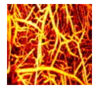
Laser Optoacoustic + Ultrasonic Imaging System Assembly (*LOUISA*) for Functional-Anatomical Mapping

Alexander A. Oraevsky

Seeing through the body
by listening to the **sound** of **light**



TomoWave Laboratories, Inc.

NIH Grants: R01CA167446, R43EB015287, R44CA110137, R44CA110137-S1, R44CA128196, R43ES021629

Arrrays of OptoAcoustic Transducers:
- Andre Conjusteau

Analog and Digital Electronics
- Vassili Ivanov

FiberOptics and Mechanics
- Peter Brecht

Firmware and Software
Pratik Talole, Ketan Mehta

Modeling, Math-Physics, Tomography
- Sergey Ermilov, Slava Nadvoretsky,
- Mark Anastasio, Wash U St. Louis

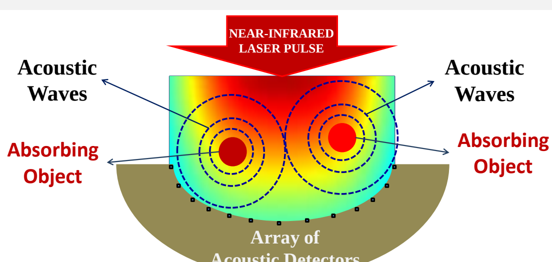
Experimental Imaging, Data Processing
- Richard Su, Dmitri Tsyboulski

Animal Studies, Nanotechnology
- Anton Liopo

Clinical imaging of breast cancer
- Wei Yang, MD Anderson Cancer Cntr

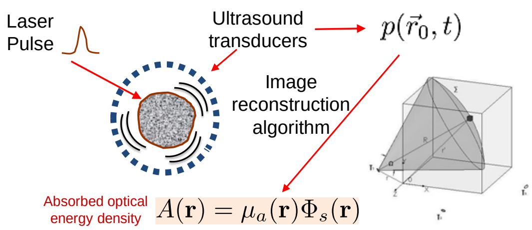
Students, Post Docs, Scientists, Engineers and Faculty Collaborators

Listening to Light with OptoAcoustics



$$\Delta P = \frac{1}{\gamma}\frac{\Delta V}{V} = \frac{1}{\gamma}\beta\Delta T = \frac{1}{\gamma}\frac{\beta E_{abs}(z)}{\rho c_V} = \frac{\beta C_S^2}{c_p} F_0\mu_a = \Gamma(T)F_0\mu_a$$

Algorithm of OptoAcoustic Tomography



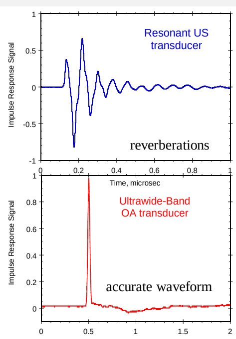
Absorbed optical energy density $A(\mathbf{r}) = \mu_a(\mathbf{r})\Phi_s(\mathbf{r})$

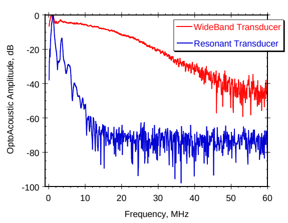
3D OAT $A(\mathbf{r}) = -\frac{C_p}{2\pi\beta c_0^2 R_s}\int_S d\mathbf{r}^s \left[\frac{2p(\mathbf{r}^s,t)}{|\mathbf{r}-\mathbf{r}^s|} + \frac{1}{c_0}\frac{\partial p(\mathbf{r}^s,t)}{\partial t}\right]_{t=\frac{|\mathbf{r}-\mathbf{r}^s|}{c_0}}$

2D OAT $A(\mathbf{r}) = \frac{C_p}{\pi c_0^2 \beta R_s}\int_S d\mathbf{r}^s \int_0^{\frac{2R_s}{c_0}} dt \frac{\partial}{\partial t} t \frac{\partial}{\partial t}\int_0^t d\tau p(\mathbf{r}_s,\tau)\log|c_0^2\tau^2 - |\mathbf{r}^s-\mathbf{r}|^2|$

Finch et. al., SIMA 2004

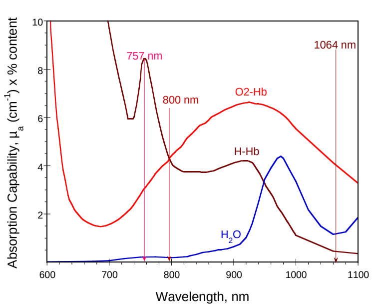
Impulse Responses OA/US transducers



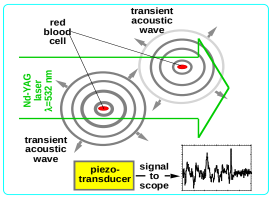


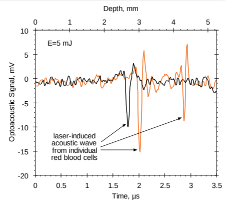
Sensitivity = NEP = 1Pa

Biophotonic Imaging Technology based on Optical Absorption in Tissues

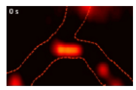


Optoacoustic Detection of Erythrocytes:
demonstration of a single red blood cell detection





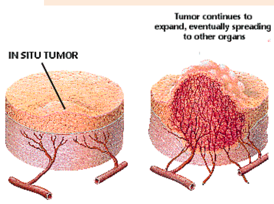
A.A. Oraevsky, E.V. Savateeva, A. Karabutov, V.G. Andreev: "Optoacoustic imaging of blood for visualization and diagnostics of breast cancer", ***Proc. SPIE*** 2002; **4619**: 81-94.



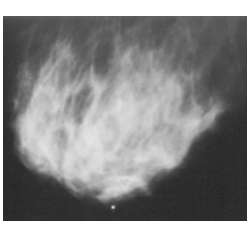
L.D. Wang, K Maslov, *L.V. Wang*, Pros NAS 110, 5759, **2013**

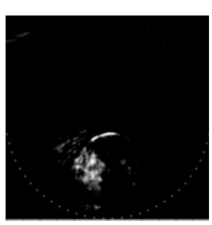
Rationale for Imaging of Cancerous Tumors based on Angiogenesis

"Without a private supply of new microscopic blood vessels cancerous tumors can not grow larger than the head of a pin and are unlikely to become lethal. Without blood vessels to feed them oxygen and nutrients, these tumors remain tiny and unable to spread…"
Judah Folkman, MD



Breast Cancer Imaging (X-ray Mammography vs. LOIS)



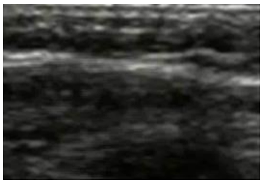


MAMMOGRAPHY IMAGE
Low Contrast: dense breast
Missing 20% of cancerous tumors

OPTOACOUSTIC IMAGE
High Contrast: 2x-3x
Resolution: 0.5 mm

Real-time Opto-Acoustic & Ultrasound Imaging

Ulnar Artery in Human Arm



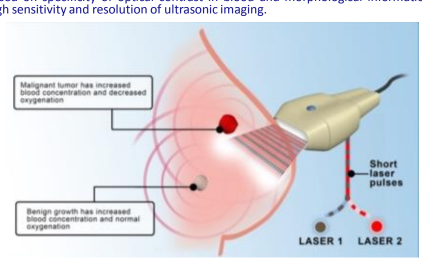
Ultrasound – anatomical information on tissue structure (morphology)

Optoacoustics – functional information about [tHb] and [SO2] (molecular)

M. Frenz et al., Proc. SPIE, vol. 4960, 2003
A. Oraevsky, S. Emelianov et al., Proc. SPIE, vol. 5320, 2004

Co-registration of OptoAcoustic and Ultrasound Images

- This technology combines and co-registers images based on optical and acoustical contrast to improve the accuracy of cancer detection and diagnosis.
- Co-registered OA+US imaging has the merit of providing both, functional information based on specificity of optical contrast in blood and morphological information with high sensitivity and resolution of ultrasonic imaging.



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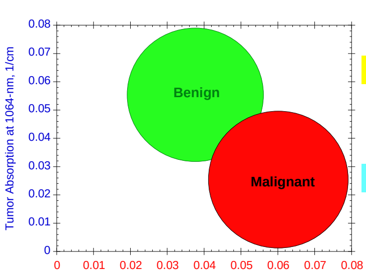
Method of Tumor Differentiation



[THb]=[Hb]+[HbO2]

[SO2]=[HbO2]/[THb]

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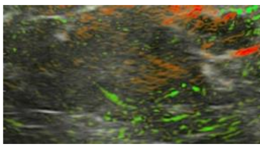
Hand-held Opto-Acoustic / Ultrasound Probe

and Method of Co-registered Functional+Anatomical Imaging



US+[tHb]

+

US+[SO2]

×

US B-mode

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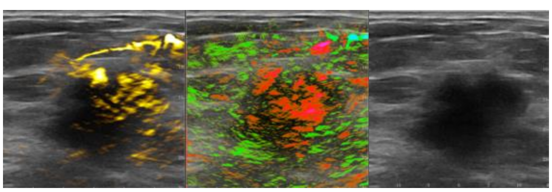
Invasive Carcinoma:

Enhanced concentration of deoxygenated blood



[tHb]	[SO2]	[USI]
Total Hemoglobin	Blood Oxygenation	B-mode Ultrasound

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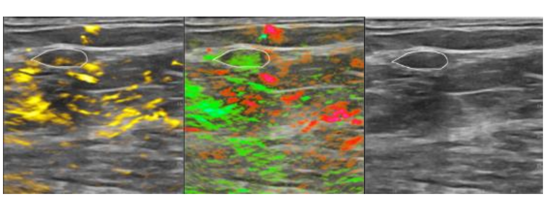
Benign FibroAdenoma:

normal blood oxygenation, not significant angiogenesis



[tHb]	[SO2]	[USI]
Total Hemoglobin	Blood Oxygenation	B-mode Ultrasound

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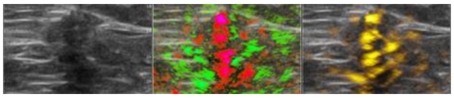
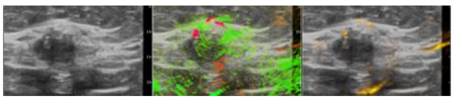
Co-registration of OA and US
for diagnostic imaging of breast cancer



Invasive Ductal Carcinoma, malignant tumor
with high concentration of (deoxy)hemoglobin



Fibroadenoma, benign tumor
with normal blood oxygenation and and low total hemoglobin

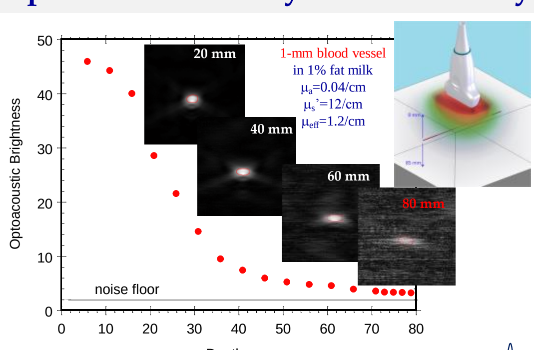
Key Features of Breast Imaging with Imagio™ *versus* the Current Standard of Care*

Key Properties	Gold Standard (X-ray mammo)	Imagio (OA+US)	Significance Benefits
Morphology and function	Only morphology	Yes Both	High sensitivity and specificity
False Negative	25%	<3%	Early detection
False Positive	82%	<36%	Minimum Negative biopsy
Safety	Carcinogenic radiation	Safe Light & Sound	More frequent procedures
Convenience	Pain of compression	No compression	Better acceptance

* Projections based on preliminary analysis of initial clinical data of 79 patients

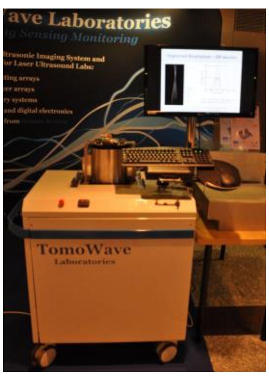
Diagnoses BIRADS-4A and BIRADS-4B cases 30% more accurately

Depth Limit of OA System Sensitivity



Tomography with LOUISA
2D *versus* 3D

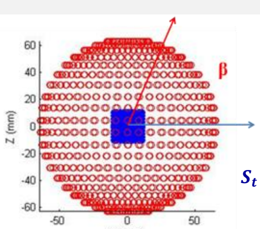
- 2D is conveniently performed with hand-held probe, but can not be used for full organ screening, sensitivity (contrast) is limited.
- 2D delivers real time video rate images that can be important for imaging rapid physiological changes, but small aperture of the ultrasonic transducer array provides limited lateral resolution and relatively inaccurate quantitative brightness of image pixels
- 3D with provides solutions for problems of 2D imaging (low background, high resolution in all directions) at the cost of time for data acquisition and image reconstruction.



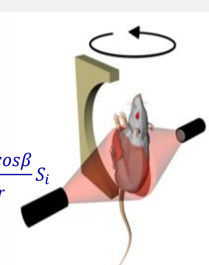
TomoWave
Laboratories, Inc.

Laser Optoacoustic Imaging System LOIS-3D a new technology for preclinical research

Quantitative OptoAcoustic Tomography



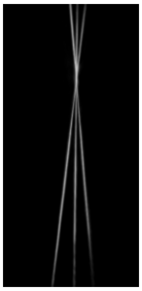
$$S_t = \frac{2\pi\ R\ cos\beta}{N_{Tr}} S_i$$



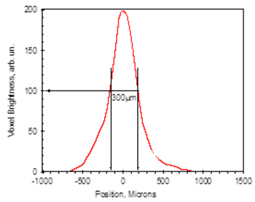
Specifications:

150 deg arc, **65mm** dia array, **128** of wideband **0.1 to 8 MHz** transducers
38400 virtual transducers on spherical surface – rigorous reconstruction
Minimal Imaging Time: **30 sec** acquisition + **20 sec** image reconstruction

Spatial Resolution in 3D



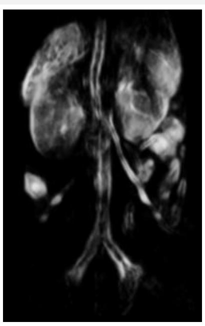
3 horse hairs with diam 150 micron



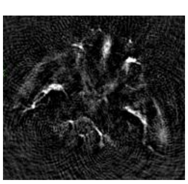
A hair cross-section of the optoacoustic image acquired with LOUIS-3D

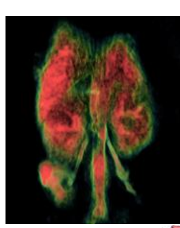
Image brightness shows Gaussian shape with FWHM of 300 micron.

Anatomical OptoAcoustic Imaging tissue structures: organs, bones

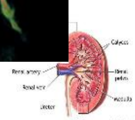


3D OptoAcoustic Imaging of blood vessels, internal organs and kidney



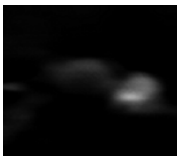


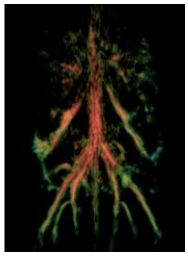
Kidney

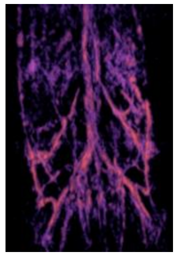


Functional OptoAcoustic Imaging
1064nm / 757nm - arterial/venous systems

1064 nm

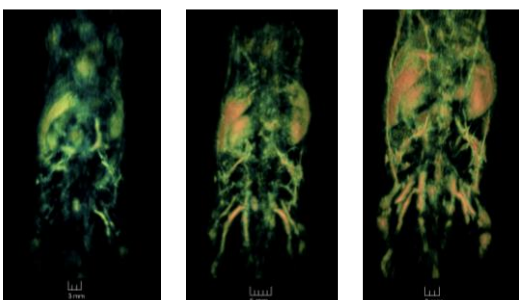




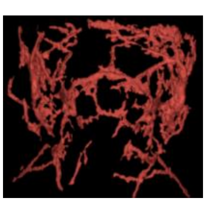


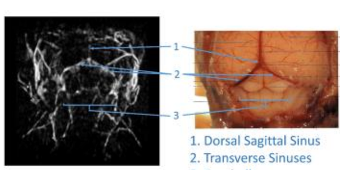
Veins @ 760 nm   Arteries @ 1064 nm

Functional OptoAcoustic Imaging at 760 nm
gradual decrease of blood oxygenation

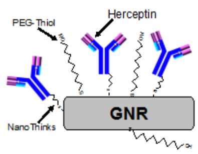


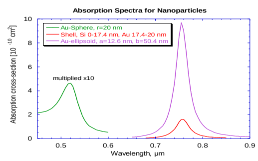
OptoAcoustic Imaging of Mouse Brain
Live Mouse, Total Hemoglobin Map

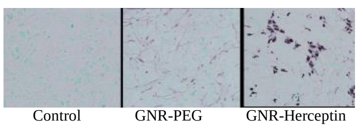


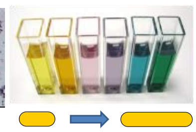


Molecular Imaging using Gold Nanorods



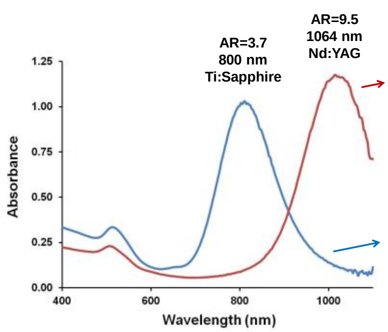


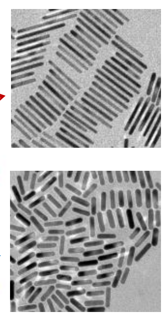




J.A. Copland, M. Eghtedari, V.L. Popov, N. Kotov, N., A.A. Oraevsky: Bioconjugated gold nanoparticles as a molecular based contrast agent: Implications for imaging of deep tumors using optoacoustic tomography, *Molecular Imaging and Biology* 2004; **6**(5): 341-349.

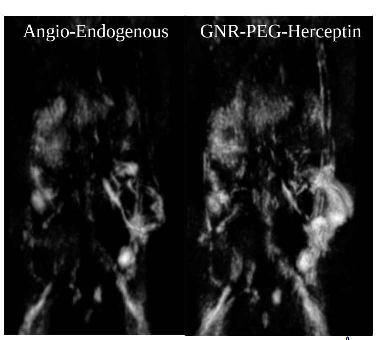
GNRs as OptoAcoustic Contrast Agents





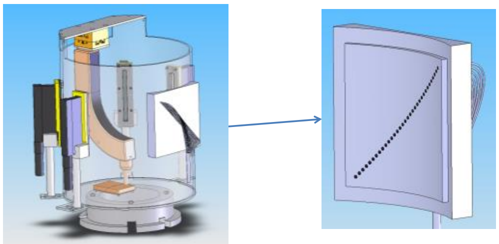
Molecular OptoAcoustic Imaging of a Tumor

BT474 Tumor
HER2 receptors
Injected iv
200 μL of targeted GNR-Herceptin
C=7x10¹²/mL



Design of Imaging Module

OA scan is followed by LU scan



Optoacoustic PLUS Laser Ultrasound Tomography enables 5 images:
Functional [Hb], [HbO2], [H2O] and morphology: SoS and UA

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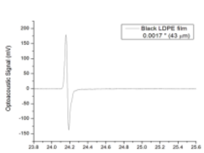
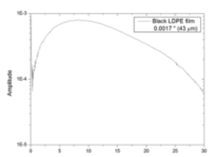
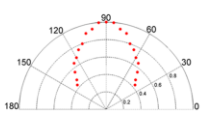
Laser Generated Ultrasound







LUE=5 kPa / [mJ/cm^2]

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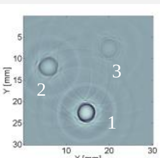
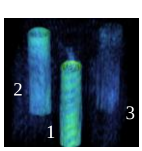
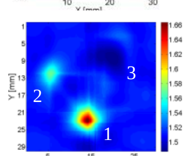
OA-US Tube Phantom

- 300 rotation steps, 16 averages
- 3 ∅4.7mm PTFE tubes filled with NaCl + $CuSO_4$
- SoS: Tube1 – 1.7, Tube2 – 1.6, Tube 3 – 1.5 mm/μs
- μa: Tube1 – 2.4, Tube2 – 2.2, Tube3 – 1.1 cm^{-1}







Viewed from the LU emitter perspective

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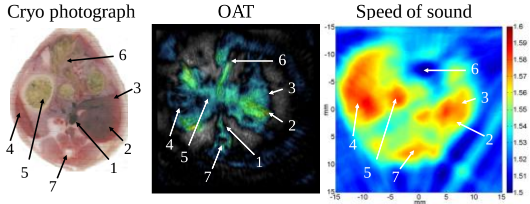
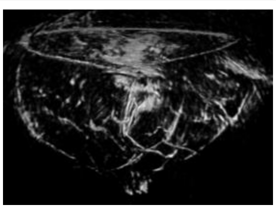
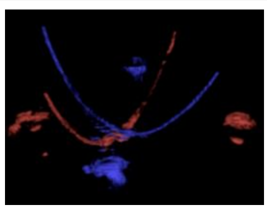
Co-registered OA & SoS Images liver/spleen level slice



1 – Abdominal aorta/caudal vena cava, 2 – Right kidney, 3 – Liver, 4 – Spleen, 5 – Stomach, 6 – Intestines/abdominal fat, 7 – Vertebrae/back muscles

From LOIS-3D to LOUISA-3D
translation to diagnostic imaging of breast cancer





Breast Screening, Diagnostics and Monitoring System

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SUMMARY

- **OptoAcoustic Tomography provides images with high optical contrast of [Hb] and [HbO2] and excellent ultrasonic resolution (<0.3mm)**
  - Most sensitive and accurate approach to quantitative imaging
  - Rapid image acquisition and reconstruction (down to 40 sec)
  - Multiwavelength spectroscopic capability
- **Functional OptoAcoustic Imaging**
  - Measurement of [Hb] and [HbO] (hematocrit) in tissues and blood vessels, assessment of heart function and blood flow.
  - Assessment of tumor angiogenesis, angiography, detection and characterization of stroke and traumatic injury of the brain
- **Molecular Imaging**
  - Distribution of cellular receptors with targeted nanoparticle agents
  - Studies into kinetic and dynamic distribution of contrast agents
- **Combination of OptoAcoustic and Ultrasonic Imaging**
  - Provides coregistered maps of anatomy and functional parameters
  - Laser generated ultrasound: 3x resolution, 3x contrast, USI spectroscopy

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