By Dr R Daoudi and Prof W Steenbergen

Handheld probe for ultrasound/ photoacoustic dual modality imaging

In this article we present a recently developed portable imaging system designed for point of care diagnostics. The system provides two imaging modalities: the well known ultrasound technique which provides anatomical and structural information and the newly emerging technique called photoacoustics which provides vascular bed and functional information, all in a portable and cost-effective scanner. The system was recently described in full (Optics Express 2014 doi: 10.1364/oe.22.026365.)

INTRODUCTION

Over the last decade, photoacoustic (PA) imaging has become an important field of investigation triggering tremendous interest among biomedical researchers and clinical physicians.

Photoacosutic imaging is based on the photoacoustic effect, that is the generation of ultrasound waves by the means of light. A short pulse of light is absorbed by a tissue chromophore. The volume containing the chromophore (e.g. blood vessels) will experience an instantaneous increase in temperature and volume and will consequently build up pressure via the thermoelastic effect. This pressure will propagate through the tissue and can be detected by an ultrasound transducer array placed at the tissue surface. An image reconstruction algorithm can then be utilized to ascertain the location of the ultrasound sources allowing for three-dimensional visualization of chromophore distribution. Unlike other optical techniques such as Optical Coherence tomography, or Diffuse Optical Tomography, photoacousics has the ability to probe optically diffuse media with high penetration depth and ultrasound sub-millimeter resolution. Photoacoustics is capable of imaging the blood vessel network with sub-millimeter resolution at a depth of several centimeters in tissue, without use of contrast agents, which is particularly important in revealing angiogenesis around tumors [1]. The use of multiple wavelength photoacoustics can further detect the presence of different tissue chromophores such as hemoglobin, lipid and melanin, thanks to their physiologically specific absorption signatures. More importantly, with spectroscopic measurements, photoacoustics can quantify hemoglobin oxygen saturation within single vessels, providing metabolic information about the microcirculation. The potential of PA has been demonstrated in several applications ranging from macroscopic to microscopic scale [2] such as oncology [3], ophthalmology [4], dermatology and cardiology [5].

The recent interest on photoacoustics was materialized by the development of commercialized imaging systems by several spin-off and existing companies. However, unlike ultrasound (US), which of course is well established in clinical use and applications, photoacoustics still has some limitations such as lack of real time imaging, high cost and impracticability due to the imposing dimensions of the lasers used [6]. These constraints are limiting the widespread use of photacoustics and prevent it from being a standard imaging modality for point of care and treatment monitoring.

PROJECT RATIONALE

Our work was motivated by the necessity to develop photoacoustic imaging systems that are compact, affordable and offering real-time imaging (translation of research into clinical practice). We have focused on these aspects with the objective of bringing photoacoustics into clinical practice. The project started as collaboration between our research group (BioMedical Photonic Imaging) led by Prof. Wiendelt Steenbergen and three European companies: ESAOTE, the manufacturer of ultrasound systems, Quantel Laser Diodes, a manufacturer of solid state lasers, and SILIOS Technologies, a manufacturer of optical equipment

To overcome the limitations mentioned above we designed and developed a handheld probe integrating an ultrasound transducer array and pulsed diode laser that combines photoacoustics and ultrasound imaging modalities. The key innovation which allowed shrinking the size of the system is the use of a diode laser instead of solid stat lasers. We took advantage of the continuing development of efficient and cost-effective pulsed diode lasers and their use as a source for photoacoustics.

The author

Dr R. Daoudi and **Prof. W. Steenbergen** are at :

Faculty of Science and Technology

Biomedical Photonic Imaging, Zuidhorst ZH263, P.O. Box 217

7500 AE Enschede, The Netherlands

emails:

k.daoudi@utwente.nl

w.steenbergen@utwente.nl

FIGURE 1. The key components of the new system are lap-top sized ultrasound scanner (Esaote, MyLab One) and a hybrid probe. The probe includes both ultrasound and laser modules in a small and ergonomic design.

SYSTEM DESCRIPTION

The imaging system is composed of a laptop sized ultrasound scanner with a 12" full touch-screen display developed by Esaote (MyLab_One) and the hybrid probe attached to it. The probe integrates both ultrasound and laser modules in small and ergonomic design [Figure 1]. The scanner can be easily transported between rooms in clinical sitting.

The integration of both ultrasound/laser modules in small and ergonomic design involved the investigation of several aspects. These included the optimization of the beam illumination shape and ultrasound detection, generation of short high energy pulses with low heat dissipation, miniaturization of the diode driver, communication between the laser module and ultrasound acquisition system, and the suppression of electrical noise generated by the proximity of the diode driver and ultrasound detector. The emitting source consists of highly efficient diode arrays (Osram, Regensburg, Germany) mounted in a stack and emitting light at a wavelength of 805 nm. The total delivered energy is around 0.56 mJ per pulse. The diodes are driven by a customized laser driver (Brightloop, France), allowing a pulse width of 130 ns at half maximum and a maximum 10 kHz pulse repetition rate which allows high frame rate imaging. The undesirable pronounced divergence of diode lasers was overcome by a meticulous optical beam shaping design composed of cylindrical micro-lenses and diffractive optical elements composed of 400 μm diffractive cells and 8 discrete phase levels placed in front of the diodes. The beam, is afterwards deflected by means of a glass prism illuminating the medium at an angle. At the front-end of the probe we obtain a homogenized beam of 20 mm by 2.5 mm. On the other hand, the scanner underwent substantial modifications to allow photoacoustic imaging. This was done first by providing an external signal to trigger the laser driver in order to synchronize between the detection and illumination, then by allowing the blocking of the US transmission during photoacoustic measurements to switch between ultrasound and photoacoustic imaging and finally by modifying the ultrasound beam-forming reconstruction allowing image reconstruction of both imaging modalities.

TESTING AND SYSTEM PERFORMANCE

The first prototype was tested and characterized using tissue mimicking phantoms. The tests included, among others, the verification of the illumination beam achieved at the frontend of the probe, the electrical noise level generated by the proximity of the diode driver and ultrasound detector, the co-registration of ultrasound and photoacoustic images and the temperature increase inside the probe caused by heat dissipation due to the generation of high energy pulses.

One of the important questions to investigate when developing a new imaging system is the resolution and imaging depth. The latter point depends mainly on the pulse energy and averaging. Unfortunately there are regulations in term of maximum permissible exposure which restrict the illumination features. It depends on the laser energy per pulse, the illumination area and laser pulse repetition frequency. This is one of the limitations when combining high laser pulse energy and high frequency repetition rate. Taking into account these limitations, we have investigated the imaging depth of our system in tissue mimicking phantom. The phantom used for these experiments consists of a bulk of Agarose gel with a mixture of Intralipid 20% and Ecoline black in water, leading to a tissue mimicking reduced scattering coefficient and absorption coefficient. Polyethylene tubing of 0.58 mm inner diameter was embedded at eight different depths. The measurement showed a possible imaging depth of 10 to 15 mm for a frame rate of 0.5 Hz. This depth reduces to 4 mm in real time imaging of 20 frames

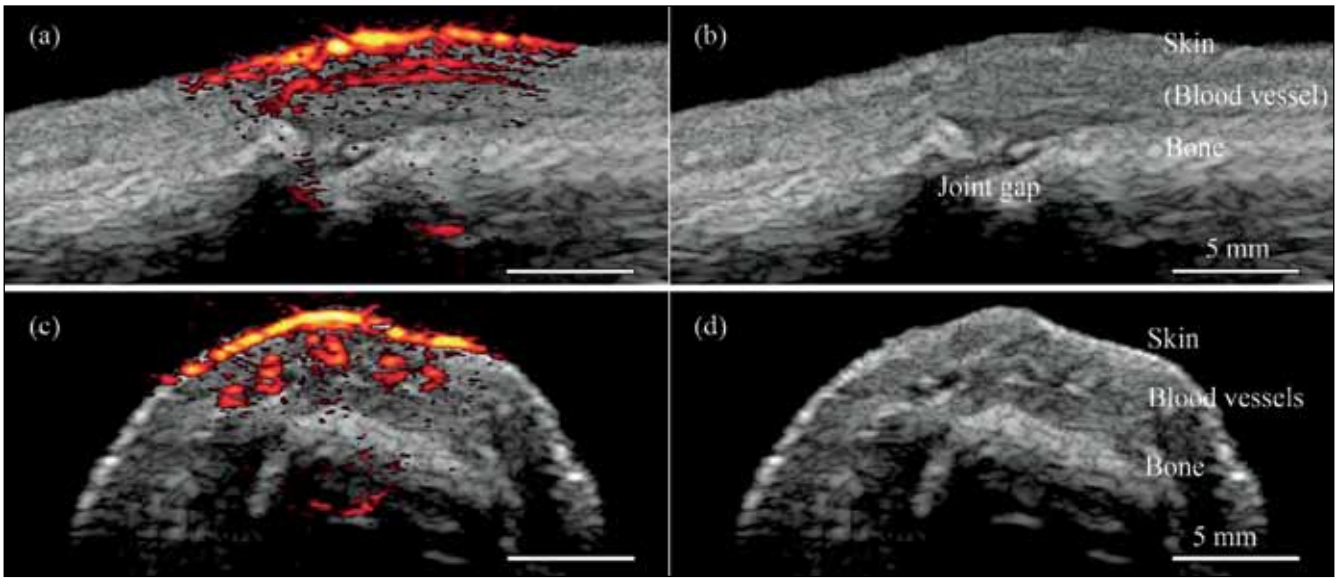

FIGURE 2. Combined PA/US images of the sagittal and transverse plane of the proximal interphalangeal (PIP) finger joint of a healthy volunteer The transverse slice is located near the joint gap. In these images the grayscale pixels correspond to US data whereas the heat-colored pixels correspond to PA data.
The image shows a detailed absorption distribution alongside the anatomical structure of the finger joint. Several blood vessels can be seen lying under the skin running parallel to the finger which are difficult to pinpoint in ultrasound images.

per second. To achieve a high penetration depth and real time imaging a measurement strategy can be used by firing the laser at high repetition rate during short time lapse. We also investigated the system resolution in different axes in a phantom study. The results showed a lateral resolution of 0.4 mm which degrades to 0.6 mm with depth and the position off axis due to limited numerical aperture of the ultrasonic transducer, whereas the axial resolution was around 0.28 mm with negligible variation.

The *in vivo* testing of the combined ultrasound and photoacoustic imaging system was performed on proximal interphalangeal (PIP) finger joints of a healthy volunteer. Figure 2 shows the combined PA/US images of the sagittal and transverse plane of the PIP joint. The transverse slice is located near the joint gap. The image shows a detailed absorption distribution alongside the anatomical structure of the finger joint. In these images the grayscale pixels correspond to US data whereas the heat-colored pixels correspond to PA data. Several blood vessels can be seen lying under the skin running parallel to the finger which are difficult to pinpoint in ultrasound images.

Different applications are currently being investigated using the new system. For instance, inflammation caused by rheumatoid arthritis in finger joints can be revealed with photoacoustics due to the increase in blood flow during the inflammation, Oncology, cardiovascular disease and burn wounds are other areas where the approach is being investigated.

FUTURE OUTLOOK

Photoacoustics is emerging as an essential tool in both biology and medicine at multiscale imaging. PA is expected to find broad applications in medicine. Some of them are in advanced stage of research such as breast imaging [7], melanoma detection, endoscopic imaging and intravascular catheter imaging. The number of research groups and published articles reflects its rapid development. The size and cost of the available systems are yet factors hindering the wide spread clinical use of photoacoustics, however with the new imaging system we hope to overcome these limitations.

The encouraging results obtained with the new portable system and the potential of PA technique to become essential in medical diagnosis and therapy monitoring has encouraged the team to take part in a European consortium composed of several industrial and academic partners to take the next steps. The project which is named FullPhase, standing for "Fully integrated real time multi-wavelength photoacoustics for early disease detection", (http://www.fullphase-fp7.eu/) is aiming to upgrade the system to several wavelengths with higher pulse energy to allow photoacoustic multi wavelength functional imaging.

REFERENCES

[1] Siphanto RI, Thumma KK, Kolkman RGM, van Leeuwen TG, de Mul FFM, van Neck JW, et al. Serial noninvasive photoacoustic imaging of neovascularization in tumor angiogenesis. Opt Express. 2005;13:89-95.

[2] Wang LHV, Hu S. Photoacoustic Tomography: In Vivo Imaging from Organelles to Organs. Science. 2012;335:1458-62.

[3] Erpelding TN, Kim C, Pramanik M, Jankovic L, Maslov K, Guo ZJ, et al. Sentinel Lymph Nodes in the Rat: Noninvasive Photoacoustic and US Imaging with a Clinical US System. Radiology. 2010;256:102-10.

[4] Jiao SL, Jiang MS, Hu JM, Fawzi A, Zhou QF, Shung KK, et al. Photoacoustic ophthalmoscopy for in vivo retinal imaging. Opt Express. 2010;18:3967-72.

[5] Wang B, Yantsen E, Larson T, Karpiouk AB, Sethuraman S, Su JL, et al. Plasmonic Intravascular Photoacoustic Imaging for Detection of Macrophages in Atherosclerotic Plaques. Nano Lett. 2009;9:2212-7.

[6] Kim C, Erpelding TN, Jankovic L, Pashley MD, Wang LHV. Deeply penetrating in vivo photoacoustic imaging using a clinical ultrasound array system. Biomed Opt Express. 2010;1:278-84.

[7] Heijblom M, Piras D, Xia W, van Hespen JCG, Klaase JM, van den Engh FM, et al. Visualizing breast cancer using the Twente photoacoustic mammoscope: What do we learn from twelve new patient measurements? Opt Express. 2012;20:11582-97.