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Calibrating reconstruction radius in a multi single-element ultrasound transducer based photoacoustic computed tomography system

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In a circular scanning photoacoustic computed tomography (PAT/PACT) system, a single-element ultrasound transducer (SUT) (rotates in full 360° around the sample) or a full-ring array transducer is used to acquire the photoacoustic (PA) data from the target object. SUT takes several minutes to acquire the PA data whereas the full-ring array transducer takes only few seconds. Hence, for real time imaging full-ring circular array transducers are preferred. However, these are custom built, very expensive and are not available readily in the market, whereas, SUTs are cheap and easily available. Thus, PACT systems can be made cost effective by using SUTs. To improve the data acquisition speed multiple SUTs can be employed at the same time. This will reduce the acquisition time by N-fold if N number of SUTs are used: each rotating 360/N degree. Experimentally all SUTs cannot be placed exactly at the same distance from the scanning center. Hence, the acquired PA data from each transducer needs to be reconstructed with their corresponding radius in a delay-and-sum reconstruction algorithm. This needs exact location of each SUT from the scanning center. Here, we propose a calibration method to find out the distance from the scanning center at which each SUT acquires the PA data. Three numerical phantoms were used to show the efficacy of the proposed method, and later it was validated with experimental data (point source phantom).

OCIS codes: (170.5120) Photoacoustic imaging; (170.3010) Image reconstruction techniques; (110.6960) Tomography; (110.6955) Tomographic imaging;

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1. INTRODUCTION

Over the past two decades, photoacoustic imaging (PAI) has been emerging as a novel multimodal multiscale biomedical imaging modality [1-5]. Due to its rich optical contrast and high ultrasonic resolution, this modality finds applications in breast cancer imaging [6, 7], in vivo small animal whole body imaging [8], molecular imaging [9], monitoring of oxygenated and deoxygenated blood levels [10], thyroid imaging [11], carotid imaging [12] and so on [13-17]. PAI works on the principle of photoacoustic (PA) effect. When a pulsed laser beam is incident on biological tissue, the endogenous chromophores present in the tissue such as haemoglobin, lipids, water etc., absorb the optical energy resulting in local temperature rise (in the order of milli Kelvin). This leads to thermoelastic expansion of the tissue resulting in generation of pressure waves known as photoacoustic waves. These generated PA waves are detected by ultrasound transducer. Various reconstruction algorithms [18-28] can be used to reconstruct the initial pressure rise representing the optical absorption map inside the biological tissue.

Circular scanning photoacoustic tomography (PAT/PACT) in orthogonal mode is used for deep tissue imaging [29]. Here, single-element ultrasound transducer (SUT) rotates a full 360 degree around the sample for data acquisition. It takes several minutes to few seconds to acquire the data depending on the repetition rate of the pulsed laser (10-100 Hz in case of Q-switched Nd:YAG laser [30] and 7 KHz in case of state-of-the-art PLD laser [31-33]). This inhibits real-time monitoring of biological processes occurring in fraction of a second. To circumvent this limitation, state-of-the-art PACT system uses circular ring array transducer offering 50 Hz frame rate (0.02 s per frame) [1]. However, these full-ring array transducers are custom-made and need complex back-end parallel signal amplifiers and digitizer electronics, making them complex and expensive. Hence, SUTs are still preferred due to easy availability at a very low price. To achieve the frame rate as that of the ring array transducer PACT system, multiple SUTs can be employed. The schematic of the multi-SUT based PACT system is shown in Fig. 2 (a). The configuration of these SUTs is different from that of full-ring circular array-based PACT system (Fig. 1 in Ref. [34]). In full-ring circular array based PACT system, the scanning radius of the...
A transducer is fixed and it need not rotate around the sample. In multi-SUT based PACT system, the transducers can be used at any desired radius depending on the sample size and each transducer need to rotate around the sample partially depending on the number of SUTs used. Integrating high frame rate PLD laser with cheap, multiple SUTs for PA data acquisition will find applications in monitoring neurofunctional activities such as epilepsy, and in characterization of pharmacokinetic, biodistribution profiles in the development process of drugs or contrast agents in small animal study. Fast imaging applications of this system would also include reducing motion artifacts by respiration or heartbeat in human as well as small animal studies.

![Fig. 1.](image)

Fig. 1. (a) Schematic diagram of k-wave simulation geometry in MATLAB. 900 × 900 pixels (0.1 mm/pixel) was used in all simulations. SUT: Single-element Ultrasound Transducer. (b) Quantifying the scanning radius using a point source 'P' placed at (550,550) pixel location in the simulation geometry. r1 is nearest distance between the point source 'P' and SUT. r2 is farthest distance between the point source 'P' and SUT. (c) Point source numerical phantom. Five points located one at the scanning center and remaining four at 1 cm away from the center. (d) Derenzo numerical phantom. (e) Blood vessel network numerical phantom.

In multi-SUT PACT system, if N number of SUT's are used then each transducer needs to rotate only 360/N degree around the sample. This improves the data acquisition time N-fold. One major limitation in using these several SUTs is that experimentally it is very difficult to place all transducers exactly at the same distance from the scanning center. Each SUT rotates in concentric circles with slight difference in scanning radius resulting in an experimental error of approximately 1 to 3 mm. In full-rings circular array transducer, this problem doesn’t exist as all the transducer array elements are exactly at the same radius from the scanning center. Usually a simple delay-and-sum method implementing back-projection algorithm is used for reconstructing cross-sectional PA images in PACT system. In this method, we need to input the scanning radius for reconstructing the PA image which is conventionally calibrated by trial and error method. For a circular ring array transducer and single element ultrasound transducer PACT systems, only one reconstruction radius is needed. Whereas, in a multi-SUT PACT system, individual reconstruction radius for each SUT is needed because if a single reconstruction radius is used for the combined PA data from all SUTs, the reconstructed PA image is distorted. This distortion increases as the number of transducers used increases. The target image can be perfectly reconstructed by using the corresponding radius of each SUT. Conventional trial and error method to find out these scanning radii is inefficient and time-consuming as it involves human training to assess the quality of the reconstructed images. This difficulty increases further in case of multi-SUT PACT system compared to full ring array transducer and single-SUT PACT systems. To overcome these limitations, there is a need to automate the process of finding the scanning radius for each SUT in a PACT system with circular scanning geometry.

In this work, a simple calibration technique has been proposed to automatically find the scanning radius for each SUT. The importance of using different scanning radius for different transducers in a multi-SUT PACT system also has been demonstrated. Three different numerical phantoms (point source, derenzo, and blood vessel network) and experimental point target phantom were used to show the efficacy of the proposed method. Pearson correlation (PC) coefficient metric was used to compare the quality of the reconstructed images for numerical phantoms and signal to noise ratio (SNR) was used for experimental phantoms.

### 2. METHODS

#### A. Numerical simulations

<table>
<thead>
<tr>
<th>Transducer #</th>
<th>Radius (mm)</th>
<th>Bandwidth (%)</th>
<th>SNR (dB)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUT1</td>
<td>40</td>
<td>70</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>SUT2</td>
<td>41</td>
<td>68</td>
<td>31</td>
<td>97</td>
</tr>
<tr>
<td>SUT3</td>
<td>37</td>
<td>72</td>
<td>25</td>
<td>95</td>
</tr>
<tr>
<td>SUT4</td>
<td>43</td>
<td>74</td>
<td>37</td>
<td>94</td>
</tr>
<tr>
<td>SUT5</td>
<td>39</td>
<td>66</td>
<td>34</td>
<td>93</td>
</tr>
<tr>
<td>SUT6</td>
<td>42</td>
<td>71</td>
<td>26</td>
<td>96</td>
</tr>
<tr>
<td>SUT7</td>
<td>38</td>
<td>69</td>
<td>28</td>
<td>92</td>
</tr>
<tr>
<td>SUT8</td>
<td>40</td>
<td>73</td>
<td>32</td>
<td>91</td>
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All numerical simulations were done using *k*-wave toolbox [35] in MATLAB. The simulation geometry used is shown in Fig. 1(a). The computational grid consists of 900 X 900 pixels (0.1 mm/pixel) with a perfectly matched boundary layer. Table 1 shows the different parameters used for the transducers SUT1 to SUT8 to generate the PA data. We have used 2.25 MHz centre frequency transducers with 13 mm diameter. To simulate real time scenario where the transducers in a multi-SUT PACT system rotate in concentric circles around the sample with slight difference in the radius, we have simulated the PA data with different scanning radius as well as different bandwidth, SNR levels and sensitivity for each transducer as shown in Table 1. The numerical phantoms used were point source phantom consisting of one point target at the scanning centre and remaining four at 1 cm far from the scanning centre [Fig. 1(c)], derenzo phantom [Fig. 1(d)], and blood vessel network phantom [Fig. 1(e)]. In case of 2-SUT PACT system SUT1 and SUT2 (each 200 detecting locations) were used for generating simulated PA data, similarly for 4-SUT PACT system SUT1, SUT2, SUT3 and SUT4 (each 100 detecting locations) were used and for 8-SUT PACT system, SUT1 to SUT8 (each 50 detecting locations) were used. The simulated PA data were generated with a time step size of 40 ns and a total of 11.00 time steps for point source phantom and 1350 time steps for derenzo and blood vessel network phantoms. The reconstructed images in all these scenarios were compared with that of single-SUT acquiring the PA data at 400 locations around the sample in 360 degree. Modified delay-and-sum algorithm was used for all the reconstructed PA images [20].
The optical energy density on the sample surface pr beam is guided on to the sample through three uncoated right angle repetition rate at 532 nm wavelength on to the sample. The laser switch Nd:YAG laser delivers pulses of 5ns duration with 10 Hz C. Experimental Method

The degree of correlation between the target phantom and the reconstructed image was evaluated using PC coefficient defined as:

\[ PC = \frac{\text{cov}(t_i, t_\text{r})}{\sigma(t_i)\sigma(t_\text{r})} \]  

where, \( t_i \) is target initial pressure rise distribution, \( t_\text{r} \) is target reconstructed initial pressure distribution, \( \sigma \) is the standard deviation and \( \text{cov} \) is the covariance.

For experimental point target phantom images, SNR was used as a comparison metric for the quality of images. SNR for each reconstructed PA image was computed as:

\[ SNR (in \, dB) = 20 \log(V/n) \]  

where, \( V \) is PA amplitude on the object and \( n \) is the standard deviation of the background noise.
3. RESULTS AND DISCUSSION

Figure 3 shows the reconstructed cross-sectional PA images of five point targets in numerical phantom (one located at the scanning center and rest four located at 10 mm distance from the center). Figure 3(a) shows the reconstructed PA image obtained using SUT1 for a full 360° rotation. Figures 3(b)-3(d) show the reconstructed PA images obtained for 2-SUT PACT system configuration (using SUT1 and SUT2). In this configuration, each transducer collects the PA data around the sample for 180° rotation. Figure 3(b) is the reconstructed PA image obtained using SUT1 from 0° to 180° around the target phantom. Figures 3(c) and 3(d) show the reconstructed PA images for the combined PA data from SUT1 and SUT2 without and with radius compensation, respectively. Similarly, Figs. 3(e, f, g) and 3(h, i, j) represent the reconstructed PA images for 4-SUT PACT and 8-SUT PACT system configurations respectively. In Figs. 3(b, e, h), the target object information was lost as the data collected around the sample for one SUT is limited (180°, 90°, 45°) as shown by the red arrow marks. The point targets were not reconstructed properly in Fig. 3(e) as compared to Fig. 3(a) whereas the point targets 1 and 5 were not visible in Fig. 3(h). This is the limited view problem [37] where the transducer does not collect the information around the sample in full 360°. This limited view problem can be overcome by employing multiple SUTs to cover around the sample in full 360° degree. Reconstructing the PA data collected from all transducers in each of the 2, 4, 8-SUT configurations by using single reconstruction radius, the shape of the target phantom looks distorted [Figs. 3(c, f, i)]. This distortion in shape was high when more number of SUTs were used. By compensating the reconstruction radius, i.e., by using corresponding reconstruction radius for each SUT (calculated using the calibration method proposed earlier), the shape of the target phantom can be preserved [Figs. 3(d, g, j)]. These reconstructed images were similar in quality as that of the reconstructed image obtained using SUT1 in case of single-SUT PACT scenario. To compare the quality of the reconstructed images Pearson correlation coefficients (PCC) were calculated for point target phantom. From Table 2, it can be observed that the PCC values for multi-SUT PACT scenarios (0.19 for 2-SUTs, 0.19 for 4-SUTs and 0.134 for 8-SUTs) are quite close to that of the PCC value of 0.19 for single-SUT PACT configuration.

Another type of numerical phantom used was derenzo phantom [Fig 1 (d)]. It consists of various sized circular target objects at various locations. Figure 4 shows reconstructed PA images. Figure 4(a) shows the reconstructed PA image of derenzo phantom obtained using SUT1 for a full 2π rad. Figures 4(b, c, d) show the reconstructed PA images obtained for 2-SUT PACT scenario. The reconstructed PA image obtained using SUT1 from 0° to 180° around the sample is shown in Fig. 4(b). The reconstructed PA images for the combined PA data from SUT1 and SUT2 without and with radius compensation are shown in Figs. 4(c) and 4(d), respectively. Similarly, the reconstructed PA images for 4-SUT PACT and 8-SUT PACT system configurations are represented in Figs. 4(e, f, g) and 4(h, i, j), respectively. As the acquired PA data for each SUT was only 180°, 90°, 45° in case of 2, 4, 8-SUT scenarios, limited view problem is posed. Hence, the target object...
information contains small artefacts [red arrow marks in Fig. 4(b)]. All the circular objects were not reconstructed in Figs. 4(e, h) [red arrow marks] as compared to Fig. 4(a). This limited view problem can be avoided by using multiple SUTs. Cross-sectional reconstructed PA images using a single reconstruction radius for all transducers in each of the 2, 4, 8-SUT configurations is shown in Figs. 4(c, f, i). This distortion in shape was high in case of 8-SUT compared to 4-SUT and 2-SUT scenarios. The shape of the circular objects can be preserved [Figs. 4(d, g, j)] by using individual reconstruction radius for each SUT (obtained using the calibration method proposed earlier). PCC were calculated for all the reconstructed PA images of the derenzo numerical phantom [Table 2]. The PCC values for multi-SUT PACT scenarios were 0.59 for 2-SUTs, 0.62 for 4-SUTs and 0.58 for 8-SUTs PACT system scenarios. These values were matching with that of the PCC value of 0.59 in case of single-SUT PACT configuration.

Fig. 4. Reconstructed PA images for derenzo numerical phantom using modified delay-and-sum reconstruction algorithm (a) for single-SUT PACT configuration (360° rotation) (b-d) for 2-SUT PACT configuration (each SUT: 180° rotation) (e-g) for 4-SUT PACT configuration (each SUT: 90° rotation) (h-j) for 8-SUT PACT configuration (each SUT: 45° rotation): (b) reconstructed image for PA data obtained using SUT1 (c) reconstructed image for combined PA data obtained using SUT1 and SUT2 without radius compensation (d) reconstructed image for combined PA data obtained using SUT1 and SUT2 with radius compensation (e) reconstructed image for PA data obtained using SUT1 (f) reconstructed image for combined PA data obtained using SUT1 to SUT4 without radius compensation (g) reconstructed image for combined PA data obtained using SUT1 to SUT4 with radius compensation (h) reconstructed image for PA data obtained using SUT1 to SUT4 without radius compensation (i) reconstructed image for combined PA data obtained using SUT1 to SUT4 with radius compensation. PC coefficients are shown at the bottom in each image. Color bar is shown for all images on the left. Scale bar is shown in (a).

Next a complex blood vessel network numerical phantom [Fig. 1(e)] was used to show the efficacy of the proposed algorithm. Figure 4 shows reconstructed PA images for the blood vessel network phantom. Figure 5(a) shows the reconstructed PA image obtained using SUT1 for a full 360-degree rotation. Figures 5(b, c, d) show the reconstructed PA images for 2-SUT PACT system configuration. The reconstructed PA image obtained using SUT1 from 0° to 180° around the sample is shown in Fig. 5(b). The reconstructed PA images without and with radius compensation for the combined PA data from SUT1 and SUT2 are shown in Figs. 5(c) and 5(d), respectively. Similarly, the reconstructed PA images for 4-SUT PACT system configuration are represented in Figs. 5(e, f, g) and for 8-SUT PACT system scenario are represented in Figs. 5(h, i, j). Due to the acquired PA data by each SUT was limited for 180°, 90°, 45° in case of 2, 4, 8-SUT scenarios, the target object information was lost partially as shown in Figs. 5(b, e, h). Entire blood vessel network was not reconstructed in Figs. 5(e, h) (red arrow marks) as compared to Fig. 5(a). This problem can be avoided by using multiple SUTs. During reconstruction, when a single reconstruction radius is used for all transducers in each of the 2, 4, 8-SUT configurations, the shape of the network gets distorted as shown in Figs. 5(c, f, i). This distortion in shape was high in case of 8-SUT and 4-SUT compared to 2-SUT system scenarios. The shape of the target object can be retained [Figs. 5(d, g, j)] by employing individual calibrated reconstruction radius computed for single point source 'P' [Fig. 1(b)] using the proposed algorithm for each SUT. To study the quality of the reconstructed images, PCC values were calculated as shown in Table 2. The PCC values for multi-SUT PACT scenarios were 0.44 for 2-SUTs, 0.46 for 4-SUTs and 0.40 for 8-SUTs PACT system scenarios. These values were approximately similar to that of the PCC (0.46) for single-SUT PACT system configuration.

Next to validate our proposed calibration method experimentally, we have used a pencil lead phantom [Fig. 2(c)]. The reconstructed PA images are shown in Fig. 6. Figure 6(a) shows the reconstructed cross-sectional PA image obtained using SUT1 for full circular scan (Single-SUT scenario). For 2-SUT scenario, Figs. 6(b, c, d) represent the reconstructed PA images. The reconstructed PA image obtained using SUT1 from 0° to 180° around the sample is shown in Fig. 6(b). Figures 6(c) and 6(d) show the reconstructed PA images for the combined PA data from SUT1 and SUT2 without and with radius compensation, respectively. Similarly, Figs. 6(e, f, g) represent the reconstructed PA images for 4-SUT PACT system configuration. Due to the rotation of the transducers for only 180° and 90° in case of 2, 4-SUT scenarios, the point targets were not perfectly reconstructed in Figs. 6(b, e) as that of Fig. 6(a). This is due to the limited view problem which can be overcome by using multiple SUTs. The reconstructed images in Figs. 6(c, f) look distorted as they are reconstructed without any radius compensation. This distortion is high for 4-SUT scenario compared to 2-SUT scenario. By using individual reconstruction radius [computed for single point target [Fig. 2(b)] using the proposed calibration method], the point targets were perfectly reconstructed [Figs. 6(d, g)] as that in Fig. 6(a). SNR values obtained for reconstructed images in case of 2-SUT and 4-SUT PACT system configurations were 34.69 dB and 35.06 dB which were similar to that of SNR (34.88 dB) for Single-SUT PACT system configuration.

High temporal resolution is always a priority for better diagnosis and continual monitoring of any biological changes happening inside the body. Researchers are always trying to improve the acquisition speed for PA imaging. Multiple SUTs for a circular scanning PACT system are more effective and economic in improving the temporal resolution. For instance, when a single SUT takes 't' sec to acquire the PA data in full 360 degree around the sample, N number of SUTs take...
only 't/N' sec. Therefore, we can save 't'/(N-1)/N sec for each frame. Instead of acquiring one frame in 't' sec with one SUT, we can acquire N frames in the same time using N-SUTs thereby increasing the temporal resolution N-fold. State-of-the-art PLD-PAT system [38] using a single SUT demonstrated imaging speed up to 0.33 Hz frame rate (3 sec for one frame). By using 8-SUTs imaging speed can be improved to 2.67 Hz frame rate (0.375 sec for each frame) which is 8 times of the imaging speed obtained using the single SUT based PLD-PAT system. Hence, we can save 2.625 sec for each frame using 8-SUT based PLD-PAT system.

4. CONCLUSION

The scanning radius is an important parameter in a delay-and-sum reconstruction algorithm to obtain optimally reconstructed cross-sectional PA image. We have come up with an algorithm to calibrate the scanning radius for a single-element ultrasound transducer in circular scanning geometry. This circumvents the limitations in finding the reconstruction radius using conventional trial-and-error method. This is very helpful when multiple SUTs are

Fig. 5. Reconstructed PA images for blood vessel network numerical phantom using modified delay-and-sum reconstruction algorithm (a) for single-SUT PACT configuration (360° rotation) (b-d) for 2-SUT PACT configuration (e-g) for 4-SUT PACT configuration (h-j) for 8-SUT PACT configuration (each SUT- 90° rotation). (a) reconstructed image for PA data obtained using SUT1 (b) reconstructed image for combined PA data obtained using SUT1 and SUT2 without radius compensation (c) reconstructed image for combined PA data obtained using SUT1 and SUT2 with radius compensation (d) reconstructed image for combined PA data obtained using SUT1 (e) reconstructed image for combined PA data obtained using SUT1 to SUT4 without radius compensation (f) reconstructed image for combined PA data obtained using SUT1 to SUT8 without radius compensation (g) reconstructed image for combined PA data obtained using SUT1 to SUT4 with radius compensation (h) reconstructed image for combined PA data obtained using SUT1 (i) reconstructed image for combined PA data obtained using SUT1 to SUT8 without radius compensation (j) reconstructed image for combined PA data obtained using SUT1 to SUT8 with radius compensation. PC coefficients are shown at the bottom in each image. Color bar is shown for all images on the left. Scale bar is shown in (a).

Fig. 6. Reconstructed PA images for point target phantom (made of five pencil leads of 0.5 mm diameter, one at the scanning center and remaining at ~1 cm from the scanning center) using modified delay-and-sum reconstruction algorithm (a) for single-SUT PACT configuration (360° rotation) (b-d) for 2-SUT PACT configuration (e-g) for 4-SUT PACT configuration (h-j) for 8-SUT PACT configuration (each SUT- 90° rotation). (a) reconstructed image for PA data obtained using SUT1 (b) reconstructed image for combined PA data obtained using SUT1 and SUT2 without radius compensation (c) reconstructed image for combined PA data obtained using SUT1 and SUT2 with radius compensation (d) reconstructed image for combined PA data obtained using SUT1 (e) reconstructed image for combined PA data obtained using SUT1 to SUT4 without radius compensation (f) reconstructed image for combined PA data obtained using SUT1 to SUT4 with radius compensation. SNR values are shown at the bottom in each image. Color bar is shown for all images on the left. Scale bar is shown in (a).
used in circular scanning PACT system as each PA data from individual SUT needs to be reconstructed with its own corresponding radius. We have shown the effectiveness of the proposed method using three numerical phantoms (point source, derenzo, blood vessel) in case of 2, 4, and 8 – SUT PACT system configurations and a point source phantom in case of 2 and 4 – SUT PACT system configurations.

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**References**


