Diagnostics of Prostate Cancer based on Ultrasonic Multifeature Tissue Characterization

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Abstract— **Diagnostics of prostate carcinoma using ultrasonic multifeature tissue characterization allows the computerized detection of tumors. Malignant areas within the prostate can be located with a high degree of accuracy while keeping the system independent of the diagnostic skills of the operator. Radio-frequency ultrasonic echo data of the prostate are captured during the examination of the patient with standard ultrasound equipment. Several features describing the histological characteristics of the underlying tissue are estimated after dividing each ultrasound data frame in up to 1000 regions of interest and compensating the echo data for diffraction and system dependent effects. Spectral features, textural features of first and second order, clinical variables and morphological descriptors are applied. In comparison to former work of the same group, additional spectral features that evaluate phase information of the echo signal were calculated using the generalized spectrum (spectral autocorrelation) approach. In addition, spectral features based on autoregressive (AR) models were evaluated for comparative reasons. Two network-based fuzzy inference systems working in parallel classify and separate the regions of interest. Following morphological analysis combines clusters within the malignancy maps, which consist of conventional grey-scaled B-mode images with areas of high cancer probability marked in red color. During a clinical study, radio-frequency ultrasonic echo data of 100 patients have been recorded. Prostate slices with histological diagnosis following radical prostatectomies are used as gold standard. The mean area under the ROC curve is between A_{ROC}=0.84 and A_{ROC}=0.86 for isoechoic tumors and for hypo- and hyperechoic tumors, respectively. Standard deviations are as low as σ_{ROC}=0.02 for isoechoic tumors and σ_{ROC}=0.01 for hyper- and hypoechoic tumors. All three spectral approaches evaluated in this work, conventional Fourier spectrum parameters, generalized spectrum parameters and AR parameters, yield comparable classification rates for the underlying prostate data sets.**

Keywords- tissue characterization; spectrum parameters; autoregression; generalized spectrum; sonohistology; prostate, urology

I. INTRODUCTION

Successful treatment of prostate cancer is only possible if tumors are detected at an early stage. The recurrence rate of prostate cancer treated at later stages is high. The different types of diagnostics that are used today (digital rectal examination, transrectal ultrasound and PSA value analysis) lack reliability, even if used in combination, and are therefore not sufficient. Results of diagnostics using conventional B-mode ultrasound are highly dependent on the physician's skills. Digital rectal examination might easily miss smaller tumors at deeper positions within the prostate. PSA values are dependent on several factors that are hard to comprise into diagnostics. Real-time strain imaging has not found wide acceptance yet and is so far only applied in certain clinics conducting studies.

Diagnosis of the prostate carcinoma using ultrasonic tissue characterization allows the detection of tumors at an early stage. The application of adaptive network-based fuzzy inference systems as nonlinear classifiers can automate the process of finding prostate cancer and can therefore help closing the gap between different results of diagnostics between sophisticated and novice physicians using ultrasound as a diagnostic modality.

II. METHODS

In the underlying system, radio-frequency ultrasonic echo data of the prostate are captured during the usual examination of the patient with standard ultrasound equipment (Kretz Combison 330, 7.5 MHz transrectal transducer). After amplification by a custom made hardware TGC (time gain compensation), data is directly transmitted to a PC by ADC at 33 MHz and subdivided into up to 1000 regions of interest (ROI) per prostate slice to yield spatially distributed classification results. The size of the ROIs used in this approach is 128 sample points at 16 echo lines with 75 % and 50 % overlap, respectively. The data is compensated for TGC amplification and for system induced effects using wire phantom measurements at different depths.

Several parameters describing the histological characteristics of the underlying tissue are calculated for each ROI and fed into two adaptive network-based fuzzy inference systems working in parallel. One system is used to classify hypo- and hyperechoic tumors, the other system is used to find isoechoic tumors inside of normal prostate tissue areas.

The systems are trained by using subtractive clustering as the first step followed by a modified backpropagation algorithm. Following morphological analysis combines clusters to mark areas of similar tissue characteristics.

As the fuzzy inference systems used in this setting were found to underestimate the size of malignant areas, morphological post processing is used to compensate the effects of underestimation. Morphological post processing is performed by two dimensional filtering of the output of the two fuzzy inference systems by previously determined filter kernels and cut off thresholds.

The results of the two fuzzy inference systems are combined to create a malignancy map, which consists of a conventional B-mode ultrasound image in which areas of high cancer probability are marked. The malignancy map can be presented to the physician during the examination on a PC screen. Volume renderings of the prostate can be calculated off-line for further diagnostics, setting up needle biopsies and therapy planning.

A. Fourier Spectrum Parameters

Fourier spectrum parameters are calculated after applying a Hamming window to the TGC-compensated RF data of each ROI, computing the Fourier transform (FT) and converting the resultant power spectrum to dB. Results of spectral estimation of each scan line are averaged to form an estimate of the average power spectrum [1].

The primary set of spectrum parameters consists of four measures of backscatter calculated within the signal bandwidth. The parameters used in this approach are: slope, axis intercept, midband value, and square deviation of the linear regression spectrum fit [2-7].

It has been shown earlier, that the extraction of features based on the backscattered echo signal is a valuable tool for discriminating different tissue types [3-6]. In most cases this feature extraction is based on conventional Fourier transform to convert the underlying echo signals into the frequency domain and to calculate the power spectrum from which the features are extracted.

The measures of backscatter are compensated for attenuation effects using an attenuation model, which is based on the multi narrow band method [8-10].

B. AR-Model Parameters

The goal of ultrasound tissue characterization is finding even small lesions within the prostate. Thus the spatial resolution of the malignancy maps plays an important role. However, there is a discrepancy between the accuracy of the feature estimations and the underlying size of the ROIs. On one side, as much data as possible is needed for an accurate parameter estimation, which requires large-size ROIs, on the other side, the resolution of the malignancy maps is wanted to be as high as possible to achieve highly resolved tumor areas and to keep the detectable lesion size as small as possible.

When using Fourier transform, the underlying time series have to be windowed to cope with spectral leakage, which may occur when a rectangular window is used for sliding window technique. During the windowing process, a certain amount of information is lost, due to the masking effect of the window. Because of this loss of information, it is advantageous to use techniques that bypass the windowing process. The most popular one of these techniques that is used in the field of tissue characterization is the autoregressive (AR) analysis or system identification technique [11, 12].

Next to autoregression parameters the order of the autoregressive process has to be determined. Some methods have been proposed to determine the order minimally needed to model the process sufficiently well. The straightforward method is to calculate the autoregression parameters for several orders and to compare the resultant impulse response with the original time series using an error measure like the mean square error (MSE) and deciding which MSE can be tolerated for the problem. Next to this straightforward approach, other analytical methods like the Akaike information criterion (AIC), the minimum description length (MDL) and the final prediction error (FPE) have been proposed to estimate the optimal order of the autoregressive process. All four methods have been applied on the underlying data in order to estimate the optimal order of the autoregressive process. According to the estimates, a model order of 15 was chosen for the following calculations.

Four autoregressive spectral parameters were calculated from the estimated spectrum and from the linear regression spectrum fit: slope, intercept, mid band value and square deviation of the spectrum fit. Parameters extracted from autoregressive models have been extensively used in the field of arterial plaque characterization by Nair et al. [12].

The tissue characterization system described in this paper is typically running on features extracted by Fourier transform [3-6]. For comparison with the conventional features, additional spectrum parameters were extracted by autoregressive models. Actually, autoregressive parameters are used for window sizes smaller than the 128 samples used in this approach. Nevertheless, the performance of AR parameters in comparison to conventional FT parameters should be examined for lengths of 128 samples.

C. Spectral Autocorrelation Parameters

As has been shown earlier [2-8], the analysis of the power spectral density of ultrasonic echo data can yield parameters that are successfully used in ultrasonic tissue characterization for the classification of prostate tissue. Both feature extraction approaches described above, one based on conventional Fourier transform, the other one based on autoregressive models, have one property in common: Both approaches only incorporate the magnitude of the frequency spectrum. The phase of the underlying echo signal, which might contain additional information about the underlying tissue, is not analyzed in these approaches.

In contrast to conventional spectral parameters, which usually are extracted after calculating the squared magnitude of the tissue response, parameters that are based on the generalized spectrum (GS) take into account the phase of the RF echo signal [13-15]. The generalized spectrum is also referred to as spectral auto correlation function (SACF).

Parameters extracted from the generalized spectrum have been used in the field of breast tissue characterization by Donohue et al. [13] and in the field of liver diagnostics by Vargese and Donohue [15].

For an RF signal segment in time $y(t)$ and its spectral component $Y(j\omega)$ the generalized spectrum at frequencies ω_i and ω_j is defined over the so-called bifrequency plane by:

$$G\left(j\omega_i, j\omega_j\right) = E\left[Y\left(j\omega_i\right)\cdot Y^*\left(j\omega_j\right)\right], \qquad (1)$$

where E is the expected value operator and the superscript * denotes the complex conjugate.

In discrete form, the expected value resolves to the average or first moment over the echo lines and frequencies ω_i and ω_j resolve to frequency positions n and m. The vector multiplication (outer product) results in a matrix with real values (zero phase) along the main diagonal and with complex values in the off diagonal elements. While the main diagonal consists of the magnitude of the Fourier spectrum, the off-diagonal magnitude components of the generalized spectrum depend on the degree of coherence between different frequency components from different regions of the Fourier spectrum and on the original spectrum magnitudes. According to these assumptions, the coherence of the backscattered echo signal, which is said to be an indicator for different tissue types, can be analyzed by the generalized spectrum.

To extract a reduced set of parameters from the generalized spectrum, a collapsed average (CA) is applied over the bifrequency plane [12]. The collapsed average over a discrete generalized spectrum is given by:

$$\hat{C}(h) = \frac{1}{M(h)}\left|\sum_{m-n=h}\hat{G}(n,m)\right|, \qquad (2)$$

where $\hat{G}$ is the discrete generalized spectrum over the ROI to be analyzed, $M(h)$ denotes the number of generalized spectrum off-diagonal elements satisfying m-n=h, and h is an index ranging from 0 to m=n indicating the frequency difference corresponding to each off-diagonal in the bifrequency plane.

As normalization for the system's point spread function is applied in the approach described in this work, magnitude normalization, as suggested in other approaches [13], has not been found useful and thus has not been used here.

Generalized spectrum parameters were directly extracted from the collapsed average. After applying a least squares fit to the collapsed average, the axis intercept, the slope, and the mid band value, which is the same as the integrated area under the collapsed average, are extracted. In addition, the maximum value of the collapsed average is used as a feature.

Regions containing strong isolated scatterers or boundaries with sharp changes in density yield high values for the integrated area under the collapsed average. Specular echoes directly affect the slope and intercept values, too. The slope indicates the rate at which coherence is lost as a function of frequency difference, and the intercept value relates to both, the area under the collapsed average and the slope.

Important features of the collapsed average for detecting and estimating regularly spaced or periodic scatterers are the integrated areas under the collapsed average separated into several sub bands. The collapsed average curve is linearly divided into ten sub bands within the transducer bandwidth, because different sized structures, e.g. spacings, layers, scatterer pairs, correspond to different regions under the curve.

III. Results

During the clinical study, radio-frequency ultrasonic echo data of 100 patients were acquired. Prostate slices with histological diagnosis following radical prostatectomies are used as the reference and gold standard. The ROC curve area is A_{ROC}=0.86 for hypo- and hyperechoic tumors and A_{ROC}=0.84 for isoechoic tumors with standard deviations of σ_{ROC}=0.01 and σ_{ROC}=0.02, respectively, using leave-one-out cross validation over patient datasets.

Next to spectrum parameters, texture parameters of first and second order, clinical variables and morphological features are used in this approach. The complete parameter extraction procedure and the nonlinear classification engine are described in detail in [3-6].

Autoregressive parameters or generalized spectrum parameters were not used in the final calculations as they did not add significantly to the final classification rates. AR and GS parameters are only stated here for reasons of comparison.

TABLE I. Results of Fourier Transform based Parameters

FT-Parameters	hyper- & hypoechoic		isoechoic	
	A_{ROC}	σ_{ROC}	A_{ROC}	σ_{ROC}
Axis intercept	0.590	0.014	0.550	0.014
Slope	0.558	0.007	0.510	0.014
Mid band value	0.622	0.015	0.558	0.032
Square deviation	0.512	0.001	0.500	0.006
Combination	0.658	0.005	0.574	0.027

The results of the FT based parameters are displayed in Table 1. The performance of the AR based parameters is given in Table 2 and the results of the GS based parameters are given in Table 3. For all parameters, the single classification results are given as the mean area under the ROC curve and its standard deviation for five fold cross validation over patients.

Next to single parameter classification results, the classification results of fuzzy inference systems that have been trained on a combination of all parameters of one group are given under 'Combination' within the tables.

TABLE II. Results of Autoregressive Model Parameters

AR-Parameters	hyper- & hypoechoic		isoechoic	
	A_{ROC}	σ_{ROC}	A_{ROC}	σ_{ROC}
Axis intercept	0.583	0.028	0.567	0.034
Slope	0.592	0.046	0.550	0.060
Mid band value	0.626	0.025	0.564	0.035
Square deviation	0.512	0.016	0.527	0.015
Combination	0.642	0.049	0.577	0.020

From the results of the combination experiments shown in tables 1, 2, and 3, it can be seen, that the FT based parameters perform slightly better for hyper- and hypoechoic tumors, when considering the mean value of the five fold cross validation results only. For hyper- and hypoechoic tumors, the standard deviation of the AR based parameters is about ten times larger and the standard deviation of the GS based parameters is about six times larger than the standard deviation of the FT based parameters. Consequently, the use of FT parameters should be preferred. Taking a look at isoechoic tumors, it is apparent, that both the mean classification rate and the standard deviation perform slightly better for the AR and GS based parameters, though the differences are only minimal.

TABLE III. RESULTS OF SPECTRAL AUTOCORRELATIONPARAMETERS

GS-Parameters	hyper- & hypoechoic		isoechoic	
	A_{ROC}	σ_{ROC}	A_{ROC}	σ_{ROC}
Axis intercept	0.620	0.015	0.516	0.012
Slope	0.528	0.013	0.546	0.022
Mid band value	0.628	0.034	0.559	0.028
Maximum	0.628	0.028	0.546	0.030
0.00 - 0.75 MHz	0.622	0.028	0.542	0.026
0.75 - 1.50 MHz	0.623	0.027	0.544	0.029
1.50 - 2.25 MHz	0.625	0.025	0.544	0.031
2.25 - 3.00 MHz	0.629	0.027	0.546	0.030
3.00 - 3.75 MHz	0.633	0.030	0.547	0.026
3.75 - 4.50 MHz	0.630	0.030	0.551	0.023
4.50 - 5.25 MHz	0.626	0.033	0.552	0.021
5.25 - 6.00 MHz	0.615	0.039	0.557	0.024
6.00 - 6.75 MHz	0.590	0.026	0.560	0.022
6.75 - 7.50 MHz	0.581	0.025	0.562	0.022
Combination	0.638	0.030	0.573	0.020

IV. CONCLUSION

Classification results of A_{ROC}=0.86 for hypo- and hyperechoic tumors and A_{ROC}=0.84 for isoechoic tumors with standard deviations of σ_{ROC}=0.01 and σ_{ROC}=0.02, respectively, using leave-one-out cross validation over patient datasets prove the ability of the described system to improve the early detection of prostate cancer. Biopsy and therapy planning can be improved. By using volume reconstructions of malignant regions within the prostate capsule even the staging of the disease might be improved.

It was shown that the use of autoregressive models and generalized spectrum approaches instead of conventional Fourier transform cannot significantly improve the classification rates when classifying the underlying prostate tissue and using time series or window lengths of 128 sample points.

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