BMO

BioMedical Optics

BioMedical Optics

New developments in Non-invasive Biomedical Optics

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BioMedical Optics

Non-invasive Biomedical Optics

- optical (or optically-based) techniques and instruments,
- to extract physiologically relevant information,
- from measuring physical quantities in tissue,
- in a non-invasive way, *i.e.* from the outside of the body,
- avoiding oppressing the patient ;
- quantities are:

  optical or opto-acoustical characteristics of the tissue sample (scattering, absorption, fluorescence data, molecular composition (with Raman), or velocity of blood cells or temperature etc.)

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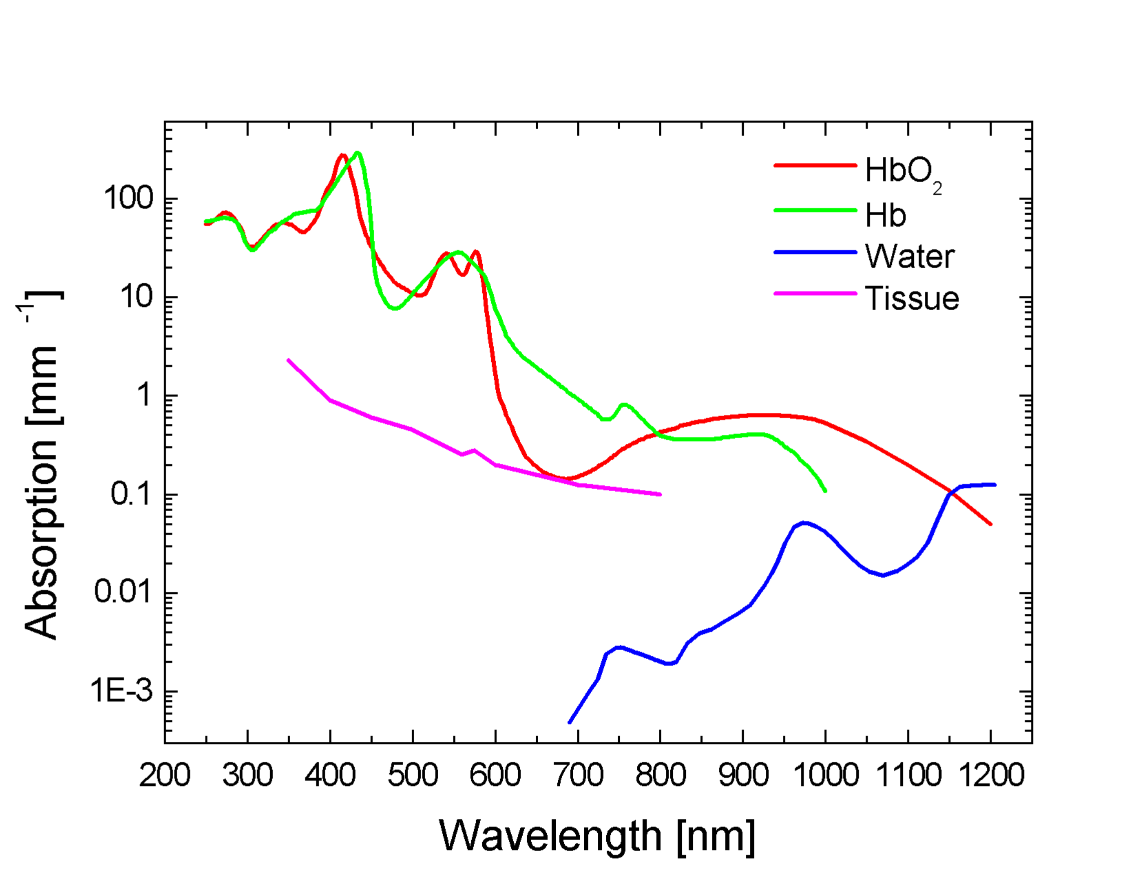
Optical properties of tissue and blood



(Reduced)
Scattering coefficient:

- λ = 580 nm:

    Dermis: 3 mm^{-1}

    Blood: 1 …

- λ = 850 nm:

    Dermis: 1 …

    Blood: 0.5 …

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Non-invasive Biomedical Optics

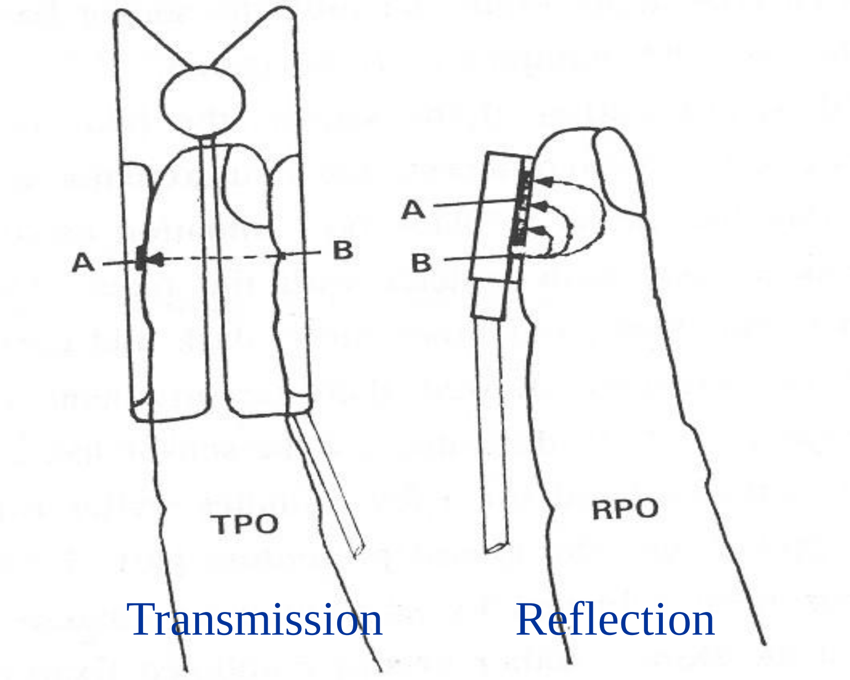
In this talk:

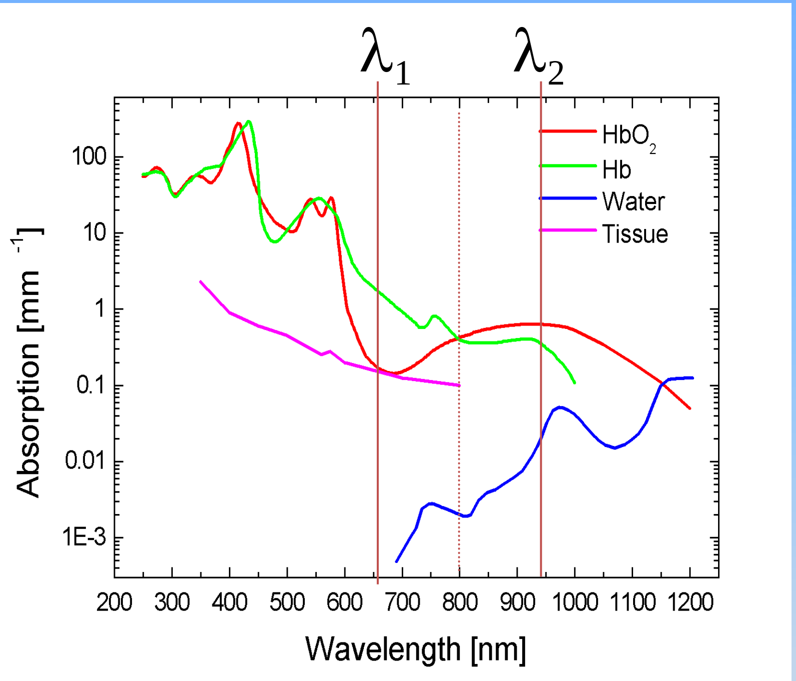
- oximetry
- *optical tomographic methods:*
  1. optical coherence tomography
  2. orthogonal polarization spectral imaging
  3. transillumination tomography:
     - time-of-flight, high-frequency modulation, continuous-wave
  4. photoacoustics
- *dynamic scattering: laser-Doppler:*
  1. laser-Doppler perfusion monitoring and imaging
  2. self-mixing laser-Doppler blood flowmetry

Oximetry

Oxygen Saturation:

$$Sa_{O_2} = \frac{c_{HbO_2}}{c_{HbO_2} + c_{Hb}}$$





Preferred wavelengths:

- 660 nm (red) ; ≈0 absorption by HbO_2
- 940 nm (IR) ; ≈ equal absorption by Hb and HbO_2

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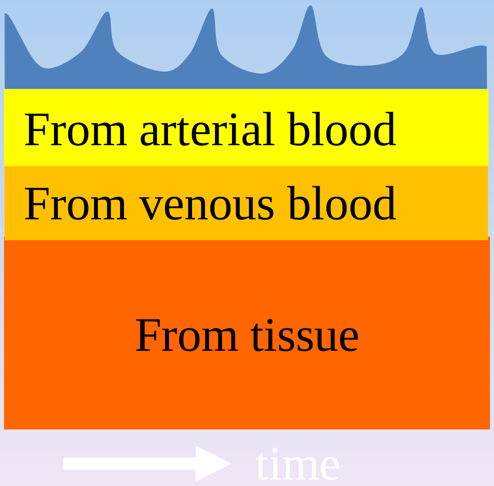
Oximetry

Pulse oximetry:

measuring pulsatile and constant blood flow.

Contributions to absorption:

From pulsatile part of arterial blood



Theory : Lambert - Beer law :

$$I(d) = I(0).\exp(-\mu_a d)$$

$$\frac{\Delta I(d)}{I(d)} = \Delta\left(\frac{\ln I(d)}{I(0)}\right) = -\mu_a.d$$

$$\frac{\Delta I_R / I_R}{\Delta I_{IR} / I_{IR}} = \frac{\mu_{a,R}}{\mu_{a,IR}}$$

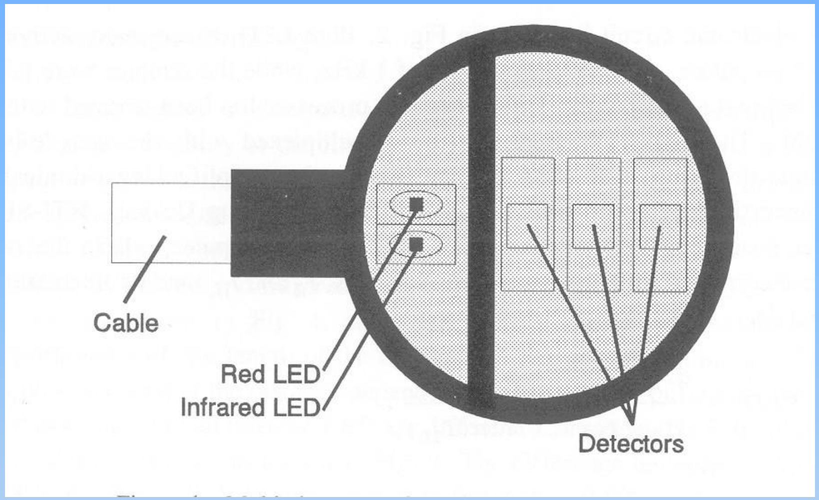
Experiment :

$$\frac{\Delta \ln I_R}{\Delta \ln I_{IR}} = \frac{\Delta I_R / I_R}{\Delta I_{IR} / I_{IR}} = \frac{(AC/DC)_R}{(AC/DC)_{IR}} = \frac{R}{IR}$$

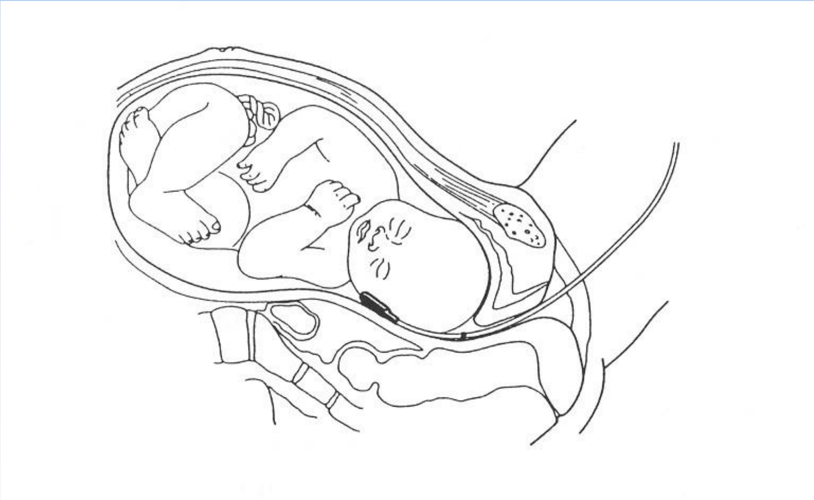
$$\Rightarrow \quad \frac{R}{IR} = \frac{\mu_{a,R}}{\mu_{a,IR}} = \frac{c_{Hb}}{c_{HbO_2} + k c_{Hb}} \quad ; \quad k \approx 1.$$

$$Sa_{O_2} = \frac{c_{HbO_2}}{c_{HbO_2} + c_{Hb}}$$

Oximetry



Reflection Pulse Oximetry
Dual-wavelength probe (*)



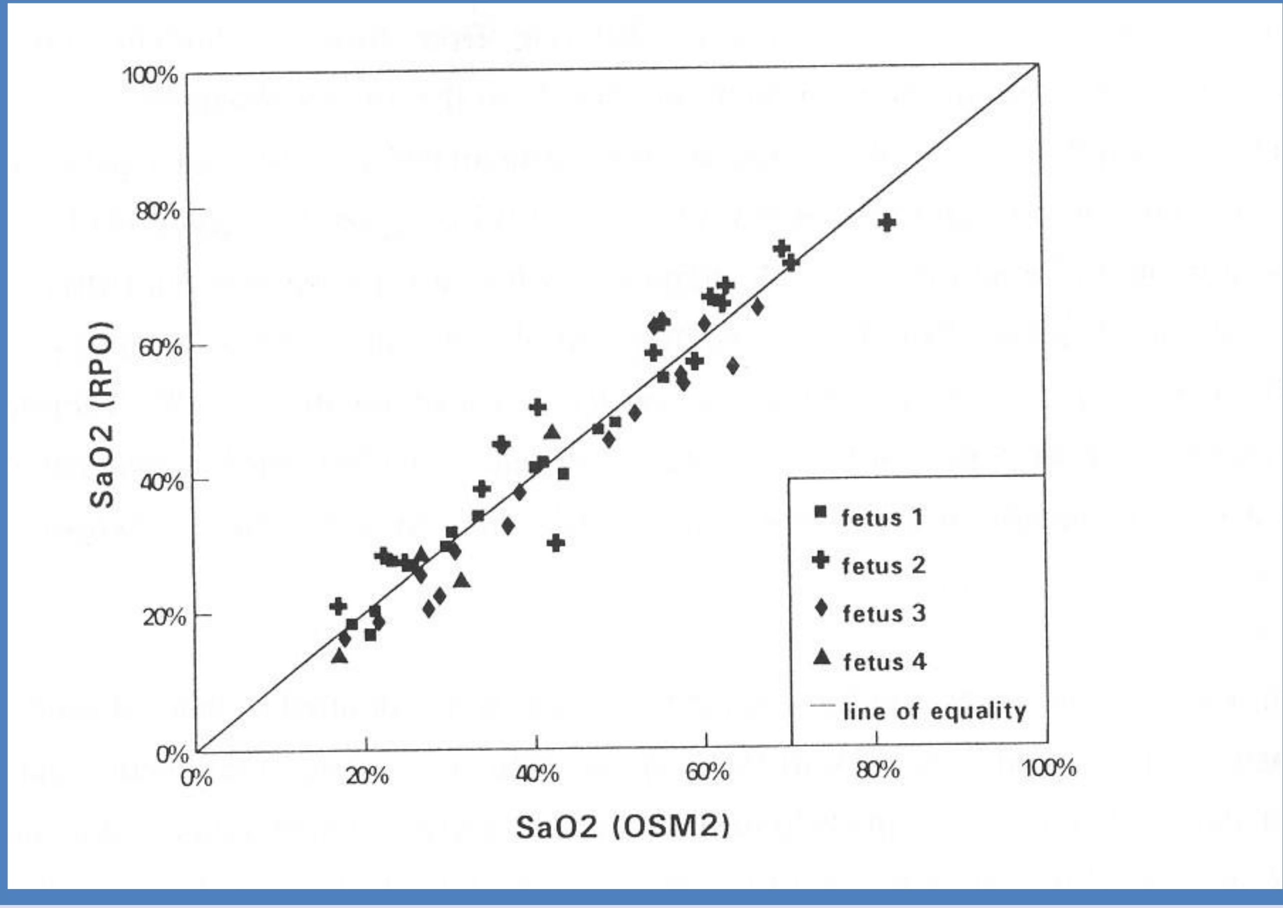
Position of the probe at fetal head

(*) Courtesy: R. Graaff, Academic Hospital Groningen, Netherlands

Oximetry

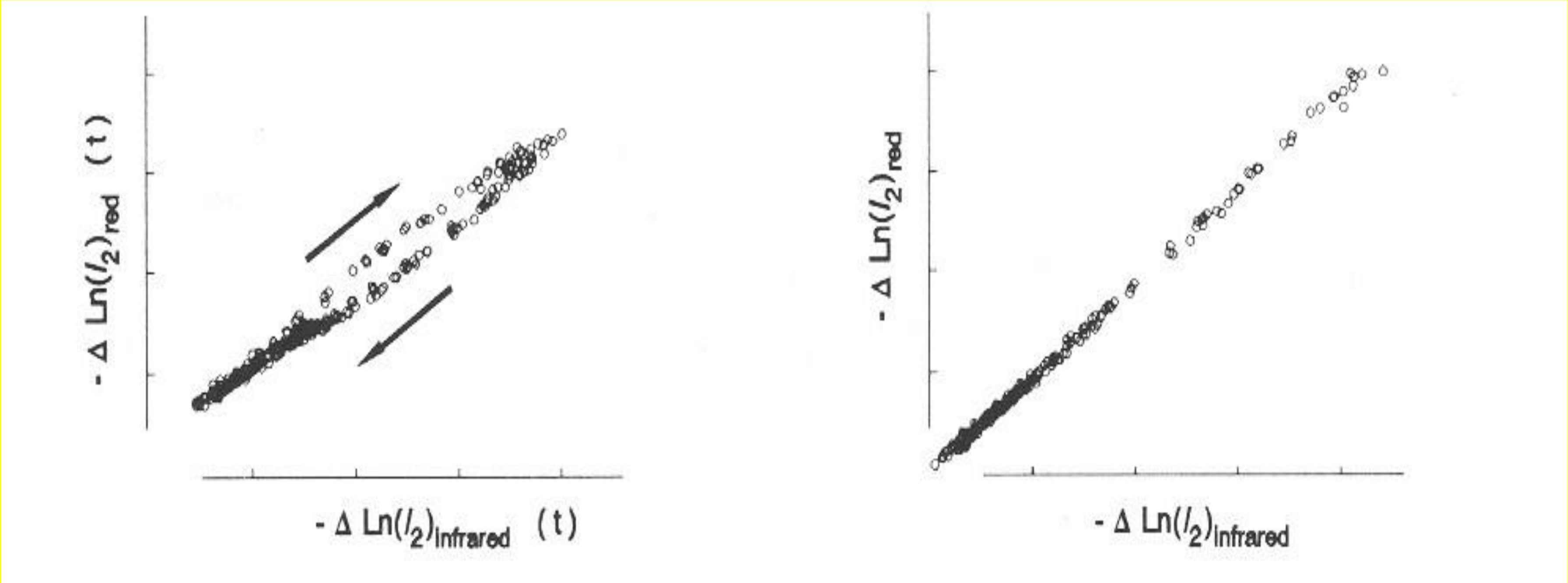
Fetal scalp

Calibration against blood samples



Courtesy: R. Graaff, C. Dassel, Academic Hospital Groningen, Netherlands

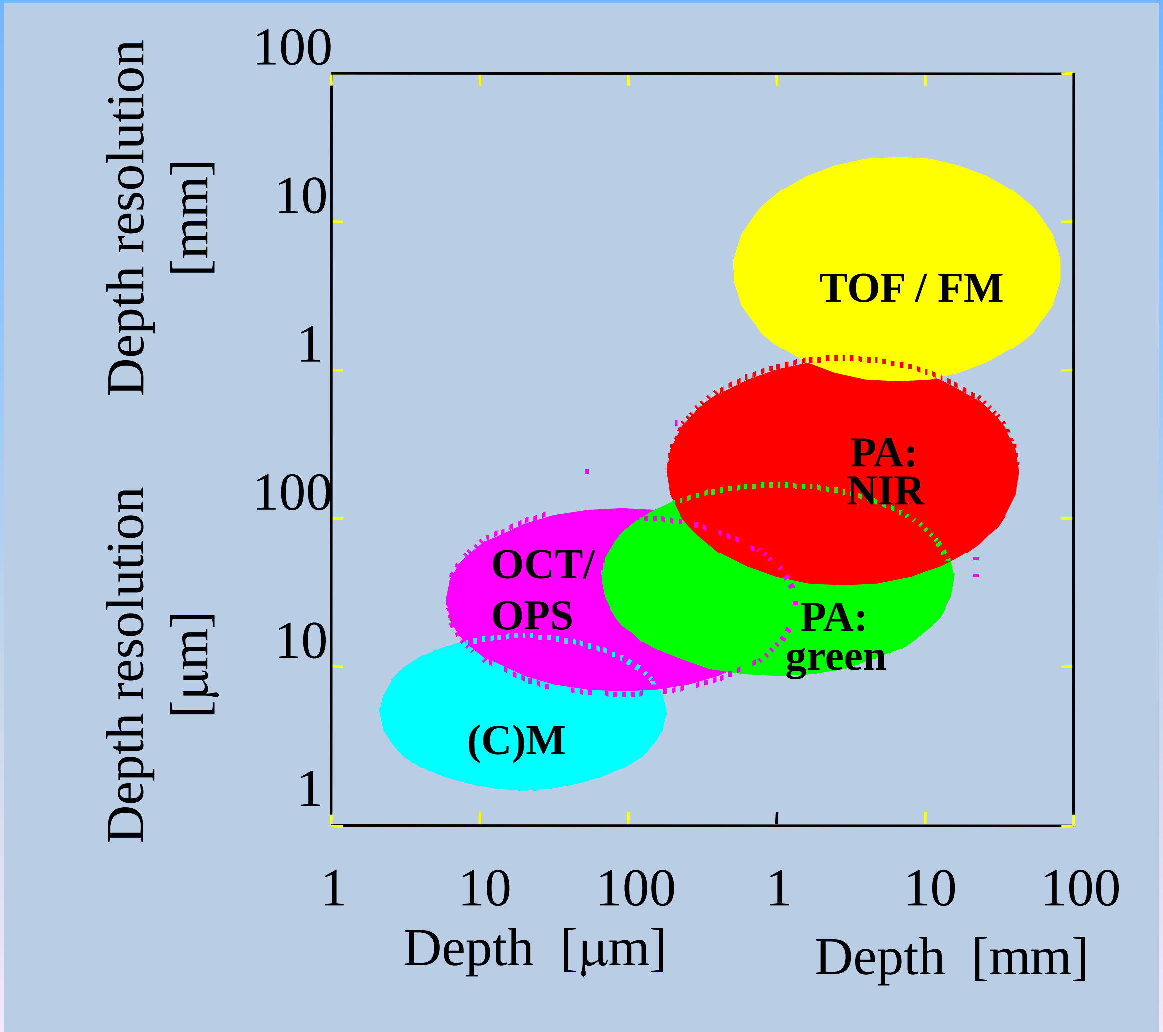
Oximetry



Heart-cycle fluctuations in red vs. infrared signal, measured at index finger of healthy subject.
Left vs. right panel: without / with pressure on the probe
More "red" means: less saturation

Courtesy: R. Graaff, C. Dassel, Academic Hospital Groningen, Netherlands

Imaging methods for hidden structures in turbid media (tissue)



C(M) : (confocal) microscopy

OCT: optical coherence tomography

OPS: orthogonal polarization spectral imaging

PA: photoacoustics

TOF: time-of-flight tomography

FM: frequency-modulated tomography

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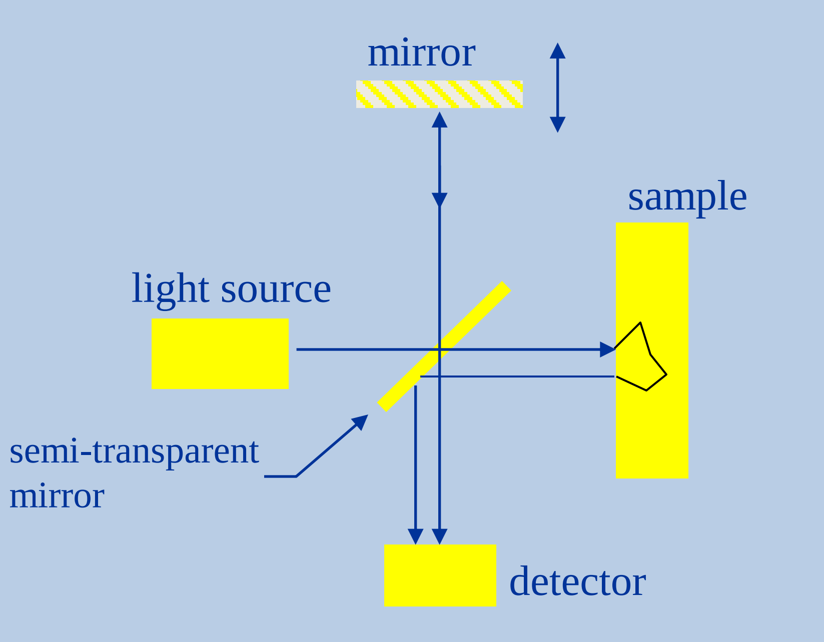
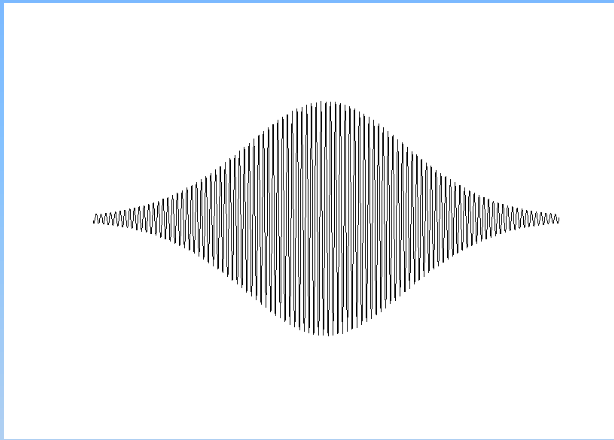
Optical Tomographic Methods:
1. Optical Coherence Tomography

Interferometer





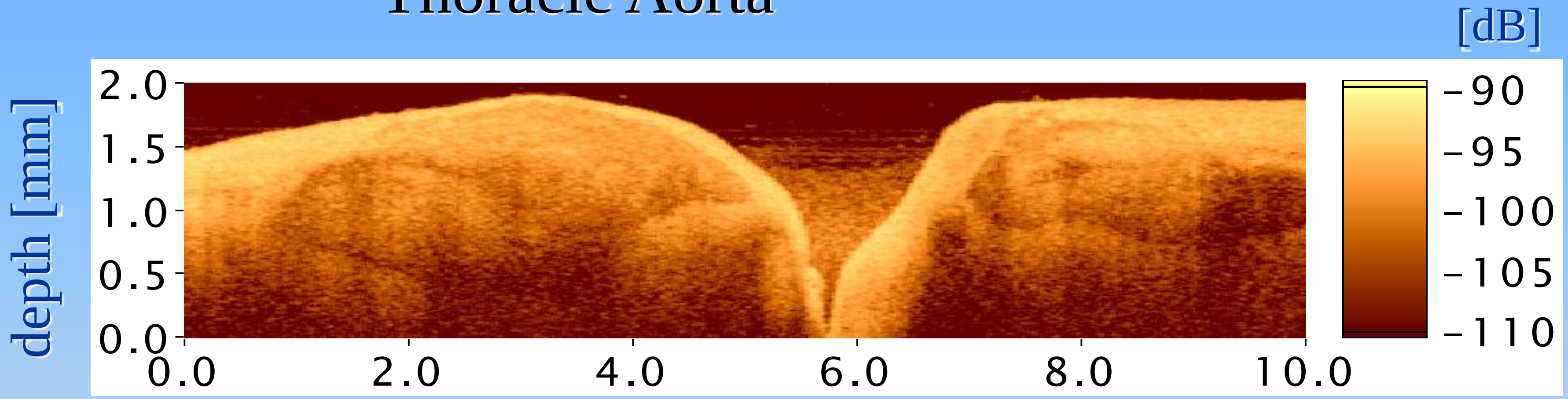
Wave package of a short-coherence light source

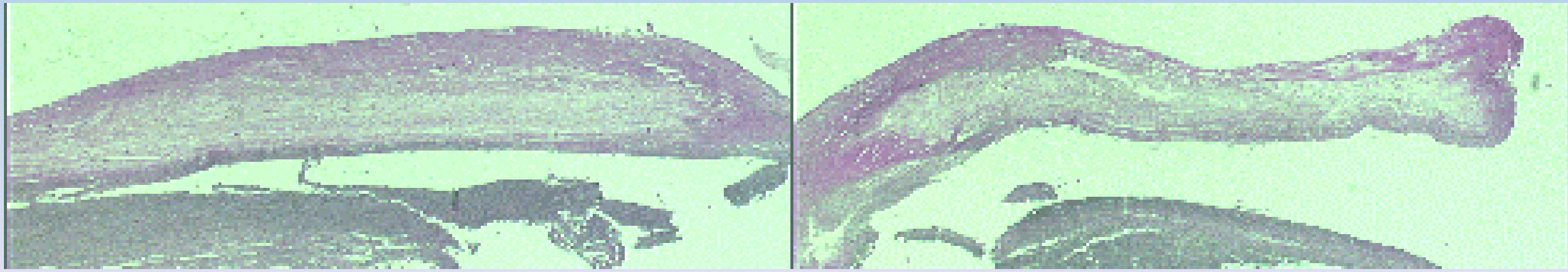
Interferometer setup:

- Detector will record only when signals from reference mirror and from sample overlap
- Scanning mirror enables depth resolution (≈ 10 μm)
- Maximum depth ≈ 1.0 mm

Optical Tomographic Methods:
1. Optical Coherence Tomography

Thoracic Aorta





histology

(T. Van Leeuwen, Acad. Med. Centr. Amsterdam)

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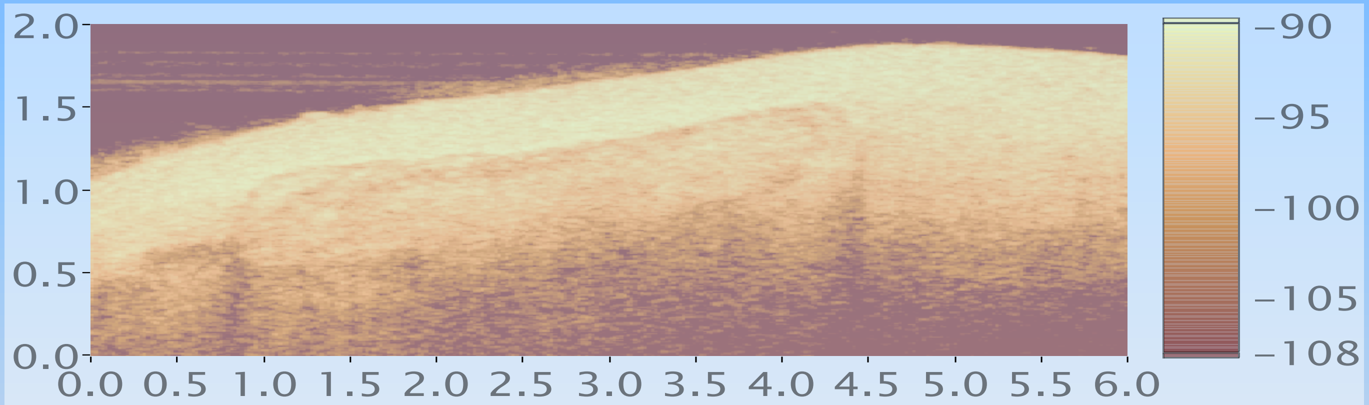
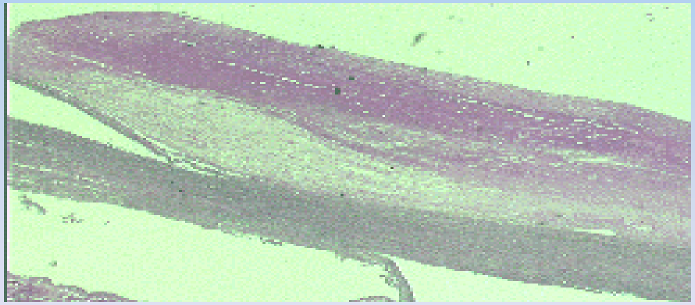
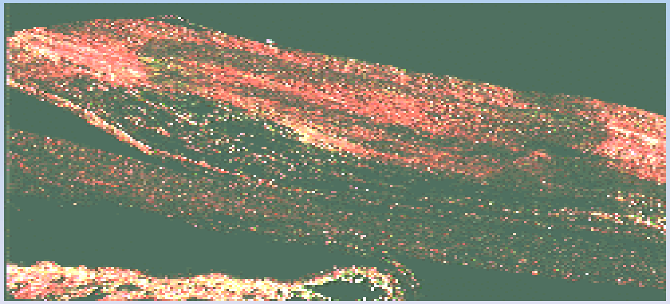
Optical Tomographic Methods: 1. Optical Coherence Tomography

Lesion in intima vessel

OCT-image







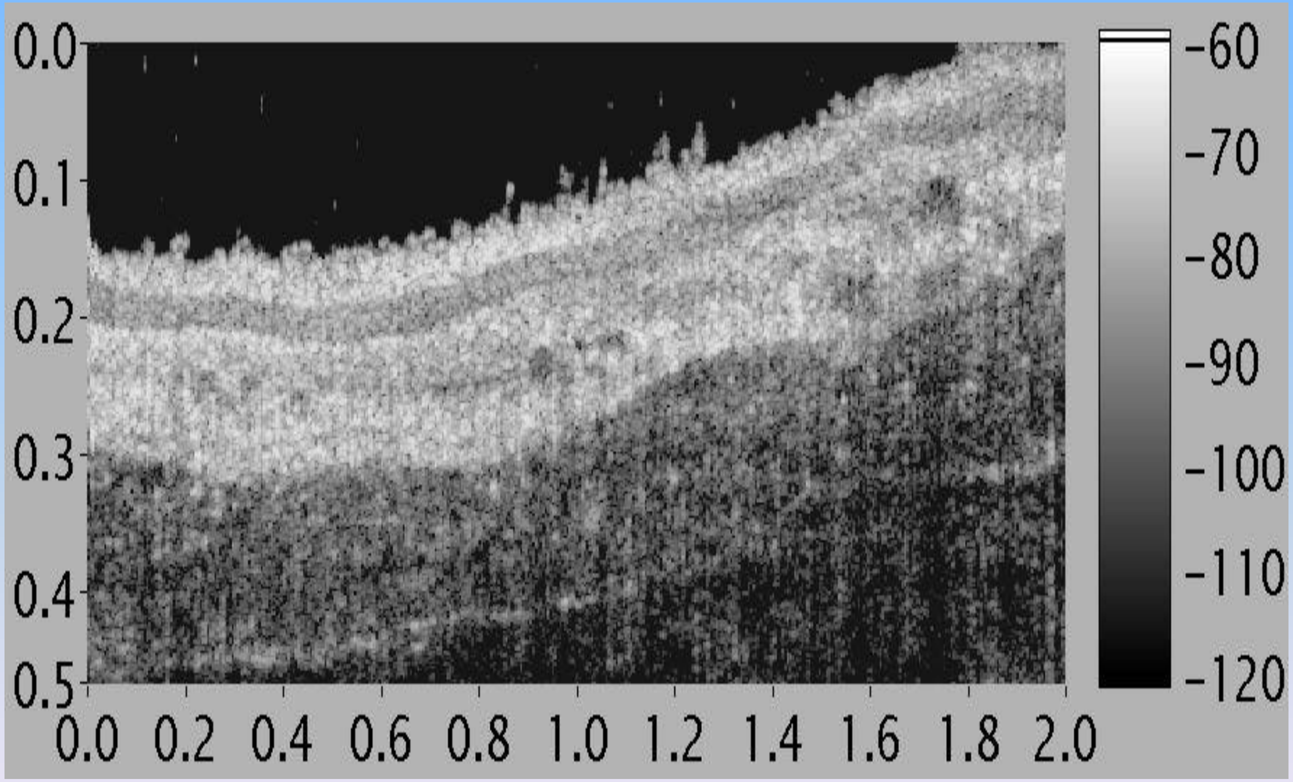
Histology

Birefringe microscopy

(T. Van Leeuwen, Acad. Med. Centr. Amsterdam)

Optical Tomographic Methods:
1. Optical Coherence Tomography

Rat Esophagus



Depth [mm]

Width [mm]

(T. Van Leeuwen, Acad. Med. Centr. Amsterdam)

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Optical Tomographic Methods:
1. Optical Coherence Tomography

Options :

- Color Doppler OCT
  (measures blood velocity profiles)
- Elastographic OCT
  (measures blood shear rates)
- Polarization OCT
  (measures birefringe effects in tissue layers)

Optical Tomographic Methods:
1. Optical Coherence Tomography

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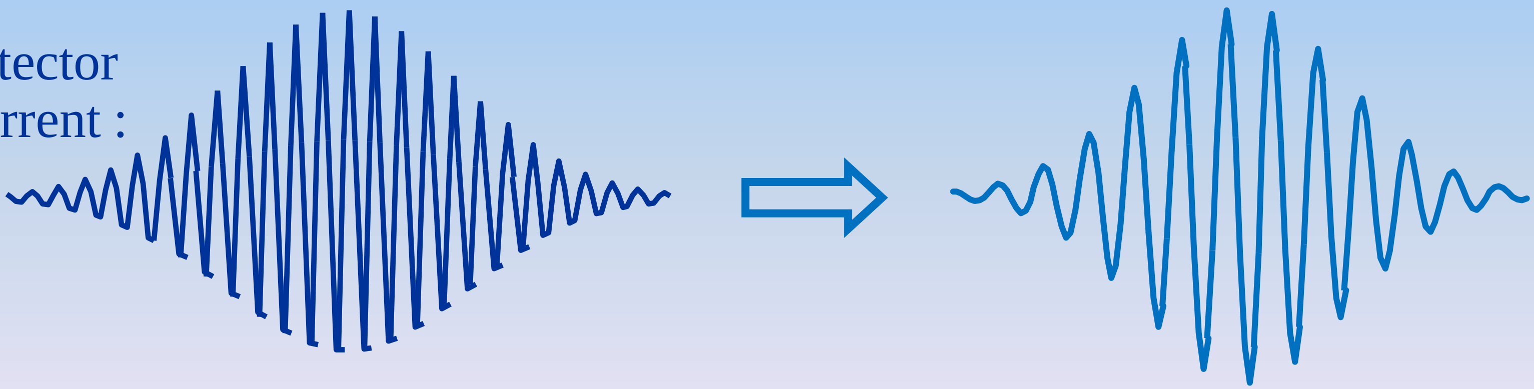
Option: Color Doppler OCT measures velocity V_s of blood cells, flowing under angle θ with direction of incident laser beam

$$\text{Doppler frequency} = \frac{2\,V\,n\cos\theta}{\lambda}$$

wavelength = λ
medium :
refract.index = n

Detector Current :

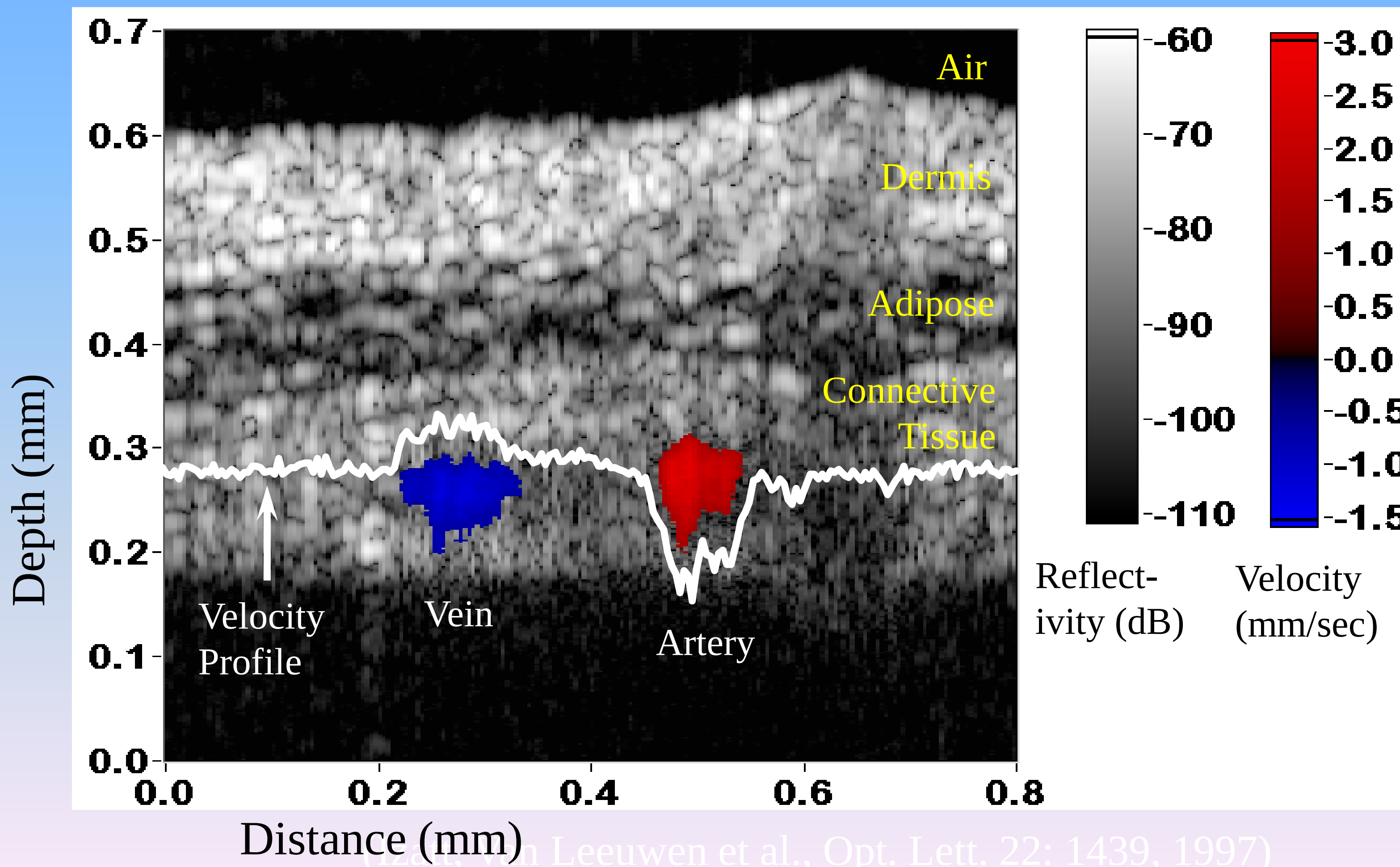


Doppler frequency = frequency difference.

(T. Van Leeuwen, Acad. Med. Centr. Amsterdam)

Optical Tomographic Methods:
1. Optical Coherence Tomography

Doppler OCT in intact *in vivo* Hamster skin tissue



(Izatt, van Leeuwen et al., Opt. Lett. 22: 1439, 1997)

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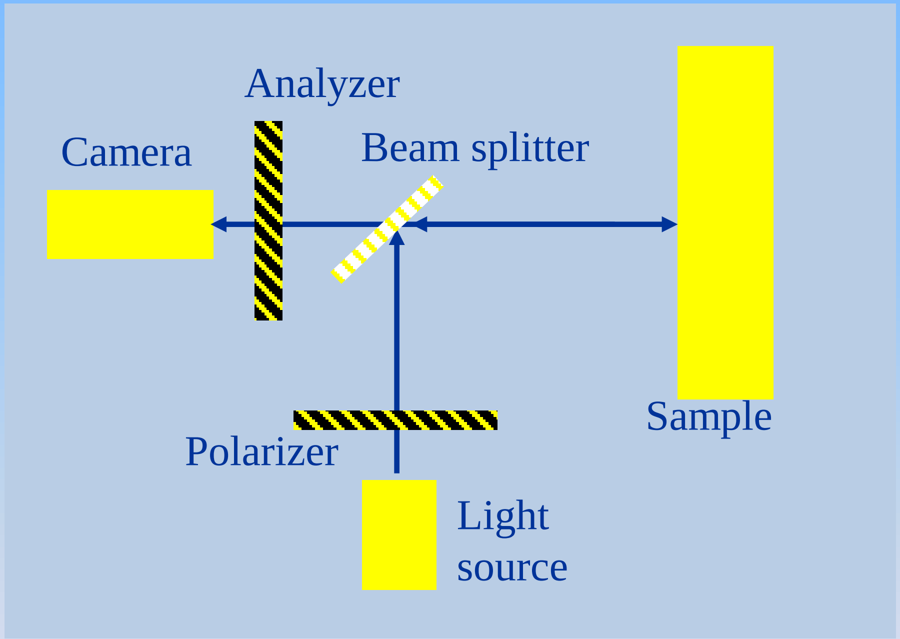
Optical Tomographic Methods: 2. Orthogonal Polarization Spectral Imaging



Analyzer and polarizer orthogonal

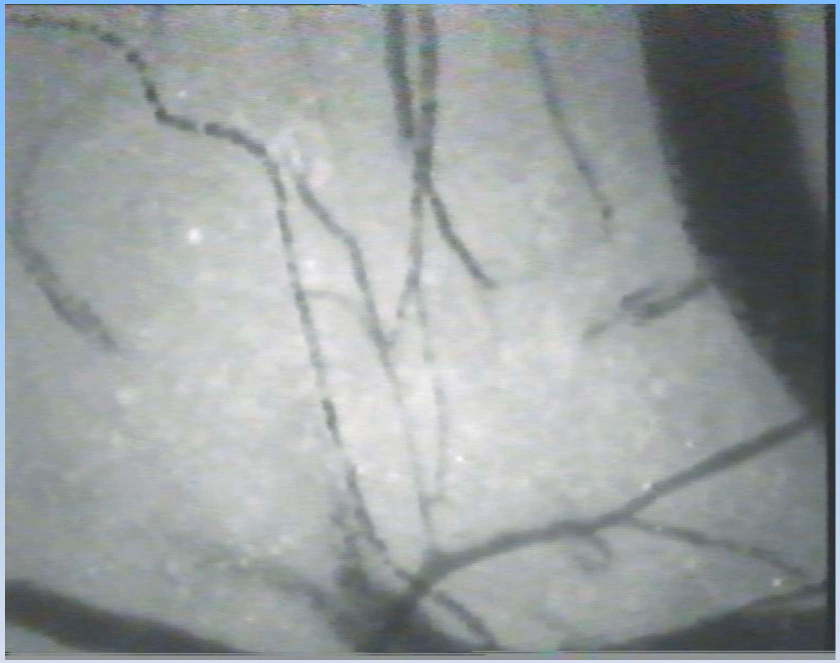
About 10 scattering events needed for complete de-polarization.

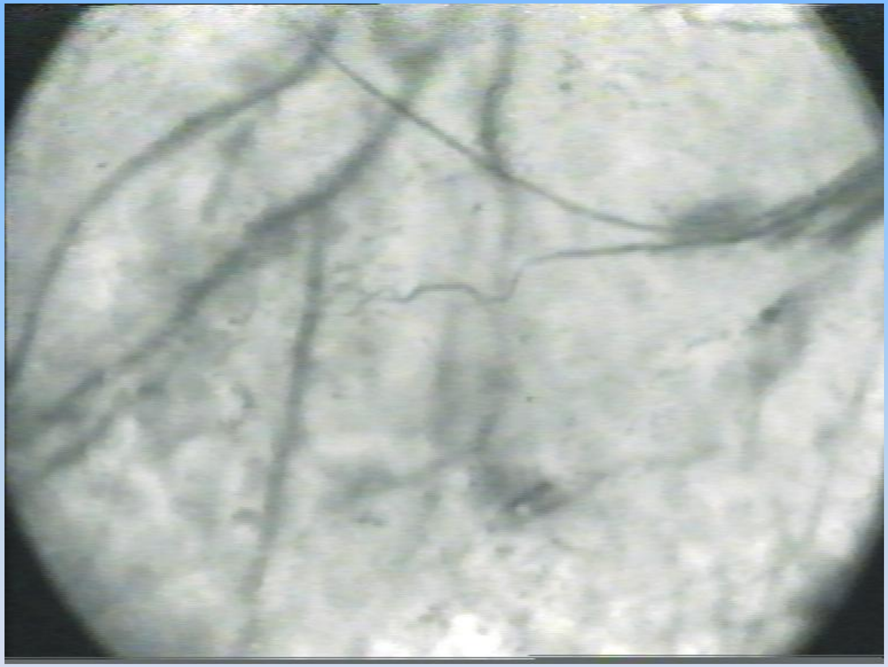
Green light: preferentially absorbed in blood cells (=> shadow view)

View field ≈ 1 mm ∅

Maximum Depth ≈ 0.5 mm

Optical Tomographic Methods:
2. Orthogonal Polarization Spectral Imaging

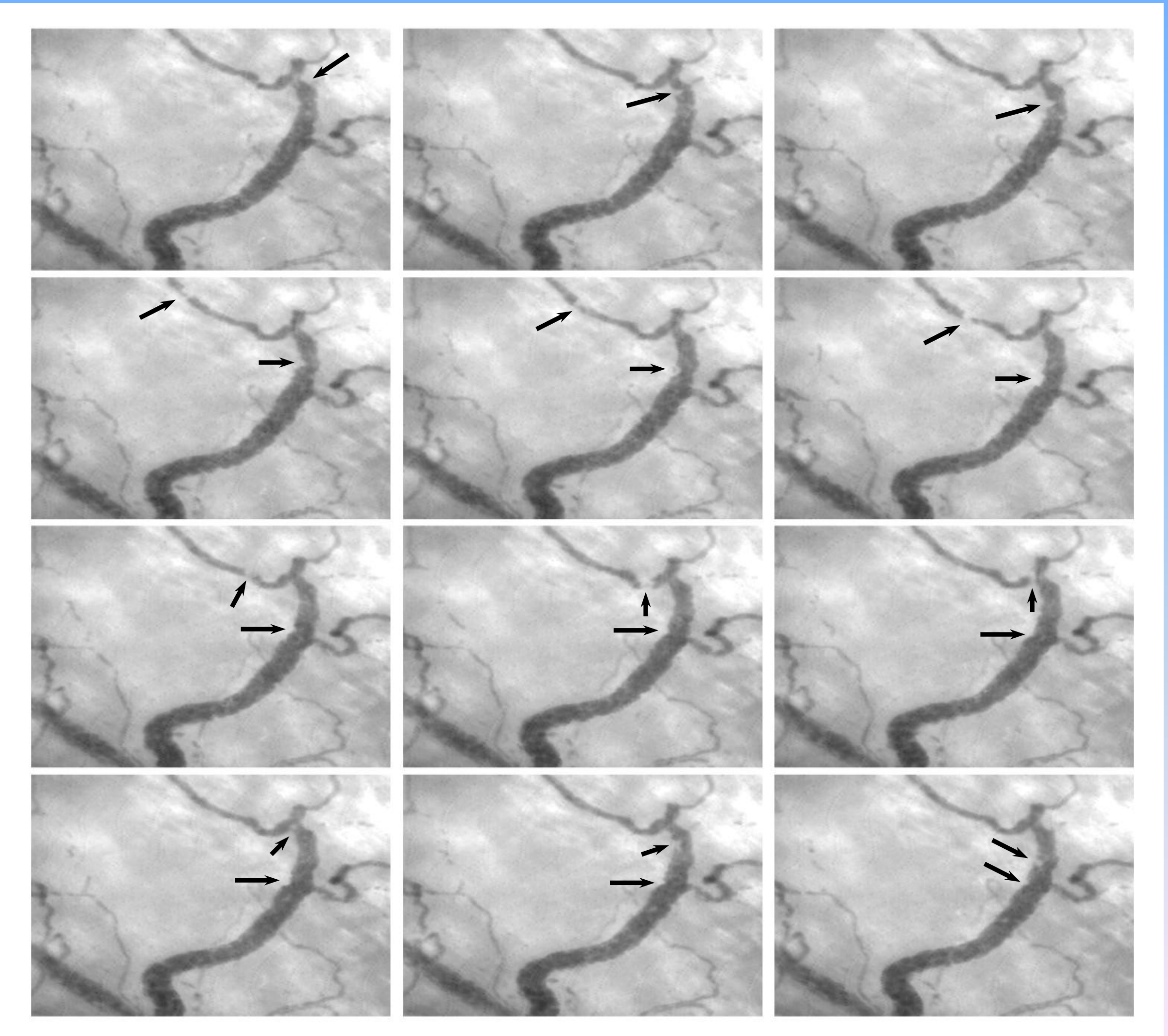




Capillary structure from under tongue of healthy person.

(T. Van Leeuwen, Acad. Med. Centr. Amsterdam)

Optical Tomographic Methods:
2. Orthogonal Polarization Spectral Imaging



Rolling and sticking leukocytes

Mathura K and Ince C (2000)
In: Prog. Appl. Microcirc.,
Ed. K. Messmer, Publ. Karger, Vol. 24

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Non-invasive Biomedical Optics

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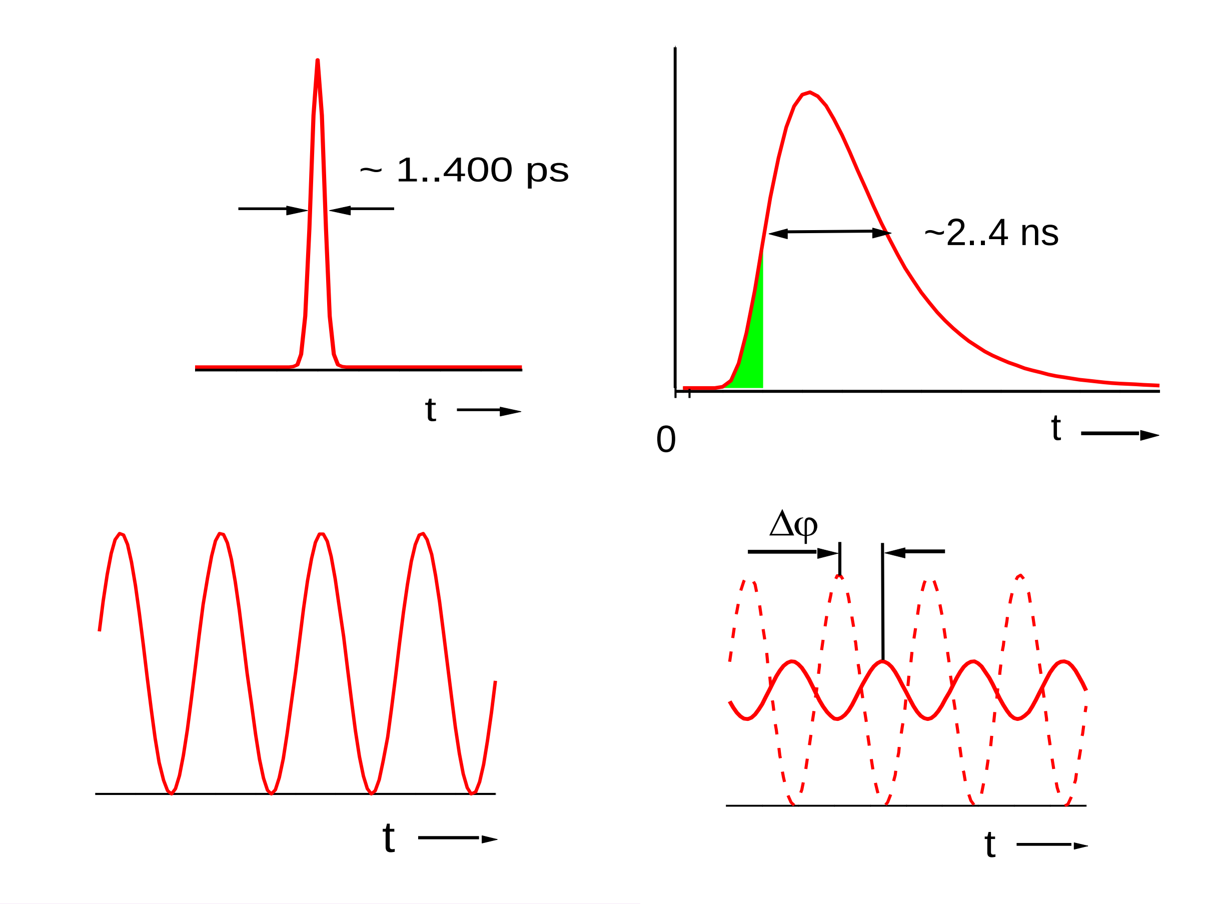
Optical Tomographic Methods:
3. Photon-transillumination methods



Time-of-flight:
emerging photons delayed by scattering

Frequency modulation:
phase lagging due to path length

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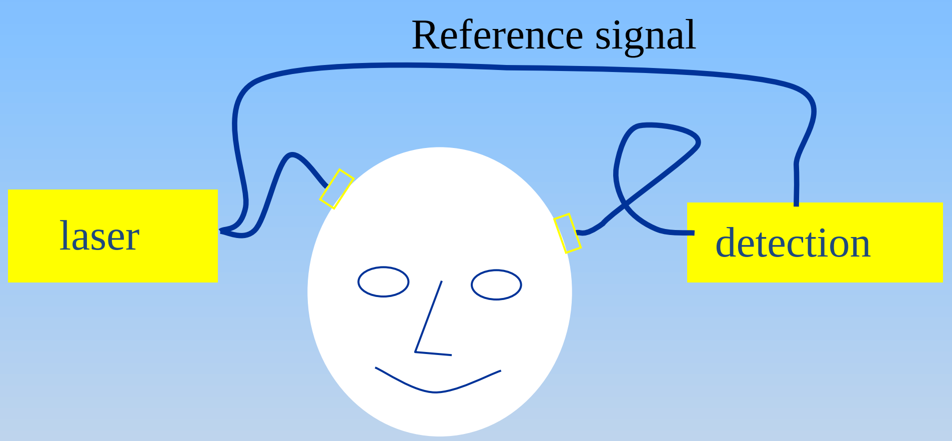
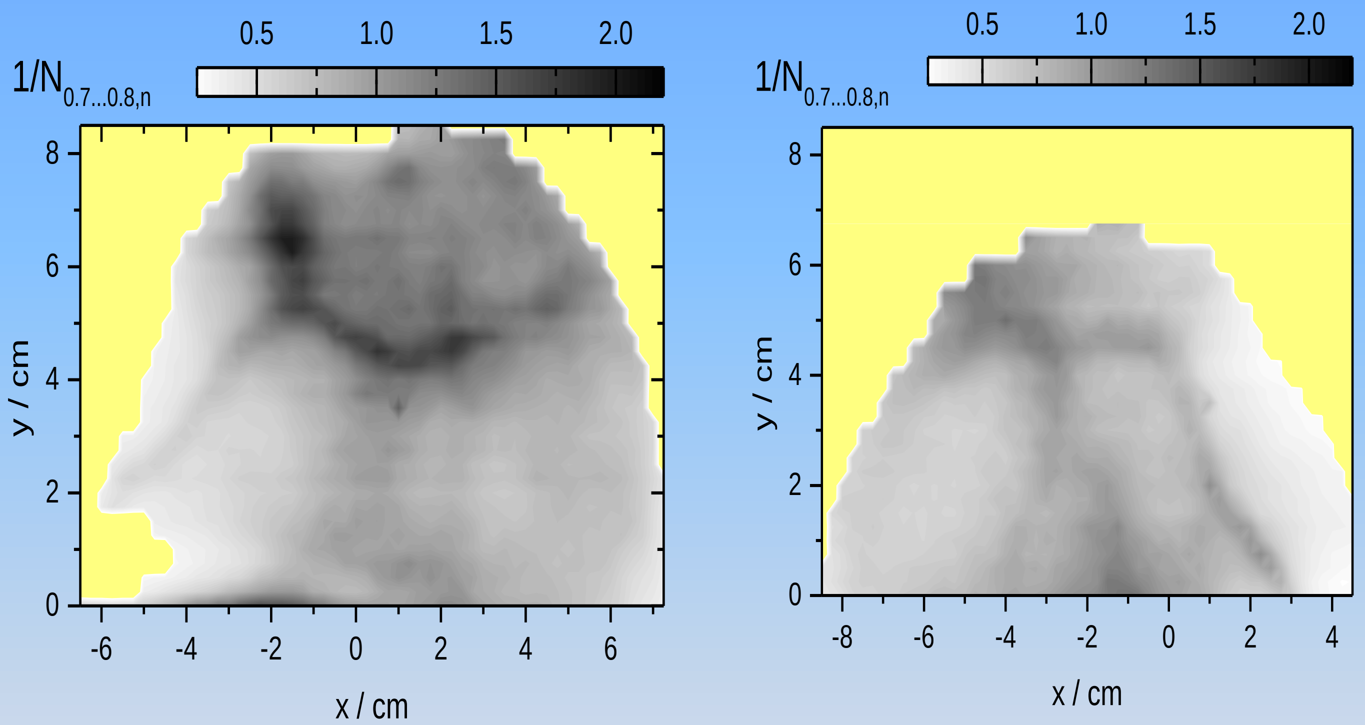
Optical Tomographic Methods:
3. Photon-transillumination methods



Either the time-of-flight or the phase/modulation depth differences between the scattered signal and the reference signal are measured.

Light transport preferentially using glass fibers.

Optical Tomographic Methods: 3. Photon-transillumination methods



Optical Mammography using pulsed time-of-flight technique.

Left: left breast with invasive ductal carcinoma and blood vessels;

Right: healthy breast

(courtesy prof. H. Rinneberg, Physikalisch Technische Bundesanstalt Berlin)

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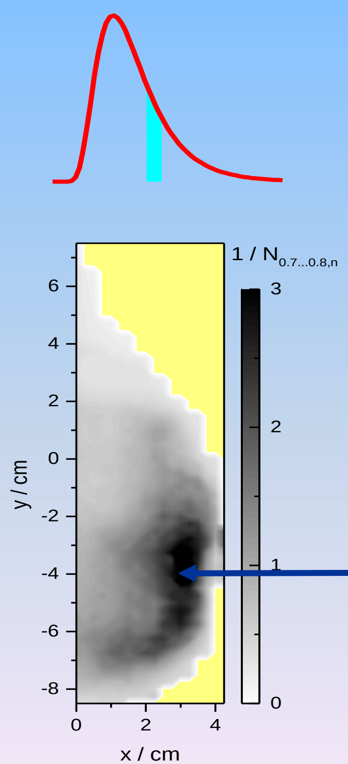
Optical Tomographic Methods:
3. Photon-transillumination methods

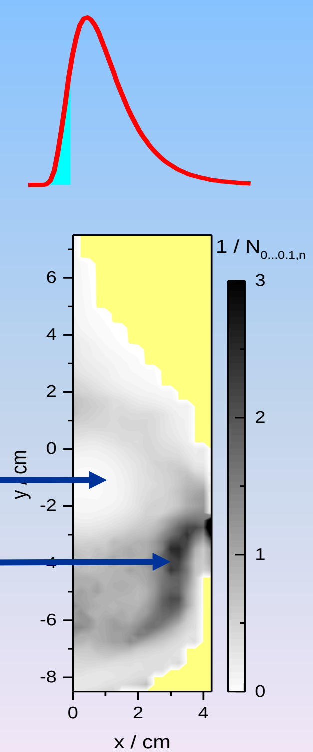
Optical Mammography:

Patient · 50 years old · invasive ductal carcinoma

(pT2, G2) 4 x 4 x 2.5 cm^3 ; cyst ∅ 3 cm ; breast thickness 6.2 cm / 5.7 cm



late time window



early time window

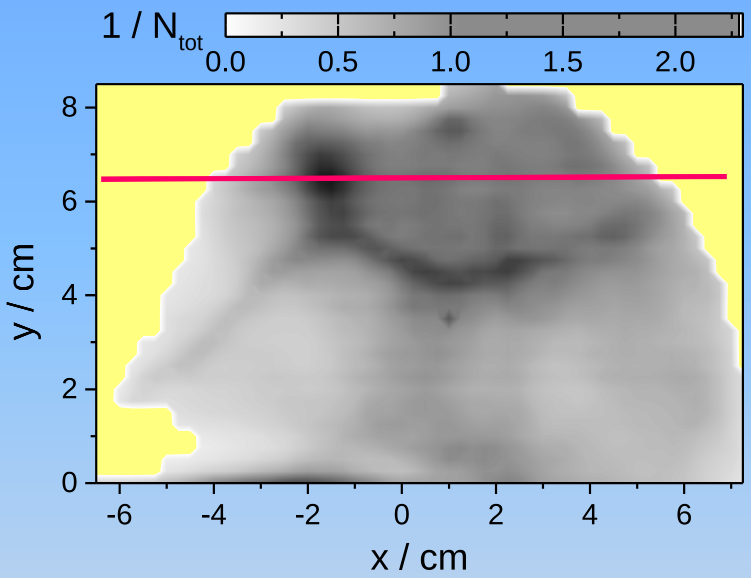
cyst

tumor

λ = 785 nm

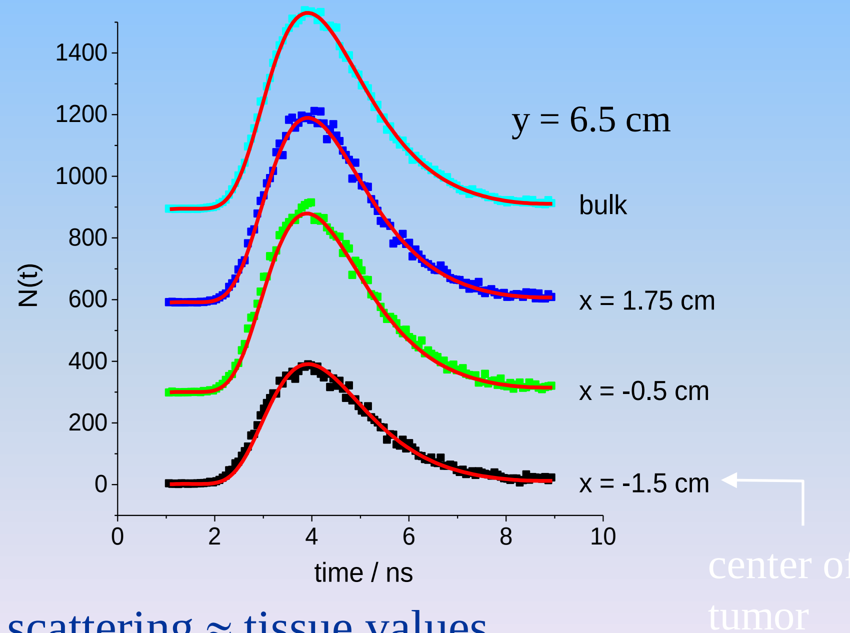
(courtesy prof. H. Rinneberg, Physikalisch Technische Bundesanstalt Berlin)

Optical Tomographic Methods:
3. Photon-transillumination methods



Line scan across breast tumor

right breast
(total photon counts, corrected for edge effects)



Diffusion theory:

homogeneous infinite slab with spherical inhomogenity

Fit to measured distributions

(10 distributions simultaneously)

Results: in tumor: absorption ≈ 2.5 x as high, scattering ≈ tissue values

(courtesy prof. H. Rinneberg, Physikalisch Technische Bundesanstalt Berlin)

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Optical Tomographic Methods: 3. Photon-transillumination methods

Oxygen saturation in tissue

$$\mu_a = \left(c_{HbO_2}\varepsilon_{HbO_2} + c_{Hb}\varepsilon_{Hb}\right)\cdot \ln 10 + \kappa_{H_2O}\cdot \mu_{a,H_2O}$$

$\rightarrow \geq 3$ wavelengths necessary , or ...

- 2 wavelengths (670 nm, 785 nm)
- assumption: $\kappa_{H2O} = 30\ \%$
- slab with sphere $\rightarrow \mu_{a,tumor}(\lambda), \mu_{a,normal}(\lambda)$

$$S = \frac{c_{HbO_2}}{c_{Hb} + c_{HbO_2}}$$

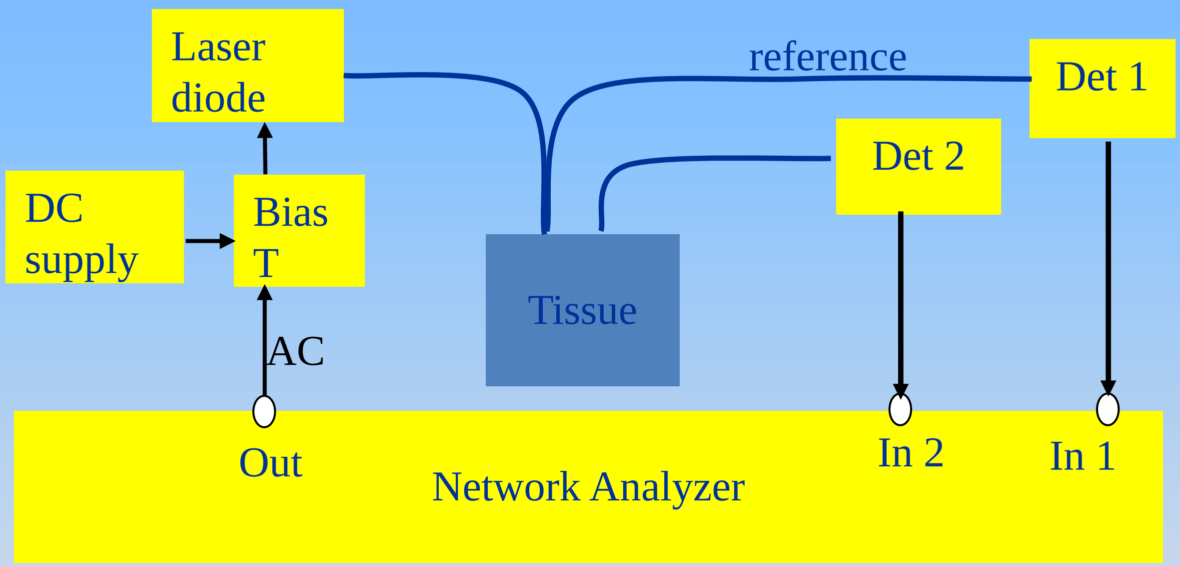
Normal tissue		Tumor tissue	
c_{tHb} (µmol/l)	S (%)	c_{tHb} (µmol/l)	S (%)
14	63	25	55

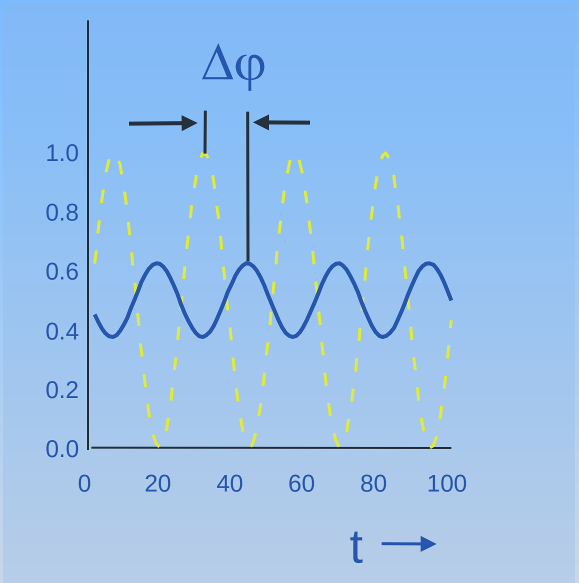
tumor hypoxic

(courtesy prof. H. Rinneberg, Physikalisch Technische Bundesanstalt Berlin)

Optical Tomographic Methods:
3. Photon-transillumination methods

High-frequency modulation provides phase and path information





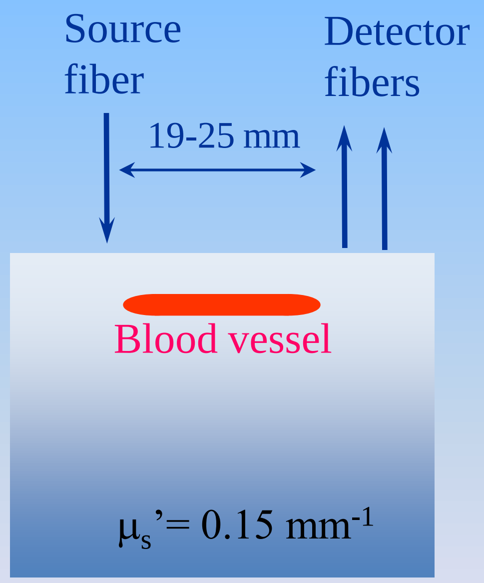
Differences in composition of the tissue sample
causes differences in phase $\Delta\varphi$ as function of frequency

Actual accuracy at 100 MHz: 1 % in scattering → 10-30 mM glucose
Expected at 1 GHz: factor 10 better

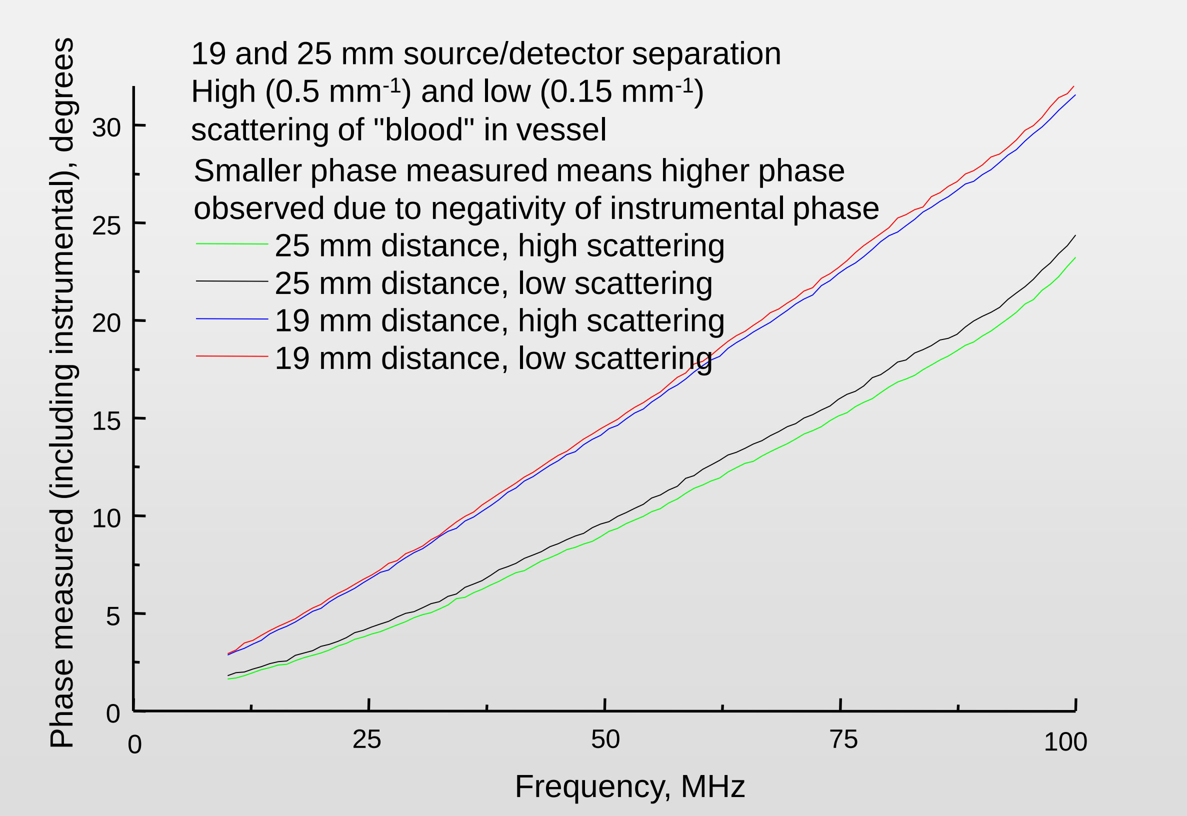
Optical Tomographic Methods:
3. Photon-transillumination methods

High-frequency modulation provides phase and path information,

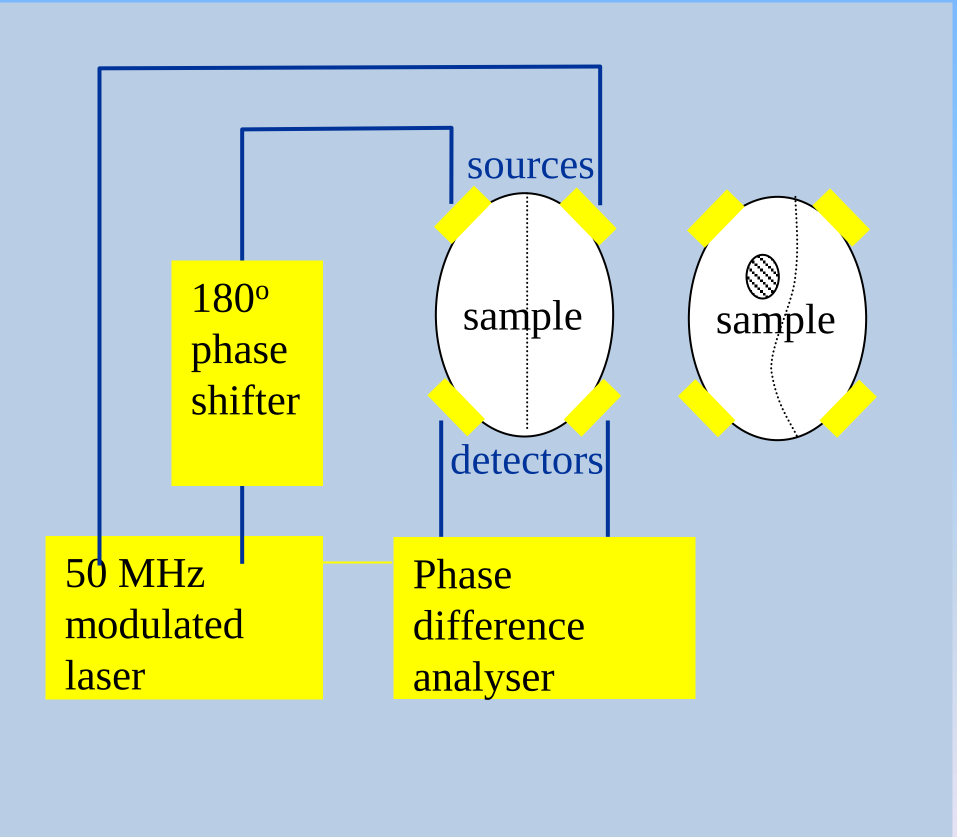
=> Scattering and absorption data => localisation of inhomogeneities



Blood vessel:
diameter 2 mm,
depth 2 mm



Optical Tomographic Methods:
3. Photon-transillumination methods



Frequency modulation:

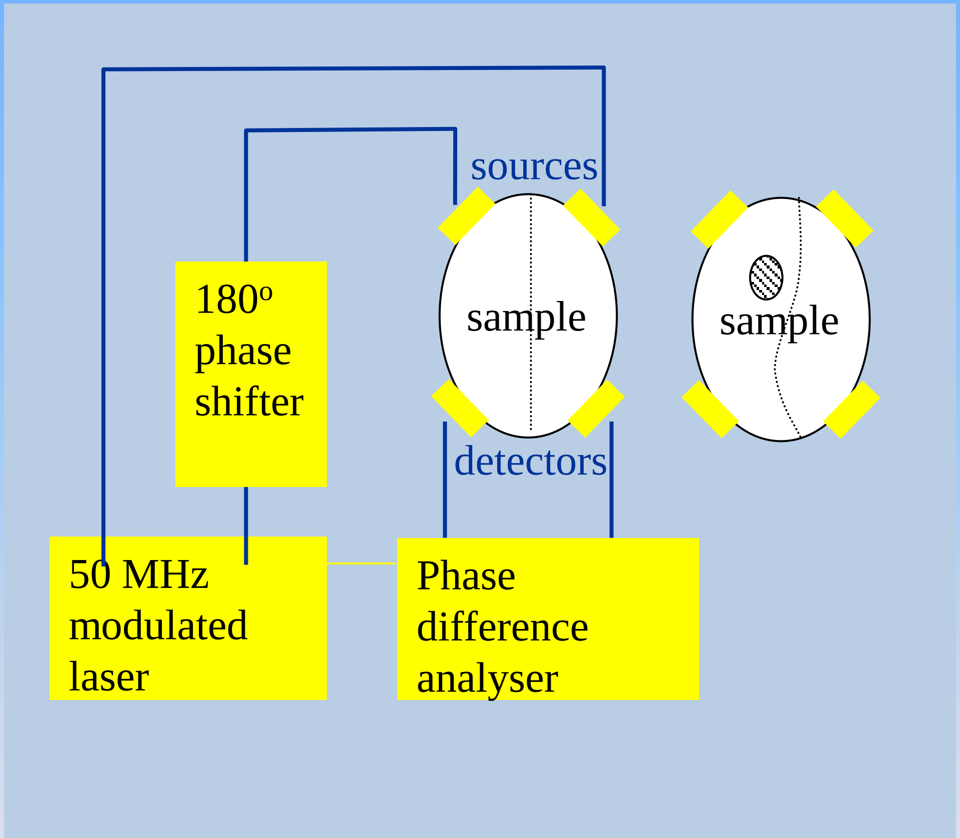
Phased Array Detection

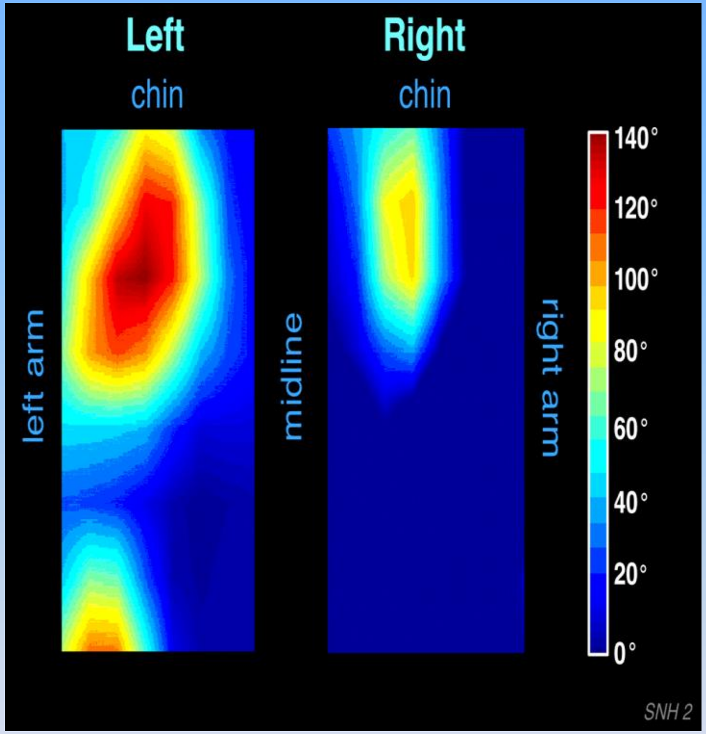
Dashed line: null-signal plane

Homogeneous sample:
detectors no difference

Inhomogeneities present:
phase difference detected

Optical Tomographic Methods:
3. Photon-transillumination methods

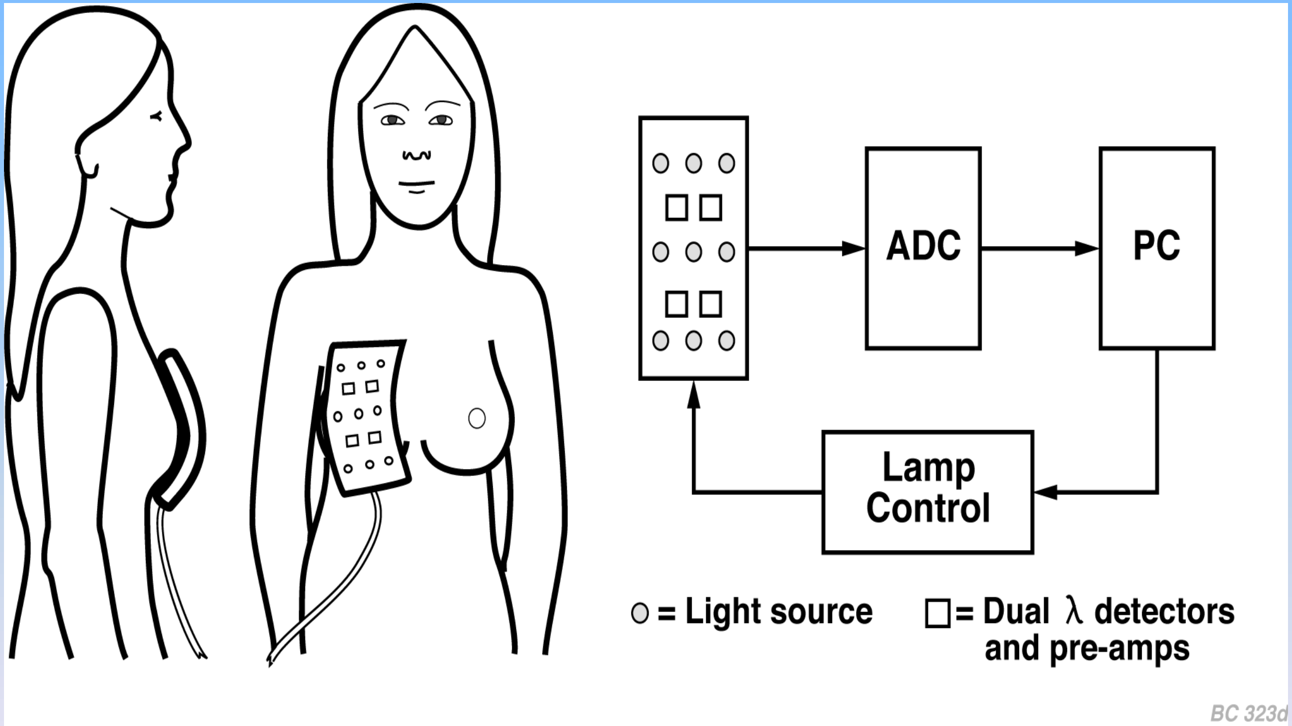




Phased-array breasts scan, showing presence of inhomogeneities
(Courtesy: B. Chance, University of Pennsylvania, School of Medicine, Philadelphia, USA)

Optical Tomographic Methods:
3. Photon-transillumination methods

Functional Near-Infrared Imaging



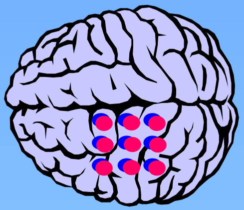
Unlike with X-rays, Photon transillumination enables to measure in reflection, thus avoiding oppressing the patient

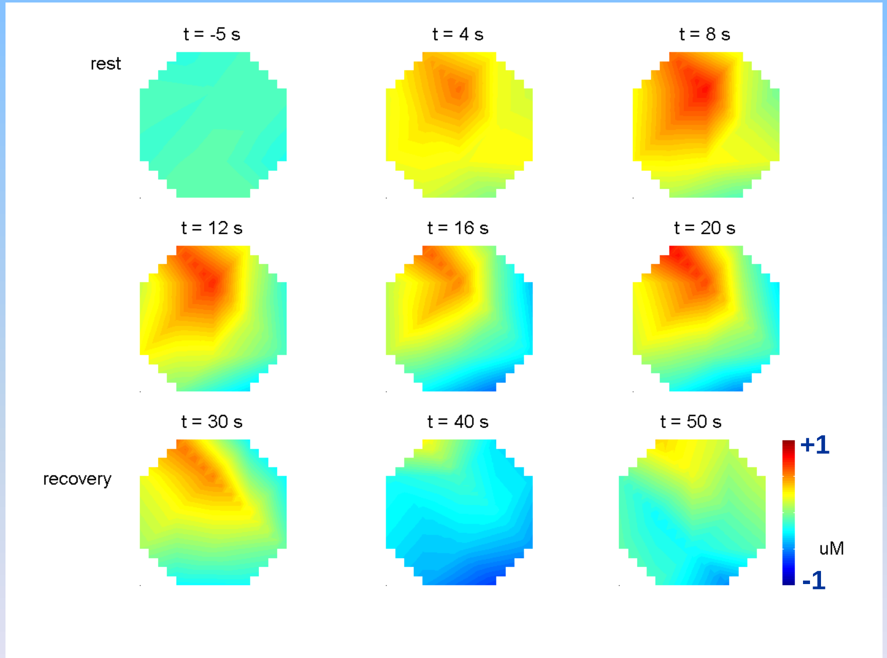
(Courtesy: B. Chance, University of Pennsylvania, School of Medicine, Philadelphia, USA)

Optical Tomographic Methods:
3. Photon-transillumination methods

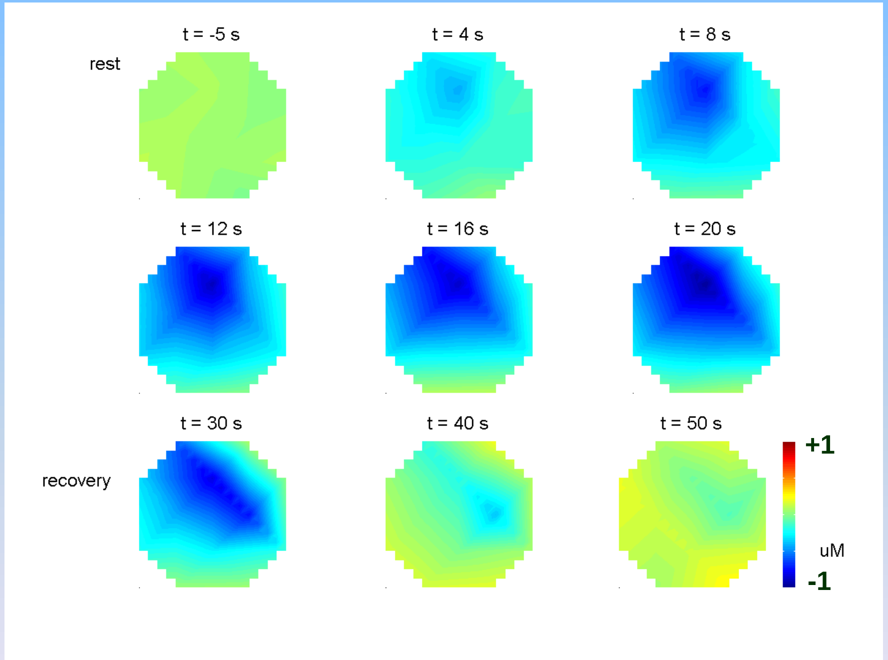
Functional Near-Infrared Imaging

7 x 7 cm maps of the left motor cortex area during
20 sec finger tapping (rate 2 Hz)





O_2Hb



HHb

(courtesy: W. Colier & B. Oeseburg, Physiology, Univ. Med. Centre Nijmegen)

Non-invasive Biomedical Optics

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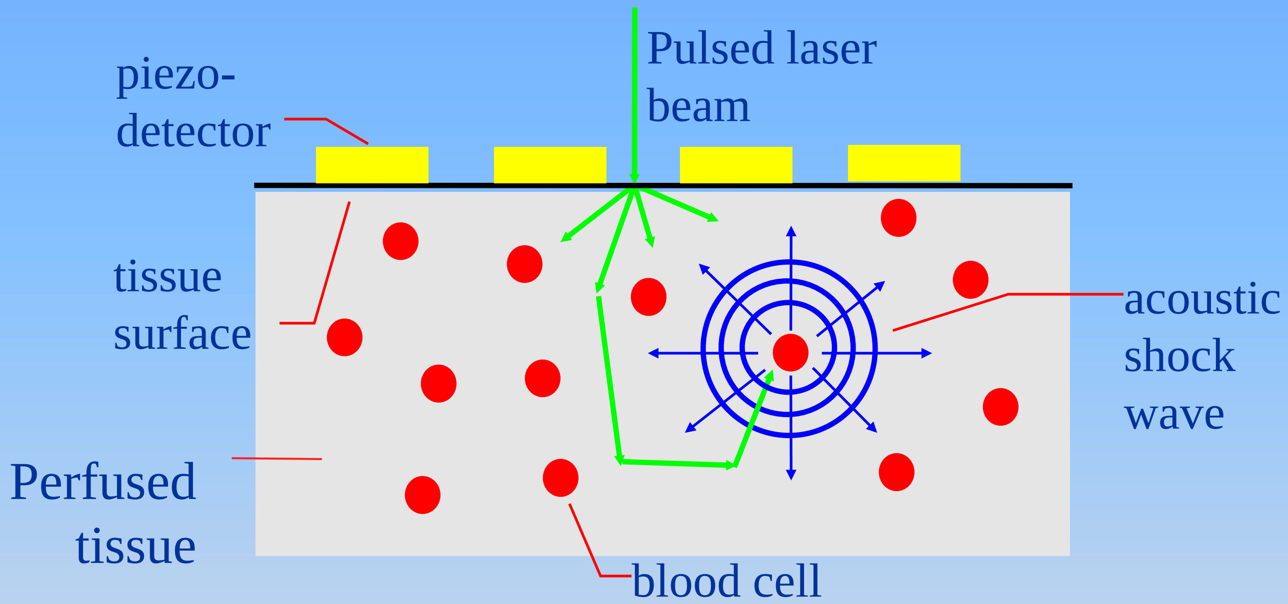
Optical Tomographic Methods: 4. Photoacoustic Imaging



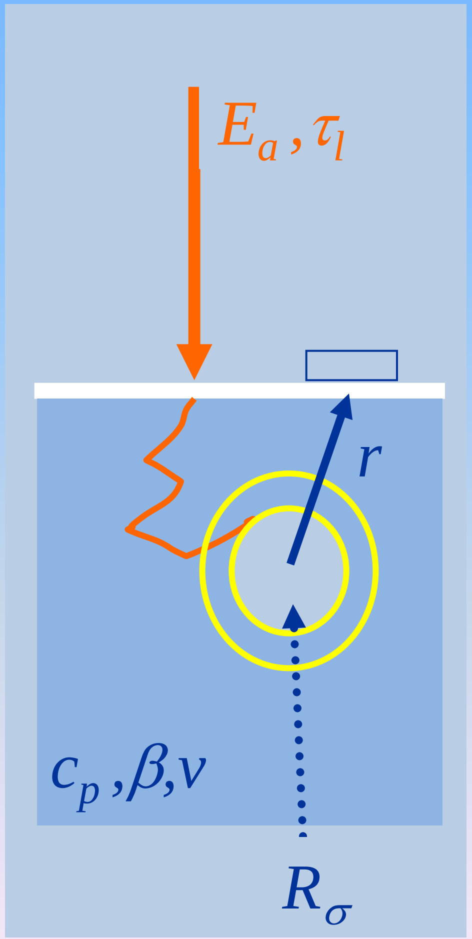
- light pulse is absorbed in blood cell
- adiabatic heating
- pressure pulse emerging (≈ 1500 m/s)
- detection at tissue surface

Depth:

- Green light: ≈ 0 - 9 mm
- Near-infrared: ≈ 0 – 30 mm

Depth resolution: ≈ 10 μm

Optical Tomographic Methods:
4. Photoacoustic Imaging



Bipolar PA-signal generated by a spherical Gaussian Source

$$\tau_a = \frac{R_\sigma}{v}$$

$$\tau_e = \sqrt{\tau_a^{\ 2} + \tau_l^{\ 2}}$$

$$P(r,t) = -P_{\max}(r)\sqrt{e}\,\frac{t-\tau}{\tau_e}\exp\left\{-\tfrac{1}{2}\frac{(t-\tau)}{\tau_e}\right\}$$

$$P_{\max}(r) = \frac{\beta\, E_a}{2\sqrt{e}(2\pi)^{3/2} c_p \tau_e^{\ 2} r}$$

$$\tau = \frac{r}{v}$$

Optical Tomographic Methods: 4. Photoacoustic Imaging

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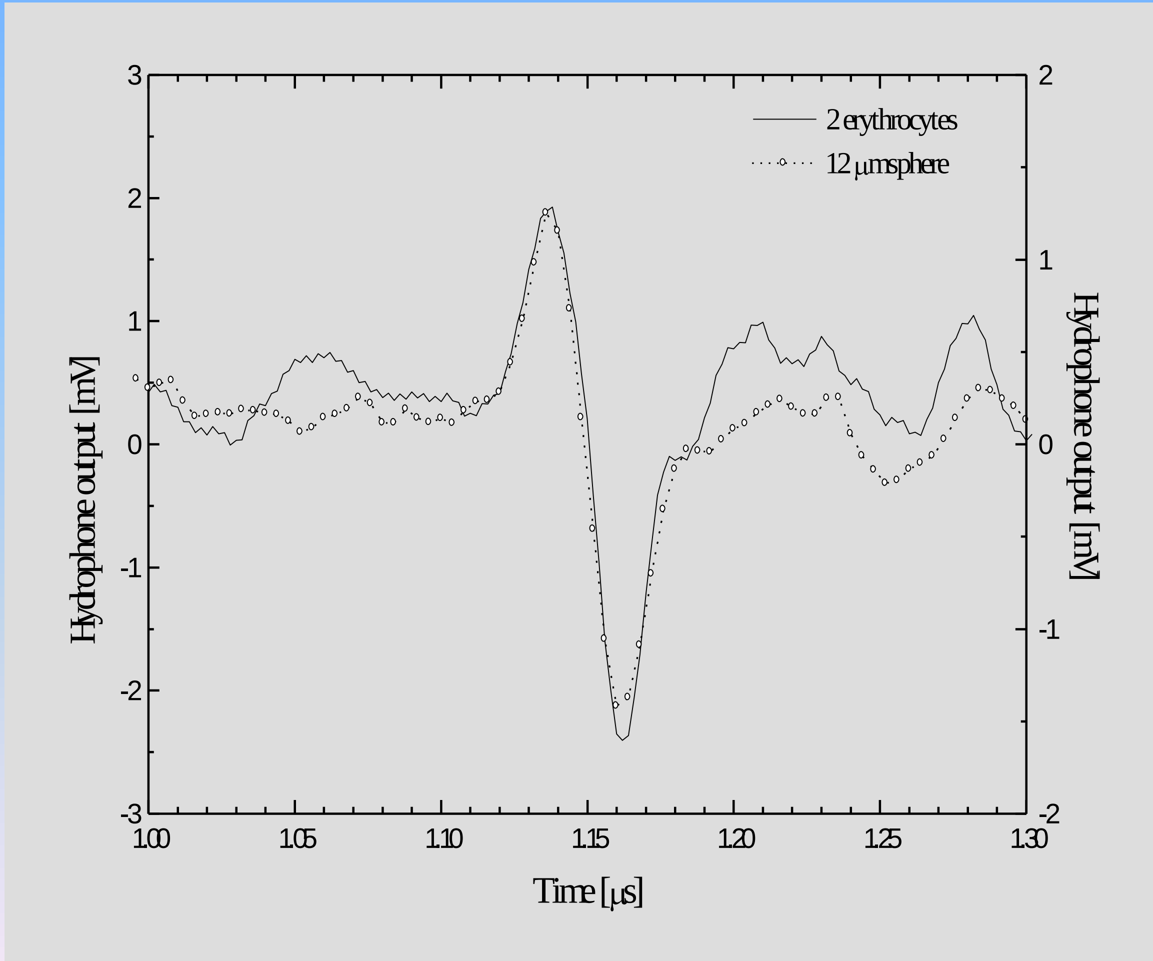
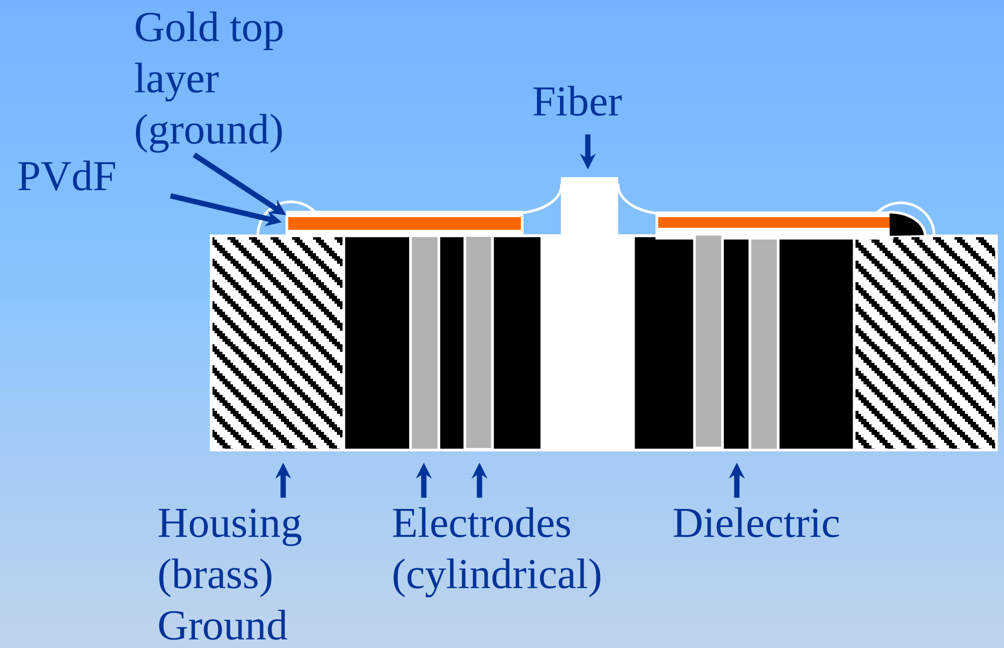


Two erythrocytes

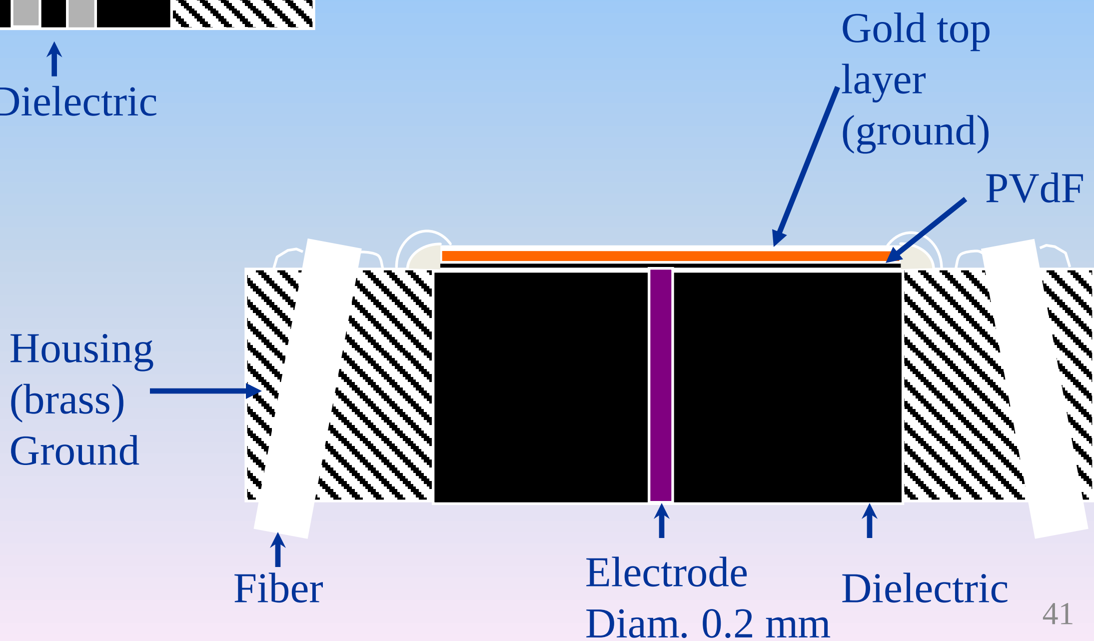
Diameter: ≈ 10 μm (compared with a 12 μm blue polystyrene sphere)
detection distance: ≈ 1.7 mm (= 1.15 μs x 1500 m/s)
medium: water/PBS

Optical Tomographic Methods:
4. Photoacoustic Imaging

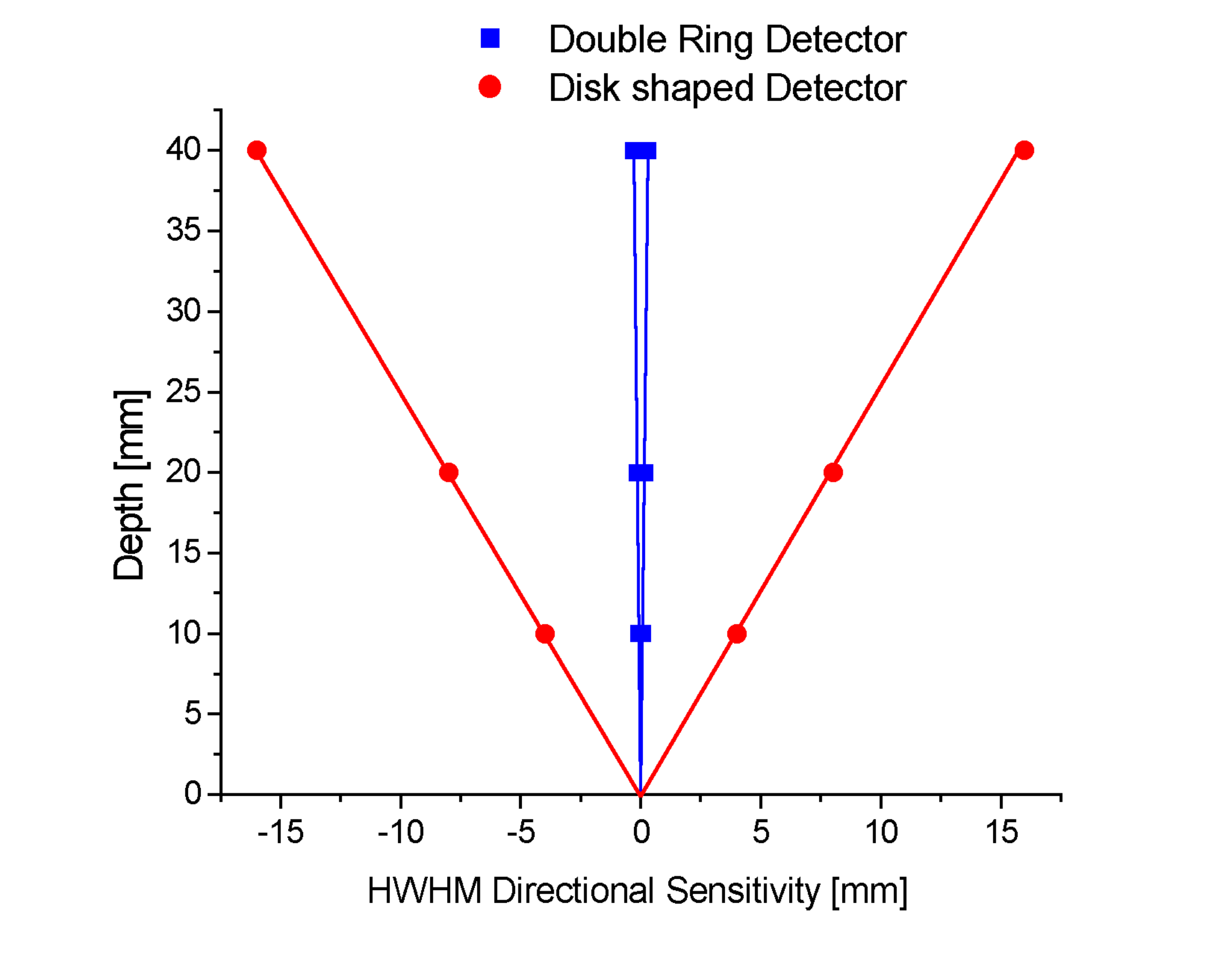
Double-Ring Detector
One-fiber illumination



Disk-shaped Detector
Ring illuminator



Optical Tomographic Methods: 4. Photoacoustic Imaging

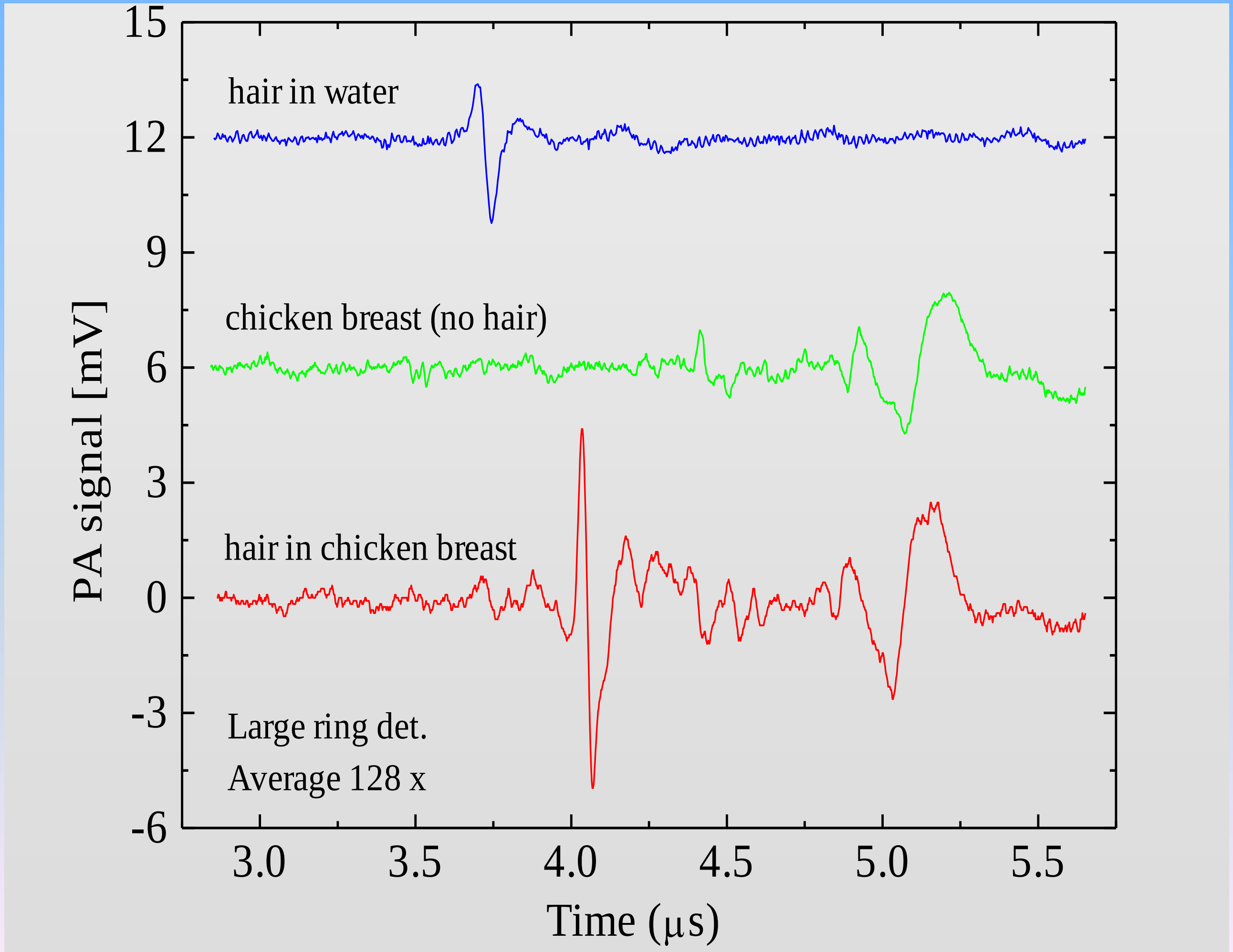


Directional Sensitivity

Disk Detector:
FWHM : Depth
1 : 5

Ring Detector:
FWHM : Depth
1 : 70

Optical Tomographic Methods:
4. Photoacoustic Imaging



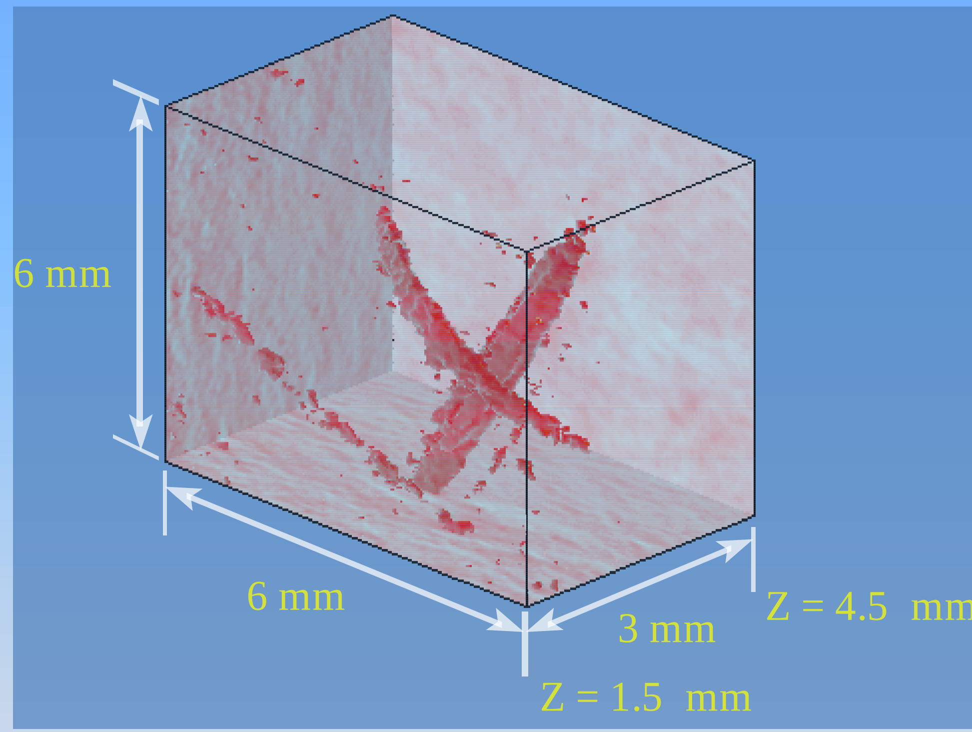
A human hair in chicken breast tissue.

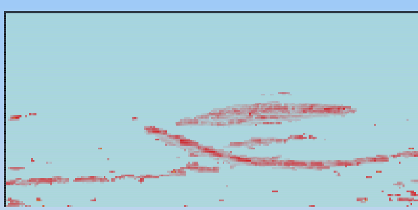
Depth: ≈ 6 mm (≈ 4 µs x 1500 m/s)

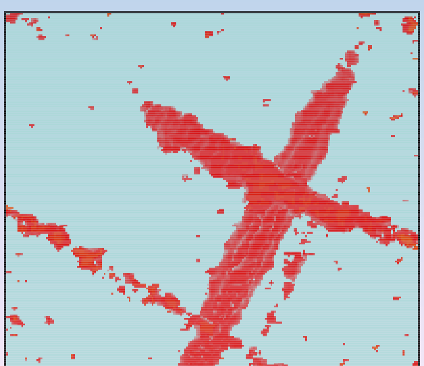
BioMedical Optics

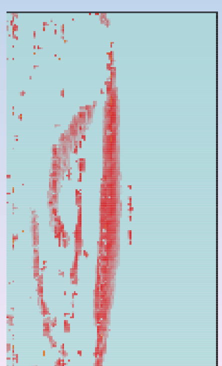
Optical Tomographic Methods: 4. Photoacoustic Imaging

Vessels in chicken breast tissue



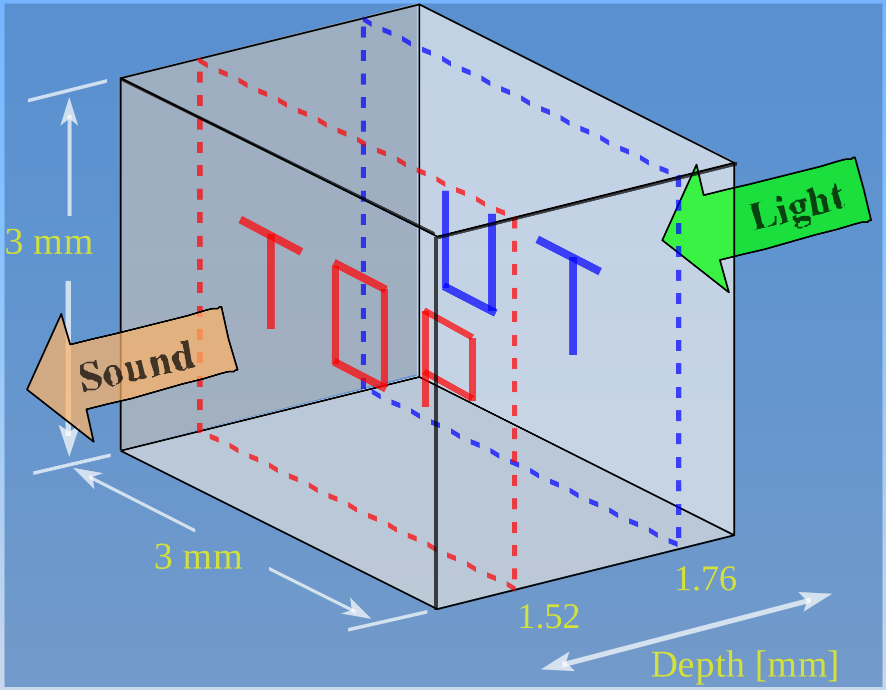




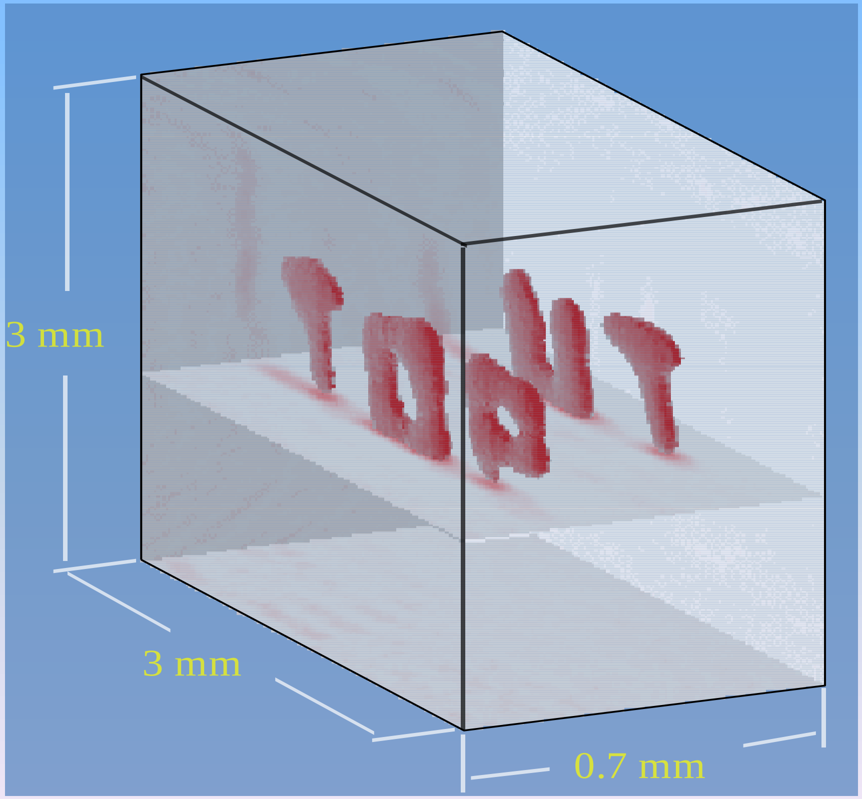


Sample : 5 mm thick chicken breast tissue in water
Image : 663 mm, inside sample, 35 % isosurface threshold
Vessels : 3 Nylon capillaries, 0.28 0.40 mm diameter
Absorber : Evans Blue, flowing, a = 300 cm-1
Detection : at Z = 0 mm, 51 51 points, 0.15 mm spacing

Optical Tomographic Methods:
4. Photoacoustic Imaging

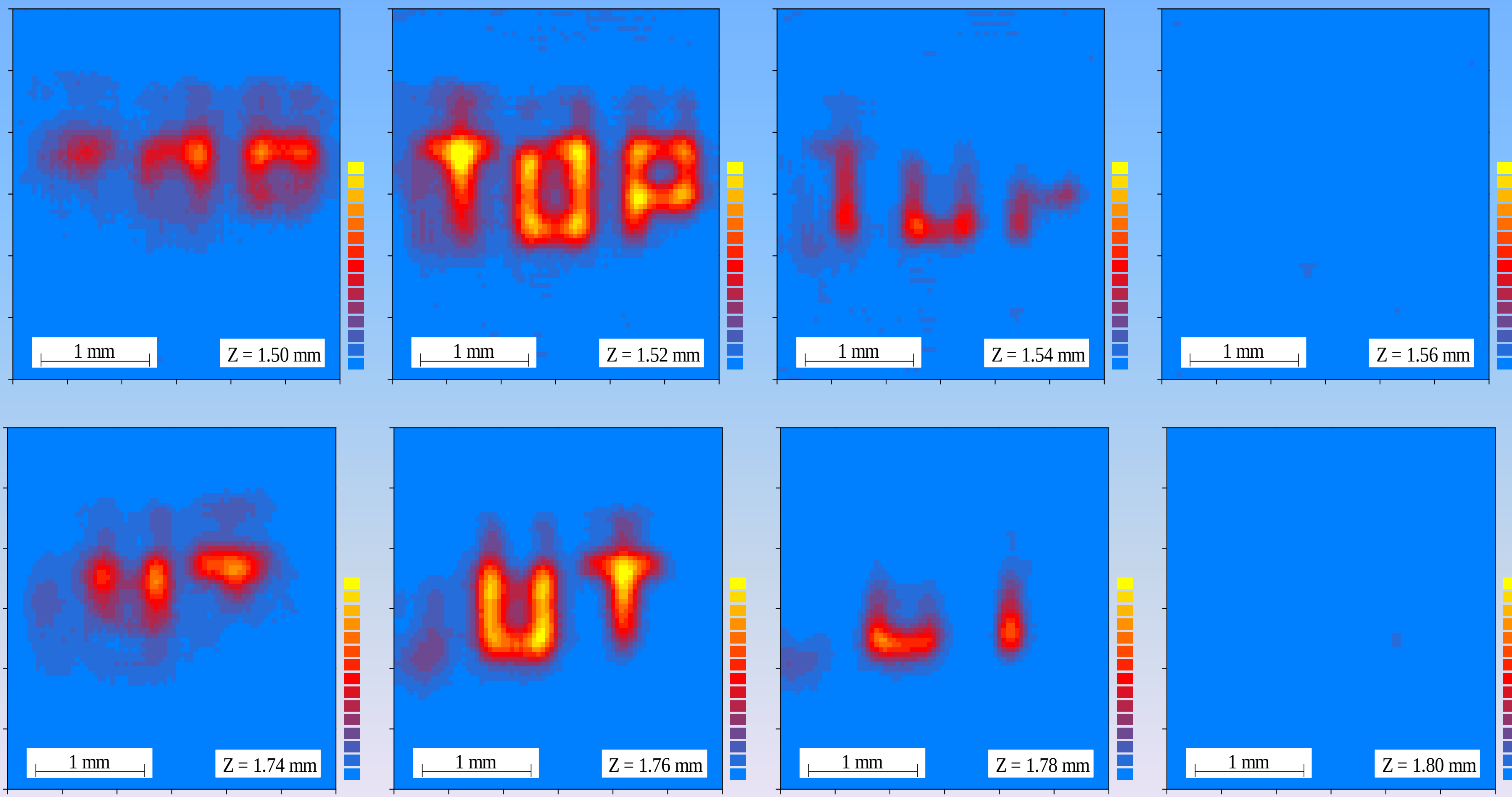


Reconstruction of hidden objects



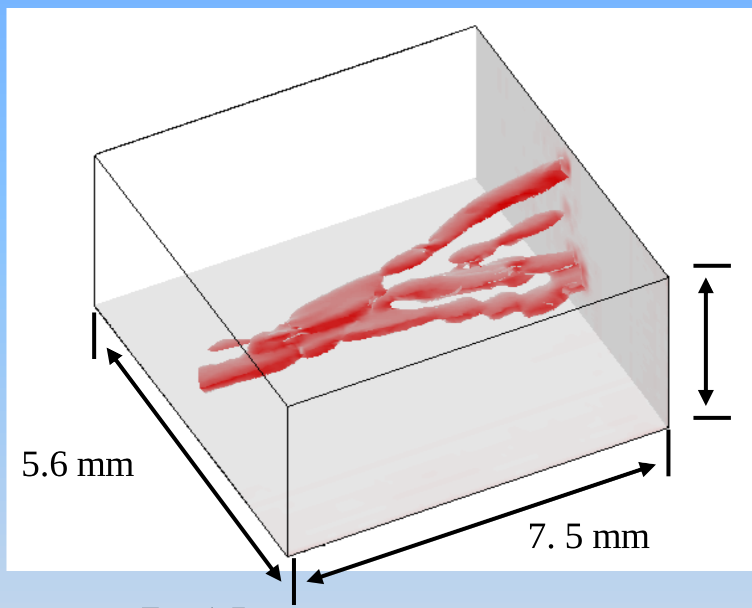
Material: carbon threads (10 µm) on transparent sheets,
in 10 % Intralipid-10%
(resembles human tissue scattering)

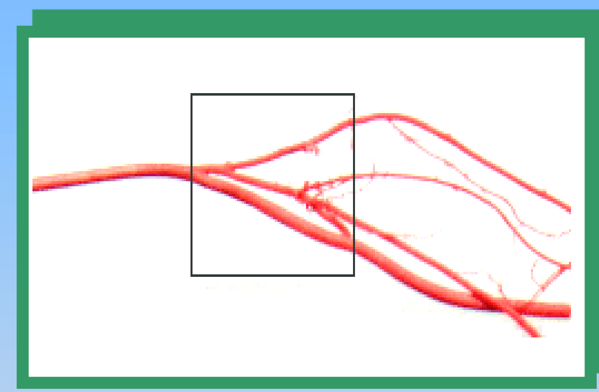
Optical Tomographic Methods: 4. Photoacoustic Imaging



Depth resolution: ≈ 10 μ m

Optical Tomographic Methods: 4. Photoacoustic Imaging





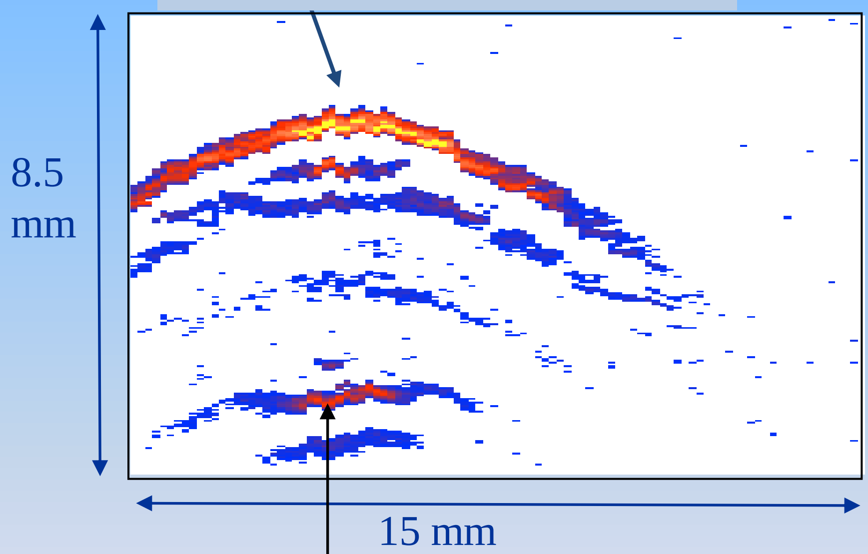
Photograph

Vascular tree from a branching epigastric artery of a rat.
Ex-vivo; medium: intralipid 1 % (≈ tissue).
Depth (Z-coord.) ≈ 5 mm : indicated in figure.
Laser power 532 nm, 2mJ/pulse through fiber ∅ 600 µm.
Depth resolution / lateral resolution: 10 / 100 µm respectively.

Optical Tomographic Methods: 4. Photoacoustic Imaging

Measuring tissue thickness above bone

Signal from Tissue Surface



Bone (Reflection of signal from tissue-surface)

Photoacoustic line scan of a finger,
perpendicular to the finger axis.

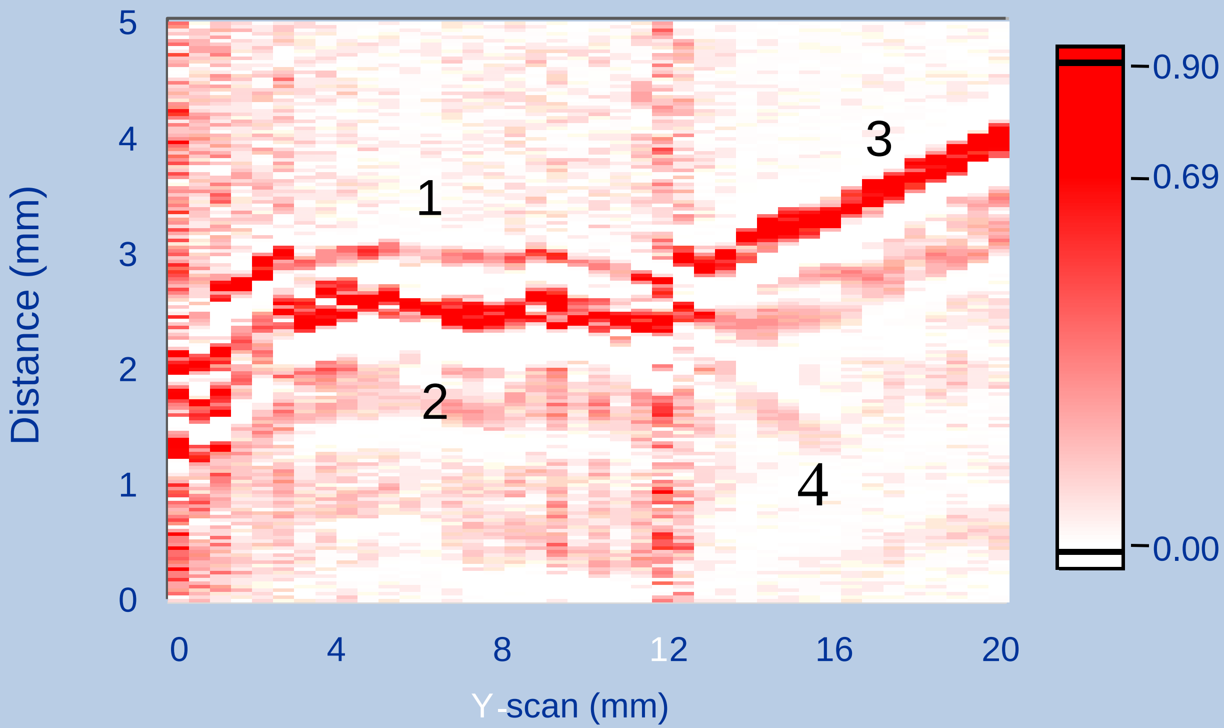
The surface of the tissue and the reflection from the bone can clearly be distinguished.

In between structures are seen that may be blood vessels.

- 100 scan lines; scan step 150 µm
- ~6 mJ/cm^2 at skin surface

Optical Tomographic Methods: 4. Photoacoustic Imaging

Line scan across finger nail



1: nail top
2: nail bottom
3: finger skin
4: reflections or blood vessels

Optical Tomographic Methods: 4. Photoacoustic Imaging

	Green 550 nm		NIR 850 nm	
	dermis	blood	dermis	blood
• Absorption coefficient [1/mm]	0.03	32	0.01	1.2
• Scattering coefficient (reduced) [1/mm]	3	1	1	0.5
• Absorption Contrast	1000		100	
• Penetration into tissue [mm]	≈ 10		≈ 30	
• Applications	Cutaneous perfusion Wound healing Diabetes Vascular malformations Skin tumours		Cerebral perfusion Muscular perfusion Mammography Angiogenese	

BioMedical Optics

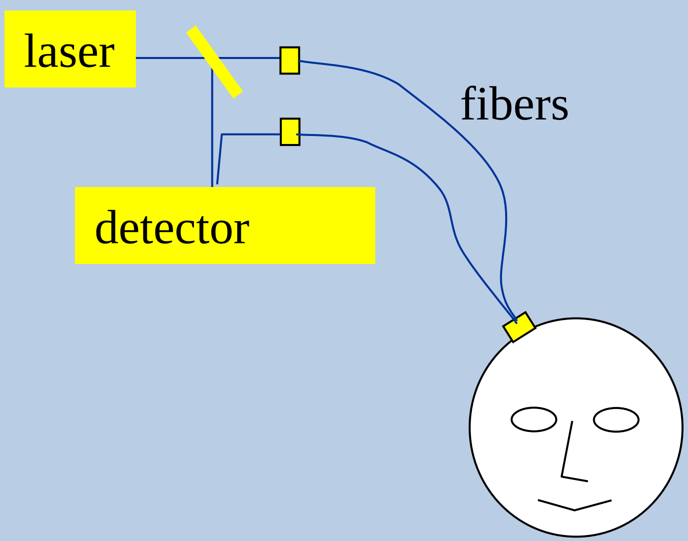
Non-invasive Biomedical Optics

In this talk:

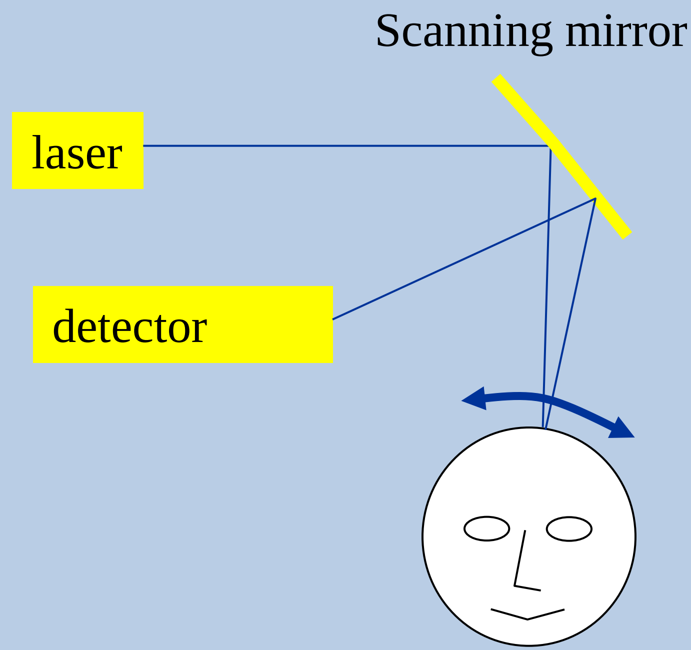
- *oximetry*
- *optical tomographic methods:*
  1. optical coherence tomography
  2. orthogonal polarization spectral imaging
  3. transillumination tomography:
     - time-of-flight, high-frequency modulation, continuous-wave
  4. photoacoustics
- *dynamic scattering: laser-Doppler:*
  1. laser-Doppler perfusion monitoring and imaging
  2. self-mixing laser-Doppler blood flowmetry

Dynamic scattering:
1. Laser Doppler Perfusion

Scattering at moving cells causes Doppler frequency shift



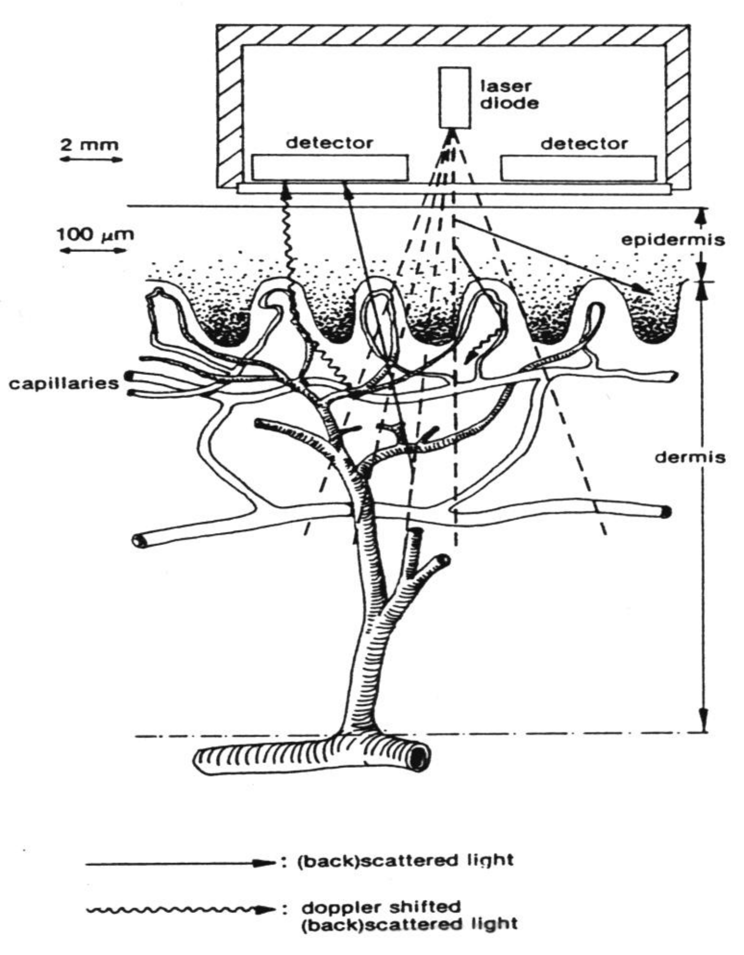
monitoring

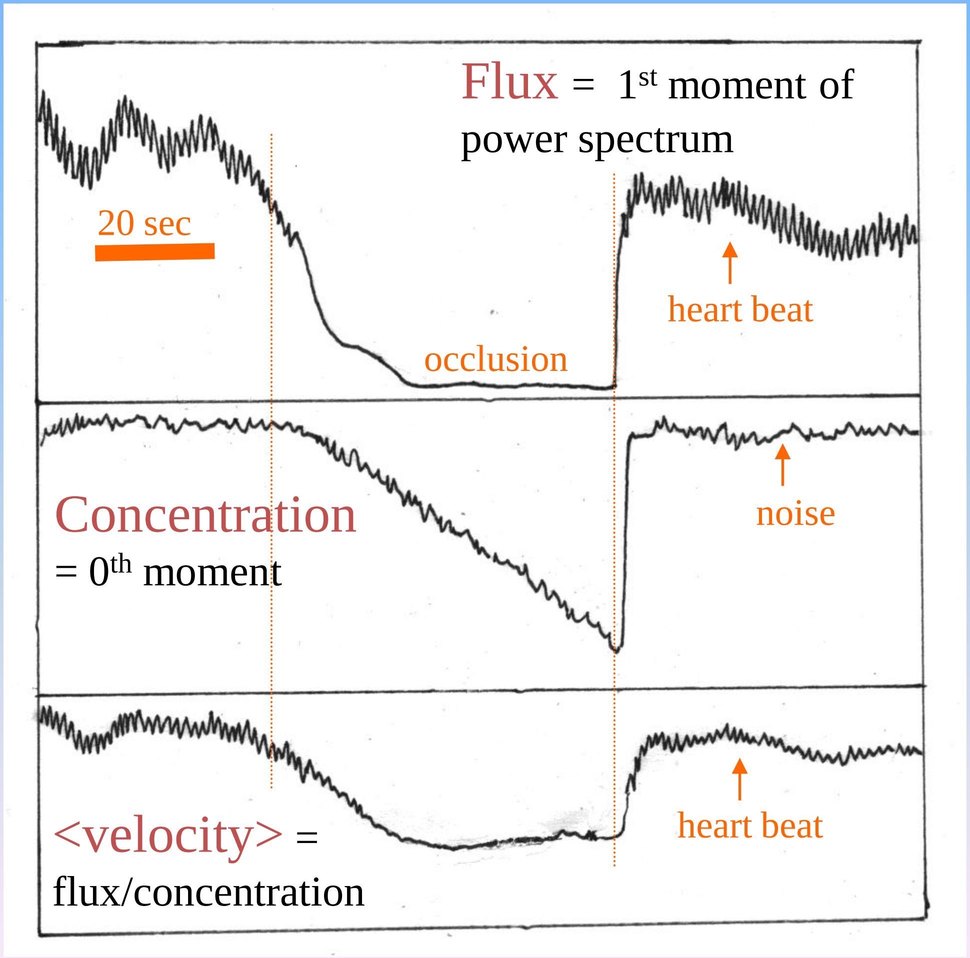


imaging

Dynamic scattering:
1. Laser Doppler Perfusion Monitoring

LD spectra of finger tip upon occlusion of upper arm





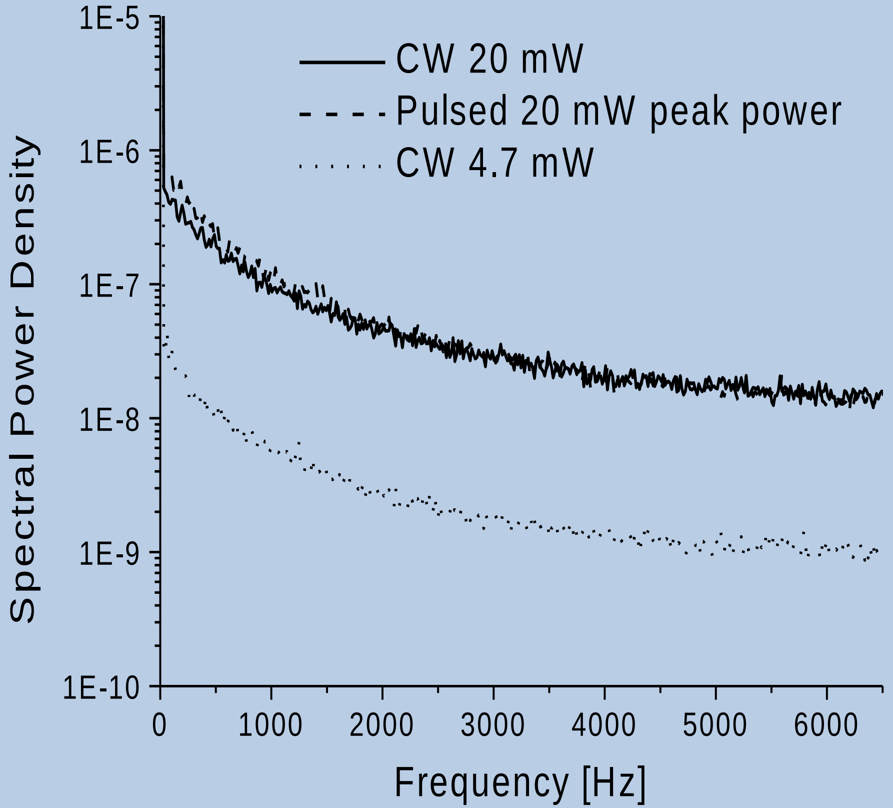
BioMedical Optics

Dynamic scattering:
1. Laser Doppler Perfusion (Monitoring)

New in LD-monitoring:

- Pulsed LD-monitoring
- Depth-sensitive LD-monitor on-a-chip
- Standardization of instruments and procedures
- Low-coherent depth-sensitive LD-monitor

Dynamic scattering:
1. Laser Doppler Perfusion (Monitoring)



Pulsed LD-monitoring

- ➔ higher powers
- ➔ larger measuring distances
- ➔ larger depths

LD-spectrum: 0-20 kHz

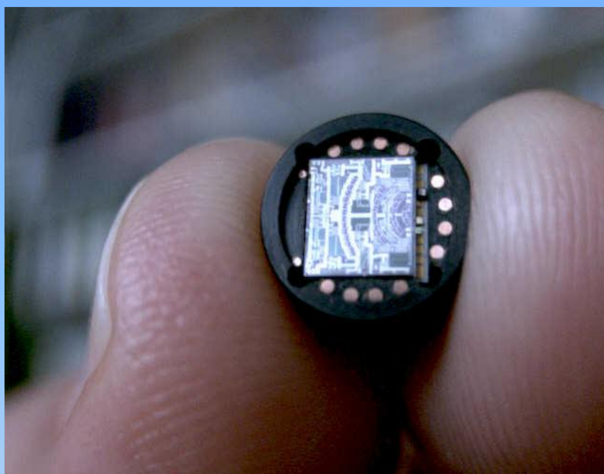
Pulse frequency: 50 kHz.

Pulse width / period = 0.24

(4.7 / 20)

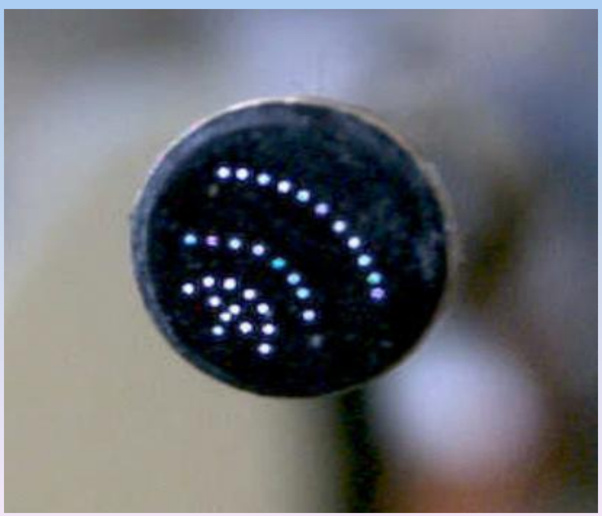
BioMedical Optics

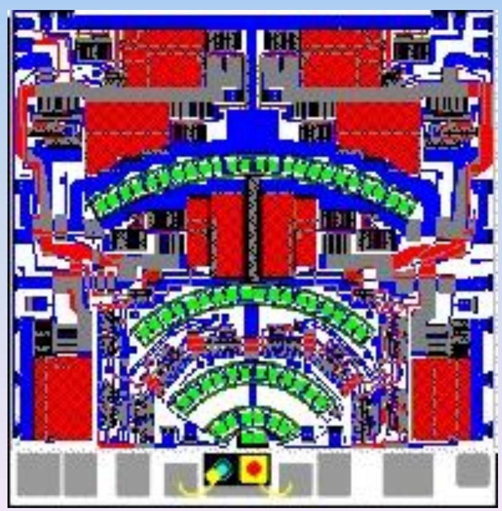
Dynamic scattering:
1. Laser Doppler Perfusion (Monitoring)



LD-monitor on-a-chip

provides miniature depth-sensitive sensor.





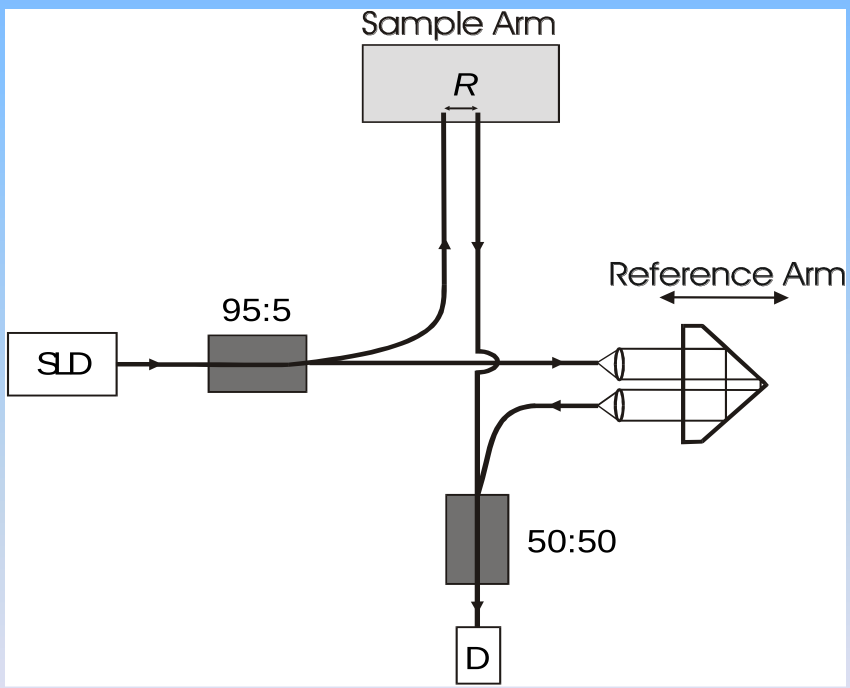
Green: photodiode rows

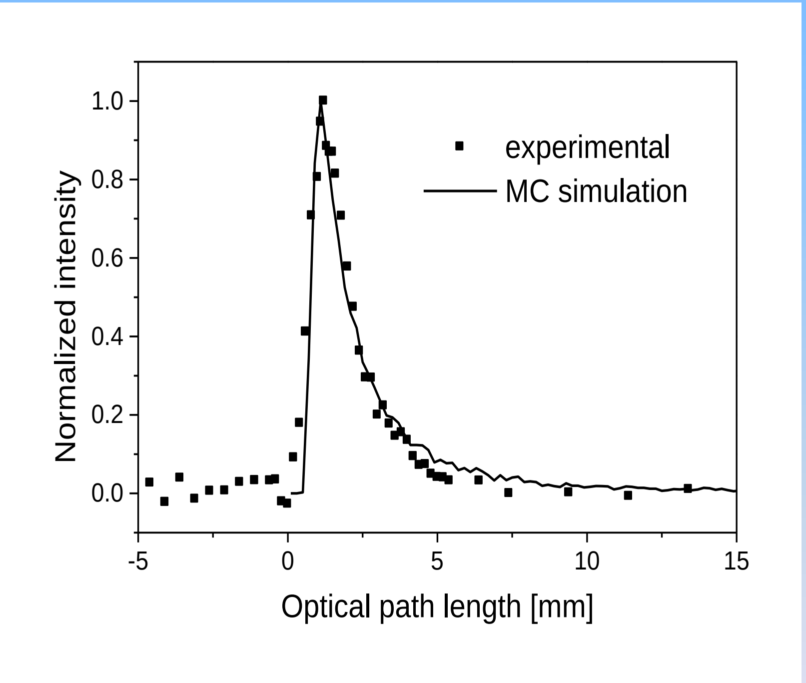
Blue/red: *electronics*: amplifiers/multiplexers

Red dot in **yellow** area: VCSEL- laser diode

Dynamic scattering:
1. Laser Doppler Perfusion (Monitoring)

Low-coherent depth-sensitive LD-Monitoring





The reference mirror selects the depth in the sample from which a coherent Doppler-shift signal will be measured.

BioMedical Optics

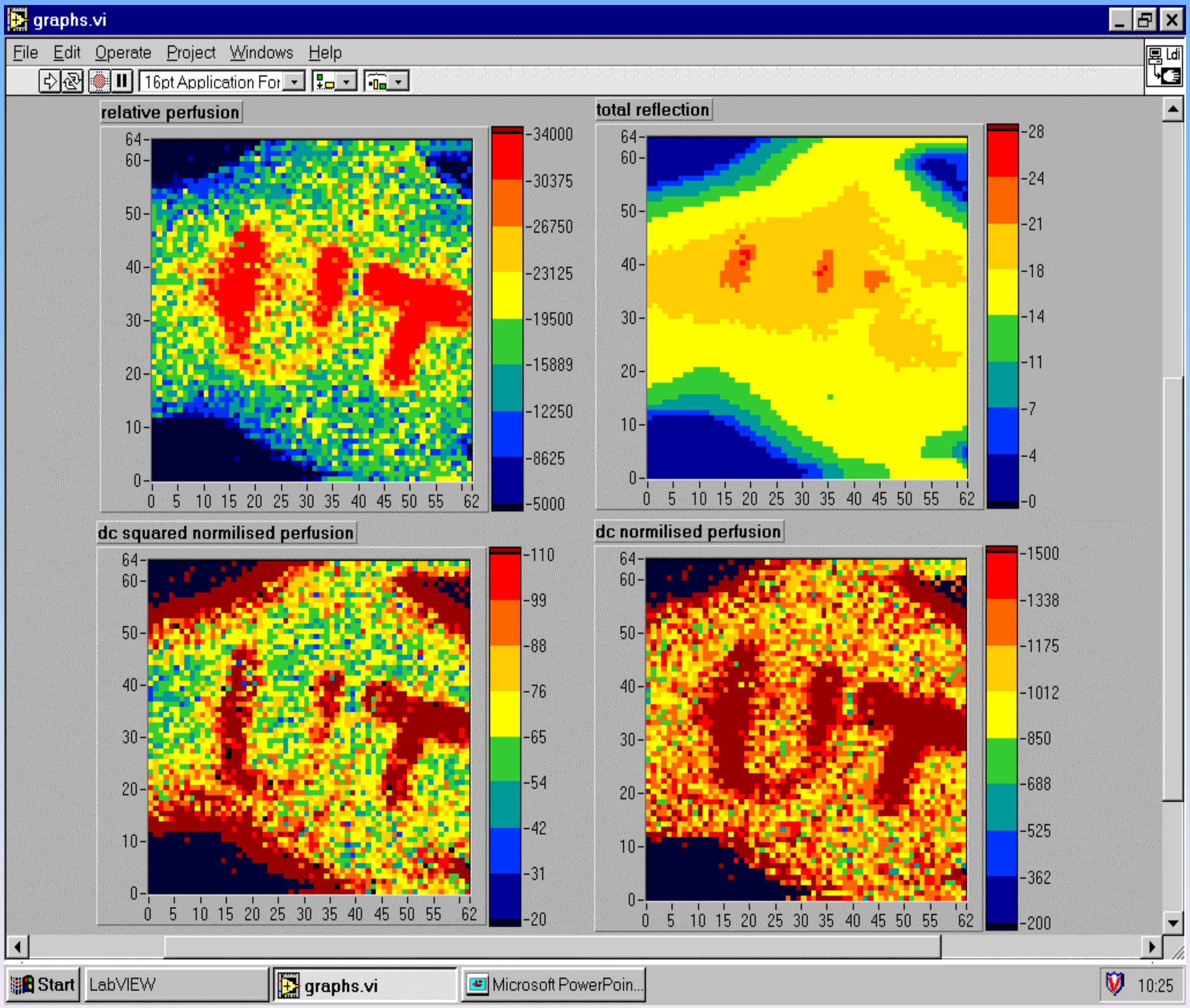
Dynamic scattering:
1. Laser Doppler Perfusion (Monitoring)

Monte-Carlo photon transport simulations

Tissue considered as

- Layered structure
- Including blocks, spheres, tubes, cones, mirror planes
- Varying scattering and absorption coefficients
- Varying scattering functions (Mie, Rayleigh,…)
- Reflection and refraction
- Rectangular or ring-shaped detectors
- Scattered, transmitted or absorbed photons detected
- Doppler spectra: varying velocity profiles

Dynamic scattering:
1. Laser Doppler Perfusion (Imaging)



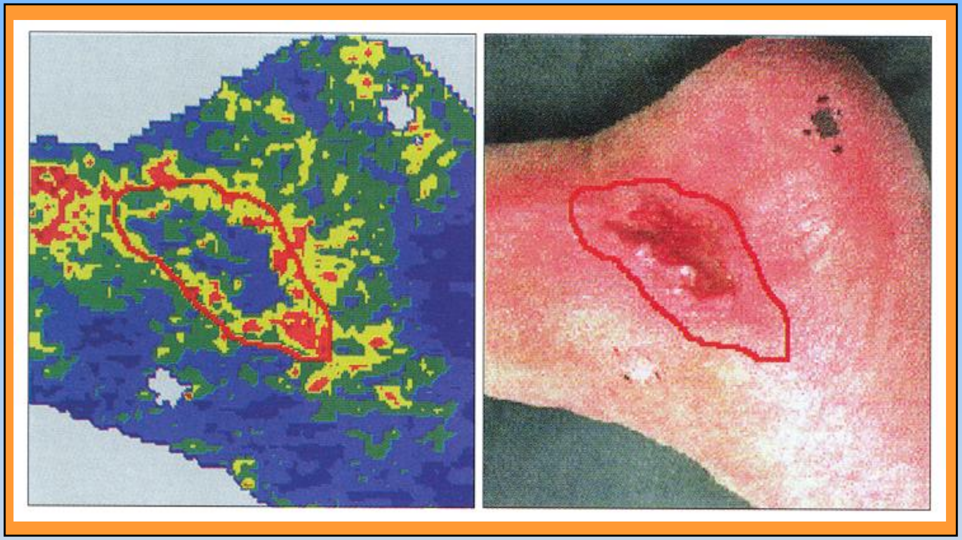
Superficial perfusion of the dorsal side of the hand,

characters UT written using muscular balm.

Upper left: perfusion, not normalized;
Upper right: DC-reflection from tissue;
Lower left: perfusion, normalized with DC
Lower right: perfusion, normalized with DC^2 .

Dynamic scattering:
1. Laser Doppler Perfusion (Imaging)

Perfusion Image of a foot ulcer

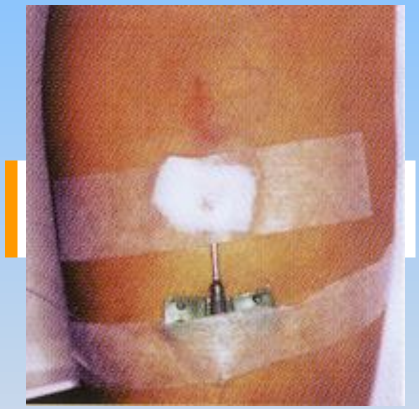


Typically the highest perfusion is in the boundary around the ulcer, in inflammatory skin and in granulating tissue inside the ulcer area.

From: Bornmyr, “Laser Doppler flowmetry and imaging - methodological studies. Dep of clinical hysiology”,thesis, Malmö, Sweden (1998);
Figure: courtesy: prof. G. Nilsson, Lisca, Linkoping, Sweden)

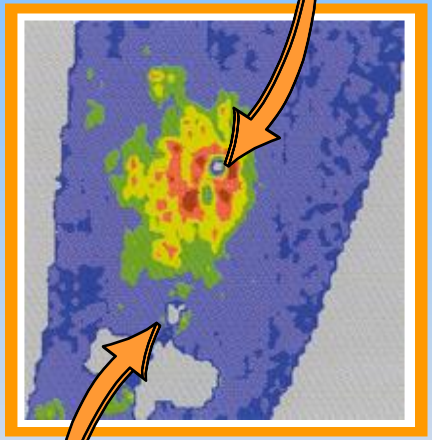
Dynamic scattering:
1. Laser Doppler Perfusion (Imaging)

The effect of micro-trauma

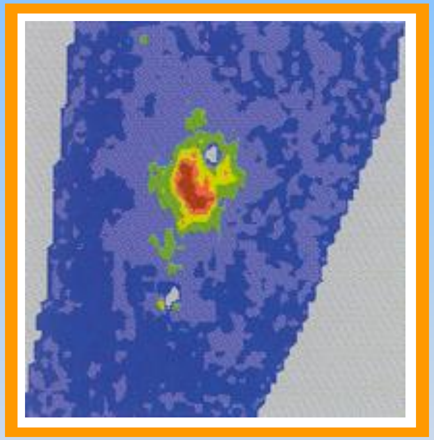


Insertion of a micro-dialysis fibre into the skin.

The dialysis fibre probe tip causes hyperperfusion



No hyperperfusion at the point of introduction because the skin is anesthetized.



After 30 minutes the hyperperfusion is reduced.

(Courtesy: Lisca Sweden)

Dynamic scattering:
1. Laser Doppler Perfusion (Imaging)

Basal cell carcinoma

(Courtesy: Lisca Sweden)

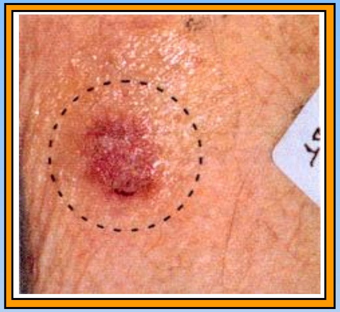
Before treatment

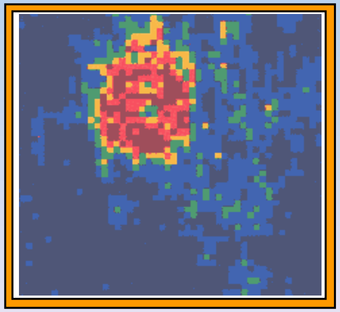
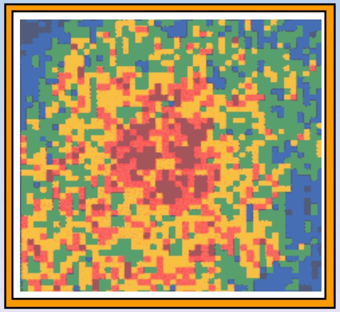
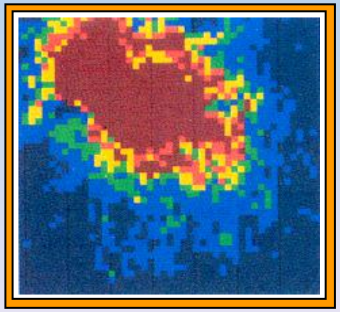
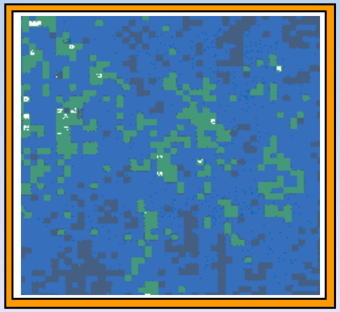
After treatment

Immediately

One week

8.5 months later

Neo-vascularisation in tumour area.

Inflammatory response.

Inflammatory response with excessive perfusion.

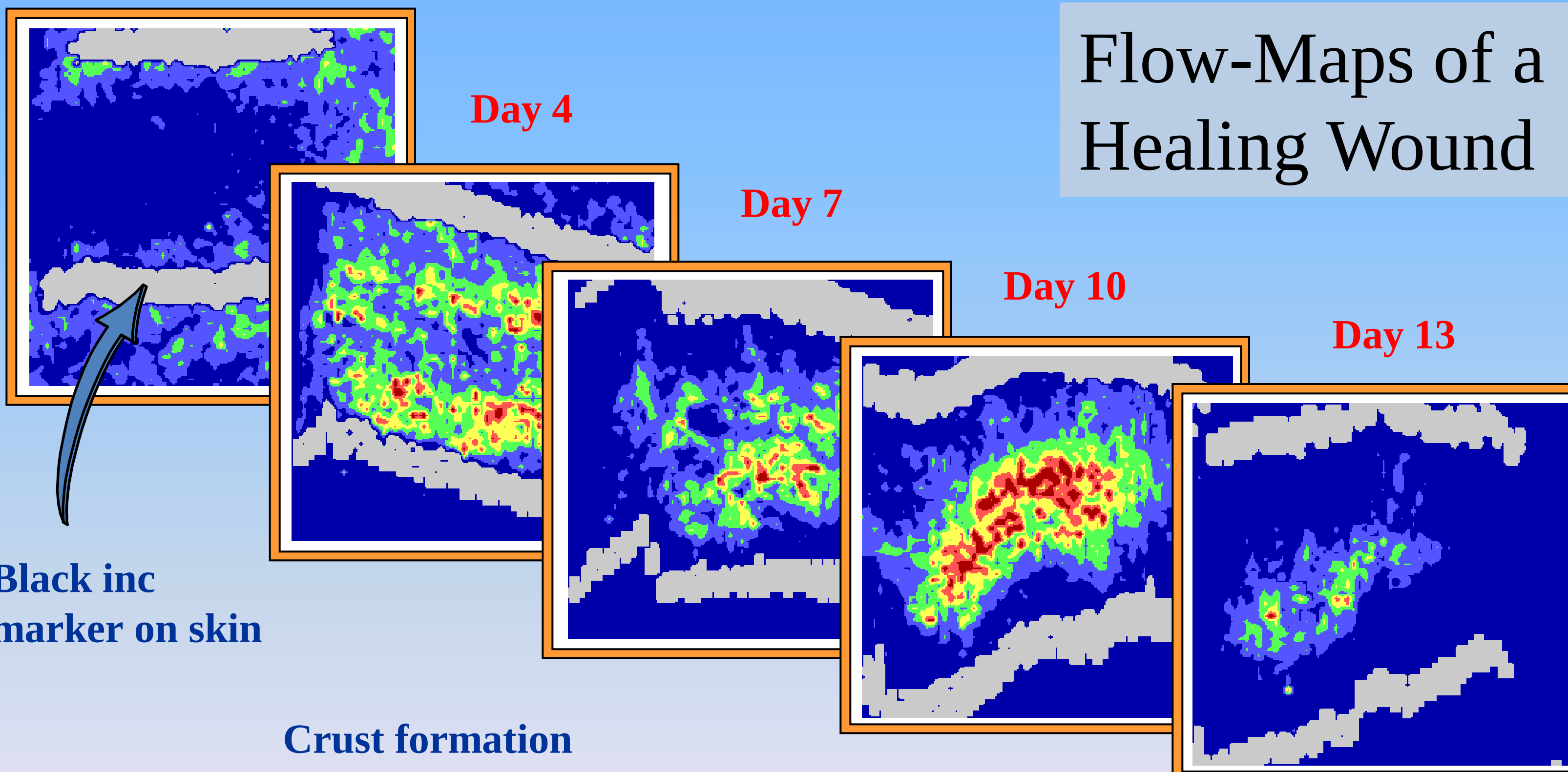
Back to normal.

BioMedical Optics

Dynamic scattering:
1. Laser Doppler Perfusion (Imaging)

Day 1: wound creation

Flow-Maps of a Healing Wound



Black inc marker on skin

Crust formation in centre of wound

Crust off

Perfusion returning to normal

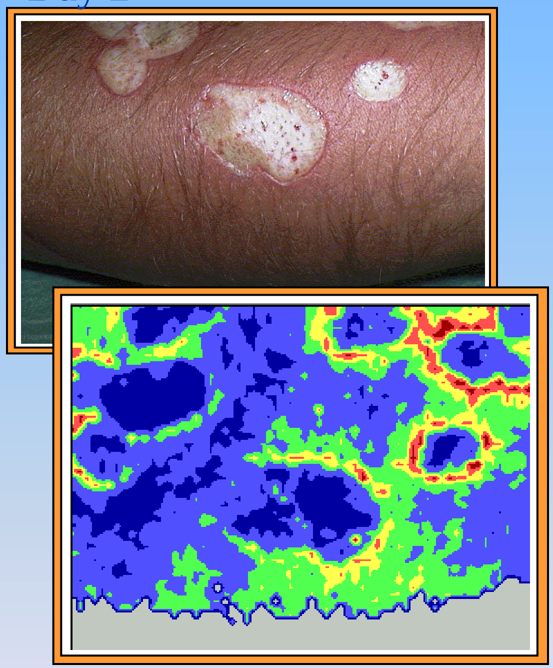
(Courtesy: Lisca Sweden)

BioMedical Optics

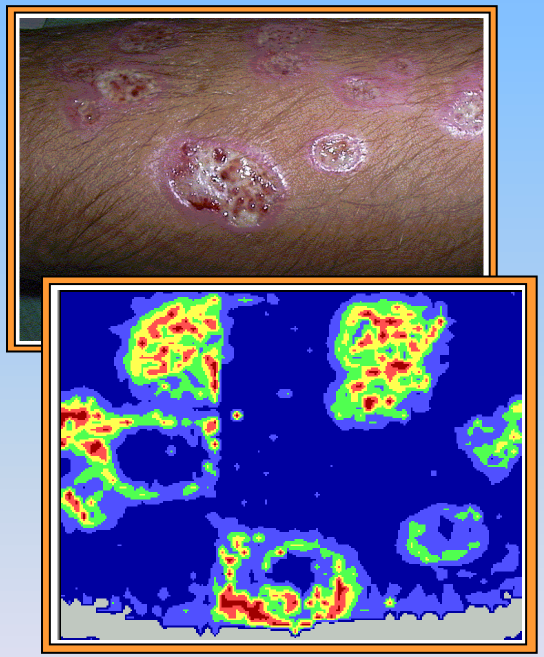
Dynamic scattering:
1. Laser Doppler Perfusion (Imaging)

The healing process of a burn wound

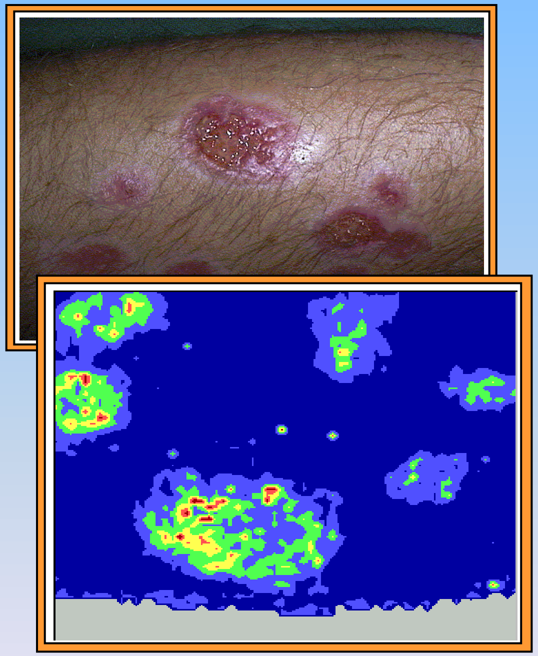
Day 2



Day 13



Day 28



Reduced perfusion
in burnt areas.
Increased perfusion
in surrounding skin.

Towards normalisation.

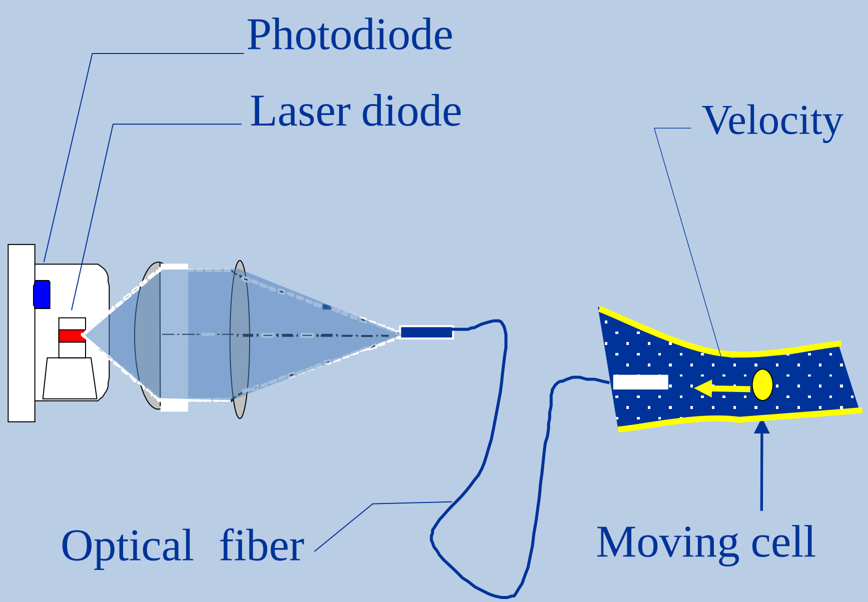
(Courtesy: Lisca Sweden)

Non-invasive Biomedical Optics

In this talk:

- *oximetry*
- *optical tomographic methods:*
  1. optical coherence tomography
  2. orthogonal polarization spectral imaging
  3. transillumination tomography:
     - time-of-flight, high-frequency modulation, continuous-wave
  4. photoacoustics
- *dynamic scattering: laser-Doppler:*
  1. laser-Doppler perfusion monitoring and imaging
  2. self-mixing laser-Doppler blood flowmetry

Dynamic scattering:
2. Self-mixing Laser-Doppler Flowmetry

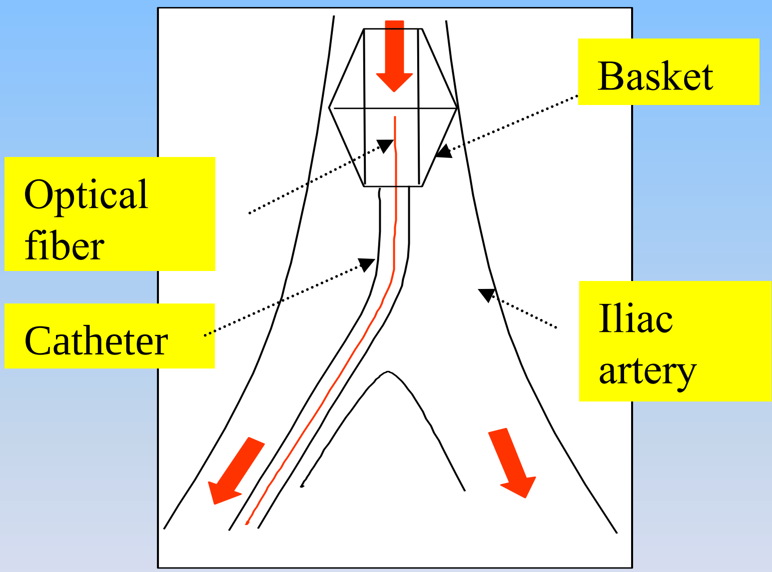


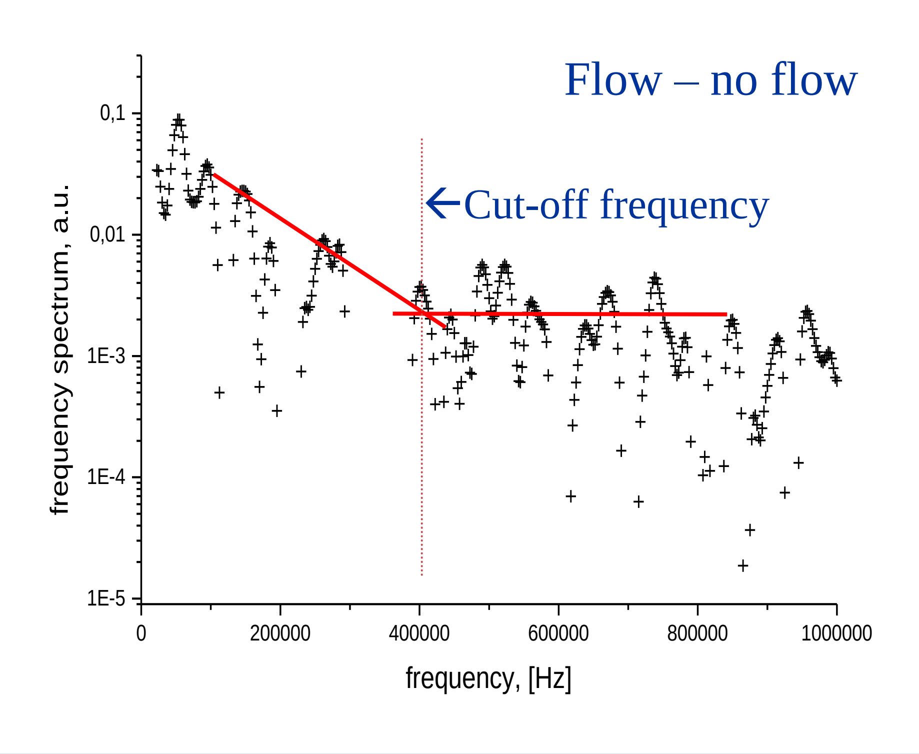
Principle:

- laser light reflected/scattered by moving blood cells,
- partly back-reflected into laser cavity,
- with Doppler-shifted frequency,
- in cavity: mixing with "original" light,
- Doppler signal results,
- can be measured with photodiode

Dynamic scattering:
2. Self-mixing Laser-Doppler Flowmetry

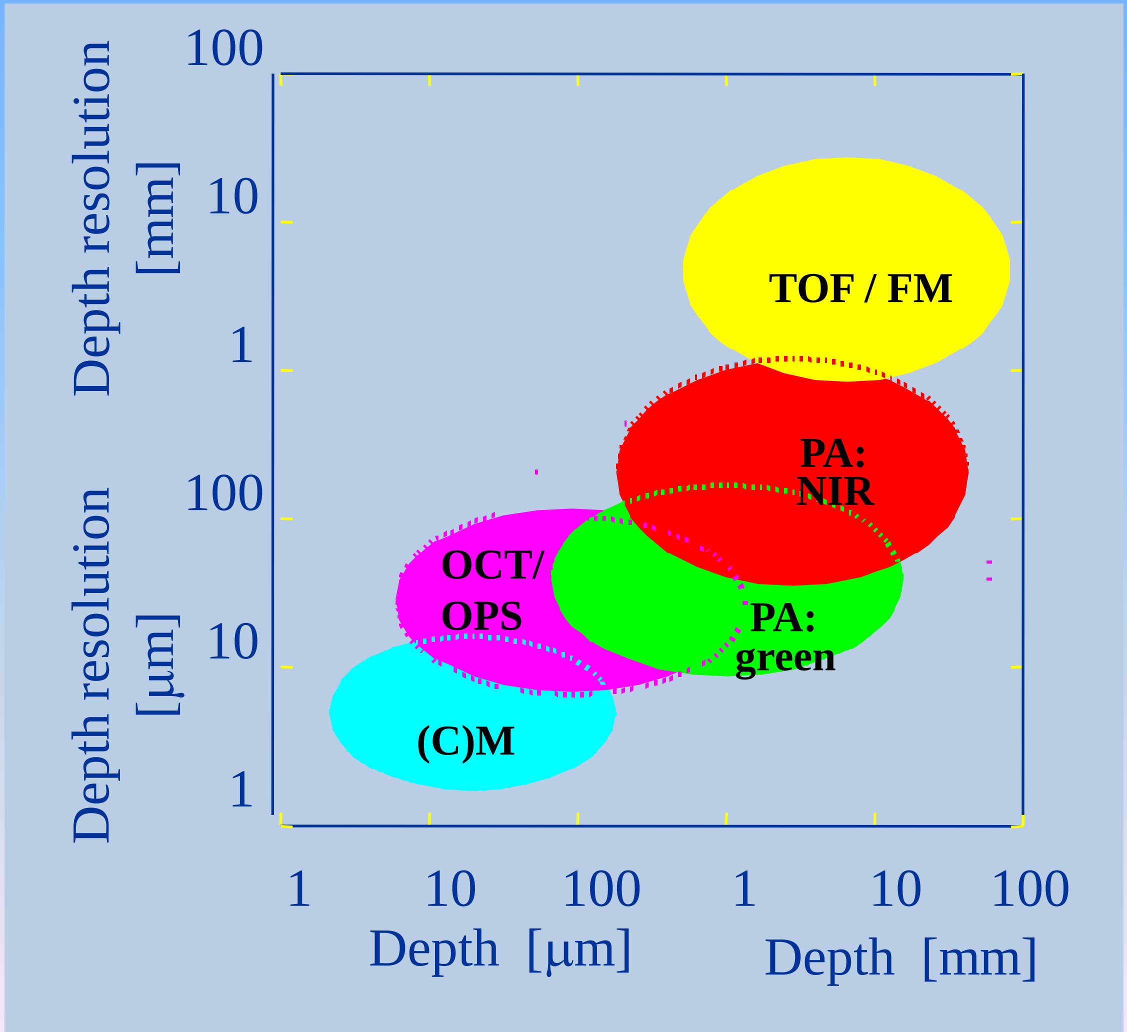
Branching in iliac artery of healthy pig





Cut-off frequency at 400 kHz corresponds with a velocity of 16 cm/s.
(Independent measurement using an electromagnetic probe: 14.5 ± 1.0 cm/s)
(L. Scalise & F.F.M. de Mul).

Imaging methods for hidden structures in turbid media (tissue)



C(M) : (confocal) microscopy

OCT: optical coherence tomography

OPS: orthogonal polarization spectral imaging

PA: photoacoustics

TOF: time-of-flight tomography

FM: frequency-modulated tomography

BioMedical Optics

Non-invasive Biomedical Optics

Conclusions:

- several techniques available, at various depths,

    to 1 mm : OCT, OPS

    to 10 mm : PA – green

    to 50 mm : TOF, FM, PA-infrared.

- resolution / depth ≈ *1 / 10* (with OCT, OPS, PA: *1/100*)

BioMedical Optics

Non-invasive Biomedical Optics

In our lab (UT – Applied Physics – Biomedical Optics)

- Laser-Doppler Monitoring / Imaging

  (chip design, calibration, speckle optics, low-coherence)
- Photon transillumination (…1.8 Ghz frequency modulation)
- Photo-acoustic imaging (blood in tissue -> mammography)
- Compound concentration determination by light scattering
- Monte-Carlo light transport simulations

Non-invasive Biomedical Optics

the end