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Investigation on the effect of spatial compounding on photoacoustic images of carotid plaques in the \textit{in vivo} available rotational range

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Abstract

Photoacoustic imaging (PA) is a promising imaging modality due to its high optical specificity. However, the low signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of \textit{in vivo} PA images are major challenges that prevent PA imaging from finding its place in clinics. This study investigates the merit of spatial compounding of PA images in arterial phantoms and the achievable improvements of SNR when \textit{in vivo} conditions are mimicked. The analysis of the compounding technique was performed on a polyvinyl alcohol vessel phantom with black threads embedded in its wall. The \textit{in vivo} conditions were mimicked by limiting the rotation range in $\pm 30^\circ$, adding turbid surrounding medium, and filling the lumen with porcine blood. Finally, the performance of the technique was evaluated in \textit{ex vivo} human carotid plaque samples. Results showed that spatial compounding elevates the SNR by 5 to 10 dB and CNR by 1 to 5, depending on the location of the absorbers. This study elucidates prospective \textit{in vivo} PA characterization of carotid plaques by proposing a method to enhance PA image quality.

\textit{Photoacoustic imaging, spatial compounding, carotid plaques, ultrasound.}
1 Introduction

Recent developments in photoacoustic imaging (PAI) have demonstrated promising results in various studies targeting cardiovascular diseases [1, 2, 3, 4, 5, 6]. Combining the anatomical information obtained from ultrasound (US) with the tissue composition obtained from PAI, the complete morphology of atherosclerotic plaques can be revealed. This morphological information might be used to assess the content of the plaque, which is one of the markers for rupture risk of a plaque and a subsequent stroke [7, 8].

In previous studies, PAI was used for ex vivo imaging of atherosclerotic plaques in coronaries [2] and carotid arteries [5], while steps toward non-invasive imaging of carotid arteries were being taken [9, 3]. For plaques in coronary arteries, intra-vascular imaging using PAI can be beneficial. Previously, a few studies have shown the feasibility of PAI in the detection of lipid pools in coronary arteries [10, 11, 12]. However, due to the superficial anatomy of carotid arteries, non-invasive PAI is more suitable for carotid plaque assessment. Nevertheless, the attempts at in vivo PAI of carotid arteries are sparse [9, 3]. The typical challenge of in vivo PAI is the low signal-to-noise ratio (SNR) due to optical and acoustic energy losses in the tissue. Moreover, the complexity of the plaque composition and the inter-subject variability in tissue properties, such as different calcification densities, impose fundamental limitations on in vivo PAI of atherosclerosis, due to the acoustic scattering of photoacoustic (PA) waves. Therefore, the complexity of the problem increases without a priori knowledge of the exact content of the plaque. Additional complexity is found in vivo due to the absorption by luminal blood and the pulsation of the arterial wall caused by the varying blood pressure.

To eliminate the causes of artifacts in vivo such as pulsation, luminal blood, and surrounding scattering medium, we previously performed an ex vivo feasibility study [5]. Isolating the plaques from its surroundings simplified the identification of the tissue-of-interest and showed the feasibility of PAI in the detection of intraplaque hemorrhages. For proof of concept, we investigated human plaque samples ex vivo and imaged each sample from multiple angles for a full 360° rotation. This range of rotation is not available in vivo and was intended for research and validation purposes only. However, the increase in both SNR and CNR after compounding was significant and would certainly be desirable in vivo. Compounding of multi-angle PA data for a limited range of angles could partially recreate this effect.

Spatial compounding of multiple images has been extensively used in plane-wave US imaging [13, 14, 15] to elevate image resolution or to estimate the speed of sound differences in tissue [16]. However, until recently, the effect of spatial compounding in PA has not been characterized for different acquisition geometries. Recently, the necessity of a multi-angle photoacoustic acquisition has been studied for the accurate reconstruction of absorber
distribution [17]. There are studies that adopted a multi-orientation approach in PA. Omar et al. utilized high frequency wide band single element transducers to acquire PA signals that are generated under the same light illumination. Their study aimed for the accurate reconstruction of a wide range of absorbing structures in small animals [18]. However, single element systems are less suitable for clinical use. Gateau et al. used a linear array transducer for whole body tomographic PA imaging [19]. They adopted a scanning scheme that required translation and rotation of the probe to 1140 different positions to reconstruct a single frame, which slows down image reconstruction significantly. Moreover, the laser source was positioned on the opposite side of the object, which is not feasible for carotid scanning. Aforementioned studies were mainly aimed for small animal imaging and clinical applicability is not considered. The study of Kang et al. investigated the effect of spatial compounding of PA images, which are acquired in different imaging planes by tilting the probe around its elevational axis. They also used a fixed laser illumination and a variable acquisition geometry to reconstruct the spatial distribution of the absorbers.

In this study, we investigated the effects of multi-angle spatial compounding on PA images that are acquired from different rotational positions with respect to the axis of the vessel sample. We aimed to investigate the merit of PA compounding for non-invasive in vivo plaque imaging. We used an integrated PA probe [20]; therefore, both the illumination geometry and the ultrasonic acquisition geometry were altered together during rotation as opposed to previous studies (see previous paragraph). Since a full rotation of the sample as performed in ex vivo experiments [5] is not possible in vivo, the effect of compounding was analyzed for a limited range of rotation. The effects of angular spatial compounding were investigated and quantified in polyvinyl alcohol (PVA) phantoms for in vivo mimicking conditions, such as a limited range of rotation, turbid surrounding medium and the presence of blood in the lumen of the samples. Finally, the proof of principle was shown in available ex vivo data of human carotid plaques (n = 4). A quantitative analysis was performed by comparing SNR and CNR of PA images for various cases.

2 Materials and Methods

2.1 Phantoms and Plaque Samples

A black thread-embedded polyvinyl alcohol (PVA) phantom was designed to characterize the performance of the spatial compounding technique to detect plaque hemorrhages in the vessel wall. The PVA gel was prepared by dissolving 15 wt% crystal PVA (Mowiol 28-99, Sigma-Aldrich, Zwijndrecht, The Netherlands) in demineralized water at 90°C. Thereafter, 1 wt% Orgasol (ELF Atochem, Paris, France) was added to the gel for acoustic scattering.
Next, the PVA gel was molded in a cylindrical mold, where black threads were attached along the height of the cylinder (see Figure 1c). Finally, molded PVA was frozen and thawed for four consecutive cycles (16 hours freeze and 8 hours thaw duration for 1 cycle) to approach stiffness of a generic vessel [21].

Next, the performance of spatial compounding were investigated on existing ex vivo atherosclerotic plaque data [5]. The samples were obtained from the Department of Vascular Surgery of the Catharina Hospital Eindhoven. Informed consent was obtained from the patients in a study approved by the local ethics committee. Analysis was performed on 4 plaque samples having intraplaque hemorrhages, which provided detectable PA signals. A total of 20 distinct cross-sections were included for the compounding analysis.

2.2 Experiment Setup and Imaging Device

For each specimen, imaging was performed in a custom-designed immersion chamber (see Figure 1). The setup consisted of a water tank with two steel pipes attached to its sides. The steel pipes were coupled via a gear system and a secondary steel rod, which allowed a synchronized rotation of both ends of the sample. A motorized rotation stage was concentrically mounted to the secondary rod. Additionally, a three-dimensional (3-D) linear stage (M-403.2DG, Physik Instrumente, Germany) was attached to the setup to control the position of the imaging probe with respect to the sample. Both the Cartesian position of the probe and the angular position of the specimen were controlled by a PC using LabVIEW software (National Instruments, Austin, Texas, USA).

The PA imaging probe consisted of a diode laser (QUANTEL, Paris, France) with a wavelength of 808 nm, a pulse duration of 130 ns, and a pulse energy of 1 mJ. The wavelength of the laser was chosen a) to target blood for various applications (see Daoudi et al. [20]), including the detection of intraplaque hemorrhage [5], and b) to maximize optical fluence in the elevational focal depth of the US acquisition. The acoustic signals were acquired by the linear array transducer with a center frequency of 7.5 MHz and bandwidth of 9 MHz (SL3323 ESAOTE Maastricht, The Netherlands) that was integrated into the PA probe. Due to the limited channels available, the middle 64 elements were activated for the acquisition; therefore, the total aperture was $64 \times 0.245 = 15.68$ mm wide by 5 mm in height. For data acquisition, the PA probe was attached to an US scanner (MyLabOne, ESAOTE, The Netherlands), and the raw data were digitized at a sample frequency of 50 MHz and transferred to the PC via a USB connection. The mean resolution of the imaging probe based on point spread function was measured to be 0.39 mm the performance of the hand-held probe designed characterized and reported in the study by Daoudi et al. [20].
Figure 1: Illustration of the experimental setup from (a) the top view and (b) the side view; (c) the mold and the polyvinyl alcohol (PVA) phantom. The sample was immersed in a phosphate-buffered-saline (PBS) solution. The imaging probe was positioned in the cross-section of the sample for photoacoustic (PA) imaging and translated along the longitudinal axis of the vessel.

2.3 Experimental Procedure

2.3.1 Phantom Experiments

Three different sets of phantom experiments (PE1-PE3) were performed as seen in Table 1. During all the experiments, the PA probe was positioned in the transverse cross-section of the vessel. A total of 500 PA frames were acquired with a pulse repetition frequency (PRF) of 100 Hz. Although the maximum PRF of the system is 10 kHz, the experiments were performed at 100 Hz to keep pace with the mechanical scanning. The design of the probe acts as a heatsink to release the heat from laser diodes. Therefore, heat dissipation and allows the system to function without any disturbance. The reduction in PRF led to an additional reduction in heat dissipation in the probe. Next, the sample was rotated by 10° and acquisition was repeated for 36 different angular positions. The same acquisition protocol was repeated for plane-wave US. Since less averaging is required for US, PRF of the acquisition was reduced to 50 Hz. A total of 10 frames were acquired at each cross-section. Since the PRF of the acquisitions do not have any effect on the parameters that is investigated in this study, they were kept low considering the data rate.

In the first set of experiments (PE1), the voltage of the high voltage capacitors of the laser driver circuit was varied from 30V to 100V to tune
Table 1: The experiments and corresponding parameters

<table>
<thead>
<tr>
<th>Experiment Name</th>
<th>Surrounding Medium</th>
<th>Lumen</th>
<th>Depth of Sample Center (mm)</th>
<th>Laser Pulse Energy (µJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE1</td>
<td>Demi-water</td>
<td>Demi-water</td>
<td>8.85</td>
<td>84 - 1045</td>
</tr>
<tr>
<td>PE2</td>
<td>Intralipid + India Ink Solution</td>
<td>Intralipid + India Ink Solution</td>
<td>8.45 - 18.85</td>
<td>1045</td>
</tr>
<tr>
<td>PE3</td>
<td>Intralipid + India Ink Solution</td>
<td>Porcine Blood</td>
<td>8.25 and 15.50</td>
<td>1045</td>
</tr>
<tr>
<td>ExPLQ</td>
<td>PBS</td>
<td>PBS</td>
<td>~8.5</td>
<td>1045</td>
</tr>
</tbody>
</table>

the optical output energy of the laser diode between 84 µJ to 1045 µJ. Thereby, a lower optical absorption was mimicked, which was validated by the linear change in the intensity of PA signals (data are not shown). During PE1, the sample was immersed in water at 8.85 mm depth.

In the second set of experiments (PE2), the immersion medium was changed to a tissue mimicking liquid obtained by mixing 1 V/V % Intralipid (20%, Fresenius Kabi BV, Zeist, The Netherlands, Batch No: 10I5853) [22] and 0.001% of Indian Ink (Talens, Apeldoorn, The Netherlands) [23, 24] in demineralized water. The resulting optical properties represent a generic soft tissue ($\mu_s = 10 \text{ cm}^{-1}$ and $\mu_a = 0.5 \text{ cm}^{-1}$). Additionally, the depth of the sample was increased from 8.45 mm to 18.85 mm in four steps, to investigate performance of compounding with increasing tissue depth.

In the final set of experiments (PE3), the effect of luminal blood was investigated by replacing the medium in the lumen by porcine blood obtained from local slaughterhouse. The measurements were performed at two different depths ($z = 8.25 \text{ mm}, 15.20 \text{ mm}$). Due to the manual adjustments during experiments, the initial position of the samples deviated slightly between the experiments. However, the effects of the deviation in depth were eliminated by considering only the relative changes in each experiment.

2.3.2 Ex vivo Human Plaques Experiments

The ex vivo measurements of human plaque samples (ExPLQ) were explained previously, in detail [5]. The samples were immersed in phosphate-buffered-saline (PBS) solution at approximately 8.5 mm depth, and at a laser pulse energy of 1045 µJ. Differently, the probe position was mechani-
cally scanned along the z axis (see Figure 1a) during acquisition of PA data. Therefore, temporal averaging was kept at 20 frames to prevent artifacts due to motion. Finally, the measurements were repeated for 36 angles.

2.4 Compounding Method

Data were filtered with a DC-blocking filter by subtracting the mean value of each channel. Afterwards, time frames were averaged into a single frame depending on the averaging window size (see Figure 4). Next, different band-pass filters were applied to each modality (PA vs. US) due to the spectral differences between the modalities [5]. While the pulse-echo signals were in the bandwidth of the transducer (\(f_c = 7.5\) MHz), the main frequency content of the PA signals was in the range of 0.8 - 5 MHz which is expected considering the laser pulse duration of 130 ns [25].

The spatial compounding process is illustrated in Figure 2. Upon acquisition, the raw channel data were reconstructed using k-space reconstruction [26] and radio-frequency (RF) data were obtained prior to envelope detection. The spatial sampling in the axial direction (\(c/f_s = 30.8\) \(\mu m\)) was 8 times higher than the lateral spatial sampling (\(d_{pitch} = 245\) \(\mu m\)). Therefore, images were mapped to a 50 \(\mu m\) equispaced grid using bi-cubic interpolation. Next, the images acquired at different angular positions were rotated back to the reference position of the sample at 0°. Consequently, a multi-angle acquisition, where the sample is fixed and the probe rotates, was mimicked. Finally, pixel values in the rotated images were summed and the envelope of the final image was detected, resulting in the final compounded images. The compounding procedure after re-meshing step can be formulated as follows:

\[
C = \frac{1}{N} \sum_{i=1}^{N} A_i \times T_i \tag{1}
\]

where \(A_i\) denotes the 2-D PA data from the angular position \(\theta_i\) and \(T_i\) denotes the affine transformation matrix that rotates the images by \(\theta_i\), \(N\) is the total number of angular positions, and finally, \(C\) is the resulting compounded image.
2.5 Image Quantification

The contribution of spatial compounding to the image quality was quantified by comparing the SNR and CNR of the absorbers in the images. In the data of the PVA phantom, a circular region of interest (ROI) was manually selected around each thread to obtain the signal power locally. Next, the region without black threads in the vessel wall was considered as background (see the dashed lines in Figure 3a).

In the data of the ex vivo carotid plaque samples, the segmentation was performed on the compounded US images based on the geometric similarity of the cross-sectional vessel contours in the US image and the histology pictures [5]. The hemorrhage regions were identified in the histology pictures, and the corresponding areas in the US image were segmented as the signal ROI. However, in order to improve the registration of the US and PA data, ROIs were manually adjusted by enlarging and translating the ROI.

Lastly, the SNR was calculated as,

$$SNR = 20 \log_{10} \left( \frac{S_{\text{rms}}}{N_{\text{rms}}} \right),$$

and the CNR was calculated as,

$$CNR = \frac{S_{\text{rms}} - N_{\text{rms}}}{N_{\text{rms}}},$$

where $S_{\text{rms}}$ represents the root-mean-square (RMS) of the signal ROI and $N_{\text{rms}}$ represents the RMS value of the background ROI.

Quantitative analysis was performed for the compounded data for two cases: a) complete rotation and b) the in vivo available rotation range (angles between -30 to 30°). Since spatial compounding could be considered a form of averaging in space domain, the total number of frames was kept constant for temporal averaging and spatial compounding to make a fair comparison between the two. Finally, the SNR and CNR values of each thread were analyzed separately to assess the effect of the absorber location.

3 Results

3.1 PVA Phantom Experiments

A qualitative representation of the effect of spatial compounding is demonstrated in Figure 3. The illustration in Figure 3a shows the geometry, orientation of the threads, and the segmented ROIs for the threads. The single frame plane-wave US image of the phantom (Figure 3b) revealed the geometry of the phantom with blurry edges at the sides. The black threads were not clearly visible in a single frame US image. However, spatial compounding increased the resolution and the contrast of the US images as expected.
Since the focus of this study is the improvement in PA image quality, no further quantitative analysis was performed on the US images. The signal levels in each single-shot PA image (Figure 3d) were insufficient to obtain a clear contrast at the absorber locations. Therefore, multiple acquisitions were temporally averaged to increase the signal quality of PA images (Figure 3e). Spatial compounding of averaged frames further increased image quality with higher resolution, contrast, and signal levels (Figure 3e). The separation and the size of the threads were not perfectly uniform, which affected the PA signals of each thread as seen in the compounded PA image (Figure 3f).

Figure 3: (a) Illustration of the phantom and embedded black threads labeled from T1 to T7, (b) conventional single-frame plane-wave US image of the phantom, (c) The resultant US image of PVA phantom after spatial compounding of all 36 angular positions, (d) Single frame photoacoustic (PA) image, (e) Photoacoustic image of the phantom after 500 frames temporal averaging, (f) The resultant PA image of PVA phantom after spatial compounding over 36 angular positions.

Figure 4a shows that increasing the number of frames averaged improves the SNR of the PA images of the PVA phantom; however, the rate of improvement decreases. The SNR of the averaged images follows the general shape of \(20 \log_{10} \sqrt{N}\) as the theory of temporal averaging of random signals states [27].

In Figures 4b to 4d, the effect of temporal averaging on the SNR of the PA images is shown (dashed lines) for increasing number of averaged frames \((N = 70, 210, 350, 490\) frames). Similarly, the effect of spatial compounding on SNR is shown (solid lines) for increasing range of rotation \((0, \pm 10, \pm 20, \pm 30)\) and equivalent total number of frames.

The SNR improvement of spatial compounding in the limited range of rotation outperforms temporal averaging by 4 dB in the case of 1 mJ optical illumination (see Figure 4d). As seen in Figure 4b, when the generated PA pressure is low and the initial SNR of the image is lower than \(\sim 2\) dB, temporal averaging is performing better than spatial compounding in
terms of SNR improvement. This shows that the initial SNR values of the compounded images should be sufficiently high for compounding to be effective.

Figure 4: (a) The dashed line is the mean of the SNRs of individual threads and the shaded area shows the limits of the maximum and minimum SNR values of each thread in PA images after temporal averaging. Plots (b), (c), and (d) show a comparison of the effect of temporal averaging ($N_{avg} = 70, 210, 350, 490$) and spatial compounding ($N_{avg} = 70, \theta_{Range} = 0, \pm 10, \pm 20, \pm 30$) for an equal total number of frames on the SNR of the PA images. The PA images of the PVA phantom were obtained for optical pulse energies of (b) 208 $\mu$J, (c) 332 $\mu$J, and (d) 1045 $\mu$J.

The results of PE2 showed that changing the surrounding medium from water to tissue mimicking fluid decreased the SNR by 3 dB and CNR by 2, see Figure 5a. Furthermore, the SNR of a single position PA image dropped by 11 dB at approximately 2 cm imaging depth. However, compounding the 7 angular positions between -30 and +30 degrees increased the SNR by 7 dB again.

Focusing on the individual absorbers for the lowest SNR case (I4), Figures 5b and 5c show that spatial compounding in the $in vivo$ available range ($\pm 30$ degrees) increases the mean SNR by 6.5 dB and the CNR by 3.

The results of the final set of experiments with the PVA phantom (PE3) shows that the presence of blood in the lumen instead of the turbid medium decreases the SNR by 3.7 dB (Figure 6a, SNR Single for the cases I1 and B1). However, the contribution of spatial compounding is larger (9.1 dB) compared to the loss in signal due to the presence of luminal blood (see Figure 6a, case B1). In conditions most similar to $in vivo$, in which the lumen
Figure 5: (a) SNR and CNR of the PA images of the PVA phantom in water (W, at 8.45 mm), and in Intralipid-Ink mixture (I1 at 8.45 mm, I2 at 11.60 mm, I3 at 15.75 mm, I4 at 18.85 mm). The dotted lines show the values of the single position acquisition and solid lines show the values of compounded images in the range of ±30 degrees. The SNR and CNR values of individual threads for the case of I4 was demonstrated in (b) and (c), respectively. The dashed lines show the mean value of individual threads.

is filled with blood and the surrounding medium is turbid, compounding already improved the SNR from 8.7 dB to 16.4 dB (see Figure 6a, case B2). In the end, the SNR and CNR of observers, in general, improve when compounding data obtained from different angles.

In Figure 7, resultant PA images were presented for a more qualitative illustration of the effect of spatial compounding for the extreme cases of PE2 (I4) and PE3 (B2). In the presence of a turbid surrounding medium, spatial compounding increased the quality of the images while the threads initially had a poor contrast (see Figure 7a and 7b). In the case of a lumen filled with blood, spatial compounding elevated the SNR of the distal threads (T6 and T7) by \( \sim 8 \) dB and the CNR by \( \sim 1 \) (see solid arrows in Figure 7). Moreover, the lumen border becomes clearer after spatial compounding in the limited range (see dashed arrows in Figure 7).

3.2 Ex vivo Plaque Samples

In Figure 8, two different cross-sections of a plaque are selected to illustrate the image qualities for single angle acquisition, limited angle compounding, and complete rotational compounding. In the first cross-section (Figure 8a-e), the dominant absorber was located proximal to the PA probe at the initial position. Therefore, the SNR of the image was highest at zero position (16.2 dB). Compounding of all the rotational positions increased the background noise and eventually decreased the SNR by 6 dB.

In the second cross-section (Figures 8f-j), the SNR of the absorber that is proximal to the imaging probe dropped from 13.3 dB to 10.6 dB for limited
Figure 6: (a) SNR and CNR of the PA images of the PVA phantom where the surrounding and the lumen are both filled with Intralipid-Ink mixture (I1, at 8.25 mm), and with the lumen porcine blood (B1 at 8.25 mm, B2 at 15.55 mm). The dotted lines show the values of the single position acquisition and the solid lines show the values of the compounded images in the range of ±30 degrees. The SNR and CNR values of the individual threads for the case of B2 was demonstrated in (b) and (c), respectively. The dashed lines show the mean value of individual threads.

Figure 7: Single frame (a and c) and compounded (b and d) in the range of ±30° PA images of the PVA phantom in the tissue-mimicking liquid (Intralipid-Ink mixture) at 18.85 mm central depth (a and b), and with the presence of blood in lumen at 15.75 mm central depth (c and d).
range compounding, and to 11.5 dB for complete rotational compounding. However, the benefit of spatial compounding was significant for the absorber distal to the probe. The SNR of the absorber increased drastically from -2.4 dB to 12.7 dB. Additionally, the CNR values of the PA images revealed similar behavior with the SNR values. The CNR of the first cross-section (Figure 8a-e) dropped from 5.4 to 2.8 and 2.3 respectively for the limited range compounding and full range compounding cases. However, the CNR of the distal absorber in the second cross-section (Figure 8f-j) raised from -0.2 to 3.3.

The relative changes of SNR and CNR of individual absorber regions in all 20 cross-sections were represented in Figure 9. Spatial compounding for the full rotational range elevated the mean SNR by $\sim 7$ dB and CNR by 1. However, for the limited rotational range case, improvements were significant only for the distal absorbers, which was indicated by the outliers in the box-plot.

4 Discussion

In this study, we investigated the effects of multi-angle spatial compounding on the quality of PA images of a PVA vessel phantom. We demonstrated that spatial compounding of the acquisitions from different angular positions improved the quality of PA images in terms of higher SNR and CNR. The improvements introduced by spatial compounding are due to an increase in PA signal intensities of absorbers which were achieved by the rise of optical power at the far absorbers location. Therefore, spatial compounding
outperforms temporal averaging, which increases the SNR by suppressing the variance of the white-noise.

We further investigated the performance of compounding for \textit{in vivo} mimicking conditions, such as turbid surrounding medium, the presence of blood in the lumen of the vessel, and limited angular rotation. The results illustrated that spatial compounding yielded a significant improvement for the limited range of rotation. The addition of tissue mimicking fluid to the surroundings, and porcine blood to the lumen of the phantom, reduced the SNR and CNR of the images. Especially the distal absorbers (T6 and T7) disappeared in the presence of luminal blood. However, spatial compounding, even for the limited \textit{in vivo} range, compensated these losses, thereby improving the image quality.

Finally, we performed a reanalysis of previously published human plaque data to quantify the effect of spatial compounding on \textit{ex vivo} PA images. The SNR improvement after spatial compounding of PA images in the range of ±30° was as high as 20 dB for distal absorbers; however, the SNR change was observed to be negative for the most proximal absorbers. This drop can be caused by two factors: (1) deviating from the 0° position reduces the optical fluence at the absorber and reduces the SNR, and (2) inhomogeneities such as calcifications, lipid pools, and intraplaque hemorrhages in human plaque samples create artifacts due to multiple reflections. Therefore, the image quality improvement of spatial compounding is highly dependent on the location of the absorber and more beneficial for the more distal absorbers, which was the rationale behind this development.

Since all the plaque samples were dissected during the histological examination, it was not possible to repeat measurements with different conditions as in the PVA phantom. However, relative losses in the SNR values can be assumed to apply to human plaque samples. Adding surrounding medium, increasing the depth, and adding luminal blood would potentially decrease the SNR of the plaque samples by approximately 12 dB. This shows that 2 cm depth will be the limit of this technique when applied \textit{in vivo}. The authors acknowledge that in patients with high body-mass index this depth will probably not be sufficient. Moreover, the available data allowed for
temporal averaging with 20 frames, and as Figure 4a shows, acquiring a higher number of frames could have drastically increased the SNR of plaque images.

In our method, the samples were rotated instead of the transducer, and the acquisition geometry of Gateau et al. were mimicked without the need of translation. For the complete 360 degrees, a total of 36 different rotational positions were used, whereas for the limited range (+-30 degrees) only 7 different positions were required to reconstruct a PA frame. *In vivo*, the latter will also be encountered, since the range of angles and the number of acquisitions will be limited due to respectively anatomical and practical constraints. Additionally, the use of the well-established k-space reconstruction method leads to a less computational complexity and increases the possibility of translation this method into current clinical US systems.

One limitation of the system is the discrepancy in the frequency spectrum of the generated PA signals and the bandwidth of the transducer. The laser pulse of 130 ns generates PA signals below 5 MHz. Using digital filters for post-processing, data were successfully retrieved and images were reconstructed with sufficient SNR and CNR. However, the central frequency of the transducer will cause a loss of sensitivity. We strongly believe that use of a lower band transducer would increase the imaging performance and consider to perform an analysis on the effect of the bandwidth of the transducer in future studies.

For future *in vivo* experiments, additional challenges are expected to be faced. The first challenge is the registration of the images acquired from different angles. Since the current clinical practice in the US is the use of hand-held probes, for our system a method for registration of the data should be developed for hand-held use, possibly in combination with a probe tracking device. The second challenge would be the effect of the location of the absorbers on the performance of spatial compounding. As the reanalysis of the *ex vivo* plaque data showed, single shot PA images can provide higher SNR compared to the limited range of compounding for proximal absorbers. However, the change in the SNR can be quantified during the compounding process and any loss in the SNR can be avoided using a selective compounding approach for proximal absorbers. Nevertheless, the initial goal was to achieve an enhancement in the SNR for distal absorbers, which makes the spatial compounding advantageous. Another challenge would be to achieve sufficient optical fluence at the absorber site *in vivo*. The presence of multi-layer surrounding tissue, such as skin, subcutaneous fat and muscle might have more significant effects on optical losses than homogeneous tissue mimicking fluid used in this study. Therefore, a higher optical pulse energy within the safety limits may be necessary for *in vivo* experiments.

This study elucidates the future experimental designs by showing the benefit of spatial compounding even in the limited range to further improve the image quality. Despite the potential challenges, there are additional
methods to improve the image quality that can be applied in future studies. In order to increase the performance of compounding, the directionality of the elements can be taken into account and prefiltering methods such as Wiener weighting filtering and apodization can be used to improve the image quality prior to spatial compounding [18, 19].

For the aimed clinical application, carotid plaque morphology assessment, a multi-wavelength approach should be developed to reveal the complete composition of the plaques including lipid content. The findings of this study are independent of the wavelength used and can be applied to multi-wavelength PA as well.

5 Conclusion

We showed that the quality of PA images in terms of SNR and CNR can be improved by compounding PA data from multiple angular positions. We presented the significance of the improvements in image quality on PVA phantom, and on the ex vivo human plaque data. Carotid arteries are in the range of 10 to 30 mm depth from the skin surface and the rotation of 30 degrees over the neck would be possible in vivo. Since the optical fluence on the carotid plaque will also vary with the change of position of the probe, higher signals from absorbers in the plaque are expected. In combination with suitable pulse energy and wave lengths, the limited range of rotation may allow for non-invasive imaging and characterization of atherosclerotic plaques in vivo.

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