Computational Physics – Lecture 15: Diffusion equation I

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  - Definition
  - In physics
- Application: Time-resolved optical imaging
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- Breast cancer imaging
  - Limitations of existing techniques
  - “New” technique: Optical imaging
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  - Model
  - Determination of tissue properties

Some pictures are taken from the internet for illustrational and educational purposes

Contents

- Optical properties of human tissue
- Detection of objects in turbid media
  - Comparison of experiment and simulation
  - Direct imaging
  - Image processing technique
- Market situation

Some pictures are taken from the internet for illustrational and educational purposes

Diffusion: Some definitions

- Diffusion (Wikipedia):
  - net movement of a substance (e.g., an atom, ion or molecule) from a region of high concentration to a region of low concentration
  - movement of a substance down a concentration gradient
  - results in mixing or mass transport, without requiring bulk motion (bulk flow)

Diffusion

Diffusion

- Two ways to introduce the notion of diffusion:
  - a phenomenological approach: diffusion is the movement of a substance from a region of high concentration to a region of low concentration without bulk motion
    - Fick's law, 1855: the diffusion flux is proportional to the negative gradient of concentrations $\boxed{J = -D\nabla n}$
  - a physical and atomistic approach: diffusion is considered as a result of the random walk of the diffusing particles
    - Robert Brown, 1827: discovery of random walk of small particles in suspension in a fluid
    - Albert Einstein, 1905: theory of the Brownian motion and the atomistic backgrounds of diffusion

Diffusion equation

$$\frac{\partial}{\partial t}P(\vec{r},t) = \vec{\nabla}\cdot\left(D(P(\vec{r},t),\vec{r})\vec{\nabla}P(\vec{r},t)\right)$$

$$D(P(\vec{r},t),\vec{r}) = D \quad = D\nabla^2 P(\vec{r},t)$$

$$= D\left(\frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial y^2}+\frac{\partial^2}{\partial z^2}\right)P(\vec{r},t)$$

nabla or del operator

divergence operator

Laplace operator

partial differential equation

$$\vec{\nabla} = \hat{\vec{x}}\frac{\partial}{\partial x}+\hat{\vec{y}}\frac{\partial}{\partial y}+\hat{\vec{z}}\frac{\partial}{\partial z}$$

$$\vec{\nabla}\cdot\vec{F} = \frac{\partial F_x}{\partial x}+\frac{\partial F_y}{\partial y}+\frac{\partial F_z}{\partial z}$$

$$\nabla^2 = \vec{\nabla}\cdot\vec{\nabla} = \frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial y^2}+\frac{\partial^2}{\partial z^2} \equiv \Delta$$

- describes the transport of the density $P(\vec{r},t)$ of "stuff" of which the motion depends on many external factors which act as "noise"
- D denotes the diffusion coefficient

Diffusion equation

- Can be derived from
  - the continuity equation, which states that a change in density in any part of the system is due to inflow and outflow of material into and out of that part of the system
    $\partial P / \partial t + \vec{\nabla} \cdot \vec{j} = 0$, where $\vec{j}$ is the flux of diffusing material
  - in combination with Fick's first law, assuming that the flux of diffusing material in any part of the system is proportional to the local density gradient: $\vec{j} = -D\vec{\nabla}P(\vec{r},t)$

Diffusion in physics

- Diffusion in gases
- Atomic diffusion (in solids)
- Electronic diffusion (diffusion current)
- Diffusion of thermal energy (heat equation)
- Plasma diffusion
- Photon diffusion
- …

Photon diffusion

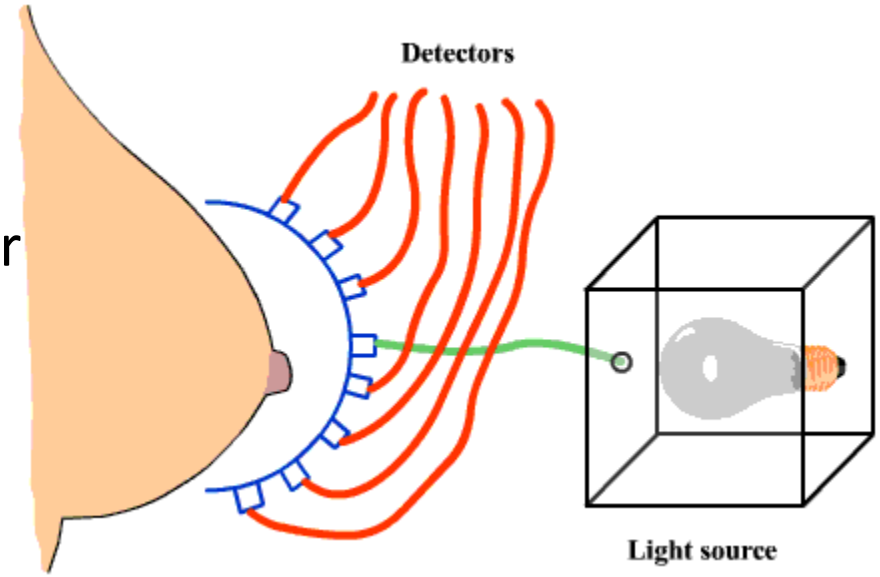
- Photons travel through a material
  - without being absorbed
  - by undergoing repeated scattering which changes the direction of their path
- The path of any single photon can be described by a random walk
- The ensemble of photons exhibits diffusion in the material and can be described with a diffusion equation
- Application in medical science: diffuse optical imaging

Time-resolved optical imaging

- Applications
  - Human tissue
    - Time-resolved Infrared Mammograph (TIM)
    - Functional and diagnostic imaging of the brain (epileptic sites)
    - Skin cancer detection
  - Soft materials
    - Quality control
    - Characterization of optical properties

Time-resolved infrared mammograph

- Apparatus
  - Components
    - picosecond pulsed NIR laser
    - NIR detectors (≥ 128)
    - software



Properties of photon scattering must be understood before devices can be designed to produce clinically useful images

Time-resolved infrared mammograph

- Market
  - Massive preventive screening for breast cancers
    - can replace X-ray mammography
  - ~~High-end mammography~~ (X-ray, MRI) at ~~Academic Hospitals~~, …

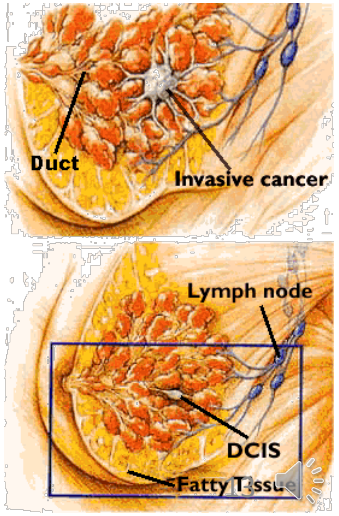
Time-resolved infrared mammograph: Motivation

- Breast cancer:
  - most common cancer in women
    - Women's (men's) lifetime risk of breast cancer is about 12% (0.1%)
  - one of the leading causes of death in women
  - can be cured in many cases when the tumors are small (before metastasis sets in)

Non-invasive diagnostic methods for detection of breast cancer at an early stage are of great importance

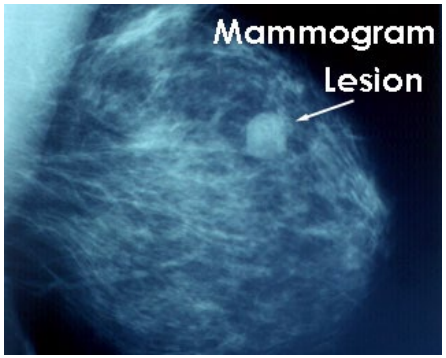
Ultimate goal:

- **Detect mm-sized lesions in 40-100 mm thick human tissue**
- **Discriminate between benign and malignant lesions**

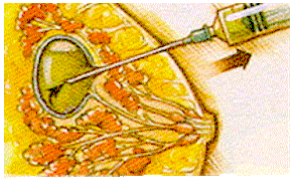


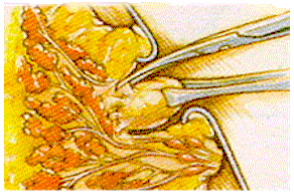
Breast Cancer Diagnosis

- Lump detection during self examination or suspicious spot on screening mammogram



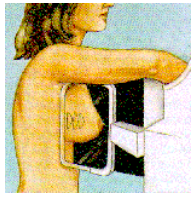
- Diagnostic mammogram
- Breast ultrasound helps determine if a mass is solid or cystic
- Needle aspiration biopsy or surgical biopsy

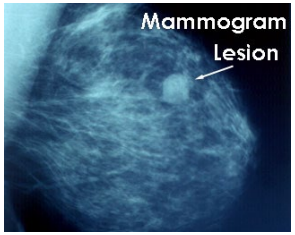

Needle Aspiration


Surgical Biopsy

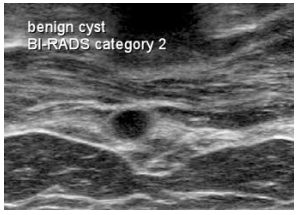
Breast cancer imaging: Existing techniques

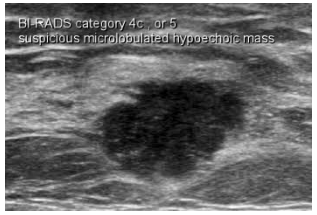
- X-ray mammography:
  - breast is compressed to spread the tissue and to allow a lower dose of x-ray
  - produces a black-and-white image of the breast tissue which is interpreted by a radiologist
  - reading mammograms is difficult
    - changes seen on mammograms:
      - calcifications (tiny mineral deposits within the breast tissue)
      - mass





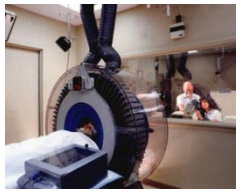
- Ultrasound imaging:
  - high-frequency sound waves are transmitted through the breast
  - the sound wave echoes are picked up and translated by a computer into an image
  - NO radiation





Breast cancer imaging: Existing techniques

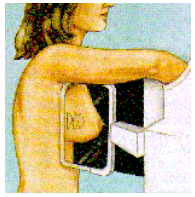
- Radioisotope imaging:
  - records radiation emitting from within the body rather than radiation that is generated by external sources
  - gamma rays emitted from inside the body are detected by a gamma camera, are converted into an electrical signal, and sent to a computer

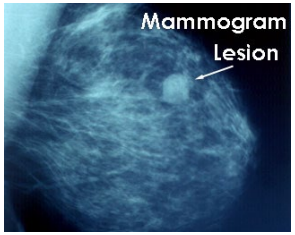


- Magnetic Resonance Imaging (MRI):
  - uses magnetization and radio waves
  - most useful MRI examinations use a contrast material
  - submillimeter spatial resolution
  - ability to define local anatomic tumor extent, critical for treatment planning

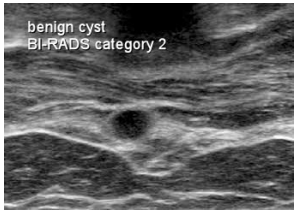
Breast cancer imaging: Limitations of existing techniques

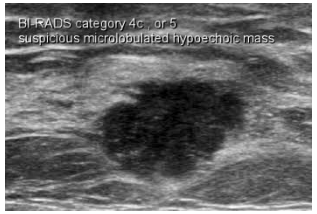
- X-ray mammography:
  - may not detect tumors in their early stage when they are small and most treatable
  - not suitable for imaging young dense breasts
  - cannot distinguish between benign and malignant tumors
  - uses ionizing radiation: Potentially harmful if used too often for routine screening





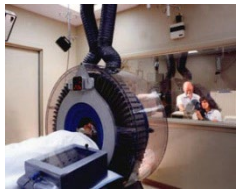
- Ultrasound imaging:
  - lacks the resolution to detect objects with linear dimension smaller than a few millimeters
    - Small calcium deposits and very small tumors are not visible
  - Useful for evaluation of breast masses: Cyst ←→ cancerous tumor





Breast cancer imaging: Limitations of existing techniques

- Radioisotope imaging:



  - exposes the body to radioactivity
  - Positron emission tomography (PET) scanning highlights cancerous tissue BUT does not reliably detect tumors smaller than 1 cm

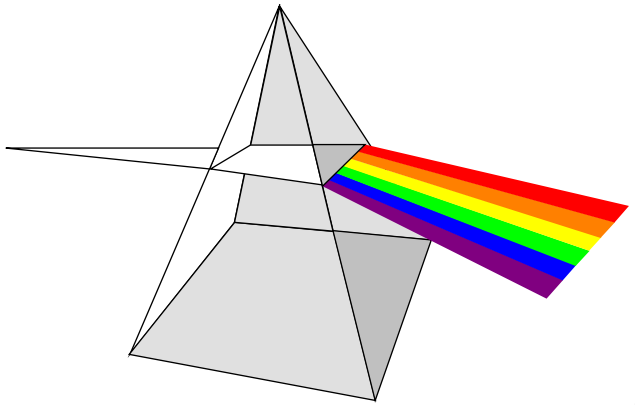
- Magnetic Resonance Imaging (MRI):

  - cannot detect microcalcifications
  - ability to detect specific chemicals, but not oxygen
  - cost of superconducting magnets needed for its operation makes it highly expensive

NEED FOR A NEW IMAGING MODALITY !

“New” Imaging Technique

- Properties: non-invasive, safe, inexpensive, compact, capable of monitoring tissue chemistry *in vivo*
- Candidate: Optical imaging



Optical imaging

- Simplest form: Illuminate part of the body to be imaged with bright light and search for indication of pathology in the observed transillumination or reflection pattern
- Physical basis: Difference in propagation of light through normal tissue and a tumor
  - absorption: Caused by chromophores, such as hemoglobin, cytochromes, and pigments
  - scattering: Originates from fluctuations of the refractive index of connective tissues and cell constituents

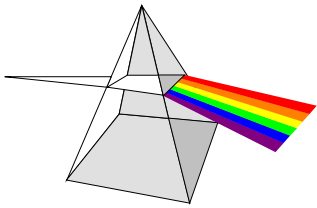
  $\rightarrow$ look for ‘‘shadow image’’ of the tumor
- Observation of a tumor ``shadow image’’ is difficult or even impossible due to the scattering by the tissue

Light

- Visible part of the spectrum is a very small portion of the entire electromagnetic radiation spectrum

$$\nu = c / \lambda$$

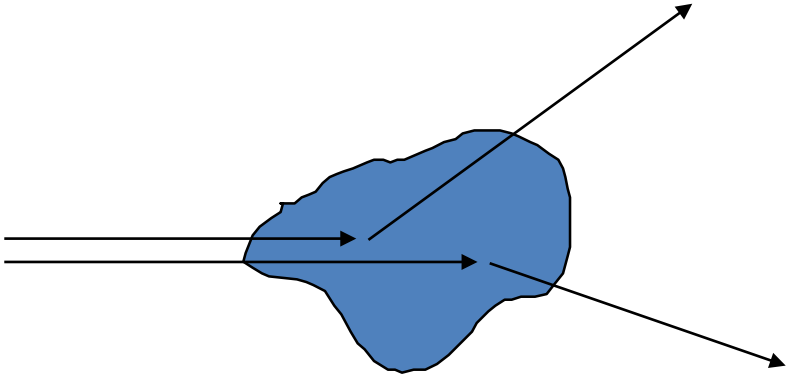
Infrared Red Green Blue Ultraviolet



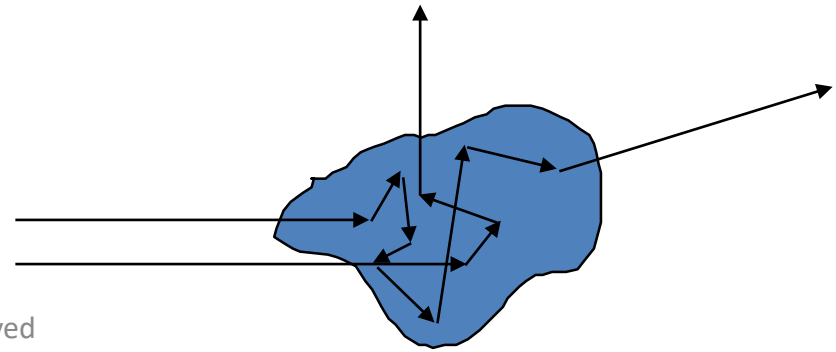
- Photon energy: $E = h\nu$
- "Non-ionizing radiation": individual photons do not have sufficient energy to ionize matter
- (Non-)ionizing radiation has (not) enough energy in each photon for a beam to pass straight through matter

X-ray versus visible and NIR light

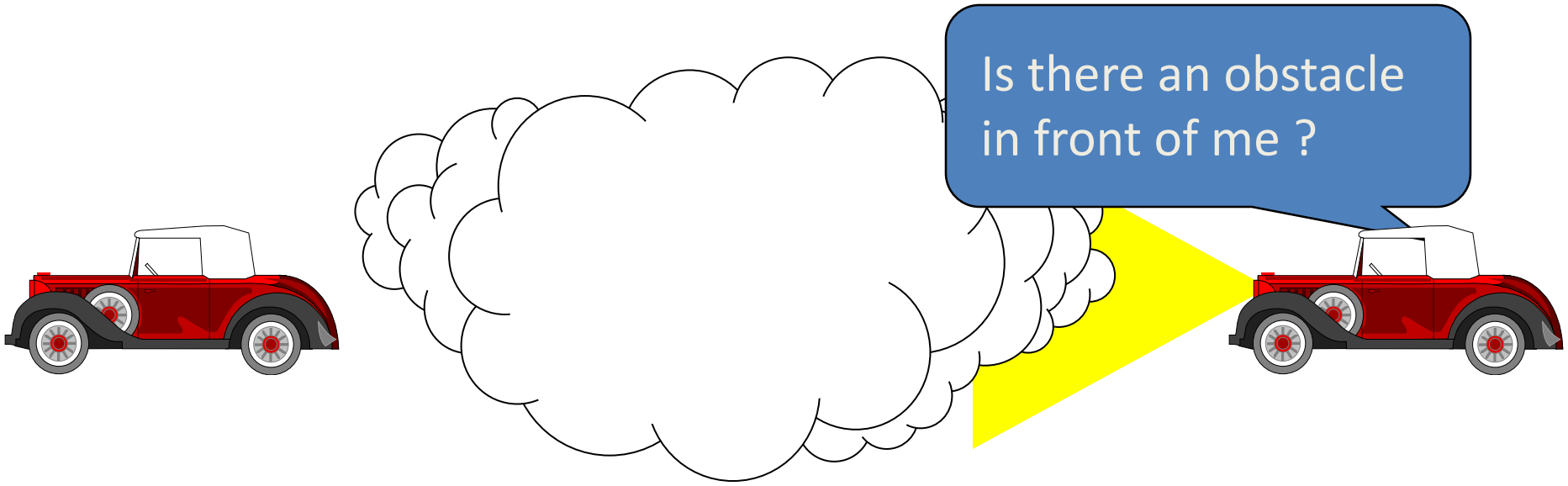
- X-Ray scattering: Single scattering event



- Light scattering: Multiple scattering events

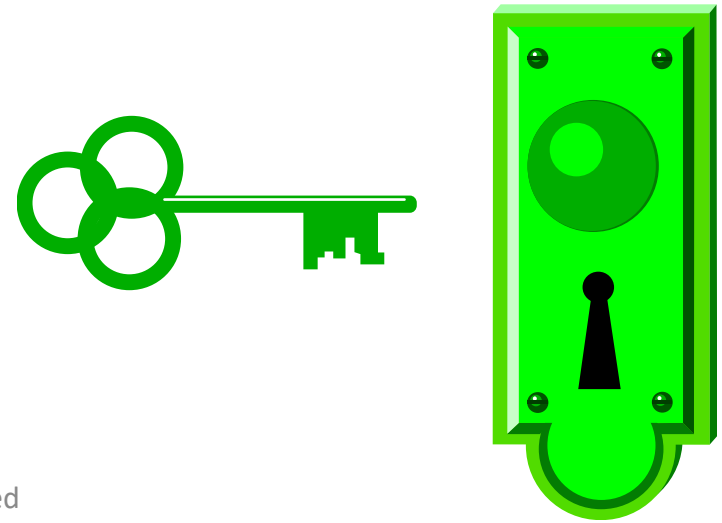


Main problem: analogy



Optical imaging

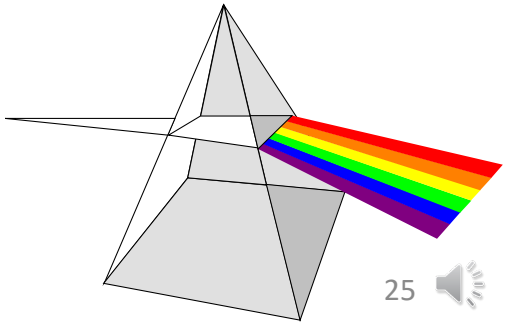
One of the keys to successful development of medical optical imaging (MOI) techniques is to deal with the problem of light scattering effectively



Medical optical imaging

What light to use?

- Near-infrared light: 700-1300nm
  - not as strongly absorbed by tissue as visible light
    - higher transmission
    - less likelihood of causing burns
  - availability of broadly wavelength-tuneable solid-state lasers, such as Ti:sapphire and Cr:forsterite, to cover this spectral range

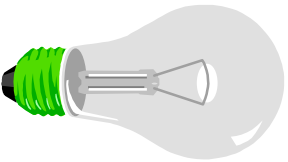


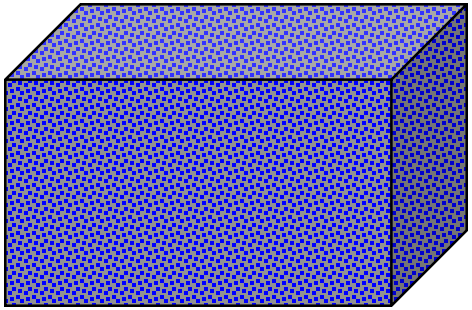
Medical optical imaging

Techniques:

- Continuous spectrum light source (photons flow in a steady stream)
  - Spatial resolution is limited by photon scattering to about 1 cm
- Time-resolved optical imaging: pulsed light sources and time-gated detectors
  - Individual photons do require different times to travel through the breast
    - Use “first” photons: low signal-to-noise ratio
    - Diffusive light imaging

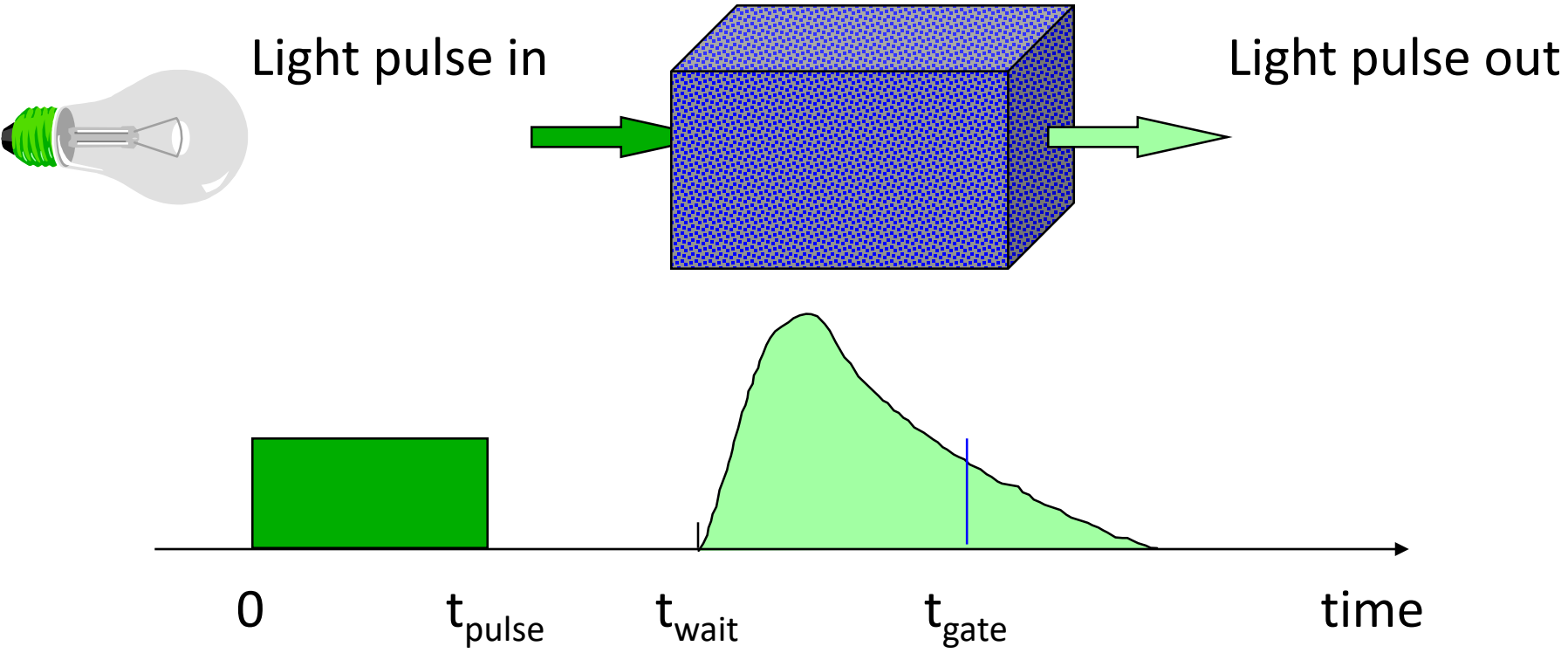
Time-resolved optical imaging





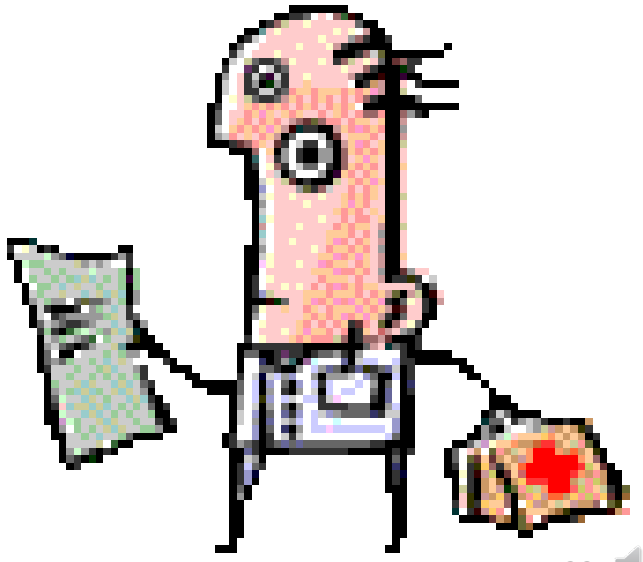
Detector

Time-resolved optical imaging



Medical optical imaging

The physics of photon scattering must be understood before clinical apparatuses can be designed.



Model

- Description of light migration in biological tissue by:
  - Maxwell equations: Rigorous BUT the structure of tissues is extremely complex and the dielectric properties of their components is not known
  - Radiative transfer equation: Simplification BUT still too complicated for application to breast tissue imaging
  - Diffusion equation (deterministic)
  - Monte Carlo simulations and random walk models (stochastic)

Model

For weakly absorbing media the propagation of light is, to a good approximation, described by the time-dependent diffusion equation:

$$\frac{\partial I(\mathbf{r},t)}{\partial t} = \nabla \cdot D(\mathbf{r}) \nabla I(\mathbf{r},t) - v\mu_a(\mathbf{r}) I(\mathbf{r},t) + S(\mathbf{r},t)$$

nabla or del operator

where: $I(\mathbf{r},t)$: light intensity at a point $\mathbf{r}$ and at time t

$D(\mathbf{r}) = \dfrac{v}{3(\mu_s'(\mathbf{r}) + \mu_a(\mathbf{r}))}$: diffusion coefficient

$\mu_a(\mathbf{r})$: absorption coefficient

$\mu_s'(\mathbf{r})$: reduced scattering coefficient

v: velocity of light in the medium in the absence of objects

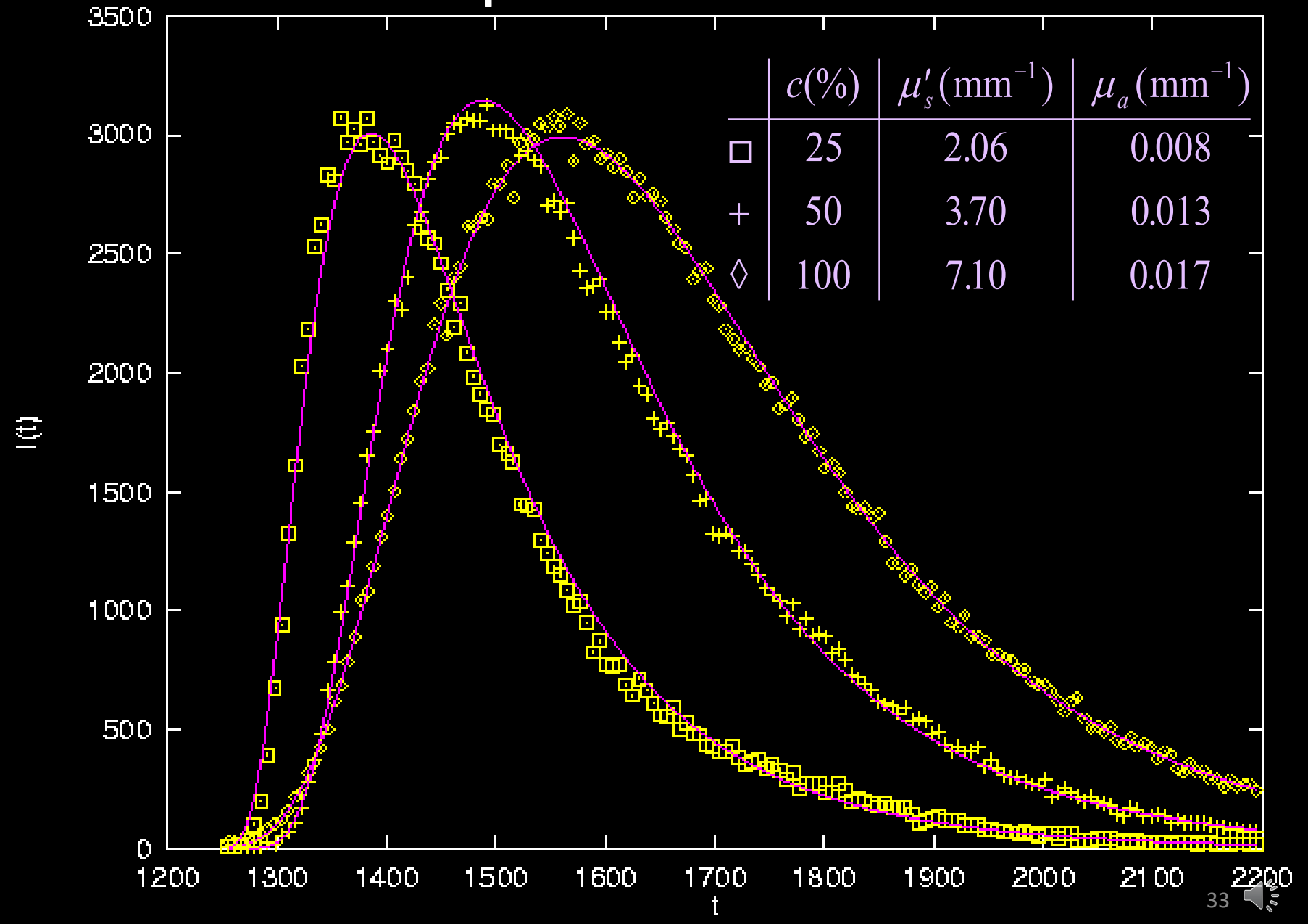
$S(\mathbf{r},t)$: light source

$$\vec{\nabla} = \vec{x}\frac{\partial}{\partial x} + \vec{y}\frac{\partial}{\partial y} + \vec{z}\frac{\partial}{\partial z}$$

Determination of tissue optical properties

- Important in diagnostic and therapeutic applications of light in medicine
  - e.g. in laser surgery, photodynamic therapy, monitoring changes in blood oxygenation and tissue metabolism
- Time-resolved optical experiments
  - analytical expression for the transillumination and/or reflection curves, depending on the optical parameters and boundary conditions (e.g. from diffusion theory)
  - estimation of optical parameters of the tissue by fitting the theoretical curve to the experimental data

Latex spheres in solution



	$c(\%)$	$\mu_s'(\mathrm{mm}^{-1})$	$\mu_a(\mathrm{mm}^{-1})$
□	25	2.06	0.008
+	50	3.70	0.013
◊	100	7.10	0.017

Optical properties of human tissue

- Breast tissue
  - *In vitro:*

λ(nm)	$\mu_a(1/\text{mm})$	$\mu_s'(1/\text{mm})$
800	$0.02-0.07$	$0.7-1.4$ [1]
653	<0.02	0.4 [2]

  - *In vivo:*

λ(nm)	$\mu_a(1/\text{mm})$	$\mu_s'(1/\text{mm})$
800	$0.0017-0.0032$	$0.72-1.22$ [3]
753	0.0028 ; 0.0068	0.76 ; 1.13 [4]

(1) V.G. Peters *et al*., Phys. Med. Biol. **9**, 1317-1334, 1990;
H. Key *et al*., Phys. Med. Biol. **36**, 579-590, 1991
(2) R. Marchesini *et al.*, Appl. Opt. **28**, 2318-2324, 1989
(3) G. Mitic. *et al*., Appl. Opt. **33**, 6699-6710, 1994
(4) K. Suzuki *et al*, Invest. Radiol. **29**, 410-414, 1994

Optical properties of human tissue

- In vivo back and abdomen tumor(5)
  - absorption factors of tumor tissue are 2-3 times larger than the absorption factor of normal tissue
  - scattering factors of tumor tissue are somewhat smaller than the scattering factor of normal tissue

→ In time resolved optical imaging experiments on breast phantoms:

Tissue : $\mu_a \approx 0.01\text{mm}^{-1}$; $\mu_s \approx 1\text{mm}^{-1}$ for $\lambda = 800\text{nm}$

Tumor : $\mu_a \approx 0.1\text{mm}^{-1}$; $\mu_s \approx 1\text{mm}^{-1}$ for $\lambda = 800\text{nm}$

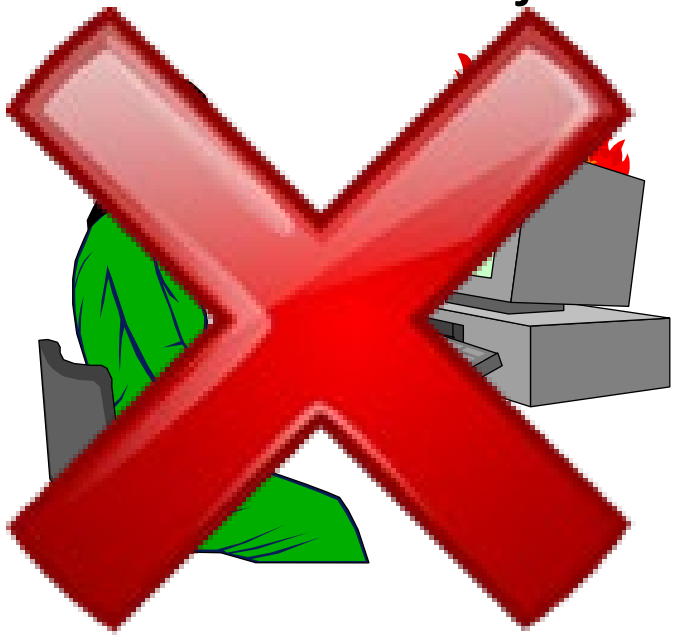
(5) J.B. Fishkin *et al*., Appl. Opt. **36**, 10-20, 1997

Numerically solving the diffusion equation

- How? See later

K. Michielsen, H. De Raedt, J. Przeslawski, N. Garcia, Phys. Rep. 304, 89-144 (1998)

- Practical applications:
  - Accurate results
  - Possibility to detect small objects
  - CPU time

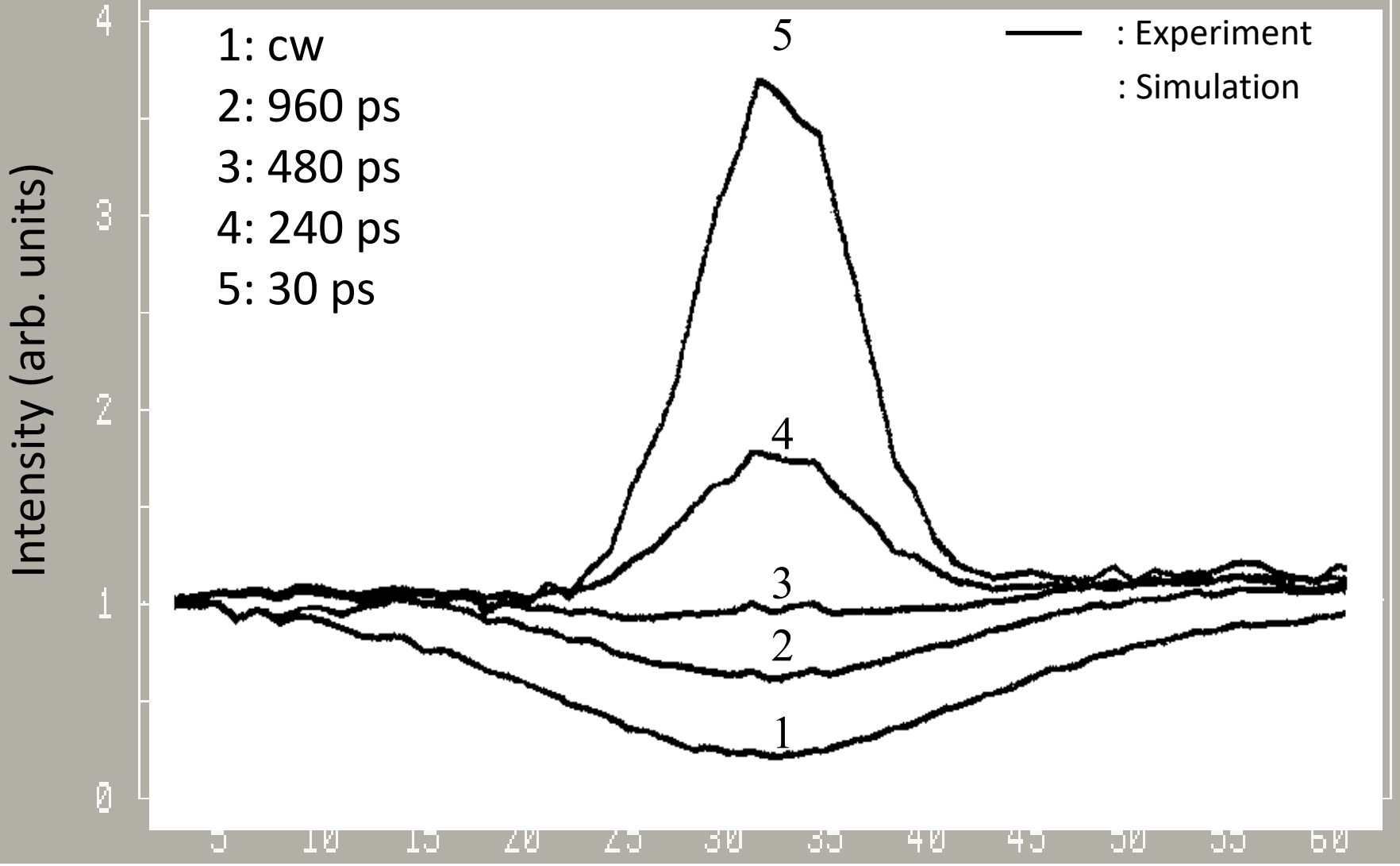


Comparison between simulation and experiment

- Use geometry, values of the model parameters etc. as determined from experiment (G. Mitic et al., Appl. Opt. 33, 6699, 1994)
  - Scattering and absorption coefficients correspond to those of mammalian tissue and tumors
- Simulate the experiment
- Compare to experimental data
  - No fitting !

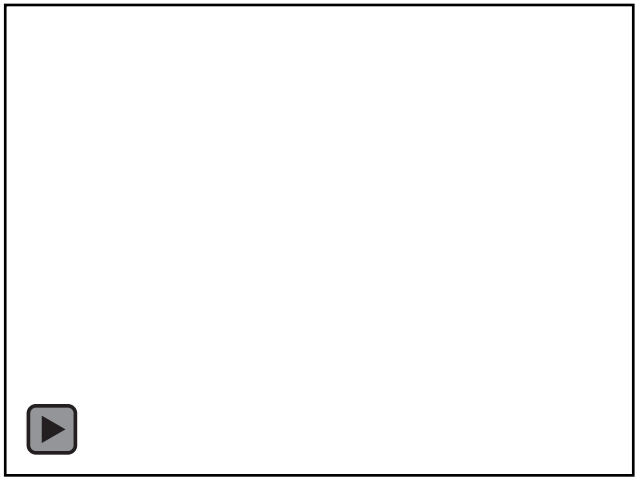
Medium : $\mu_s' = 0.9\,\mathrm{mm}^{-1}$; $\mu_a = 0.0005\,\mathrm{mm}^{-1}$

Object : $\mu_s' = 0\,\mathrm{mm}^{-1}$; $\mu_a = 0.13\,\mathrm{mm}^{-1}$



Direct imaging of objects

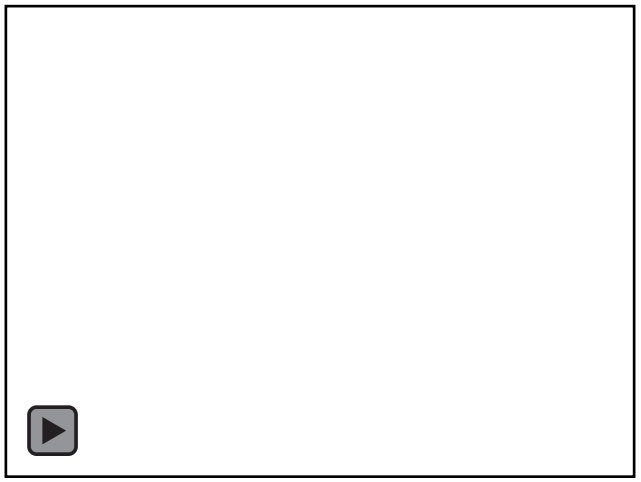
- A 4mm-radius tumor in a model breast of size 63mm x 63mm x 63mm, positioned right at the middle



- The tumor can be detected in the transmitted but not in the reflected light intensity

Direct imaging of small objects

- A 1mm-radius tumor in a model breast of size 63mm x 63mm x 63mm, positioned right at the middle



- No trace of the tumor in the transmitted and reflected light intensity.

Direct imaging of objects in turbid media is difficult

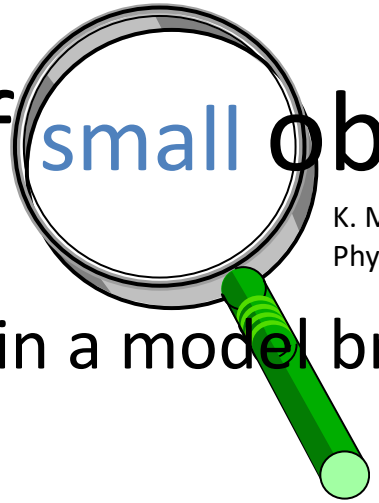
- Success depends on
  - scattering and absorption factors of the medium & objects
  - the size of the objects
  - the thickness of the tissue
  - procedure of taking data: Time-gate, time delay
- There is no obvious, systematic relation between the properties of the object and the measured intensity
- Simulation may be essential to interpret the data

Image processing technique

- Measure the integrated intensity I of the sample
- Calculate or measure the reference signal corresponding to a ``test model''
- Compute $\ln(I / I_0)$ or $I - I_0$ for various source and detector positions

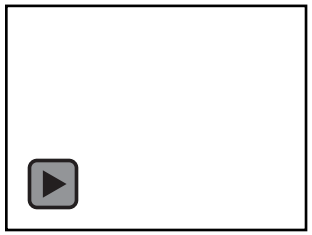
$\rightarrow$The resulting distribution should reveal whether there are hidden objects or not

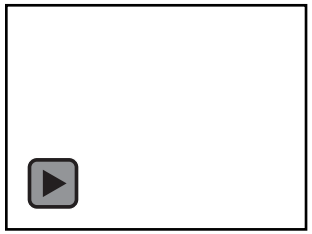
Imaging of small objects

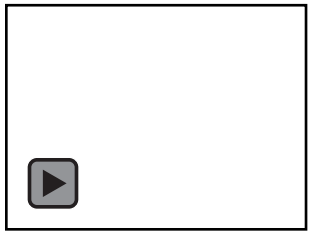


K. Michielsen, H. De Raedt, J. Przeslawski, N. Garcia, Phys. Rep. 304, 89-144 (1998)

- A 0.5mm-radius tumor in a model breast of size 63mm x 63mm x 63mm
  - Direct imaging :
  - Using image processing :
    - without noise :
    - with noise :

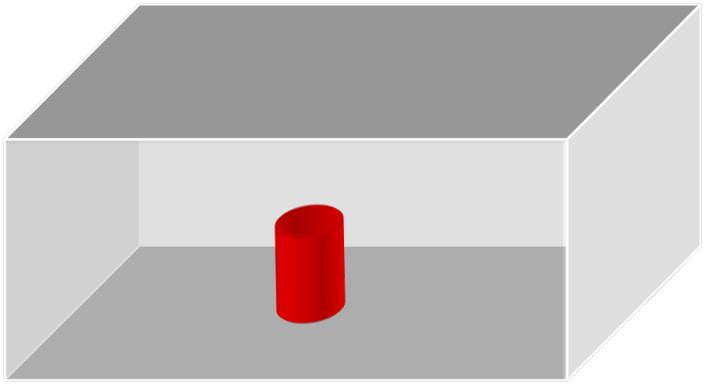




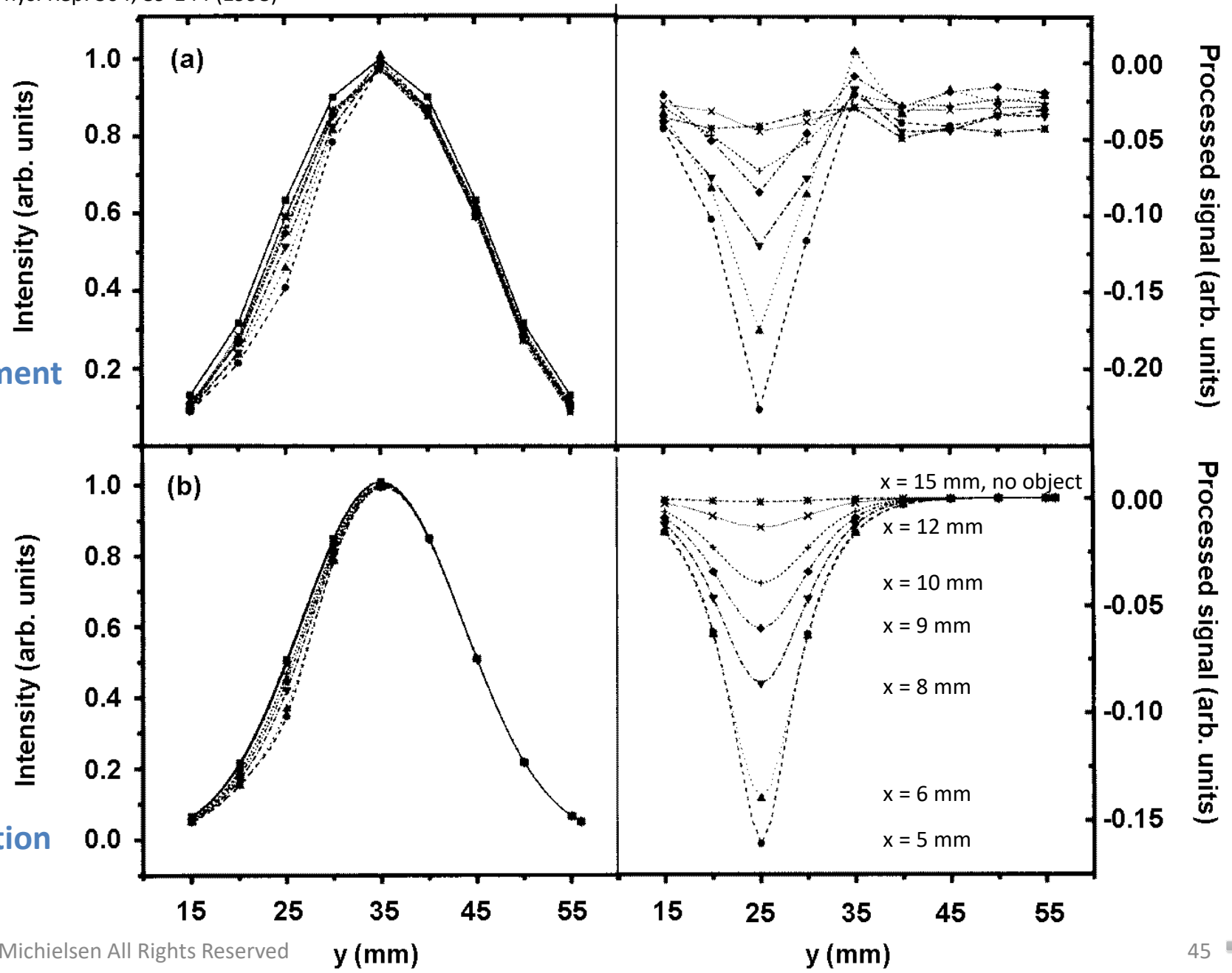


Comparison with experiment

- Experimental (reflection) results on the time-resolved optical imaging of a blood tube (1 mm diameter) immersed in intralipid agree with theoretical results.



K. Michielsen, H. De Raedt, J. Przeslawski, N. Garcia, Phys. Rep. 304, 89-144 (1998)



Time-resolved imaging: Summary

- Simulation of diffusion process reproduces and predicts experimental results of time-gated transillumination and reflection measurements of tissue-like phantoms
  - Conditions for imaging tumors can now be studied systematically, with less resort to actual experiments
    - Speed up and improve design of diagnostic equipment
- mm-sized objects can be detected through appropriate image processing

MOI: Possible Advantages Over X-ray Mammography

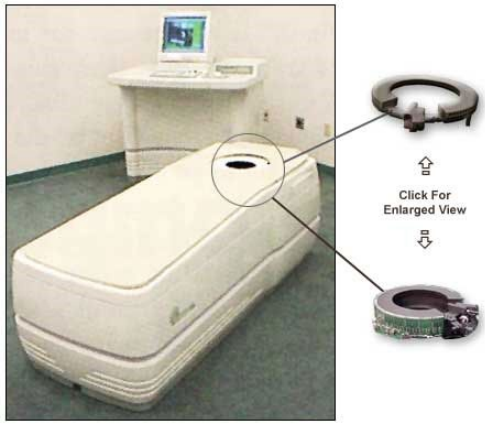
- Ability to differentiate a cyst from a solid lesion
- Higher specificity than x-ray mammography
- Breast protheses are easily and quickly examined (reduce the need for MRI)
- Breast density is no issue
- Examination time is about the same or less than that of a conventional mammogram
- No use of ionizing radiation

MOI: Market Situation

- Market
  - Philips (The Netherlands)
    - Continuous-wave optical mammography (+ fluorescent chemical)
    - 2000: Philips withdraws from optical mammography market
  - IMDS (Imaging Diagnostic Systems, USA)
    - Computed Tomography Laser Breast Imaging System (CTLM®).
      - Continuous-wave imaging
      - Time-resolved imaging
      - Fluorescence imaging
    - 2021: FDA process pending, available internationally
  - ART (Advanced Research and Technology Inc, Canada)
    - Optical mammography SoftScan®

MOI: Market Situation

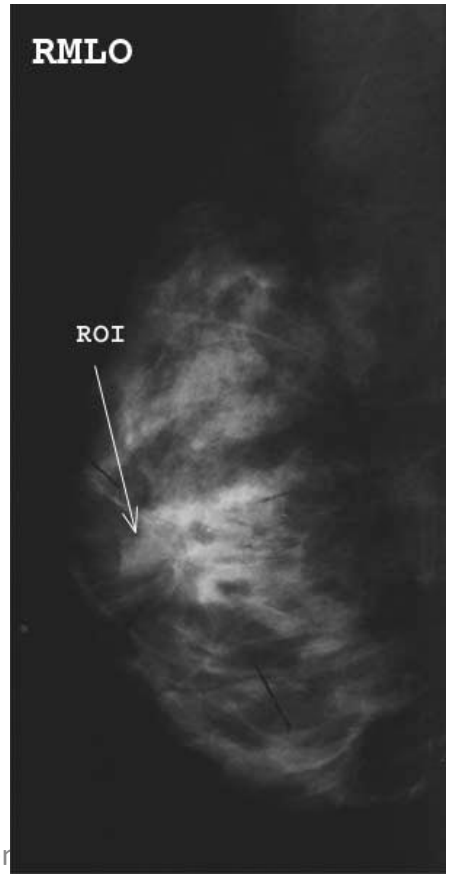
- CTLM® system (IMDS): How does it work?
  - The patient lies comfortably in the prone position with one breast suspended in the scanning chamber.
  - The laser beam sweeps 360 degrees around the breast starting from the chest wall moving forward until the entire breast is scanned.
  - The data is acquired by an array of specialized detectors, where it is reconstructed by computer algorithms to create three-dimensional cross sectional images of the breast.
  - The examination takes approximately 10-12 minutes to perform.
  - No breast compression is required and no ionizing radiation is used.

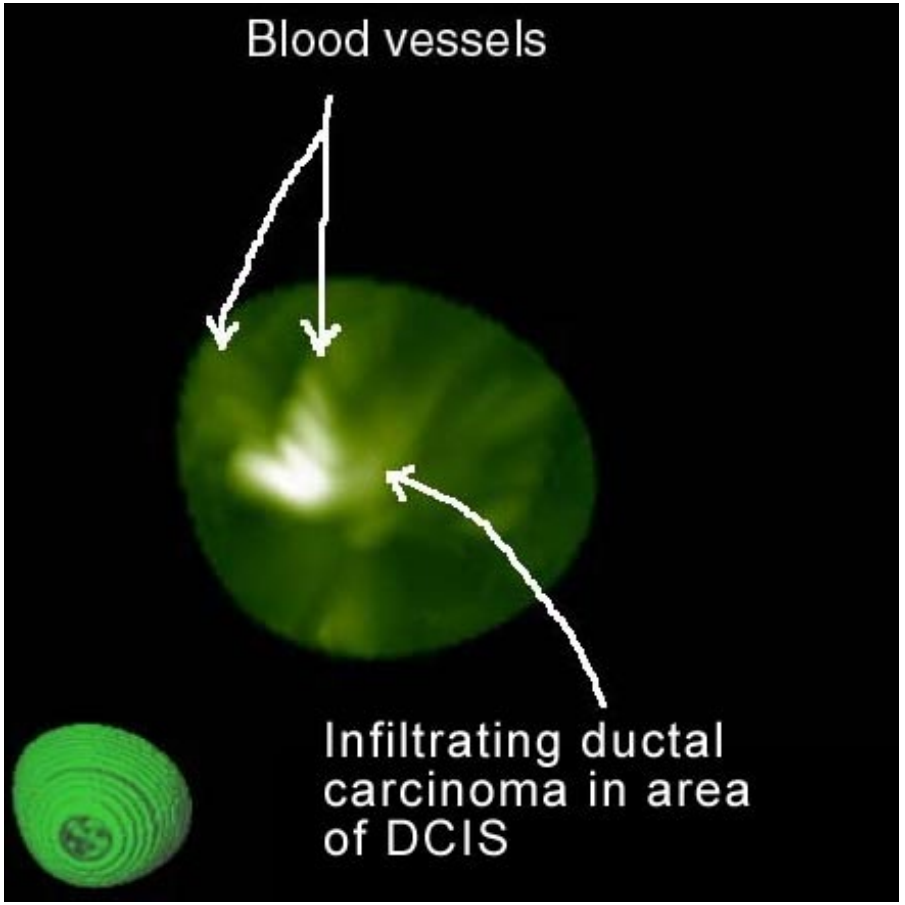


MOI: Market Situation

- CTLM® system (IMDS): Case studies

CASE 2

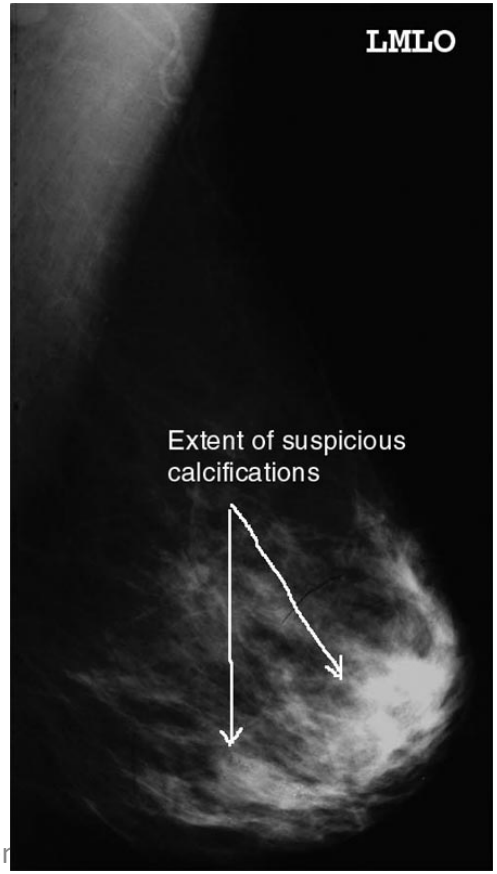


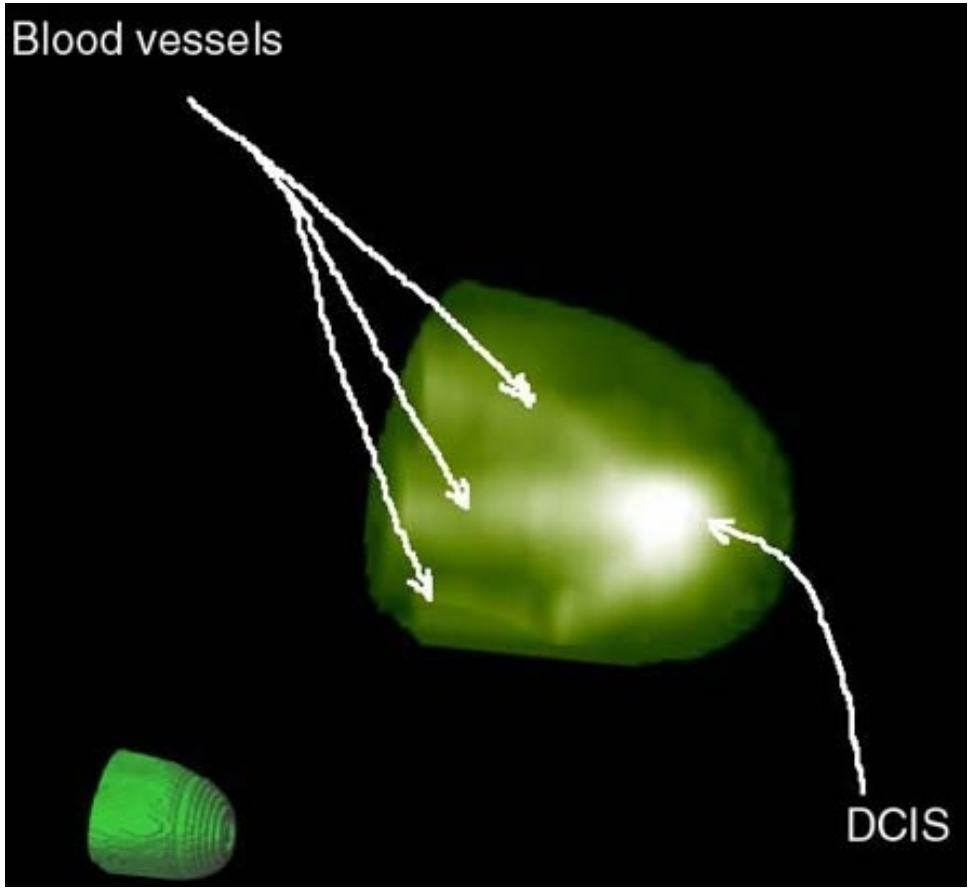


MOI: Market Situation

- CTLM® system (IMDS): Case studies

CASE 3

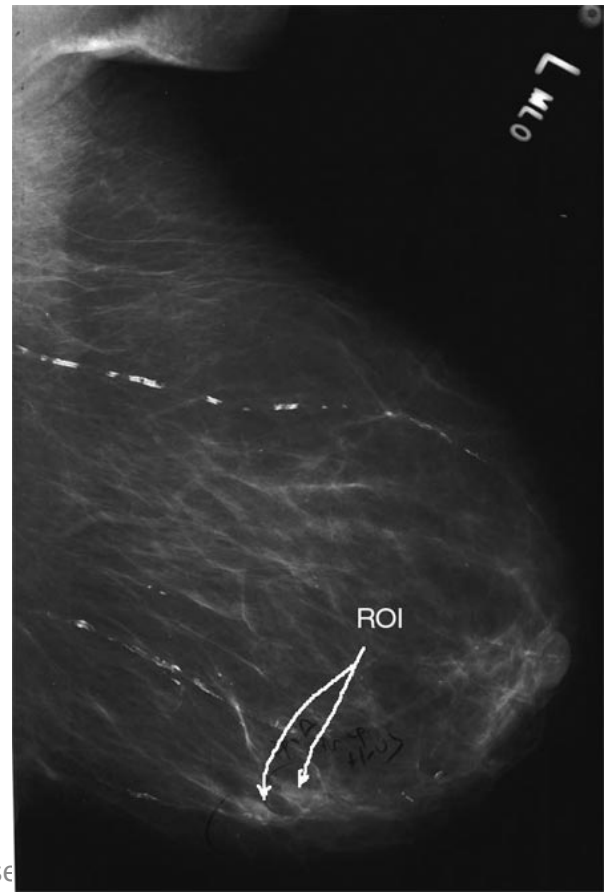


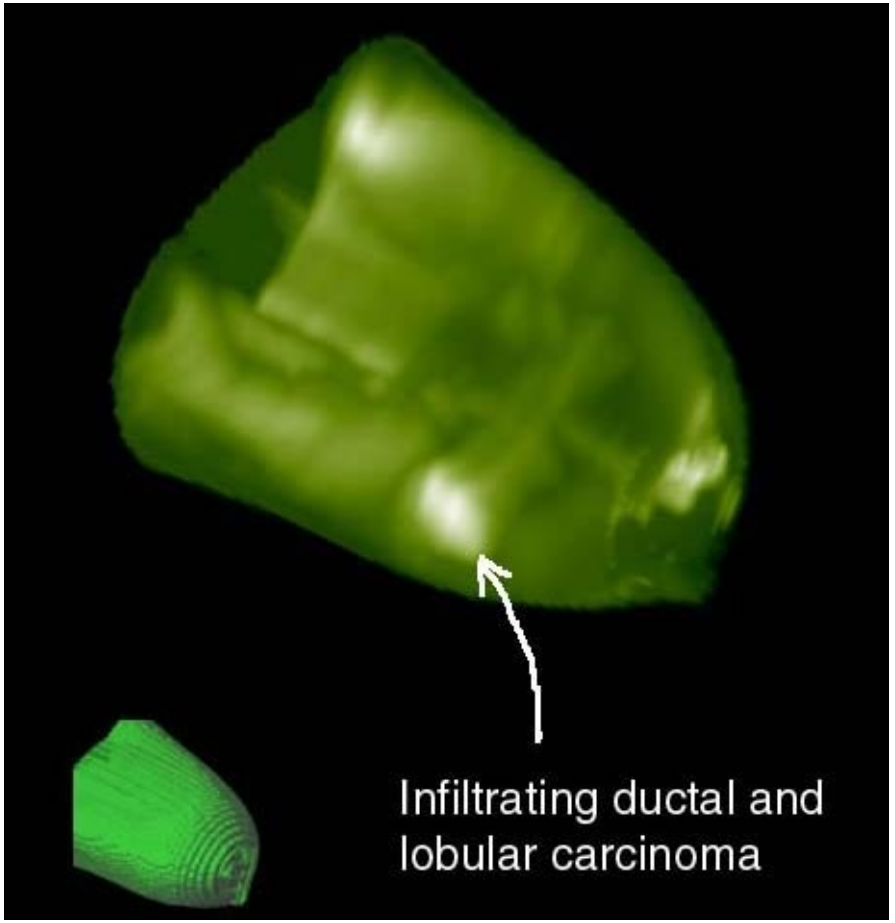


MOI: Market Situation

- CTLM® system (IMDS): Case studies

CASE 4

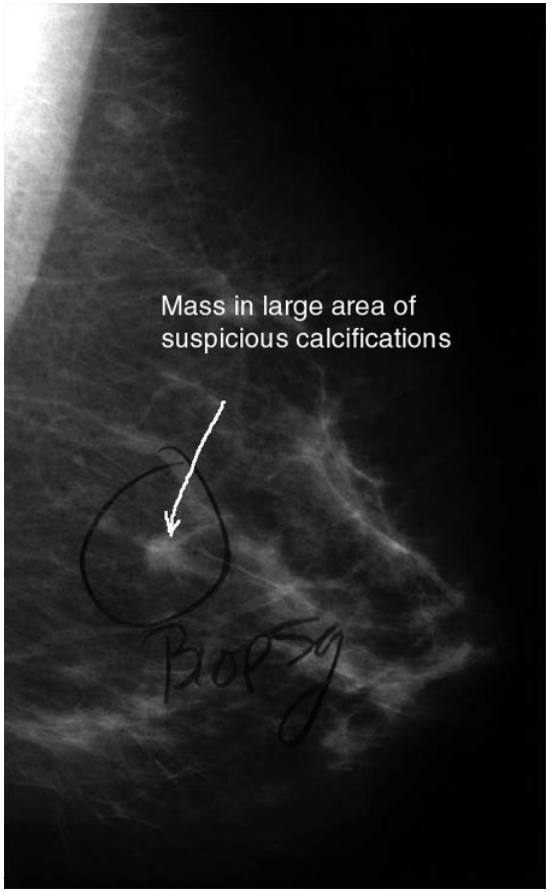


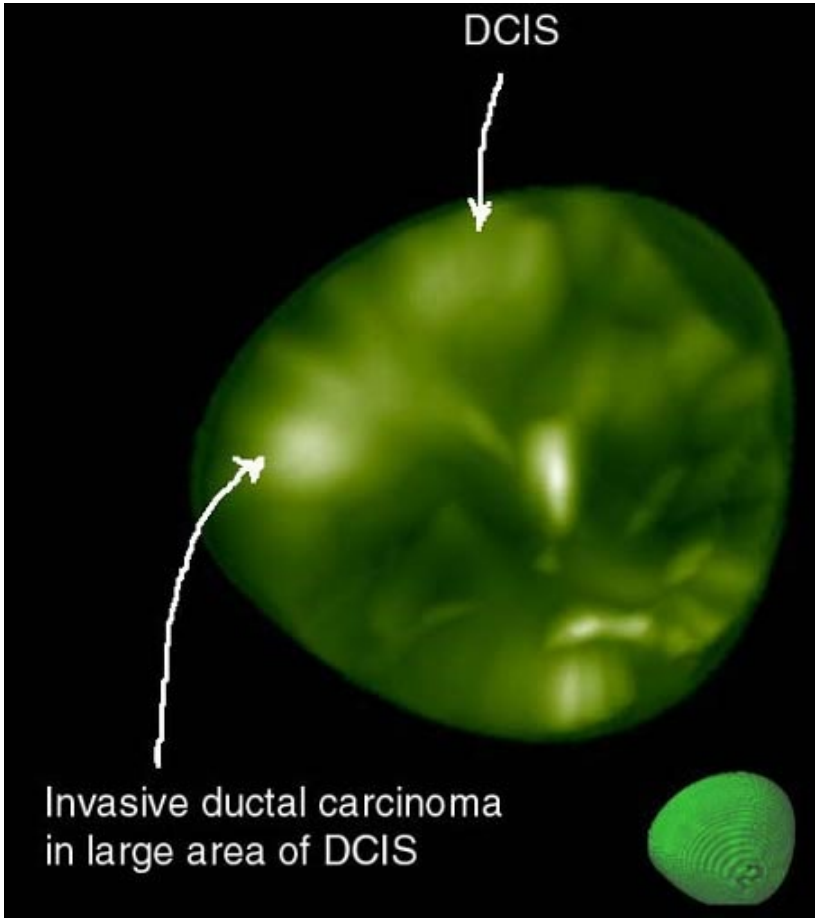


MOI: Market Situation

- CTLM® system (IMDS): Case studies

CASE 5





MOI: Market Situation

- CTLM® system (IMDS): Case studies

CASE 6