Inverse Problems for Biomedical Systems

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What is an inverse problem?

A physical phenomenon: interactions between systems, can be measured.

We can create **physical laws** which provide a model for the phenomenon,

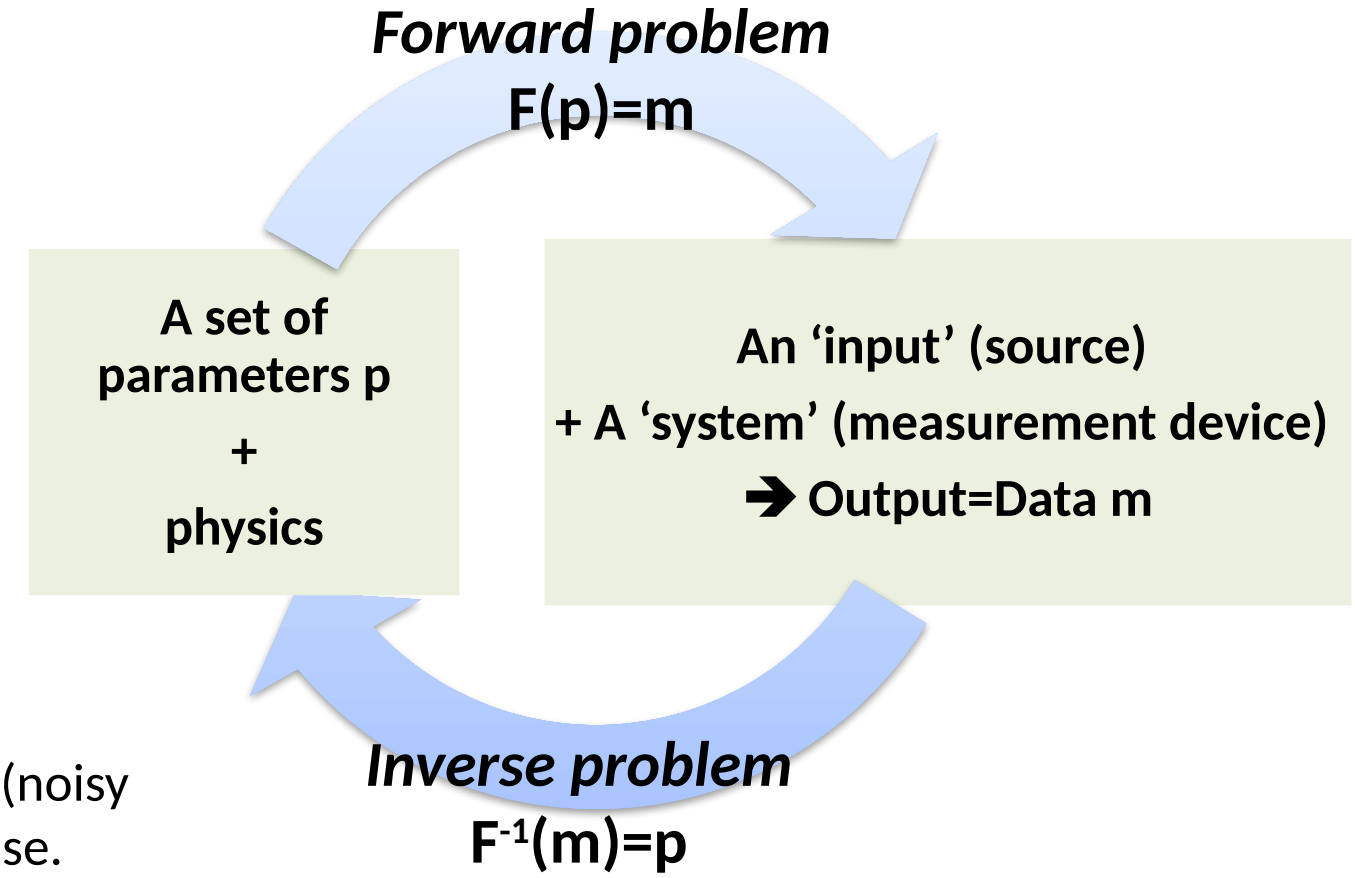
A model is determined by **parameters** and an **internal state.**

$$m = F(p, x)$$

Examples: Wave propagation, light-matter interactions, gravity.

What is an inverse problem?

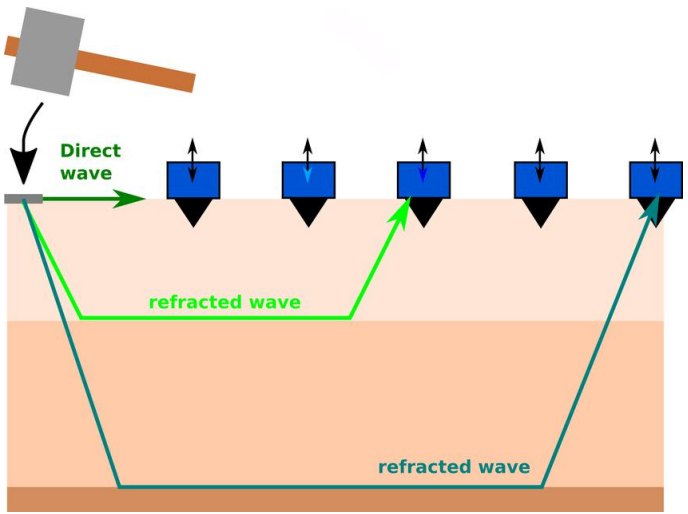
Given known causes (initial conditions, material properties, other model parameters), determine the effects (data/measurements).

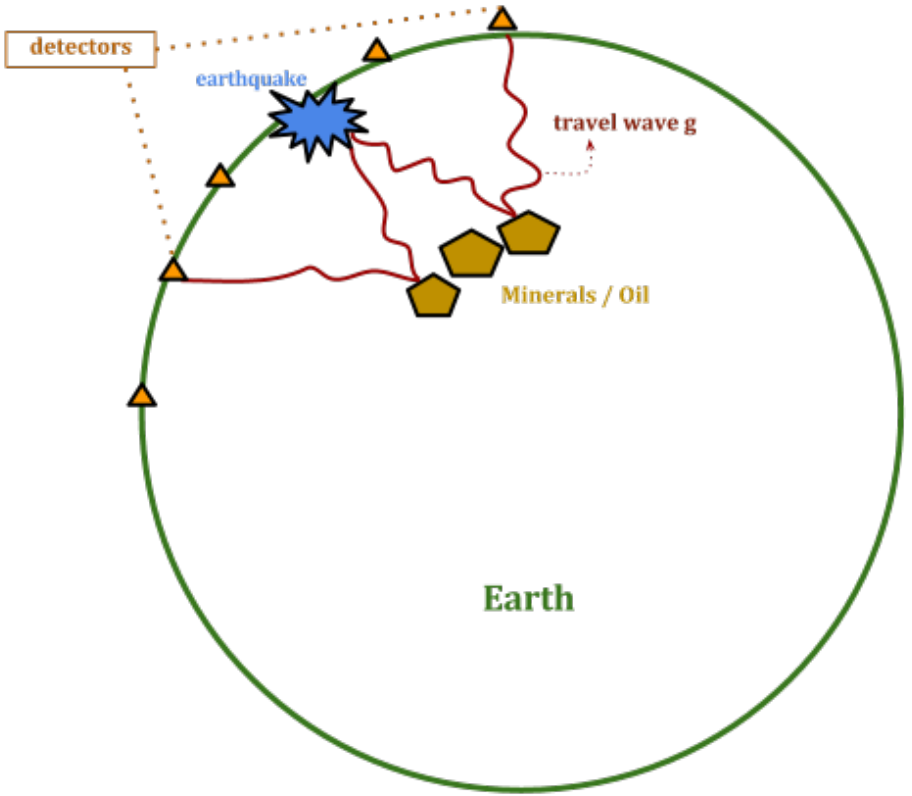


Observing the effects (noisy data), recover the cause.

Examples

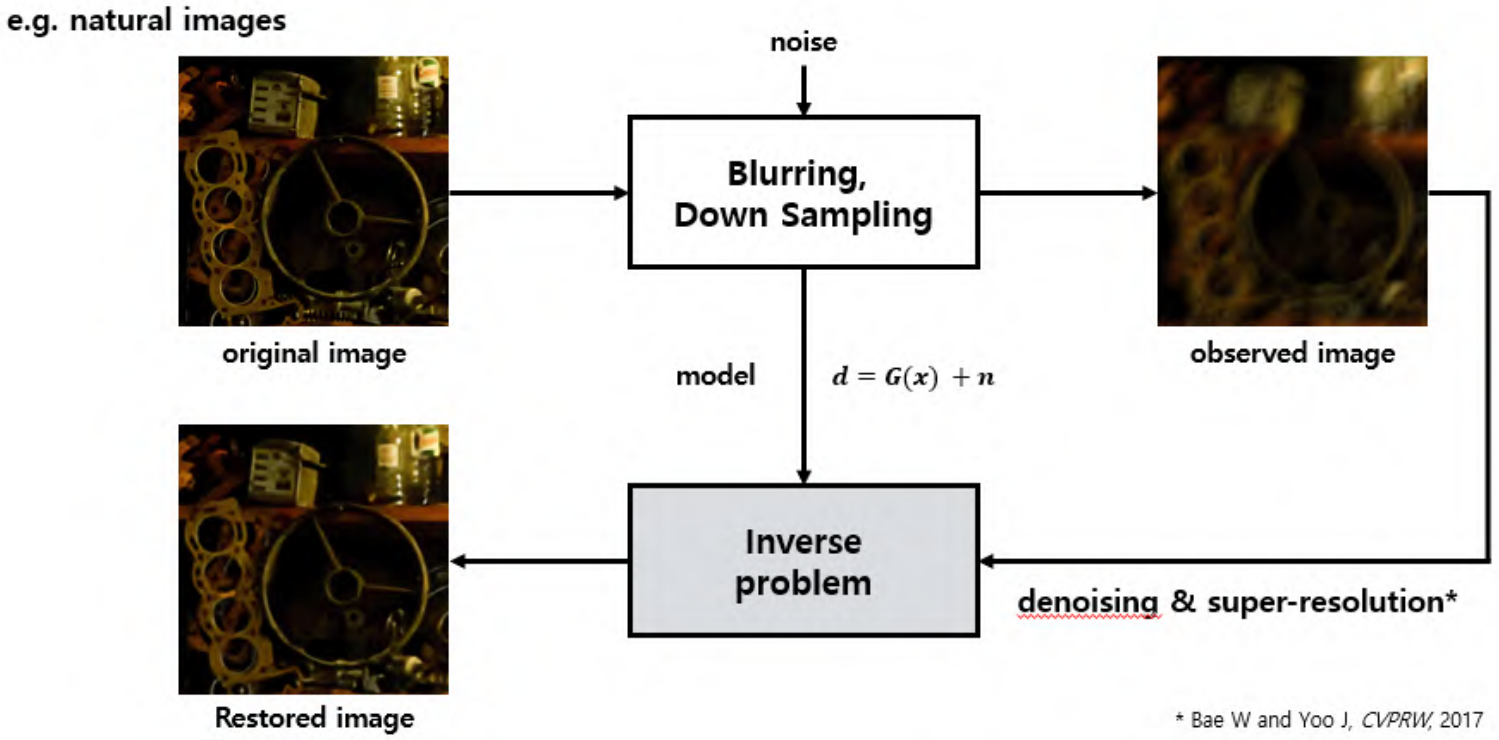
Geology - Seismology





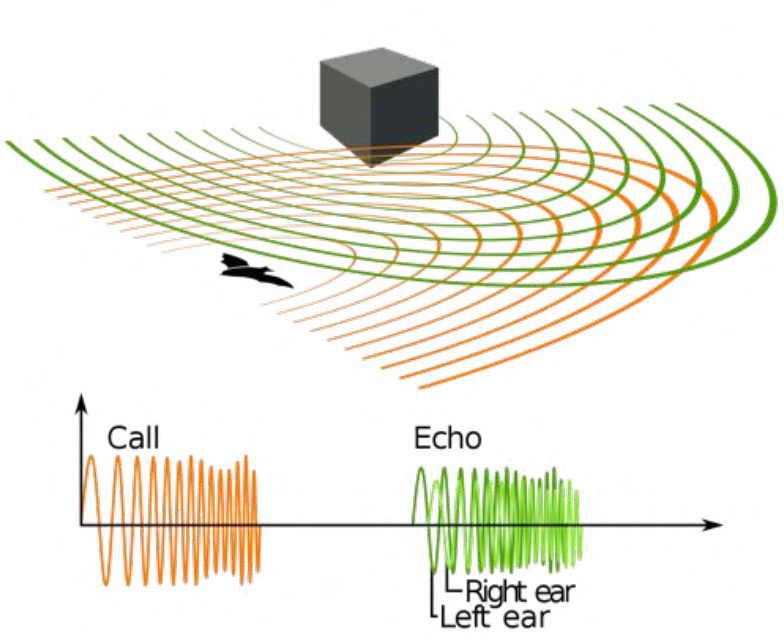
Examples

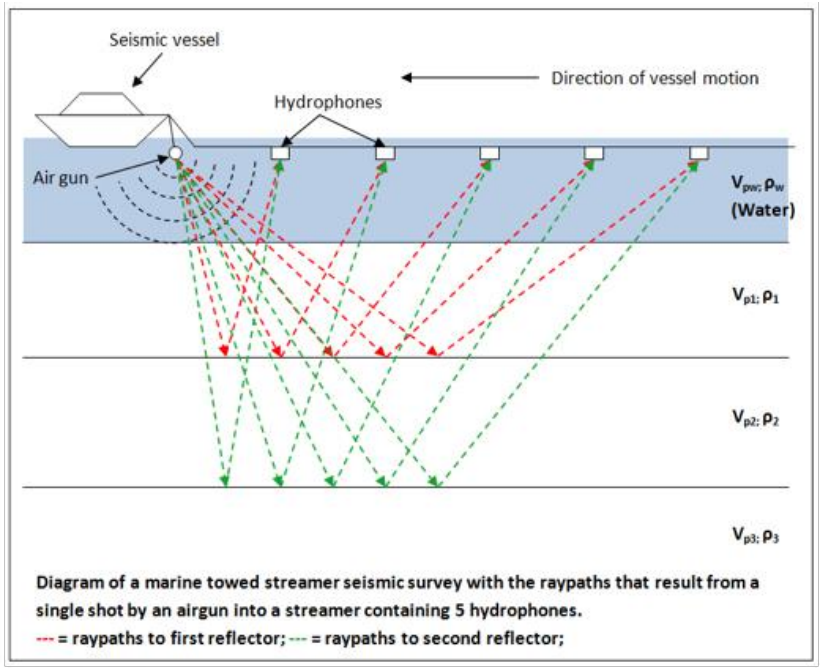
Signal processing / Imaging



Examples

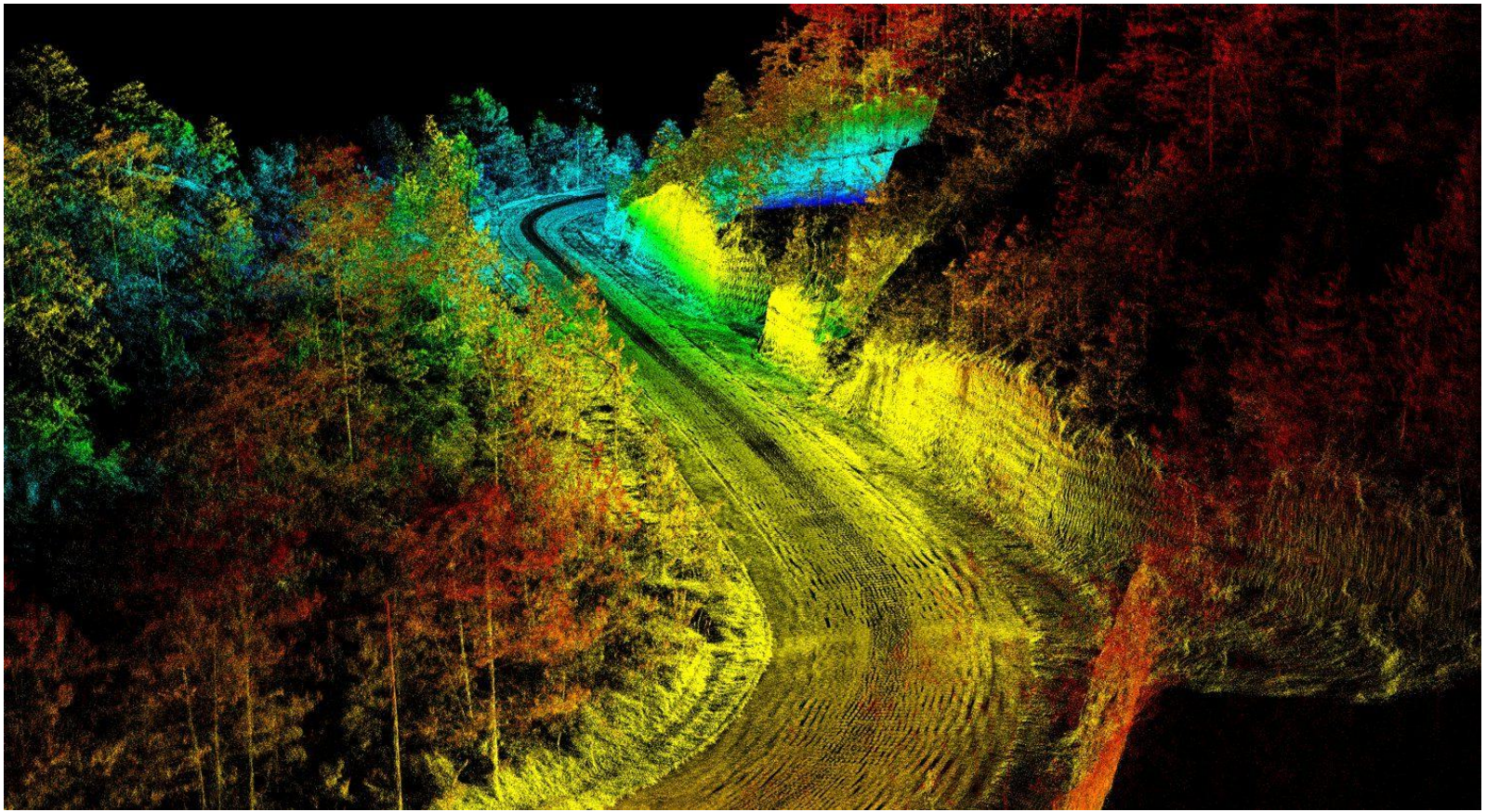
Positioning / Navigation





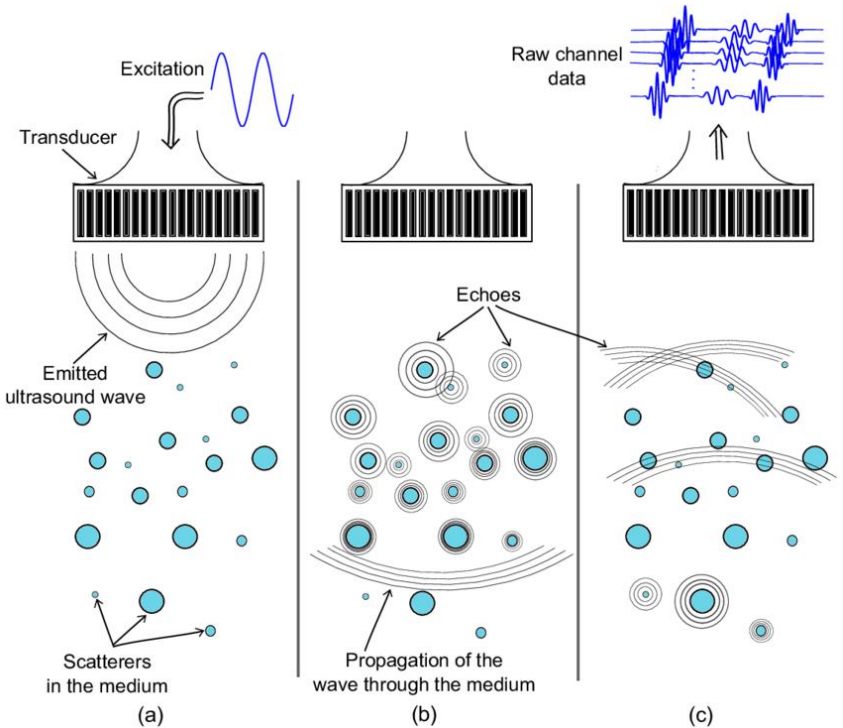
Examples

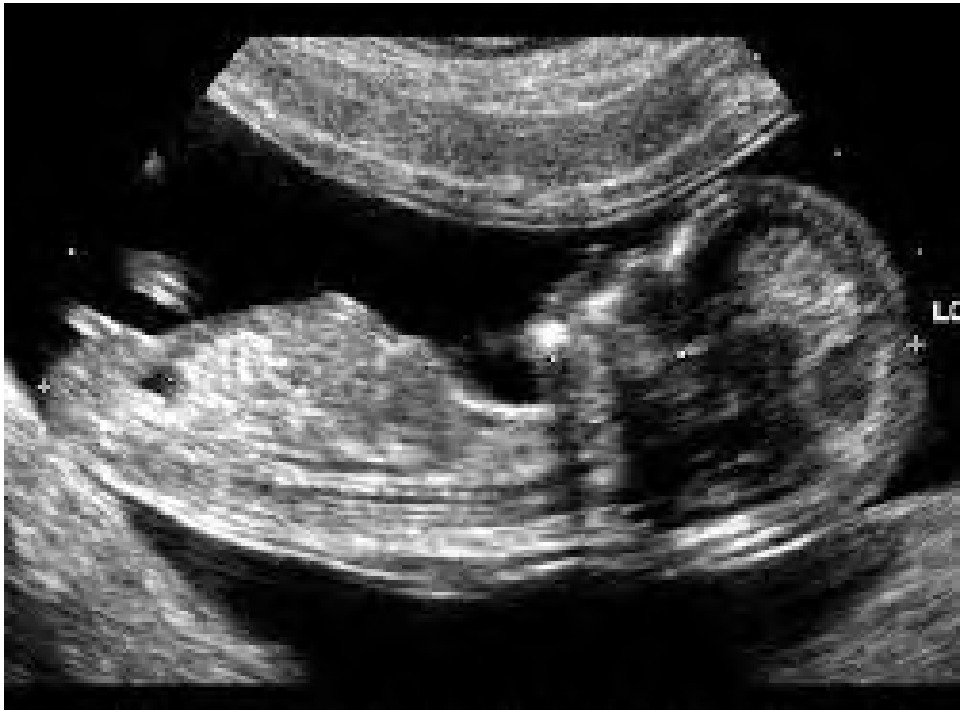
LIDAR



Examples

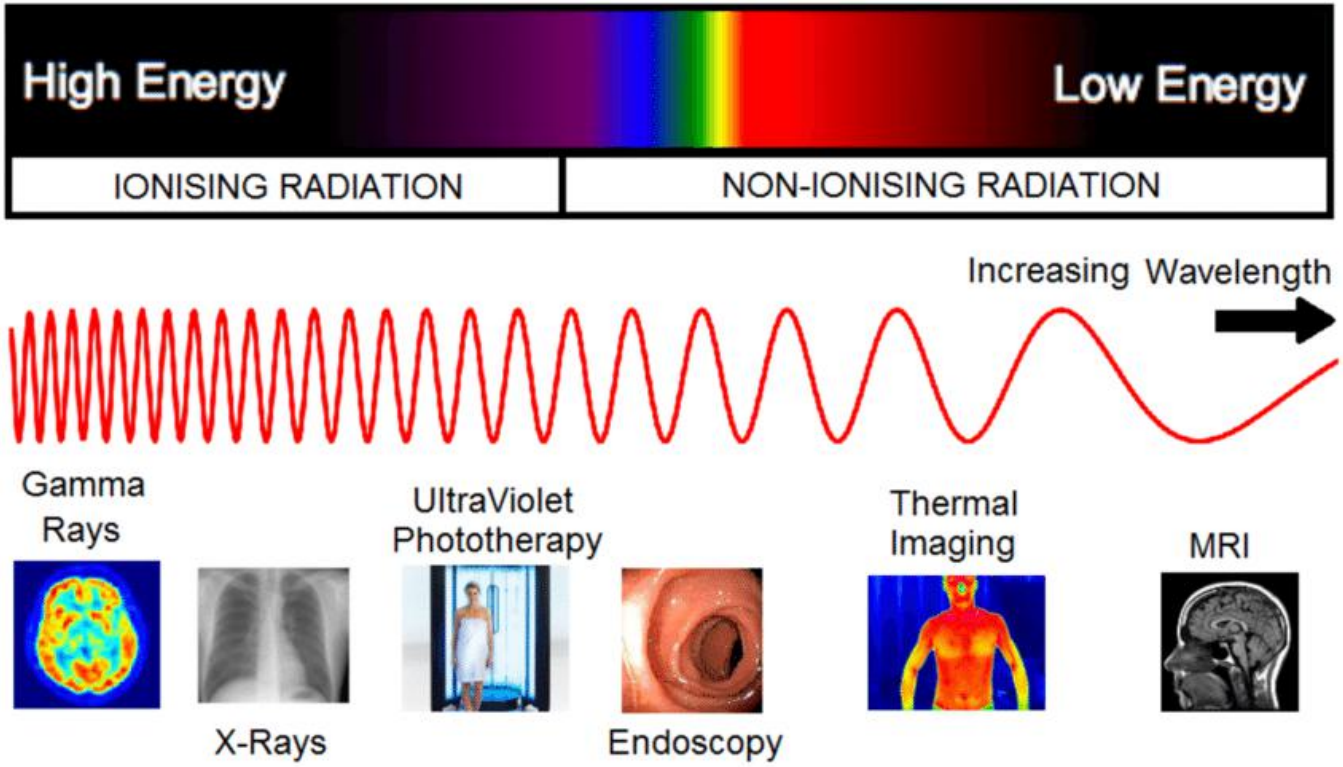
Biomedical imaging - Echography





Examples

Biomedical Imaging – Use of the electromagnetic spectrum

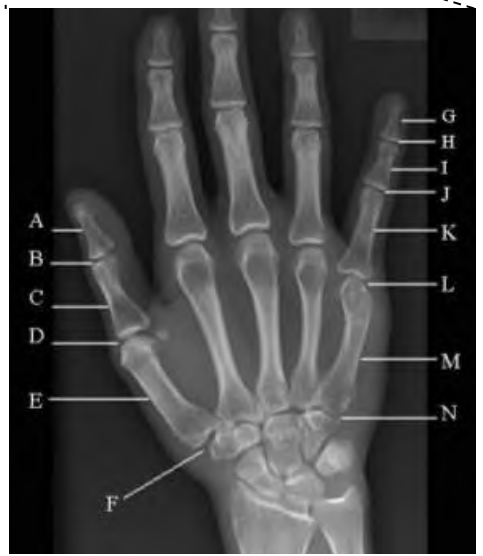


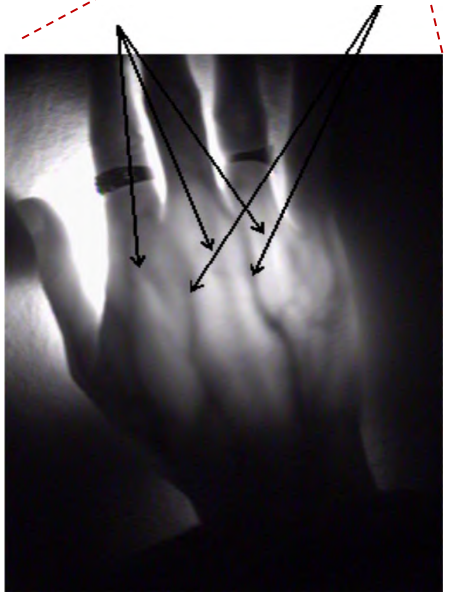
X Rays

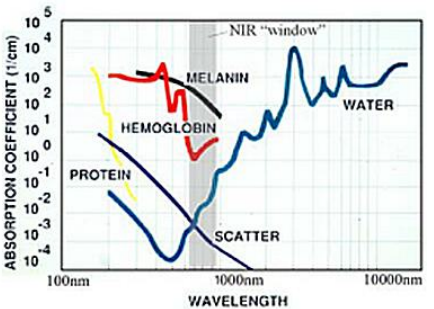
Ultraviolet Visible Infrared

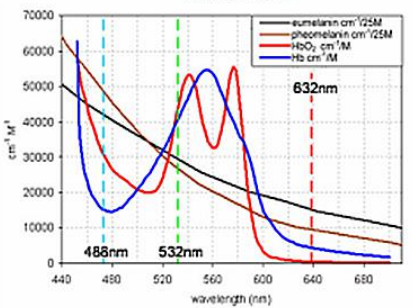
Blood vessels

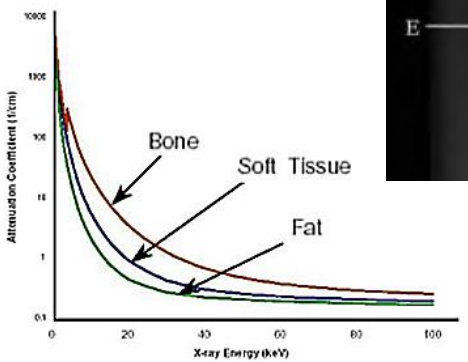
tendons







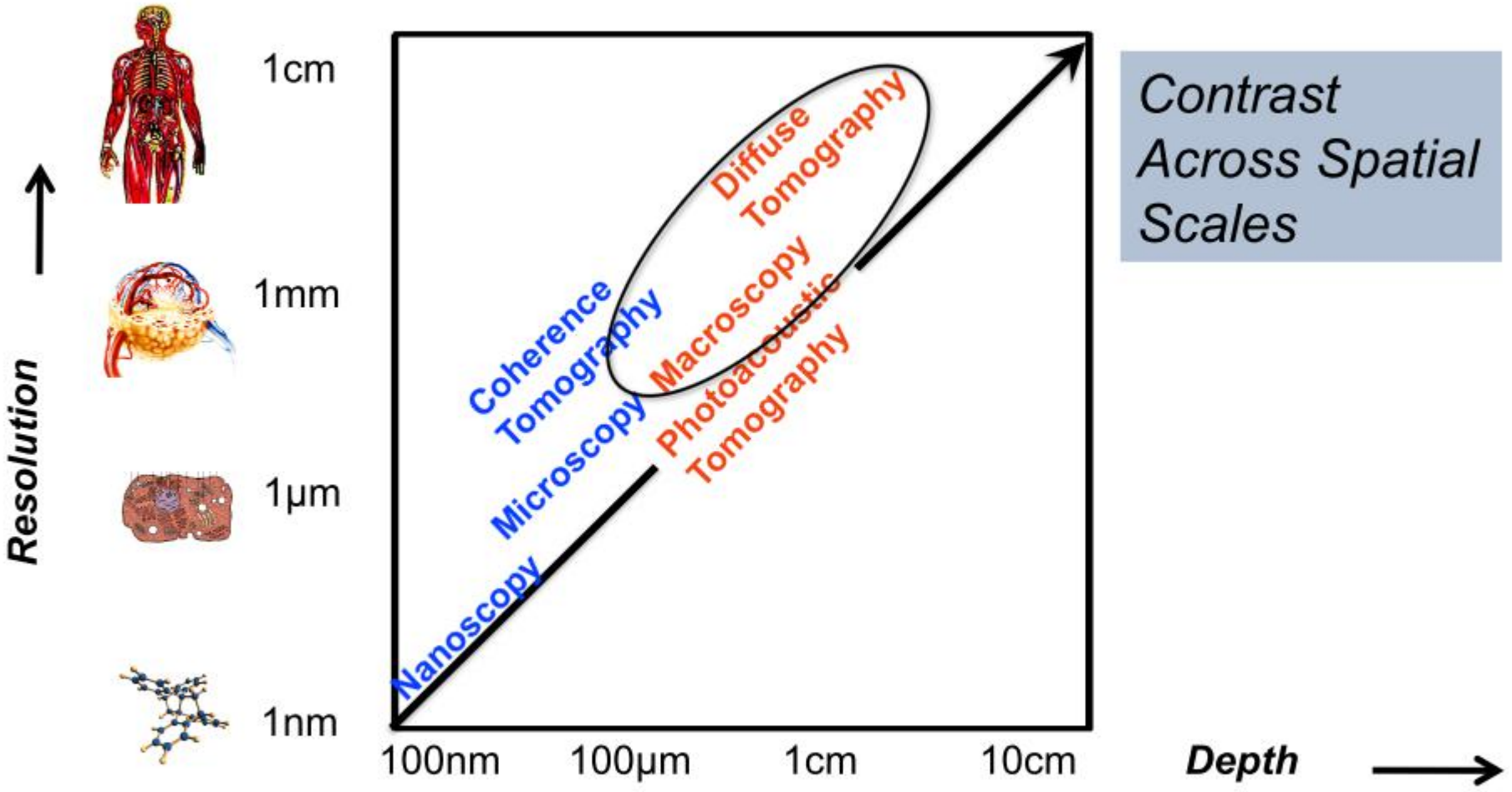


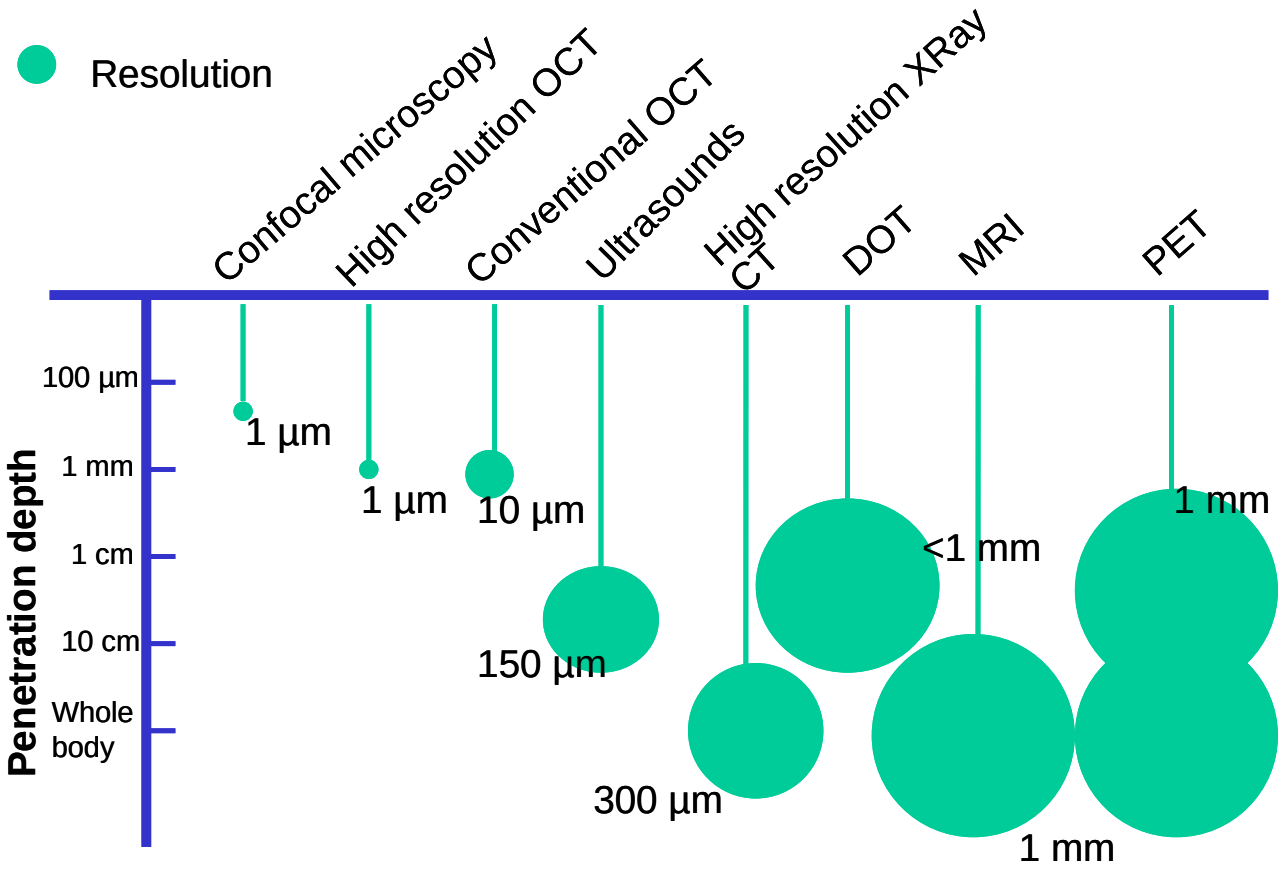


Morphology

Physiology

Different scales/different resolutions

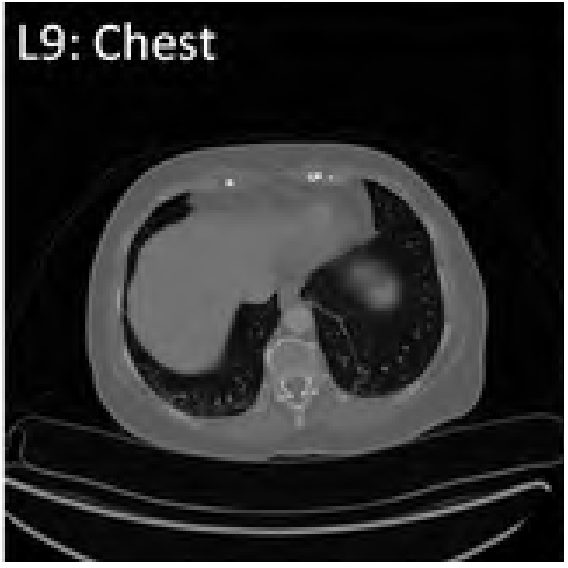



Resolution
Confocal microscopy
High resolution OCT
Conventional OCT
Ultrasounds
High resolution XRay CT
DOT
MRI
PET
Penetration depth
100 µm
1 mm
1 cm
10 cm
Whole body
1 µm
1 µm
10 µm
150 µm
300 µm
<1 mm
1 mm
1 mm

Examples

Computerized tomography

$F(p)=m$

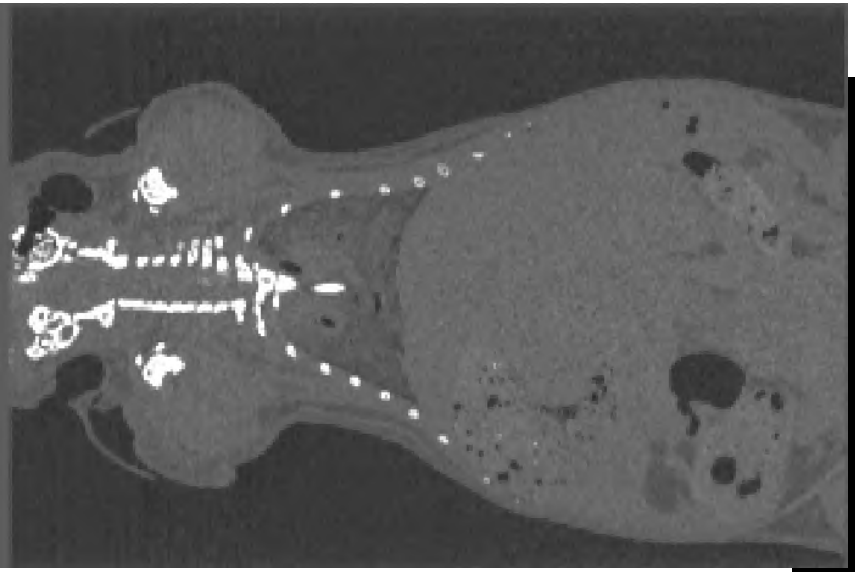


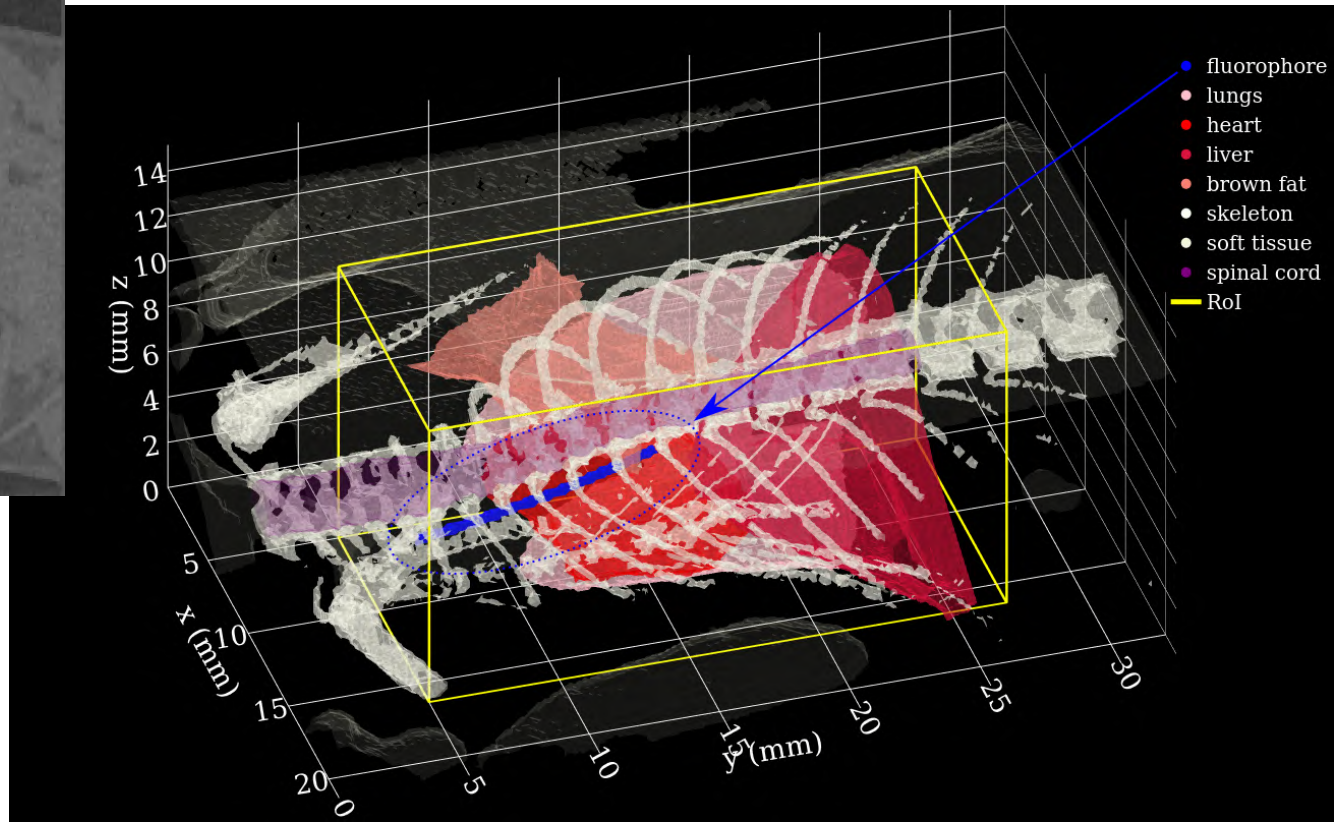
Volumetric distribution of soft and hard tissues/organs

sinograms

$F^{-1}(m)=p$

Computerized tomography





Why using light (optical) for tissue screening?

Major challenge:

Measuring physiological functions without disturbing or damaging *in vivo* functions of the organ

➔ Visible and NIR light

- Non invasive

Photons in the visible wavelengths range have insufficient energy to cause ionization and therefore produce little or no damage to the sample.

- Good penetration in tissues

Longer wavelength (NIR) can penetrate several centimeters into tissue.

- Instrumentation simple and inexpensive

Light sources (LEDs, lamps, lasers) and detectors (phototubes, photodiodes, CCDs).

- Easy to manipulate

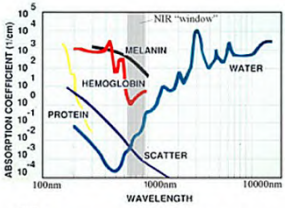
turned with mirrors, focused with lenses, piped through fibers, wavelength selected with filters, time selected with optical gates, etc.

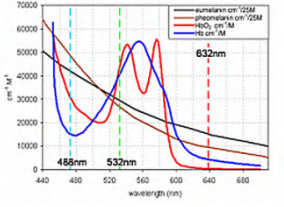
- Tissues have unique intrinsic optical signatures

Biomolecules, cells, tissues➔ specific identification.

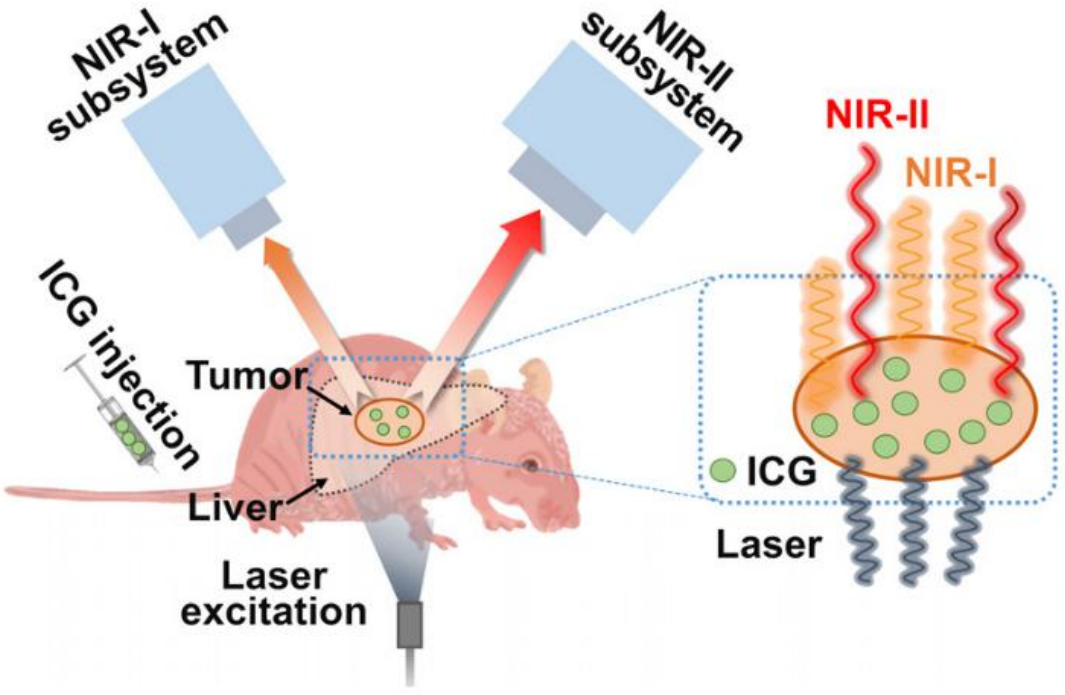
- Wide variety of extrinsic contrast agents

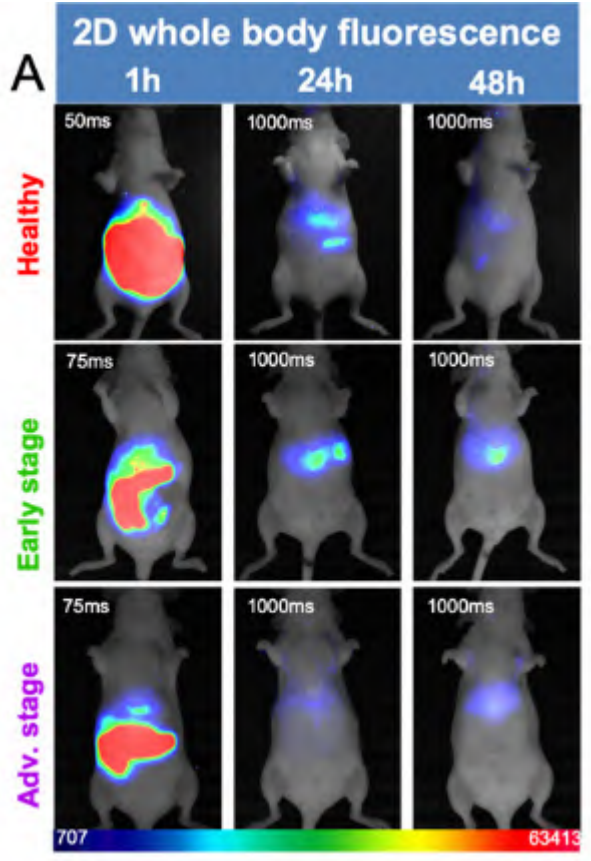
Optical bioimaging can often be aided by labels (also called probes, e.g. fluorescent dyes, quantum dots, metal nanoparticles, etc.) that attach to specific structures of interest and enhance contrast.





Examples

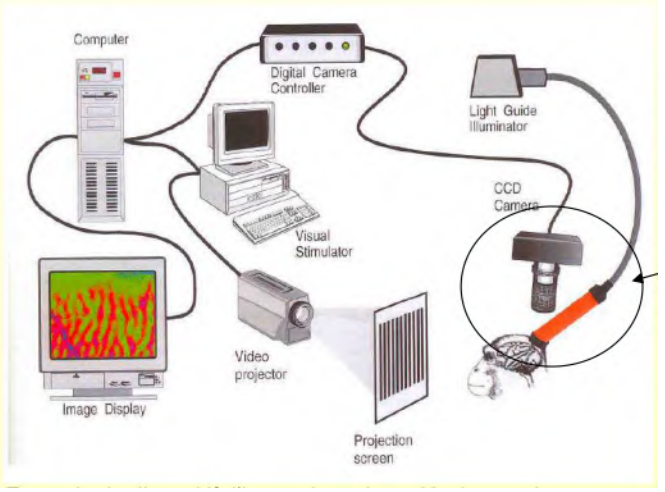

NIR-I subsystem
NIR-II subsystem
ICG injection
Tumor
Liver
Laser excitation
NIR-II
NIR-I
ICG
Laser


A
2D whole body fluorescence
1h
24h
48h
Healthy
Early stage
Adv. stage
50ms
1000ms
1000ms
75ms
1000ms
1000ms
75ms
1000ms
1000ms
707
63413

Diffuse Optical Tomography (DOT)

Bilicheck
for biliribin monitoring

Pulse oximeter for
O2 saturation monitoring



Intrinsic Optical Imaging (IOI)

Involved disciplines

Physical Modelling:

- Specific knowledge: Physics, Biology, Seismology, Telecommunications, etc
- Differential Equations: Continuity equations, hyperbolic systems, Conservation laws.

Forward Problem:

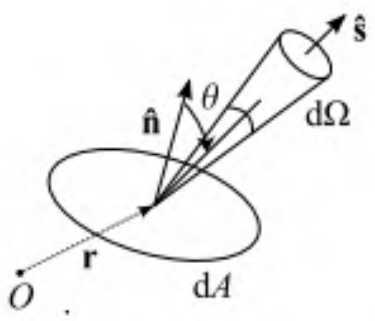
- Numerical methods
- Linear algebra

Inverse Problem:

- Optimization problems
- Probability theory and statistical methods
- Multi-variable calculus
- Numerical analysis and linear algebra

Physical model for light propagation

Photometric Quantities (states)



$$\cos\theta = \hat{\mathbf{s}}\cdot\hat{\mathbf{n}}$$

$$d\Omega = \sin\theta\, d\theta\, d\phi$$

$$\hat{\mathbf{s}} = (\sin\theta\cos\phi, \sin\theta\sin\phi, \cos\theta)$$

$L(\mathbf{r},\hat{\boldsymbol{s}},t)$: **Specific intensity** (Radiance, Irradiance…) [W.m^{-2}.sr^{-1}]:
power (or flux) per unit surface and solide angle at time t (and wavelength λ)

$\phi(\mathbf{r},t)$: **Fluence Rate** [W.m^{-2}]: $\phi(\mathbf{r},t)=\int_{4\pi} L(\mathbf{r},\hat{\boldsymbol{s}},t)d\Omega$

$F(\mathbf{r},t)$: **Net Flux** [W.m^{-2}]: $F(\mathbf{r},t)=\int_{4\pi} L(\mathbf{r},\hat{\boldsymbol{s}},t)(\hat{\boldsymbol{s}}.\hat{\boldsymbol{n}})d\Omega=(\int_{4\pi} L(\mathbf{r},\hat{\boldsymbol{s}},t)\hat{\boldsymbol{s}}d\Omega).\hat{\boldsymbol{n}}$

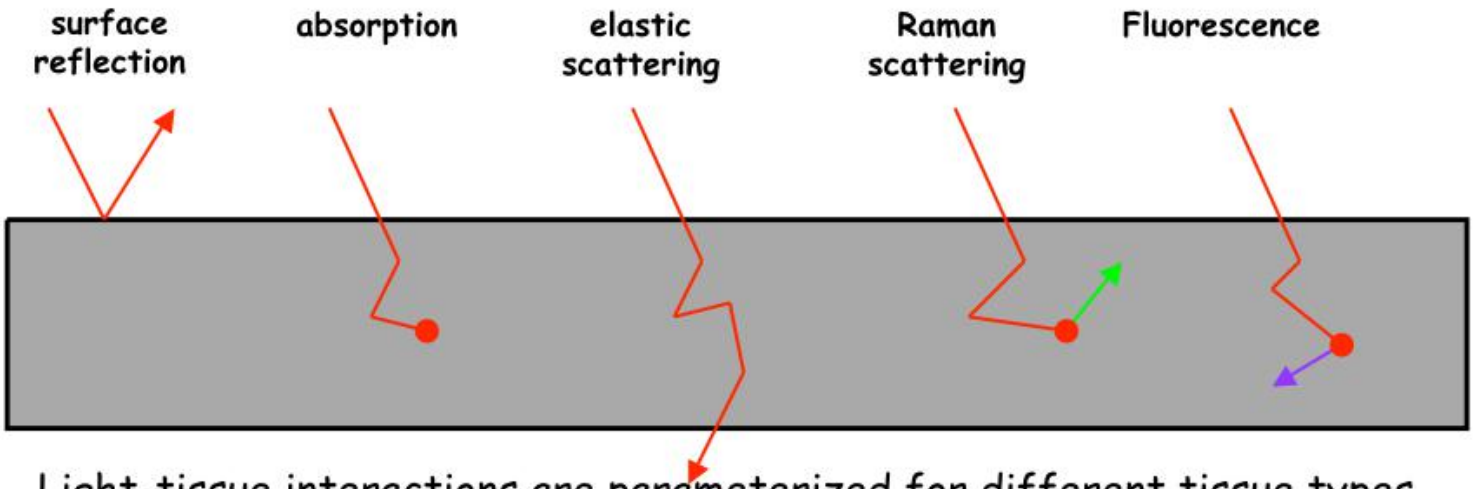
$\boldsymbol{J}(\mathbf{r},t)$: **Current Density Vector** [W.m^{-2}]: $\boldsymbol{J}(\mathbf{r},t)=\int_{4\pi} L(\mathbf{r},\hat{\boldsymbol{s}},t)\hat{\boldsymbol{s}}d\Omega$ (points in the direction the net flux of radiation)

Light propagation

Based on a conservation law:

A conserved quantity in a volume, for instance mass and energy. Changes in time are due to source, sinks or flows.

Light interaction with tissue

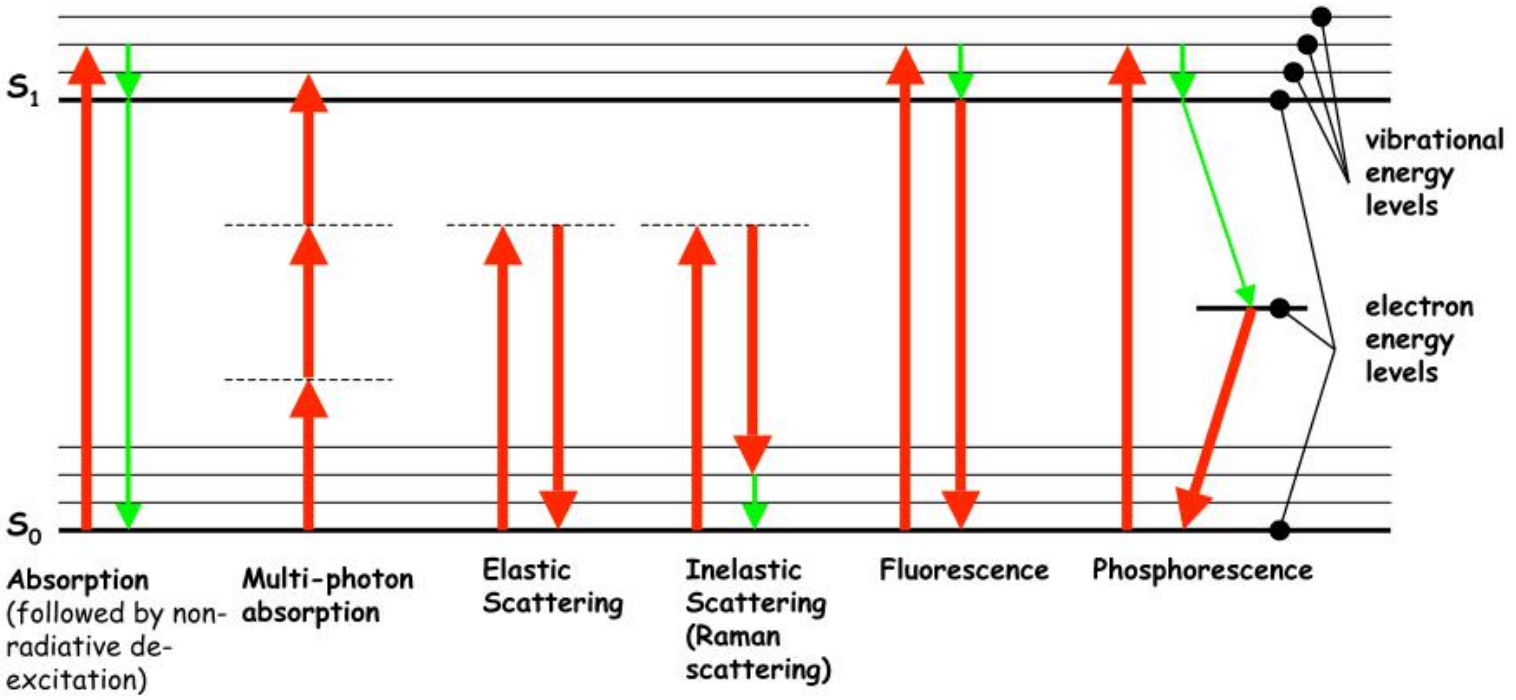


Light-tissue interactions are parameterized for different tissue types

$\mu_s(\lambda)$	scattering coefficient [cm^{-1}]
$\mu_a(\lambda)$	absorption coefficient [cm^{-1}]
$g(\lambda)$	average cosine HG parameter
$\mu_f(\lambda)$	fluorescence coefficient [cm^{-1}]
$\mu_R(\lambda)$	Raman coefficient [cm^{-1}]

$\mu_{total} = \mu_s + \mu_a + \mu_f + \mu_R$ total interaction coefficient [cm^{-1}]

Jablonsky Diagram



Absorption

- Conversion of energy into something else (mostly heat)
-
- Absorption is the primary event to cause a potentially therapeutic (or damaging) effect on a tissue.
  - Energy transfer is due to absorption

- Diagnostic, chemical composition of a tissue, optical contrast during imaging.

Absorption coefficient μ_a [cm^{-1}]

➔ The probability of a photon to be absorbed per unit length

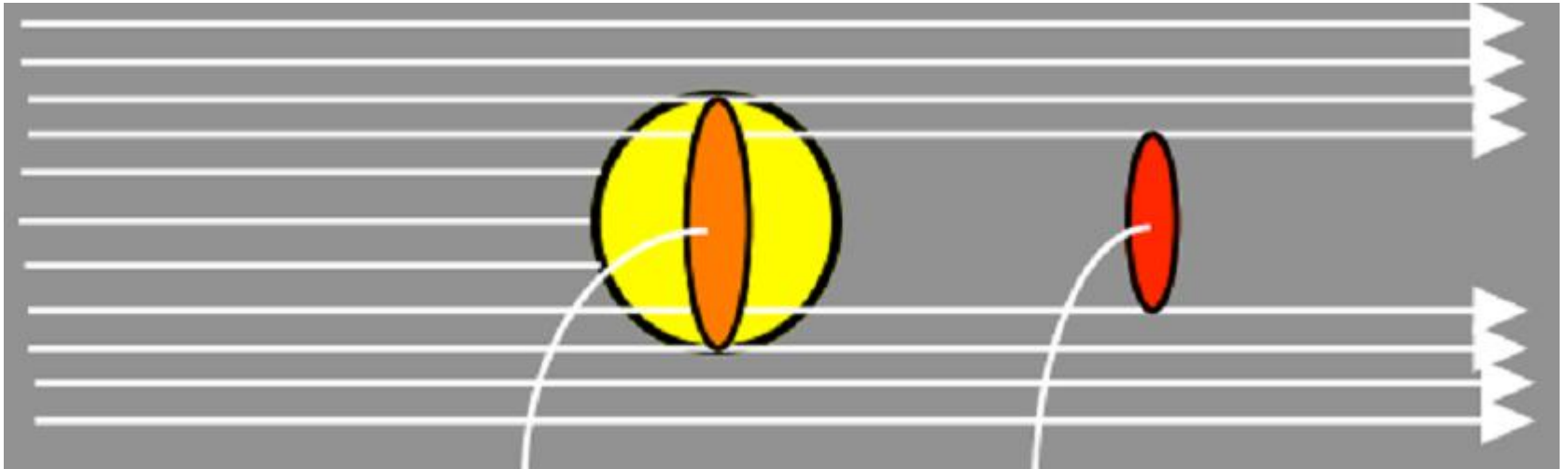
Absorption mean free path $mfp=1/\mu_a$ [cm]

➔ Mean path-length between photon absorption:

$mfp=1/\mu_a \sim 1\text{-}10$ cm for biological tissues.

Definition and Units of Absorption Coefficient [cm^{-1}]

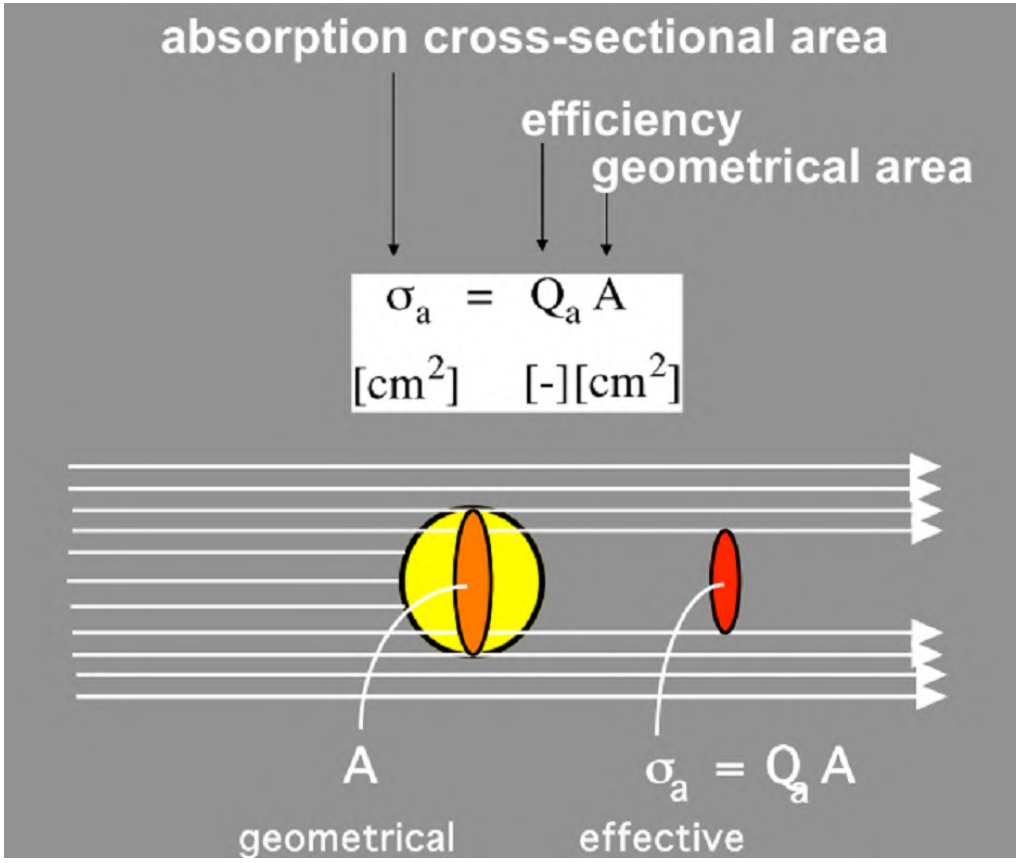
- Idealized chromophore=sphere
- Sphere blocks incident light and casts a shadow-absorption.
- This description is of course an incorrect and schematicized version of the real situation.



Definition and Units of Absorption Coefficient [cm^{-1}]

The size of the absorption shadow is called the **absorption cross-section** (σ_a [cm^2]) and can be smaller or larger than the geometrical size of the chromophore (A [cm^2]).

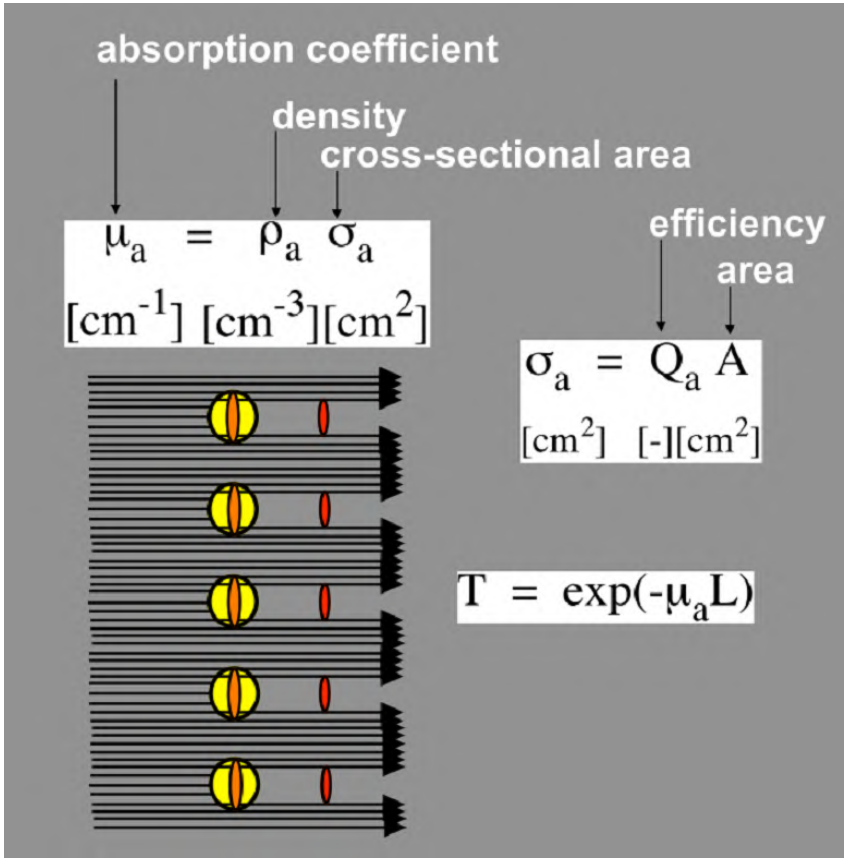
It is related by the proportionality constant called **absorption efficiency** Q_a [-].

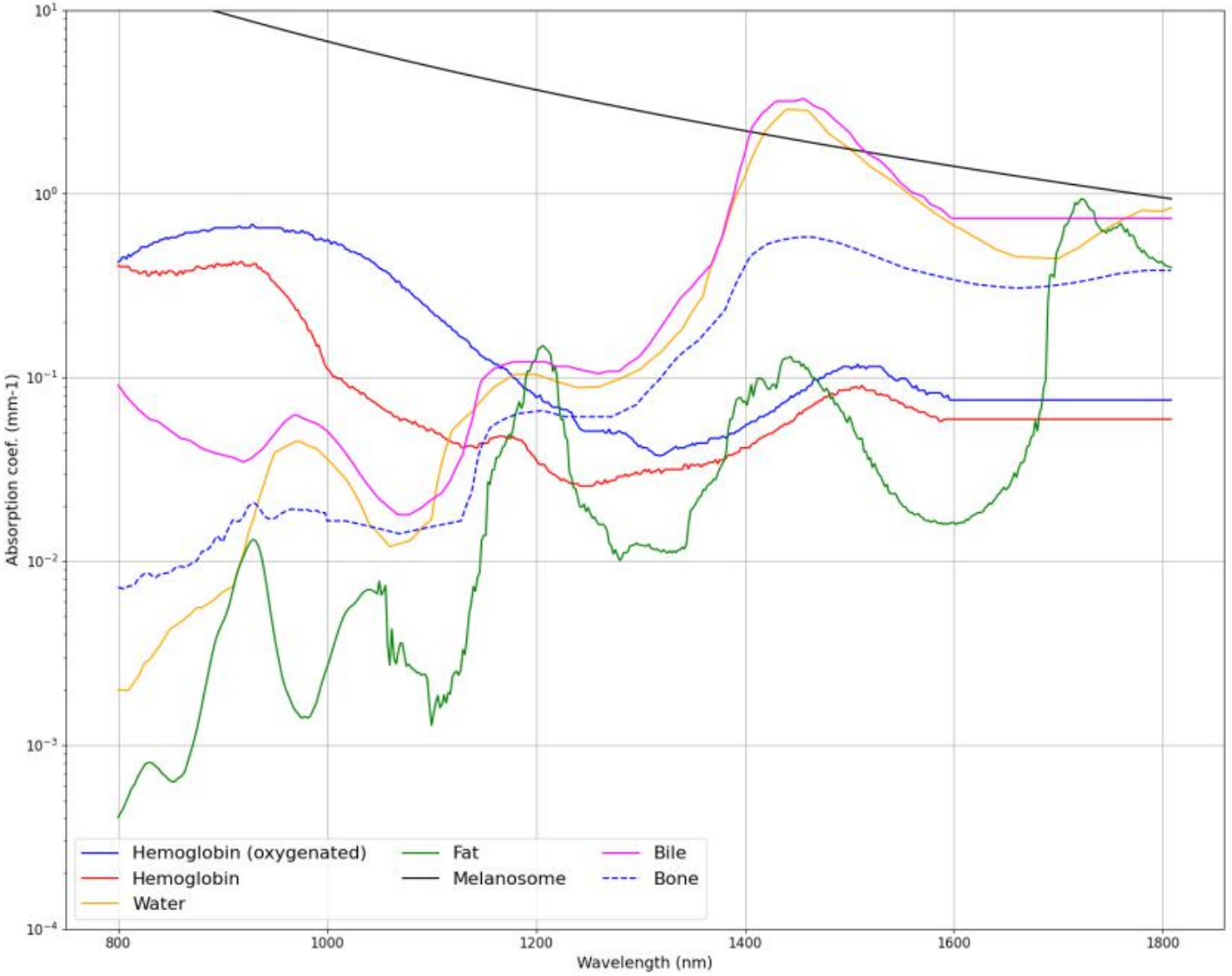


Definition and Units of Absorption Coefficient [cm^{-1}]

The **absorption coefficient μ_a [cm^{-1}]** describes a medium containing many chromophores at a concentration described as a **volume density ρ [cm^{-3}]**.

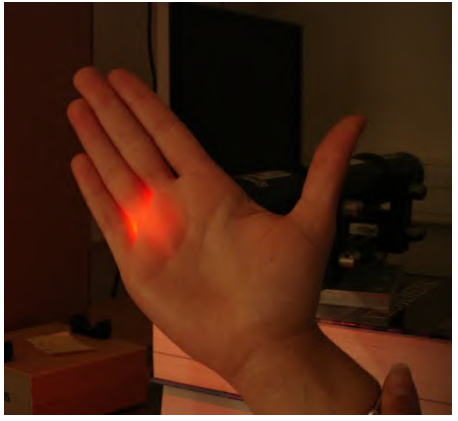
The absorption coefficient is the cross-sectional area per unit volume of medium.




Absorption coef. (mm-1)
Wavelength (nm)
Hemoglobin (oxygenated)
Hemoglobin
Water
Fat
Melanosome
Bile
Bone

Scattering

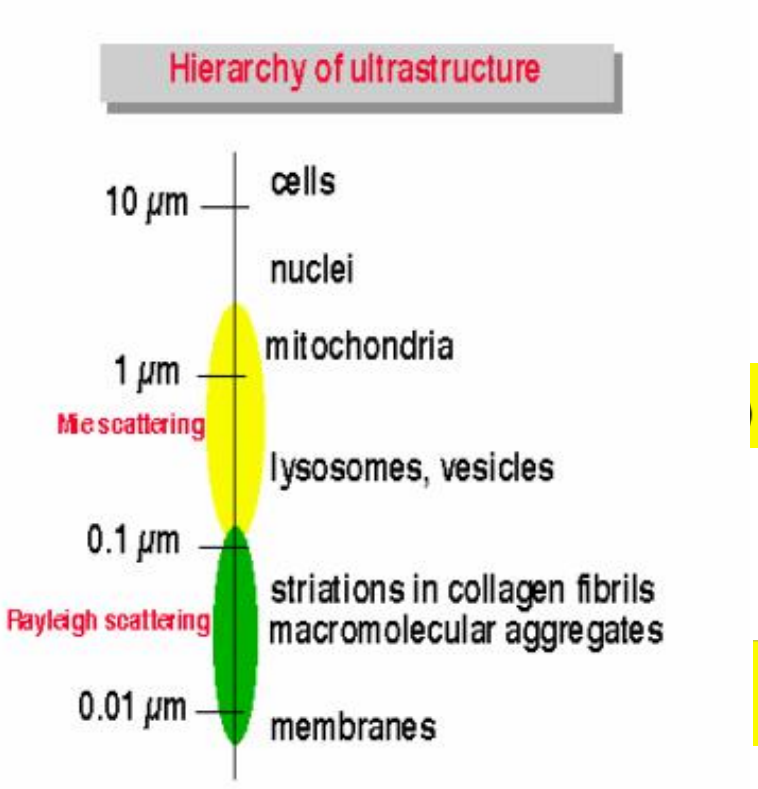
- The deflection of light from its original path.
- Occurs in media which contain fluctuations in the refractive index n, whether such fluctuations are discrete particles or more continuous variations in n.



Some Biological Scatterers

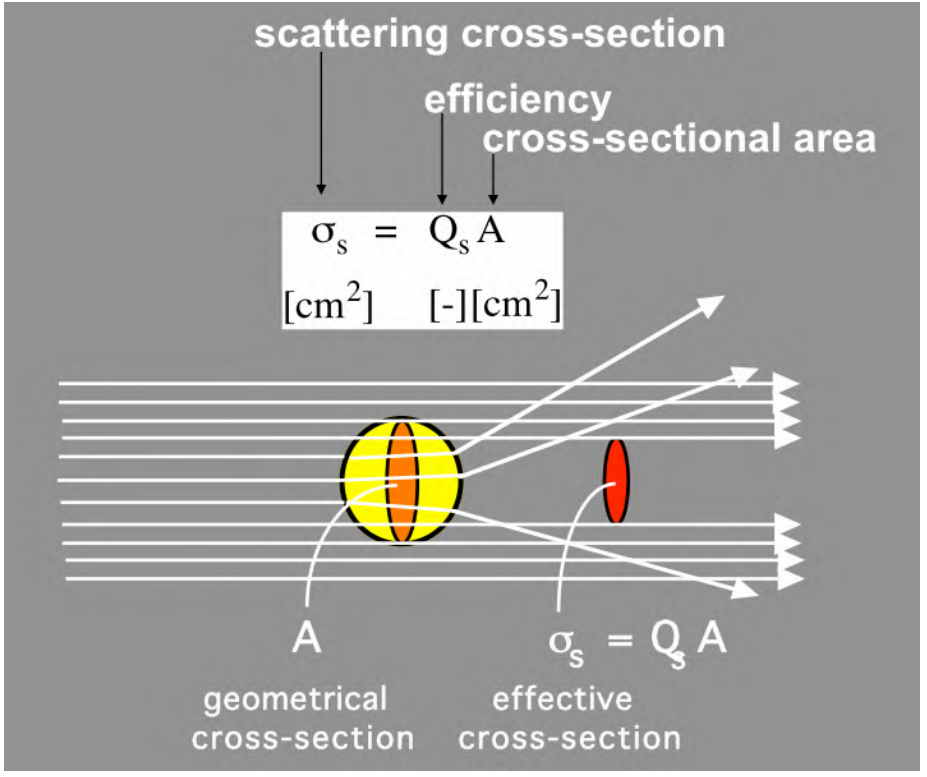
- Scattering of light by structures on **the same size** scale as (or **bigger than**) the photon wavelength is described by **Mie theory**.

- Scattering of light by structures much **smaller** than the photon wavelength is called the Rayleigh limit of Mie scattering, or simply **Rayleigh scattering**.



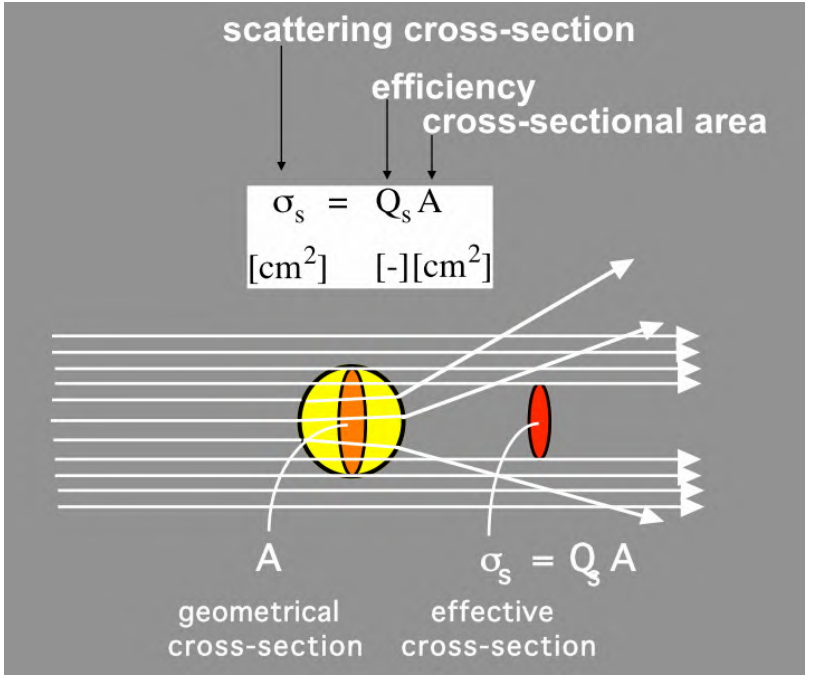
Light scattering by a single particle Modelling

- Scattering particle idealized as a sphere with a particular geometrical size.
- Sphere redirects incident photons into new directions casting a shadow.
- Oversimplified version of the real situation.



Light scattering by a single particle Quantifying

- The size of the scattering shadow is called the scattering cross-section (σ_s [cm^2])
- Can be smaller or larger than the geometrical size of the scattering particle (A [cm^2])
- Scattering efficiency (Q_s [dimensionless]).



Light scattering by tissues scattering coefficient

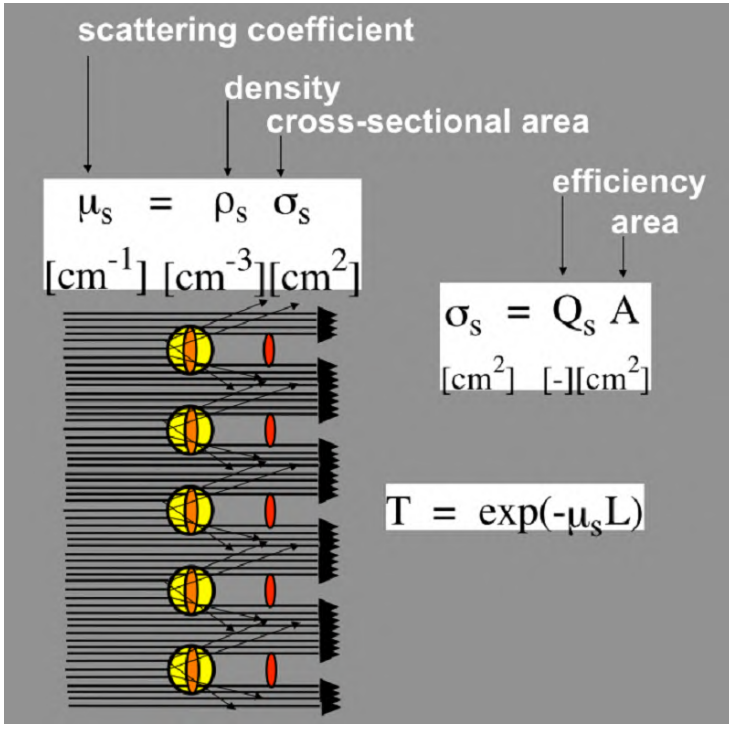
The **scattering coefficient μ_s** [cm^{-1}] describes a medium containing many scattering particles at a concentration described as a **volume density ρ_s** [cm^3]. The scattering coefficient is essentially the cross-sectional area per unit volume of medium.

The probability of a photon being scattered per unit path-length:

- $1/\mu_s$ mean path-length between photon scattering [cm] = **scattering mean free path**
- **$1/\mu_s \sim 0.01$ cm** for biological tissue

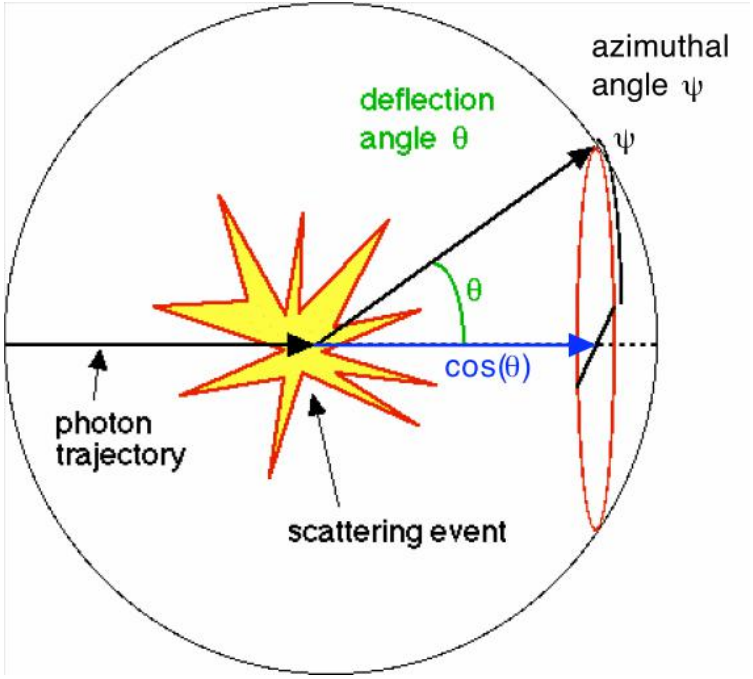
The probability of **transmission T** of the photon **without redirection by scattering** after a pathlength L is:

$$T=\exp[-\mu_s L]$$



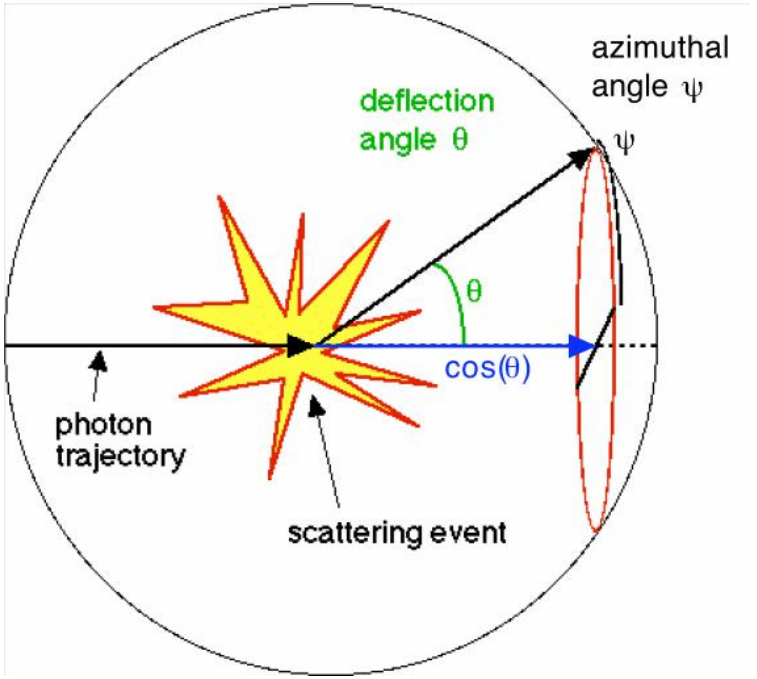
Light scattering by a single particle

- A scattering event causes a deflection at angle θ from the original forward trajectory.
- Azimuthal angle of scattering ψ.
- The deflection angle θ affects the amount of forward direction, cos(θ), retained by the photon.



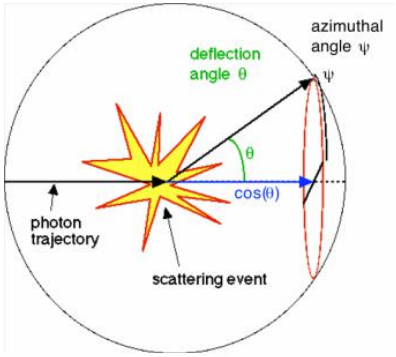
Light scattering by a single particle
Phase function

- **Scattering function – Phase function**
- Angular dependence of scattering, $p(\theta)$.
- Has units of [sr^{-1}], describes the probability of a photon scattering into a unit solid angle oriented at an angle θ relative to the photons original trajectory.
- The $p(\theta)$ has historically been also called **scattering phase function**.



Light scattering by a single particle
Anisotropy factor g

g [-] is a measure of the amount of forward direction retained after a single scattering event.



$$g = \langle \cos\theta \rangle = \int_0^{\pi} p(\theta)\cos\theta \, 2\pi\sin\theta \, d\theta$$

where $\int_0^{\pi} p(\theta) \, 2\pi\sin\theta \, d\theta = 1$

$\Leftrightarrow$

$$g = \int_{-1}^{1} p(\cos\theta)\cos\theta \, d(\cos\theta)$$

$$\int_{-1}^{1} p(\cos\theta) \, d(\cos\theta) = 1$$

$g \in [-1;1]$

$g = 0$ *isotropic scattering*

$g = 1$ *forward scattering*

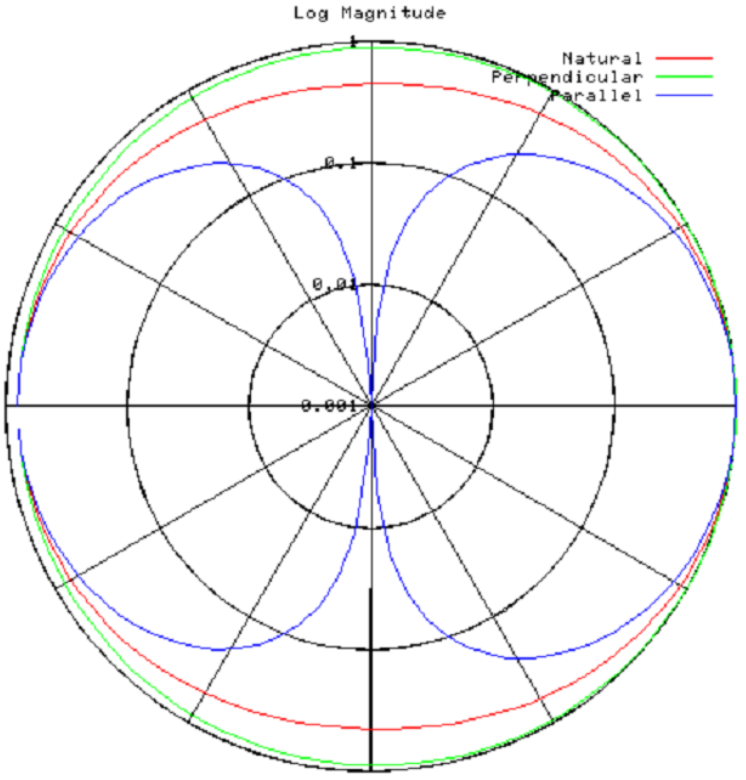
$g = -1$ *backward scattering*

Light scattering by a single particle phase functions with different anisotropy factors g

D=0.2 μm
n_medium=1.0
n_sphere=1.5
λ=0.6328 μm

➔ g=0.04

$$g = \langle \cos\theta \rangle = \int_0^{\pi} p(\theta)\cos\theta \, 2\pi\sin\theta \, d\theta$$



Light scattering by a single particle phase functions with different anisotropy factors g

D=1.0 μm

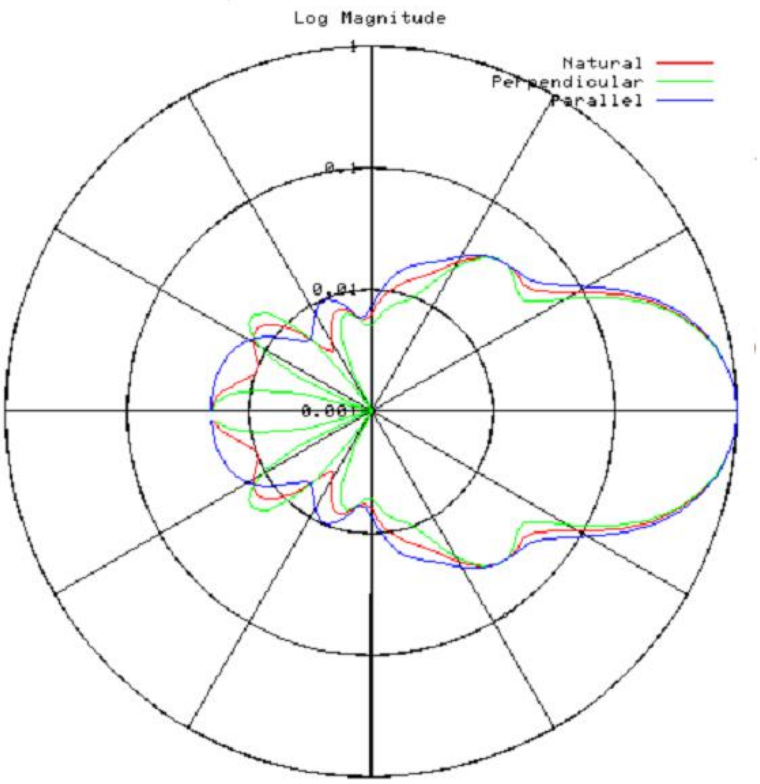
n_medium=1.0

n_sphere=1.5

λ=0.6328 μm

➔ g=0.7

$$g = \langle \cos\theta \rangle = \int_0^{\pi} p(\theta)\cos\theta \, 2\pi\sin\theta \, d\theta$$



Light scattering by a single particle phase functions with different anisotropy factors g

D=2.0 μm

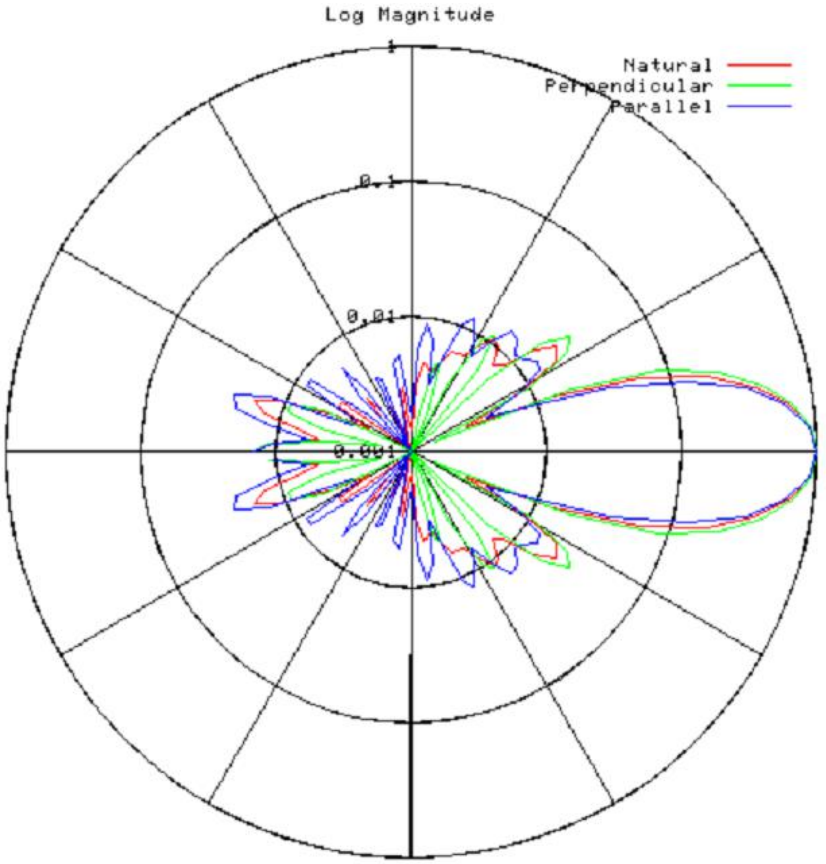
n_medium=1.0

n_sphere=1.5

λ=0.6328 μm

➔ g=0.714

$$g = \langle\cos\theta\rangle = \int_0^{\pi} p(\theta)\cos\theta \, 2\pi\sin\theta \, d\theta$$



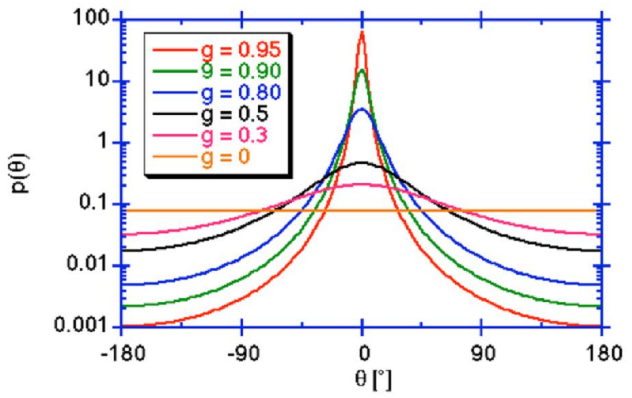
Light scattering by a single particle
Henyey-Greenstein scattering function

- [L. G. Henyey, J.L. Greenstein, Diffuse radiation in the galaxy, Astrophysical Journal 93:70-83, 1941].
- Most popular scattering function in tissue optics.
- Henyey and Greenstein (1941) devised an expression which mimics the angular dependence of light scattering by small particles, which they used to describe scattering of light by interstellar dust clouds.
- The HG scattering function is useful in approximating the angular scattering dependence of single scattering events in biological tissues.

$$p(\theta) = \frac{1}{4\pi} \frac{1-g^2}{(1+g^2-2g\cos\theta)^{3/2}}$$

$$\int_0^{\pi} p(\theta) 2\pi \sin\theta d\theta = 1$$

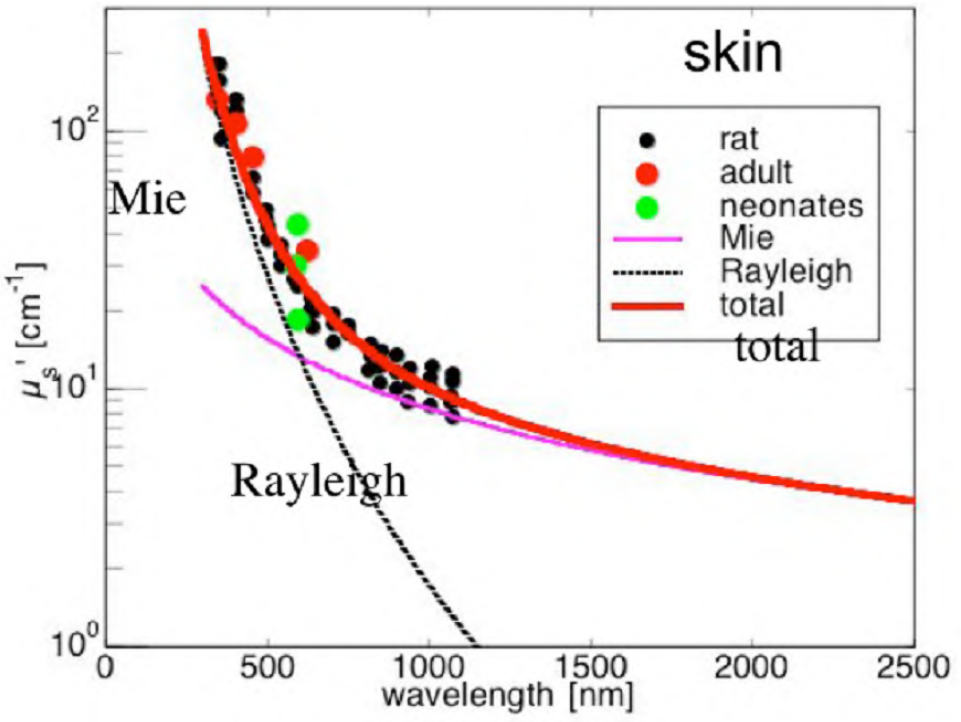
$$\int_0^{\pi} p(\theta) \cos\theta \, 2\pi \sin\theta d\theta = g$$



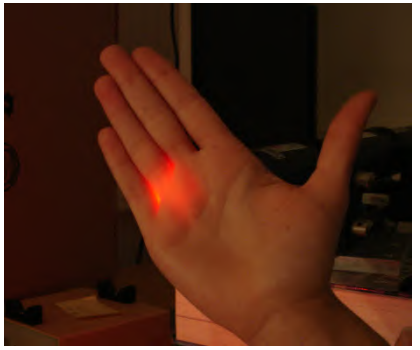
43 cm^{-1} 0.62 1 - 0.62 0.7 < ~1 < 1.3

$$\mu_s' = \mu_{s.500nm}' \left(f \left(\frac{\lambda}{500nm} \right)^{-4} + (1-f) \left(\frac{\lambda}{500nm} \right)^{-1} \right)$$

Rayleigh Mie



Typical optical properties (400 nm-1350 nm)



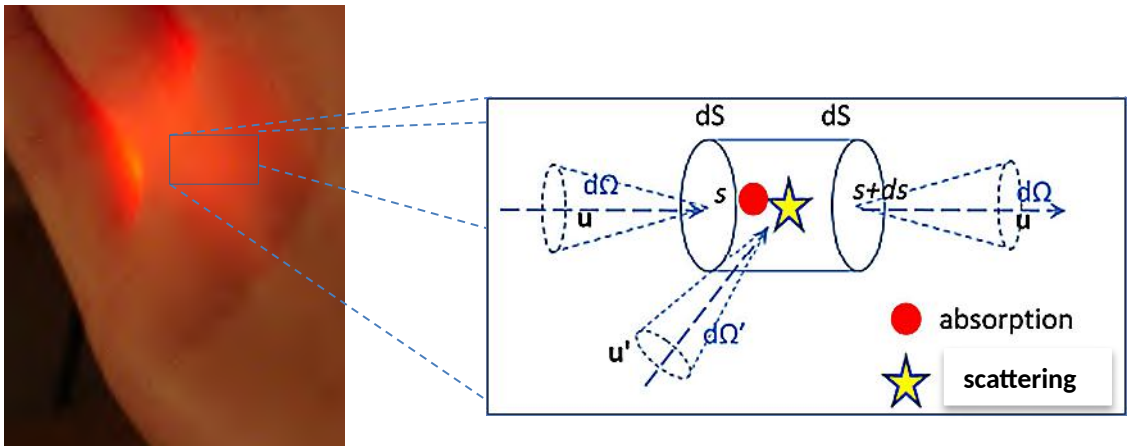
- Absorption coefficient μ_a=0.1 cm^{-1}
- Scattering coefficient μ_s=100 cm^{-1}

➔ T (L=1cm) ~ 0!

- Index of refraction n=1.38
- Anisotropy factor g=0.9

➔ Highly anisotropic scattering particles (=large)

Model: Radiative Transfer Equation



Volume: dV = ds dA

Balance of energy within volume element dV, in the direction of observation **u**:

$L_\nu(s + c\,dt, \boldsymbol{u}, t + dt) - L_\nu(s, \boldsymbol{u}, t)$ *Specific intencity* $[\mathcal{W}\,m^{-2}sr^{-1}]$

$= -(\mu_a + \mu_s) L_\nu(s, \boldsymbol{u}, t)\,cdt$ **losses**

$+\frac{\mu_s}{4\pi}\int_{4\pi} ph_\nu(s, \boldsymbol{u}', \boldsymbol{u})\, L_\nu(s, \boldsymbol{u}', t) cdt d\Omega' ds$ **gains**

$+Q(\boldsymbol{r}, \boldsymbol{u}, t)$

➔ Parameters characterising the medium:
$\mu_a(s), \mu_s(s)$ **and** $ph_\nu(s, \boldsymbol{u}', \boldsymbol{u})$

[1] S. Chandrasekhar, Radiative Transfer (Dover, New York, 1960).
[2] K.M. Case and P.F. Zweifel, Linear Transport Theory (Addison-Wesley, Reading, Massachusetts, 1967).
[3] A. Ishimaru, Wave Propagation and Scattering in Random Media (Academic Press, New York, 1978).

Model : RTE

Evaluation of the integral

$$\frac{1}{c}\frac{\partial L_\nu(s,\boldsymbol{u},t)}{\partial t} + \boldsymbol{u}.\boldsymbol{\nabla} L_\nu(s,\boldsymbol{u},t) = -(\mu_a + \mu_s) L_\nu(s,\boldsymbol{u},t) + \frac{\mu_s}{4\pi}\int_{4\pi} ph_\nu(s,\boldsymbol{u}',\boldsymbol{u})\, L_\nu(s,\boldsymbol{u}',t) d\Omega' ds + Q(\boldsymbol{r},\boldsymbol{u},t)$$

Developments:
PN Approximations
P1: Diffusing wave theory
P3:…
Diffusion Approximation

Stochastics
Monte Carlo simulations
Random walk

Discretizations (space, angular)
Discrete Ordinates Method(DOM=SN)
Kubelka-Munk (2Flux)
Adding-doubling
FDM,FEM

+ Hybrid Methods