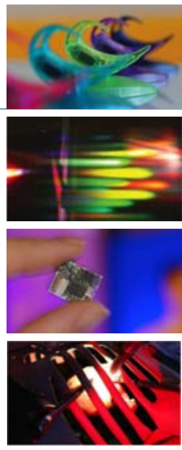
Molecular, morphological and structural imaging using light

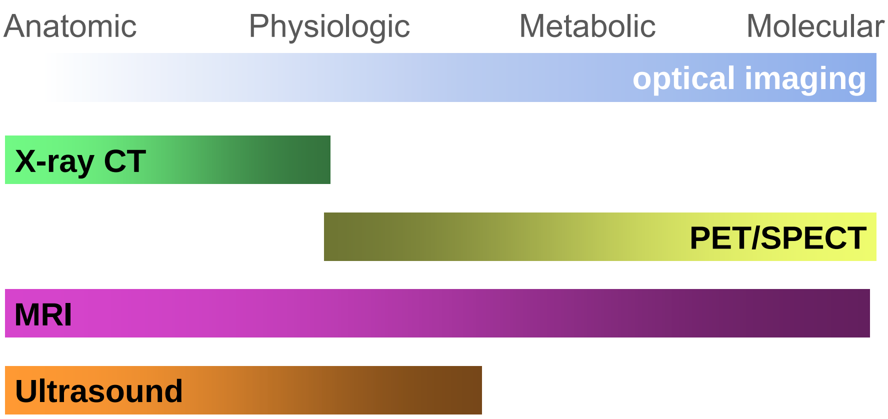


Dr Daniel Elson
Senior Lecturer in Surgical Imaging
Hamlyn Centre for Medical Robotics and Department of Surgery and Cancer
Wednesday 18th January 2012

The Hamlyn Centre
The Institute of Global Health Innovation

Imperial College London

In vivo imaging methods



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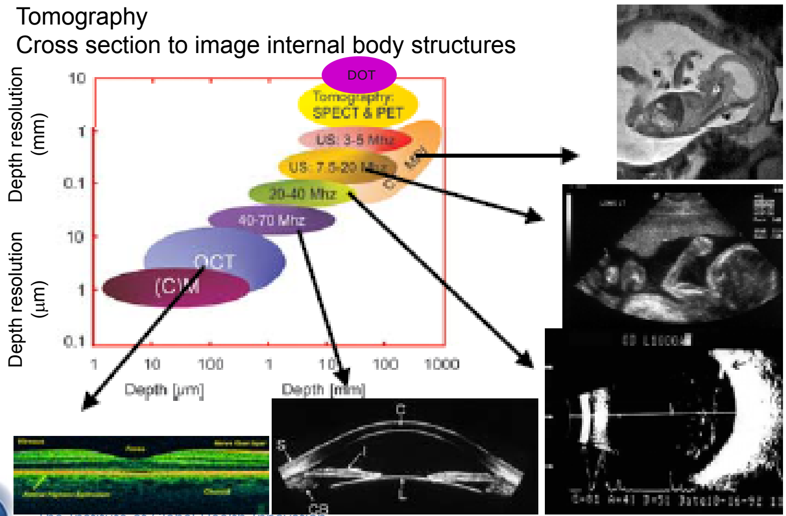
Courtesy Simon Cherry, UCD

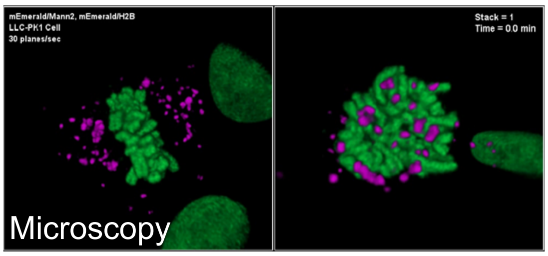
Medical Imaging and optical imaging

Tomography
Cross section to image internal body structures



Maurice Aalders, University of Amsterdam

Optical imaging in the life sciences

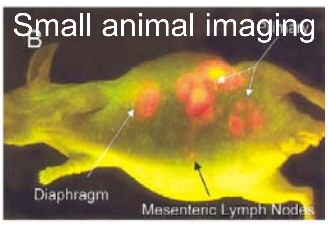


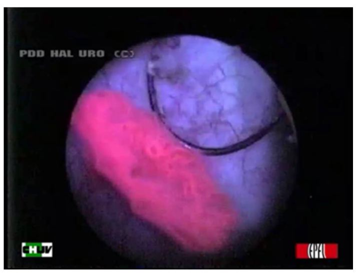
Basic research

Pre-clinical testing

Assessment of
tissue, disease
Response to therapy

Clinical





Content

- The basic interaction of light with tissue
- Tomographic imaging
- Endoscopic imaging
- Fluorescence
- Advanced endoscopic techniques

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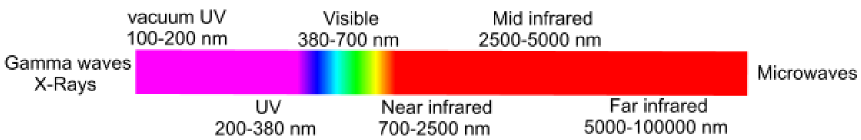
Properties of light 1: the light spectrum

- Light is an oscillating electromagnetic field that has a wavelength between 100 nm – 100 microns



- This field may strongly interact with the electrons in certain materials, usually causing a change in the speed of light (as well as other possible interactions) described by the refractive index:

$$n = \frac{speed\ of\ light\ in\ vacuum}{speed\ of\ light\ in\ medium} = \frac{c}{v}$$

- This field contains energy, and has a dual-character whereby it can be considered to have wave-like and particle-like properties. E.g. this energy may be considered to exist in energy packets, or photons.

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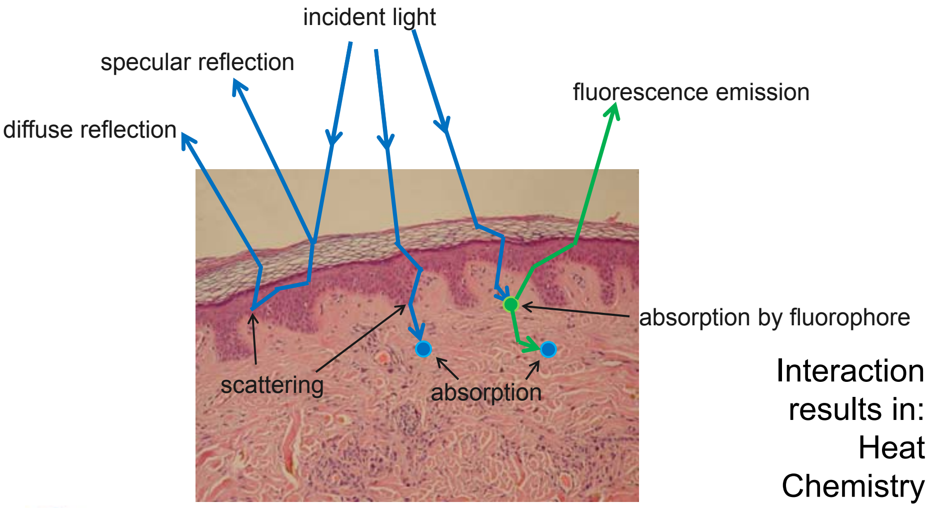
Main light-tissue interactions

Imperial College London



Interaction results in:
Heat
Chemistry
Light
Motion

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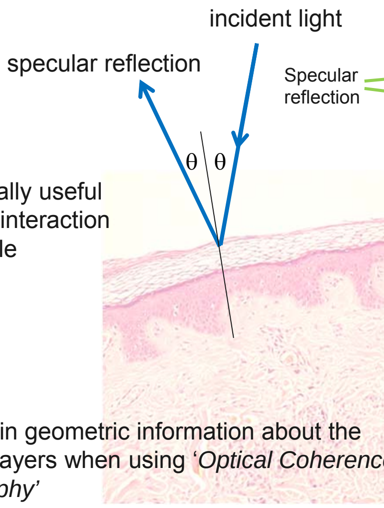
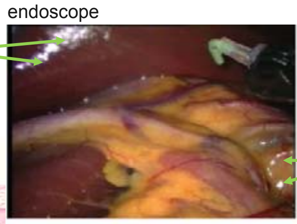
Specular reflection

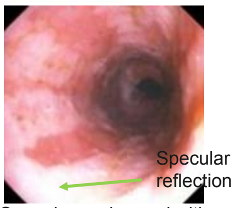
Imperial College London



Not generally useful – minimal interaction with sample

Cardiac surface imaged with rigid endoscope





Oesophagus imaged with flexible endoscope

Can obtain geometric information about the surface/ layers when using *'Optical Coherence Tomography'*

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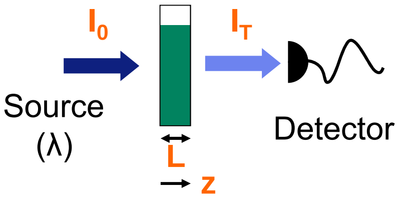
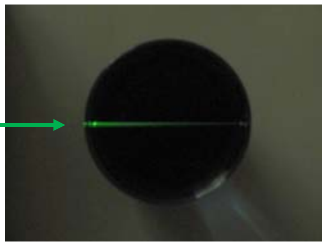
Optical absorption



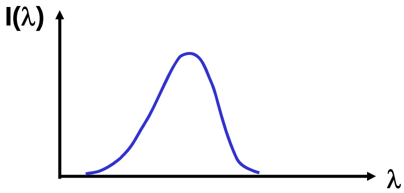


$\partial I = -I \times \mu_a \times \partial z$

Where μ_a is the absorption coefficient

$\Rightarrow I_Z = I_0 \, e^{(-\mu_a z)}$

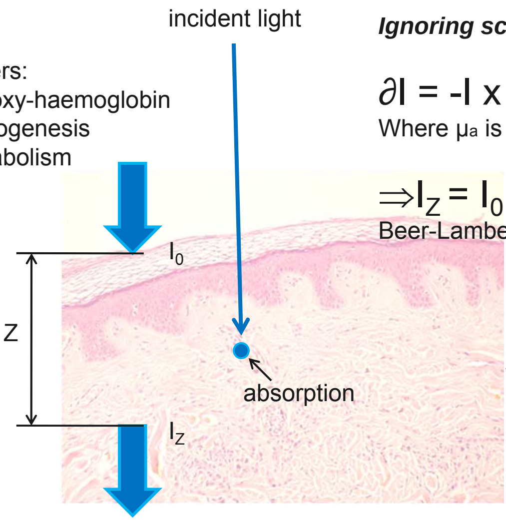
Beer-Lambert law



Absorption of a particular chemical is wavelength dependent

Absorption in tissue (in the absence of scattering)

Tissue absorbers:
- Oxy- and deoxy-haemoglobin
  - angiogenesis
  - metabolism
- Water
- Lipids



Ignoring scattering for now…

$\partial I = -I \times \mu_a \times \partial z$

Where μ_a is the absorption coefficient

$\Rightarrow I_Z = I_0 \, e^{(-\mu_a z)}$

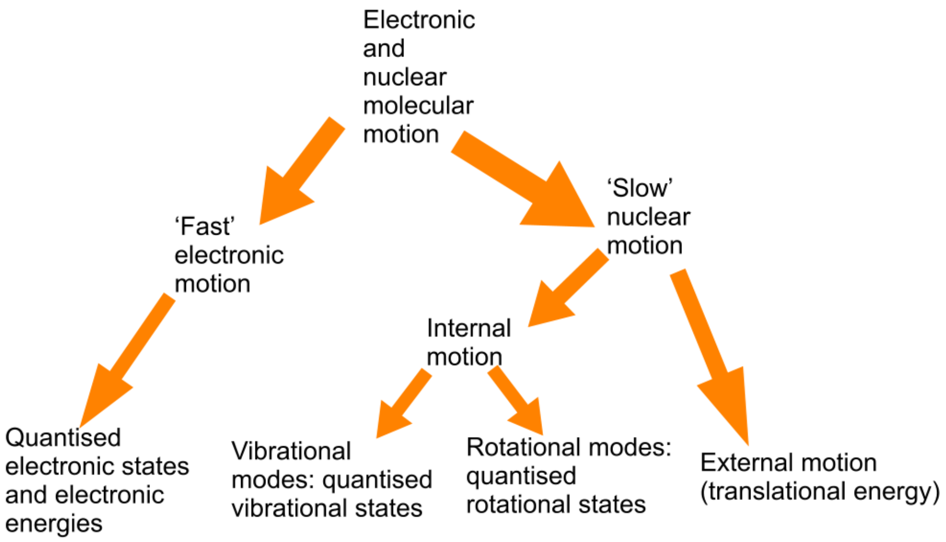
Beer-Lambert law

μ_a > 1-10 /mm in tissue

Absorption mean free path
$d_a = 1/\mu_a < 1$ mm

Strong absorption!
μ_a function of wavelength

Quantised states of a molecule



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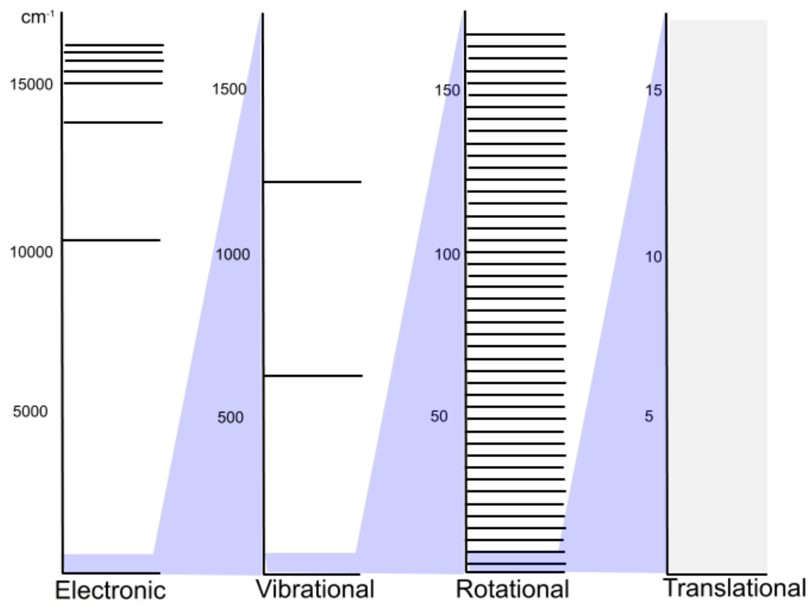
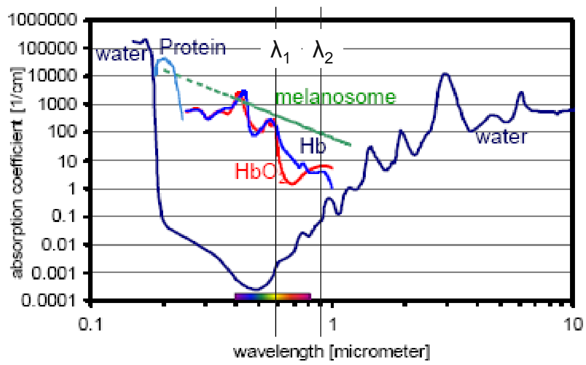
Molecular energy levels



Absorption spectra of tissue components

Imperial College London



- There is an optical transmission window at 600-1100 nm where oxyhaemoglobin absorption is low
- Can make absorption measurement at two wavelengths to record the relative concentrations of oxy- and deoxy-haemoglobin
- Problem: Scattering of light makes accurate measurements of absorption difficult

Sources of scattering in biological tissue

Imperial College London

Scattering occurs due to changes in the refractive index, for instance:

Collagen fibrils

Macromolecular aggregates

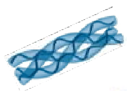
Lysosomes, vesicles

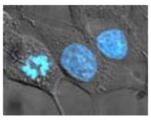
Mitochondria

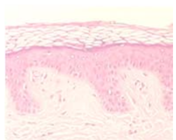
Nuclei

Cells

Bulk properties of tissue layers



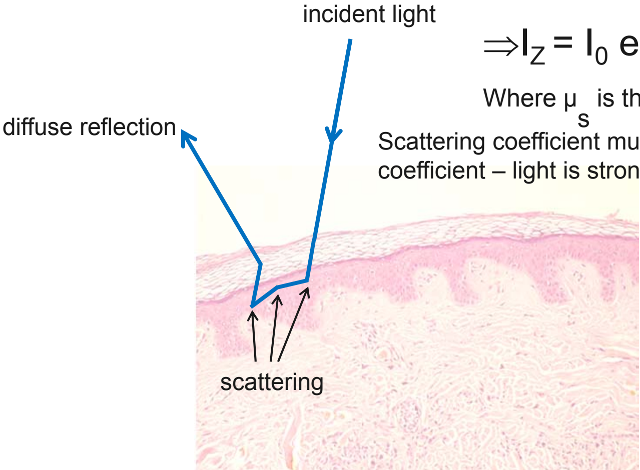




Scattering in bulk tissue

Imperial College London

Ignoring absorption for now…



Different tissue layers have different scattering properties

Elastic scattering…

$$\Rightarrow I_Z = I_0\, e^{(-\mu_s . z)}$$

Where μ_s is the scattering coefficient

Scattering coefficient much higher than absorption coefficient – light is strongly scattered.

$\mu_s > 10$ /mm in tissue

Scattering mean free path

$d_s = 1/\mu_s < 0.1$ mm

Makes tomographic imaging using light difficult (cf X-rays)

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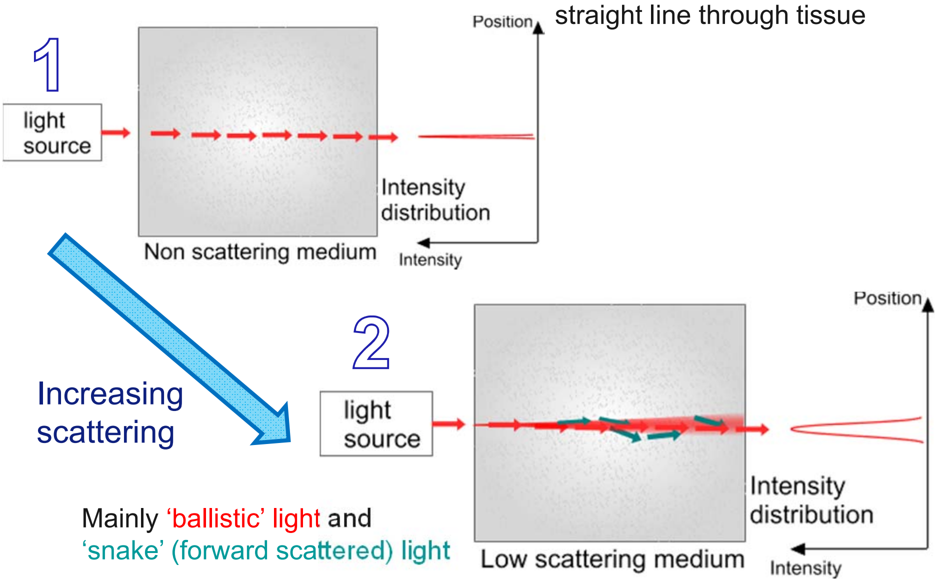
The effect of scattering on absorption measurements in tissue (1)

Imperial College London

All 'ballistic' light, propagates in straight line through tissue



Mainly 'ballistic' light and 'snake' (forward scattered) light

Optical projection tomography

- With low amount of scattering and small (<10 mm) samples, it is possible to carry out projection imaging
- Currently used in developmental biology studies

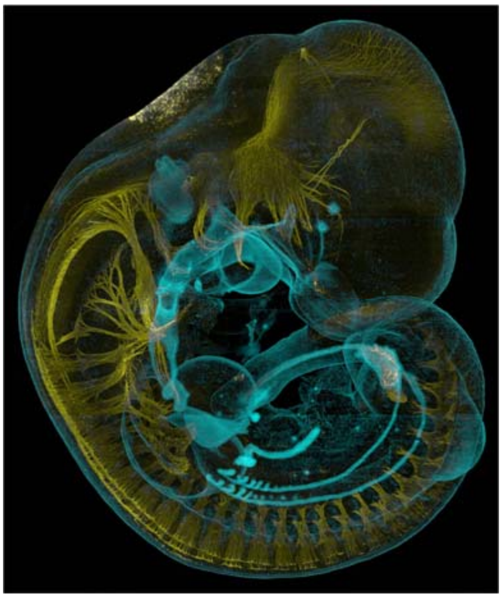
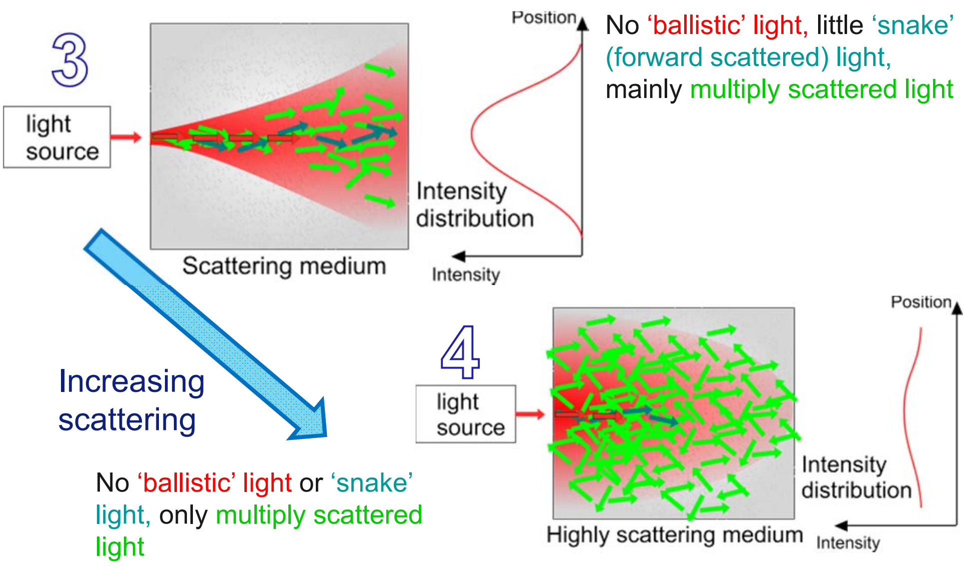
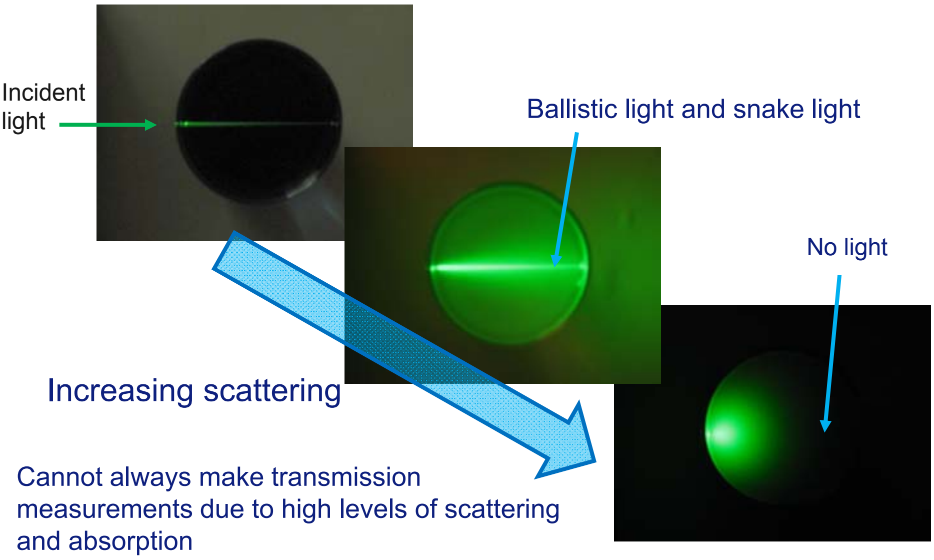


Image courtesy Jim Swoger/James Sharpe

The effect of scattering on absorption measurements in tissue (2)



Demonstration in phantoms with different scattering properties



Cannot always make transmission measurements due to high levels of scattering and absorption

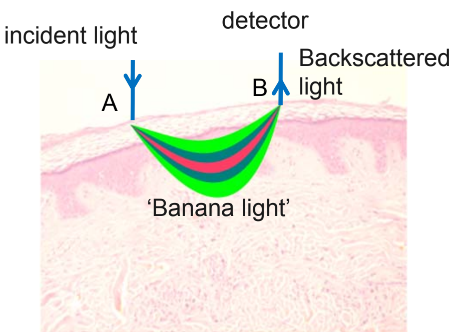
Making absorption measurements with backscatter

What happens between point A and point B?

Modelling shows that the light probes a 'banana' shaped volume of the tissue

DPF can be calculated for a particular tissue type and A-B distance by Monte Carlo methods, where a statistical simulation allows the average distance travelled by a huge number of photons to be calculated

Alternatively DPF it may be approximated using the diffusion equation



Application: Pulse oximetry

- Absorption varies depending on the concentration of oxy- and deoxy-haemoglobin
- Monitor optical absorption at two wavelengths (e.g. 650 nm, 900 nm)
- Blood volume varies depending on the phase of the heart beat
- By monitoring the temporally changing (AC) component, absorption due to other tissues may be factored out
- May also be used to monitor heart beat

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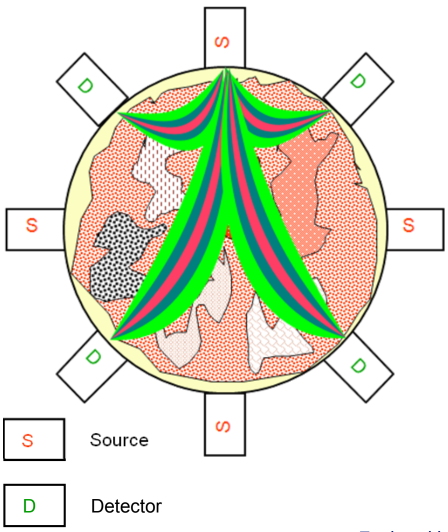
Diffuse optical tomography (DOT)

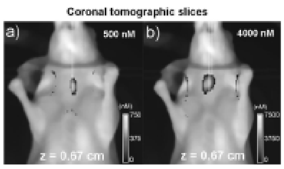


Actively developed for small animal imaging, e.g. for drug testing

Fluorescence contrast agents (molecular beacons) are being developed for clinical imaging

Small animals (e.g. rodents) are relatively easy compared with human tissue

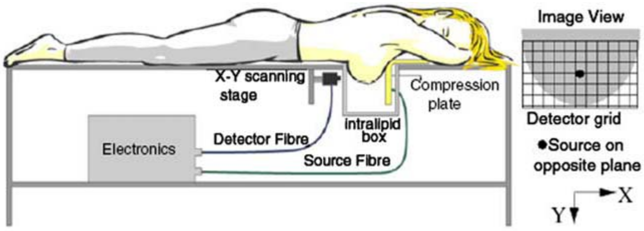
Also possible to image human brain and breast

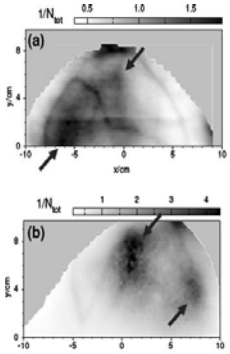


Zacharakis et al. IEEE Trans. Med. Imaging, 24 (205) 878-885

Application to breast imaging

- Possible to detect lesions in the breast by detecting increased haemoglobin
- Other applications of tomographic techniques are limited by strong tissue absorption

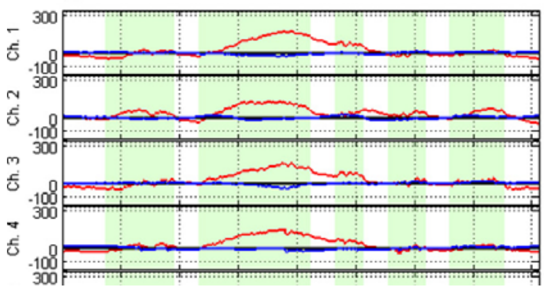




Leff et al. Breast Cancer Res Treat (2008) 108:9–22

Near infrared spectroscopy (NIRS)

- Example application: NIRS
- Can study brain activation by detecting absorption at different wavelengths to detect total blood volume, and oxy- and deoxy- haemoglobin levels



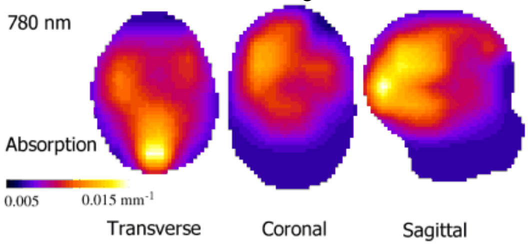
D.R. Leff et al. / NeuroImage 39 (2008) 805–813

Measurements in neonates

Imperial College London

In vivo imaging

In vivo images



http://www.medphys.ucl.ac.uk/research/borl/research/monstir/neonatal.htm

Difficult to resolve heterogeneities smaller than ~ 1 cm

Not very specific: absorption and scattering data

- OK using blood, oxygen but often *not* able to contrast diseased and healthy tissue

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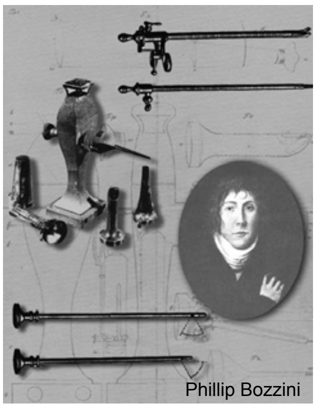
Early Optical imaging in minimally invasive surgery

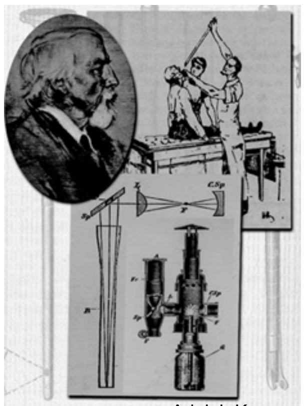
Imperial College London



Light sources mounted at the tip of the endoscopy (candle, gas lamp or electric bulb).

Rigid instruments

Could access oesophagus, stomach and bronchus



Adolph Kussmaul

Constant drive to extend diagnostic capabilities to the lumen of the human body.

From the Lumen to the Laparoscope, *Irvin M. Modlin et al. Surgical Endoscopy*

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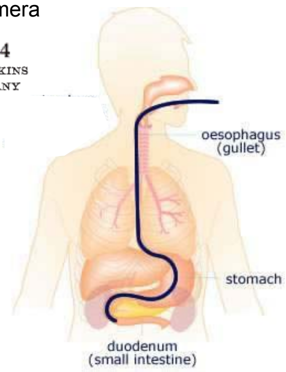
Development of fibrescopic endoscopy

Image is relayed from (internal) sample via fibre bundle (*~ 1 m long, 0.5 – 12 mm diameter*) to eyepiece or CCD camera

NATURE January 2, 1954
H. H. HOPKINS
N. S. KAPANY
Department of Physics,
Imperial College of Science and Technology,
London, S.W.7.

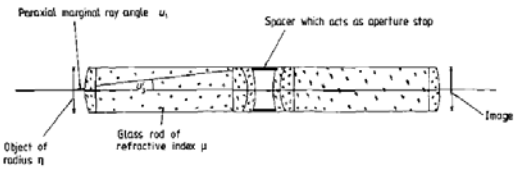


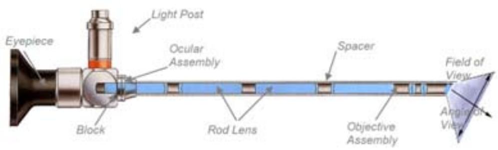
Illumination source (often Xenon lamp) is coupled in via 2nd fibre bundle or liquid light guide

"wet" end of endoscope can be articulated so fibre bundle needs to be very flexible
- limits diameter (*< 3mm*) and number of fibres
- typically ~ 12,000 fibres

Hopkins' rod lens endoscope

Imperial College London

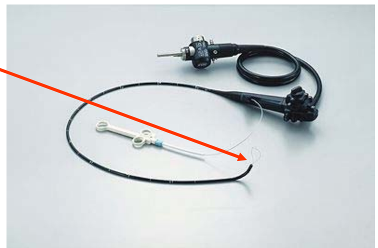




High resolution optical system
Wide field of view (100 degrees)
Wide range of working distances (10 - >100 mm)
Good colour performance (low chromatic aberrations)

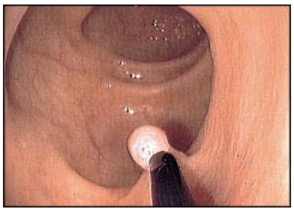
Flexible wide-field video endoscopes

Image is captured by miniature CCD camera at (internal) sample and transmitted via cable to monitor



Illumination source (often Xenon lamp) is coupled in via fibre bundle

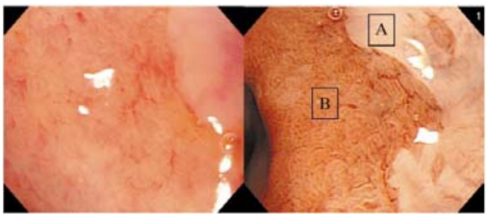
Superior resolution to flexible fibre endoscope



Narrow band imaging

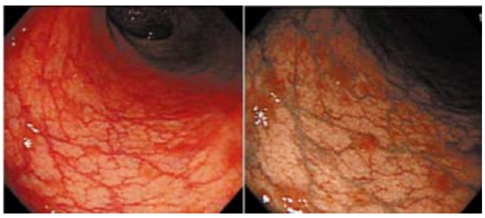
Use narrow (30 nm FWHM) sub-bands of light, instead of full white light spectrum

Conventional NBI



Barrett's Oesophagus

Blue light – high haemoglobin absorption
Green and red light – higher tissue penetration



Adenomatous colon

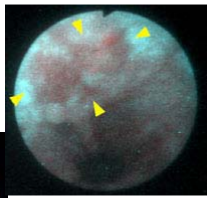
Gono et al. Journal of Biomedical Optics 9(3), 568–577 (May/June 2004)

Fluorescence imaging

Imperial College London

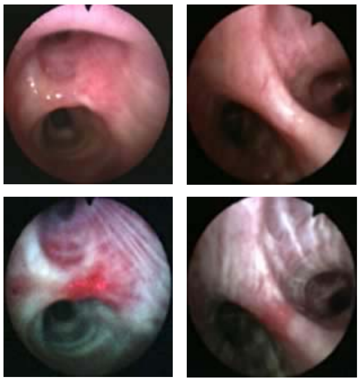
Olympus Lucera system

Fluorescence



White light

Xillix LIFE-GI Endoscope system



Richard Wolf DAFE system

High sensitivity (>90%) but lower specificity (<70%)

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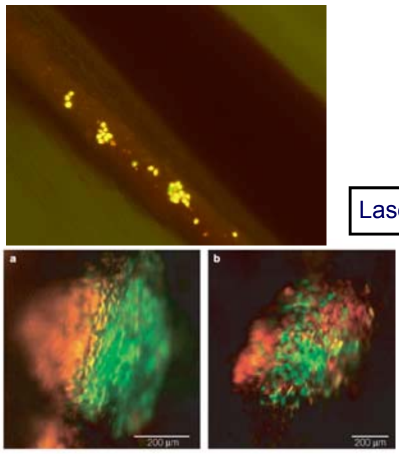
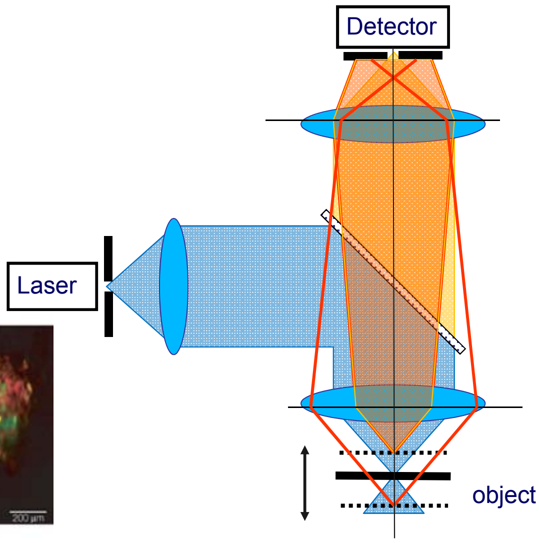
Confocal scanning laser microscopy (reminder)

Imperial College London

- Depth resolution – 3D imaging
- Digital image acquisition

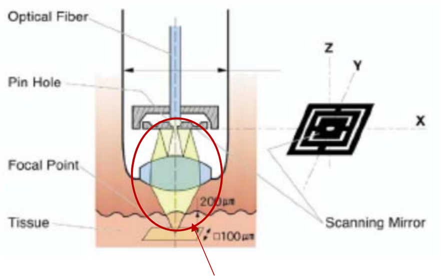




Endoconfocal microscopy: scanning 1

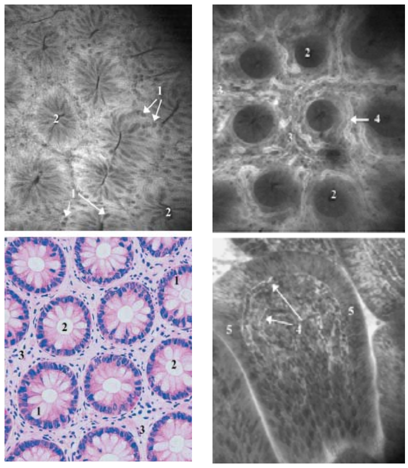
Imperial College London

Approach 1: distil scanning (Pentax system)
Mirror activated by electrostatic effect



Miniature confocal microscope

Pentax system



Polglase et al. Gastrointestinal Endoscopy Volume 62, No. 5 : 2005

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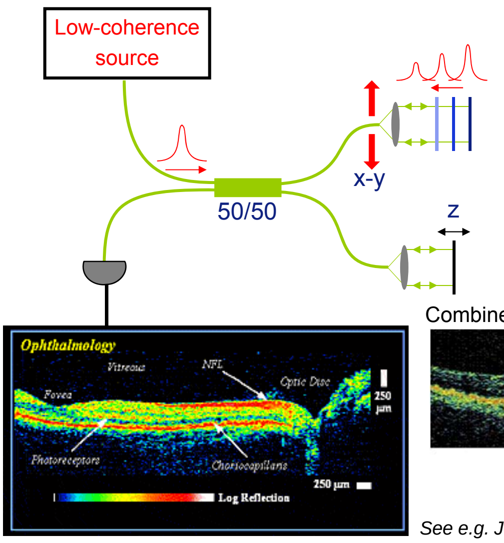
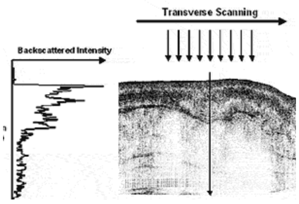
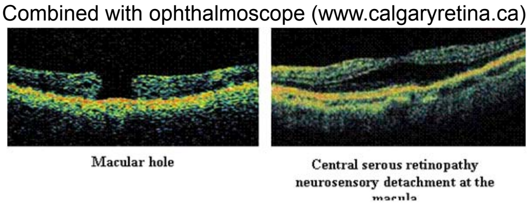
Ophthalmic applications

Imperial College London





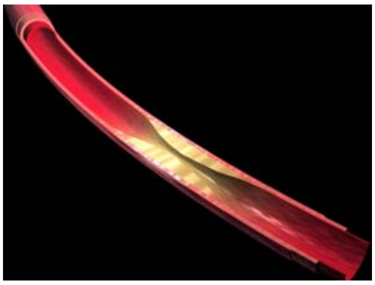
Combined with ophthalmoscope (www.calgaryretina.ca)



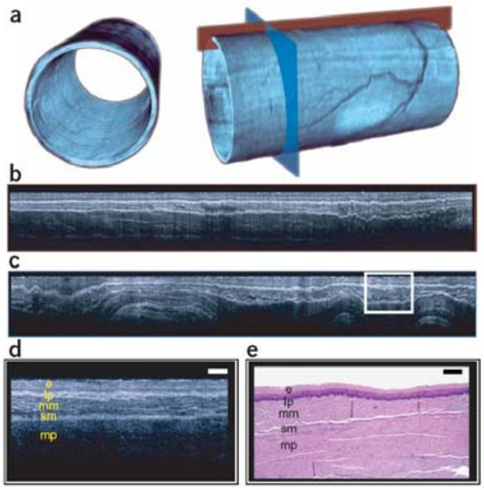
See e.g. J. G. Fujimoto, Nat. Biotech. 21(2003) 1361

Examples: In vivo endovascular OCT

NATURE MEDICINE 12(12), pp. 1430, 2006
http://dx.doi.org/10.1038/nm1450
Figure 2



http://www.lightlabimaging.com/intl/prodsrv/cathetermovie.htm



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Summary

- Tissue scatters and absorbs light strongly, so it is difficult to make tomographic reconstructions
- However, it is possible to combine some tomographic information with functional information, e.g. NIRS, detecting breast lesions
- Also has advantage of being non-ionising and minimally invasive
- Superficial imaging of tissue surface can yield high spatial resolution, e.g. endoscopy
- Different endoscopy modalities can determine different information about the sample
- Photodynamic detection allows fluorescence demarcation of tumours and image-guided treatment

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