Temporal stability of therapeutic microbubbles

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Non-invasive blood-brain barrier (BBB) opening using focused ultrasound (FUS) requires intravenous injection of pre-formed microbubbles. Although microbubble behavior during exposure to imaging sequences has been studied extensively, our understanding of microbubble stability within a therapeutic field is still incomplete. Here, we studied the temporal stability of microbubbles during therapeutic FUS exposure in two timescales: the short time scale (i.e., μs of low-frequency ultrasound exposure) and the long time scale (i.e., days post-activation). Microbubbles had a concentration decay constant of 0.02 d^{-1} but maintained a stable size distribution for up to 3 weeks (< 10% variation). Microbubbles flowing through a 4-mm vessel within a tissue-mimicking phantom (5% gelatin) were exposed to therapeutic pulses (f_c: 0.5 MHz, peak-negative pressure: 300 kPa, pulse length: 1 ms, pulse repetition frequency: 1 Hz, n=10). We recorded and analyzed the microbubble acoustic emissions with concentration-matched samples (10^7 microbubbles/ml) on day 0, 7, 14, and 21 after activation. Temporal stability decreased while inertial cavitation increased over time both *in vitro* and *in vivo*, possibly due to changes in the lipid shell. BBB opening volume in mice (n=3) measured through T_1-weighted contrast-enhanced MRI was equal to 19.1 ± 7.1 mm^3, 21.8 ± 14 mm^3, 29.3 ± 2.5 mm^3, and 38 ± 20.1 mm^3 on day 0, 7, 14, and 21, respectively, showing no significant difference over time (p-value: 0.49). In conclusion, microbubbles maintain their capacity to produce similar therapeutic effects over a period of 3 weeks after activation, as long as the natural concentration decay is accounted for.

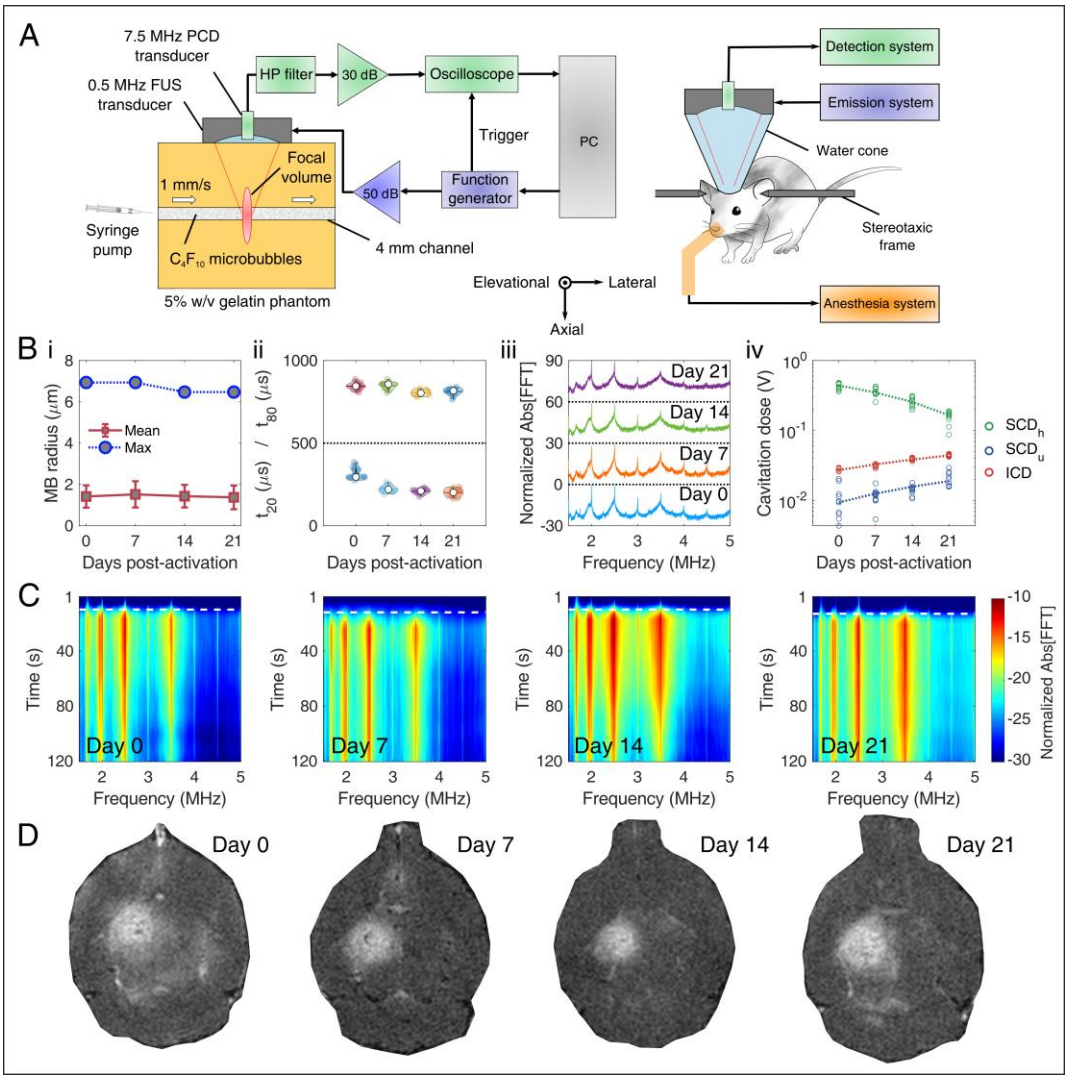

Figure: A) In vitro and in vivo experimental setup. B) In vitro microbubble stability. i) Mean and maximum microbubble size evolution. ii) Microbubble lifetime over time, expressed as the time required for 20% or 80% of the total energy to be emitted (i.e., t_{20} and t_{80}). iii) Normalized spectra over time. iv) Cavitation doses evolution. SCDh: harmonic stable cavitation dose, SCDu: ultraharmonic cavitation dose, ICD: inertial cavitation dose. C) In vivo microbubble stability. Spectrogram evolution, showing increase of broadband emissions with storage time. D) BBB opening evolution over time.

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