Breaking the Limits in Photoacoustic Imaging: Deeper, Smaller, and More Colorful

Junjie Yao, Duke University
The OSA Imaging Optical Design Technical Group Welcomes You!

BREAKING THE LIMITS IN PHOTOACOUSTIC IMAGING: DEEPER, SMALLER, AND MORE COLORFUL

28 April 2020 • 14:00 EDT
The OSA Imaging Optical Design Technical Group

This group encompasses the design and characterization of traditional optical systems utilizing lens design, geometric ray-tracing, and physical optics modeling.

The evolution and development of design codes and software to assist in designing components and systems are included here.

Typical applications include astronomical telescopes, microscopes, cameras, stray light, and adaptive optics.
Technical Group Leadership 2020

Chair
Dr. Maryna L. Meretska

Vice Chair
Dr. Xusan Yang

Social Media Officer
Dr. Marie-Anne Burcklen

Event Officer
Dr. Sarmishtha Satphaty
Our Technical Group at a Glance

Our Focus

• “Physics of nonlinear optical materials, processes, devices, & applications”
• 2000 members

Our Mission

• To benefit YOU
• Webinars, social media, publications, technical events, business events, outreach
• Interested in presenting your research? Have ideas for TG events? Contact us at: TGactivities@osa.org.

Where To Find Us

• Website: https://www.osa.org/fd
• Facebook: https://www.facebook.com/groups/OSAImagingOpticalDesign/
• LinkedIn: https://www.linkedin.com/groups/8113351/
Today’s Webinar

Breaking the limits in photoacoustic imaging: deeper, smaller, and more colorful

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Speaker’s Short Bio:
Graduation in Physics at Tsinghua University, China
Ph.D. degree from Washington University, USA
Breaking the Limits in Photoacoustic Imaging: Smaller, Deeper, and More Colorful

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OSA
April 28th, 2020
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More than 300 years, optical imaging stays similar!

1665 - Robert Hooke's microscope.
When light meets tissue: scattering and absorption

Optical penetration depth

- Planar optical microscopy
- Aberration limit
  - Confocal or two-photon microscopy
  - Optical coherence tomography
  - Optical-resolution photoacoustic tomography
- Diffusion limit
  - Diffuse optical tomography
  - Ultrasound-modulated optical tomography
  - Acoustic-resolution photoacoustic tomography
- Dissipation limit
  - Wavefront engineering
- Absorption limit

https://photoacoustics.pratt.duke.edu/
Light is like life, going in all directions

Before clearing

The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.

After clearing

The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.
Photoacoustic effect: Listening to absorbed light
When light is absorbed, it is fluorescence and/or heat.

Excited state

- One-photon fluorescence
  - Radiative relaxation
  - Fluorescence

- Two-photon fluorescence
  - Radiative relaxation
  - Fluorescence

- Photoacoustic effect
  - Nonradiative relaxation
  - Heat
  - Sound

Ground state
Photoacoustic tomography: from energy to image

(1) ns laser pulse (e.g., 20 mJ/cm$^2$)

(2) Light absorption & heating (~ mK)

(3) Ultrasonic emission (~ mbar)

(4) Ultrasonic detection & reconstruction

http://appshopper.com/entertainment/x-ray-hd-free

J Yao et al., Nature Methods 13(8), 2016

https://photoacoustics.pratt.duke.edu/
Photoacoustic imaging: Listening to light whispering in tissues

Reference: Canon Inc.

https://photoacoustics.pratt.duke.edu/
Optical imaging of the tissue: from shallow to deep

- **Confocal microscopy**
  - Penetration limit: ~200 µm

- **Two-photon microscopy**
  - Penetration limit: ~1.5 mm

- **Photoacoustic microscopy**
  - Penetration limit: ~5 mm

- **Diffuse Optical tomography**
  - Penetration limit: ~1 cm

- **Photoacoustic tomography**
  - Penetration limit: ~7 cm

**Excitation laser beam** → **Fluorescence**

*Acoustic wave*
Implementations of photoacoustic tomography

Optical-resolution photoacoustic microscopy
- Ultrasonic transducer
- Focusing lens (NA: 0.1)
- Acoustic lens
- Correction lens
- Resolution: 0.2-10 µm
- Penetration: 1-2 mm

Acoustic-resolution photoacoustic microscopy
- Conical lens
- Condenser
- Ultrasonic transducer
- Resolution: 15-50 µm
- Penetration: 3-10 mm

Photoacoustic computed tomography
- Difuser
- Ultrasonic transducer array
- Resolution: 100-500 µm
- Penetration: 10-100 mm

J Yao et al., Nature Methods 13(8), 2016
Endogenous contrast for photoacoustic imaging

Exogenous contrast for photoacoustic imaging

Size (nm)

1 5 10 50 100 1000

Reporter gene products
Organic dyes
Nanoparticles/Quantum dots

Sensitivity (nM)

$10^6$ $10^3$ $10^0$ $10^{-3}$

BphP1
IRDye-800
Nanoparticles

J Yao et al., Nature Methods 13(8), 2016

https://photoacoustics.pratt.duke.edu/
Duke photoacoustic-imaging Lab in 3 years!

July, Nov. 2016

Oct, 2019
Example 1: High-resolution photoacoustic microscopy

J Yao et al. Optics Letters, 35(9), 2010

https://photoacoustics.pratt.duke.edu/
Photoacoustic microscopy of glass frog in resting/active states

H. Fleischmanni

Oxygenation map (PAM)  Anatomy (US imaging)

Oxygenation

0.4  1.0

1 mm

Unpublished, Duke Photoacoustic Lab; Collaborator, Carlos Taboada

https://photoacoustics.pratt.duke.edu/
Monitoring blood ‘storage’ of glass frog from awake to asleep

Unpublished, Duke Photoacoustic Lab; Collaborator, Carlos Taboada

https://photoacoustics.pratt.duke.edu/
Example 2: Whole-body small-animal photoacoustic tomography

Penetration depth
3 cm

Time = 0.00 s

L Li, J. Yao et al. Nature Biomedical Engineering, 1, 0071 (2017)
Our missions at Duke PI-Lab

**Smaller** for high throughput

**Deeper** for clinical impact

**Colorful** for molecular sensitivity

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https://photoacoustics.pratt.duke.edu/
High-speed MEMS-based benchtop photoacoustic imaging


https://photoacoustics.pratt.duke.edu/
MEMS-based benchtop PAM of brain’s hemodynamic response


https://photoacoustics.pratt.duke.edu/
Polygon-scanner PAM with ultrawide scanning range of 10 mm

Unpublished, Duke Photoacoustic Lab

https://photoacoustics.pratt.duke.edu/
Vessel constrictions induced by Epinephrine in skin and brain

Lan et al., BOE, 2018, 9(10), 4689-4701

https://photoacoustics.pratt.duke.edu/
Brain microvasculature hemodynamics induced by Cardiac Arrest

Time: 18.0 s
Handheld photoacoustic microscopy for skin lesion imaging
Label-free wearable photoacoustic imaging and treatment of circulating melanoma cells
Wearable photoacoustic watch for circulating melanoma detection during immune therapy

Unpublished, Duke Photoacoustic Lab

https://photoacoustics.pratt.duke.edu/
Multiplexing the miniaturized photoacoustic imaging

Single PA unit

Laser

MEMS driving

Fluidic controlling

DAQ

Day 0

Day 3

Day 7

Unpublished, Duke Photoacoustic Lab

https://photoacoustics.pratt.duke.edu/
Head-mounted photoacoustic imaging of neural activities on freely-behaving aged animals

GCaMP6 mouse

PA detection spot

Fractional change in PA signal (%)

Unpublished, Duke Photoacoustic Lab

https://photoacoustics.pratt.duke.edu/
PAM/Fluorescence imaging of near-infrared calcium indicator (iGECI, ex: 670 nm)

Blood oxygenation (PAM)

iGECI (fluorescence)

Paw stimulation

Nature Biotechnology, under review. Collaborator, Vlad Verkhusha

https://photoacoustics.pratt.duke.edu/
Our missions at Duke PI-Lab

Smaller for high throughput

Deeper for clinical impact

Colorful for molecular sensitivity

https://photoacoustics.pratt.duke.edu/
Lighting up from inside: Super-deep PAT with internal light

- Human whole-body imaging needs a penetration of more than 10 cm
- Photon penetration is limited to about 5 cm by optical attenuation
A graded-scattering based optical fiber diffuser

Li et al., IEEE transactions on medical imaging, 2019

https://photoacoustics.pratt.duke.edu/
Deep PAT with internal light illumination in pig models during shockwave treatment
Deep PAT with internal light illumination in pig models during shockwave treatment
Thermal-memory-based PAT (TEMPT) of temperature during focused ultrasound therapy

Step 1
- Multiple laser pulse excitation
- Multiple PA measurement

Step 2
- Grüneisen parameter reconstruction
- Ratiometric measurement

\[ \Gamma_0(T_0) \propto \sqrt{\frac{p_1^2 b(N-1)}{P_N - P_1}} \]

Step 3
- Temperature map at a single time point
- Repeated temperature monitoring

Zhou, et al., Optica, 2019, 6(2), 198-205

https://photoacoustics.pratt.duke.edu/
Correcting the skull’s aberration to ultrasound waves

Skull’s acoustic distortion

Liang, et al., J of Biophotonics, 2019, e201800466

https://photoacoustics.pratt.duke.edu/
Correcting the skull’s aberration to ultrasound waves

Liang, et al., J of Biophotonics, 2019, e201800466

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**Smaller** for high throughput

**Deeper** for clinical impact

**Colorful** for molecular sensitivity

https://photoacoustics.pratt.duke.edu/
Overwhelming endogenous biomolecules in deep-tissue PAT

Volumetric rendering

J Yao et al., Nature Methods, 13 (1), 2016

https://photoacoustics.pratt.duke.edu/
Weak molecular signals are overwhelmed by strong background blood signals
Photoswitchable non-fluorescent NIR bacterial phytochrome BphP1


https://photoacoustics.pratt.duke.edu/
Differential PAT of BphP1: improved contrast and sensitivity

ON

HbO\textsubscript{2}

BphP1

OFF

Norm. PA amplitude

1

5 mm

Contrast to noise ratio

ON

OFF

Diff

BphP1


https://photoacoustics.pratt.duke.edu/
Multi-scale differential PAT: from single cells to whole-body

J Yao et al., Nature methods 13 (1), 67-73 (2016);
https://photoacoustics.pratt.duke.edu/
Longitudinal RS-PACT of cancer metastasis in mouse liver

Detection sensitivity: 200 cancer cells at 10 mm depth

J Yao et al., Nature methods 13 (1), 67-73 (2016);
https://photoacoustics.pratt.duke.edu/
Imaging protein-protein interactions by using a split version of BphP

Lei Li et al., Nature communication, 9, 2734 (2018)

https://photoacoustics.pratt.duke.edu/
Bio-switchable hypoxia-sensitive dye Hyp-650

Chen et al., Optics Letters, 44(15), 2019; Collaborator, Jeff Chan, UIUC

https://photoacoustics.pratt.duke.edu/
Quantify the tissue’s hypoxia under ischemia

Chen et al., Optics Letters, 44(15), 2019; Collaborator, Jeff Chan, UIUC

https://photoacoustics.pratt.duke.edu/
Conclusions

- Photoacoustic imaging is intrinsically sensitive to tissue’s functional molecular information, based on optical absorption contrast.
- A variety of functional and molecular probes (endogenous or exogenous) can be imaged by photoacoustic imaging, with high sensitivity and deep penetration.
- Photoacoustic-imaging-specific functional molecular imaging strategies and toolkits have been developed and applied in life science.
- Clinical translation of photoacoustic imaging is on the horizon and will bring its unique impact to the medical imaging playground.
Welcome to visit us at Duke PI-Lab