# 3aBB5. Acoustic Targeted Drug Delivery In Neurological Tissue

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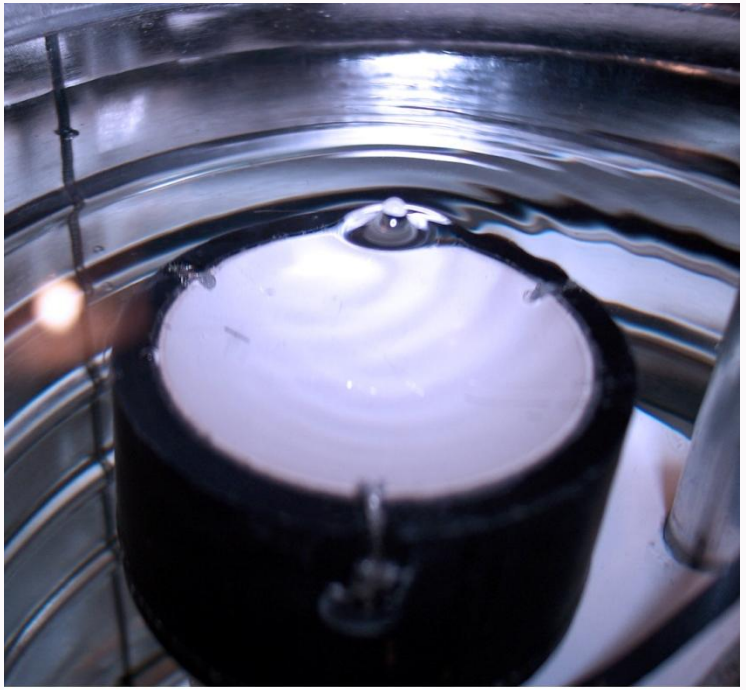
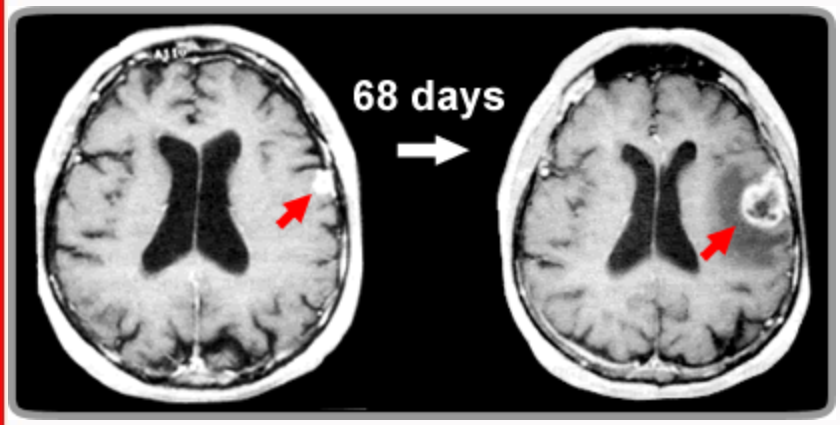
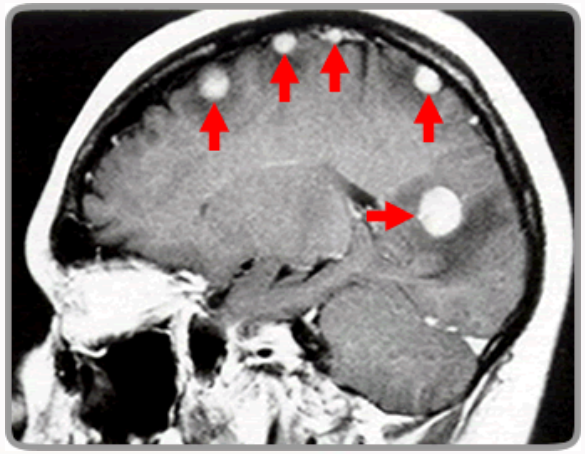
# Presentation Outline

- Purpose of the research
- Background of therapeutic acoustics
- Methods used in the study
- Results from the laboratory
- Conclusions
- Future directions



# Purpose of the Research



- Brain cancer is the leading cause of cancer related deaths for patients younger then age 35.
- For children brain cancer is usually inoperable because the brain is not fully developed.
- Current treatments for brain cancer involve a combination of:

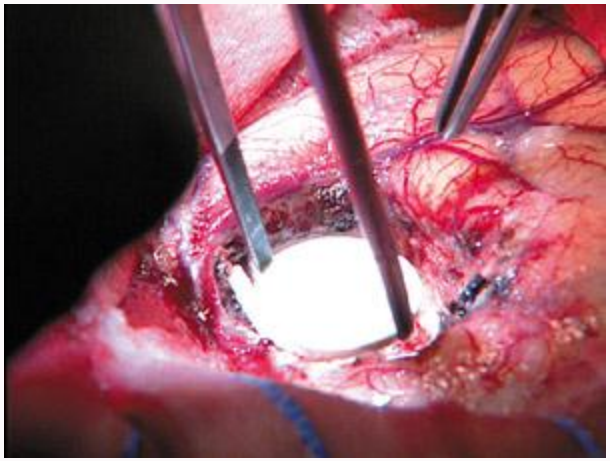
  -Removal of the tissue

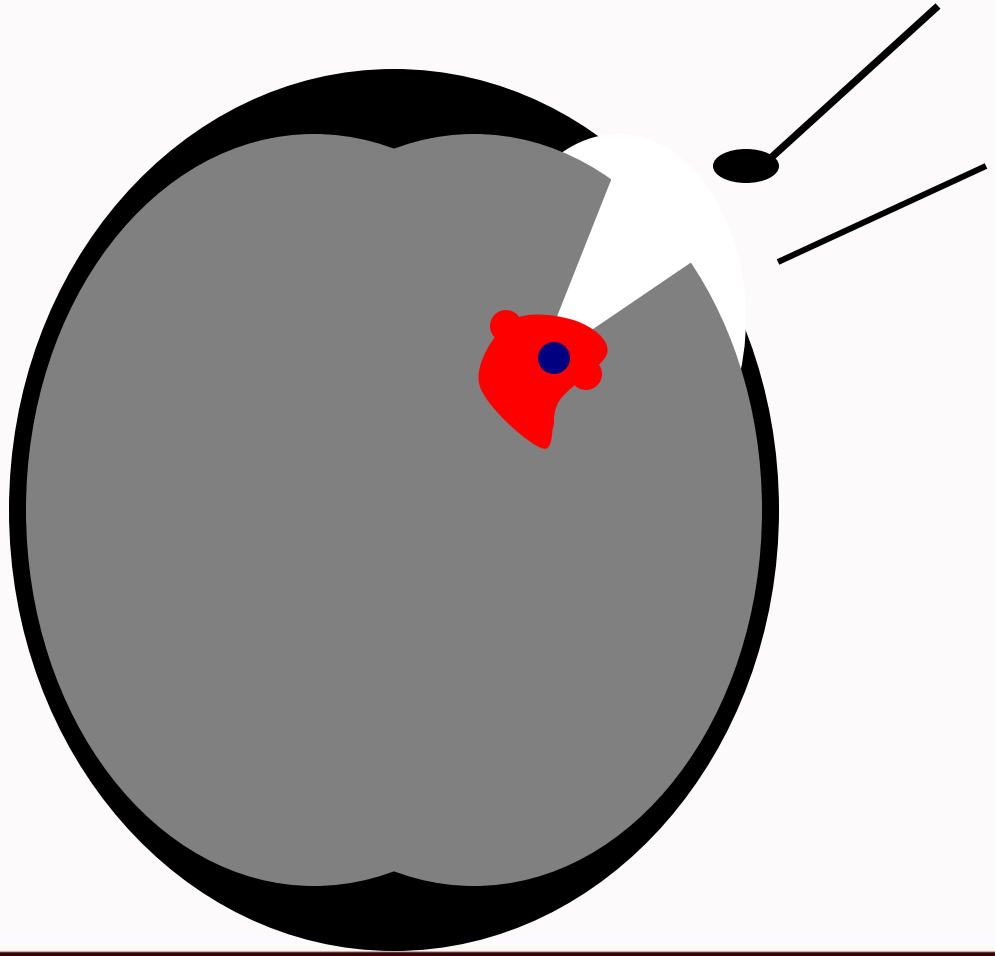
  -Gamma knife treatment

  -Chemotherapy

# Brain Cancer Treatment

Generally, tumors are treated with radiation and/or surgery. Chemotherapy is not used for benign tumors and is generally not a very effective treatment for most malignant primary brain tumors or metastatic tumors. – Oncology channel





# Background of Therapeutic Acoustics

- The first study to show the biological effects of “focused ultrasound” was conducted in 1926.
- By the 1970s focused ultrasound and high intensity ultrasound surgeries had evolved into clinical use: used to disintegrate gall bladder stones and break down various tumors in the brain and pancreas.
- Termed “therapeutic ultrasound,” the mid-level ultrasonic waves are utilized to treat tissues directly and enhance the successful outcomes of other treatments.

  -used to deliver drugs through the skin without needles, to enhance bone healing and growth, to provide arthritis relief and reduce joint inflammation.

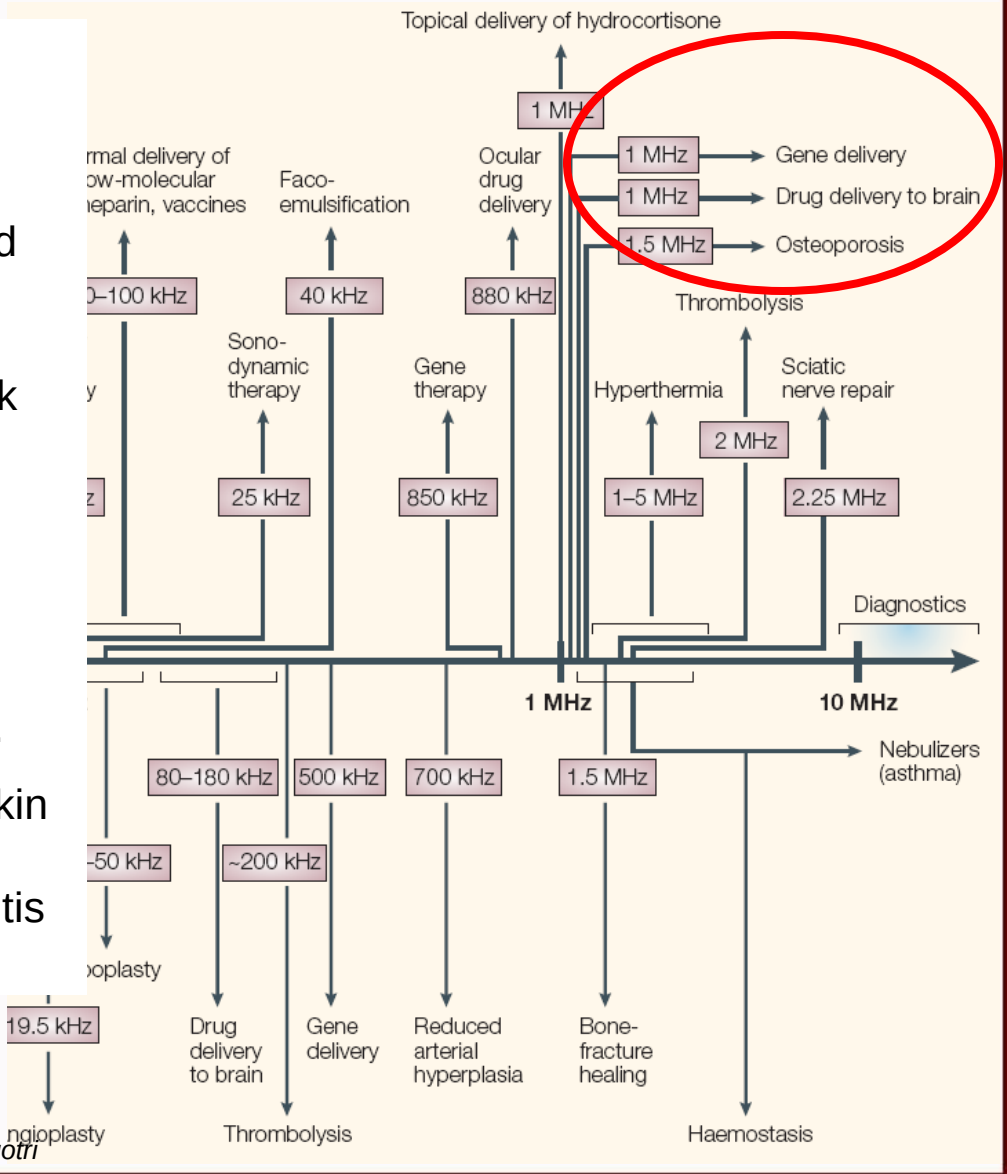
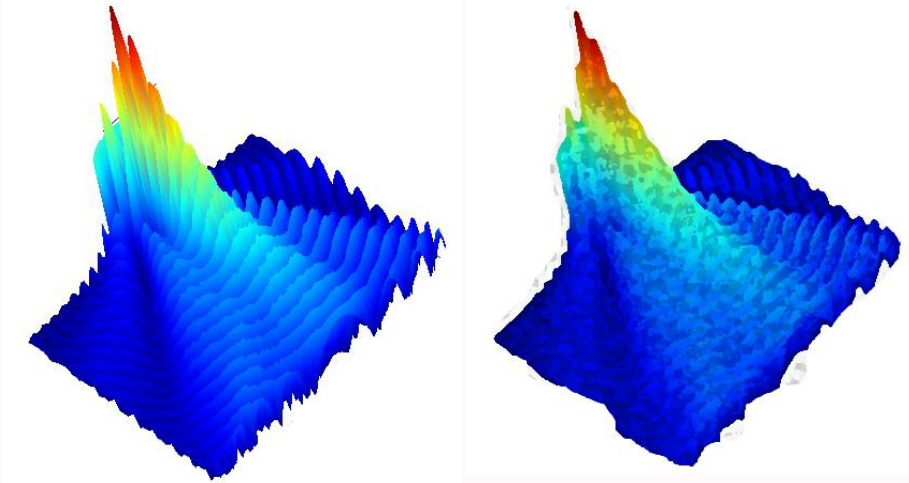



*Image credit: Samir Mitragotri*

# Effects of Sound on Tissue

- **The Sponge Effect**

- **The Radiation Pressure**



- **Controlled Cavitation**

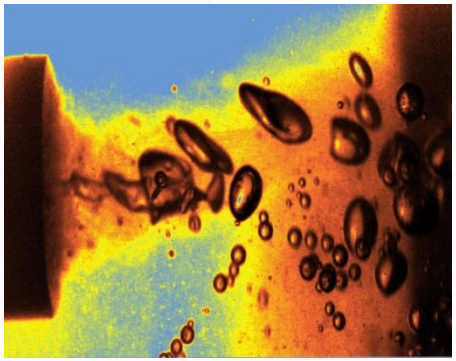
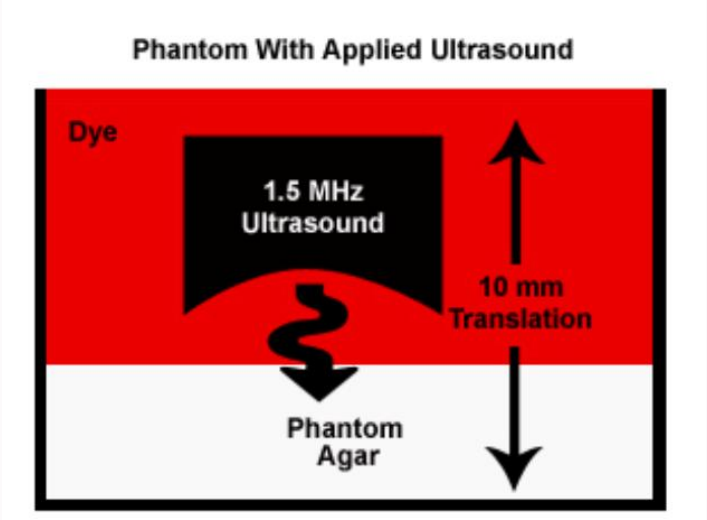


*Image credit: K. S. Suslick and K. J. Kolbeck, University of Illinois*

# Methods Used

- Neurological tissue mimicking phantoms were prepared by filling Petri dishes with a solution of 0.6 wt% agar.
- Fresh excised equine brain and avian muscle tissue was harvested.
- Evans blue dye, diluted in distilled water to 0.25 wt% was used to mimic water soluble drug and to determine the extent of perfusion.
- 6.8 watts of ultrasound energy was generated by a lead zirconate titanate (PZT-4), 1.5 MHz, 20mm diameter piezoelectric ceramic with a radius of curvature corresponding to 40mm



# Methods Used

- Acoustic output power was determined using the “Mason Model” for a piezoelectric equivalent circuit, and a calibrated pzt sonophone

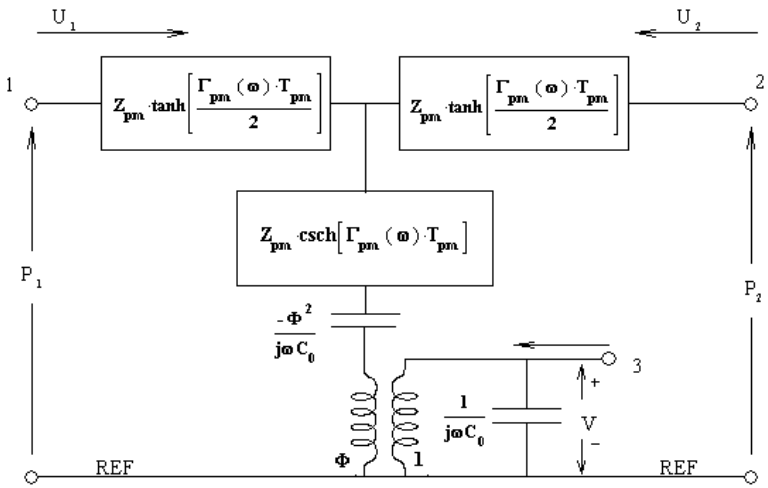
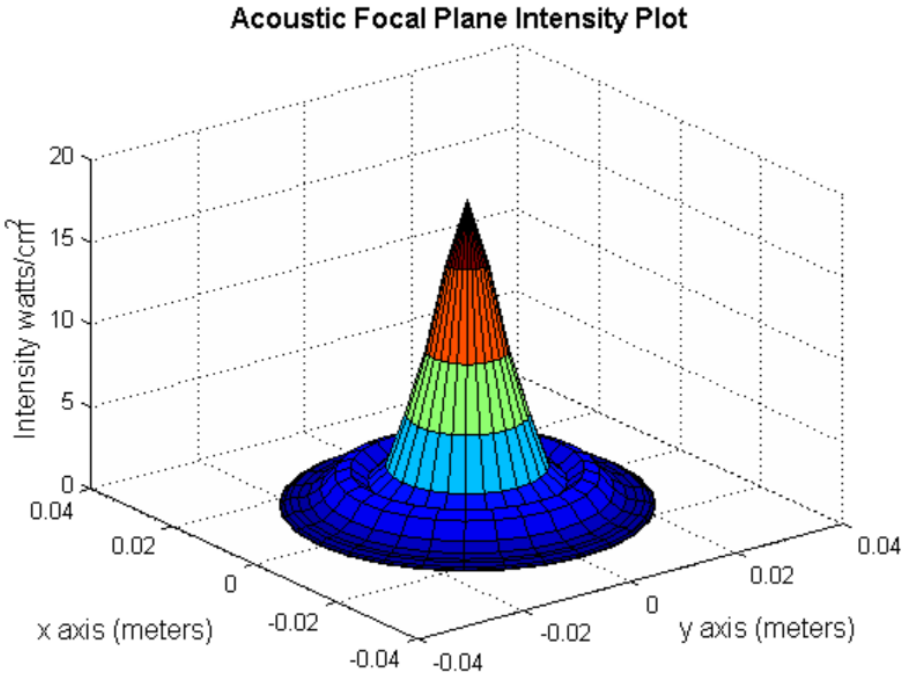



Fig. 2 Piezoelectric element equivalent circuit.



# Methods Used

- Phantoms/tissue was sonicated on and off (15 seconds each) at their geometric center for durations of 1-4 minutes
- The transducer was oscillated at 0.25 Hz over a 10mm translation
- Histology on the phantoms was preformed by taking a 2mm geometric center slice from the phantom/tissue and imaging it with a ccd camera/microscope system
- Using a least squares approach, we parametrically fit the experimental data to the theoretical diffusion equation to compare differences in diffusion between the sonicated and control phantoms.

$$N(x,t) = N_0 erfc\left(\frac{x}{2\sqrt{Dt}}\right)$$

where: $N_0$ is the source concentration,
$x$ is the diffusion distance,
$Dt$ is the diffusion time product and
*erfc* is the complimentary error function.

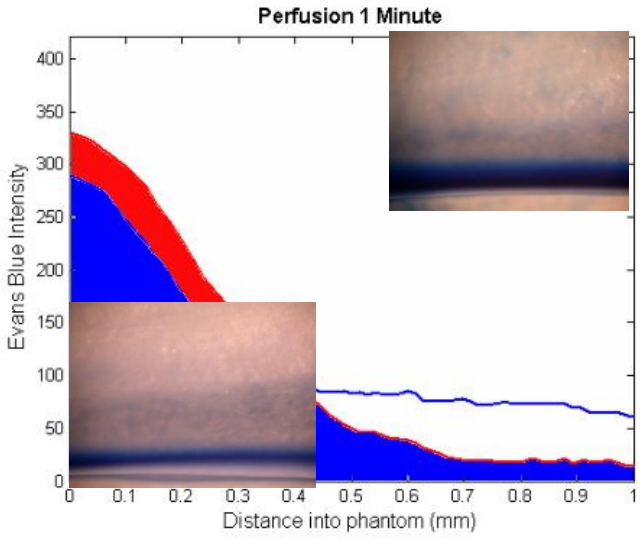


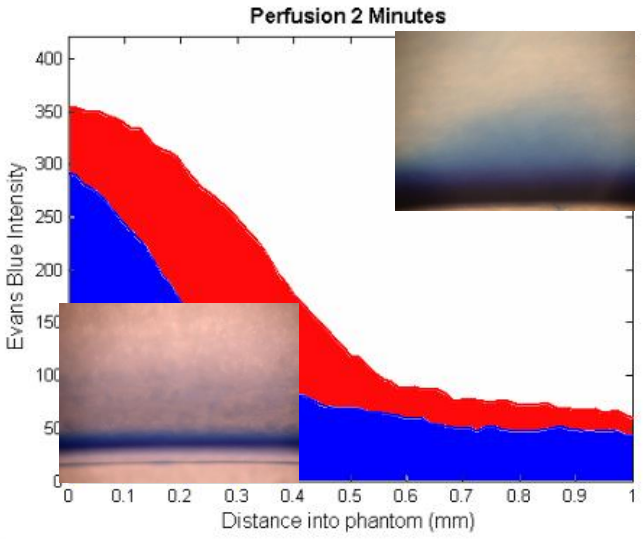
Equation: Crank J. *The Mathematics of Diffusion,* Oxford University Press, 1975

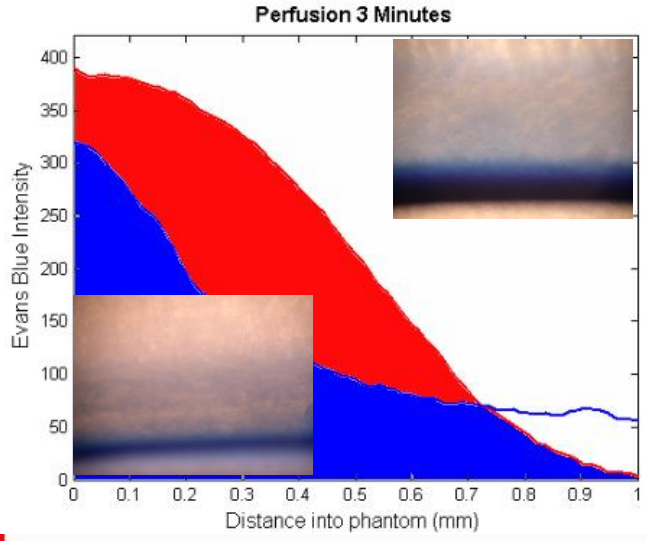
# Results: Phantoms

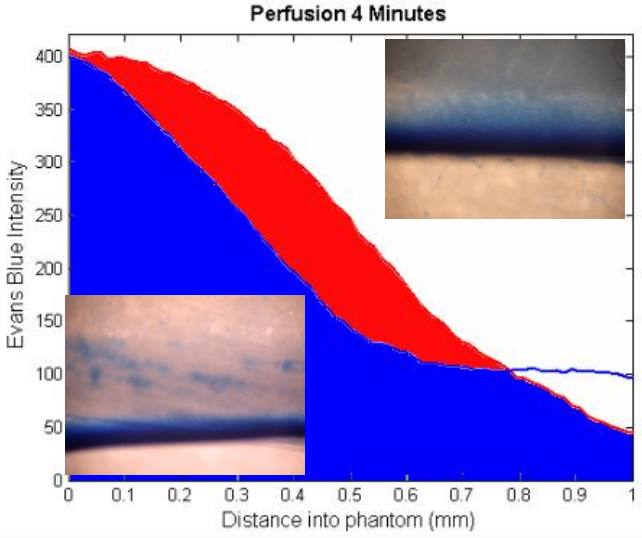
Evans Blue dye uptake increase of:

1min: 13.7%
2min: 61.5%
3min: 74.8%
4min: 27.8%



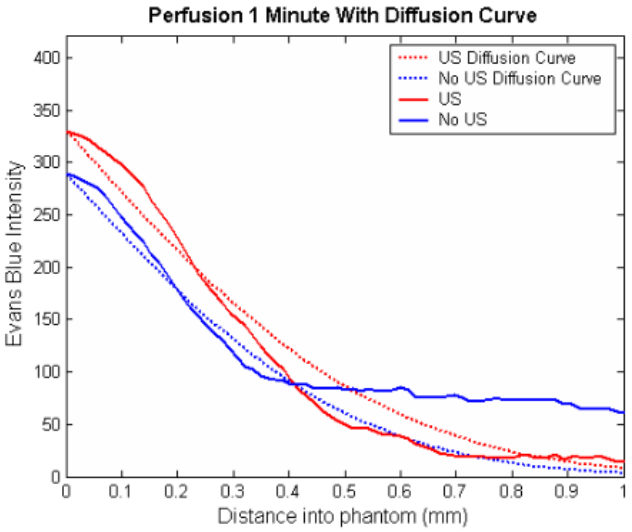



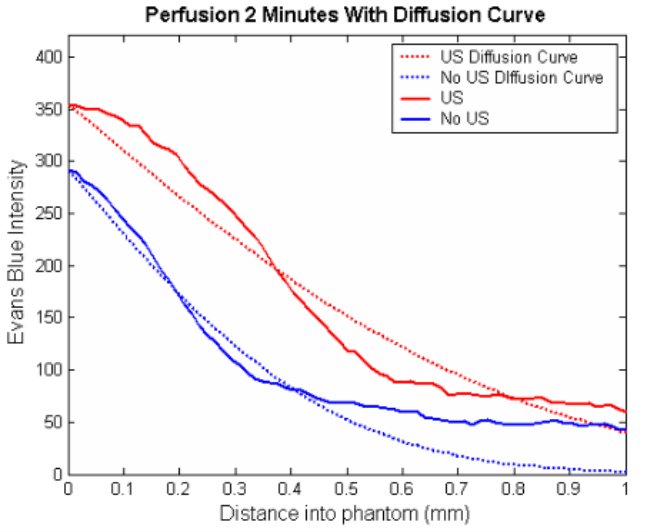



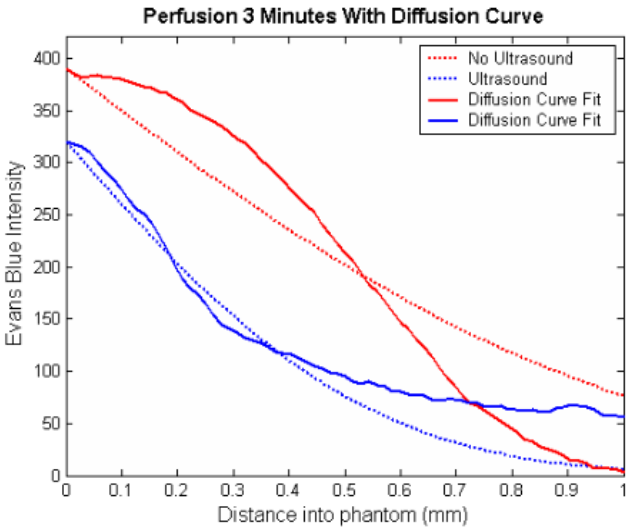



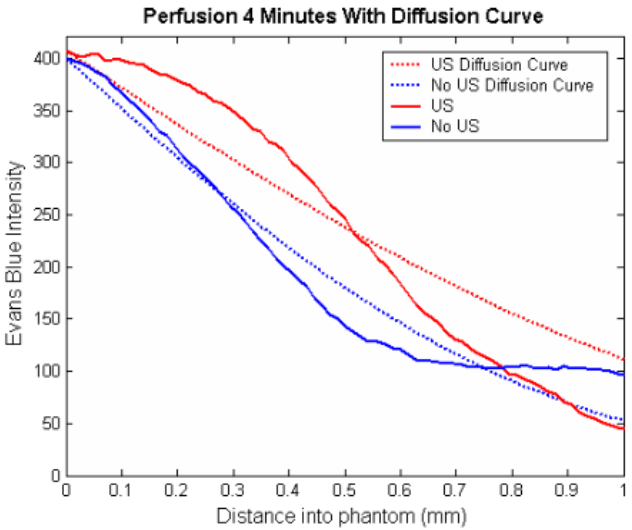
# Results : Phantoms

| | 1 Min No US | 1 Min US |
|---|---|---|
| $C_o$ | 289 | 330 |
| Dt | 0.09 | **0.07** |
| | **2 Min No US** | **2 Min US** |
| $C_o$ | 291 | 354 |
| Dt | 0.19 | 0.06 |
| | **3 Min No US** | **3 Min US** |
| $C_o$ | 319 | 389 |
| Dt | 0.29 | 0.08 |
| | **4 Min No US** | **4 Min US** |
| $C_o$ | 399 | 406 |
| Dt | 0.41 | 0.21 |

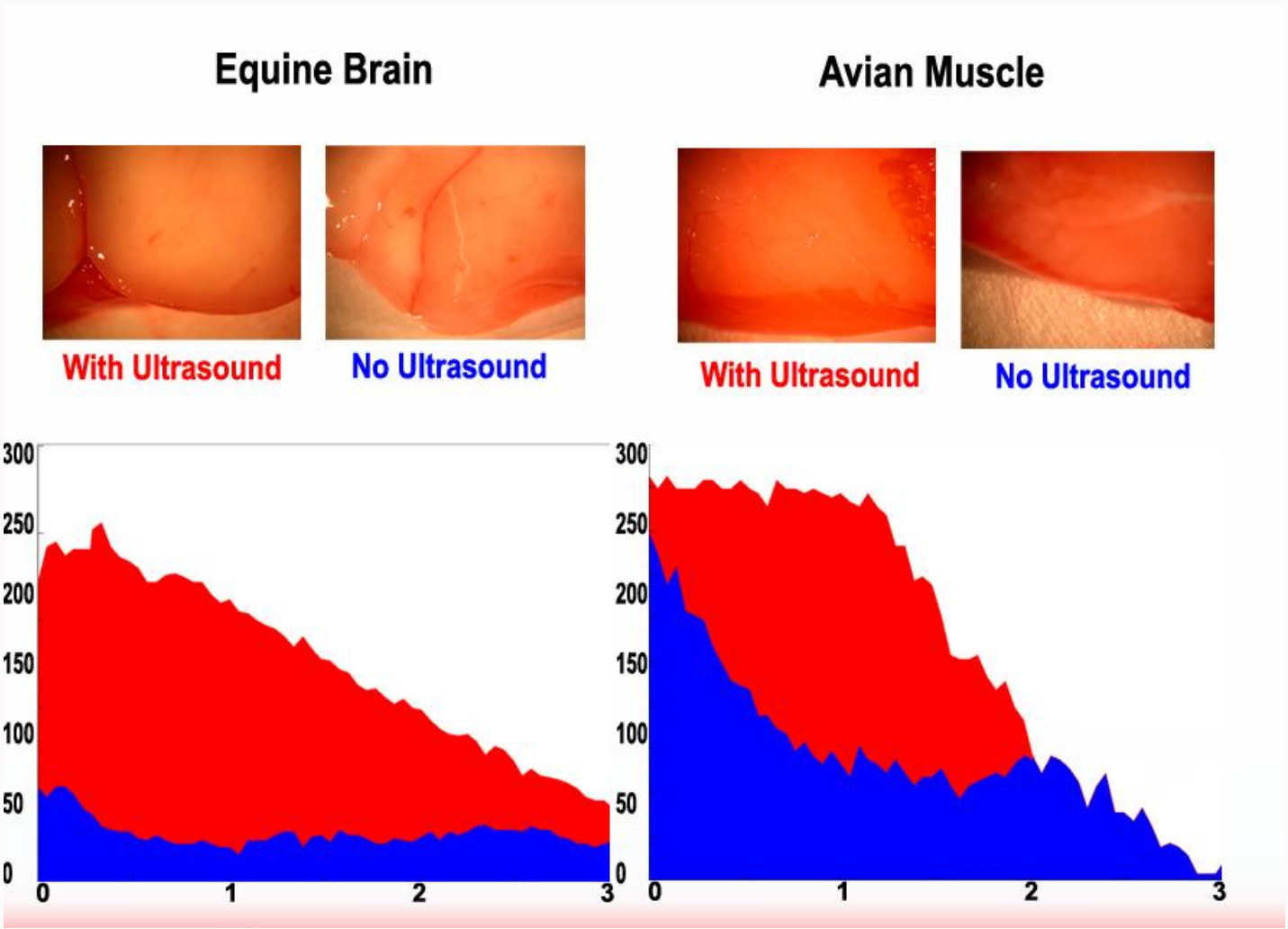


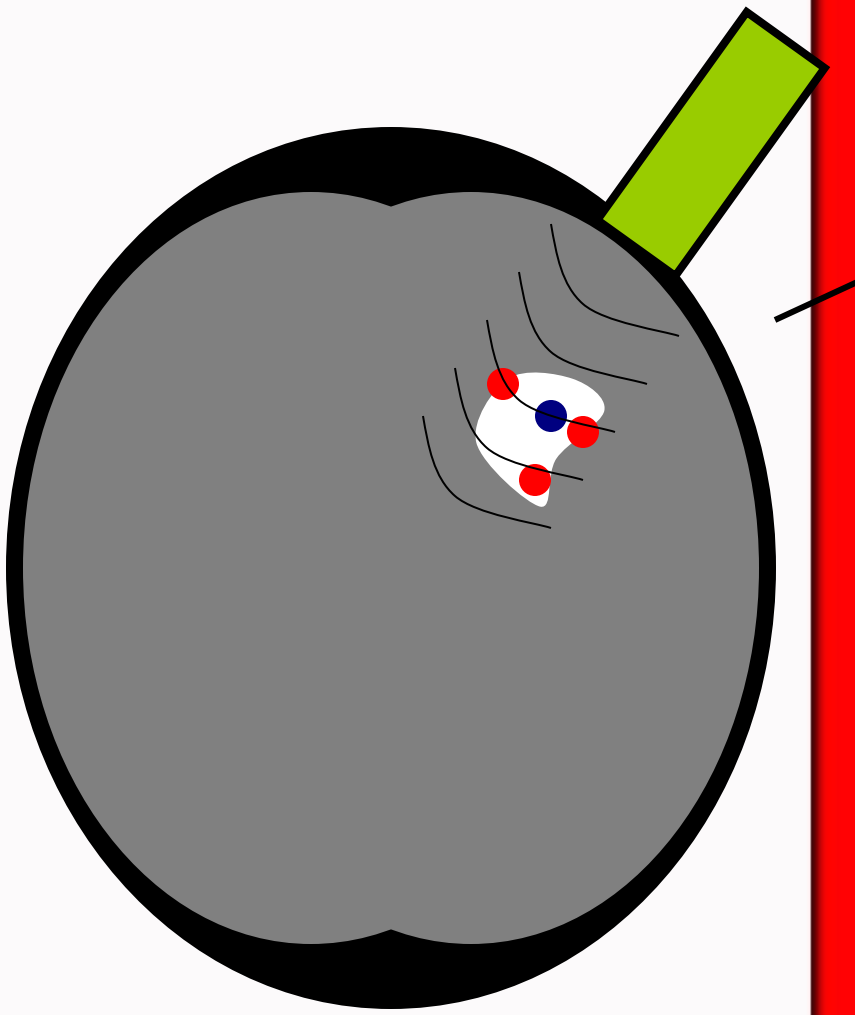



# Results : Equine and Avian, 1 min



# Conclusions

- Using 1.5MHz sonication techniques we have successfully shown enhancement of Evans blue dye perfusion into tissue mimicking phantoms
- Mechanisms besides simple diffusion are in action
- Therapeutic ultrasound holds the possibility to enhance drug perfusion and uptake in the brain.
- This initial study suggests that application of ultrasound in conjunction with convection enhanced delivery, gliadel wafers and systemic chemotherapy/neuro-pharmacological agents could enhance treatment success.





*Full Article: G.Lewis and W.Olbricht "A phantom feasibility study of acoustic enhanced drug perfusion in neurological tissue" IEEE LISA, November 2007*

# Future Directions

- We are in the process of conducting a similar study using mammalian brain tissue and commassie blue stain
- Then we plan to combine convection enhanced delivery with sonication on a living animal model.
- The use of therapeutic ultrasound to enhance drug and nutrient perfusion in living tissues hold many practical applications, and is the continuing focus of the laboratory.

# Questions on the Study


- Research was supported by the Graduate Fellowship from the National Science Foundation.
- The work was also supported in part by the National Institute of Health Grant NS-045236, and Transducer Engineering Inc.

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