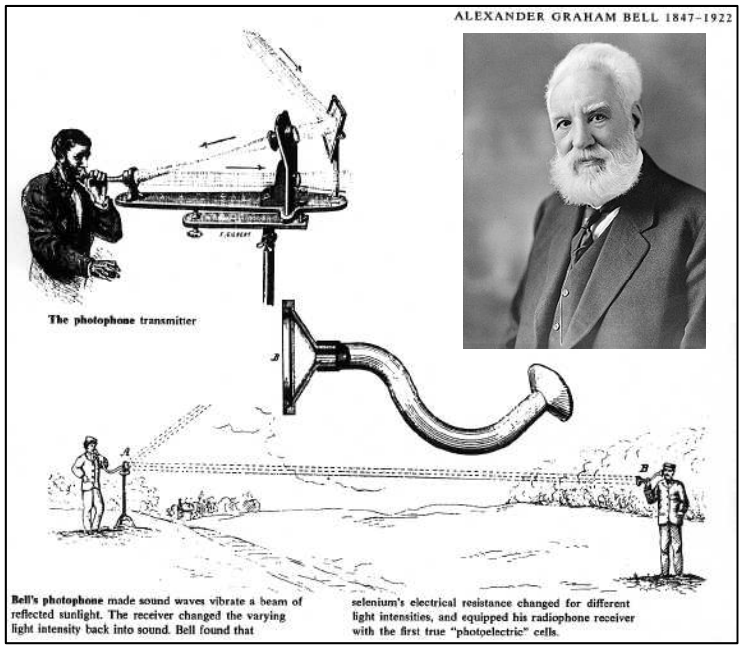
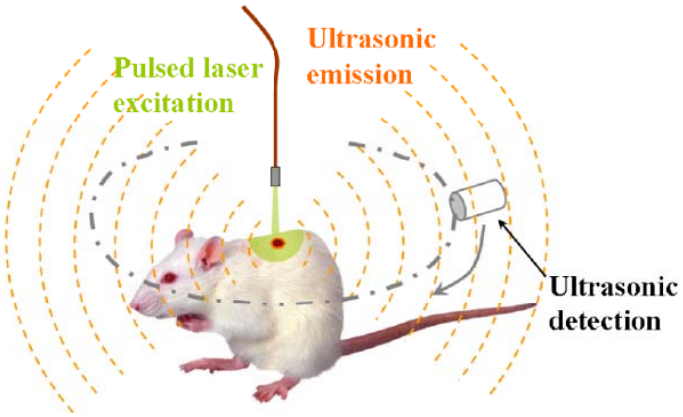
Photoacoustic Tomography

Ultrasound-Modulated Optical Tomography

PAT Introduction

- **Photoacoustic (PA) tomography (PAT)**
  - Also referred to as optoacoustic tomography
  - Emerging biomedical imaging method based on the PA effect
    - Rapid theoretical and technological development in the 1990s
  - Advantages
    - Image deeper into tissue because multiple scattered photons are utilized
    - Suitable for functional and molecular imaging
  - Disadvantages
    - Requires sensitive excitation and emission equipment
- **PA effect**
  - Alexander Graham Bell, 1880 → photophone
  - Generation of acoustic waves by substances
  - Illumination with electromagnetic (EM) waves of varying power → Absorption → Variational thermal expansion → Acoustic wave
  - Predominant tissue absorbers:
    - Blood (Hemoglobin)
    - Melanosomes (Melanin)
    - Water
  - Physical and chemical information in PA signals.





PAT Theory

- **PAT Theory**
  - Excitation: Short EM pulses
    - Short duration → thermal confinement (i.e. ignore thermal diffusion)

$$\tau \ll \tau_{th} = \frac{d_c^2}{D_T}$$

    - where
      - τ_{th} is the thermal confinement threshold
      - d_c is the characteristic dimension size (targeted spatial resolution)
      - D_T is thermal diffusivity (~0.14 mm^2/s for soft tissue)
    - Acoustic stress confinement → The expansion of the object is negligible compared to the size

$$\tau \ll \tau_{st} = \frac{d_c}{v_s}$$

    - where
      - τ_{st} is the acoustic stress confinement threshold
      - v_s is the acoustic velocity
  - Heating function

$$H(\mathrm{r},t) = \begin{cases} \mu_a(\mathrm{r})\Phi(\mathrm{r},t) & \text{(for optical illumination)} \\ \sigma(\mathrm{r})\langle \mathrm{E}^2(\mathrm{r},t)\rangle & \text{(for RF wave illumination)} \end{cases}$$

    - where
      - Φ is the optical fluence rate in W/m^2
      - σ is the electrical conductivity in S/m
      - E is the electrical field
      - <·> represents short-time averaging

- Initial pressure after illumination:

$$p_0(\mathrm{r}) = \Gamma A(\mathrm{r})$$

  - where
    - Γ is a dimensionless parameter (Grueneisen parameter)

$$\Gamma = \frac{v_s^2 \beta}{C_p}$$

    - A(r) is the total energy converted into heat at location r

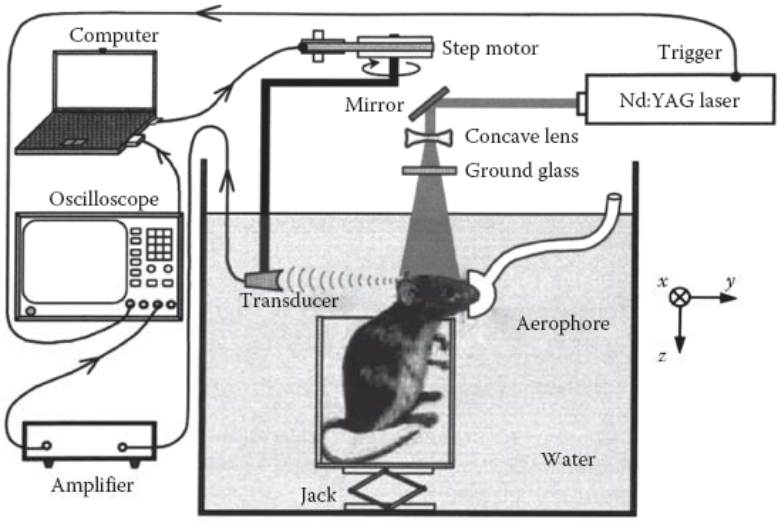
$$H(\mathbf{r},t) \approx \mathrm{A}(\mathbf{r})\ \ \delta(t)$$

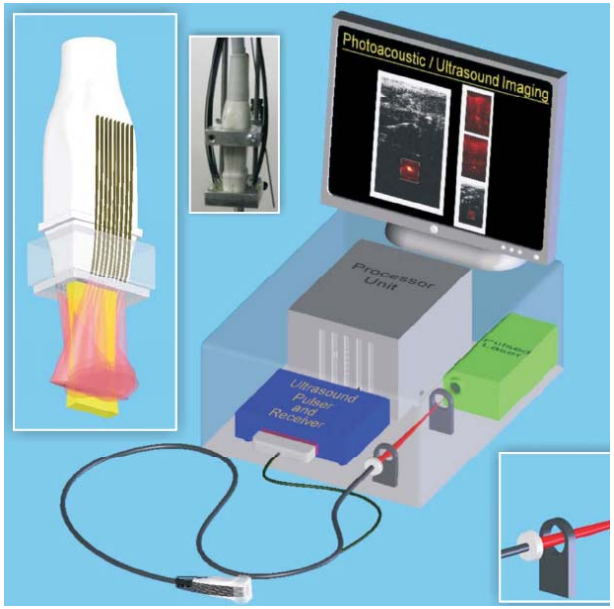
    - β is the isobaric volume expansion coefficient in K^{-1}
    - Cp is the isobaric specific heat in J/K·kg
- Solution
  - After simplifications

$$p(\mathrm{r},t) = \frac{v_s^2}{4\pi}\frac{\partial}{\partial t}\frac{1}{v_s t}\iint_{|r-r'|=v_s t} p_0(\mathrm{r}')ds'$$

PA computed tomography (PAT)

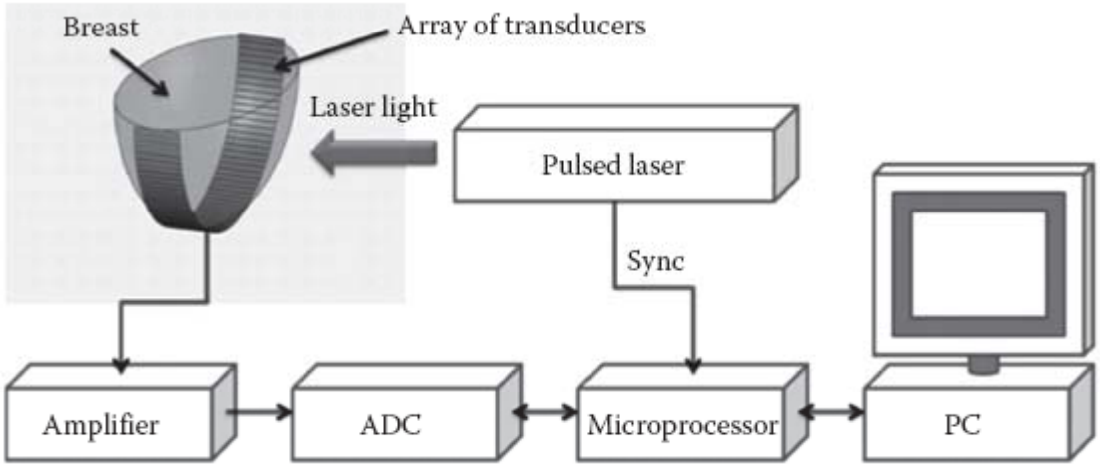
- **Basics**
  - Illuminate with laser
  - Scan a single-element ultrasonic transducer over the tissue surface or use ultrasound array
    - The weak PA signal generally has a wide spectrum → The ultrasonic detector must have high sensitivity and wide band detection
- **Reconstruction Algorithms**
  - Reconstruction of the initial PA absorption distribution → inverse spherical Radon transformation
  - Exact, approximate, and numerical reconstruction algorithms

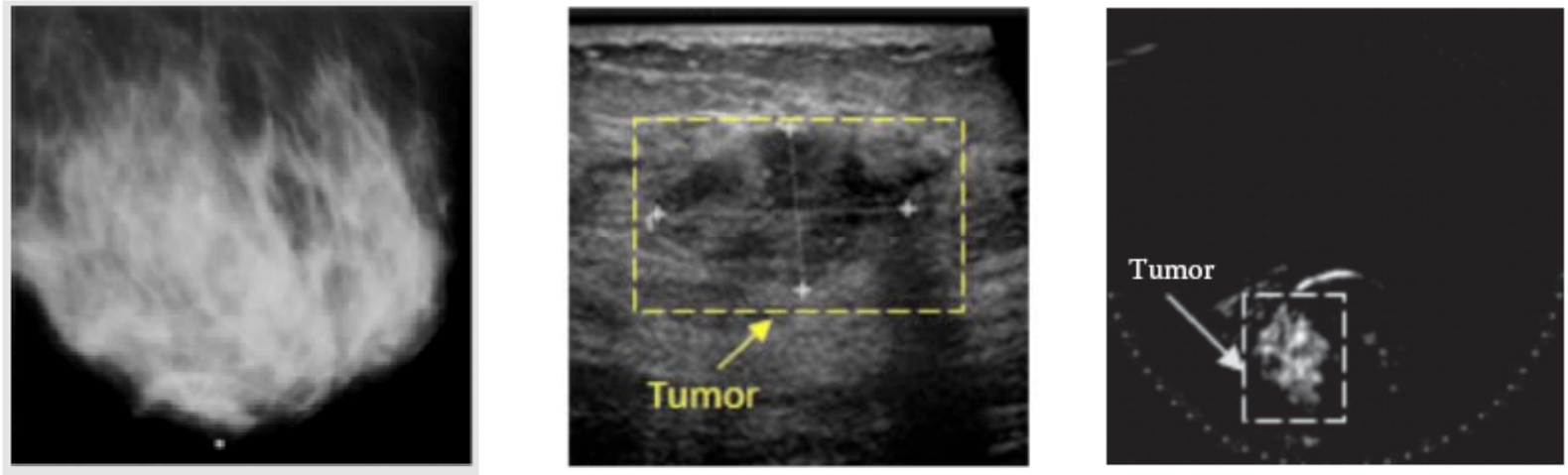




PA computed tomography (PAT)

- **Applications**
  - Breast imaging

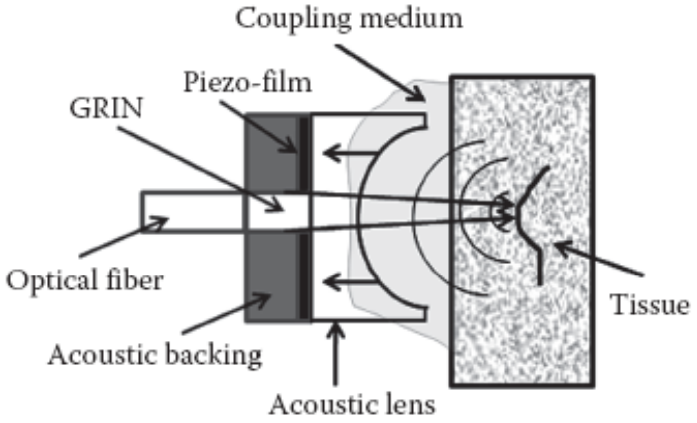


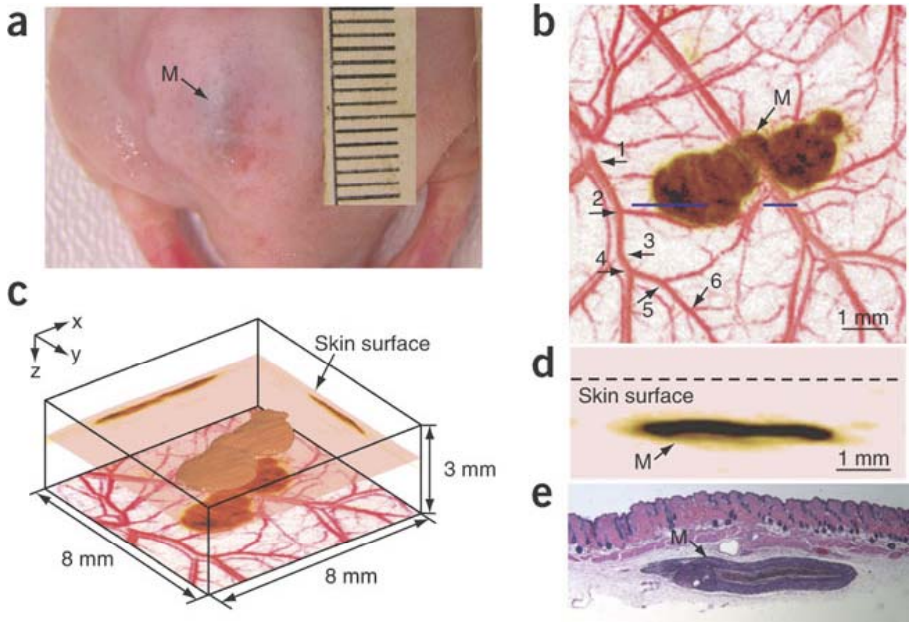


X-ray mammography of a dense breast does not show signs of a tumor; Doppler ultrasonography shows an increased blood flow; PAT clearly shows a tumor (JBO, 14, 024007 (2009))

PA Microscopy

- **Basics**
  - Detects signals with a positively focused ultrasonic transducer
    - Focusing ultrasound in the tissue is much easier than focusing light at depths
  - Direct imaging (no reconstruction)
  - Scanning the transducer in 2 or 3 dimensions
  - Transmission or reflection mode (more convenient for tissue)
  - Limitations
    - Less penetration than PACT

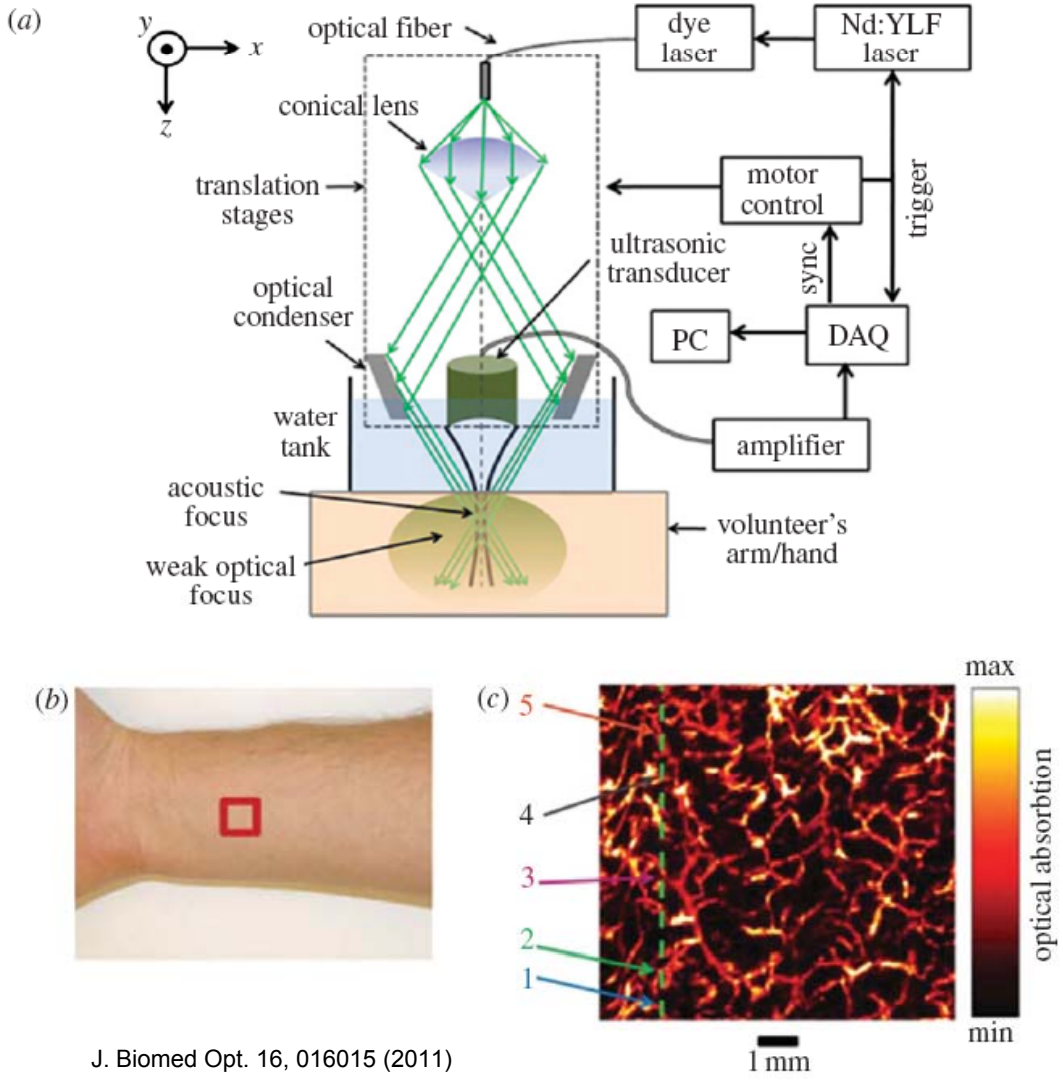




Nature Biotechnology 24, 848 - 851 (2006)

PA Microscopy

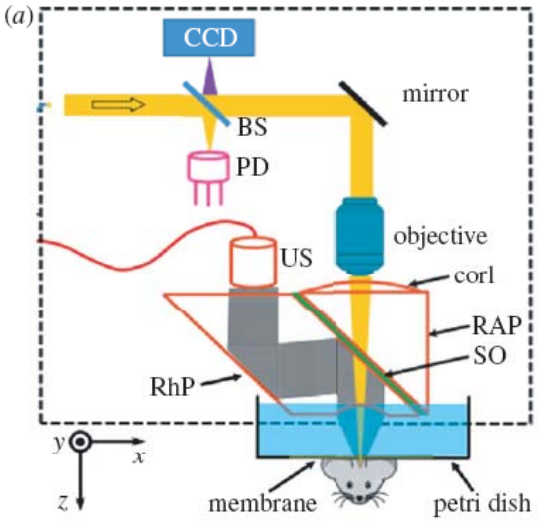
- **Acoustic-resolution photoacoustic microscopy (AR-PAM)**
  - Dark Field PAM
    - Avoid US reverberations from near the surface
  - Lateral resolution at the focus of 45 μm and a vertical resolution of 15 μm for an 8 x 8 mm FOV
  - Limitations
    - Resolutions degrades rapidly away from the focus

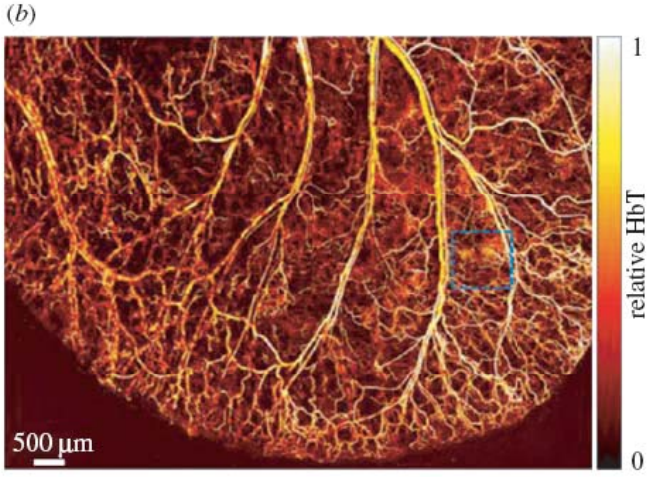


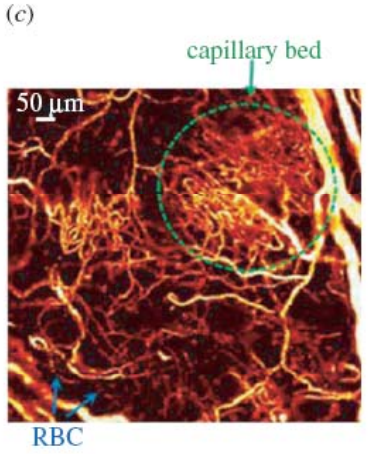
J. Biomed Opt. 16, 016015 (2011)

PA Microscopy

- **Optical-resolution photoacoustic microscopy (OR-PAM)**
  - Light focusing → Determines the lateral resolution
  - More like an optical microscope measuring absorption
  - Better lateral resolution (10 μm)
  - Limitations
    - Less penetrations than AR-PAM → very superficial imaging



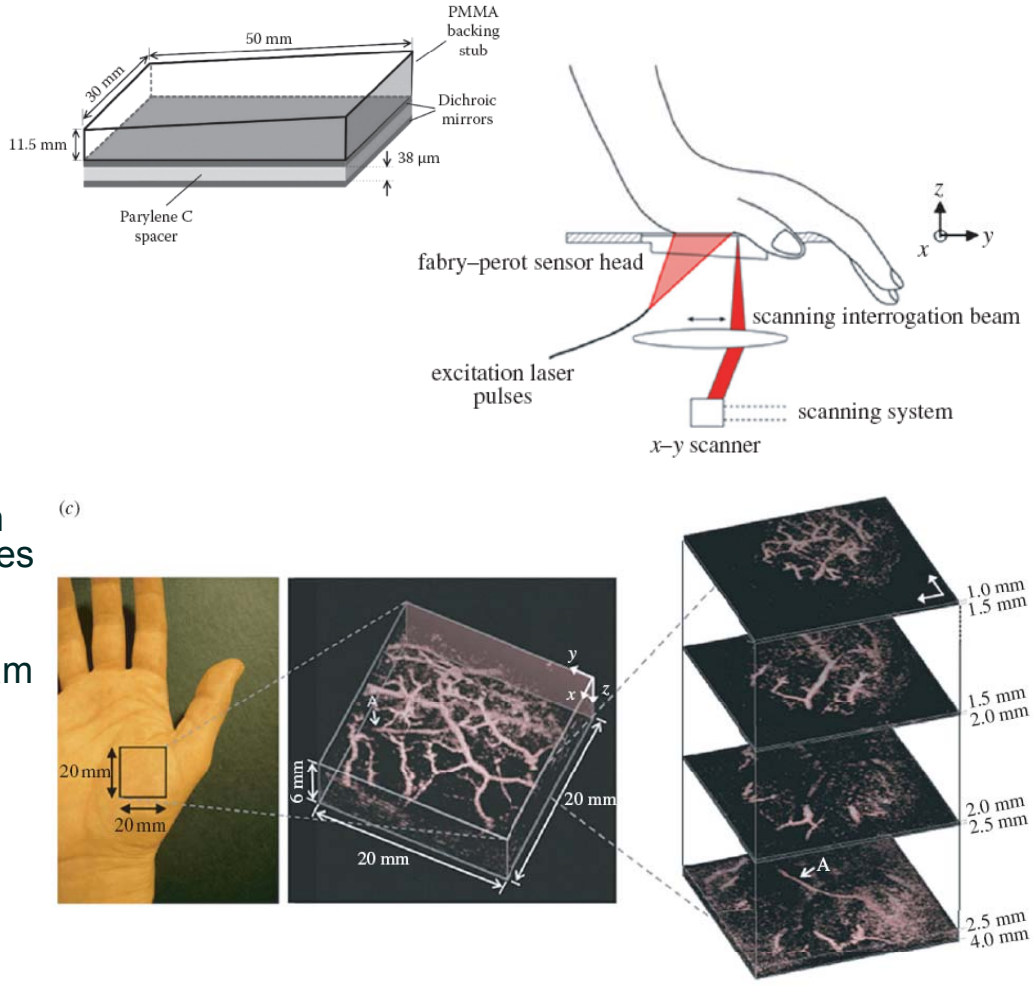




Opt. Lett. 36, 134–1136 (2011)

All optical PA

- **Optical ultrasound detection**
  - Overcoming the limitations of piezoelectric-based detection for planar geometries
    - Low, non-uniform sensitivity
    - Limited bandwidth
  - Transparent Fabry–Perot (FP) polymer film etalon
    - Polymer film spacer sandwiched between a pair of mirrors
    - Acoustically induced changes in the optical thickness of the spacer → modulate the reflectivity of the etalon → detected by measuring the changes in the reflected power of an incident laser beam
    - Raster scanning a focused laser beam across the surface of the sensor →Incident PA wavefront spatially mapped in 2D.
  - Advantages
    - No aperture limatations
    - Broadband response
    - Fine sampling

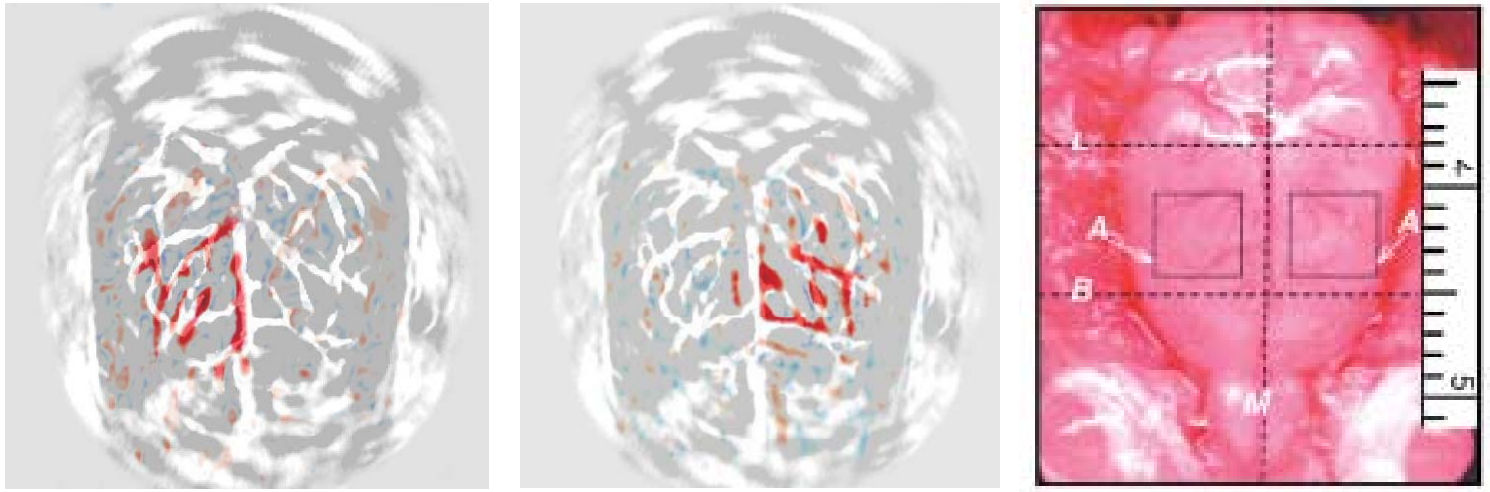


Phys. Med. Biol. 54, 1035–1046 (2009)

PA Spectroscopy and Functional Imaging

- **Absorption**
  - Wavelength and environment sensitive
- **Spectrally dependent absorption of blood**
  - Functional imaging of SO_2

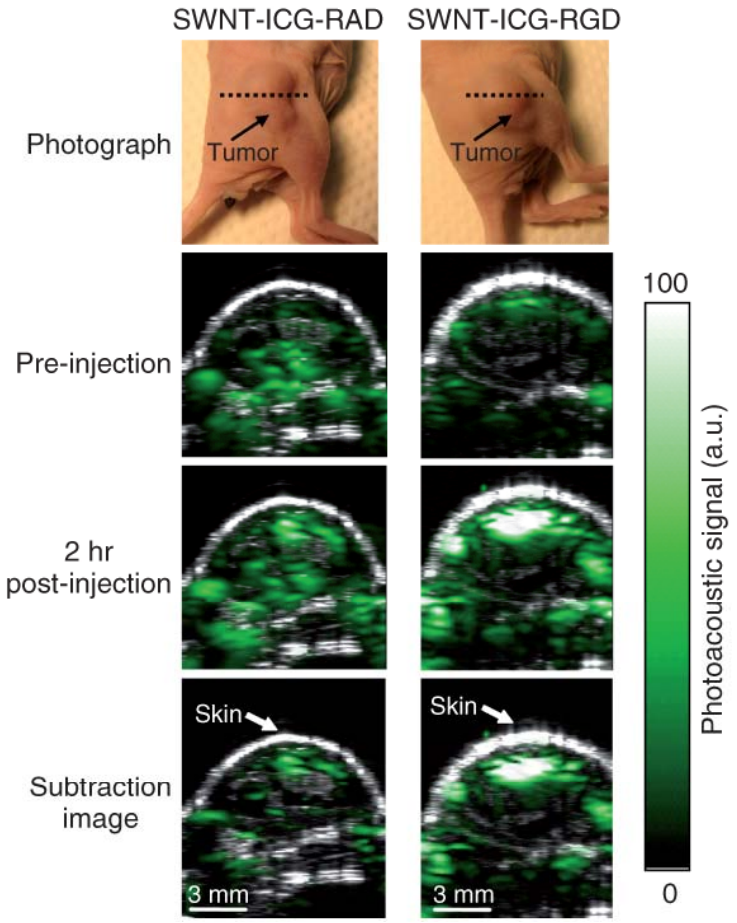
Left whisker stimulation **Right whisker stimulation**



The regions of high differential absorption indicate regions of oxygen utilization. (X. Wang et al., Nat. Biotechnol. 21, 803 (2003))

PA Contrast Agents and Molecular Imaging

- **Contrast agents**
  - Exogenous
  - Enhance the image quality and specificity
  - Dyes
    - E.g. indocyanine green (ICG)
      - FDA approved by FDA
      - High absorption in the NIR spectral region
      - Increase contrast in blood vessels
  - Nanoparticles
    - Absorption peak is tunable by changing the shape and size of the particle
    - Without bio-conjugation →accumulate in tumor sites due to the enhanced vascular permeability and retention
- **PA molecular imaging mechanisms**
  1. Changes at the molecular level → optical or RF absorption properties of contrast agents change
  2. Contrast agents (with specific absorption spectra) bio-conjugated with certain proteins (such as antibodies) → targeting specific molecules



Tumor targeting in living mice with RGD-functionalized carbon nanotubes. Ultrasound image (gray) with photoacoustic overlay (green) at one transverse slice through the tumor (dotted black line). (Nano Lett 2010, 10:2168–217)

Comparison

Imaging modality	Primary contrast	Imaging depth	Resolution
Confocal microscopy	Fluorescence/scattering	~0.2 mm	~1-2 microns
Two-photon microscopy	Fluorescence	~0.5 mm	~1-2 microns
Optical coherence tomography	Optical scattering	~1-2 mm	~10 microns
Ultrasonography (5 MHz)	Ultrasonic scattering	~60 mm	~300 microns
Photoacoustic microscopy (50 MHz)	Optical absorption	~3 mm	~15 microns
Photoacoustic tomography (3.5 MHz)	Optical absorption	~50 mm	~700 microns

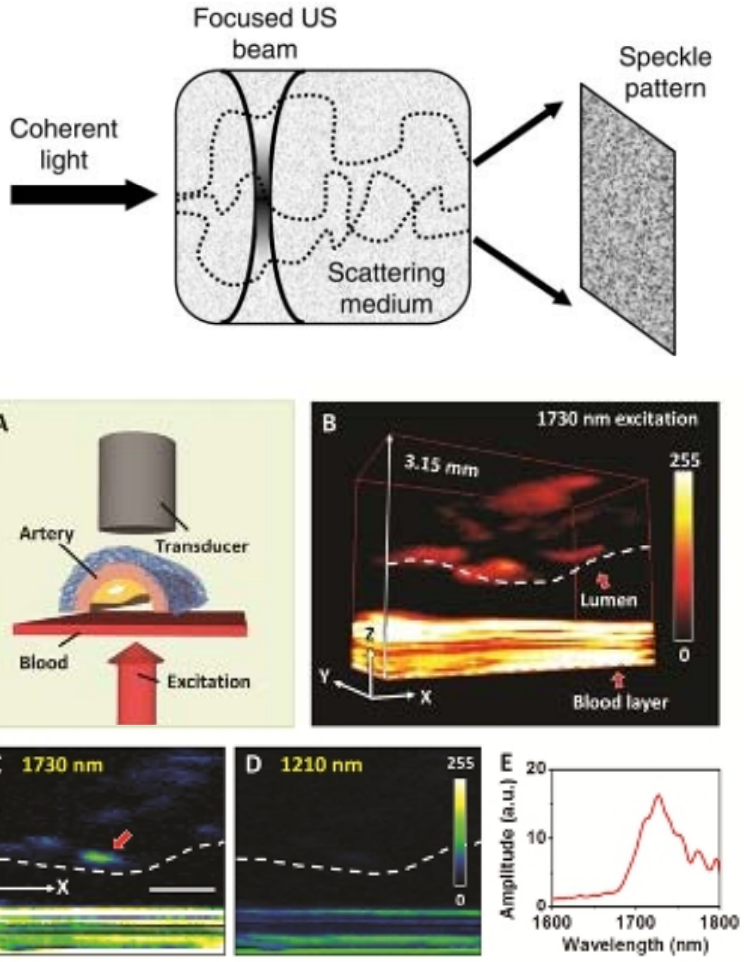
UOT Introduction

- **Ultrasound-Modulated Optical Tomography (UOT)**
  - Why combine light with ultrasound?

Properties	*Diffuse optical tomography*	*Ultrasonic imaging*	*Ultrasound-modulated optical tomography*
Contrast	Excellent (functional)	Poor in early cancers	Excellent (= DOT)
Resolution	Poor (~5-10 mm)	Excellent & scalable	Excellent (= US)
Imaging depth	Good (~5 cm)	Good & scalable	Good
Speckle artifacts	None	Strong	None
Scattering coefficient	Strong (~100 /cm)	Weak (~0.3 /cm)	

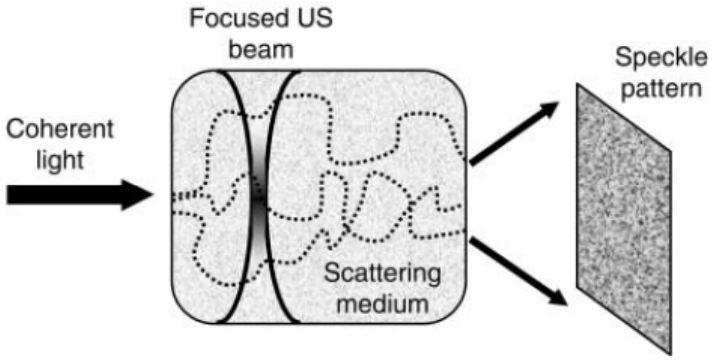
UOT Introduction

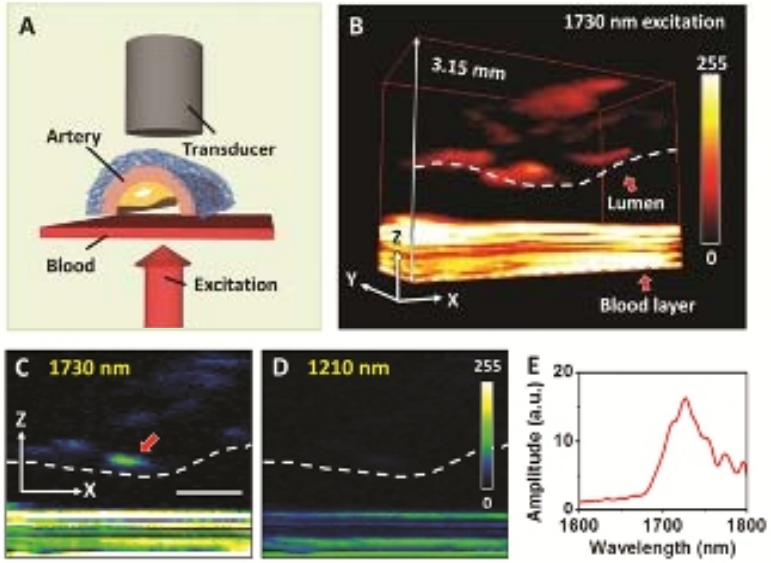
- **Tissues are highly scattering media**
  - DOT unable to provide good-quality images.
  - Use ultrasonic waves, which scatter much less than light waves, to provide better localization
- **Ultrasound-Modulated Optical Tomography (UOT)**
  - Part of the light is modulated by an ultrasonic beam focused inside the biological tissue
  - Modulated photons can be discriminated from background-unmodulated photons → their origin can be directly derived from the position of the focused ultrasonic beam.
  - Three-dimensional (3D) images can be built up by moving the focused ultrasonic beam.
  - Strong optical contrast with high ultrasonic spatial resolution



UOT Introduction

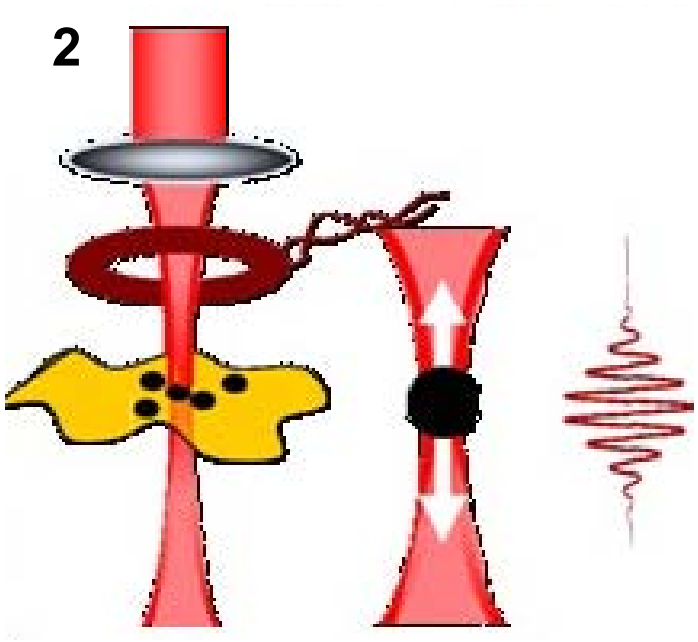
- **UOT Advantages**
  - Image contrast based on optical properties → morphological and functional information of biological
- **UOT Challenges**
  - A major challenge in UOT is the low signal-to-noise ratio (SNR)
    - From low modulation efficiency and uncorrelated phases between speckle grains.
    - Detection techniques
      - Parallel detection with CCD cameras,
      - Speckle contrast detection with CCD cameras,
      - Interferometric techniques
    - Intense ultrasound bursts instead of continuous-wave or pulsed ultrasound





UOT Theory

- **UOT Mechanisms of Contrast**
  1. Incoherent intensity modulation of light due to variations of the optical properties of a medium caused by ultrasound
     - Too weak to be detected experimentally
  2. Changes in the optical phase due to ultrasound-induced displacements of optical scatterers
     - Multiply scattered light accumulates modulation
     - The intensity of the speckles formed by the multiply scattered light fluctuates with the ultrasonic wave
  3. Changes in the optical phase due to ultrasonic modulation of the optical refractive index of the medium
     - As in number 2
  - 2 and 3 require coherent light



UOT Theory

- **The spectral intensity at frequency $n\omega_a$ can be calculated by**

$$I_n = \frac{1}{T_a}\int_0^{T_a} \cos(n\omega_a\tau)G_1(\tau)d\tau$$

  - where
    - T_a is the acoustic period
    - ω_a is the acoustic angular frequency
    - n is an integer
    - $G_1(\tau)$ is the autocorrelation function of the scalar electric field, E(t)

$$G_1(\tau) = \int_0^{\infty} p(s) < E_s{}^*(t+\tau)E_s(t) > ds$$

$$G_1(\tau) = \frac{(L/l)\sinh\left(\left\{\varepsilon\left[1-\cos(\omega_a\tau)\right]\right\}^{1/2}\right)}{\sinh\left((L/l)\left\{\varepsilon\left[1-\cos(\omega_a\tau)\right]\right\}^{1/2}\right)}$$

  - where
    - n_o is the background refractive index
    - k_o is the optical wave vector in vacuo
    - A is the acoustic amplitude, proportional to the acoustic pressure
    - k_a is the acoustic wave vector
    - l is the optical transport mean free path
    - η is the elasto-optical coefficient
    - L is the thickness of the slab

$$\varepsilon = 6(\delta_n + \delta_d)(n_0 k_0 A)^2$$

$$\delta_n = (\alpha_{n1} + \alpha_{n2})\eta^2$$

$$\delta_d = \frac{1}{6}$$

$$\alpha_{n1} = \frac{k_a l \tan^{-1}(k_a l)}{2}$$

$$\alpha_{n2} = \frac{\alpha_{n1}}{\left[(k_a l)/\tan^{-1}(k_a l) - 1\right]}$$

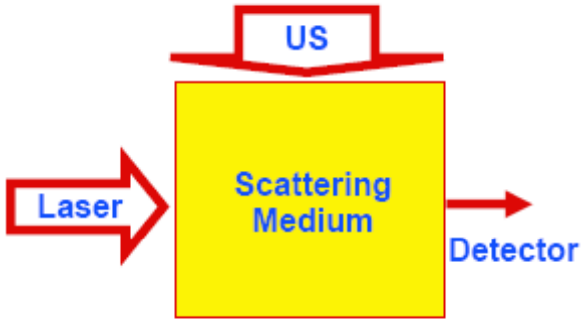
UOT Theory

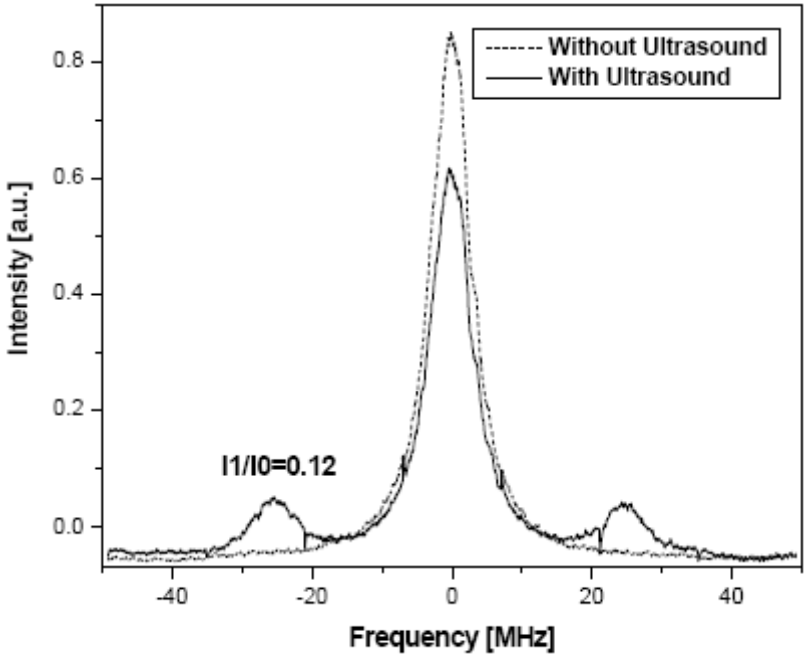
- **Under the weak-modulation approximation (i.e., (L/l) $\varepsilon^{1/2}$ = $\ll$ 1)**

$$G_1(\tau) = 1 - \frac{1}{6}\left(\frac{L}{l}\right)^2 \varepsilon\left[1 - \cos(\omega_a \tau)\right]$$

- **Thus, the modulation depth can be obtained as follows**

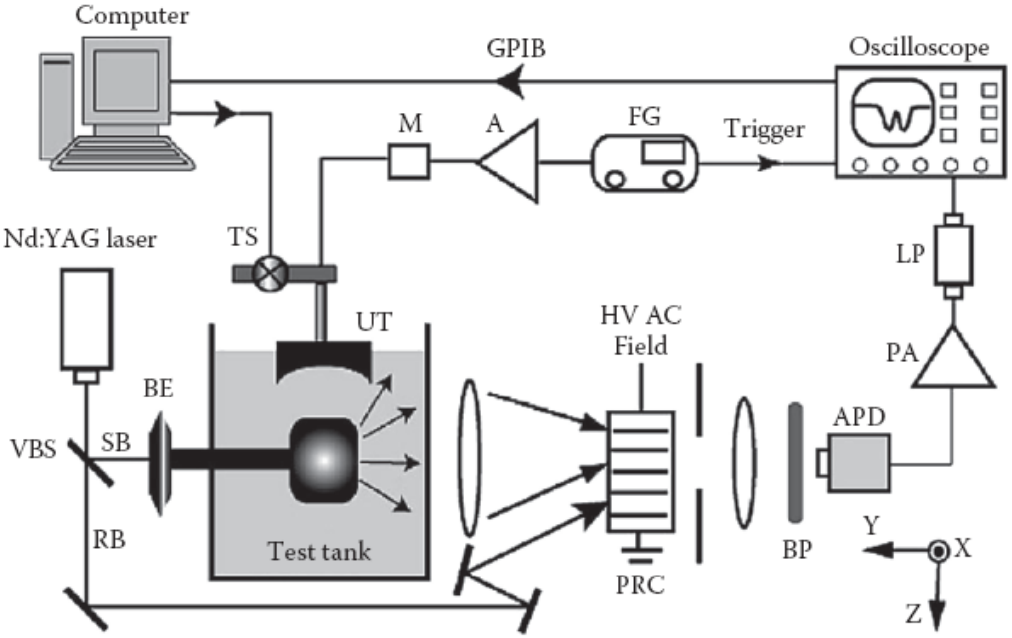
$$M = \frac{1}{12}\left(\frac{L}{l}\right)^2 \varepsilon \propto A^2$$

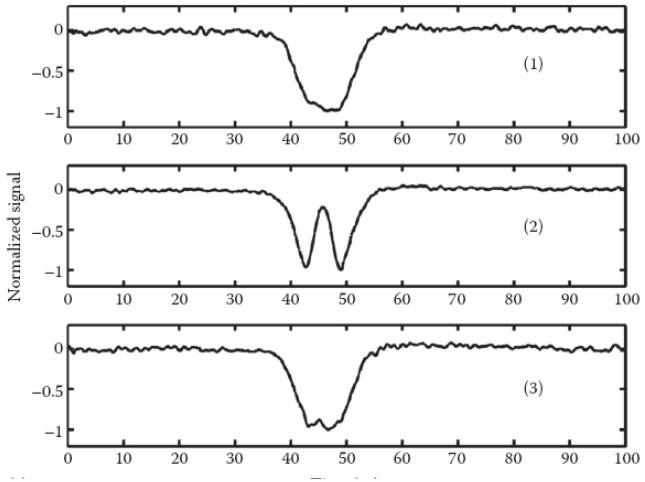


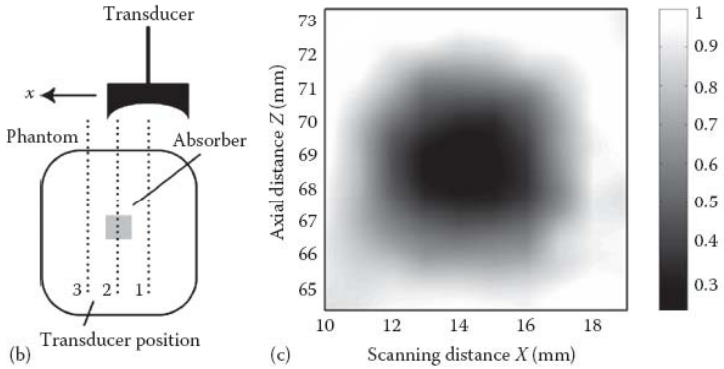


Detection Techniques in UOT

- **Photorefractive Interferometer–Based Detection**
  - The signal beam and the reference interfere at the photodetector → ultrasonic phase modulation in the signal beam converted to an intensity modulation
  - Measuring ultrasound-modulated light intensity during the time of ultrasound flight → A-lines
  - Scanning the sample along the X direction and acquiring each corresponding A-line → B-scan images can be obtained

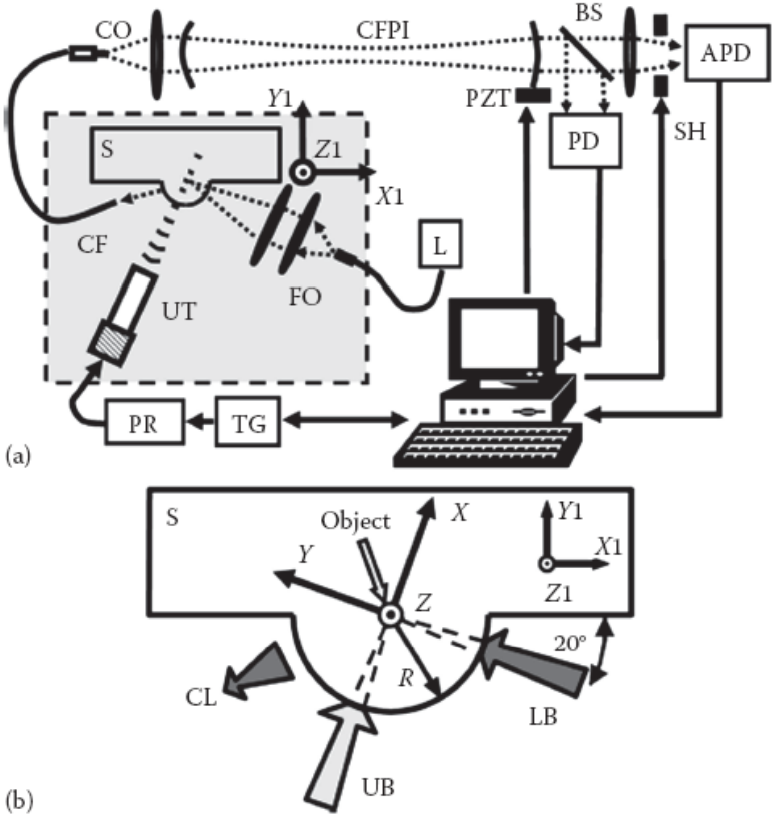


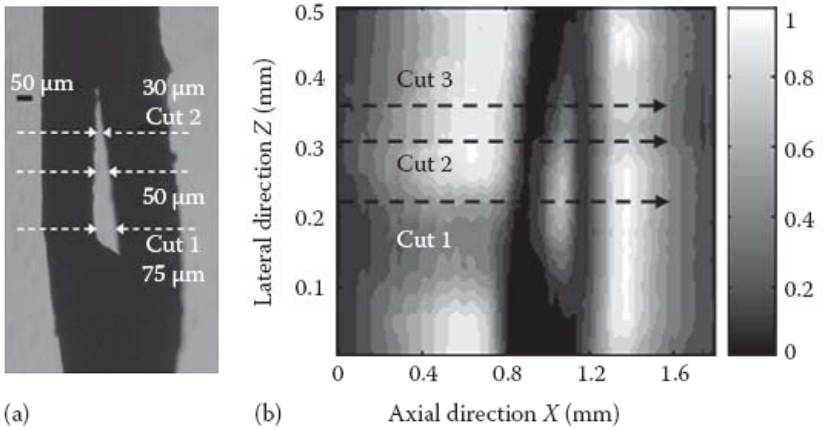


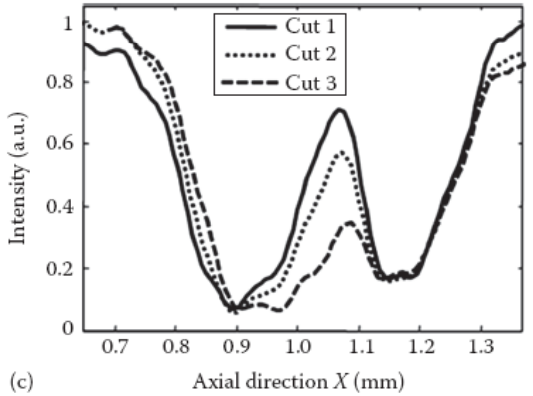


Detection Techniques in UOT

- **Confocal Fabry–Perot Interferometer–Based Detection**
  - The cavity is tuned to the frequency of one sideband of the ultrasound-modulated light
  - Measuring ultrasound-modulated light intensity during the time of ultrasound flight → A-lines
  - Scanning the sample along the Z direction and acquiring each corresponding A-line → B-scan images can be obtained.







Detection Techniques in UOT

- **Spectral-Hole-Burning-Based Detection**
  - SHB crystal tuned to a frequency f_2
  - Ultrasound modulation at f_m with sidebands at f_1 and f_2
  - Only f_2 arrives at the detector

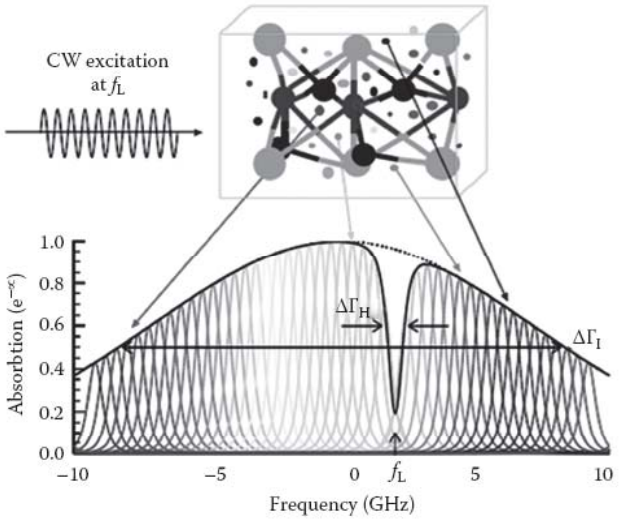
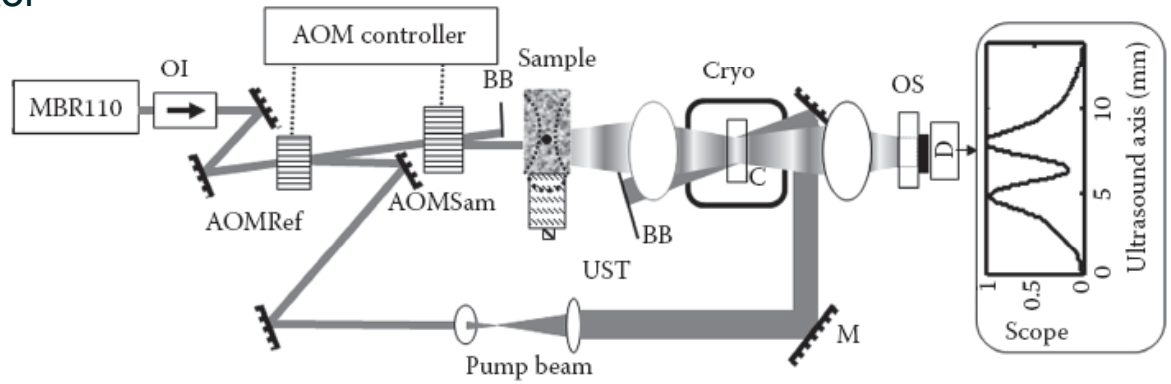
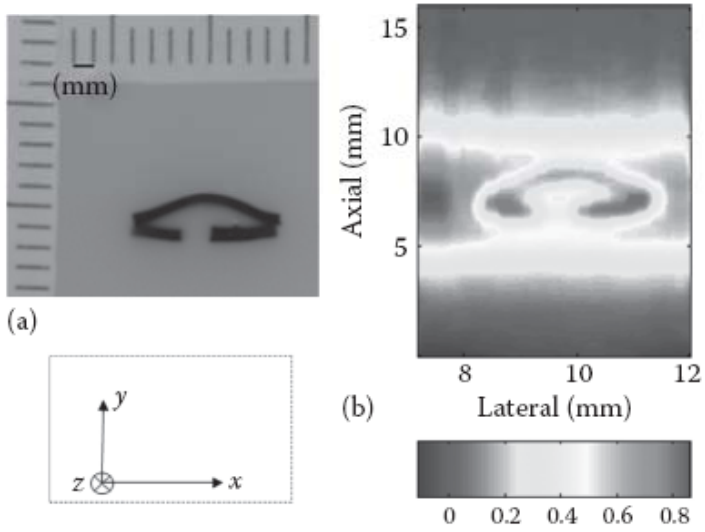


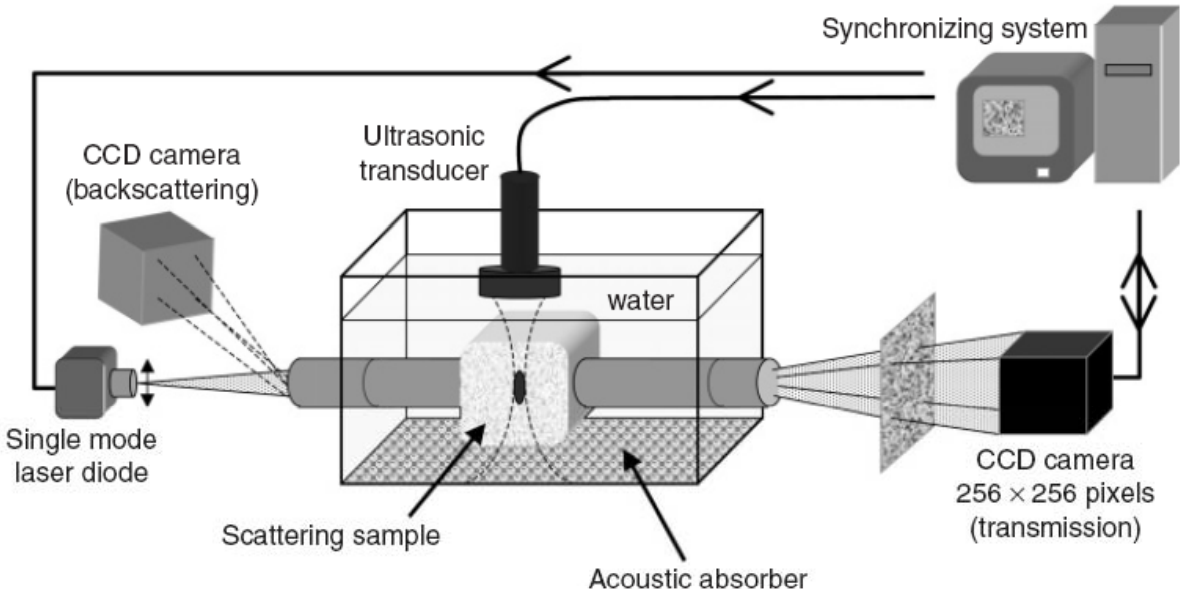
FIGURE 21.18 Normalized spectral absorption profile of an SHB crystal with a spectral hole burned at f_L. $\Delta\Gamma_I$: inhomogeneous bandwidth. $\Delta\Gamma_H$: homogeneous linewidth. (Reproduced from Li, Y. et al., *Opt. Express*, 16, 14862, 2008b. With permission.)

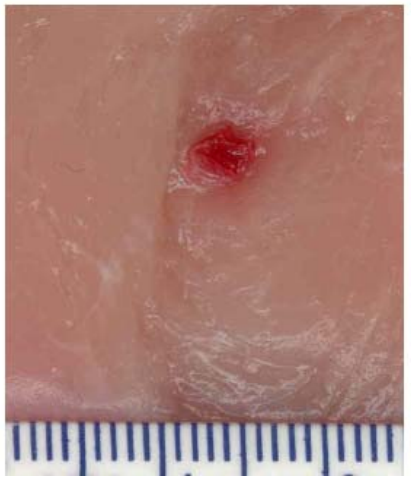


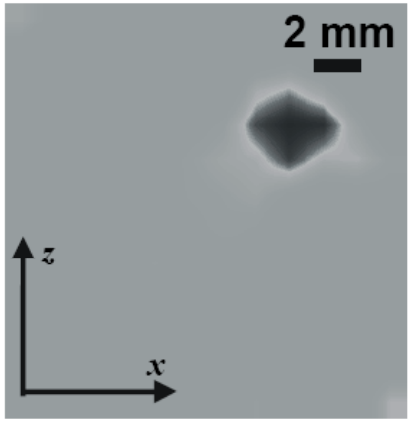


Detection Techniques in UOT

- **Parallel detection using a CCD camera**
  - Dramatic increase in the SNR
  - The intensity of the speckle pattern is modulated at the US frequency
  - The amplitude of the speckle modulation is directly related to the optical properties of the medium inside the US focal zone.
  - The US focus is scan to create image







Detection Techniques in UOT

- **Frequency Sweeping (Chirping)**
  - Frequency encoding along the ultrasonic axis (z)
  - Location encoded in frequency (analogous to MRI)