ULTRASONIC TISSUE CHARACTERIZATION

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ABSTRACT

A definition of UTC could be: "The assessment by ultrasound of quantitative information about histo-pathological changes of biological tissues". This quantitative information is extracted from the echographic data at two different levels. First, the raw data, i.e. the radiofrequency rf-signals corresponding to single transmit- receive echo lines in an image. Second, the 2-D echographic images, which are constructed by the scanner from the rf-signals (image texture analysis).

INTRODUCTION

The analysis of rf-signals is discussed in the contribution. Prior to image construction, the echo data have been not only demodulated but also, compressed and filtered. A basic problem inherent in both levels of data analysis is the so-called beam diffraction: due to the limited transmit- and receive apertures of the US transducer and additional transmit/receive focussing regimes, the spatial and spectral beam characteristics are depth dependent. This means that even in an isotropic and homogeneous medium the backscattered signals are depth dependent. The position and width of the corresponding amplitude spectrum, but also the "speckle" pattern in images, change from the transducer face to greater depth. Furthermore, amplitude decay due to attenuation in the examined tissues is compensated by time gain compensation (TGC) setting of the receiving amplifier. These problems can be accounted for by adequate calibration measurements when rf-signals are processed [11].
In case of image texture analysis, the derived UTC parameters have to be corrected, or *a posteriori* calibrated [31,32].
The information that can be extracted by analysis of the rf-data concerns primarily the acoustic characteristics of tissues: the attenuation coefficient and backscattering coefficient, both as function of frequency. Because of the relatively limited frequency range comprised by the transmitted US pulse, generally linear with frequency relations are assumed for soft tissues. The speed of sound cannot be estimated from single and coincident transmit/receive scan lines. For this reason, techniques were developed using linear array transducers, where separate transmit and receive angles were employed, directed to the same region-of-interest (ROI) [2]. Alternatively, through-transmission techniques are used for bone characterization, where the travel time between two transducers is measured through the heel bone or a finger phalange and compared to a reference measurement in water. For this clinical application, also the attenuation coefficient is measured by US transmission [16,17].
Analysis of rf-data is also performed in "elastography" [21]. Here the backscattered rf-signals are acquired prior to and after a slight compression of the tissues. The rf-signals are correlated and the

relative compression, i.e. the tissue strain, is estimated vs. depth. This strain is related to the elasticity of the tissue (i.e. Young's modulus), hence the terms elastography, elasticity imaging, or sonoelasticity. The latter technique is using a low frequency vibrator (<1000Hz) and imaging is performed with conventional color Doppler techniques [18].
Finally, it may be remarked that the rf-based techniques are used to estimate the discussed acoustic tissue parameters locally ("sliding window") and to produce so-called parametric images. This might be identified as the ultimate goal of innovation in medical ultrasound!
A second part of UTC is based on the analysis of the texture in 2-D echographic images. It was shown by realistic simulations, that the statistical and speckle characteristics of echographic texture are systematically dependent on the "number density" of the scattering sites within a medium. In other words, the gray level statistics [19,4,26] and the speckle size [19] change continuously when the number of scatterers, on average, within the resolution cell corresponding to the transmitted beam width and pulse length increases from one to approximately ten. In the latter case "fully developed" speckle occurs. This result shows that image analysis could in principle reveal the effective number density of tissues, as well as pathological changes of this parameter. The number density may be considered as a histological characteristic of tissues.
Another method was devised to reveal eventual spatial regularity in the histology, e.g. the lobular structure of the liver parenchyma [35, 20]. Based on second order statistical texture analysis some evidence for its usefulness could be shown.
Further texture analysis methods are not making use of any a priori assumptions about tissue histology but merely use methods developed in other, generally technical, fields of image analysis. Although, success has been claimed in several clinical studies, the patient numbers are generally too low and the calibrations, or corrections of transducer and equipment performance too limited, to be able to generalize and find optimal strategies from existing literature. Adequate preconditioning and calibration should preferably be incorporated within commercial equipment thus enabling exchange of data and of results between institutions.

PHYSICAL BACKGROUNDS.

Acoustic Tissue model

A general model suitable for most parenchymal tissues (i.e., constituting organs like liver, spleen, etc.), is assuming homogeneity and isotropy. Acoustically it is characterized by a fixed speed of sound (on the order of 1540 m/s in soft tissues) and by absorption and scattering. Absorption is due to relaxation phenomena of translational and rotational vibration modes of biological macromolecules. Scattering is considered to obey the Born approximation (i.e., single scattering, undisturbed wave propagation) and is related to small inhomogeneities in acoustic impedance, which are randomly

distributed in 3D space. For instance, the microvasculature (arterioles), and the collagen meshwork of parenchymal tissues are producing relatively strong scattering contributions as
compared to individual cells (e.g., blood cells). The overall attenuation due to absorption and scattering is accessible for estimation from backscattering. In terms of backscattered echo amplitude e(t, z):

$$e(t,z) = e(t,o)\exp\{-m(f)2z\} \qquad (1)$$

where: f= frequency [MHz]
z= depth (i.e., 2z= two-way travel path of scattered wave) [cm]
μ= attenuation coefficient [nepers/cm].
In addition to the random (= diffuse) scattering, in some tissues small range order is present which is related to structural regularity on a millimeter scale, e.g., the triads of Kiernan constituting the portal system of the liver. So, in addition to diffuse scattering, a structural scattering component is present which is revealed in the texture of 2D echographic images [12].

Preprocessing

The characteristics of the ultrasound beam are depth dependent, both in continuous wave- and in pulsed mode. The limited dimensions of the transducer cause this. The resulting intensity distribution is called the "beam diffraction pattern", or "directivity function", which applies both in transmission-

and in reception mode of the transducer (reciprocity principle). Generally, the directivity effects and the additional depth effects of transmit- and receive focusing are summarized in the same term: beam diffraction. Furthermore, it was shown experimentally [28, 3] that the received echographic spectra, calculated from the radiofrequency data, are highly depth dependent and, therefore, influence the estimates of the frequency dependence of the attenuation- and backscattering coefficients[7, 23, 34]. Finally, it was shown by experiments and simulations [19] that also the texture features estimated from echographic images display a significant depth dependence (see also section Processing: Texture analysis).

The tissue attenuation yields both an amplitude decay of the echographic signals, as well as an effective downshift of the spectral information. The latter effect is not shown in echographic images, due to the amplitude demodulation. It is, however, used in acoustospectrographic approaches to estimate the frequency dependence of the attenuation coefficient.

It can be concluded that prior to UTC the signals have to be corrected, in the frequency domain, for the influence of beam diffraction [28, 3, 7, 34, 24, 25, 20, 11] and, in addition, for the time-gain-compensation amplifier (TGC).

Equation (1) is obviously too simple to describe the real world conditions in echography. After transforming Eq (1) to the frequency domain and insertion of transducer performance, the backscattered spectrum E (f, z) becomes:

$$E(f,z) = P^2(f)D^2(f,z)T^2(f,z)S(f) \tag{2}$$

where: P(f) = electro-acoustic transfer function of transducer
D(f,z) = beam diffraction transfer function (spectrogram)
T(f,z)= tissue transfer function (attenuation)
S(f)= backscatter transfer function.

In Eq. (2) it is assumed that the time gain compensation amplification has been corrected for. The diffraction correction consists of the estimation of P(f) from a (perfect) reflector in focus in a medium with known acoustic characteristics and of $D^2(f,z)$ from the average backscatter vs. depth of a medium with known backscatter characteristics [24, 11].

The next step is to analyse the corrected spectra vs. depth:

$$E_c(f,z) = T^2(f,z)S(f) \tag{3}$$

By taking the logarithmic spectra (in dB) and differentiating with respect to depth z:

$$\frac{d}{dz}\{\log_{10}[E_c(f,z)]\} = 2\frac{d}{dz}\{log_{10}[T(f,z)]\} \tag{4}$$

In this way, the tissue transfer function is obtained, which is then used to compensate the spectrogram for the effects of attenuation and resulting is:

$$E_c^*(f,z) = S(f) \tag{5}$$

So, the homogeneous backscattering vs. frequency is obtained over the whole depth range that is being analysed.

Finally, these attenuation-compensated data can be software AM-demodulated and a corrected echographic image can be constructed ready for texture analysis [25, 20].

When radiofrequency signals are not available, a pragmatic approach for pre-processing the video images prior to analysis is the use of a reference measurement on a tissue-mimicking phantom with known acoustic characteristics. This method allows for correction of the diffraction and attenuation effects in the axial direction, i.e. along the scan lines and for the equipment settings of overall gain and TGC [31, 33]. In the past, many authors neglected position dependencies of the areas in the image selected for analyse, or they restricted the analysis to a single Region of Interest (ROI) in the focal transmit zone of the transducer.

ACOUSTIC SPECTROSCOPY.

Acoustic spectroscopy is concerned with the analysis of the frequency dependence of the attenuation- and backscattering coefficient.

Attenuation coefficient

The attenuation as given by Eq. (1) can be written in the frequency domain, while replacing the echo by the tissue transfer function:

$$T(f, z) = \exp\{-2\mu(f)\, z\} \tag{6}$$

Transferring to decibells:

$$20\log_{10}[T(f, z)] = -2\alpha(f)z \tag{7}$$

Where: $\mathbf{I}(f) = [20\log_{10}(e)]\mathbf{T}(f) \quad 8.68\mathbf{T}(f)$.
Insertion of Eq. (7) into Eq. (4) yields the attenuation coefficient from the measured logarithmic echo spectrogram.

It has been shown in many studies that in the low megahertz (1-10MHz) frequency range the attenuation coefficient α (f) is linearly dependent on frequency :

$$\alpha(f) = \alpha_1(f - f_c) + \alpha_0 \tag{8}$$

Where: α_0 = midband value (i.e., at $f=f_c$)
α_1 = slope.
The attenuation coefficient can be estimated in various ways, generally by using a “sliding” window technique. The rf-lines of an echographic image are segmented by suitable window functions (e.g., Hanning windows) of length D samples and which are overlapping each other by 50 percent. The amplitude spectra of the windows are calculated (yielding the Spectrogram) at discrete frequencies f_i. Eq. (7) is calculated at each frequency, yielding a set of values $\alpha(f_i)$ by linear regression analysis. Finally, the linear regression according to Eq. (8) is calculated of α (f_i) vs. f_i yielding α_0 and α_1. This method is called the “multi-narrow band” technique [3]. An alternative method is making use of the property given by Eq. (8) that the higher frequencies of the received spectrum of the echo signals are attenuated more than the low frequencies. This results in an effective “down ward” shift of the spectrum with increasing depth. This so-called “centroid shift” method [13, 6] can applied in case the spectrum corresponding to the transmitted ultrasound pulse is Gaussian shaped and Eq. (8) is taken:

$$\alpha(f) = \alpha_1 f \tag{9}$$

then it can be shown that::

$$\alpha_1 = \frac{f_c' - f_c}{2z\sigma_f^2} \tag{10}$$

where: f_c'= centroid frequency at depth z.
σ_f = “standard deviation” of (Gaussian) spectrum.

Backscatter coefficient

The spectrographic data are corrected for the attenuation, by using the estimated α(f, z) and subsequently averaged over all windows in the ROI, yielding one single backscatter (amplitude-) spectrum: S (f). Again, this can be approximated by a straight line when plotting the log-spectral amplitude vs. frequency:

$$S(f) = b_1(f - f_c) + b_0 \tag{11}$$

The estimated slope of the backscatter coefficient may be used to assess the (effective) size of the scatterers in the tissue. The backsattering coefficient vs. frequency curve changes both in position and shape with the size of the scatterer when calculated for a particular model. The model often used was the spherical scatterer [30, 24].
The slope of the linear approximation decreases in a monotonous fashion when changing the size from 20 to 500 μm. So the slope estimate yields a unique size estimate. This idea was successfully applied in the assessment of an animal model of melanomas [24], in clinical studies of eye tumours [5, 25, 29] and for estimating the size of renal glomeruli [9].

Elastography

Elastography, or Elasticity Imaging is a rather new field of UTC [21, 27, 8]. The basic principle is, that a radiofrequency echogram is acquired two times: once before and once after a small indentation of the tissue by the transducer (e.g., 0.2 mm). By comparing the signals at two depths within the analysis window, the relative change in mutual distance due to the external force yields an estimate of the strain. When denoting the distance prior to force: *l*, and after applying the force: $l - \Delta l$, the strain s is given by:

$$s = \frac{\{l - (l - \Delta l)\}}{l} = \frac{\Delta l}{l} \tag{12}$$

A problem with the use of rf-data for the estimation is the deformation, even within an analysis window, of the signal at larger compressions (>>1%). The correlation algorithm is not finding the correct time shift any more. This so-called signal decorrelation imposes a theoretical limit on the accuracy of strain estimation as well. Recently, Ophir and colleagues investigated two new methods for strain estimation. The use of the signal envelope (i.e., demodulated rf-signals) in the correlation resulted in improved accuracy for larger compressions as compared to rf-based methods, and the reverse for small compressions [33].
The second method employs the power spectrum estimate vs. depth, where it could be shown that the compression results in a small upward shift of the mean frequency (centroid) due to compression. This method is far more robust than time domain correlation methods [14]. The authors anticipate to enhance clinical applicability of elastography by these techniques, such as enabling “free hand” elastography.
The promising aspect of elastography is, that it yields 2D images with relatively large contrasts and high signal-to-noise ratio [1, 33]. Moreover, the range of tissue stiffness’ is relatively large [15]. So, it seems evident that elastography has a potential of becoming a quantitative method of "palpation", where the grey level in the images is indicative of the hardness of a lesion.

A rather innovative technique was introduced recently by Heimdal et al., (1998): strain rate imaging (SRI). Basically, it is derived from a correlation technique of ultrasound velocity estimation, which is called Tissue Doppler Imaging. The low velocity, high amplitude Doppler signals obtained from the heart walls, or from arterial walls, are used to calculate the local velocity gradient along scan lines in 2D velocity images. This local velocity gradient can be rewritten:

$$SRI = \frac{\partial v_{z_i}}{\partial z} = \frac{\partial (\frac{dz}{dt})_{z=z_i}}{\partial z} = \frac{ds_{z_i}}{dt} \tag{13}$$

where: v_{zi} = velocity of (heart wall) movement at depth z
s_{zi}= strain at z_i

The technique is being evaluated for the assessment of regional myocardial disturbances.

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