Improved Detection of Nanoparticle-Based Contrast Agents in Tumors

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Previous results on use of joint entropy for detection of targeted nanoparticles accumulating in the neovasculature of MDA435 tumors are extended.[M.S. Hughes *et al.*, J. Acoust. Soc. Am. 133, 283-300 (2013), Figure (7)], improving sensitivity by nearly another factor of two using a "quasi-optimal" waveform.

I. RESULTS

In this letter we report on a further improvement in sensitivity of ultrasonic detection of targeted nanoparticle contrast agents *in vivo* beyond that reported in Figure (7) of a recent publication in this journal[1]. These results were obtained using the joint entropy, $H_{f,g}$ (Eq. (4)[1]) of the backscattered radio frequency ultrasound (RF) 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)[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.

The color lookup table of Fig. (1) is chosen to be the same as that of Figure (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]

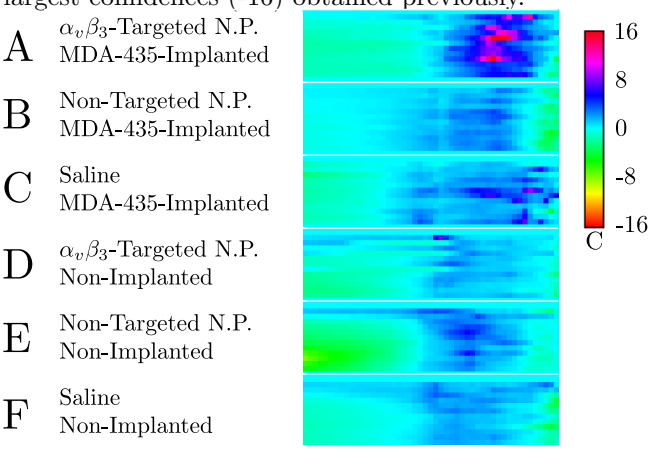

FIG. 1. Confidence, **c**, panels for $\Delta H_{f,g}$ for all groups used in our study. (A)MDA 435-implanted mice injected with $\alpha_v\beta_3$-targeted nanoparticles ($N = 5$), (B)MDA 435-implanted mice injected with non-targeted nanoparticles ($N = 5$), (C) MDA 435-implanted mice injected with saline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

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