Turbid tissue optics II: Time-resolved methods & Instrumentation and measurements

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Abbe lecture #3

14.01.2014

Roadmap for introductory lecture

μ_a ⟷ absorption

μ_s, μ_s' ⟷ scattering

L ⟷ radiance

ϕ ⟷ fluence (energy density)

radiative transport equation

diffusion equation

boundary conditions

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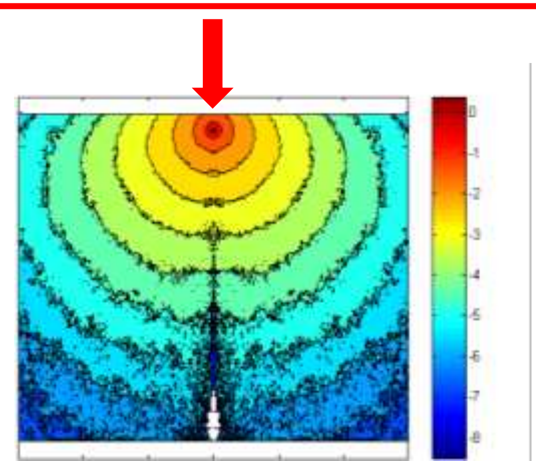
reflectance measurements in space and time

steady-state

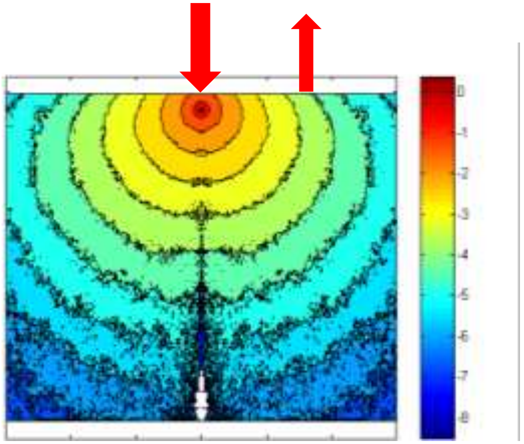
pulsed

sinusoidally-modulated



Roadmap for today

- review of basic concepts from last time

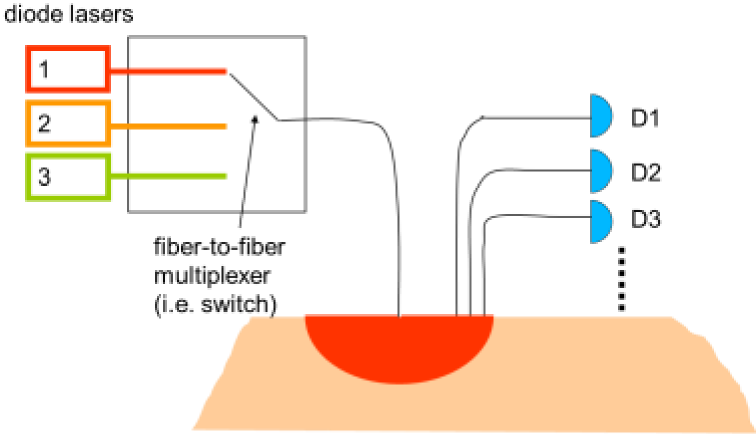


the Virtual Tissue Simulator

reflectance measurements: three types

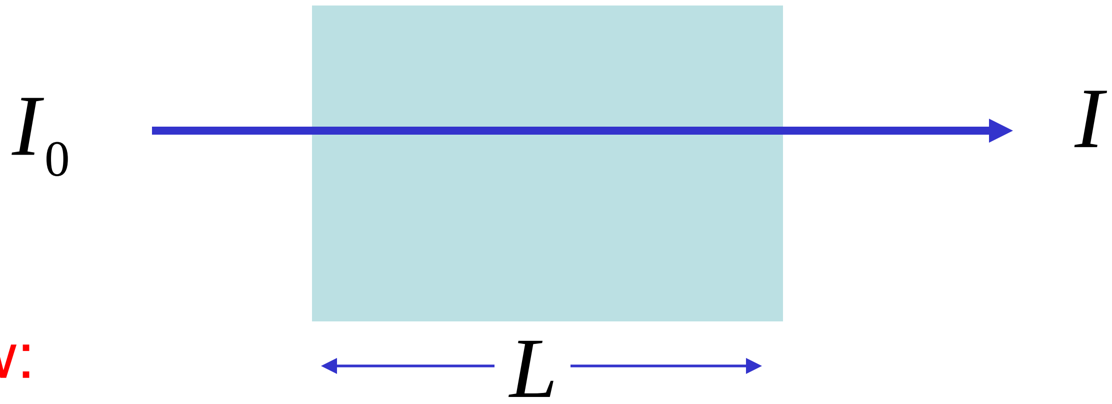
- steady-state
- pulsed
- sinusoidally-modulated *("frequency domain")*

instrument design considerations



various applications

Reminder: absorption coefficient



Beer's Law:

$$\frac{I}{I_0} = 10^{-\varepsilon cL} = e^{-\mu_a L}$$

molar extinction

$$\left(\frac{1}{\text{length} \cdot \text{molarity}}\right)$$

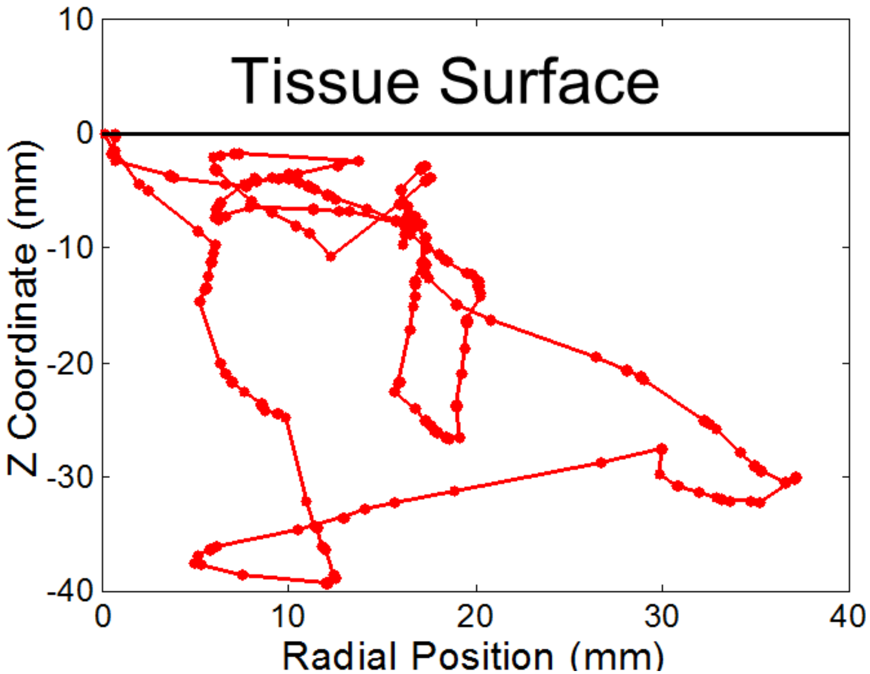
concentration
(molarity)

$$\mu_a \equiv \ln 10 \cdot \varepsilon c$$

"absorption coefficient" [1/length]

$\frac{1}{\mu_a}$ = absorption mean free path

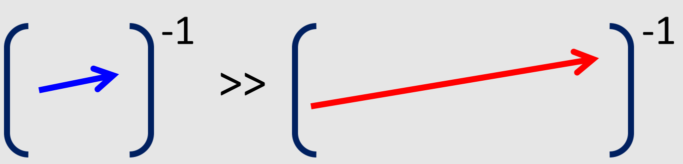
Reminder: absorption vs. scattering in the near-infrared



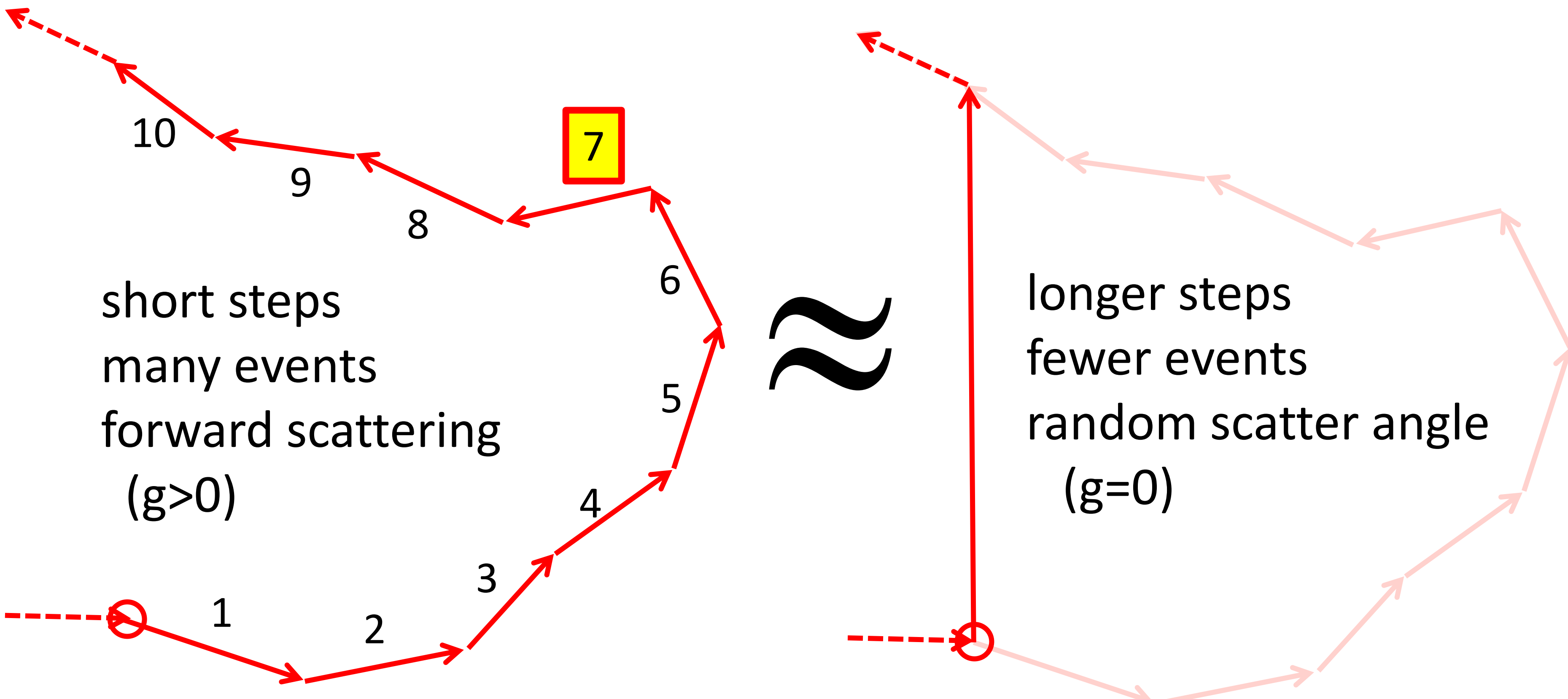
Many more scattering events than absorption events

scattering length << absorption length

μ_s >> μ_a

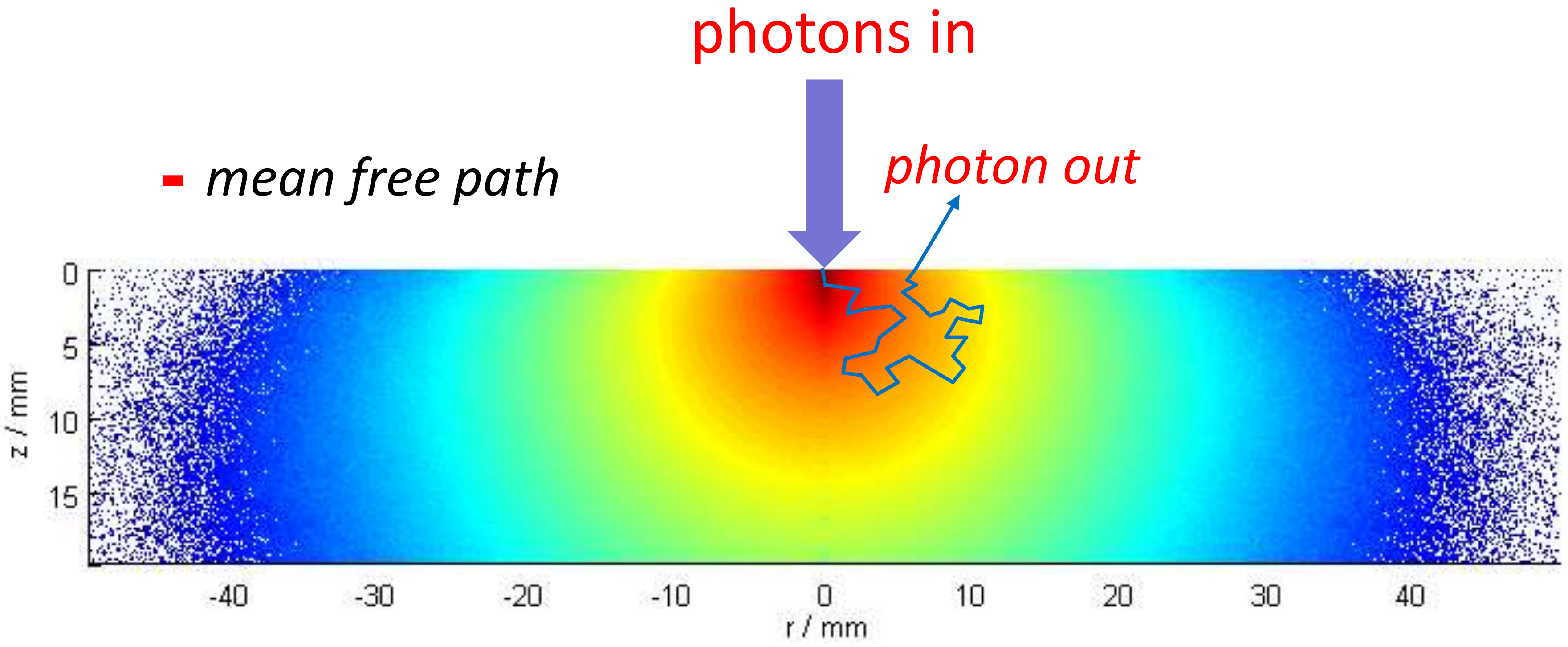


"Reduced scattering" substitution



Reduced-scattering coefficient: $\boxed{\mu_s'} \equiv \mu_s(1-g)$

Reminder: fluence and reflectance



Reminder: steady-state diffusion equation

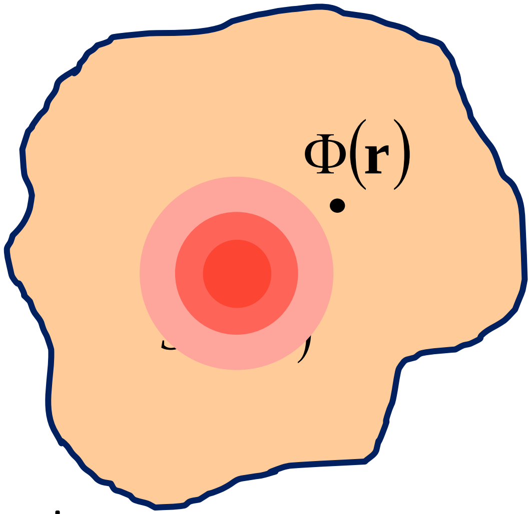
Dropping time-dependent terms and assuming an isotropic source yields:

$$-D\nabla^2\Phi(\mathbf{r},t)+\mu_a\Phi(\mathbf{r},t)=S_0(\mathbf{r},t)$$

where $D=1/[3(\mu_a+\mu_s')]$

The Green's function for this equation is

$$\Phi_G=\frac{1}{4\pi D}\frac{e^{-\mu_{eff}r}}{r}$$



where μ_{eff} is the 'effective attenuation coefficient':

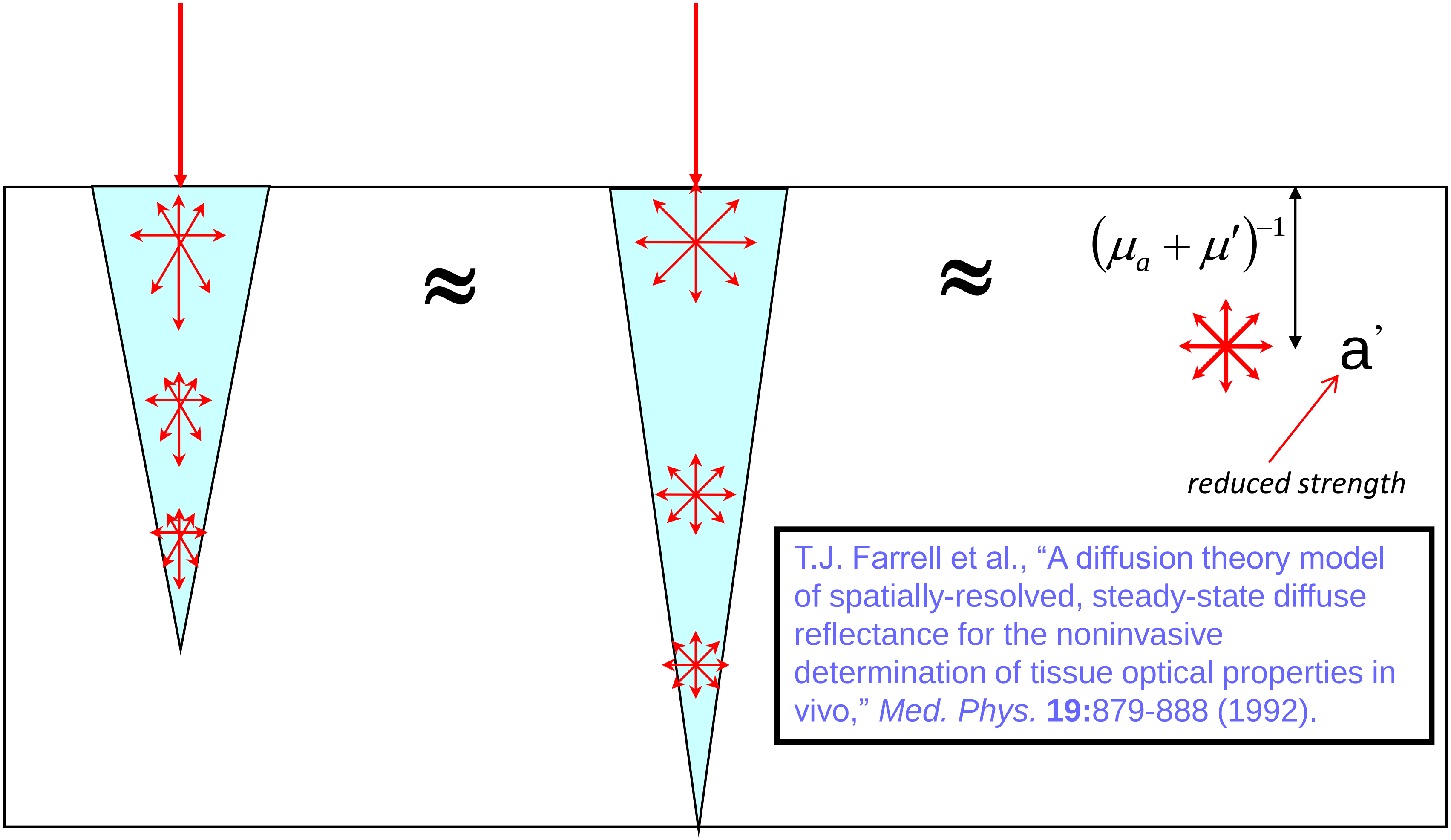
$$\mu_{eff}=\left[3\mu_a(\mu_a+\mu_s')\right]^{1/2}$$

Reminder: how to model the sources of scattered light

$$I(z) = I_0 e^{-(\mu_a + \mu_s) z}$$

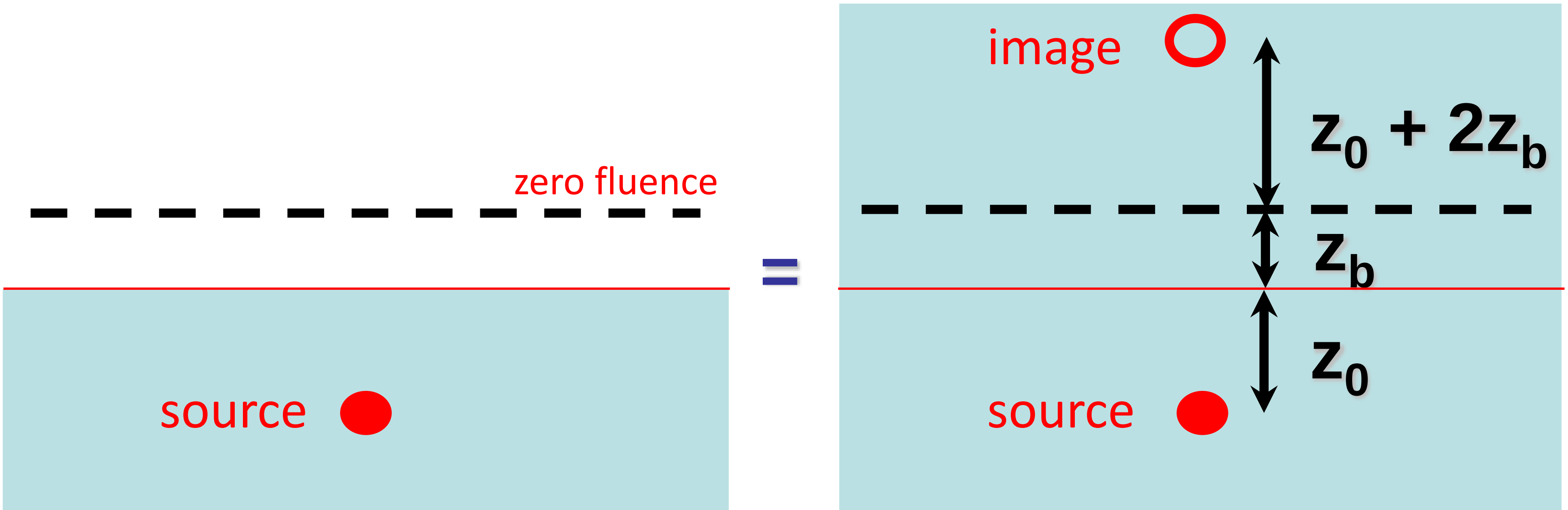
$$I(z) = I_0 e^{-(\mu_a + \mu_s') z}$$

buried point source



T.J. Farrell et al., "A diffusion theory model of spatially-resolved, steady-state diffuse reflectance for the noninvasive determination of tissue optical properties in vivo," *Med. Phys.* **19:**879-888 (1992).

Reminder: "extrapolated boundary" solution



$$\Phi_{in} = \Phi_{source} + \Phi_{image}$$

$$= \frac{1}{4\pi D}\left(\frac{\exp(-\mu_{eff} r_{source})}{r_{source}} - \frac{\exp(-\mu_{eff} r_{image})}{r_{image}}\right)$$

infinite-boundary Green's function

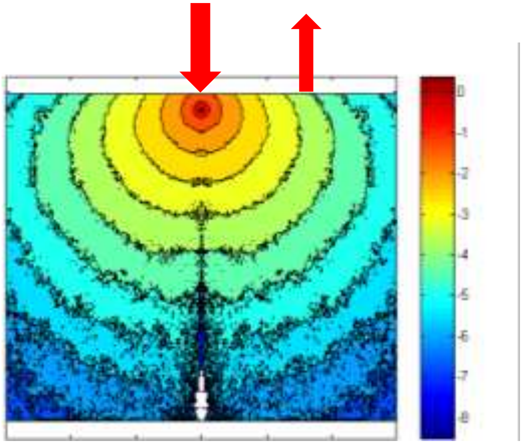
Roadmap for today

review of basic concepts from last time

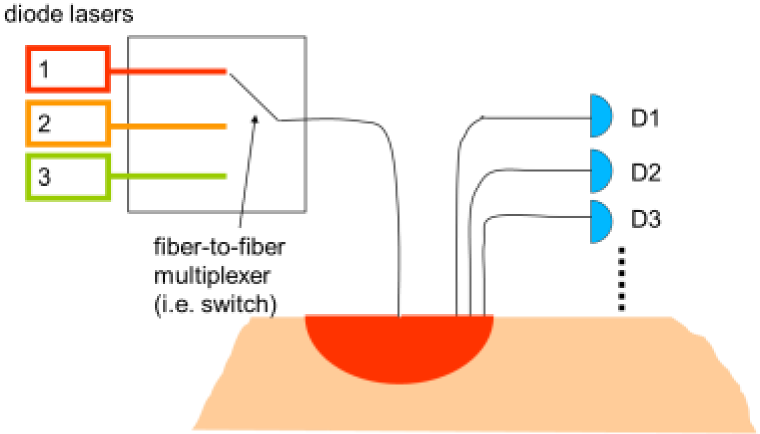
the Virtual Tissue Simulator

reflectance measurements: three types

- steady-state
- pulsed
- sinusoidally-modulated *("frequency domain")*



instrument design considerations



various applications

Virtual tissue simulator

- http://www.virtualphotonics.org/vts/

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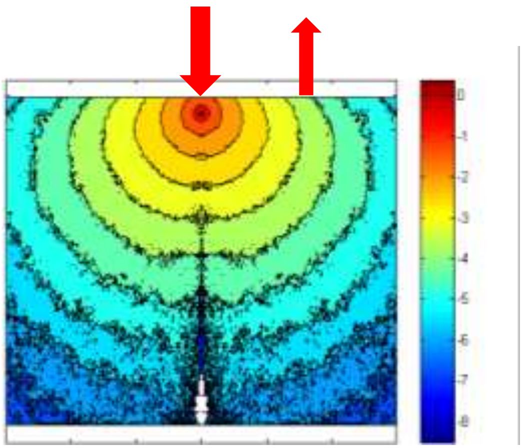

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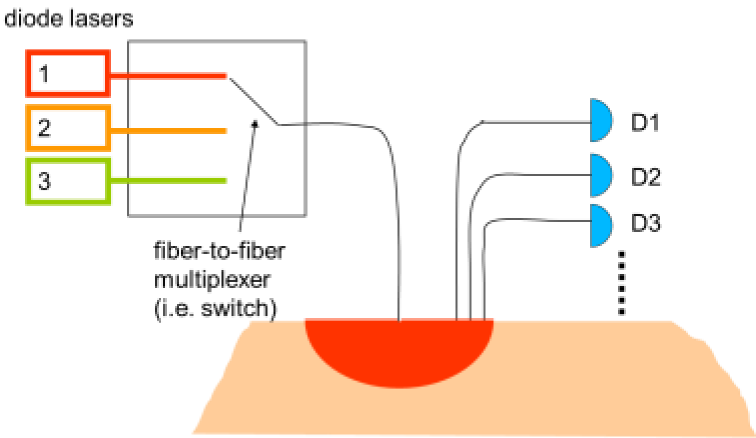


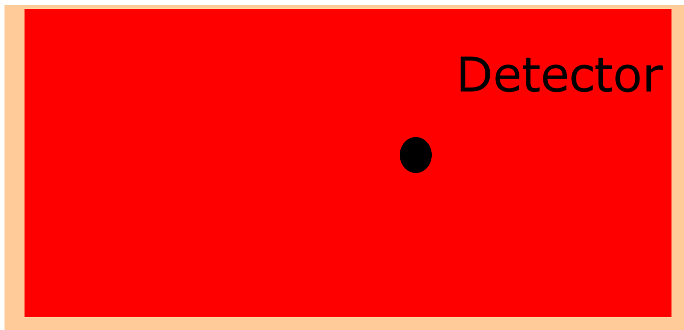
instrument design considerations

various applications

Time-resolved photon detection: extreme examples

in the limit of:

no scattering

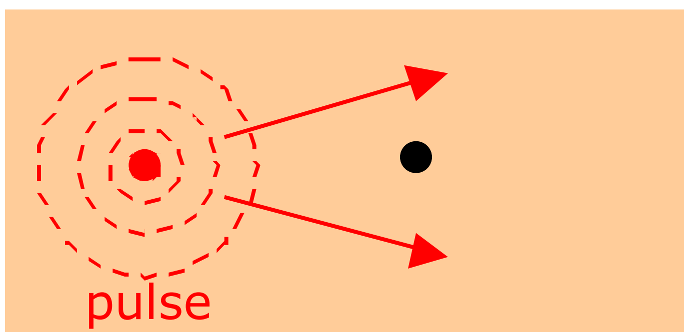


signal at detector decays according to

$$e^{-\mu_a ct}$$

absorption

no absorption



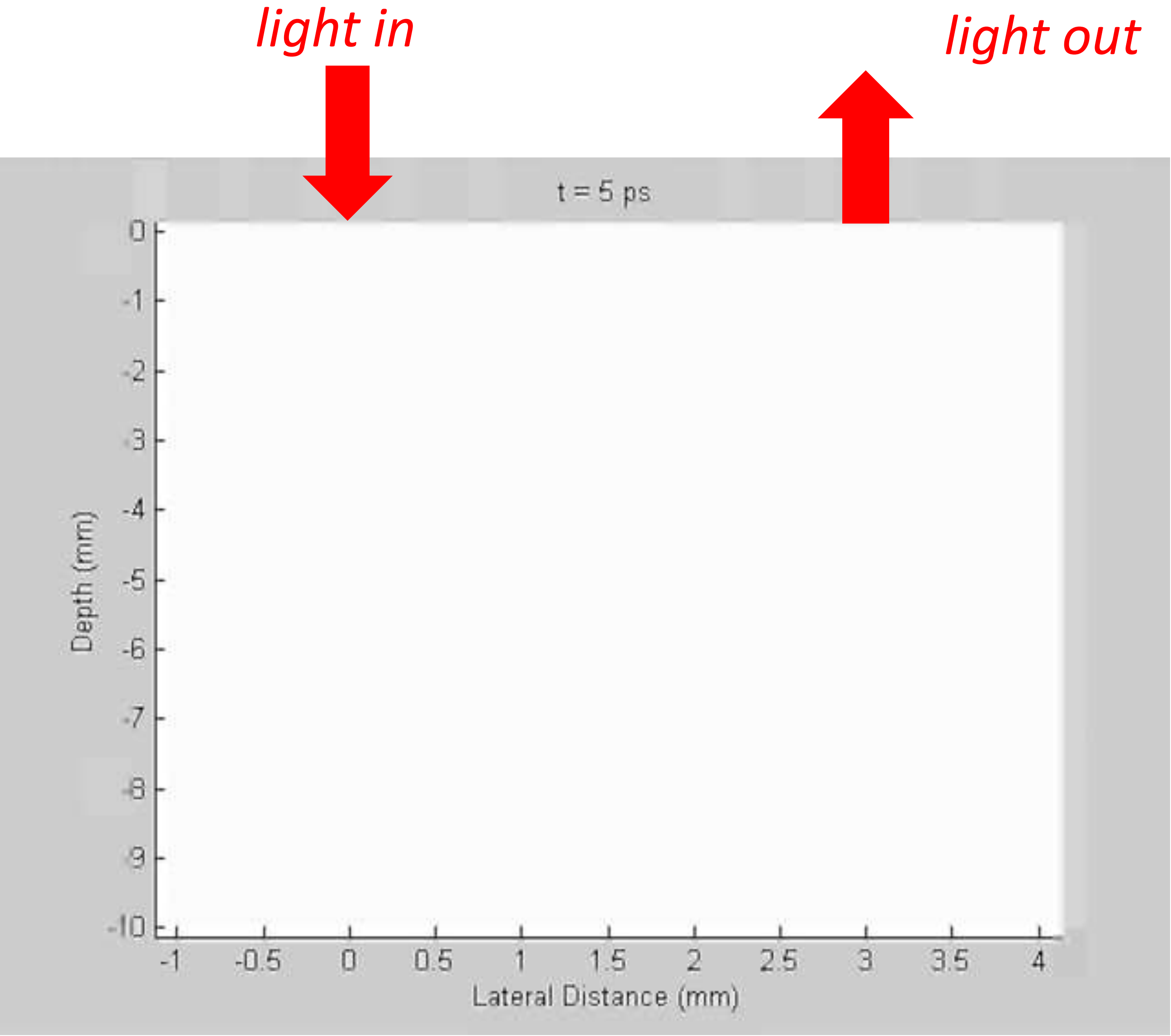
RMS distance from origin ("random walk") increases according to

$$\sqrt{\frac{1}{3(\mu_s' + \mu_a)}ct} = \sqrt{Dct}$$

scattering

diffusion coefficient [m^2/sec]

Reminder: time-resolved photon detection paths



Reminder: the ugly mathematics

Time-resolved radiative transport equation:

$$-D\nabla^2\Phi(\mathbf{r},t)+\mu_a\Phi(\mathbf{r},t)+\frac{1}{c}\frac{\partial\Phi(\mathbf{r},t)}{\partial t}+\frac{3D}{c}\left[\mu_a\frac{\partial\Phi}{\partial t}+\frac{1}{c}\frac{\partial^2\Phi}{\partial t^2}\right]=$$

$$S_0(\mathbf{r},t)-3D\nabla\cdot\mathbf{S_1}(\mathbf{r},t)+\frac{3D}{c}\frac{\partial S_0(\mathbf{r},t)}{\partial t},$$

where D is the optical diffusion coefficient:

$$D=\frac{1}{3(\mu_a+\mu_s(1-g))}$$

Time-domain

Approximations to the radiative transport equation:

1. reduced-scattering similarity: $\mu_s' = \mu_s(1-g)$
2. scattering dominates over absorption: $\mu_a << \mu_{tr}$
3. photons scatter many times before next pulse is launched $\omega_{\text{modulation}} << c\mu_{tr}$
4. isotropic sources of diffuse light

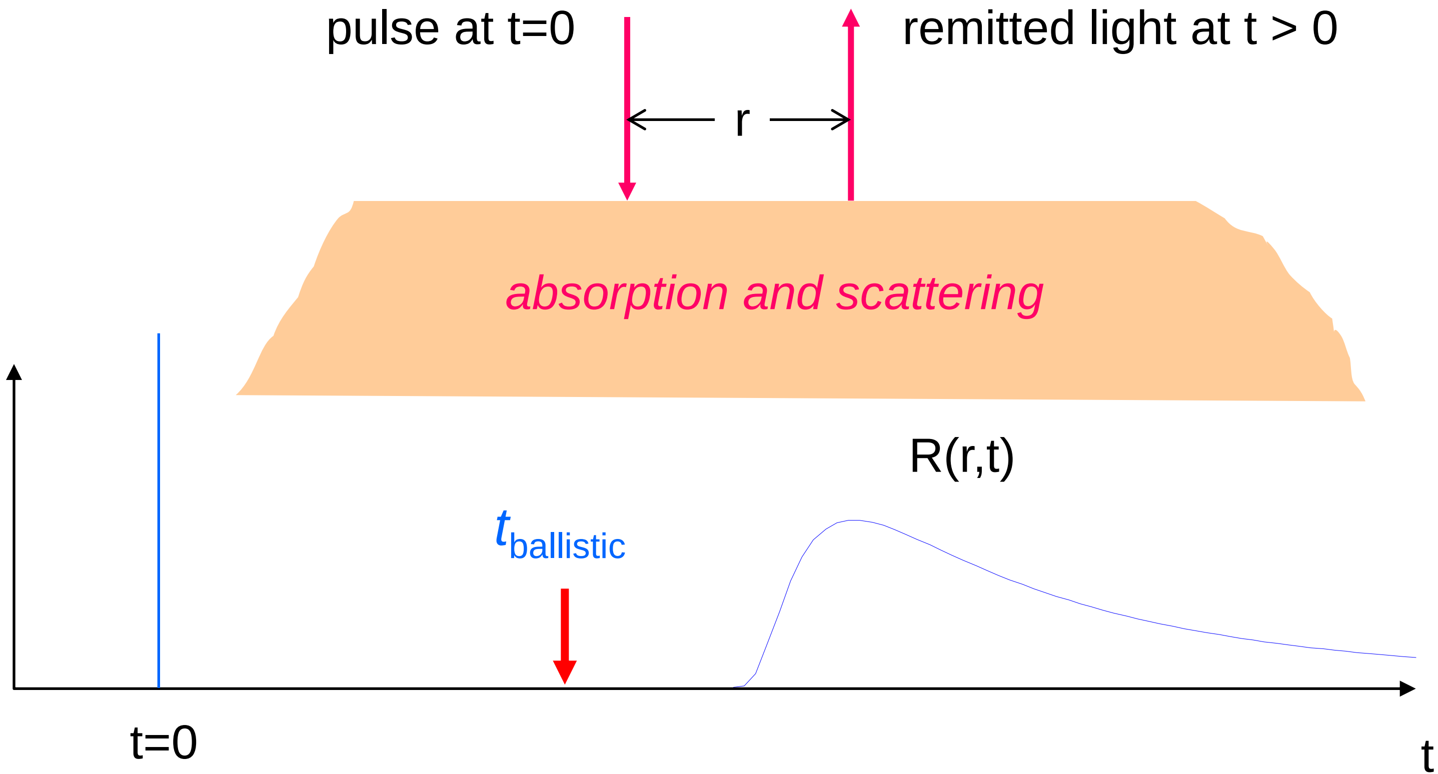
Leads to the following *time-resolved diffusion equation:*

$$\left(D\nabla^2 - \mu_a\right)\Phi - \frac{1}{c}\cdot\frac{\partial\Phi}{\partial t} = -S$$

Infinite geometry Green's function (point source at origin and at *t*=0):

$$\Phi(\mathbf{r}, t) = c(4\pi Dct)^{-3/2}\exp\left(-\frac{r^2}{4Dct} - \mu_a ct\right)$$

Time-resolved measurements



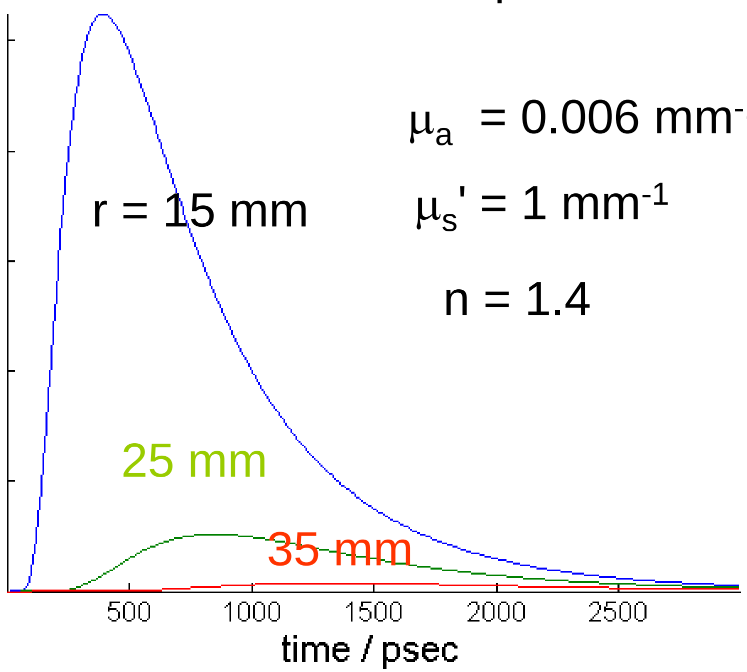
Infinite geometry: $$\Phi(\mathbf{r},t) = c(4\pi Dct)^{-3/2} \exp\left(-\frac{r^2}{4Dct} - \mu_a ct\right)$$

Time-resolved measurements

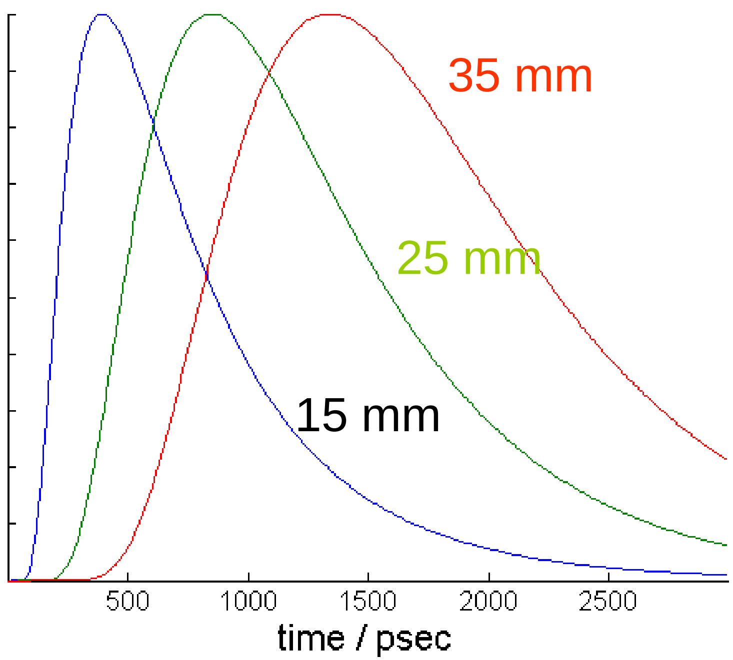
Infinite geometry: $$\Phi(\mathbf{r},t) = c(4\pi Dct)^{-3/2} \exp\left(-\frac{r^2}{4Dct} - \mu_a ct\right)$$

(similar curves for semi-infinite reflectance)

different source-detector separations



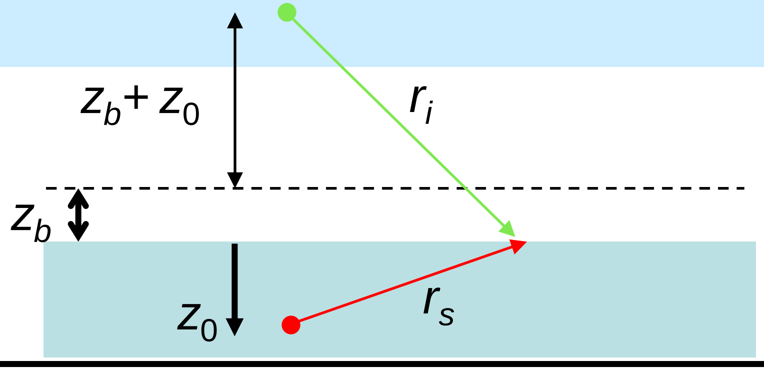
normalized



time resolution needed: psec scale; integration time needed: 100's-1000’s of psec

Measured reflectance: time-domain

For semi-infinite boundary, use extrapolated boundary condition (as in steady state analysis)



Full expressions for fluence and flux:

$$\Phi(r,z,t) = \frac{c}{(4\pi Dct)^{3/2}} \exp(-\mu_a ct) \times \left\{ \exp\left[-\frac{(z-z_o)^2 + r^2}{4Dct}\right] - \exp\left[-\frac{(z+z_o+2z_b)^2 + r^2}{4Dct}\right] \right\}$$

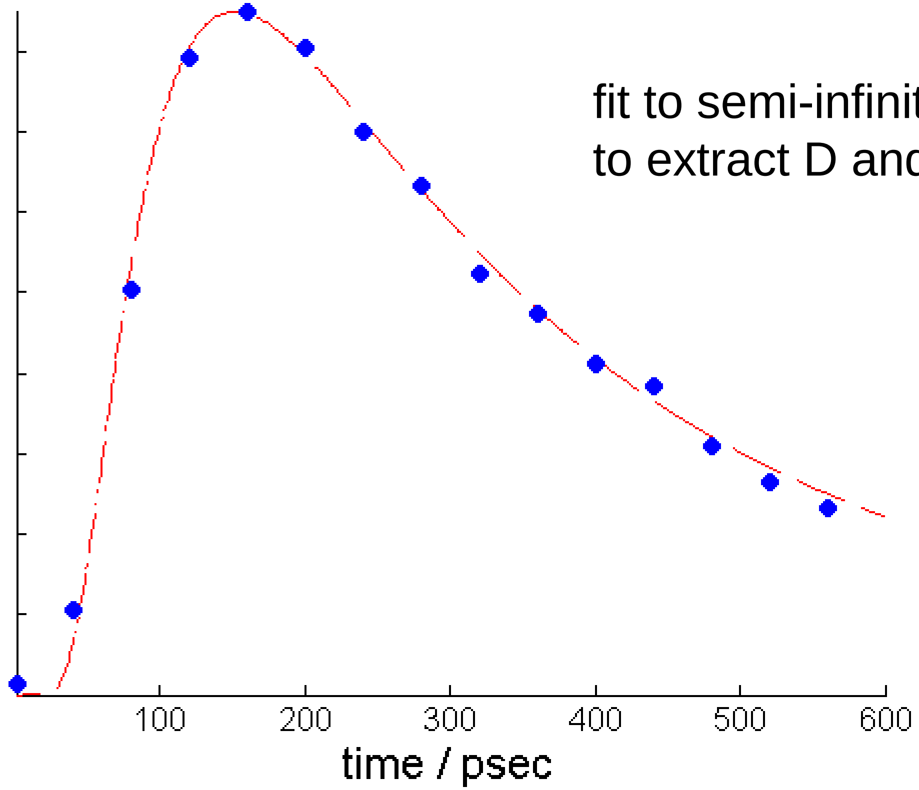
$$R_f = \frac{1}{2}(4\pi Dc)^{-3/2} t^{-5/2} \exp(-\mu_a ct) \left[z_o \exp\left(-\frac{{r_s}^2}{4Dct}\right) + (z_o + 2z_b) \exp\left(-\frac{{r_i}^2}{4Dct}\right) \right]$$

Formula for measured reflectance (particular case of index mismatch 1.0/1.4):

$$R = 0.118\Phi + 0.306 R_f$$

A. Kienle and M. S. Patterson, "Improved solutions of the steady-state and the time-resolved diffusion equations for reflectance from a semi-infinite turbid medium," JOSA A 14(1), 246-254 (1997).
R. C. Haskell et al., "Boundary conditions for the diffusion equation in radiative transfer," JOSA A 11(10), 2727-2741 (1994).

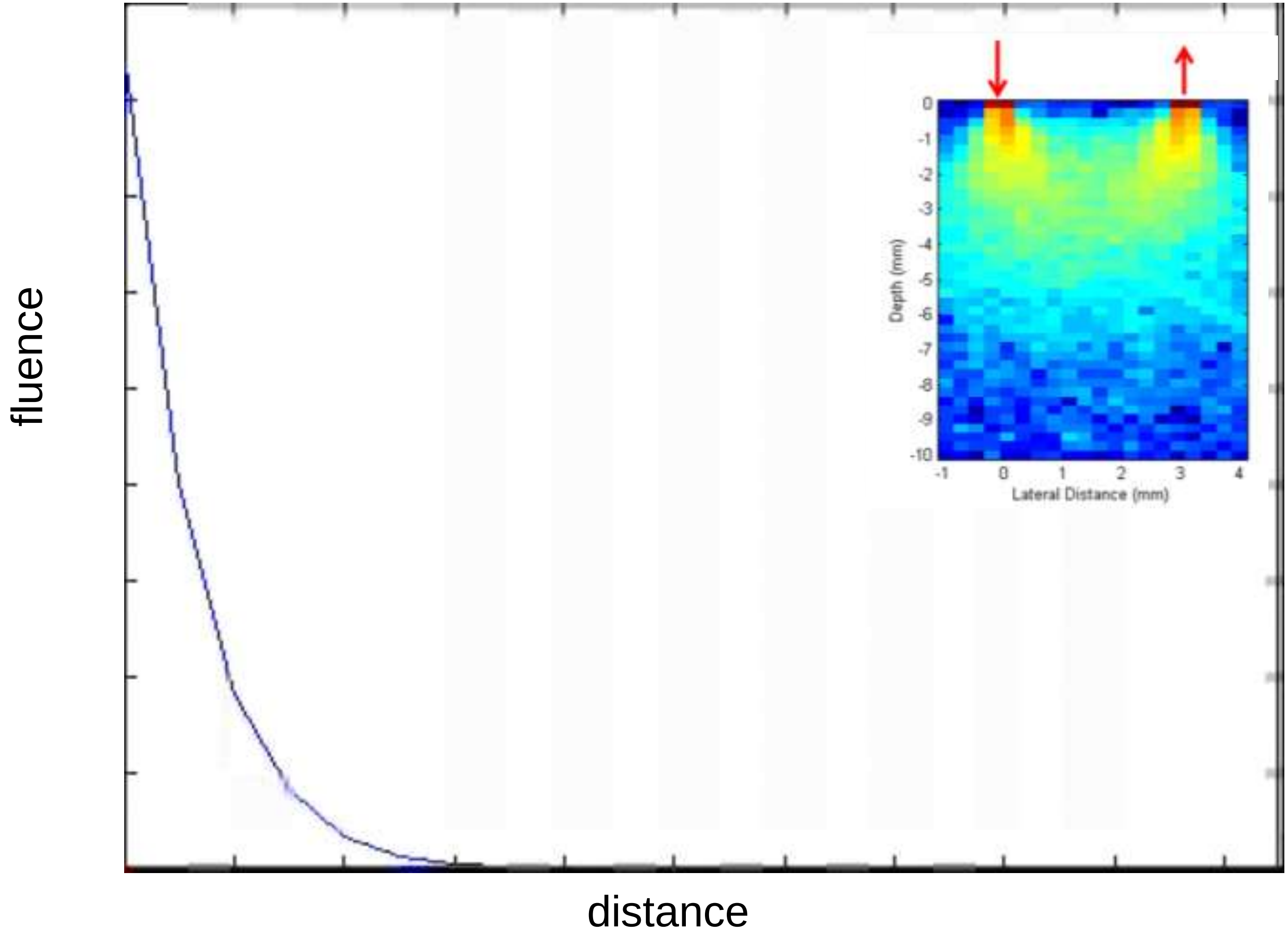
Time-resolved data



fit to semi-infinite theory (or match to Monte Carlo) to extract D and μ_a (2-parameter fit)

Larger distance: “smoother” time response

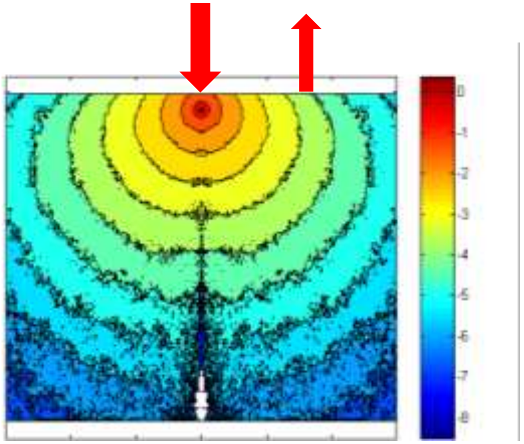
$$\Phi(\mathbf{r},t) = c(4\pi Dct)^{-3/2} \exp\left(-\frac{r^2}{4Dct} - \mu_a ct\right)$$



Roadmap for today

review of basic concepts from last time

the Virtual Tissue Simulator



reflectance measurements: three types

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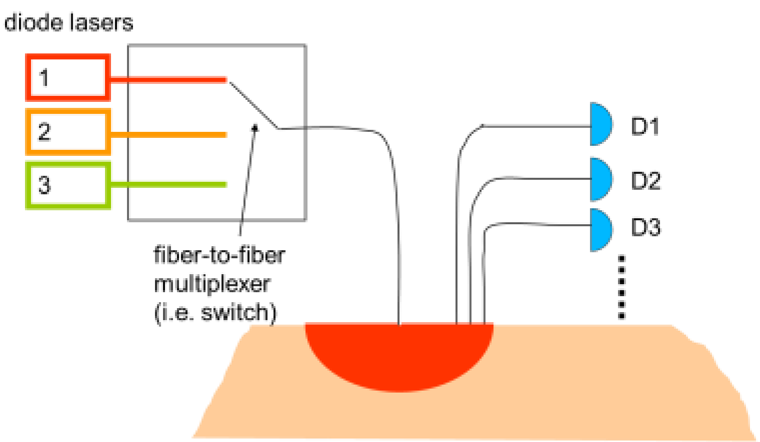
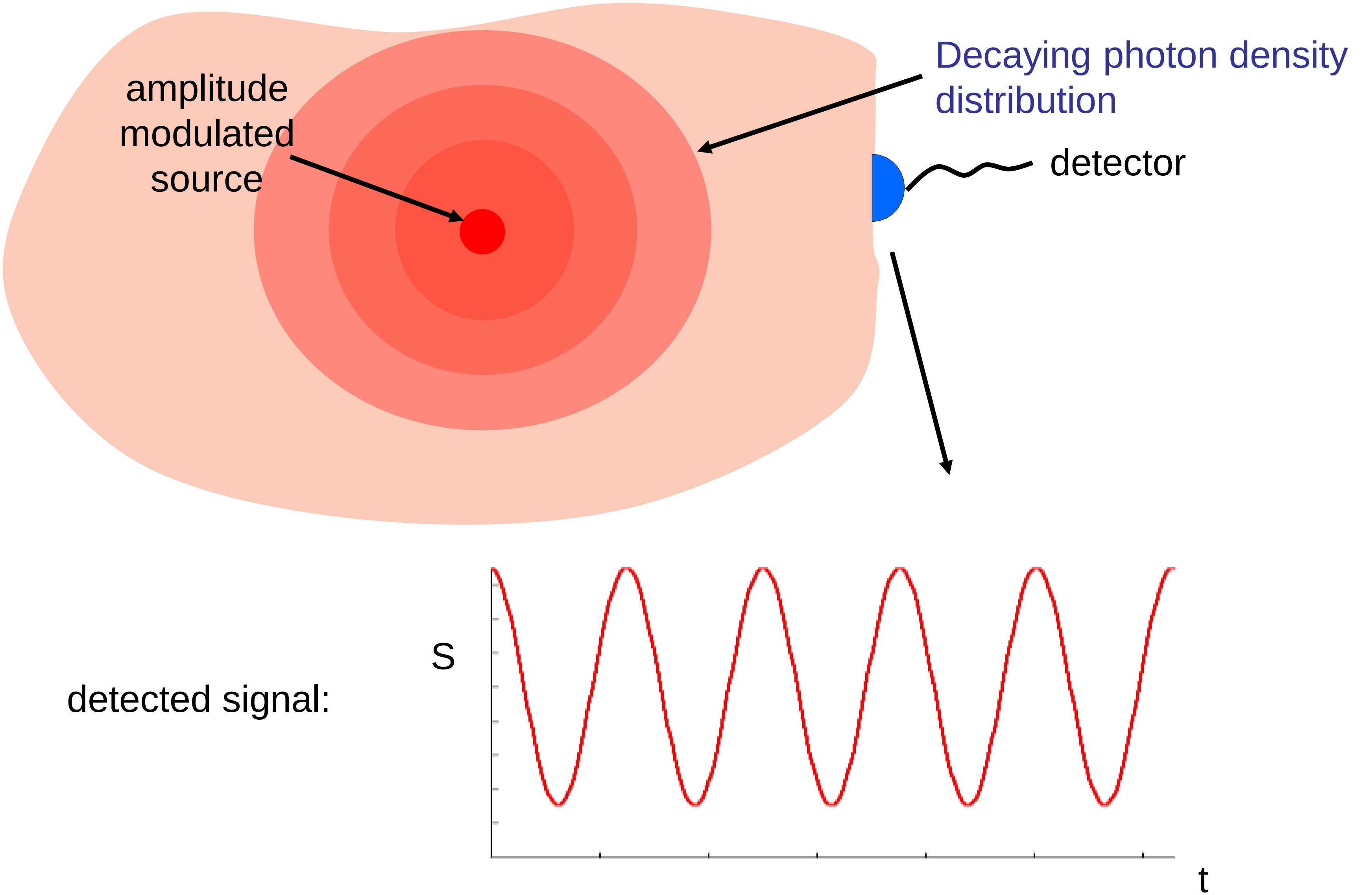


instrument design considerations

various applications

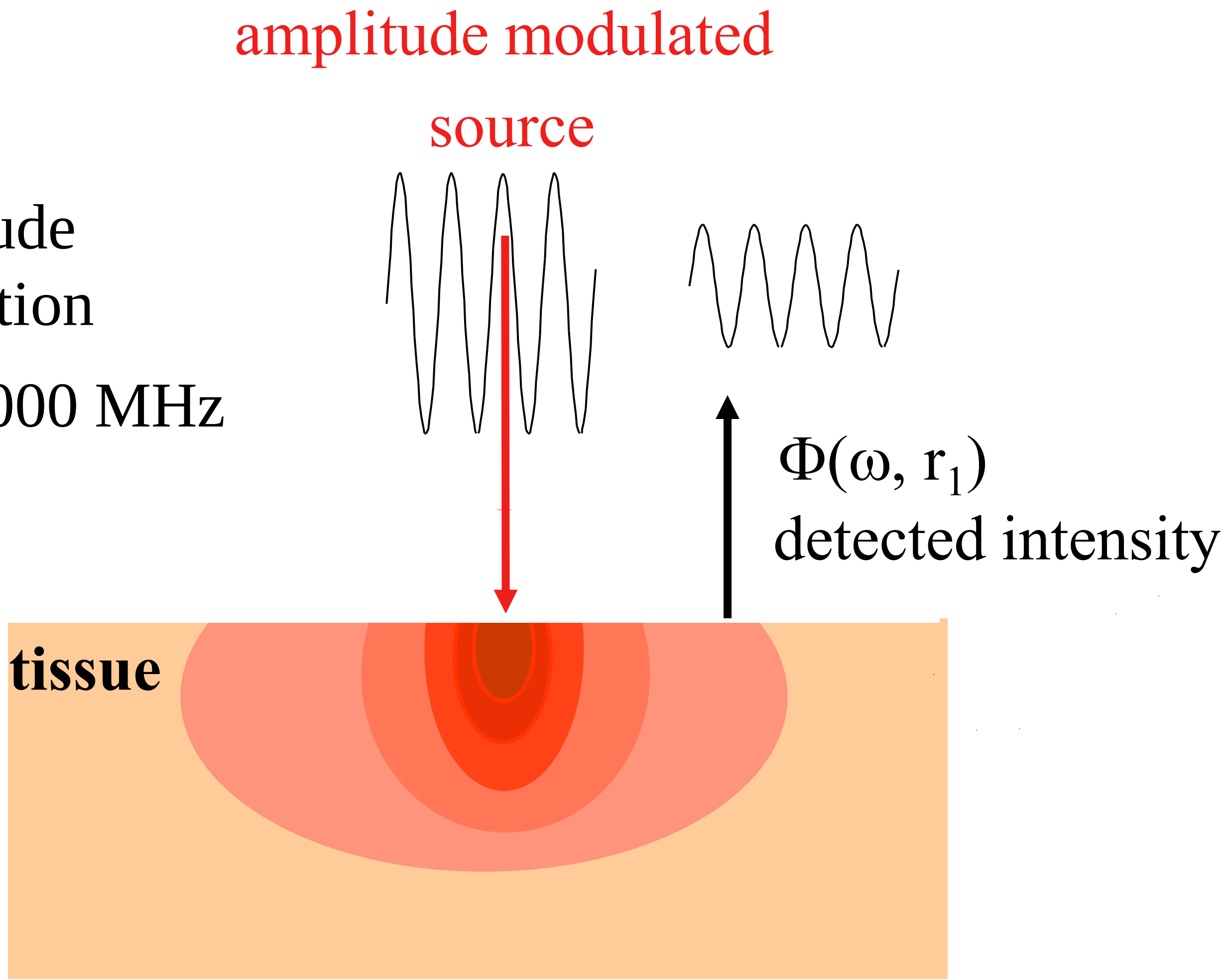
Frequency domain diffusion



Frequency domain diffusion

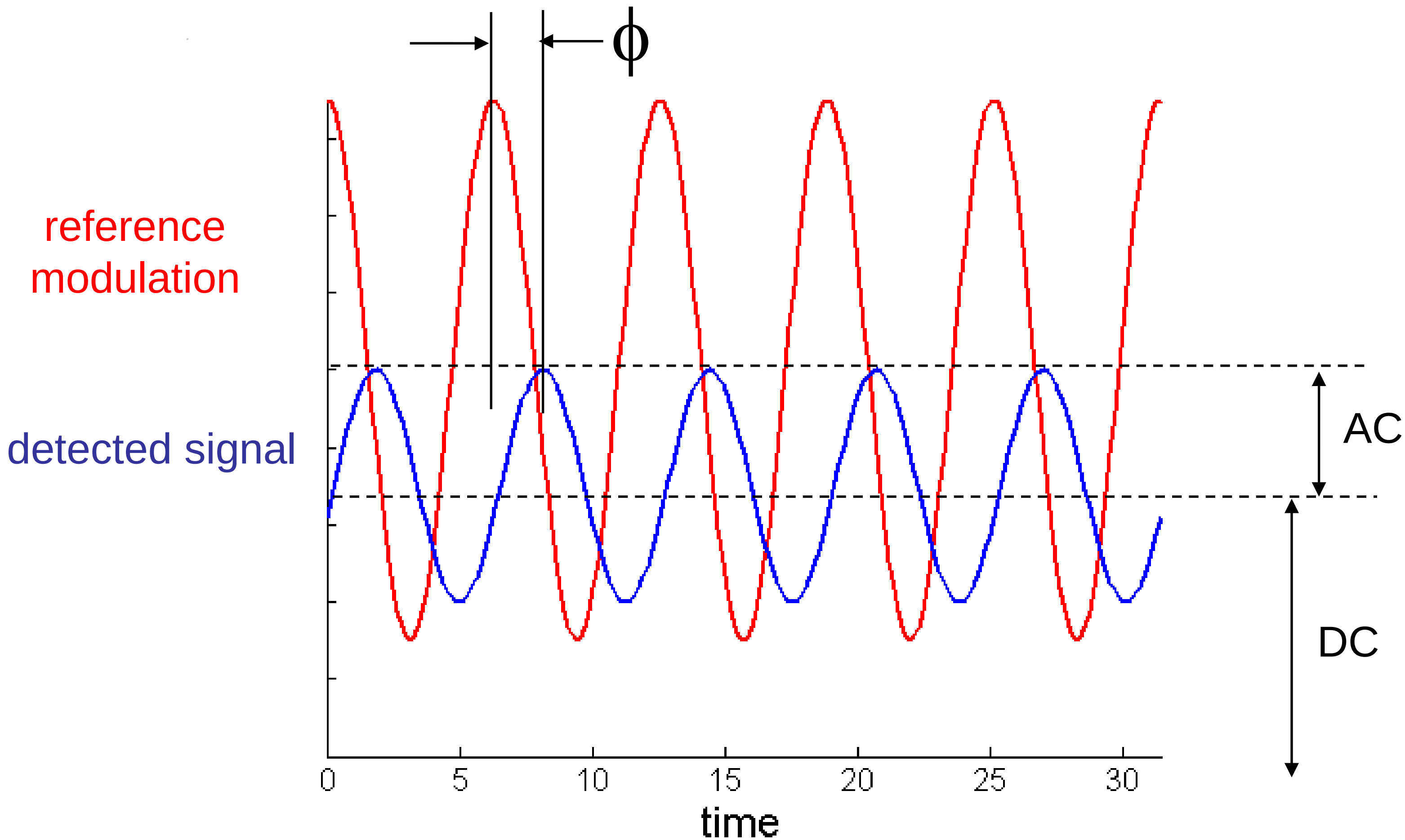
Amplitude modulation

50 MHz - 1000 MHz



Frequency-resolved

The observables:



Frequency-domain diffusion

Time-dependent diffusion equation, as before:

$$\left(D\nabla^2 - \mu_a\right)\Phi - \frac{1}{c}\cdot\frac{\partial\Phi}{\partial t} = -S$$

Oscillating source term (photon density wave):

$$S = S_o[1 + A\exp\left(-i\omega t\right)]\delta(\vec{r})$$

"DC" term

"AC" term
(complex notation)

point source
at the origin

Frequency domain: theory

Assert that the solution takes the form

$$\Phi = \Phi_{DC} + \Phi_{AC} \exp\left(-i\omega t\right)$$

Diffusion equation becomes separable:

$$\left(D\nabla^2 - \mu_a\right)\Phi_{DC} = -S_o\delta(\vec{r})$$

$$\left[D\nabla^2 - (\mu_a - i\omega/c)\right]\Phi_{AC} = -AS_o\delta(\vec{r})$$

"effective" absorption coefficient: frequency-dependent and complex!

$1/\mu_a$ ↔ absorption m.f.p.

c/ω ↔ "wave blurring" m.f.p.

Frequency domain Green's functions

Green's functions, point source in an infinite medium:

$$\Phi_{DC} = \frac{S}{4\pi D r} \exp\left(-r\sqrt{\mu_a/D}\right)$$

$$\Phi_{AC} = \frac{AS}{4\pi D r} \exp\left[-r\sqrt{\left(\mu_a - \frac{i\omega}{c}\right)/D}\right]$$

As in time domain, use extrapolated boundary condition to determine measured reflectance emerging from the surface

Frequency domain Green's functions

Rewrite AC solution as:

decay factor

$$\Phi_{AC}\exp(-i\omega t) = \frac{AS}{4\pi D}\cdot\frac{\exp(-\kappa r)}{r}\cdot\exp\left[i(kr-\omega t)\right]$$

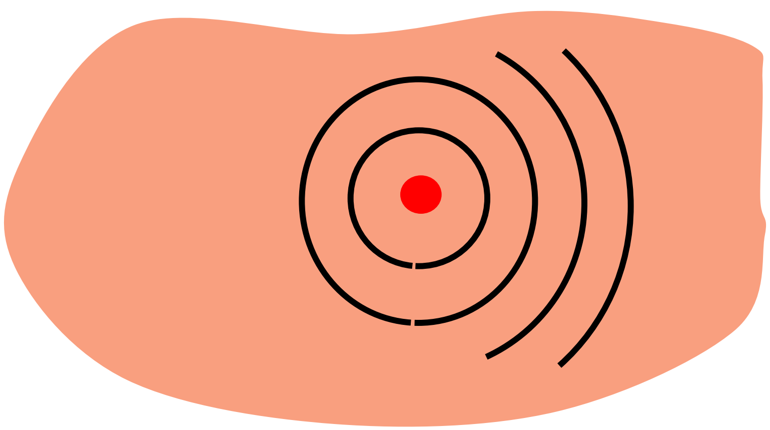
magnitude

phase relative to the point source modulation

where

$$(\kappa - ik)^2 = (\mu_a - i\omega/c)/D = \mu_{\text{eff}}^2(1 - i\omega/\mu_a c)$$

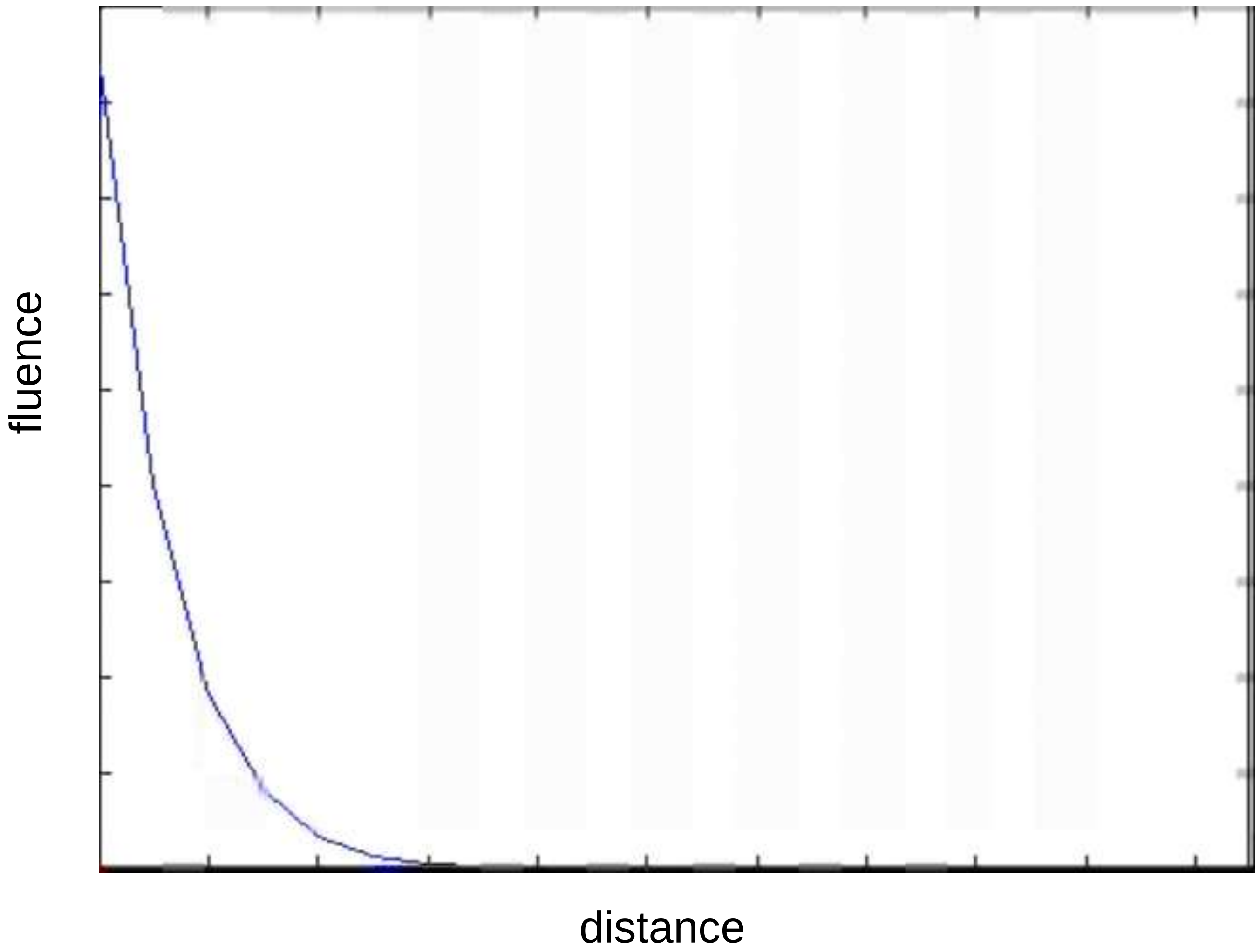
imaginary term is significant when photons "survive" for more than one oscillation period



- propagation speed of photon density wavefronts is ω/k
- "speed" means phase advance; there is *not* a local maximum of photon density

Photon density waves do not have local maxima in *space*!

$$\Phi(\mathbf{r},t) = c(4\pi Dct)^{-3/2}\exp\left(-\frac{r^2}{4Dct} - \mu_a ct\right)$$



Frequency domain

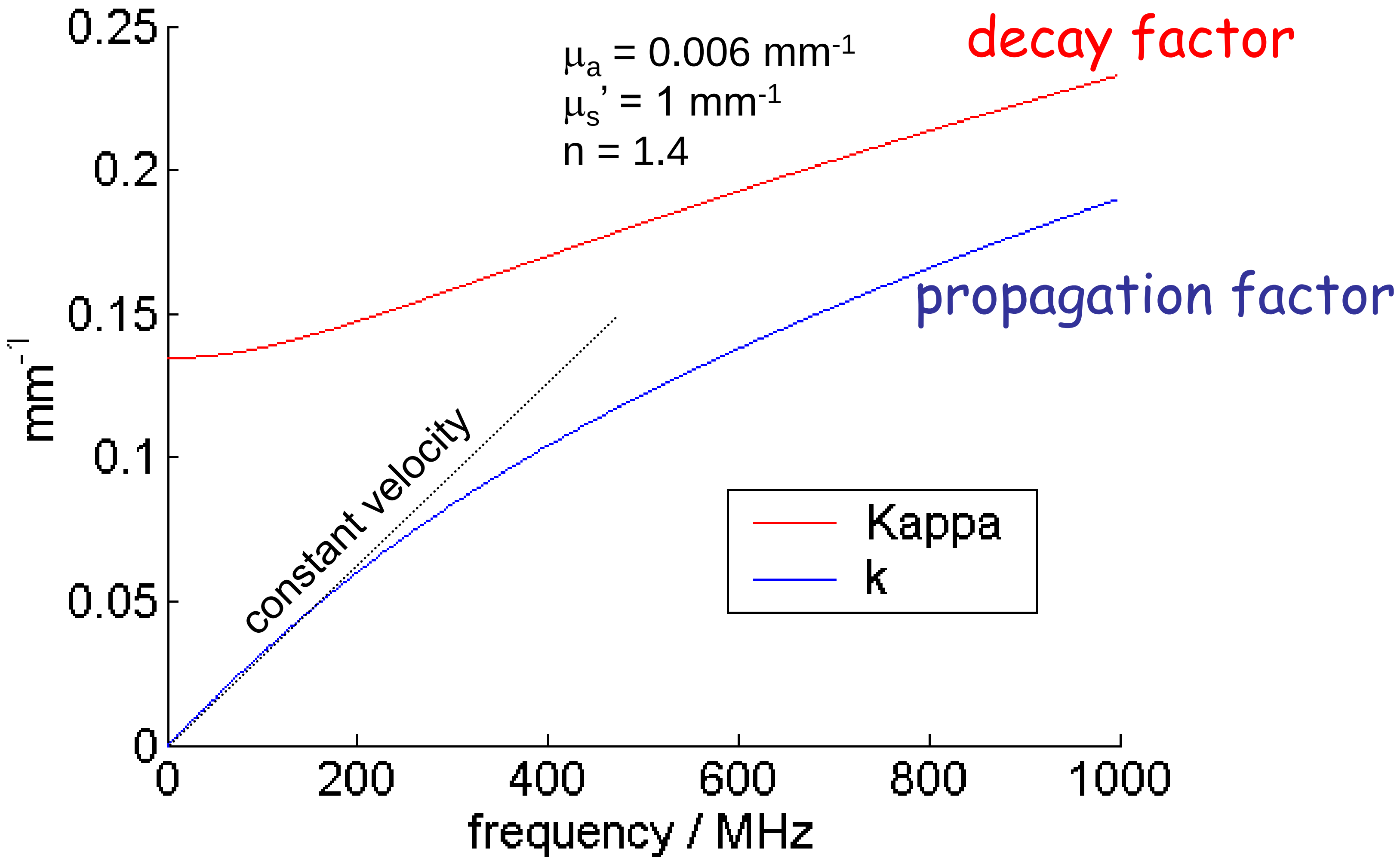
Solutions for real and imaginary exponential coefficients:

$$\kappa^2 = \mu_{\text{eff}}^2 \left[\frac{\sqrt{1+(\omega/\mu_a c)^2}+1}{2}\right]$$

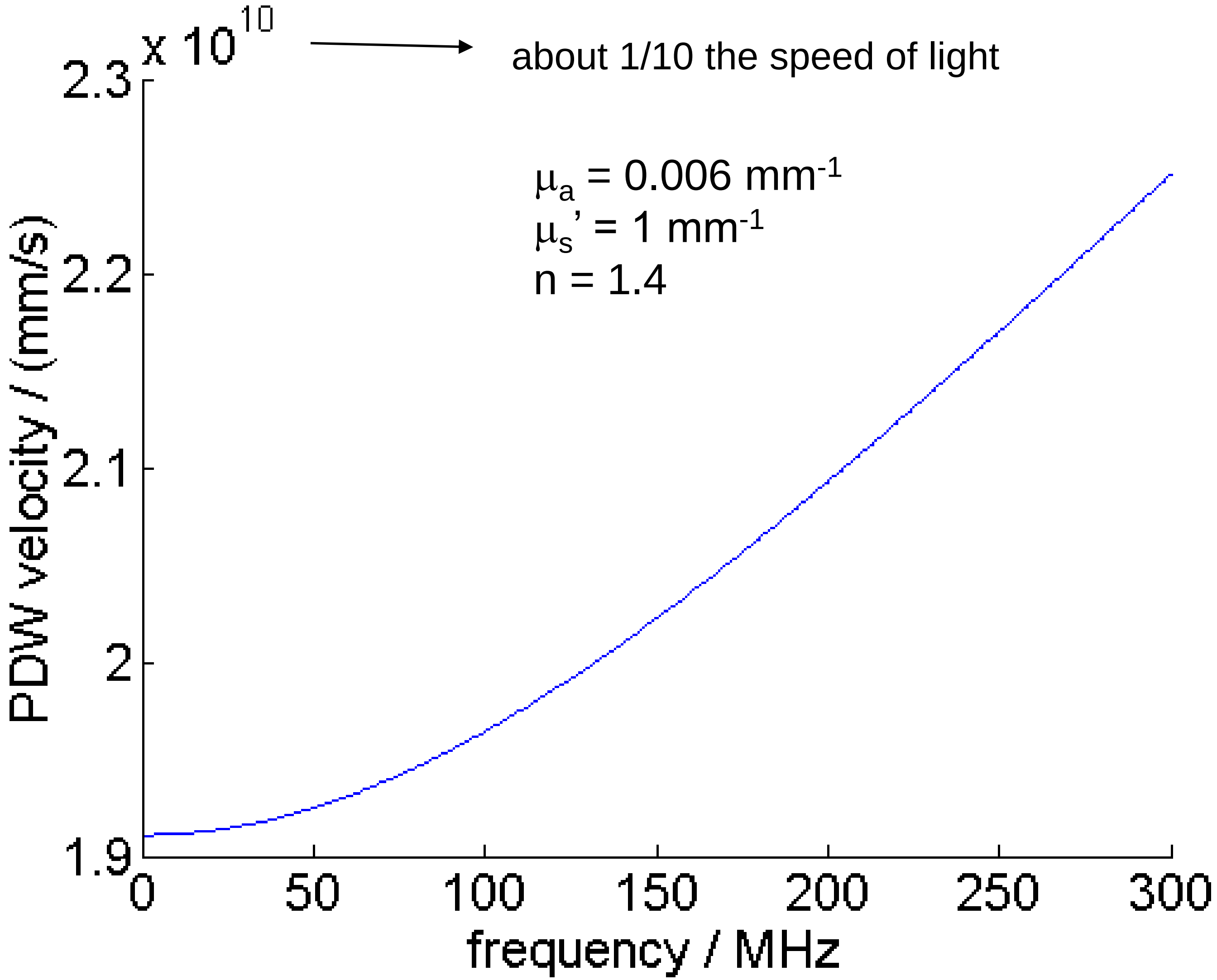
$$k^2 = \mu_{\text{eff}}^2 \left[\frac{\sqrt{1+(\omega/\mu_a c)^2}-1}{2}\right]$$

- K (kappa) larger at high frequencies: greater attenuation
- *k* scales as ω at low frequencies: $v=\omega/k$ is constant
- *k* scales as $\omega^{1/2}$ at high frequencies: $v=\omega/k$ gets larger

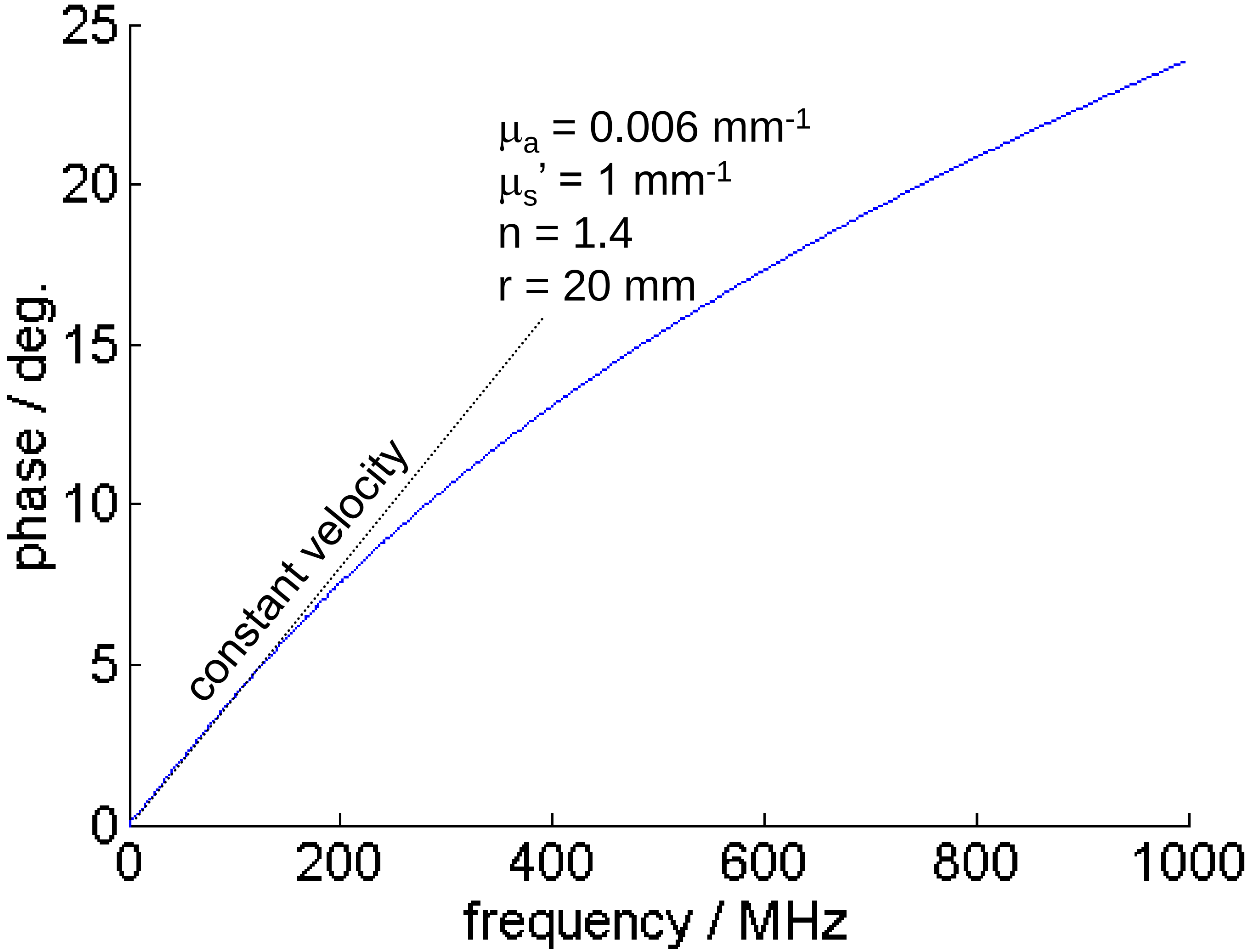
Frequency-dependent wave properties: i.e, dispersion!



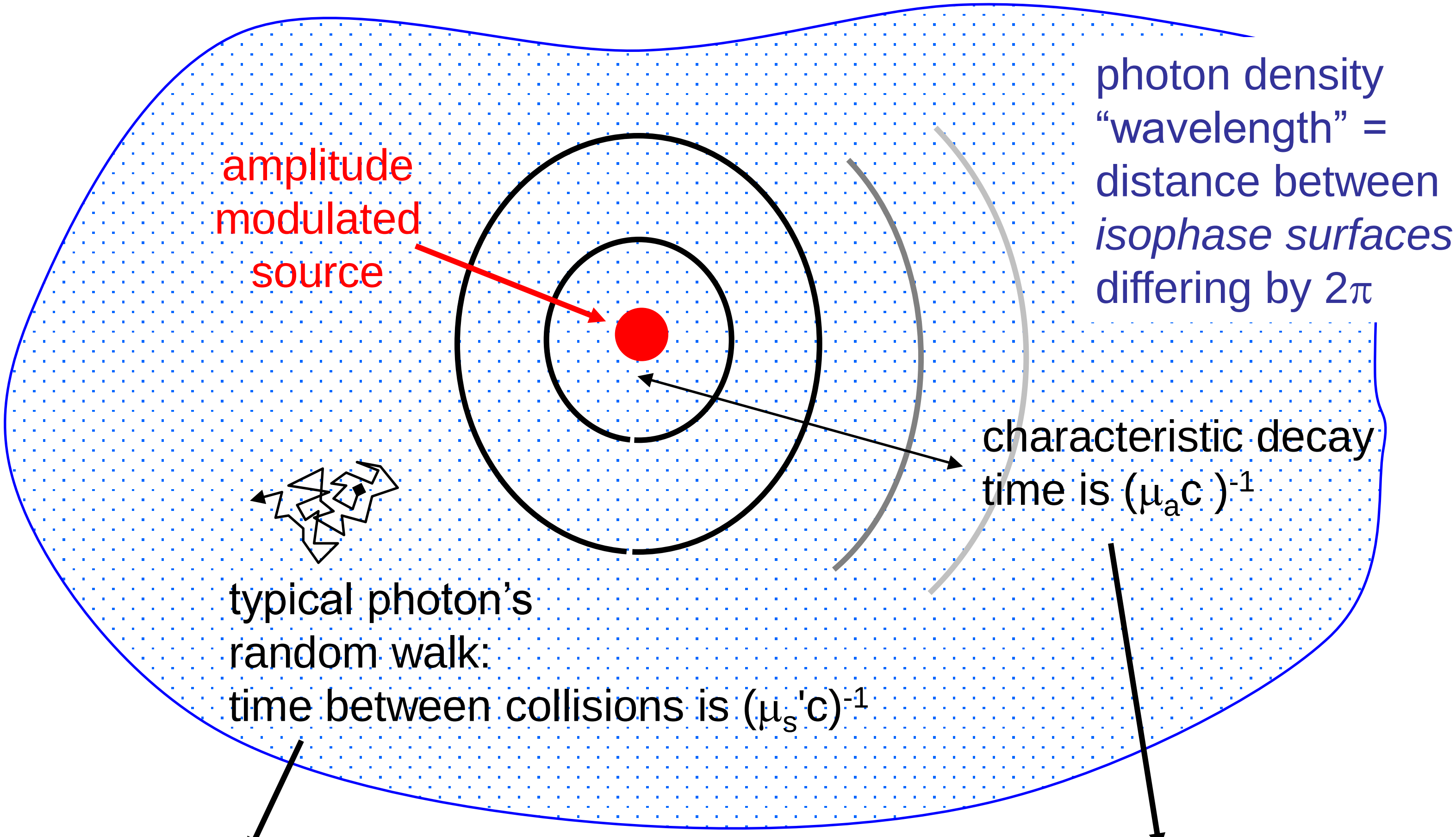
Velocity of photon density "waves"



Therefore, the measured phase shift depends upon the optical properties of the medium



Validity of photon density wave picture



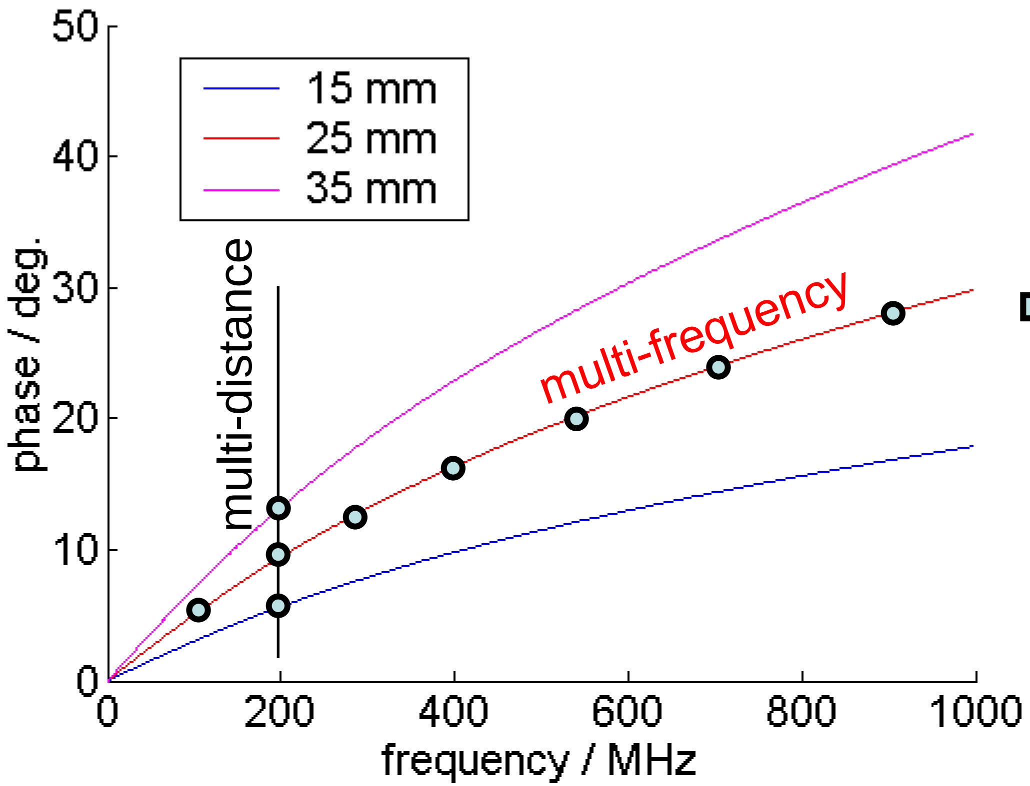
if only a few collisions occur during a source modulation cycle, diffusion model does not approximate reality (>10 GHz)

if photons “survive” for only a few oscillation cycles, AC effects are no different from DC effects (<10 MHz)

Frequency domain

Ways to make measurements:

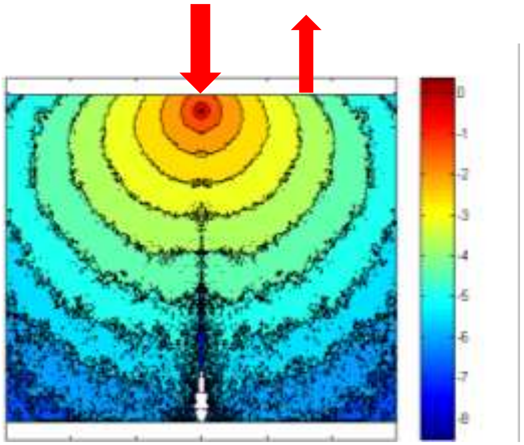
1) phase and/or amplitude vs. distance
2) phase and/or amplitude vs. frequency



fit to a model
to get absorption
and scattering
coefficients

Roadmap for today

review of basic concepts from last time



the Virtual Tissue Simulator

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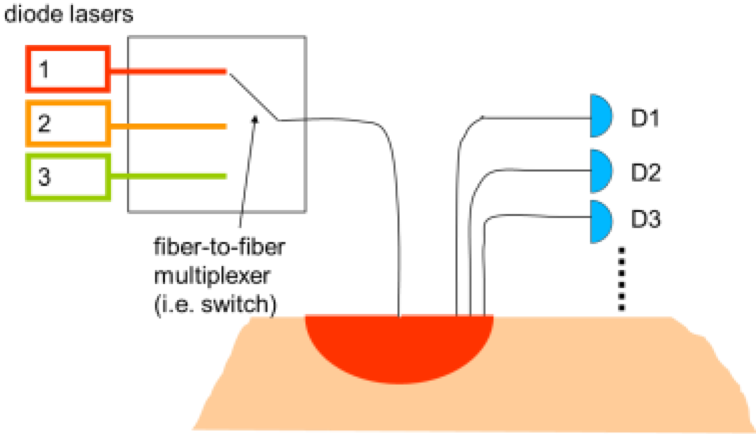
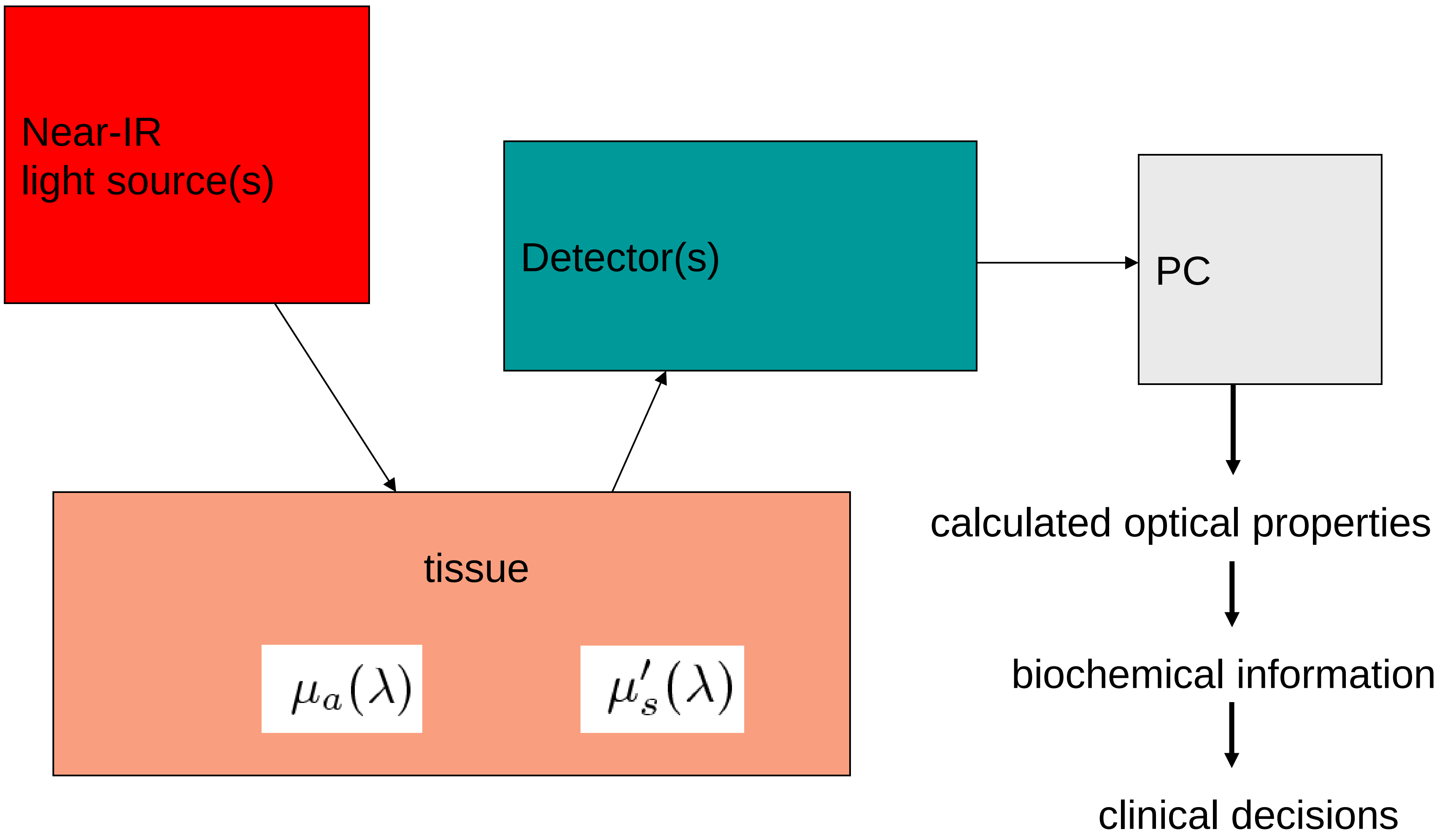
instrument design considerations

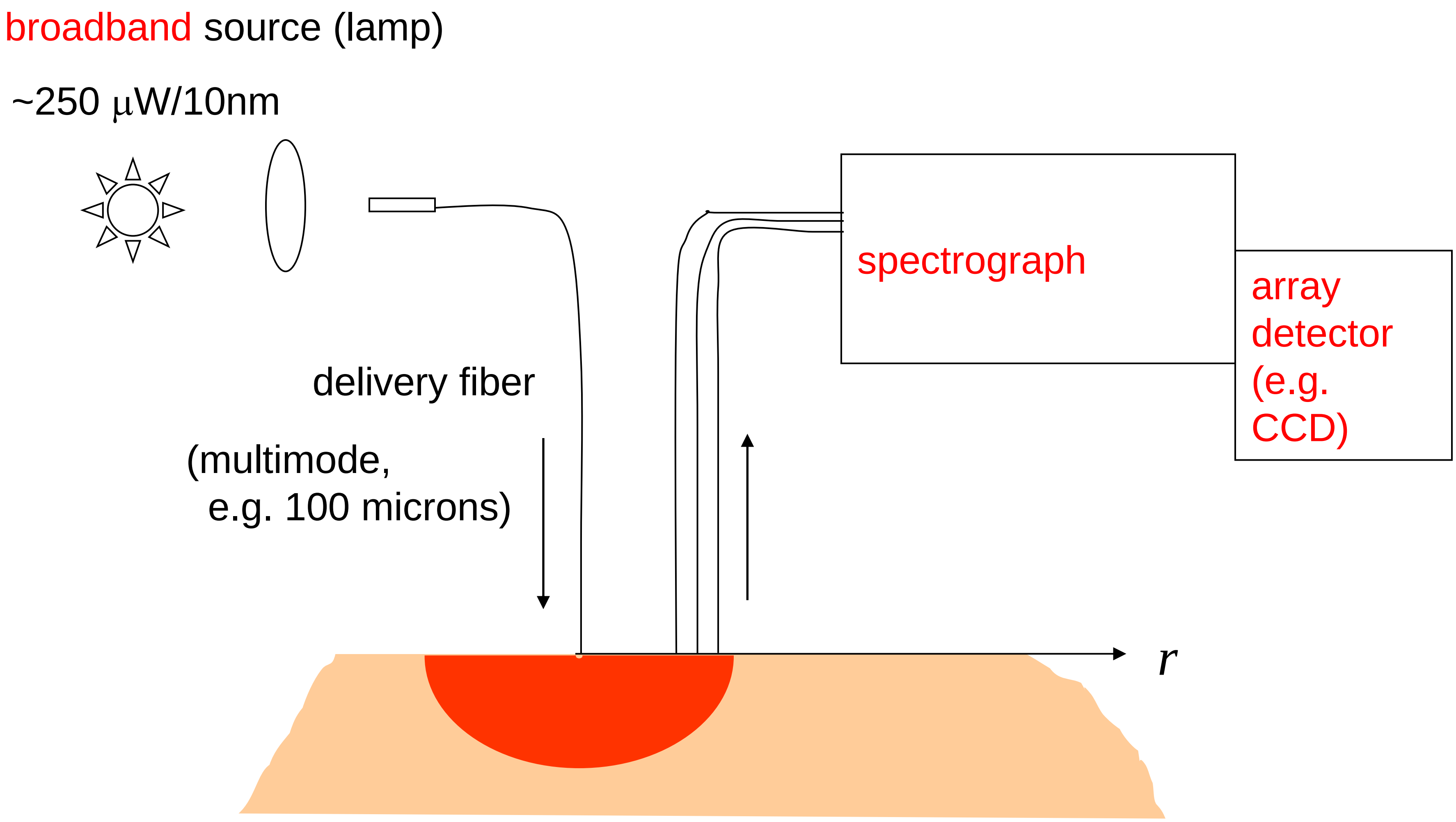


various applications

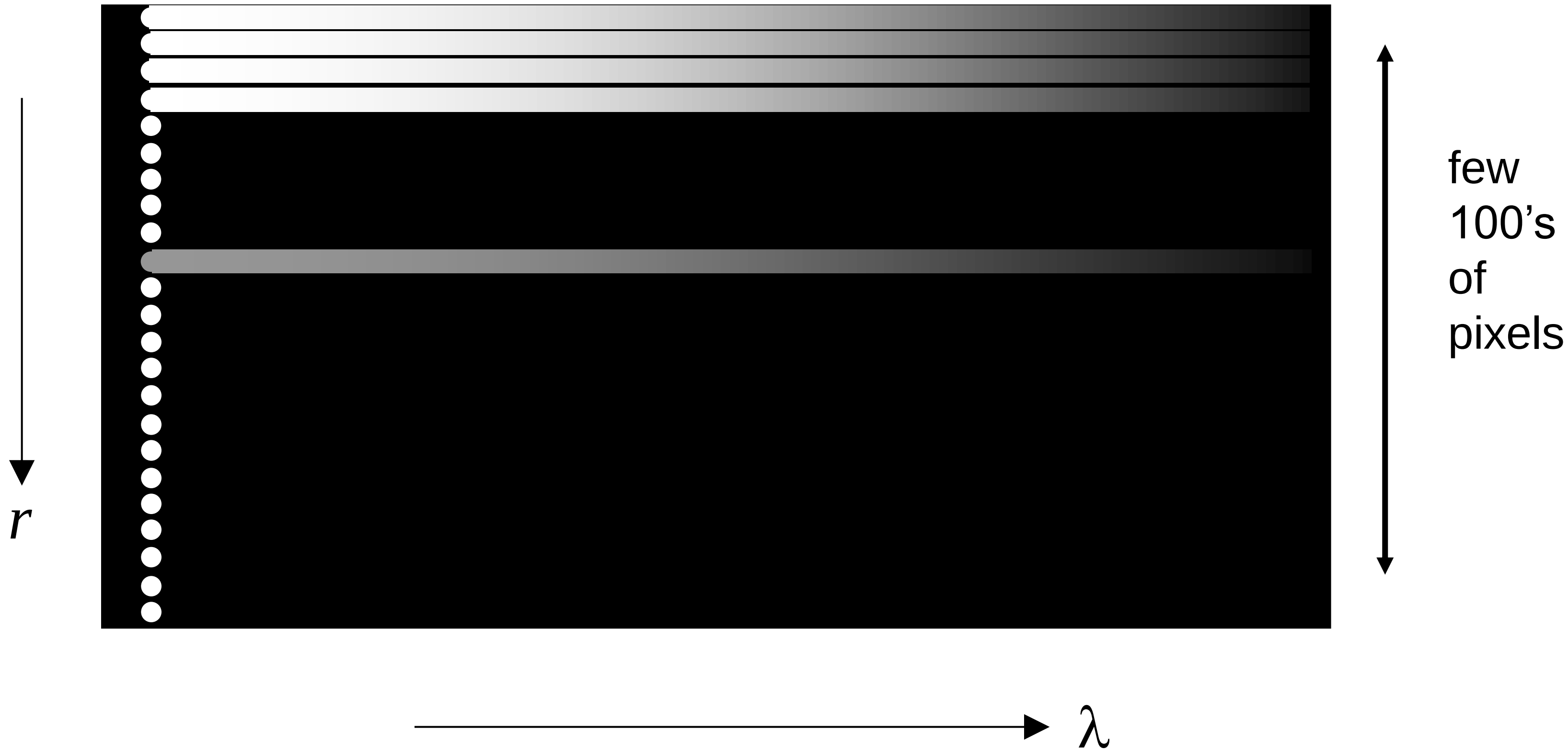
Basic instrumentation for all cases



Steady state (“CW”) + spectrometer



Spectrographic CCD display

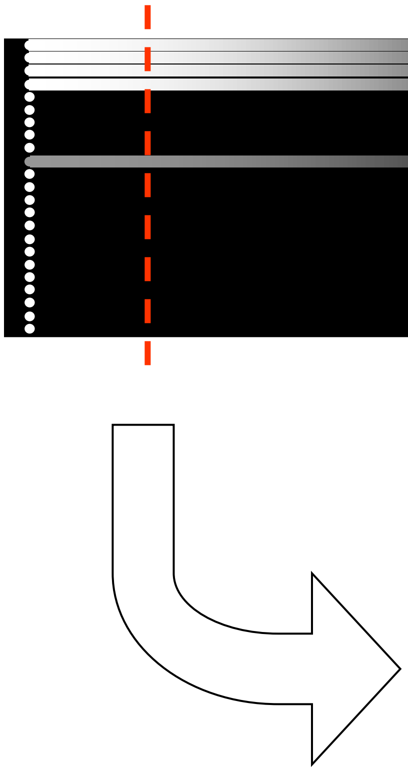


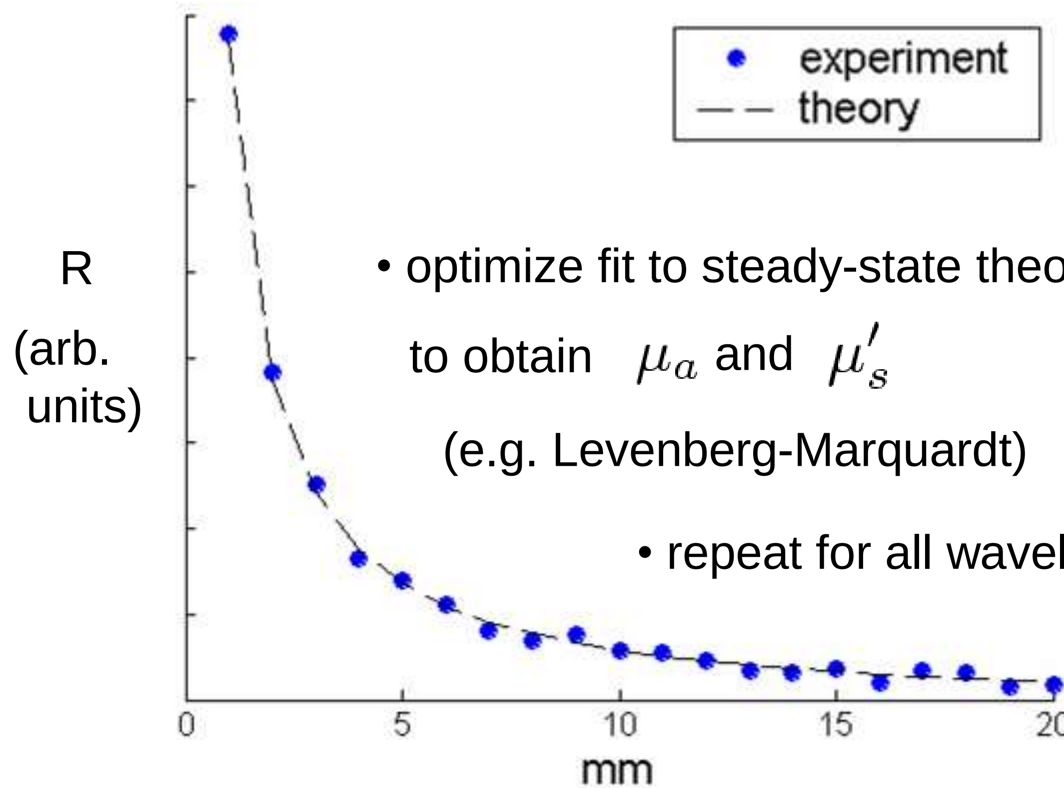
$$\text{fiber image: } \frac{150\,\mu\text{m}}{\text{fiber}} \cdot \frac{1\text{ pixel}}{25\,\mu\text{m}} = 6\text{ pixels/fiber}$$

integration time: 10's of seconds

calibration: shine equal light into all channels

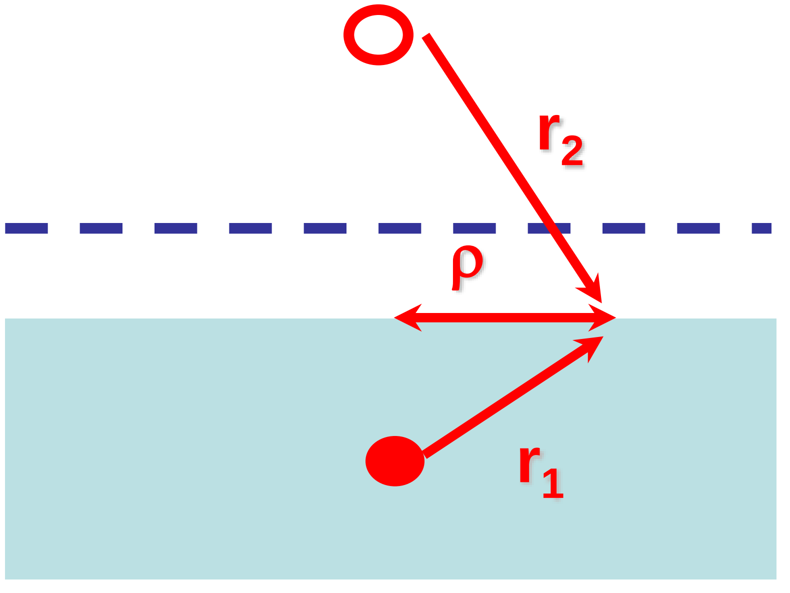
Steady state reflectance data

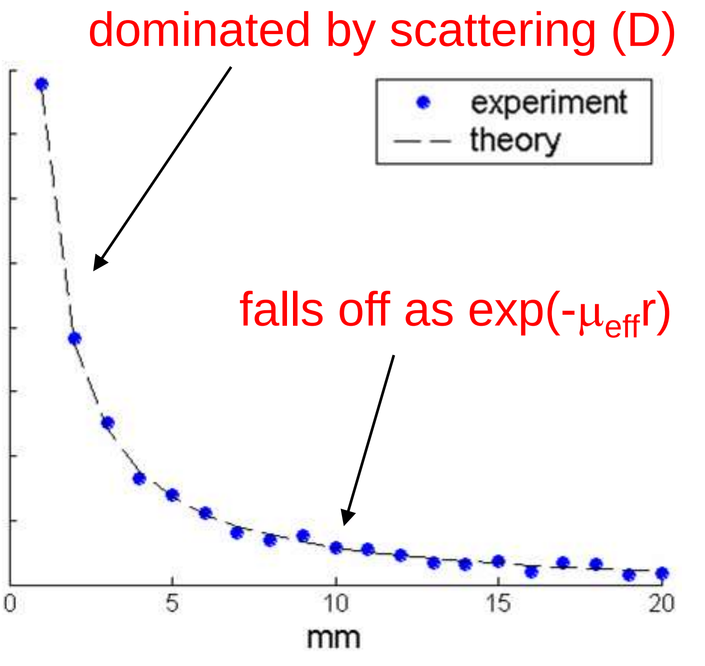




- optimize fit to steady-state theory to obtain μ_a and μ_s' (e.g. Levenberg-Marquardt)
- repeat for all wavelengths

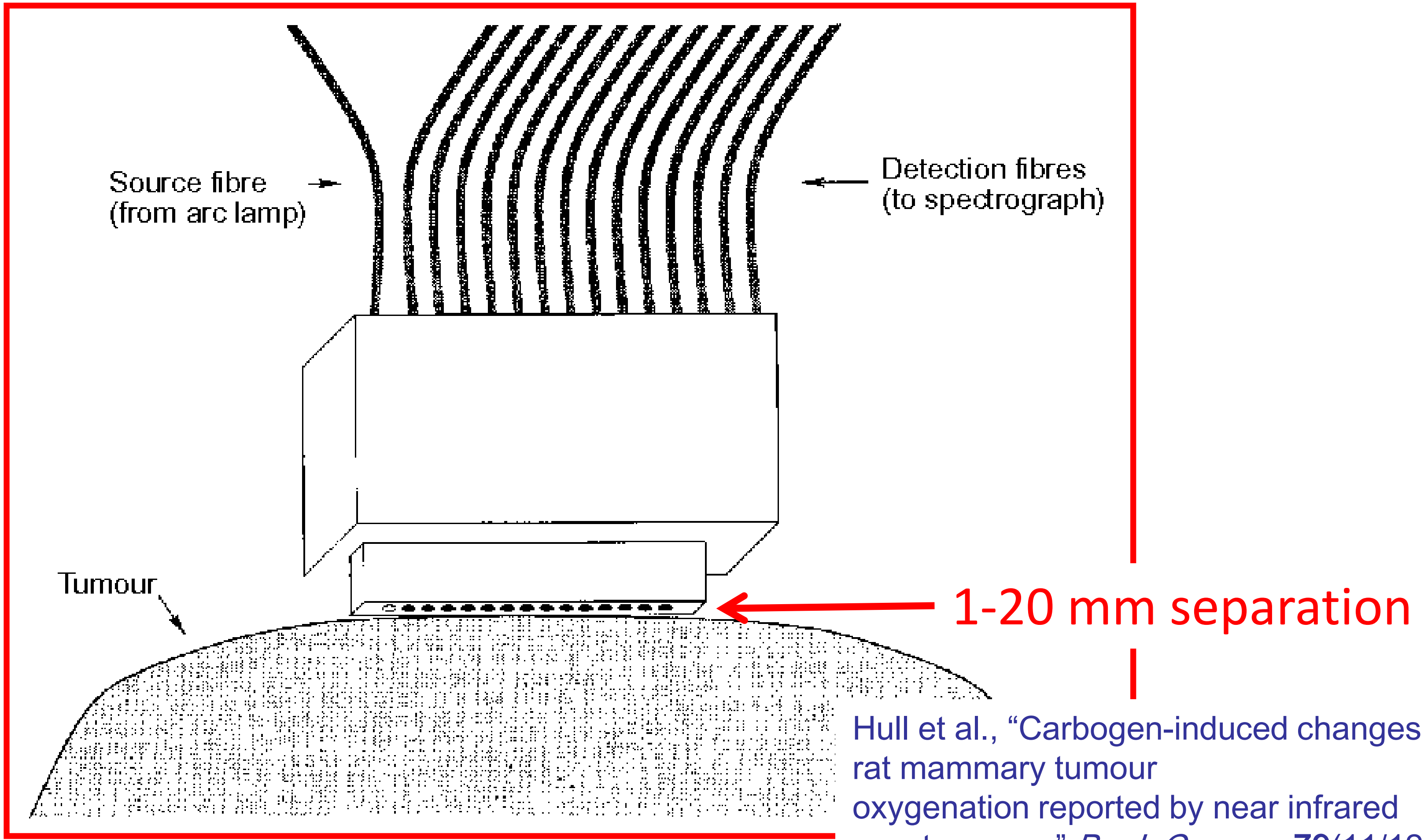
Need to measure both "near" and "far"





$$\Phi(\rho) = \frac{1}{4\pi D}\left(\frac{\exp(-\mu_{eff} r_1(\rho))}{r_1(\rho)} - \frac{\exp(-\mu_{eff} r_2(\rho))}{r_2(\rho)}\right)$$

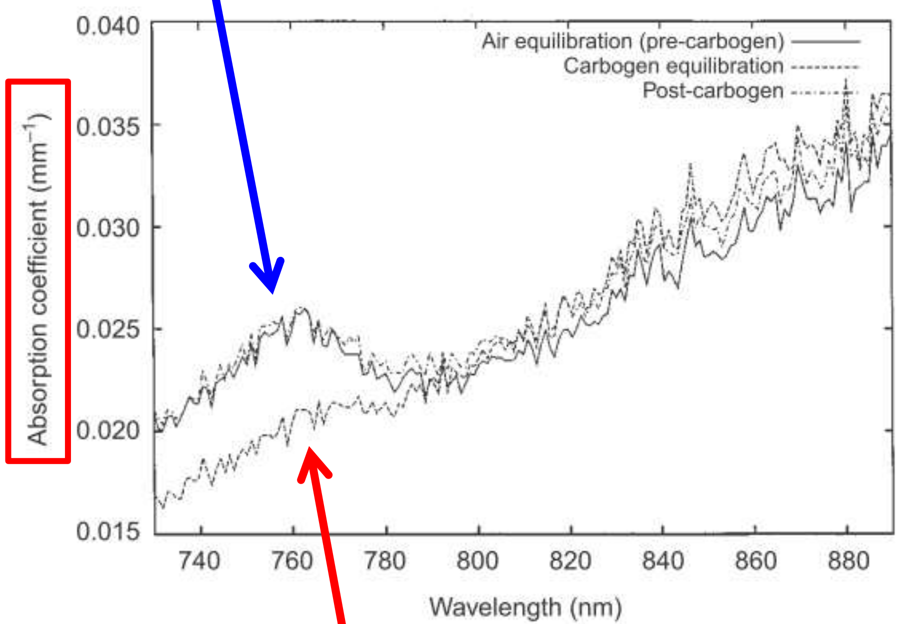
Linear probe for *in vivo* diffuse reflectance spectroscopy



Hull et al., "Carbogen-induced changes in rat mammary tumour oxygenation reported by near infrared spectroscopy," *Br. J. Cancer*, **79**(11/12), 1709-1716 (1999).

Seeing blood oxygenation change

normal air



when rat is breathing 95% O_2

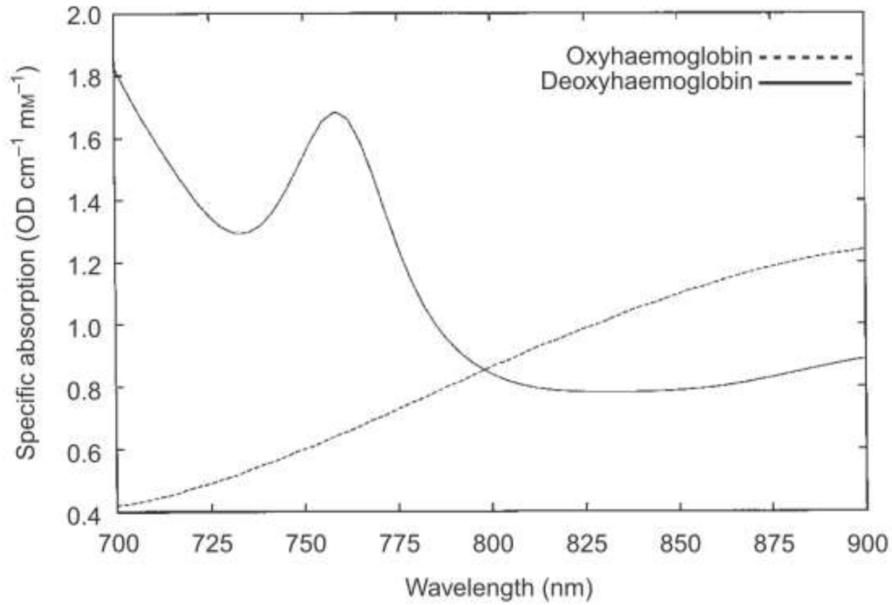


Figure 2 Near infrared absorption spectra of deoxy- (—) and oxyhaemoglobin (- - -). The oxyhaemoglobin spectrum is from Wray et al (1988); the deoxyhaemoglobin spectrum is from Matcher et al (1995)

Hull et al., *Br. J. Cancer*, **79**(11/12), 1709-1716 (1999).