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Additional results for "Joint entropy of continuously differentiable ultrasonic waveforms" [J. Acoust. Soc. Am. 133(1), 283-300 (2013)]

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Additional results for "Joint entropy of continuously differentiable ultrasonic waveforms" [J. Acoust. Soc. Am. 133(1), 283–300 (2013)] (L)

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Previous results on the use of joint entropy for detection of targeted nanoparticles accumulating in the neovasculature of MDA435 tumors [Fig. 7 of M. S. Hughes *et al.*, J. Acoust. Soc. Am. **133**, 283–300 (2013)] are extended, with sensitivity improving by nearly another factor of 2. This result is obtained using a "quasi-optimal" reference waveform in the computation of the joint entropy imaging technique used to image the accumulating nanoparticles.
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In this Comment we report on a further improvement in sensitivity of ultrasonic detection of targeted nanoparticle contrast agents *in vivo* beyond that reported in Fig. 7 of a recent publication in this journal.[1] These results were obtained using the joint entropy, $H_{f,g}$ [Eq. (4) of Ref. 1], of the backscattered radio frequency ultrasound and a reflection of the insonifying pulse, $g(t)$, as a reference waveform.

A theoretical analysis of average performance of this type of signal processing in the presence of Gaussian noise leads to a general strategy for finding a much better choice of reference in many experimental circumstances.[2] This search requires extensive computer time but results in a further *2.5-fold* increase in sensitivity as quantified by the statistical confidence of the measurements means and standard deviations [Eq. (6) of Ref. 1].

All data acquisition and analysis parameters are the same as described previously.[1] The new feature of the analysis presented here is the use of a more nearly optimum reference waveform, $g(t)$, for the computation of joint entropy, $H_{f,g}$.

The reference, $g(t)$, was found by searching for the maximum confidence obtained using step-like functions having jumps at the extrema of the reflection of the transducer insonifying pulse from a stainless steel-reflector. These functions are specified by location of jumps, low-value, and high-value. The search spanned the following parameter ranges. Shift values: from −0.02 to 0.10 in increments of 0.01, high-values: from 100.0 to 10000.0 in decades, low-values: from 0.01 to 0.001 in decades values.

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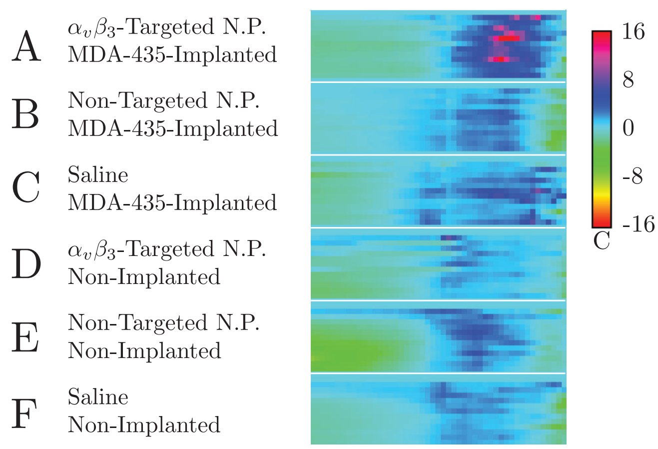

FIG. 1. Confidence, **c**, panels for $\Delta H_{f,g}$ for all groups used in our study. (A) MDA 435-implanted mice injected with $\alpha_v\beta_3$-targeted nanoparticles ($N = 5$); (B) MDA 435-implanted mice injected with non-targeted nanoparticles ($N = 5$); (C) MDA 435-implanted mice injected with saline ($N = 5$); (D),(E),(F) same injections into $N = 5$ tumor-free mice.

The color lookup table of Fig. 1 is chosen to be the same as that of Fig. 7 published previously.[1] However, the confidence values in the panels cover the range −7.7 to 30.1 so that the upper range of values, which appear on the upper right of panel (A) are actually saturated. These are roughly twice the magnitude of the largest confidences (−16) obtained previously.[1]

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[1]M. Hughes, J. McCarthy, J. Marsh, and S. Wickline, "Joint entropy of continuously differentiable ultrasonic waveforms," J. Acoust. Soc. Am. **133**(1), 283–300 (2013).
[2]M. Hughes, J. McCarthy, J. Marsh, and S. Wickline, "Entropic vs. energy waveform processing: A comparison based on the heat equation," in *Proceedings of the Fall 2014 Acoustical Society Meeting*, 2014.