TECHNOLOGY INNOVATIONS

ULTRASOUND IMAGING GOES ULTRAFAST A CHANGE IN PARADIGM IN MEDICAL ULTRASOUND

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Abstract— **As ultrasonic waves penetrate deep into tissues ultrasound imaging is able to image invisible things by "seeing through tissues" in real time. With the advent of ultrafast ultrasound imaging, the modality can reach thousands of frames per second, much faster than what the human eye can see. A completely new world is revealed as most important physiological processes in the human body occur in this temporal range. This article shows how ultrafast can bring clinical value and change the paradigm in medical ultrasound. From virtual and quantitative palpation to assess tissue stiffness to micro-vascularization imaging, cardiovascular risk assessment and brain functional investigation, ultrafast imaging breaks the traditional barriers of the ultrasound field.**

Keywords— **Ultrasound, Ultrafast Imaging, Shear wave Elastography, Vascularization, Functional Ultrasound.**

I. INTRODUCTION

By filming inside the human body, ultrasound imaging has deeply changed our fundamental understanding and clinical management of pathologies, acting as a virtual human eye that looks at tissue and flow dynamics in real time.

The concept of an ultrasound system is to transform non-audible sound (ultrasound waves) into clinically relevant images of the body. Despite the physics behind it is very well known, ultrasound imaging has been constantly progressing in quality and clinical relevance through technology enablers from other industries. Very schematically, the ultrasound industry has passed through three technological eras [1, 2]:

- *The analogical era (70's and 80's): building the foundations of ultrasound imaging.*

Technically, real time ultrasound imaging has been possible thanks to the manufacturing of efficient piezoelectric materials capable of transforming electrical signal into acoustic waves (and vice versa) and the development of electronic components that are fast enough to process signals in a few microseconds and small enough to fit into transportable volumes;

In the first generation of ultrasound systems, most of the processing, and more particularly the heart of the ultrasound system – the beamforming (or image formation), was performed on analog hardware boards. Despite limited versatility and quality, ultrasound imaging was made possible at an affordable price. Real time analysis of tissue morphology and blood flow revolutionized the medical field such as cardiology or obstetrics;

- *The digital era (90's and 00's): The quintessence of real time imaging*

The move to digital processing started in the late 80s with high quality digital signal processing chips (DSP's) and the significant price reduction of Analog to Digital converters (ADCs) thanks to its democratization in the consumer electronic industry. Ultrasound signals were early digitized and processed numerically to output the final image, enabling new processing techniques that drastically increased the image quality and performances of systems: dynamic beamforming (each pixel data is perfectly realigned and processed), spatial and frequency compounding, second harmonic imaging...

- *The software era (from 10's): from real time to ultrafast imaging.*

In the last decade, the increase in processing power of computer processors and the advent of graphic boards dedicated to massive parallel computing allowed the design of a full software based ultrasound system. The processing – including the beamforming- is now done on a computer reducing the electronic boards to acquisition, digitization and data routing functions.

Coupled with smart techniques to send ultrasound waves in the medium, this architecture pushed the barriers of ultrasound machines, and enabled ultrafast ultrasound

imaging. The body can now be imaged at frame rates 1000 times faster than what the human eye can catch.

Whereas all imaging modalities strongly benefited from the Moore's law [1], the impact of multicore CPU and GPU boards on ultrasound imaging is the most effective. The move from hardware to software beamforming enabled researchers to dramatically change the way ultrasonic waves are transmitted in the human body. Such re-foundation of ultrasound basics paves the way to completely new clinical imaging modes and provides new information and biomarkers for diagnosis.

This article shows how ultrafast imaging is changing the way ultrasound is used, by looking at new phenomena, by displaying new clinically relevant information, by significantly enhancing its performance and clinical impact, by opening new clinical fields to ultrasound and by making the modality safer and easier to use.

The first section explains how ultrafast imaging works. The second section shows how ultrafast ultrasound can be used to discover new properties of the human body. The third section will discuss concrete and potential clinical benefits of these discoveries. The fourth section will present ultrafast perspectives for the next years.

II. IMAGING THE BODY AT ULTRA-HIGH SPEED

To build an ultrafast ultrasound camera, the way ultrasound waves are sent into the body must be rethought. Ultrasound machines are today designed in what is called a serial architecture. The image area is sliced into small vertical bands and the machine successively interrogates those bands by sending focused ultrasound beams.
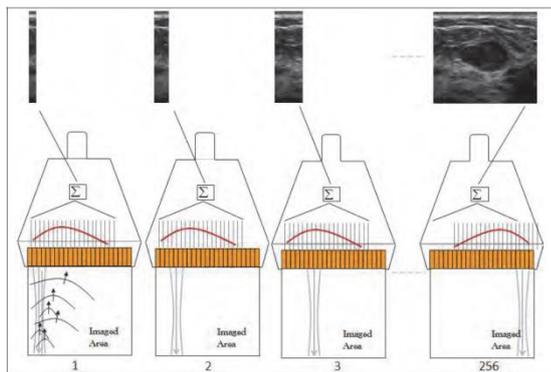
Fig. 1 Conventional ultrasound imaging (from ref [2])

The image is then reconstructed by band, each ultrasound wave getting information from the specific band being insonified. A 2D image is usually reconstructed using a few hundreds of firing beams. The time needed to reconstruct a full image (or volume) is around a few tens of milliseconds, leading to imaging frame rates of a few tens of Hz – perfectly fitting the human eye ability.

This serial design makes perfect sense for ultrasound machines derived from the hardware eras (analogic or digital). The hardware boards were built to compute an image band and this processing was iteratively used for all image bands. Moving to parallel processing of all image lines would require to duplicate the hardware hundreds of time and significantly increase the cost of the system. Despite interesting perspectives shown by academia [3], this move did not make sense from a clinical product standpoint.

The equation is completely different now that software ultrasound machines are technically possible. Parallelization in software is almost for free and a full image or volume could be reconstructed in one shot.

To achieve that, the body should not be insonified anymore by lines but by waves able to cover the whole imaged area. Such waves are either plane waves or divergent waves, propagating over the entire targeted area.
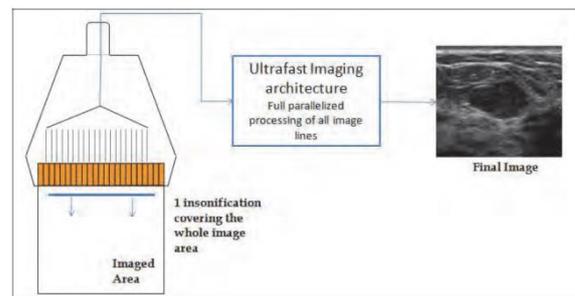
Fig. 2 Basic Principle of Ultrafast Imaging scanners (from ref [2])

On ultrafast machines, each ultrasound wave sent into the body leads to fully reconstructed image of the area of interest. As the wave propagation happens is a few tens of microseconds, frame rates of several thousands of Hz can be reached, way above human eye perception.

This is in perfect analogy with what is done in optics. Conventional cameras reconstruct images line by line, while ultrafast – or high speed – cameras are able to build images in a fully parallelized manner. Today ultrafast cameras can reach billions of images per second, thanks to the much higher speed of propagation of light.

Many concrete applications of such devices exist today such as the monitoring of car crashes to improve car safety, or the recording of object weak movements to better understand their properties or their environment [4].

Similarly we will see that ultrafast ultrasound cameras allow very fine analysis of body's motion leading to clinical breakthroughs in safety and effectiveness.

One of the drawbacks of high-speed cameras is the low image quality, due to weak exposure time. An equivalent problem is faced in ultrasound. Images recovered from flat waves are lower in signal to noise ratio, contrast and resolution compared to classical focused images.

However in the ultrasound world, and contrary to optics, signals are perfectly digitized in time leading to new possibilities to improve ultrafast image quality. The concept

of coherent plane wave compound has been introduced in order to solve this drawback [5]. Instead of reconstructing an image from a single plane wave transmission, several plane waves with different steering angles are sent into the body. Images computed from all steered waves are coherently summed to output a single high quality image. Like in optics, the exposure time is increased, recovering signal over noise but – unlike in optics - the contrast and the resolution are dramatically improved from the coherent summation of steered ultrasound images.
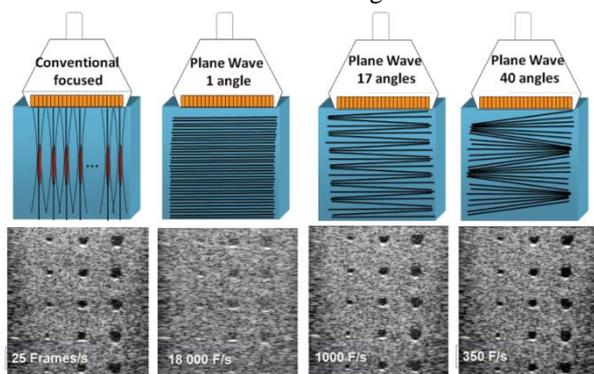
Fig. 3 From conventional line per line imaging to ultrafast coherent compound (from ref [3]))

The beauty of the plane wave compound approach is that with a few tens of angles, very high quality images can be recovered, higher than classical focused images requiring hundreds of firings. Thanks to bi-directional dynamic focusing (in transmit and receive), superb images can then be displayed at much higher frame rate than in a conventional architecture.

In summary, the use of plane wave combined with massive processing parallelization allowed by software platforms enable ultrafast ultrasound imaging.

Very high frame rates can be achieved (up to 20 or 30 kHz) with a limited image quality or ultra-high image quality can be obtained by decreasing the maximum frame rate achievable through the plane wave compounding technique (fig. 3).

There is a continuum of trade-off between frame rate and image quality depending on the number of angles used to compute the final ultrasound frame. The trade-off will be chosen according to the imaging goals.

The Aixplorer scanner from Supersonic Imagine is the first commercially available ultrafast ultrasound system, introduced in 2009. The next section shows concrete examples of how ultrafast imaging can benefit clinical practice on the Aixplorer. Catching small vibrations to measure tissue stiffness, imaging blood pulse to assess cardiovascular risk, imaging of micro-vascularization for pathology characterization.

III. DISCOVERING NEW CLINICAL RELEVANT INFORMATION

The ability to look at phenomena at temporal scale much smaller than what the human eye is able to catch open many perspectives to enrich our understanding of the body. Our ultrafast camera can be used to revisit what classic ultrasound is used to do: image soft tissues, blood flow, or contrast agents. Looking at them at a different time scales reveals new information with significant value for the clinician.

A. Adding a new sense to ultrasound: touch

Ultrasound is originally intended to show tissue morphology in real time. The reference imaging mode, the B mode, display echoes of different intensities depending on tissue ultrasound property, called echogenicity. As a complement to this information, flow information can be derived from ultrasound signals leveraging the Doppler effect of moving red blood cells. The information is displayed as color-coded images, temporal spectra and audio files.

Ultrafast imaging brings an additional sense to ultrasound, in addition to vision (b mode) and hearing (audio Doppler): the sense of touch. With an ultrafast camera it is possible to detect and quantify very subtle and fast tissue motion (a few micrometer displacement) occurring inside the body. This motion, well processed, reveals the inner elastic structure of the analyzed organ. Leveraging these ideas, Shear Wave Elastography (SWE) has been introduced in clinics in 2009 on the Aixplorer scanner to quantify and image in real time tissue stiffness.

- *Shear Wave Elastography: Principles*

To achieve its goal, the ultrasound system will act the same way the physician does when trying to assess tissue stiffness: palpate the organ to feel elasticity contrasts.

In SWE, the palpation relies on a side effect of ultrasound waves: the acoustic radiation force. Like the wind acting on a sail, the ultrasound radiation force pushes the tissue in the direction of the wave propagation. Then, by focusing beams at specific locations deep in tissue it is possible to create virtual fingers remotely palpating tissue at the beam focuses. This concept was introduced by A. Sarvazyan in 1998 [6].
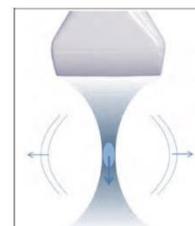
Fig. 1 Acoustic radiation from an ultrasound beam (from ref [3]))

The figure above shows the method to generate a shear wave source inside the body: focus an ultrasound beam using a long pulse: between 100 to 150 μs, 100 times longer than for imaging the tissue.

The virtual fingers will create low frequency mechanical shear waves inside tissues having propagation speeds directly related to tissue stiffness (shear waves propagate slowly in a soft medium and faster in a harder tissue). In a purely elastic tissue, the stiffness is quantified by the Young's modulus E, that can be written $E=3\rho c^2$, p being the body density (assumed as a constant) and c the shear wave speed.

Contrary to ultrasound waves, shear waves are sensitive to tissue elastic properties and their analysis appears as a smart way to quantify tissue stiffness non-invasively.

However, those waves are very weak (only a few micrometer displacement amplitude) and fast, passing through the image area in a few tens of milliseconds, less than the time required for an ultrasound machine to build a single image.

An ultrafast system is required to properly follow their propagation in tissues. The figure below shows the propagation of a shear wave imaged by the ultrafast scanner at 4000 images/s.
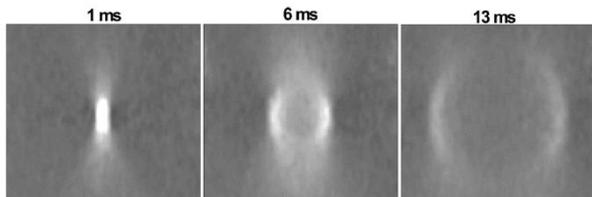
Fig. 2 Shear wave induced by an ultrasound beam focused in the center of the image (from ref [8]))

The tissue elasticity is deduced by measuring at each location the shear wave propagation speed (typically time of flights estimation algorithms are used).

The weakness of the shear wave displacements raises two issues: first it makes the shear wave detection a challenge in real tissue, secondly it limits the distance of propagation of the wave, reducing the explored area (typically to a few millimeters). A trivial solution would be to increase the energy of the ultrasound pushing beams but it raises safety concerns, as the amount of acoustic energy allowed at a given location is limited by international acoustic standards [7]. We found [8] a much smarter way to address this issue by creating a moving shear wave source travelling at a supersonic speed. This is made possible by successively focusing pushing beams at different depths, the beams being moved at a speed higher than the shear wave propagation speed. In such a supersonic regime, and similarly to a supersonic airplane creating an acoustic bang, the shear waves will sum up naturally along a Mach cone to create a higher amplitude plane shear wave as illustrated on the figure below.
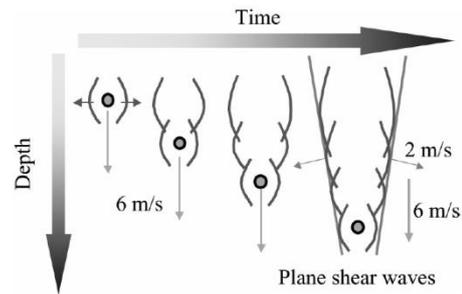
Fig. 3 Supersonic source (from ref [8]))

Thanks to this "bang" effect, the amplitude of the shear wave is multiplied by a factor of 5 to 10 without increasing proportionally the local acoustic power delivered in the medium [9]. With such a method a large shear wave can be generated in the medium able to propagate over several centimeters across tissue.
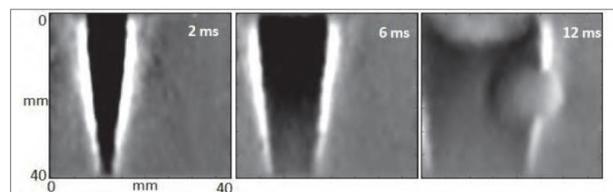
Fig. 4 Plane shear wave along a Mach cone from a supersonic source propagating in a heterogenous phantom (from ref [2]))
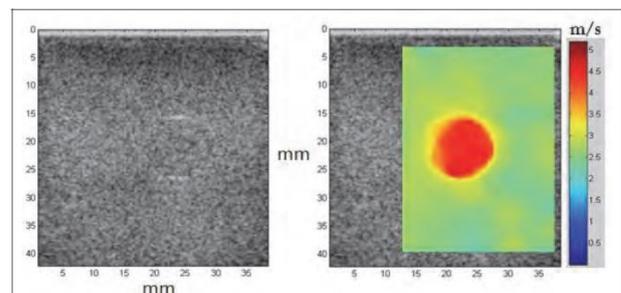
Fig. 5 Map of shear wave velocity deduced from previous movie (ref [2])

To build an image, several supersonic lines laterally separated by a few centimeters (typically 2 to 4) are generated and the deduced elasticity maps is concatenated to build a final elasticity map covering the full image area.

This mode is implemented in real time on the Aixplorer machine and provides quantitative elasticity maps of all organs (Breast, small parts, prostate, MSK, Liver …).

For precise quantification the user can place a Q-box on the image to measure local elasticity values.

In summary, the coupling of radiation force-based supersonic sources and ultrafast imaging allowed the creation of a new imaging mode in ultrasound providing real-time and quantitative elasticity imaging.
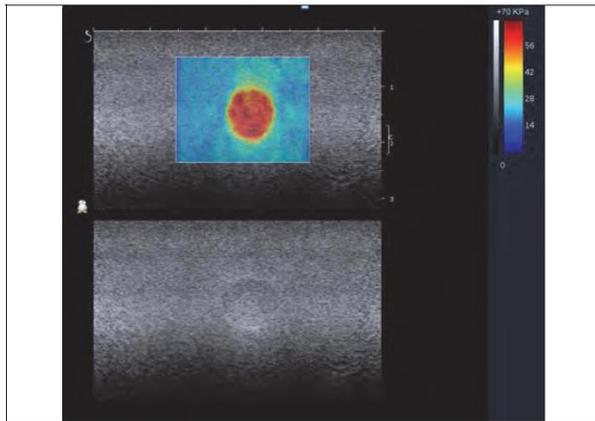
Fig. 6 Shear Wave Elastography mode on Aixplorer (from ref [2]))

- *Shear Wave Elastography: maturity and clinical value*

On Aixplorer, SWE is today a mature mode performing in a robust and a reliable way on most of human organs. It is available in 2D and 3D. It can be used for focal or diffuse disease diagnostic. It is a very powerful tool for therapy monitoring thanks to its quantitative aspect. It can also be used for functional assessment, like in the MSK application for example.

Many clinical studies have been performed since its introduction in 2009 and have proven its robustness and clinical utility. Below some highlights on the main organ studied:

§ On breast, more than 75 peer review clinical articles have been published [10,11]. SWE has been proven to be reproducible with a near perfect intra-observer reproducibility [12]. In the diagnostic workflow it increases ultrasound specificity by 34% without loss in sensitivity when trying to classify BI-RADS 3 and 4a lesions [13]. In the monitoring of therapeutic treatments, it allows early and accurate assessment of chemotherapy efficiency thanks to volumetric implementation for breast.
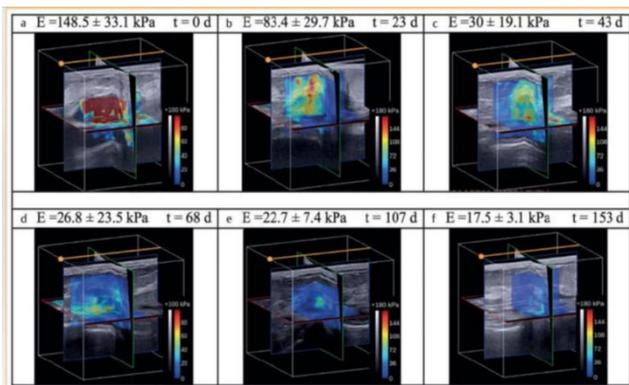
Fig. 7 3D SWE of a lesion treated by chemotherapy at different times

§ On Liver diseases, SWE showed excellent accuracy in detecting severe fibrosis, and exhibited good to excellent performances in staging fibrosis in Hepatitis B, C and NAFDL diseases [14-19]. Cut offs for each etiologies has been found and published. It has also been proven useful in oesophageal varices detection and distinction of compensate from decompensate liver fibrosis through the estimation of spleen elasticity [20].

§ On Prostate, SWE has been proven effective to better target the biopsies (the cancer detection rate being improved by a factor of 3 and showed excellent specificity for lesion characterization [21].

- *Shear Wave Elastography and competition*

SWE was the first real-time quantitative elasticity-imaging mode on the market. Since then all manufacturers have implemented their version of shear wave imaging. Still not relying on ultrafast imaging or supersonic sources these techniques lack of robustness or usability as they need to sacrifice performance. They can either sacrifice the imaging capability (giving only a single point measurement), the real time aspect or the quantitative aspect [22].

From a scientific standpoint the coupling of ultrafast imaging and supersonic sources is the safest and most efficient way to measure elasticity.

§ the safest approach thanks to the supersonic effect that reduces the local acoustic power delivered to the minimum required, staying in compliance with international standards and with ALARA (*as low as reasonably achievable*) principle.

§ the most efficient, as it gives optimal signal to noise ratio and therefore reduces the operator dependency and operation time while providing maximum imaging robustness and stability.

It is highly desirable and probable to see this technique standardized similarly to what happened to the color mode in the 80s/90, the standardization and the extension of the clinical proofs will insert the mode in the mainstream clinical routine of all applications.

- *Shear Wave Elastography: perspectives*

As one elasticity image is computed in a few tens of milliseconds, one potential feature of SWE, unused so far, is to monitor elasticity as function of time. Elasticity of organs can change over time under external or internal solicitation. Dynamic SWE analysis gives another dimension to the understanding of body organs:

§ In the heart, researchers showed that it was possible to monitor evolution of myocardial stiffness while the heart is beating. They measured stiffness at 10 different times during the heart cycle. While diastolic elasticity could help detection of infarct, systolic elasticity is a way to measure heart contractility non-invasively [23]. In the same path, monitoring muscle or tendon stiffness under contraction could help assess their viability and strength and monitor myopathologies [24,25].

§ On external organs, applying a compression hardens them. Quantifying this hardening is a new piece of information to further help characterizing lesions, more particularly small ones where the elastic contrast remains small. Research is going on investigating the possibility of computing hardening maps and assess their clinical relevance.

Finally 3D SWE will provide a unique tool to monitor effectiveness to non invasive or minimally invasive therapies (RF or cryo ablation, Hifu…).

B. Breaking the limits in blood flow imaging.

Blood flow information is assessed today through 2 distinct ultrasound modes. Color flow imaging provides visualization of flow on a color-coded image in real time while PW Doppler gives quantitative and precise flow information at a specific location as a function of time. The existence of two separate modes is a non-sense and a waist of time for the user. And the only reason for that is the technical limitations due to the lack of ultrafast imaging on existing systems. Indeed, properly quantifying blood flow requires high frame rates, typically between 500 and 20000 Hz (the frame rate should be at least twice the Doppler frequency shift induced by the moving red cells). Unreachable for conventional systems these frame rates are only available along a given line where a focused beam is repeatedly fired (PW mode). To get a flow image, compromises are taken and each line is partially sampled during a short duration. These compromises induce many limitations on the color flow imaging mode:

- lack of sensitivity
- Unability to image slow flow
- lack of quantitativeness: only a mean velocity at the central frequency can be estimated.
- Low frame rates of large areas of interest

The PW mode also suffers from limitations

- Availability only at given location
- System dependent spectral broadening due to focused beam geometry inducing bias in the maximum velocity measurements.

Rethinking blood flow imaging with ultrafast is an opportunity to break all these limitations. Using ultrafast frame rates, flow can be correctly sampled over the entire area of interest thus providing highly sensitive and quantitative imaging [26]. The figure below compares sequences of conventional and ultrafast Doppler.
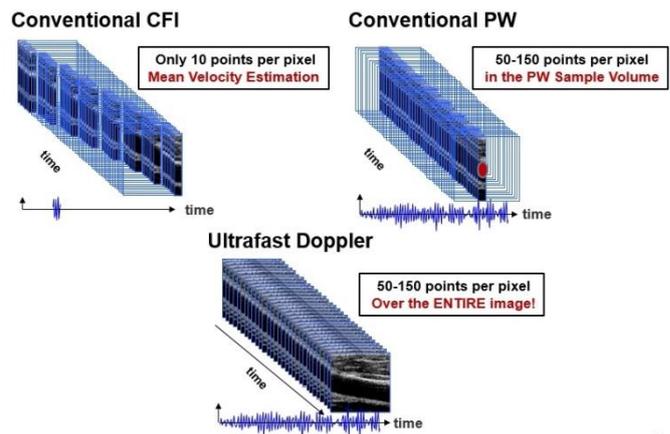
Fig. 8 Doppler mode acquisition sequences

- *Providing quantification anywhere*

As flow is correctly quantified anywhere, launching an acquisition of ultrafast Doppler data allow reconstruction of the color flow images while enabling the possibility to compute PW spectra anywhere on the image [27]. The color imaging frame rate is much higher (typically a factor of 10 is provided) and Doppler signals can be computed from multiple points and compared between them as illustrated on image below.
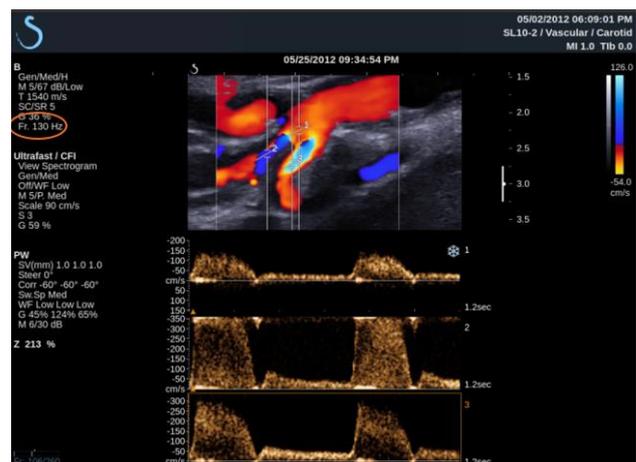
Fig. 9 Ultrafast Doppler of a carotid stenosis (from ref [27])

Comparing multiple spectra from the same acquisition increases diagnostic robustness (the comparison is done on the same plane and same cardiac cycle) and allows a significant gain in scanning time increasing therefore the patient throughput. This is particularly true for carotid and liver scanning.

- *Increasing quantification accuracy*

Doppler quantification is usually performed via spectrum computation of flow signals. The spectrum gives the distribution of Doppler frequencies and therefore the flow velocities at a given location. Most of clinical indicators are based on the maximum velocity measurement or the ratio of maximum velocities (at systole and diastole). However velocity measurements are biased due to geometrical spectral broadening effects. Indeed, a given and constant flow velocity will not give one Doppler frequency as expected but a distribution of Doppler frequencies corresponding to its projection along all angles of the transducer aperture. This artefact depends on the transducer and ultrasound beam geometry and may vary from one manufacturer to the other (literature reported a 20 % uncertainty in the maximum velocity measurements).

Ultrafast Doppler offers the opportunity to avoid this bias by displaying not the spectrum but the distribution of mean velocities over time in a given sample volume. Thanks to the high spatial and temporal resolution, this distribution is much more representative of the true velocity flow pattern [28]. The figure below show an example in the carotid:
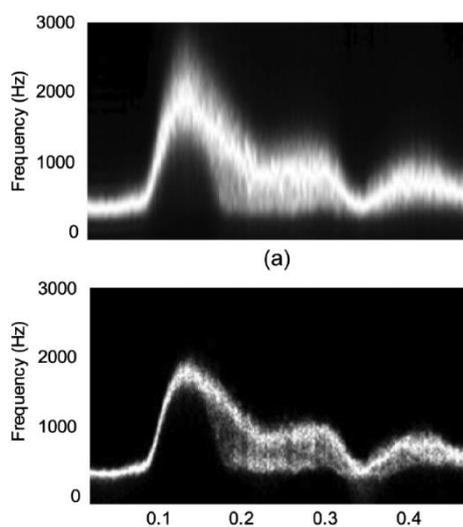
Fig. 10 Classical PW spectrum compared to ultrafast histogram (from ref [28])

Despite its potential clinical impact, this feature is still not available commercially as extensive clinical validation is required to replace maximum velocities cut off in the clinical workflow.

- *Increasing sensitivity and resolution to image micro-vascularization*

Slow flows are today hardly detected by color flow imaging mainly for two reasons. First, the lack of sensitivity and resolution of the mode. Second, because slow flows move at the same speed as tissue and classical recipes (temporal wall filtering) to filter blood from tissue motion do not work anymore;

Ultrafast Doppler is able to overcome those limitations. As for slow flows the sampling rate required in way lower than the maximum capabilities of the ultrafast system (typically 500 Hz for velocities of a few cm/s), the plane wave compound technique can be implemented. Each image is deduced from a set (between 5 and 15 depending on time availability) of several tilted plane waves summed coherently. This significantly enhances the resolution and signal to noise of ultrasound images resulting in a color flow image of very high resolution and sensitivity.

Furthermore, as ultrafast imaging provides simultaneously Doppler data over the full image, smarter filters can be used to separate tissue from flow motion. Conventionally, this separation using temporal filters that assume the flow faster than the tissue. In ultrafast Doppler, the spatial information is used to filter tissue from flow as tissue motion has a much larger spatial coherence than flow motion. Using a filter that use both the temporal and the spatial information allows the extraction of slow flow with speeds similar to tissue's, enhancing the sensitivity of the mode.

Examples below show conventional and ultrafast color images on different pathologies.
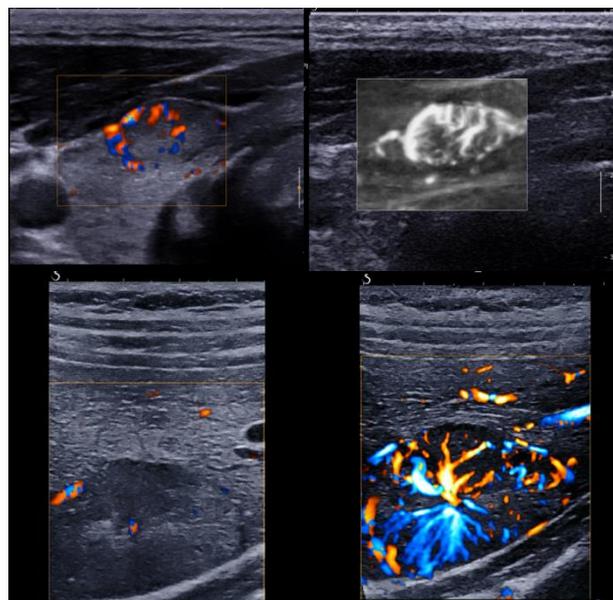
Fig. 11 Example of sensitive ultrafast Doppler (Angio Plus) compared to classical Doppler o clinical cases: thyoid nodule (up) and transplanted kidney (bottom)

Ultrafast Doppler (and its sensitive version called Angio PLUS) was recently introduced. Despite the lack of clinical studies, the first clinical images demonstrate the significant improvement in performance of the mode compared to classical flow imaging opening many clinical perspectives: better lesions characterization, inflammation quantification etc...

- *Perspectives: parametric maps for better and faster workflow*

Leveraging the quantitativeness of ultrafast Doppler, it becomes possible in a single cardiac cycle acquisition to access in all pixels quantitative hemodynamic parameters such as the resistivity or pulsatility indexes, which were estimated up to date at a single location at a time. 2D and soon 3D maps of these parameters could be provided as already demonstrated in the brain of human newborns [29]. Resistivity maps can be used to monitor resistivity variations due to changes of intracranial pressure or controlled hypothermia during the follow up of newborns. It could also provide very informative maps of arterial resistivity in transplanted kidney.
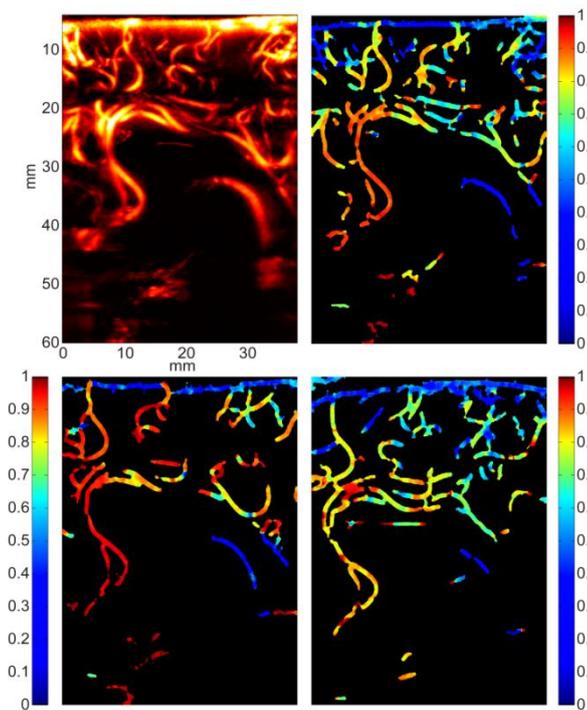
Fig. 12 Changes of resistivity observed in the medial sagittal plane of the human newborn brain during a mild fontanelle compression. Top: the Doppler image and its corresponding resistivity m map at baseline without fontanelle compression. (from ref [29])

C. Recording the living body:

Another way to clinically leverage the ultrafast system is to use it to analyze natural motion occurring in the body. One example is the propagation of the blood flow pulse wave at each heart beat in the arteries. The pulse wave velocity is an established criterion to assess cardiovascular risk. It is usually measured with dedicated tonometry devices (Complior®, Alam Medical and the SphygmoCor, ArtCor Medical) measuring an average value between the carotid and femoral artery. The reproducibility and clinical value of the technique is proven [30]. It suffers from a lack of accuracy as it measures an average speed over many arteries while being a time consuming act (10 - 15 minutes)
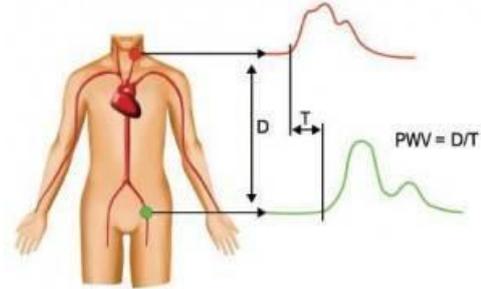
Fig. 13 Classical tonometry measurement methodology (from ref [31]))

Ultrafast imaging allows precise tracking of the pulse wave in vessels and therefore local assessment of pulse wave velocity (PWV) in targeted arteries, such as carotid or aorta. The figure below shows the pulse wave track on the carotid and the velocities estimation derived from the data. Two velocities can be measured: the velocity at artery dilatation and the one at artery retraction (after the blood pulse wave is gone). Interestingly, both velocities can be different, revealing inner elastic and geometric properties of arteries.
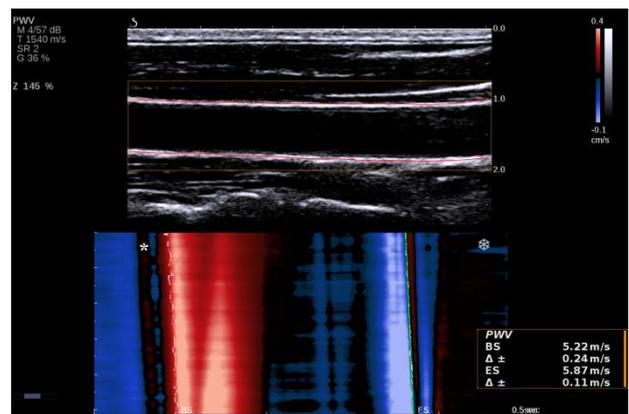
Fig. 14 PWV on Aixplorer

The feature is currently under clinical investigation and comparison with the standards [31]. Its clinical benefit was already demonstrated in the framework of Ehler Danlos pathology, a rare disease affecting Collagen Type III in arteries [32].

IV. PERSPECTIVES FOR ULTRAFAST IMAGING

If ultrafast imaging has already a strong clinical impact in the ultrasound field through applications presented in the previous paragraph, it also opens many other possibilities currently investigated in research that may revolutionize the

use of ultrasound in medicine. We present below an overview of the most promising trends.

A. Exploring human brain activity

The most fascinating impact of ultrafast imaging is probably in neuroscience. At the frontier of physics, biology, computer science and sociology, the quest for understanding the human mind is one of the biggest challenges of the 21st century. So far, brain exploration has been dominated by MRI [33] and more particularly by functional MRI. The use of ultrasound is a challenge in the brain due to the strong attenuation of waves through the skull and is until today dedicated to specific transcranial Doppler exams in vascular.

Interestingly ultrasound could play a role where MRI has limitations: small animals (due to lack of resolution), children (due to confinement requirements) and intra-operative scans. In small animals, the very high sensitivity and resolution of ultrafast Doppler enables for the first time live functional imaging of the brain. The first in vivo experiments were performed on trepanned rats by imaging functional changes of cerebral blow volume (CBV) in the brain micro-vascularization during whisker stimulation [34].
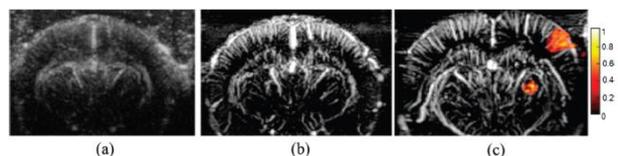
Fig. 15 Functional ultrasound imaging during whisker stimulation a) Doppler, b) Ultrafast Doppler, c) brain activity (from ref [34]))

Similar experiments were performed in intact rats (with skull) using ultrafast Doppler and contrast agents [35]. Functional ultrasound can also be used to monitor brain diseases such as epileptic seizures [34, 36].

Today functional ultrasound can be performed on freely moving small animals by just plugging a small transducer in animal's head [37]. A new field of investigation is here open for research - unreachable by other imaging modalities that require an immobilization of the animal.

Back to clinical diagnosis, functional ultrafast ultrasound can provide a unique bedside neuro-imaging system during neurosurgery for predicting the remodeling of cortical mapping resulting from tumor development. Finally, in newborns, brain activity monitoring is possible through the fontanel window to enable assessment of neonatal seizures and hemorrhage.

Fig. 16 Portable functional brain imaging system (from ref [37])

B. Transforming contrast agents into spy agents

Ultrasound contrast agents are usually injected in the body to increase back-scattered signals from blood flow vascularization. Ultrasound wave makes bubbles resonate at the wave frequency and higher harmonics. The very specific ultrasound signature of bubbles gives access to flow dynamics and can help lesion characterization, in liver for example, or to diagnosis cardiac pathologies.

So far, contrast agents have not been used in the mainstream clinical routine because their clinical benefit does not counterbalance the invasiveness of the technique.

This will not be the case anymore when coupled with ultrafast imaging.

Indeed, ultrafast imaging allows the measurement of the dissolution time of a bubble under high acoustic pressure. The clinical interest of the dissolution time is currently under investigation. It seems strongly correlated to the bubble environment. The figure below shows the difference between bounded and free bubbles in a phantom experiment after a disruption pulse over a few millisecond timescale [38].
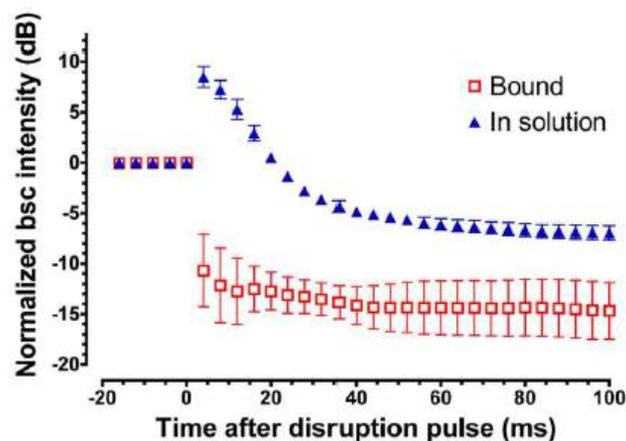
Fig. 17 Dissolution time of bounded and free bubbles in a phantom after a disruption pulse (from ref [38])

Ultrafast bubbles dissolution imaging could help differentiated free bubbles from sticky bubbles and be the first step for ultrafast molecular imaging. It could also be a way to measure intra-vascular pressure while reducing invasiveness to minimum [38,39].

Finally catching bubbles at ultrafast frame rate allows isolation of each bubble signal from the others giving rise to bubble super-localization and what we can call ultrasound microscopy [40].

This has been demsontrated in vitro on a microfluidic setup having channels at least 10 times smaller than the ultrasound resolution, shown on figure below. While the classical ultrasound image blurries all the information, the ultrafast imaging of bubbles allows proper imaging of the channel nerwork, leveraging an increased resolution by at least a factor of 10. This revolutionnary approach, earlier applied in optics and rewarded by the chemistry nobel prize [41], can be applied to ultrasound thanks to ultrafast imaging and is currently under investigation in vivo.
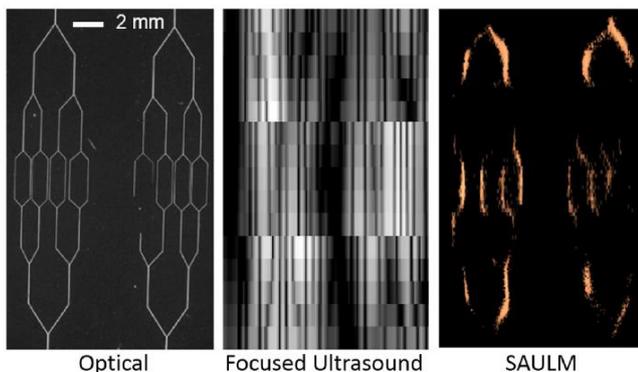
Fig. 18 Optical imaging, ultrasound imaging (center) and ultrasound microscopy (from ref [40])

Given the potential clinical benefit, these three potential applications could give another dimension to ultrasound contrast agents spreading its use in clinical routine.

C. Handheld ultrafast

One of the big trends of ultrasound industry since the 90s is miniaturization. From the big cart used in specific scanning rooms, ultrasound moved to light laptop format used in point of care and emergency. Ultrasound machines are now ready to be embedded on handheld systems, integrated on a tablet or in a probe plugged to a smartphone through usb or wireless connection. Ultrafast imaging will follow that trend. The increasing efficiency of tablet processors will open the road to ultrafast handheld system.

All benefits listed above will be available in the palm of the hand.

The miniaturization will also trigger progress on the road to 4D ultrafast imaging. Expected to be a breakthrough for cardiac imaging, 4D ultrafast still requires another level of technological evolution and miniaturization to be achievable.

V. CONCLUSIONS

With recent technological evolution clinical Ultrasound is currently entering the era of ultrafast imaging. Already bringing significant clinical benefit thanks to SWE mode and ultrafast Doppler, ultrafast imaging breaks the traditional limitations of ultrasound, provides several new applications and opens new avenues for a better understanding and clinical management of the human body.
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