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

M. S. Hughes,^{a)} J. N. Marsh, and S. A. Wickline

Washington University School of Medicine, Washington University in St. Louis, St. Louis, Missouri 63110

J. E. McCarthy

Department of Mathematics, Washington University in St. Louis, St. Louis, Missouri 63110

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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.

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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¹M. Hughes, J. McCarthy, J. Marsh, and S. Wickline, “Joint entropy of continuously differentiable ultrasonic waveforms,” J. Acoust. Soc. Am. **133**(1), 283–300 (2013).

²M. 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.

^{a)}Author to whom correspondence should be addressed. Electronic mail: mshatctrain@gmail.com