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Effects of Signal Saturation on QUS Parameter Estimates Based on High-frequency-ultrasound Signals Acquired from Isolated Cancerous Lymph Nodes

Kazuki Tamura [Student Member, IEEE],

Graduate School of Engineering, Chiba University, Chiba, Japan

Jonathan Mamou [Senior Member, IEEE],

Lizzi Center for Biomedical Engineering, Riverside Research, New York

Alain Coron [Member, IEEE],

Laboratoire d'Imagerie Biomédicale, CNRS, INSERM, Sorbonne Universités, UPMC Univ Paris 06, Paris, France

Kenji Yoshida [Member, IEEE],

Center for Frontier Medical Engineering, Chiba University, Chiba, Japan

Ernest J. Feleppa [Fellow, IEEE], and

Lizzi Center for Biomedical Engineering, Riverside Research, New York

Tadashi Yamaguchi [Member, IEEE]

Center for Frontier Medical Engineering, Chiba University, Chiba, Japan

Abstract

Choosing an appropriate dynamic range for acquiring radio-frequency (RF) data from a high-frequency ultrasound (HFU) system is challenging because signals can vary greatly in amplitude as a result of focusing and attenuation effects. In addition, quantitative ultrasound (QUS) results are altered by saturated data. In this study, the effects of saturation on QUS estimates of effective scatterer diameter (ESD) and effective acoustic concentration (EAC) were quantified using simulated and experimental RF data. Experimental data were acquired from 69 dissected human lymph nodes using a single-element transducer with a 26-MHz center frequency. Artificially saturated signals (x_c) were produced by thresholding the original unsaturated RF echo signals. Saturation severity was expressed using a quantity called saturate-SNR (SSNR). Results indicated that saturation has little effect on ESD estimates. However, EAC estimates decreased significantly with decreasing SSNR. An EAC correction algorithm exploiting a linear relationship between EAC values over a range of SSNR values and l^1 -norm of x_c (i.e., the sum of absolute values of the true RF echo signal) is developed. The maximal errors in EAC estimates resulting from saturation were -8.05 dB/mm³, -3.59 dB/mm³ and -0.93 dB/mm³ with the RF echo signals thresholded to keep 5, 6 and 7 bits from the original 8-bit dynamic range, respectively. The EAC correction algorithm reduced maximal errors to -3.71 dB/mm³, -0.89 dB/mm³ and -0.26 dB/mm³ when signals were thresholded at 5, 6 and 7 bits, respectively.

Index Terms

high-frequency ultrasound; quantitative ultrasound; cancerous lymph nodes; lymphnode metastases; signal saturation

I. Introduction

Quantitative ultrasound (QUS) methods based on the backscatter coefficient can be used to characterize tissue microstructure using a scattering model [1] and successful QUS studies have been performed to assess various organs. High frequency (i.e., >20 MHz) ultrasound (HFU) permits fine-resolution imaging of tissue features because its wave-length is short (e.g., 75 μm at 20 MHz) and it typically uses focused beams with low F-numbers.

Also, HFU data have been successfully exploited to quantify ultrasound scattering in soft tissues using spectral-based QUS methods. For example, a study used neural network classification based on spectral parameters [2] to tissue type imaging. In another study, Ghoshal et. al. [3] assessed fat amount in liver tissues. Oelze et al. [4] investigated animal models of fibroadenomas and carcinomas using effective acoustic concentration (EAC) and effective scatterer diameter (ESD).

The exponential, Gaussian and fluid-filled sphere form factors were investigated to develop QUS methods to investigate human thyroids. The exponential form factor showed the best goodness fit and estimated scatterer diameter ranged from 44 μm to 56 μm [5]. Lavarello et al. [6] were able to detect and classify diseased thyroid tissues (normal, C-Cell adenoma, papillary thyroid carcinoma and follicular variant papillary thyroid carcinoma) using ESD and EAC, homodyned-K parameters. ESD and EAC showed significant difference among normal, papillary thyroid carcinoma and follicular variant papillary thyroid carcinoma.

Recently, new QUS methods were developed to describe ultrasound scattering in dense media using structure form factor based method [7]. These dense form factor could prove highly relevant to cancer studies.

However, QUS using HFU remains challenging because of acoustic attenuation and focusing effects. Specifically, HFU, radio-frequency (RF), echo signals often have a large dynamic range because of high frequency-dependent attenuation along the propagation path and strong focusing. The RF signal amplitude typically covers several orders of magnitude between the sample surface and the deepest imaged regions. Single-element, spherically-focused HFU transducers have small F-numbers because a high sound pressure is required to obtain adequate echo-signal data in attenuating media. Therefore, diffraction effects associated with strong focusing become significant and greatly affect the dynamic range of the transmitted and received RF signals, even if the depth range of interest is small. It is one of the reasons why QUS methods are often limited to superficial tissues and why applying QUS clinically can be challenging [5].

Attenuation and diffraction effects create challenging experimental conditions for digitizing RF echo-signal data with 8-bit, or even 12-bit, A/D cards. If the voltage range is set too high,

then the signal-to-noise ratio (SNR) of small signals (e.g., from deep regions or weak scatterers) becomes too low. Conversely, if the range is set too low, then large signals are clipped creating non-linear signals and signal-saturation issues.

In clinical ultrasound, saturation can be reduced by adjusting TGC, gain, dynamic range, and other scan settings, but because the latest generation of clinical ultrasound systems are fully digital, saturation still occurs at the digitization step and are related to the assigned digitizer dynamic range. So, a tradeoff exists between the ability to acquire unsaturated RF data for QUS processing as a function of location in the imaged field of view. This problem also exists at typical clinical frequencies, but its investigation in the case of an HFU system is the focus of this study.

Signal saturation will affect the frequency contents of RF signals. The Fourier transform of a saturated signal contains harmonics and nonlinear components; therefore, saturation is expected to affect QUS estimates based on the backscatter coefficient. The present study determines the effect of saturation on QUS-parameter estimates and investigates possible correction methods for affected QUS parameters. Recent work by our group demonstrated how QUS estimates were able to distinguish metastatic regions within freshly-excised lymph nodes (LNs) using a single-element, HFU transducer [8]–[10]. Acquiring the LN data was time consuming because it required careful adjustment of several parameters (e.g. dynamic range, gain, attenuation) to obtain unsaturated RF data. The present study examines the effects of saturation on two QUS parameters proven to be useful for cancer detection in LNs: ESD and EAC. The study also presents an original method to mitigate the effects of saturation on these parameters. The study is performed first on simulated data that mimics experimental data from LNs and then on experimental data acquired from human LNs excised from cancer patients. EAC and ESD also are useful in various other tissue-evaluation applications (e.g., distinguishing among different types of rat mammary tumors[11], or assessing types and degrees of fatty liver[3]).

Accurate knowledge of whether LNs contain metastases is mandatory for staging cancer using the American Joint Committee on Cancer tumor-node-metastases (TNM) staging system. The method requests to make a lot of histological samples for definitive diagnosis.

Therefore, because the pathologist cannot evaluate every LN in its entirety, these approaches suffer serious sampling inadequacies. Inadequate LNs sampling results in a large number of false-negative determinations and can greatly affect outcomes. A purpose of our QUS studies of LNs was to develop QUS-based methods to guide the pathologist to the optimal plane for cutting and microscopically examining the LN and thereby reducing the chance of missing small, otherwise occult metastases and the rate of false-negative determinations without increasing the labor load on the pathologists. Our studies to date demonstrated that we have made encouraging progress toward this end [8], [12], [13].

Our approach requires scanning LNs using HFU and acquiring and processing individual LN RF data. Therefore, if the investigated methods are successful, a significant improvement in scanning could be achieved by reducing the time currently needed to pre-scan the LN in order to set the digitizer dynamic range to avoid saturation.

Although the investigated methods were evaluated on simulated and clinical human LN data, the methods can be applied to all studies using ESD and EAC. Therefore, if successful, the methods could be invaluable for a wide range of preclinical as well as clinical QUS studies.

The goal of the present study was to rigorously investigate the effects of saturation on two clinically-important QUS estimates and to devise, if possible, corrections methods to mitigate these effects. If successful, these methods would permit relaxing experimental constraints on data collection and processing at no detriment to the QUS results. In addition, application of QUS approaches to deeper organs would become easier and more reliable. The paper presents methods and results applied to simulated data, experimental data from a glass bead phantom, and experimental data from a representative clinical database of 69 LNs acquired from 48 colorectal-cancer patients.

II. Materials and Methods

A. ESD and EAC Estimation

Estimates of ESD and EAC were computed using a spherical Gaussian scattering model[1]. The Gaussian scattering model permits efficient implementation and has been used successfully in numerous studies[11] [14].

For a single-element, spherically-focused transducer, the normalized theoretical power spectrum obtained from random medium filled with Gaussian scatterers is given by[11].

$$W_{theor}(f) = \frac{185Lq^2a_{eff}^6\rho Z_{var}^2f^4}{1+2.66(fqa_{eff})^2}e^{-12.159f^2a_{eff}^2}, \quad (1)$$

where f is frequency [MHz], L is the gate length [mm], q is the ratio of transducer diameter to the distance between the transducer and the region of interest (ROI), a_{eff} is the effective scatterer radius (i.e., $2a_{eff}$ is ESD), and ρZ_{var}^2 is EAC. Also, ρ is number of scatterers per mm^3 and $Z_{var} = (Z - Z_0)/Z_0$ is commonly termed the “relative acoustic impedance where Z and Z_0 are the acoustic impedances of the scatterers and the surrounding medium, respectively. After removing, the f^4 dependence, the logarithm of the experimentally-measured normalized power spectrum is fit to an affine function of f^2 at the frequency band 14.5 to 35 MHz, i.e., $Q(f) \approx Af^2 + B$ when $Q(f) = W(f) - 40\log(f)$, and ESD is estimated from A [12].

$$ESD = 2a_{eff} = 2 \times \sim \sqrt{\frac{A}{-4.3[12.159 + 2.66q^2]}}. \quad (2)$$

EAC is estimated from B and a_{eff} .

$$EAC = B - 10 \log[185 L q^2 a_{eff}^6]. \quad (3)$$

B. Artificial Saturation

Signal saturation occurs when the RF signal exceeds the digitizer dynamic range. We considered two types of artificial saturation, which are illustrated in Figure 1. Both saturation processes are fully characterized using a parameter τ (0 to 2^{N-1}) where N is the quantization bit number.

1) Natural artificial saturation (NAS, Fig. 1a)—In this type of artificial saturation, the quantization bit number remains fixed to N and the dynamic range (DR) of the digitizer was reduced and defined as

$$DR = \max(|RF|) \frac{\tau}{2^{N-1}}, \quad (4)$$

$$x_c = \begin{cases} x > DR: & DR \\ |x| \leq DR: & \text{int} \left(\frac{x 2^{N-1}}{DR} \right) \frac{DR}{2^{N-1}} \\ x < -DR: & -DR, \end{cases} \quad (5)$$

where *int* represents the integer part of its argument and x is the original, unsaturated RF signal.

2) Loss-of-bit artificial saturation (LAS, Fig. 1c)—This LAS method can be applied to RF echo signal which have already been acquired with an N -bit digitizer. An M -bit ($M < N$) artificially saturated RF signal is obtained using:

$$x_c = \begin{cases} x > \tau: & \tau \\ |x| \leq \tau: & x \\ x < -\tau: & -\tau \end{cases} \quad (6)$$

The investigated values of τ were 2^{N-4} , 2^{N-3} and 2^{N-2} . These values mean that the dynamic ranges were artificially limited to 1/8, 1/4 or 1/2 of full range (i.e., loss of 3 bits, 2 bits, or 1 bit, respectively).

3) Saturate-SNR (SSNR)—Saturation effects of NAS and LAS were quantified using saturate-SNR (SSNR):

$$SSNR = 20 \log \left(\frac{\|x\|_2}{\|x - x_c\|_2} \right). \quad (7)$$

where $\|x\|_2$ is the ℓ^2 -norm of x . Note that if x and x_c are identical (i.e., no saturation effects), then SSNR becomes infinite. The use of SSNR is well established in audio signal restoration and was therefore also used here [15].

C. Spline interpolation

A possible approach to mitigating saturation effects is interpolation. We investigated cubic spline interpolation as a means of correcting saturated RF points because it is an easy method that often provides satisfactory results [16]. The control points were defined as sampled points not affected by artificial saturation (i.e., with absolute values less than τ in LAS and less than DR in NAS)

Figure 2 shows a result of cubic spline interpolation applied to an RF signal acquired from a human LN. Figure 2(a) and (b) depict time-domain and frequency-domain signals, respectively. The black, blue, and green lines show the original unsaturated RF signal, the artificially-saturated RF signal (with NAS and $\tau = 32$ when $N = 8$), and the restored (i.e., interpolated) RF signal.

D. EAC Correction Method

To correct the effects of saturation on EAC, we took advantage of the empirical linear relationship between the ℓ^1 -norm of saturated RF signals and EAC. The correction method estimates EACs from saturated RF data and spline interpolation.

Figure 3 illustrates the EAC-correction method applied to an ROI (which was acquired using an 8-bit digitizer) from a human LN. The RF signal was generated using LAS with $\tau=2^{8-3}=32$. A representative (unsaturated) RF segment from this ROI is shown in gray in Figs. 3(a)–(c), and its saturated version is shown in green.

The method requires the restored signal (Fig. 3(b)), the sub RF plots (Fig. 3(c1)–(c4)) and the correction plot (Fig. 3 (d)). Figure 3(b) shows the restored signal (magenta) computed using cubic spline interpolation. The ℓ^1 -norm of restored signal was plotted as a cross in Fig. 3(d).

Sub RF plots (blue lines in Fig. 3) were artificially saturated versions of the (already) saturated signal (Fig. 3(a)) obtained with lower thresholds. They were obtained by using LAS or NAS on the green signal with L (number of sub RF plots) thresholds which were

$\tau_i (= \frac{\tau}{L+1} \cdot i)$ or $DR_i (= \frac{DR}{L+1} \cdot i = \max(|RF|) \cdot \frac{\tau_i}{2^{N-1}})$ in LAS or NAS, respectively, where i was between 1 and L . Sub EAC values ($c1_{EAC} c2_{EAC} c3_{EAC} c4_{EAC}$) and ℓ^1 -norm ($c1_{norm} c2_{norm} c3_{norm} c4_{norm}$) values were calculated from each sub-RF plot and added to the Fig. 3(d). B_{EAC} and B_{norm} (computed from the saturated signal) were also shown as the green star in Fig. 3(d). A least-square linear fit was performed in the correction plot to calculate the slope of the linear fit to the green star and the blue circles (slope of the blue line). Then, the red line was obtained using the slope of the fit and forcing it to go through the green star derived from the saturated normalized spectrum. The vertical magenta line in the correction plot was extended vertically from the magenta X. In a final step, the cross point of the extended red line and extended magenta line indicated the corrected EAC value.

In this example, the value of L was 4 and the values of τ_i were 6, 13, 19 and 26 when LAS was applied with $\tau = 32$ on $N = 8$. The parameters used for the experimental data are shown in table I.

E. Simulations

Simulated RF signals were computed for random media containing scatterers that followed a Gaussian scattering model. The simulated signals were used to assess the effects of LAS and NAS saturation as well as to evaluate the performance of our EAC correction method under well-controlled conditions.

Backscatter signals were generated in the frequency domain Transducer pulse-echo impulse-response (Rayleigh pulse modulation) and scatterer locations were converted to the frequency domain with a Fourier transform (FT) and multiplied. The scatterer locations were set on an axial line as arbitrary number of scatterer density randomly. The resultant spectra were converted to the time domain by an inverse FT. The beam profile was calculated from theoretical equations [17] using the transducer dimensions which was used for LNs measurement and its experimentally-measured bandwidth.

The simulated RF signal was then quantified to 8 bits (i.e., constrained to be a signed integer between -128 and 127). For LAS, quantization of the simulated signals was based on maximum $|\text{RF}(t)|$. The simulation parameters shown in Table II were chosen to mimic the experimental human LN data. The simulation used a single-element focused transducer with an aperture of 6.1 mm, f-number of 2, and a center frequency of 26 MHz. The simulated scan was 1,256 lines with 325 points per line sampled at 400 MHz (i.e., 1 mm for depth of computed area). The number of lines and depth were the same as in the ROIs used on human LN data. Random Gaussian white noise was added to the simulated RF signals to yield an SNR of 31.2 dB, which was the average SNR in the experimental data. Simulations were performed to mimic non-metastatic and fully-metastatic LNs. To that end, EAC and ESD values were -3.57 dB/mm³ and 26.3 μm for the non-metastatic simulations and EAC and ESD were -7.45 dB/mm³ and 37.1 μm for the metastatic simulations. These values were the average values for these QUS estimates in our experimental LN data [12]. Each generated RF echo signal was artificially saturated using τ values ranging from 2^{N-5} to 2^{N-2} using LAS (e.g., DR on NAS were 2^{-4} to 2^{-1} times maximum RF signal) and to permit statistical analysis, each simulation case was conducted 100 times.

F. Glass bead phantom Data

Ultrasound RF data were collected from a scattering phantom with glass beads of known average diameter (i.e., 15.9 μm) and number density (i.e., 1.99×10^4 scat/mm³). The phantom speed of sound and acoustic attenuation were measured to be 1560 m/s and 0.5 dB/MHz/cm, respectively. RF data were acquired using a single-element, focused transducer (Panametrics-NDT, V328) with an aperture of 9.5 mm, a focal length of 19 mm, a center frequency of 14.4 MHz, and a -6 dB bandwidth extending from 9.6 MHz to 18.8 MHz. The theoretical axial and lateral resolutions were 78.6 μm and 208 μm , respectively. RF echo signals were digitized at 250 MS/s with a 12-bit A/D board. The DR was set 800 mV for non-saturated RF data and 400 mV, 200 mV, 100 mV and 50 mV for NAS data. Data were

acquired in 31 planes composed of 301 A-lines. Adjacent A-lines were 30 μm apart. The purpose of this experiment was to compare and evaluate the effects of the two artificial saturation methods on ESD and EAC estimates.

G. Experimental Human-LN Data

LNs were dissected from patients with colorectal and gastric cancers at Kuakini Medical Center in Honolulu, HI. Echosignal data acquisition and histological analysis have been described in detail[8]–[10], and are summarized here. After gross preparation, individual LNs were placed in a saline bath at room temperature for HFU scanning and data acquisition. RF echo signals were acquired using a single-element, focused transducer (Olympus, PI35-2-R0.50 IN) with an aperture of 6.1 mm, a focal length of 12.2 mm, a center frequency of 25.6 MHz, and a -6 dB bandwidth extending from 16.4 MHz to 33.6 MHz. The theoretical axial and lateral resolutions were 86 μm and 116 μm , respectively. RF echo signals were digitized at 400 MS/s with an 8-bit A/D board. The transducer scanned in X and Y directions with 25 μm between scan positions to acquire RF echo signals over the full 3D volume of the LN. A representative dataset consisting of 50 non-metastatic LNs and 19 fully metastatic LNs was used for this study. The size of LNs varied, but they usually ranged between 5 and 10 mm in their largest dimension. Because the LN project investigated QUS-based methods to differentiate metastatic LNs from nonmetastatic LNs, all experimental setting were set to prevent saturation of RF data acquired from LN tissue. As a result, only the LAS method could be performed on the clinical LN data.

The Institutional Review Boards (IRBs) of the University of Hawaii and the Kuakini medical Center (KMC) approved the participation of human subject in the study. All participants were recruited at KMC and gave written informed consent as required by both IRBs.

III. Results

A. NAS and LAS effects on ESD and EAC

1) Simulation results—Figure 4 illustrates the effects of NAS (a) and LAS (b) in the frequency band used for ESD and EAC estimation for the simulated non-metastatic data. The figure displays $Q(f)$ (solid curves) and the Gaussian scattering model fit (dashed curves) as a function of τ and DR. As expected, the amplitude of the normalized spectrum decreased as τ and DR decreased because they result in decreased energy in the RF signal. Interestingly, the frequency dependence of the normalized spectra was not strongly affected by LAS or NAS.

Therefore, EAC also decreased with decreasing τ (e.g., from -3.66 dB/mm³ to -16.39 dB/mm³ for LAS), while ESD remained mainly unaffected with values remaining within 4% of 26 μm for non-metastatic LN

Figure 5(a) shows the ESD error as a function of SSNR with green lines. The error was defined as the difference between the estimated and the simulated ESD. Figure 5(a) demonstrates that LAS and NAS effects on ESD estimation errors are identical. The estimation errors without saturation (i.e., infinite SSNR) were 0.41 ± 0.45 μm and -0.13 ± 0.30 μm for non-metastatic and metastatic simulations, respectively. ESD was not affected

by saturation using LAS or NAS and a comparison between ESD estimates obtained using saturated data (SSNR > 12.7 dB) and those obtained with non-saturated data failed to yield a statistically-significant difference. Student's t -test p -values ranged between 0.059 and 0.913 ($p < 0.05$ was the chosen threshold for statistical significance). Therefore, we concluded that both saturation methods had non-significant effects on ESD and we did not investigate an ESD-correction algorithm.

Figure 5(b) shows the EAC error as a function of SSNR. The error was defined as the difference between the estimated and simulated EAC. EAC errors obtained using saturated signals increased exponentially as SSNR decreased for non-metastatic as well as metastatic simulations. The EAC correction method reduced the errors. For example, for metastatic simulations with SSNR = 6.76 dB, EAC error reduced from -4.02 dB/mm^3 to -0.37 dB/mm^3 with LAS. Similarly, for non-metastatic simulations with SSNR = 6.92 dB, EAC error reduced from -4.27 dB/mm^3 to -1.52 dB/mm^3 .

The magenta line in Fig. 5 shows the error in ESD and EAC as a function of SSNRs using interpolated RF signals. Maximal ESD errors (percentages of theoretical values) of the interpolated RF signals were $13.32 (50.08 \%) \pm 0.22 \mu\text{m}$ and $2.05 (5.55 \%) \pm 0.21 \mu\text{m}$ occurred when $\tau = 8$ (i.e., SSNR ≈ 3 dB) for non-metastatic and metastatic LNs with LAS, respectively. Spline interpolation reduced EAC estimation errors when the SSNR was greater than 15 dB. However, the error increased rapidly when SSNR decreased below 15 dB for both saturation methods.

2) Glass-bead-phantom results—Figures 6(a) and (b) respectively illustrate the effects of NAS and LAS in the frequency band used for ESD and EAC estimation from glass-bead-phantom data. The figure displays $Q(f)$ (solid curves) and the Gaussian scattering model fit (dashed curves) as a function of τ and DR. Results follow trends similar to those obtained from simulations.

Figures 7(a) and (b) show the ESD error as a function of SSNR with NAS and LAS method. Overall, ESD error increased with decreasing SSNR. The NAS and LAS results were nearly identical although ESD error from LAS was larger than that obtained from NAS for intermediate values of SSNR (i.e., between 1.0 and 7.3 dB).

Figures 7(c) and (d) show the EAC error as a function of SSNR. EAC errors were different for LAS and NAS. For instance, NAS yielded a lower EAC error than LAS for SSNR values between 7 dB and 4 dB. The proposed EAC correction method (Fig. 7(c)) applied to NAS data reduced errors to 0.13 dB/mm^3 , -2.15 dB/mm^3 from -7.68 dB/mm^3 , -1.05 dB/mm^3 when DR was 200 mV (i.e., $\tau = 32$) and 400 mV ($\tau = 64$), respectively. In addition, the corrected EAC value $\tau = 32$ was not statistically different from 0. The proposed EAC correction method applied to LAS data (Fig. 7(d)) reduced error to -6.54 dB/mm^3 , -3.39 dB/mm^3 , -1.73 dB/mm^3 from -14.75 dB/mm^3 , -7.88 dB/mm^3 , -1.60 dB/mm^3 when τ was 16, 32, and 64, respectively.

3) Summary of results—The previous two results sections demonstrate that NAS and LAS methods have nearly identical effects on estimated values of ESD and EAC (with or without correction).

B. Human-LN-dataset results

1) Illustrative effects in the frequency domain—Figure 8 illustrates the effects of LAS in the frequency band used for QUS estimation on a representative human LN dataset. The figure displays the normalized spectrum and the Gaussian scattering-model fit (dashed) as a function of τ . The results are very similar to those of Figs. 4 and 6. The magnitudes of the normalized spectra decrease with decreasing τ , but the effect of LAS on the frequency dependence of the normalized spectra is very limited. Therefore, as expected, EAC also decreased with decreasing τ (for values of SSNR from infinity to 1.2 dB), while ESD is essentially unaffected with values remaining within 4.3 % of 25.7 μm .

2) Effective scatterer-diameter estimation—Figure 9(a) illustrates the impact of LAS on ESD estimates. SSNR values were distributed from infinity to 3.26 dB. The error was defined as the difference between the ESD value computed with and without LAS. Estimate values were very robust to LAS effects, with relative errors smaller than 1.65 μm , which is 4.5 % of the original ESD. Figure 9(b) demonstrates that non-significant differences (t-test, $p > 0.05$) existed for SSNR values ranging from infinity to 3.9 dB. (The effects were so small that investigation of a correction method was not warranted in the present study, but may be the subject of a future study.)

3) Effective-acoustic-concentration estimation—Figure 10 (a) illustrates the effect of LAS on EAC estimates. The errors are defined as the difference between the value of the EAC estimate in the presence and absence of LAS. EAC values decreased as SSNR values decreased. The maximal errors were -8.05 dB/mm^3 , -3.59 dB/mm^3 , -0.93 dB/mm^3 when τ was 16, 32, and 64, respectively. Figure 10(c) illustrates the result of the EAC-correction algorithm. The maximal errors (after correction) were -3.71 dB/mm^3 , -0.89 dB/mm^3 , -0.26 dB/mm^3 when τ was 16, 32, and 64, respectively. Figures 10(b) and 10(d), which were extracted from Figs. 10(a) and 10(c) respectively, show EAC error values that were not statistically different from 0 (i.e., t-test yielded $p > 0.05$). The lower bound of the SSNR range of non-significant effects decreased from 22.78 dB to 3.99 dB using the proposed correction method. Finally, Fig. 10(e) shows the mean and standard-deviation values around SSNR values from 2 dB to 30 dB in steps of 2 dB. This figure clearly demonstrates the reduction in EAC error and shows that, for SSNR > 10 dB, the corrected EAC can be assumed to be accurate.

4) Effects on cancer detection—Ultimately, EAC and ESD values are intended to identify metastatic regions within LNs. Therefore, this section evaluates the effects of LAS on cancer detection before and after EAC correction.

Figure 11 shows means and standard deviations of the corrected EAC values of metastatic and non-metastatic LNs for each threshold value. The mean value of corrected EAC values

for metastatic LNs at $\tau = 16$ was approximately -8 dB/mm^3 . A non-significant difference (t -test, $p > 0.05$) existed between the mean EAC values of non-metastatic and metastatic LNs.

Table III shows the effect of LAS on EAC estimates and the performance of the correction method for the purpose of cancerous LN detection. The highest mean error caused by LAS was -3.83 dB/mm^3 and the maximal error was -8.05 dB/mm^3 . In comparison, the difference in the mean values of EAC estimates in the original unsaturated signals from non-metastatic and metastatic LNs was 4.18 dB/mm^3 . However, after correction, the mean errors in values of the EAC estimate were less than -1.06 dB/mm^3 and the maximal error was less than -4 dB/mm^3 .

IV. Discussion

A. Effect on QUS Parameters

The effects of LAS saturation on ESD and EAC has the same trend on simulated RF data (Fig. 5) and human LNs RF data (Fig. 9–10). In particular, these studies demonstrated that saturation effects on ESD estimates were limited regardless of the saturation method because the frequency dependence of the normalized spectrum used for QUS estimation was not affected. In contrary, EAC was strongly affected because of the amplitude decrease of the normalized spectrum in the presence of signal saturation.

Nevertheless, Eqs. (2) and (3) indicate that EAC depends on the amplitude of the normalized spectrum as well as its frequency dependence. In particular, a small error in ESD can greatly affect EAC because of the 6th power of a_{eff} in Eq. (3). The EAC values were still significantly reduced even if the a_{eff} used in Eq. (3) was fixed to the value obtained from unsaturated data. Therefore, the main cause of EAC reduction is the signal power loss caused by saturation and not the small errors on ESD.

Our proposed correction algorithm has value in reducing the need to optimize the voltage range on the A/D card used to digitize RF echo signals or to use multiple voltage ranges to assure acquisition of unsaturated signals. The algorithm can be seen as a means to enhance the dynamic range of the RF data for QUS estimation, which could prove invaluable in fast-paced clinical use of these techniques.

A significant difference in the EAC values was not apparent in non-metastatic and metastatic LNs when echo signals were saturated, as indicated in Fig. 11. However, the EAC values of non-metastatic LNs were affected more strongly than those of metastatic LNs because the normalized spectra of non-metastatic LNs were typically larger than those of metastatic LNs. Note that in our LN studies, ESD was the single QUS parameter which permitted cancer detection the most effectively[12]. Therefore, this study also confirms that cancer detection in human LNs using ESD could be performed directly without the need for any correction and without careful optimization of the digitizer range.

Nevertheless, this study also suggests that detection of cancer in LNs using uncorrected EAC estimates from saturated signals could increase false-negative determinations. This is particularly true for the LNs excised from breast-cancer patients where EAC could be an

important contributor to cancer detection[13] This hypothesis will be tested in subsequent studies performed on our extensive database of LN excised from breast-cancer patients.

The EAC correction method was carefully demonstrated on single-element data. In addition, our results also demonstrated that no ESD correction was needed. Nevertheless, clinical ultrasound data is most often acquired using array transducer and while we are encouraged by our results to hypothesize that they may generalize to array data, further investigations are needed and will be the subject of subsequent studies.

In conclusion, the proposed correction algorithm has value in QUS-based diagnosis because: 1) ESD values can be used without correction as shown in Sec. III B.2). and 2) EAC values can be used following our correction algorithm.

B. On the use of the interpolated RF signal to estimate ESD and EAC

In this study, we also investigated the use of the interpolated RF signal to estimate EAC and ESD (Fig. 5); however, QUS estimates were found to be unsatisfactory. In fact, ESD errors were found to be larger than those obtained from saturated signals and EAC errors were larger than those obtained after our EAC correction method.

As expected, with the proposed method and the interpolation method, EAC errors increased as SSNR decreased. The proposed EAC correction method produced a smaller EAC error than the interpolation method did when SSNR ranged from infinity to 3.19 dB for non-metastatic LNs and from infinity to 8.11 dB for metastatic LNs (See Fig. 5c). In addition, our method is more adapted to QUS studies because, saturation effects can greatly vary within an ROI (i.e., each RF segment has its own SSNR) Therefore, the optimal correction method must be effective over a wide range of SSNR values. When SSNR values span a wide range, the correction method described here is superior to the spline-only interpolation method.

C. Robustness and effective bit gain

The result of EAC correction (Simulation: Fig. 5(b), Glass bead phantom: Figs. 7(c) and 7(d), human LN dataset: Fig. 10) shows satisfactory results for SSNR greater than 7 dB. To illustrate the limitations of our EAC correction methods, Figure 12 shows results obtained from simulated RF data saturated with LAS using a τ value of 12, 20 and 32. As expected, this figure shows that for the lowest threshold, the correction is ineffective. Satisfactory results were obtained with $\tau = 20$, and nearly perfect correction was achieved with $\tau = 32$. These results demonstrate that estimating the unsaturated l^1 -norm is critical for accurate EAC correction and that the cubic spline interpolation is unable to provide accurate l^1 -norm estimates when τ is too small.

To further investigate how the l^1 -norm estimates degrade as SSNR decreases, Fig. 13 displays the ratio of the l^1 - norms of the saturated and interpolated signals against the original unsaturated l^1 -norm. These plots show means and standard deviations obtained from 100 random simulations. Both plots show positive correlation against SSNR The l^1 -norm ratio of interpolation shows higher value than saturation on a wide SSNR range (i.e., between infinity and 1.03 dB) and drops rapidly when SSNR<5 dB. It means that the

accuracy of l^1 -norm estimation decreased sharply when SSNR was <5 dB. These results demonstrate that our EAC correction method is stable and robust and can be used for $\text{SSNR} > 5\text{dB}$,

Based on our representative data sets of 69 LNs an SSNR of 5 dB is achieved with $\tau = 16$ in LAS, which means that our correction methods virtually extended the dynamic range by 3 bits (i.e., $\log_2(128/16)$). This feature could prove critical in clinical implementations of these methods were time might not be available to optimally set the digitizer range or could permit the proper QUS processing of deeper suspicious regions.

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Biographies

Kazuki Tamura (M'14) was born in Yamagata, Japan in 1992. He received the M.E. degree from Chiba University, Chiba, Japan, in 2016. He is currently Ph.D course student.

Mr. Tamura is a member of IEEE, the Acoustical Society of Japan and the Japan Society of Ultrasonics in Medicine.

Jonathan Mamou (S'03–M'05–SM'11) graduated in 2000 from the Ecole Nationale Supérieure des Télécommunications in Paris, France. In January 2001, he began his graduate studies in electrical and computer engineering at the University of Illinois at Urbana-Champaign, Urbana, IL. He received his M.S. and Ph.D. degrees in May 2002 and 2005, respectively. He is now Research Manager of the F. L. Lizzi Center for Biomedical Engineering at Riverside Research in New York, NY. His fields of interest include theoretical aspects of ultrasonic scattering, ultrasonic medical imaging, ultrasound contrast agents, and biomedical image processing. He is the co-editor of the book *Quantitative Ultrasound in Soft Tissues* published by Springer in 2013. Jonathan Mamou is a Senior Member of IEEE, a Fellow of the American Institute of Ultrasound in Medicine (AIUM), and a Member of the Acoustical Society of America. Dr. Mamou served as the Chair of the AIUM High-Frequency Clinical and Preclinical Imaging Community of Practice. He is an Associate Editor for *Ultrasonic Imaging* and the *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control* and a reviewer for numerous journals.

Alain Coron was born in 1971 in Saint-Etienne, France. He graduated from the electronics and information department of the Institut de Chimie et Physique Industrielles, Lyon, France, in 1994. Then he received the Ph.D degree in signal processing from the Institut National Polytechnique de Grenoble, France in 1998.

From Spring 1998 to summer 2001 he was successively a postdoctoral fellow at Universit Catholique de Louvain in Louvain-la-Neuve, Belgium and at Technische Universiteit Delft in Delft. He studied magnetic resonance spectroscopy and magnetic resonance imaging (MRI) with time frequency and wavelet transforms and also sparse sampling of 3D MRI. He is now a research engineer at CNRS, Paris, France and interested in analysing and processing data from high-frequency ultrasound, Dynamic Contrast-Enhanced Ultrasound or histology. Dr Coron is a member of the IEEE and IEEE SPS.

Kenji Yoshida was born in Nara, Japan, in 1980. He received a Dr. Eng. degree from Doshisha University in 2009. From 2009 to 2013 he worked as research assistant in Doshisha University, Kyoto, Japan. He is currently an assistant professor for Center for Frontier Medical Engineering (CFME), Chiba University. He received the Best Paper Award at the Symposium on Ultrasonic Electronics in 2007, the Awaya Kiyoshi Award for encouragement of research from the Acoustical Society of Japan in 2007, the 56th Sato Award from the Acoustical Society of Japan. Since graduate school, he has been studied microbubble dynamics and contrast enhanced ultrasound. The present main field of his research is quantitative ultrasound for tissue characterization, it includes measurement of acoustic properties of the tissue by high-frequency ultrasound.

Dr. Yoshida is a member of the IEEE, the acoustical Society of Japan, the Japan Society of Applied Physics, the Japan Society of Ultrasonics in Medicine and the Japan Society of Endoscopic Surgery.

Ernest J. Feleppa, PhD, was born in 1940 in New York City. He received his baccalaureate in physics at Cornell University, Ithaca, NY, in 1961, and his doctorate in biophysics at Columbia University, New York, NY, in 1968. After a year of post-doctoral research in physiology and genetics, Dr. Feleppa became a member of the research staff at Riverside Research in 1969 where he pursued research in coherent optics, environmental systems, and education-management systems before joining the biomedical-engineering laboratory at Riverside Research. As a member of the biomedical engineering laboratory, Dr. Feleppa undertook research in ultrasonic tissue characterization applied to the eye, liver, kidney, thrombi, plaque, prostate, and lymph nodes that laid the foundation for modern quantitative ultrasound. After serving as assistant manager, manager, and associate director of the biomedical engineering laboratory, he became its research director in 2005.

Tadashi Yamaguchi was born in Ibaraki, Japan, on 1971. He received a B.E., M.E. and the Ph. D. degrees, from Chiba University, in 1996, 1998 and in 2001 in Information Science, respectively. From 2001 to 2007 he worked for Department of Information and Image Science, Faculty of Engineering, Chiba University as an Assistant Professor. He was a Visiting Researcher of Bioacoustic Research Laboratory, University of Illinois at Urbana-Champaign from 2003 to 2004. From 2007 to 2008 he worked for Department of Information, Processing and Computer Science, Graduate School of Advanced Integration Science, Chiba University as an Assistant Professor. From 2008 to 2013 he worked for Research Center for Frontier Medical engineering, Chiba University as an Associate Professor. From 2013 he has been a Professor of Center for Frontier Medical Engineering (CFME), Chiba University, and the Director of Ultrasonics and Medical Imaging Laboratory in CFME.

His present interests are in tissue characterization of the organs by ultrasound, it includes the analysis of acoustic properties of tissues by ultra-high ultrasound, and development of quantitative diagnosis method for internal organs by estimation of scattering features of target tissues.

Dr. Yamaguchi is a member of IEEE, the Acoustical Society of Japan, The Japan society of Ultrasound in Medicine, Electronics Information and Communication Engineering of Japan, Marine Acoustics Society of Japan, and Japan Society of Endoscopic Surgery.

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Fig. 1.
Two-way artificial saturation,

Fig. 2.
Example of signal restoration using cubic spline interpolation. The circles show control point for spline interpolation when $\tau = 32$ using LAS.

Fig. 3.

Correction method for EAC. The green star was plotted right down panel using the estimated EAC value and l^1 -norm of the saturated data. Additional saturated points (blue circle) were plotted using signals which were artificially saturated with threshold τ_i . The blue line illustrates a least-squares fit to the green star and blue circle. The red line is the identical with slope as the blue line and passes through the green star. The magenta line shows the l^1 -norm of the restored data obtained using cubic-spline interpolation. The value of EAC at the intersection point of the red and magenta lines is the corrected EAC value.

Fig. 4.

Effect of saturation on $Q(F)$ and estimated of EAC and ESD on simulated data. The line colors were saturation level (dynamic range (a) and threshold (b)). Line styles illustrate spectrum (continues line) and Gaussian fitting result (dashed line).

Fig. 5.

ESD errors (a) and EAC error (b) as a function of SSNR obtained using simulated data. Saturation method were NAS (broken lines) and LAS (continues line). Circle and cross marks were metastatic and non-metastatic, respectively. Means and standard deviations were obtained from 100 independent random simulations. EAC errors as a function of SSNR before and after application of our EAC correction algorithm. Magenta lines were estimated using interpolated RF echo signal

Fig. 6. Effect of saturation on $Q(f)$ and estimated of EAC and ESD on phantom data.

Fig. 7.

ESD errors (a)(b) and EAC error (c)(d) as a function of SSNR obtained using phantom data. (a) and (c) are saturated using NAS. (b) and (d) are saturated using LAS. Means and standard deviations were obtained from 231 ROIs. EAC errors as a function of SSNR before and after application of our EAC correction algorithm

Fig. 8.

Effect of saturation on $Q(F)$ and estimated of EAC and ESD on representative experimental data.

Fig. 9.

ESD estimation errors as a function of saturation. Error is defined as mean of $ESD_{\tau} - ESD_{ori}$, where ESD_{τ} and ESD_{ori} are the means of estimated ESD value using saturated data at τ and original non-saturated data, respectively. (a) ESD errors from all lymph nodes. (b) ESD errors from LNs selected from (a) for which non-significant errors were found (i.e., t-test yielded $p > 0.05$). (Symbols and error bars are the mean and standard deviation of the ESD errors obtained from each LN, respectively).

Fig. 10.

(a) and (b) Estimated acoustic concentration before correction. (c) and (d) Estimated acoustic concentration after correction. (b) and (d) shows the extract plots which were showing non-significant difference (t-test, $p > 0.05$). (e) shows combined data from (a) and (c) where results were averaged binned every 2 dB in SSNR to permit easy visualization of the EAC correction effects.

Fig. 11.
Mean and standard deviation of EAC estimates in non-metastatic and metastatic LNs.

Fig. 12. Robustness of EAC correction algorithm presented in the same format as Figure 3(d). (a) Deficient correction, (b) satisfactory correction, (c) best correction.

Fig. 13. l_1 -norm ratios as a function of SSNR. They were calculated as the l_1 -norm obtained from saturated or interpolated data divided the l_1 -norm of the original unsaturated data. Mean and standard deviation were obtained from 100 random simulations.

TABLE I τ_1 Values for Correction for Experimental Signal($N=8$)

	τ_1	τ_2	τ_3	τ_4
$\tau = 16$	3	6	10	13
$\tau = 32$	6	13	19	26
$\tau = 64$	13	26	38	51

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TABLE II

Simulation Parameters

Speed of sound		1540	m/s
Aperture		6.1	mm
f-number		2	
Center frequency		26	MHz
Number of lines		1256	lines
Number of RF points per line		325	points
SNR		31.2	dB
Non – metastatic	Number of scatterers	534	Scat/pl
	Diameter	26.2	μm
	ESD	26.3	μm
	KAC	-3.57	dB/mm ³
Metastatic	Number of scatterers	219	Scat/pl
	Diameter	37.1	μm
	ESD	37.1	μm
	EAC	-7.45	dB/mm ³

Saturation Effect and Correction Performance. Errors Are Saturation or Correction Minus Original. Mean Error Is the Difference Between Mean of Saturation or Correction and Original. Error Maximum (Max.) Is Maximum of Absolute Error. the Figures Show Mean Values $\pm$ Standard Deviation Values.

TABLE III

	Original [dB/nm ³]	Saturation Error		Correction Error				
		Mean	Max.	Correction [dB/nm ³]	Mean	Max.		
$\tau=16$	Non-meta.	-3.88 ± 2.38	-7.71 ± 1.88	-3.83	-8.05	-4.79 ± 2.10	-0.91	-3.71
	Meta.	-8.06 ± 4.69	-10.87 ± 3.97	-2.81	-5.73	-8.27 ± 4.63	-0.22	2.24
$\tau=32$	Non-meta.	–	-4.94 ± 2.07	-1.06	-3.59	-3.99 ± 2.37	-0.11	-0.60
	Meta.	–	-8.88 ± 4.35	-0.82	-2.72	-8.18 ± 4.57	-0.13	-0.89
$\tau=64$	Non-meta.	–	-4.03 ± 2.31	-0.15	-0.09	-3.88 ± 2.39	0.00	0.11
	Meta.	–	-8.21 ± 4.60	-0.15	-0.89	-8.08 ± 2.39	-0.03	-0.26