Biomedical Optics

Laser Doppler Velocimetry

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Biomedical Optics : course

Contents

1. - General Introduction
   - Overview of existing techniques

2. - Light scattering, theoretical background
   - Monte-Carlo + numerical assignment
   - Photoacoustics

3. Experimental: focus on some techniques:
   - Laser-Doppler perfusion
   - Self-mixing velocimetry

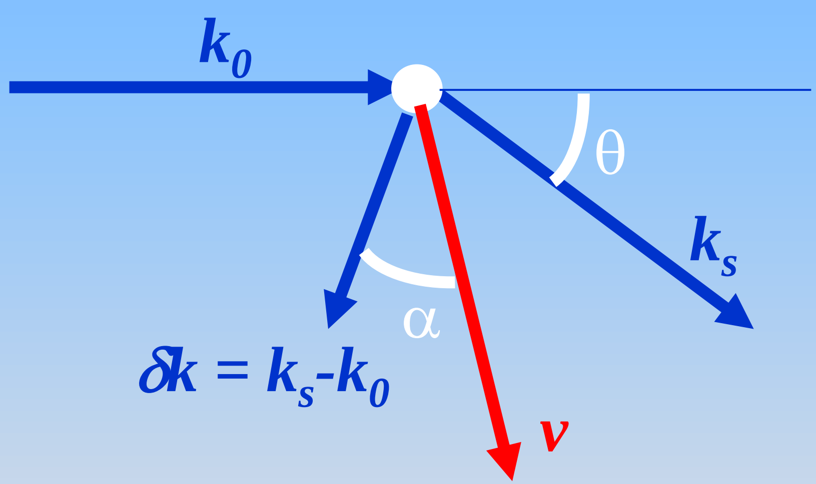
Laser Doppler Velocimetry

Contents:

1. LD for blood perfusion
   - Principles
   - Monitoring
   - Imaging
2. Self-mixing LD
   - Principles
   - Experimental aspects
   - Flow velocities
   - Intra-arterial use

LDV: Principles

Principle of laser Doppler:



$\boldsymbol{k_0}$ and $\boldsymbol{k_s}$: incoming and scattered wavevectors

$\boldsymbol{v}$: particle velocity

$\omega_D = 2\pi f_D$: Doppler frequency

$$\omega_D = \left(\vec{\boldsymbol{k}}_s - \vec{\boldsymbol{k}}_0\right) \bullet \vec{\boldsymbol{v}}$$

$$\left|\delta\vec{\boldsymbol{k}}\right| = 2k.\sin\tfrac{1}{2}\theta$$

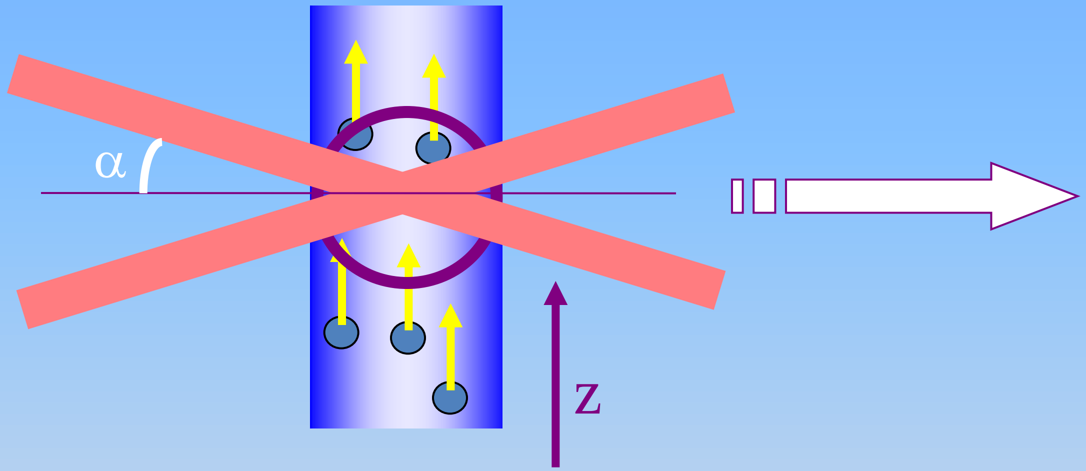
$$f_D = \frac{kv}{\pi}\sin\tfrac{1}{2}\theta\cos\alpha$$

Normally in tissue: θ is small : $\langle\cos\theta\rangle \approx 0.95$ ➔ $\theta < 15^{o}$

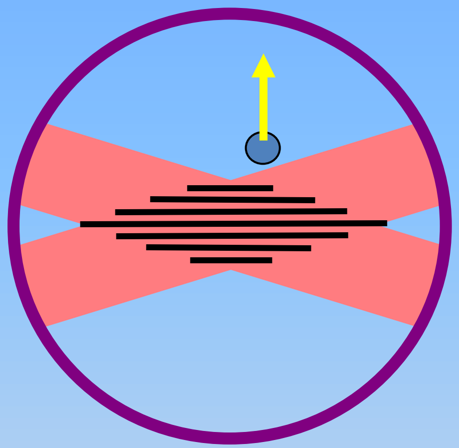
➔ approx. $\boldsymbol{\delta k_0}$ // $\boldsymbol{v}$: only $\boldsymbol{v}$-component $\perp$ $\boldsymbol{k_0}$ measured

LDV: Types of Instruments (1)

(A) Differential (Dual-beam) Laser Doppler Velocimetry



Interference fringe pattern



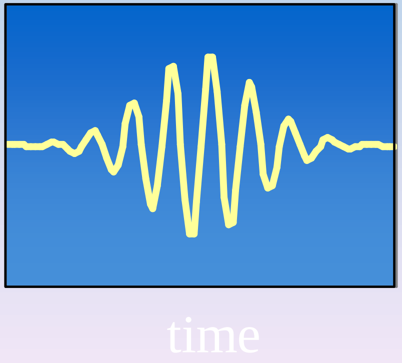
Fringe spacing $s = \frac{\lambda}{2\sin\alpha}$

Detection preferentially in forward direction

Doppler frequency

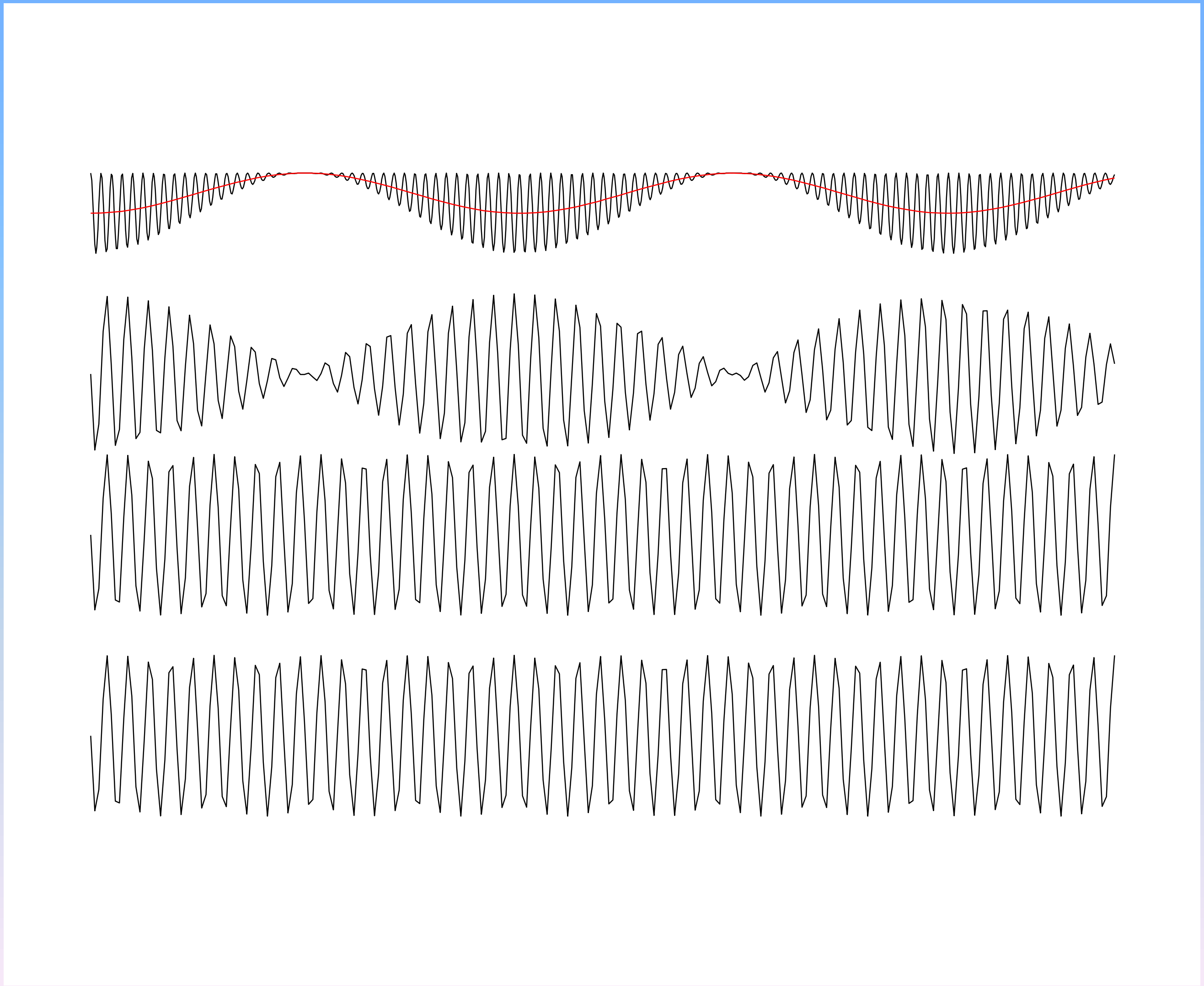
$$f = 2.v_z(\sin\alpha)/\lambda$$

Scattered intensity burst



LDV: Types of Instruments (2)

(A) Differential (Dual-beam) Laser Doppler Velocimetry



Original frequency
ω [≈ 10^{14} Hz]

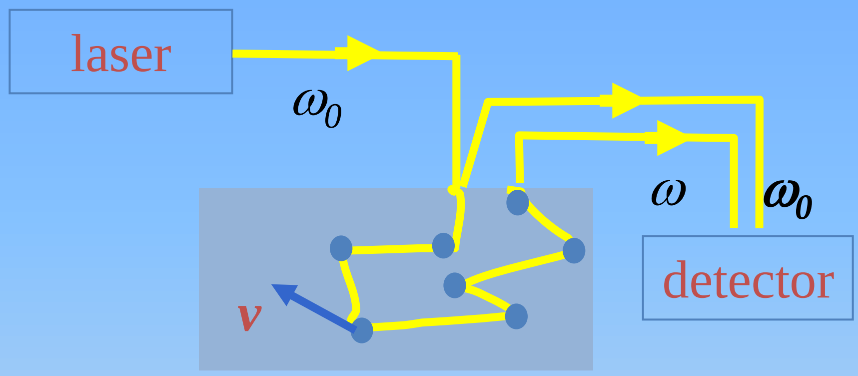
Doppler-shifted frequency
$\omega + \omega_D$ [≈ 10^{14} Hz]

Doppler frequency
ω_D [<≈ 20 kHz]

Doppler intensity signal :
~ (freq.sign)^2

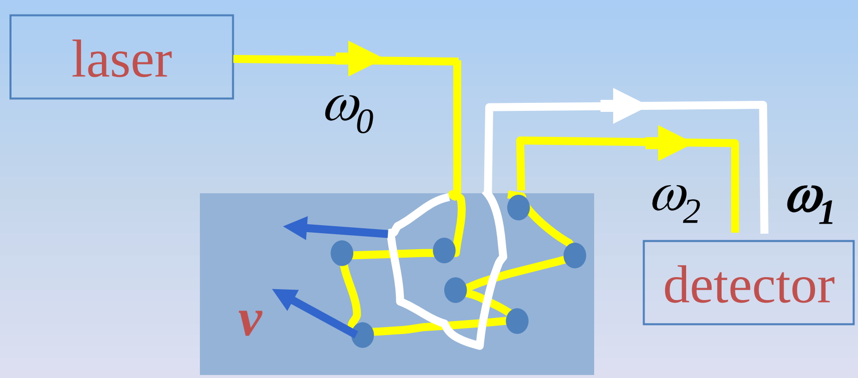
LDV: Types of Instruments (3)

(B) Laser Doppler Perfusion Velocimetry



Averaged Doppler frequency:

Heterodyne mixing
$\Delta\omega = \omega - \omega_0$



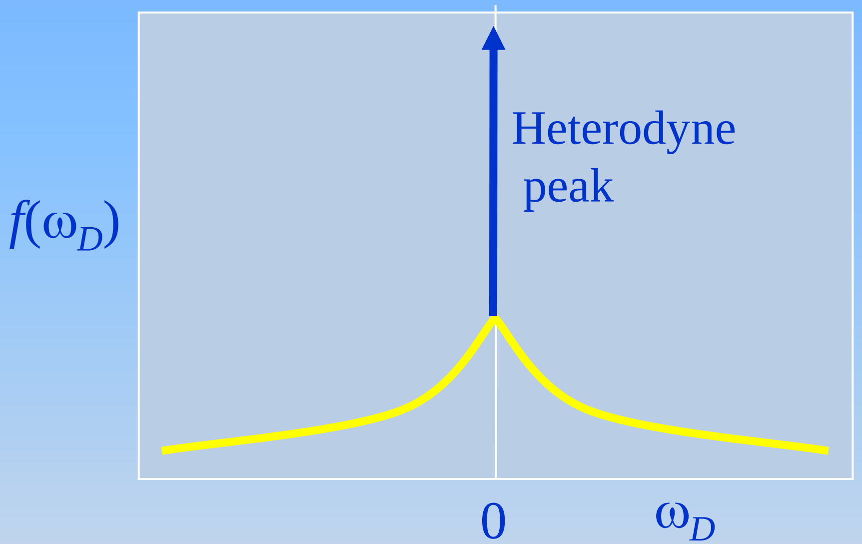
Homodyne mixing
$\Delta\omega = \omega_1 - \omega_2$

Averaging by:
- random velocities
- (multiple) scattering in random directions

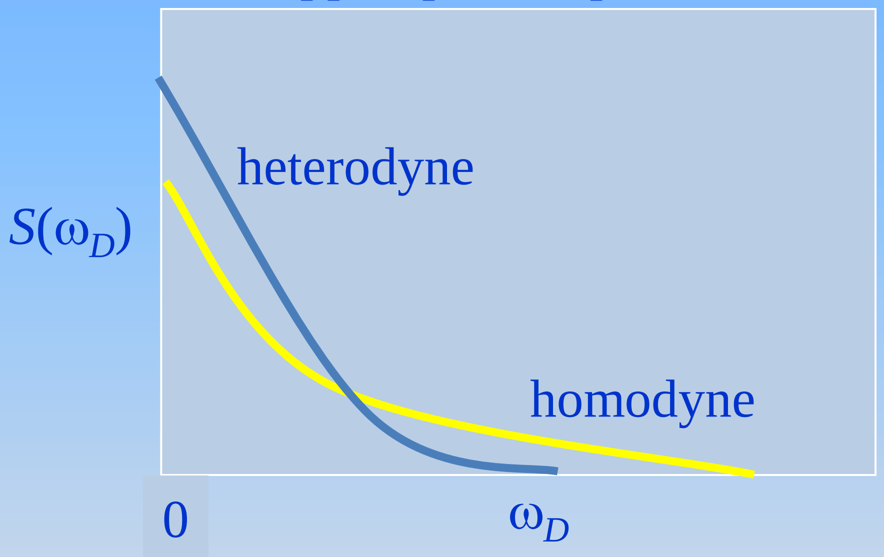
LDPV: Spectra (1)

(B) Laser Doppler Perfusion Velocimetry

Doppler frequency spectrum



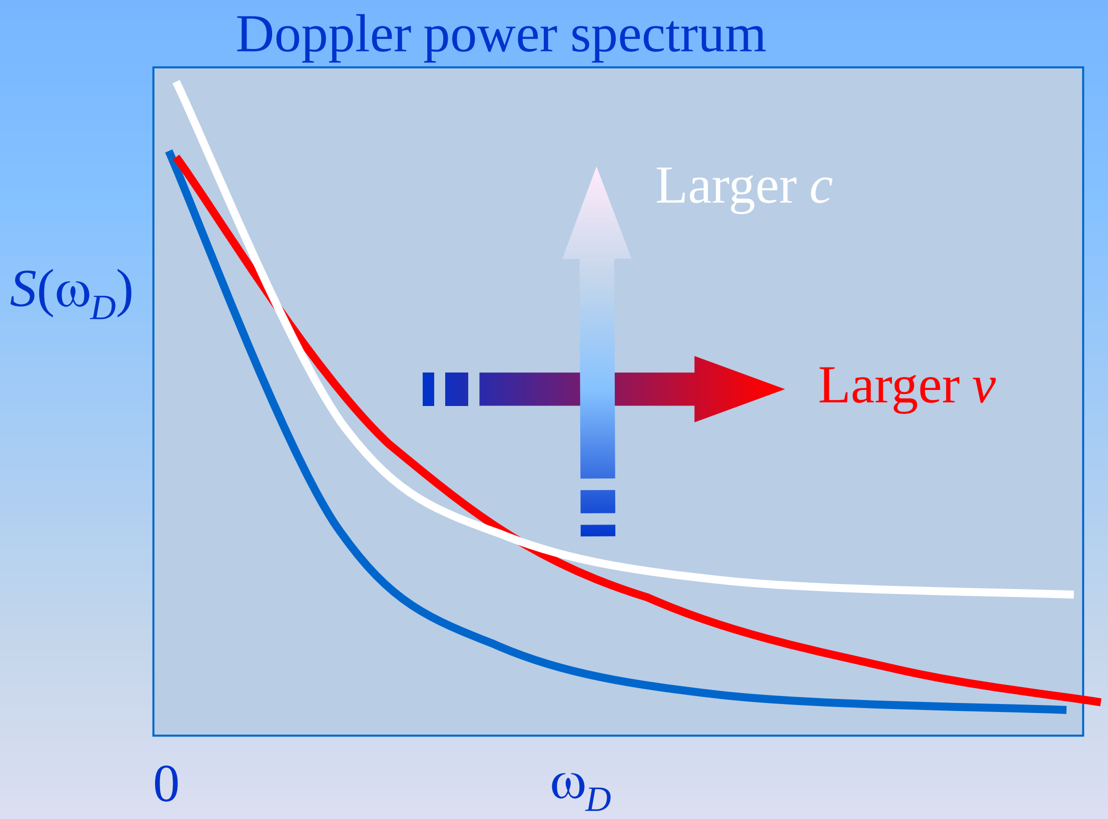
Doppler power spectrum



Heterodyne peak: due to large amount of non-Doppler shifted scattered photons.

LDPV: Spectra (2)

(B) Laser Doppler Perfusion Velocimetry



Power spectrum dependent on:

- concentration *c*
- velocity *v*

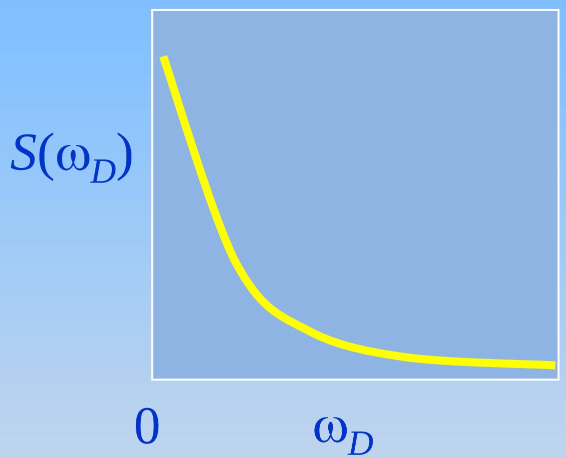
Moments of Power spectrum :

$$M_n = \int_0^\infty \omega^n . S(\omega) d\omega$$

LDPV: Spectra (3)

(B) Laser Doppler Perfusion Velocimetry

Doppler power spectrum



Power spectrum dependent on:

- concentration *c*
- velocity *v*

Moments of Power spectrum:

$$M_n = \int_0^\infty \omega^n . S(\omega) d\omega$$

Moments:

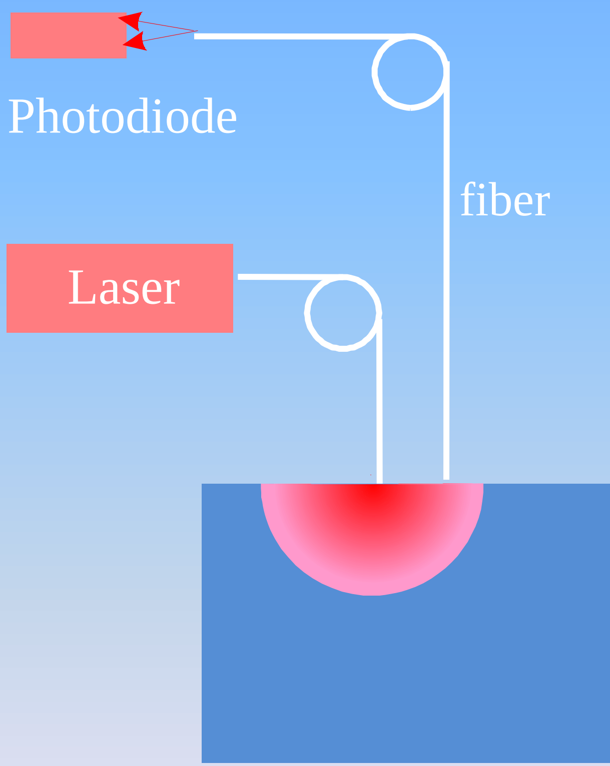
$n = 0$: ~ concentration of moving scatterers

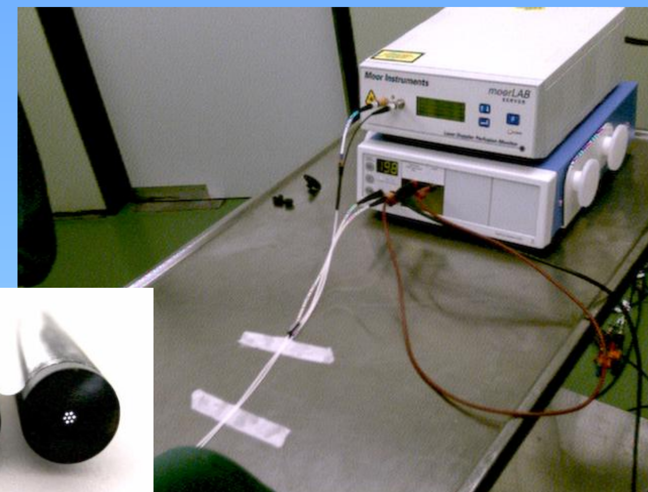
$n = 1$: ~ flux of moving scatterers

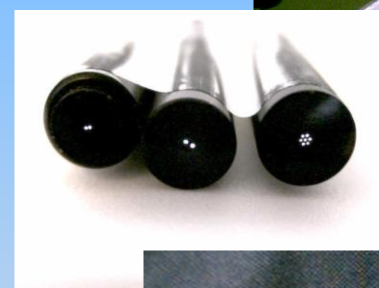
M_1 / M_0 : ~ velocity

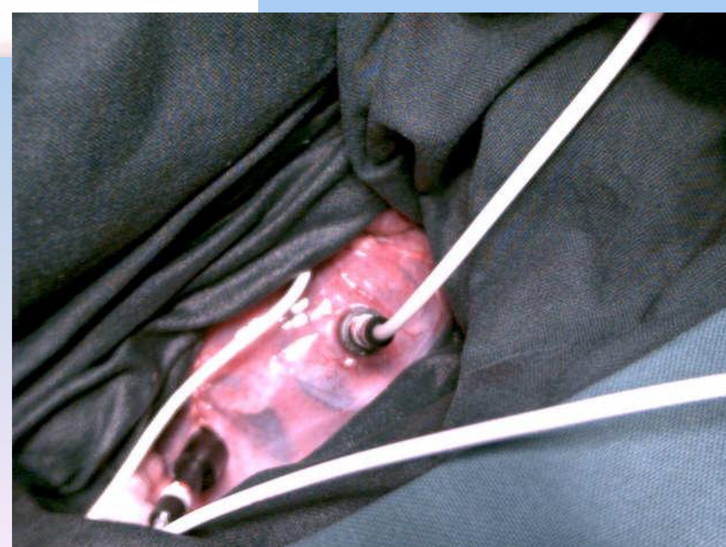
LDPV

(B) Laser Doppler Perfusion Velocimetry

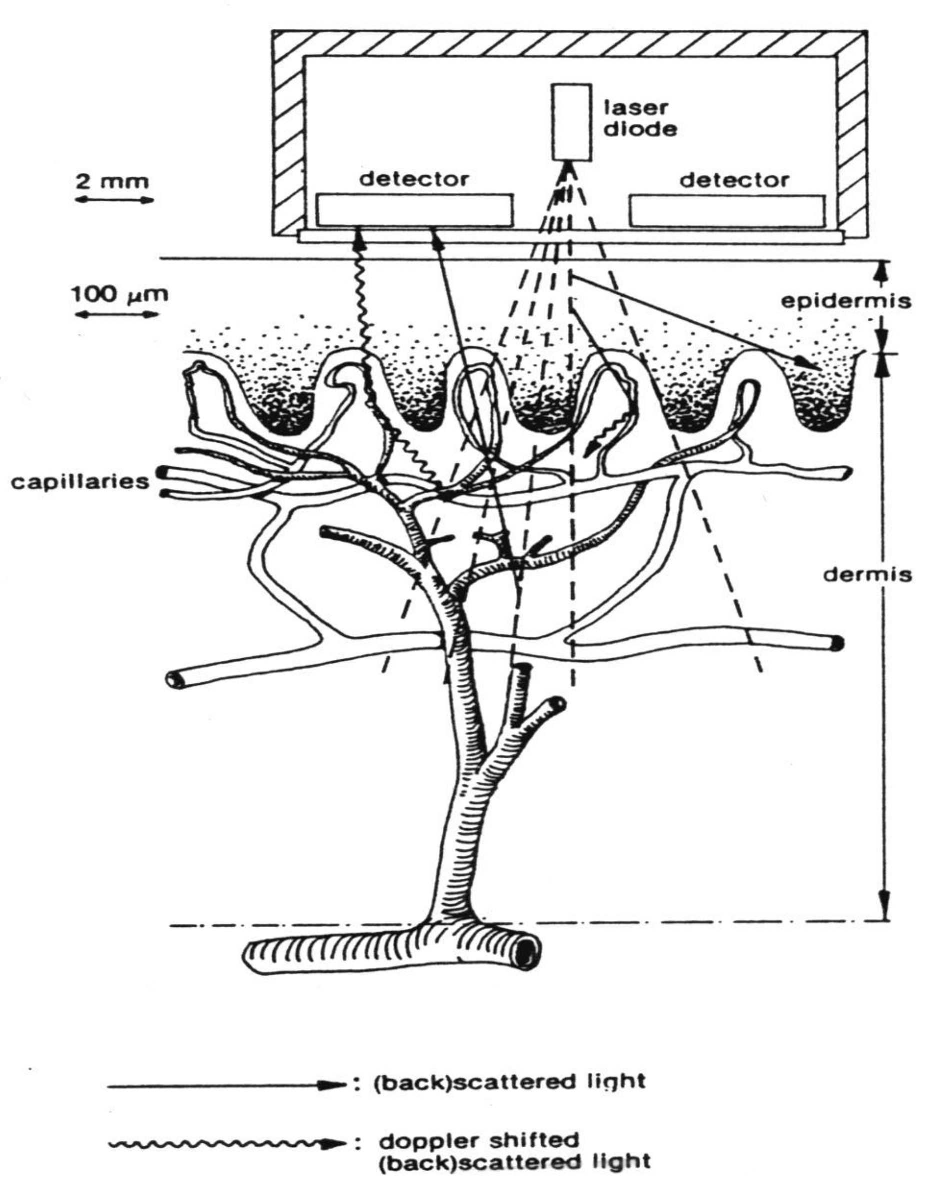








LDPV: Skin Tissue

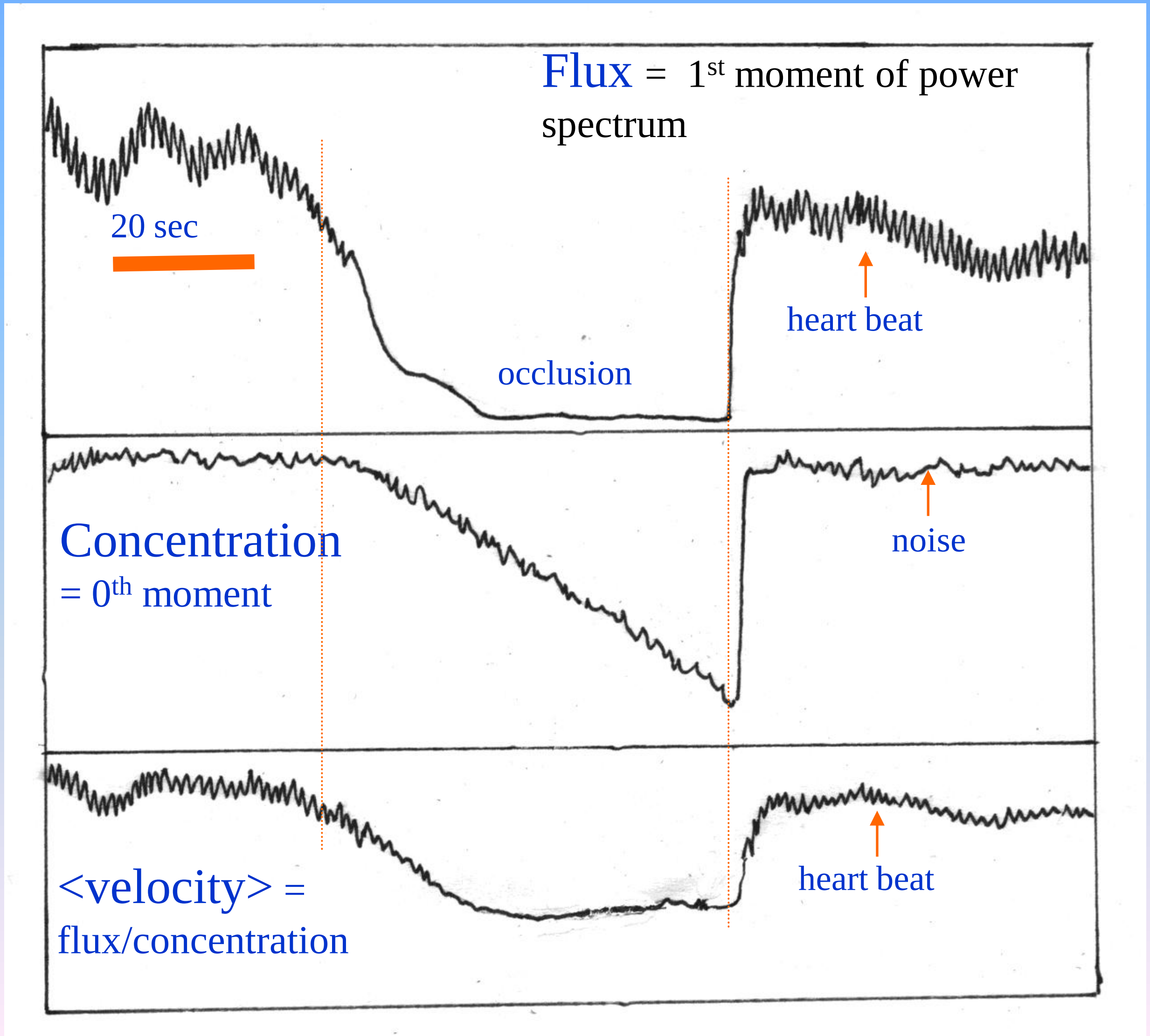


(B) Laser Doppler Perfusion Velocimetry

Schematic cross section of Skin tissue

LDPV: Signals

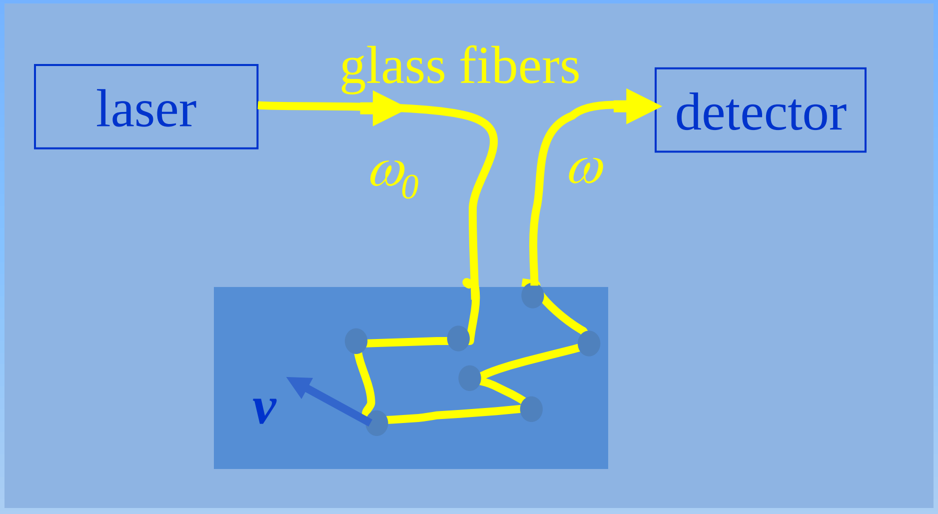
(B) Laser Doppler Perfusion Velocimetry



LD spectra of finger tip upon occlusion of upper arm

LDPV: Types of Instruments

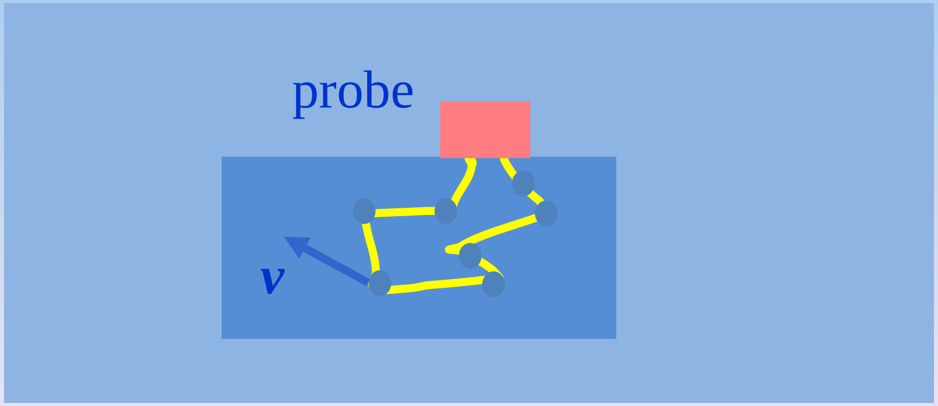
(B) Laser Doppler Perfusion Velocimetry: Instrument design



(a) Glass fibers for light transport

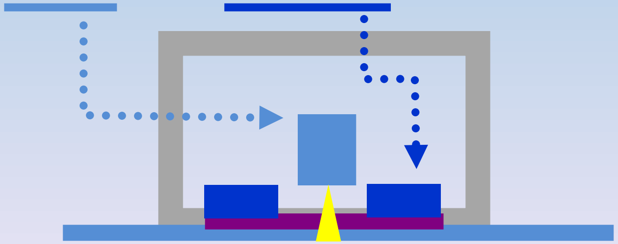
Disadvantages:

- motional artefacts
- sensitive for local variations



(b) Direct-contact velocimetry:

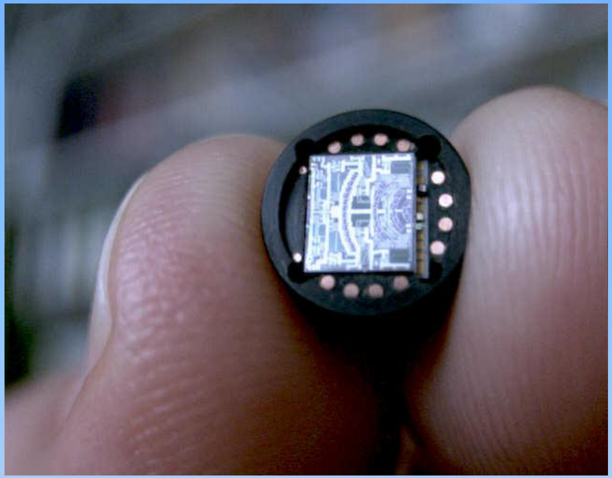
Laser and detector in one probe



- no motional artefacts
- local averaging

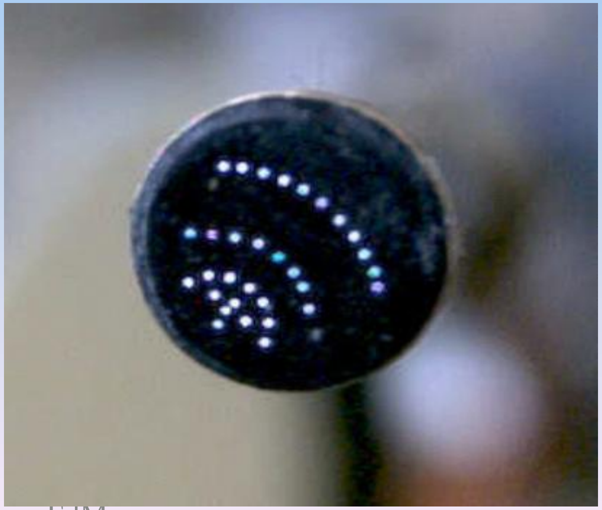
LDPV: New Instruments

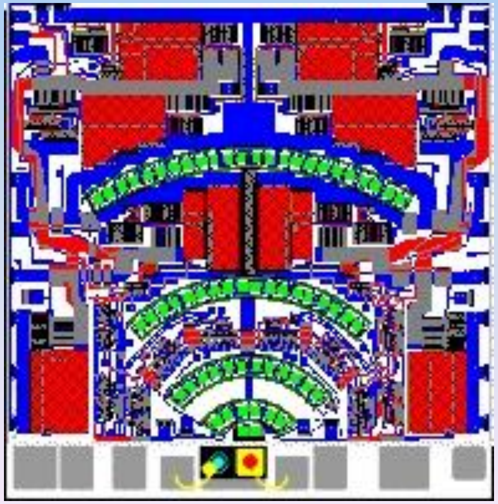
(B) Laser Doppler Perfusion Velocimetry: Instrument design



LD-monitor on-a-chip

provides miniature depth-sensitive sensor.





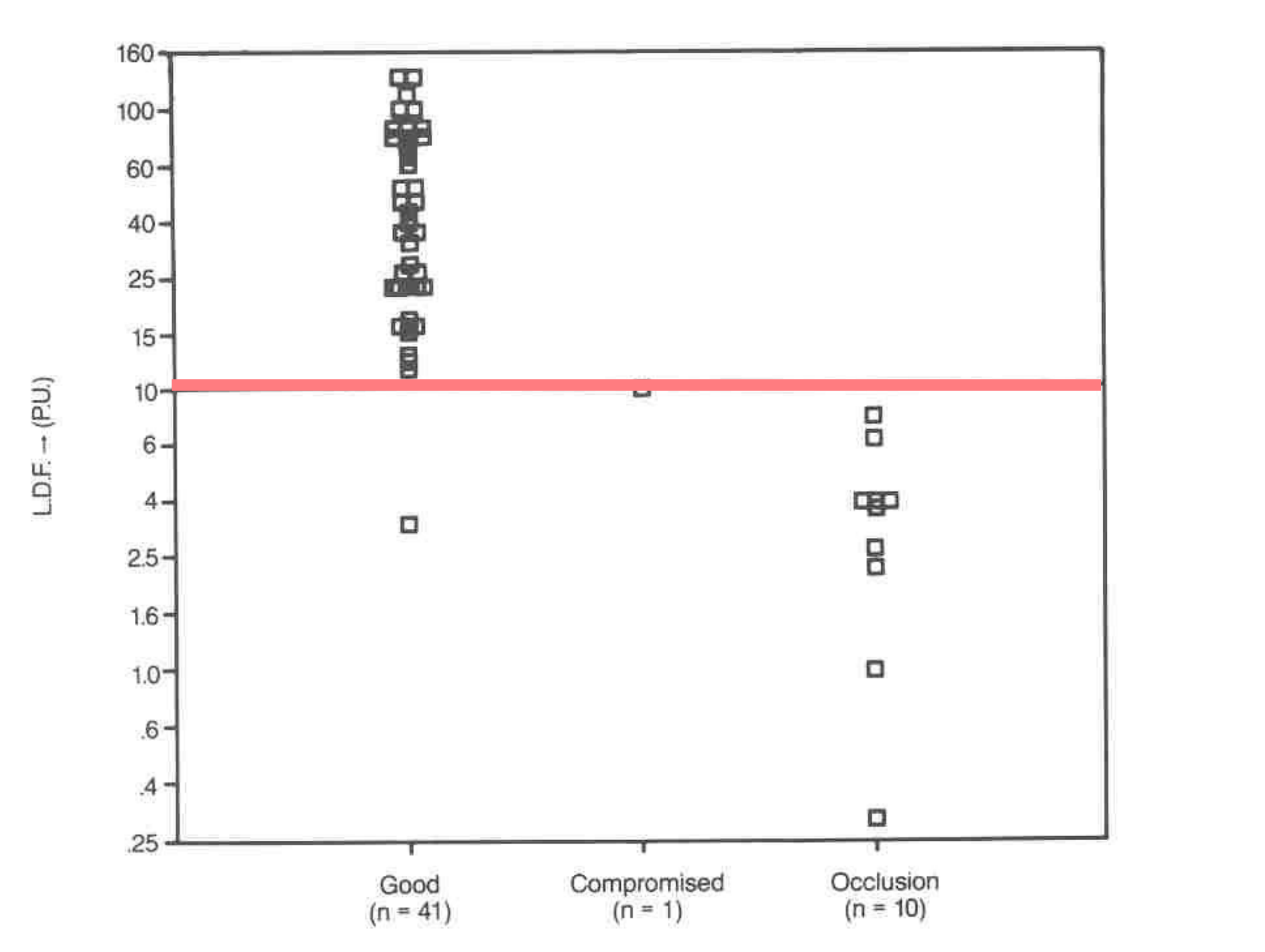
Green: photodiode rows

Blue/**red**: electronics: amplifiers/multiplexers

Red dot in **yellow** area: VCSEL- laser diode

Clinical applications: (1) Plastic Surgery

(B) Plastic and Reconstructive Surgery



Replantation and Revascularization

N=68
Flaps: forearm, toe, thumb, lateral arm, fibula

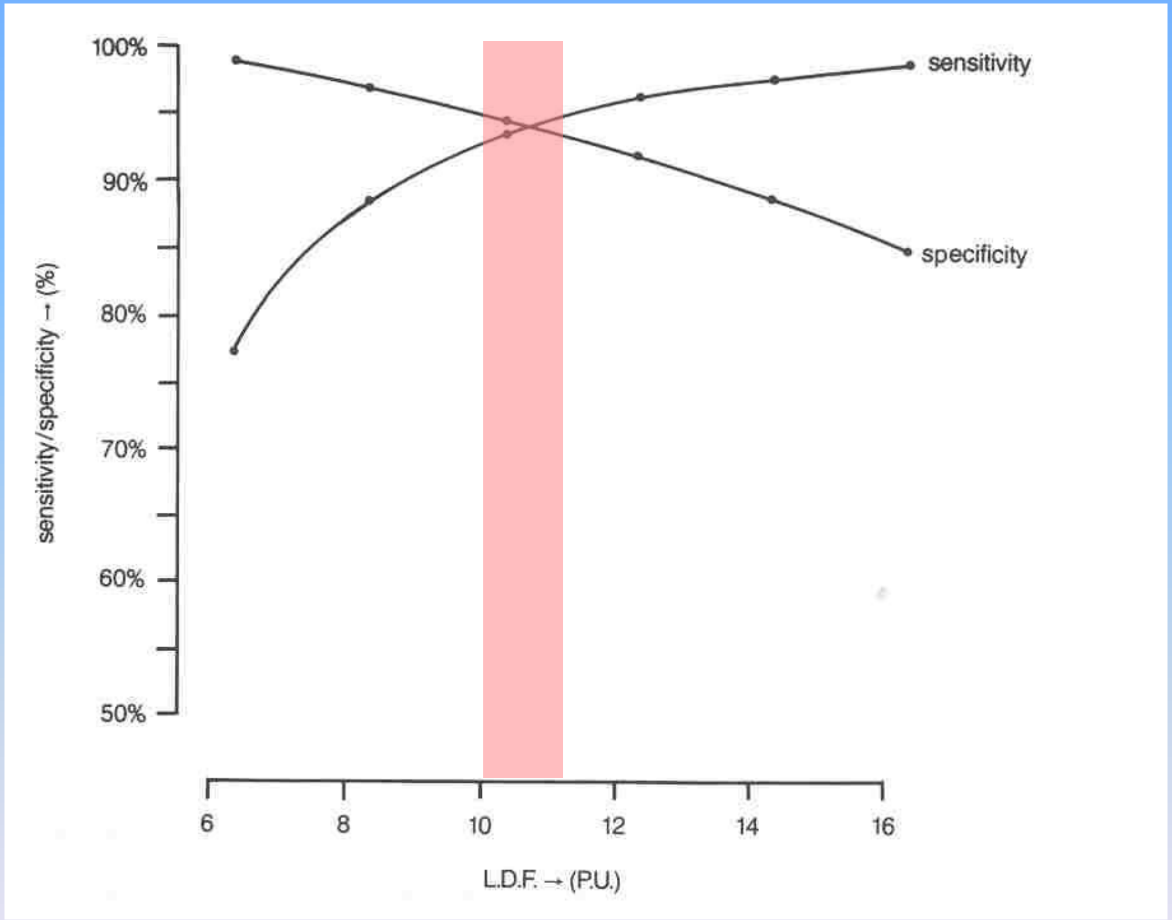
Effects after first half hour

Resulting Inter-vention level ("alarm value") = 10

Courtesy: L. van Adrichem, University Hospital Rotterdam

Clinical applications: (1) Plastic Surgery

(B) Plastic and Reconstructive Surgery



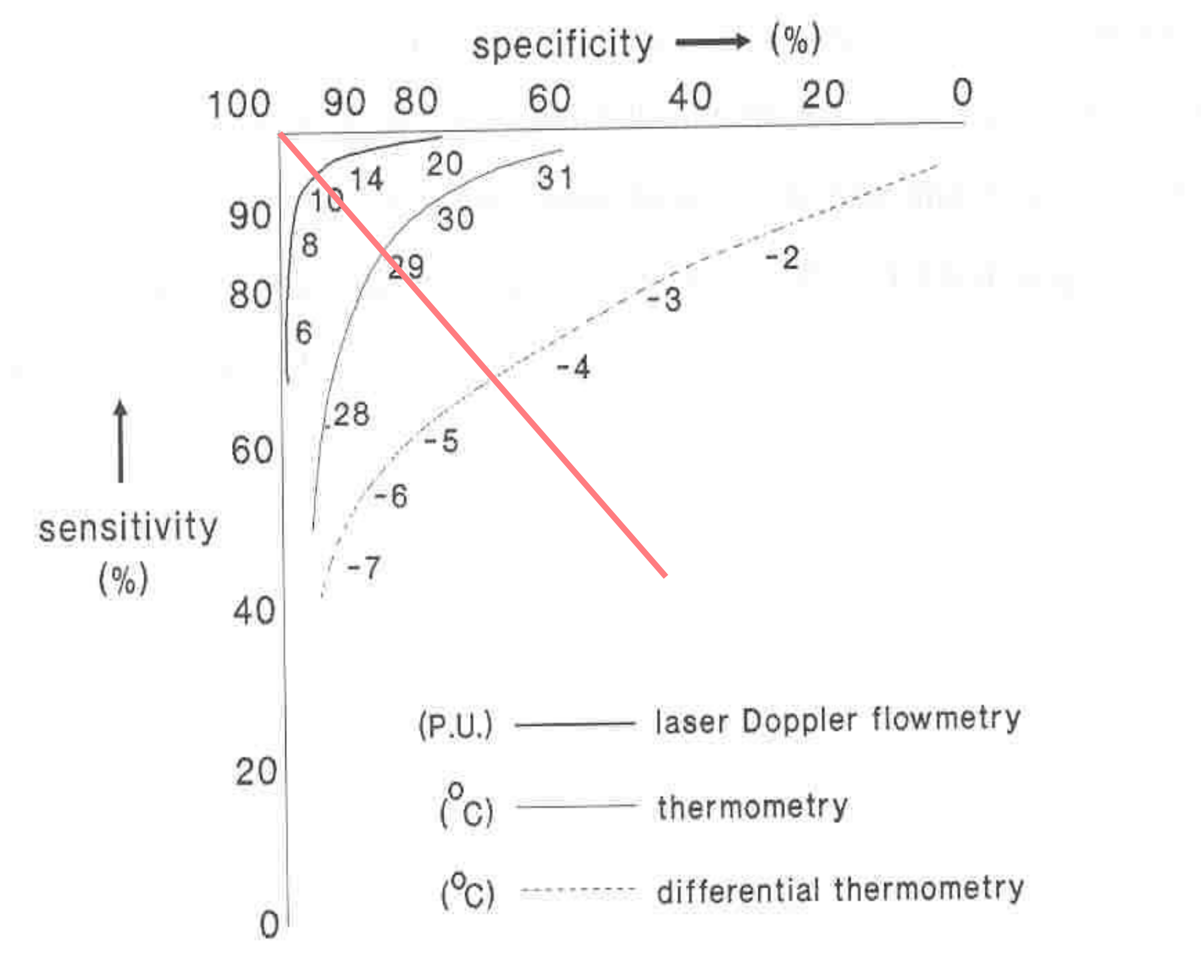
Specificity and Sensitivity of LD Perfusion flowmetry in the replantation/ revascularization group

 "alarm value", intervention level

Courtesy: L. van Adrichem, University Hospital Rotterdam

Clinical applications: (1) Plastic Surgery

(B) Plastic and Reconstructive Surgery



Characteristics of Post-operative monitoring devices

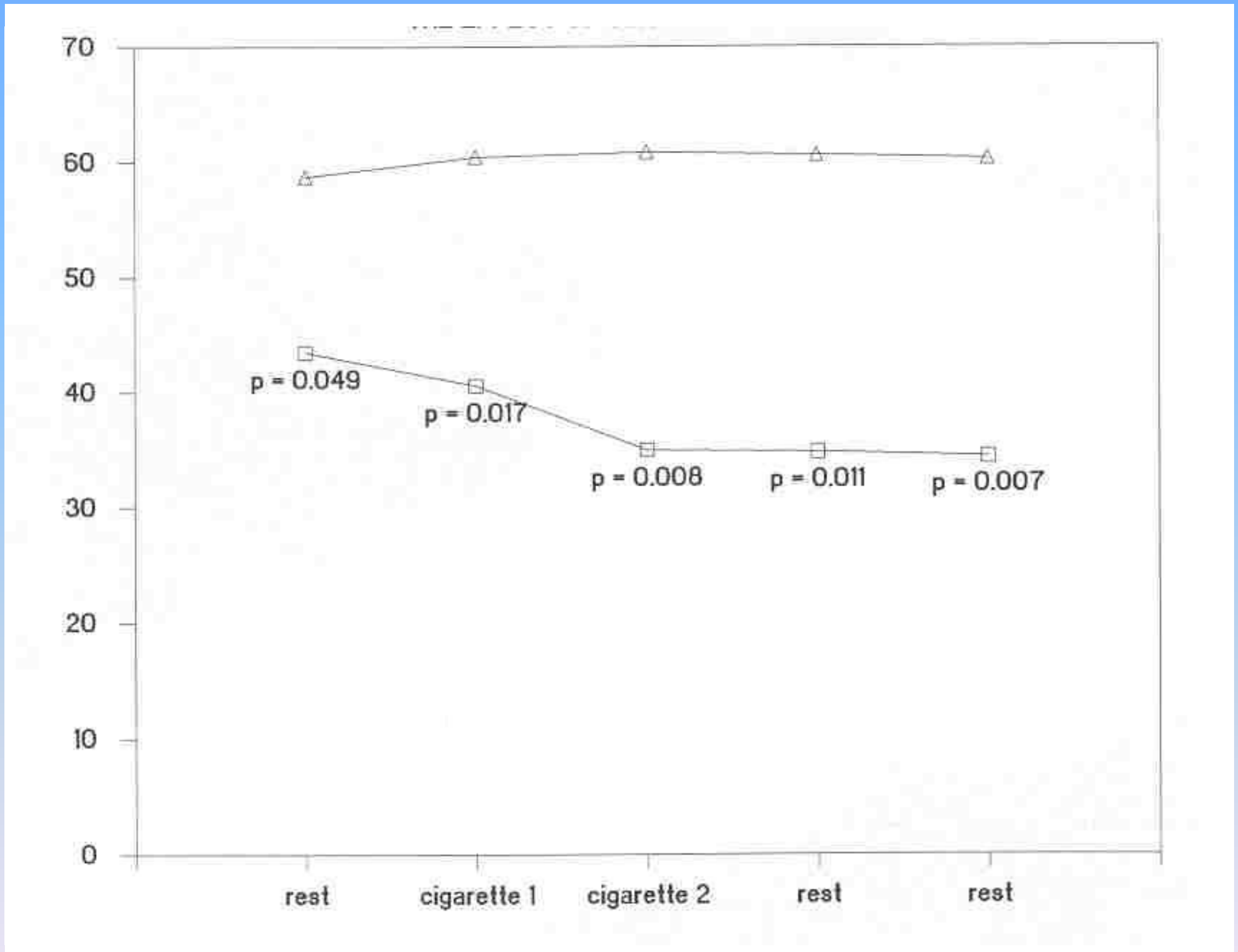
Figures: instruments read-out

Red line: Intervention level

Courtesy: L. van Adrichem, University Hospital Rotterdam

Clinical applications: (1) Plastic Surgery

(B) Plastic and Reconstructive Surgery



Cigarette smoking:

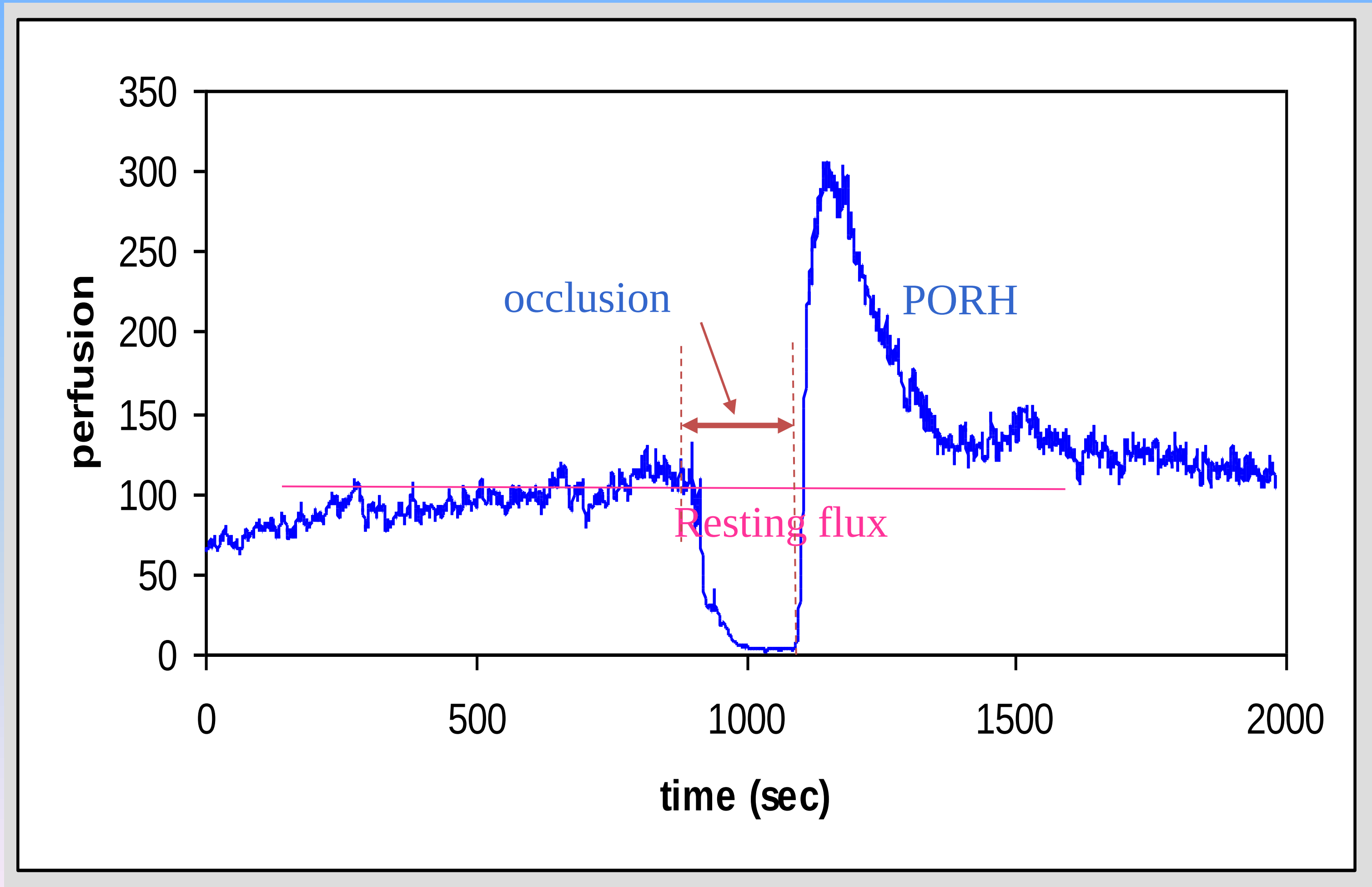
1.
Effect on flow through healthy thumb.

2.
Effect on flow through replanted digit.

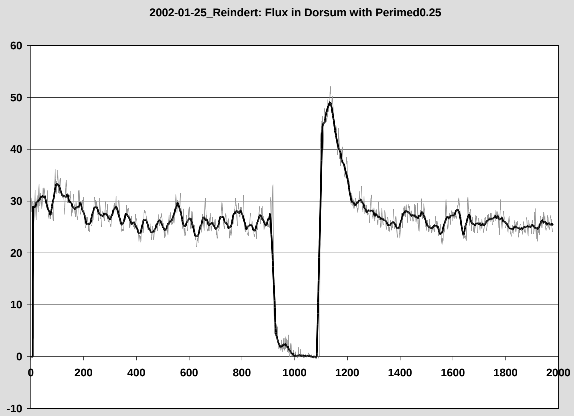
Courtesy: L. van Adrichem, University Hospital Rotterdam

Clinical Applications (2): PORH: Post-Occlusive Reactive Hyperemia

Healthy person

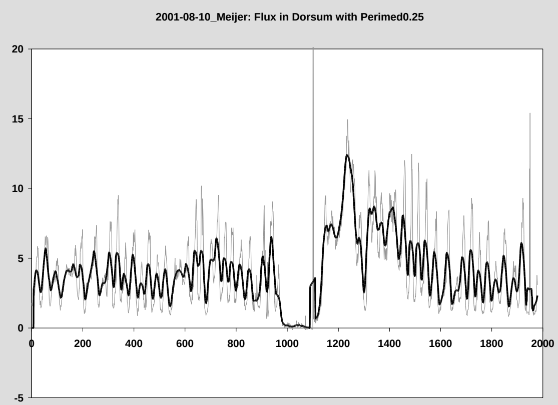


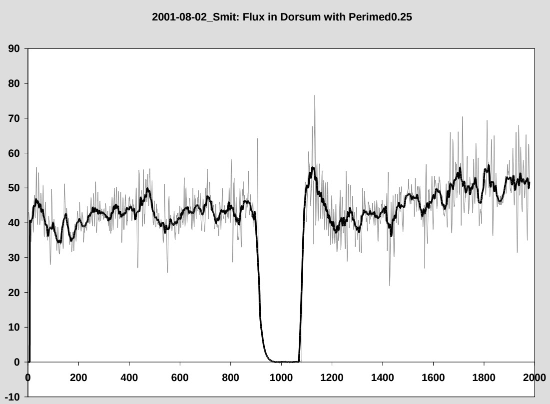
PORH:



Control group:

Fast rise, high top





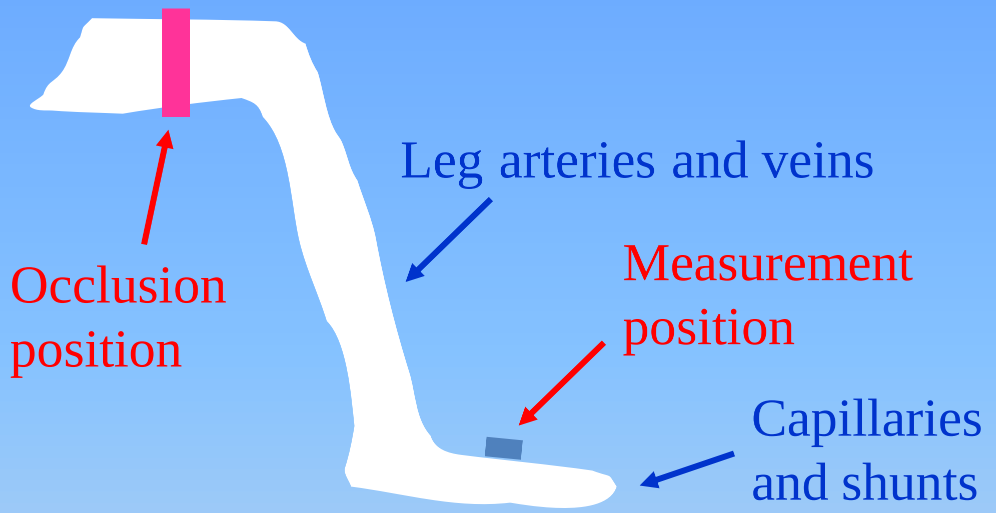
PAOD:

Slow rise, low top

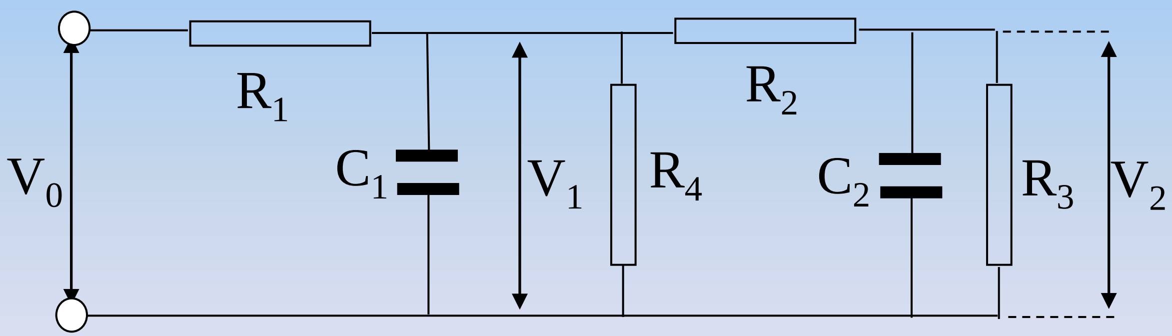
Diabetes Mellitus:

Medium rise, low top

PORH:
Post-Occlusive Reactive Hyperemia



Model: jump-response after occlusion:



Leg arteries and veins:

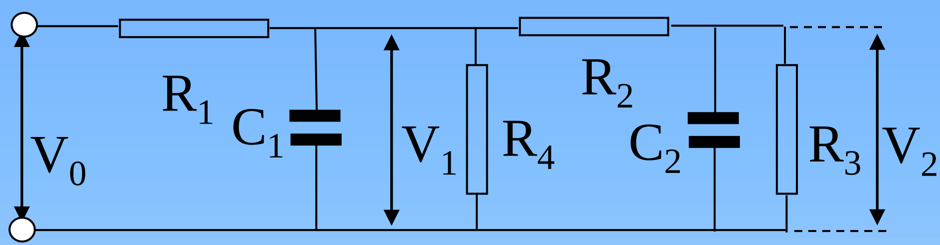
- Resistance R_1
- Capacitance or compliance C_1

Capillaries/ shunts:

- Resistance R_2 .. R_4
- Capacitance or compliance C_2

PORH:
Post-Occlusive Reactive Hyperemia

Model: jump-response after occlusion:



$$R = \frac{8\mu l}{\pi r_0^{\,4}} \quad ; \quad C = \frac{3\pi r_0^{\,3} l}{2E_\gamma h}$$

RC- circuits behave in time like : exp($-t\,/\,\tau$):
with characteristic time constant τ .

$$\tau = RC = \frac{12\mu l^2}{r_0 E_\gamma h}$$

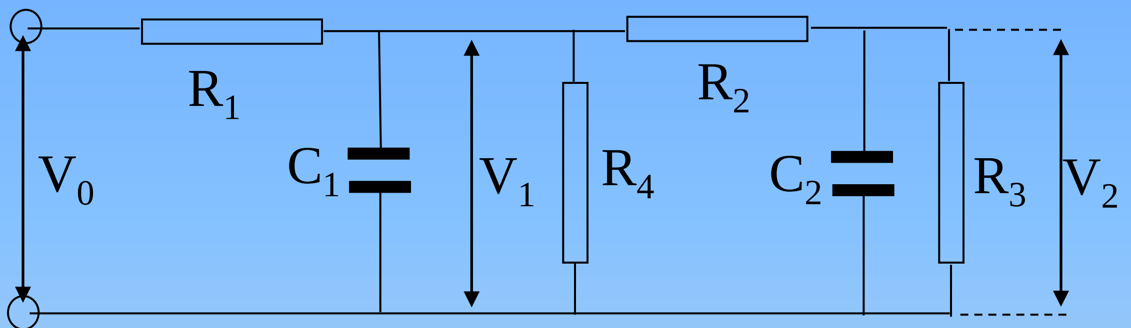
V = pressure (voltage) [N/m^2]
I = flow (current) [m^3/s]
Q = volume (charge) [m^3]

R = resistance = V / I [Ns/m^5]
C = capacitance = Q / V [m^5/N]

l = length of tube
r_0 = radius
μ = viscosity [Ns/m^2]
h = wall thickness
E_γ = Young's modulus [N/m^2]

Post-Occlusive Reactive Hyperemia

Model: jump-response after occlusion:



Measured perfusion:
Current I through R_2.

Exact model:

$$I = I_{rest}\left[1 + k_1 . e^{-t/\tau_1} + k_2 . e^{-t/\tau_2}\right] \quad ; \quad k_2 = -1 - k_1$$

$$\text{with} \quad k_1 \,, k_2 = f\left(R_1 .. R_4 \,, C_1 .. C_2\right)$$

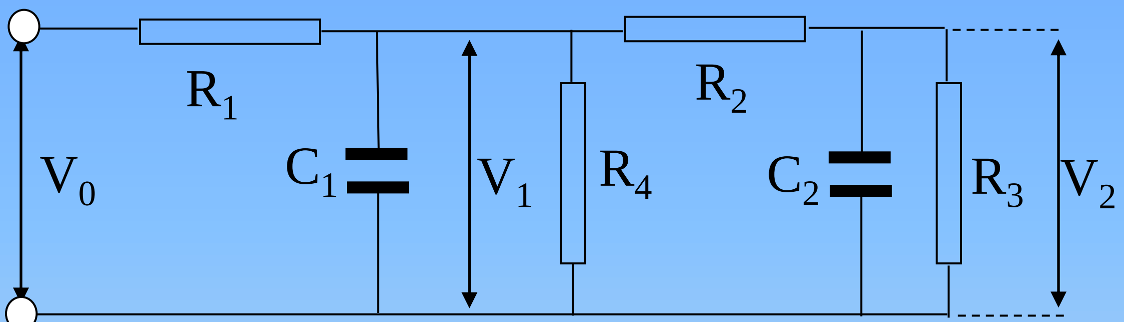
Approximation: $R_4 >> R_1 .. R_3$ (no shunts before entrance in capillary bed)
$R_1\, C_1 << (R_2 + R_3)\, C_2$ (leg filled much faster than capillaries)

$$I_{approx} = I_{rest}\left(1 - e^{-t/\tau_1}\right)\left[1 + \left(MR - 1\right) e^{-t/\tau_2}\right]$$

MR = ratio of maximum and resting flux

Post-Occlusive Reactive Hyperemia

Model: jump-response after occlusion:



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$$I_{approx} = I_{rest}\left(1 - e^{-t/\tau_1}\right)\left[1 + \left(MR - 1\right)e^{-t/\tau_2}\right]$$

MR = ratio of maximum and resting flux

$$\tau_1 = R_1 C_1 \quad ; \quad \tau_2 = C_2 \frac{R_2 R_3}{R_2 + R_3} \quad ; \quad MR = \frac{R_2 + R_3}{R_2}$$

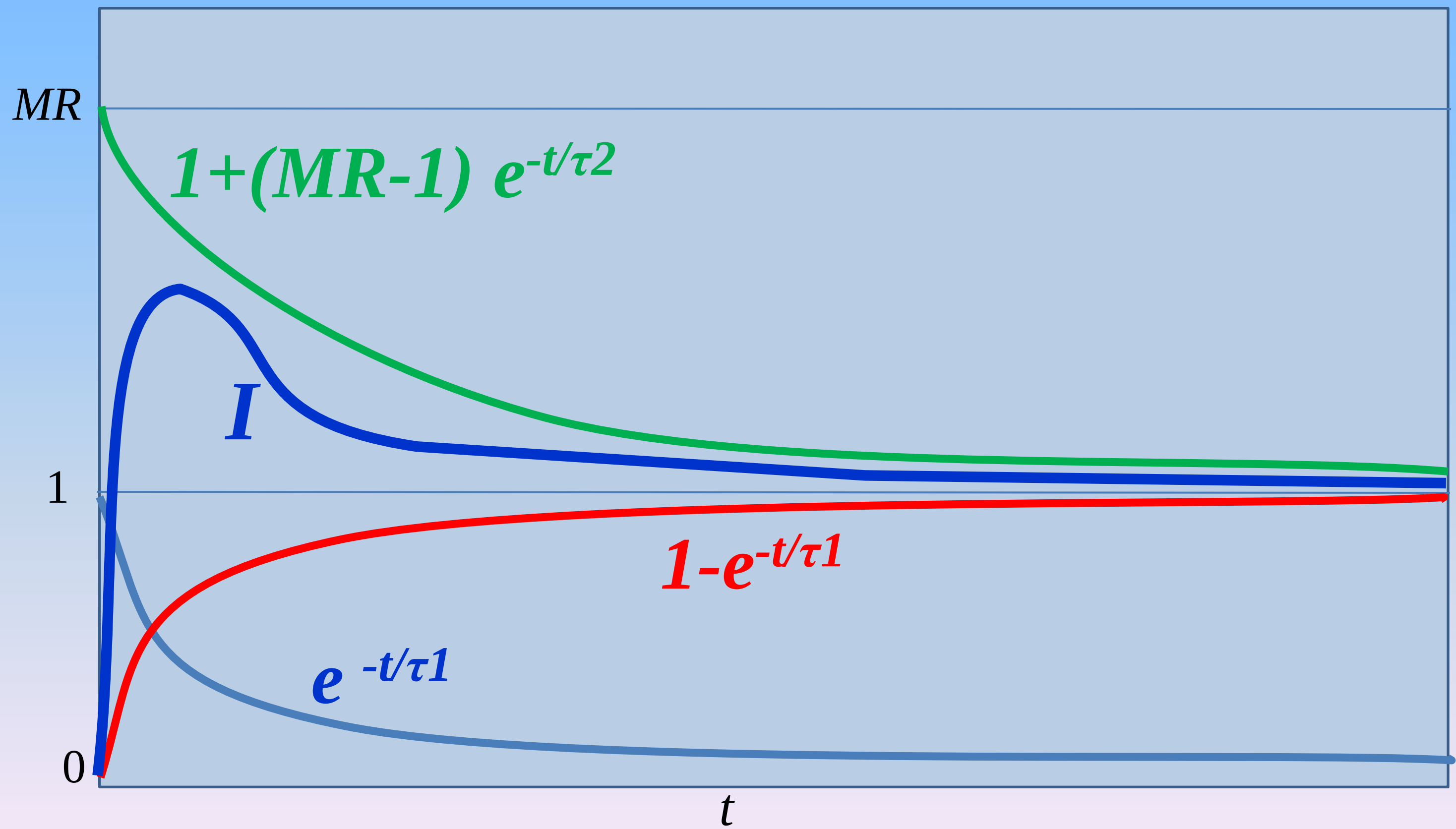
Post-Occlusive Reactive Hyperemia

Model: jump-response after occlusion:
Approximation:

$$I_{approx} = I_{rest}\left(1-e^{-t/\tau_1}\right)\left[1+\left(MR-1\right)e^{-t/\tau_2}\right]$$

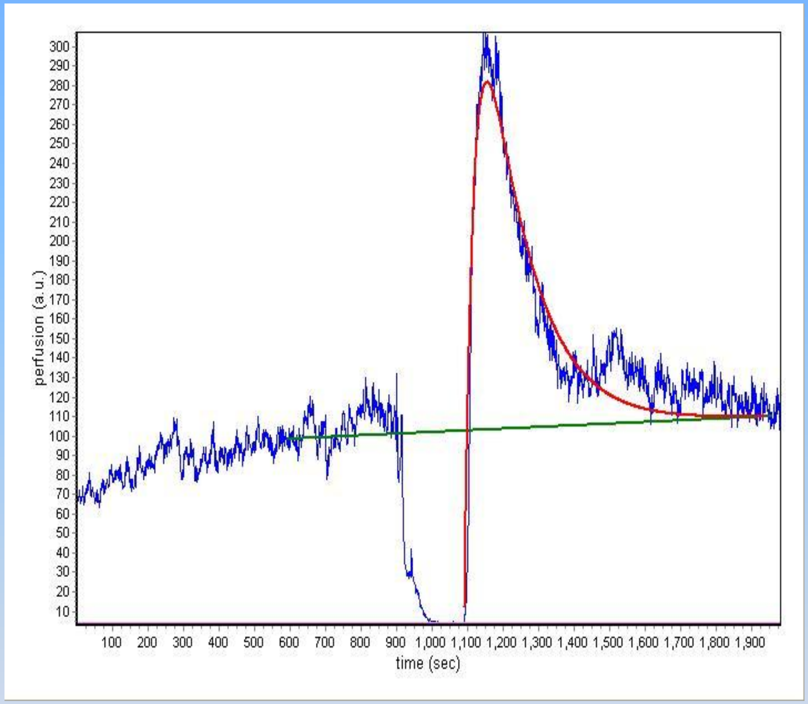
Measured perfusion:
Current I through R_2.

Assume: $\tau_1 << \tau_2$

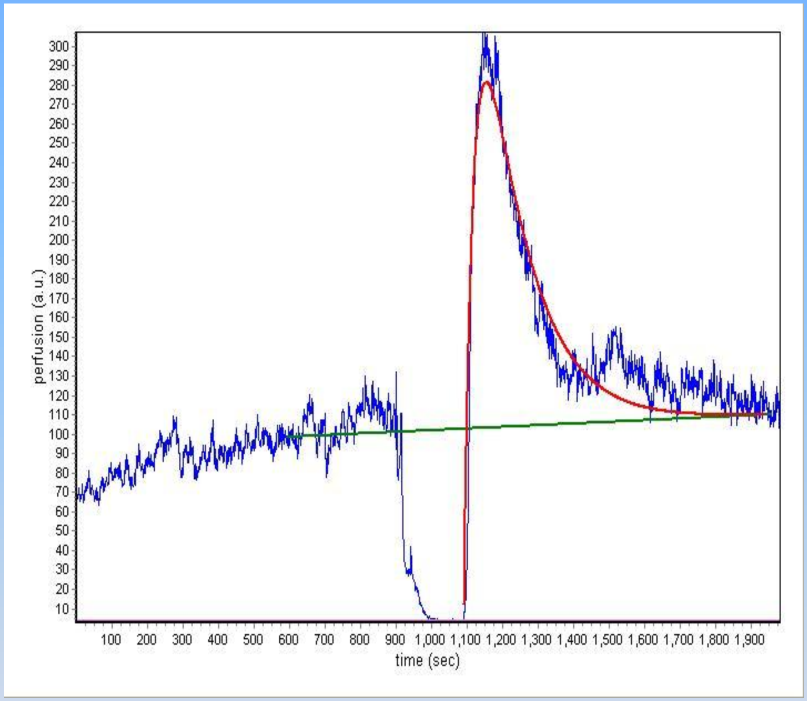


Post-Occlusive Reactive Hyperemia

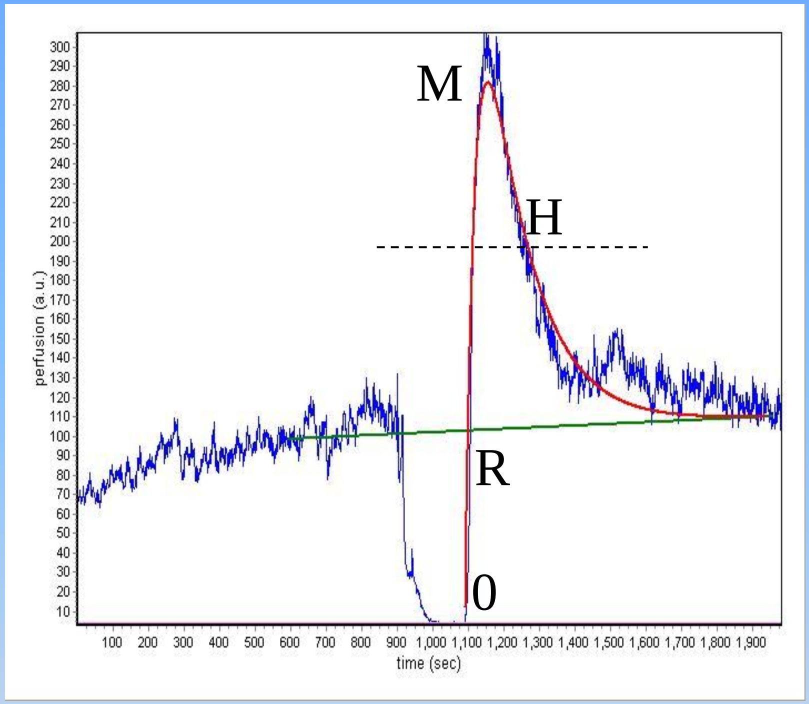
Exact model



Approximation



Post-Occlusive Reactive Hyperemia



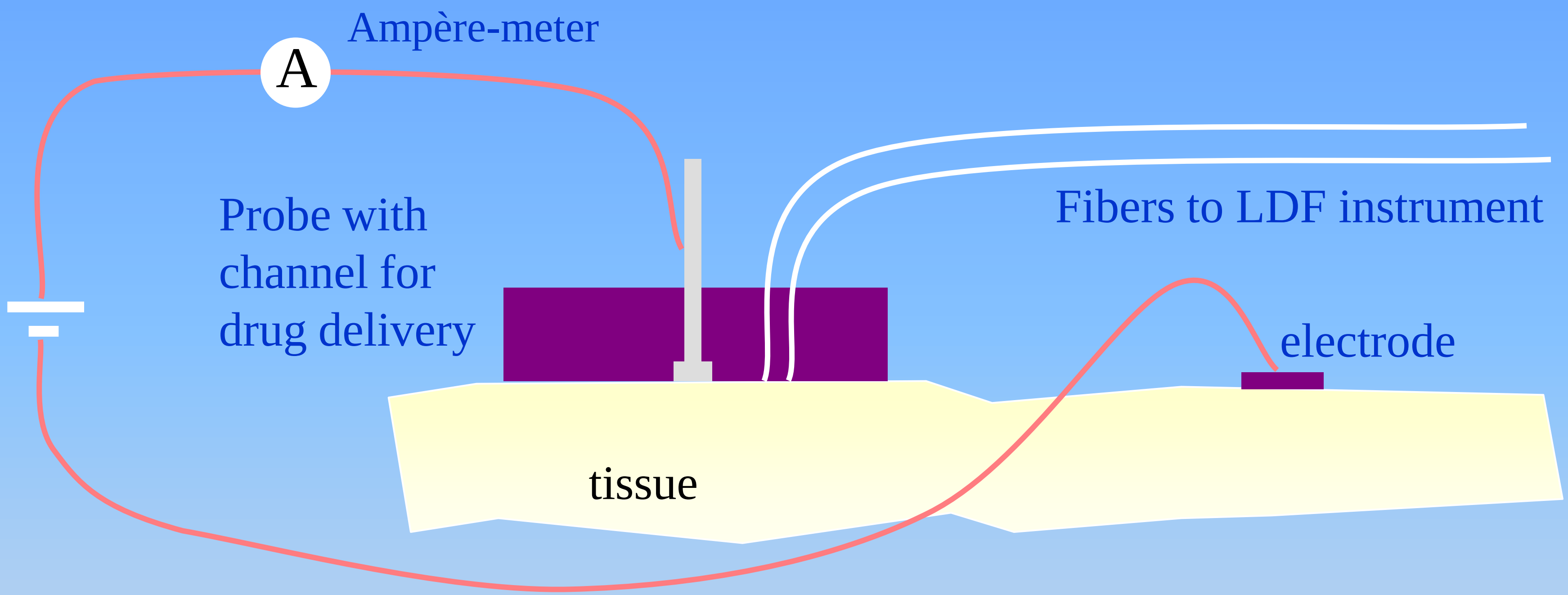
Conclusions from the model:
(times in sec)

	t_R	t_M	t_H	M/R
PAOD	6.5	58	149	3.1
Controls	<0.5	24	74	5.8

(PAOD = post arterial-occlusion disease)

PAOD-patients react much slower after occlusion.
Their reaction amplitude is smaller.

Clinical applications (3): Iontophoresis



Measured:

Influence of drug delivery on flow.

Amp-meter measures amount of injected molecules.

Measure for diffusion coefficient of drug in tissue.

Clinical applications (3): Iontophoresis

Measured:
Influence of drug delivery on flow.
Amp-meter measures amount of injected molecules.

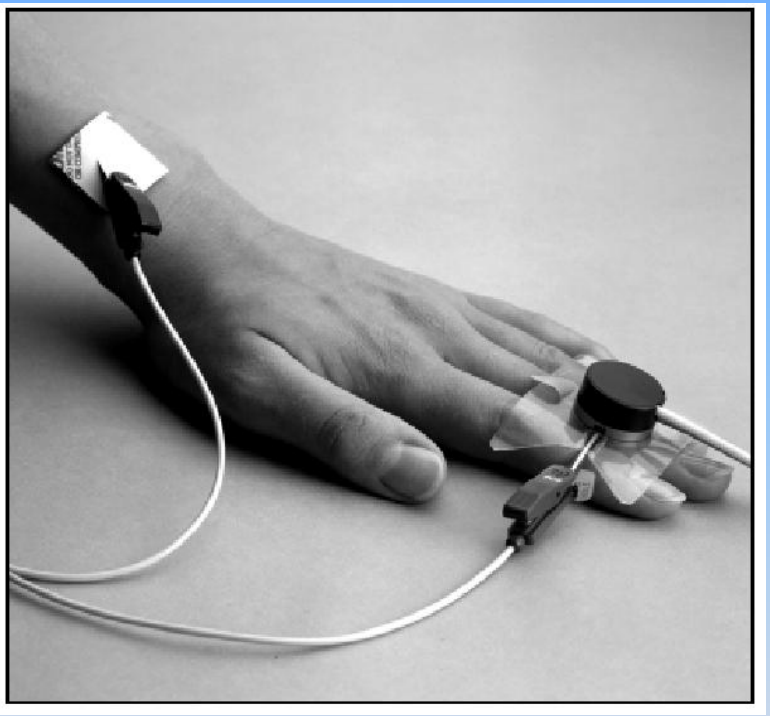
Measure for diffusion coefficient of drug in tissue.

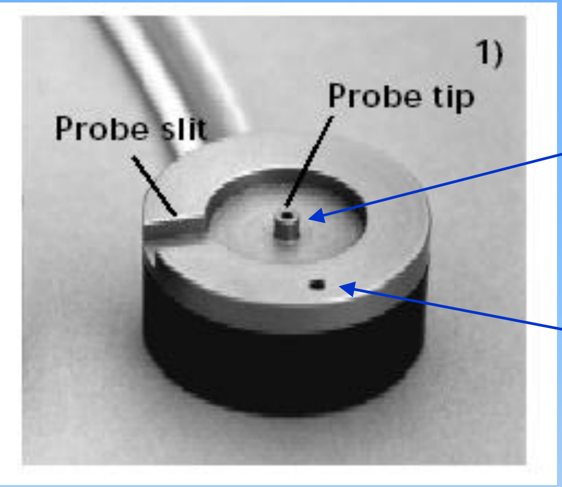
Example:
Women with pre-eclampsia (pregnancy poisoning):
- hypertension, proteinuria, oedema,
- due to endothelial dysfunction, changes in vascular reactivity and permeability for macromolecules

Vasodilatation can be enforced by drugs:
- endothelial-dependent drugs: acetylcholine
- endothelial-independent drugs: nitroprusside

Question: relation between flow change and drug delivery.

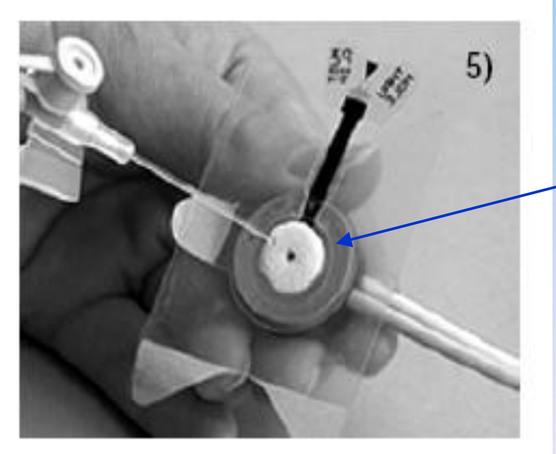
Clinical applications (3): Iontophoresis





LDF-probe (measurement)

LDF-probe (reference)

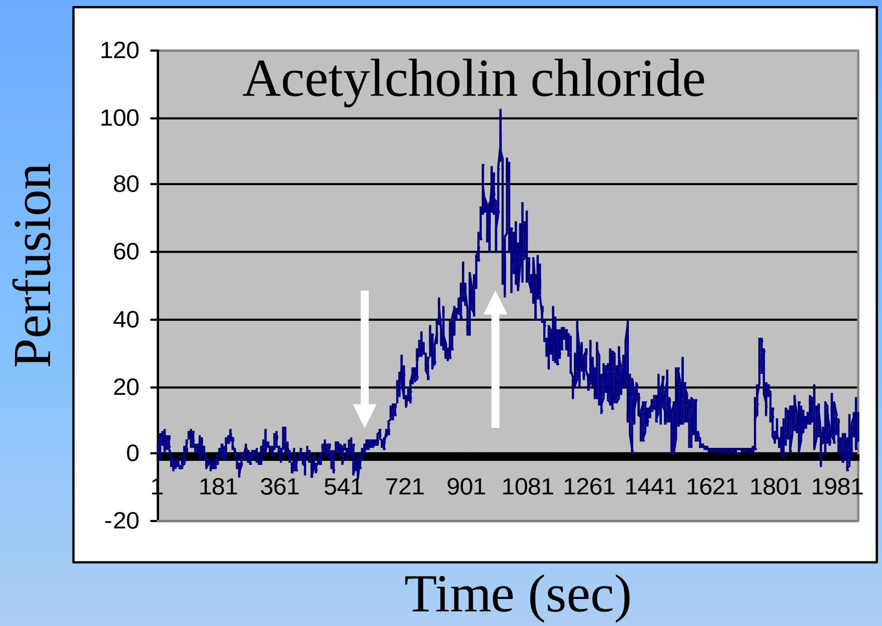


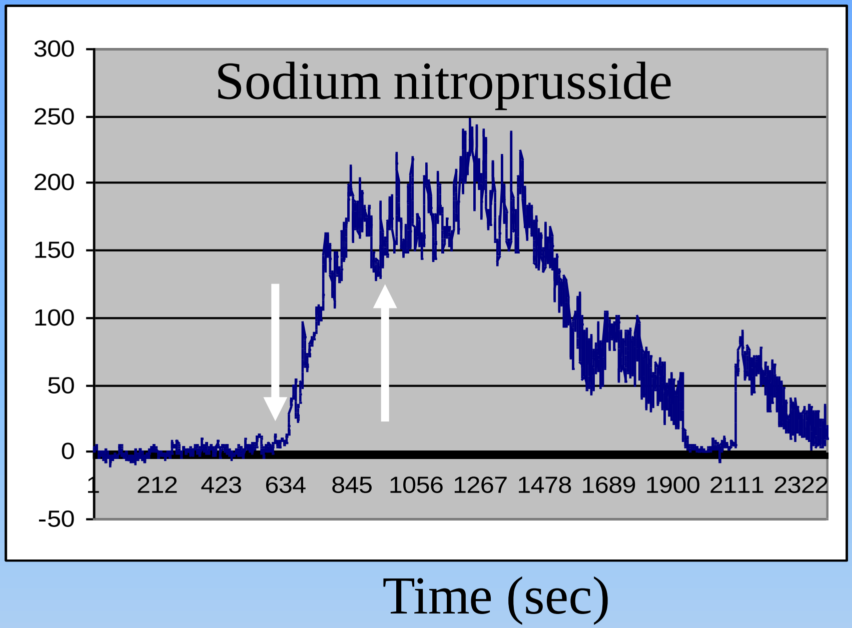
Sponge pad

Clinical applications (3): Iontophoresis

Compounds in iontophoresis	Activity
Capsaicin	Neuropeptides
(Nor)epinephrine hydrochloride	Vasoconstrictor
Sodium nitroprusside	Vasodilator, to smooth muscle walls
Acetylcholin chloride	Vasodilator, activating endothelial vessel cells
Histamine	Oedema and vasodilation

Clinical applications (3): Iontoforesis





5 Shots: Start (↓) at 600 sec, duration 20 sec each, intervals 90 sec
End (↑) at 960 sec

At end of recording: arterial occlusion.

Shown signal = measuring probe – reference probe

Acetylcholine washes out faster, due to vasodilation, especially with women with pre-eclampsia.

LD - Diffusion model for Iontophoresis

1. 1-Dimensional diffusion : c = concentration

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial z^2}$$

D = diffusion constant

$$c(z,t) = \frac{Q}{\sqrt{\pi D t}}\exp\{-\frac{z^2}{4Dt}\}$$

2. Decrease too slow: add decay term: $-\lambda c$

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial z^2} - \lambda c$$

λ = decay constant

$$c(z,t) = \frac{Q}{\sqrt{\pi D t}}\exp\{-\frac{z^2}{4Dt} - \lambda t\}$$

3. Assume: N shots with interval Δt

$$\Delta F(t) = \sum_{n=1}^{N}\exp[-(n-1)s]\ \frac{Q_0}{\sqrt{\pi D t_n}}\ \exp\left(-\frac{z^2}{4Dt_n} - \lambda t_n\right)$$

$$t_n = t - (n-1)\Delta t$$

s = shot saturation constant;

if $s = 0$: all shots contribute equally

if $s >> 1$: only first shot contributes

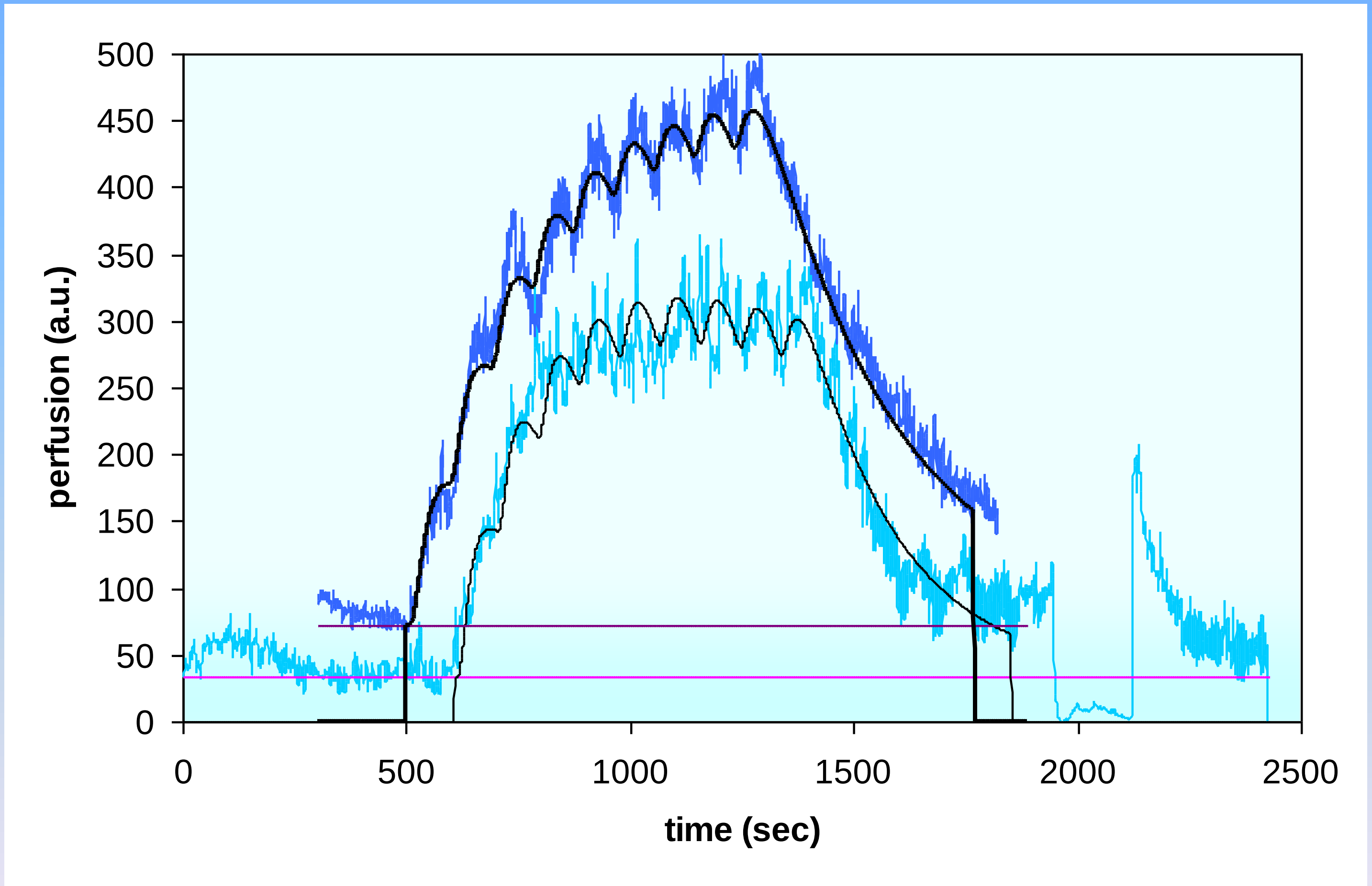
Assume: excess (*) flow $\Delta F(t)$ ~ concentration

(*) = above resting flux level.

LD - Diffusion model for Iontophoresis

Fit results (2 Pre-eclampsia patients; SNP-administration):

9 shots; 90 sec. apart.



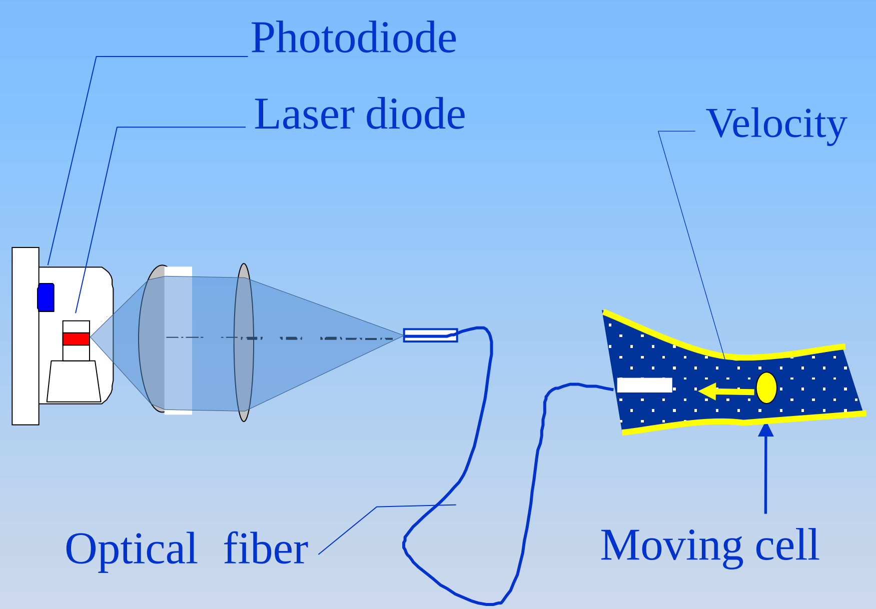
,

Parameters: χ_{2red} = 1.15; $\tau 1$ = 76 ± 10 s ; $\tau 2$ = 408 ± 30 s ; s = 0.029 ± 0.014

χ_{2red} = 1.90; $\tau 1$ = 65 ± 12 s ; $\tau 2$ = 252 ± 30 s ; s = 0.048 ± 0.028

SM-LDV: Self-mixing (1)

(C) Self-mixing Laser Doppler Velocimetry: Principle

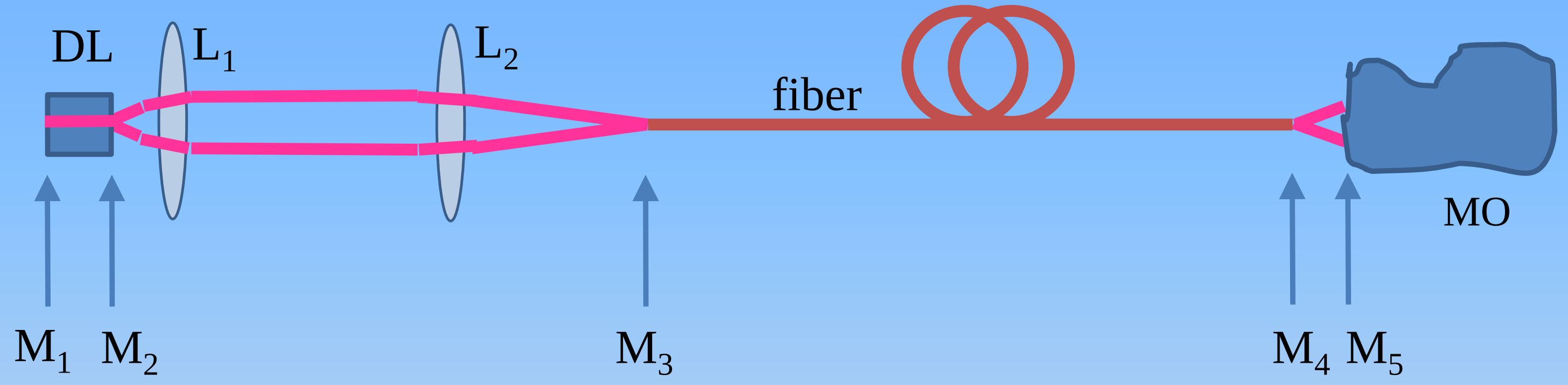


Principle:

- laser light reflected/scattered by moving blood cells,
- partly back-reflected into laser cavity,
- with Doppler-shifted frequency,
- in cavity: mixing with "original" light,
- Doppler signal results,
- can be measured with photodiode

SM-LDV: Self-mixing (2)

(C) Self-mixing Laser Doppler Velocimetry: Principle



Five-mirror setup:

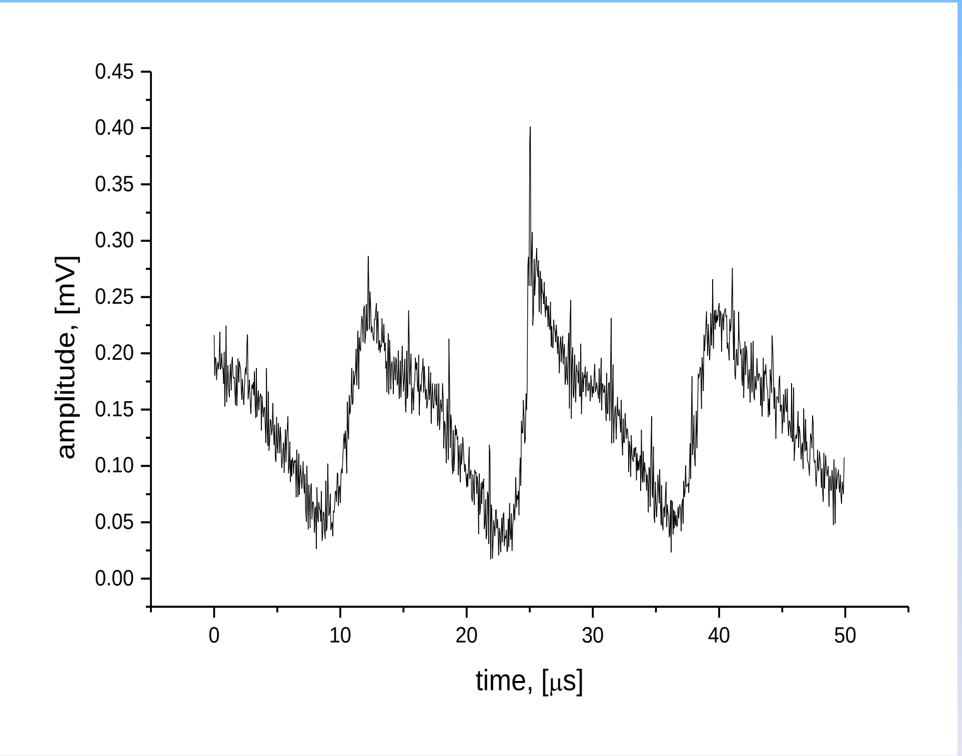
- M_1 and M_2 : facets of laser crystal
- M_3 and M_4 : facets of fiber
- M_5 : reflection at / scattering in moving object MO

MO: moving object
L_1 and L_2 : lenses
DL: diode laser + photodiode

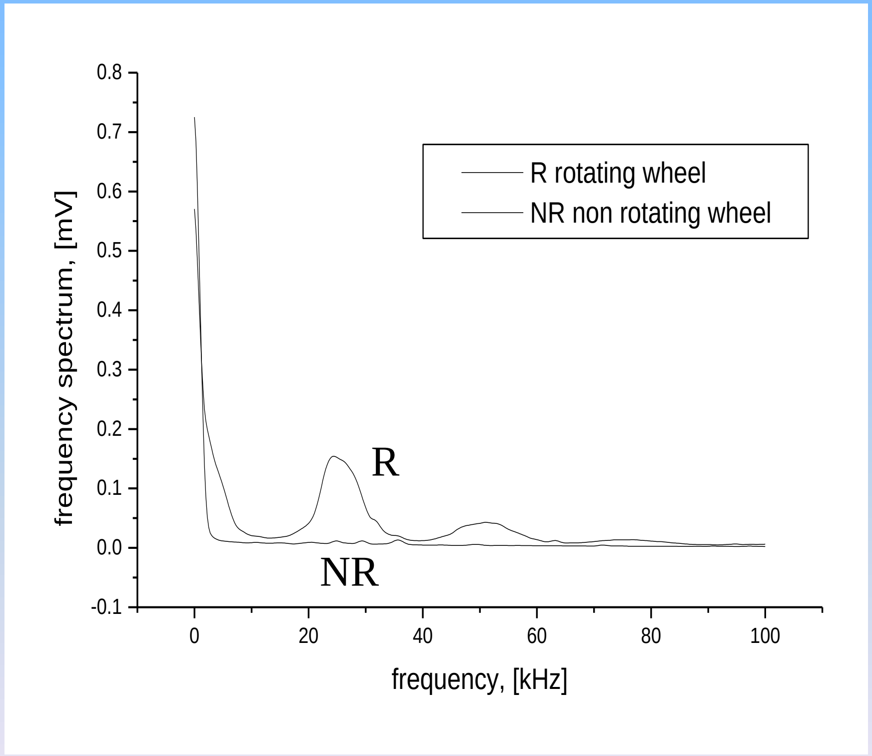
SM-LDV: Self-mixing (3)

(C) Self-mixing Laser Doppler Velocimetry: Principle

Time signal

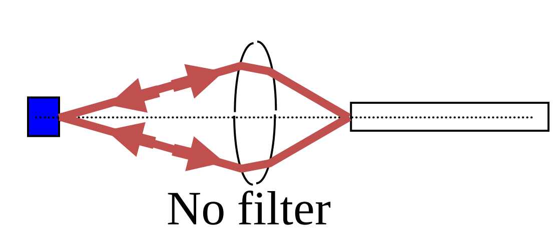


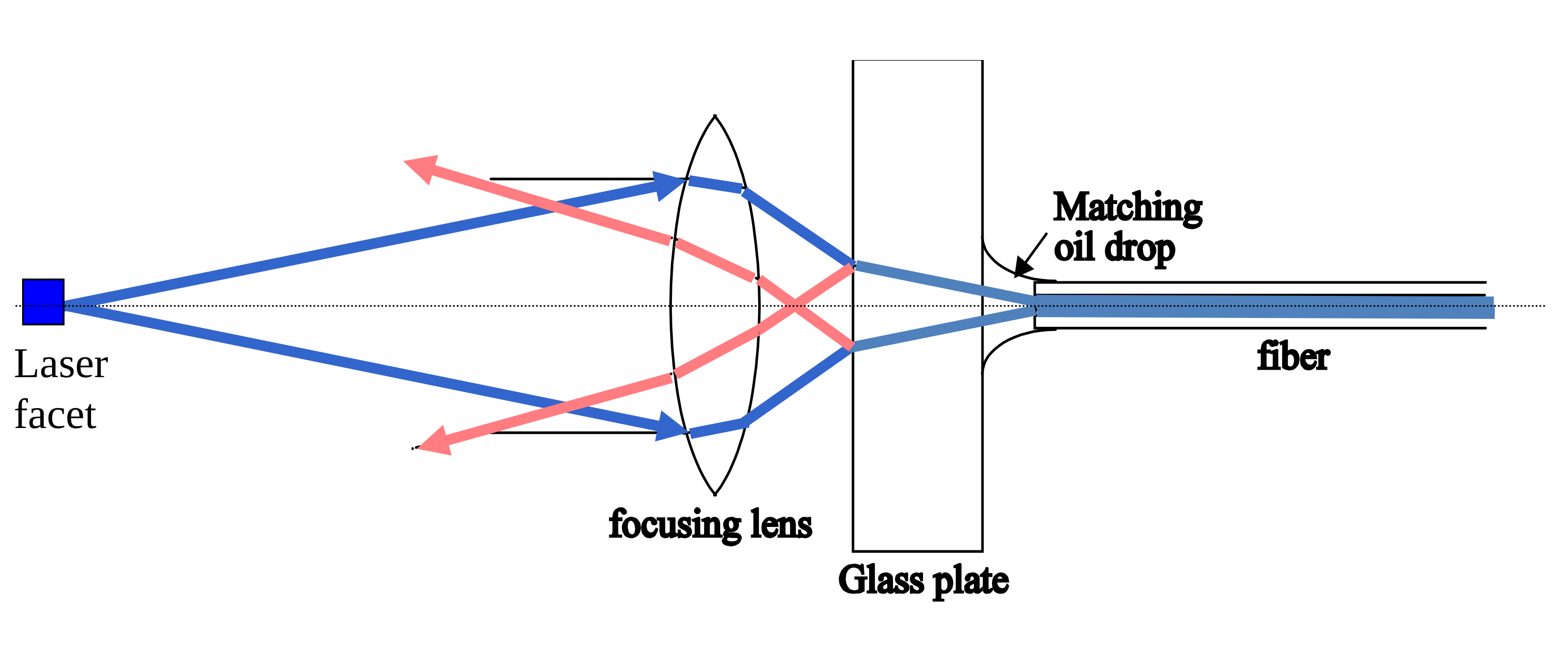
Frequency signal



SM-LDV: Self-mixing (4)

(C) Self-mixing Laser Doppler Velocimetry:
Filter for directly reflected light



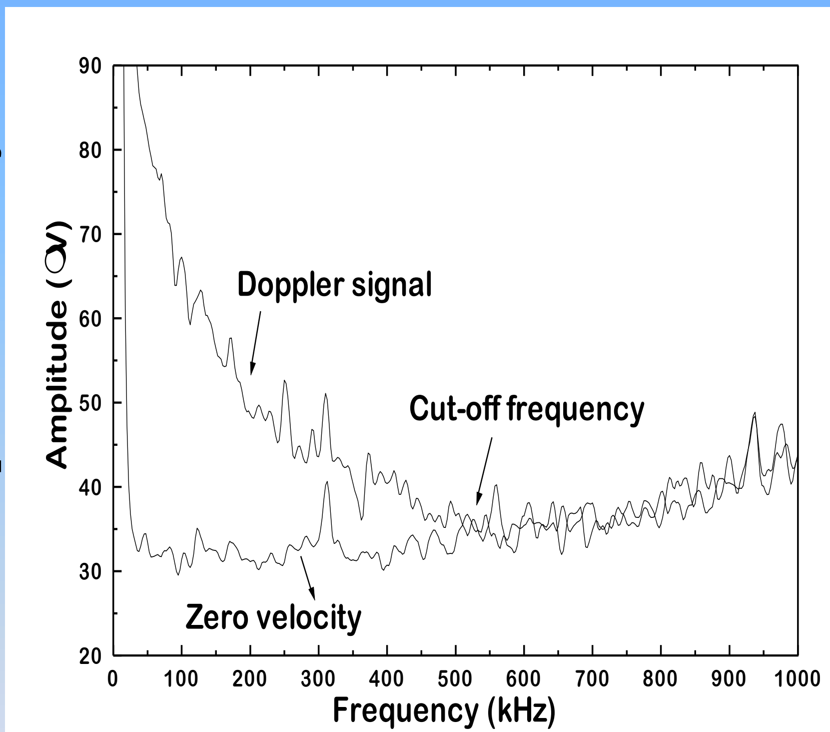


Reflected light will not be focussed onto laser crystal facet.
Only light returning through the fiber will be fed back into the laser cavity.

SM-LDV: Self-mixing (5)

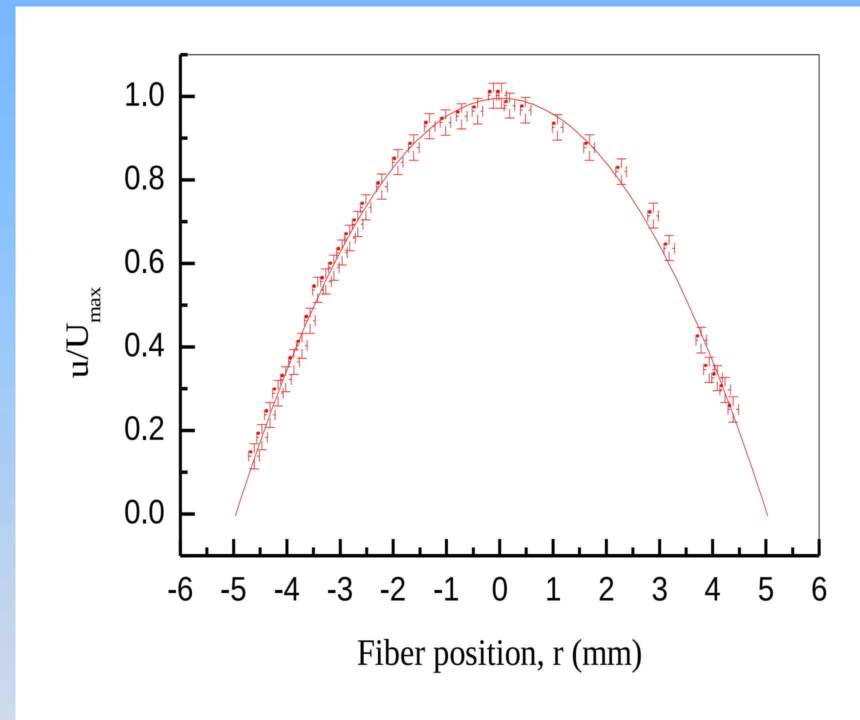
(C) Self-mixing Laser Doppler Velocimetry

Spectral intensity



Frequency / kHz

Liquid flow: Cut-off frequency provides maximum flow velocity

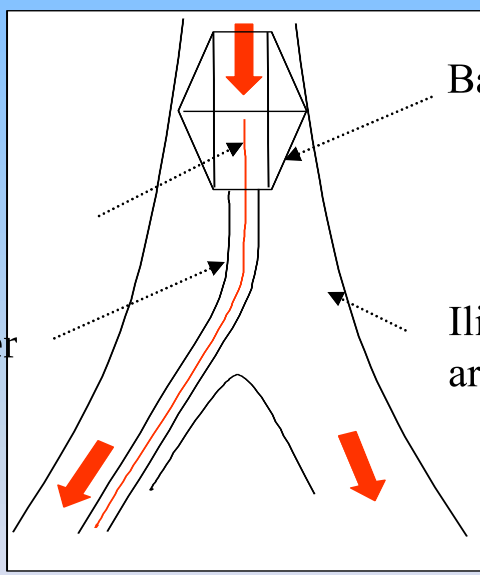


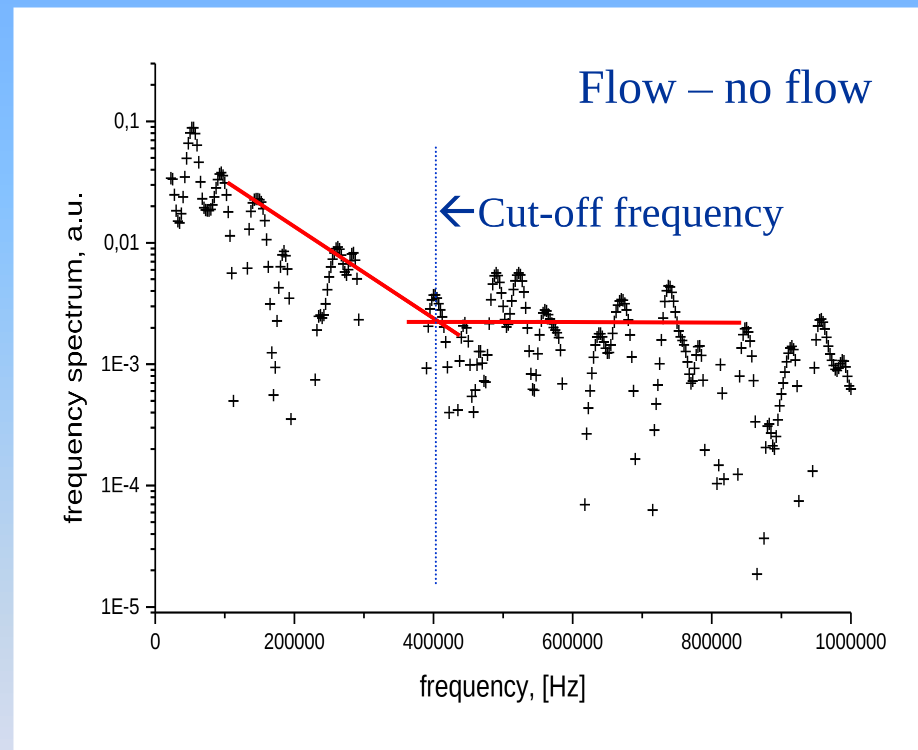
Flow profile in whole milk, normalised on maximum value

SM-LDV: Self-mixing (6)

(C) Self-mixing Laser Doppler Velocimetry

Branching in iliac artery of healthy pig



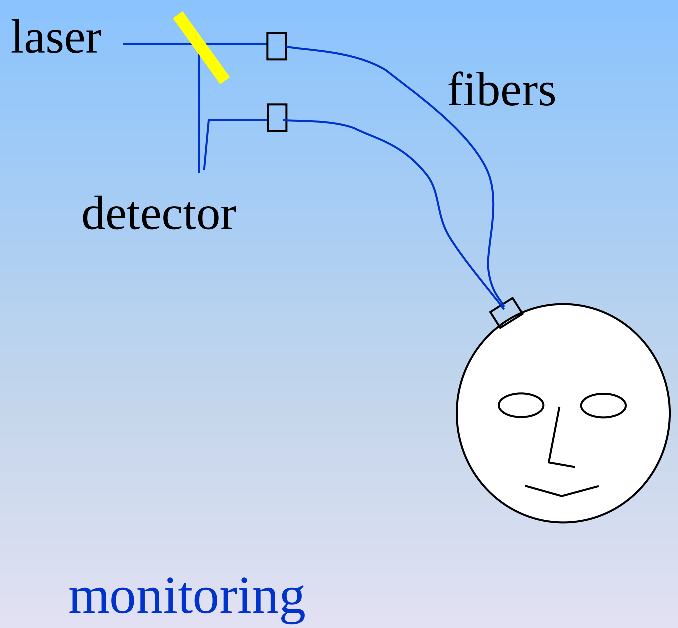


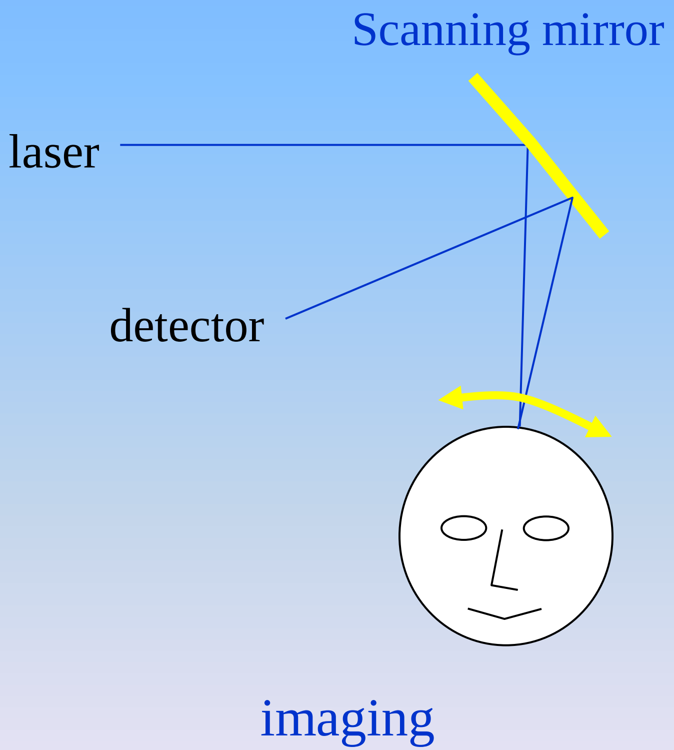
Cut-off frequency at 400 kHz corresponds with a velocity of 16 cm/s.

(Independent measurement using an electromagnetic probe: 14.5 ± 1.0 cm/s)

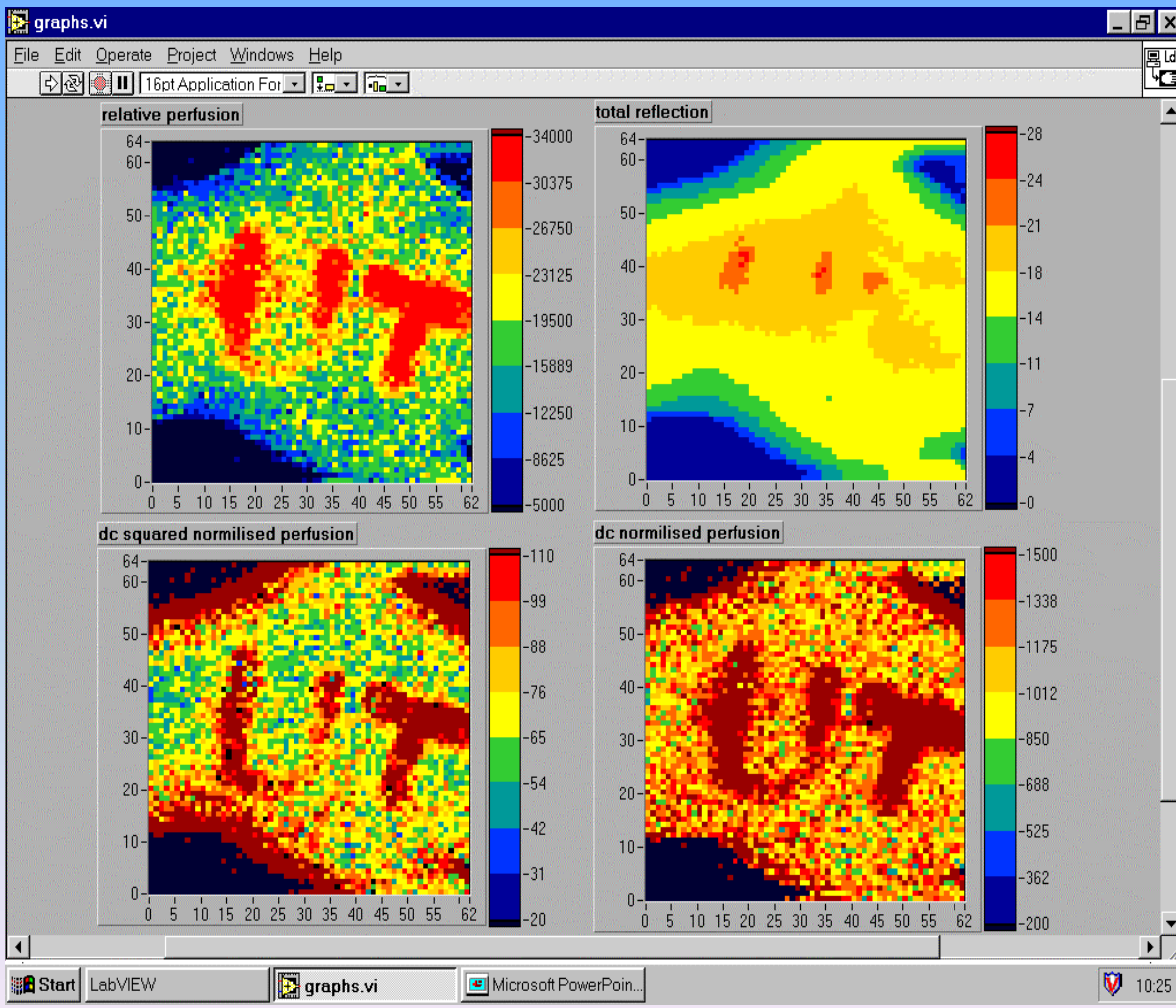
Laser Doppler Perfusion: Monitoring vs. Imaging

Scattering at moving cells causes Doppler frequency shift





Laser Doppler Perfusion (Imaging)



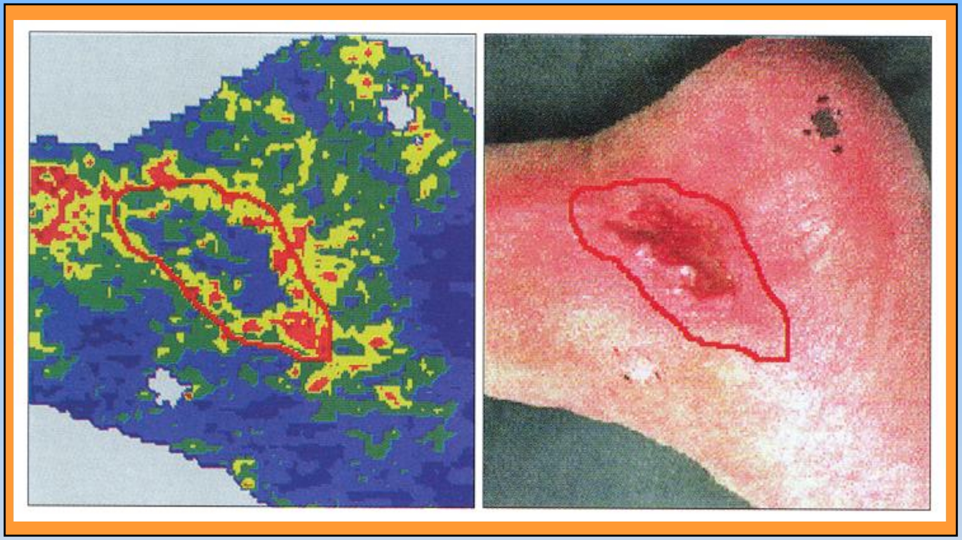
Superficial perfusion of the dorsal side of the hand,

characters UT written using muscular balm.

Upper left: perfusion, not normalized;
Upper right: DC-reflection from tissue;
Lower left: perfusion, normalized with DC
Lower right: perfusion, normalized with DC^2 .

Laser Doppler Perfusion (Imaging)

Perfusion Image of a foot ulcer



Typically the highest perfusion is in the boundary around the ulcer, in inflammatory skin and in granulating tissue inside the ulcer area.

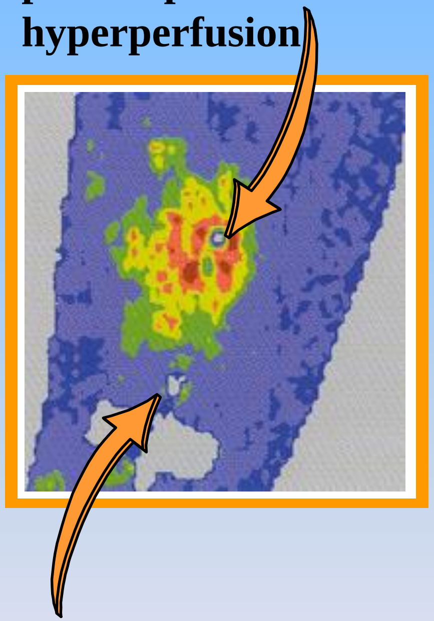
From: Bornmyr, "Laser Doppler flowmetry and imaging - methodological studies. Dep of clinical hysiology",thesis, Malmö, Sweden (1998);
Figure: courtesy: prof. G. Nilsson, Lisca, Linkoping, Sweden)

Laser Doppler Perfusion (Imaging)

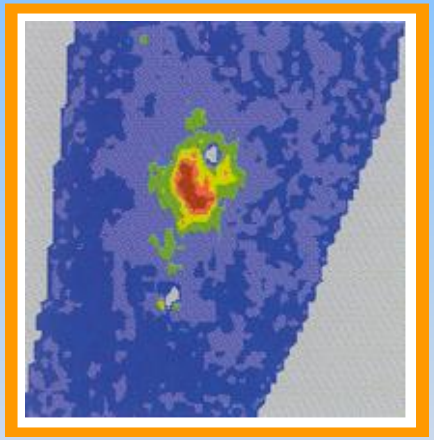
The effect of micro-trauma

The dialysis fibre probe tip causes hyperperfusion

Insertion of a micro-dialysis fibre into the skin.



No hyperperfusion at the point of introduction because the skin is anesthetized.



After 30 minutes the hyperperfusion is reduced.

(Courtesy: Lisca Sweden)

Laser Doppler Perfusion (Imaging)

Basal cell carcinoma

(Courtesy: Lisca Sweden)

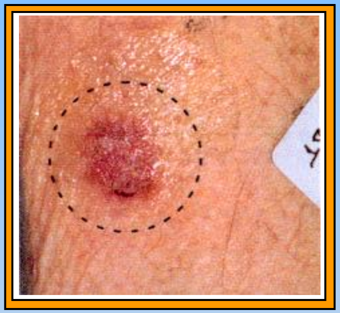
Before treatment

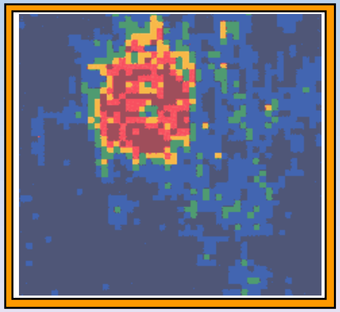
After treatment

Immediately

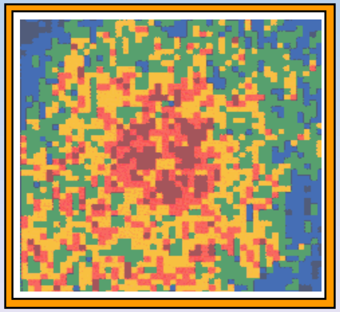
One week

8.5 months later

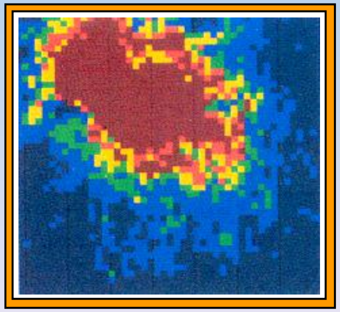




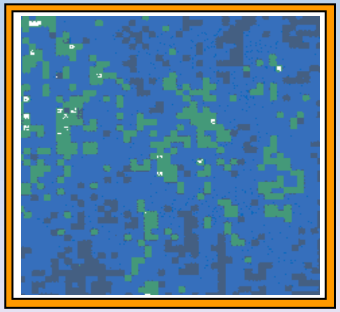
Neo-vascularisation in tumour area.



Inflammatory response.



Inflammatory response with excessive perfusion.



Back to normal.

Laser Doppler Perfusion (Imaging)

Flow-Maps of a Healing Wound

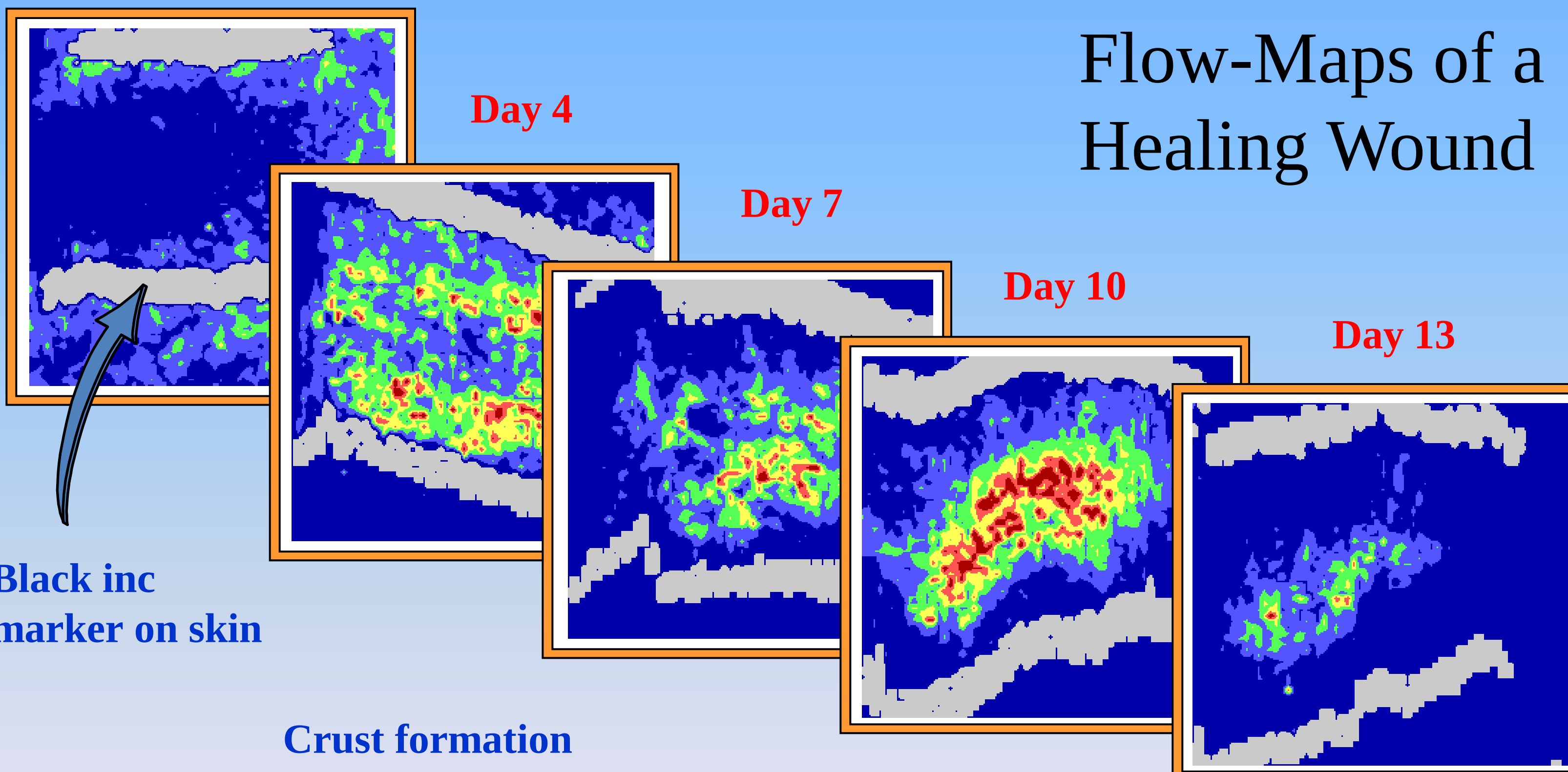
Day 1: wound creation

Day 4

Day 7

Day 10

Day 13



Black inc marker on skin

Crust formation in centre of wound

Crust off

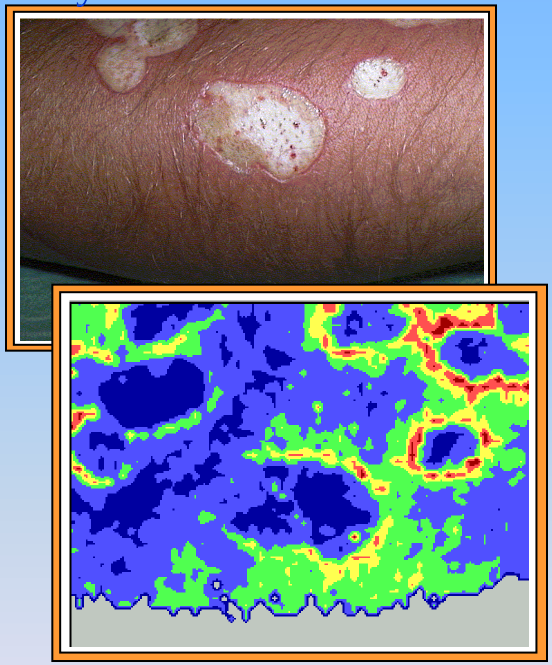
Perfusion returning to normal

(Courtesy: Lisca Sweden)

Laser Doppler Perfusion (Imaging)

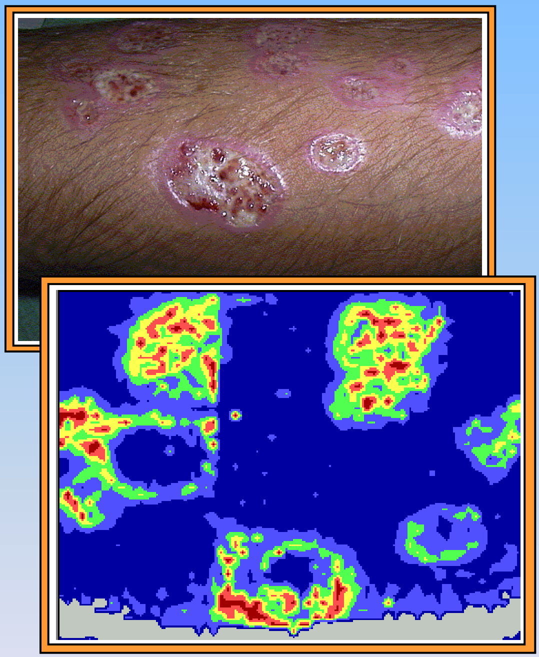
The healing process of a burn wound

Day 2

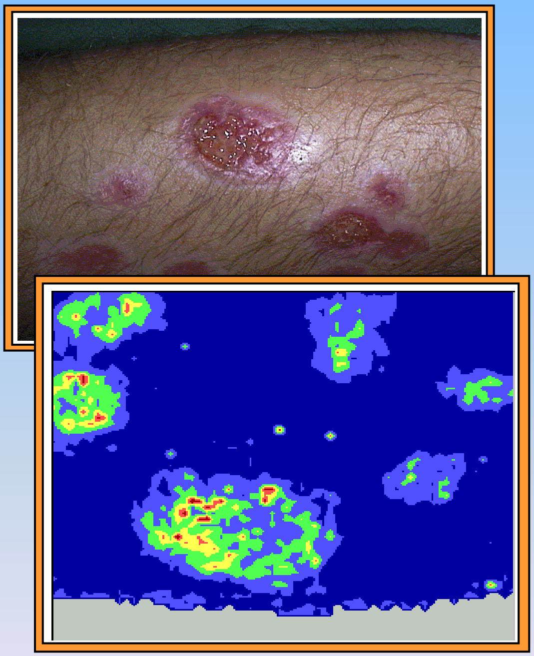


Reduced perfusion
in burnt areas.
Increased perfusion
in surrounding skin.

Day 13



Day 28

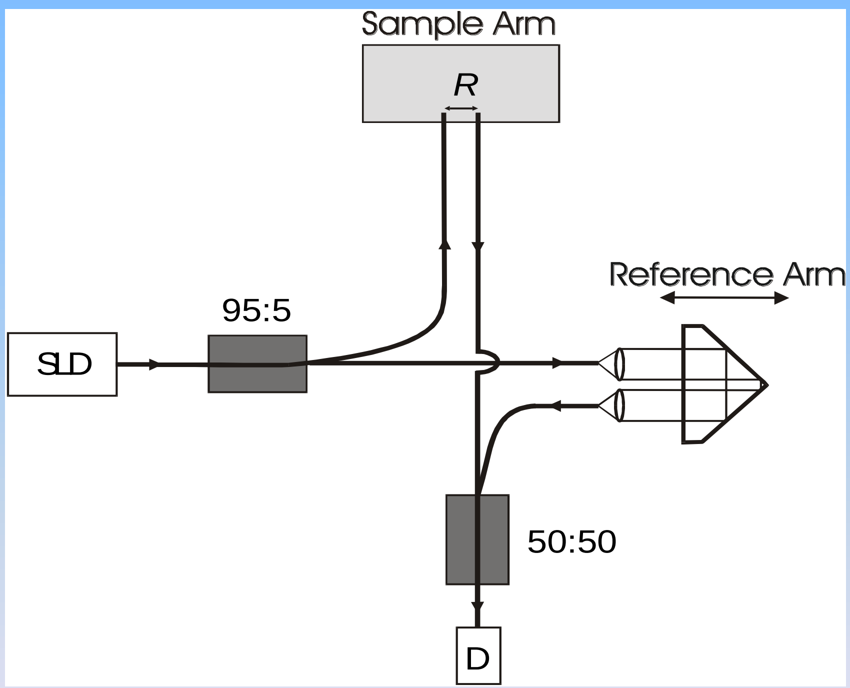


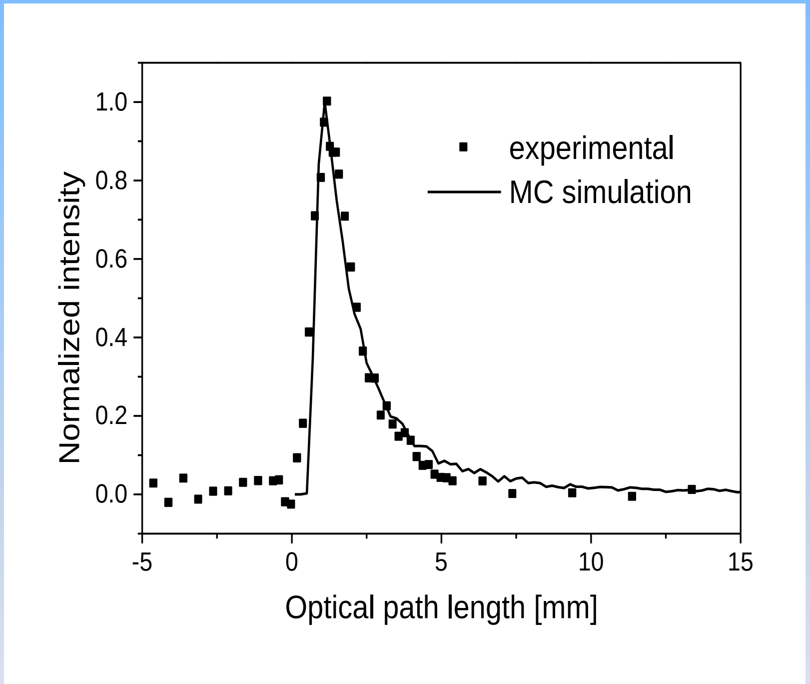
Towards normalisation.

(Courtesy: Lisca Sweden)

Laser Doppler Perfusion (Monitoring)
New developments

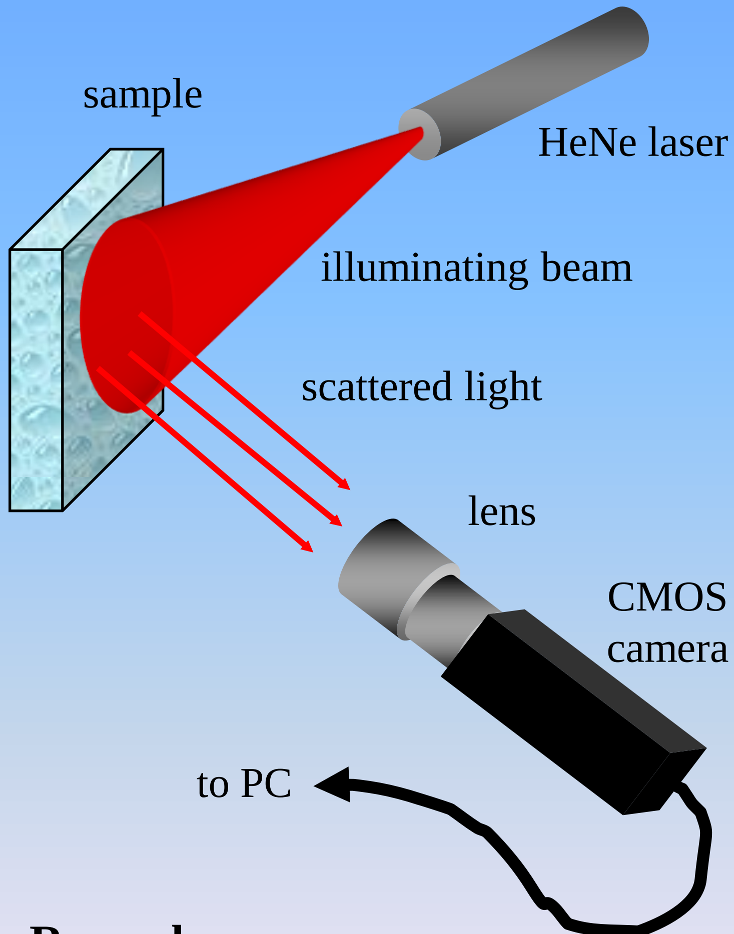
Low-coherent depth-sensitive LD-Monitoring





The reference mirror selects the depth in the sample from which a coherent Doppler-shift signal will be measured.

Laser Doppler Perfusion (Imaging)
New developments:



Imaging using CMOS camera

Advantage of CMOS over CCD camera:

CCD: serial read-out of collected photons
using shift registers
=> slow read-out
=> no dynamic response possible

CMOS: each pixel can be addressed separately,
enables fast dynamic 2D-response

Advantage of CMOS over scanning detector:

Scanning detector:
= measures dynamic signal
= slow imaging due to scanning

Remarks:

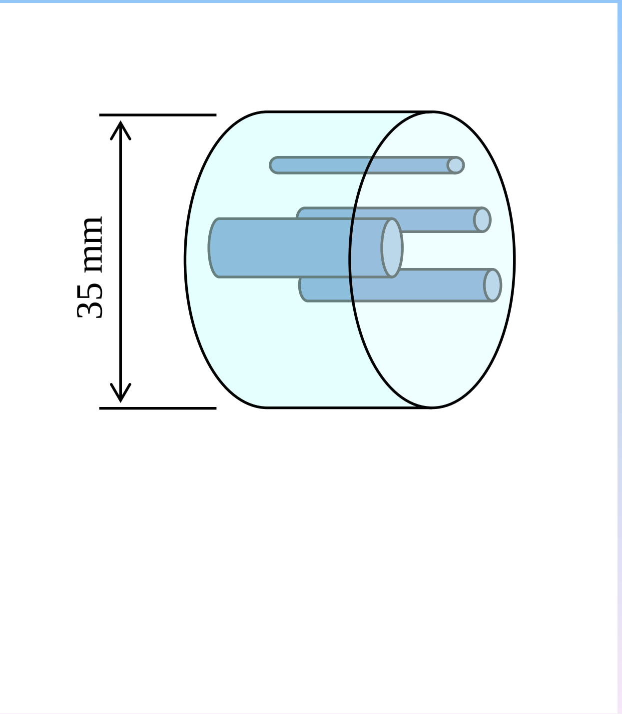
- Beam diameter on the sample.....±5 cm
- Sample-to-camera distance..........60cm

Laser Doppler Perfusion (Imaging)

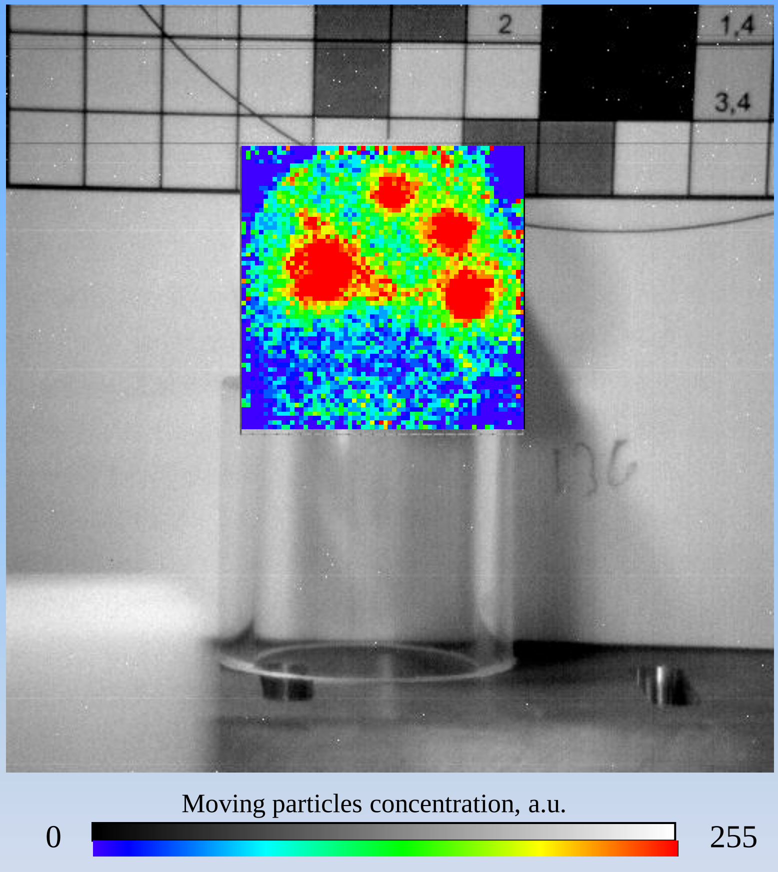
New development:

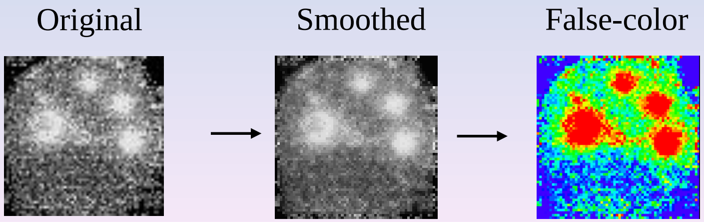
Imaging using CMOS camera

Sample : Plastic box with 4 cylindrical holes filled with *Intralipid*™ (moving particles)



Full frame

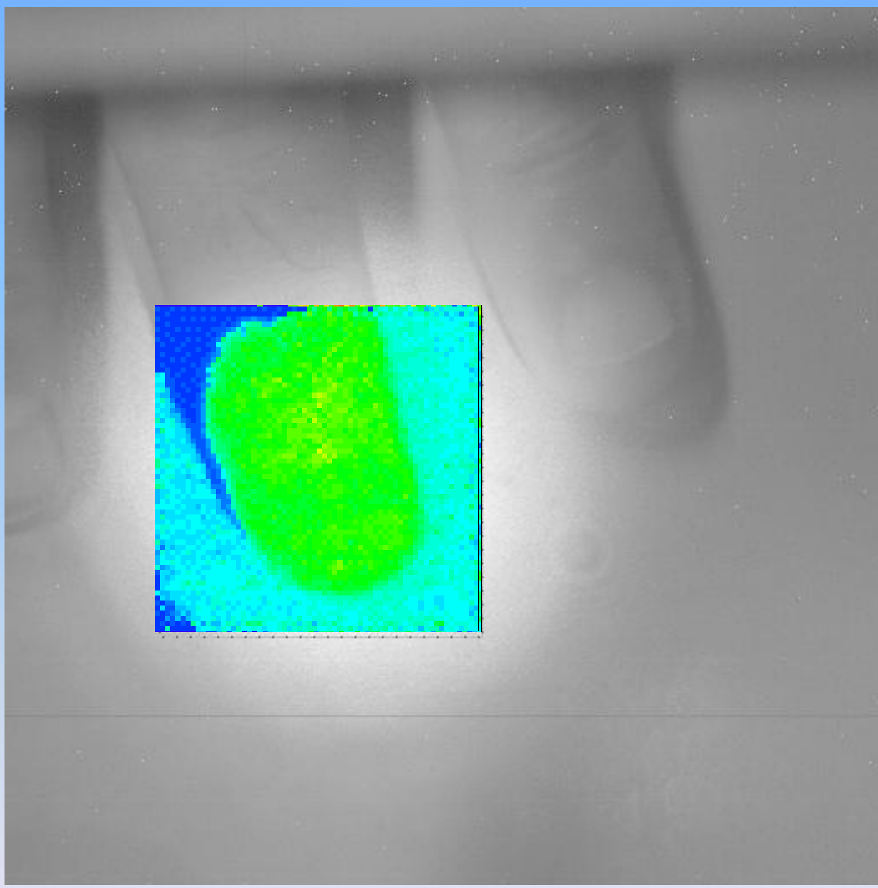


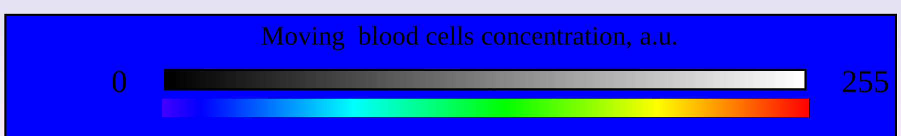


Laser Doppler Perfusion (Imaging)

New development:

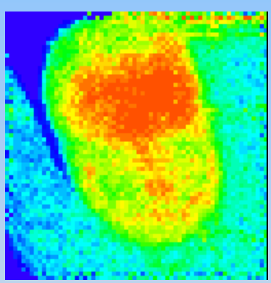
Imaging using CMOS camera



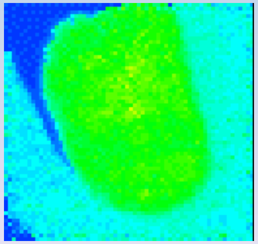


Before image processing

After image processing



No occlusion



Occlusion

Laser Doppler Velocimetry

Summary:

1. LD for blood perfusion
   - Principles
   - Monitoring
   - Imaging
2. Self-mixing LD
   - Principles
   - Experimental aspects
   - Flow velocities
   - Intra-arterial use

The End