Feedback control of microbubble cavitation for ultrasound-mediated blood-brain barrier disruption in non-human primates under magnetic resonance guidance

Hermes A. S. Kamimura[1,2], Julien Flament[1,3], Julien Valette[1], Andrea Cafarelli[2,4], Romina Aron Badin[1], Philippe Hantraye[1], & Benoît Larrat[2*]

[1]Molecular Imaging Research Center, Institut de Biologie François Jacob, Commissariat à l'énergie atomique et aux énergies alternatives (CEA), Fontenay-aux-Roses, France

[2]NeuroSpin, Institut des sciences du vivant Frédéric Joliot, Commissariat à l'énergie atomique et aux énergies alternatives (CEA), Gif-sur-Yvette, France

[3]Institut national de la santé et de la recherche médicale (Inserm), UMS 27, Fontenay-aux-Roses, France

[4]The BioRobotics Institute, Scuola Superiore Sant'Anna, Pontedera, Italy

* Corresponding author

Centre CEA Saclay-Neurospin Bat 145

RD306 – 91191 Gif-sur- Yvette, France

Phone: +33 1 69 08 93 78

E-mail: benoit.larrat@cea.fr

Running headline: Feedback controlled US-mediated BBB opening in NHP

Supplementary Materials

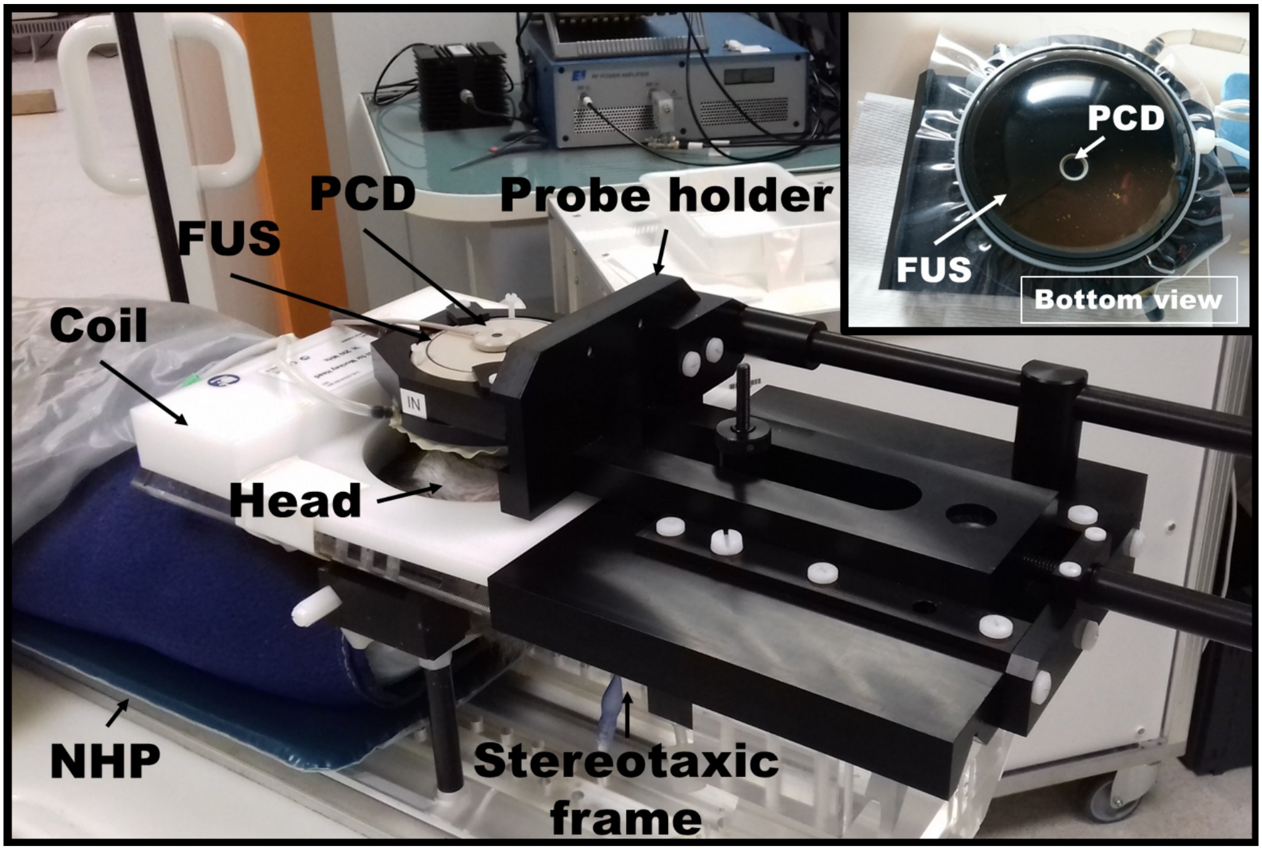


Fig. S1: MRgFUS experimental setup dedicated for non-human primate (NHP). The animal is placed in sphinx position with the head shaved and coupled to the transducers with a water balloon. The stereotaxic frame allow the positioning of the transducers in 2D. The depth of focus is controlled electronically using phase shifting. The whole setup is placed inside the magnet.

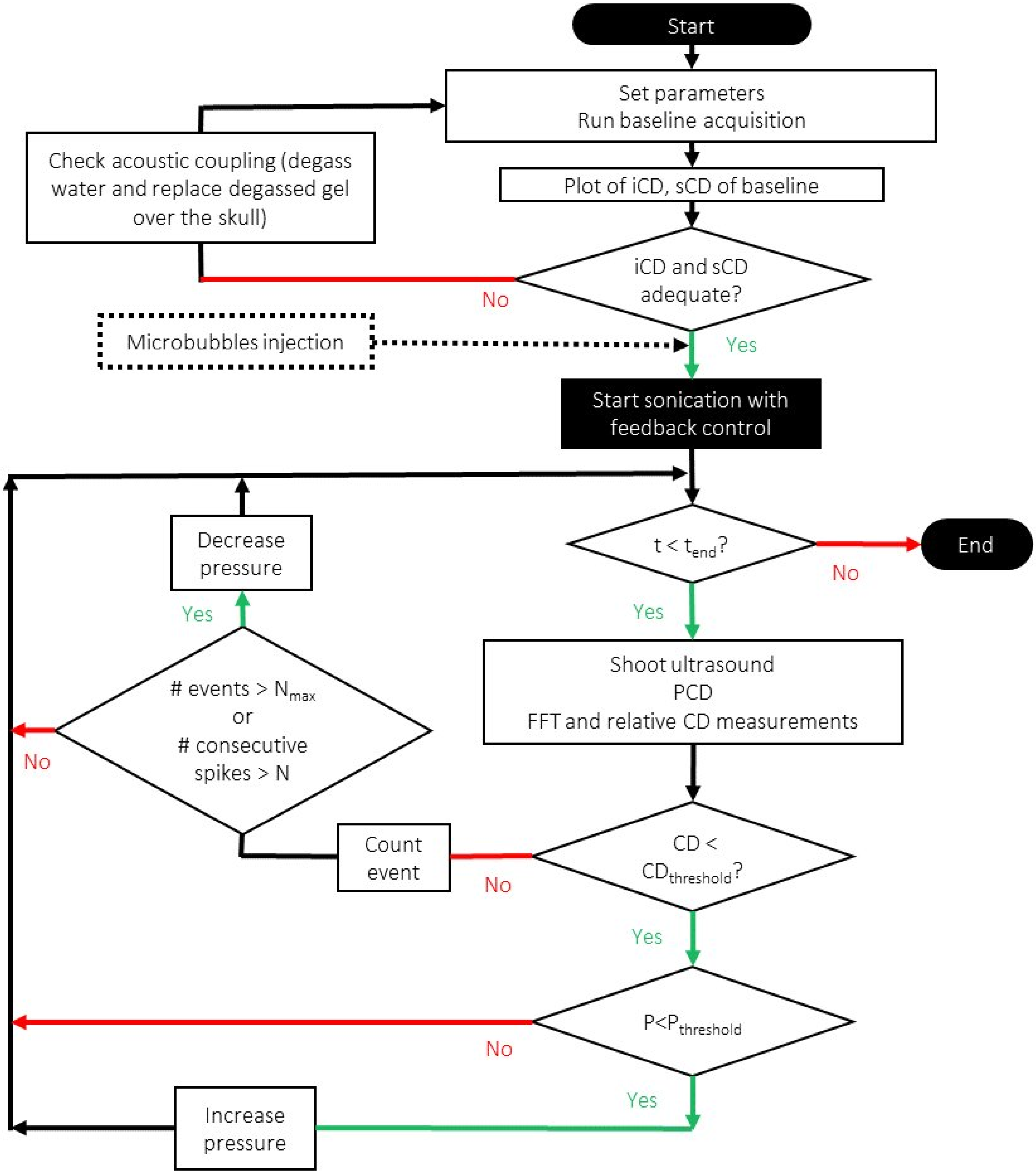
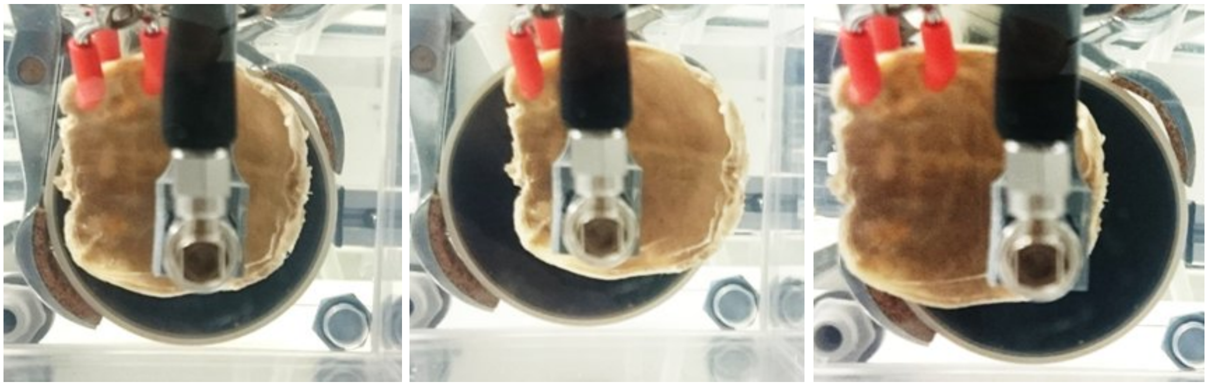
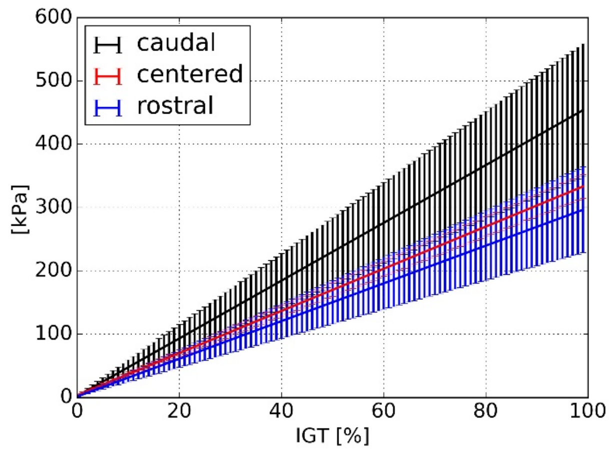


Fig. S2 – Algorithm for real-time feedback control of the acoustic pressure.

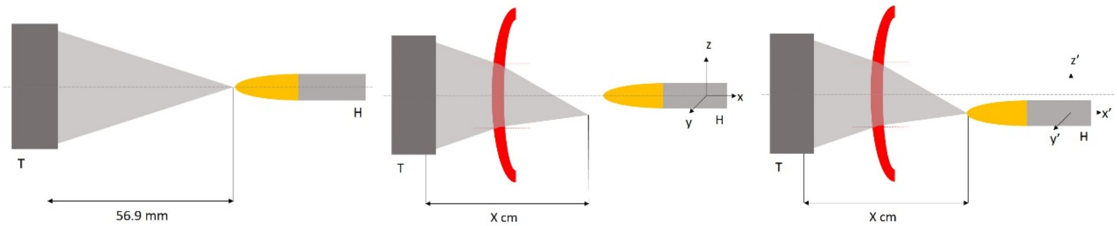


(a) **(b)** **(c)**

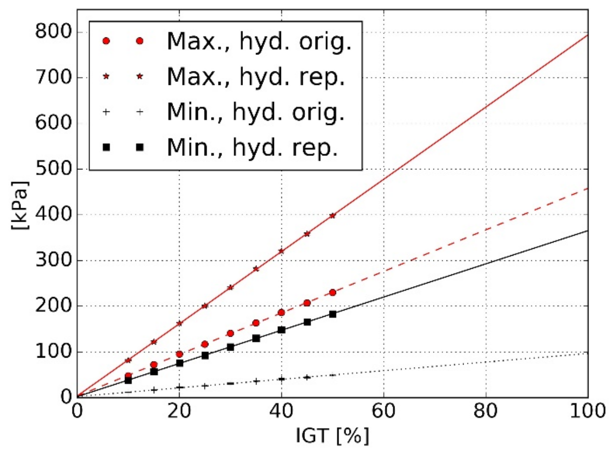


(d)

Fig. S3: Skull effects on ultrasound transmission. Three anatomical regions were evaluated in 3 skull samples: (a) centered at hippocampus, (b) 2 cm caudal from (a), and (c) 2 cm rostral from (a). The ultrasound pressure at the focus in the three different locations are shown in (d) with the error bars indicating the standard deviation of measurements of 3 samples.



(a) (b) (c)



(d)

Fig. S4: Measurement of skull aberration. (a) Hydrophone (H) at the focus of the transducer (T) in free water. (b) Skull specimen positioned between the transducer (T) and hydrophone (H) causing focus aberration. (c) The three-dimensional coordinates and signals were recorded with the transducer repositioned at the relocated focus region after aberration. (d) Acoustic pressure measured at different locations of the hydrophone and skull specimen. Skull aberration were evaluated at positions where the maximum and the minimum signals were observed around hippocampus with the hydrophone at the original position of the focus in free water (b), “Max., hyd. Orig.” and “Min., hyd. Orig.”, respectively. The hydrophone was repositioned to the relocated focus for each case providing signals “Max., hyd. rep.” and “Min., hyd. rep.”, respectively. The estimated focus shift for the two conditions were 1.40 to 2.10 mm.

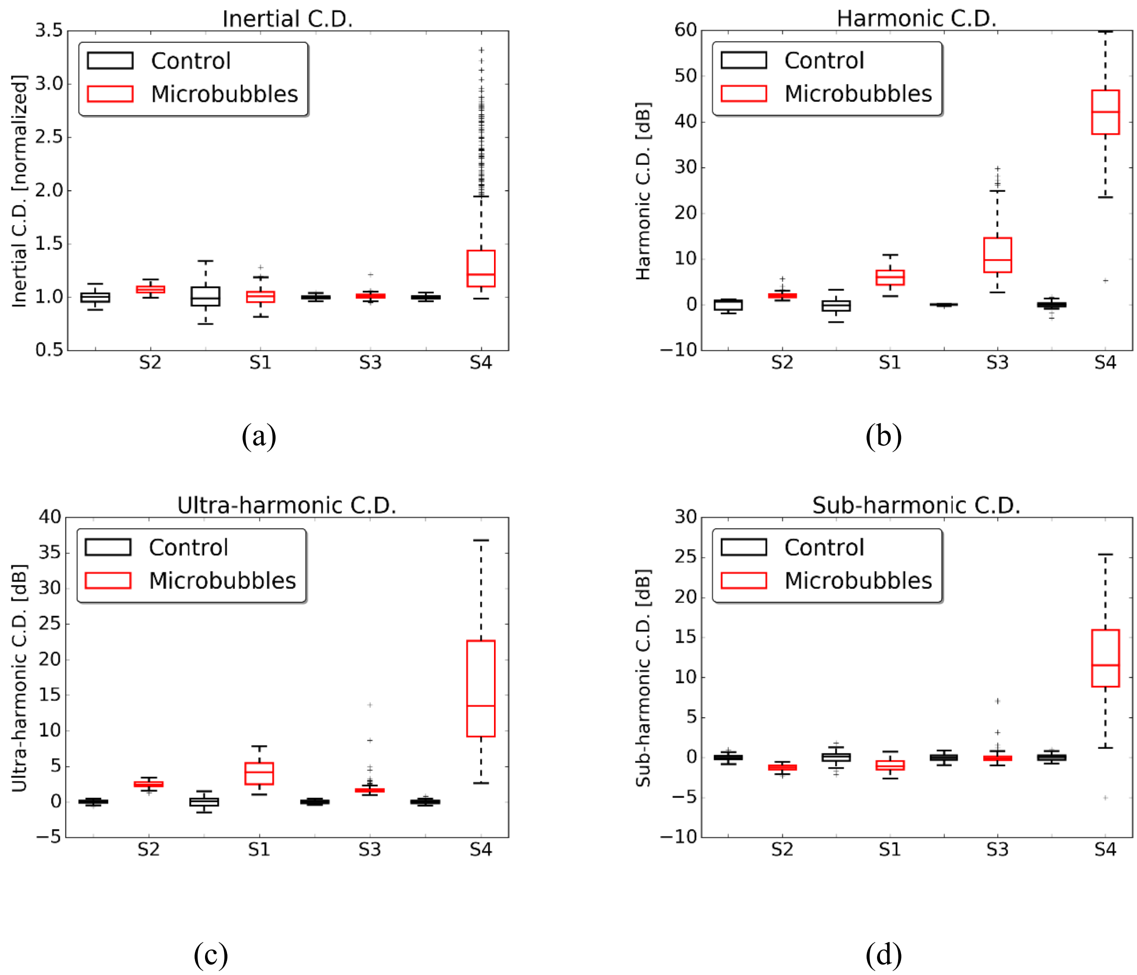
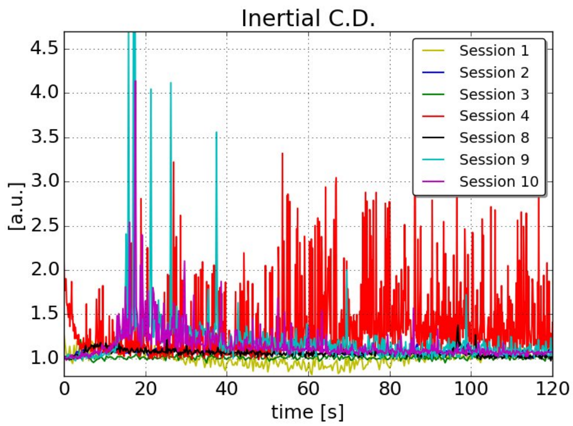
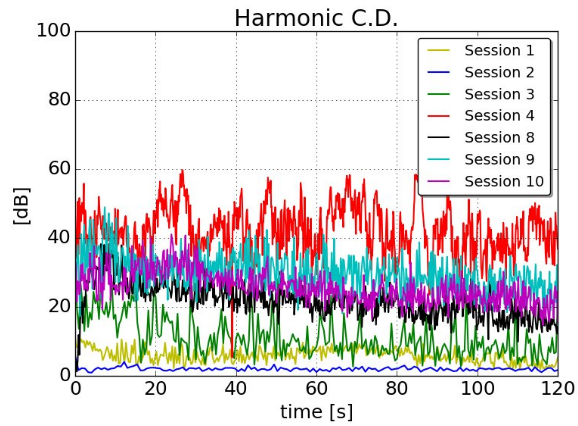


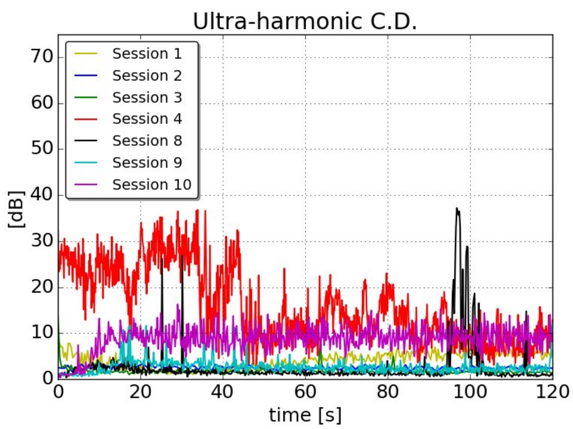
Fig. S5: Summary of relative inertial (a), harmonic (b), ultra-harmonic (c), and sub-harmonic (d) cavitation doses (C.D.) using constant acoustic pressure (no feedback control) across experimental sessions 1-4 (S1-S4).



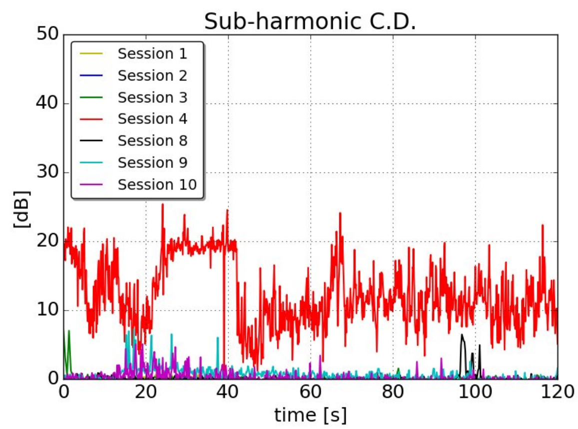
(a)



(b)



(c)



(d)

Fig. S6: Time series of cavitation doses (C.D.) during 2-min sonication after microbubble injection normalized to the baseline acquisition before microbubble injection for each experimental session (1-10). (a) Inertial C.D. associated with broadband emissions, (b) harmonic C.D. associated with stable cavitation, (c) ultra-harmonic C.D. associated with stable cavitation, and (d) sub-harmonic C.D. associated with transient cavitation events.

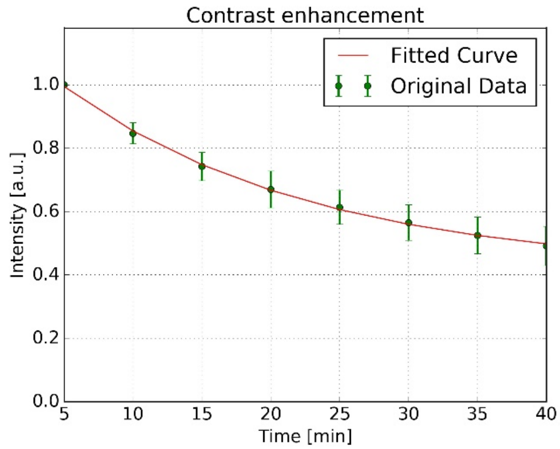


Fig. S7: Exponential fit of the gadolinium decay in muscles. The intensity I decays with: $I = 0.765 * e^{-0.055*t} + 0.414$. The half-life in muscles is 40 min.

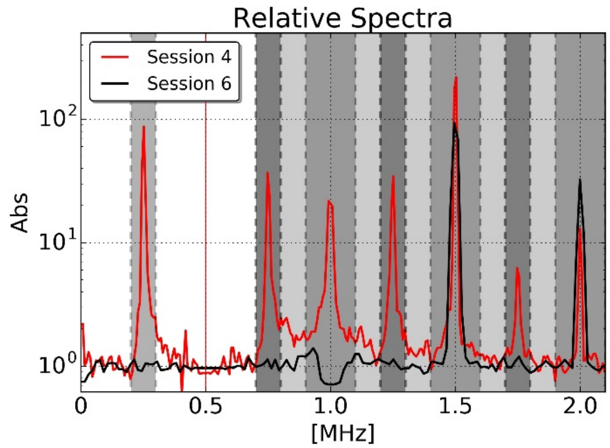


Fig. S8: Examples of relative spectra obtained from experimental session 4 that resulted in a permanent lesion compared to a session performed under feedback control of acoustic pressure (session 6).