Super-Resolution Ultrasound Imaging: The Quest for Microvessels

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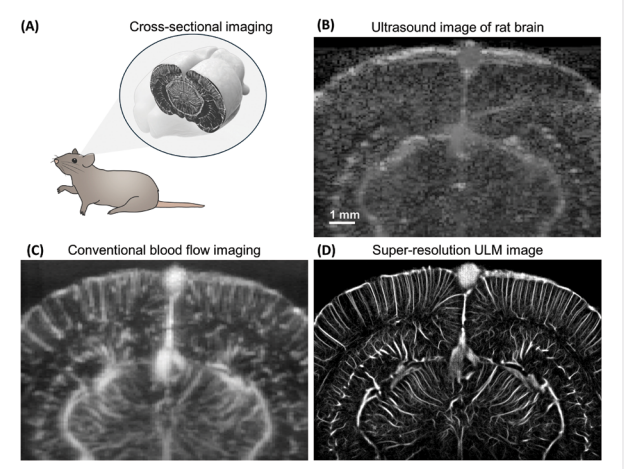
Everything you do, from climbing stairs to drinking a cup of coffee to reading this article, relies on oxygen to fuel your actions. Oxygen is delivered throughout your body via red blood cells that travel along the highway of your vascular system. The last stop in their journey are the microvessels, small blood vessels where oxygen and other gases are exchanged with the cells in your body. Understanding this microvessel blood flow is critical to the treatment and monitoring of numerous pathologies, from heart disease to cancer to dementia. However, microvessels are very small and often very deep in tissues, making them especially difficult to see using conventional biomedical imaging technologies. So, there is an ongoing pursuit to give clinicians ready access to microvascular flow information.

One potential approach to solve this critical imaging issue is a technique referred to as super resolution ultrasound imaging, often referred to as ultrasound localization microscopy (ULM). ULM is a recently developed solution to this "quest for microvessels" that uses FDA-approved microbubbles to greatly improve imaging resolution without losing imaging depth (**Figure 1**). But how does ULM do this? In this article, we discuss the ULM image reconstruction process using real in vivo example data taken from one of the most metabolically demanding organs, the brain.

Figure 1. ***A:*** *example of cross-sectional imaging of a rat brain.* ***B:*** *ultrasound tissue imaging gives a view of the different types of tissue where the differences in image intensity depend on changes in acoustic properties (e.g., density, sound speed).* ***C:*** *conventional blood flow imaging, such as power Doppler processing, reveals vasculature but is still limited by the wavelength of ultrasound.* ***D:*** *super-resolution ultrasound localization microscopy (ULM) imaging can break past this barrier and provide an imaging resolution at the microvascular scale.*



The "Crowd" Inside Our Body

Envision yourself lost in a crowd surrounded by people who are talking. Close your eyes and rely on your ears to distinguish individual voices and identify your colleagues. If everyone is speaking at once, distinguishing and locating specific individuals becomes a formidable challenge (**Figure 2**). But if only a handful of people are speaking, the task is much more manageable because of the separation and isolation of sound sources. Likewise, if your colleagues use something to help them stick out in the crowd (e.g., a whistle, which has a different pitch and volume from voices), the task of finding them is also more manageable. Super-resolution ULM imaging works in a similar way, detecting and localizing isolated microbubble signals that are distinct from tissue to generate detailed microvascular images.

Consider biomedical ultrasound imaging in this context of mapping the location of voices in this crowd. You are the ultrasound transducer, positioned on the surface of the body, and the various tissues and organs inside our body are the various individuals. (Of course, a caveat with this analogy is that we do not have active "voices"

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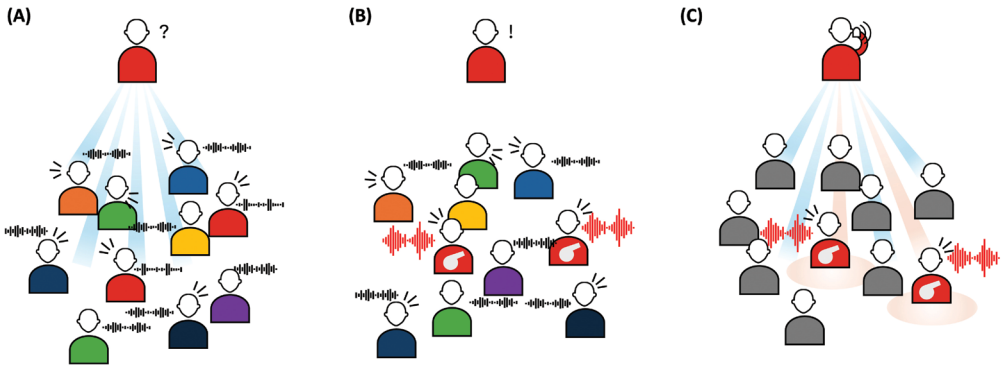


Figure 2. *Lost in the crowd.* ***A:*** *with everyone speaking at once, it is impossible to identify the locations of individual voices based on sound alone.* ***B:*** *if we give our colleagues (**red shirts**) a whistle, then we can locate them based on the pitch and loudness of the sound (**C**). Identifying each person's individual location is easier if our colleagues are far apart from one another or if they are moving around in the crowd.*

that speak in our body; specifically, ultrasound has a frequency range of ~1-15 MHz, well above the human voice frequency range of 90-255 Hz and the upper human audible range of 20 kHz). The transducer sends an ultrasound wave into the body to generate echoes from tissue(s) that consist of tiny "scatterers." Scatterers arise from changes in the acoustic impedance of tissue (which depends on tissue density and tissue sound speed) as the ultrasound wave travels through the body (e.g., different cell types, different orientations of tissues, different tissue structures such as connective tissues).

As one can probably guess, there are too many voices, all speaking at once and with similar tones and timbres, making the task of localizing each scatterer difficult. In real biological tissues, the number of scatterers is several orders of magnitude higher than we have considered in this analogy, presenting an even larger challenge to differentiating between tissues. The best we can hope to accomplish is to map out the general location(s) of a group of voices. For example, there may be denser groups where voices are loudest or the pitch of voices can provide us with information about the composition of the group (such as the ratio of men to women to children in our crowded room analogy). But the "problem" is that it is impossible to pinpoint the location of a single voice or scatterer with conventional ultrasound imaging. Our ability to resolve these fine details is compromised.

Microbubbles as Unique "Colleagues"

So how do we improve the technology? Can we pinpoint our colleagues within the crowd if they are all simultaneously speaking? No. We need a way for our colleagues to stick out in the crowd. And so, continuing with our analogy, we hand our colleagues a whistle (microbubble) to play. We are also asking them to walk around in the crowd and, ideally, to stay far apart from one another to make our task easier.

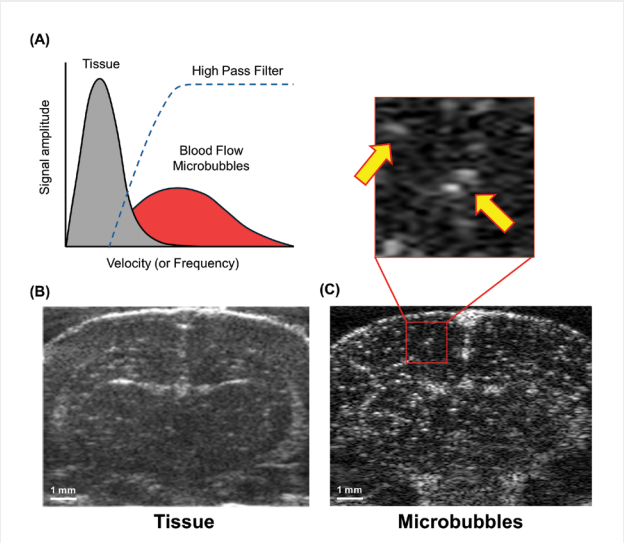
In biomedical ultrasound imaging, there is a well-established technology called contrast-enhanced ultrasound (CEUS) in which tiny microbubbles are injected into the bloodstream to enhance blood flow signals; these microbubbles function as the whistle in our crowded room analogy. Blood flow signals tend to be much weaker than the surrounding tissue(s), so microbubbles were designed to help image the vasculature. These microbubbles are typically 2-5 μm in size and made from lipid shells encapsulating an inert gas (e.g., perfluorocarbon). The size of the microbubbles was specifically chosen to mimic the size of red blood cells. This design ensures that microbubbles are small enough to smoothly circulate in the blood flow system without blocking vessels (even capillaries) but are also too large to leak out of the vascular space. Microbubbles are clinically approved around the world and are widely and safely used for numerous clinical applications such as cardiac imaging and cancer diagnosis.

Microbubbles have some unique acoustic properties that distinguish them from tissue scatterers. First, they are highly compressible, approximately four orders of magnitude more compressible than regular soft tissue. This makes microbubbles very bright under ultrasound imaging because ultrasound backscattering intensity is proportional to the difference of compressibility between microbubbles and the surrounding medium (i.e., blood). In our analogy, this means that the whistle is louder than the surrounding voices.

Second, microbubbles are highly nonlinear acoustic resonators. When hit with ultrasound waves, microbubbles generate nonlinear signals that are not produced by soft tissue. This unique property provides an opportunity to separate microbubble signals from native tissue signals during ultrasound imaging (the whistle is a much higher pitch than a typical voice, making it stand out in the crowd). Isolation is also essential to the task of pinpointing the individual locations of our microbubbles and colleagues. That is, if the whistles are too close together, the sounds overlap, causing confusion and impairing our ability to locate each individual precisely.

Third, microbubbles are highly mobile because they circulate within the body via the bloodstream; similarly, our colleagues with whistles are walking around while others remain stationary. This property provides another opportunity for creating separation between the microbubble signal and native tissue signal by means of filtering based on motion (**Figure 3**).

Figure 3. ***A:*** *using filtering, we can separate out the tissue components in the data (**B**) from a video of moving microbubbles (**C**).* ***C, inset:*** *handful of isolated microbubbles in one imaging frame (**yellow arrows**).*



Combining the three unique properties of microbubbles and envisioning their behavior in biological tissues, microbubbles manifest as a group of sounds that are loud (Property 1), with distinct tones (Property 2), and are constantly moving (Property 3) within the crowd. Importantly, the typical microbubble concentration in the bloodstream is several orders of magnitude lower than that of red blood cells, which gives rise to much greater distances between microbubbles, making them easier to localize in vivo (e.g., **Figure 3C**, *yellow arrows*, highlights the microbubbles).

Recognizing these unique advantages provided by microbubbles, Couture et al. (2011) and Siepmann et al. (2011) first introduced the idea of super-resolution imaging based on localizing microbubbles (ULM). The seminal papers by Christensen-Jeffries et al. (2015) and Errico et al. (2015) then marked the beginning of a new era of deep tissue microvascular imaging enabled by the combination of ultrasound and microbubbles. We detail how ULM imaging works, how it impacts basic science and clinical research, what shortcomings and limitations need to be overcome, and what is on the horizon for super-resolution ultrasound imaging.

How Does Localization of Microbubbles Work?

Microbubble "localization" is the process of estimating the subwavelength position of an individual microbubble within an ultrasound image, pinpointing the position of this whistle in the crowd. The usual workflow involves two main stages: an initial, quick estimate of the rough position of some "candidate" microbubbles and then a finer, subpixel algorithm of these candidates to get the super-resolved location.

It is important to note that there are usually several microbubbles within an ultrasound imaging frame (**Figure 4**), so we need a strategy for getting that first rough estimate of all microbubble positions simultaneously. A simple method is to identify isolated bright spots in the ultrasound image, which is sometimes called

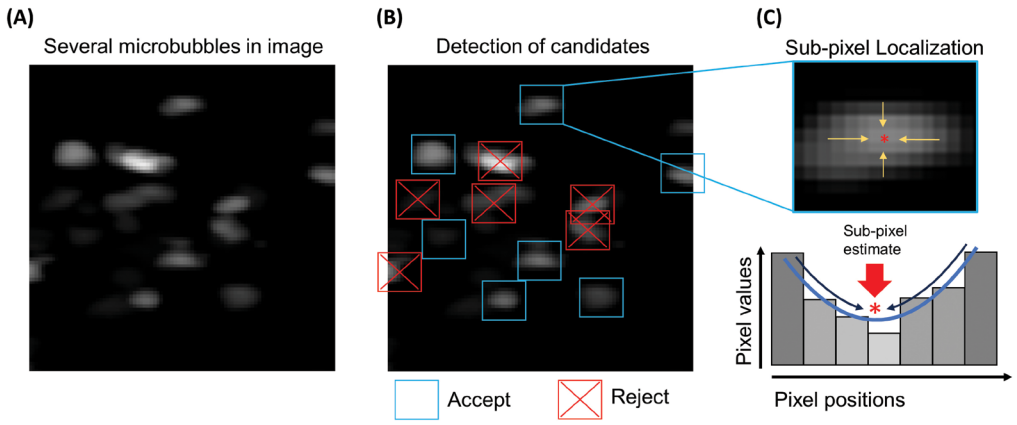


Figure 4. *Two phases of microbubble localization.* ***A:*** *example image with several microbubbles within the field of view from which the first stage of localization is applied to identify microbubble candidates (**B**). Some candidates may be rejected at this stage before being passed to the second stage that calculates the subpixel position of each valid candidate (**C**).*

a local maxima search. Other strategies include cross-correlation with a hypothetical microbubble point spread function, sometimes referred to as template matching. Deep learning plays a role here, with many networks designed to perform both microbubble detection and subpixel localization in a single step, as demonstrated by van Sloun et al. (2021) and Shin et al. (2024). Each strategy has several parameters that must be tuned for the specific imaging setup. Generally, there are assumptions made about the shape and size of a microbubble, how bright it is in comparison to the background, and the variability of the appearance of the microbubble. These assumptions are used to exclude candidates that seem too different than expected, with the assumption that these are likely false detections due to noise and other sources of error.

These candidate microbubble positions are then processed using a subpixel algorithm to achieve super-resolution. One of the most common super localization strategies for microbubble images is the "intensity weighted centroid" algorithm, sometimes also referred to as the "center of mass," in which a subpixel microbubble position is inferred based on the pixel intensities within a local region of interest surrounding the microbubble image. Other strategies to estimate the subwavelength position have been proposed, each with different advantages and disadvantages, such as processing time required, appropriateness of microbubble physical model, and assumptions made to simplify the problem. These new subpixel positions are then fed into the next stage of super-resolution ultrasound processing, a microbubble tracking algorithm.

How Does Microbubble Tracking Work?

As mentioned in **Microbubbles as Unique "Colleagues,"** microbubbles travel inside blood vessels, following the flow of blood plasma to circulate through the body. One of the conditions for good microbubble localization is that they are relatively spatially sparse to avoid any distortion of the microbubble shape by other nearby microbubbles. If we were to only accumulate the microbubble positions on every frame into an image, we would end up with a collection of discontinuous points within the lumen of blood vessels. Luckily, we know that the microbubbles are only within the vascular flow so we can make some assumptions about their locations between imaging frames and then use this information to interpolate or "fill in" the missing space between positions, a process often referred to as microbubble linking and tracking.

The simplest form of microbubble tracking is a nearest-neighbor search. For every imaging frame, we take each microbubble and pair it with the closest microbubble in the next imaging frame and then continue this process iteratively until all microbubbles within our reference frame are either paired or until we have exhausted all

potential candidates. We then move onto the next frame and pair those microbubbles with the candidates in the frame after that and so on until we run out of imaging frames. Each "chain" of pairs becomes a track, which can then be interpolated to get the super-resolved spatial positions.

From this track data, we can estimate valuable physiological metrics of the vasculature. The distance traveled by the microbubble over time is the flow velocity. Tortuosity, a measure of the "disorganization" of the vasculature, can be estimated by how chaotic the trajectory is and has applications in cancer and neuroimaging.

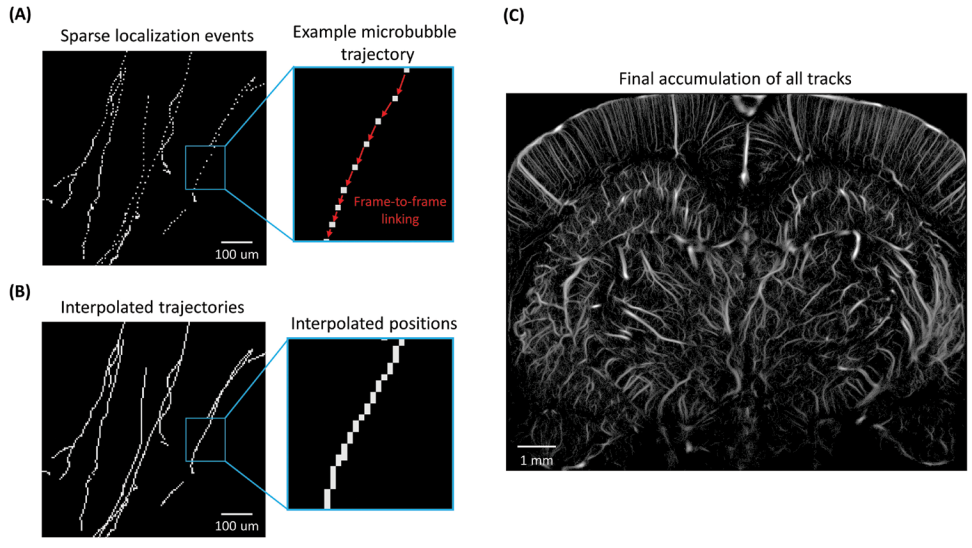
There are also features in addition to position that can be used for pairing. Several algorithms have been used that also match microbubbles, characterized by intensity, shape, or cross-correlation based on the assumption that a microbubble will look most similar to itself in the next imaging frame.

As with microbubble localization, there are several parameters that must be selected to complete this process. Some of these include the maximum allowable velocity of a microbubble, the minimum track length that is considered valid (i.e., short tracks are probably noise), the amount of acceleration and/or changes in direction in the microbubble flow, and threshold value(s) for the microbubble "similarity" metrics used to pair microbubbles. More advanced tracking algorithms also have a "gap filling" option in the pairing step that allows a microbubble to be paired with another that is more than one frame away to account for the occasional missed detection.

Now that we have the microbubble tracks, the final step is to convert it into a super-resolution image. This is done by selecting a desired interpolation factor to generate a pixel grid and then filling in all of the pixel positions for each track. The selection of the interpolation factor needs to be done judiciously because a pixel grid that is too coarse will lead to loss of information (separate blood vessels being merged together) and a pixel grid that is too fine will leave spaces inside vessels.

The ULM microbubble tracking is demonstrated using a real-world experimental dataset from a rat brain (**Figure 5**). In **Figure 5A**, we see an example accumulation of microbubble localization events for a single 1,000 frame acquisition of data from the cortical region. Although there are obvious vessel-like features,

Figure 5. *In vivo example of microbubble tracking.* ***A:*** *in this accumulation image, the sparse localizations of microbubbles lead to discontinuous vessel segments. The zoomed-in subregion demonstrates a chain of microbubbles that can be linked frame-by-frame into a trajectory.* ***B:*** *this microbubble track is interpolated to fill in these gaps in the data.* ***C:*** *this process is repeated for every microbubble track in the dataset, accumulating all the track data to produce the final super-resolution image.*



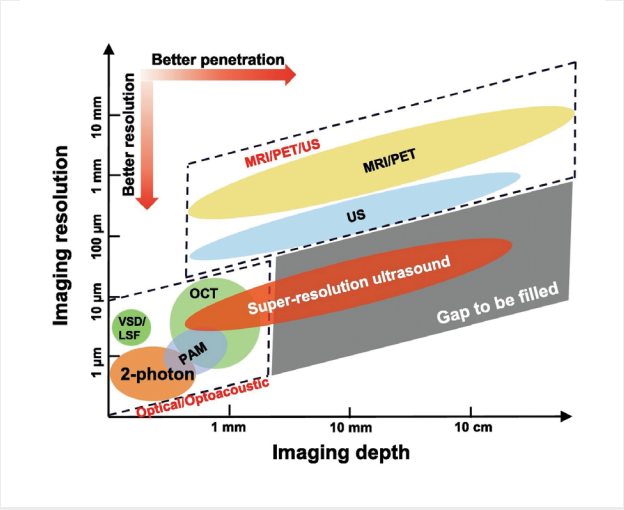


Figure 6. *Comparison of imaging resolution and penetration depth across various vascular imaging modalities, including two-photon microscopy (2-photon), laser speckle-flow imaging (LSF), magnetic resonance imaging (MRI), optical coherence tomography (OCT), photoacoustic microscopy (PAM), positron emission tomography (PET), ultrasound (US), and voltage-sensitive dye imaging (VSD). Reprinted from Song et al., 2023, licensed under CC BY-NC-ND 4.0 (see creativecommons.org/licenses/by-nc-nd/4.0h).*

the sparse microbubble data have led to discontinuous vessel segments that can be difficult to interpret. A subregion was selected to show diagrammatically the process of frame-to-frame microbubble linking to produce a trajectory. This trajectory is then interpolated to fill in the missing microbubble positions and plotted onto a pixel grid (**Figure 5B**). Finally, all the interpolated track data is accumulated across all acquisitions into a final super-resolution ULM reconstruction (**Figure 5C**), which required 50,000 frames in total.

What Are the Representative Applications of Super-Resolution Imaging?

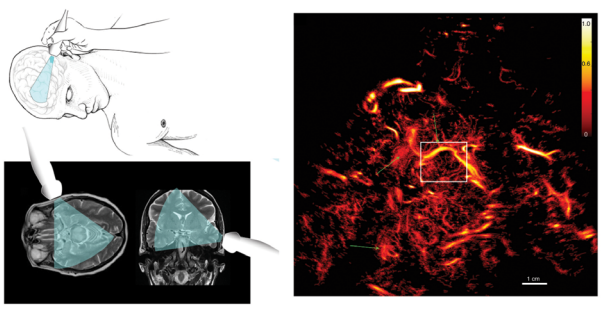
Super-resolution ULM imaging is essentially a microvascular imaging technique. Therefore, any applications that benefit from in vivo imaging of the tissue microvasculature are candidate applications for super-resolution ultrasound. Detailed summaries of preclinical and clinical applications of super-resolution imaging are provided in these reviews by Christensen-Jeffries et al. (2020), Chen et al. (2021), and Song et al. (2023). Here we provide a brief overview of some of the most prominent ones.

The brain has been one of the most popular organs for super-resolution imaging because of the importance of cerebral blood flow (CBF). This is not surprising because the brain is one of the most metabolically demanding organs, requiring a tightly regulated CBF to maintain normal function. CBF is a highly complex process that spans many different brain regions and across many different size vessels; thus imaging and monitoring of CBF presents a formidable challenge because it demands an imaging modality that has both large imaging territory and high spatial resolution.

Over the past several decades, many brain vascular imaging technologies have been developed, including optical imaging, photoacoustic imaging, magnetic resonance imaging (MRI), X-ray computed tomography (CT), and Doppler ultrasound. However, none of these methods provide both brain-wide imaging coverage (e.g., whole brain imaging provided by MRI and CT) and high spatial resolution (e.g., at micrometer scale provided by optical imaging) at the same time. Super-resolution ultrasound, on the other hand, nicely bridged this gap (**Figure 6**); it allows brain-wide spatial coverage while providing a micrometer-scale spatial resolution as well as the capability of measuring blood flow velocity for individual vessels.

These new imaging capabilities have created many new possibilities in many brain applications such as a stroke (**Figure 7**), shown by Demené et al. (2021) and Chavignon et al. (2022), aging by Lowerison et al. (2022), Alzheimer's disease by Lowerison et al. (2024), hydrocephalus and ischemia by Zhang et al. (2022), and functional imaging

Figure 7. *In vivo human brain super-resolution imaging. The schematic diagram depicts the handheld ultrasound imaging setup and reconstructed microvessel density map. Adapted from Demené et al., 2021, with permission. © Springer Nature.*



of neural activities in the brain by Renaudin et al. (2022). Both animal and human brain imaging results have been reported (see Song et al., 2023), and the brain remains as one of most promising and active areas of research for super-resolution ultrasound.

Another prominent application of super-resolution ultrasound is associated with cancer imaging. As aberrant growth of microvessels is one of the hallmarks of cancer, super-resolution ultrasound presents an enticing tool from cancer basic research to clinical management of cancer (e.g., early detection, diagnosis, and therapy response evaluation). Thanks to the high spatial resolution, super-resolution ultrasound is capable of characterizing and quantifying the abnormal microvascular flow, which serves as a functional tumor microenvironment biomarker because impaired flow is indicative of elevated intratumoral pressure and hypoxia, reported by Lowerison et al. (2020). Translational research of cancer super-resolution ULM in humans is under way and early promising results have been reported in breast (Opacic et al., 2018) and lymph node (Zhu et al., 2022) tissues.

What Are the Limitations?

Similar to its optical counterpart, fluorescence photoactivation localization microscopy, the primary limitation of super-resolution ULM lies in its slow imaging speed or low temporal resolution. In contrast to conventional ultrasound imaging, which is known for providing real-time imaging speed, ULM requires tens of seconds for data acquisition and hours for postprocessing to generate a single image. The slow imaging speed poses a formidable challenge for practical application because ultrasound imaging is typically conducted via free-hand scanning, and therefore the long data acquisition time makes ULM very susceptible to probe and tissue motion. Pragmatic solutions to this problem have included fixation of the transducer to reduce motion and correction of motion artifacts in postprocessing, although this is ideally done with three-dimensional (3D) imaging that is not as accessible as two-dimensional (2D) imaging in practice.

However, despite the low imaging speed, significant progress has been made in accelerating data acquisition. This includes developing algorithms for identifying overlapping signals under high microbubble concentration, boosting localization rates with high-frame-rate ultrasound imaging, exploiting temporal and spatial correlation of microbubbles, and inventing new super-resolution techniques that bypass microbubble localization or tracking. Hardware approaches, such parallel computing and algorithmic improvements driven by deep learning, have also been implemented to achieve faster postprocessing. Although real-time ULM without compromising spatial resolution remains a challenge, ongoing advancements hold the promise to narrow this gap and ultimately establish super-resolution ultrasound as a routine tool in biomedical research and clinical practice.

Another pragmatic challenge of ULM imaging is its dependence on microbubbles, which are intravenously injected into the bloodstream in vivo. Although intravenous injection is not an inherently complicated procedure, it is invasive and requires knowledge of anatomy and proper techniques to ensure it is done correctly and safely. In small animals such as mice, tail vein or jugular vein injections can be challenging because of the small vessel size. In humans, intravenous injections require designated medical staff and monitoring of adverse reactions to microbubbles. Contrast microbubble-free super-resolution imaging approaches offer the best practicality (and also real-time imaging), but they do not yet provide the same spatial resolution as microbubble-based techniques (demonstrated by You et al., 2023).

The next frontier of ULM is to extend its capabilities beyond imaging tissue microvasculature. Microbubbles only travel within blood vessels, which precludes super-resolution ultrasound from imaging the extravascular (outside blood vessel) space. The next-generation ultrasound contrast agents based on nanoparticles, nanodroplets (Thomas et al., 2021), and gas vesicles (Bourdeau et al., 2018) are being actively developed to open new doors for future, extravascular super-resolution ultrasound imaging.

The Outlook

Since 2015, the field of super-resolution ultrasound imaging has been experiencing an exponential growth propelled by advancements in techniques and their consequential impact on both preclinical and clinical domains. Looking ahead, a pivotal area for further development lies in high throughput imaging, enabling swift in vivo examination of tissue microvasculature. This endeavor necessitates overcoming two primary obstacles: long data acquisition (e.g., from tens of

seconds to several seconds or less) and postprocessing time (e.g., from hours to minutes or even seconds). Enhanced microbubble localization and tracking techniques that sustain a high-fidelity performance under high microbubble concentrations remains the key to shortening the data-acquisition time. Although real-time ULM based on localizing individual microbubbles faces challenges due to the inherent slowness of accumulating sparse signals (similar to coloring a picture with ultrafine tipped markers), alternative techniques that bypass localization or tracking offer real-time imaging capabilities but sacrifice spatial resolution (demonstrated by Chen et al., 2023). The different available super-resolution techniques provide a complementary set of tools for effective imaging. For example, one can utilize the localization-free approach to obtain a real-time, comprehensive view of the vasculature, while employing localization-based methods to capture "close-up," high-resolution details of tissue microvasculature. For both approaches, a robust computational resource with adequate computing power to handle the high data rate associated with ultrafast imaging (e.g., several to tens of gigabytes per second) and postprocessing pipeline for super-resolution imaging (e.g., beamforming, tissue clutter filter, microbubble localization and tracking, neural networks for deep learning-based algorithms, and other ancillary processing steps) is necessary. In the meantime, ongoing efforts will focus on the continual development of more efficient algorithms aimed at reducing the computational expenses associated with super-resolution imaging.

Once high throughput imaging becomes available, super-resolution ultrasound will transition into a much more practical technology and be utilized by a much broader user base in both basic and translational research. On successful commercialization and integration into clinical ultrasound scanners, super-resolution imaging will become readily available to clinicians worldwide. This accessibility will enable clinicians to explore a myriad of clinical applications, ultimately revealing the clinical impact of super-resolution ultrasound. Another promising avenue for future growth of super-resolution ultrasound imaging lies in the domain of neuroscience, particularly in brain imaging. The unique combination of a large imaging territory (e.g., whole brain), ultrafine spatial resolution, and the portable and wearable nature of ultrasound imaging renders a compelling vision of a wearable brain imaging device that provides real-time, high-fidelity functional brain imaging in freely moving and naturally behaving subjects, including animals and humans. The longitudinal, in vivo imaging capability also presents a crucial tool for investigating the progression of neurological diseases and responses to therapy, particularly in relation to cerebral blood flow. Moreover, when coupled with therapeutic ultrasound techniques, such as focused ultrasound-based drug delivery, ablation, and neuromodulation, super-resolution ultrasound offers a compelling avenue for monitoring and assessing responses, including the opening of the blood-brain barrier, passive cavitation detection and localization, and neural activities triggered by focused ultrasound stimulation. By reducing reliance on MRI for imaging guidance and response monitoring and offering an all-acoustic solution for both therapy and imaging, super-resolution ultrasound holds the potential to significantly enhance the accessibility of these innovative therapeutic techniques, benefiting diverse populations worldwide across various demographics.

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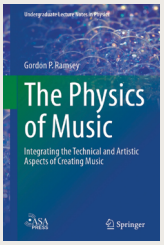

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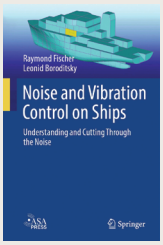

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