Bayesian spectrum analysis of non-linear ultrasound contrast microbubble signals

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***Abstract*—The localization of individual contrast microbubbles (MBs) is key to the emerging field of super-resolution ultrasound. The Fourier Transform (FT) is typically used for the frequency domain analysis of MB signals in ultrasound contrast imaging. Bayesian spectrum analysis offers a viable solution to overcome the limited frequency resolution achieved by the FT for MB scatterers. A typical MB signal sampled at 20 MHz and consisting of approximately 80 samples was investigated. The conventional frequency resolution for Fourier-based methods in this instance was 241 kHz. The Bayesian spectral estimation resulted in 12 distinct frequency components many of which were separated by less than 241 kHz. The smallest separation was 52 kHz. The resulting frequency and amplitude estimates matched relatively well with the Fast Fourier Transform (FFT) spectral peaks. Using these estimates the MB signal was reconstructed, and a correlation coefficient of approximately 0.99 was achieved between original and reconstructed signals. The result was reproduced in the analysis of a synthetic MB signal, similar to the original one, and all 12 frequencies were always resolved. Overall, the method promises high spectral resolution without sacrificing the temporal one, and provides information that may be used to differentiate the MB non-linear signal from that of linear scatterers.**

I. Introduction

Super-resolution ultrasound allows the reconstruction of the micro-vasculature by localizing individual contrast microbubbles (MBs) that are injected into the micro-circulation [1]–[5]. Techniques that aim to improve spatial or frequency resolution may add to current super-resolution methods and increase their precision [6]–[9]. The reflected echoes from MB scatterers, are short sinusoidal signals with many closely spaced frequency components. The frequency resolution attained by the Fourier Transform or other Fourier-based methods in general that are commonly used in ultrasound imaging for the frequency analysis of such signals, is limited due to the small number of signal samples.

A parametric spectral estimation method within a Bayesian framework, was developed for the frequency analysis of ultrasound echo signals in [10]–[13]. The method employed a reversible jump Markov Chain Monte Carlo (rjMCMC) technique [14] to provide distinct frequency values of a signal instead of a continuous spectrum provided by the non-parametric methods such as the FT. The rationale for the proposed method was that by changing the spectral estimation problem to that of parameter estimation and by incorporating already known echo-signal characteristics, improved frequency resolution can be achieved [15]–[17].

In [18], the parametric frequency estimation method was applied on ultrasound echo signals from both linear and non-linear (MB) scatterers, revealing previously hidden frequency information, which resulted in approximately 80% correct signal classification for the two types of echo signals. The method was expanded in [19] to include amplitude, noise, and phase estimation, which enabled signal reconstruction and was tested with ultrasound signals from linear scatterers. At least two-fold resolution gains were reported in [19], which led to revealing new frequencies. The objective of this work is to provide an assessment of such a parametric spectral estimation method for the reconstruction of non-linear MB signals. It also investigates the uniqueness, robustness, and parsimoniousness of the solution derived by the Bayesian spectrum analysis by employing a synthetic MB signal.

II. Methods

A. Bayesian Spectral Estimation

The Bayesian method attempts to represent any given input signal as a sum of sinusoids in noise [20]. The number of frequencies, their values, their associated amplitude and phase are all unknown parameters that are being estimated. The algorithm is based on the selection of prior distributions for each of the parameters to be estimated, and on repetitive realizations for a more robust estimation. In particular, multiple rjMCMC realizations are used to draw samples from the posterior distribution and subsequently to estimate the unknown parameters. The posterior distribution is the product of the joint prior distribution and the likelihood function. The joint prior distribution is formulated by the product of all individual prior distributions. The likelihood function depends on the signal type, while the signal noise is considered independent, and evenly distributed. More information and a detailed description of the method can be found in [13], [18].

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The resulting frequency, amplitude, phase and noise estimates from all rjMCMC realizations are further processed in order to provide the final parameter values that will result in signal reconstruction. Similar to the work presented in [19], the parameter estimates are grouped depending on the number of identified frequency components. The frequency estimates in each group are then ordered from the lowest to the highest frequency and the remaining parameters (amplitude, phase) associated to the frequency values are also positioned in separate matrices accordingly. The next step involves the mean value calculation for each set of frequency estimates and their associated amplitudes/phases. Furthermore, several realization estimates may be rejected as outliers and excluded from the mean calculation, if they are found significantly different than the mean values. Finally, the estimated noise variance (power) is used alongside the power of the reconstructed signal to provide an estimate of the original signal's Signal-to-Noise-Ratio (SNR).

B. Experimental Setup

A phased array (S3, Philips, Andover, MA, USA) was used to acquire echo signals from individual MB scatterers, and all acquisitions were performed using a modified ultrasound scanner (Sonos5500 Philips Medical Systems, Andover, MA, USA). Transmission of ultrasound was implemented by focused beams where the transmit focus was set to 60 mm depth. The data were acquired between depths of 70 mm and 80 mm, as at this depth range, the peak negative pressure was low enough (550 kPa) to ensure the survival of the MBs. The excitation pulse was a 6-cycle sinusoid around the transmit frequency (f_0), which was equal to 1.62 MHz. Importantly, the transducer was operated at the low edge of its bandwidth. The sampling frequency (f_s) was 20 MHz, and the raw ultrasound signals were stored for further processing. The acquisition setup was previously used to provide absolute calibration of MB signals, and more information can be found in [21].

C. Data Analysis

The Bayesian method is employed to calculate all signal parameters which lead to signal reconstruction. The estimation method is applied 5000 times to a single MB signal, to ensure that there is an adequate number of estimates for data analysis, since many estimates are rejected during the post-processing described above. The similarity between the original MB echo and the reconstructed signals is measured using the correlation coefficient, r. From a set of 5000 realizations, multiple signals can be reconstructed, depending on the number of identified frequency components, to approximate the original MB echo. The approximation that results into the highest r value with the original signal is considered correct. The same estimation method is then applied to the reconstructed signal, again with 5000 realizations. The reconstructed signal is in essence a synthetic signal which resembles to an MB signal, hence a synthetic MB signal. This second round of reconstruction allows the one to one comparison of all estimated parameters, and is used for the robust assessment of the method's reproducibility.

III. Results and Discussion

Fig. 1 shows a typical MB signal, which was analysed using the Bayesian spectral estimation method. The signal consisted of 83 sample points, which combined with the f_s used here, resulted in a frequency resolution (δf) equal to 20 MHz / 83 samples $= 0.241$ MHz for all non-parametric spectrum analysis methods. Each of the 5000 rjMCMC realizations provided estimates with a specific number of frequency components for the MB signal as seen in the histogram displayed in Fig. 2(a). The most common number of frequency components was 14, which accounted for 54.2% of the realizations (2712 out of 5000), while the numbers 15 and 16 accounted for 31.4% and 9.6% respectively.

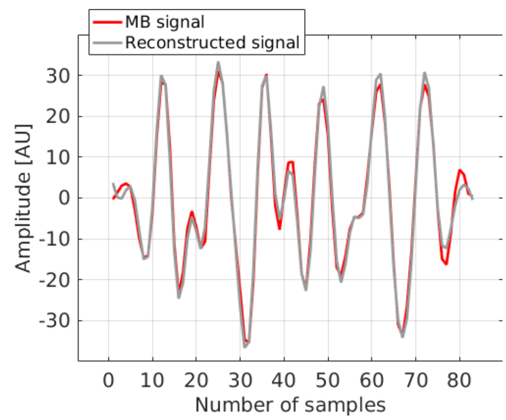

Fig. 1. An example of a single MB signal (red), and its reconstruction (gray) as obtained using the Bayesian spectral estimation. The resemblance between the two signals is quantified by the correlation coefficient that was measured to 0.99.

However, signal reconstruction using the estimated parameters from the realizations that identified 14 frequency components did not lead to a correlation coefficient (r) higher than 0.92 with the original MB signal. Similar r values were obtained from those realizations that resulted into 15 or 16 frequency components, which were the next two groups that were examined. On the other hand, the representation of the original MB signal by a sum of 12 sinusoids in noise with SNR $= 23.63$ dB, resulted in a r value equal to 0.99 between the two signals. Fig. 1 also displays the reconstructed signal that was closest to the original one, on top of it for comparisons. From a visual inspection the two signals closely resemble, which was confirmed by the high r (1 is for identical signals). Note that despite the fact that the number 12 accounted for only 53 times, a value that corresponds to $\approx 1\%$ of the total number of realizations, it provided the closest approximation to the original MB signal. Importantly, this was not an unexpected result, since it is common for such methods to provide some non-accurate results [22]. This result highlights the significance of the post-processing that is required before a reasonable solution is obtained.

Fig. 3 displays the resulting frequency and amplitude values from all the realizations that resulted in 12 diffrent frequency components alongside the FFT of the MB signal. The results

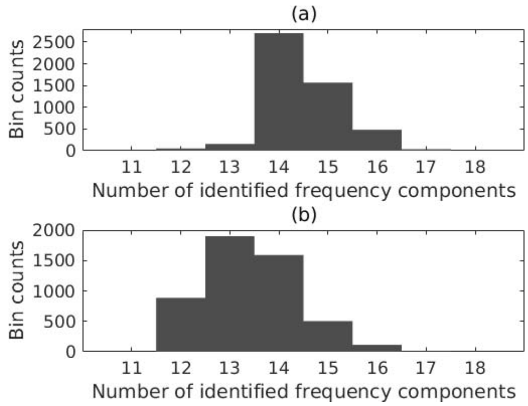

Fig. 2. Histograms showing the number of detected frequency components using 5000 rjMCMC realizations for (a) the original MB signal (1^{st} round of signal reconstruction), and (b) the synthetic MB signal (2^{nd} round of reconstruction).

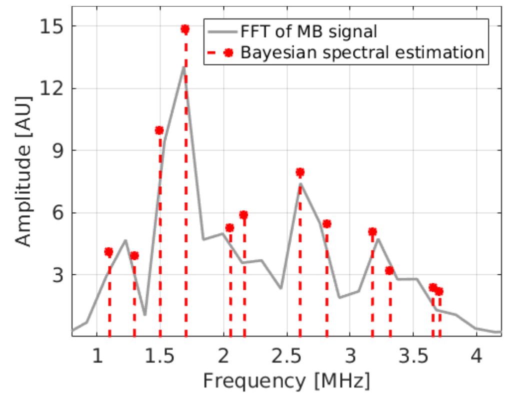

Fig. 3. The FFT of the original MB signal displayed in Fig. 1 alongside with the output of the parametric spectral estimation algorithm. The Bayesian spectrum analysis provided individual frequency, and amplitude (and phase) values instead of a continuous spectrum.

of the Bayesian spectral estimation method also including the phase estimates are shown in Table I. Given the δf limitation, the FFT did not result in more than 4 clearly defined peaks. The 12 distinct peaks identified by the Bayesian spectrum analysis presented good resemblance with the FFT. The 52 kHz that separated the 11^{th} and 12^{th} frequency components as shown in Fig. 3 and Table I was the smallest difference noted between successive frequency estimates and are an indicator of the method's achieved frequency resolution in this instance. In theory, an almost 5 time longer pulse length (duration) would be required to resolve such differences using the FFT. However such choice would deteriorate the temporal resolution which is also significant in ultrasound imaging. In addition, among the 12 estimates, there were 5 more frequency pairs that were separated by less than 241 kHz, that couldn't have been distinguished as separate spectral peaks using the FFT or any other Fourier-based method. Furthermore, Table I showed that instead of a single frequency component at 1.620 MHz, which was the f_0 used here, the parametric estimation resulted in 2 other frequencies around this value that were also associated with the largest estimated amplitudes. These were found at 1.495 MHz and 1.700 MHz, and were separated by 205 kHz.

TABLE I
FREQUENCY, AMPLITUDE, AND PHASE ESTIMATES OF A MB SIGNAL USING BAYESIAN SPECTRUM ANALYSIS

Component	Frequency [MHz]	Amplitude [AU]	Phase [deg]
1^{st}	1.096	4.12	106.5
2^{nd}	1.295	3.92	−84.1
3^{rd}	1.495	9.95	−85.0
4^{th}	1.700	14.88	74.9
5^{th}	2.053	5.28	133.1
6^{th}	2.162	5.91	−12.9
7^{th}	2.605	7.96	−164.7
8^{th}	2.815	5.44	−22.9
9^{th}	3.174	5.05	−29.4
10^{th}	3.314	3.21	10.9
11^{th}	3.652	2.38	−122.7
12^{th}	3.704	2.18	159.7

Fig. 2(b) and Table II show the results of the parametric spectral estimation method when using the frequency, amplitude and phase values shown in Table I to create and subsequently analyse a MB-like synthetic signal. The number of signal samples and the sampling frequency were kept unchanged for a fair comparison. Similar to the previous case, each of the 5000 rjMCMC realizations provided estimates with a specific number of frequency components as displayed in the histogram displayed in Fig. 2(a). The most common number of frequency components was 13 in this instance, which accounted for 38.1% of the realizations (1903 out of 5000), while the numbers 14 and 12 accounted for 31.8% and 17.7% respectively. However, signal reconstruction using the estimated parameters from the realizations that identified 13 or 14 frequency components led to r values ≈ 0.92 with the synthetic MB signal. The representation of the synthetic MB signal again by a sum of 12 sinusoids in noise with SNR $= 23.76$ dB, resulted in the highest r value (0.99) between the two signals. Tables I and II are in direct comparison and the displayed results were insignificantly different. The highest difference between the frequency values was noticed for the 11^{th} component and was ≈ 10 kHz. Similarly the highest difference for the amplitudes was 0.83, noticed for the same frequency component. Finally, no difference higher than 19.6 degrees was found during the phase comparison.

Overall, the findings of the current work demonstrate that the parametric spectral estimation method combined with a r-oriented post-processing, provides consistent signal reconstruction and does not result into different representations of the same signal. However, the above statement is not conclusive and further work is required involving a significantly larger signal sample size for both types of ultrasound signals, from linear and non-linear scatterers. In addition a thorough study using synthetic signals is necessary. The concept of using as synthetic signal, a reconstructed signal that is the output of the Bayesian method to a real MB response may prove to be useful as it enables both the simulation of signals that look like the real ones, and the one to one comparisons of the results for better and more detailed performance evaluation.

TABLE II
FREQUENCY, AMPLITUDE, AND PHASE ESTIMATES OF A SYNTHETIC MB SIGNAL USING BAYESIAN SPECTRUM ANALYSIS

Component	Frequency [MHz]	Amplitude [AU]	Phase [deg]
1^{st}	1.099	3.97	111.8
2^{nd}	1.305	3.78	−99.2
3^{rd}	1.492	9.84	−82.9
4^{th}	1.700	15.13	74.7
5^{th}	2.047	5.10	127.0
6^{th}	2.163	5.89	−11.1
7^{th}	2.599	8.26	−167.2
8^{th}	2.816	5.23	−16.9
9^{th}	3.168	5.14	−22.3
10^{th}	3.308	3.46	9.5
11^{th}	3.661	1.55	−120.8
12^{th}	3.710	1.59	179.3

In addition, the SNR must be examined extensively, as it is likely that there is an effective SNR range where the method performs best and allows for higher r values to be obtained during the signal reconstruction stage. Besides that, the choice of the best signal approximation based on the correlation coefficient must also be further investigated as the use of a different criterion might provide different results of this parametric estimation. In that case, the signal similarity between original and reconstructed signals might be lower but the different results may provide additional ways to analyse the spectral content of a signal, and more importantly to differentiate the responses of linear and non-linear signals which is the long term objective of developing such a tool. The optimization of the method also involves measurements using real imaging conditions, implementations of reduced computational complexity, and tests with different lengths of transmitted pulses in order to further enhance and expand the signal classification achieved in [18].

IV. CONCLUSION

The Bayesian spectrum analysis was found to be well-suited for the frequency estimation of non-linear ultrasound signals from microbubble (MB) scatterers, providing a reconstructed signal with close resemblance to an original MB signal. The method assumes a signal model and estimates the model parameters (frequencies, amplitudes, phase) by exploiting any prior information that may be available regarding these parameters. The minimum frequency separation was improved by a factor of five using the parametric method compared to Fast Fourier Transform (FFT). As a consequence, the number of identified frequency components was more than double compared to the number of FFT spectrum peaks. The Bayesian spectrum analysis may significantly improve the sensitivity and the specificity of existing diagnostic examinations, and may be particularly relevant in applications that deploy MBs and MB localization, such as in ultrasound super-resolution.

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