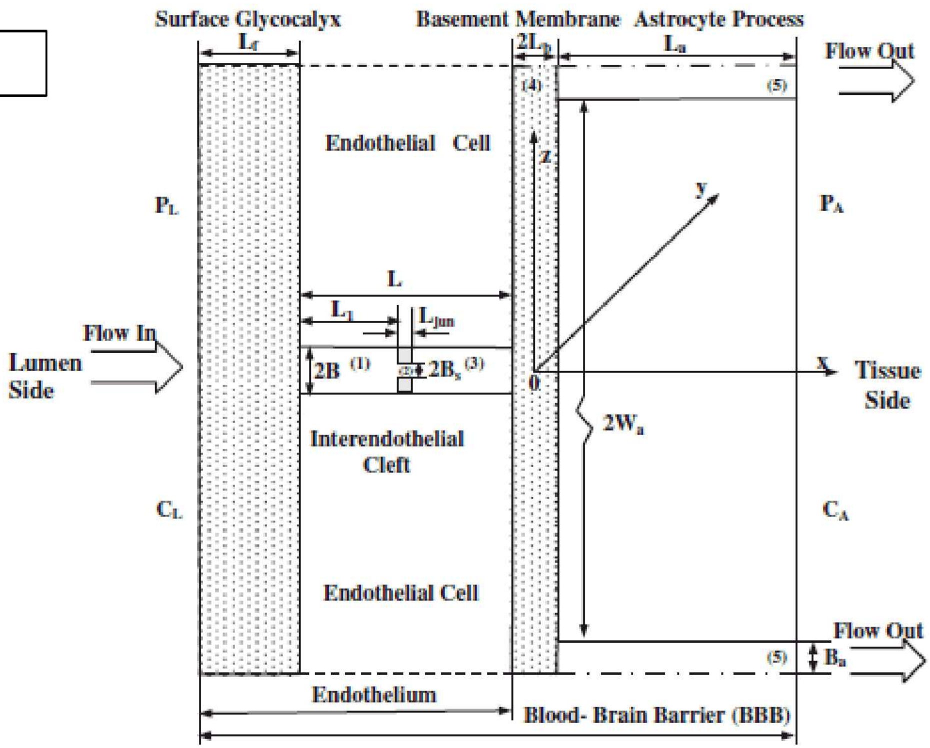
Parameters:
Compressive wave amplitude – 0, 400, 700 kPa
Bubble Diameter – 0.3 µm, 0.6 µm

If bubble collapse causes a member of the BBB to fail, the barrier breaks down, which could lead to neuroinflammation (meningitis) or neurodegeneration

Microscale Modeling & Simulation
Blood-Brain Barrier

Inter-Endothelial Clefts & Tight Junctions adjacent to our bubbles modeled after structures described papers of Sugihara-Seki, et.al. [1], & Li, et.al. [2]





[1] Sugihara-Seki, M., Akinaga ,T., Itano, T., 2008, "Flow across microvessel walls through the endothelial surface glycocalyx and the interendothelial cleft," J. Fluid Mech., **601**, pp. 229-252.

[2] Li, G., Yuan, W., Fu, B. M., 2010, "A model for the blood-brain barrier permeability to water and small solutes," J. Biomechanics., **43**, pp. 2133-2140.

Microscale Modeling & Simulation
Blood-Brain Barrier

Investigate cavitation bubble collapse adjacent to Blood Vessel Wall

- No compressive wave
- Compressive Wave loading (400, 700 kPa)

Hypotheses:

- **Cavitation bubble collapse dependent on:**
  - Bubble diameter
  - Bubble location
  - Bubble density
  - Strength of intracranial stress wave (related to blast strength)

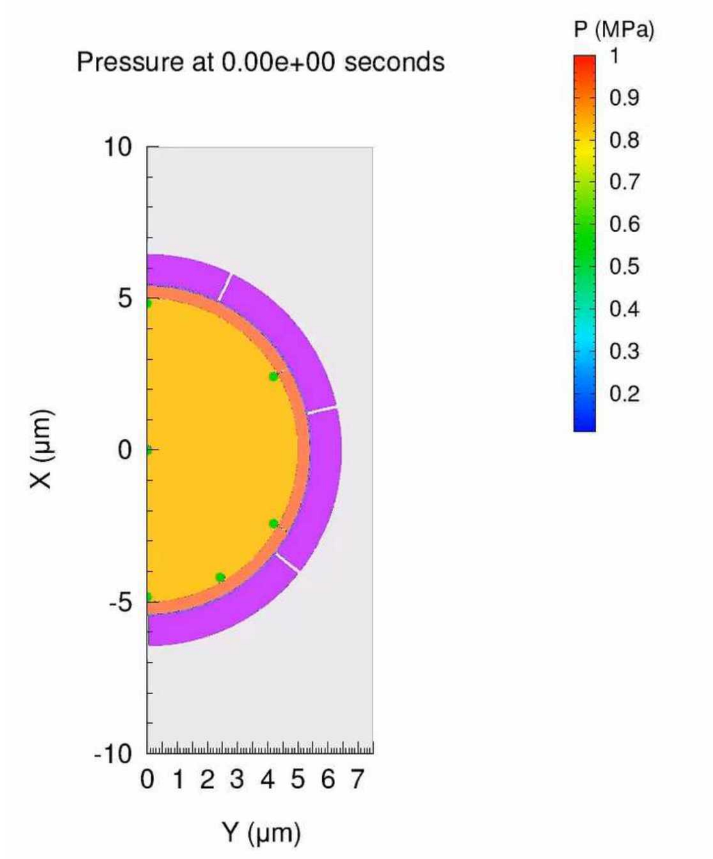
- **Anticipated effects of cavitation bubble collapse:**
  - Increase in pressure and von Mises stress in endothelial layer of vessel wall adjacent to bubbles after collapse
  - Micro-jetting of fluid across bubble into endothelial layer for scenarios with a follow-on compressive wave of 400 or 700 kPa
  - Potential damage to Tight Junctions (TJ) in endothelial layer creating pathways for toxin mobility

Microscale Modeling & Simulation
Blood-Brain Barrier

Investigation of cavitation bubble diameter

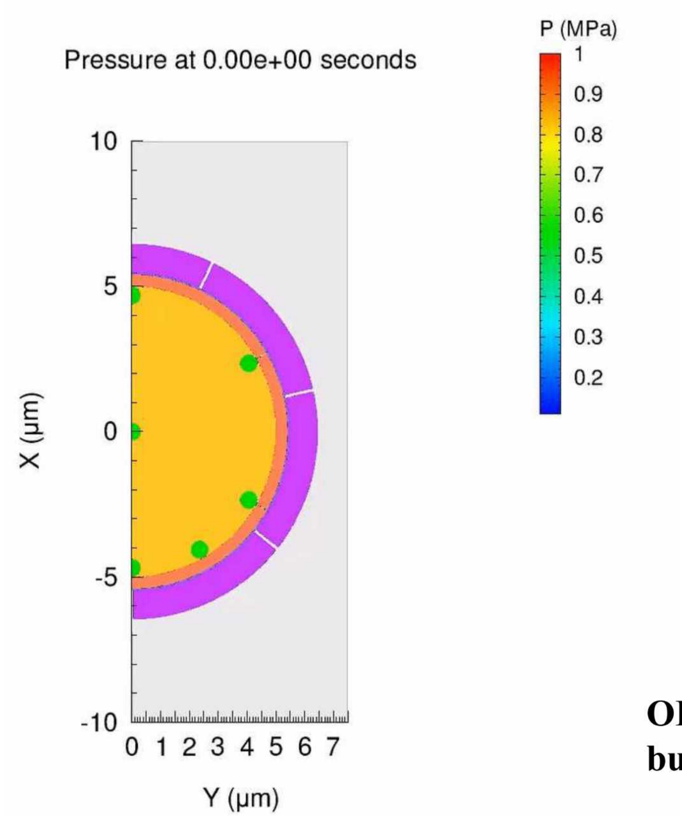
0 kPa Compressive Wave

0.3 µm diameter bubble



OBC = 14 ns

0.6 µm diameter bubble

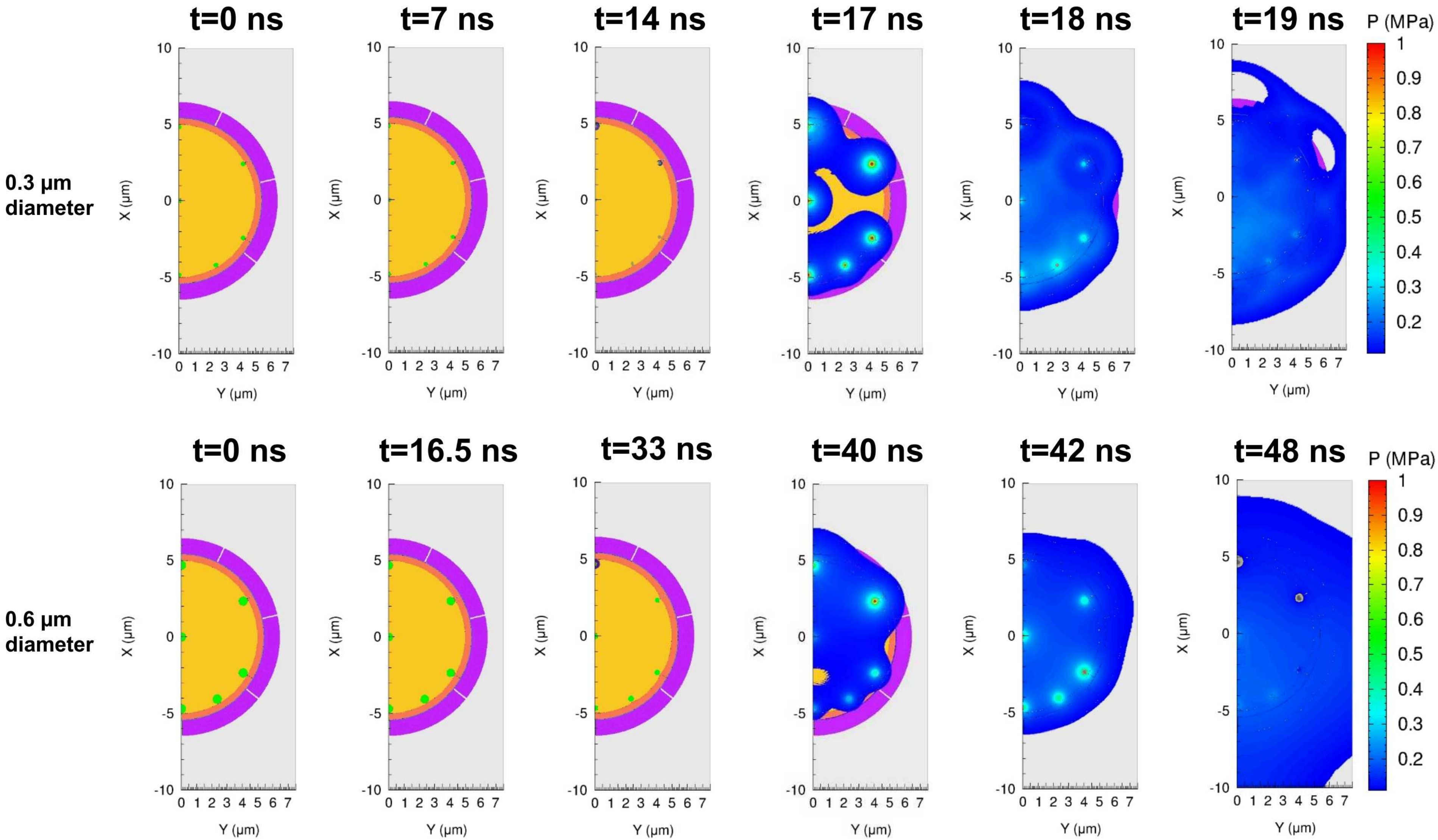


OBC = 33 ns

OBC = Onset of bubble collapse

Microscale Modeling & Simulation
Blood-Brain Barrier

Investigation of cavitation bubble diameter (0 kPa wave)

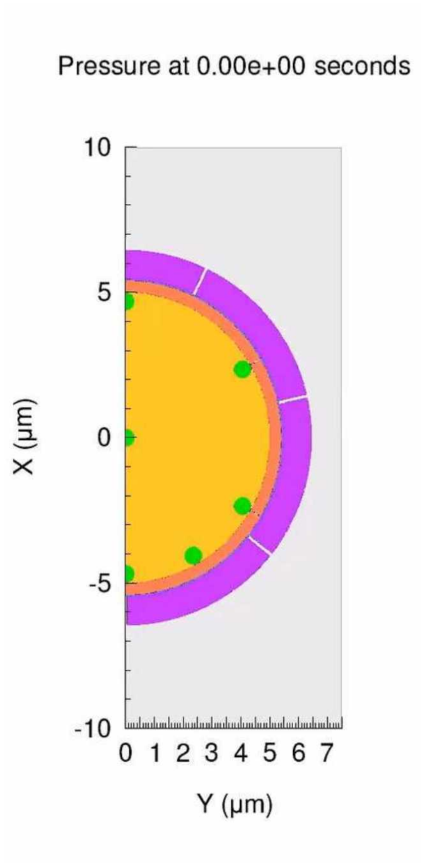


Microscale Modeling & Simulation
Blood-Brain Barrier (BBB)

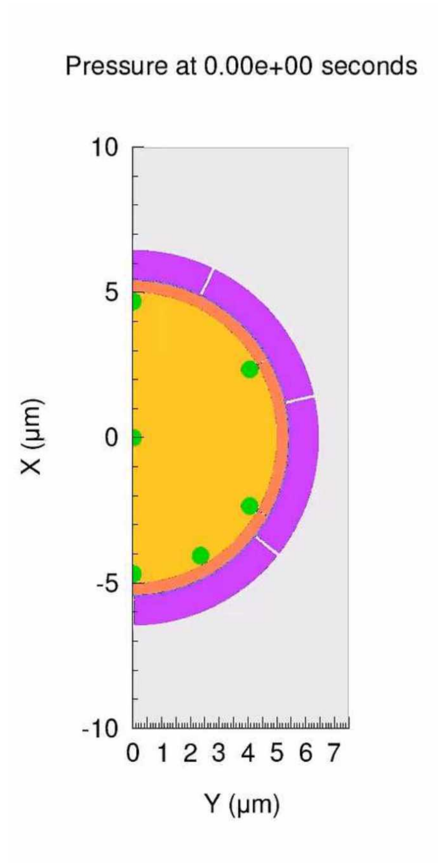
Investigation of compressive wave amplitude

0.6 µm diameter bubbles

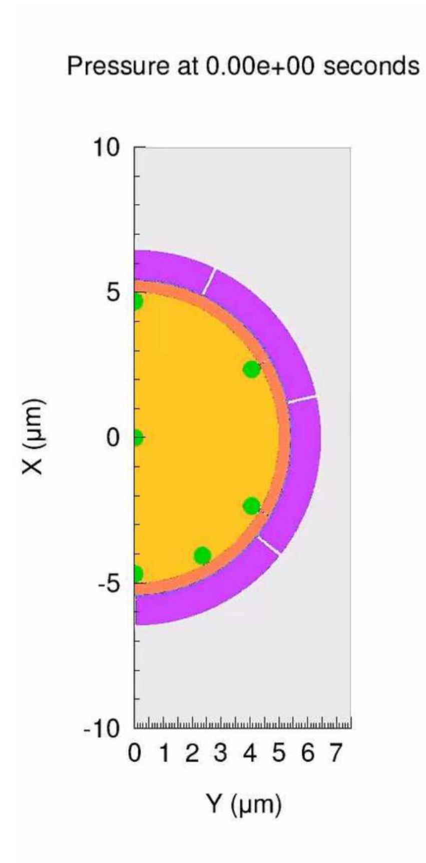
0 kPa	400 kPa wave	700 kPa wave



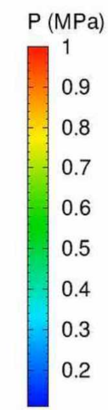
OBC = 33 ns



OBC = 24 ns



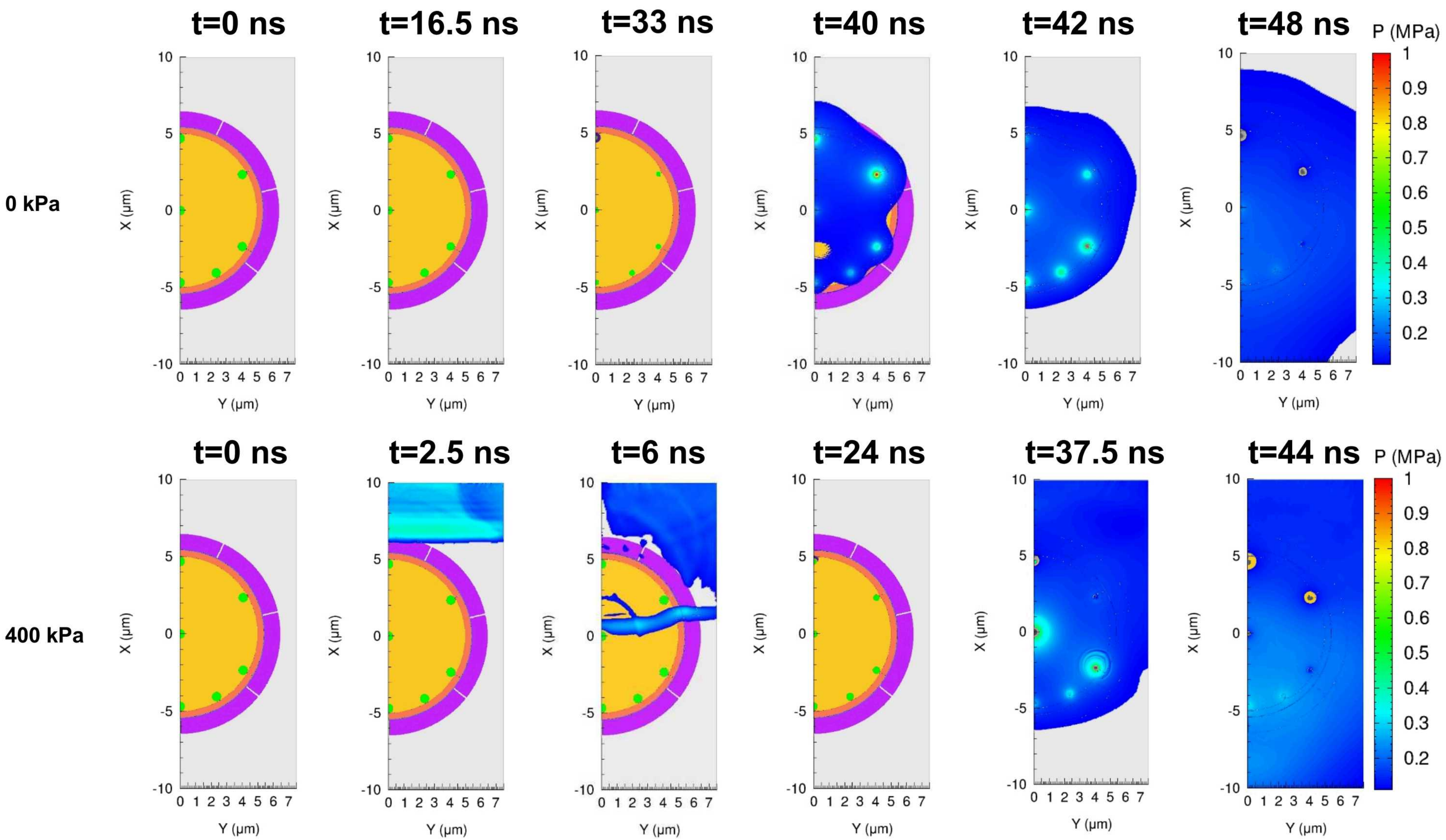
OBC = 20.5 ns



OBC = Onset of bubble collapse

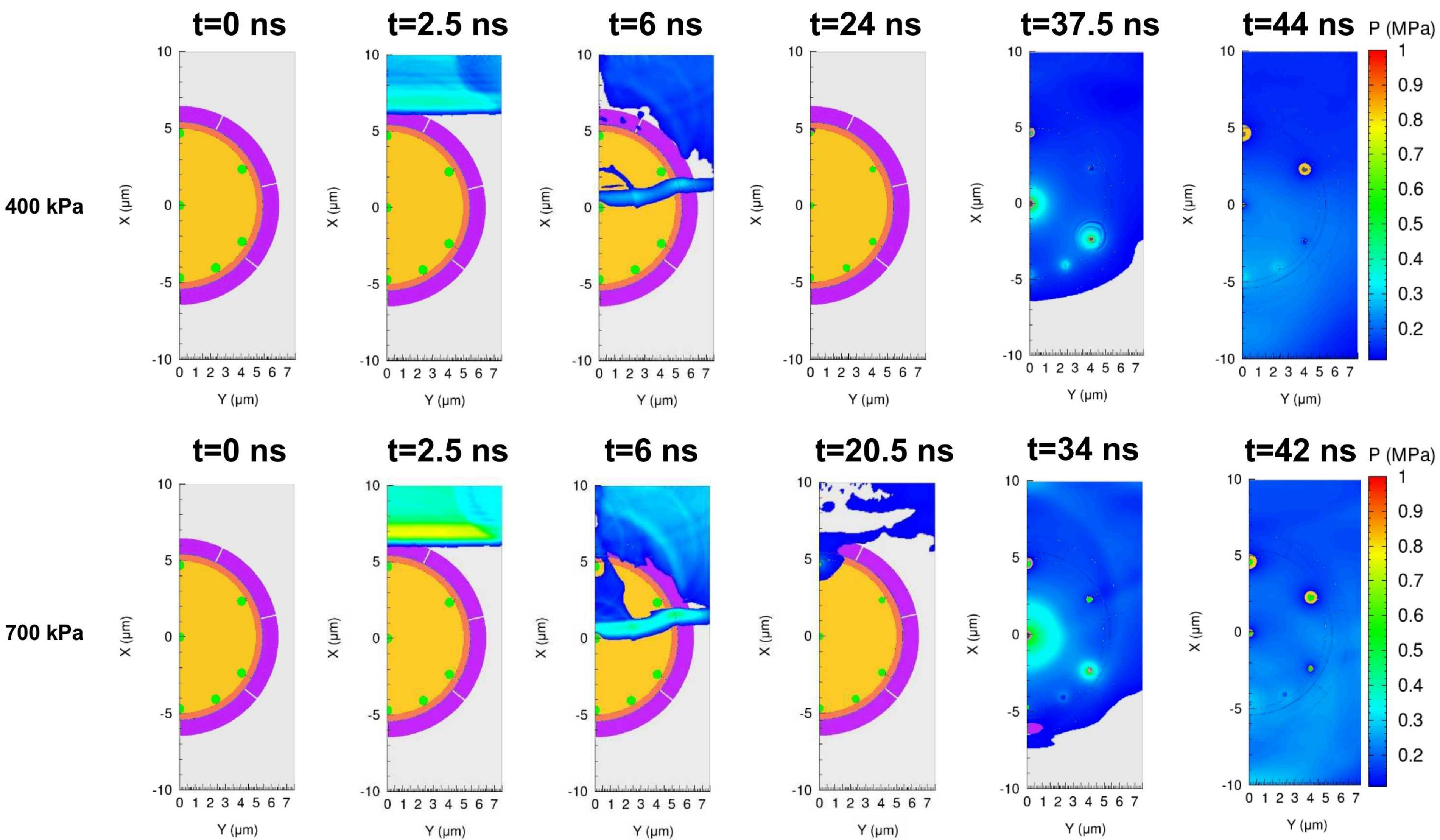
Microscale Modeling & Simulation
Blood-Brain Barrier (BBB)

Investigation of compressive wave amplitude (0.6 μm diameter bubbles)



Microscale Modeling & Simulation
Blood-Brain Barrier (BBB)

Investigation of compressive wave amplitude (0.6 µm diameter bubbles)



ACCOMPLISHMENTS

- **Presented at the American Society of Mechanical Engineers (ASME) International Mechanical Engineering Congress & Exposition (IMECE), November 6, Tampa, FL. Haniff S, Taylor P (2017) Blast-induced cavitation leading to damage of the blood-brain barrier. (IMECE2017-72677)**
- **Completed SNL-UNMHSC SAND Report SAND2018-7333**
- **C2B2 Project Funding Received April 2018**
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- **Performed single element testing of Tillotson EOS (Task 2)**

ISSUES

- **Delays in funding caused delays in technical progress.**

- **Considering how to increase models' credibility through verification with cavitation experiments.**

CONCLUSIONS

- Anticipated findings:
  - Quantify vascular structure damage as functions of bubble diameter, location, and density
  - Verification: The models reproduce results from bubble collapse experiment (e.g., *Controlled single bubble cavitation collapse results in jet-induced injury brain tissue**).
- Anticipated impact:
  - Protection: Quantify to what degree (if any), personal protective equipment (e.g., helmet) can protect from effects of bubble collapse.

* Canchi S, Kelly K, Hong Y, King MA, Subhash G, Sarntinoranont M. Controlled single bubble cavitation collapse results in jet-induced injury in brain tissue. Journal of the mechanical behavior of biomedical materials. 2017 Oct 1;74:261-73.

PATH FORWARD

- Complete BBB model and simulation work.
  - Finalize damage versus bubble characteristic relationships.
  - Memorialize findings in a SAND report.
- Verification effort: Reproduce results from bubble collapse experiment on human (or surrogate) brain.

PUBLICATIONS, PATENTS, PRESENTATIONS & AWARDS

- **Presented *Blast-induced cavitation leading to damage of the blood-brain barrier*. (IMECE2017-72677)**

- **Completed SNL-UNMHSC SAND Report SAND2018-7333**

- **Anticipate SAND report to share work with scientific community.**

COOPERATIVE DEVELOPMENT

- The current work builds on previous development
  - Head/Neck model supported by James Mackiewicz ONR Code 30.
  - Head/Neck/Torso model supported by Sandia's Laboratory Directed Research and Development grant.

COLLABORATION & DISCUSSION

- **Model credibility requires experimental verification.**
- **If the gold-standard experiment**
  Measurement of a phenomenon (e.g., bubble formation, collapse, micro-jetting) in a living human being **is currently not possible, what is the next closest experiment that has been complete?**
- **Would simulation of the Canchi experiment be useful in general and useful to humans in particular?**
  - **Rate hippocampal ex vivo slice (350 um), single seed bubble (Ø 0.2 mm), split Hopkinson bar "blast"**
  - **Results: pressure v time, DIC displacements, strains, bubble growth/collapse/jet.**

Backup Slides

Correlation of Intracranial Cavitation Predictions with Clinical Data on TBI Subjects

- Mild TBI (n=27) from blunt impact, controls (n=27), “no discernible evidence of brain injury in our mild TBI cohort using functional MRI.”
- Moderate TBI
  - (n=6) DTI “detected no areas displaying significant differences in the [Fractional Anisotropy] between the TBI cohort and the normal controls.”
  - (n=7) fMRI with ICA “did not identify any brain injury” which could be used to correlate with simulation
  - (n=1) 37 yom, blunt trauma R parietal lobe
    - decreases in FA

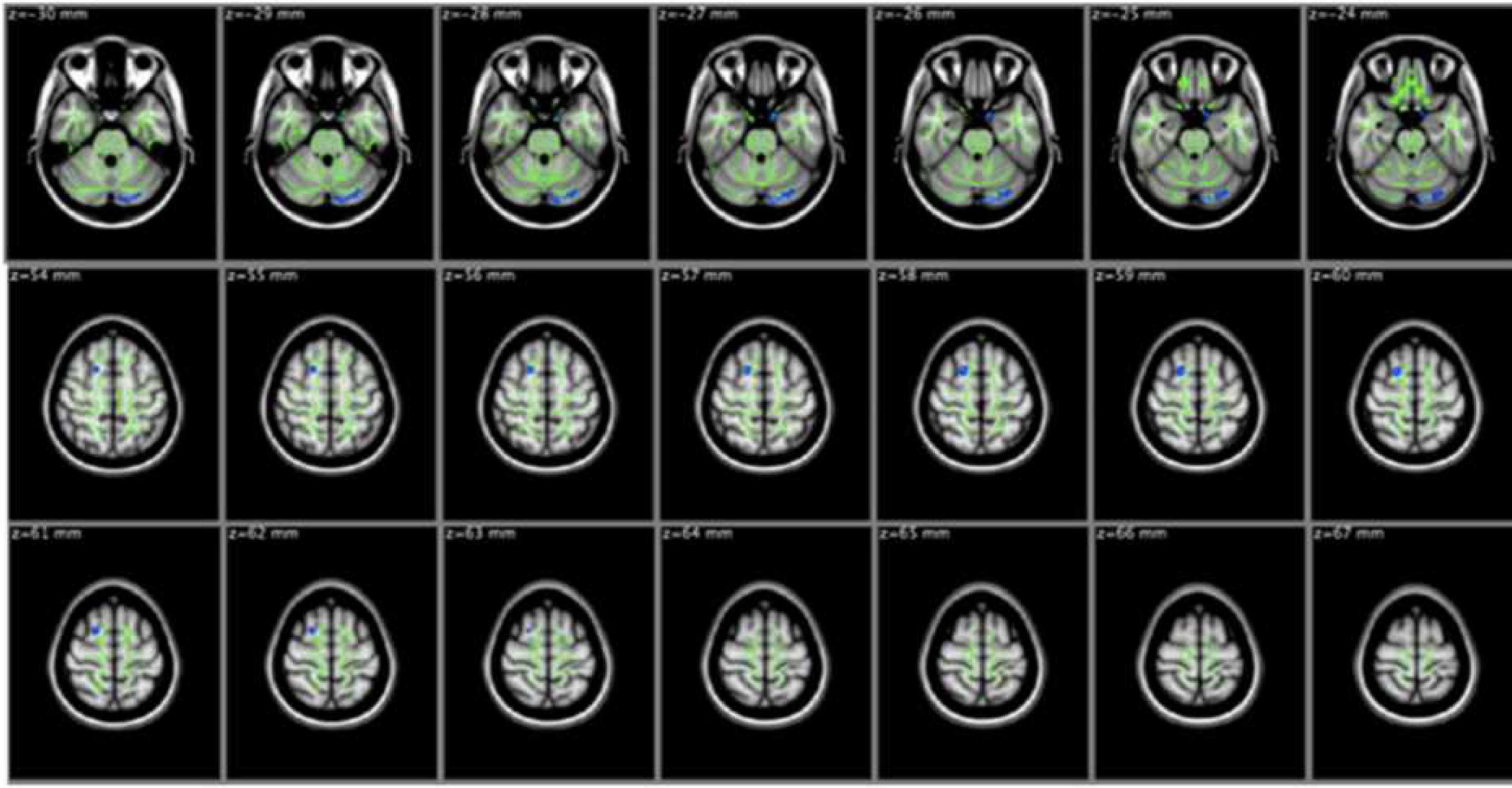

Figure 2. Tract-based spatial statistics (TBSS) results comparing a single parietal impact TBI subject with a group of age and sex-matched healthy controls. Results are filtered using a threshold significance level of p=0.5 and are corrected for multiple comparisons using threshold-free cluster enhancement. Green regions represent the white matter tracts within which all comparisons were conducted. Blue regions specify areas in which the TBI patient displayed decreased levels of fractional anisotropy (FA) relative to controls. The data are presented in radiological space, with the right hemisphere being shown on the left in each image.

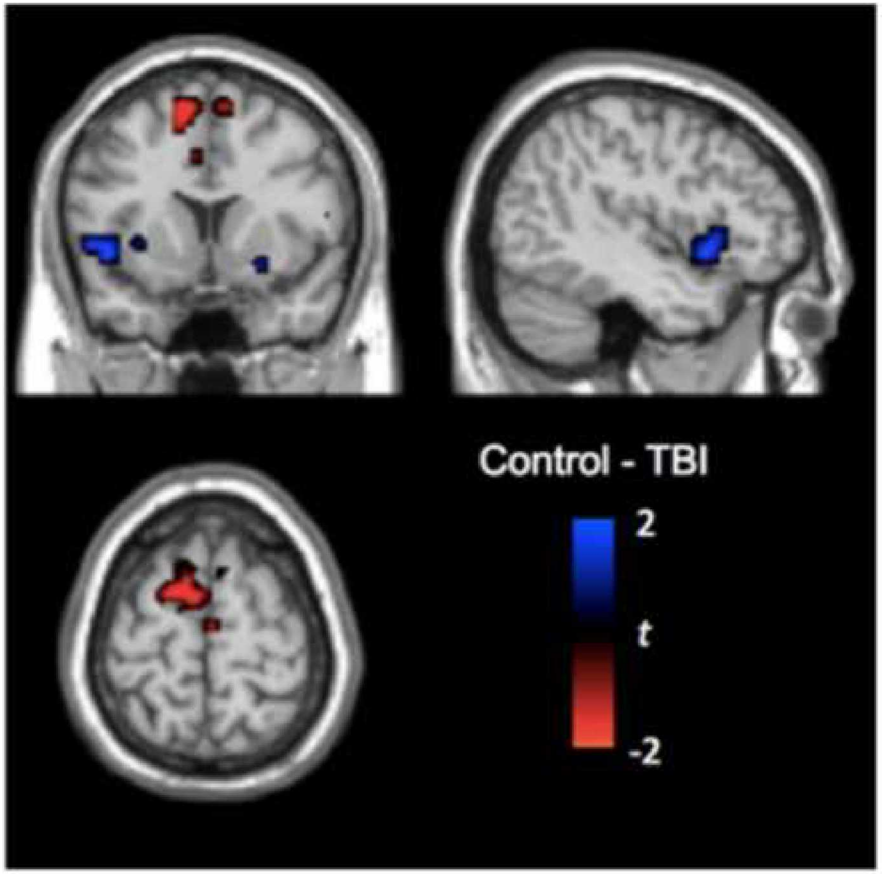

Figure 3. Independent component analysis results comparing a single parietal impact TBI subject with a group of 10 age- and sex-matched healthy controls. The red color specifies the left supplementary motor region on which elevated levels of activity were detected relative to controls. This difference was detected in the sensorimotor network. The blue region near Broca's area displayed decreased activity levels relative to controls and belongs to a larger network that spans the temporo-frontal regions.

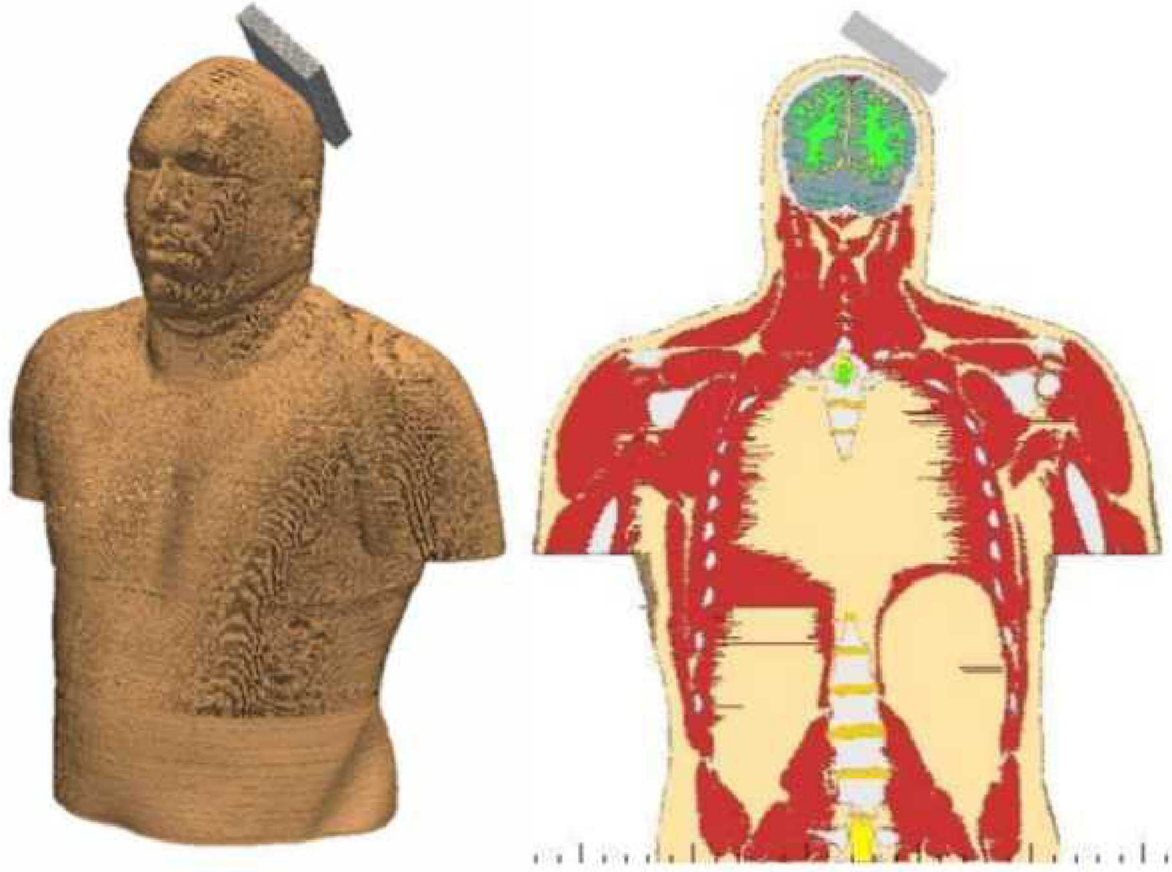

Figure 4. Sandia head-neck-torso model used to simulate head impact mimicking the injury scenario experienced by our single TBI subject. Initial condition of injury scenario: exterior view (left); coronal cut view (right).

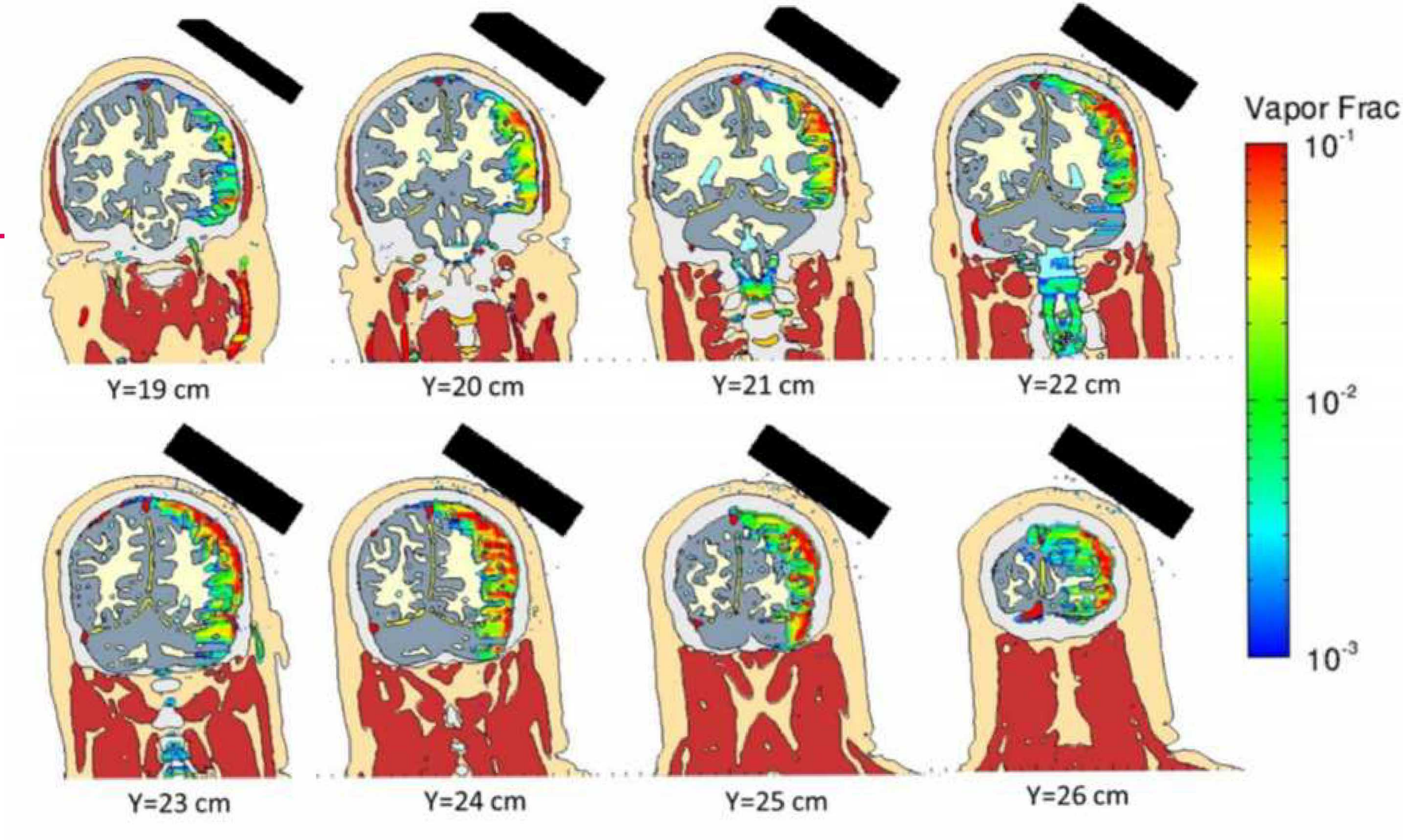

Figure 6. Predictions of maximum cavitation vapor volume fraction plotted in a select number of coronal sections as a result of blunt impact to the left rear parietal region of the head. All plots correspond to the simulation time of 5.9 milliseconds, roughly 0.75 milliseconds after initiation of rebound from the impactor. The coronal cuts are ordered front to back with Y=19 cm to 26 cm.

DISCUSSION

To date, we have not attempted to quantify a spatial correlation of our single-subject cavitation predictions with the clinical DTI and fMRI results presented in Figure 2 and Figure 3, identifying regions of the brain displaying structural injury and functional deficits in the parietal and occipital regions of the brain. Although the results from our single subject study are encouraging, far more work needs to be performed on both the clinical and M&S aspects of this project before we can apply statistical methods to attempt correlation of simulation prediction with clinical measurements of TBI. Unfortunately, with the loss of one of our key UNMHSC personnel (Vakhtin), we have had to postpone continuance of this work.