

# **THE ABUNDANT PROMISE OF ULTRASOUND IN NEUROSURGERY**

A Broad Overview and Thoughts on  
Ethical Paths to Realizing Its Benefits



# **THE ABUNDANT PROMISE OF ULTRASOUND IN NEUROSURGERY**

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Ethical Paths to Realizing Its Benefits

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**SPIE.**

*“Shipwrecked we just float, O favorable wind arise,  
May we one more time gaze upon that familiar trait.”*

*“For years my heart was in search of the Grail  
What was inside me, it searched for, on the trail.”*

– Hafiz

## Dedication

*Amir Manbachi would like to dedicate this book*

To the women in our lives, and in support of the feminism movements around the world!

Especially for:

“*Woman, Life, Freedom*”  
(*Femme, Vie, Liberté*)  
(آزادی زندگی زن)

May we keep learning from our failures as a society:

From the story of Mahsa Amini, the young Persian woman who lost her life because she showed an inch of hair in 2022; or the woman who had to flee her birth country in fear, without her husband’s legal *travel permission* amidst the pandemic lockdowns, just to save her life from domestic abuse and non-supportive, anti-feministic laws.

Here’s to all the men, women, and others who stand up for a more fair, inclusive, and empowering society for all of us!

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# Preface: The Personal Applications of Ultrasound in My Life

## First Exposures to Neurological Disorders

*“Proud of you and everything you have accomplished! I’m sure between your education ingenuity and your artistic music talents, you and agha Reza\* will have a great life ahead of you! If we don’t see each other again, I want you to—”*

I interrupted my uncle halfway through his sentence, even though interrupting an elder was a major no-no in the Persian culture. But I had no choice. I was afraid to hear the rest of what he had to say!

To the best of my memory, these were the last words spoken to me by my uncle, as our family departed Iran to embark on our immigration journey to Canada. My uncle’s name was *Mansoor* (meaning “victorious” in Farsi). He had gone through a lot and was a man of great integrity. Uncle Mansoor had lost his father at a young age and had managed to support himself, his mother, and his siblings through craftsmanship during his childhood. After suffering a work-related eye injury, he would eventually find his way to working in healthcare in Iran. Given my age, I couldn’t comprehend the depth of the traumas he had experienced. Despite myriad obstacles, Uncle Mansoor single-handedly supported his elderly mother, my grandmother, through her final moments—with no governmental assistance or support from the rest of the family. If he had a middle name, it should have been *Righteousness*. He lived a simple life, full of love. He had a heart of gold and was sincere, pure, and down to earth.

My brother and I have many cherished memories of Uncle Mansoor. I remember his retirement when I was around 10 years old—as he had more free time, he visited our family often. Uncle Mansoor used to take us to hike the

---

\*The word “*agha*” means “Mr.” in Farsi. “Reza” is my older brother’s name; it means “content,” and that is exactly how I would describe him: wise, calm, and content.

have more and will be able to do more than we did. It is my fervent hope that projects like this book will take us one step farther in terms of leaving the world better than we found it. I believe in the power of sound, ultrasound, and acoustics—especially in a field of much necessity, such as neurosurgery. If this book helps you to think the same way, or if you already do, please join me to partner up and aim to make an impact in this field.



**Amir Manbachi, Ph.D.** is a Persian-Canadian Ultrasound Engineer and Biomedical Engineer from Toronto. He is an Assistant Professor of Neurosurgery, Biomedical Engineering, Mechanical Engineering, Electrical and Computer Engineering at Johns Hopkins University, focusing on studying the fundamentals and novel clinical applications of ultrasound. He is the engineering co-PI on a \$13.48M award from Department of Defense and is responsible for the assembly of a world-class team of pioneers, including 60 individuals from clinical, academic, and industry settings. He is the co-Director and founder of the HEPIUS Innovation Labs, focusing on the next generation of wearables and implantable medical ultrasound devices for spinal cord injury patients: [HopkinsMedicine.org/Neuro/HEPIUS](http://HopkinsMedicine.org/Neuro/HEPIUS)

# Chapter 1

## Introduction to Applications of Ultrasound in Neurosurgery

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- 1.1 Introduction
  - 1.1.1 Overview
- 1.2 Fabrication Strategies and Operational Principles for Ultrasound Transducers
- 1.3 Diagnostic Ultrasound in Neurosurgery: An Overview of Various Imaging Modalities and State-of-the-Art Microflow Sensing
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References

### 1.1 Introduction

Since the advent of diagnostic ultrasound for detecting brain tumors in 1948, the applications of ultrasound in neurosurgery have grown tremendously.<sup>1</sup> While the original application of ultrasound focused on diagnostic applications, ultrasound has since been employed in applications ranging from tumor ablation and piezo-surgery to tissue regeneration as well as real-time physiological monitoring.<sup>2-5</sup> While the applications of ultrasound in medicine keep expanding, the field of neurosurgery has been rather slow to adopt this promising technology when compared to other fields of medicine

## 1.5 Intraoperative Ultrasound Guidance in Neurosurgical Procedures

Intraoperative ultrasound (IoUS) provides neurosurgeons with the ability to identify, localize, and characterize intra-cranial and –spinal abnormalities.<sup>28</sup> IoUS has several advantages over other imaging modalities, such as CT or MRI. For example, its ability to provide true real-time imaging can account for brain shift, which refers to the intraoperative displacement of brain tissue from preoperative images.<sup>29</sup> This makes IoUS particularly well suited for navigation systems, where fusing imaging can be done by mapping preoperative CT or MRI images onto the IoUS scans.<sup>6,30</sup> IoUS has shown utility in many different interventions, including lesion identification and biopsy, catheter insertion, foreign body identification, and decompression.<sup>28,31–33</sup> Several different components are necessary for implementing IoUS, including bony exposure via craniotomy or laminectomy and probe sterilization.<sup>34</sup> Choosing the right probe is essential for different applications, with higher- and lower-frequency probes more suitable for superficial and deep visualization, respectively.<sup>32,35</sup> Chapter 5 discusses the different ultrasound modalities that can be used for IoUS, its utility in various neurosurgical procedures, and requirements for its implementation. The chapter concludes with a discussion of the advantages, limitations, and future potential of IoUS. Overall, the chapter demonstrates the potential of IoUS to greatly assist neurosurgeons in decision making and surgical planning.

## 1.6 Contrast-Enhanced Ultrasound Imaging

Contrast-enhanced ultrasound (CEUS) is able to address several of the limitations with conventional B-mode imaging, such as differentiating tissues with similar acoustic properties and improving visualization. CEUS typically involves the intravenous infusion of microbubbles, ranging in size from 1 to 10  $\mu\text{m}$ , that can help depict microvasculature. These agents take advantage of the difference in echogenicity between microbubbles and the surrounding tissue to improve the signal-to-noise ratio.<sup>6</sup> CEUS has utility in many neurosurgical operations, such as resecting brain tumors, evaluating aneurysms before and after clipping, and visualizing occlusion of the carotid arteries.<sup>32</sup> In the spine, CEUS can be used for intramedullary spinal cord tumor resection, vascular malformation repairs, and evaluation of blood flow following spinal cord injury.<sup>36,37</sup> Chapter 6 discusses the principles behind CEUS and its application in spine surgery. The chapter demonstrates how CEUS can serve as a useful adjunct to other ultrasound modalities in neurosurgical procedures.<sup>38</sup>

## 1.9 Novel Applications of Ultrasound in Neurosurgery

The applications of ultrasound in neurosurgery are continuously growing. Chapter 9 introduces new, state-of-the-art neurosurgical applications that include ultrasound computed tomography, real-time ultrasound thermography and thermometry, and non-invasive intracranial pressure monitoring. Thermography refers to recording surface temperature changes using heat-sensing infrared cameras. Ultrasound has the ability to recognize temperature changes due to the temperature dependence of speed of sound.<sup>51</sup> Ultrasound provides a non-invasive, real-time measurement of temperature changes that could be indicative of inflammation and metabolic rate intraoperatively.<sup>51</sup> Furthermore, this chapter discusses how artificial intelligence and machine learning are increasingly being used in conjunction with ultrasound imaging to improve image quality and increase diagnostic accuracy.<sup>52</sup> The future of ultrasound in neurosurgery has limitless possibilities to provide patients with real-time diagnostic and therapeutic applications without exposing patients or clinicians to ionizing radiation.

## 1.10 The Abundant Promise of Ultrasound in Neurosurgery: The Ethical Path to Claiming the Potentials

Ethical considerations are critically important when advancing the medical field. Chapter 10 details the ethics of ultrasound, including the discussions of informed consent as well as potential risks of harm. In addition to ensuring safe ultrasound practices, there are also justice considerations regarding whether advancements in neurosurgical ultrasound are accessible to all groups of people. For cases where medical advancements are more accessible to the affluent, what pathways allow for transition to wide access to the broader public nationally and globally? Finally, this chapter discusses author and editor Dr. Amir Manbachi's personal experiences and motivations for advancing the field of ultrasound in neurosurgery.

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# Chapter 2

## Fabrication Strategies and Operational Principles for Ultrasound Transducers

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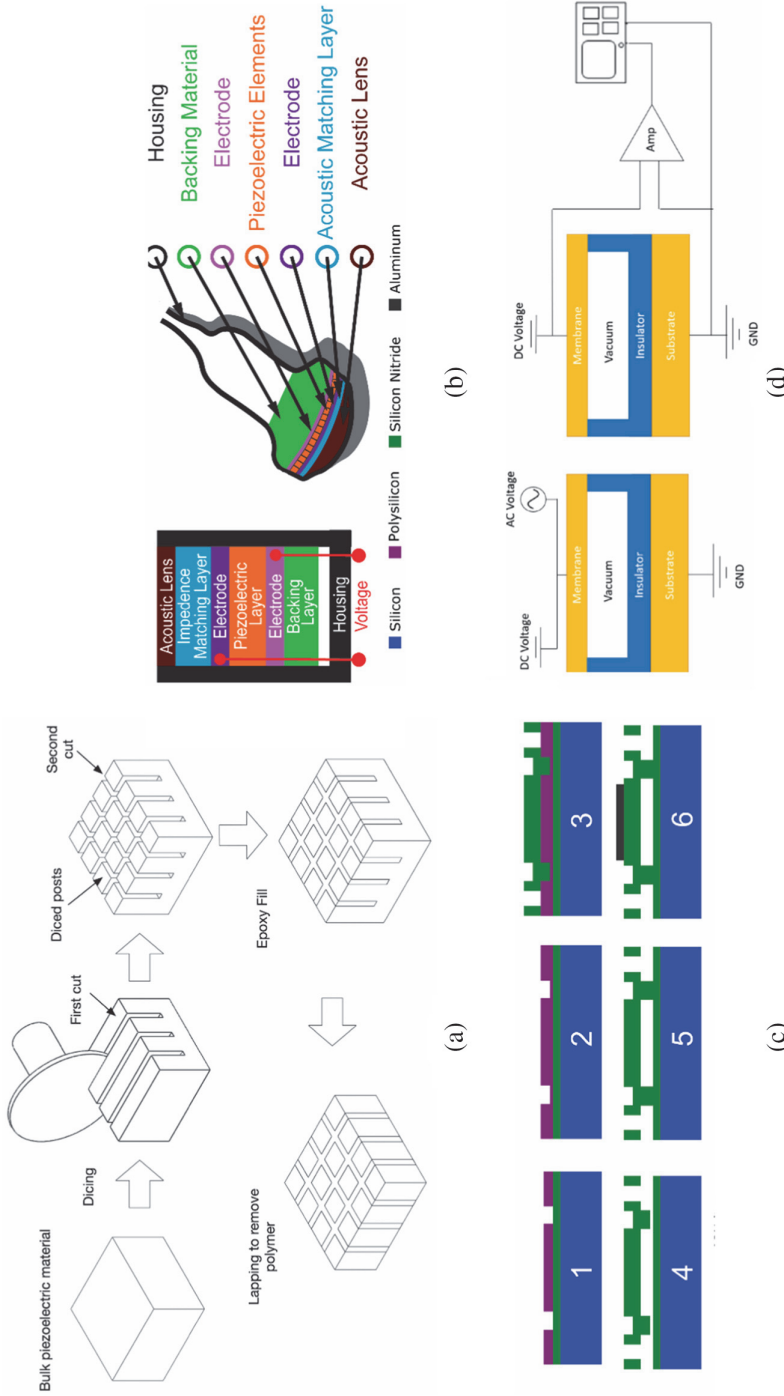
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- 2.1 Introduction
  - 2.2 Introduction to Piezoelectricity
    - 2.2.1 Types of piezoelectric materials
    - 2.2.2 Piezoelectric transducer fabrication strategies
  - 2.3 Introduction to Electrostriction
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    - 2.5.2 Future directions
- References

### 2.1 Introduction

In 1917, during World War I, Paul Langevin reported on the development of the first ultrasound transducer for the detection of submarines.<sup>1,2</sup> Since then,





**Figure 2.3** Fabrication processes for PMUT and CMUT transducers. (a) Method of creating composite piezoelectric transducer arrays by alternating dicing the piezoelectric crystal and filling in the kerfs with epoxy. (Drawings adapted from Ref. 33.) (b) Simplified schematic for the structure of a PMUT transducer element (left) and a curvilinear ultrasound transducer (right). (c) Sacrificial release method for fabricating CMUT transducer arrays. First, silicon nitride is deposited, then polysilicon is patterned on top of the silicon nitride layer. Next, a sacrificial layer of polysilicon is deposited for the etch channels into the arrays. Subsequently, a silicon nitride layer, which will become the top plate layer of the transducer, is deposited. This is followed by the sacrificial layer of polysilicon being deposited. Next, a layer of silicon nitride is deposited to seal the arrays. Finally, aluminum electrodes and interconnects are deposited. (Image adapted from Ref. 34.) (d) Simplified schematic of a CMUT transducer fabricated using the sacrificial release method in transmit (left) and CMUT receive (right) modes. (Image adapted from Ref. 35.)

# Chapter 3

## Diagnostic Ultrasound in Neurosurgery: An Overview of Various Imaging Modalities and State-of-the-Art Microflow Sensing

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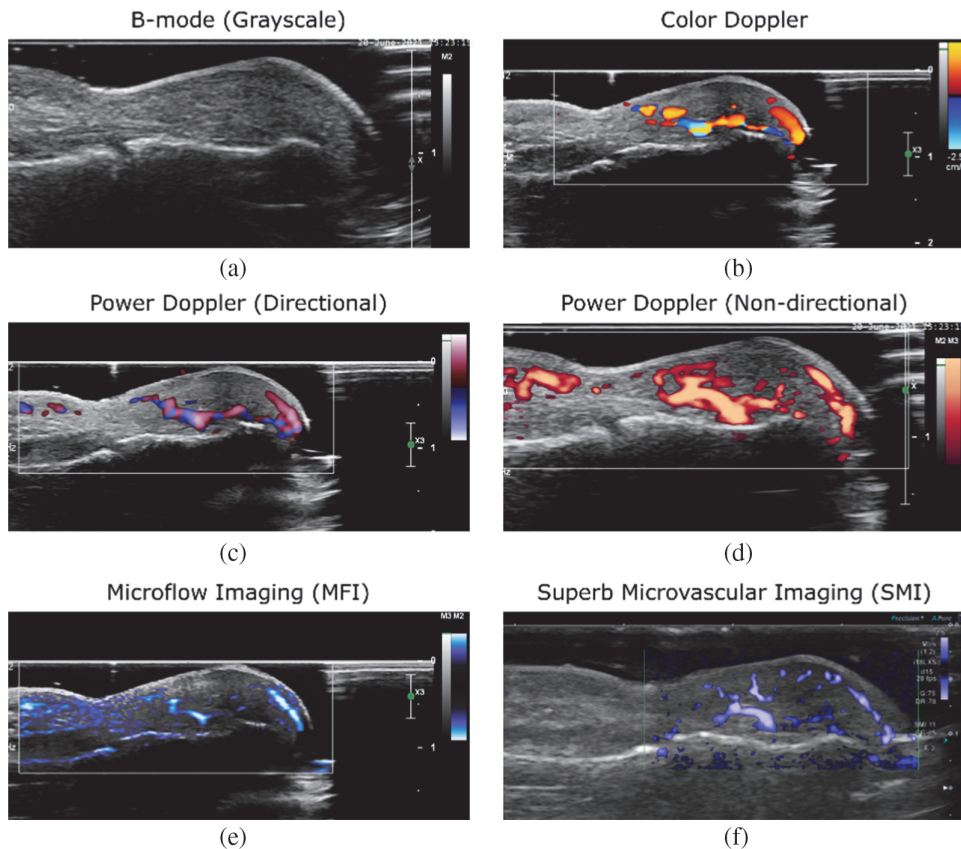
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  - 3.3.3 C-mode
  - 3.2.4 M-mode
  - 3.2.5 Doppler imaging
    - 3.2.5.1 Spectral Doppler
    - 3.2.5.2 Color Doppler
    - 3.2.5.3 Power Doppler



**Figure 3.2** Representative images for diagnostic ultrasonic modalities in the fingertip. (a) B-mode. (b)–(f) Doppler imaging modes that visualize blood flow. (e) and (f) are proprietary imaging techniques by Philips and Canon, respectively, that pick up slow blood flows often found in microvasculature. (Images adapted from Ref. 33.)

### 3.2.3 C-mode

C-mode scans provide a 2D visualization across an area of constant depth [Fig. 3.1(c)]. Although not often employed in medical ultrasound since the development of 3D B-mode, C-mode has been shown to aid in diagnosing bone fractures and viewing the ventricles of the heart.<sup>14,15</sup>

### 3.2.4 M-mode

In M-mode, or motion-mode, a single scan line is repeatedly sent through the same location in the body. Depth is represented along the  $y$ -axis where the signal amplitude impacts pixel brightness [Fig. 3.1(c)]. Uniquely, the  $x$ -axis represents time, thus capturing the motion of a single area of the body (e.g., the heart throughout the cardiac cycle).<sup>1</sup> Although not typically

# Chapter 5

## Intraoperative Ultrasound Guidance in Neurosurgical Procedures

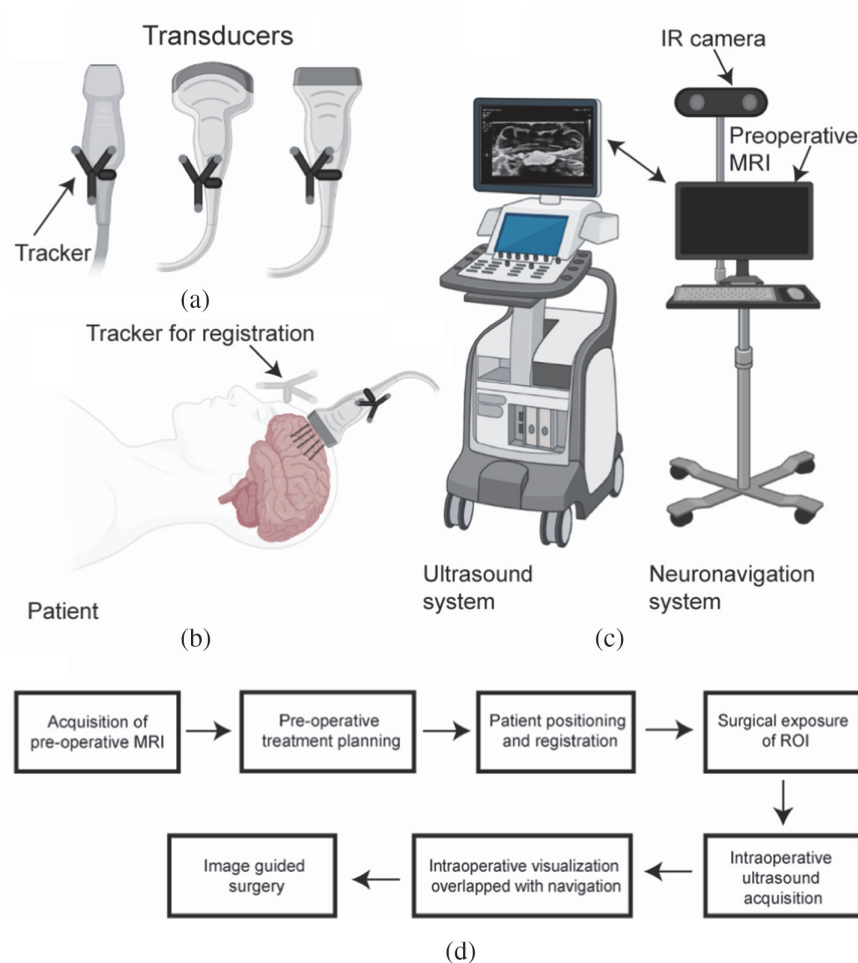
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- 5.1 Introduction
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  - 5.6.2 Lesion biopsy and catheter insertion
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- 5.7 Requirements for Implementing Intraoperative Ultrasound
  - 5.7.1 Impact of bone
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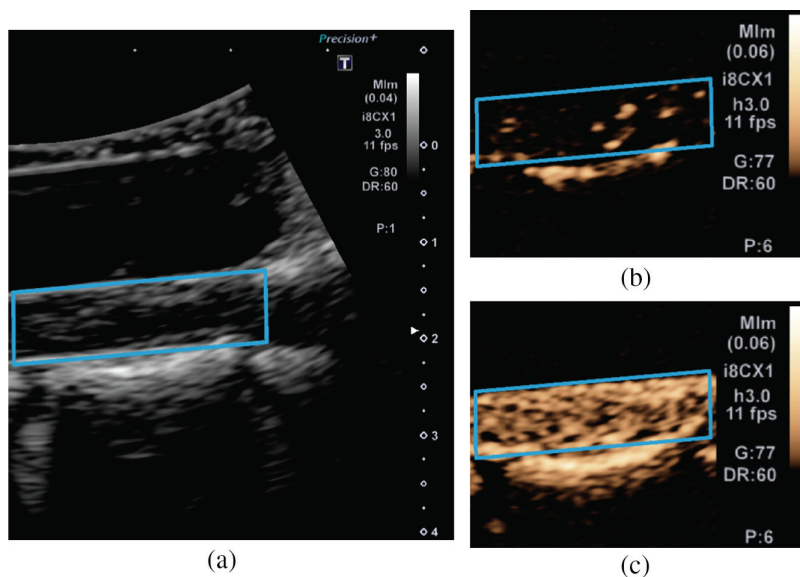
**Figure 5.1** Overview of the technique of intraoperative ultrasound and fusion imaging. (a) Phased, convex and linear array attached to a tracker allowing localization in navigation space. (b) The exposed dura of the patient registered to the pre-operative MRI is imaged using the desired probe. (c) Ultrasound imaging system showing a foreign body object along with a neuronavigational system and infrared (IR) camera that tracks the patient and probe location. (d) Flowchart depicting the technique of intraoperative ultrasound used with pre-operative MR imaging. (Illustration created with BioRender with permission.)

image transformations to create a link between the anatomical structures and the image data.<sup>12</sup> This process allows the surgeons to visualize the exact target location and plan the patient-specific surgical trajectory. Thus, neuronavigation follows a definite sequence of steps, starting with obtaining preoperative images, registration, intraoperative localization, fusion with the preoperative images, and visualization-guided surgery (Fig. 5.1).<sup>13</sup> While these systems can be initially time-consuming due to registration and calibration, surgical navigation is transforming the field of neurosurgery.<sup>13</sup>

### 6.3.3 Spinal cord injury

Spinal cord injury (SCI) is characterized by a secondary phase of inflammation, neurotoxicity, and ischemia following the initial mechanical damage. CEUS can play a role in the workup of SCI and determining severity by displaying in real-time a high-resolution topographical map of tissue hypoperfusion.<sup>25</sup> Most of this work has thus far been performed in rodent models.<sup>25</sup> Although ultrasound of the spinal cord is generally prevented by the bony elements of the spine, surgical laminectomy and decompression is a standard treatment of SCI, allowing for CEUS after removal of the laminae.<sup>25</sup> Khaing et al. illustrate in a rodent model that CEUS can be performed not only intraoperatively, but weeks after the initial laminectomy using a transcutaneous approach. Using this approach, they found that the area of local hypoperfusion had decreased over 10 weeks.<sup>26</sup> This finding indicates that CEUS can be used postoperatively for monitoring the response to injury.

Additionally, CEUS can be used to monitor spinal cord blood flow intraoperatively and ensure adequate perfusion during spine surgery. Figure 6.2 illustrates CEUS in a porcine model of SCI. Other groups including Yang et al. evaluated the use of CEUS for circumferential decompression for myelopathy resulting from ossification of the posterior longitudinal ligament, and found that CEUS can supplement intraoperative neuromonitoring to detect preservation of spinal cord function.<sup>27</sup>



**Figure 6.2** Sagittal cross-section of the porcine spinal cord with contrast microbubbles. The spinal cord region of interest is outlined in blue. (a) B-mode image prior to contrast injection. (b) CEUS image immediately after injection of contrast and (c) 17 s after contrast injection. The orange colormap depicts the location of contrast agents at a given time; within the spinal cord, contrast agents travel through the vasculature due to blood flow. The detection of contrast agents beyond the ROI box illustrates surrounding tissues. (The methods used to collect these images were approved by JHMI IACUC protocol SW20M221.)

# Chapter 9

## Other Emerging Novel Applications of Ultrasound in Neurosurgery: Ultrasound Computed Tomography, Thermometry, and Thermography; Intracranial Pressure Monitoring; and Artificial Intelligence

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  - 9.5.3 Surface segmentation
  - 9.5.4 Computer-aided diagnosis



accuracy of the neuronavigation.<sup>16</sup> This navigation is similar to those described in Chapter 5, but the use of USCT algorithms may improve registration accuracy compared with traditional ultrasound imaging. USCT is less applicable in the context of spine surgery because of the longitudinal shape of the spinal column.<sup>17</sup> However, intraoperative tools are starting to be developed that can more easily access spinal anatomy.<sup>17</sup> USCT methods of combing several slices of ultrasound may prove useful in improving the usability of the imaging for spinal surgery.<sup>17</sup>

### 9.3 Ultrasonic Thermometry and Thermography

Ultrasound thermometry is a method of non-invasively measuring the temperature of tissues based on changes to the SoS.<sup>3</sup> When the temperatures are being mapped over an image, the technique is called ultrasonic thermography.<sup>3</sup> The first ultrasound thermography method was published in 1998, and the practicality of ultrasound thermography has increased with modern GPU-enabled systems.<sup>18</sup> However, these early methods performed poorly in the presence of sharp lateral temperature gradients or significant tissue deformation.<sup>18</sup> Temperature measurements are highly sensitive to the tissue under consideration and are consequently inaccurate when the underlying tissue changes.<sup>18</sup> Today, better imaging of tissue deformation and modeling of the tissue interfaces has improved the accuracy of ultrasonic thermometry.<sup>18</sup> Most applications will have spatial and temporal resolutions on the order of millimeters and milliseconds, respectively.<sup>19</sup>

There are four principle methods for estimating temperature with ultrasound.<sup>19</sup> These techniques rely on changes to the SoS, so Miller et al. proposed a model for estimating the SoS in various tissues based on the temperature:<sup>19</sup>

$$\frac{1}{c(T)} = \frac{1}{c_w(T)} + \frac{1}{c_f(T)} + \frac{1}{c_r(T)}, \quad (9.1)$$

$$c_w(T) = \sum_{i=1}^5 k_w^i T^i, \quad c_f(T) = k_f^0 - k_f^1 T, \quad c_r(T) = k_r^0 - k_r^1 T, \quad (9.2)$$

where the subscripts “w,” “f,” and “r” represent water, fat, and residual material, respectively,  $c$  represents the SoS,  $T$  is the temperature, and  $k^i$  is a set of tissue-specific constants for fitting a polynomial. Equation (9.1) describes the overall SoS as the result of the waves passing through different material types in parallel. Equation (9.2) is an estimation of the SoS as a function of temperature, so the temperature could also be estimated from a SoS measurement. However, more-sophisticated techniques are based on the physical sequelae of the changing SoS.<sup>19</sup> One impact is that the mean resonant



# Chapter 10

## The Abundant Promise of Ultrasound in Neurosurgery: The Ethical Path to Claiming the Potentials

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- 10.1 Ethics of Ultrasound
  - 10.2 Safety Considerations
    - 10.2.1 Risk of harm and accuracy
    - 10.2.2 Ethics of consent (patient's voluntary choice)
    - 10.2.3 Undesirable outcomes
  - 10.3 Justice Considerations
  - 10.4 Conclusion: Past, Present, and Future
- References

### 10.1 Ethics of Ultrasound

Over the course of this book, I hope that we have managed to make the readers excited about the many potential applications of ultrasound, specifically within a relatively unexplored medical field, such as neurosurgery. In this final chapter, I would like to start the conversation on the ethical considerations of claiming such rich potentials. It goes without saying that little is known about both the risks and the benefits of therapeutic ultrasound applications relative to diagnostic tools, such as elastography or thermometry. Over several decades, the FDA has had the chance to develop a number of guidelines on how to safely obtain images of bodily organs—for example, keeping the thermal index (TI) and mechanical index (MI) beneath certain thresholds. Although therapeutic ultrasound has a great promise for

As a field, we have not conducted enough studies to understand whether focused ultrasound could have similar long-term implications. I understand that this statement may cause backlash within our community, and for the record, I personally have no technical reason to believe that it would. For example, the blood–brain barrier opening application of ultrasound, if done properly, is reversible and does not need to lead to stroke. I hope you noted that the statement “*if done properly*” is a high bar, which makes a number of assumptions. To draw a parallel example from another field, a surgeon who leaves behind a foreign body in a surgery knows how *not* to do it. And yet, it still happens. It could be due to fatigue, device-specific training, or many other factors. Such a scenario is statistically so rare in medicine that it is categorized as a *never-event*. Despite its rarity, when it happens, the consequences are devastating. The question presented here is: What are we doing as a field to make sure medical errors (or undesirable outcomes) are minimized when applying focused ultrasound treatment?

There are perhaps too many issues being addressed/run together here, namely: (1) Are there any theoretical concerns about personality changes here akin to with DBS? (2) What are the likely risks and how likely are they to occur? (3) Which of these risks would be from preventable surgeon mistakes and which are inherent? (4) What needs to be in place to reduce the likelihood of medical mistakes?

### 10.3 Justice Considerations

As mentioned previously, many millions of dollars must be spent on the necessary resources to set up MRI-guided focused ultrasound (MRgFUS) systems. As lucky as I have been in my career, and securing our multi-million DARPA funding at Hopkins, even our group cannot easily afford such a system. The extremely high price makes the system difficult to access, whether for patient care providers or for scientific researchers.

This inaccessibility prompts certain ethical questions: (1) Does the price of this system disproportionately help the affluent? In other words, does the cost of the system exacerbate the already-existing gap between patients from various backgrounds? (2) What is the pathway to fair scalability and wide access based on need, both nationally and globally? Of course, the global health aspects of such a question could be a whole book on its own, specifically as related to low-resource–setting healthcare systems. (3) Could such pricey treatments take away resources from other health interventions that offer far more bang for our buck, given the limited resources of all healthcare systems? Interestingly, the answers may lie in non-financial ethical considerations. For example, does ultrasound provide a path for a cure, or does it simply prolong an already-short life expectancy by a few weeks? If it is the latter, as may be the case for patients with glioblastoma multiforme brain