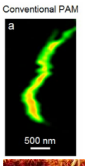
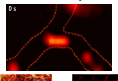
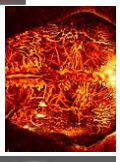
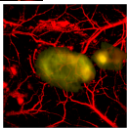
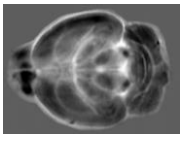
Photoacoustic Tomography:
Multiscale Imaging from Organelles to Patients by Ultrasonically Beating the Optical Diffusion Limit











Lihong V. Wang
Gene K. Beare Distinguished Professor
Optical Imaging Laboratory
Departments of Biomedical Engineering and Radiology
Washington University in St. Louis
Email: Photoacoustics@gmail.com

Disclosure Statement

Lihong Wang

Dr. Lihong Wang has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

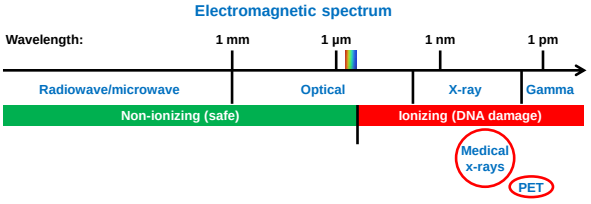
Affiliation/Financial Interest	Organization
Consultant/Share	Microphotoacoustics, Inc.

Outline

- Motivations and challenges
- Photoacoustic tomography
  - Photoacoustic computed tomography
  - Photoacoustic microscopy
- Time-reversal wavefront engineering
- Compressed ultrafast photography

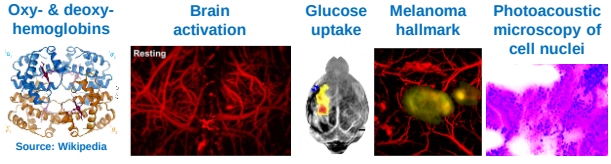
Motivations for Imaging with Light

- Light-matter interaction uniquely positioned at the molecular level

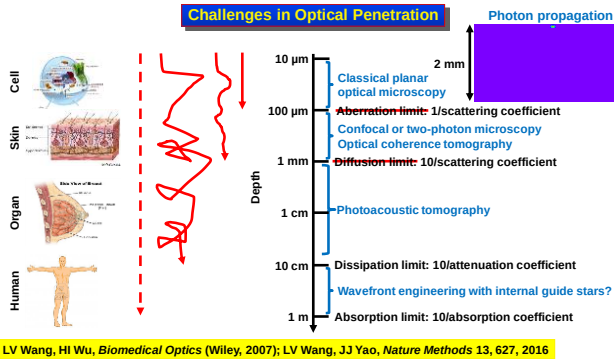


Motivations for Imaging with Light

- 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



Challenges in Optical Penetration



LV Wang, HI Wu, *Biomedical Optics* (Wiley, 2007); LV Wang, JJ Yao, *Nature Methods* 13, 627, 2016

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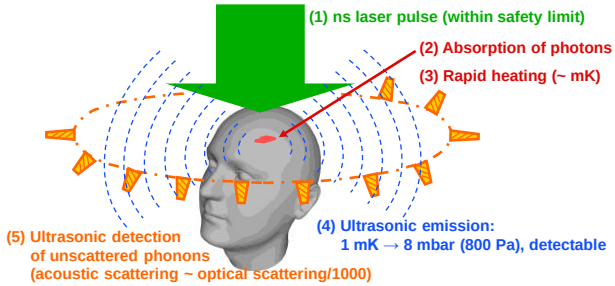
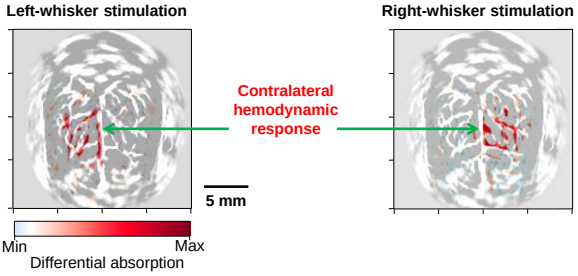
Photoacoustic Computed Tomography: Deep Penetration with Optical Contrast and Ultrasonic Resolution



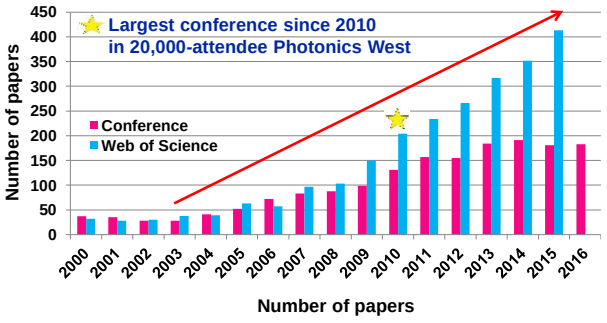
X Wang, Y Pang, G Ku, G Stoica, LV Wang, *Nature Biotech* 21, 803, 2003

First Functional (Also First *In Vivo*) Photoacoustic Tomography in Small Animals with Intact Scalp and Skull

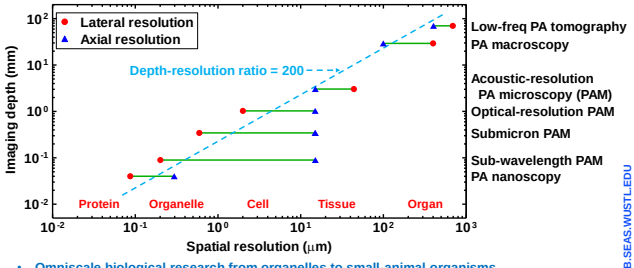


X Wang, Y Pang, G Ku, G Stoica, LV Wang, *Nature Biotech* 21, 803, 2003

Growth of Photoacoustic Tomography



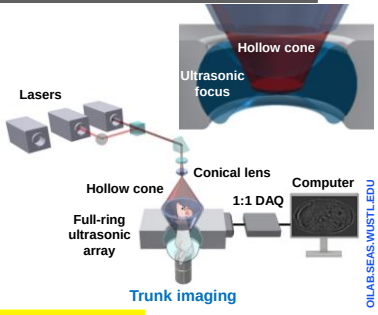
Omniscale *In Vivo* Photoacoustic (PA) Tomography with Consistent Contrast



- Omniscale biological research from organelles to small-animal organisms
- Translation of microscopic lab discoveries to macroscopic clinical practice

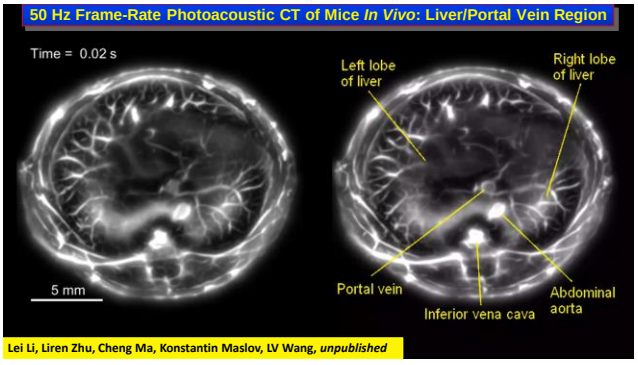
LV Wang, S Hu, *Science* 335, 1458, 2012; LV Wang, *Nature Photon* 3, 503, 2009

Single Impulse Panoramic Photoacoustic Computed Tomography



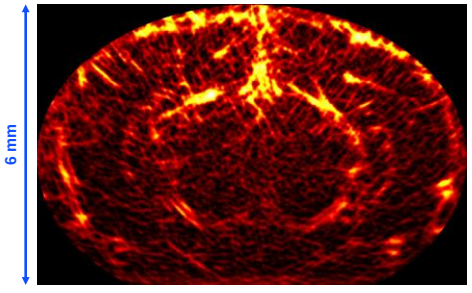
Lei Li, Liren Zhu, Cheng Ma, Konstantin Maslov, LV Wang, *unpublished*

50 Hz Frame-Rate Photoacoustic CT of Mice *In Vivo*: Liver/Portal Vein Region



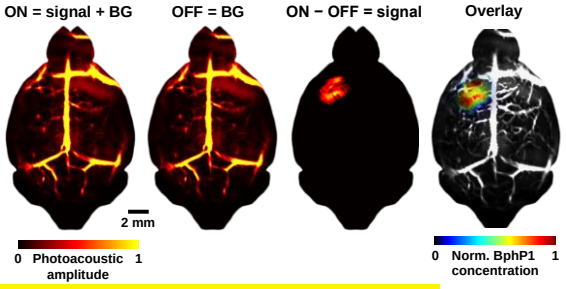
Lei Li, Liren Zhu, Cheng Ma, Konstantin Maslov, LV Wang, *unpublished*

Photoacoustic Computed Tomography of the Whole Brain of a Mouse *In Vivo*



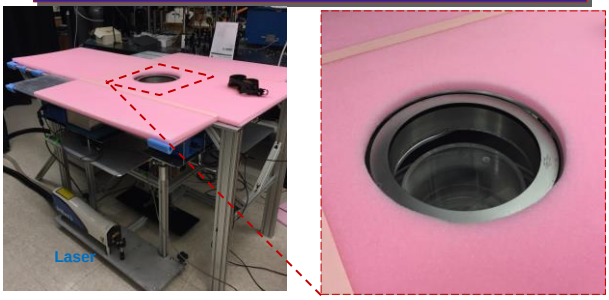
Pengfei Zhang, ..., LV Wang, *unpublished*

Reversibly Switchable Photoacoustic Genetic Imaging of Mouse Brain Tumor



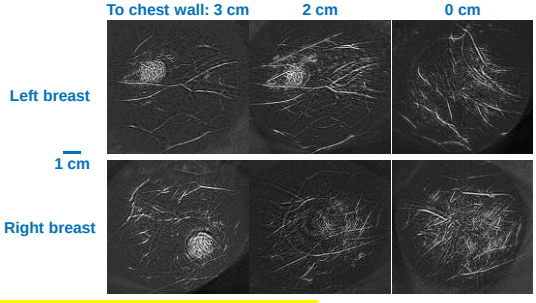
[JJ Yao, AA Kaberniuk], L Li, DM Shcherbakova, R Zhang, LD Wang, G Li, VV Verkhusha@Einstein, LV Wang, *Nature Methods* 13, 67, 2016

In Vivo Human Breast Panoramic Photoacoustic Computed Tomography



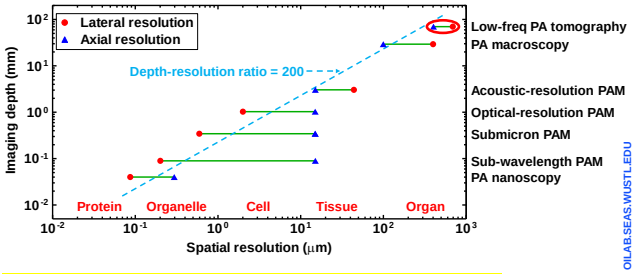
Li Lin, Junhui Shi, Konstantin Maslov, ... LV Wang, *unpublished*

Photoacoustic Computed Tomography of Human Breast In Vivo: Volunteer #1



Li Lin, Junhui Shi, Konstantin Maslov, ... LV Wang, *unpublished*

Omniscale *In Vivo* Photoacoustic (PA) Tomography with Consistent Contrast



LV Wang, S Hu, *Science* 335, 1458, 2012; LV Wang, *Nature Photon* 3, 503, 2009

Outline

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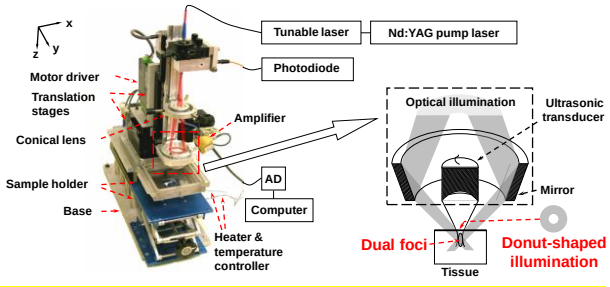
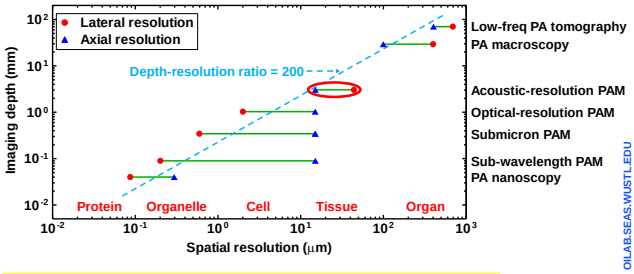
First 3D Photoacoustic Microscope



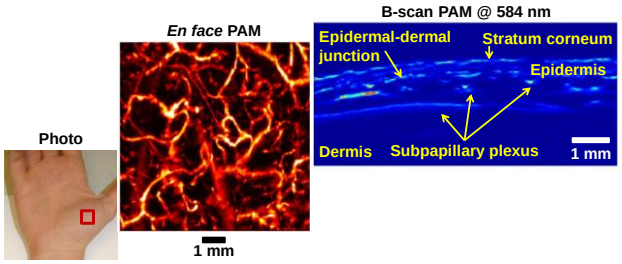
K Maslov, G Stoica, LV Wang, *Optics Lett* 30, 625, 2005
H Zhang, K Maslov, G Stoica, LV Wang, *Nature Biotech* 24, 848, 2006; *Nature Protoc* 2, 797, 2007

Omniscale *In Vivo* Photoacoustic (PA) Tomography with Consistent Contrast



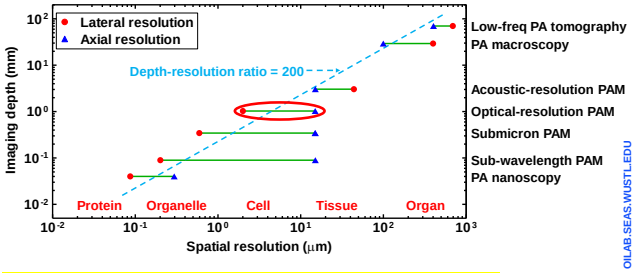
LV Wang, S Hu, *Science* 335, 1458, 2012; LV Wang, *Nature Photon* 3, 503, 2009

In Vivo Photoacoustic Microscopy of the Human Skin



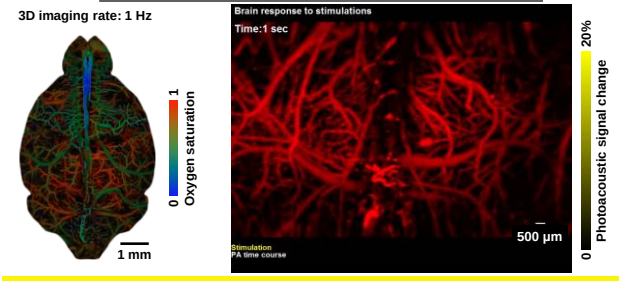
C Favazza, O Jassim, LA Cornelius, LV Wang, *J Biomed Optics* 16, 016015, 2011;
Collaboration: LA Cornelius

Omniscale *In Vivo* Photoacoustic (PA) Tomography with Consistent Contrast



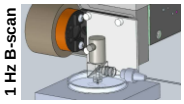
LV Wang, S Hu, *Science* 335, 1458, 2012; LV Wang, *Nature Photon* 3, 503, 2009

In Vivo Photoacoustic Microscopy of Cerebral Hemodynamic Response to Electric Hindpaw Stimulation

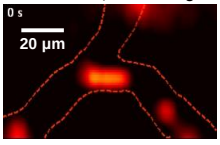


JJ Yao, LD Wang, JM Yang, KI Maslov, TTW Wong, Lei Li, CH Huang, J Zou@TAMU, LV Wang, *Nature Methods* 12, 407, 2015; Featured by *Science*, doi:10.1126/science.aab0393

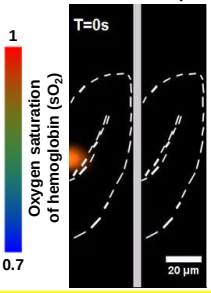
In Vivo Single-Cell Photoacoustic Flowoxigraphy: Flow and Oxygenation Imaging



Single red blood cells
(200 Hz B-scan, 20 3D images/s)

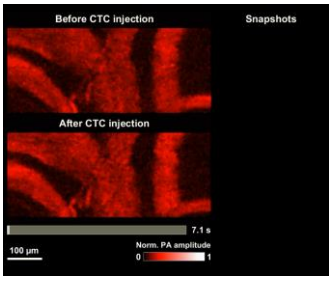


Human cuticle capillary



LD Wang, K Maslov, LV Wang, *PNAS* 110, 5759, 2013; HC Hsu, LD Wang, LV Wang, *JBO* 21, 056004, 2016

In Vivo Photoacoustic Microscopy and Short-Pulsed Laser Therapy of Single Circulating Tumor Cells



Goals:

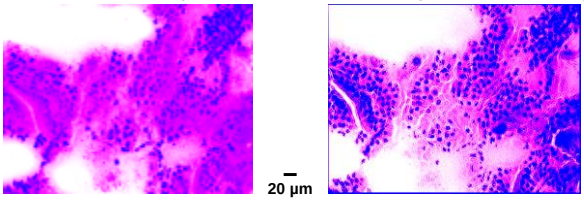
1. Remove primary melanoma
2. Clear circulating tumor cells
3. Uncage antigens alive
4. Elicit immunoresponse
5. Destroy metastases

Yun He, LD Wang, J Shi, J Zou @ TAMU, … LV Wang, *unpublished*

Label-Free Photoacoustic Histology by Imaging DNA & RNA in Cell Nuclei

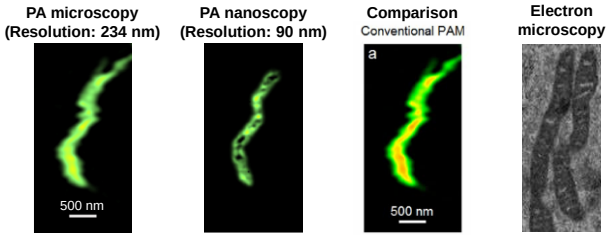
Photoacoustic microscopy without staining

Histology with hematoxylin and eosin staining



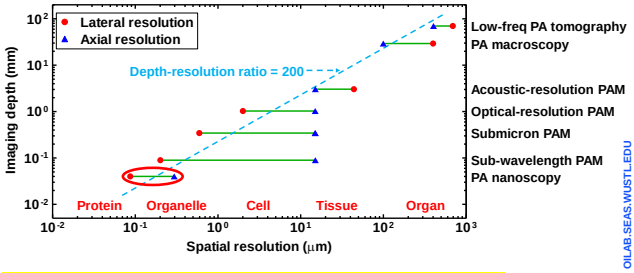
D Yao, R Chen, K Maslov, Q Zhou, LV Wang, *J Biomed Optics* 17, 056004, 2012;
Collaboration: Q Zhou @ USC

Label-Free Photoacoustic (PA) Nanoscopy of a Mitochondrion with Sub-Organelle Resolution: Beat Optical Diffraction Nonlinearly



A Danielli, K Maslov, A Garcia-Uribe, A Winkler, CY Li, LD Wang, Y Chen, G Dorn, LV Wang, *J Biomed Optics* 19, 086006, 2014; Collaboration: G Dorn;
J Yao, LD Wang, CY Li, C Zhang, LV Wang, *Phys Rev Lett* 112, 014302, 2014

Omniscale *In Vivo* Photoacoustic (PA) Tomography with Consistent Contrast



LV Wang, S Hu, *Science* 335, 1458, 2012; LV Wang, *Nature Photon* 3, 503, 2009

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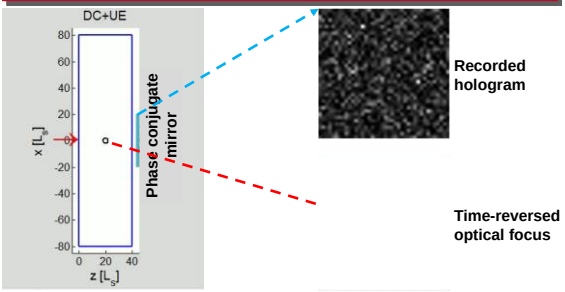
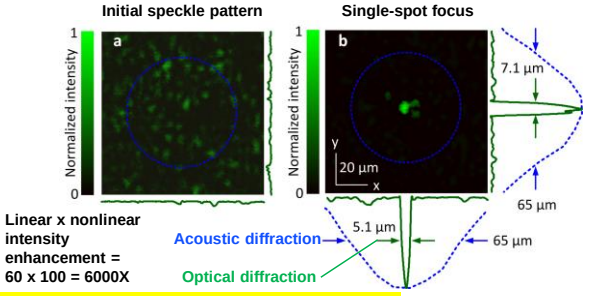
Time-Reversed Ultrasound-Encoded (TRUE) Optical Focusing



[X Xu, H Liu], LV Wang, *Nature Photon* 5, 154, 2011; [Y Liu, P Lai], C Ma, X Xu, AA Grabar, LV Wang, *Nature Comm* 6, 5904, 2015; Featured by *Nature*, 518, 158, 2015

Speckle Pattern Concentration by Photoacoustic Wavefront Shaping (PAWS)



[PX Lai, LD Wang, JW Tay], LV Wang, *Nature Photon* 9, 126, 2015
LD Wang, C Zhang, LV Wang, *Phys Rev Lett* 113, 174301, 2014

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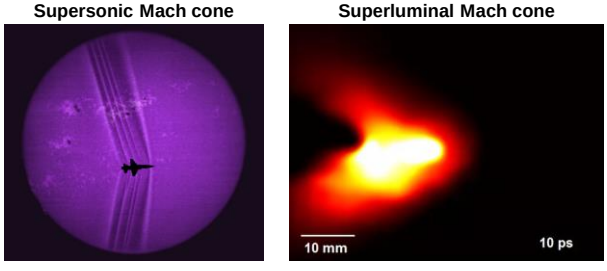
Watch a Flying Laser Pulse with Single-Shot Compressed Ultrafast Photography at 100 Billion Frames/Second

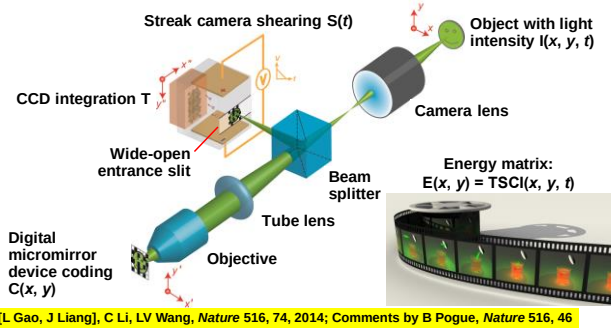
[L Gao, J Liang], C Li, LV Wang, *Nature* 516, 74, 2014 Video slowdown: 10 billion X

Watch a Flying Superluminal Mach Cone with Single-Shot Compressed Ultrafast Photography at 100 Billion Frames/Second



[J Liang, C Ma, L Zhu], *LV Wang*, unpublished

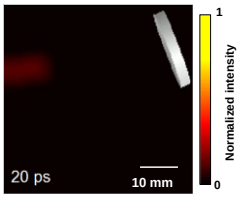
Single-Shot Compressed Ultrafast Photography: 100 Billion Frames per Second



[L Gao, J Liang], C Li, LV Wang, *Nature* 516, 74, 2014; Comments by B Pogue, *Nature* 516, 46

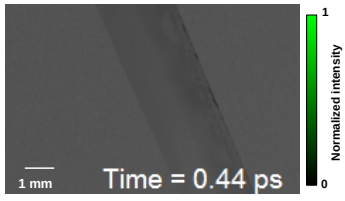
Boost from 100 Billion to 10 Trillion Frames per Second

100 GHz



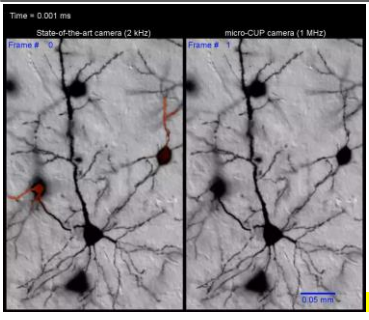
[L Gao, J Liang], C Li, *LV Wang*, Nature 516, 74, 2014

2.3 THz



J Liang, ..., *LV Wang*, unpublished

Simulated Ultrafast Imaging of Action Potential Propagation: Fastest 2-KHz Commercial Camera versus the Proposed 1 MHz CUP Camera



Liren Zhu, *LV Wang*, unpublished

Financial Interest Disclosure and Funding Sources

FINANCIAL INTEREST

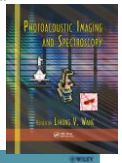
- **Microphotoacoustics, Inc.**

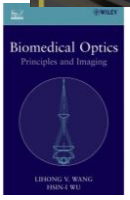
ACTIVE GRANTS

- **NIH DP1 EB016986: NIH Director's Pioneer Award**
  Program Directors: Richard Conroy/Ravi Basavappa
- **NIH R01 CA186567: NIH Director's Transformative Research Award**
  Program Directors: Bob Nordstrom/Ravi Basavappa
- **NIH R01 EB016963: Ring PACT**
  Program Director: Richard Conroy
- **NIH U01 NS090579: BRAIN Initiative**
  Program Director: Ned Talley
- **March of Dimes: Prematurity Birth**
  Program Director: Joe Leigh Simpson

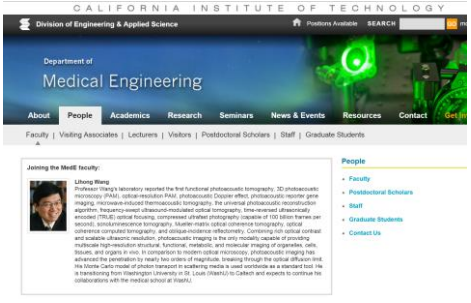
Further Information

- YouTube videos on "Photoacoustic tomography"
- Web at HTTP://OILAB.SEAS.WUSTL.EDU
- Books





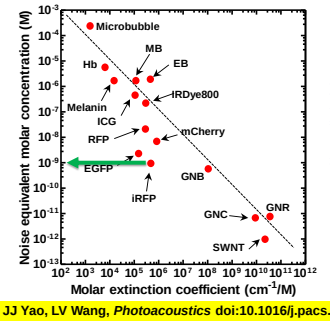
Relocation to Caltech

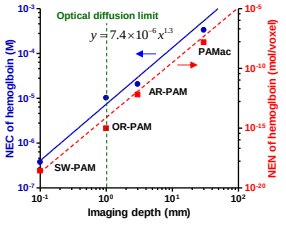


http://www.mede.caltech.edu/people

HIRING:
Postdocs
Students
Technicians

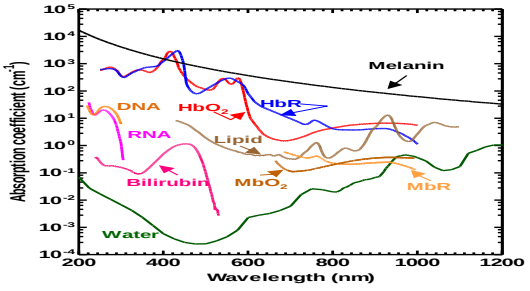
Noise Equivalent Concentration or Number





JJ Yao, LV Wang, *Photoacoustics* doi:10.1016/j.pacs.2014.04.002

Endogenous Absorbers



JJ Yao, LV Wang, *Photoacoustics* doi:10.1016/j.pacs.2014.04.002

Scalability of Resolution and Penetration

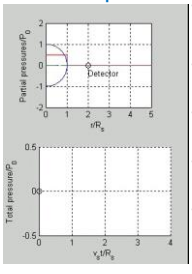
$$\text{Acoustic spatial resolution} \propto \frac{1}{\text{Acoustic bandwidth}}$$

$$\text{Acoustic penetration limit} \propto \frac{1}{\text{Acoustic bandwidth}}$$

$$\frac{\text{Penetration limit}}{\text{Spatial resolution}} = \text{Constant}$$

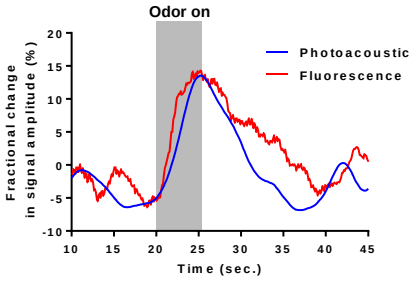
Photoacoustic Conversion Efficiency and SNR

Photoacoustic wave from a sphere



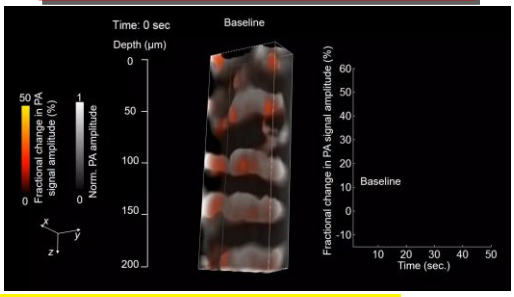
- $\frac{\text{Thermal expansion coefficient}}{\text{Compressibility}} \approx 8$ mbars/mK
- Noise equivalent pressure ~ sub mbar
- SNR at photoacoustic source ~ 10^5
- Attenuation over a 10^2 voxel range ~ 10^3
- SNR at tissue surface ~ 10^2

Photoacoustic and Fluorescence Detection of Calcium-Sensitive Protein GCaMP5G in the Fruit Fly Brain *In Vivo*



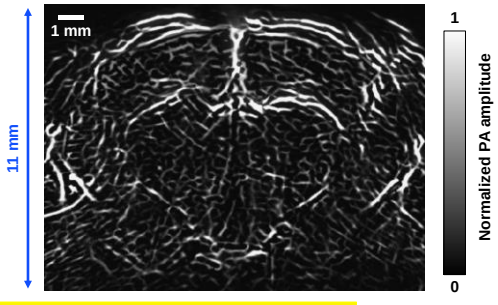
RY Zhang, B Rao, HY Rong, B Raman@WUSTL, LV Wang, *unpublished*

Photoacoustic Microscopy of Calcium-Sensitive Protein GCaMP5G in the Fruit Fly Brain *In Vivo*



RY Zhang, B Rao, HY Rong, B Raman@WUSTL, LV Wang, *unpublished*

Photoacoustic Computed Tomography of the Whole Brain of a Rat *In Vivo*



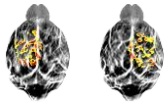
Li Lin, Lei Li, Liren Zhu, Cheng Ma, Konstantin Maslov, LV Wang, *unpublished*

Photoacoustic Imaging of Hemoglobin and Glucose Metabolism in Mouse Brain *In Vivo* with Electric Forepaw Stimulation

Analogous to fMRI

[Hemoglobin] @ 570 nm
(Isosbestic wavelength)

Right paw stimulation | Left paw stimulation



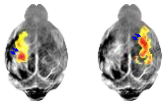
1 mm

0 10%
Photoacoustic change

Analogous to PET

[2-NBDG] @ 478 nm
(Glucose analog)

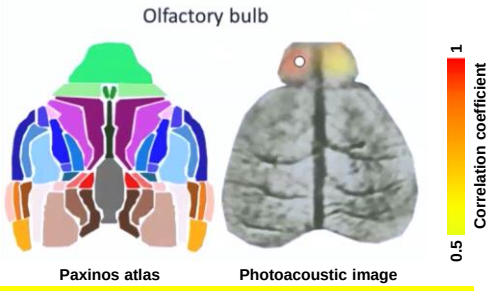
Right paw stimulation | Left paw stimulation



Glucose analog:
2-NBDG = 2-deoxy-2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-D-glucopyranose

[J Yao, J Xia], K Maslov, M Naziriavanaki, V Tsytsarev, AV Demchenko, LV Wang, *NeuroImage* 64, 257, 2013; Collaboration: AV Demchenko @ UMSL

Noninvasive *In Vivo* Photoacoustic Tomography of Resting-State Functional Connectivity in Mouse Brain



Paxinos atlas | Photoacoustic image

[M Nasiriavanaki, J Xia], H Wan, A Bauer, J Culver@WUSTL, LV Wang, *PNAS* 111, 21, 2014