Can We Use Ultrasound to Monitor and Diagnose Lung Diseases?[1]

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Challenges of Lung Ultrasound

Ultrasound imaging is highly effective in the medical investigation of most human organs, and, naturally, doctors and scientists have attempted to apply it to lung assessment. The first studies on lung ultrasound date back to the 1960s with work by Floyd Dunn (O'Brien, 2018). In this earlier work, researchers tried to characterize lung tissue by means of standard acoustic properties such as the speed of sound and attenuation. However, these approaches showed a large variability in the reported values (Dunn and Fry, 1961; Dunn, 1998), severely affecting the clinical applicability of this type of characterization.

The reason behind this variability has to do with the most important difference between the lungs and soft tissues: the presence of air. Although all soft tissues share very similar acoustic properties, air stands out significantly. And the lung is filled with it. As an example, speed of sound values in soft tissues are in the 1,500 m/s range, whereas air shows speed of sound values in the 300 m/s range (Wong, 1986).

The Lung

The lungs are formed by a distribution of many tiny air sacs, the alveoli, embedded in soft tissue. To picture the structure of the lung, one could use the analogy of a bunch of grapes immersed in water where the grapes would be filled with air and the surrounding water would be soft tissue. In this analogy, the grapes represent the 600 million lung alveoli, which have a diameter on the order of 280 μm.

It is easy to understand how big of an approximation it would be to attribute macroscopic acoustic properties to such a complex, heterogeneous medium. Moreover, the ratio of lung volume occupied by soft tissue to that occupied by air is not the only parameter that matters in lung ultrasound propagation. The shape, dimension, and spatial distribution of the air spaces will also strongly influence ultrasound propagation (Soldati et al., 2016). Moreover, all of these parameters change during breathing as the air spaces expand and contract with inspiration and expiration, thereby adding extra issues when considering imaging the lung with ultrasound. To make things even more challenging, such a large difference in acoustic properties between air and soft tissues implies that ultrasound waves are essentially fully reflected by the alveoli because the transmission coefficient is approximately zero (Szabo, 2004).

The first important lesson to learn is that the lungs cannot be modeled as soft tissue.

Conventional Ultrasound Imaging

Let us first review the basics of ultrasound imaging. To reconstruct an ultrasound image, acoustic waves in the megahertz range are transmitted into the body by an ultrasound probe. These waves are partly reflected back to the probe by acoustic interfaces within the tissue (discontinuities in acoustic properties). If the speed of sound was constant and known, as it is in most soft tissues, it would be possible to convert the time traveled by the wave to a specific depth to reconstruct an image representing the volume of interest (Szabo, 2004).

Conventional ultrasound imaging therefore relies on two main hypotheses. First, an effective speed of sound in the imaging volume must be assumed and known. Second, one must assume that higher order scattering can be neglected. This means that significant echoes are generated only from the interaction between the incident field (transmitted by

1 For additional information on lung ultrasound, see the special issue of The Journal of the Acoustical Society of America *at* acousticstoday.org/jasa-lung-ultrasound.

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the probe) and one acoustic interface and not by the interaction between "echoes" and an acoustic interface.

These two hypotheses are valid for most biological tissues. As an example, in tissues such as blood, brain, muscle, fat, breast, heart, kidney, liver, and spleen, errors smaller than ±7.5% would be made assuming a homogeneous speed of 1,546 m/s (Szabo, 2004). This also implies that echo intensities are generally small, given that the reflection coefficients at these interfaces are small (Szabo, 2004). In those tissues, higher order scattering can be ignored.

With higher order scattering, the linear relationship between time of flight (i.e., the interval between the transmission of the ultrasound pulse and the reception of its echo) and the actual distance of the interface responsible for that echo is lost. In other words, strong higher order scattering means that the echolocation principle is fundamentally inapplicable. This is precisely what happens in the lungs.

Clinical Lung Ultrasound

The fact that echolocation cannot be used in lungs is presumably the reason why the interest from the scientific community in lung ultrasound has faded until new developments from the clinical world came in the late 1990s (Lichtenstein et al., 1997). Fortunately, blind to the fact that the basic assumptions behind standard ultrasound imaging did not apply to lung tissue, clinicians began imaging lungs with ultrasound clinical scanners and started to report and describe the presence of "signs" that appeared on their screens with a wide variety of lung diseases.

All lung images exhibited *imaging artifacts*, but striking differences were observed between ultrasound images in healthy aerated lungs and in diseased lungs (Soldati et al., 2016). An imaging artifact is a feature that appears in an image (intended as an anatomical representation of internal body parts) but that is not actually present in the imaged volume. It is, in fact, the imaging system that generates these artifacts because it applies predefined processing operations to signals that do not verify the assumptions made by the system.

Although conventional ultrasound images fail to provide an anatomical description of the lungs, artifacts still convey information in the sense that they signal that something particular is happening. The question is, what use can be made of these artifacts?

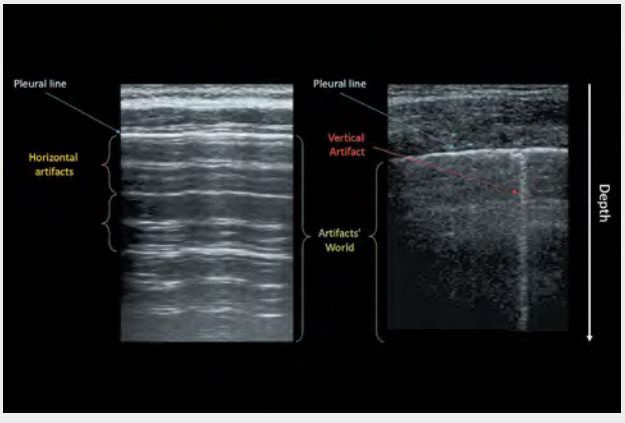
Artifacts Provide Relevant Information

To introduce a practical example, **Figure 1** shows lung ultrasound images exhibiting horizontal (called A-lines) and vertical (called B-lines) artifacts. In both images, it is possible to clearly distinguish the intercostal tissue layers (between the probe and the lung surface) and a first horizontal structure, known as the pleural line, which is the anatomical representation of the lung surface and which separates the image into two parts. Up to the pleural line, the two fundamental assumptions necessary to ultrasound imaging still hold. Below the pleural line is a world of artifacts because the wave is encountering lung tissue and the imaging volume is filled with air. These images can be distinguished by the differences in their artifactual patterns.

Horizontal artifacts (**Figure 1**, *left*) are reverberation artifacts resulting from the high reflectivity of the surface of the normally aerated lung. This series of horizontal lines is the visual representation of the multiple reflections occurring between the ultrasound probe and the lung surface. A sort of pinball effect between the probe and the lung surface that, if the lung is fully aerated, acts as an impenetrable wall to ultrasound waves.

In contrast, vertical artifacts (**Figure 1**, *right*) are attributed to local alterations in the acoustical properties of the lung surface, such as the replacement of volumes normally occupied by air in favor of media that are acoustically more similar to the intercostal tissue (water, blood, and tissue), resulting in an increased transmission coefficient. These alterations are typical of a wide range of pathological conditions that opens channels through

Figure 1. *Lung ultrasound images displaying horizontal (**left**) and vertical (**right**) artifacts. See text for detailed explanations.*



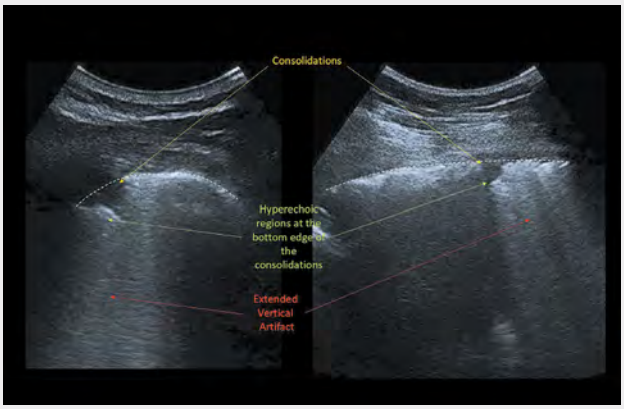


Figure 2. *Lung ultrasound images from two different Covid-19 patients displaying consolidations and extended vertical artifacts. The* ***white dashed lines*** *overlaid on each image are indicative of the original location of the pleural line.*

which ultrasound waves can penetrate and in which they are trapped. The pinball effect in that case occurs inside these structures because the ultrasound wave finds itself surrounded by "air walls." Given the size of these structures, which can be close to the wavelength at the imaging frequency, resonance rather than reverberation phenomena can occur. This currently represents the main hypothesis behind the visualization of vertical artifacts (Demi et al., 2020; Mento et al., 2020).

It is clinically relevant that although horizontal artifacts are generally associated with a healthy lung, a correlation exists between vertical artifacts and many lung conditions, including Covid-19 (**Figure 2**) (Soldati et al., 2020). It should also be noted that lung ultrasound imaging can only detect alterations that occur close the lung surface. That is the only part of the lung that can be explored because the presence of air significantly hinders ultrasound propagation. In the case of a more critical lack of aeration, such as with lung consolidation, ultrasound waves can penetrate deeper into the lung and the surface of discontinuity between dense nonaerated areas and aerated areas moves deeper with respect to the original location of the pleural line.

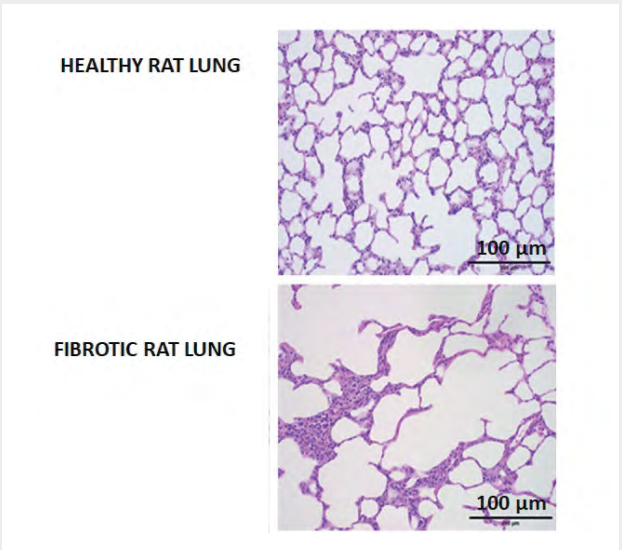
Figure 2 shows examples of lung ultrasound images displaying consolidations in a Covid-19 patient. Consolidations can be defined as large areas (at least one order of magnitude larger than the wavelength at the imaging frequency) of the lung, originally occupied by air, that become filled with denser media such as blood and inflammatory liquids. These images show that beyond consolidations, vertical artifacts extend from the bottom edge of the hypoechoic areas (displaying low intensities). These are signs of partial, although pathological, aeration levels. Consolidations are typical in Covid-19 patients but do not represent a specific sign (Soldati et al., 2020) because they can be observed with many other lung conditions.

Chronic Lung Diseases: The Example of Pulmonary Fibrosis and Pulmonary Edema

Idiopathic pulmonary fibrosis (IPF) is a chronic condition that affects 200,000 Americans (Raghu et al., 2018). With IPF, scarring in lung tissue occurs progressively (**Figure 3**), leading to serious breathing difficulties. IPF is lethal but can be mitigated with new drugs. Pulmonary fibrosis can be monitored by periodic high-resolution computed tomography (HRCT) scanning and pulmonary function tests. HRCT is costly and ionizing and pulmonary function tests need to be performed in a hospital for accuracy.

Developing quantitative ultrasound methods for the quantification of pulmonary fibrosis would enable an inexpensive point-of-care monitoring of the disease progression and response to treatment. Pulmonary edema is another interstitial lung disease. It is related to heart

Figure 3. ***Top:*** *histology of a healthy rat lung. The alveolar density is high.* ***Bottom:*** *histology of a fibrotic rat lung. The alveolar density is significantly lower.*



failure and affects 6.2 million Americans (Benjamin et al., 2019). Pulmonary edema leads to the accumulation of lung fluid, making breathing difficult. The methods currently available to monitor pulmonary edema are invasive, such as intracardiac devices that monitor pulmonary artery pressure (Abraham et al., 2011) or inaccurate and ionizing (chest X-ray).

Both pulmonary edema and pulmonary fibrosis need to be monitored closely. Both affect the lung microstructure. In pulmonary fibrosis, progressive thickening of the alveolar walls will increase the mean distance between the alveoli (Crouch, 1990). In pulmonary edema, an increase in interstitial fluid and in the size of the interstitial space will also affect alveolar density (Gehlbach and Geppert, 2004). Those changes in microstructure are bound to affect ultrasound propagation and scattering. This should be explored using ultrasound to quantify those changes.

Using Artifacts to Develop Semiquantitative Parameters

In medicine, ultrasound is mainly used for imaging. There are two main reasons why, in addition to imaging, extracting quantitative ultrasound parameters from reflected ultrasound signals is highly advantageous. First, in the context of monitoring chronic diseases, it is necessary to be able to compare quantitative markers of the disease from one week to the next or from one month to the next. Second, because comparing numbers is more robust than comparing images, assessing lung tissue with quantitative ultrasound markers is highly relevant for monitoring chronic lung conditions. With quantitative biomarkers, it will become possible to follow the severity of a condition or the quality of the response to treatment in a more objective and reproducible manner.

We now understand that standard ultrasound imaging of the lungs can demonstrate the loss of aeration if the loss of aeration reaches the surface of the lung. It can localize less aerated regions as well as inform on their extent. For example, consolidations indicate a more severe loss of aeration compared with small and isolated vertical artifacts. One approach is to use the imaging patterns (e.g., horizontal and vertical artifacts in **Figure 1**) to grade the state of the lung in a semiquantitative manner.

As an example of a clinical application, a lung ultrasound imaging protocol and a scoring system have been developed for Covid-19 evaluation (Soldati et al., 2020). Following these semiquantitative approaches, clinicians can assess the probability of worsening of the condition of a patient (Perrone et al., 2020) and thus act accordingly. This type of information has been a great help in handling large patients' influx during the pandemic. Thus, with these semiquantitative methods, visual interpretation of imaging findings are associated with a score. Surely, computer-aided methods can help interpreting the data, providing a fast and more reproducible analysis and supporting the reduction in the subjectivity intrinsic to this type of evaluation (Mento et al., 2021). But these are not fully quantitative methods. And that is a challenge.

The Path to Quantitative Lung Ultrasound

To transform lung ultrasound into a quantitative technique, it is necessary to identify measurable physical quantities that reflect the alterations in lung tissue. Two families of parameters have been explored by recent research: parameters related to the frequency content of vertical artifacts and parameters leveraging scattering by the alveoli.

Parameters Related to Vertical Artifacts

Recent research efforts are emerging in this direction. As an example, if it is true that vertical artifacts are generated by resonance phenomena, characterizing them based on their frequency content would allow us to indirectly characterize the "acoustic traps" responsible for their generation. In fact, it is the dimension, shape, and content of these traps that would define its resonance frequency (Demi et al., 2020; Mento et al., 2020).

Figure 4 shows lung ultrasound images obtained from a recent clinical study (Demi et al., 2020) in which a dedicated lung ultrasound imaging approach based on these concepts was developed and tested. Each row shows images generated at different imaging frequencies but obtained at the same time and from the very same point on the chest of a patient. It is visible that vertical artifacts strongly depend on the imaging frequency because Patient 1 shows vertical artifacts only at 3 MHz, Patient 2 at 4 and 5 MHz, and Patient 3 at 3, 4, and 5 MHz. This result is consistent with the hypothesis that these artifacts are generated by resonance phenomena. Moreover, this result tells us that simply counting these artifacts when imaging with a clinical scanner can be misleading. For example, if Patient 1 had been imaged only at 4 MHz, the artifact would have been missed altogether.

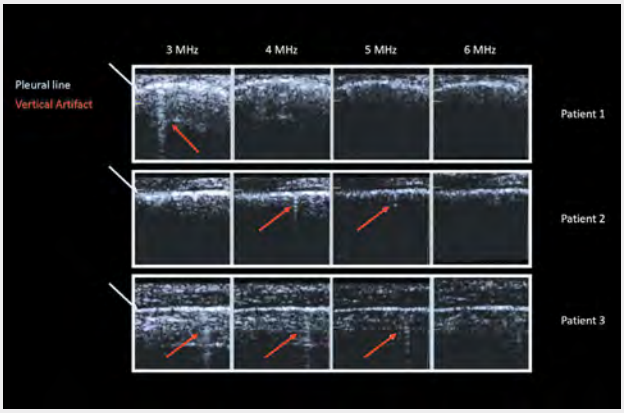


Figure 4. *Examples of lung ultrasound images obtained with a multifrequency imaging approach in three different patients. From* ***left to right****, images formed with ultrasound pulses at a different center frequency (i.e., 3, 4, 5, and 6 MHz).* ***Light blue arrows****, pleural line;* ***red arrows****, vertical artifacts.*

Scattering and Diffusion by the Alveoli

In the lungs, alveoli scatter ultrasound waves due to their shape, size, and the strong acoustic impedance difference between air and tissue. The portion of the wave that is able to penetrate the lungs is scattered back in the form of a highly complex signal. This is a significant challenge because it prevents ultrasound imaging. However, each scattering event is, in fact, an opportunity, leaving the signature of the microstructure within the ultrasound signals. One way to leverage this information is to use a mathematical analysis to extract information from raw ultrasound data as opposed to interpreting features from ultrasound images in which the ultrasound data have already been processed.

Because of the large numbers of scattering events by the millions of air-filled alveoli, ultrasound waves do not propagate straight at a constant speed. Instead, they are subjected to diffusion. One can exploit the physics of diffusion and scattering to extract new parameters that could be used as quantitative biomarkers for lung diseases such as fibrosis or edema.

In a process dominated by multiple scattering and diffusion, the incoherent contribution of the ultrasound signals is stronger. To describe the principle of how this could be leveraged, one can use an analogy with a group a people walking in a forest. The walkers walk straight from tree to tree but randomly change direction at each tree encounter. In a very dense forest (e.g., healthy lung), the walkers would quickly forget where they came from after a few tree encounters. As a group, they would make slow progress in the forest. In contrast, in a sparse forest (diseased lung), they would make quicker progress and the group would quickly spread apart.

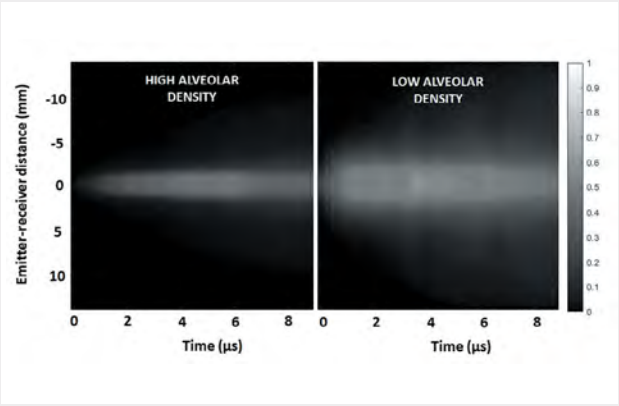
Parameters Related to Scattering and Diffusion

In the lungs, the air-filled alveoli play the role of the aforementioned trees. Measuring the rate of spread of the diffusive halo (**Figure 5**) provides an indirect measurement of the density of alveoli, which is affected by interstitial lung diseases such as pulmonary fibrosis and pulmonary edema. The rate of growth of the diffusive halo is the diffusion constant.

For spherical air-filled scatterers, the diffusion constant is proportional to the scattering mean free path (SMFP), which represents the mean distance between scattering events and is a measure of the mean distance between healthy alveoli (Mohanty et al., 2017). In a rodent study on rats with pulmonary fibrosis, rats with pulmonary edema, and healthy rats, it was demonstrated that the SMFP was significantly lower in healthy animals than in animals with fibrosis or edema (**Figure 6**) (Mohanty et al., 2020). It has also been showed that the SMFP was significantly correlated to the severity of fibrosis as measured by histology, the gold standard for pulmonary fibrosis.

In addition to the diffusion constant and SMFP, the ultrasound backscatter coefficient (BSC) and ultrasound signal

Figure 5. *Growth of the diffusive halo over time in a healthy lung (****left****) and in a lung with edema (****right****). Because the density of air-filled alveoli is lower in edematous lungs, the diffusive halo grows faster.* ***Color scale,*** *normalized incoherent intensity.*



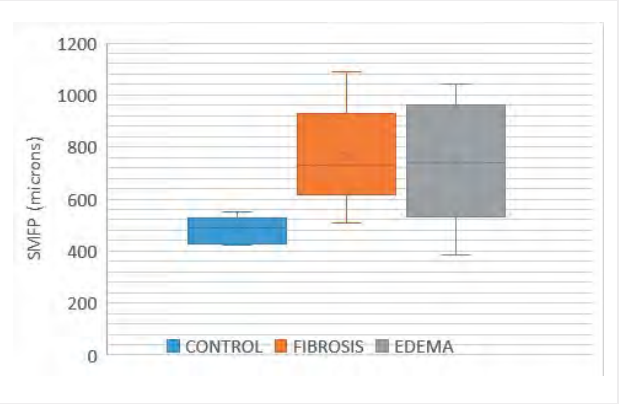


Figure 6. *The scattering mean free path (SMFP) is significantly lower in healthy rat lungs than in edematous and fibrotic rat lungs.* ***Horizontal bar*** *and* ***X in the center****, the median.* ***Vertical lines*** *(****bottom*** *to* ***top****): minimum, first quartile, third quartile, and maximum.*

envelope statistics are also highly relevant for assessing and monitoring changes in lung structure because they are bound to be influenced by the distribution and size of the alveoli. The BSC is used to extract parameters of tissue microstructure by analyzing the power spectra of raw ultrasound data. Theoretical models of BSC accounting for scatterer properties, such as scatterer diameter and scatterer concentration, are fitted to real ultrasound data, which allows one to estimate the parameters of the microstructure such as the size and density of the alveoli (Oelze and Mamou, 2016).

In a study on a rodent model of pulmonary fibrosis, it was demonstrated that ultrasound parameters related to the BSC and envelope statistics all showed significant differences between control lungs and edematous lungs and between control lungs and fibrotic lungs. These parameters also correlated to the severity of pulmonary fibrosis as determined by histology (Lye et al., 2021).

Finally, ultrasound attenuation also reflects scattering and absorption and can therefore be used to interrogate lung tissue. Lungs exhibiting edema are less attenuating than fibrotic lungs due to the presence of fluid buildup. Higher frequencies are attenuated faster than lower frequencies. It is therefore possible to measure the downward shift in frequency content in backscattered ultrasound signals in the form of a parameter called the backscatter frequency shift (BFS) to quantify ultrasound attenuation in the lungs (Zenteno et al., 2016). In a study on rats with edematous or fibrotic lungs, the BFS proved able to discriminate between fibrosis and edematous lungs, suggesting that it could be used to increase the specificity of diagnosis (Mohanty et al., 2020).

Can Specificity Be Achieved?

The question of diagnosis specificity is critical in lung ultrasound. Not only it is important to differentiate a healthy lung from a diseased lung, but it is also crucial to develop parameters that would be different for different interstitial diseases such as fibrosis and edema. This should be the pathway to true lung ultrasound diagnosis. Currently, in conventional ultrasound imaging of the lung, many interstitial diseases lead to the presence of B-lines, vertical artifacts that arise in a nonfully aerated lung.

However, by analyzing the raw ultrasound data, it becomes possible to characterize these artifacts based on their intensity, bandwidth, and native frequency (Demi et al., 2020; Mento et al., 2020). And what has emerged is that this kind of characterization has an impact in the discrimination of patients affected by fibrosis from patients affected by other lung pathologies. In other words, this type of approach adds specificity.

Figure 7, *top left*, shows Gaussian distributions for native frequency and bandwidth representing 13 fibrotic patients. Results from 26 patients are then jointly depicted in the two-dimensional (2-D) plot (**Figure 7**, *top right*), where the *x*-axis and the *y*-axis represent the mean native frequency and the mean bandwidth, respectively, of the B-lines observed in each patient. The patient IDs are written near the corresponding marker. In **Figure 7**, *bottom left*, histograms of the vertical artifacts total intensity for fibrotic and nonfibrotic patients are shown. The total intensity (I_{tot}) is a recently introduced metric designed to study the vertical artifact dependency on several imaging parameters (Demi et al., 2020; Mento et al., 2020). **Figure 7**, *bottom right*, shows the 2-D plot of the patients' distribution as a function of the mean native frequency and mean bandwidth of the vertical artifacts observed in each patient after the application of a 1.6 dB threshold to the mean total intensity. As seen, accounting for the total intensity has the effect of further improving the method's specificity (Mento et al., 2020). Indeed, because of increasing absorption with fibrotic tissue, it is expected that a reduction in artifact intensity would be displayed in fibrotic patients.

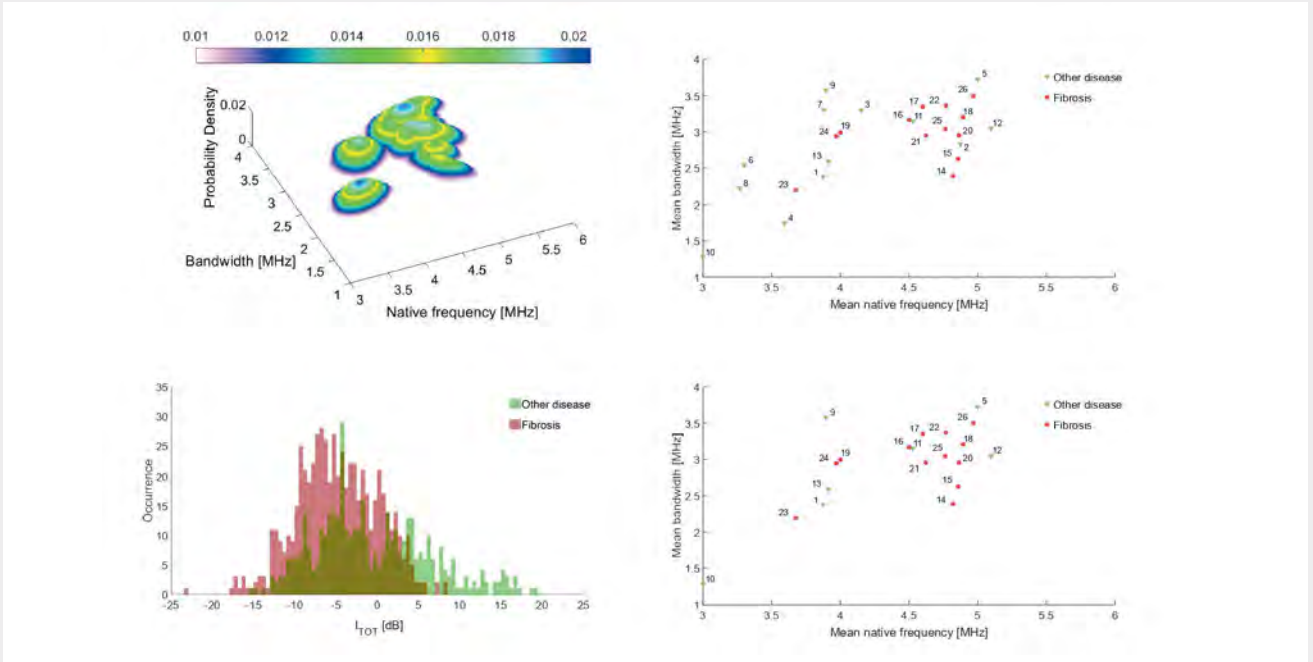


Figure 7. ***Top left:*** *Gaussian distributions of native frequency and bandwidth representing 13 fibrotic patients.* ***Color scale****, probability density (unitless),* ***Top right:*** *two-dimensional (2-D) plot representing 26 patients with respect to the mean bandwidth and native frequency of their vertical artifacts,* ***Bottom left:*** *histograms of the vertical artifact total intensity as obtained from fibrotic (**red**) and nonfibrotic (**light green**) patients.* I_{tot}*, total intensity* ***Bottom right:*** *2-D plot representing 26 patients with respect to the mean bandwidth and native frequency of their vertical artifacts after a threshold of vertical artifact intensity was applied.*

Multiple Ultrasound-Based Parameters to Increase Specificity

Another highly relevant way to achieve specificity is to combine multiple parameters. In that sense, the physics-based ultrasound parameters described in ***Parameters Related to Scattering and Diffusion***, which are related to diffusion, scattering models, and attenuation, respectively, are not redundant and will reflect different and independent properties of the lung structure. Using them in combination is a path that should be considered to increase the specificity of diagnosis.

For example, pulmonary fibrosis and pulmonary edema both increase the diffusion constant because they both lower the alveolar density. As a result, the measurement of the SMFP is not sufficient to discriminate between them (**Figure 6**). The BFS, on the other hand, is lower in edematous lungs (low attenuation) than in fibrotic lungs (high attenuation). Moreover, vertical artifact native frequency and bandwidth provide an indirect estimation of the acoustic channel size and geometries, whereas the total intensity helps in discriminating the channel content (**Figure 7**). As a consequence of these differences in approaches, it is possible to envision a multiparameter space that would allow simultaneous quantifying of alveolar density, mean alveolar size, and tissue characteristics (interstitial fluid, fibrotic tissue, or air).

This new research suggests that ultrasound can be utilized to monitor and diagnose lung diseases. Clinical applications are currently limited to semiquantitative methods that can, however, provide important information on the level of aeration of the superficial lung. But promising developments (Demi, 2020; Mento et al., 2020; Mohanty et al., 2020; Lye et al., 2021) suggest that quantitative and specific ultrasound characterization of lung tissue is within reach.

The Potential of Portability: What Could It Look Like?

Compared with other diagnostic modalities, ultrasound has the significant advantage of allowing relatively inexpensive and portable care (Everbach, 2006; Ketterling and Silverman, 2017; Simon et al., 2017; Smallwood and Dachsel,

2018). This has become even truer with the recent development of miniaturized ultrasound scanners and ultraportable ultrasound probes that can be connected to a tablet or a phone. All physical parameters developed so far, and the ones that will be developed in the future, can be obtained using a conventional ultrasound probe to acquire the raw data that would be processed by dedicated software. The quantitative characteristics of these parameters ensure that a highly skilled, highly trained technician is not needed to interpret the images. In this context, developing quantitative biomarkers of lung diseases that could be monitored at home, as frequently as needed, has become even more significant.

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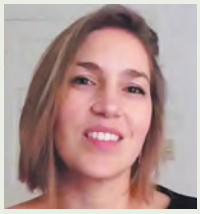

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