Challenges in Biophotonics

Therapeutic and Diagnostic applications of light in medicine

Laser therapy

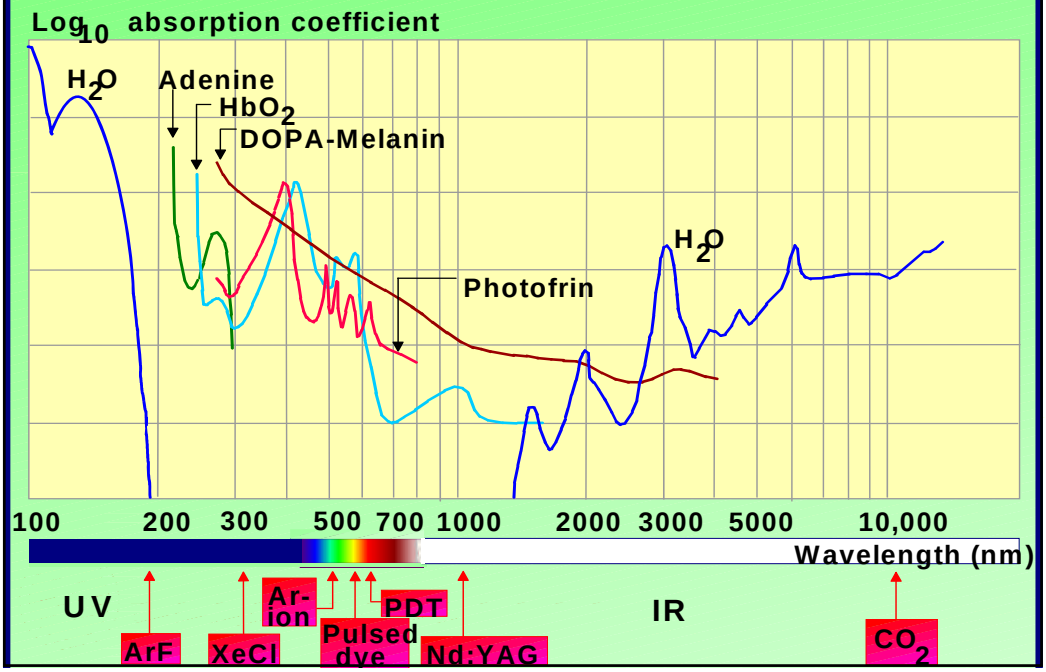
- **Laser surgery and ablation**
- **Thermo therapy and photocoagulation therapy**
- **Tatoo removal**
- **Cosmetic hair removal**
- **Photodynamic therapy**

Why are lasers used for medical treatments?

- Effective local treatment
- Minimally invasive
- Minimal side-effects
- No bleeding
- Non-contact

Lund University Medical Laser Centre, Sweden

Absorption spectra of tissue chromophores



Medical Laser Therapy

- Laser surgery
  - Eye (Ar-ion , Nd:YAG, Excimer lasers)
  - Dermatological (CO_2, Dye, Ruby, Ar-ion lasers)
  - General surgery (Nd:YAG, diode, CO_2 lasers)
- Thermo therapy
- Photodynamic therapy

Dosimetry is essential!!

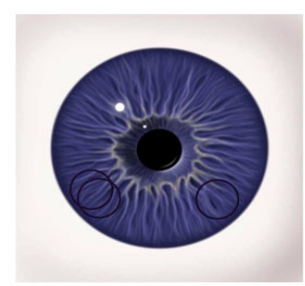
LASIK

***L**aser-**A**ssited **I**n **S**itu **K**eratomileusis*

LASIK

Laser-Assited In Situ Keratomileusis

Seven steps towards a perfect sight



1. Mark the cornea with inc. Apply anaesthetic eye drops!

From www.eyesurgeryeducation.com

Lund University Medical Laser Centre, Sweden

LASIK

Laser-Assited In Situ Keratomileusis

Seven steps towards a perfect sight

2a. Fixate the eye with a suction ring
(Option: 2b. Wavefront analysis of the eye)

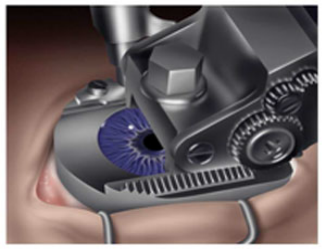
From www.eyesurgeryeducation.com

Lund University Medical Laser Centre, Sweden

LASIK

Laser-Assited In Situ Keratomileusis

Seven steps towards a perfect sight



3. Peel a slice of the cornea with a *microkeratome*

From www.eyesurgeryeducation.com

Lund University Medical Laser Centre, Sweden

LASIK

Laser-Assited In Situ Keratomileusis

Seven steps towards a perfect sight

4. Expose the underlying layer of the cornea.

From www.eyesurgeryeducation.com

Lund University Medical Laser Centre, Sweden

LASIK

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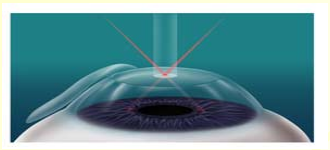
Seven steps towards a perfect sight



5. Laser alignment of the eye.

From www.eyesurgeryeducation.com

Lund University Medical Laser Centre, Sweden

LASIK

Laser-Assited In Situ Keratomileusis

Seven steps towards a perfect sight

Typical values

W_{pulse}= 3mJ, t_{pulse}= 18 ns

λ=193 nm f = 50Hz

$\varnothing_{beam}$= 0.9 mm

6. Reshape the cornea! (Excimer laser)

From www.eyesurgeryeducation.com

Lund University Medical Laser Centre, Sweden

LASIK

Laser-Assited In Situ Keratomileusis

Seven steps towards a perfect sight

7. Put the flap back, wait 5 minutes, then go home!

From www.eyesurgeryeducation.com

Medical Laser Therapy

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- Thermo therapy
- Photodynamic therapy

  Dosimetry is essential!!

Laser Skin Resurfacing

Wrinkles

Lund University Medical Laser Centre, Sweden

Courtesy: Stuart Nelson, UC Irvine

Laser Skin Resurfacing

Rhinophyma

Lund University Medical Laser Centre, Sweden

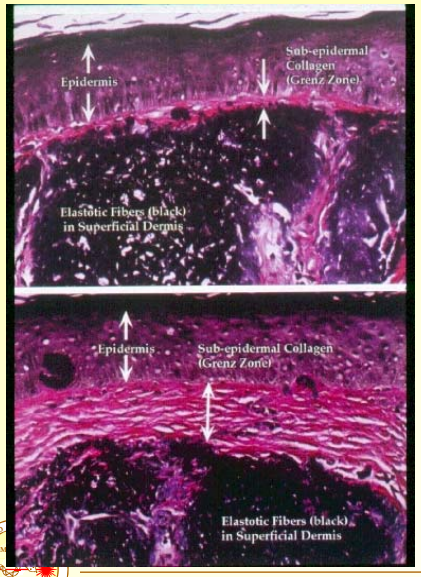
Courtesy: Stuart Nelson, UC Irvine

Laser Skin Resurfacing

Lund University Medical Laser Centre, Sweden

Courtesy: Stuart Nelson, UC Irvine

Formation of New Collagen



Pre Treatment

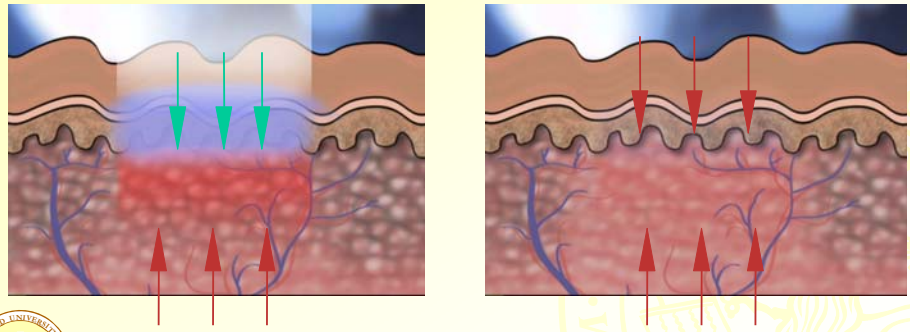
6 Months Post Treatment

Lund University Medical Laser Centre, Sweden

Courtesy: Stuart Nelson, UC Irvine

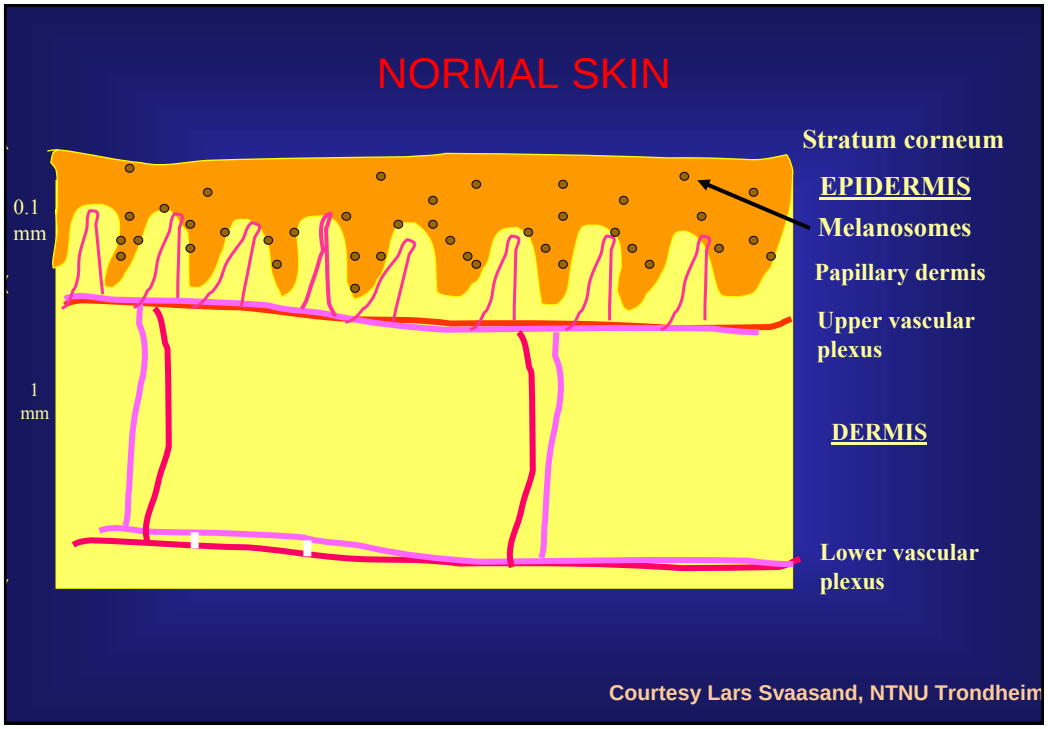
What is Non-Ablative Skin Rejuvenation?

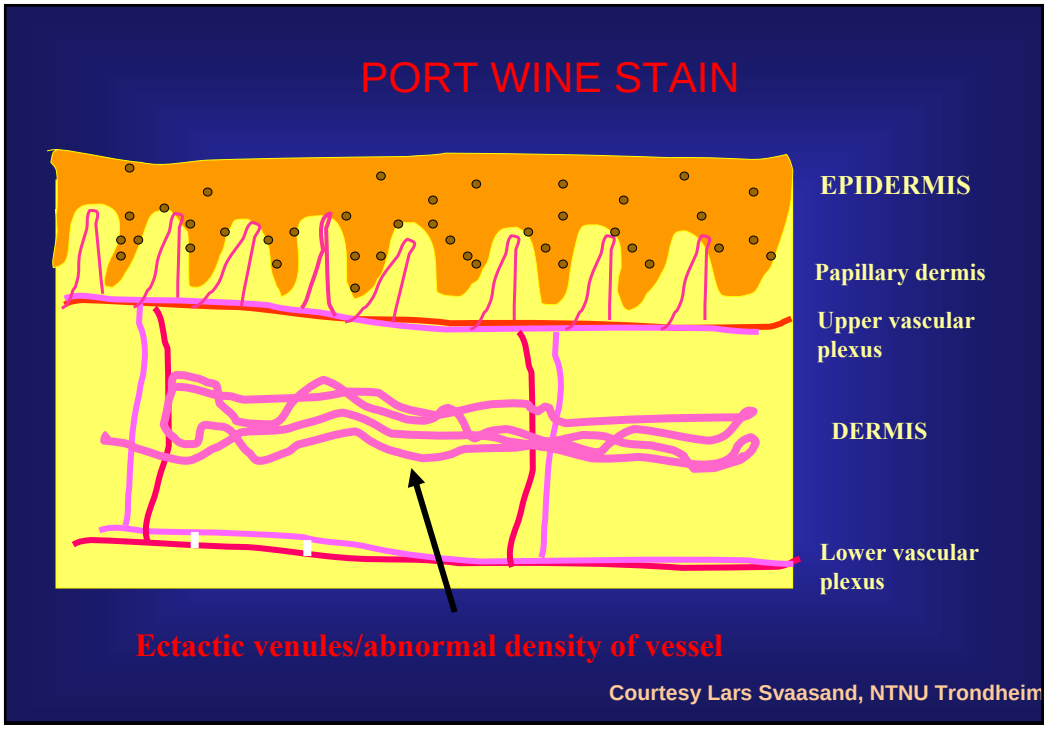
Epidermal protection **New collagen deposition**

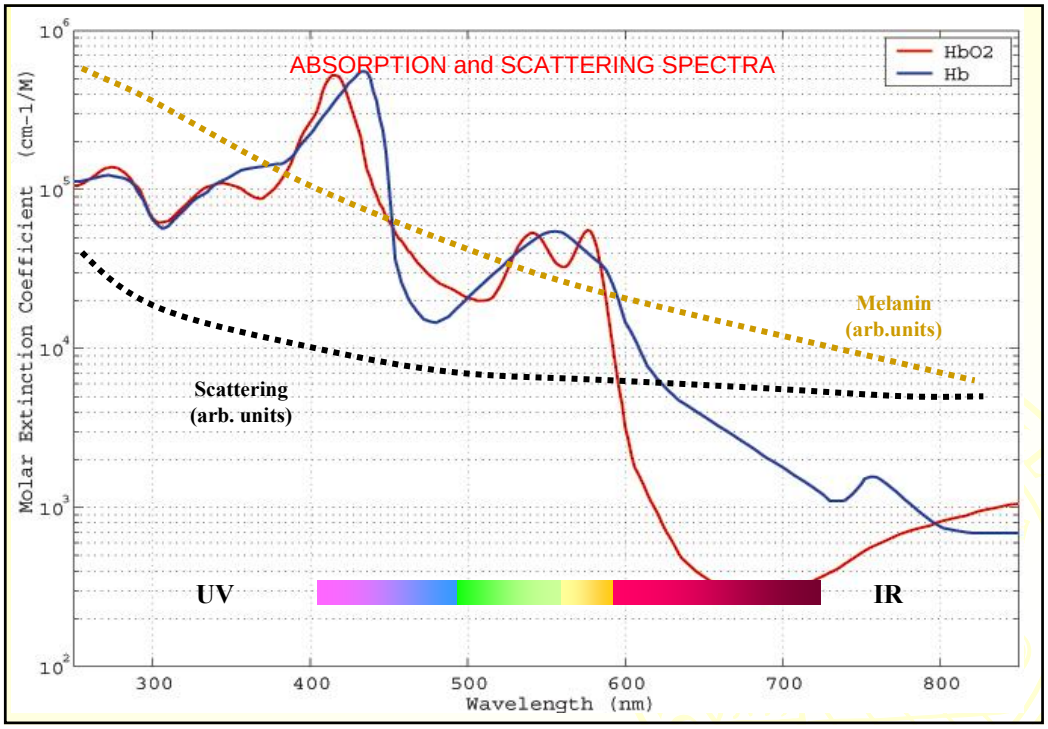


Lund University Medical Laser Centre, Sweden

Courtesy: Stuart Nelson, UC Irvine


NORMAL SKIN
Stratum corneum
EPIDERMIS
Melanosomes
Papillary dermis
Upper vascular plexus
DERMIS
Lower vascular plexus
0.1 mm
1 mm
Courtesy Lars Svaasand, NTNU Trondheim


PORT WINE STAIN
EPIDERMIS
Papillary dermis
Upper vascular plexus
DERMIS
Lower vascular plexus
Ectactic venules/abnormal density of vessel
Courtesy Lars Svaasand, NTNU Trondheim



Medical Laser Therapy

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- **Thermo therapy**
- **Photodynamic therapy**

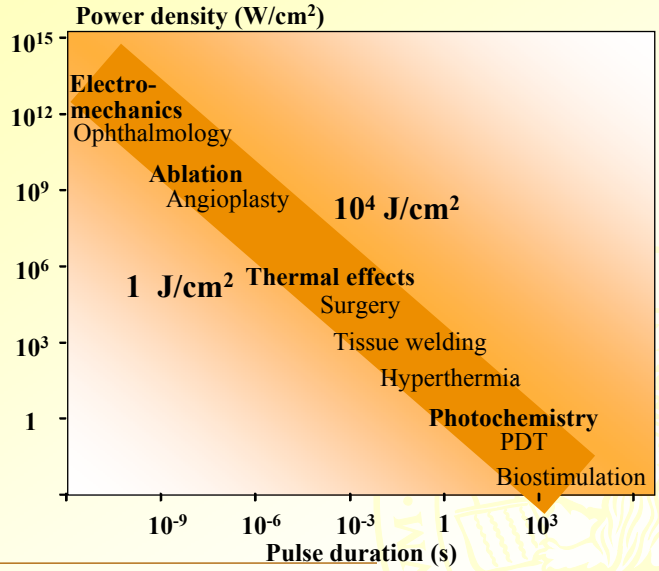
Dosimetry is essential!!

Laser Medical pen

- Both for cutting tissue and for coagulation of bleedings
- Laser characteristics: P = 5W, λ = 980 nm

Developed by the US Air Force

Laser-Tissue Interaction Mechanisms

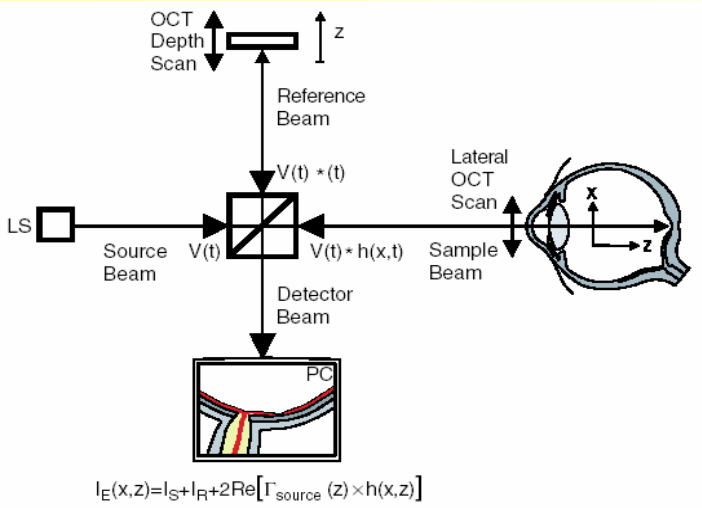


Optical measurements of tissue

- **Morphological measurements**
  - White light imaging and Microscopy
  - Optical coherence tomography (OCT)
  - Optical mammography
- **Physiological measurements**
  - Oxygenation
  - Optical biopsy
  - Transcutaneous glucose measurements
  - Body fluid constituents (dialysis monitoring, blood vials analysis)
- **Velocity measurements**
  - Laser Doppler
  - Breathing
  - Photoplethysmography (PPG)

"OCT for dummies"

Optical **C**oherence **T**omography

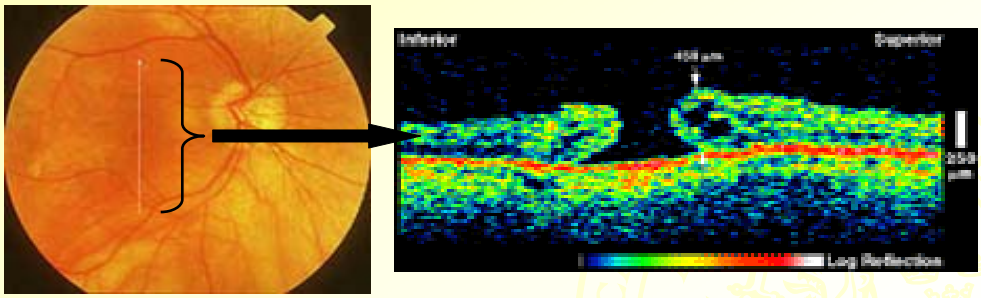


Commercial OCT system

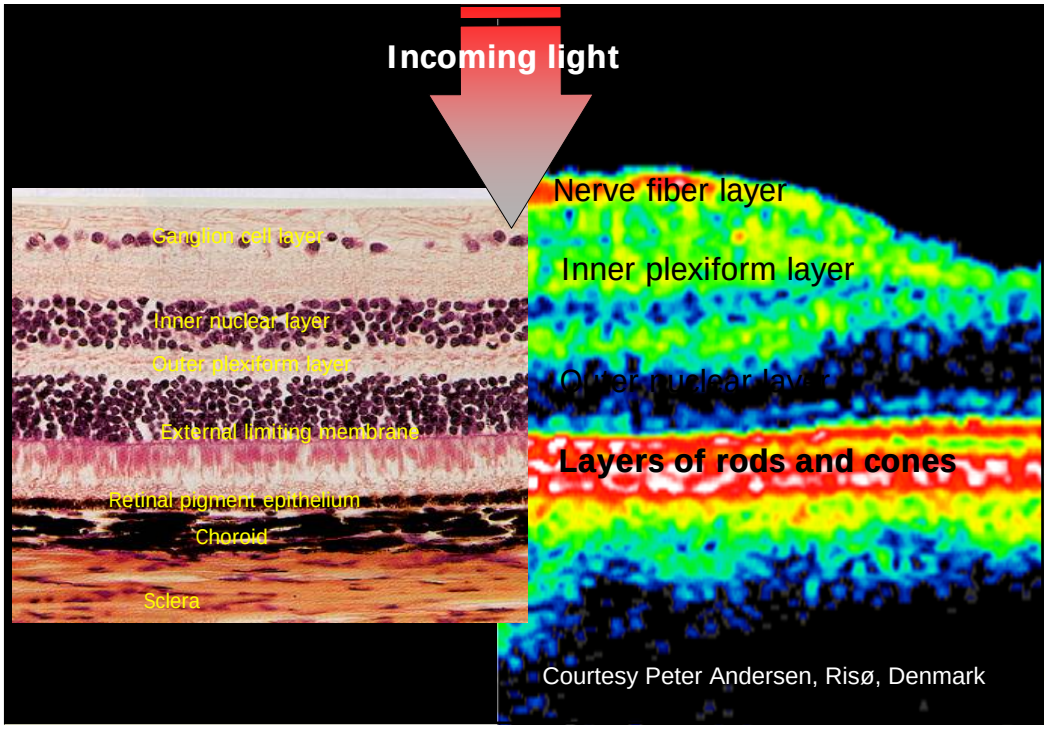
Humphrey® Optical Coherence Tomography Scanner at Herlev Hospital.

Courtesy Peter Andersen, Risø, Denmark

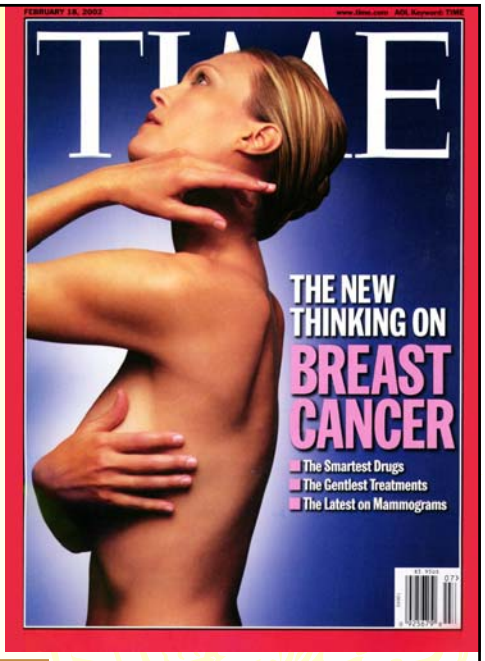
Applications: Ophthalmology



Courtesy Peter Andersen, Risø, Denmark

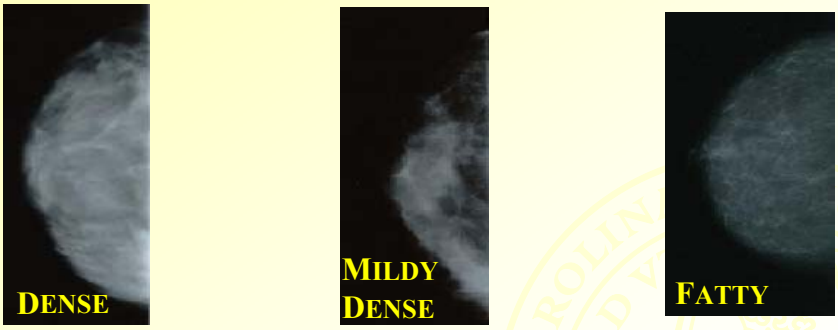


Opportunities for New Technologies



Consequences of Age Related Changes

x-ray mammograms (normal breasts)



AGE

http://homearts.com/depts/health/a8bhty51.htm

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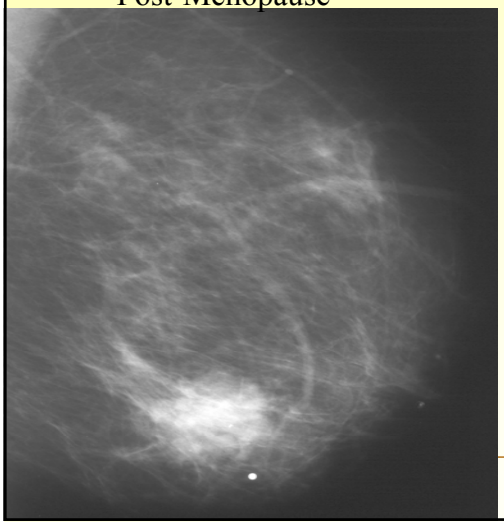
Mammography: Good and Bad

Overall ~90% sensitivity, specificity

Post-Menopause



Pre-Menopause

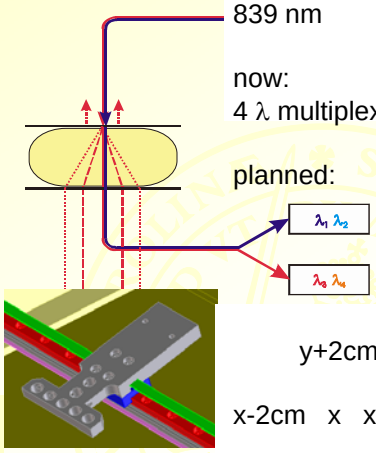
PTB Multi-Channel Scanning Laser Pulse Mammograph (mark #2, 2003)

- 4 (8) detection channels → off-axis data (z_T)
- 4 wavelengths →cHb, $cHbO_2$ + water + lipid
  →scatter power

652 nm
684 nm
797 nm
839 nm

now:
4 λ multiplexed

planned:



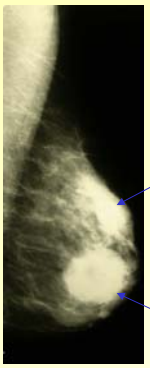
y+2cm

x-2cm x x+2cm

PTB

Patients #144: Cysts (Mammot3)

Thickness: 4.8 cm (CC)
5.0 cm (OB)



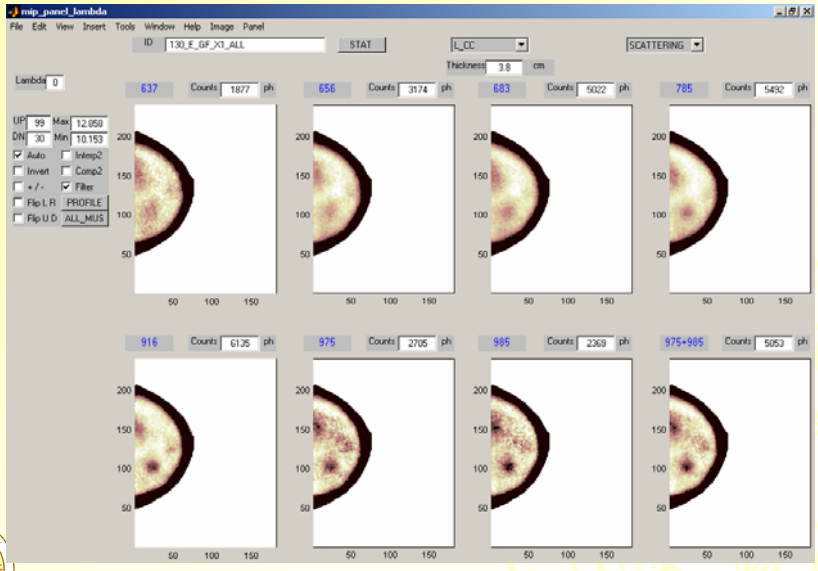
Scattering

637 nm 656 nm 683 nm 785 nm

Lund University Medical Laser Centre, Sweden

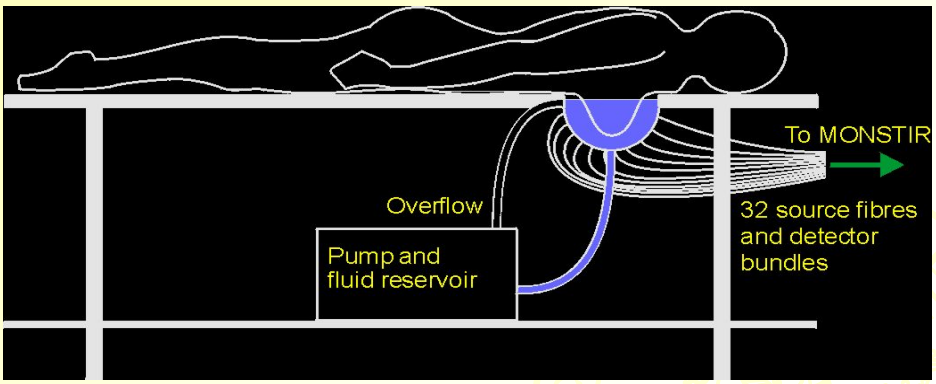
Courtesy Alessandro Torrecelli, POLIMI

Patient #130: Cyst (Scattering)



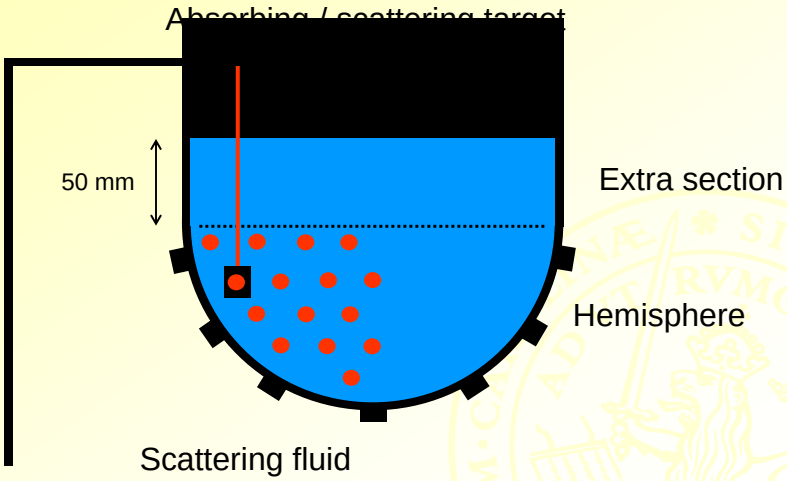
Courtesy Alessandro Torrecelli, POLIMI

Construction of 3D scanning bed



Courtesy Jeremy Hebden, UCL London

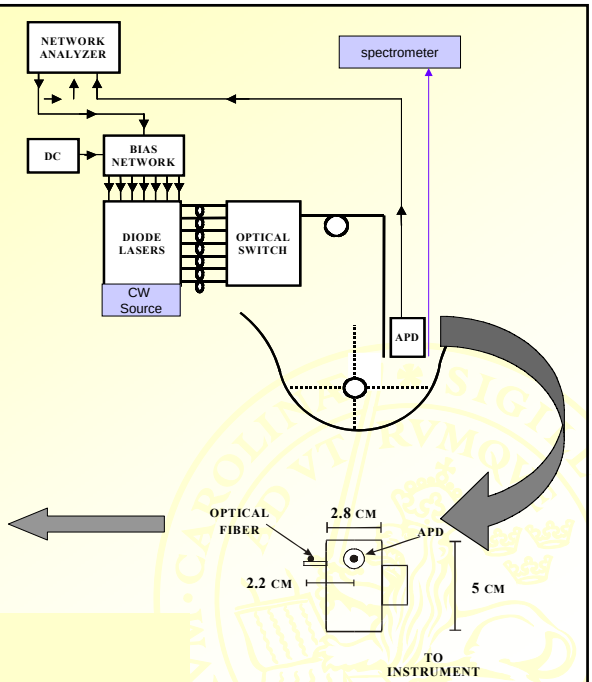
Evaluation of contrast & spatial resolution



Lund University Medical Laser Centre, Sweden

Courtesy Jeremy Hebden, UCL London

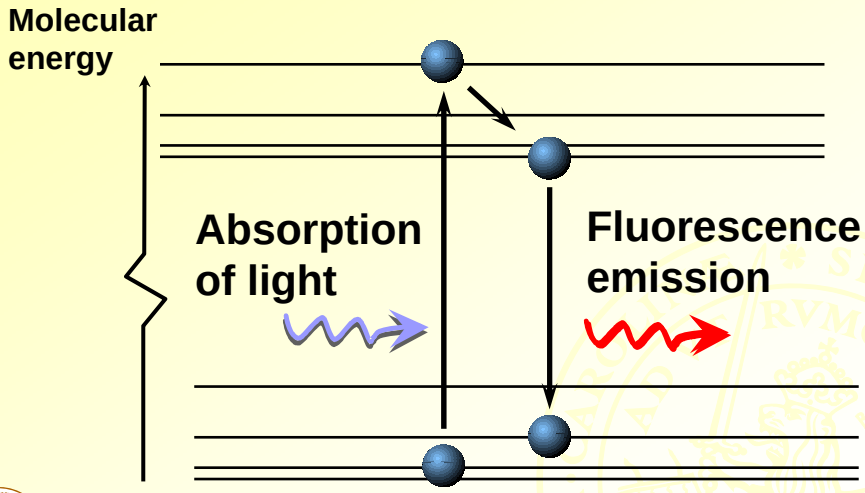
Hand-Held Optical Scanner



Pham, TH., et al. Review of Scientific Instruments, 71 , 1 – 14, (2000).
Bevilacqua, F., et al. Applied Optics, 39, 6498-6507, (2000).

Courtesy Bruce Tromberg, UC Irvine

Fluorescence?



Clinical questions

* Discriminate adenoumatous and hyperplastic polyps in the **colon**
* Identify premalignant and malignant lesions of the **vocal fold**
* Identify malignant tissue in the **brain**
* Visualize the borders of malignant **skin** lesions

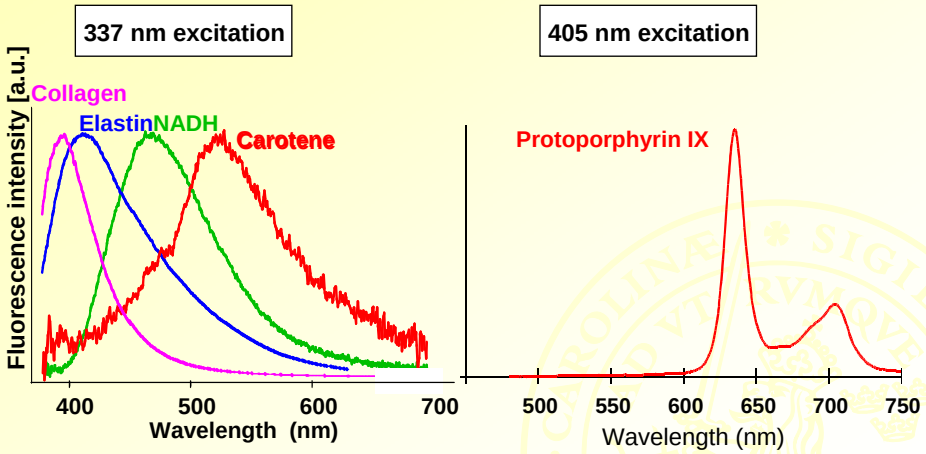
Fluorescence diagnostics

- Optical contact fibre or through surgical microscope
- Non-invasive
- Real-time diagnosis
- Provide “optical biopsy” information
- Endoscopy

- Autofluorescence
  - Collagen
  - Elastin
  - NADH...

Fluorescence:

Tissue autofluorescence Protoporphyrin IX



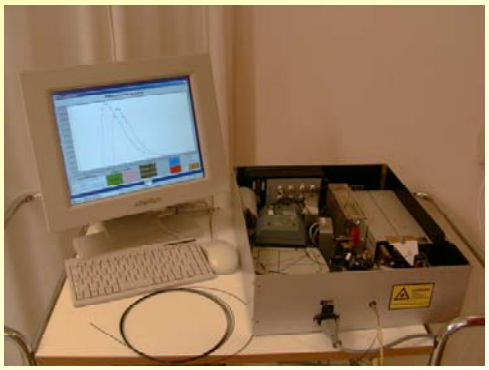
J. Johansson, Dissertation thesis, LTH (1993).
af Klinteberg *et al.* (1999)

Clinical measurements

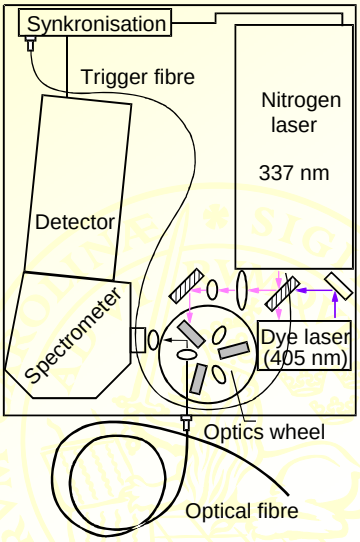
Hyperplastic:

Adenomatous:

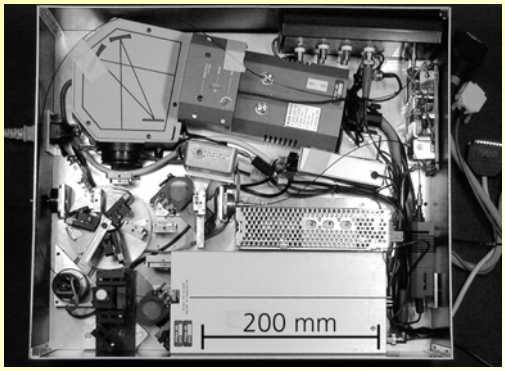
Gated Fluorosensor



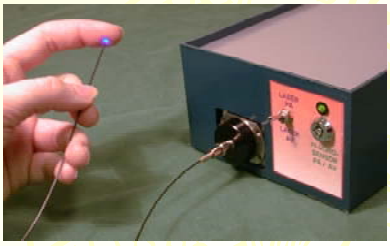
1998-



Fluorosensors

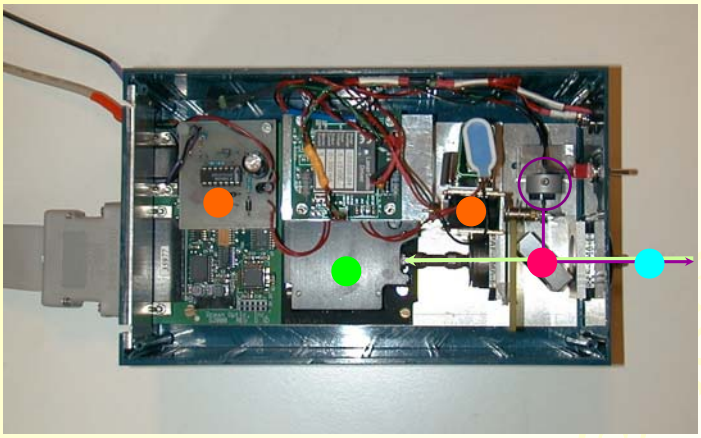


Nitrogen laser based fluorosensor



Diode laser based fluorosensor

Diode laser fluorosensor



1999

- Diode laser 396 nm
- Beam splitter
- Optical fibre
- Spectrometer

2001

- Shutter

Software

Lap top controlled

Old, old systems

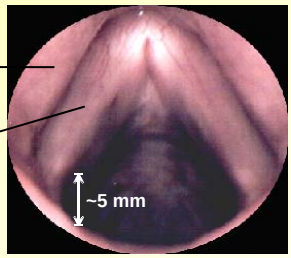
1986

1999
R.I.P.

1990

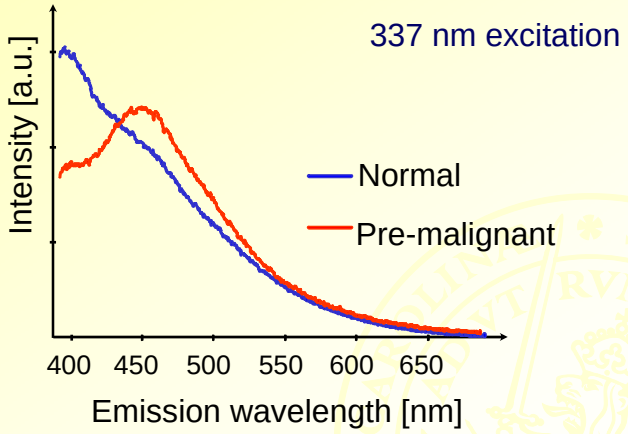
2003
R.I.P.

Fluorescence larynx



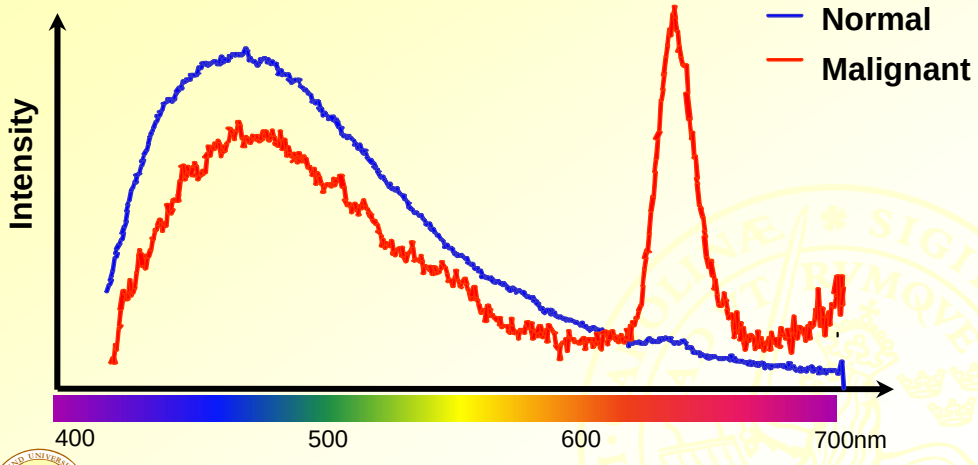
- 337 nm excitation
- Multivariate methods for classification: SIMCA, PCA, PLS, logistic regression.
- Malignant and premalignant lesions vs. normal tissue
  ⇒ up to 88% sens. and 93% spec.

Autofluorescence spectra from tissue

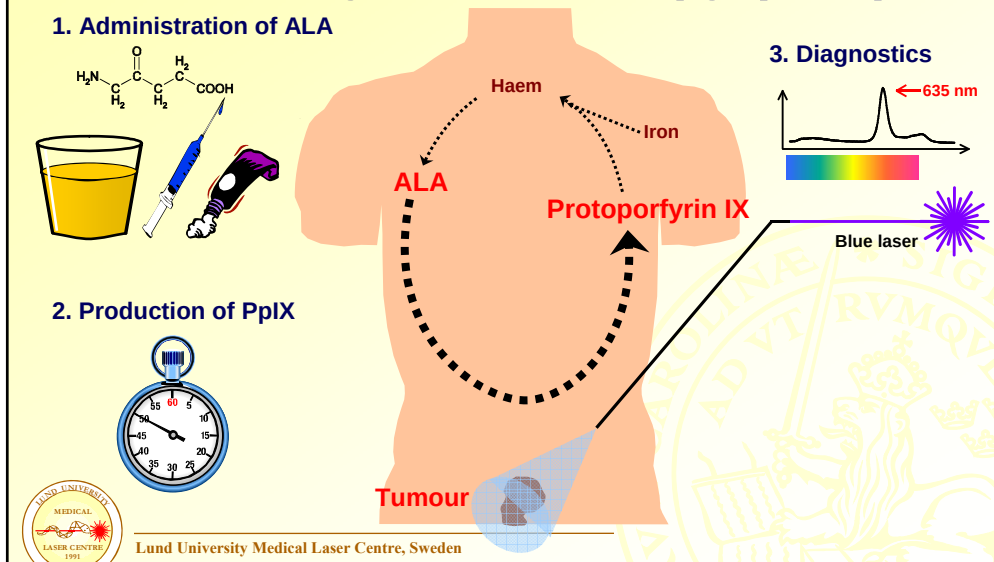


- Autofluorescence
  - Collagen
  - Elastin
  - NADH...
- Fluorescence induced by tumour marker
  - e.g. ALA-induced PpIX

Typical fluorescence spectra



Exogenous fluorescence and Photodynamic therapy (PDT)



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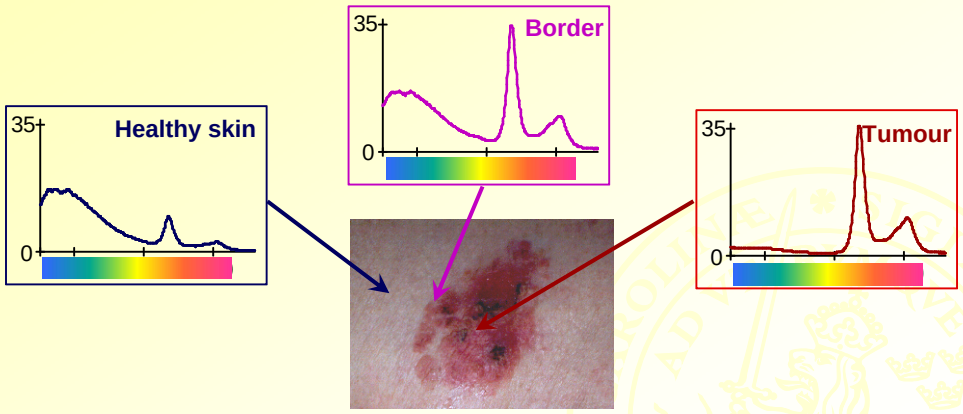
Fluorescence diagnostics of skin tumour following ALA administration

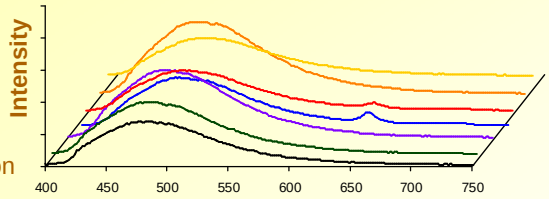


Basal Cell Carcinoma of the skin

Lund University Medical Laser Centre, Sweden

Fluorescence spectra

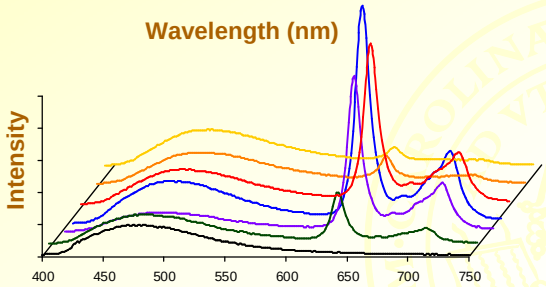
Normal skin
10 mm outside lesion



1 hour post PDT
Post PDT
Pre PDT
4 hours post ALA
2 hours post ALA
1 hour post ALA
Pre ALA

Wavelength (nm)

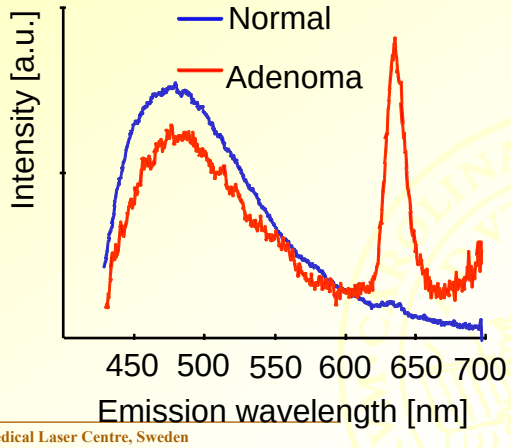
BCC
Centre of lesion



Lund University Medical Laser Centre, Sweden

Tissue fluorescence with ALA-PpIX as tumour marker

405 nm excitation



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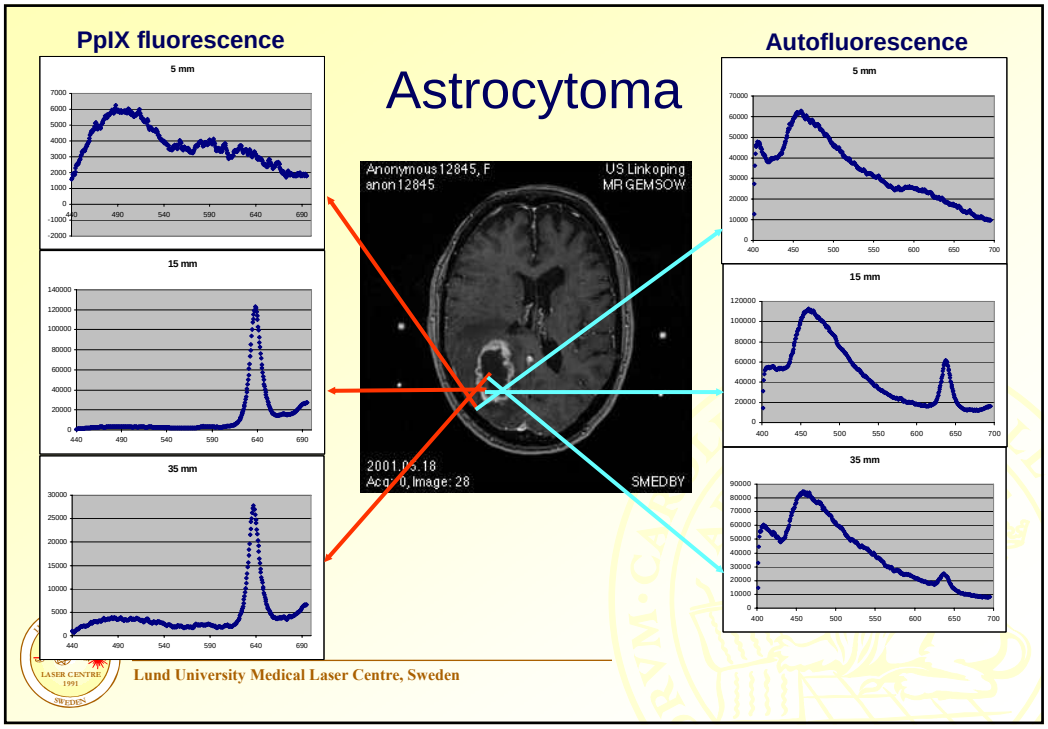
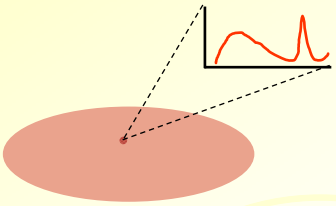
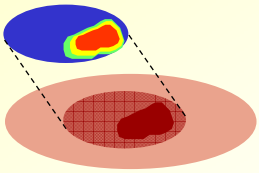

PpIX fluorescence
Astrocytoma
Autofluorescence
5 mm
15 mm
35 mm
Anonymous12845, F
anon12845
US Linkoping
MR GEMSOW
2001.03.18
Acq: 0, Image: 28
SMEDBY
Lund University Medical Laser Centre, Sweden

Fluorescence diagnostics

Point monitoring:
Whole spectrum in
one small tissue site

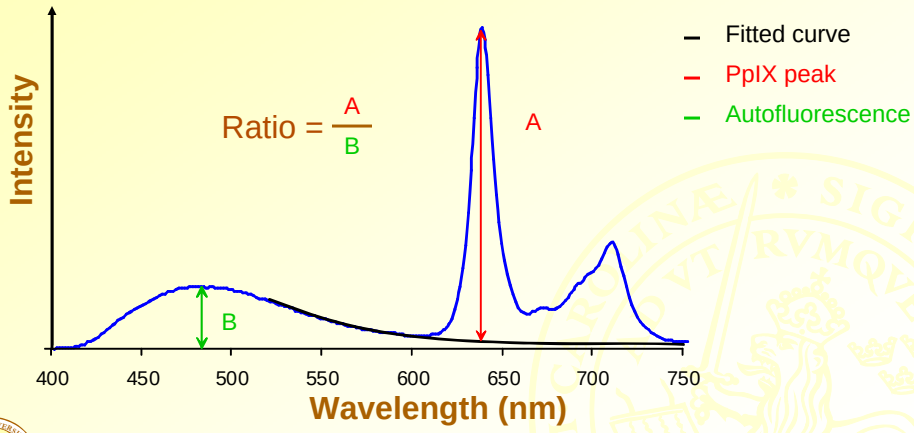




Imaging:
Less spectral information
but in larger area

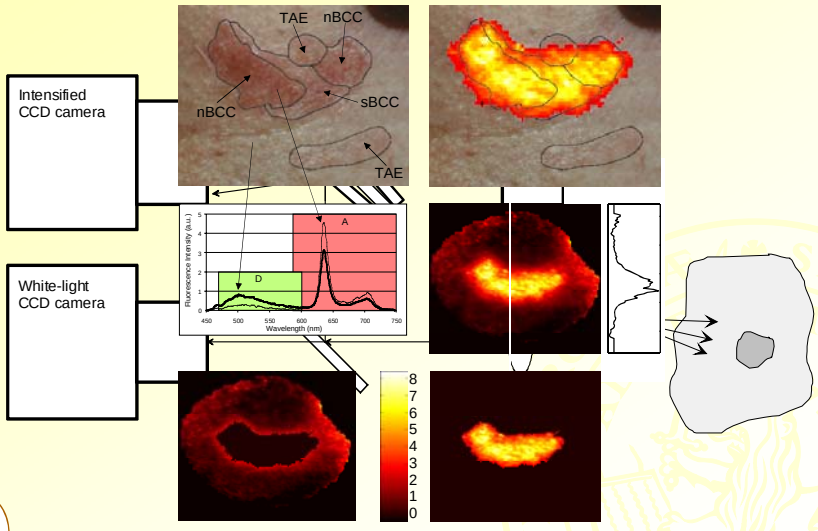
Lund University Medical Laser Centre, Sweden

Fluorescence specrum



Lund University Medical Laser Centre, Sweden

Fluorescence imaging



Lund University Medical Laser Centre, Sweden

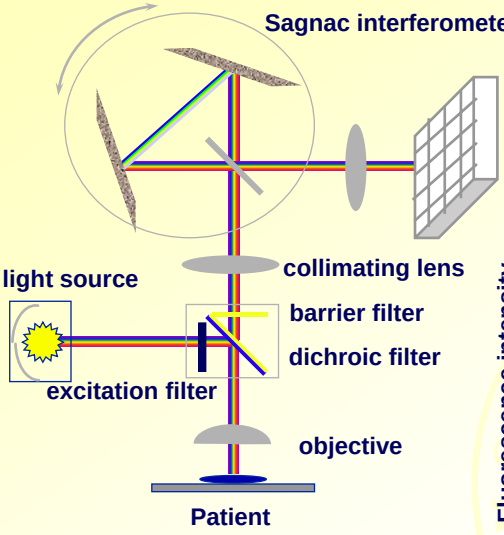
Multicolour Fluorescence Imaging

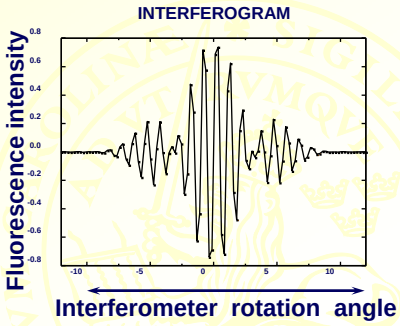
White light image

Digitally processed image

Lund University Medical Laser Centre, Sweden

Hyperspectral imaging system





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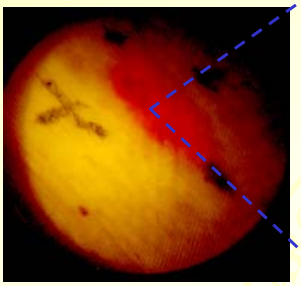
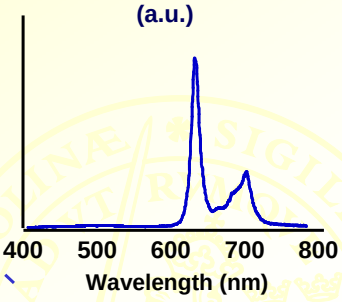
Hyperspectral imaging

White light photo

Fluorescence image using visual colour scale



Fluorescence intensity (a.u.)



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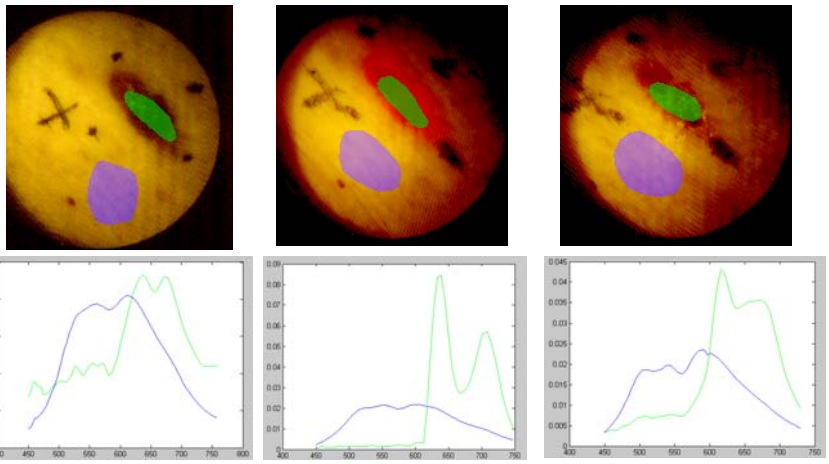
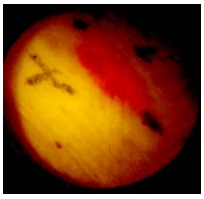
Hyperspectral fluorescence imaging of a Basal Cell Carcinoma

Pre ALA | Pre PDT | Post PDT



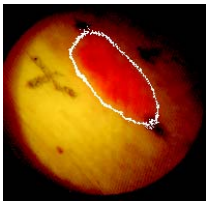
Hyperspectral fluorescence imaging of a BCC pre PDT

Photo



Visual colour coding

Similarity plot



PLS analysis

Hyper Spectral Diagnostic Imager

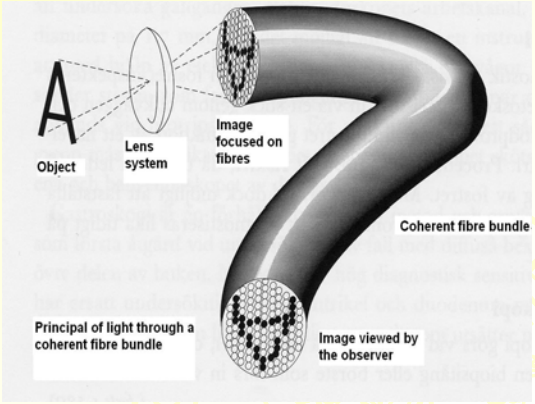
Combines:
- video image
- reflectance scan
- fluorescence scan

Aim:
- interactive diagnostics
- integrated colposcope

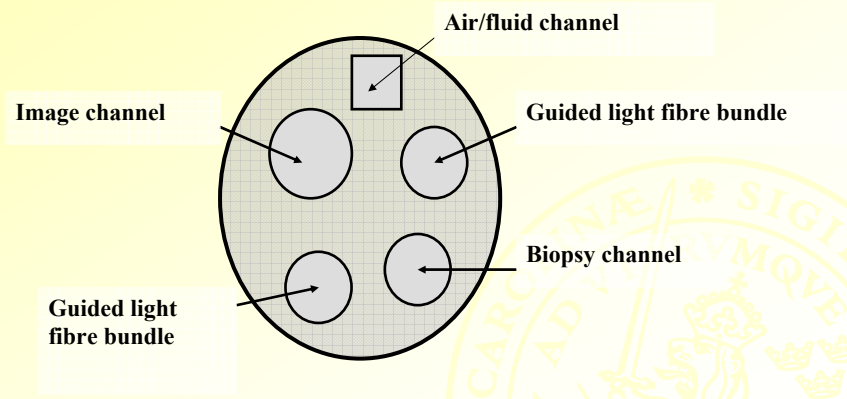
Under development by Science & Technology Inc, USA

Fibre endoscope

- Coherent fibre bundle



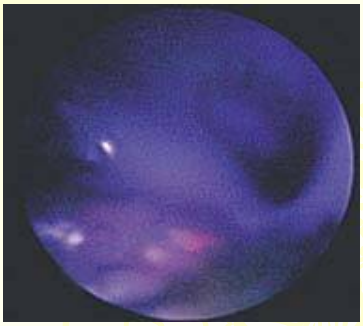
Cross-section of the distal end



The diagnosis

White-light mode

Blue-light mode



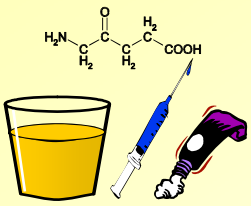
Measurements at Ear-Nose-Throat clinic

Larynx

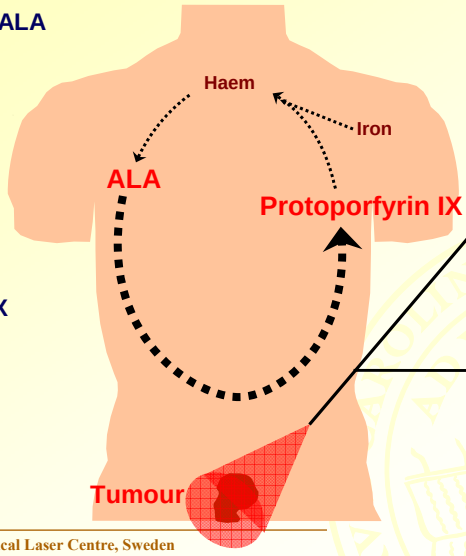
Lund University Medical Laser Centre, Sweden

Fluorescence diagnostics of skin tumour following ALA administration

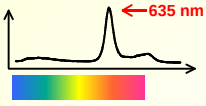
1. Administration of ALA



2. Production of PpIX



3. Diagnostics



Blue laser

4. Treatment

Red laser

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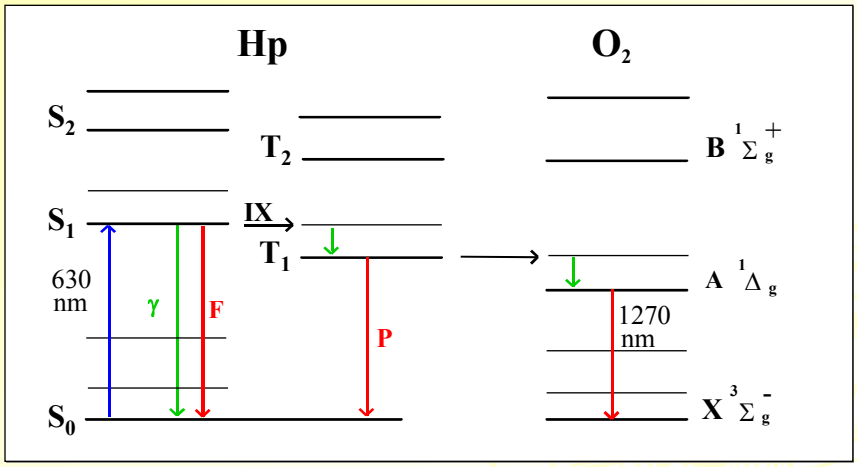
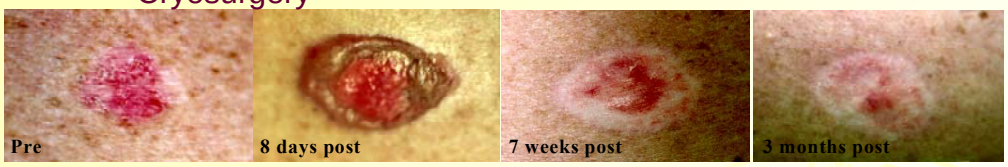
Energy level diagram for PDT



Course of healing

Cryosurgery



ALA-PDT

ALA-PDT of non-melanoma malignant lesions in the region close to the eye

Pre treatment

Post treatment

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Parameters of concern in photodynamic therapy

PHOTOSENSITIZER

Pre-formed agent/porphyrin precursor

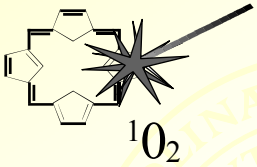
Dose

Mode of administration

Tissue localization

Selectivity

Kinetics



ILLUMINATION

Wavelength

Light dose

Fluence rate

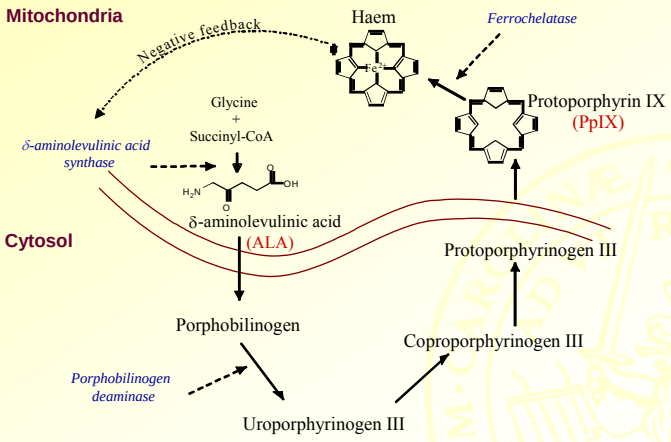
Split-dose regimen

Photoproduct generation

OPTIMIZED TREATMENT OUTCOME

Lund University Medical Laser Centre, Sweden

The synthesis of haem



Benefits & Disadvantages of PDT

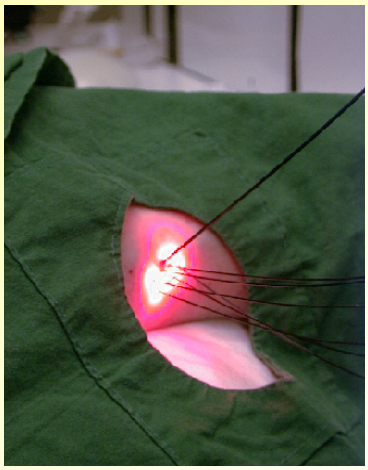
Superficial PDT

+ Selective treatment
+ Good cosmetic results
+ Fast healing
+ Repeated many times
+ Outpatient basis
+ "Simple" method (cooling with water as anaesthetics, occasionally)

– Thin and superficial tumours

…compared to conventional methods

Benefits & Disadvantages of I-PDT



Interstitial PDT

+ Large and/or **deeply** lying tumours

– Mechanical damage
– Insertion of fibres
– Dosimetry

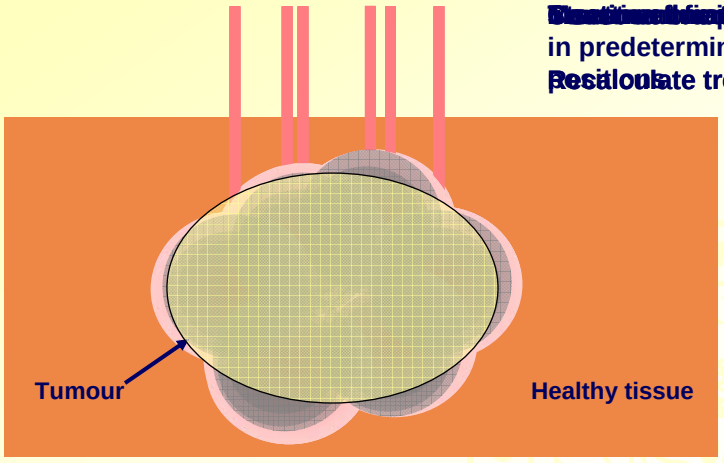
...compared to superficial PDT

Concept

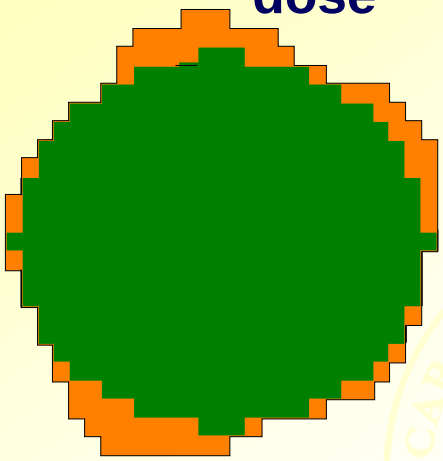
Action:

Placement of light fibres in predetermined position

Calculate treatment time



Calculations of delivered light dose



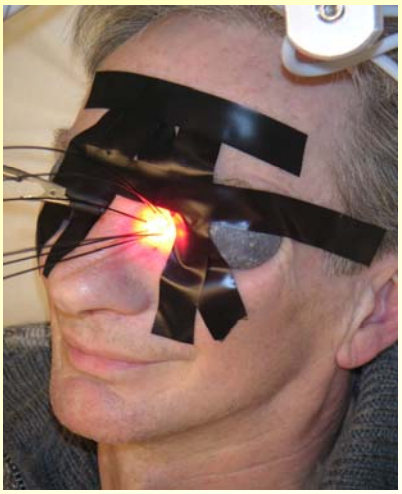
Not fully treated tumour tissue

Treated tumour tissue

High dose surrounding tissue

20 minutes

Benefits & Disadvantages of IPDT



Interstitial PDT

+ Large and/or **deeply** lying tumours

– Minimally invasive
– Positioning of the fibres
– Dosimetry

...compared to superficial PDT

Our patented technology

Dosimetry measurements during treatment

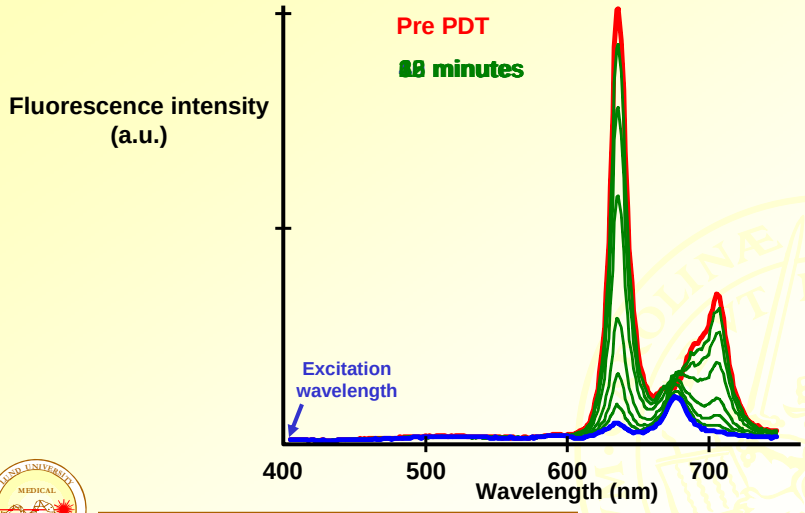
Fluence rate
- fibre positions
- optical feedback

Fluorescence
- build-up of PpIX
- PpIX bleaching

Temperature
- IR camera

Tissue perfusion
- laser Doppler imaging

PpIX photobleaching

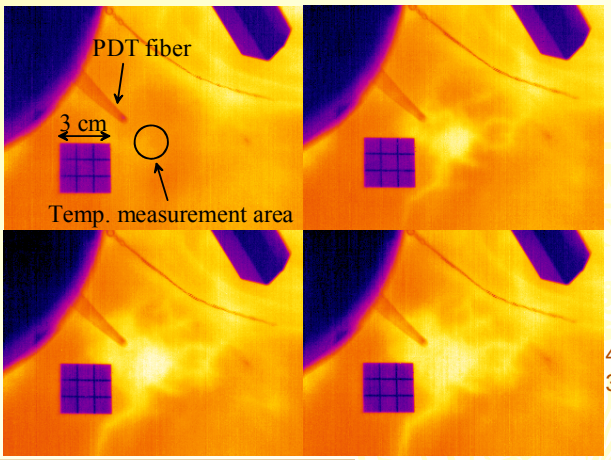


Temperature measurements

- Monitor the heating during PDT
- Observe vascular effects
- Thermal imaging camera (AGEMA
- Resolution 0.1 ºC

Temperature measurements

Basal cell carcinoma on the chest. 127 mW/cm^2, 60 J/cm^2



Pre PDT
33,6ºC

140 s
36,4ºC

320 s
37,0ºC

480 s, post PDT
36,7ºC

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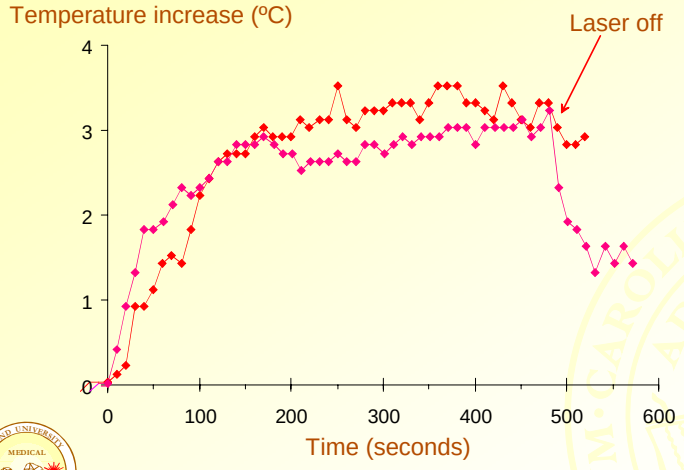
Temperature measurement



Basal cells cancer
127 mW/cm^2

Chest, ALA
Back, ALA-ME

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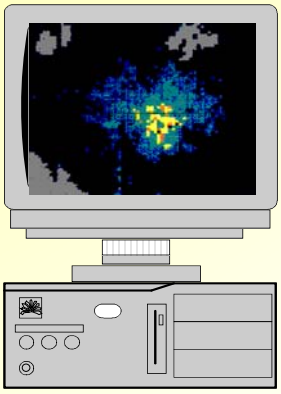
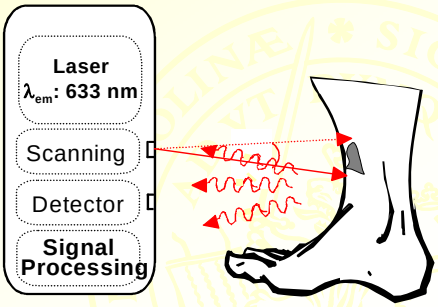
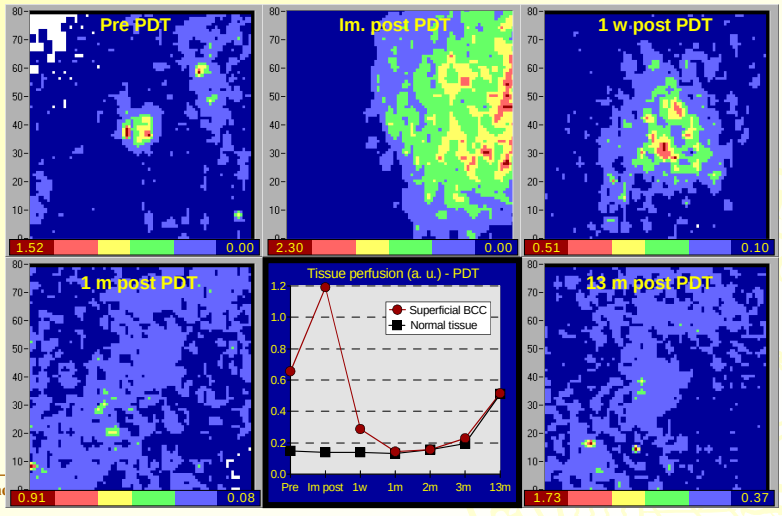
Laser Doppler Perfusion Imaging



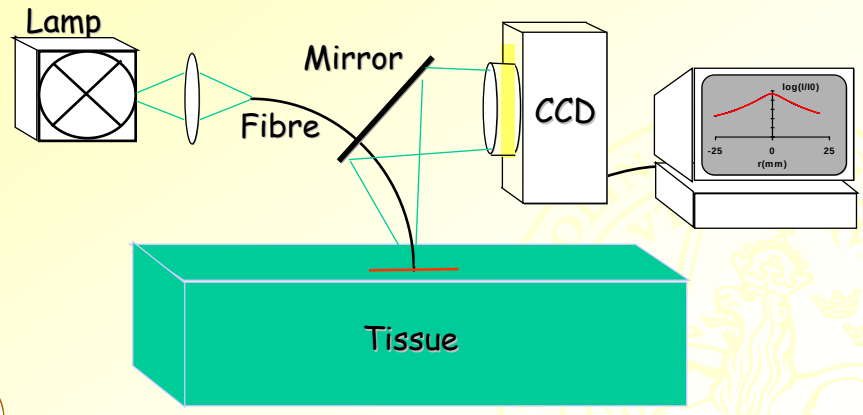
Computer



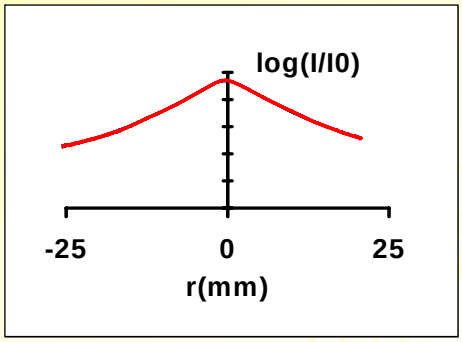
Laser Doppler Perfusion Imaging



Set-up for spatially resolved diffuse reflectance



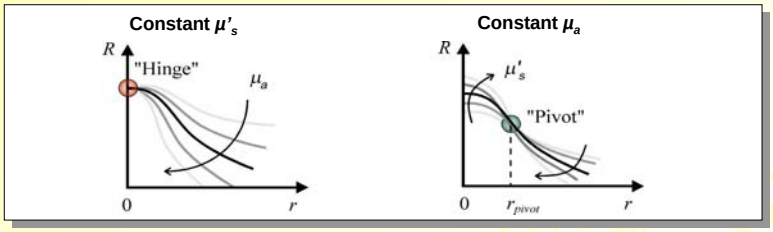
Diffuse Reflectance from Skin at 630 nm

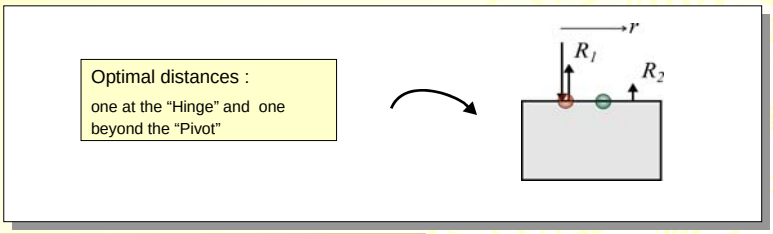


Diffuse reflectance of normal skin irradiated with a pencil beam of light at 630 nm, measured as line across the irradiated spot.

Models and methods

- Spatially resolved CW reflectance



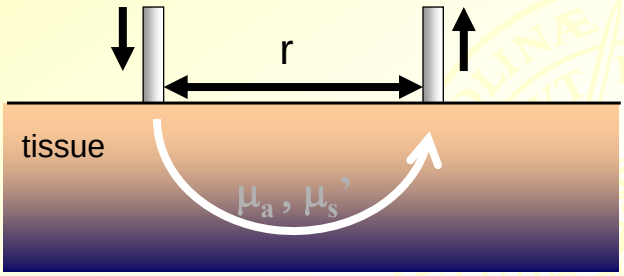


Spatially resolved CW measurements

Diffusion equation - curve fitting

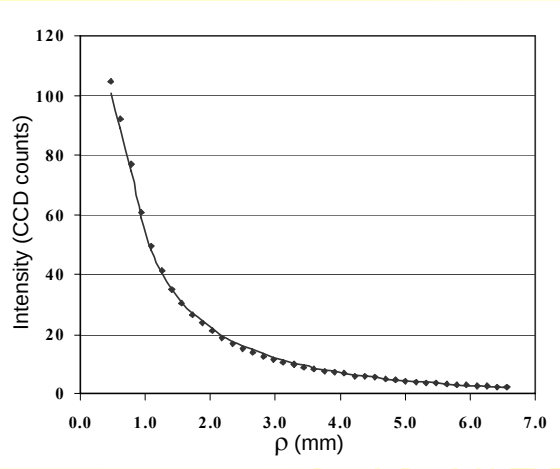
Monte Carlo method - curve fitting

Calibration against known standards



Results

Fit of MCS to diffuse reflectance



Results

Fit versus expected optical properties