Research article

Photoacoustic-guided focused ultrasound (PAFUSion) for identifying reflection artifacts in photoacoustic imaging

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ABSTRACT

Influence of acoustic inhomogeneities and resulting reflection artifacts is an important problem in reflection-mode photoacoustic imaging. Absorption of light by skin and superficial optical absorbers will generate photoacoustic transients, which traverse into the tissue and get reflected from structures having different acoustic impedance. These reflected photoacoustic signals, when reconstructed, may appear in the region of interest, which causes difficulties in image interpretation. We propose a novel method to identify and potentially eliminate reflection artifacts in photoacoustic images using photoacoustic-guided focused ultrasound [PAFUSion]. Our method uses focused ultrasound pulses to mimic the wave field produced by photoacoustic sources and thus provides a way to identify reflection artifacts in clinical combined photoacoustic and pulse-echo ultrasound. Simulation and phantom results are presented to demonstrate the validity and impact of this method. Results show that PAFUSion can identify reflections in photoacoustic images and thus envisages potential for improving photoacoustic imaging of acoustically inhomogeneous tissue.

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1. Introduction

Photoacoustic (PA) imaging is a promising biomedical imaging modality that has emerged over the last decade. In PA imaging, pulsed light absorbed by the target emits thermo-elastically generated ultrasound (US). This data can be detected using US probes allowing the reconstruction of location and spatial details of the light-absorbing target [1,2]. PA imaging thus combines the advantages of US and optical imaging, providing excellent optical contrast with ultrasonic resolution. While US imaging makes use of acoustic scattering and reflection in tissue to provide structural details, PA imaging extracts functional information based on optical absorption by tissue chromophores such as blood. Since PA imaging involves US detection, it can be realized in a commercially available US scanner to perform dual mode PA/US imaging [3–5]. These dual mode systems preferably utilize a scheme in which tissue is irradiated from the same side where PA signals are detected (reflection-mode, epi-mode PA imaging) [6]. This mode in which optical components and US transducers are combined, aids the clinician to perform single hand guidance of the probe during imaging. In addition, epi-illumination mode facilitates the imaging of body parts where bones or acoustically attenuating soft tissue would obstruct propagation of acoustic waves from the illuminated tissue region to the acoustic probe.

In many of the reported handheld probe-based PA/US systems, light illumination for PA imaging is done at an oblique angle in such a way that it coincides with the US imaging plane [3–5] with the goal to maximize fluence and thus signal-to-noise ratio. On the downside this results in a high light fluence on the surface of the tissue just beneath the US probe, such that melanin and superficial blood vessels generate strong PA transients which propagate into the tissue and reflect back from acoustically dense structures [7–9]. These reflected signals appear as artifacts in the reconstructed PA images. The reflection artifacts significantly reduce the contrast, and thus the imaging depth, which is critical [7,8]. Since these artifacts are triggered by the properties of the tissue, simple signal averaging is not effective for reducing them. Because of the strong optical attenuation in tissue [1], reflection artifacts that show up in a certain depth can become stronger than the PA signals of interest in spite of the low level of acoustic scattering [10], which can limit the imaging depth. As an example, when imaging structures like finger joints (multiple light absorbers and acoustic reflectors), signals of interest may get mixed with the reflections from bone or tendon, which results in the wrong interpretation of images. To
achieve clinically relevant PA imaging depth, it is vital to develop methods for eliminating reflection artifacts. Another key reason for limited PA imaging depth is the clutter caused by PA sources outside the imaging plane. These sources may produce high PA transients that could reach the imaging probe directly (direct clutter) or could get reflected on structures inside the imaging plane (echo clutter). PAFUSion deals with identifying reflections caused by PA sources within the imaging plane.

Different techniques have been reported to reduce clutter in PA imaging [7,8,10–13]. Deformation Compensated Averaging (DCA) [8] employs the artifact decorrelation, which is the result of tissue deformation when tissue is slightly palpated with the imaging probe. Although this technique showed promising results, notable disadvantages have been reported: 1) controlled probe motion can be performed only by an experienced person and this technique can be employed only for easily deformable tissue, and 2) the maximum achievable tissue deformation on one side limited by the tissue mechanical properties, and the minimum deformation required for artifact decorrelation on the other side, determines the contrast improvement. Another technique employs localized vibration tagging [LOVIT] of tissue using acoustic radiation force [ARF] for reducing clutter in the focal region of a long-pulsed ultrasonic beam [7]. While claiming nearly full artifact elimination, authors also reported the difficulty in eliminating echo clutter completely using LOVIT. For successful echo clutter reduction, LOVIT prefers a small ARF displacement region, which sets a limitation to the real-time capability because extensive scanning is then required to achieve clutter reduction in a large field-of-view. This method also requires transducers that are capable of transmitting ARF pulses and is limited by the US safety regulations.

In this paper, we investigate a novel method that can identify and potentially eliminate reflection artifacts in PA images. We specifically aim at reducing the reflection artifacts caused by PA sources within the imaging plane. Our technique ultrasonically simulates the PA signal from an optical absorber and uncovers PA signal reflections caused by acoustic reflectors beneath or around the absorber. The described method does not require any additional transducers or computationally intense algorithm to identify reflection artifacts, thus foresees good potential in improving real-time clinical PA imaging. Compared to LOVIT, our method works with low ultrasound power and thus does not pose any risks in clinical application. Because the focused pulse-echo acquisitions in PAFUSion can be performed at a much higher frame rate than PA imaging, it holds potential to be fast and real-time capable. Compared to DCA, it is not limited by tissue deformability and can thus even be used when e.g. imaging close to bone as in finger joint imaging. PA sources located outside the imaging plane are not directly observable and thus are not amenable to PAFUSion. Therefore, PAFUSion specifically targets at identifying and potentially reducing the reflection artifacts in a situation where tissue is irradiated as close as possible to the imaging plane with the goal to optimize signal-to-noise ratio, where out-of-plane clutter plays an inferior role.

The main goal of this paper is to present the first simulations and experimental results as a proof-of-principle of ‘PAFUSion’.

2. Theory

Fig. 1a illustrates the generation of a PA signal from an optical absorber, and the resulting PA reflection signal caused by an acoustic reflector deeper inside the tissue. In PAFUSion (Fig. 1b), we transmit a focused US pulse, with the focal position adjusted to the location of the optical absorber by using guidance of PA data. The focused US pulse, at the time of arrival in the focal position, mimics the part of the PA wave that was traversing towards the reflector. Under the assumption that signal acquisition starts at the time when the focused US pulse arrives at the PA source (t = 0), the resulting signal will show the US reflections at the same time where they show up in the PA signal. When reconstructing a PA image from the US data, it will thus mimic the reflection artifacts in terms of shape and depth without containing the real PA signal itself.

Thus, instead of identifying reflectors, which would be done with normal US imaging, with PAFUSion we identify PA signal reflections, which then can be used to correct PA images for reflection artifacts.

3. Methods and materials

3.1. PAFUSion – Processing steps

The processing steps of PAFUSion are schematically illustrated in Fig. 2. Let us consider a simple medium with two optical absorbers and one acoustic reflector in between them. The distance between optical absorber 1 and the acoustic reflector is d as shown in Fig. 2a. Once after collecting PA data, an image can be reconstructed using any reconstruction algorithm. Fig. 2b shows the schematic of the reconstructed PA image, in which three high intensity points P1, P2, and P3 are visible. Points P1, P2, and P3 have intensities I1, I2, and I3 respectively. Intensity for a particular point

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**Fig. 1.** (a) Illustration of photoacoustic signal generation and signal causing reflection artifacts (b) Principle of PAFUSion: Focusing ultrasound to the photoacoustic source mimics the reflection caused by it.
is defined here as the maximum value of the reconstructed image envelope at the location of that point. The distance between $P_1$ and $P_2$ is 2d. This PA image is used as the guidance for further steps in the technique. PA-UFUSion is applied on points from top to bottom in PA image.

In the example in Fig. 2 three high intensity points are identified in the PA image, thus two steps are required to perform PA-UFUSion. It is not necessary to apply PA-UFUSion on $P_3$, as this deepest feature in the PA image will never lead to the identification of another new reflection. In the first step, US is focused onto $P_1$ (Fig. 2c), and the resulting echoes are acquired. Reconstruction from this echo data is performed considering one-way propagation of sound and by setting the acquisition start ($t = 0$) to the time at which US reaches the focus distance. By this way, reconstruction treats the spatial pressure distribution of the focused US pulse as the initial pressure distribution of a virtual PA source, and thus will be able to mimic the reflection artifacts caused by that PA source. The image obtained by this step is saved for further processing. In the second step, the same procedure is repeated for $P_2$ (Fig. 2d). Since there is no acoustic reflector beneath $P_2$ in this example, resultant image of the second step will be blank without any echoes. During each step, US reflections from the depth of focus as well as above it are omitted from the reconstructed image. The next step is weighted addition of images obtained in step 1 and step 2 for obtaining the PA-UFUSion image (Fig. 2e), which reveals only the reflection artifacts. The weights for the images obtained in steps 1 and 2 are chosen to be proportional to the intensities $I_1$ and $I_2$ respectively in the PA image in Fig. 2a. As a final step, we envisage that the PA-UFUSion image can be used to correct the PA image for obtaining a reflection artifact-free PA image (Fig. 2f). However, this proof-of-principle study focuses only on identifying the reflection artifacts in PA images. Correcting the PA images using PA-UFUSion images will be realized as a next stage of improvement.

### 3.2. Equipment and Setup

A handheld dual-mode PA/US system which was already reported by our group [5] was used for all the experiments in this study. Fig. 3 shows the photograph of the system in which a commercial US scanner (MyLabOne, ESAOTE Europe BV, The Netherlands) was used along with a probe that integrates an US array with a diode laser module emitting pulses at 805 nm wavelength, 130 ns pulse width and pulse energy of 0.56 mJ. The US probe has a -6 dB fractional bandwidth of around 100% and center frequency of 7.5 MHz.

The system was used in research mode where US transmission, laser pulse transmission, and data acquisition were controlled using custom-made software running on a PC. The same software also controlled the switching between PA imaging and US focusing for PA-UFUSion technique. In addition, plane-wave US images were acquired as a reference to monitor reflector positions. US focusing was achieved by adjusting the transmission delays of the different transducer elements in the linear array. By this way, it is possible to scan the focus to any point in the imaging plane. A one-cycle transmission pulse shape was applied to each transducer element. In plane-wave US, PA, and PA-UFUSion imaging, RF data of all US transducer elements were saved after being acquired by the scanner with 50 MHz sampling frequency and digitized with a

![Fig. 2. Step-by-step schematic illustration of data processing steps in PA-UFUSion. (a) Simple medium with two optical absorbers and one acoustic reflector, (b) Photoacoustic image, (c) PA-UFUSion imaging step 1 – US focus on first high-intensity point in the PA image, (d) PA-UFUSion imaging step 2 – US focus on second high-intensity point in the PA image, (e) PA-UFUSion image obtained using weighted addition of images obtained in (c) and (d), (f) PA image corrected using PA-UFUSion image.](image)

![Fig. 3. Portable ultrasound scanner (left) and the hybrid probe (right) integrating laser module and US transducer array [5].](image)
dynamic range of 12 bits. PA images and reference plane-wave US images, were reconstructed using a frequency domain reconstruction algorithm [14]. PAFUSion data was processed using the PA reconstruction algorithm by following the steps mentioned in section 3.1.

3.3. PAFUSion k-Wave simulation

A 3-D simulation of the PAFUSion algorithm was performed using the k-Wave toolbox [15]. Fig. 4a shows the geometry of the digital phantom and the acoustic parameters that were defined for the simulation. Simulation involved three steps: 1) photoacoustic imaging and reconstruction 2) focused US imaging 1 (focus to first high intensity point in the PA image), and 3) focused US imaging 2 (focus to second high intensity point in the PA image). Finally weighted addition of images (weight proportional to the PA intensity at the depths of focus) obtained in step 2 and 3 was performed for obtaining the PAFUSion image. For all the steps, reconstruction was done using a 2-D frequency domain reconstruction algorithm [14].

3.4. Phantom measurements

Three phantom measurements were performed for proving the validity of the PAFUSion technique to identify reflection artifacts in PA imaging. Before all experiments, measurements were done by moving the US/PA probe forth and back axially to identify potential reflection artifacts caused by optical absorption on the transducer surface that would move relative to the PA signal. In that way we made sure that all the reflection artifacts are really caused by PA sources inside the phantom. The first phantom was similar to the digital phantom in the simulation study. Fig. 5a shows the schematic of this phantom in which one optical absorber (nylon thread) and acoustic reflector (delrin rod) was used. Both the optical absorber and acoustic reflector were positioned inside a tank filled with water in such a way that they were perpendicular to the imaging plane of the US/PA probe that was immersed in water (Fig. 5a). This phantom was used to study a simple situation with a single photoacoustic reflection and its identification using the PAFUSion technique. Water without any scattering was chosen as the medium in this phantom for obtaining maximum PA signal (and thereby PA reflection) from the absorber positioned at the top part of the phantom.

The second phantom (Fig. 6a) contained two optical absorbers and one acoustic reflector. Again, nylon threads and delrin rod were used as optical absorbers and acoustic reflector respectively. The second nylon thread was placed deep inside the phantom in such a way that a PA reflection artifact (caused by first nylon thread PA signal reflecting on delrin rod) would almost overlap with the PA signal from this second thread. This phantom was intended to study the fusion of PA reflections with signals of interest. This is a critical problem in imaging structures like finger joints, where multiple absorbers and acoustic reflectors are present. Water mixed with Intralipid (μs = 6 cm⁻¹) was used as the medium in this phantom to make sure that both nylon threads generated a significant PA signal.

The nylon thread that was used as the optical absorber was itself acoustically reflective, thus it can cause reflection artifacts even in the absence of additional acoustic reflectors. The third phantom (Fig. 7a) represents the condition in which optical absorbers themselves are acoustically reflective, and was meant to study and identify the resulting reflection artifacts. Two nylon threads were kept at different depths in water and were perpendicular to the US/PA probe (Fig. 7a). Water without any scattering was chosen as the medium in this phantom for obtaining a strong PA signal from the first nylon thread (and thereby a strong reflection interfering with the second nylon thread) by directing the light to the top part of the phantom.

4. Results

In all the results, lateral and axial coordinates are represented by x and z respectively and the envelope of the images (PA, PAFUSion and US) are plotted in linear amplitude scale. Image reconstruction assumed constant speed of sound in the medium for all phantom measurements, which may have resulted in a slight deviation of the depth of reconstructed features compared to the physical depth owing to the inhomogeneous speed of sound of the embedded inclusions.

Fig. 4. (a) Digital phantom used for simulation, including the acoustic properties, (b) photoacoustic image and enlarged region of interest, which shows the reverberation-like details of the reflection artifacts, (c) PAFUSion image.
4.1. **PAFUSion simulation**

Fig. 4a shows the details about the phantom and US probe positioning used for the PAFUSion simulation. Fig. 4b shows the reconstructed PA image. The PA source ($x = 8$ mm, $z = 4.5$ mm) and its reflection on the acoustic reflector which occurs at position ($x = 8$ mm, $z = 9.5$ mm) are evident in the PA image. Limited view artifacts in the shape of circular streaks are visible in both PA image and PAFUSion images. The PAFUSion image (Fig. 4c) clearly identifies the PA reflection artifact by reproducing the correct depth and approximately the correct shape. It is evident from the results that PAFUSion could reproduce even the minute layered artifacts seen below the high intensity reflection ($x = 8$ mm, $z = 9.5$ mm). The intensity of the artifacts is different in the PAFUSion image than in the PA image because the simulated US transmission pressure amplitude was chosen independent from the PA signal amplitude.

4.2. **Phantom experiments**

Fig. 5a shows the details about the first phantom and the schematic of the measurement setup. This phantom had only one optical absorber embedded and an artifact-free PA image would have only one high intensity spot. Fig. 5b shows the reconstructed PA image in which the signal from the nylon thread ($x = 8$ mm, $z = 4.5$ mm) and two other signals ($x = 8$ mm, $z = 7$ mm and $x = 8$ mm, $z = 9.5$ mm) are visible. The nylon thread itself ($x = 8$ mm, $z = 4.5$ mm) and two surfaces of delrin rod ($x = 8$ mm, $z = 5.9$ mm and $x = 8$ mm, $z = 7.3$ mm) are observable in the plane-wave US image (Fig. 5c). The PAFUSion image (Fig. 5d) evidently revealed two reflection signals and confirmed that signals at $x = 8$ mm, $z = 7$ mm and $x = 8$ mm, $z = 9.5$ mm in the PA image are reflection artifacts. It is worth mentioning that reflection artifacts identified by PAFUSion reproduced the shape and spatial details of the actual PA reflection artifacts quite well. The second reflection

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**Fig. 5.** (a) Scheme of phantom 1 and experimental setup, (b) photoacoustic image, (c) plane-wave ultrasound image, (d) PAFUSion image.

**Fig. 6.** (a) Scheme of phantom 2 and experimental setup, (b) photoacoustic image, (c) plane-wave ultrasound image, (d) PAFUSion image.
artifact \((x = 8 \text{ mm}, z = 9.5 \text{ mm})\) is caused by the echo of the nylon thread PA signal on the second surface of the delrin rod. An extended horizontal feature can be seen right to the first identified reflection artifact \((x = 8 \text{ mm}, z = 7 \text{ mm})\) in the PAFUSion image (Fig. 5d). This is potentially a reconstruction artifact common to the frequency-domain algorithm, which is better visible in the PAFUSion image than in the PA image owing to a higher center frequency of the transmitted US compared to the PA signal. These artifacts occur outside the region of interest and are thus not critical for this experiment. The intensity ratio of the two identified reflections \((x = 8 \text{ mm}, z = 7 \text{ mm} \text{ and } x = 8, z = 9.5 \text{ mm})\) in the PAFUSion image ideally would be the same as the ratio of reflection intensities in the PA image. However, this ratio was found to be different in the PAFUSion and PA experiments (10 times higher in PAFUSion images). The intensities of the second reflections appear similar in the PA image and the PAFUSion image, because the color map in the PAFUSion image was chosen such that the pixel intensity of the first artifact was saturated to portray both artifacts clearly.

Fig. 6a shows the details about the second phantom and the schematic of the arrangement used for the measurement. This phantom consisted of two optical absorbers and an acoustic reflector. Ideally, one would expect only two high intensity spots in the PA image. Fig. 6b shows the reconstructed PA image in which the signals from the two nylon threads \((x = 8 \text{ mm}, z = 5 \text{ mm} \text{ and } x = 9.065 \text{ mm}, z = 10.4 \text{ mm})\) and two other signals \((x = 8, z = 7.4 \text{ and } x = 8, z = 9.8)\) are visible. Both nylon threads \((x = 8 \text{ mm}, z = 5 \text{ mm} \text{ and } x = 9.065, z = 10.4 \text{ mm})\) and two surfaces of delrin rod \((x = 8 \text{ mm}, z = 6.3 \text{ mm} \text{ and } x = 8, z = 7.7 \text{ mm})\) are noticeable in the plane-wave US image (Fig. 6c). The PAFUSion image (Fig. 6d) clearly revealed two reflection signals and confirmed that signals at \(x = 8 \text{ mm}, z = 7.4 \text{ mm} \text{ and } x = 8 \text{ mm}, z = 9.8 \text{ mm} \) in PA image are reflection artifacts. The second reflection artifact \((x = 8 \text{ mm}, z = 9.8 \text{ mm})\) is almost fused with the signal from the second nylon thread \((x = 9.065 \text{ mm}, z = 10.4 \text{ mm})\), mimicking a clinical scenario where identification of such an artifact would be crucial. The extended horizontal feature right to the first reflection in the PAFUSion image is again visible. This feature occurs outside the region of interest and thus does not prevent the identification of reflection artifacts. The distance between the first nylon thread and the delrin rod in this phantom is the same as for the first phantom. Also the intensity ratios of the two identified reflections \((x = 8 \text{ mm}, z = 7.4 \text{ mm} \text{ and } x = 8 \text{ mm}, z = 9.8 \text{ mm})\) were similar to the ones found in phantom 1. This is reasonable because the distance travelled by the US (PAFUSion, PA imaging) and thus the attenuation was similar in phantom 1 and phantom 2.

The third phantom was designed to simulate the condition of optical absorbers that themselves reflect PA signals from other PA sources. Recent studies shown that in PA finger imaging, the tendon shows contrast in PA as well as US imaging [16]. If the skin/blood vessel signal gets reflected on the tendon, the resulting artifacts can make image interpretation difficult.

Fig. 7a shows the details of the third phantom and the schematic of the measurement setup. Fig. 7b shows the reconstructed PA image (zoomed in for more details) in which signals from the two nylon threads \((x = 8 \text{ mm}, z = 4 \text{ mm} \text{ and } x = 8 \text{ mm}, z = 6.2 \text{ mm})\) and another signal \((x = 8 \text{ mm}, z = 8.5 \text{ mm})\) are evident. Both nylon threads are visible in the plane-wave US image (Fig. 7c). The PAFUSion image (Fig. 7d) clearly exposes the reflection signal and confirms that the feature at \(x = 8 \text{ mm}, z = 8.5 \text{ mm} \) in the PA image is a reflection artifact. It is worth mentioning that the PAFUSion image reproduces the depth and shape of the reflection artifact.

5. Discussion

For the simulation and all phantom measurements, our results show that PAFUSion is capable of identifying all the reflection artifacts present in the PA image. Our phantom measurements led to promising results for structures separated by around 1.5 mm, which is quite close to the clinically relevant scenario in finger joint imaging (distance between a blood vessel and a tendon, see further below). A straightforward method to identify reflection artifacts would be to use the B-mode US image and to identify potential acoustic reflectors in them, and then use this information together with simulations to identify reflections in the PA image. However, the US simulations would then rely on an imperfect input dataset, and furthermore the type of ultrasound
acquisition used in the US image (center frequency, number of cycles, transmission angle) is often different from the type used in the PA image. Furthermore, the computational cost of a wave-field simulation would limit the real-time applicability of such an approach. For these reasons, it can be advantageous to physically mimic the reflection artifacts instead, by using ultrasound transmissions that match the wave field of the PA sources in a physical back-propagation approach. The key aspect in the PAFUSion process is that the zero time has to be defined at the moment when the US pulse reaches the absorber, rather than when the pulse is injected in the tissue as in normal US imaging. Hence, in the PAFUSion algorithm, the tissue itself reveals the PA reflections by applying US imaging in a manner that simulates the timing of PA images. Another critical feature in the PAFUSion process is that the US pressure distribution matches the PA initial pressure distribution. If the shapes of US and PA initial pressure distributions are not matched, it will result in wrong arrival time of the transient at different reflectors, because the wave front curvature of the diverging US wave front will be different from the PA wave front.

Any dual mode PA/US system can incorporate the PAFUSion technique without any special changes to the system. The software requirements are quite similar to those of normal line-by-line US imaging, which makes clinical implementation straightforward. There is no training required to use this technique since everything can be software controlled just as in US imaging. In this work, the PAFUSion image was obtained by weighted addition of images obtained in different steps, in which the weight is proportional to the PA signal intensity. In a variation on this procedure, the US pulse amplitude can also be varied based on the PA signal intensity. This will reduce the overhead of doing weighted addition of images during processing. Another practical limitation is that PAFUSion requires an extra measurement and computation step, which may make the total imaging procedure slower. However, we expect that developments in GPU (Graphical Processing Unit) and FPGA (Field Programmable Gate Array) technology can overcome this, as parallel acquisition and processing is feasible using these high-speed techniques. Speed of sound and acoustic attenuation variations in tissue may also play a major role in accuracy of this technique when applied in vivo. Future work will also focus on considering these parameters during processing.

This work was intended for presenting the proof-of-principle of the technique and therefore concentrated on a comparably simplified scenario where the reflection artifacts were present in the center part of the US imaging plane, and PAFUSion was applied on PA images containing concentrated features (nylon thread). However, the choice of the phantom is not a limitation to the validity of the technique. Features with a more complicated shape, and features that are spatially extended are expected in an in vivo scenario. We envisage solving these in our future studies by transmitting US pulses with the shape of the identified PA feature, and then applying PAFUSion algorithm to identify reflection artifacts.

This work targeted only at identifying the reflection artifacts, but not at their elimination. Elimination of artifacts requires further investigation into a thorough calibration of pulse shape and amplitude of the focused US transmissions. Such an effort was beyond the goal of this study, but will be realized as a next step of improvement. Two critical aspects to consider for making the reflection-artifact elimination work in our next step are: Shape of US focus: The characteristics of the US focus have an impact on the shape and intensity of identified reflection artifacts in PAFUSion. It is critical to have a narrow focus axially and laterally to mimic small PA features like blood vessels. Using a Schlieren-imaging setup, we characterized the size and shape of the US focus. When focusing US to a depth of 4.5 mm, we achieved a focus with length of 0.2 mm and width 0.4 mm in the imaging plane. This shows that, using our system, we will be able to apply PAFUSion on small blood vessels. In the range of depth that we target (until 15 mm), change in shape of the focus with respect to the depth was found to be negligible.

Frequency content: The pulse shape of the transmitted US in PAFUSion must be ideally the same as the PA pulse shape to be able to coherently subtract PA reflections and PAFUSion-identified reflections. In this study, the frequency content of the US focused at a PA feature in the PAFUSion procedure is not matched with the frequency content of the PA signals coming from these features. Considering the pulse width of laser diode in our integrated probe (130 ns), there may be a low pass filtering effect. Thus, the reflections in PA images are of lower frequency (4 MHz), partly outside the bandwidth of the transmitted US in PAFUSion measurements. The low frequency of the PA signals might be one of the reasons for the reflection-intensity ratio difference seen in the PA image and PAFUSion image in the phantom experiments. Matching the frequency content will be one focus of future investigation, and can be achieved either physically by adapting the US transmission spectrum, or in software by filtering.

At this point, we would like to draw attention to the side-constraints and further steps that will be important when moving towards a clinical implementation of the proposed technique.

First of all, we remind the reader that PAFUSion can only identify and compensate for reflection artifacts caused by PA signals generated inside the imaging plane, but not out-of-plane clutter. This is not a strong limitation, because PAFUSion is specifically designed for a setup where the tissue is irradiated directly below the probe to maximize SNR. Normally, the resulting strong reflection artifacts inhibit the use of such a setup, and the optimum irradiation distance is determined by a trade-off between in-plane reflection artifacts and out-of-plane clutter and SNR [12]. If PAFUSion manages to reduce the in-plane reflection artifacts, irradiation directly below the probe will become an option again, and then out-of-plane clutter will be insignificant.

Second, PAFUSion can only identify and compensate for the inward propagating part of PA signals that can be mimicked using the limited range of possible US transmission angles. A typical ultrasound probe has an angular aperture in the range of 30° to 30°, whereas typical PA sources (cylindrical blood vessels) radiate into an angle range of 360°, which leads to a limitation of the method. If an acoustic reflector and optical absorber are positioned side by side, then the reflection artifact caused by these will be impossible to identify using this technique. Considering the fact that most of the echo producing structures (tendon, bone) lie beneath the superficial optical absorbers that generate strong PA transients (skin, blood vessels), this limitation is not critical.

Also, when using a linear array probe, PAFUSion is limited to mimicking PA transients that propagate parallel to the imaging plane. Therefore, the probe must be oriented such that artifact-generating PA sources are oriented perpendicular to the imaging plane in order to obtain optimum performance. This can be easily achieved in free-hand probe guidance, and will be even less of a limitation if 1.5D or 2D arrays are used.

With increasing number of PA absorbers (skin, multiple blood vessels) and many possible reflection angles (angle between absorber to bone/tendons), identification of all the reflection artifacts may become challenging. However, it is vital to mention that an artifact reduction by 75% facilitates an increase in signal to artifact ratio by 12 dB. Clinical PA imaging suffers from poor deep-tissue contrast because of optical attenuation and reflection artifacts, and
a 12 dB increase in signal to artifact ratio itself will have a significant impact on image contrast.

In this work, PAFUision was performed after manually identifying the high intensity points in the PA image. Manual identification might not be an option in a real-time application, but this is not a limitation as it is possible to automate the process of PA source identification as long as the number of strong PA sources is small. With a non-sparse distribution of PA sources, it might though be advantageous to automatically scan a large number of pixels in a region of interest in the imaging plane. To minimize the number of focused US acquisitions in view of real-time imaging, there is a possibility to use a synthetic aperture approach, where US can be synthetically focused to any desired point in the imaging plane. Instead of physically scanning e.g.100×100 pixels with a focused beam, the focused acquisitions can be synthetically generated in software processing from e.g. just 100 plane-wave transmissions using different transmit angles.

Time reversal of photoacoustic signals could also be an alternative for reducing acquisition time in comparison to separately focusing on multiple PA sources. Time reversal could be a solution for two problems: (1) the PA images often show spread-out features rather than point-like features, and (2) the different spectral contents of PA and US signals. Time reversal may lead to ingoing US signals which are spectral copies of outgoing PA signals. The only problem to which time reversal is not a solution is that of frequency-dependent attenuation. Our future research will therefore focus on studying the feasibility of using the PA time reversal approach in PAFUision. Most of the commercially available US systems may not be capable of pulsing the transducer elements with non-periodic pulses, which would be the technical challenge in using PA time reversal. This limitation can also be solved by using a synthetic approach where the US transmission pulse shape is matched with the PA signal shape using software processing.

At this stage of PAFUision implementation, one of the clinical applications we foresee is finger joint PA imaging. For instance, if the distance between a superficial blood vessel and a tendon is the same as the distance between the tendon and synovium, the blood vessel signal reflects on the tendon to generate reflection artifact at almost the same depth as the synovium is located. This is critical in rheumatoid arthritis imaging where inflammation of synovium is the marker. The second phantom experiment was intended to mimic this situation and it is clear that PAFUision can be useful in these circumstances. The third phantom experiment represents the condition in which optical absorbers are by themselves acoustically reflective. These features with contrast in PA and US imaging might create problems in accurate interpretation of clinical PA images. One of the important reflection artifact sources is the skin because of its high melanin content. In any clinical applications, skin is expected to generate high PA transients, which triggers the generation of reflection artifacts. PAFUision will help to avoid the exclusion of patients with high melanin content, from deep-tissue PA imaging. Reflection artifacts generated by small moles or hair, which is directly under the probe can also be potentially identified by using PAFUision.

6. Conclusions

PAFUision allows the identification of reflection artifacts in photoacoustic images by ultrasonically simulating the PA waves from the optical absorber, traversing towards the acoustic reflectors and thus by mimicking the PA reflection signals. In this proof-of-principle study, a simulation of a simple virtual phantom and three phantom experiments were performed to confirm the validity of this novel technique. Results demonstrate that PAFUision can separate reflection signals generated inside the imaging plane from the signals of interest, and thus envisions good potential for improving photoacoustic imaging of acoustically inhomogeneous tissue.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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