Ultrasonic imaging is versatile, noninvasive, portable, relatively inexpensive, and is second only to X-ray in annual procedural volume. Optical imaging continues to search for an identity in the medical arena. Opto-acoustic tomography combines the merits and most compelling features of both technologies.

LASER OPTO-ACOUSTIC IMAGING: LET THERE BE LIGHT THAT SOUNDS!

By Howard Nathel

Light and sound, both "non-ionizing" energy sources, are used to look inside the body. Conventional ultrasound[1] is a cornerstone for the radiologist and other medical practitioners performing non- and minimally invasive diagnostic procedures. In spite of widespread use, common complaints regarding ultrasound include lack of contrast and resolution. Contrast is limited to several percent differences from reflected ultrasonic waves because tissue densities and the speed of sound do not vary significantly from one tissue type to the next. Resolution degrades because high frequency ultrasonic waves diffract substantially at penetration depths greater than several millimeters.

1047-6938/99/6/0027/06-$0015.00

Optical radiation,[2,3] in particular red and near-IR wavelengths (600–1400 nm), penetrate tissue and provide contrast resulting from differential absorption (and scattering to a lesser extent) of specific tissue types. At 1064 nm, differences in absorption coefficients result in optical contrast of approximately 400% between cancerous and normal breast tissue (0.015 cm^{-1} and 0.6 cm^{-1}, respectively).[4] However, because scattering is the dominant attenuation mechanism, penetration to depths where imaging capabilities are useful is limited even with the use of intricate scatter reduction (hardware)[5–8] and/or image reconstruction[9,10] (algorithmic) techniques.

Light with sound

As optical scientists, we often search for methods to increase signal sensitivity to enhance visualization of physical, chemical, and biological processes. A common technique is energy down-conversion, whereby a high-energy photon is converted to a lower energy photon via both linear and nonlinear phenomena. In 1880, Alexander Graham Bell discovered a down-conversion mechanism that permits one to listen to optically induced physical phenomena with tremendous sensitivity.[11] Bell measured sound being generated from a rubber sheet that was illuminated by an intermittent beam of sunlight. Approximately a century later,[12] after the invention of the laser, the photo-acoustic effect has become a useful scientific tool. High fluence, monochromatic optical excitation sources, in consort with high sensitivity ultrasonic detectors (piezo-electric crystals or microphones), have allowed spectroscopic measurements of very low cross-section absorption bands, such as vibrational overtones, in transparent, or nearly transparent, media. Additionally, detection of extremely low concentrations of materials for sensing and monitoring applications[13–16] have become facile and very useful practical measurements.

Several techniques that combine light and sound with the prospect of new medical imaging modalities have become areas of active research.[17,18] The focus here is on opto-acoustics[19–26] as the most promising in the list of technologies that combine light and sound.

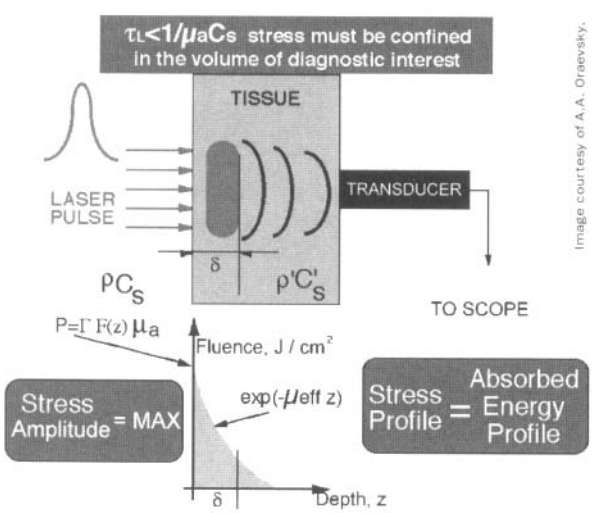

Figure 1. Principles of opto-acoustic signal generation.

Principles

During the opto-acoustic effect, a laser light pulse upon absorption induces an adiabatic temperature rise resulting in a pressure build-up, followed by an acoustic shock wave propagating to the surface (see Fig. 1). The amplitude of the generated photo-acoustic signal is determined by the product of the absorption coefficient and local fluence rate, as well as thermophysical properties of the medium. The preceding light path of the photon, caused by scattering, before being absorbed, is therefore not relevant. Ultrasonic transduction is used for detection.

Opto-acoustic imaging can be performed in continuous wave amplitude modulation mode or pulse mode operation. The latter generates the highest signal amplitudes and broadest ultrasonic frequency spectrum, yielding greater resolution and sensitivity. The opto-acoustic signal, expressed as a pressure, is determined by the thermo-elastic expansion coefficient, β, optical absorption coefficient, μ_a, and distribution of the absorbed photons, $H(z)$.

$$P(z) = \frac{\beta_{cS}^2}{C_P} H(z)\mu_a = \Gamma(T)H(z)\mu_a \qquad (1)$$

The simple expression demonstrates that opto-acoustic imaging can provide information on tissue optical properties at a given tissue temperature.[26] Equation 1 is strictly valid only when the heating process is instantaneous compared to the medium expansion resulting in instant stress generation. Temporal stress confinement requires laser pulse durations much shorter than the time of stress propagation across the light penetration depth in the medium. For typical sonic velocities in tissue and optical absorption, coefficients for hemoglobin, melanin, and porphyrins laser pulses with several nanosecond duration provide ideal excitation sources for the application. The sharp temporal pressure profile will carry both very high and low ultrasonic frequencies. The high frequency components are capable of delivering high-resolution information. Lower frequencies deliver dimensions of larger objects. High frequencies attenuate more rapidly and therefore sensitivity at greater depths is limited.

Opto-acoustic waves generated by nanosecond laser pulses contain frequency components up to several 100 MHz. Detection requires broader bandwidth transducers than used in conventional ultrasound. By measuring the pressure in a detection plane (either by scanning a single element or using a transducer array) as function of position and time, an image can be constructed. Time-of-flight detection of broadband ultrasonic waves gives rise to enhanced longitudinal (depth) resolution. For dermatological and other subsurface (several millimeter deep) applications, 300 MHz detection yields a depth resolution of 10 μm provided the ultrasound transducer has temporal resolution of several nanoseconds and assuming sound speeds on the order of millimeters per microseconds. Medical ultrasonic imaging systems using piezoelectric transducers as the ultrasound source and receiver typically create images with 10 times less resolution because they use lower frequencies.

Irradiation wavelengths may be chosen in the range

from near-UV to near-IR to achieve desirable depths of light penetration in tissues, and to provide optical contrast for tissue differentiation. Wavelength and pulse width requirements make opto-acoustic imaging applications very amenable to any one of a variety of *Q*-switched solid-state lasers and optical parametric oscillators (OPO) as the irradiation source.

Laser opto-acoustic tomography can be performed in either forward mode for deep tissue applications[22, 24, 27] (two surface access, see Figure 2a) or in backward mode for surface and sub-surface applications (single surface access, see Fig. 2b).[19, 28, 29] The two modes of detection permit substantial flexibility for *in vivo* imaging of various human organs. Transmission mode can be applied in breast cancer diagnosis. Reflection mode detects pressure transients generated in tissue layers propagated backward to the same site as the irradiated surface emphasizing high spatial resolution images (up to 10 μm) of thin layers, and detection of early subsurface lesions in various organs or dermatology. Restraints on the acoustic detector for reflection mode require the incoming laser pulse to illuminate the tissue without being obstructed by the acoustic transducer. All applications benefit from placing the transducer in the acoustic near field because acoustic diffraction attenuates the amplitude and changes the shape of the waves as they propagate from their origin.

Current interest and applications

Historically, the "Holy Grail" for transillumination has been mammography with the hope of replacing X-rays with a nonionizing and noninvasive diagnostic. Not surprisingly, this turns out to be a Herculean task because of the large amount of breast tissue—up to 6 cm—the light must pass through and retain image information. Preservation of image information, not only for diagnostic (resolution requirement of ≤ 1 mm), but even for screening (resolution requirement of ~ 1 cm) purposes typically requires a combination of techniques mentioned previously.[5–10] Opto-acoustics does not rely on these methods because of light path indifference.

Light-based tissue imaging techniques use blood as the major contrast agent. Developing tumors exhibit an advanced microcirculation network inside and around the affected area (angiogenesis).[30] This finding may be used in opto-acoustic tomography for sensitive detection of tumors and is presently a major emphasis of Alexander Oraevsky's research group at the University of Texas Medical Branch (UTMB).[27, 31–32] Angiogenesis in malignant and benign tumors can result in different structure of the microcapillary networks between the two tumor types. Medical imaging with opto-acoustics may be able to distinguish malignancies, reducing the number of unnecessary biopsies, potentially an advantage over conventional imaging modalities such as X-ray radiography, magnetic resonance imaging, and ultrasound.

Robert Kruger and colleagues at the University of Indiana Department of Radiology are applying radio frequency (rf) energy as the excitation source in their development of a thermo-acoustic computed tomographic (TCT) device.[33] Although the use of microwaves to induce ultrasonic signals in tissue has been extensively studied,[34–37] they believe the use of longer wavelength rf waves (434 MHz) has advantages in that they, like microwaves, penetrate many centimeters of breast tissue, provide sufficient contrast, and are already approved by the Federal Communications Commission (FCC) for medical applications. They have constructed a 64-channel TCT scanner and have recorded tomographic images of the human breast.

Other biopsy applications the UTMB group is exploring with opto-acoustics include detection of early cancers and lesions of internal organs such as the oral cavity, esophagus, and gastrointestinal tract using opto-

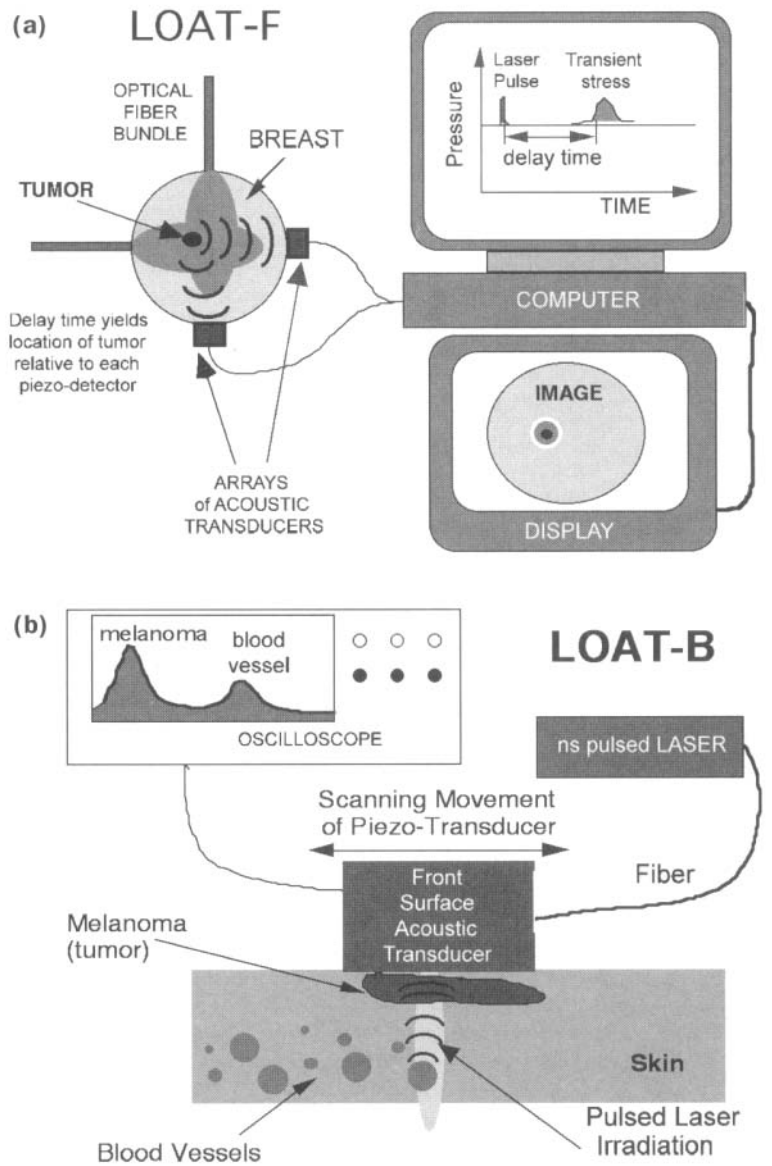

Figure 2. (a) Schematic diagrams of the LOAT-F (Laser Opto-acoustic Tomography in Forward Mode), (b) The LOAT-B (Laser Opto-acoustic Imaging in Backward Mode). A typical laser-induced ultrasonic wave in LOAT-F has a frequency of 100 kHz to 5 MHz and can propagate in tissues with minimal attenuation, providing high sensitivity for the imaging of deeply located tumors. A typical ultrasonic wave in LOAT-B has a frequency of 5 MHz to 100 MHz and can propagate in tissues with minimal acoustic diffraction delivering information with high spatial resolution.

acoustic endoscopy,[38] and high resolution characterization of skin lesions, such as vascular (port wine stains) and pigmented (melanomas) lesions.[39] Figure 3 (page 31) shows comparative results of opto-acoustic imaging of normal and early cancer stages of squamous cell carcinoma produced in a hamster cheek pouch model. Pronounced changes in subsurface tissue structures that occur in the course of cancer development in hamsters treated with DMBA carcinogenic substance were not detected upon gross examination.

When tissue undergoes coagulation in the course of thermal treatment, optical properties and thermo-elastic properties change dramatically.[40] Opto-acoustic imaging, that uses both optical and thermo-elastic contrast, is therefore a strong candidate for monitoring tissue coagulation. Presently opto-acoustics is being investigated as a means of noninvasive monitoring of tumor ablation with rf or cryogenic procedures, and as a source of feedback information that will help to refine laser dermatological procedures as these procedures move from the doctor's office to the salon. Recently the UTMB research group used the laser opto-acoustic technique for real-time measurements of thermal damage in tissues as a means of controlling the extent of tissue coagulation.[41,42]

Differentiation and enhanced contrast using opto-acoustics for an optically inhomogeneous material with a layer structure such as human skin and water, bone, and cartilage, has been investigated by Martin Frenz and colleagues at the University of Berne in a collaboration with Guenther Paltauf's group at the Karl-Franzens-Universität.[43,44] Bone, normally inaccessible by conventional ultrasound imaging, holds promise as an application for opto-acoustics due to the reliance on optical, not ultrasonic, differences for contrast. Using tunable nanosecond pulses from an optical parametric oscillator to target specific absorbers in multi-layered tissue, differentiation is achieved. Figure 4 depicts an *in vivo* measurement in human skin showing a depth profile through the epidermis (peak 1), where absorption in melanin is dominant, and the dermis, where absorbing blood vessels are present (peak 2). Changing the wavelength between 500 and 550 nm reduces the blood absorption, thereby decreasing the amplitude of peak 2 in relation to peak 1. This example demonstrates the possibility of selective imaging using a tunable laser source.

F.F.M. de Mul and his colleagues from the University of Twente have produced 3-D images of deep lying blood vessels and hairs in real tissue samples[45,46] by processing photo-acoustic time-of-flight signals with a beam-focusing algorithm that accommodates spherical waves and works properly in retrieving the sources from the acoustic signals. Depths down to about 10 mm have been imaged with resolutions of about 10μm axially and 200 μm laterally. Lateral resolution is determined by the dimensions of the detectors.

The group of Tim Mills at the University College London has developed an all-optical, fiber, photo-acoustic/photo-thermal sensor,[47,48] that is small in diameter (250 μm), and has a high frequency and wide bandwidth response. The acoustic sensor uses a Fabry-Perot interferometer bonded to the distal end and a photodiode positioned at the proximal end of the fiber as the acoustic wave detector. Originally the device was developed for the time-resolved, photo-acoustic, spectroscopic analysis of the arterial wall during laser angioplasty. Presently, the optical fiber sensor is being developed as a topical, endoscopic, or interstitial detector for the assessment of suspected malignant tumors and other tissue pathologies by measuring the amplitude, rise, and decay times of the photothermal responses of cancer and normal tissue.

Commercial prospects: What is needed?

For any new modality to have commercial prospects it must meet the criteria of clinical utility and viability. These are 1) it must compete with or compliment existing modalities; 2) it must not be cost prohibitive; and 3) it must be user friendly.

With other optical technologies,[5–7] progress has been made in realistic clinical situations where a resolution of approximately 5 mm is obtained at a depth of a few centimeters. Optical Coherence Tomography[8] (OCT) provides resolutions of 10 μm, but only at depths on the order of a millimeter in turbid tissue. Opto-acoustics can fill the gap between OCT and other photon transillumination techniques. With green light, a resolution of approximately 10 μm can be expected at a depth of several millimeters. With near-IR light, both penetration depth will increase and resolution will degrade by approximately a factor of five. In other photon transillumination methods (either in the time or frequency domain), the scattering of light by the medium has an extremely deleterious influence on imaging and quantitative analysis. With opto-acoustics, however, scattering is advantageous, diffusing the light fluence conveniently and making the photo-acoustic process more homogeneous. The "bathing" of the sample with photons alleviates many technical difficulties associated with scanning of the irradiation source.

With respect to other more conventional modalities such as X-rays, ultrasound, and magnetic resonance imaging (MRI), comparisons depend on particular situations. Cost is comparable with X-rays with the benefit of using nonionizing radiation and similar resolutions. Prices can be higher than conventional ultrasound, however, contrast and resolution are far better. MRI is much more expensive, less versatile, and cumbersome.

The use of lasers in medical diagnostic modalities often meets resistance because criteria 2 and 3 come into question. For most opto-acoustic applications, millijoule level, *Q*-switched, near-IR lasers with reasonable repetition-rates (tens of hertz to kilohertz) allow for clinically usable energies and image acquisition times. Although the "dream machine" for such an application is an all solid-state, diode-pumped system, flashlamp pumped systems with proven track records and competitive prices will be very satisfactory. These systems will likely be adequate (at high repetition rates) for most surface and sub-surface tissue imaging. For mammography, higher energy (several hundred millijoules) will be

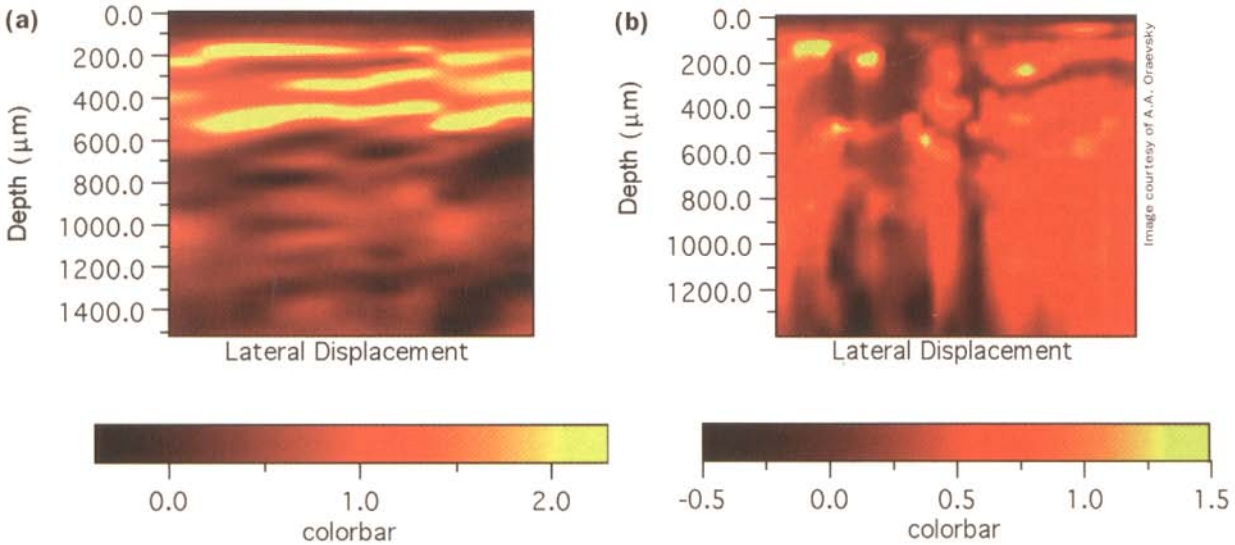

Figure 3. The opto-acoustic images depict distinct tissue layers in (a) control (normal) animals and (b) heterogeneous structureless tissue in pre-cancer and cancer stages. Imaging was performed using 12-ns Nd:YAG laser pulses (FWHM) at the wavelength of 532 nm, which provided sufficient depth of monitoring (2 mm), significant tissue contrast, and 30-μm in depth resolution.

necessary. This application can bear the increased cost. Lasers required for opto-acoustic tomography represent a mature technology and do not pose any impediment to the development of the technology for clinical use.

For clinically relevant, and therefore commercially viable systems, to become commonplace, improvements in the area of 2-D detection need to take place. To date, most 2-D images have been acquired by scanning a single detector over a surface. Although this is sufficient for some applications, to take images of larger areas, with acquisition times suited to clinical settings, multiplexed array transducers are being developed.[33, 46, 49–50]

Although optical contrast is better than ultrasound contrast using endogenous absorbers and scatterers, optical contrast can often be improved. The absorption contrast between blood and the surrounding medium varies with wavelength. The sensitivity will therefore vary accordingly, and depends on what location is being targeted in the tissue. Contrast will be diminished by approximately a factor of 10 when going from surface applications using 530 nm to deep tissue applications using 0.80–1.06 μm. Thus, for longer wavelength systems, exogenous contrast agents, such as dyes, similar to those used in other optical techniques, such as absorption and fluorescence imaging,[51, 52] will enhance performance.

A very compelling reason why opto-acoustic imaging may be accepted into the clinical environment, and thus aid in its commercialization, is the fact that ultrasound is already a fully entrenched modality. Two companies are presently pursuing the commercialization of opto-acoustics for medical imaging. Optosonics Inc. of Indianapolis is working to commercialize the TCT breast imager being developed by Robert Kruger's group at the University of Indiana School of Medicine. LaserSonix Technologies Inc., a Houston based start-up, is in the process of commercializing the research of the UTMB group.

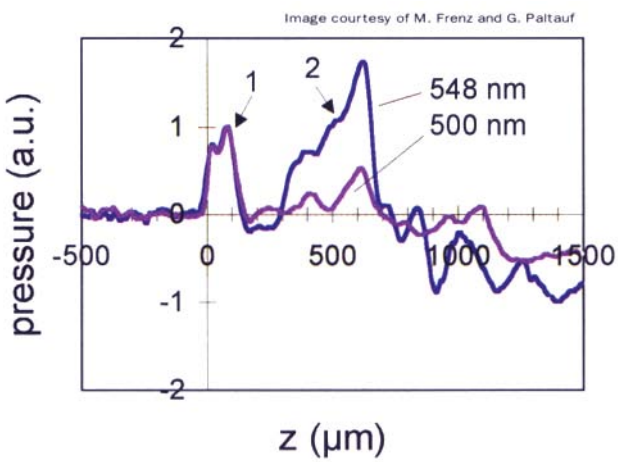

Figure 4. Opto-acoustic signals generated in human skin by absorption of OPO pulses at two different wavelengths. Peak 1 is due to absorption in the epidermis, peak 2 arises from blood absorption in capillaries.

Acknowledgments

The author would like to thank Alexander Oraevsky, Robert Kruger, Martin Frenz, Guenther Paltauf, and F.F.M. de Mul for very helpful input while preparing this article. The Opening TCT image on page 27 is courtesy of Opto-Sonics, Inc. Indianapolis, IN (http://optosonics.com).

References

1. A.L. Weber, *Diagnostic Ultrasound* (Miller Freeman, San Francisco, CA, 1995).
2. M. Cutler, "Transillumination as an aid to diagnosis of breast lesions," Surg. Gynaecol. Obstet. **48,** 721 (1929).
3. J.L. Boulnois, "Optical properties of tissue," Lasers Med. Sci. **1,** 47 (1986).
4. V.G. Peters *et al.*, "Optical properties of normal and diseased human breast tissues in the visible and near infrared," Phys. Med. Biol. **35,** 1317–1334 (1990).
5. L. Wang *et al.*, "Ballistic 2-D imaging through scattering walls using an ultrafast optical Kerr gate," Science **253,** 769–771 (1991).
6. J.C. Hebden *et al.*, "Time resolved imaging through a highly scattering medium," Appl. Opt. **30,** 788 (1991).
7. O. Coquoz *et al.*, "Frequency-domain photon migration

(FDPM) measurements of cell and tissue optical properties for biomedical diagnostics," *Biomedical Optical Spectroscopy and Diagnostics, 1996 Technical Digest* (OSA, Washington, DC, 1996), pp. 21–23.
8. D. Huang *et al.*, "Optical coherence tomography," Science **254,** 1178 (1991).
9. J.R. Singer *et al.*, "Image reconstruction of the interior bodies through diffuse radiation," Science **248,** 990 (1990).
10. E.A. Sickels, "Computed tomography scanning, transillumination, and magnetic resonance imaging," *Recent Results in Cancer Research* **105** (Springer-Verlag, Berlin-Heidelberg, Germany, 1987), p. 31.
11. A.G. Bell, "On the production of sound by light," Am. J. Sci. **20,** 324 (1880).
12. E.F. Carome *et al.*, "Generation of acoustic signals in liquids by ruby laser-induced thermal stress transients," Appl. Phys. Lett. **4,** 95–97 (1964).
13. V.P. Zarov and V.S. Letokhov, *Laser Opto-Acoustic Spectroscopy* (Springer-Verlag, New York, NY, 1984).
14. A.C. Tam, "Applications of photoacoustic sensing techniques," Rev. Mod. Phys. **58,** 381–481 (1986).
15. M.W. Sigrist, "Laser generated acoustic waves in liquids and solids," J. Appl. Phys. **60,** R83-R121 (1986).
16. A. Campbell *et al.*, "A Feasibility Study on Pulsed Photoacoustic Spectroscopy for Non-invasive Glucose Monitoring," *Biomedical Optical Spectroscopy and Diagnostics, 1996 Technical Digest* (OSA, Washington, DC, 1996), pp. 11–13.
17. F.A Marks *et al.*, "Comprehensive Approach to Breast Cancer Detection Using Light: Photon Localization by Ultrasound Modulation and Tissue Characterization by Spectral Discrimination," B. Chance and R.R. Alfano, eds., in Proc. SPIE Conference on Photon Migration and Imaging in Random Media and Tissues, **1888** (SPIE Press, Bellingham, WA, 1993), pp. 500–510.
18. L.V. Wang and Q. Shem, "Sonoluminescence Tomography of Turbid Media," B. Chance *et al.*, eds., to appear in Proc. of SPIE Conference on Optical Tomography and Spectroscopy of Tissue III (SPIE, Bellingham, WA, 1999), p. 3597.
19. A.A. Oraevsky *et al.*, "Laser-based Optoacoustic Imaging in Biological Tissues," Proc. SPIE Conference on Laser-Tissue Interaction V, S.L. Jacques, ed., **2134A** (SPIE Press, Bellingham, WA, 1994), pp. 122–128.
20. R.A. Kruger, "Photoacoustic ultrasound," Med. Phys. **21,** 127–131 (1994).
21. A.A. Oraevsky, "A nanosecond acoustic transducer with applications in laser medicine," IEEE/LEOS Newsletter **8,** 6–17 (1994).
22. A.A. Oraevsky *et al.*, "Time-resolved Optoacoustic Imaging in Layered Biological Tissues," *Advances in Optical Imaging and Photon Migration,* R.R. Alfano, ed. **21** (Academic Press, New York, NY, 1994), pp. 161–165.
23. R.A. Kruger *et al.*, "Photoacoustic ultrasound-reconstruction tomography," Med. Phys. **22,** 1605–1609 (1995).
24. A.A. Oraevsky *et al.*, "Laser Opto-acoustic Tomography for Medical Diagnostics: Principles," R.A. Lieberman *et al.*, eds., Proc. SPIE Conference on Biomedical Sensing, Imaging, and Tracking Technologies I **2676** (SPIE Press, Bellingham, WA, 1996), pp. 22–31.
25. A.A. Karabutov *et al.*, "Time-resolved laser optoacoustic tomography of inhomogeneous media," Appl. Phys. B **63,** 545–563 (1996).
26. A.A. Oraevsky *et al.*, "Measurement of tissue optical properties by time-resolved detection of laser-induced transient stress," Appl. Opt. **36,** 402–415 (1997).
27. R.O. Esenaliev *et al.*, "Laser Optoacoustic Imaging for Breast Cancer Diagnostics: Limit of Detection and Comparison with X-ray and Ultrasound Imaging," B. Chance and R.R. Alfano, eds., Proc. SPIE Conference on Optical Tomography and Spectroscopy of Tissue: Theory, Instrumentation, Model, and Human Studies II **2979** (SPIE Press, Bellingham, WA, 1997), pp. 71–82.
28. A.A. Oraevsky *et al.*, "Lateral and z-axial Resolution in Laser Optoacoustic Imaging with Ultrasonic Transducers," B. Chance and R.R. Alfano, eds., Proc. SPIE Conference on Optical Tomography and Spectroscopy of Tissue: Theory, Instrumentation, Model, and Human Studies II **2389** (SPIE Press, Bellingham, WA, 1995), pp. 198–208.
29. A.A. Oraevsky *et al.*, "Laser Optoacoustic Tomography of Layered Tissues: Signal Processing," B. Chance and R.R. Alfano, eds., Proc. SPIE Conference on Optical Tomography and Spectroscopy of Tissue: Theory, Instrumentation, Model, and Human Studies II **2979** (SPIE Press, Bellingham, WA, 1997), pp. 59–70.
30. J. Folkman, "What is the evidence that tumors are angiogenesis dependent?" J. Natl. Cancer Inst. **82,** 4–6 (1990).
31. A.A. Oraevsky *et al.*, "Breast Cancer Diagnostics by Laser Optoacoustic Tomography," *Advances in Optical Imaging and Photon Migration, 1996 Technical Digest* (OSA, Washington, DC, 1996), pp. 160–162.
32. A.A. Oraevsky *et al.*, "Laser Optoacoustic Imaging of Breast: Detection of Cancer Angiogenesis," B. Chance *et al.*, eds., Proc. SPIE Conference on Optical Tomography and Spectroscopy of Tissue III **3597** (SPIE Press, Bellingham, WA, 1999), in press.
33. R.A. Kruger, private communication.
34. K.R. Foster and N.S. Arkhipov, "Microwave hearing; Evidence for thermoacoustic auditory stimulation by pulsed microwaves," Science **185,** 256–258 (1980).
35. R.J. von Gutfield, "Thermoelastic generation of elastic waves for non-destructive testing and medical diagnostics," Ultrasonics **18,** 175–181 (1980).
36. R.G. Olsen, "Generation of Acoustic Images From the Absorption of Pulsed Microwave Energy," J.P. Powers, ed., *Acoustic Imaging* (Plenum Publishing, New York, NY, 1982).
37. J.C. Lin and K.H. Chan, "Microwave-induced thermoacoustic tissue imaging—system design," IEEE Trans. Microwave Theory Tech. **32,** 854–860 (1984).
38. A.A. Karabutov *et al.*, "Opto-acoustic Detection of Oral Cancer: Feasibility Studies in Hamster Model of Squamous Cell Carcinoma," B. Chance *et al.*, eds., Proc. SPIE Conference on Optical Tomography and Spectroscopy of Tissue III **3597** (SPIE, Bellingham, WA, 1999), in press.
39. A.A. Karabutov *et al.*, "Imaging Vascular and Layered Structures of Skin with Optoacoustic (front surface) Transducer," S.L. Jacques, ed., Proc. SPIE Conference on Laser-Tissue-Interaction X **3601** (SPIE, Bellingham, WA, 1999), in press.
40. A.A. Karabutov and V.E. Gusev, *Laser Optoacoustics* (AIP Press, New York, NY, 1993).
41. R.O. Esenaliev *et al.*, "Laser OptoAcoustic Technique for Real-time Measurement of Thermal Damage in Tissues," T.P. Ryan and T.Z. Wong, eds., Proc. SPIE Conference on Thermal Treatment of Tissue with Image Guidance **3594** (SPIE, Bellingham, WA, 1999), in press.
42. R.O. Esenaliev *et al.*, "Real Time Optoacoustic Monitoring of Photothermal Laser-tissue Interactions," S.L. Jacques, ed., Proc. SPIE Conference on Laser-Tissue-Interaction X **3601** (SPIE, Bellingham, WA, 1999), in press.
43. G. Paltauf and H. Schmidt-Kloiber, "Measurement of laser-induced acoustic waves with a calibrated optical transducer," J. Appl. Phys. **82,** 1525–1531 (1997).
44. K.P. Köstli *et al.*, "Optoacoustic Measurements of Water, Bone and Cartilage with an Infrared-OPO," S.L. Jacques, ed., Proc. SPIE Conference on Laser-Tissue-Interaction X **3601** (SPIE, Bellingham, WA, 1999), in press.
45. C.G.A. Hoelen *et al.*, "Three-dimensional photoacoustic imaging of blood vessels in tissue," Opt. Lett. **28** (1998).
46. C.G.A. Hoelen *et al.*, "Photoacoustic Tissue Scanning (PATS)," B. Chance *et al.*, eds., Proc. SPIE Conference on Optical Tomography and Spectroscopy of Tissue III **3597** (SPIE, Bellingham, WA, 1999), in press.
47. J. Laufer *et al.*, "Photoacoustic-photothermal Optical Fiber Sensor for the Minimally Invasive Detection of Cancers and Other Tissue Pathologies," A. Katzir and J.A. Harrington, eds., Proc. SPIE Conference on Specialty Fiber Optics for Medical Applications **3596** (SPIE, Bellingham, WA, 1999), in press.
48. T.N. Mills, "Pulsed photoacoustic characterization of arterial tissue," S.L. Jacques, ed., Proc. SPIE Conference on Laser-Tissue-Interaction X **3601** (SPIE, Bellingham, WA, 1999), in press.
49. A.A. Oraevsky *et al.*, "Two-dimensional Optoacoustic Tomography: Array Transducers and Image Reconstruction Algorithm," S.L. Jacques, ed., Proc. SPIE Conference on Laser-Tissue-Interaction X **3601** (SPIE, Bellingham, WA, 1999), in press.
50. G. Paltauf *et al.*, "Two-dimensional Recording of Opto-Acoustic Waves," S.L. Jacques, ed., Proc. SPIE Conference on Laser-Tissue-Interaction X **3601** (SPIE, Bellingham, WA, 1999), in press.
51. E.M. Sevick *et al.*, "Localization of absorbers using frequency-domain measurements of time-dependent photon migration," Appl. Opt. **33,** 3562–3570 (1994).
52. E.M. Sevick-Muraca *et al.*, "Fluorescence-lifetime Based Sensing in Tissues and Other Random Media with Measurement of Photon Migration," *Analytical Use of Fluorescent Probes in Oncology*, E. Kohen, ed. (Plenum Press, New York, NY, 1996).

Howard Nathel (hnathel@pipeline.com) is a consultant in the areas of laser and biomedical optics and a founder of LaserSonix Technologies Inc., Houston, TX.