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● *Original Contribution*

HETEROGENEOUS TISSUE CHARACTERIZATION USING ULTRASOUND: A COMPARISON OF FRACTAL ANALYSIS BACKSCATTER MODELS ON LIVER TUMORS

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Abstract—Assessment of tumor tissue heterogeneity via ultrasound has recently been suggested as a method for predicting early response to treatment. The ultrasound backscattering characteristics can assist in better understanding the tumor texture by highlighting the local concentration and spatial arrangement of tissue scatterers. However, it is challenging to quantify the various tissue heterogeneities ranging from fine to coarse of the echo envelope peaks in tumor texture. Local parametric fractal features extracted via maximum likelihood estimation from five well-known statistical model families are evaluated for the purpose of ultrasound tissue characterization. The fractal dimension (self-similarity measure) was used to characterize the spatial distribution of scatterers, whereas the lacunarity (sparsity measure) was applied to determine scatterer number density. Performance was assessed based on 608 cross-sectional clinical ultrasound radiofrequency images of liver tumors (230 and 378 representing respondent and non-respondent cases, respectively). Cross-validation via leave-one-tumor-out and with different *k*-fold methodologies using a Bayesian classifier was employed for validation. The fractal properties of the backscattered echoes based on the Nakagami model (Nkg) and its extend four-parameter Nakagami-generalized inverse Gaussian (NIG) distribution achieved best results—with nearly similar performance—in characterizing liver tumor tissue. The accuracy, sensitivity and specificity of Nkg/NIG were 85.6%/86.3%, 94.0%/96.0% and 73.0%/71.0%, respectively. Other statistical models, such as the Rician, Rayleigh and *K*-distribution, were found to not be as effective in characterizing subtle changes in tissue texture as an indication of response to treatment. Employing the most relevant and practical statistical model could have potential consequences for the design of an early and effective clinical therapy. (E-mail: omar.al-kadi@eng.ox.ac.uk or o.alkadi@ju.edu.jo) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasound, Tissue characterization, Liver tumor, Radio-frequency envelope, Fractal analysis, Texture analysis.**

INTRODUCTION

Ultrasound tissue characterization can provide useful quantitative assessments for understanding the state of biological disease (Mamou and Oelze 2013). With advancement in medical image analysis, it is becoming a promising non-invasive technique for early detection of tumor response to treatment (Czarnota et al. 2013; Sadeghi-Naini et al. 2013a, 2013b). It has the advantage of deriving parameters that can represent tissue properties in a fast, non-ionizing, easily operated and cost-effective way compared with other conventional follow-up imaging techniques. Soft tissue pathologies in the form of lesions tend to have scattering patterns distinct from those of normal tissue structure, and the associated acoustic properties could characterize the concentration of scatterers and microstructures; which is an indication of different tissue types. Biological tissue ultrasonic modeling followed by echo signal analysis can facilitate heterogeneity examination of tumor texture.

The interaction of an acoustic wave with different tissue regions can be modeled by the backscattered radiofrequency (RF) signal. Tissue properties based on the scatterer number density and spatial distribution can be derived subsequently for analysis. There are several approaches for which useful information can be extracted

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from the RF signal. One approach uses the local power spectral density to estimate the integrated backscatter and attenuation coefficient (Banihashemi et al. 2008; Nam et al. 2011; Rubert and Varghese 2014; Sannachi et al. 2015) or to measure the mean central frequency and scatterer size (Bridal et al. 1997; Lavarello and Oelze 2012; Nordberg and Hall 2015; Saha and Kolios 2011). Textural properties of the tissue spatial arrangement can also be estimated from the envelope-detected RF image (Bouhlel and Sevestre-Ghalila 2009; Klein et al. 2011). As the first-order statistical properties of the backscattered RF signal rely on the number density and spatial distribution of scatterers (Pereyra and Batatia 2012; Wagner et al. 1983), which may be coherent, random or a mixture of both, it would be difficult to account for all scatterer conditions using the former approaches. Therefore, others have investigated the probability density function of the backscattered echoes and proposed to account for the number, size, spacing and regularity of the scatterers in tissue. An overview of the various statistical distributions for modeling the envelope-detected RF signal can be found in Destrempes and Cloutier (2010). For the latter approach, the main objective is to provide a better characterization of the fundamental elements that form the coarse textural patterns, namely, speckles formed from the backscattered echoes. The speckle local arrangement represents the various scatterer concentrations and spatial distributions occurring in tissue, ranging from a fully developed to a partially developed to a coherent speckle pattern. In cases in which there are many randomly located scatterers per resolution cell (*i.e.*, fully developed speckle), the envelope signal statistics would follow a square root of exponential distribution, known as the Rayleigh distribution (Wagner et al. 1983). The model can be further subdivided into pre-Rayleigh, Rayleigh and post-Rayleigh for characterizing heterogeneous, homogeneous and periodic textures, respectively (Cramblitt and Parker 1999; Molthen et al. 1995; Shankar et al. 1996). Non-Rayleigh distributions can be observed when the scatterers become less condensed or have a structure with some regularity. That is, when the number of scatterers in a resolution cell is small (*i.e.*, partially developed speckle), the *K*-distribution was found to be more effective in modeling the pre-Rayleigh statistics of the RF envelope (Shankar et al. 2000). The RF envelope statistics in this case would have a shape resembling a square root of the product of gamma and exponential distributions. Whereas if the scatterers become organized with some periodicity (*i.e.*, coherent speckle), the Rician distribution, which is the generalization of the Rayleigh distribution, is more appropriate for characterizing the underlying regular structures in tissue (Sijbers et al. 1998).

Although the prior models account for specific aspects of scatterer localization, they are not general enough to model the various tissue texture conditions. This is true when a high degree of variability exists in the scattering cross-section associated with a low number of scatterers. In practice, it is very common to encounter non-Rayleigh conditions of ultrasound backscatter, such as mixtures of diffuse and coherent or periodically aligned scatterers in tissue microstructure. Therefore, a comprehensive approach is sought as in the generalized *K*-distribution (Jakeman and Tough 1987) and homodyne *K*-distribution (Dutt and Greenleaf 1994; Mamou et al. 2011). A third parameter, which represents the envelope of the coherent signal, was added to the effective number of scatterers and energy of the random scatterers to account for post-Rayleigh conditions. However, a drawback lies in the analytical complexity of these model generalizations, rendering the process of parameter estimation computationally expensive. Other models that apply a generalization approach to the Rayleigh and Rice distributions to better fit the backscattered echo include the Weibull (Raju and Srinivasan 2002), Rician inverse Gaussian (Eltoft 2005) and generalized gamma (Tunis et al. 2005) models. On the other hand, the Nakagami distribution family can provide a simpler and general model for ultrasonic tissue characterization (Shankar 2000). In addition to the scatterer density and amplitude, the regularity of the scatterer spacing is taken into consideration, making it possible to account for hypo-echoic and hyper-echoic structures (Tsui et al. 2010). The model shape equivalent to a scaled square root of a gamma distribution can better represent the backscattered RF signal envelope and can be easily fine-tuned via the shape Nakagami parameter to represent low and high number of scatterer densities with minimal error (Tsui et al. 2014). The model was further generalized as a Nakagami-generalized inverse Gaussian distribution in Karmeshu and Agrawal (2006) by including an additional shape adjustment parameter to account for the tails of the density function. However, this generalization was not investigated with real tissue, where scatterers tend to have a high degree of variability in scattering cross sections.

All aforementioned statistical models of the backscattered echo envelope in the literature claim a better characterization of texture anisotropic properties. A large number of articles address the problem of soft tissue characterization and diagnosis from ultrasound images of various internal organs, such as in kidneys (Wu et al. 2013), liver (Ghoshal et al. 2012), breast (Tadayyon et al. 2014), gallbladder (Kumon et al. 2010), pancreas (Atiee et al. 2014), spleen (Roosens et al. 2013) and abdominal aorta (Tsui et al. 2008), all of which present practical examples of, but are not limited to, recent clinical work. However, to the best of our knowledge, the