Interventional photoacoustics: Using light to sound out the path to safe, effective interventions

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Abstract: Recently there has been rapid progress with performing interventional photoacoustic imaging to guide minimally invasive clinical interventions, providing unique tissue type contrast that is highly complementary to conventional pulse-echo ultrasound imaging. This Focus Collection in Physics in Medicine and Biology presents an exciting new field in medical physics and will be useful to identify links between biomedical optics and ultrasonics.

Technological advances in medicine hold immense promise for safer, faster therapeutic interventions. Many of such technologies are minimally invasive in nature, using dedicated, slimly profiled instruments to reach their working field through a small incision. Laparoscopic technologies have fundamentally changed many abdominal and orthopaedic surgeries, while catheter-based interventions are now commonplace in the treatment of many cardiovascular disorders. Other proposals feature targeted therapeutic agents, such as nanoparticles, for local drug or gene administration, which allow for the use of much higher doses than systemic delivery because toxicity for healthy tissues is a lesser concern. In several cancers, such as prostate cancer, brachytherapy is used to irradiate a tumour from within by placing needles with radioactive sources in the tissue.

These approaches share a common aspiration of delivering targeted, focal treatment by imparting a change on tissue or implant a device, with minimal side effects and fast recovery. They also share a critical dependence on image guidance: minimally invasive instruments are employed inside the body of the patient, so there is no direct line of sight on the working field. Imaging technology is required to visualize the pathology and surrounding anatomy, the instruments themselves, and the effect of the intervention. Likewise, the most advanced new therapeutic agents are frequently activatable, so they need to be trackable in the body in the patient so energy can be delivered, for instance by light or ultrasound, to switch them “on”.

Such imaging guidance tools are of course used in many forms. Coronary or cardiac procedures are guided by X-ray fluoroscopy or angiography, needle placement in many scenarios is usually performed under ultrasound echo imaging, and laparoscopy uses video endoscopy. Virtually all of these techniques also have limitations, however. Both video endoscopy and X-ray imaging reduce a 3D mobile working field to a 2D image, which makes depth perception a challenge. Optical imaging with visible light is complicated by the presence of blood. Echo and X-ray have poor contrast for (the differences between) soft tissues, and do not excel at picking up thin instruments. As a result, instrument navigation, visualization of pathology and assessment treatment effect are complicated. Use of the images requires a large degree of interpretation, and the procedures can be performed only by highly skilled operators that have completed a long learning curve. There is room for technologies, maybe not in all but certainly in a large subset of innovative interventional fields, for improved image guidance that addresses these needs.

Photoacoustic imaging is an emerging family of technologies that have the potential to solve some of these outstanding needs. In photoacoustics, short light pulses illuminate the tissue under examination. Optical absorption transfers the energy to the tissue, where it generates a transient thermo-elastic expansion. The ensuing pressure wave can be recorded by an ultrasound transducer as in pulse-echo imaging and so a – relatively aberration-free – acoustic image can be made of – tissue-composition specific – optical absorption. This allows the visualization of optical contrast in strongly scattering tissues up to a depth of several centimetres. The use of optical absorption encourages the use of spectroscopic methods and analyses, to identify for instance the difference between a fibrous and a lipid-rich atherosclerotic plaque, or between arteries and veins. It may localize a tumour by the presence of drug-loaded nanoparticles that may deliver their contents directly to the cells they were targeted to. Optical absorption has the potential to be highly chemically specific, and photoacoustics exploits that potential in deep, highly informative, real-time images.

Since half of photoacoustic imaging is in fact ultrasound, there is a large overlap in instrumentation between photoacoustic and echo imaging. It is relatively straightforward to acquire photoacoustic images interleaved with conventional pulse-echo imaging and visualize the chemical information from photoacoustic imaging as an overlay on the structural ultrasound image, which is intrinsically co-registered. Many applications of photoacoustic imaging capitalize on this compatibility. At the same time, the contrast of the two modalities is highly complementary. Photoacoustic imaging may provide a drop-in solution for guiding interventions where the contrast offered by ultrasound alone is lacking sensitivity (for thin instruments) or specificity (for different soft tissues), and by this minimize the interpretation required to provide rapid image guidance.

Timing is a key difference between diagnostic and interventional imaging. Diagnostic imaging aims to establish the presence and nature of disease, and precedes therapy. Interventional imaging, on the other hand, needs to provide actionable information: the interventionist decides on a treatment strategy, or manoeuvres her instruments based on the data, which should thus be moving images, be immediately available, have specific contrast, and require minimal interpretation. Photoacoustics has the potential to fulfil these criteria for a number of scenarios, and photoacoustic imaging approaches that attempt to do so are what we mean by “interventional photoacoustics.”

The applications and consequent technical implementations may vary widely, but some categories of technology research and instrumentation concepts can be defined. First, there is a difference in invasiveness: some photoacoustic devices are themselves catheters or needles. Such instruments may contain both optical delivery (usually through optical fibres) and ultrasonic detection. Catheter-based imaging usually provides a highly detailed but small field of view, which is thus complementary to but also dependent on wide-field imaging. This approach has been prominent in coronary imaging, but biopsy guidance in breast tumours has also been explored.

Alternatively, the invasive imaging devices may only deliver light while a transducer elsewhere receives the ultrasound. This latter realization simplifies device design, while still managing to inject light at anatomies that can be hard to reach with light from the outside. The external transducer can also be used to visualize the surrounding tissue structure. The applications of this approach include needle placement in muscle or peripheral nerve interventions, or treatment of prostate cancer. Other implementations may use entirely non-invasive imaging instruments to visualize instruments with photoacoustic contrast, be they metallic (metals usually are effective absorbers) or coated with an optically absorbing layer. For this configuration to be effective, the working field needs to be relatively superficial.

Finally, theragnostic photoacoustic imaging, which combines localization of pathology with intervention, may also be seen as a form of interventional photoacoustics. Theragnostic imaging is usually achieved with the aid of engineered micro- or nanoparticles that provide both image contrast as well as therapeutic action by activation with light, sound, or temperature. Ideally, the effect of the treatment can also be visualized.

This focus issue presents a collection of original research papers and topical reviews which cover these topics. Photoacoustic imaging of tissues is at present not yet a clinical reality, although it is an extremely active research field. A small number of clinical studies has shown enormous promise for applications such as lymph node staging. Translation of photoacoustic technology to a clinical setting is relatively difficult because of the divergent nature of its technological components, encompassing optical, ultrasonic, and electronic technology. All-optical approaches, using interferometric detection of acoustic pressure, are being developed to provide a simpler alternative, but still are in their infancy. Routine clinical deployment also requires meticulous validation of the provided image contrast, which is not trivial because of the many factors (light, acoustic receive sensitivity, medium thermodynamic parameters) influencing the final image.

This focus issue comprises seven publications, four original research papers and three reviews, which each investigate aspects of interventional photoacoustic imaging. The reviews concern real-time image formation, discussed in the context of optimizing image contrast and registration to other (pre-acquired) image data [*Dean-Ben and Razansky 2019*]; photoacoustic guidance of cardiovascular interventions, a clinical field that boasts incredibly sophisticated minimally-invasive interventions such as valve replacements [*Iskander-Rizk, Van der Steen and Van Soest 2019*]; and the physics, chemistry and utility of exogenous contrast, discussed in the context of intravascular imaging but with myriad other applications [*Sowers and Emelianov 2018*]. The frontiers of interventional photoacoustic imaging are being pushed in new studies. Exploring a new type of multimodal contrast agents, *[Visscher et al 2019].* performed a study into the dynamics of activatable particles, that may be enhanced with diagnostic and therapeutic moieties, responding to laser excitation. Shubert and Lediju Bell investigate photoacoustic contrast in (manipulated) human vertebrae to extract features that may serve in image guidance of spinal cord surgery *[Shubert and Lediju Bell 2018]*. Francis and Manohar studied the tracking of ablation needles and the tissue changes imparted by radiofrequency ablation on tissue *[Francis and Manohar 2019],* a treatment that has applications in the liver, the heart and other organs. Cryo-ablation, another form of thermal energy to modify aberrant tissues, is a form of prostate cancer treatment that is difficult to dose. Petrova et al. examine how photoacoustic thermometry may assist in this scenario [*Petrova et al 2018*].

Together, these studies present an eclectic overview of trends in real-time photoacoustic imaging, striving to provide specific contrast and minimize interpretation. They may enable a more precise treatment by ablation therapies, delivering just the right dose in the right location, reducing the risk of collateral damage by overtreatment or poor localization. They may also light the way for exogenous contrast and effective multimodal imaging.

Technology translation in biomedical science is a conversation. Researchers with an engineering or physics background learn to listen to the demands of physicians, and those “unmet clinical needs” are almost universally recognized as a compass for engineering in medicine. Equally importantly, however, developments that are sometimes sceptically brushed aside as “technology push” or “hammers looking for a nail” may serve to educate clinical professionals about what might be possible, what they could desire for their patients. We believe that true advances and innovation in interventions will happen in that conversation, and hope that this collection can facilitate it in the area of photoacoustic guidance of medical interventions.

References

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