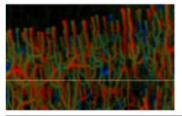
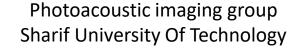
# Photoacoustic imaging

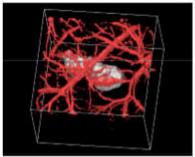
Zahra Kavehvash Sharif University of Technology

November 2023

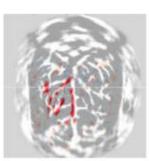
# PHOTOACOUSTIC TOMOGRAPHY: Ultrasonically Breaking through the Optical Diffusion Limit

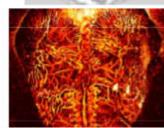


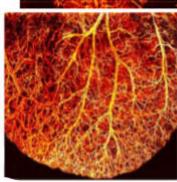




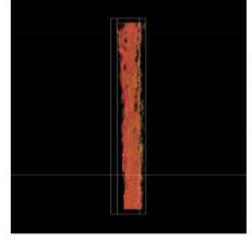


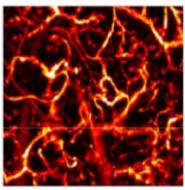


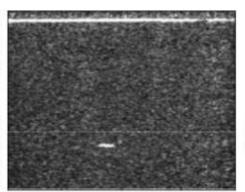




November 2023



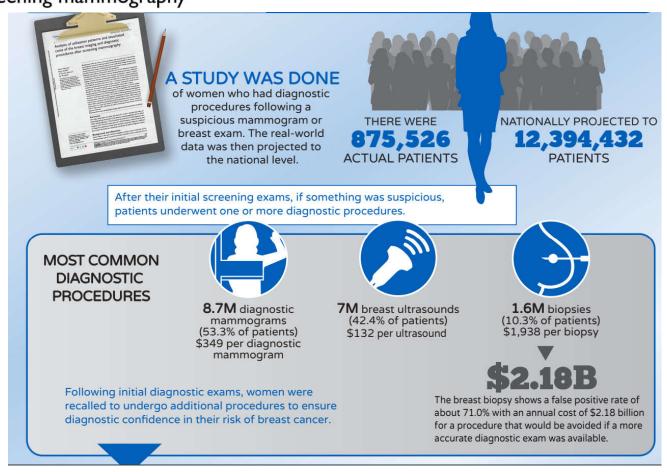




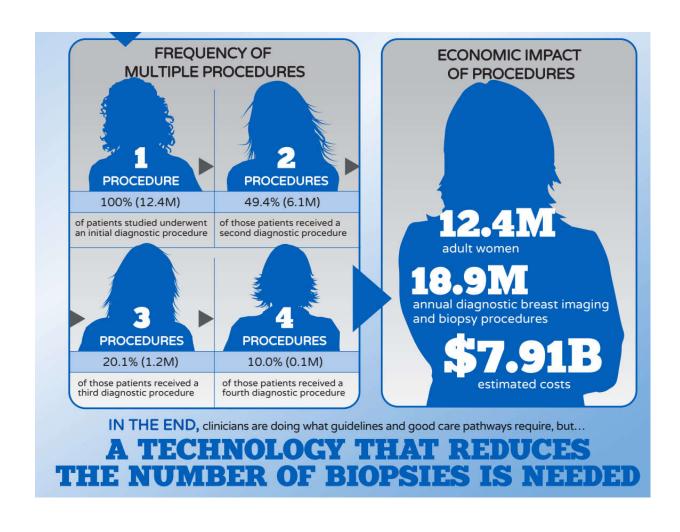
ORIGINAL RESEARCH

## Why photoacoustic imaging

Analysis of utilization patterns and associated costs of the breast imaging and diagnostic procedures after screening mammography



## Why photoacoustic imaging

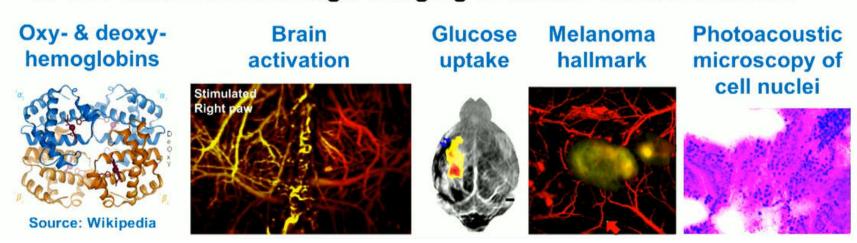


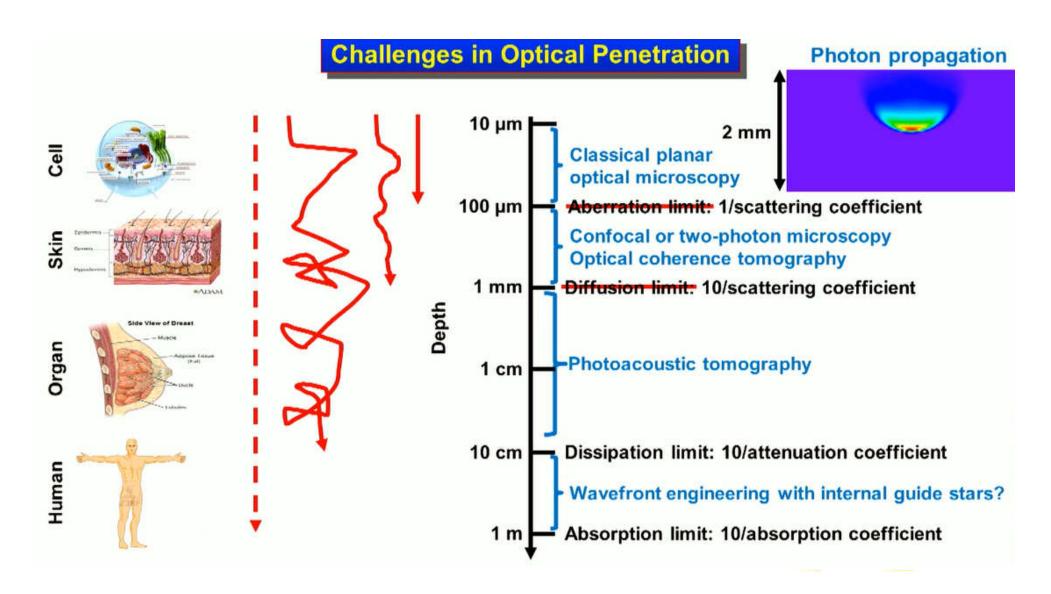


#### Motivations for Imaging with Light Light-matter interaction uniquely positioned at the molecular level Electromagnetic spectrum Wavelength: 1 mm 1 µm 1 nm 1 pm Radiowave/microwave Optical X-ray Gamma Non-ionizing (safe) Ionizing (DNA damage) Medical x-rays

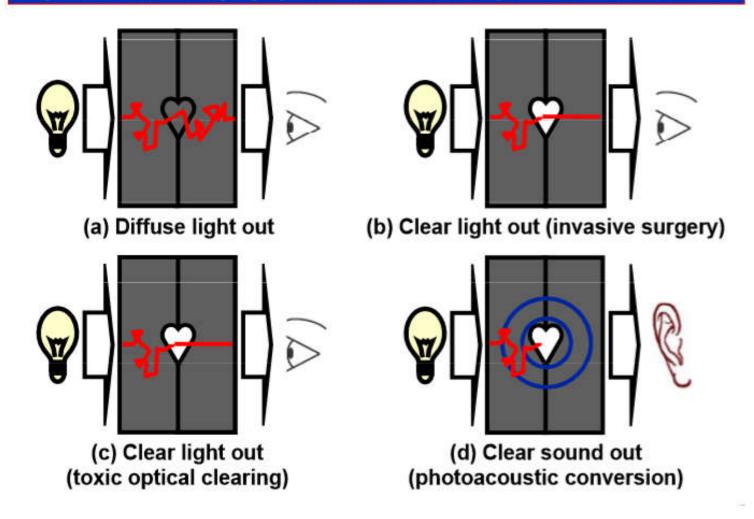
### **Motivations for Imaging with Light**

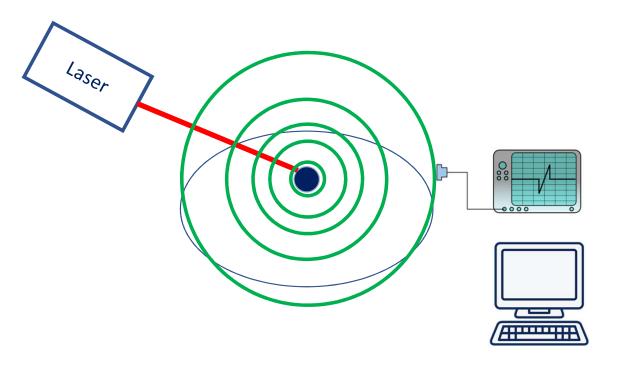
- Light-matter interaction uniquely positioned at the molecular level
- Fundamental role of molecules in biology and medicine
- In vivo functional imaging analogous to functional MRI
- In vivo metabolic imaging analogous to PET
- In vivo molecular imaging of gene expressions or disease markers
- In vivo label-free histologic imaging of cancer without excision



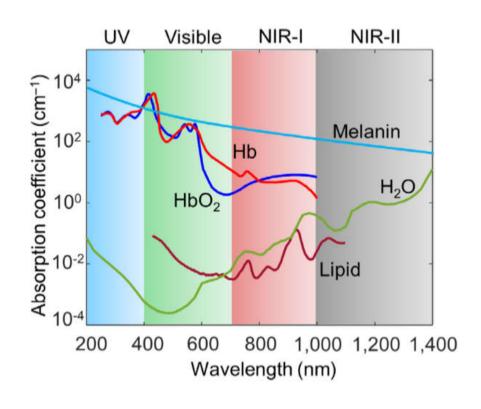


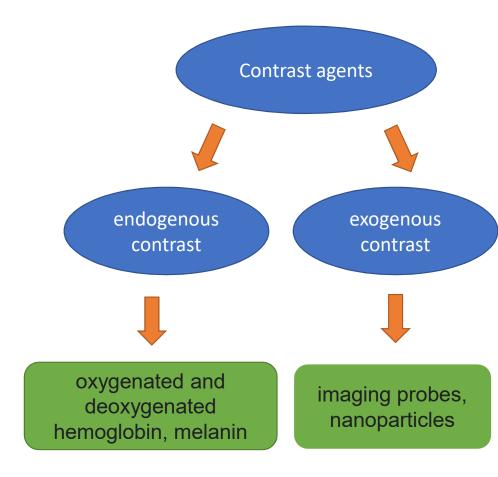
## High-resolution Imaging by Clear Detection Despite Diffuse Illumination





Laser Pulse Absorption Thermal Acoustic Ultrasound Image Detection



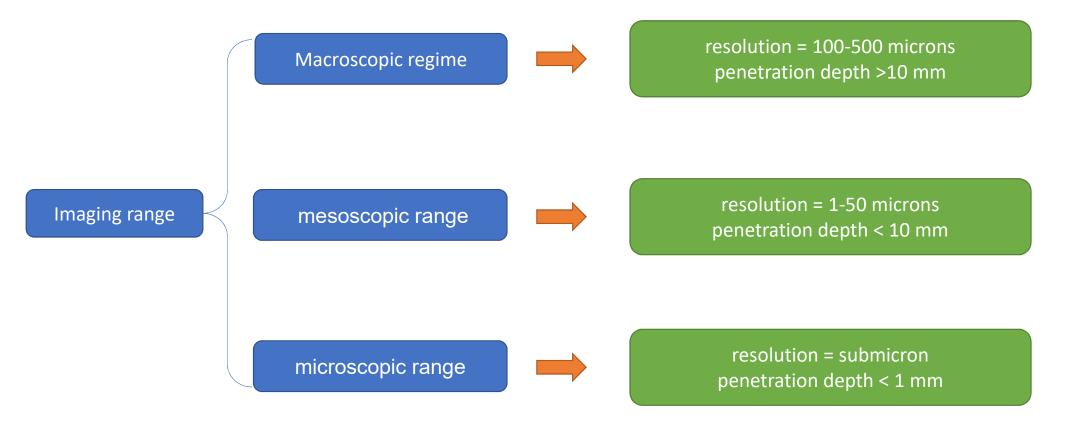


one anatomical image

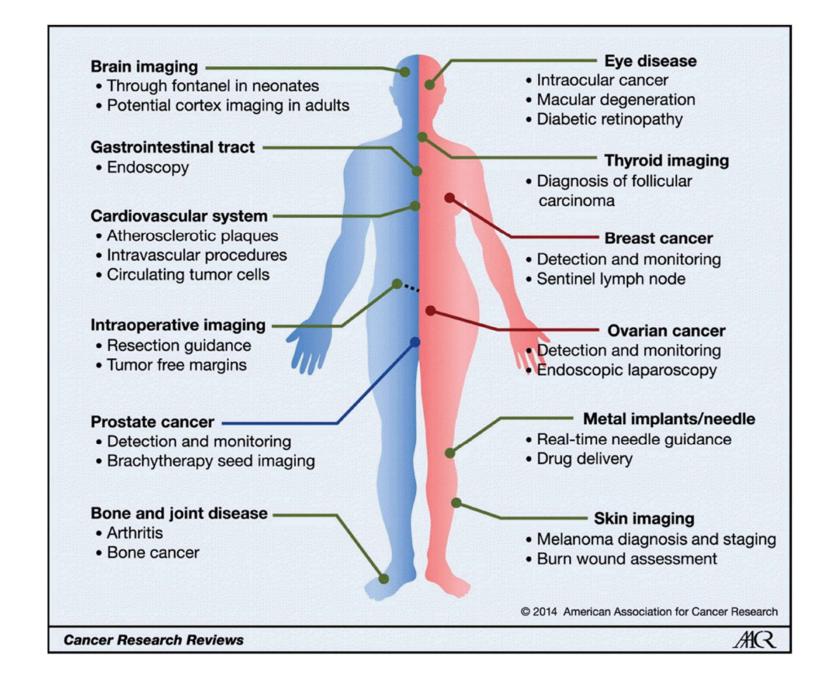
three images

one functional image resolving oxy- and deoxy-hemoglobin concentrations

a third image resolving additional target photoabsorber (contrast agents)



## **Applications**



cardiovascular disease research

biological applications

neuroimaging

cancer research

Breast imaging

Vasculature imaging

lymph nodes imaging

Skin imaging

Imaging of pharmacokinetic

Rheumatoid arthritis

Thyroid imaging

prostate imaging

• • •

real-time hand-held imaging systems

Anatomical imaging

vasculature, kidney, heart, liver, brain and muscle

Modes of operation

functional/dynamic imaging

video rates to reveal changes in tissue contrast caused by hemodynamics, motion such as vessel pulsation, and uptake of drugs

biological / molecular imaging

tissue oxygenation, reporter genes, fluorescent proteins and various exogenous agents (e.g. fluorescent dyes, nanoparticles, target-specific agents)

## The Radiologists about Photoacoustic

## New imaging technique helps radiologists downgrade benign breast masses

Michael Walter | April 18, 2018 | Radiology Business | Quality

Using optoacoustic (OA) imaging combined with conventional ultrasound (US) can help downgrade benign masses classified as BI-RADS 4A or 4B, according to a new study from Dutch researchers published in *Radiology*. This, the authors noted, could reduce the number of biopsies negative for cancer.

"The reported rates of US-guided biopsies with results positive for cancer are low, varying from 7.9 percent to 17 percent, which results in many biopsies of benign masses," wrote lead author Gisela L. G. Menezes, MD, PhD, with the department of radiology and nuclear medicine at University Medical Center Utrecht in Utrecht, Netherlands, and colleagues. "In retrospect, many of these biopsies negative for cancer might be considered unnecessary because they result in increased emotional distress for patients and higher overall costs related to interventional procedures and short-interval follow-up imaging studies.

"Among the greatest challenges in US breast imaging are to improve the differentiation between benign and malignant lesions, to concurrently maximize sensitivity and specificity, to decrease false-positive findings while minimizing false-negative findings, and to decrease the number of biopsies negative for cancer."

To see if OA/US technology could potentially help radiologists address this issue, the authors studied more than 200 breast masses evaluated with US alone and classified as BI-RADS 4A or 4B. The same masses were then evaluated a second time with OA/US.

"Regardless of the outcome at OA/US, a biopsy was performed after the OA/US examination solely on the basis of findings at conventional imaging (BI-RADS 4A or 4B)," the authors wrote. "All biopsied masses (and surgical specimens when available) underwent central pathologic review by an independent histopathologist. The central histopathologic diagnosis was considered the reference standard for OA/US comparison."

Overall, when evaluating with OA/US, more than 47 percent of benign masses classified as BI-RADS 4A and more than 11 percent of benign masses classified as BI-RADS 4B were "correctly downgraded" to BI-RADS 3 or BI-RADS 2.

Three masses, however, were "incorrectly downgraded." These masses were malignant, and their classification should not have been changed. Menezes et al. reviewed these findings and found that the radiologists, not the technique, were to blame.

"From the three false-negative masses found in our study, two masses could have been prevented if OA/US signs suggestive of malignancy had been observed at OA/US," the authors wrote. "Future analysis and studies performed to improve the scoring system used at OA/US may help to decrease the number of false-negative findings and may help us to unfold the full potential of this technology."

#### 9 technology trends and takeaways from RSNA 2022

Dave Fornell | December 06, 2022 | | Radiological Society of North America (RSNA)

#### Two new breast imaging modalities aid women with dense breasts

There were two innovative new breast imaging technologies on the floor, both using ultrasound and elastography to better understand if a suspicious area is cancer or not without the need to biopsy every patient. Both technologies are also designed to help image women with dense breasts to be able to see through the dense tissue that masks cancers on traditional mammograms.

Seno Medical showed the new breast imaging modality of opto-acoustic ultrasound (OA/US). It uses six separate images to show the functional and anatomic features of breast tissue and immediately display features that differentiate tumor neo-angiogenesis. This may prevent the need for additional testing or biopsy. The system just received U.S. FDA PMA clearance and the vendor celebrated with champagne in the booth.

#### Read more about this new technology.

The second vendor Delphinus offers whole breast 3D ultrasound tomography. To use the system the patient lays in a prone position on a table with their breast inserted into a hole in the table. It is filled with water and a light suction device pulls the breast down to elongate without compression.



Opto-acoustic Imaging: A new modality changing the future of breast imaging (radiologybusiness.com)

## Opto-acoustic Imaging: A new modality changing the future of breast imaging





And add to that a 46% reduction in first diagnostic imaging exams and a 60% reduction in unneeded second or third imaging exams (because OA/US is the stopgap in providing the needed information to send or not send a patient for biopsy) and just by making OA/US part of the care path, the total estimated savings to U.S. healthcare could amount to \$4.9 billion.

Experts see OA/US improving the breast cancer diagnosis process by reducing both duplicative diagnostic imaging exams and breast biopsies of benign masses, saving an estimated \$4.9 billion annually for the healthcare system. Early studies even indicate that OA/US can help physicians better assess the type of breast cancer, which may predict its response to treatment over time.

"This is equivalent to the step between 2D and tomography," notes Kenneth Kist, MD, a radiologist who recently retired from UT Health San Antonio who was part of the PIONEER multicenter clinical trial as well as a next-generation clinical study using OA/US technology. "It has a *lot* of additional information."



"This is game-changing for breast cancer imaging in that we get functional information—that we would normally get from advanced imaging—but

with ultrasound"

 Basak Dogan, MD, Director of Research at UT Southwestern Medical Center's Harold C. Simmons Comprehensive Cancer Center "This makes you a better radiologist, having more and deeper information," notes Jeroen Veltman, MD, PhD, a breast radiologist within MRON (Radiologie Oost-Nederland) who is also responsible for breast and prostate imaging in the ZGT Hospital in Hengelo in the Netherlands. As chair of the breast imaging section of the Dutch Radiology Society and an assistant professor within the Multi-Modality Medical Imaging (M3I) group at the Technical University of Enschede, Veltman says, "We can decide more certainly with this anatomic and functional information what is the right path for the patient."

"The primary benefit of this technology is that it can help the patients avoid the biopsy ordeal. [With OA/US], we're finding that we can more correctly categorize masses we would normally biopsy based on ultrasound features alone," says Dogan. "In the latest reader study, we found that about 15% of biopsies would have been avoided, and that's without losing significant sensitivity."



"The training was excellent, getting us comfortable with a new way of scanning. Once you scan a few patients, say five or six, you get the feel of the system and gain confidence in what you are seeing in the images."

- Thanh Van, MD, Director of Breast Imaging and Intervention at UT Health San Antonio Thanh Van, MD, director of Breast Imaging and Intervention at UT Health San Antonio who also participated in the next-generation clinical study using Imagio®, considers OA/US imaging especially helpful in women whose mass falls into the BI-RADS 3, or "probably benign," category, that can be potentially downgraded to BI-RADS 2.

"Additionally, for the BI-RADS 3 women who are really anxious about it, it could give a measure of assurance that you can follow it [instead of taking a biopsy]," she says.

"We often talk about downgrading, but I think OA/US can be very helpful in upgrading when necessary," he says. "With the press of a button, you can put it on—and if it is a very active legion, you don't even think about *not* taking the biopsy."

"Doing an ultrasound and finding a lesion in the breast can bring a lot of psychology with it," he says. "For example, if you have a young patient, you don't want to believe that it's cancer. But if you put on photoacoustics and it's very active, you know you have to biopsy. It can prevent you from thinking

# A second opinion before skipping a breast biopsy



"This makes you a better radiologist, having more and deeper information. We can decide more certainly with this anatomic and functional information what is the right path for the patient."

- Jeroen Veltman, MD, PhD, Breast Radiologist within MRON

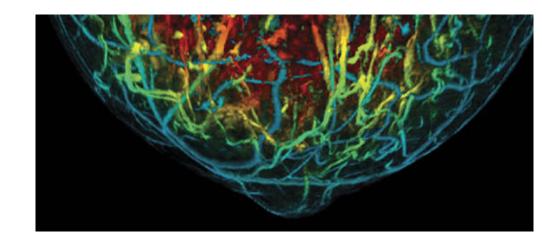
"Especially in large markets and large cities, where hospital systems compete against each other, it's nice to be able to say that our radiology practice offers the newest technology, including cutting-edge opto-acoustic imaging. When it comes to healthcare, women seek out technologies that can help them. This could be one."

Kenneth Kist, MD, Retired Radiologist at UT Health San Antonio

too lightly of a lesion."

## **Breast Cancer Imaging**

- The number of breast cancer cases was largest among the different types of cancers.
- leading cause of cancer-induced deaths among women.
- It is about 30% (or 1 in 3) of all new female cancers each year.
- In the year 2015 alone, worldwide, 523,000 women died because of breast cancer.
- In 2020, an estimated 684,996 women across the world died from breast cancer.
- In the previous 17 years (2005–2015) breast cancer cases had increased by 43%.
- We have to do something to make the world with fewer deaths



Photoacoustic Breast Imaging System can image breast cancer cells in early stage.

Low cost system, No pain, No damage

## **Breast Cancer Imaging**

## commercial products



**Emerging** applications **Breast cancer** imaging

X-ray: poor sensitivity mammography

ultrasound: low specificity

Photoacoustic: focusing on detecting the increased vascular density and correspondingly high hemoglobin concentration thought to occur in and around tumors



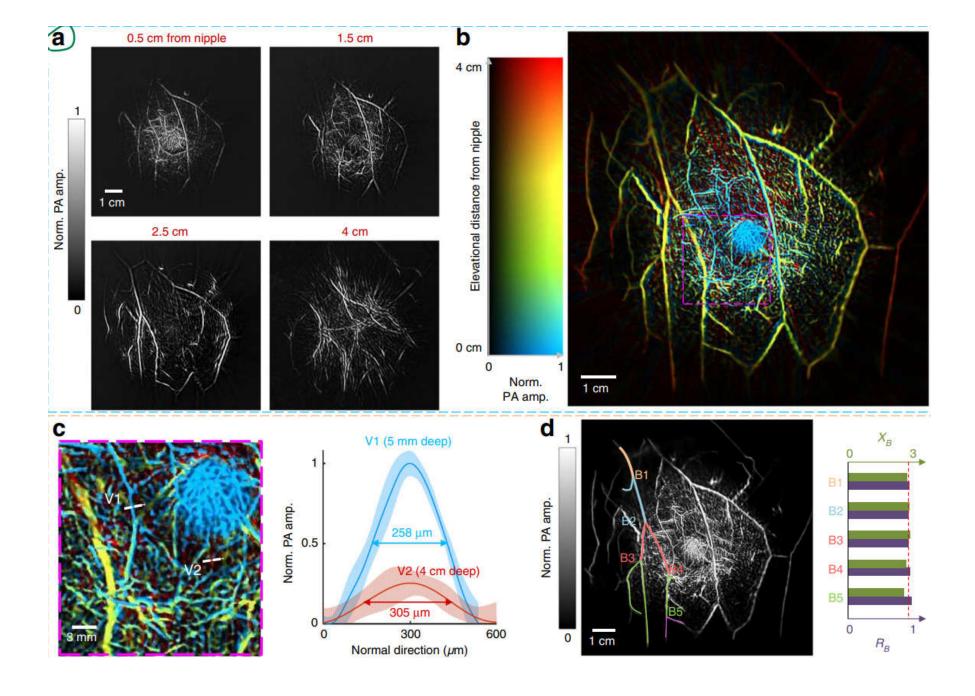


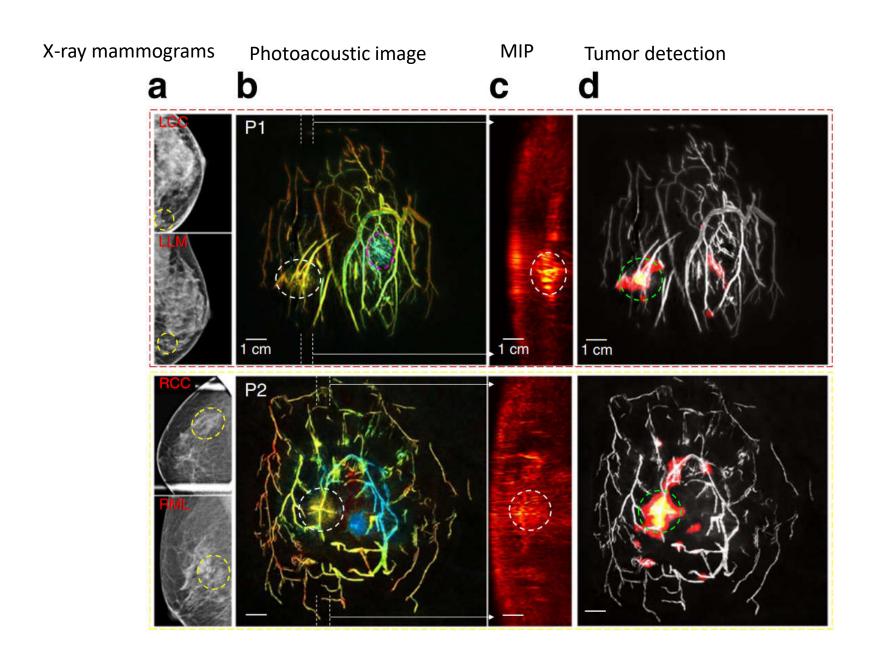
Full-ring ultrasonic transducer array

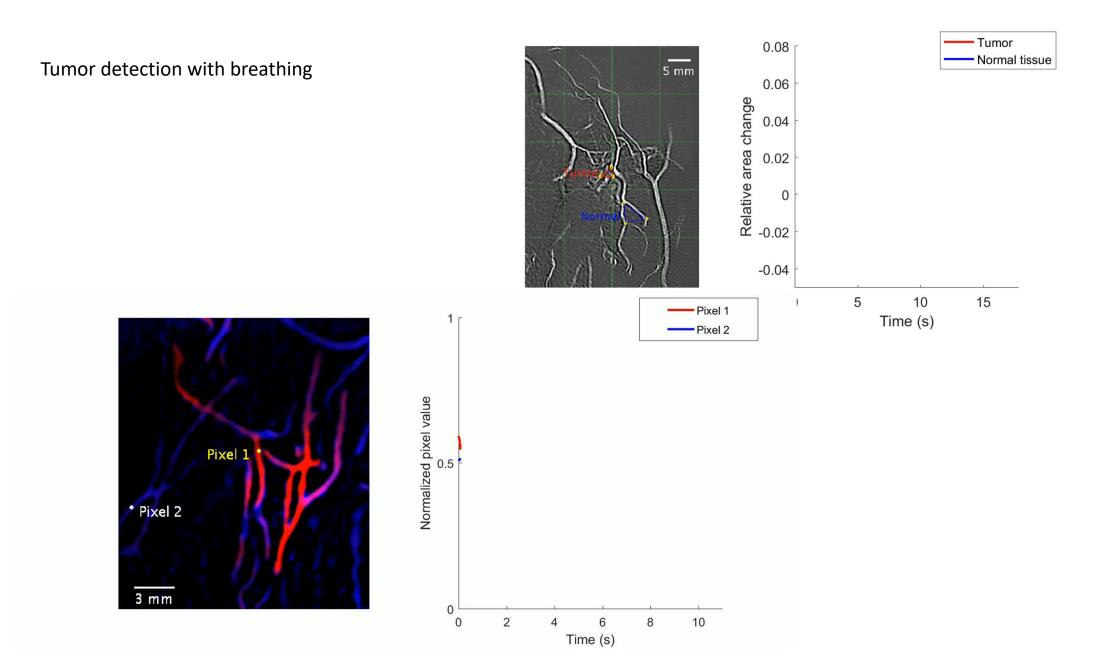


Imaging Parameter	Goals for Clinical Use
Resolution	0.3–0.5 mm
Imaging Depth	5 cm
Sensitivity to Blood Content	Δ Absorption < 0.05 cm <sup>-1</sup>
Oxygen Quantification	20% Accuracy
3D Image Co-registration	<0.1 mm
Image Acquisition Time	<1 min
Frame-to-frame Variability	<3%

L. Wang, nature, 2018

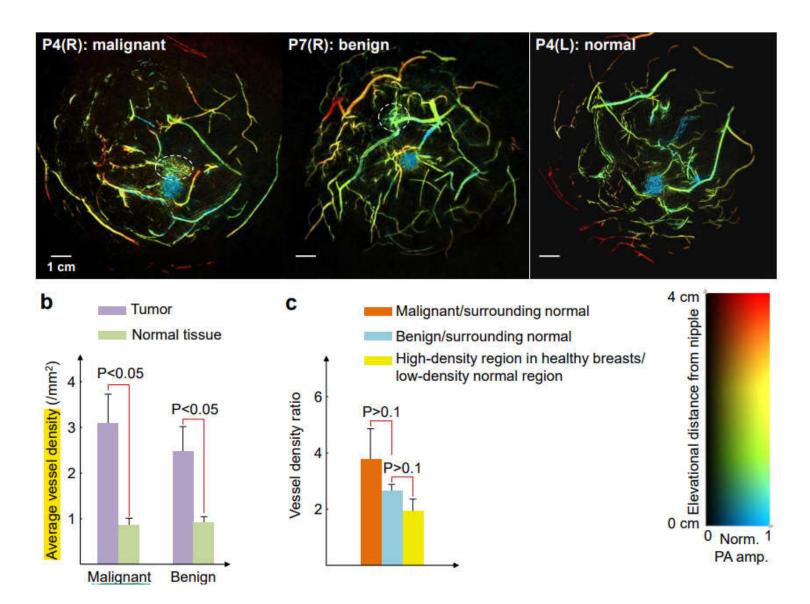


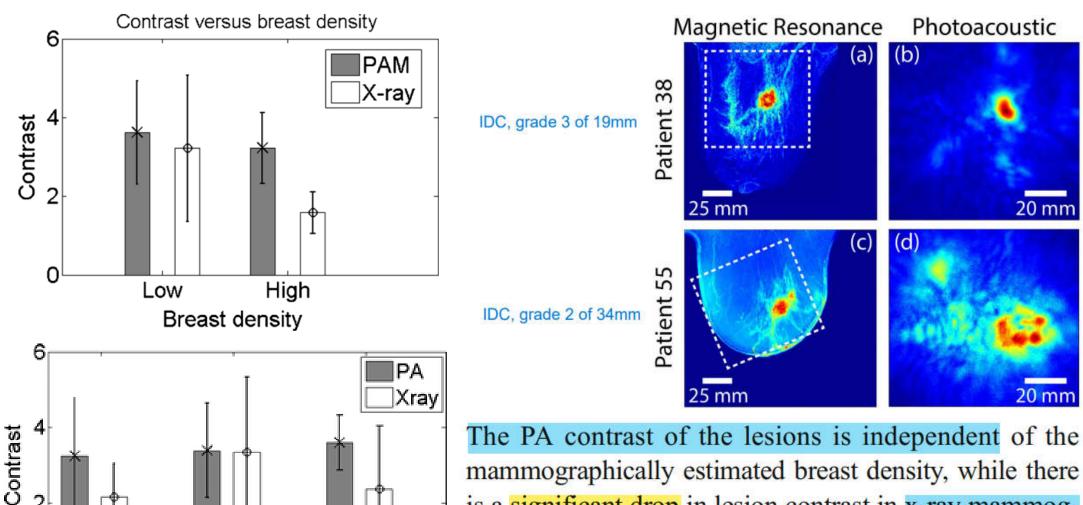




Tumor detection:

- 1- Malignant
- 2- benign



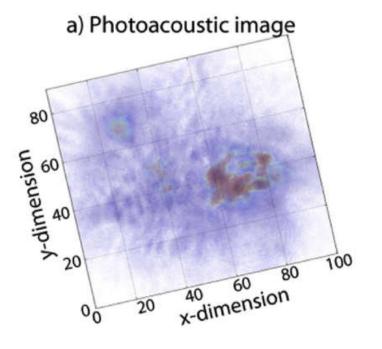


Grade 1

Grade 2

Grade 3

The PA contrast of the lesions is independent of the mammographically estimated breast density, while there is a significant drop in lesion contrast in x-ray mammography for high-density breasts compared to low density breasts;

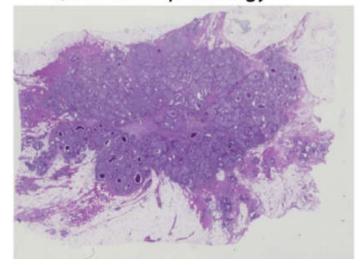


b) MR image

20 mm

c) H&E histopathology

d) CD31 histopathology



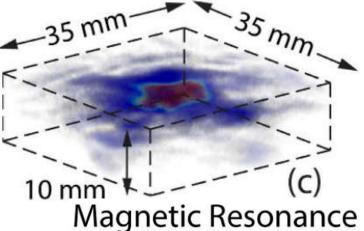


CD-31 immunohistochemistry (IHC) in histopathology, showed good correspondence between density and distribution of vascularity, and PA image patterns

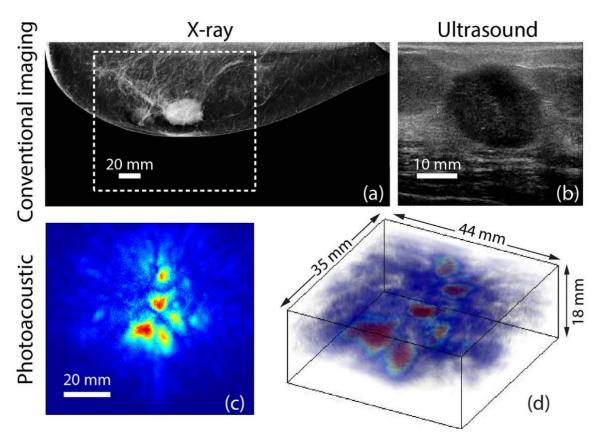
# X-ray Ultrasound The 2:00 701 30 mm (a) 10 mm (b)

Example of photoacoustic mass-like appearance seen in 44 year old patient (P38, Case 1) with infiltrating ductal carcinoma (IDC). (a) The cranio-caudal x-ray mammogram of the right breast does not show any abnormalities and is judged as BI-RADS 1. The white box indicates the field-of-view (FOV) of the PA image. (b) Ultrasound image of palpable mass, reveals 22mm highly suspect mass. (For MR image see Fig. 1(a)) (c) A volume rendering of part of the PA data reveals confined high intensity area, which we define as mass appearance.

## Photoacoustic



25 mm



Example of photoacoustic ring-like appearance observed in 69 year old (P47, Case 2) with IDC (a) The CC x-ray mammogram of the left breast **shows a highly suspect mass measuring about 24mm in diameter**. The white box indicates the FOV of PA image. (b) Ultrasound image of the palpable mass reveals **highly suspect mass measuring 29mm**. (c) MIP in CC view of PA volume presents as a collection of high intensity zones surrounding an area of low intensity. (d) A volume rendering of PA data reveals the ring appearance.

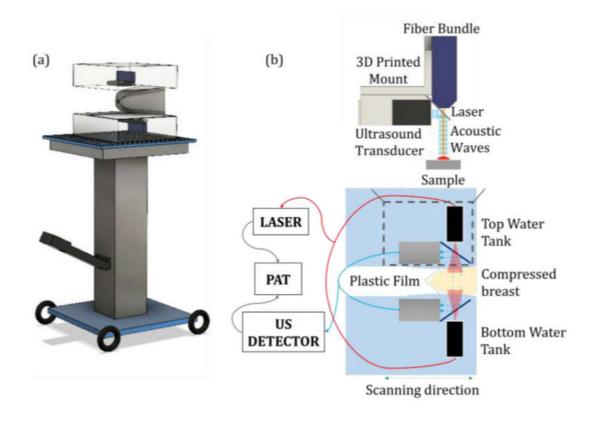


Fig. 1. Dual Scan Mammoscope (DSM), the mild compression photoacoustic breast imaging system. (a) A 3D schematic drawing of the

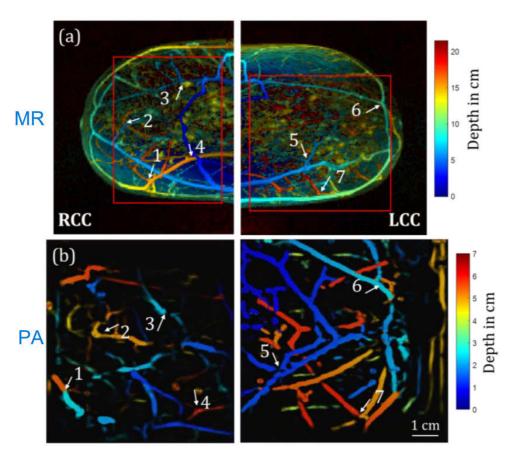
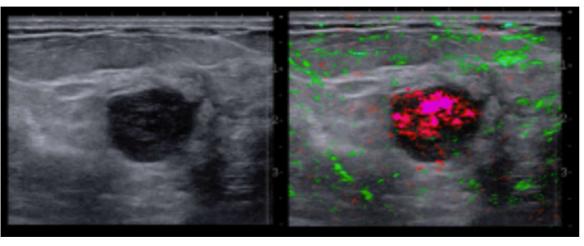


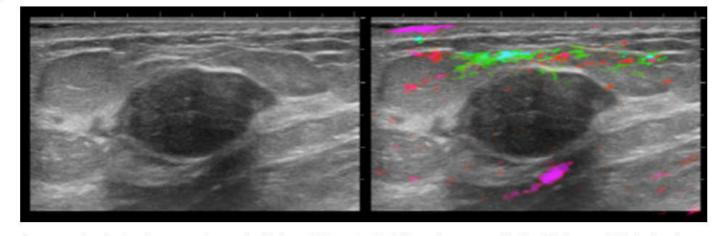
Fig. 5. Comparison of photoacoustic data with contrast-enhanced MRI



Predicting the Breast Tomur grade

An example of a triple-negative breast cancer discovered with Imagio® Imaging. The grayscale image (left) was initially reported as BI-RADS 3. The OA image (right) showed intense de-oxygenation in the central nidus, providing confidence that this mass should be biopsied.

# Preventing unnecessary Biopsies

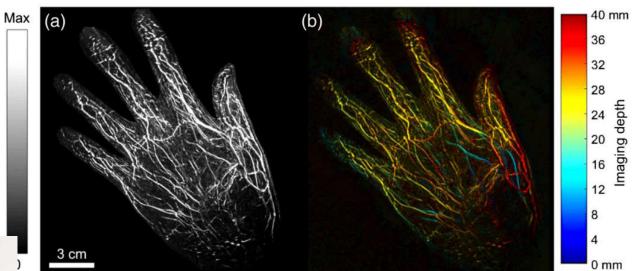


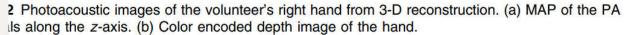
An example of a benign mass imaged with Imagio®—a typical fibroadenoma, with the OA image (right) showing a reassuring draping vessel and the very little activity in the central nidus.

Emerging applications

Vascular imaging

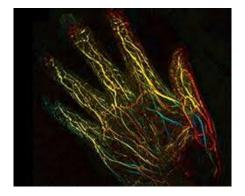
PA amplitude

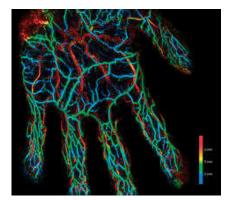






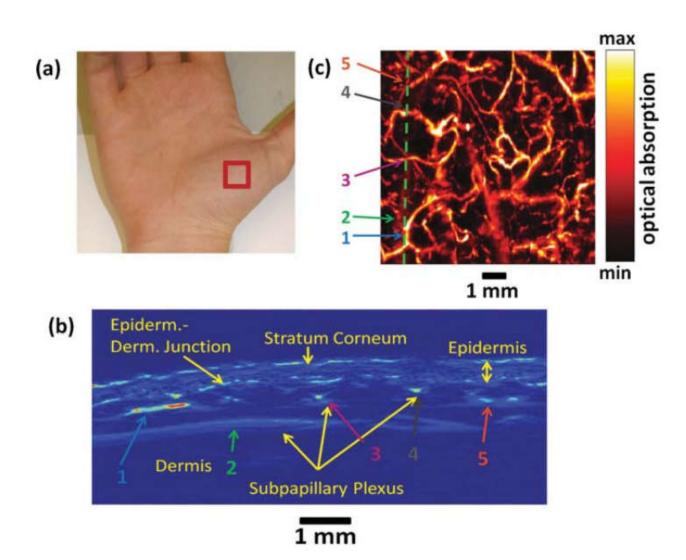
MSOT i-Thera





Emerging applications

skin imaging



Emerging applications

Thyroid imaging

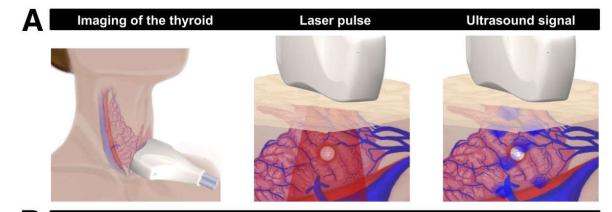
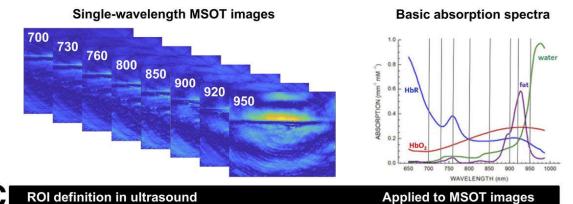


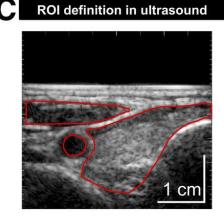
Image reconstruction and spectral unmixing

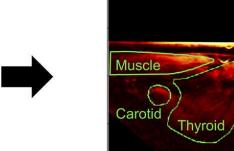
(a)
Fiber bundle
Foil

detector array

Cylindre PACT thyroid focus, Vasilis 2013











#### Rheumatoid arthritis

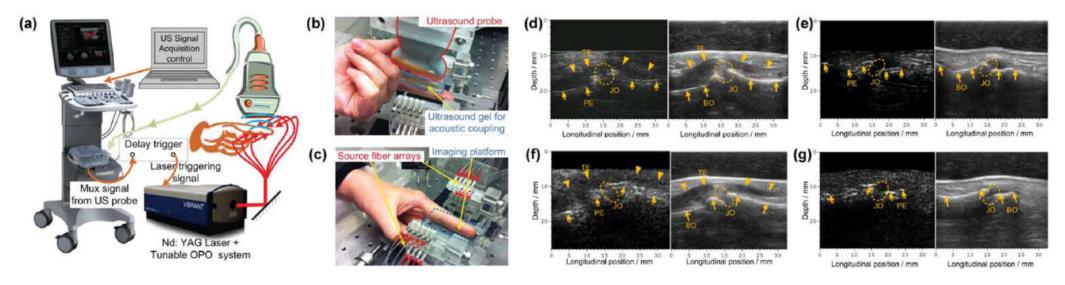
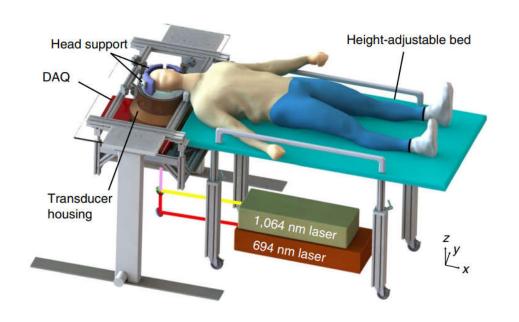


Fig. 4. (a) Schematic of a PA and US dual modality imaging system for human peripheral joints built on a commercial US unit and a linear array probe. (b) Photograph of the experimental setup for coronal middle plane from the volar side. (c) Photograph of the experimental setup for sagittal middle plane. (d) PA and US images of coronal plane (volar) of a male PIP joint. (e) PA and US images of sagittal plane of a male PIP joint. (f) PA and US images of coronal plane (volar) of female PIP joint. (g) PA and US images of sagittal plane of a female PIP joint. TE: tendon, JO: joint, PE: periosteum, BO: bone. Adapted with permission from Ref [34].

## fPAT, Functional PA brain imaging, 2022



magnetic resonance angiography (MRA)

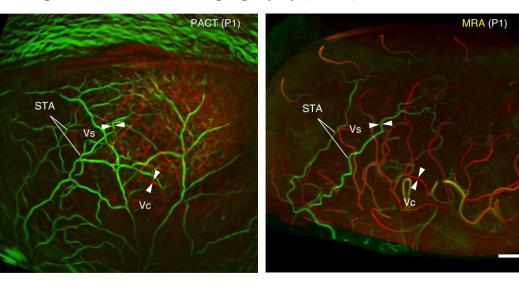
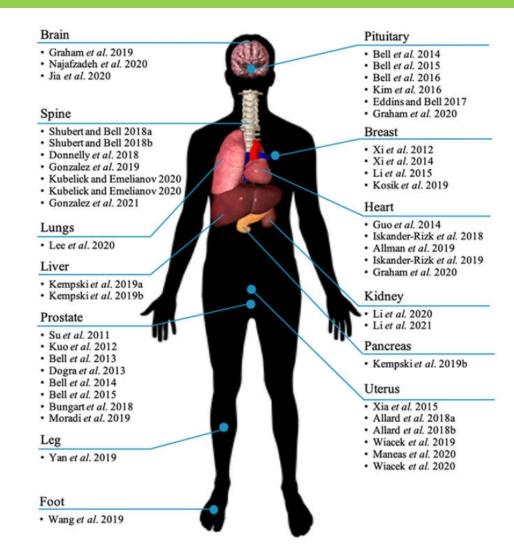


Table 1	Strengths of the	1K3D-fPACT	over BOLD	fMRI for	cortical	neuroimaging
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Modality	Contrast	Response	Background	Sensitivity	Linearity	Portability	Space	Sound	Costs	Magnet
fMRI	HbR	Early	High	Low	No	No	Closed	Loud	High	Yes
fPACT	HbR, HbO <sub>2</sub> , sO <sub>2</sub> , CBV	Earlier	Low	High	Yes	Yes	Open	Quiet	Low	No

# Other Applications

#### Photoacoustic-guided surgery from head to toe



### All in one

Table 1. Comparison of the performance of different imaging techniques

Variable	Ultrasound	Photoacoustic imaging	Fluorescence imaging	MRI	PET
Type of energy measured	High-frequency sound waves	High-frequency sound waves	Visible or near-infra- red light	Radio waves	High energy gamma rays
Spatial resolution	50–500 μm	50-500 μm	2-10 mm (depth dependent)	20–100 μm	1–2 mm
Time resolution	Seconds to minutes	Seconds to minutes	Seconds	Minutes to hours	Minutes
Sensitivity	Not well characterized	pM	nM	$\mu M$ – $mM$	pM
Depth	<5 cm	< 5 cm	< 5 mm	No limit	No limit
Type of contrast agents	Microbubble	Nanoparticle/micro- bubble	Small molecules nanoparticle	Small molecules nanoparticle	Small molecules nanoparticle
Cost	Low	Low	Medium	High	High

MRI, magnetic resonance imaging; PET, positron emission tomography.

#### **Breast Cancer Treatment Monitoring**

From the literature it was found that PA imaging can be used to monitor the efficacy of anticancer treatments, such as **chemotherapy** or **molecular targeting therapies**, through the changes in the PA images of tumor-related blood vessels.

#### Conclusion

**Ultrasound**: low specificity

X-ray: poor sensitivity mammography, damage

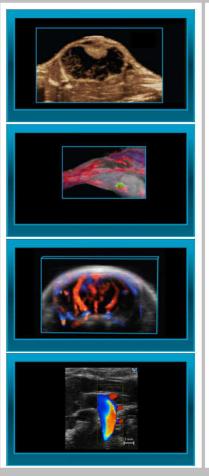
Enhanced-MRI: high-cost, contrast-agent, may damage

Photoacoustic: low-cost, NO contrast-agent, NO pain, NO damage

#### List Of TOP KEY PLAYERS in Photoacoustic Imaging Market Report are

- iThera Medical GmbH
- Kibero
- Seno Medical Instruments
- FUJIFILM VisualSonics
- TomoWave





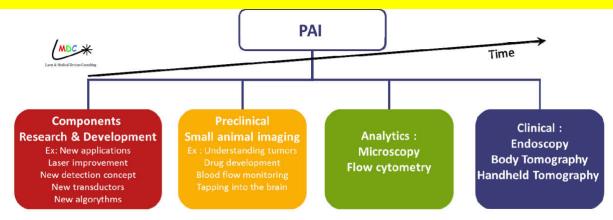




شكل ۵ محصولات كمپاني iThera

شکل ۲ دستگاه VEVO LAZR-X کمپانی

#### **Global Photoacoustic Market Size**

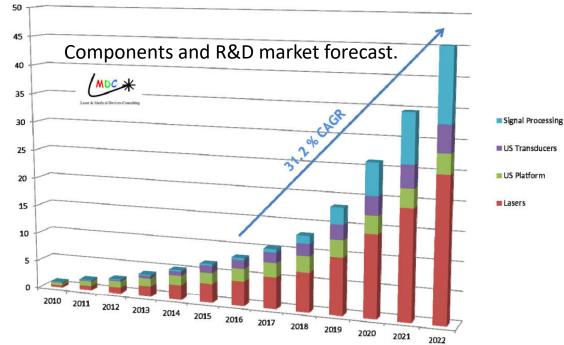


PAI market segmentation

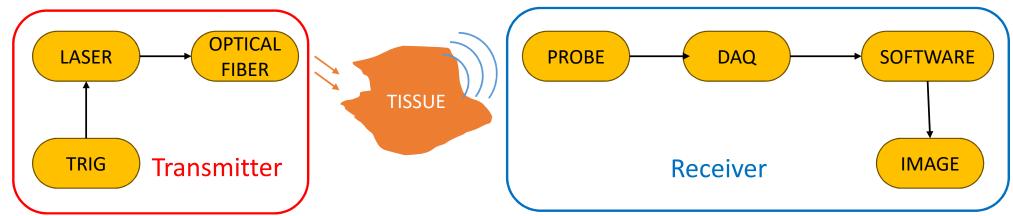
#### **Photoacoustic Imaging Market Report Scope**

Report Attribute	Details
Market size value in 2021	USD 69.8 million
Revenue forecast in 2028	USD 235.9 million
Growth rate	CAGR of 19% from 2021 to 2028

There is a sharp increase from 2018, due to the clinical approved products that should be launched on the market during 2017.

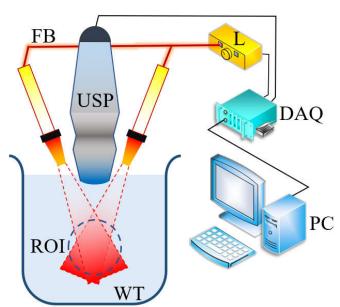


## **PAI** system



Cost estimation for a low-cost PACT system.

Component	Type	Price (USD)
Laser	PLD arrays, 20 kHz, 55 ns pulse width	10–15 K
Optical fiber bundle and optics	Dia: 1 mm, NA: 0.25, diffuser: 120 grit	~500
US transducer	8 single elements, 2-10 MHz	2-5 K
	128-channel linear arrays, 2-10 MHz	10-15 K
Amplifiers	Low-noise 40dB	~300
DAQ (single/ multi-channel)	8 channel differential, 200KS/s	~500
	128 channels, 40 MS/s (Linear array)	~30K
Servo motor	24-70 VDC	~400
Software	MATLAB	~300



## LASER

Nd:YAG – Pulsed

• PRF: 10 Hz

• Energy: 0.1 – 1 J

Wavelength: 532 nm, 1064 nm

Setup type: Hand-held

Weight: ~ 3 KG

Optical fiber



## DAQ

- 32, 64 DAQ channels (future: 128 192)
- SNR level: ~ 45 dB
- Supports up to 192 channels
- Supports up to 64 channel US transmission
- Adaptive with USCT setups



## **Probe**

Number of elements: 192

• Frequency: 4-12 MHz

• Pitch: 0.2 mm

Radius of curvature: 0

Elevation aperture: 3.5 mm

Elevation focus: 13 mm

Aperture 35 mm



#### **Improtant news**

#### iThera Medical closes €13 Million financing to fund translation of their optoacoustic imaging technology into routine clinical use

December 21, 2022

Medical device company iThera Medical announces successful closure of €13 Million investment round, led by TRUMPF Venture with participation by the EIC Fund as co-investor in addition to existing investors Mey Capital Matrix, Wachstumsfonds Bayern, BayBG, Fluxunit, Falk Strascheg Holding, and Occident. The funding will drive the company's continued innovation and commercialization of its novel medical imaging technology, with a specific goal to translate the technology into a routine clinical environment and offer clinicians worldwide a powerful new diagnostic tool.

#### iThera Medical to lead €2.3m research project to advance inflammatory bowel imaging

February 20, 2019

The European Commission has awarded a €2.3 million 'Fast Track to Innovation' project grant to a consortium led by the Munich-based medical device company iThera Medical. Funded under the European Innovation Council (EIC) pilot, the aim of the grant is to improve the sensitivity and effectiveness of MSOT, Multispectral Optoacoustic Tomography, in detecting and managing inflammatory bowel diseases (IBD). Beyond technical improvements, the new project, 'EUPHORIA' (Enhancing Ultrasound and PHOtoacoustics for Recognition of Intestinal Abnormalities) will also support the transition of MSOT from clinical research use to routine diagnosis.

#### iThera Medical leads €1.6m project to develop novel machine learning-assisted optoacoustic imaging of neuromuscular disease

May 17, 2022

Medical device company iThera Medical announces the kickoff of the technology innovation project SMART-3D funded by the Bavarian Research Foundation. Commenced on 01 May 2022, the project aims to develop an innovative new approach to monitor neuromuscular disease in pediatric patients through the company's proprietary optoacoustic imaging technology and next-generation 3D image reconstruction assisted by machine learning.

#### iThera Medical leads €1.9m research project to advance optoacoustic imaging technology towards Al-supported quantitative medical diagnosis

September 13, 2021

Medical device company iThera Medical announces the kickoff of the Bavarian state-funded technology innovation project DeepOPUS. The project aims to augment the company's proprietary optoacoustic imaging technology using Al technology, developing it into a quantitative diagnostic method for inflammatory bowel disease (IBD) and beyond.

European Commission backs biophotonics "FAMOS" consortium with €10.1M for project to develop new lasers for earlier, better diagnosis of major disease

October 24, 2012

#### **Improtant news**

iThera Medical closes €13 Million financing to fund translation of their optoacoustic imaging technology into routine clinical use

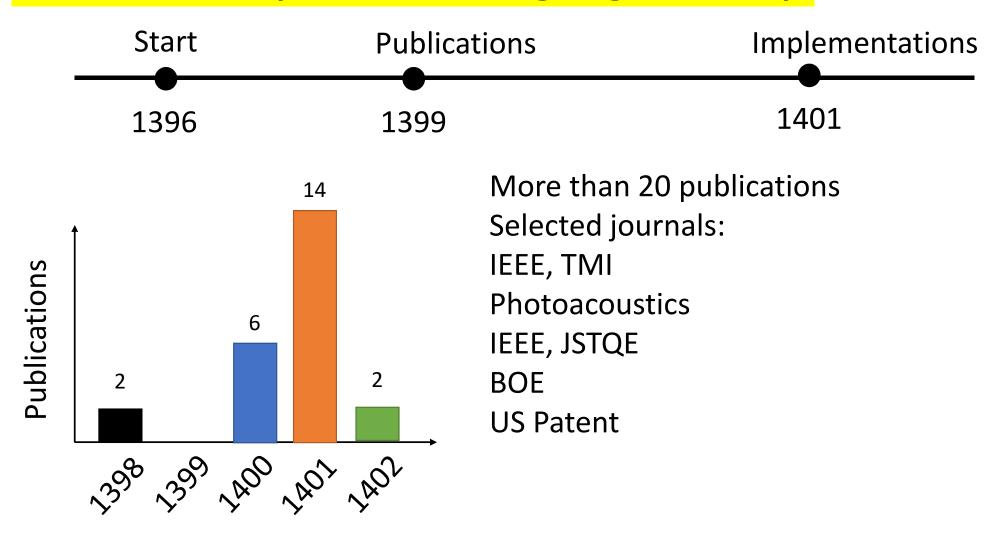
December 21, 2022

CE Mark awarded to iThera Medical's second-generation MSOT Acuity Echo optoacoustic imaging system

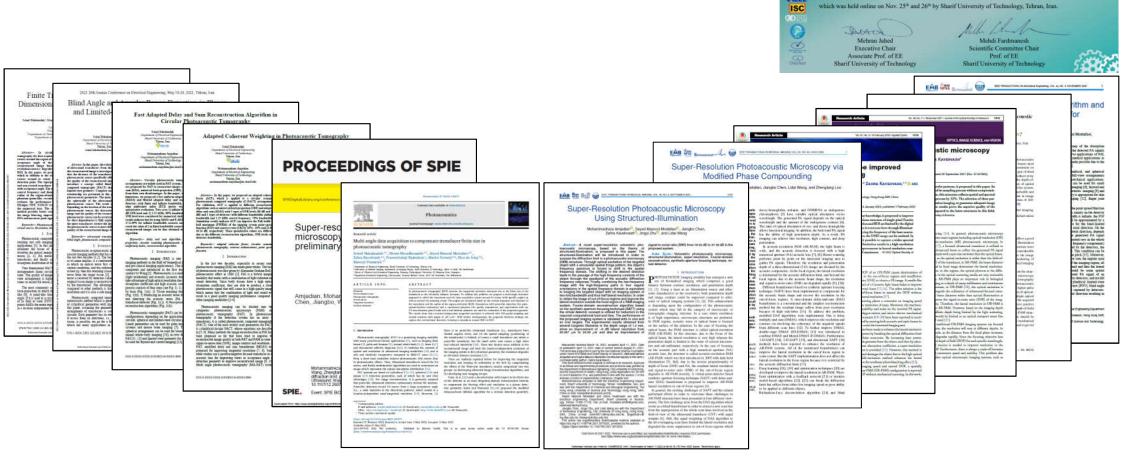
May 26, 2021

Ulrich Kruse, Investment Manager of TRUMPF Venture, describes their rationale for investing: "iThera Medical's technology is positioned to be the next breakthrough in medical imaging. As a company with deep roots in photonics and medical technology, we are thrilled to support the continued development of MSOT and anticipate an impactful launch into wider medical imaging markets."

### **SOFTWARE (Beamforming algorithms)**



#### Some 2021-2022 selected works



Distinguished Paper Certificate

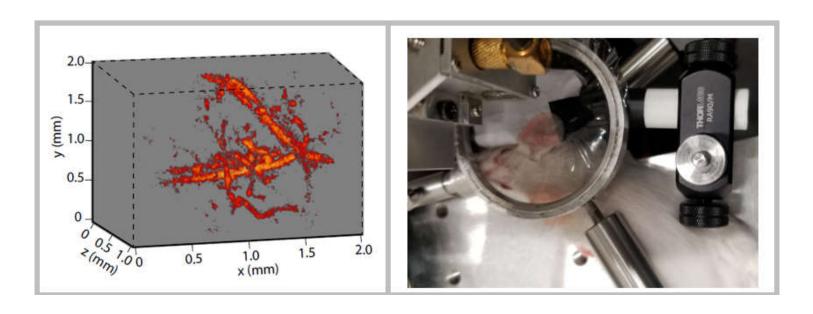
"Adapted Coherent Weighting in Photoocoustic Tomography", Soheil Hakakzadeh, Seyed Masood

This certificate is awarded to the distinguished paper, titled:

## Photoacoustic Microscopy (1)



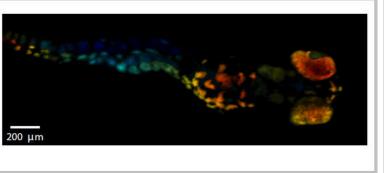
Rat liver

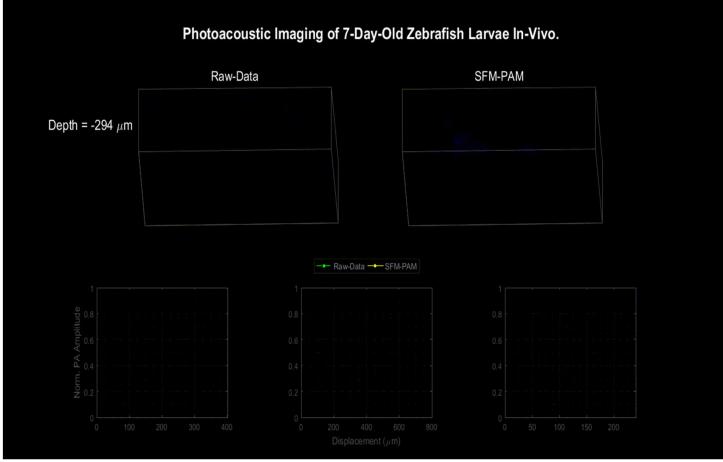


Rat Ear

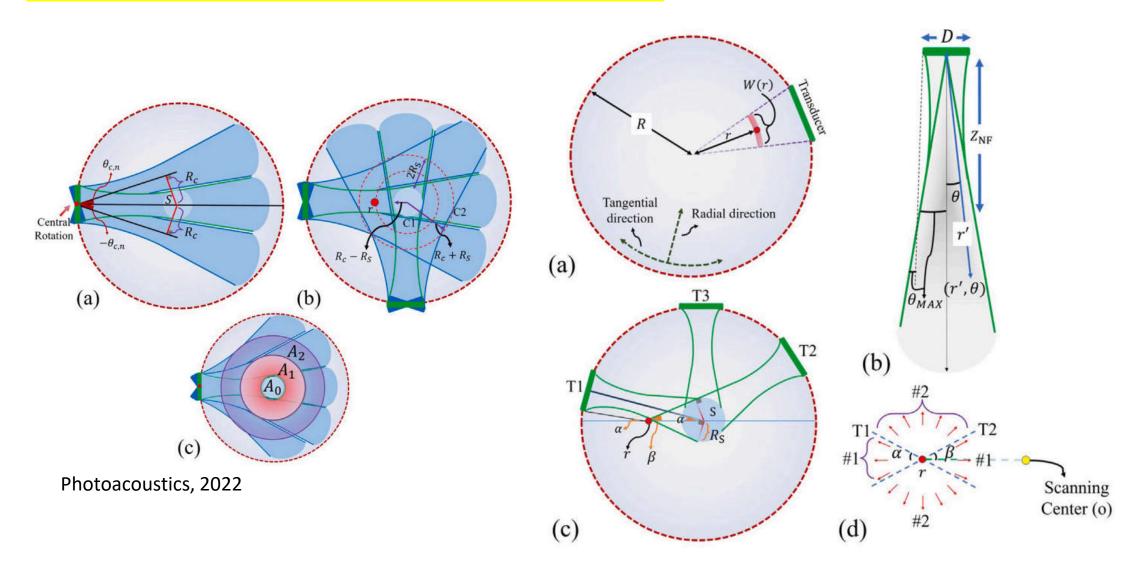
## **Photoacoustic Microscopy (2)**

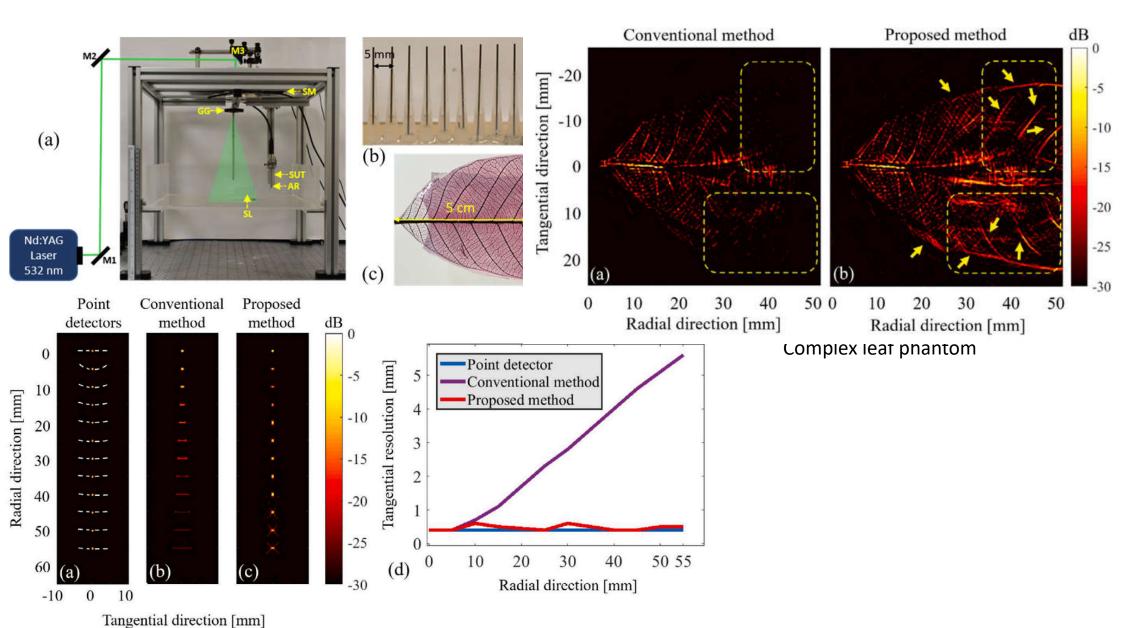


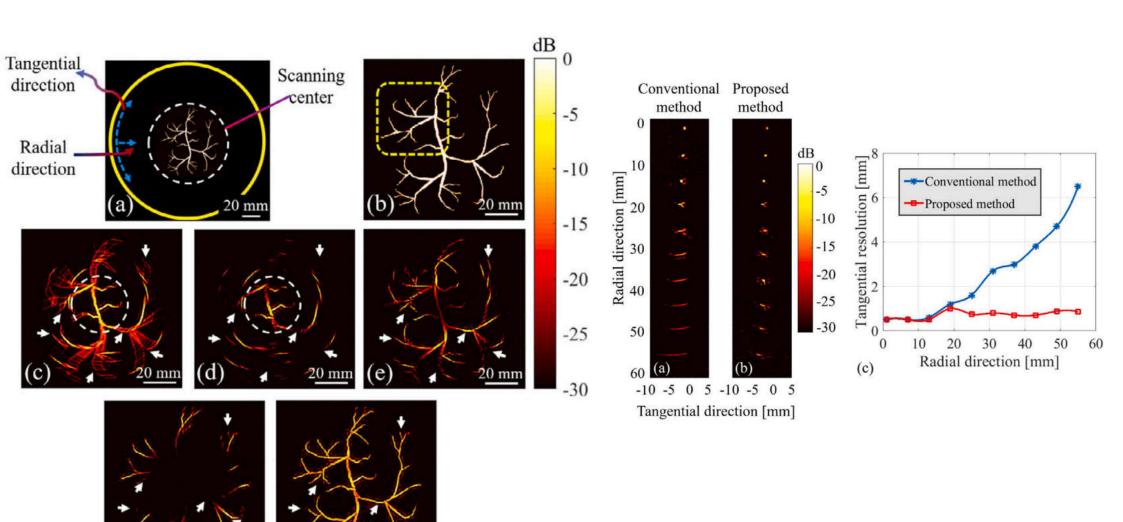




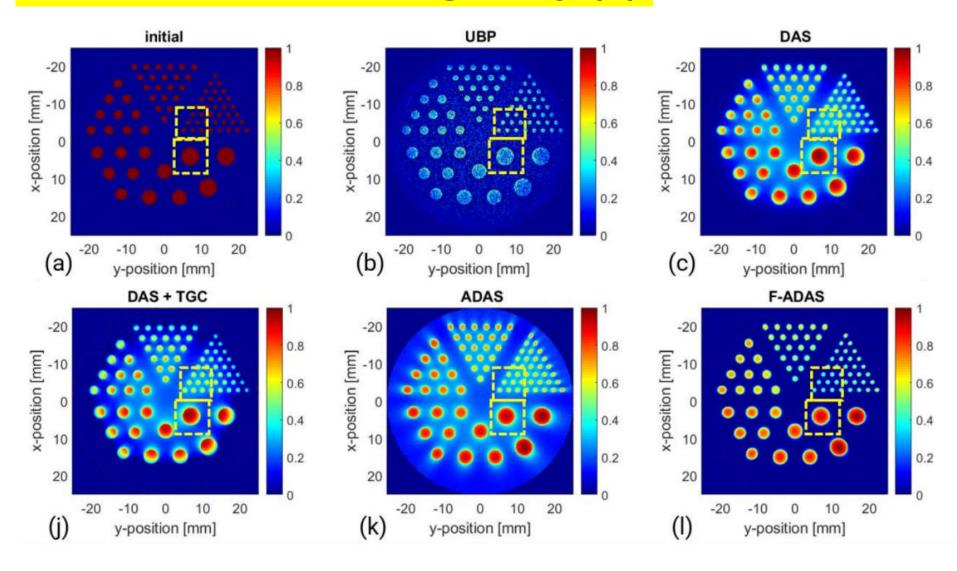
## **Photoacoustic Tomography (1)**



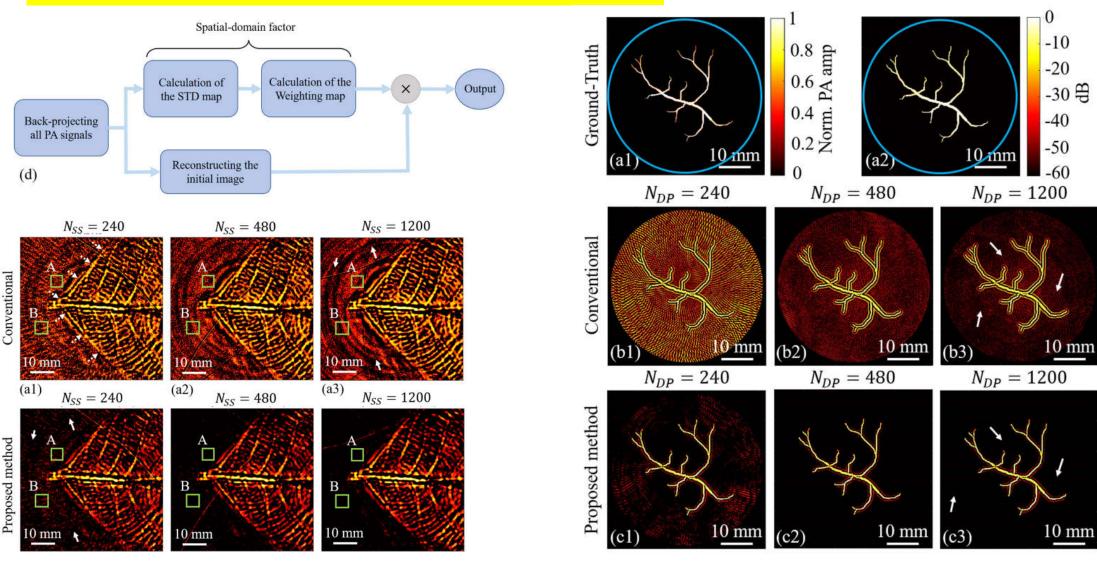




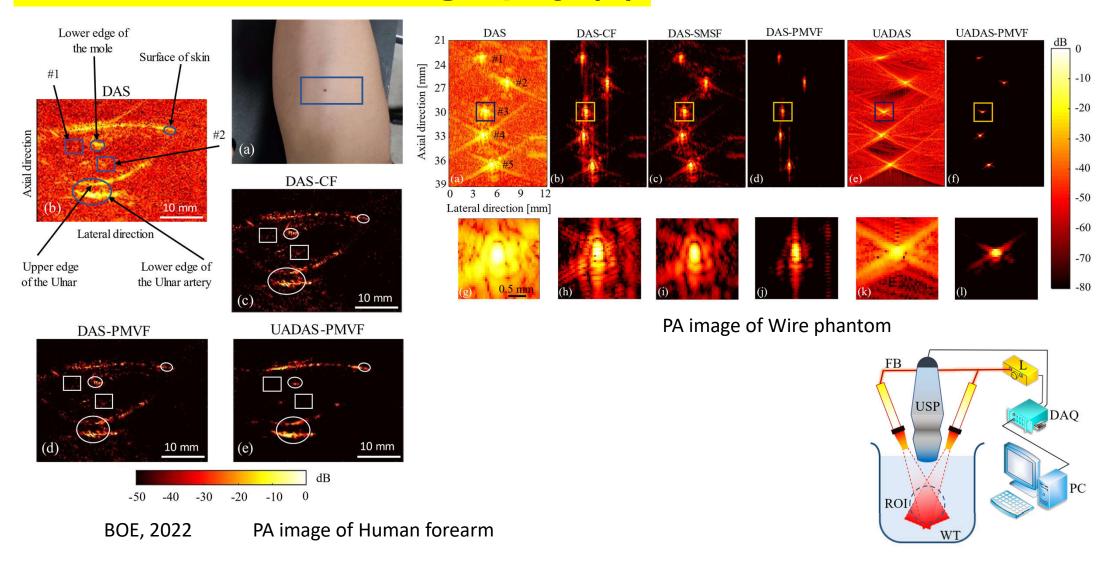
### **Photoacoustic Tomography (2)**

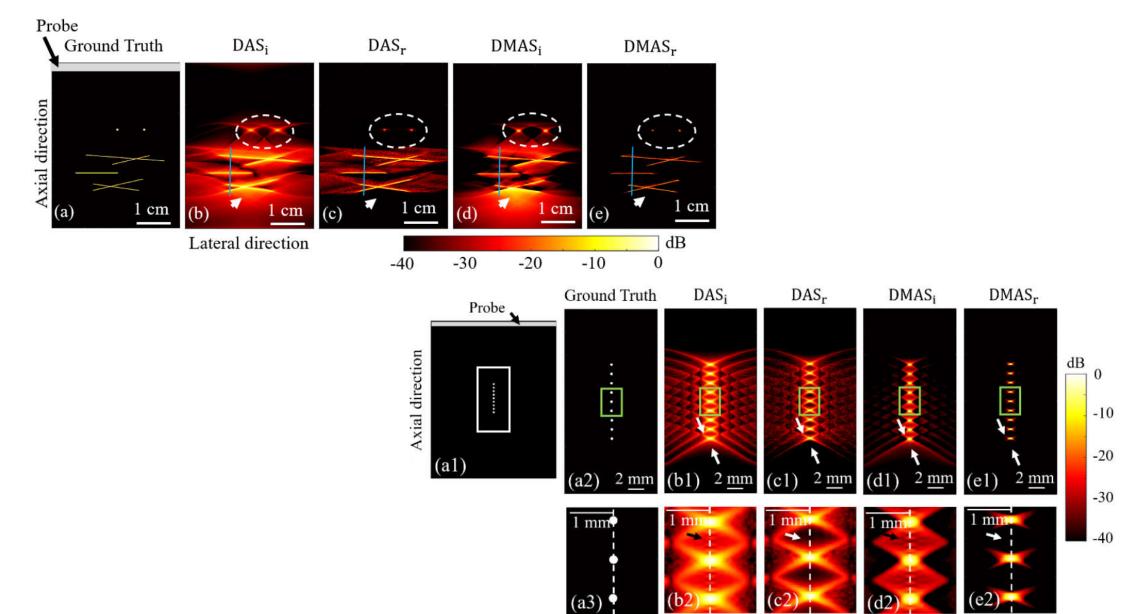


### **Photoacoustic Tomography (3)**



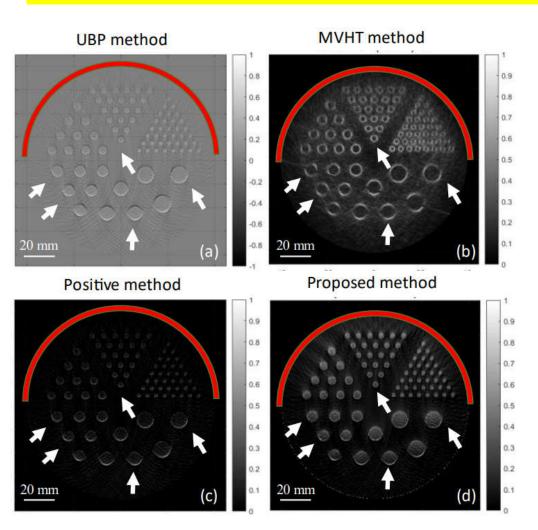
## **Photoacoustic Tomography (4)**

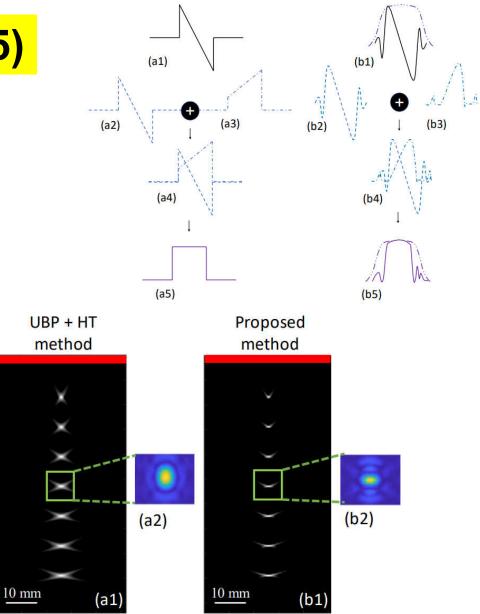




Lateral direction

## **Photoacoustic Tomography (5)**





## Matching PAI Systems with Applications

Introduction

1 Imaging depth

2

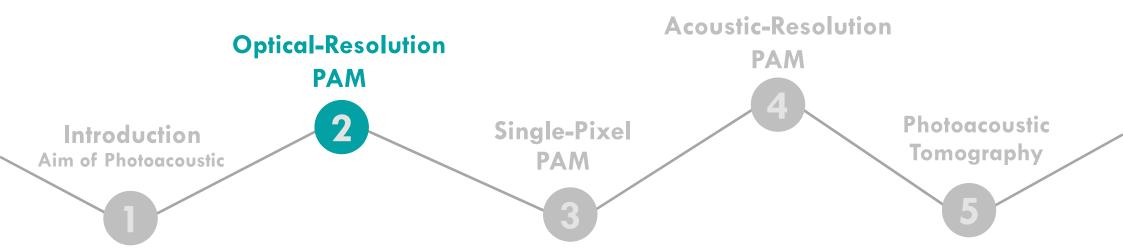
Imaging speed or temporal resolution

3 Imaging contrast

10 <sup>-7</sup>	10 <sup>-6</sup>	10 <sup>-5</sup>	10 <sup>-4</sup>	10 <sup>-3</sup>
Organelles (SR-PAM)			Spatia	Il resolution (m)
	Single cells (OR-PAM)			
		Tiss (AR-I		
			Whole-body animals or hu (PACT)	umans
10 <sup>-5</sup>	10 <sup>-4</sup>	10 <sup>-3</sup>	10 <sup>-2</sup>	10 <sup>-1</sup>
	Pen	etration limit (	m)	

Major Implementations	PAM	PACT	
Lateral Resolution	AR-PAM $\cong$ 30 $\mu$ m OR-PAM $\cong$ 3 $\mu$ m	100 - 500 μm	
Axial Resolution	< 30 μm	100 - 500 μm	
Penetration Depth	AR-PAM < 10 mm OR-PAM < 1 mm	> 10 mm	
Energy per pulse	AR-PAM < 1 mJ OR-PAM < 1 μJ	> 10 mJ	
PRF	> 1 KHz	Tens of Hertz	

# Agenda



### Optical Resolution PAM (OR-PAM)

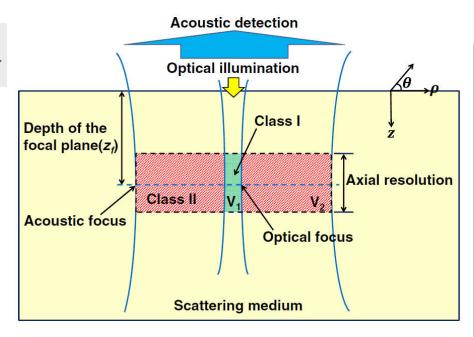




$$\delta_{OR} = 0.51 \frac{\lambda_o}{NA_o} = 0.51 \frac{532^{nm}}{0.1} = 2.7 \ \mu m$$

- Penetration depth is restricted to the mean optical path length:
- The scattering anisotropy g = 0.9
- The scattering coefficient  $\mu_s = 100 \ cm^{-1}$
- The absorption coefficient  $\mu_a = 0.1 \ cm^{-1}$

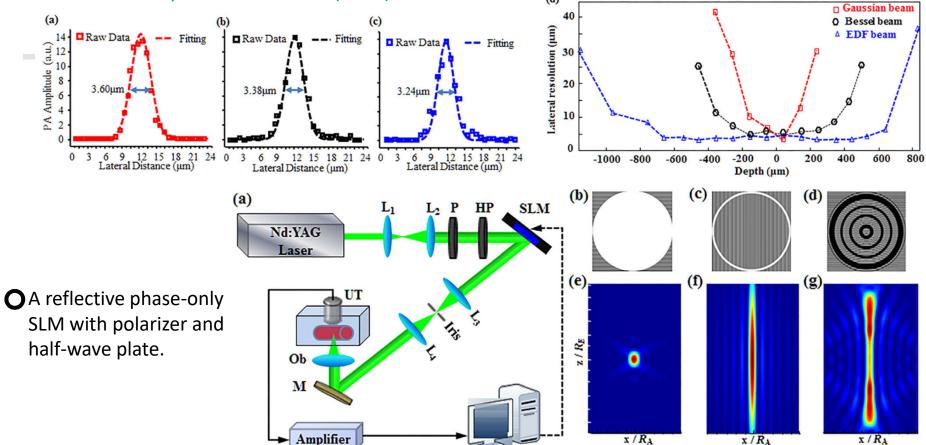
$$l'_t = \frac{1}{\mu_s(1-g) + \mu_a} = 1 \ mm$$



Optical-Resolution PAM

#### **DOF Improvement**

solution: Instead the focused Gaussian beam, we produced needle-like Bessel beam (BB), and extended depth-of-focus beam (EDFB).



Optical-Resolution PAM

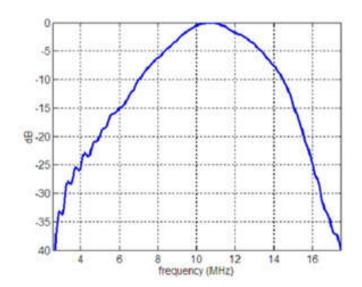
> (69/7 0)

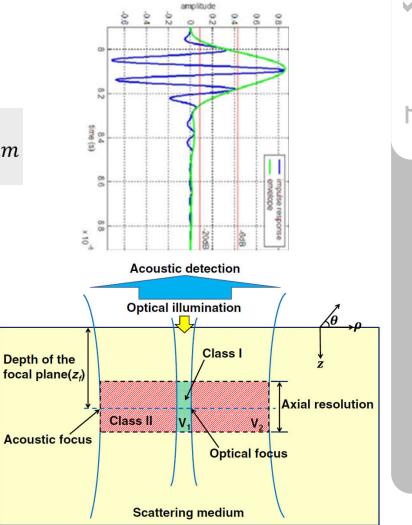
#### **Limitations of OR-PAM**





$$\delta_{axial} = 0.88 \frac{c}{\Delta f_c} = 0.88 \frac{1540^{\frac{m}{s}}}{0.78 \times 50^{MHz}} = 34.74 \ \mu m$$





Optical-Resolution PAM

(70/70)

#### Isotropic Imager



- <u>1st solution:</u> Higher frequency ultrasonic transducers and deconvolution algorithms have been utilized to achieve higher acoustically defined axial resolution.
- <u>Problems:</u> at the cost of the signal-to-noise ratio (SNR) and imaging depth.
- 2<sup>nd</sup> solution: Grueneisen Relaxation Photoacoustic Microscopy (GR-PAM).
- <u>Phenomenon:</u> The temperature-dependent property of the Grueneisen parameter has been employed in photoacoustic imaging mainly to measure tissue temperature..

Optical-Resolution PAM

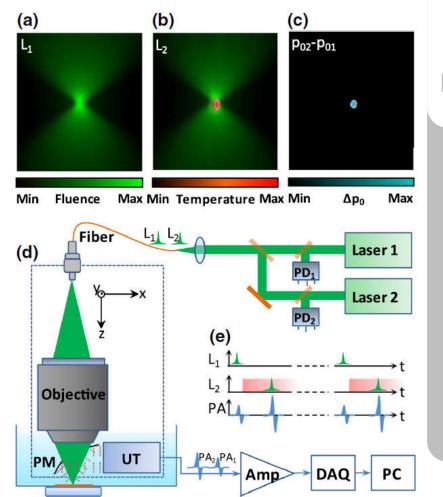
#### **GR-PAM**

- GR-PAM sequentially delivers two identical laser pulses with a microsecond-scale time delay.
- The first laser pulse generates a photoacoustic signal and thermally tags the in-focus absorbers.

$$p_{01} = \Gamma_0 \eta_{\rm th} \mu_a F$$

When the second laser pulse excites the tagged absorbers within the thermal relaxation time, a photoacoustic signal stronger than the first one is produced, owing to the temperature dependence of the Grueneisen parameter.

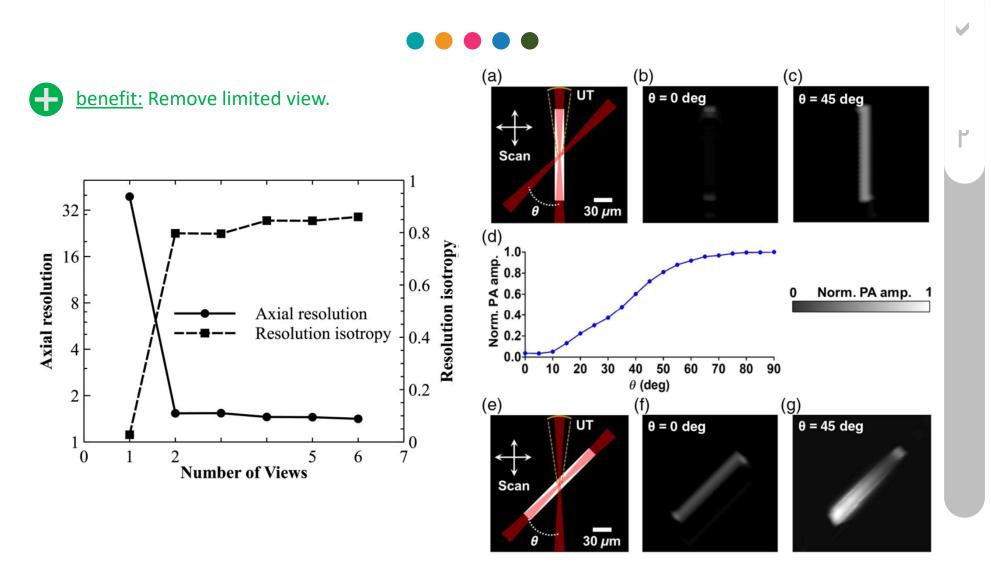
$$p_{02}=(\Gamma_0+b\eta_{
m th}\mu_aF)\eta_{
m th}\mu_aF$$



Optical-Resolution PAM

(72/70)

#### **Multiview Structure**



Optical-Resolution PAM

(73/70)

#### **Limitations of OR-PAM**

- <u>Problem:</u> Need a mechanical scanner with high speed and stability along with the high resolution.
- Problem: Noise caused by the movement of the ultrasound transducer to scan the imaging medium.
- Key Idea: Single-Pixel Photoacoustic Microscope.

#### Conventional PAM



Single-Pixel PAM

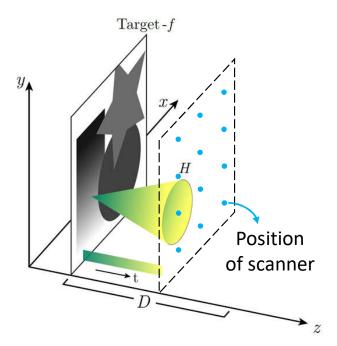
(74/70)

#### Single-Pixel Photoacoustic Microscope (SIR-PAM)

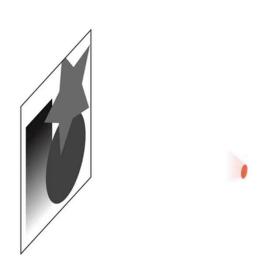


#### **Conventional PAM**

#### Single-Pixel PAM



The scene is illuminated with a pulsed source



Single-Pixel PAM

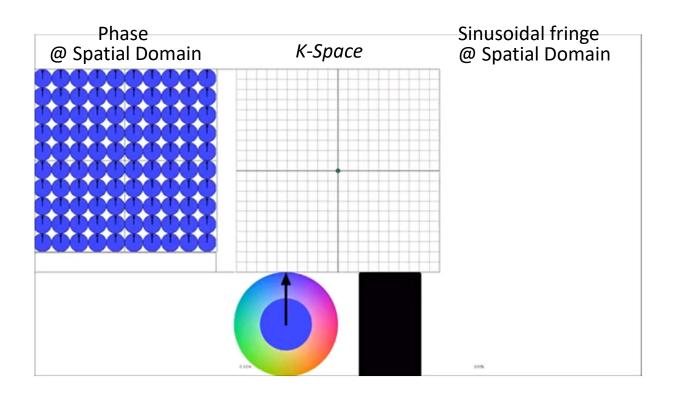
(75/70)

## Single-Pixel Photoacoustic Microscope



Orthonormal basis of two-dimensional Fourier transform:

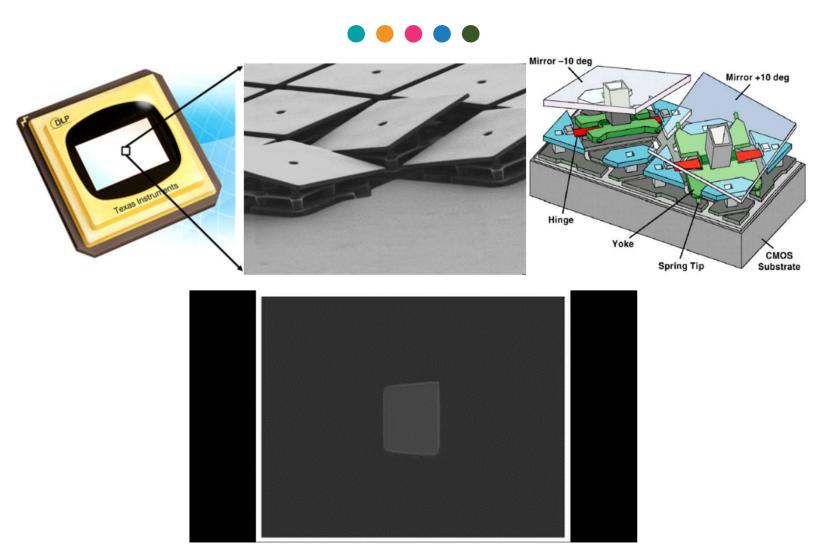
Complex exponential pattern;  $P_{\varphi}(x, y, z) = \exp[-i(k_{x_0}x + k_{y_0}y + \varphi)]$ 



Single-Pixel PAM

(76/70)

## Sinusoidal pattern generation using DMD

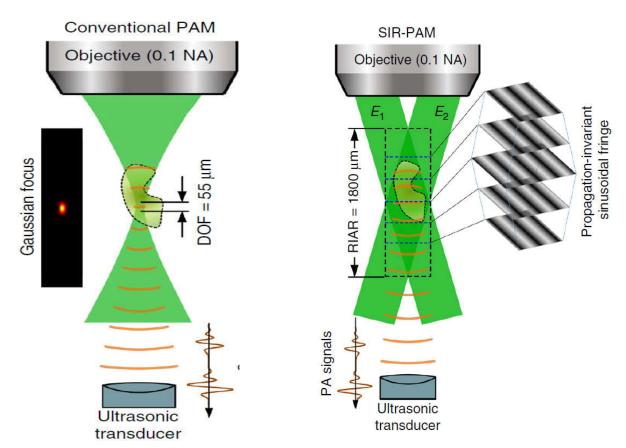


Single-Pixel PAM

(77/70)

## Region-of-Interest (ROI)

<u>Problem:</u> Trade-off between ROI and resolution; due to limitation of number of DMD pixel (dependent on scaling factor in 4f structure):



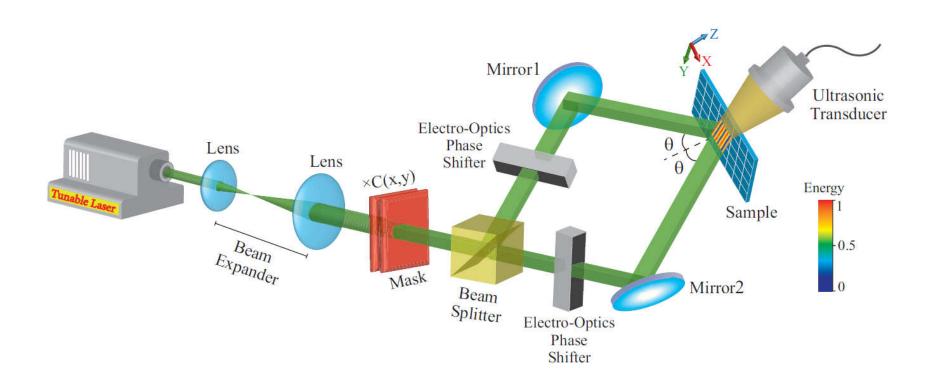
Single-Pixel PAM

(78/70)

## Setup



Proposed Structure:

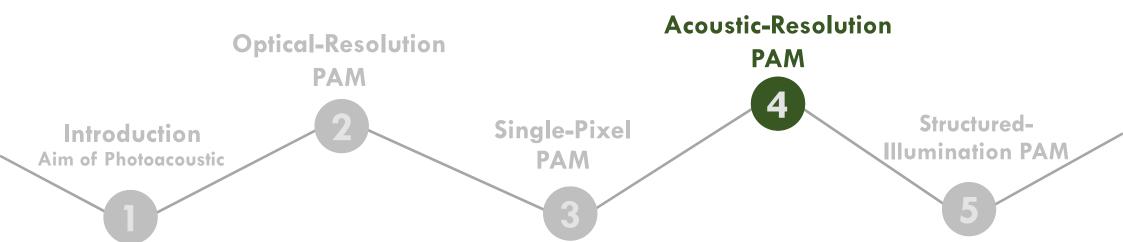


Single-Pixel PAM

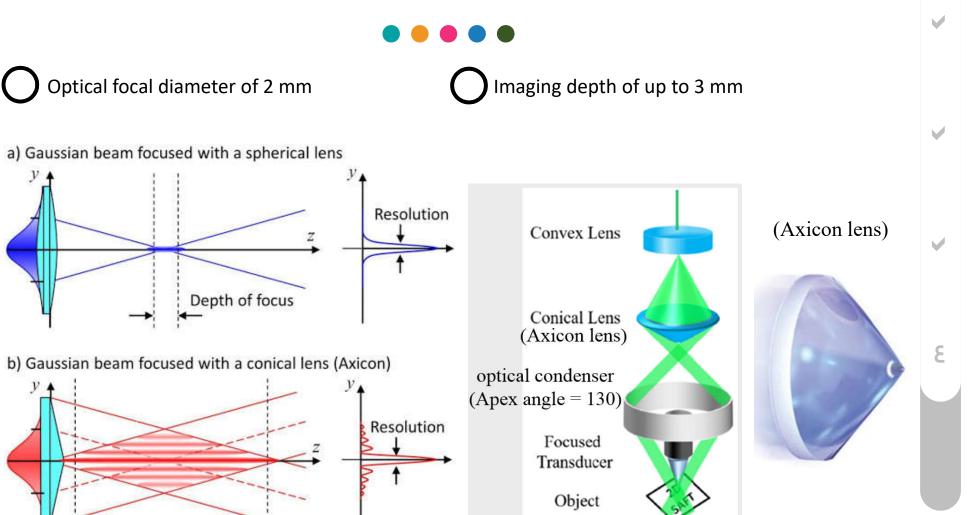
(79/70)

## Agenda





## Dark-Field and Bright-field Illumination



Depth of focus

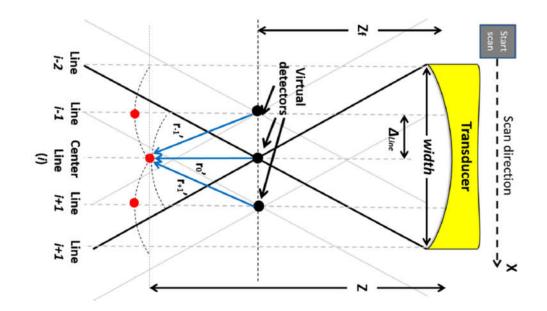
Acoustic-Resolution PAM

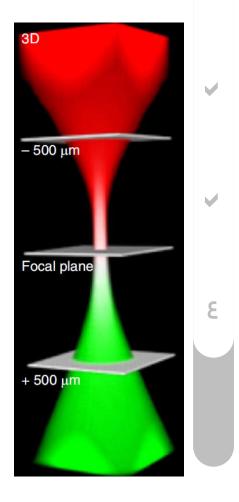
(81/70)

## Synthetic Aperture Focusing Technique (SAFT)



- <u>Profits:</u> In order to obtain an appropriate lateral resolution, the AR-PAM method takes advantage of a Large NA (for resolution improvement in the focal zone), High frequency, High sensitive, single-element focused UST.
- Problem: Large NA of this focused transducer although improves the lateral resolution in the focal-zone limits the DOF. Moreover, it deteriorates the lateral resolution and thus image quality in out-of-focus regions.





Acoustic-Resolution PAM

(82/70)

### SAFT based on Virtual Detector (VD) Concept

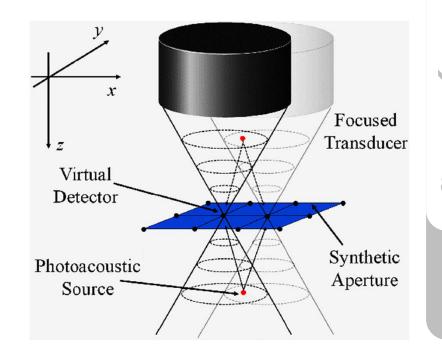


<u>Problem:</u> During conventional delay-and-sum reconstruction, large-aperture detectors are considered as a point detector, typically at the center of the transducer surface.

**Acoustic wavelenght** :  $\lambda_a = 30 \, \mu m$ ,

**Active diameter of transducer** :  $D_a = 6 mm$ 

Key Idea: The focal point of the US transducer is considered as the VD.

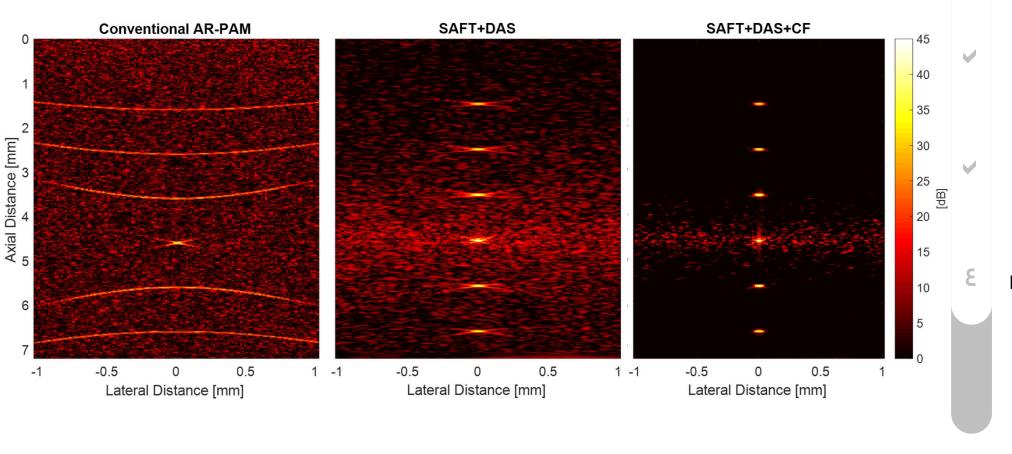


Acoustic-Resolution PAM

(83/70)

## **Numerical Simulations**





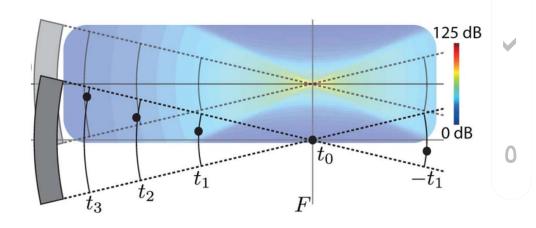
Acoustic-Resolution PAM

(84/70)

#### **Acoustic Diffraction Limit**



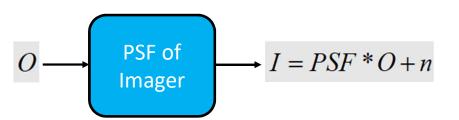
- Problem: It has been assumed that a VD acts as a point detector. Still, the finite diameter and NA of the focused ultrasound transducer makes the point detector assumption of VDs to be inexact. The lateral resolution in focal-zone is limited to  $\delta_{AR}=0.71\frac{\lambda_a}{NA_a}$  due to the acoustic diffraction limit.
- 1st Solution: Deconvolution with the PSF of the acoustic system



Structured-Illumination PAM

(85/70)

#### Richardson-Lucy Deconvolution Algorithm



$$J_{k} = [\frac{I}{PSF * J_{k-1}} * PSF ']J_{k-1}$$

One is the normalized adjacent mean square error (AMSE) of two successively restored images in adjacent iterations:

$$AMSE = \frac{\sum_{x} \sum_{y} \sum_{z} [J_{k} - J_{k-1}]^{2}}{\sum_{x} \sum_{y} \sum_{z} J_{k-1}^{2}}$$

Depth from the transducer (mm)						
5.8	6.1	6.4	6.7	7	7.3	7.6
640/40	380/35	220/42	65/40	220/42	380/42	700/42
70/42	75/42	75/42	65/42	70/39	75/39	75/42
23	20	12	0	26	25	31
20/18	21/19	20/19	24/12	29/12	22/15	24/17
31	28	17	6	30	31	36
	640/40 70/42 23 20/18	5.8     6.1       640/40     380/35       70/42     75/42       23     20       20/18     21/19	5.8     6.1     6.4       640/40     380/35     220/42       70/42     75/42     75/42       23     20     12       20/18     21/19     20/19	5.8     6.1     6.4     6.7       640/40     380/35     220/42     65/40       70/42     75/42     75/42     65/42       23     20     12     0       20/18     21/19     20/19     24/12	5.8     6.1     6.4     6.7     7       640/40     380/35     220/42     65/40     220/42       70/42     75/42     75/42     65/42     70/39       23     20     12     0     26       20/18     21/19     20/19     24/12     29/12	5.8     6.1     6.4     6.7     7     7.3       640/40     380/35     220/42     65/40     220/42     380/42       70/42     75/42     75/42     65/42     70/39     75/39       23     20     12     0     26     25       20/18     21/19     20/19     24/12     29/12     22/15

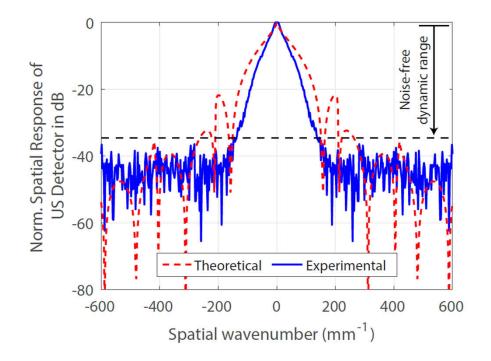
Structured-Illumination PAM

(86/70)

#### Limitation



Problem: Limitation in dynamic range.



Solution: Structured Illumination.

Structured-Illumination PAM

(87/70)

#### Aim of Structured-Illumination PAM



- Purpose: The structured-illumination will be introduced in order to surpass the diffraction limit in an AR-PAM structure.
- Through optical excitation of the targeted object with a sinusoidal spatial fringe pattern, the object's frequency spectrum is forced to shift in the spatial frequency domain.
- The shifting in the desired direction leads to the passage of the high-frequency contents of the object through the passband of the acoustic diffraction frequency response.
- Finally, combining the low-frequency image with the high-frequency parts in four regular orientations in the spatial frequency domain is equivalent to imaging the targeted object with an imaging system of two-fold bandwidth and thus half lateral resolution.

Structured-Illumination PAM

(88/70)

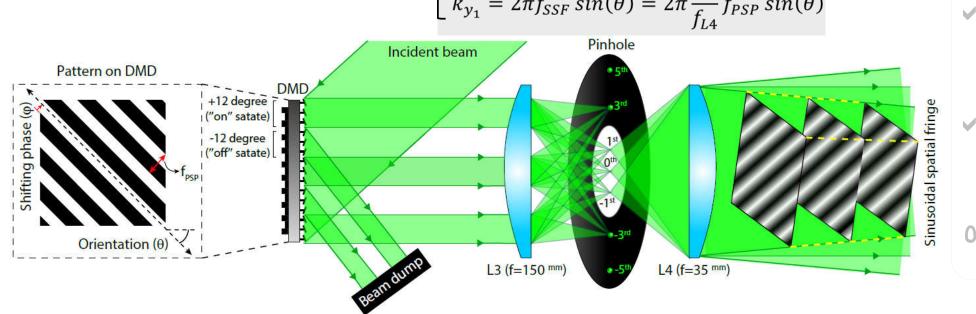
# Spatial Amplitude and Phase Modulation Using a DMD for Fringe Illumination



$$f_{SSF_{max}} = \frac{sin(\theta_{L4_{max}})}{\lambda} \approx \frac{NA_{L4}}{\lambda} = \frac{d_{L4}}{2\lambda f_{L4}} = 671.3 \ mm^{-1} \quad \rightarrow \quad r_p = \lambda f_{L3} \times (2f_{\rm SSF}) \times \frac{f_{L4}}{f_{L3}} = 445.6 \ \mu m$$

Spatial frequencies of the SSF Pattern:

$$\begin{bmatrix} k_{x_1} = 2\pi f_{SSF} \cos(\theta) = 2\pi \frac{f_{L3}}{f_{L4}} f_{PSP} \cos(\theta) \\ k_{y_1} = 2\pi f_{SSF} \sin(\theta) = 2\pi \frac{f_{L3}}{f_{L4}} f_{PSP} \sin(\theta) \end{bmatrix}$$



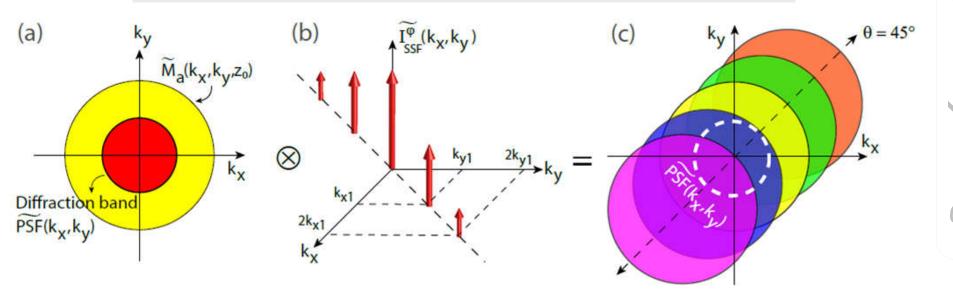
Structured-Illumination PAM

(89/70)

#### Structured-Illumination PAM



$$\begin{split} \widetilde{P_0^{\varphi}} & (k_x, k_y, z) = FT_{2D} \{ p_0(x, y, z) \}_{x,y} = \eta \Gamma [\widetilde{M_a} (k_x, k_y, z) \otimes I_{SSF}^{\widetilde{\varphi}} (k_x, k_y)] \\ & = \eta \Gamma [(\frac{1}{4} + \frac{2}{\pi^2}) \widetilde{M_a} (k_x, k_y, z) + \frac{e^{i\varphi}}{\pi} \widetilde{M_a} (k_x - k_{x_1}, k_y - k_{y_1}, z) \\ & + \frac{e^{-i\varphi}}{\pi} \widetilde{M_a} (k_x + k_{x_1}, k_y + k_{y_1}, z) + \frac{e^{i2\varphi}}{\pi^2} \widetilde{M_a} (k_x - 2k_{x_1}, k_y - 2k_{y_1}, z) \\ & + \frac{e^{-i2\varphi}}{\pi^2} \widetilde{M_a} (k_x + 2k_{x_1}, k_y + 2k_{y_1}, z) \end{split}$$



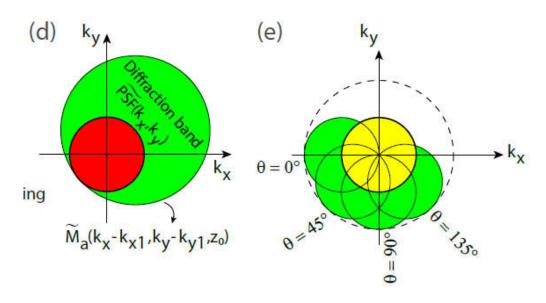
Structured-Illumination PAM

(90/70)

## Phase Compounding Method



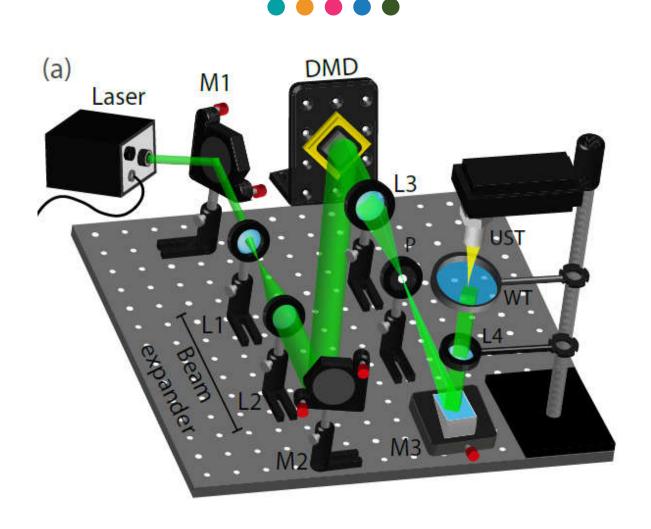
$$\begin{split} &\widetilde{\widehat{M}}_{a}(k_{x}-k_{x_{1}},k_{y}-k_{y_{1}},z) = \widetilde{M}_{a}(k_{x}-k_{x_{1}},k_{y}-k_{y_{1}},z).\widetilde{PSF}(k_{x},k_{y}) \\ &= \frac{\pi}{4\eta\Gamma} \left[ \left( \widehat{\widehat{P}}_{0}^{(\varphi=0)}(k_{x},k_{y},z) - \widehat{\widehat{P}}_{0}^{(\varphi=\pi)}(k_{x},k_{y},z) \right) \right. \\ &+ i \left( \left[ 1 + \frac{8}{\pi^{2}} \right] \widetilde{\widehat{P}}_{0}^{NI}(k_{x},k_{y},z) - \widehat{\widehat{P}}_{0}^{(\varphi=0)}(k_{x},k_{y},z) - 2\widehat{\widehat{P}}_{0}^{(\varphi=\pi/2)}(k_{x},k_{y},z) - \widehat{\widehat{P}}_{0}^{(\varphi=\pi)}(k_{x},k_{y},z) \right) \right] \end{split}$$



Structured-Illumination PAM

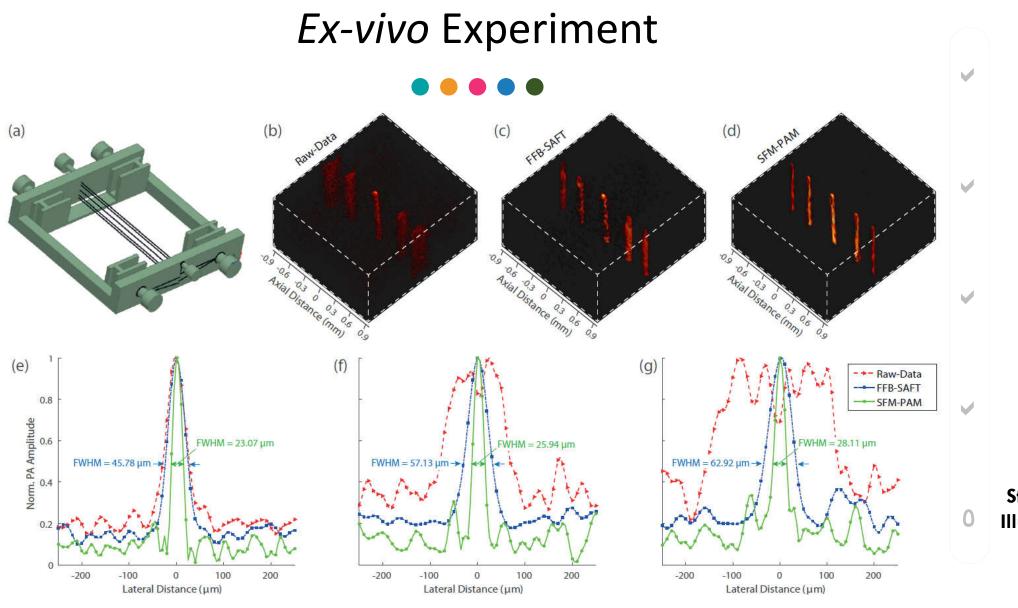
(91/70)

## **Experimental Setup**



Structured-Illumination PAM

(92/70)

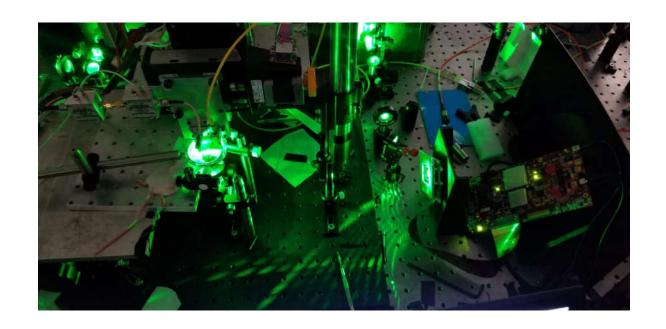


Structured-Illumination PAM

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# *In-vivo* Experiment

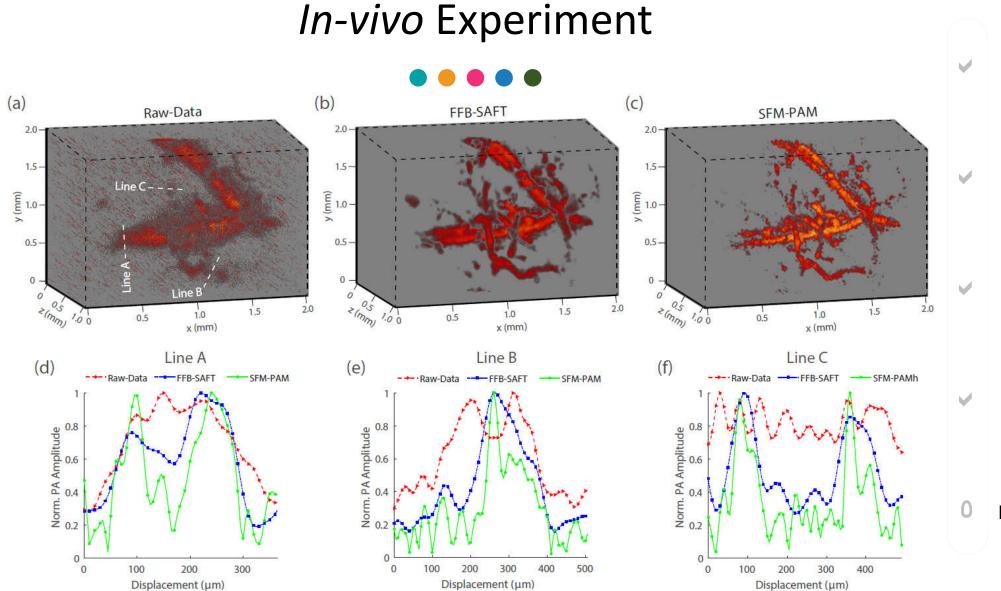






Structured-Illumination PAM

(94/71)



Structured-Illumination PAM

(95/71)