Photoacoustic imaging of a human vertebra: implications for guiding spinal fusion surgeries

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Keywords: spinal surgery, pedicle screw placement, image guided intervention, bone breaches, photoacoustic-guided spinal surgery, spinal fusions

Abstract
It is well known that there are structural differences between cortical and cancellous bone. However, spinal surgeons currently have no reliable method to non-invasively determine these differences in real-time when choosing the optimal starting point and trajectory to insert pedicle screws and avoid surgical complications associated with breached or weakened bone. This paper explores 3D photoacoustic imaging of a human vertebra to noninvasively differentiate cortical from cancellous bone for this surgical task. We observed that signals from the cortical bone tend to appear as compact, high-amplitude signals, while signals from the cancellous bone have lower amplitudes and are more diffuse. In addition, we discovered that the location of the light source for photoacoustic imaging is a critical parameter that can be adjusted to non-invasively determine the optimal entry point into the pedicle. Once inside the pedicle, statistically significant differences in the contrast and SNR of signals originating from the cancellous core of the pedicle (when compared to signals originating from the surrounding cortical bone) were obtained with laser energies of 0.23–2.08 mJ (p < 0.05). Similar quantitative differences were observed with an energy of 1.57 mJ at distances ≥6 mm from the cortical bone of the pedicle. These quantifiable differences between cortical and cancellous bone (when imaging with an ultrasound probe in direct contact with each bone type) can potentially be used to ensure an optimal trajectory during surgery. Our results are promising for the introduction and development of photoacoustic imaging systems to overcome a wide range of longstanding challenges with spinal surgeries, including challenges with the occurrence of bone breaches due to misplaced pedicle screws.

1. Introduction
Approximately 500,000 spinal fusion surgeries are performed annually in the United States (Rajaee et al 2012, Weiss and Elixhauser 2006) to alleviate pain or neurologic deficit or to repair damaged vertebrae within the spinal column. These spinal abnormalities can be caused by a trip or fall, degenerative changes, congenital deformities, or cancer that originates from or metastasizes to the spine (Faciszewski et al 1995, Manbachi et al 2014). During spinal fusion surgeries, the surgeon places screws through the pedicles of vertebrae in order to connect them with a metal rod and stabilize the spine to normal function. The pedicles are cylindrically shaped pieces of bone that connect the anterior vertebral body to the posterior aspect of the lamina and facet joint to create an arch of bone that protects the spinal cord. The outer region of the pedicle consists of cortical bone that surrounds a more porous cancellous core. Ideally, screws would be inserted in and follow this cancellous core into the vertebral body.

In order to make a pilot hole for the screw, the surgeon uses knowledge of the surrounding anatomy to locate a starting point, and then an awl, drill, or high speed burr is used to mark the starting point. A pedicle probe is then used to push through the pedicle to create the hole. These methods could lead to breaching of the bone on
any side of the pedicle because the trajectory cannot be accurately visualized by the surgeon. The pedicle wall is breached in 4%–12% of procedures (Lehman et al 2007, Samdani et al 2010), and this rate increases up to 29% for residents (Bergeson et al 2008). In addition to potential breaches, it is difficult to determine the optimal starting point without some initial drilling through bone, which further weakens the remaining bone for pedicle screw insertion, particularly if the initial position is incorrect and adjustments are required. Approximately 14%–39.8% of screws are misplaced during spinal fusion surgeries (Gertzbein and Robbins 1990, Castro et al 1996, Laine et al 1997, Abul-Kasim and Ohlin 2011), which can lead to postoperative neurological injuries, vascular injuries, blindness, or necessary reoperations (Deyo et al 1993, Bjärke et al 2002, Lee 2012).

To reduce the risk of complications related to pedicle screw misplacement, traditional navigation systems for spinal surgery use preoperative CT evaluation, which is critical when choosing the appropriate diameter, length, trajectory, and entry point for pedicle screws (Kretzer et al 2011). In the operating room, projection x-ray imaging (i.e. fluoroscopy) is currently used to non-invasively visualize the pedicle during insertion, but there are several limitations with fluoroscopy, namely the use of harmful ionizing radiation and the lack of depth information from projection x-rays. Ultrasound imaging is one alternative to intraoperative x-ray imaging (Goodwin 2003, Manbachi et al 2014), with advantages that include real-time imaging without requiring ionizing radiation. However, it is typically difficult to visualize ultrasound signals through bone, given the large acoustic impedance mismatch between bone and soft tissue and the strong dependence on the angle of incidence (Brendel et al 2002).

Photoacoustic imaging is a more promising option to overcome existing limitations with ultrasound imaging, and it generally works by transmitting light and listening for sound. The absorption of light causes thermal expansion, which then generates a sound wave that can be detected with conventional ultrasound probes (Xu and Wang 2006, Beard 2011, Bouchard et al 2014). The use of photoacoustic imaging to guide surgeries has previously been explored for neurosurgeries (Bell et al 2014b, 2015b), hysterectomies (Allard et al 2018), fetal surgeries (Xia et al 2017), and teleoperated surgeries that are performed with a da Vinci robot (Gandhi et al 2017, Allard et al 2018). Similar approaches have also been demonstrated to guide the placement of brachytherapy seeds for treating prostate cancer (Su et al 2011, Kuo et al 2012, Bell et al 2014a). In addition, custom light delivery systems have been designed and demonstrated for several of these applications including transurethral light delivery (Bell et al 2015a, Ai et al 2018), interstitial light delivery (Bell et al 2013, 2014a, Mitcham et al 2015), and light delivery systems that surround surgical tools (Eddins and Bell 2017, Allard et al 2018). It is also possible to track surgical tool tips in photoacoustic images using robotic visual servoing methods (Shubert and Bell 2017).

In the more specific context of bone imaging, photoacoustic imaging has demonstrated potential to non-invasively diagnose different types of bones, including cancerous bones (Thella et al 2016). In addition, photoacoustic technology previously proved to be sensitive to minor variations of the cortical bone density (Lashkari and Mandelis 2014). Quantitative photoacoustics was additionally used to determine bone mineral density and bone composition differences (Feng et al 2015, He et al 2017), which could be useful for avoiding pedicle breaches, as well as for determining the starting point prior to drilling or pedicle probe insertions. However, to the authors’ knowledge, photoacoustic images of the pedicles in a human vertebra have never been demonstrated, and therefore, a clinically viable photoacoustic imaging approach to guide spinal fusion surgeries has never been explored.

This paper explores the feasibility of using photoacoustic imaging to uncover expected differences between cortical and cancellous bone for the potential guidance of spinal fusion surgery. To deploy a viable clinical system, an optical fiber that delivers laser light could either be isolated from or attached to the surgical tool (e.g. a drill, burr, pedicle probe, or awl). A standard clinical ultrasound probe would then be placed with acoustic coupling gel on the vertebra of interest. The purpose of this ultrasound probe is to receive the acoustic response generated by optical absorption within the blood-rich cancellous core. This is a reasonable expectation because the optical absorption of blood is orders of magnitude higher than that of bone, and the sound is only required to travel once through the 244 μm to 1.75 mm-thick cortical bone layer (Ritzel et al 1997, Edwards et al 2001, Defino and Vendrame 2007), rather than the two-way acoustic propagation that is required for ultrasound imaging. This system also has the additional benefits of producing real-time image guidance information without requiring harmful ionizing radiation.

2. Materials and methods

2.1. Study design

We initiated our study with the overall goal of investigating four research questions:

(i) Can we distinguish cortical from cancellous bone with 3D photoacoustic imaging?
(ii) Can we visualize the boundaries of the pedicle with 3D photoacoustic imaging?
(iii) Can we use photoacoustic imaging to determine the optimal entry point for screw insertion into the pedicle?
(iv) Can we use photoacoustic imaging to determine optimal drill paths?
A fresh human spinal column from Anatomy Gifts Registry (Hanover, MD) was cut to isolate one lumbar vertebra in order to investigate these four questions and ultimately determine the feasibility of photoacoustic-guided spinal fusion surgeries. Feasibility was assessed with regard to sufficient optical and acoustic penetration through the fresh human lumbar vertebra specimen to generate photoacoustic signals. We also investigated the visualization of bone boundaries with 3D photoacoustic imaging, the spatial resolution with which we can distinguish the cortical from cancellous bone using photoacoustic imaging once inside the pedicle, and the required energy to make this distinction.

The expected benefit of photoacoustic imaging over ultrasound imaging is that light can penetrate the surface cortical bone to produce acoustic signals beyond the 244 μm to 1.75 mm-thick (Ritzel et al 1997, Edwards et al 2001, Defino and Vendrame 2007) cortical bone interface surrounding the pedicle (which indicates potential to produce photoacoustic signals within the pedicle). Ultrasound imaging is known to suffer from challenges with sound penetration, which generally impedes imaging at depths below the first cortical bone interface encountered when the ultrasound probe is placed in a clinically realistic position on a patient’s back (Brendel et al 2002). The acoustic impedance of ultrasound signals beyond the first cortical layer creates acoustic shadowing artifacts (which cause the ultrasound image to appear black after encountering the first cortical bone interface).

2.2. Imaging systems
We combined information obtained from ultrasound, photoacoustic, and CT imaging systems to investigate the feasibility of photoacoustic-guided spinal fusion surgeries. The ultrasound imaging system was an E-CUBE 12R ultrasound scanner (Alpinion Medical Systems, Seoul, Korea) connected to one of two ultrasound probes. The first ultrasound probe was an Alpinion L3-8 linear array with a bandwidth of 3–8 MHz. The second ultrasound probe was an Alpinion SP1-5 phased array with a bandwidth of 1–5 MHz. The photoacoustic imaging system consisted of the ultrasound system described above, synchronized with a Phocus mobile laser (Opotek, Carlsbad, California, U.S.A.). The laser light was delivered through a 1 mm core diameter optical fiber that was coupled to the laser with a custom adapter. The laser wavelength was 750 nm. Unless otherwise noted, the laser energy exiting the fiber was 1.57 mJ (200 mJ cm$^{-2}$ laser fluence). The CT scanner was a Siemens Arcadis Orbic 3D (Munich, Germany). The CT image resolution after reconstruction was approximately $0.5 \times 0.5 \times 0.5$ mm$^3$.

2.3. 3D image comparisons
The goal of the first experiment was to make 3D reconstructions of ultrasound, photoacoustic, and CT images of the pedicle within the vertebra sample. To avoid known challenges with acoustic shadowing and enable the acquisition of meaningful reference ultrasound images, these ultrasound images were acquired with the vertebra laying flat, and the ultrasound probe was scanned across the pedicle in the direction shown in figure 1. This orientation also enabled us to image the entire pedicle with the best ultrasound and photoacoustic resolution in the direction of the circular cross section of the pedicle. The better resolution with this probe orientation is expected because ultrasound and photoacoustic images are known to have better resolution in the axial (i.e. image depth) dimension when compared to that of the lateral dimension.

The ultrasound probe was attached to a Sawyer robot (Rethink Robotics, Boston, MA), which was programmed to translate in 1 mm increments in the scan direction shown in figure 1. Ultrasound and photoacoustic images were acquired with each increment of the ultrasound probe. The optical fiber was fixed in place until the completion of all translations. Figure 1 shows an example of the placement of the optical fiber relative to the vertebra sample. This experiment was performed with three ‘bad’ orientations and three ‘good’ orientations of the optical fiber, where examples of bad and good orientations of the optical fiber relative to the pedicle of the vertebra are shown in figure 2.

2.4. Experiments with clinically realistic probe positions
Our second experiment was designed to determine if it was possible to achieve the same results with the ultrasound probe in a more realistic orientation for clinical imaging, where the probe was moved adjacent to the optical fiber. This orientation represents a surgeon placing both the ultrasound probe and the optical fiber on a patient’s back to noninvasively examine the starting point for drilling. These experiments were performed with both the linear array and the phased array ultrasound probes. For the linear array probe, the optical fiber was moved to the three good and three bad orientations shown in figure 2, and the ultrasound probe remained stationary for all acquisitions during this experiment. Similarly, for the phased array probe, the optical fiber was moved to four good and four bad orientations while the ultrasound probe remained stationary.

2.5. Determining laser energy requirements
The goal of the third experiment was to determine the laser energy required to observe quantitative differences between the cortical and cancellous regions once a surgeon enters the pedicle. This detail would be important to deliver information to the surgeon in a quantitative format rather than relying on the visualization and
interpretation of photoacoustic images to determine these differences. The fiber was fixed to the phased array ultrasound probe with tape, and this probe-fiber pair was placed over either the cancellous or cortical region of an exposed pedicle with the specimen and probe relationship being similar to that shown in figure 1. This probe location was used instead of the clinically realistic probe location because it enables us to directly associate photoacoustic signals with either cortical or cancellous bone, and it represents signals that can be obtained after a surgeon enters the vertebra. The laser energy was varied over the range 0.12–2.72 mJ, which corresponded to 15–345 mJ cm$^{-2}$ laser fluence.

The photoacoustic signal contrast and signal-to-noise ratio (SNR) was computed for each image according to the following equations:

\[
\text{Contrast} = 20 \log_{10} \left( \frac{\mu_i}{\mu_o} \right) \tag{1}
\]

\[
\text{SNR} = \frac{\mu_i}{\sigma_o} \tag{2}
\]

Figure 1. Setup for acquiring 3D ultrasound and photoacoustic image volumes. The placement of the optical fiber produced the bad photoacoustic images shown in figures 3 and 5. With the exception of the fiber location, this same setup was used to acquire the good and bad photoacoustic images in movies S1–S3 (stacks.iop.org/PMB/63/144001/mmedia).

Figure 2. Examples of bad (top) and good (bottom) fiber orientations. The good orientations correspond with the optimal entry point into the pedicle for spinal fusion surgeries. The specific arrow placement indicates the location of the fiber for each of the six photoacoustic images shown in figure 7, and the first two positions in each row were intentionally duplicated after manually removing and replacing the optical fiber.
where $\mu_i$ and $\sigma_o$ are the mean and standard deviation of signals within a region of interest (ROI) in the photoacoustic image (centered at an axial depth of 1 cm and a lateral position associated with the brightest point in the image), and $\mu_s$ is the mean of the signals within a ROI associated with the noise floor of the photoacoustic image (centered at a depth of 3 cm and a lateral position associated with the brightest point in the image). The ROI associated with the noise floor was deeper than the 2 cm-thick vertebra specimen (measured in the axial direction of the ultrasound probe shown in figure 1). The size of each ROI was $0.8 \text{ cm} \times 0.8 \text{ cm}$.

At each energy level, a paired sample t-test was performed to determine statistically significant differences between the 15 contrast measurements from the cortical bone and the 15 contrast measurements from the cancellous bone. This process was repeated for the 15 SNR measurements per bone region per energy level. All data analysis was performed with MATLAB software (MathWorks, Natick, MA).

2.6. Determining warning distance limit for potential cortical bone breach

In the fourth experiment, we investigated the distance from the cortical bone where differences in contrast and SNR measurements could be detected once a surgeon enters the pedicle. The specimen and probe relationship was similar to that shown in figure 1. This probe location was used instead of the clinically realistic probe location because it provides more confidence of the exact region being imaged and it represents signals that can be obtained after a surgeon enters the vertebra.

The fiber remained fixed to the phased array ultrasound probe with tape, and this probe-fiber pair was placed in a starting position on one side of the exposed pedicle. The probe was then translated in 2 mm increments (which was verified using calipers), and photoacoustic images were acquired with each probe-fiber placement. The laser energy was held constant at 1.57 mJ, which corresponds to 200 mJ cm$^{-2}$ laser fluence. Contrast and SNR (equations (1) and (2), respectively) were measured for each photoacoustic image, using the same ROIs described in section 2.5.

3. Results

3.1. Comparison of co-registered photoacoustic, ultrasound, and CT images

Figure 3(A) shows a picture of a human lumbar vertebra with labels highlighting key anatomical landmarks that are referenced throughout this paper. Figure 3(B) shows a superior-inferior (SI) slice of a CT image of the ex vivo human vertebra sample. The white box indicates the region of the vertebra that was scanned to create 3D ultrasound and photoacoustic images. This region encompassed the pedicle, the transverse process and the superior articular process. To create 3D ultrasound and photoacoustic images, the vertebra was exposed and the robot-controlled ultrasound probe was placed to scan across the pedicle, from the vertebral body to the superior articular process, as indicated in figure 1. The photoacoustic and ultrasound images were inherently co-registered to each other, and the CT images were rotated by $-40^\circ$ for visual registration with the ultrasound and photoacoustic volumes, as shown for two SI plane locations in figures 3(C) and (D).

Figure 3(C) shows triplanar views of the co-registered photoacoustic, ultrasound, and CT images, from left to right, respectively. The ultrasound and photoacoustic images were acquired while the optical fiber was placed near the superior articular facet, above the pedicle, and fixed in place throughout the 3D scan. Figure 3(C) shows that the cortical bone surrounding the pedicle appears as a bright region.

Figure 3(D) shows triplanar views of the co-registered images with the SI plane moved closer into the pedicle. Comparison of figures 3(C) and (D) indicates that the cancellous core of the pedicle appears as lower-amplitude, more diffuse signals in the photoacoustic image. Videos for all ultrasound and photoacoustic axial planes and all CT SI planes are available as supplementary material (movies S1 and S2).

To provide additional confirmation that photoacoustic signals are detected in both the cortical and cancellous bone, figure 4 shows lateral-elevation slices of the photoacoustic images shown in figures 3(B) and (C) overlaid on corresponding ultrasound image slices. This alternative display format demonstrates that the photoacoustic signals shown in figure 3(B) are associated with the surface cortical bone while the photoacoustic signals shown in figure 3(C) are primarily associated with the deeper cancellous region of the pedicle, which is the region of interest when inserting pedicle screws in spinal fusion surgeries.

3.2. Fiber position affects bone visualization

Figure 5 shows co-registered photoacoustic, ultrasound, and CT images as triplanar slices. The main difference between the two photoacoustic images in figure 5 is the location of the optical fiber during image acquisition. In both locations, the fiber is touching the cortical bone near the superior articular facet, but it is not located directly above the pedicle in the ‘bad’ orientation, which represents a nonideal entry point into the pedicle for screw insertions during spinal fusion surgeries. In this bad orientation, it is difficult to see the cancellous core of the pedicle in the photoacoustic image. When the fiber is moved to the ‘good’, more optimal location directly above the cancellous core, figure 5 shows that deeper photoacoustic signals from within the cancellous core are more
visible. These signals likely originate from fresh blood within the cancellous core of the vertebra sample. A video of this result for all ultrasound and photoacoustic axial planes and all CT SI planes is available as supplementary material (movie S3).

To provide additional confirmation that the location of detected photoacoustic signals varies with fiber placement, figure 6 shows the lateral-elevation slices of the photoacoustic images in figure 5 overlaid on the corresponding ultrasound image slice in figure 5. This alternative display format demonstrates that the position of the optical fiber delivering the light causes visualization of different regions of the vertebra specimen in the photoacoustic images. The cortical bone is visualized in the photoacoustic image when the fiber is placed in the nonideal location. When the fiber is placed in a more ideal location that is directly above and pointing toward the pedicle, the signals at depths as deep as 3 cm from the top bone surface in figure 6 to appear to be associated with the cancellous region of the pedicle.

Figure 3. (A) Diagram of the human vertebra, labeled with several key anatomical landmarks. The optical fiber was placed near the superior articular facet for photoacoustic imaging. (B) Superior–inferior (SI) slice of a CT image of the fresh cadaveric human vertebra that was imaged in our experiments. (C) Triplanar views of the co-registered photoacoustic (left), ultrasound (center) and CT images (right). (D) Triplanar views with a SI slice that intersects the pedicle. The orange and blue arrows indicate signals associated with the cortical bone and cancellous core of the pedicle, respectively, in photoacoustic, ultrasound, and CT images. Videos for all ultrasound and photoacoustic axial planes and all CT SI planes are available as supplementary material (movies S1 and S2).

Figure 4. Lateral-elevation slices of the photoacoustic images shown in figures 3(C) and (D) overlaid on corresponding ultrasound image slices provide an alternative display format to demonstrate the source of the photoacoustic signals in the cortical and cancellous regions of the vertebra specimen, respectively. The photoacoustic images were normalized to the brightest signal in the 3D volume and displayed on an amplitude scale ranging from 0 to 1.
3.3. Results with clinically realistic probe position

The images in figures 3–6 were acquired with the ultrasound probe placed directly on top of the exposed vertebra, which is useful for characterizing the photoacoustic signals with sufficient resolution, but is not a realistic position for clinical imaging. The ultrasound probe was moved to a more clinically realistic position for determining the ideal entry point into the pedicle, as shown in figure 7(A). In this position, the probe is hovering over the superior articular facet and the optical fiber is placed next to the probe.

Figure 7(B) shows several images with the fiber in the bad orientation, which is defined above. In all cases, the signal from the deeper cancellous core is not visible. We saw signals from the cancellous core region with the fiber located more directly above the cancellous core (i.e. good fiber orientation), as demonstrated in figure 7(C). These signals were observed as deep as 3 cm from the surface of the ultrasound probe. Note that ultrasound gel was placed between the vertebra and ultrasound probe, which resulted in a gap of approximately 5 mm between the top of the images in figure 7 and the start of the specimen surface.

The first two fiber positions indicated in the first and second row of figure 2 were similarly placed to assess the consistency of our results, and the order of these fiber positions correspond to the order of the results shown in
Overall, there are subtle differences in the photoacoustic images in figure 7 achieved with either all of the good cases or all of the bad cases. In particular, the first two images in figure 7(B) are similar to each other, and the first two images in figure 7(C) are similar to each other. Thus, there is a qualitatively similar signal appearance for the intentionally repeated manual fiber placement locations shown in figure 2. The third image in each case is less similar to the first two images in each case, which is consistent with the dissimilarity in the manually placed fiber positions shown in figure 2. In all cases, deeper signals were obtained with the fiber position that corresponds with an ideal entry point into the pedicle.

Figure 8 demonstrates that our results are repeatable with a lower resolution, phased array ultrasound probe (see figure 8(A)), rather than the linear array ultrasound probe used to obtain the results in figures 3–7. When the fiber is in the bad orientation (figure 8(B)), the signal from the cancellous core is not visible. Similar to the results in figure 7(C), additional signals from the cancellous core region are observed with the fiber located more directly above the cancellous core, as shown in figure 8(C). These signals are observed as deep as 5 cm from the probe surface, which is deeper than the 3 cm observed with the linear array, likely because the phased array ultrasound probe is sensitive to lower acoustic frequencies (which are known to have deeper penetration depths when imaging through bone).

3.4. Quantification of observed signals

Contrast and SNR were measured to demonstrate that the deeper signals observed at depths as large as 3 cm produce quantifiably different results when the fiber is located within the cortical region compared to the cancellous region. Therefore, these measurements were obtained at the same image depth with the phased array probe placed next to the optical fiber and on top of the annotated dots in figure 9(A), which denote the interrogated cortical and cancellous regions in the exposed vertebra. Figure 9(B) shows example photoacoustic images and corresponding ROIs for contrast and SNR measurements.

Figure 9(C) shows the contrast and SNR results obtained as energy was increased (i.e. the fluence incident on the vertebra ranged from 15 mJ cm\(^{-2}\) to 345 mJ cm\(^{-2}\)). The mean contrast difference between the photoacoustic signals from the cortical and cancellous bone at a laser fluence of 200 mJ cm\(^{-2}\) is 2.4 dB, and the corresponding mean SNR difference is 2.1. These quantitative results confirm our observations in figures 3–6, which were acquired with 200 mJ cm\(^{-2}\) fluence and show consistent signal differences when imaging the cortical and cancellous bone.
cancellous regions of the human vertebra sample. Statistically significant differences in both contrast and SNR measurements were obtained with fluence values of $29.8-264 \text{ mJ cm}^{-2}$, which correspond to energies of $0.23-2.08 \text{ mJ}$ ($p < 0.05$). This range of energy levels is consistent with our ability to observe qualitative differences in the signals from cortical and cancellous bone, with the exception that we also observed differences at the highest energy level (i.e. $2.72 \text{ mJ}$, which corresponds to $346 \text{ mJ cm}^{-2}$ fluence).

In addition to fixing the cortical and cancellous region locations when measuring contrast and SNR, these metrics were calculated as the fiber-probe pair was translated from the cortical to the cancellous region in the scan direction shown in figure 10(A) to provide an assessment of possible expectations once the ultrasound receivers are modified to accommodate insertion into a pedicle. Contrast and SNR are displayed as a function of distance in figures 10(B) and (C), respectively. At $0-10 \text{ mm}$ from the starting point of the scan direction, the probe-fiber pair was touching the exposed cortical bone. At $12-26 \text{ mm}$ from the starting point of the scan direction, the probe-fiber pair was touching the cancellous region. The mean contrast and SNR difference between the photoacoustic signal at a distance of $16 \text{ mm}$ from the starting point of the scan direction (i.e. approximately
6 mm from the inner edge cortical bone along the scan direction) and that at position 4 mm (i.e. the first positive contrast position) is 2.7 dB and 1.6, respectively, which is similar to the differences measured at the 200 mJ cm$^{-2}$ fluence level in figure 9. Therefore, this result provides some indication of the distance with which photoacoustic signal differences can be detected to avoid bone breaches once the surgeon is inside the pedicle.

4. Discussion

We demonstrated that it is possible to use photoacoustic imaging to distinguish cortical from cancellous bone without drilling or otherwise disrupting the pedicle, which provides evidence for the clinical potential to generate signals from the cancellous core of the pedicle before any surface cortical bone is removed. This evidence is significant because spinal surgeons can now consider photoacoustic imaging as a potential option to noninvasively determine the starting point for drilling or cannulating a pedicle, based solely on changes in photoacoustic signal appearance and fiber location.

After using photoacoustic imaging to determine the starting point, the results in figures 9 and 10 indicate that a smaller probe-fiber pair that fits inside a pre-drilled hole may additionally be used as a real-time indicator of the optimal drill or pedicle probe trajectory. A smaller probe was previously used to transmit and receive ultrasound signals for guiding spinal fusions (Manbachi et al 2014), which indicates that a similar photoacoustic device is clinically feasible with the addition of an optical fiber. Although the presented configuration is similar to one that would be used in practice (with the exception that fewer piezoelectric elements would be needed to provide a smaller overall footprint), the signal detection sensitivity will likely differ due to differences in overall receiver sensitivity. Despite expected system sensitivity differences, the general trends are expected to remain the same (i.e. there will be a quantifiable transition from cortical to cancellous regions to assist with the detection of possible bone breaches with sufficient distance to correct for this error in real-time before it occurs). Thus, the analysis presented in figures 9 and 10 provide an example of the type of contrast and SNR measurements that can be performed to achieve quantitative differences with other photoacoustic imaging system configurations.

In figure 9, laser fluence values of 29.8–264 mJ cm$^{-2}$ are sufficient to quantify observed differences using the contrast and SNR metrics. At a fluence level of 200 mJ cm$^{-2}$, figure 10 shows that differences in contrast and SNR can be obtained within 6 mm from the cortical bone (i.e. at a position of 16 mm on the plots in figure 10). Therefore, photoacoustic imaging can potentially be used to issue a warning that will prevent bone breaches when surgeons are as close as 6 mm to the cortical bone boundary of a pedicle when using a 750 nm laser operating at a fluence of 200 mJ cm$^{-2}$ (i.e. 1.57 mJ energy). We discuss the safety implications of this result toward the end of this section.

We hypothesize that the signals observed within the cancellous region of the fresh bone specimen are associated with fresh blood within the cancellous core of the pedicle. Interference from blood outside of the bone is not expected to limit the light that will be delivered to the cancellous region when an optical fiber is in direct contact with the bone surface because the bone surface is typically exposed during surgery. Thus, direct contact between bone and an optical fiber is expected to be feasible.

One limitation of our results is that the 3D ultrasound and photoacoustic images were not acquired with the ultrasound probe in an orientation that would be suitable for clinical translation (i.e. compare figures 7 and 8 with figure 1). However, this limitation is a benefit for the initial experiment that characterized qualitative differences between cortical and cancellous bone in 3D photoacoustic images, because this probe orientation optimized the image resolution in the dimension of interest (i.e. the cross-section of the pedicle) for comparison with the 3D CT images and enabled us to determine that it is difficult to demarcate pedicle boundaries with pho-
toacoustic imaging alone (which was one of our initial questions, as noted in section 2.1). We confirm in figures 7 and 8 that a more clinically realistic probe orientation is capable of making the same qualitative distinctions observed in the 3D images.

With regard to the safety of the proposed photoacoustic imaging technology, the laser fluence required to obtain quantifiable, statistically significant differences between cortical and cancellous bone in these studies (i.e. 29.8–264 mJ cm$^{-2}$) exceeds the current laser safety limit of 25.6 mJ cm$^{-2}$ (ANSI 2014) when imaging through skin with a 750 nm laser. However, the safety limit for bone, which has significantly different optical and thermal properties than those of skin, is currently undefined. Our future work includes more research into laser safety limits when imaging through and within bone.

Our future work also includes an exploration of a novel drill design to integrate photoacoustic imaging in a form factor that is already familiar to surgeons (Shubert and Bell 2018), although the development of this new drill design is not a requirement for implementing the proposed photoacoustic imaging approach. The minimum equipment requirements for photoacoustic-based technology to guide spinal fusion surgeries are a light source (delivered through one or more optical fibers) and acoustic receivers. There are multiple design possibilities when combining these two essential components to achieve the desired result. For example, an optical fiber could stand alone, be adhered to, or be inserted within the burr, drill, or awl that is typically used to cannulate the pedicle. If a drill is used, then the drill bit and drill can contain a hollow core to accommodate an optical fiber, and a stationary optical fiber can be air-coupled to a concentric and aligned rotating fiber inserted within the core of the drill bit. This specific prototype was previously designed and tested to demonstrate the first known detection of photoacoustic signals within the pedicle, which originated from a custom 3D printed drill bit inserted into a pre-drilled hole in the pedicle (Shubert and Bell 2018).

Additional next steps needed for these findings to be applied in the clinic include testing the approach on an intact spinal column and developing a device that will transmit information to the surgeon in multiple display formats. One example of an alternative format is an internal circuit board that converts contrast and SNR measurements into lights that change colors and/or blink to issue warnings to stop and adjust the trajectory, to alert surgeons that it is safe to continue, or to indicate proceed with caution when too close to the cortical boundary. This device would enable the surgeon to focus on the surgical field at all times and eliminate the requirement to divert attention to images on an external monitor when receiving information about the optimal starting point or the proximity to the cortical bone. This approach may also be combined with commercial robotic systems (Bourgeois et al 2015, Overley et al 2017, Fan et al 2017, Theodore and Ahmed 2018) to plan real-time trajectories for pedicle screw insertion.

5. Conclusion

This work is the first to demonstrate that 3D photoacoustic imaging can be used to noninvasively elucidate differences between cortical and cancellous bone, which has promising benefits for guiding spinal fusion surgeries. We explored the use of 3D photoacoustic imaging of a human vertebra sample to noninvasively differentiate cortical from cancellous bone for this surgical task. Although we were unable to explicitly delineate pedicle boundaries as we initially set out to explore, we found that signals from the cortical bone appeared as compact, high-amplitude signals, while signals from the cancellous bone had lower amplitudes and were more diffuse, particularly at deeper depths (i.e. 3–5 cm) within the image. In addition, we discovered that the location of the light source for photoacoustic imaging is a critical parameter that can be adjusted to assist with distinguishing cortical from cancellous bone within the pedicle when the ultrasound probe location remains unchanged. This finding can be used to noninvasively determine the optimal entry point into the pedicle. Once inside the pedicle, differences in the contrast and SNR of signals originating from the cancellous core of the pedicle (when compared to signals originating from the surrounding cortical bone) were obtained with a laser energy of 1.57 mJ (which correspond to a laser fluence of 200 mJ cm$^{-2}$ for our 1 mm core diameter fiber), at distances $\geq$6 mm from the cortical bone of the pedicle. This result can potentially be used to ensure an optimal trajectory during surgery. This initial work is generally promising for the introduction and development of photoacoustic imaging systems to overcome a wide range of longstanding challenges with spinal surgeries, including challenges with the occurrence of bone breaches due to misplaced pedicle screws.

Acknowledgments

The authors thank Mark Goodwin and Omar Mehdi for preparing the vertebra sample and Gerhard Kleinzig and Sebastian Vogt from Siemens Healthineers for making a Siemens ARCADIS Orbic 3D available. This work was funded by a sponsored research agreement with Cutting Edge Surgical, Inc, with partial support from NSF CAREER Award ECCS 1751522 and NIH R00 EB018994.
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