Mean Scatterer Spacing Estimation from Pellets Using Cepstral Analysis: A Preliminary Study

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Abstract*—Ultrasonic backscattered signals from biological tissues contain information regarding their structures, more specifically, their scatterer structures. This work investigates the use of cepstral analysis in characterizing periodicities in ultrasound A-lines due to uniformity in the scatterer distribution. The A-line is simulated as a convolution between a generated radio-frequency (RF) pulse and a scattering medium containing uniformly distributed scatterers along with randomly situated scatterers. The cepstral analysis is tested by varying the regularity of the scatterers. Simulation results indicate that the mean scatterer spacing can be estimated using both power and complex cepstrum, where it manifests itself as a peak. Experimental results conducted on cell pellets imaged at 1 and 56 hrs revealed a peak at 0.15 mm. In conclusion, a general agreement between simulation and experimental results was found. Future work include the further investigation of the use of mean scatterer spacing as a new biomarker for cancer treatment monitoring.*

Keywords—cell death; cepstral analysis; HT-29; mean scatterer spacing; quantitative ultrasound; scatterer properties; tissue characterization; ultrasound backscatter

I. INTRODUCTION

Cancer therapy consists of many types of treatment which include chemotherapy, radiation, and surgery. Recent studies have shown that responses to a given therapy vary from one patient to another due to the complexity of the biological systems [1]. Therefore, since there is no unique solution for all patients, an efficient early monitoring modality is needed to effectively evaluate the response to treatment. This can be achieved using an imaging modality through the detection of cell death; cancer imaging can monitor tumor progression under treatment which will cause structural changes that can be detected using quantitative ultrasound imaging [2–7].

Quantitative ultrasound has been successfully used to characterize tissues through scatterer properties, which are used to noninvasively monitor the response to cancer therapy [7]. Previous studies have found that these quantitative ultrasound-based biomarkers could differentiate between tumors and normal breast tissues [8]. For example, scatterer size and acoustic concentration estimates were used to differentiate fibroadenomas from mammary carcinomas and sarcomas [9].

Ultrasonic tissue characterization is based on the assumption that ultrasound signals contain considerably more information about the tissue being imaged than the B-mode images that are currently used, since ultrasound waves interact directly with tissues. Therefore, the information in the backscattered signal can be used to monitor changes in tissue structures, such as the alterations of the physical characteristics associated with disease processes. These alterations may cause observable changes in acoustic scattering properties [5].

Characterization of tissue through scatterer properties, such as scatterer spacing, has the potential to develop medically significant approaches to the diagnosis and treatment of disease. Scatterer spacing is the distance between regularly-spaced structures within soft tissues. Previous work has demonstrated that scatterer spacing is capable of differentiating between normal and cirrhotic liver [10]. In another work, scatterer spacing was recognized as an effective tool for noninvasive estimation of temperature change caused by an externally applied heating field [11]. Scatterer spacing may be computed using either spectral autocorrelation [12] or cepstral analysis [13].

In this work, cepstral analysis was used to estimate the mean scatterer spacing from simulated ultrasound backscatter radio-frequency (RF) signals to identify periodic structures. The scatterer spacing was then estimated for cell pellets over a period of time, where the spacing between the scatterers is semi-periodic and unknown.

II. MATERIALS AND METHODS

A. Cepstrum Computation

The power cepstrum of a signal is the inverse Fourier transform of the logarithm of the power spectrum of the signal:

$$C_p(n) = IFT\{Log(|X(w)|^2)\} \quad (1)$$

where $X(w) = FT\{x(n)\}$, *FT* is the Fourier Transform, *IFT* is the Inverse Fourier Transform, and *x(n)* is the signal for which the cepstrum is applied. The logarithm is performed on a real quantity, which is the magnitude of *X(w)*, discarding the phase information.

The complex cepstrum is defined as the inverse Fourier transform of the logarithm of the frequency spectrum of the signal:

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$$C_c(n) = IFT\{Log(X(w))\} \quad (2)$$

In this case, the logarithm is performed on the complex quantity *X(w)*. The logarithm of a complex number is defined as:

$$Log(X(w)) = Log(A) + j\theta \quad (3)$$

where $X(w) = Ae^{j\theta}$.

In order to test this method and validate the use of these cepstra in the mean scatterer spacing estimation, a simulation of backscattered RF signals was initially performed.

B. Simulation of Backscattered RF Signals

Backscattered RF signals were simulated in order to test the performance of the cepstrum in estimating the mean scatterer spacing, under a variety of conditions [14].

A scattering medium was first generated, which consists of 2 types of scatterers: diffuse scatterers and periodic scatterers whose spacing and strength can be controlled.

The total number of diffuse particles within the resolution volume of the imaging device can be considered a random variable having a Poisson distribution. A constant scatterer spacing was chosen and the ratio between the amplitudes of diffuse to regular scatterers varied between 0.1 and l [15].

The backscattered signal was obtained by the convolution of the scattering medium with an RF pulse, whose central frequency, bandwidth and duration can be controlled (Fig. 1). To simulate the depth-dependent attenuation, the RF signal was multiplied by an exponential decay, and finally a uniformly-distributed noise was added to simulate the measurement noise. The resulting simulated RF signal is shown in Fig. 2.

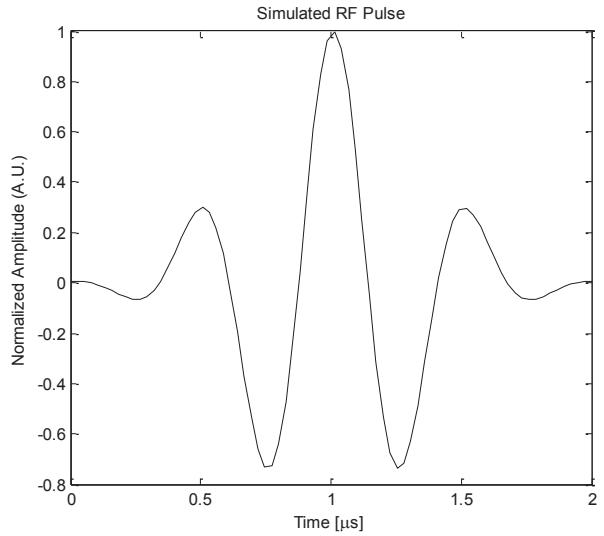


Fig. 1. A simulated RF pulse.

Both power and complex cepstra for the simulated signal were computed using (1) and (2), respectively. Since the density of the random scatterers is higher than the periodic ones, the cepstrum of a single A-line does not reveal clear periodic peaks. In order to overcome this problem, the cepstra of *N* A-line were added to increase the gain of the periodic component in the signal by a factor of √N [14].

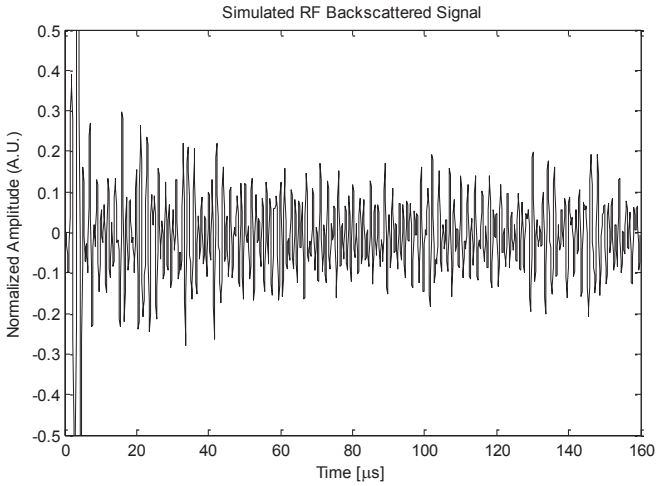


Fig. 2. A simulated RF signal produced by the convolution of the simulated RF pulse with the scattering medium containing both diffuse and uniformly spaced scatterers (spacing equal to 10 μm).

C. Pellet Model

HT-29 cells (ATCC) were grown in McCoy's 5A media prepared from powder (Gibco) at Princess Margaret Hospital (Toronto, ON), and supplemented with 10% FBS (Gibco). Cells were incubated at 37°C, 5% CO_2 in a humidified chamber and passed every 3 to 4 days to maintain the cells in the exponential growth phase until required for pellet preparation. Ten cell pellets were prepared: two in a custom stainless steel holder with three wells with depth 3.02 mm and diameter of 7.8 mm for ultrasound imaging, and eight in 8 mm diameter flat bottomed tubes for histology. For each pellet, HT-29 cells were dissociated with trypsin and 30 million cells were placed in the well, and centrifuged for 10 minutes at 200xg. Excess media was gently removed, and the pellets were carefully covered with phosphate buffered saline (PBS) and left at room temperature for the remainder of the experiment. Cells left at room temperature for long periods of time create cell starvation and hypoxia, ultimately leading to cell necrosis.

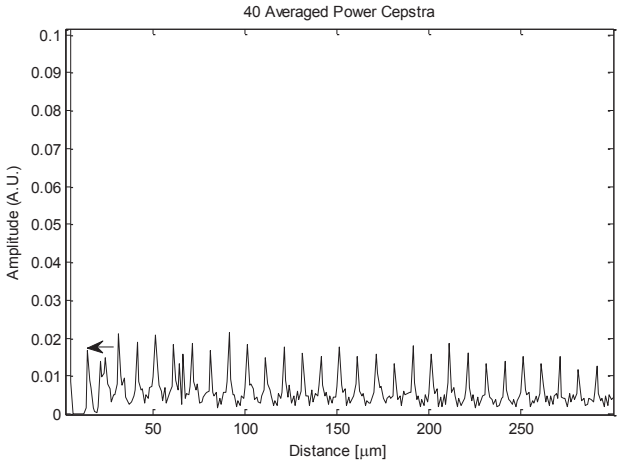
D. Data Acquisition

Ultrasound data were acquired using a Vevo770 preclinical imaging system (VisualSonics, Toronto, ON) using a nominal 55 MHz single-element mechanically-scanned transducer. Raw RF data were acquired and digitized onboard at 420 MHz. Twelve planes of 100 A-lines were acquired from the imaging pellet at each time point. Reference data were acquired from the stainless steel at the bottom of the third well, which contained only PBS in order to normalize the data [16].

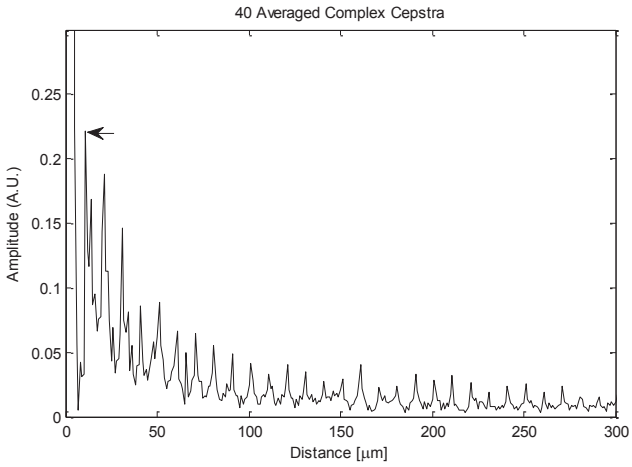
III. RESULTS

A. Simulation Results

The averaged power and complex cepstra for 40 individual A-lines are shown in Figs. 3a and 3b, respectively. The effect of the periodic scatterers is clearly visible as a peak at the characteristic spacing.



(a)



(b)

Fig. 3. The averaged power cepstra (a) and complex cepstra (b) computed from 40 individual A-lines taken from the same simulated medium.

B. *Experimental Results*

Cepstral analysis was performed on the same pellet at different time points, ranging from 1 hour to 56 hours. The ultrasound B-mode images of the pellets are shown in Fig. 4.

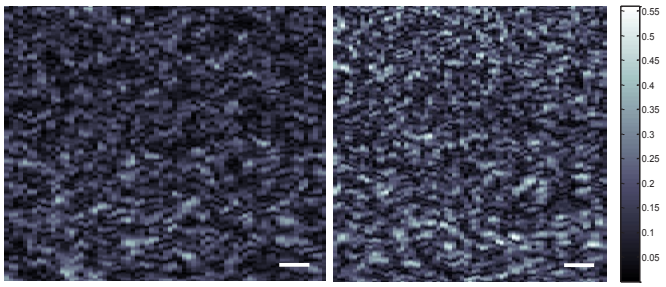
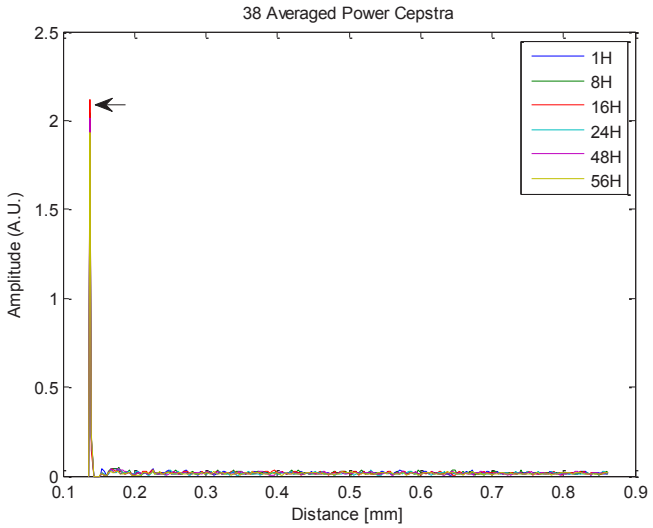
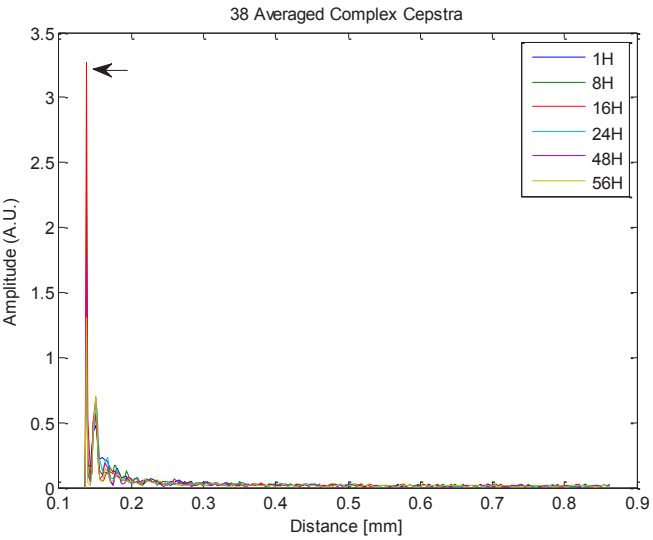


Fig. 4. B-mode images of pellet at 1 hour (left) and 56 hours (right). The scale bar represents 0.1 mm.

The results of the averaged power and complex cepstra are shown in Figs. 5 (a) and (b), respectively.



(a)



(b)

Fig. 5. The averaged power cepstra (a) and complex cepstra (b) computed from 38 individual A-lines taken from the same pellet.

IV. DISCUSSION

The goal of this work is to introduce the mean scatterer spacing as a new biomarker which could be used for characterizing tissues and cancer treatment monitoring, in the same way the scatterer properties are currently being used.

It is known that periodic components in the time domain signal manifest themselves as peaks in the cepstral domain; more precisely, at integer multiples of Δ, with Δ being the location of the dominant peak [17]. The mean scatterer spacing can be determined either from the location of the fundamental (dominant) peak or from the spacing of adjacent harmonics [13]. As shown in Figs. 3 (a) and (b), both averaged power and complex cepstra present periodic peaks, with distance between adjacent ones equal to the scatterer spacing (10 μm). This is in agreements with previous work reported in the literature [14].

Despite similarities between the averaged power and complex cepstra in terms of spacing estimation, one can notice some differences. In the power cepstrum, the fundamental peak (arrow in the figures) corresponding to the scatterer spacing has an amplitude similar to the harmonic peaks as shown in Fig. 3 (a). In the complex cepstrum however, the fundamental peak is dominant and has the largest amplitude compared to other harmonic peaks. This difference may be due to the fact that the computation of the logarithm is different in each case. The power cepstrum performs the logarithm on a real quantity, discarding any useful information that may be present in the phase component of the frequency domain. However, the complex cepstrum does utilize the phase information, since the logarithm is performed on the frequency spectrum of the RF signal, which is complex. This suggests that there may be an advantage to retaining the phase information when processing the RF signal.

The cepstral analysis was then tested on the HT-29 cells. Fig. 4 shows the B-mode images of the pellet at 1 hour and 56 hours. The difference in brightness in the images is due to cell necrosis, which has been shown to change the ultrasound backscatter [16]. Figs. 5 (a) and (b) show the averaged power and complex cepstra respectively, for 38 averaged A-lines from the same pellet. The arrows point to the fundamental peaks, which are at approximately 0.15 mm in both cepstra. Differences between both power and complex cepstra can also be seen, as in the case of the simulated signals. As shown in Fig. 5 (b), harmonic peaks are clearly visible in the complex cepstra. However, they tend to be negligible in the power cepstra as shown in Fig. 5 (a). The cause of these differences and the computation of the spacing from the peaks will be investigated in future work.

V. Conclusion

The potential of using cepstral analysis to assess the mean scatterer spacing was investigated. For this purpose, a simulation of the scatterer medium was carried out. The diffuse scatterers were generated using a Poisson distribution and the periodic ones were equally spaced. The cepstral analysis was then tested on cell pellets.

These preliminary results are promising. Peaks are detected in the cepstrum from cell ensembles, even though the scatterer spacing is not visible through the B-mode images. Potential use of this work include the use of mean scatterer spacing as a new biomarker that can be used for characterizing tissues and cancer treatment monitoring.

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