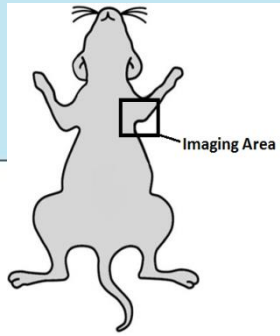
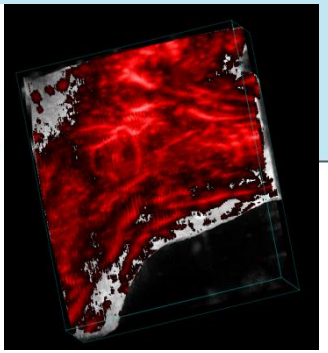
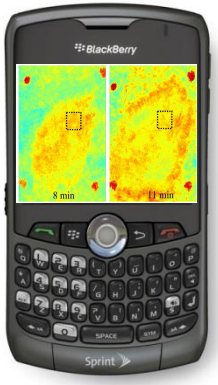
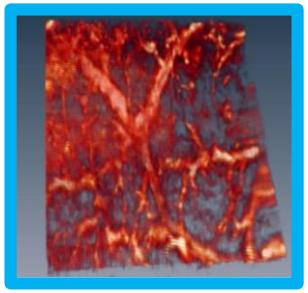
Microcirculation Imaging Techniques – TOMI lab

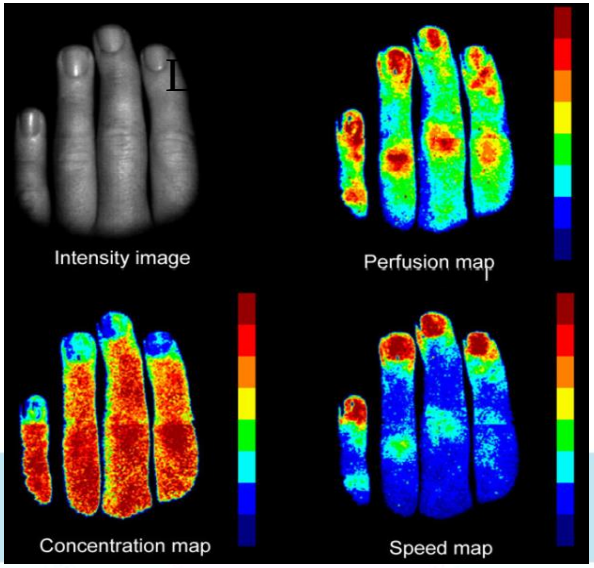
- Laser Doppler perfusion imaging (LDPI)
- Laser speckle contrast imaging (LSCI)
- Tissue viability imaging (TiVi)
- Photoacoustic Imaging (PAI)
- Optical coherence tomography (OCT)

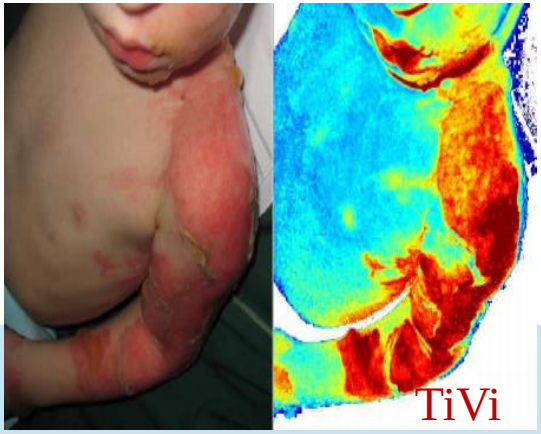


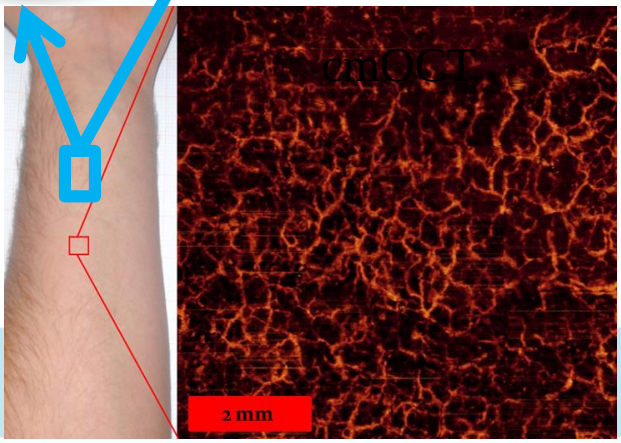




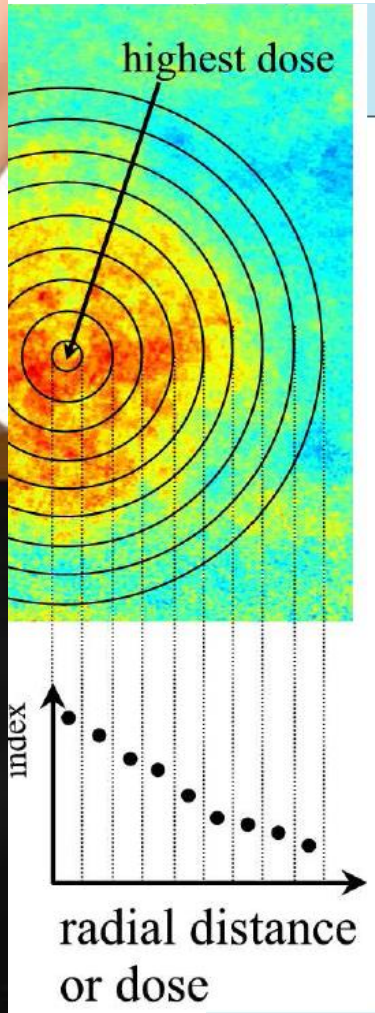








nemal



O'Doherty, J., *et al.*, 2011 .*Arch Derm Res (2010)*

Commercially available mHealth devices

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Otoscope

Dermascope

Ophthalmoscope

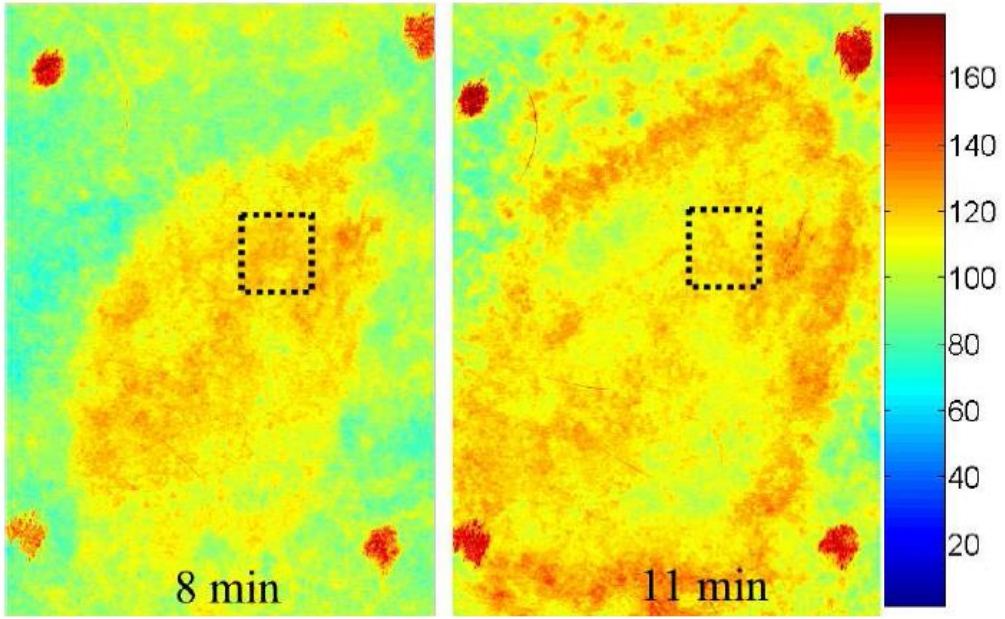
Microscope

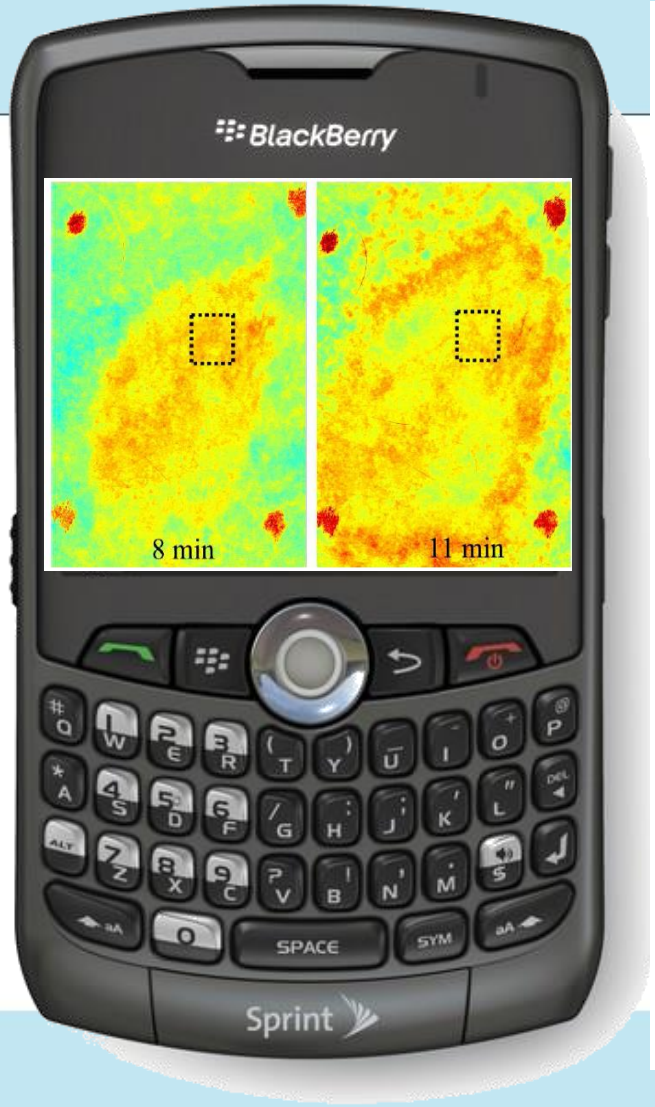
Ultrasound

Mobile platform

Swelling reduces TiVi index value

18% reduction in averaged value of dashed box while the edges increase





J. Biophotonics 1–4 (2010) / DOI 10.1002/jbio.201000050.
J. Physiological Measurement (2010)

Mobile platform

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J. Biophotonics 1–4 (2010) / **DOI** 10.1002/jbio.201000050

Journal of
BIOPHOTONICS

LETTER

Cellular phone-based photoplethysmographic imaging

Enock Jonathan and Martin J. Leahy*

Tissue Optics and Microcirculation Imaging (TOMI) Facility, National Biopho
Department of Physics, University of Limerick, Ireland

Received 4 April 2010, revised 3 August 2010, accepted 3 August 2010
Published online 6 September 2010

Key words: photoplethysmography, biophotonics, optical imaging, cel

We present study results on visible light reflection photoplethysmographic (PPG) imaging with a mobile cellular phone operated in video imaging mode. PPG signal components around 0.1 Hz attributed to the sympathetic component of the heart rate, 1 Hz as the heart rate and 2 Hz as heart rate high order harmonic were quantified on the index finger of a healthy volunteer. The green channel reported PPG signals throughout the sampled area. The blue and red channel returned plethysmographic information, but the signal strength was highly position specific. Our results obtained with a cellular phone as the data acquisition device are encouraging, especially in the broad context of personal or home-based care and the role of cellular phone technology in medical imaging.

Cellu

Spectral signature of Haemoglobin

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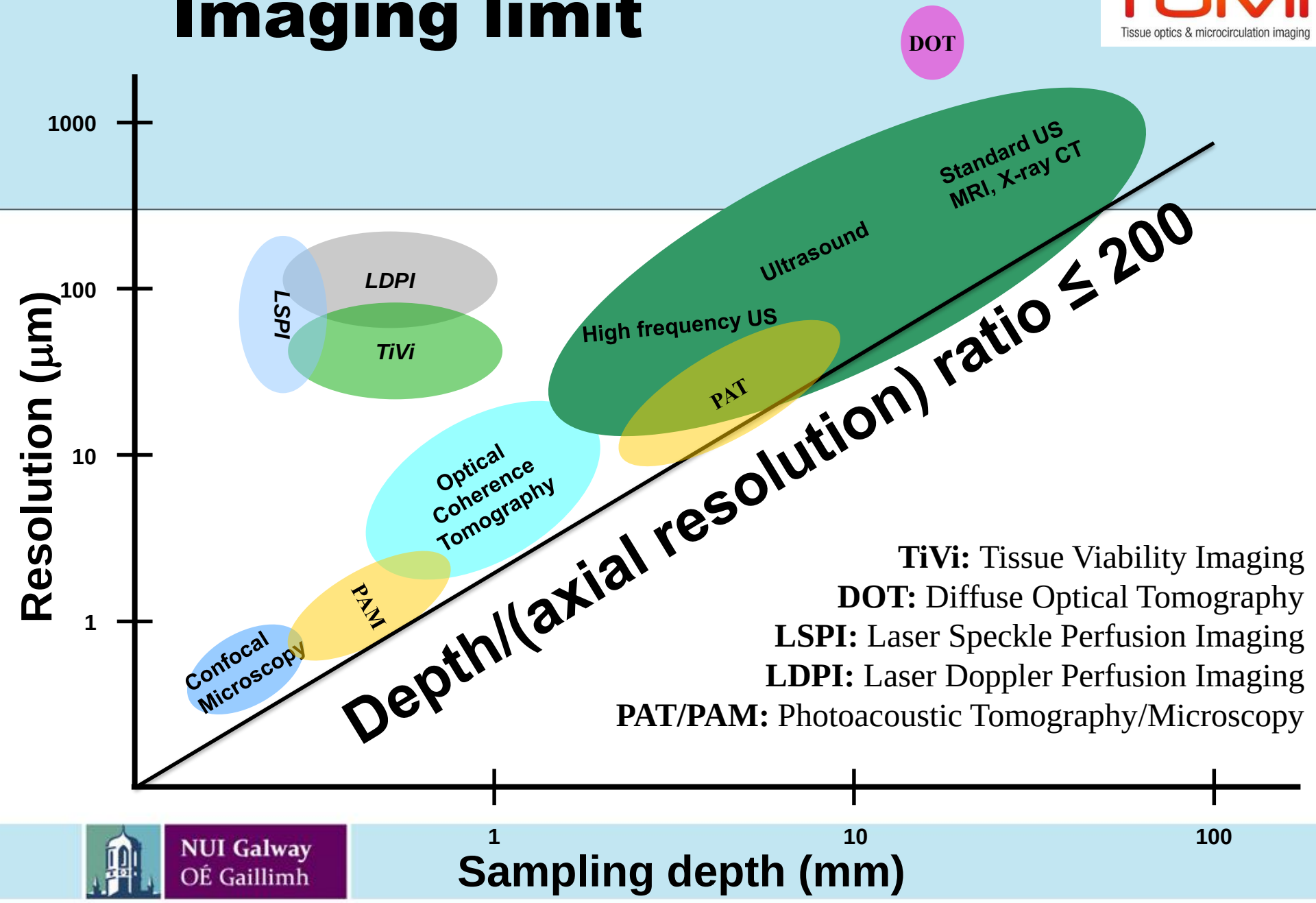
Imaging limit



TiVi: Tissue Viability Imaging
DOT: Diffuse Optical Tomography
LSPI: Laser Speckle Perfusion Imaging
LDPI: Laser Doppler Perfusion Imaging
PAT/PAM: Photoacoustic Tomography/Microscopy

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Lal C, Leahy MJ. *Microcirculation* ***23****: 345–363, 2016.*

Mobile platform

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Cellu

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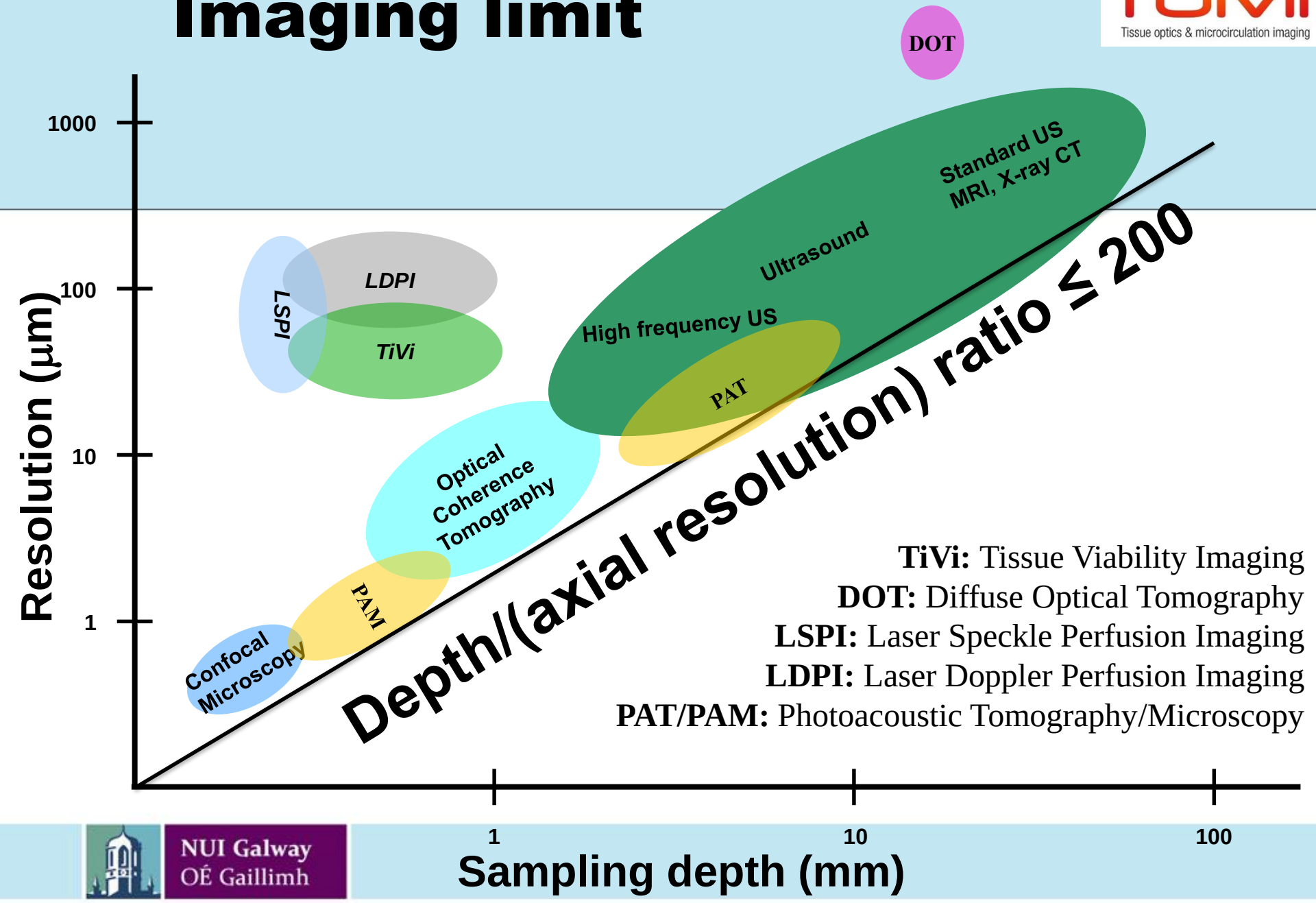

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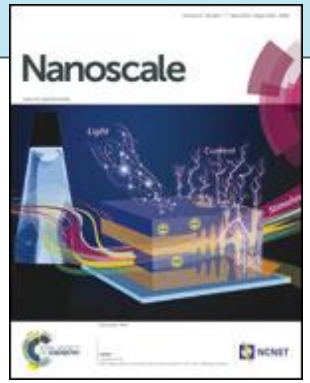
Lal C, Leahy MJ. *Microcirculation* ***23****: 345–363, 2016.*

Nanostructural sensitivity at depth



Resolution (μm)

1000
100
10
1

atoms (C H N O P S)
molecules (DNA, lipids, proteins, etc)
molecular systems
organelles (mitochondria, nuclei, etc.)
cells
tissue
organ
body

Spectral decoding

Structural Sensitivity (μm)

100
10
1

1 Sampling depth (mm) 10 100

Alexandrov et al. *Nanoscale*, **6**, 3545-3549

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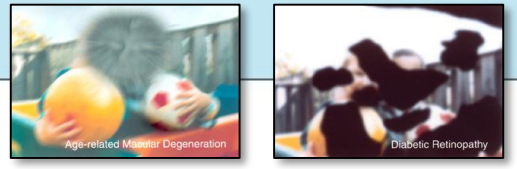
Home monitoring of retinal disease

- AMD[(a)] and DR[(b)] leading causes of blindness
  - > 40 million cases in US and Europe alone
  - Will double by 2020: demographics + diabetes



- Effective treatments exist, but burden huge and unsustainable
  - All actors want clinical need for treatment to drive visit schedule
  - However, after stabilization, necessary visit frequency varies by patient
  - So, TAE protocols constrained by need to forestall events/treat quickly

- Critical need: *Home* monitor that provides clinically useful information
  - Patients monitor as often as they want, reducing anxiety
  - Doctors see patients when clinical need exists
  - Unnecessary visits eliminated, reducing burden on all
  - *And,* outcomes should improve

[(a)] **Age-related macular degeneration**
[(b)] **Diabetic retinopathy**

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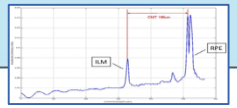
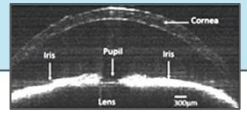
MR-OCT: one sensor, many applications

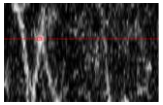
- Mobile health/fitness monitoring
  - Eye care/ophthalmology
  - Glucose concentration
  - Skin care/dermatology
  - Vital signs

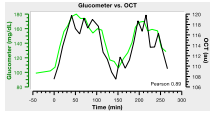


MR-OCT retinal thickness

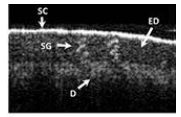


MR-OCT rat eye image


MR-OCT flow detection

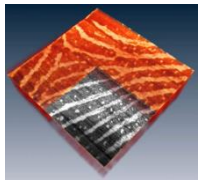


MR-OCT glucose tracking

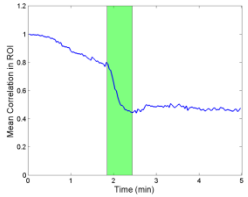


MR-OCT tissue image

- Security and NDT [a]
  - Personal authentication
  - Document verification
  - Production testing

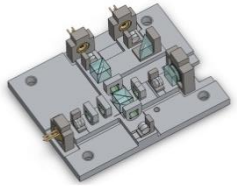

MR-OCT subdermal fingerprint


MR-OCT optical profiling



MR-OCT adhesive curing

- Key: MR-OCT suited to requirements
  - Noninvasive, subsurface
  - Sensitive, specific, fast
  - Small, low cost, battery power



[a] Non-destructive testing

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Compact Imaging

National University of Ireland, Galway

Optical Coherence Tomography

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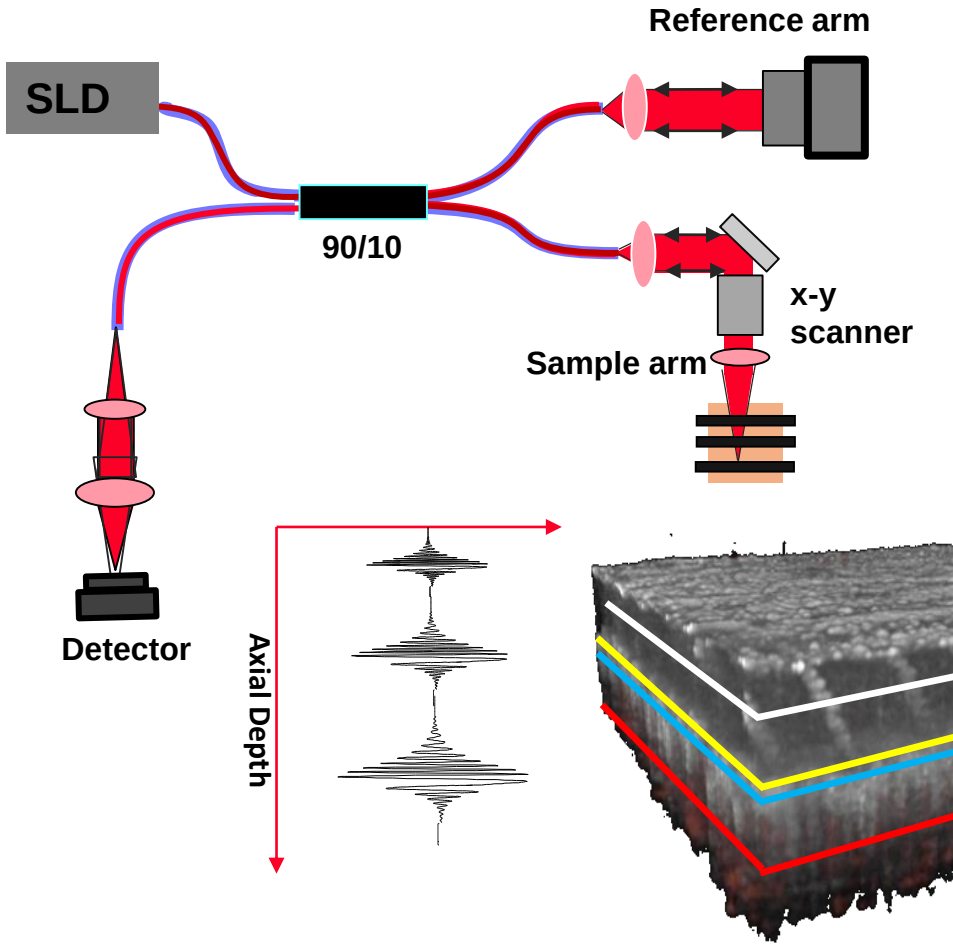
- OCT uses low coherence interferometry to produce a two or three dimensional image of optical scattering from internal tissue microstructures.
- OCT can provide both micro structural and functional information with high resolution and sensitivity
  - High resolution (2-15 μm)
  - 3D imaging in scattering tissue (2-3 mm)
  - Non invasive – “Optical Biopsy”



Commercially available OCT systems

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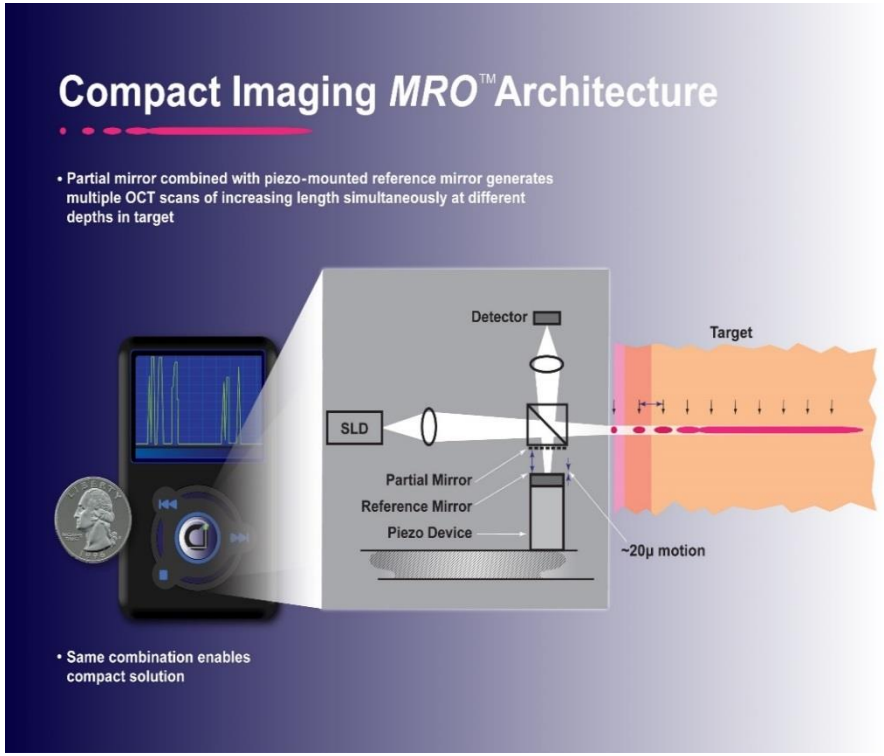
Cirrus HD-OCT

ILUMIEN

Skintell

Conventional clinic-scale OCT instruments, priced from €45,000 to over €120,000, were commercialized early in the last decade for use by ophthalmologists, dermatologist, cardiac surgeons

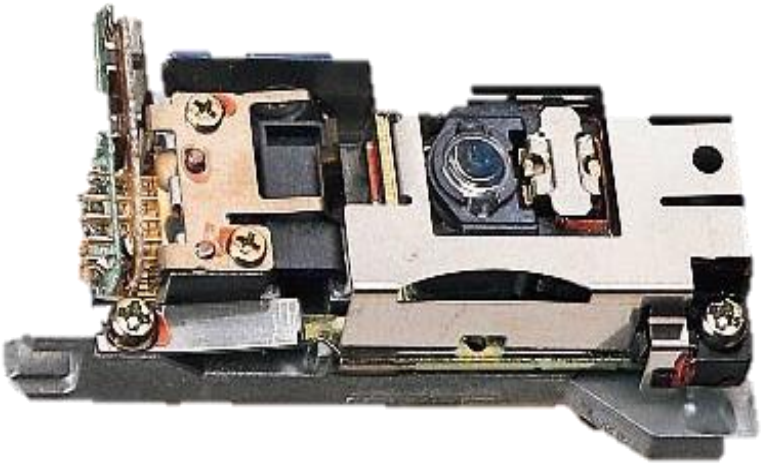
Compact imaging solution with MR-OCT



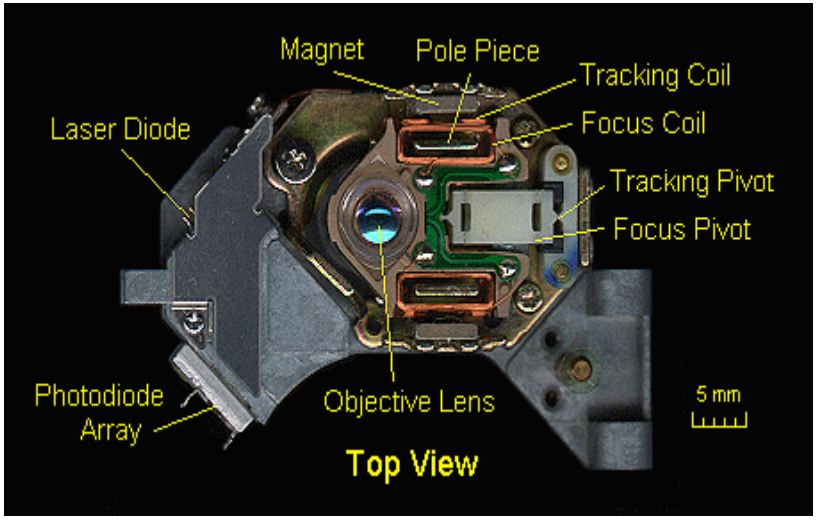
MR-OCT features

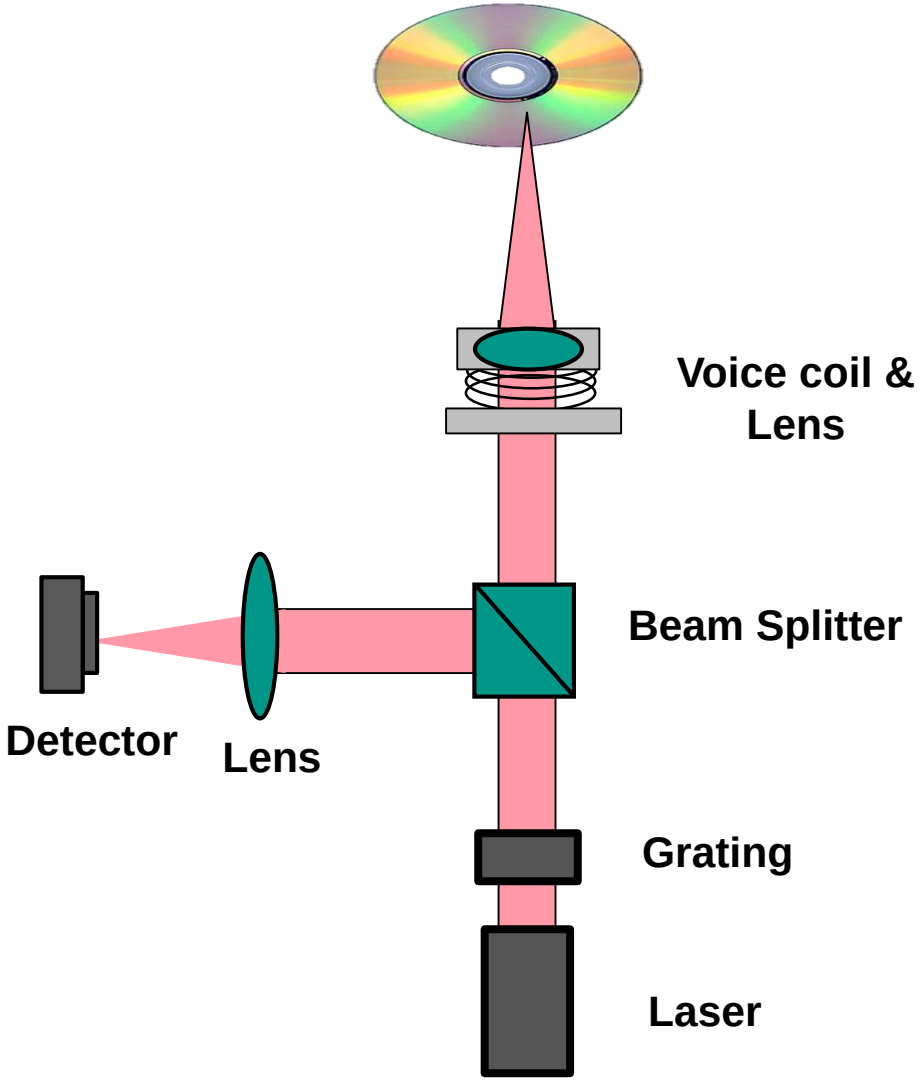
- Small form factor: About the size of a computer DVD read/write head
- Robust, cost-effective design: Virtually solid state, typical of handheld devices
- Low-operating power requirements
- Flexible “free space” optical architecture

CD ROM Pickup Unit



Cost 10$!!!





Replacing CD ROM Pickup Unit with MR-OCT

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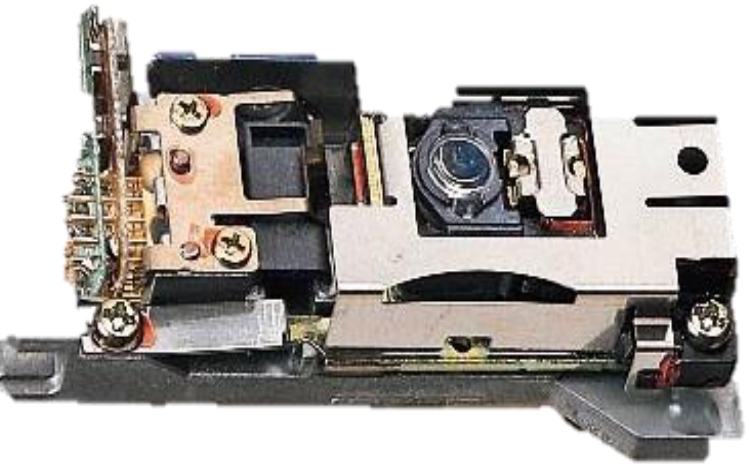

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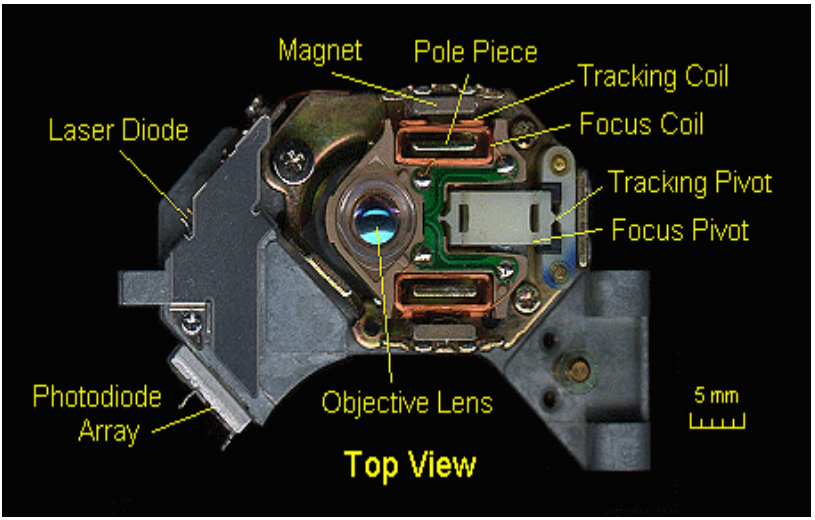
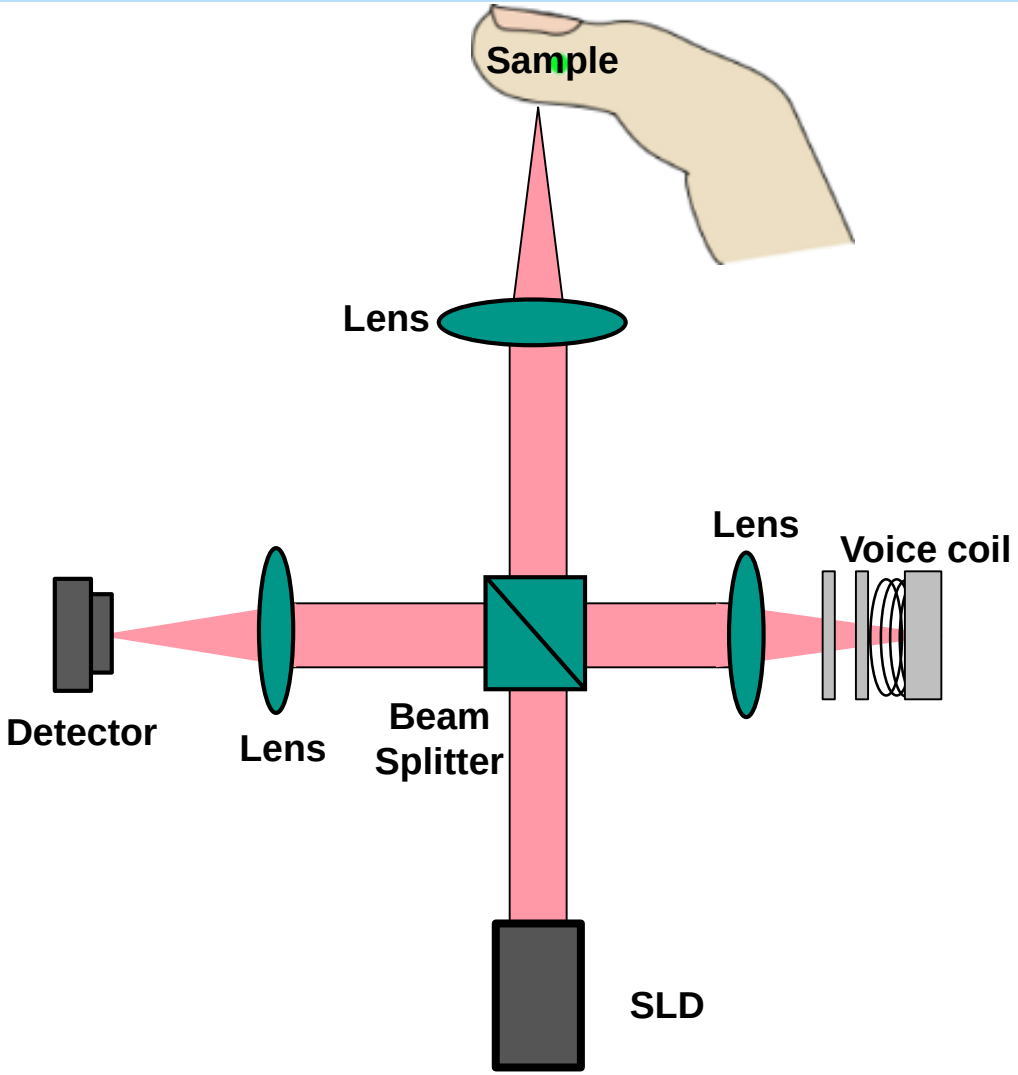
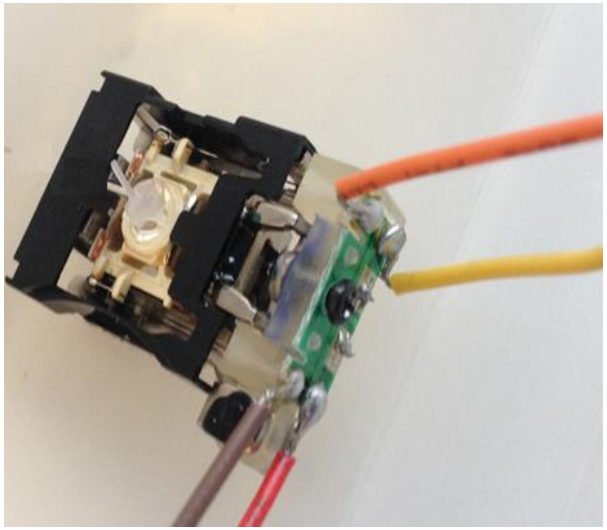
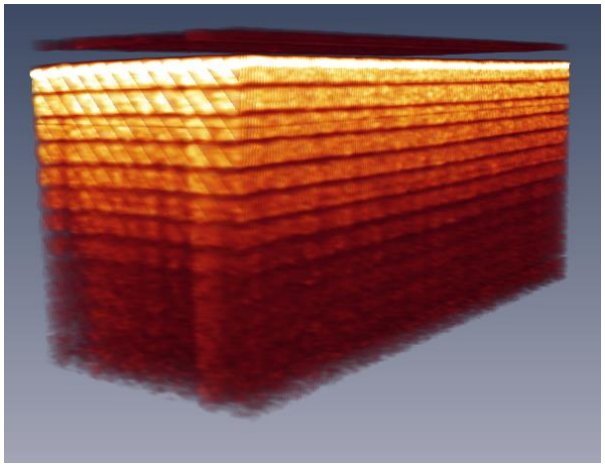




CD ROM Pickup head actuator





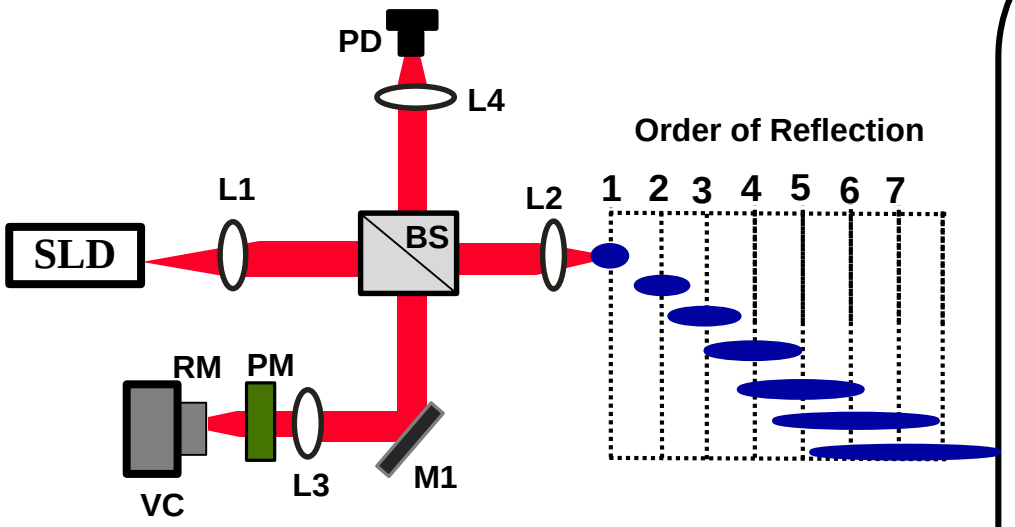
MR-OCT of Scotch tape with VCM

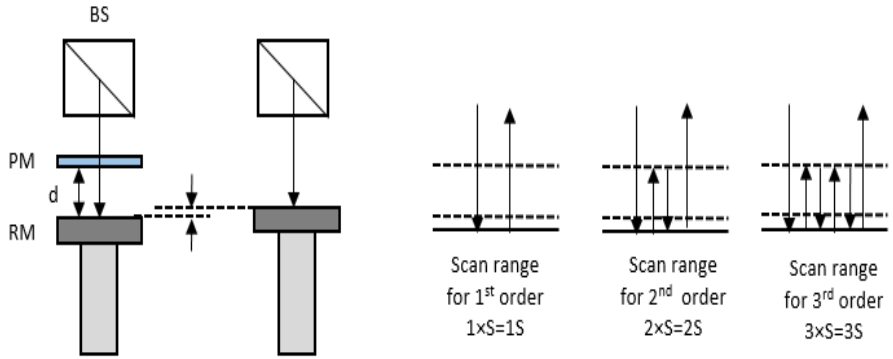
Voice coil motor (VCM) actuator used in CD pick up head to ensure the constant focus on the optical disc

Voice coil features

- Low operational voltage
- Long life
- Light weight
- Inexpensive

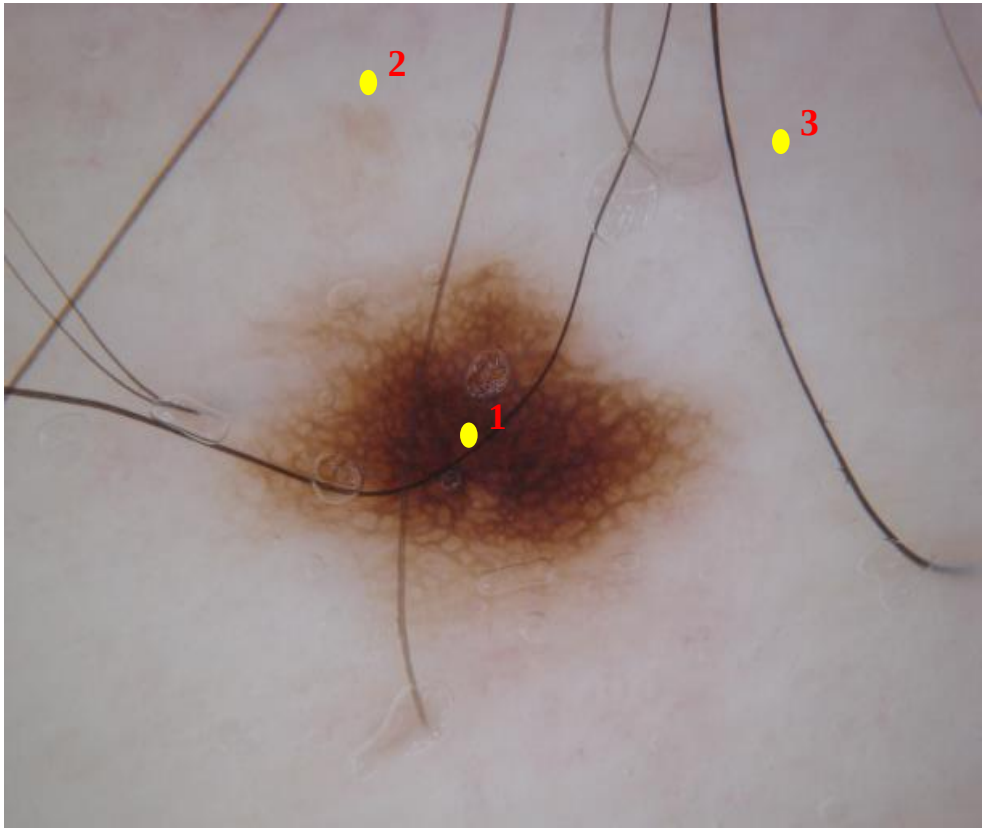
Multiple Reference Optical Coherence Tomography (MR-OCT)

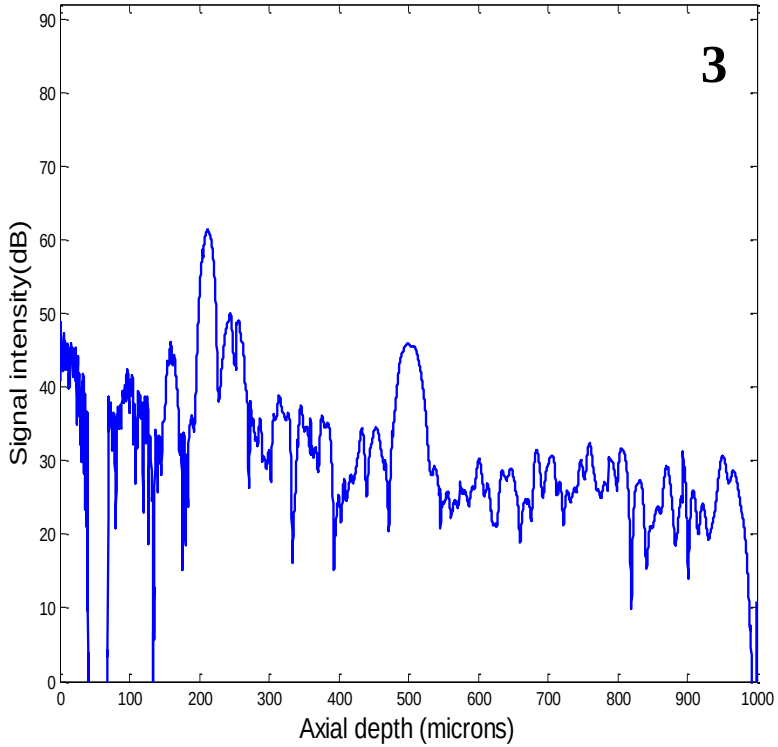




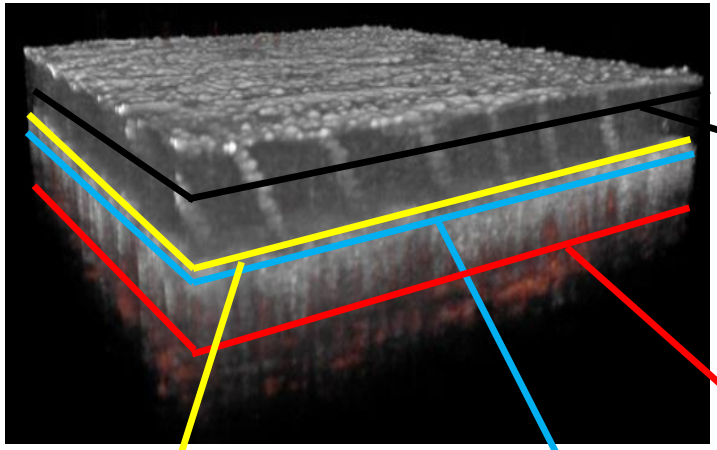
- MR-OCT is similar to conventional TD-OCT, except a partial mirror is placed very close to the reference mirror.
- The partial mirror causes the light to be reflected back and forth multiple times between the partial mirror and the reference mirror.
- Each reflection between the partial and reference mirrors is delayed by the round trip time between the two mirrors.

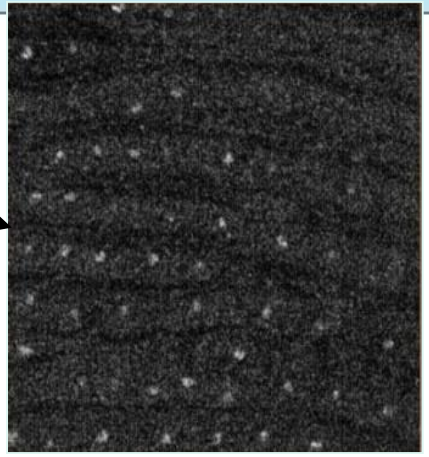
Co-registering MR-OCT beam with dermascope image



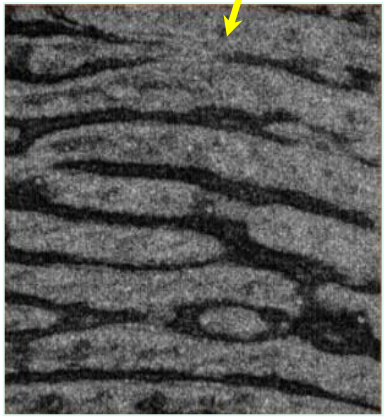


cmOCT of the thumb for a 5x5x3 mm region

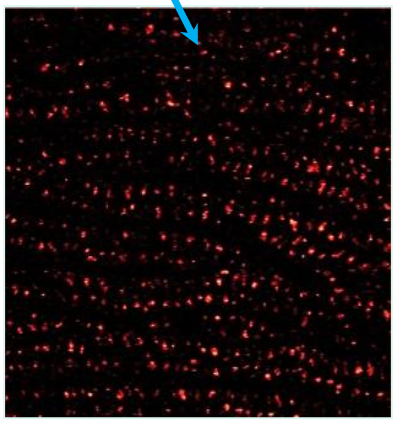




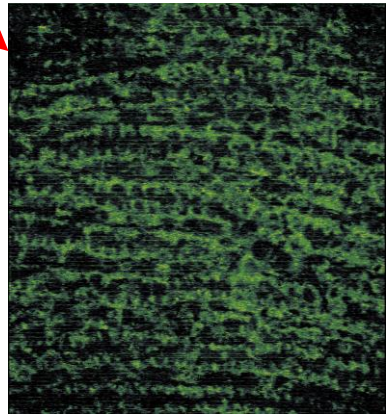
Sweat ducts



Sub-surface Fingerprint



Rising Capillary Loops



Microcirculation Map

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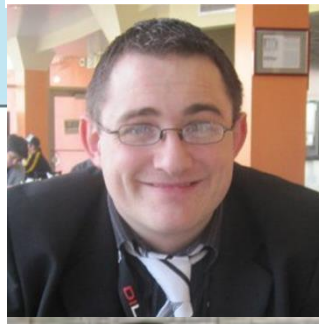

AuthenTec

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Zam et al., 2013. J. Biophoton. 6 (9) , 663-667.
McNamara et al., 2014, *J. Biomed. Opt. 18 (12), 126008*

Fingerprint Microcirculation

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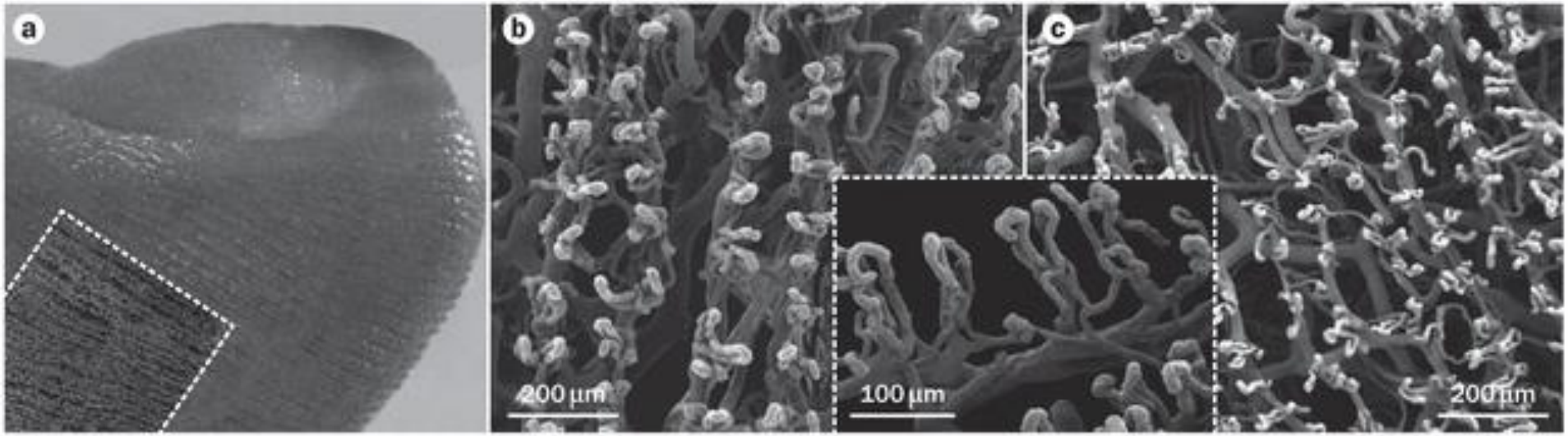

Nature Reviews | Rheumatology

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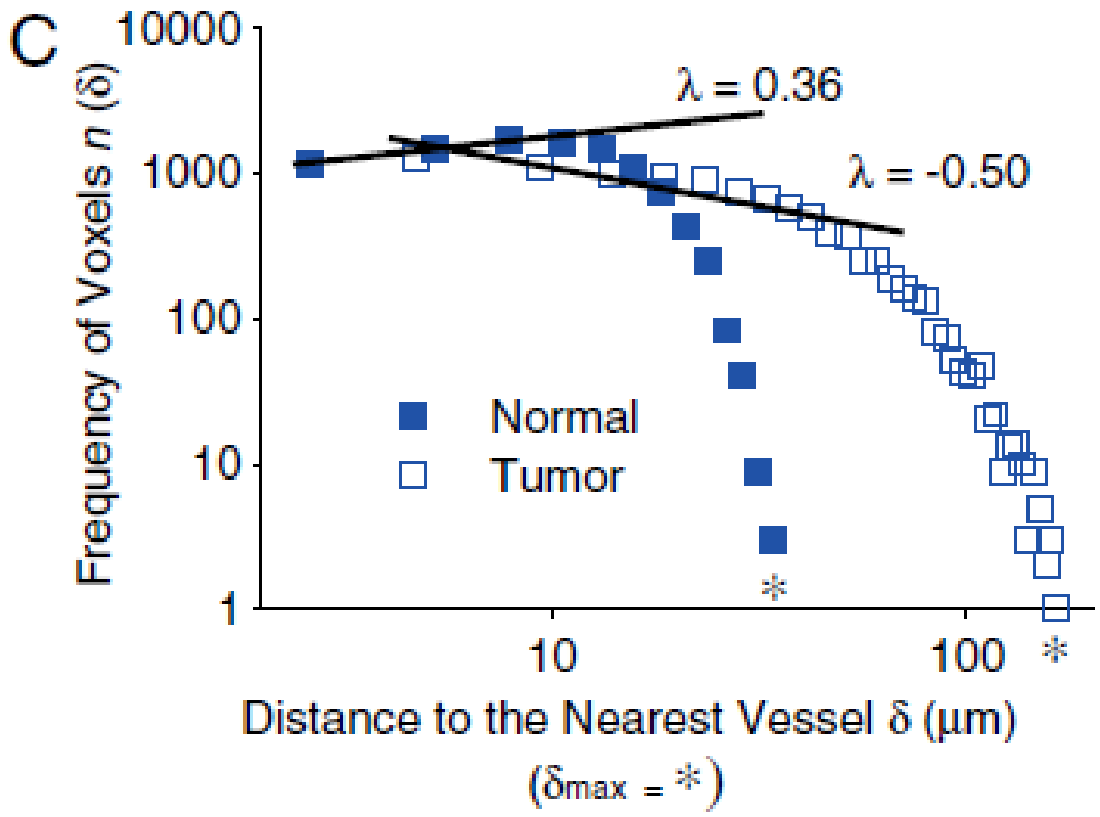
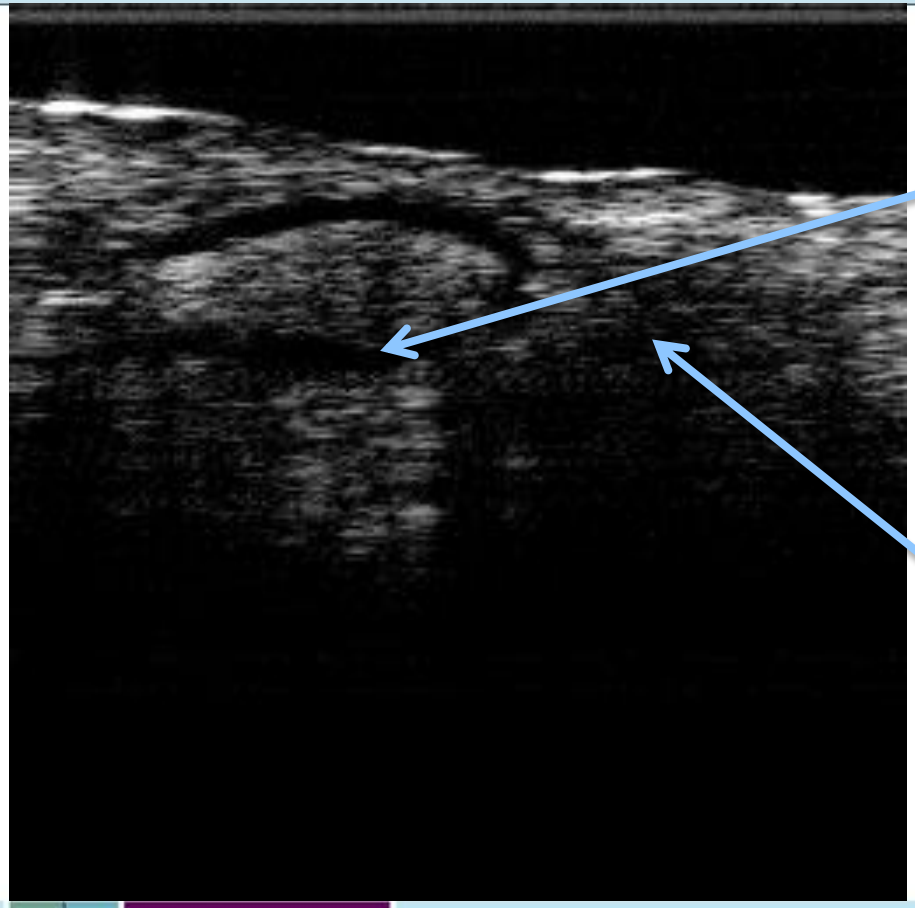
Flavahan, N Nature Reviews Rheumatology, 11, 146–158 (2015)
doi:10.1038/nrrheum.2014.195

Scaling rules for diffusive drug delivery in tumor and normal tissues



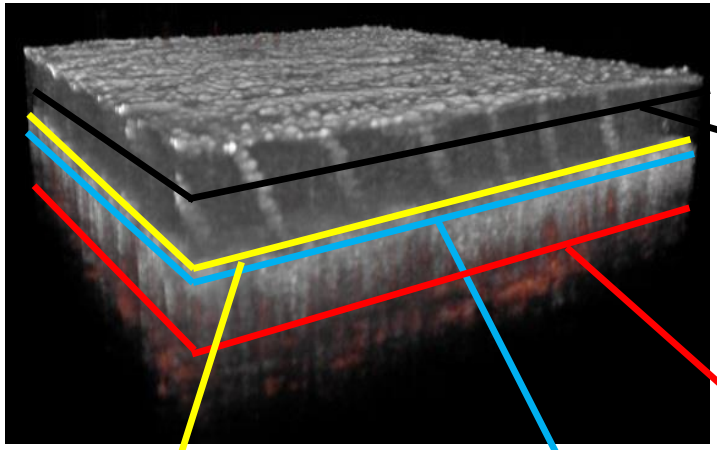
Principle of cmOCT

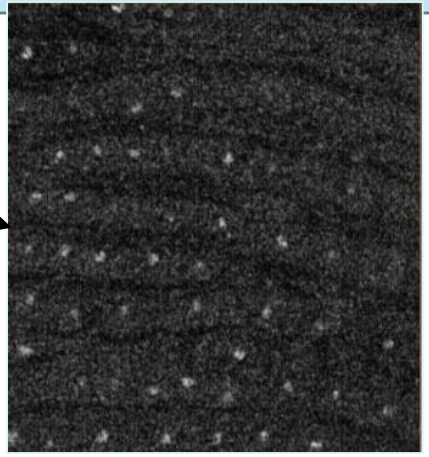


200 µm embedded capillary tube with flowing fluid

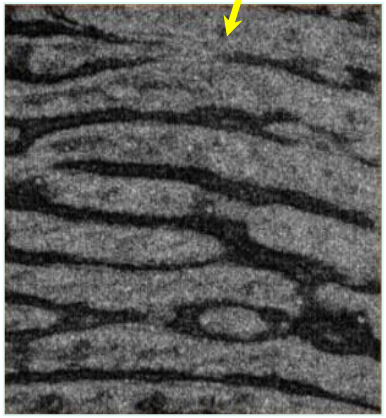
Excised section of Pig Skin

cmOCT of the thumb for a 5x5x3 mm region

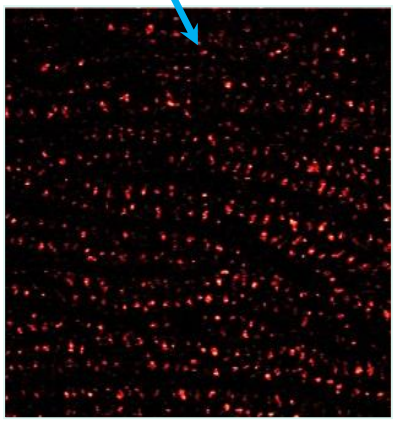




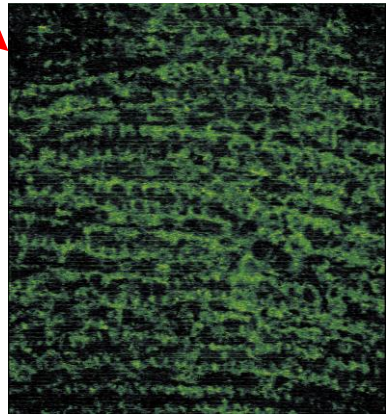
Sweat ducts



Sub-surface Fingerprint



Rising Capillary Loops



Microcirculation Map

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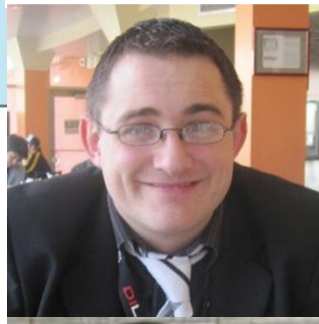

AuthenTec

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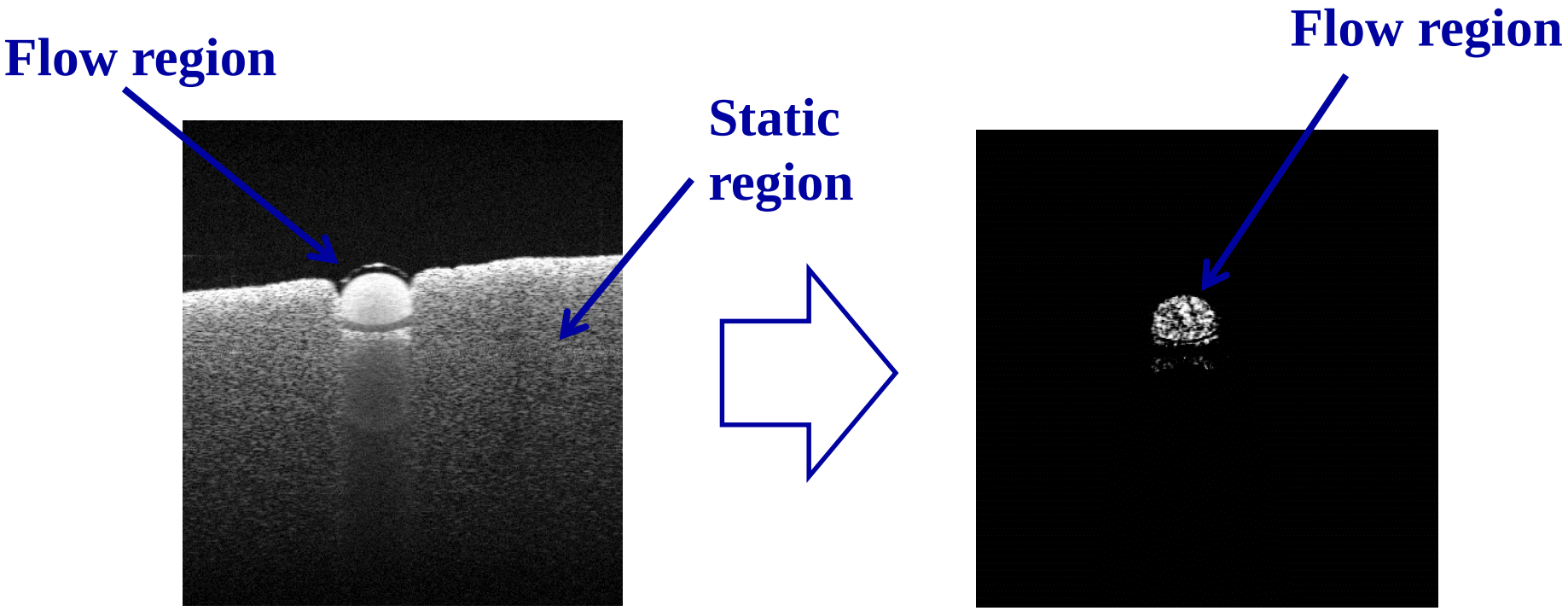
OÉ Gaillimh

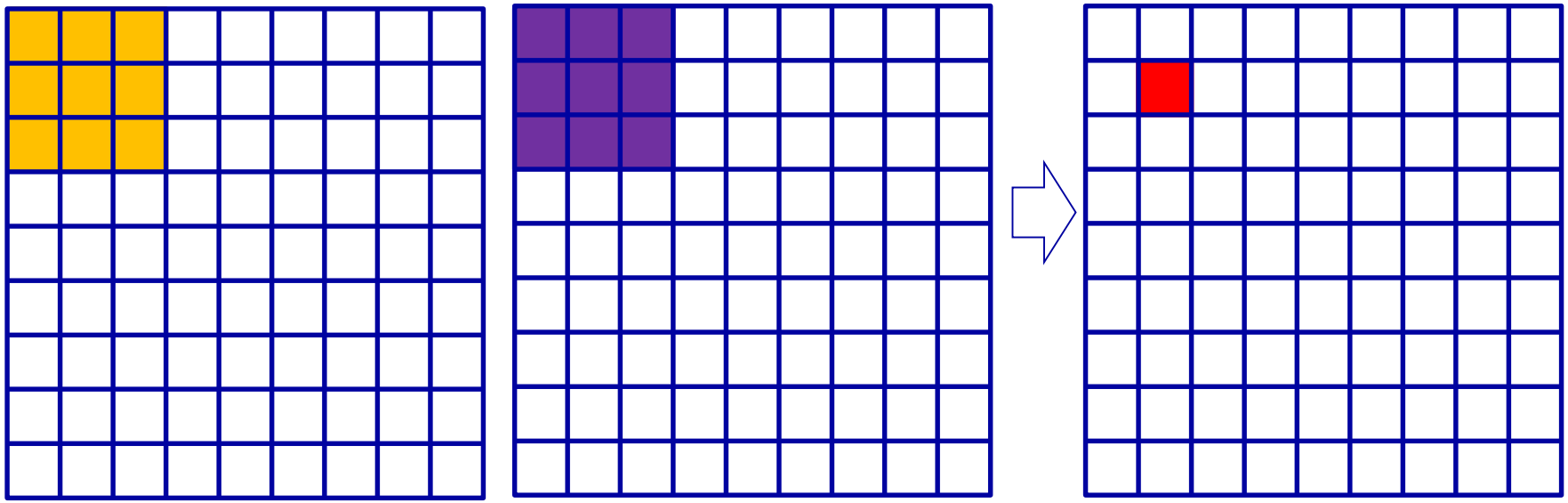
Zam et al., 2013. J. Biophoton. 6 (9) , 663-667.
McNamara et al., 2014, *J. Biomed. Opt. 18 (12), 126008*

Correlation mapping OCT (cmOCT): Principle



Joey Enfield, Enock Jonathan, and Martin Leahy, "In vivo imaging of the microcirculation of the volar forearm using correlation mapping optical coherence tomography (cmOCT)," Biomed. Opt. Express 2, 1184-1193 (2011)

Correlation mapping OCT (cmOCT): Principle

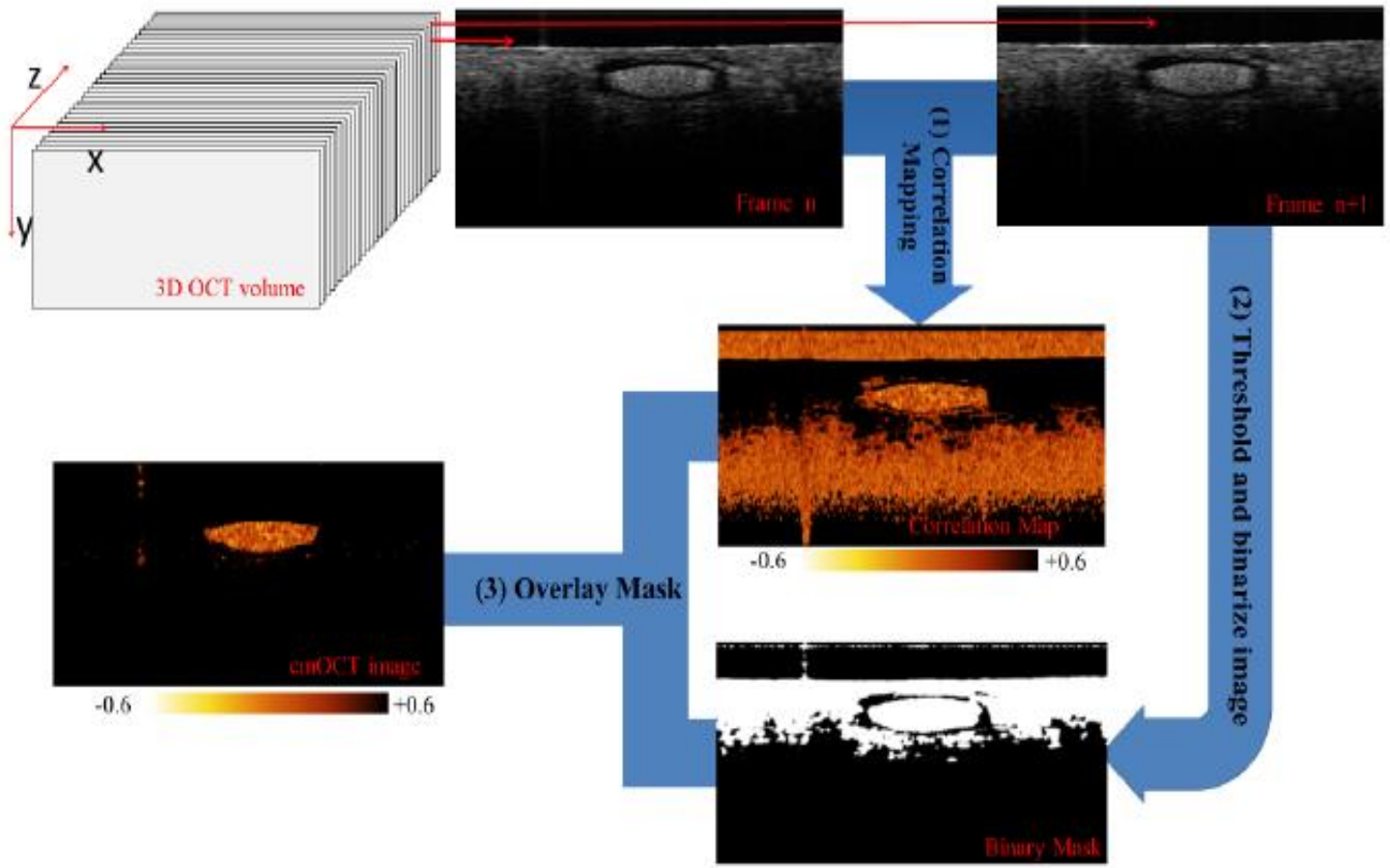


Frame A **Frame B** **Correlation Image**

$$cc(x,z) = \sum_{p=0}^{M} \sum_{q=0}^{N} \frac{\left[I_A(x+p,z+q) - \bar{I}_A(x,z)\right]\left[I_B(x+p,z+q) - \bar{I}_B(x,z)\right]}{\sqrt{\left[I_A(x+p,z+q) - \bar{I}_A(x,z)^2\right]\left[I_B(x+p,z+q) - \bar{I}_B(x,z)^2\right]}}$$

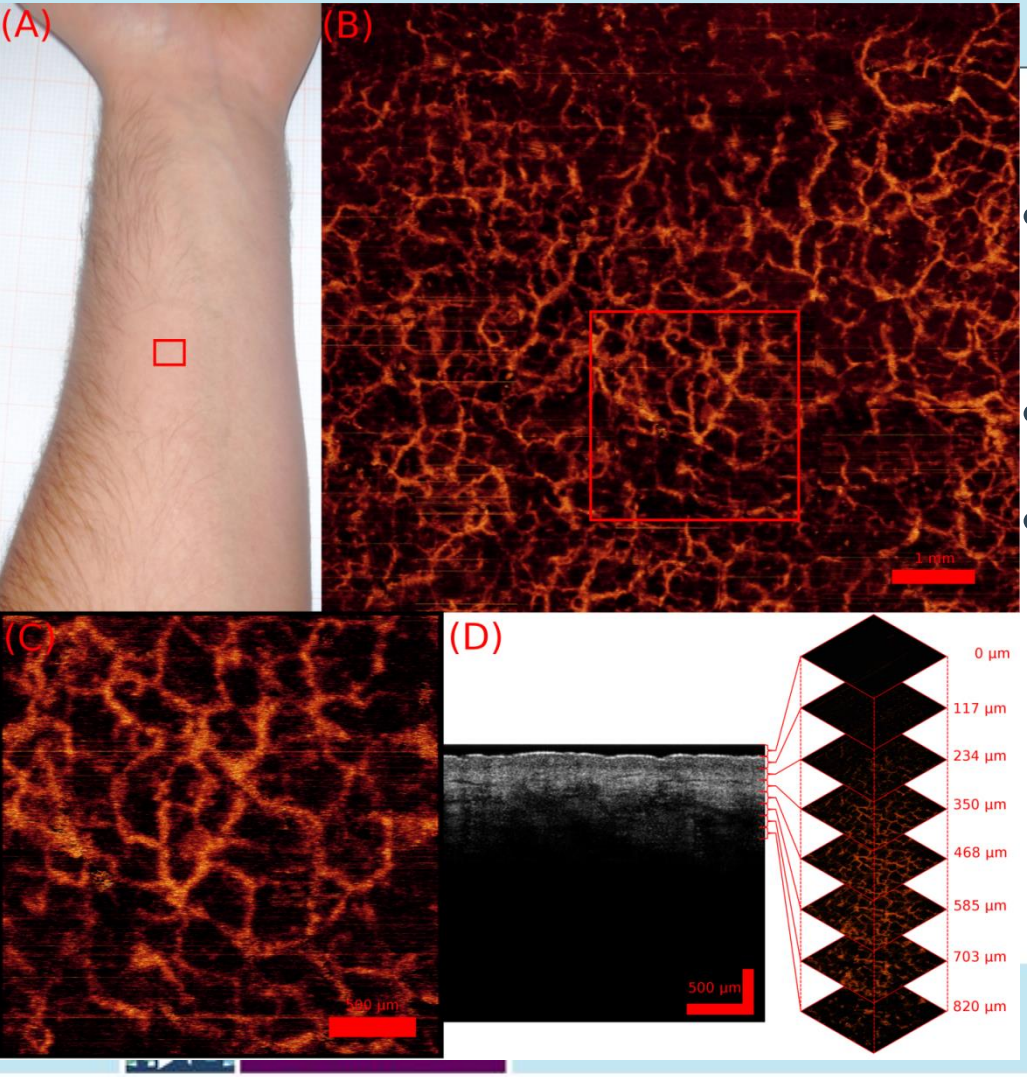
Where M, N are the grid size

Correlation mapping OCT (cmOCT): Principle



Joey Enfield, Enock Jonathan, and Martin Leahy, "In vivo imaging of the microcirculation of the volar forearm using correlation mapping optical coherence tomography (cmOCT)," Biomed. Opt. Express 2, 1184-1193 (2011)

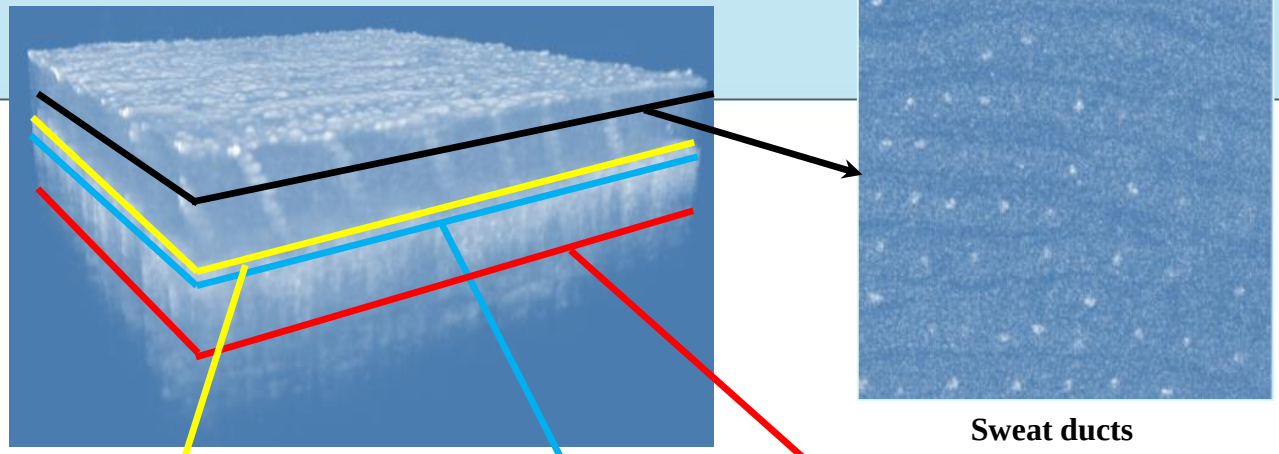
cmOCT



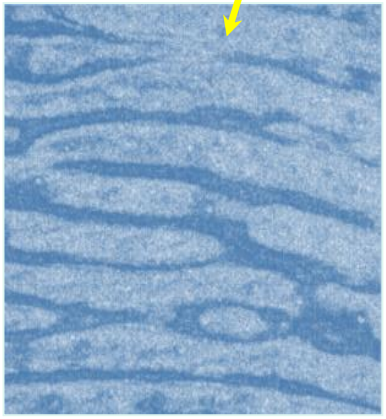
- Correlation mapping OCT
- 8 sequential frames
- 2-D correlation map average correlation value for a square grid measuring 7x7

Enfield, J. 2011 *Biomedical Optics Express* **2 (5)** 1184-1193.
Jonathan et al. 2011 J. Biophotonics 4 (5)

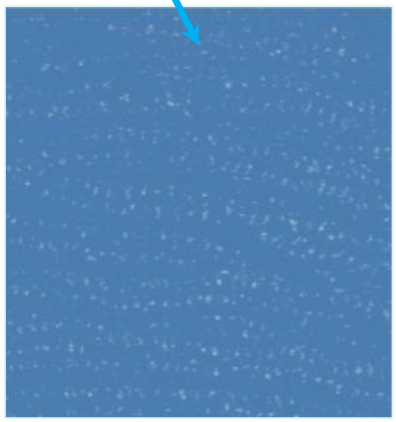
Results: cmOCT of the thumb for a 5x5x3 mm region



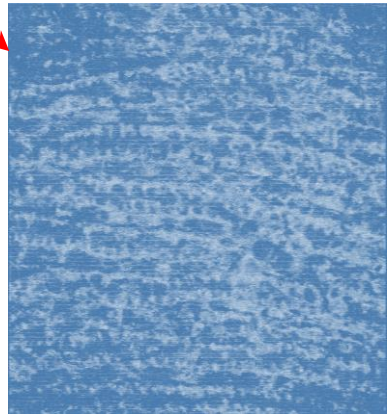
Sweat ducts



Sub-surface Fingerprint



Rising Capillary Loops



Microcirculation Map

Zam et al., 2013. J. Biophoton. **6** (9) , 663-667.
McNamara et al., 2014, *J. Biomed. Opt.* **18** *(12), 126008*

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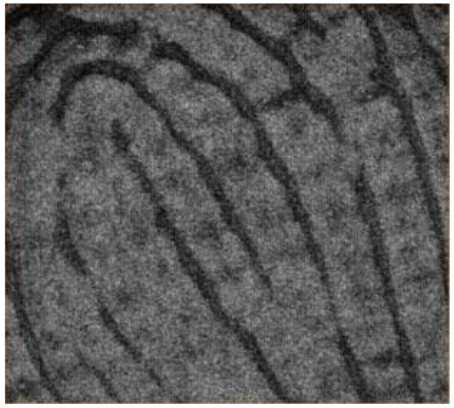
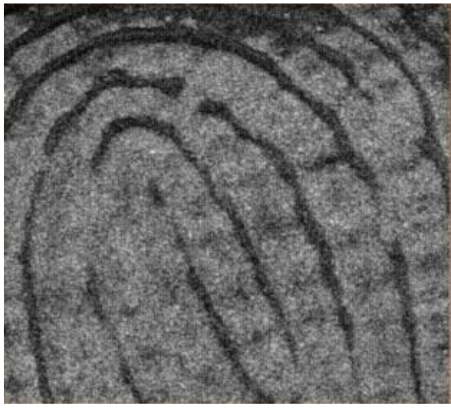
Secure biometric access to smartphones

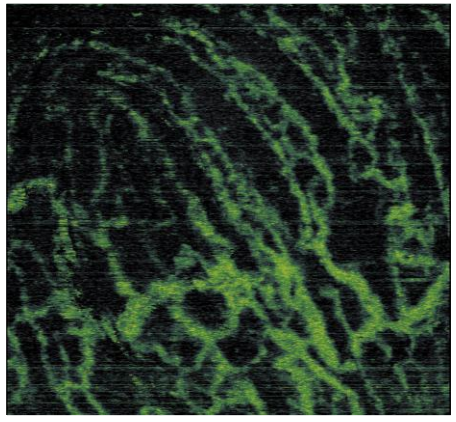
http://www.digitaltrends.com/mobile/can-apple-hand-over-your-fingerprint-to-the-nsa/

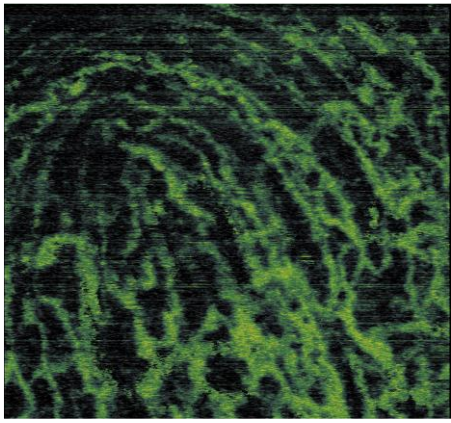
Middle finger

Day 1 Day 30









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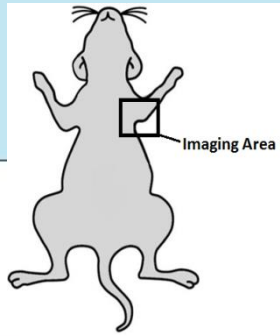
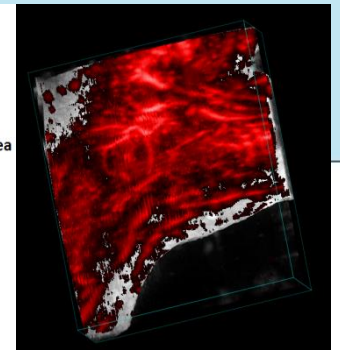
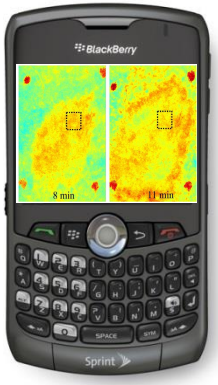
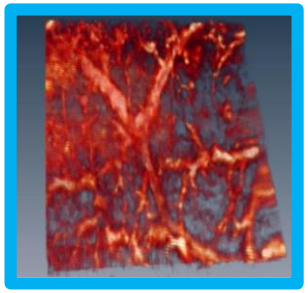
Microcirculation Imaging Techniques – TOMI lab

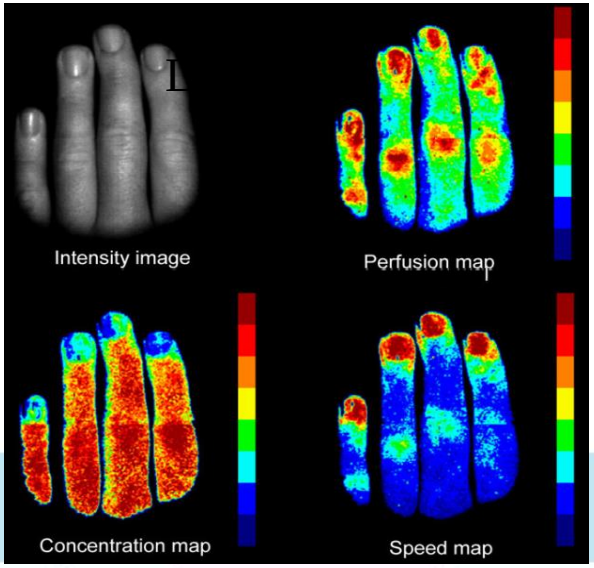
- Laser Doppler perfusion imaging (LDPI)
- Laser speckle contrast imaging (LSCI)
- Tissue viability imaging (TiVi)
- Photoacoustic tomography (PAT)
- Optical coherence tomography (OCT)

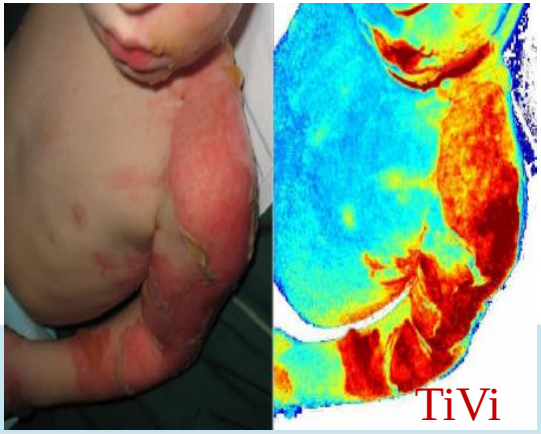


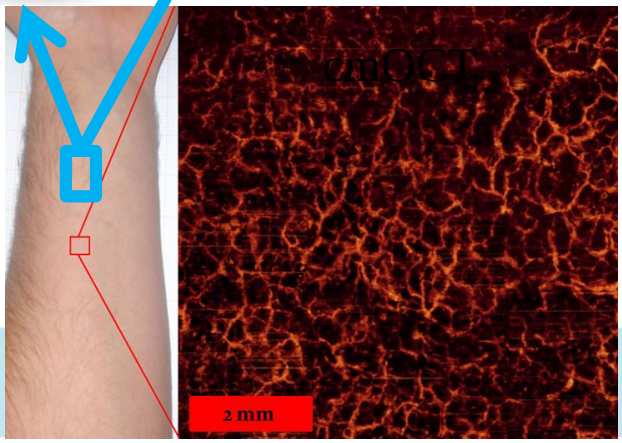












In vivo imaging of human forearm using 40 MHz transducer

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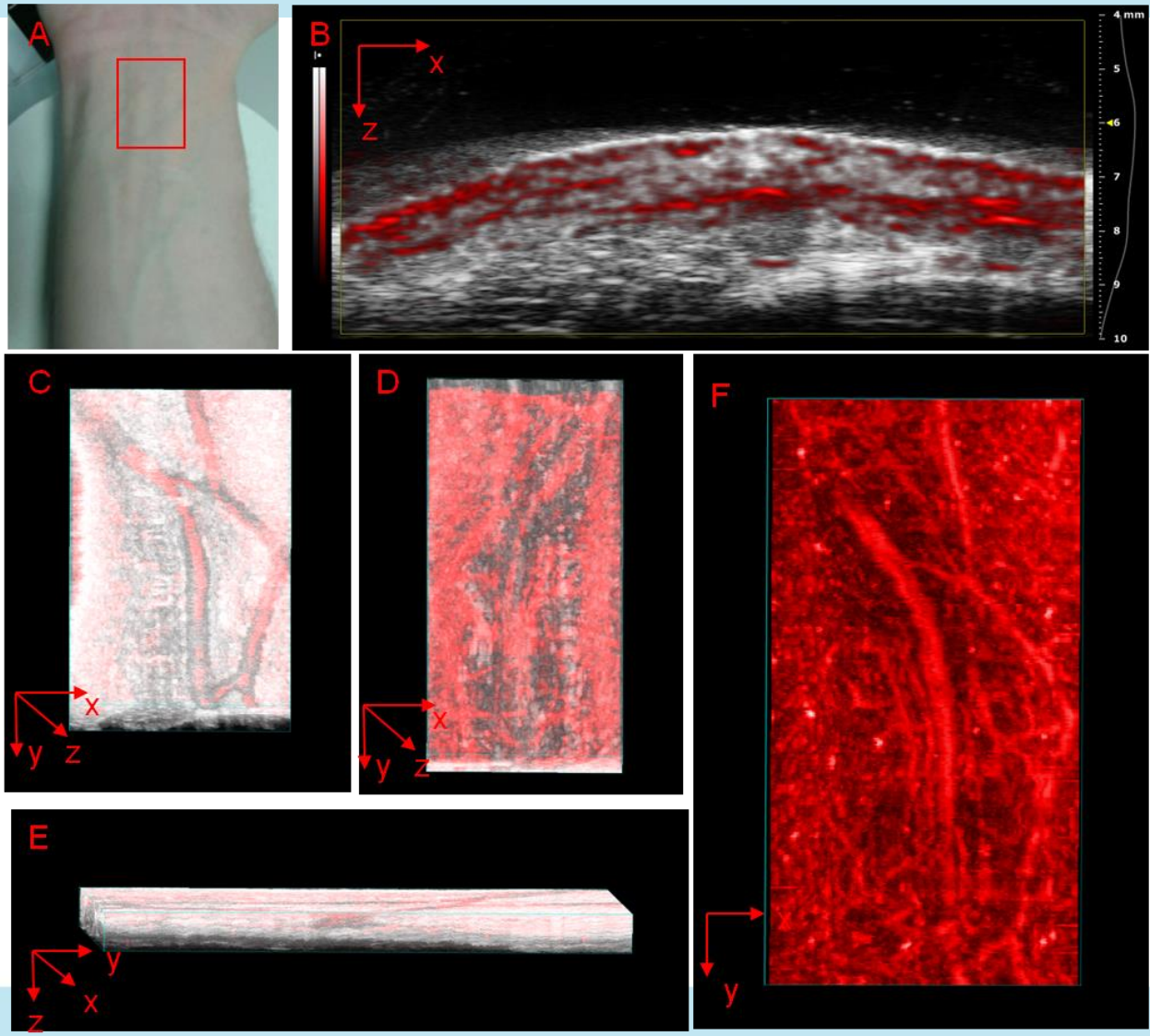
Tissue optics & microcirculation imaging

- In vivo PA and high frequency ultrasound images of the human forearm for a 30.5 (length) x 14.1 (width) x 10 (depth) region using 40 MHz probe at 860 nm.



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OÉ Gaillimh

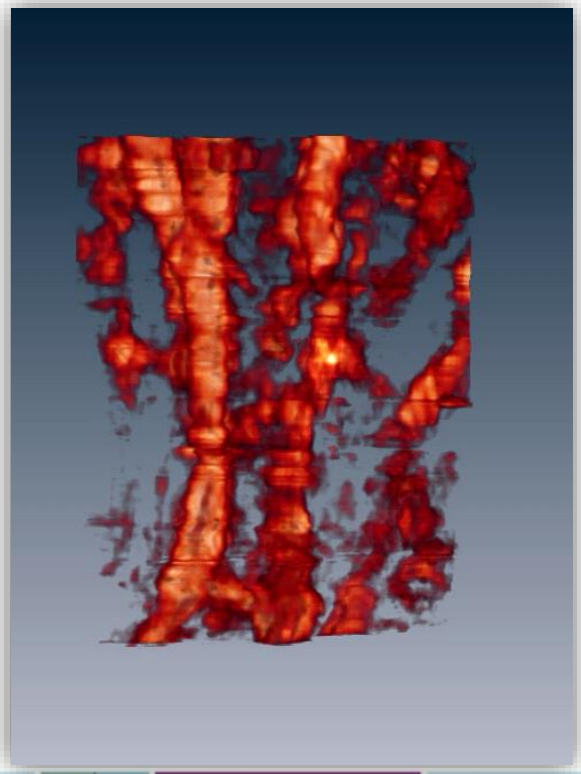
submitted to Journal of Investigative Dermatology, May 2014.

Comparison of 15, 21 & 40 MHz transducers

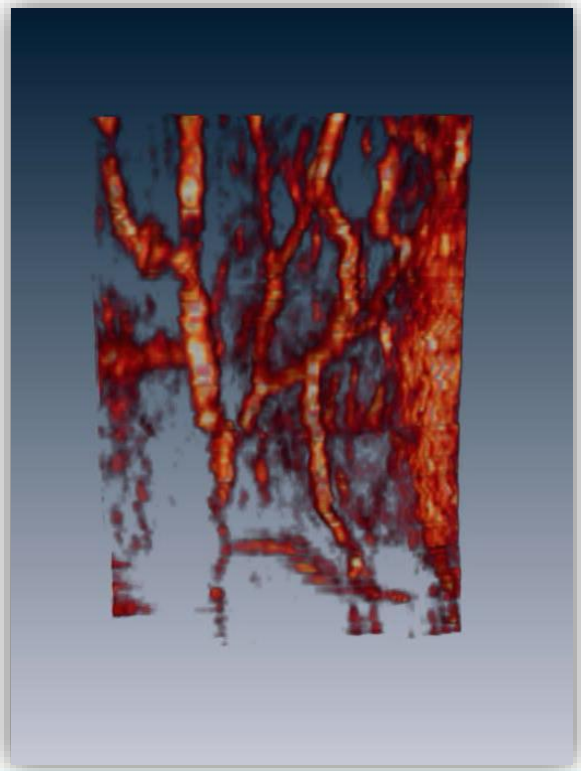
TOMI
Tissue optics & microcirculation imaging

• Comparison of *in vivo* images of the human forearm acquired at the same location using 15 MHz, 21 MHz and 40 MHz transducer probes at 1064 nm.

15 MHz (rendered)
30.5 mm x 23 mm (l x w).



21 MHz (rendered)
30.5 mm x 23 mm (l x w).



40 MHz (rendered)
30.5 mm x 14 mm (l x w).

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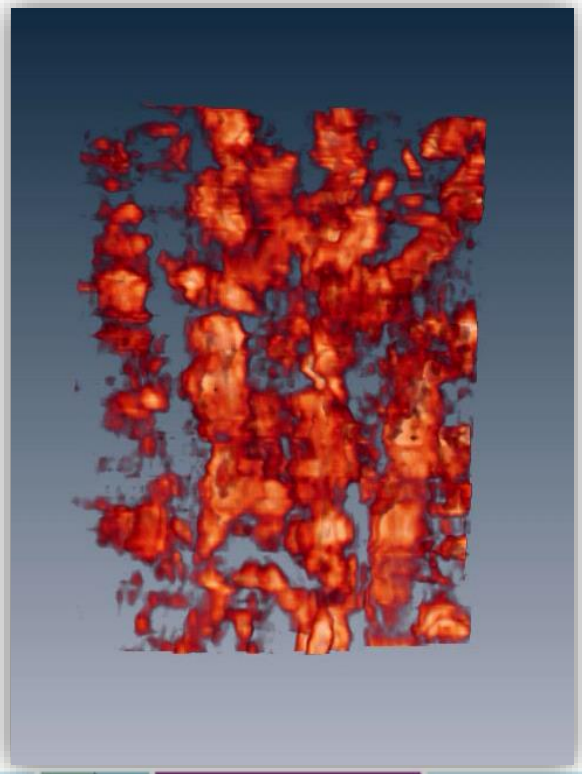
Leahy et al., submitted to Journal of Investigative Dermatology, May 2014.

Comparison of 15, 21 & 40 MHz transducers

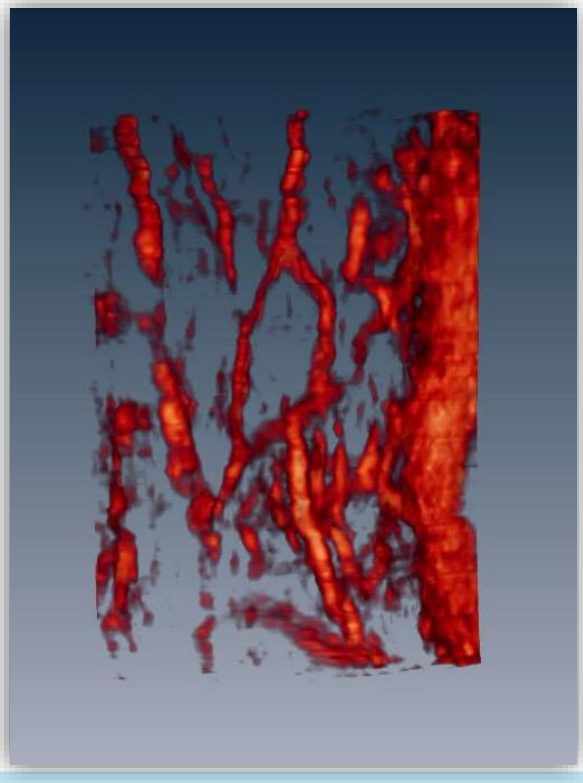
TOMI
Tissue optics & microcirculation imaging

• Comparison of *in vivo* images of the human forearm acquired at the same location using 15 MHz, 21 MHz and 40 MHz transducer probes at 800 nm.

15 MHz (rendered)
30.5 mm x 23 mm (l x w).



21 MHz (rendered)
30.5 mm x 23 mm (l x w).



40 MHz (rendered)
30.5 mm x 14 mm (l x w).

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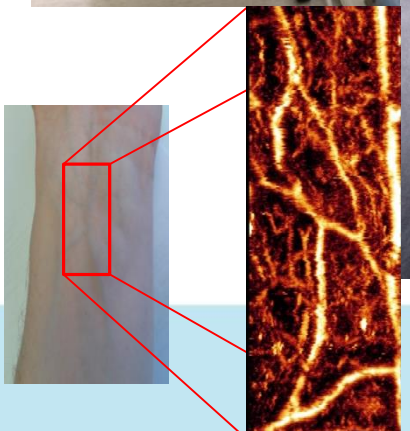
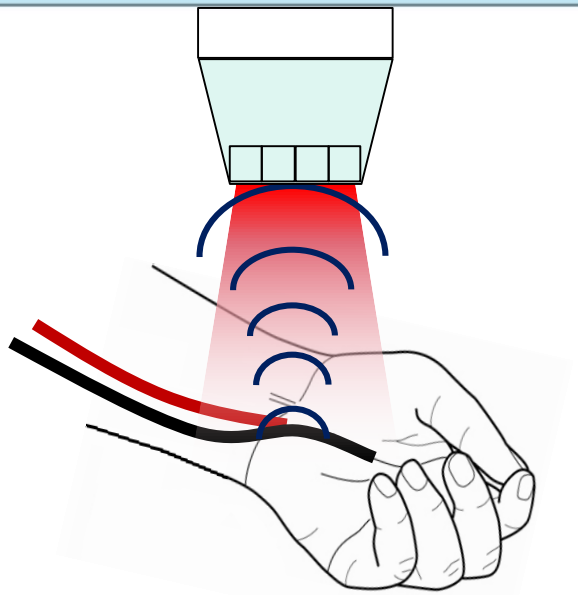
submitted to Journal of Investigative Dermatology, May 2014.

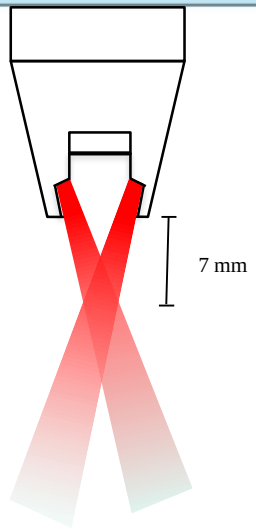
Visual Sonics Vevo® LAZR PAI System

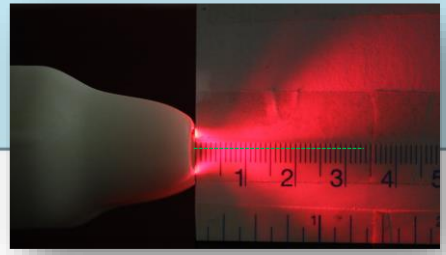
- OPO pumped by doubled Nd:YAG 680-970 nm, 20 Hz repetition rate, 5 ns pulse width, 45 +/5 mJ pulse energy
- 532 nm, 680-970 nm, 1064 nm, and 1200-2000 nm
- Real-time coregistered US and PA images
- Laser light delivery and Ultrasound (US) detection in single PA probe

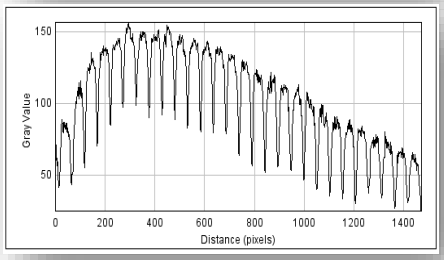


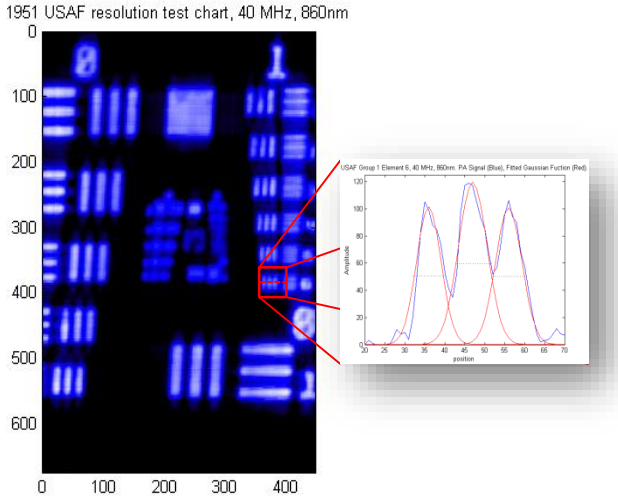
40 MHz PA probe











- 256 linear transducer array
- 7 mm laser focus
- Lateral resolution 140 µm

OCT: optical analogue of pulsed-wave ultrasound

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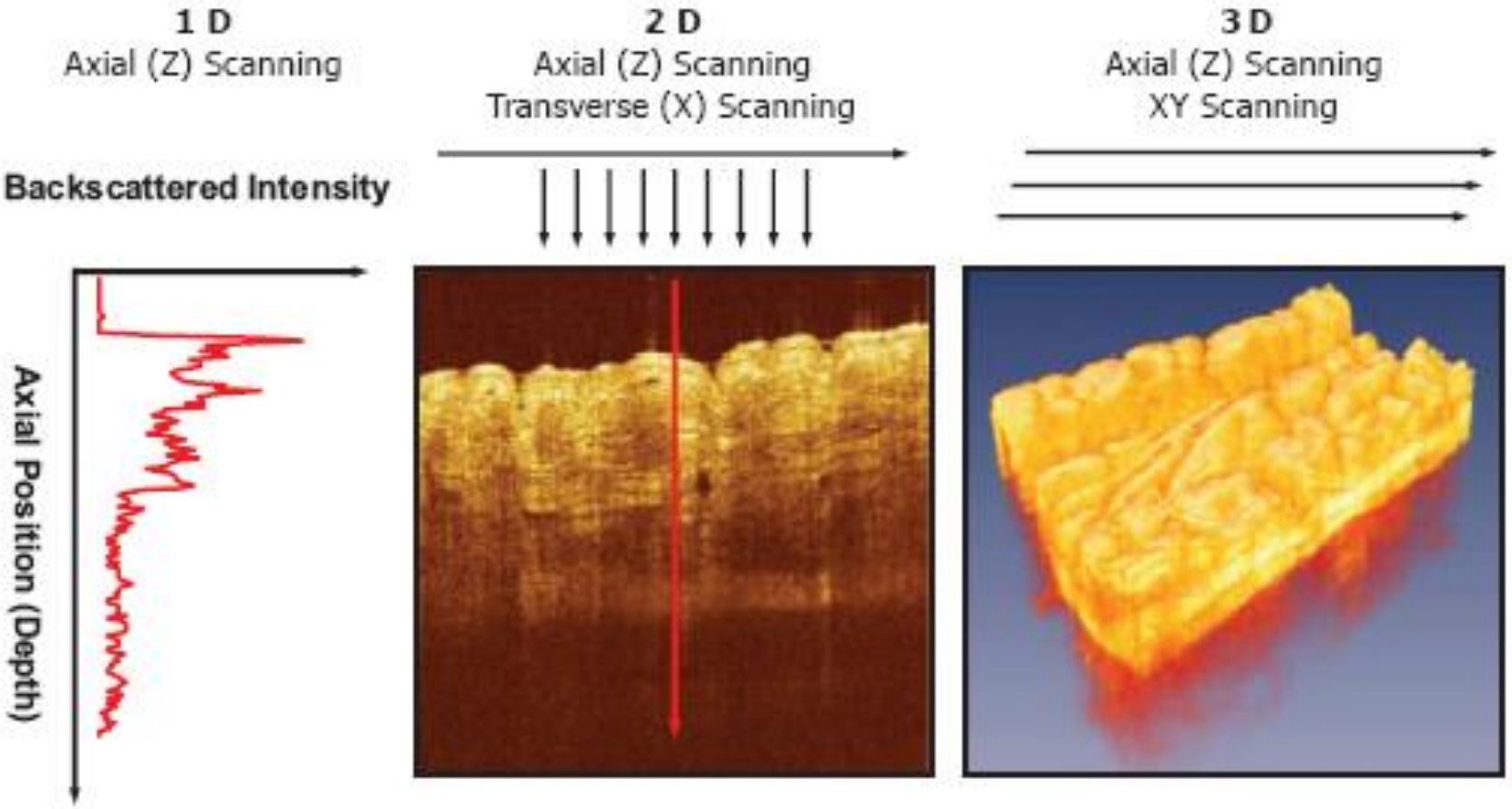
Tissue optics & microcirculation imaging



J. Fujimoto, 2008

Materials & Methods

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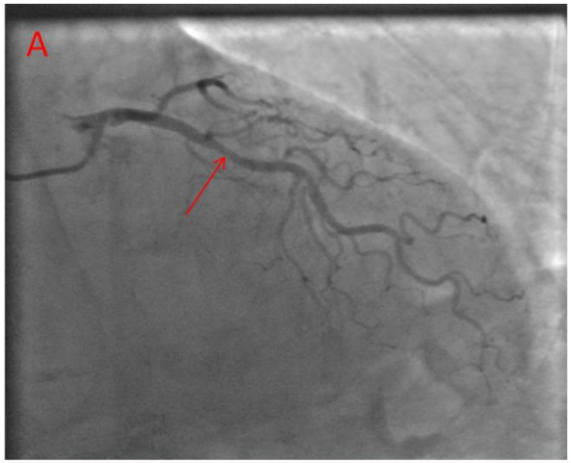
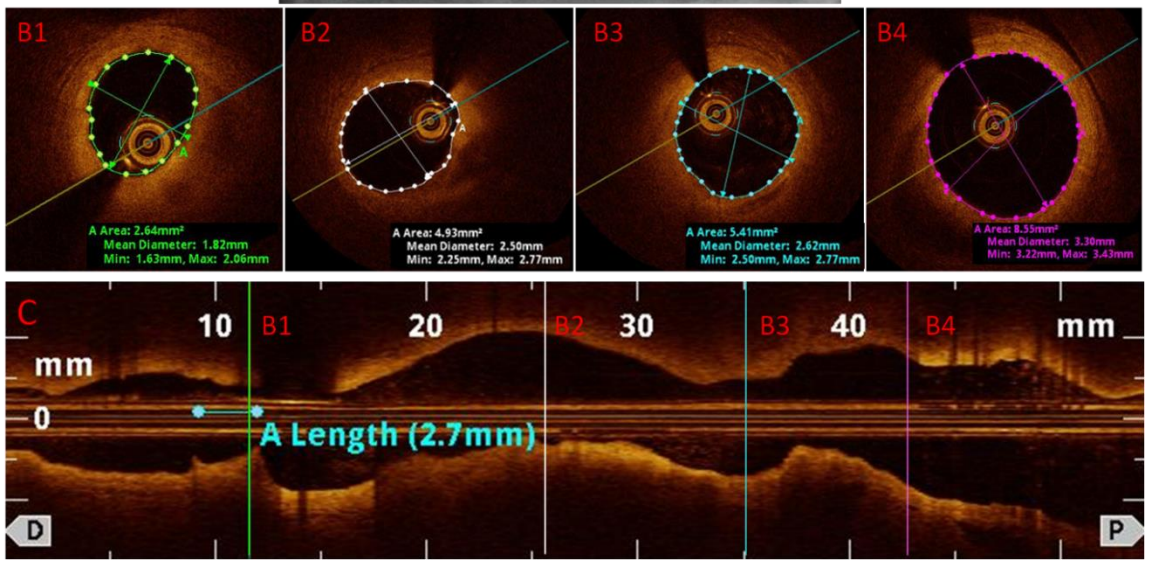
Tissue optics & microcirculation imaging

- The minimal lumen area (MLA) and minimal lumen diameter (MLD) were measured at the cross section with the smallest lumen area using FD-OCT.



NinePoint_4.mp4

- Reference lumen area (RLA) was measured at reference cross section with the largest lumen within 10 mm proximal or distal to MLA and before any side branch.



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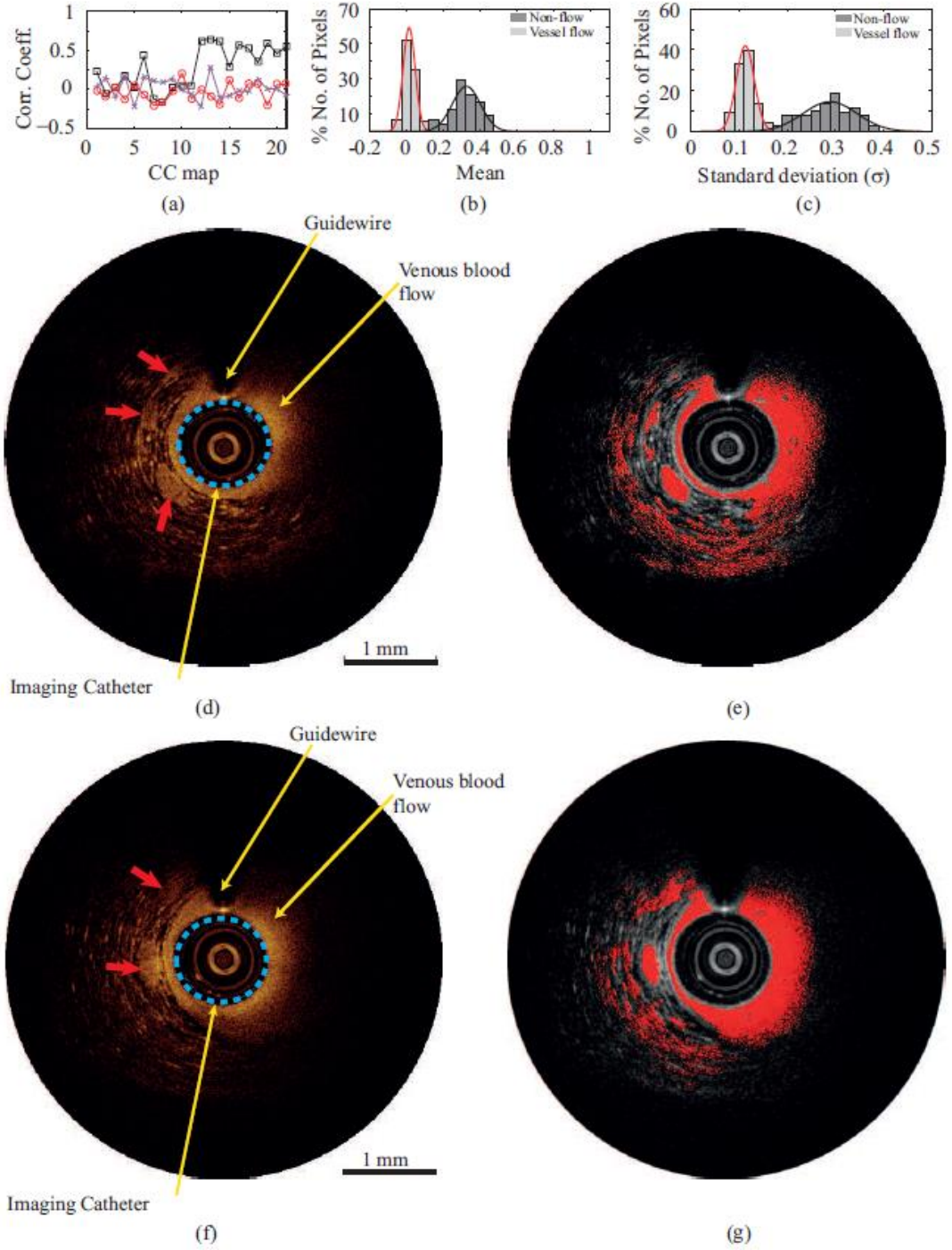
Intracoronary microcirculation

Human Coronary Sinus using the every frame CC mapping method.

(d and f) Cross-sectional OCT images obtained with zero pullback. Bold red arrows indicate the vessels. (e and g) Flow maps corresponding to (d) and (f) superimposed onto the respective OCT images. Flow regions are marked red.



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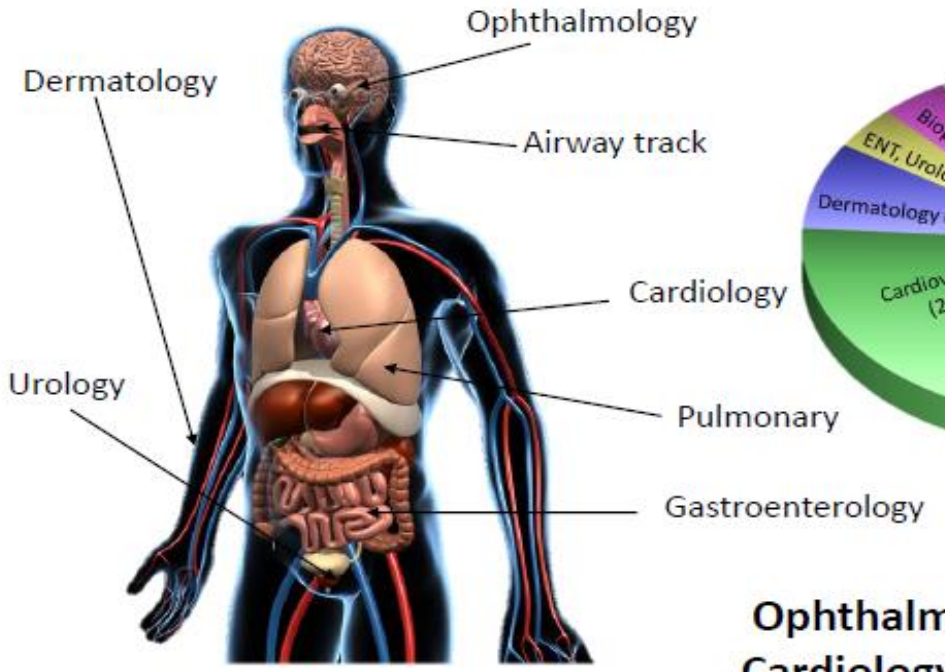
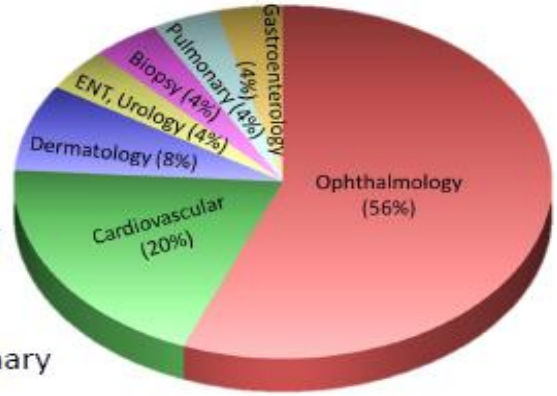
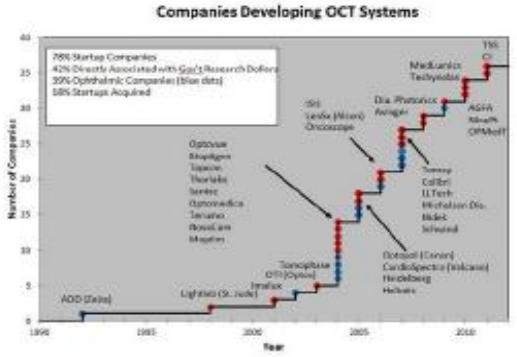
Clinical OCT Systems in the world market







~40 OCT Based Established Companies and Startups

Ophthalmology ~ 20M patients/year
Cardiology (intravascular OCT) (~100k patients/year)

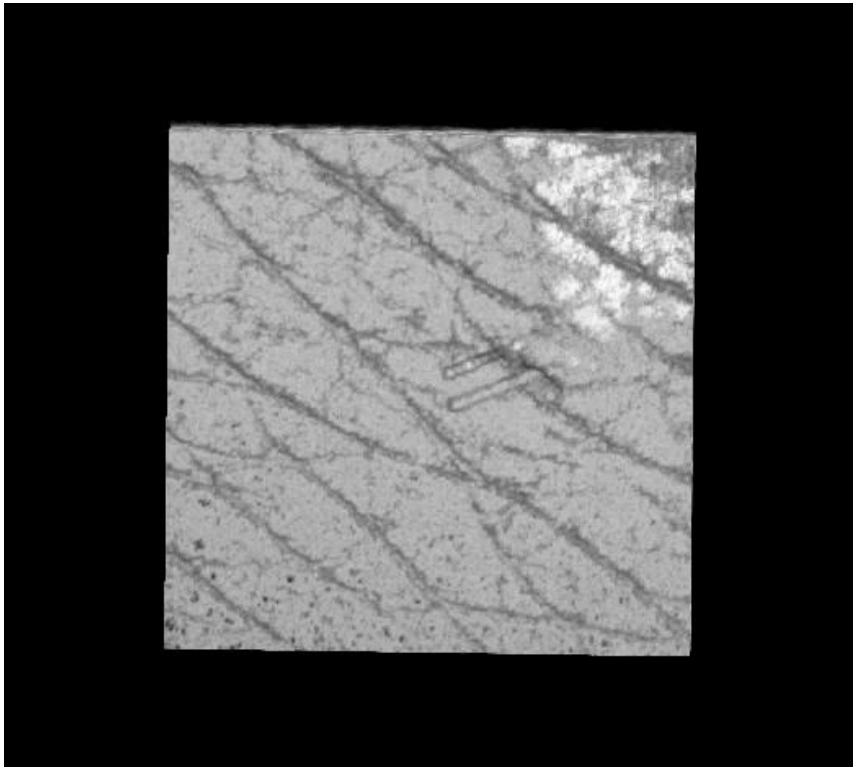
- **$6,000,000,000 in equipment sales, $10,000,000,000 in health care savings.**

http://www.octnews.org/articles/6849556/the-ecosystem-that-powered-the-translation-of-oct-

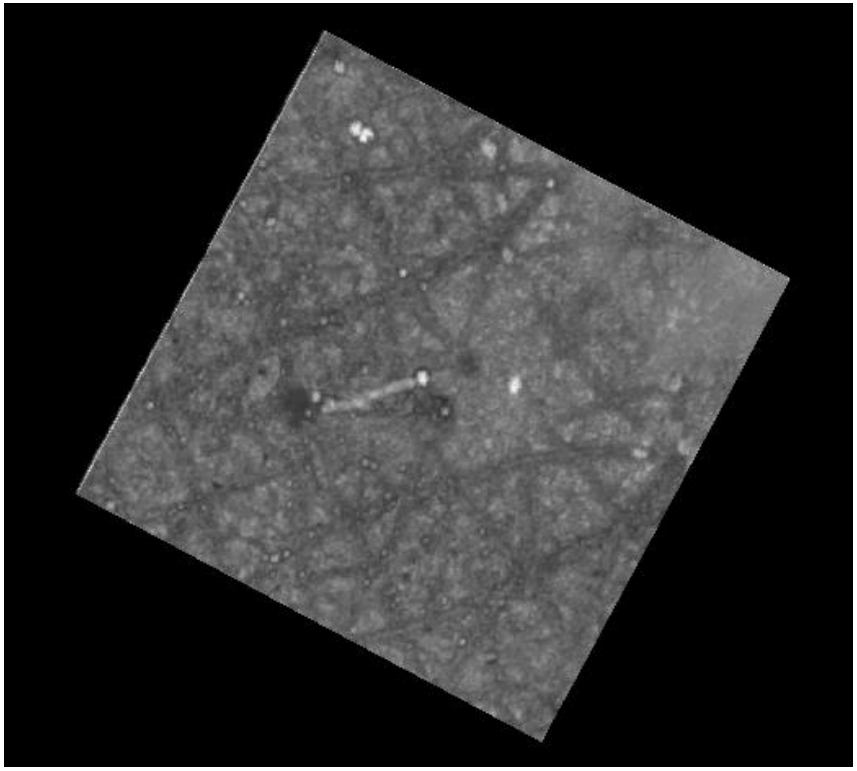
http://www.ajo.com/article/S0002-9394(17)30419-1/fulltext

In Vivo cmOCT and Optical Clearing

Before Clearing



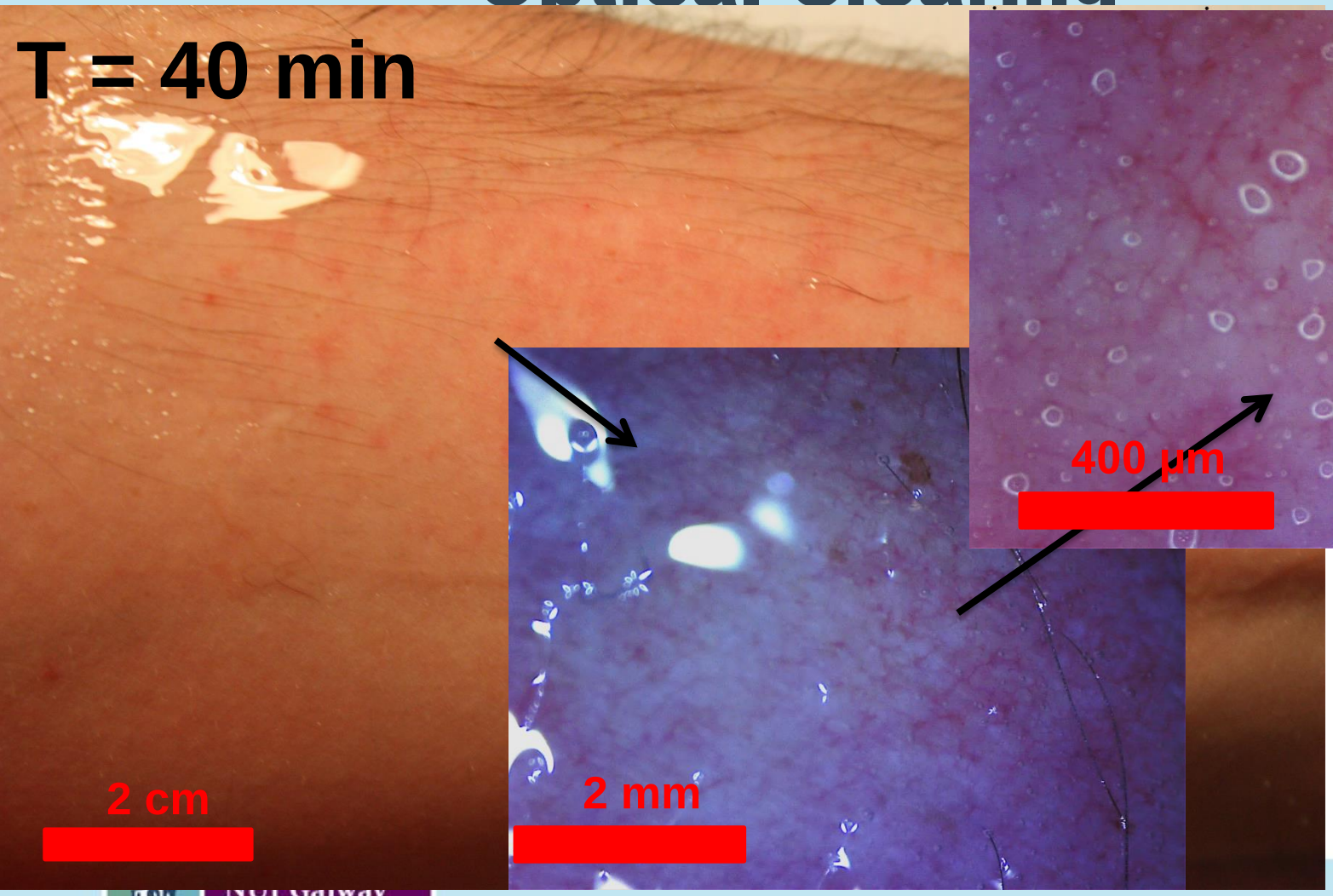
After Clearing



Region shown is a 3x3 mm region, before and after 40 min clearing

J. Biomed. Opt. 2016, 0001; **21**(8):081212

In Vivo Human
Optical Clearing



J. Biomed. Opt. 2016, 0001; **21**(8):081212

Label-free Imaging Domains

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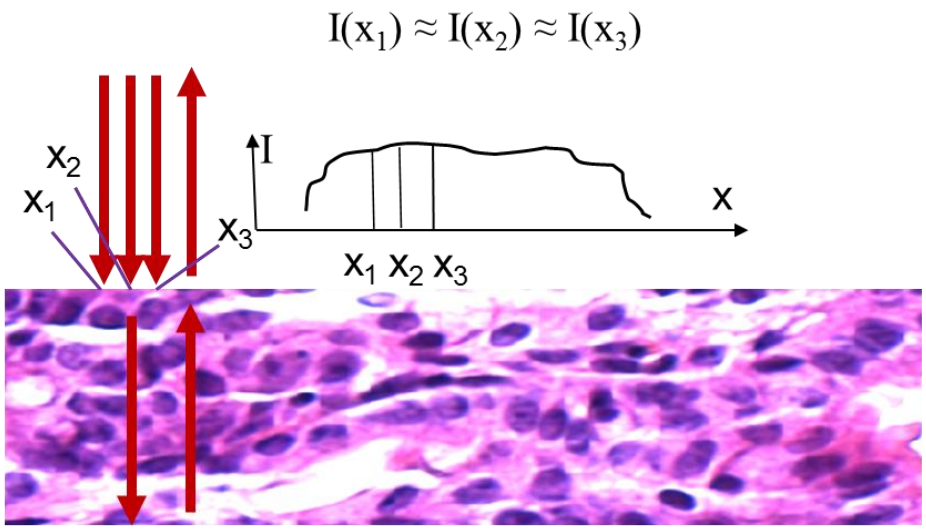
Conventional microscopy

Detector

One intensity value at each point of the image

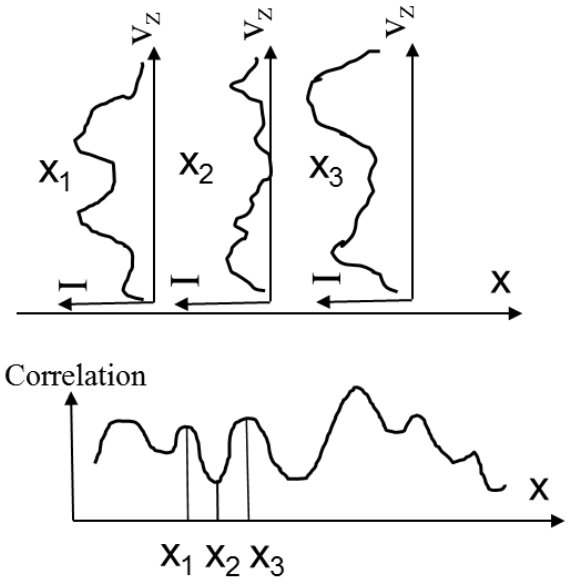


Structural features at points x_1, x_2, x_3 are unresolvable

srSESF microscopy

Spectral detector

Axial spatial frequency profile at each point of the image



Structural features at points x_1, x_2, x_3 can be resolved

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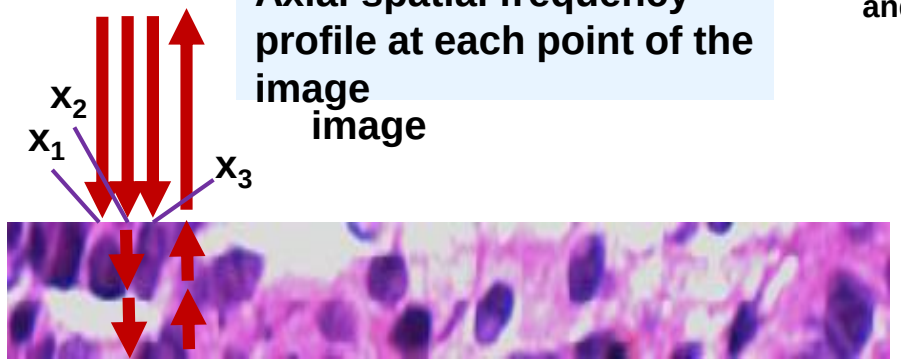
Nature Scientific Reports ***5*** 13274

sSESF approach

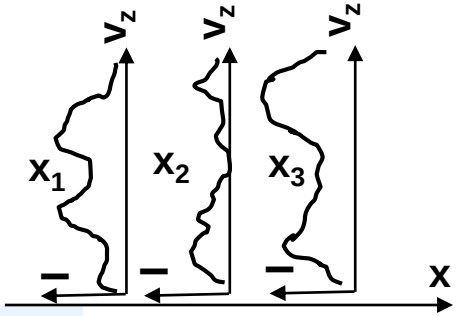
sSESF microscopy

Axial spatial frequency profile at each point of the image

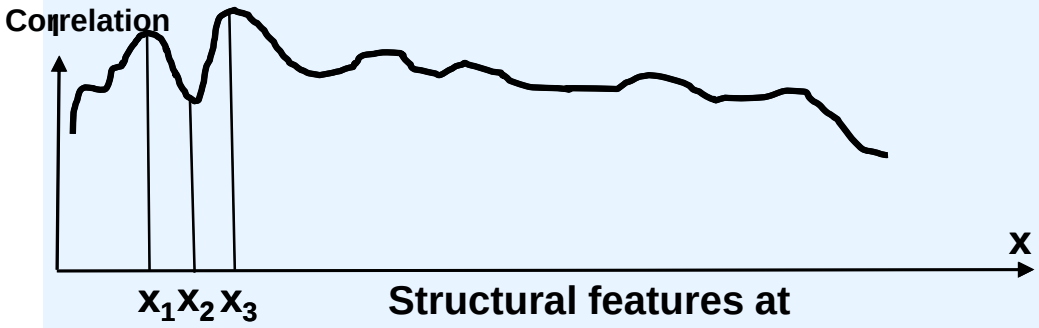
It was shown that super-resolution image can be formed as a map of correlation between frequency profile at given point and at all other points in the image.



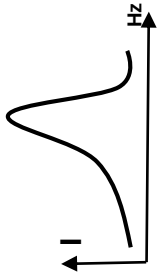
image



High frequency content



Structural features at points x_1, x_2, x_3 can be resolved



Synthesized structure

Imaging of 2D lateral structure with size beyond the diffraction resolution limit.

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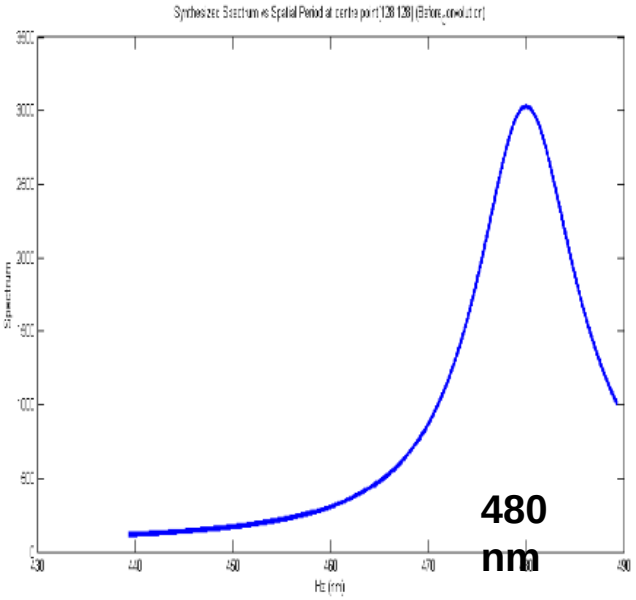
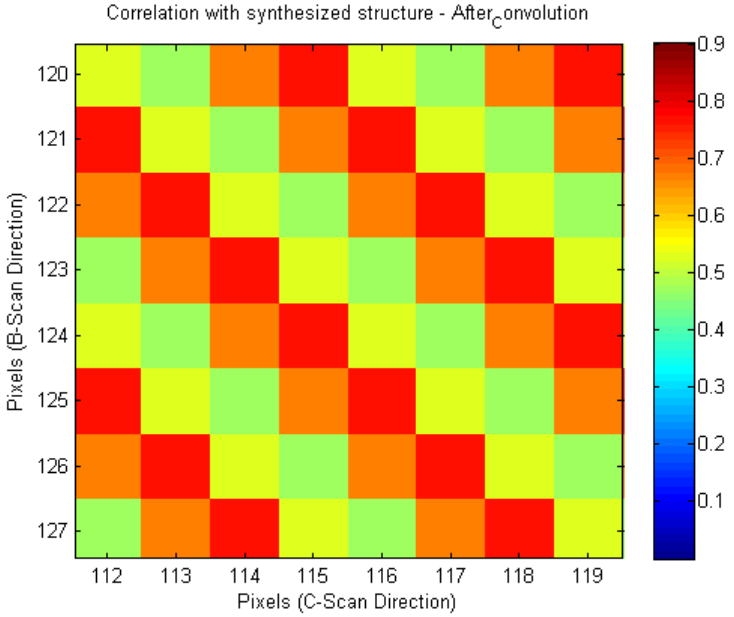
Size of each element of the lateral structure 600nm x 600nm, in 2 times smaller than diffraction resolution limit. Size difference in axial structure is 10 nm.

λ = 1300 nm, Δλ=140 nm NA = 0.5, R = 1590 nm
SNR 71 dB





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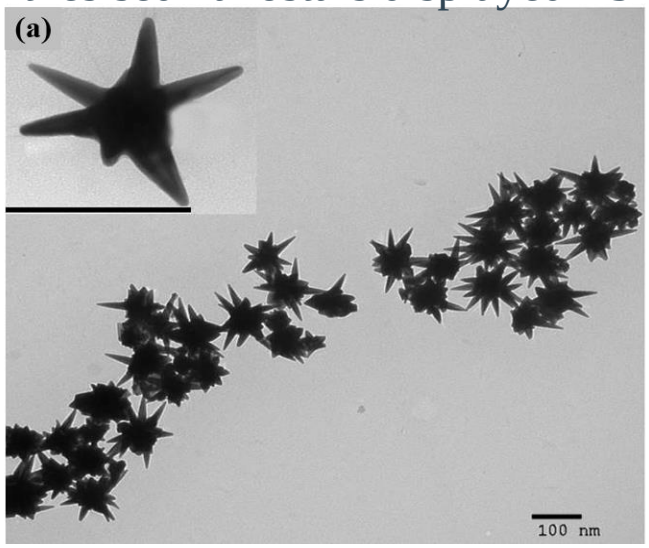
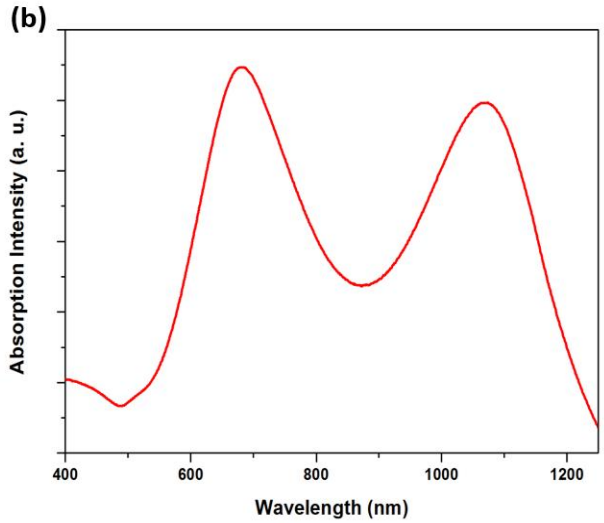
Dual Plasmonic Gold NanoStars

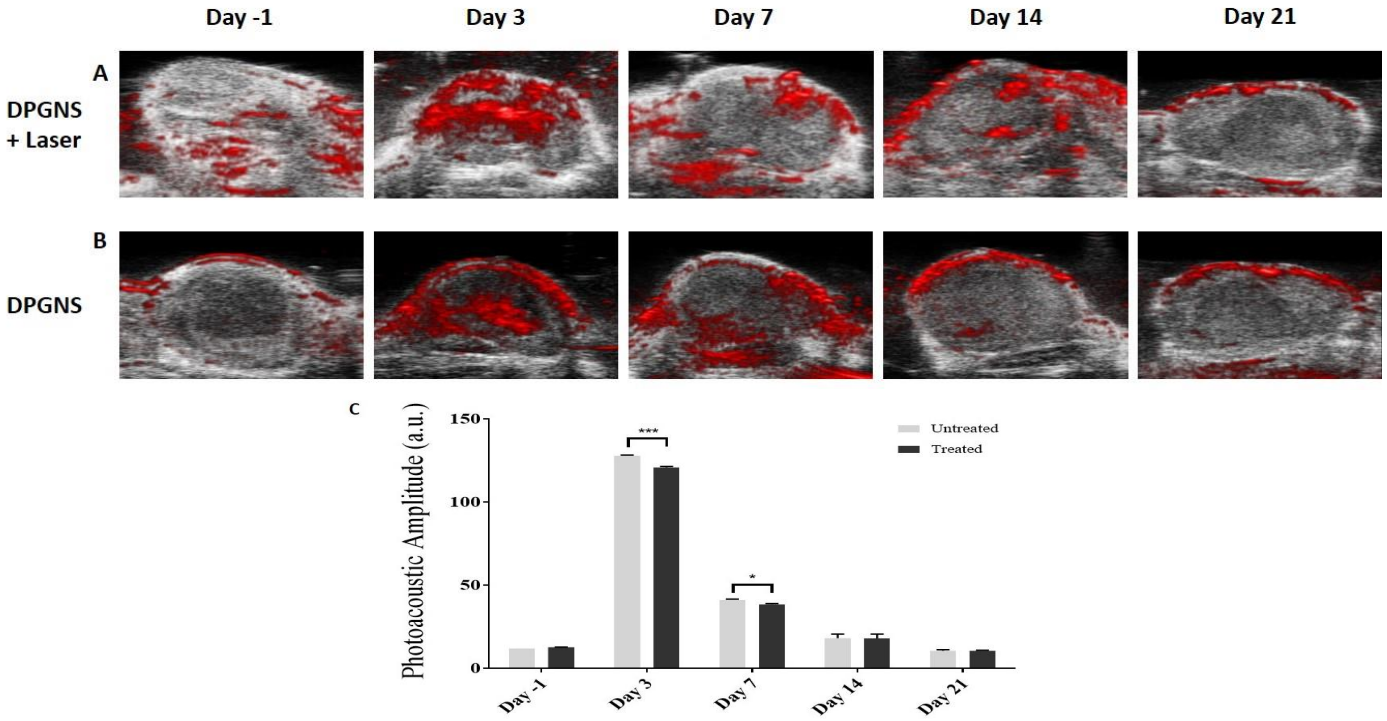
- Bimetallic configuration:
  - Silver has superior optical properties but is prone to oxidation
  - Forms FCC crystal with similar lattice constant as gold (capable of forming divisible shell geometry)
- Multibranched gold nanostars synthesised by using Ag as shape directing agents
- Synthesised nanostars displayed LSPR band in NIR





- Precursor – $HAuCl_4$ & Silver nitrate
- Reducing agent – Ascorbic acid

DPGNS – *In vivo* Photothermal Therapy



PA images of tumour administered with DPGNS followed by 1064 nm laser irradiation (A), tumour administered with only DPGNS (B); PA amplitude plot (C) for (A) and (B). Notice that the DPGNS retained in the tumour at Day 3 with optical properties intact even after laser exposure (0.5 W/cm^2 for 10 mins.)

STARSTEM

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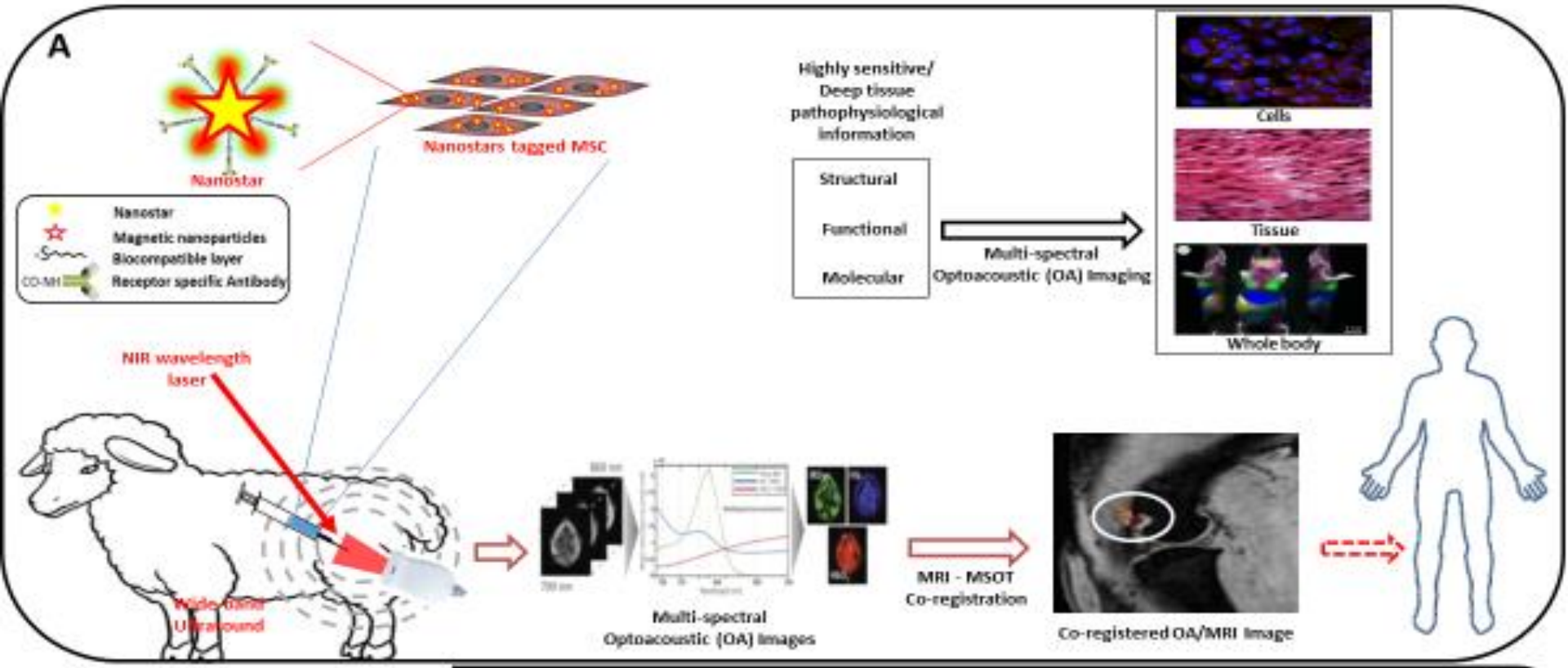

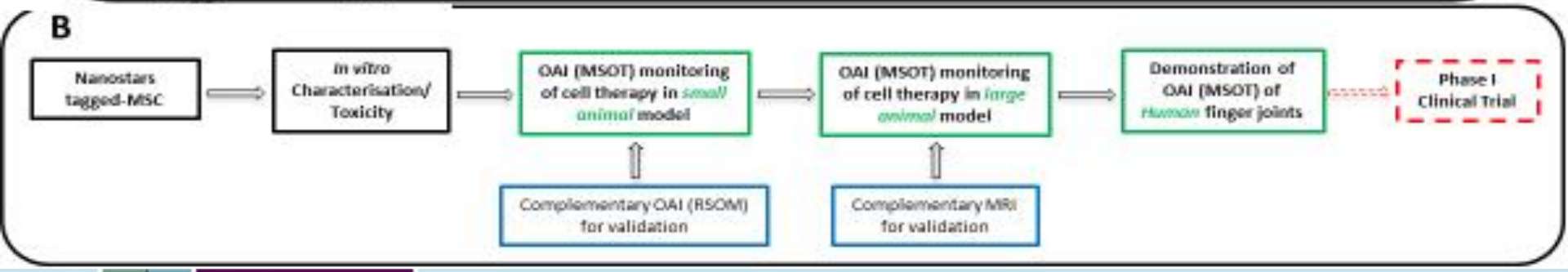

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BIGSS

BIOPHOTONICS AND IMAGING GRADUATE SUMMER SCHOOL

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2020

This is our eight Biophotonics and Imaging Graduate Summer School. It is an important opportunity for graduate students in 2020 to access the kind of close contact with leading professors that only this kind of environment facilitates. Tutors for BIGSS 2020 include:

Steve Jacques (Tufts)- Tissue optics and modelling
Wei Chen (Oklahoma) – Photothermal therapy and immunology
Paola Borri (Cardiff)– Advanced Light Microscopy.
Caroline Boudoux (Montreal)– Endoscopy
Elizabeth Hillman (Columbia)- High-speed optical imaging and microscopy of in-vivo brain function.
Stephen Boppart (Urbana-Champaign)- Optical coherence tomography
Sergio Fantini (Tufts)- Diffuse optics and applications to tissue oximetry and non-invasive brain studies
Brian Wilson (Dartmouth)- Photo Medicine, Radiation Medicine and Nano Medicine
Paul Beard + Ben Cox (London)– Photoacoustic Imaging

http://tomi.nuigalway.ie; BIGSS@nuigalway.ie

Deadline: May 16th

SPIE. The international society for optics and photonics

OSA® The Optical Society

IEEE Photonics Society *Transforming Science into Technology™*

Take away

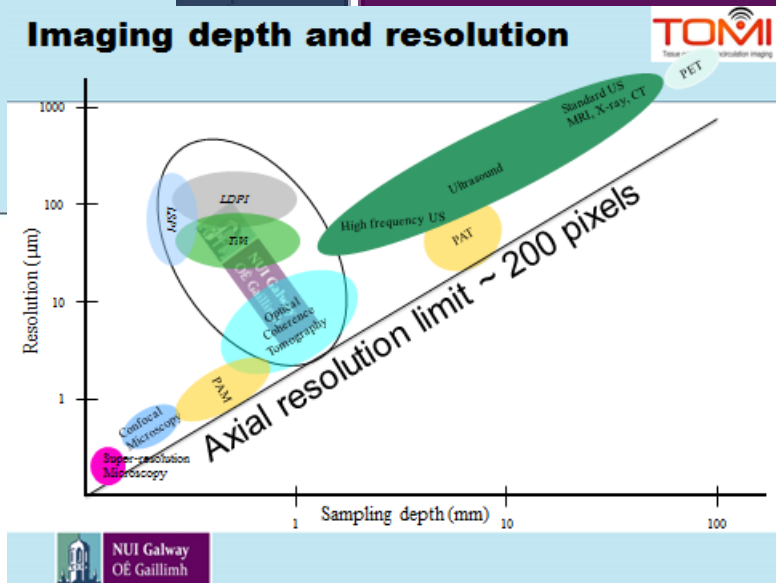
- Smallest is 1/200 of the depth
  - BUT sensitivity to smaller is possible
- Light penetration is really about scattering
- OCT decouples width from depth resolution
- FDOCT Noise advantage

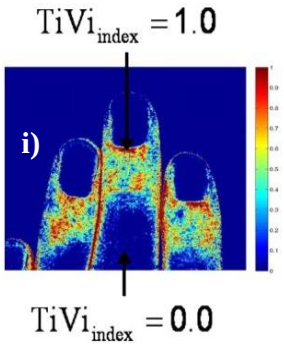
- H2020 TOPIC : Nanotechnologies for imaging cellular transplants and regenerative processes in vivo

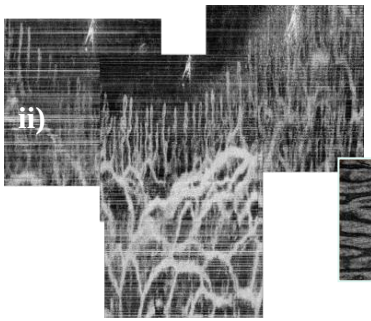
  - €6M question

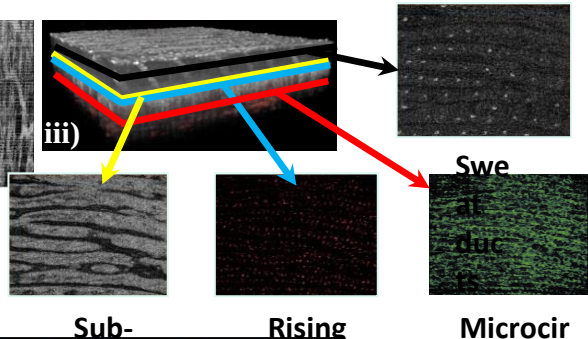
Summary

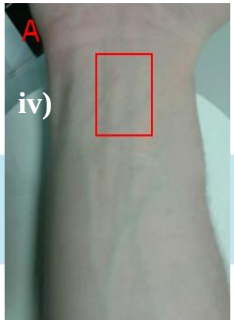
- In vivo / Ex vivo
- Scattering or non-scattering tissue?
- Depth versus resolution
- Speed – frames per second – motion?
- Functional – flow, oxygenation, molecular sensitivity
- Sub-resolution content/activity
- Fit for purpose

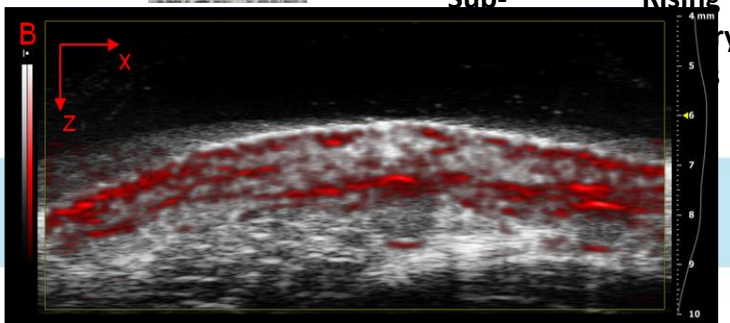


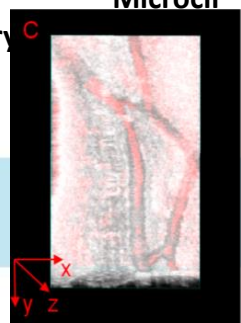












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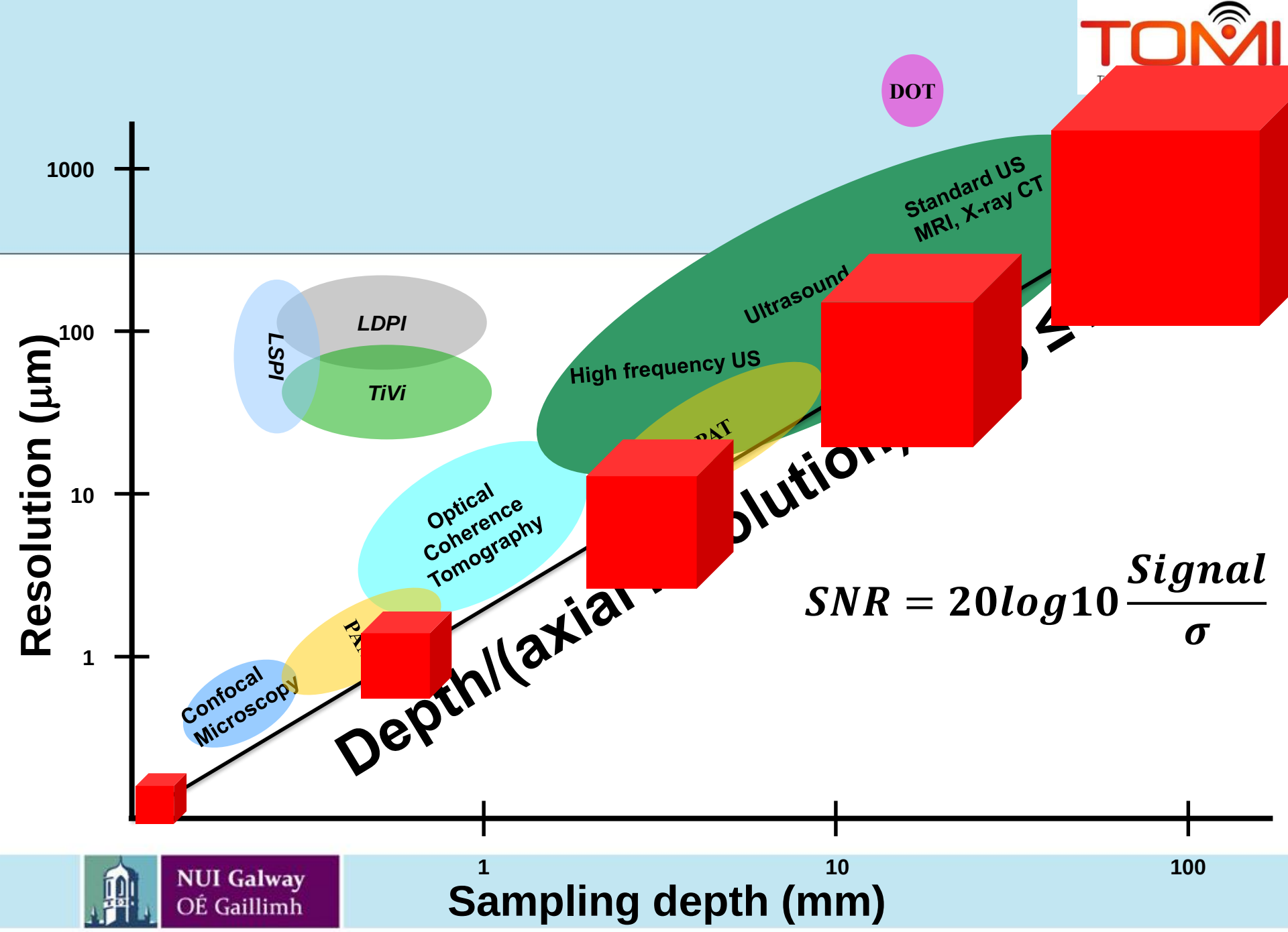

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NBIPI: Tissue Optics and Microcirculation Imag

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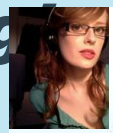
Tissue optics & microcirculation imaging



TOMI Team:

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Prof. Steve Jacques (adjunct)
Prof. Valery Tuchin (adjunct)
Dr Sergey Alexandrov
Dr Paul McNamara
Dr Nandan Das
Dr Yi Zhou
Dr Vijaya Raghavan
Rajib Dey
Seán O'Gorman

Aedán Breathnach
Anand Arangath
Soorya James
Aaron Croke
Kai Neuhaus
Cerine Lal
Gillian Lynch

Alumni:

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Dr Neil Clancy, Research Fellow, Imperial College London
Dr Joey Enfield, Senior Java Developer, Fexco
Dr David Connolly, Assistant Professor, University of Aalborg
Dr Anne-Marie Henihan, Research Fellow, University of Limerick
Dr Emmanuel Pican, Lecturer ,CIT
Dr Susan Daly, Research Fellow University of Limerick
Dr Dennis Warncke
Dr Paddy Finn, Crystal Energy
Dr Paul McNamara, NUIG - Compact Imaging
Dr Xin Gao, University of Kentucky
Dr Marie-Louise O'Connell, Irish Medicines Board
Dr Brian Kelleher, Lecturer, DCU
Dr Haroon Zafar, Galway University Hospitals
Dr Roshan Dsouza, Urbana-Champaign

Collaborators:

Fujifilm-VisualSonics, Inc.
St. Jude Medical, Inc.
Compact Imaging , Inc.
Wheelsbridge AB
iThera GmBh

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BIGSS

BIOPHOTONICS AND IMAGING GRADUATE SUMMER SCHOOL

TOMI Tissue optics & microcirculation imaging

NBIPI

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Steve Jacques (Tufts)- Tissue optics and modelling
Irving Bigio (Boston)- Nonlinear optics in spectroscopy and microscopy
Paola Borri (Cardiff)– Advanced Light Microscopy.
Caroline Boudoux (Montreal)– Endoscopy
Elizabeth Hillman (Columbia)- High-speed optical imaging and microscopy of in-vivo brain function.
Ton van Leeuwen (Amsterdam)- Optical coherence tomography
Sergio Fantini (Tufts)- Diffuse optics and applications to tissue oximetry and non-invasive brain studies
Brian Pogue (Dartmouth)- Optics in Surgery & Radiation Therapy - photochemistry/radiochemistry
Daniel Razansky (Munich)– Optoacoustic Imaging

http://tomi.nuigalway.ie; BIGSS@nuigalway.ie

Deadline: May 16th

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