Laser-Doppler Blood Perfusion Flowmetry for studying Post-Occlusion Reactive Hyperaemia and Drug Administration by Iontophoresis

Frits F.M. de Mul

Kolff Institute – Dept. Biomedical Engineering
University Medical Center Groningen
Groningen, the Netherlands

Biomedical Optics group,
Department of Applied Physics,
University of Twente, Enschede, the Netherlands

Contents:

1. Principles of Laser-Doppler Blood Perfusion Monitoring

2. Model for Post-Occlusion Reactive Hyperaemia (PORH) to study
   Peripheral Arterial Occlusive Disease (PAOD)

3. Model for Drug Administration using Iontophoresis

Publications: see website:
www.demul.net/frits, scroll to “Laser Doppler”.

LDV: Principles

Principle of
Laser-Doppler Blood Flow Perfusion Monitoring in Tissue

- A **laser beam** with pencil shape will be **scattered**
- by **structures** (particles, cells, vessels, ...) in tissue.

- If these structures have a **velocity**
- the scattered light will get a slight **Doppler frequency shift**.

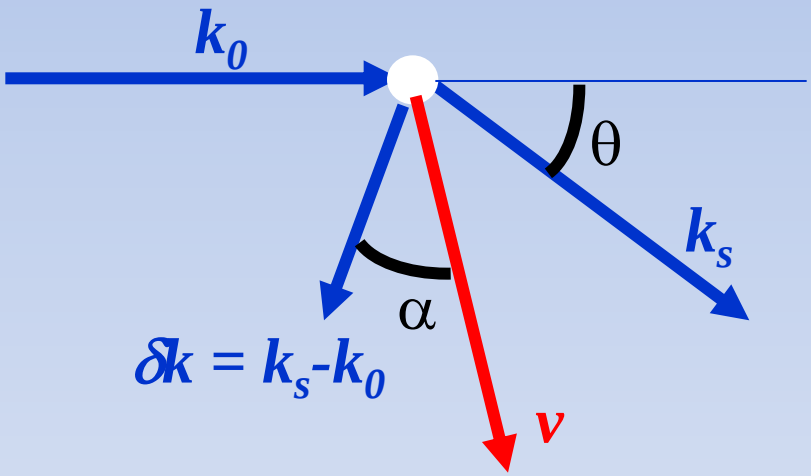
- This shift can be measured by **mixing** the emerging light
- with the original **incident** light.

- The shift is **proportional** to the averaged (*) particle **velocity**
- and the **amount** of scattering particles involved.

- (*) “averaged”: over directions and magnitudes of particle velocities

LDV: Principles

Principle of laser Doppler:



v : particle velocity

k_0 and k_s :
incoming and scattered wavevectors
$k = 2\pi/\lambda$; λ = wavelength

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

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

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

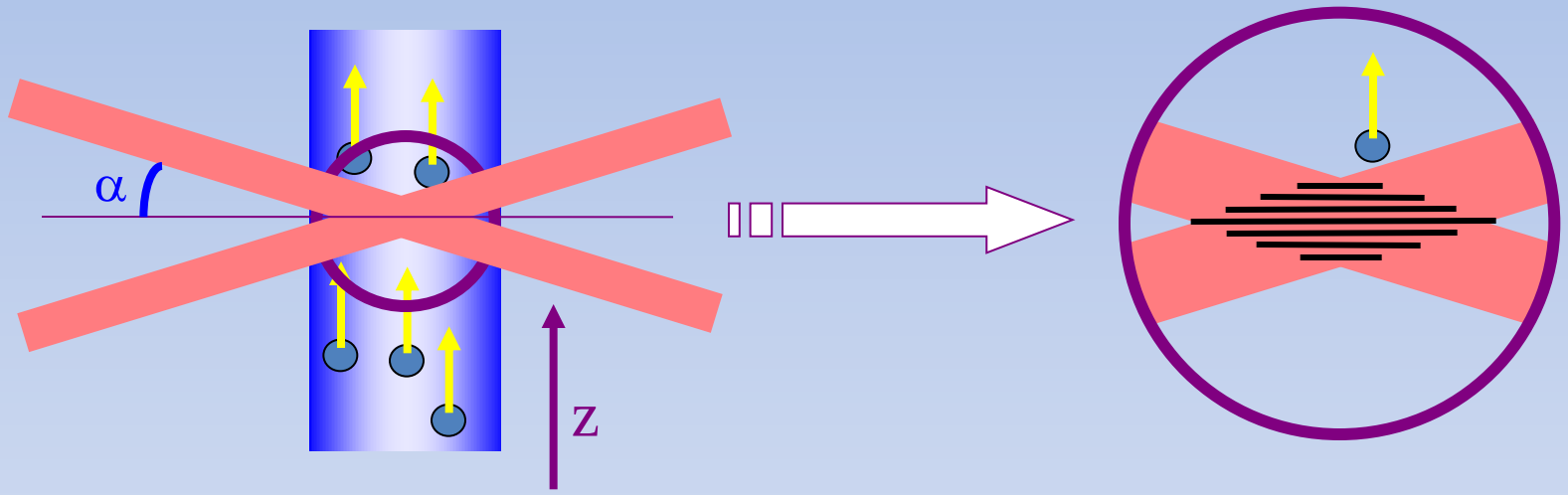
Normally in tissue: θ is small : $<\theta>$ $< \approx 10^o$

➔ approx.: $\delta k \perp k_0, k_s$: only v-component $\perp k_0$ measured

LDV: Types of Instruments (1)

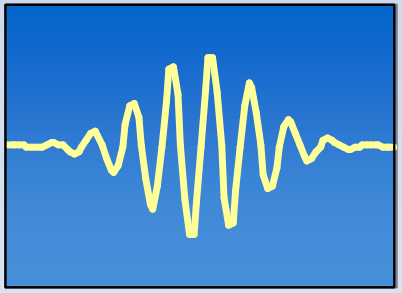
(A) Differential (Dual-beam) Laser Doppler Velocimetry

Interference fringe pattern



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

Scattered intensity burst



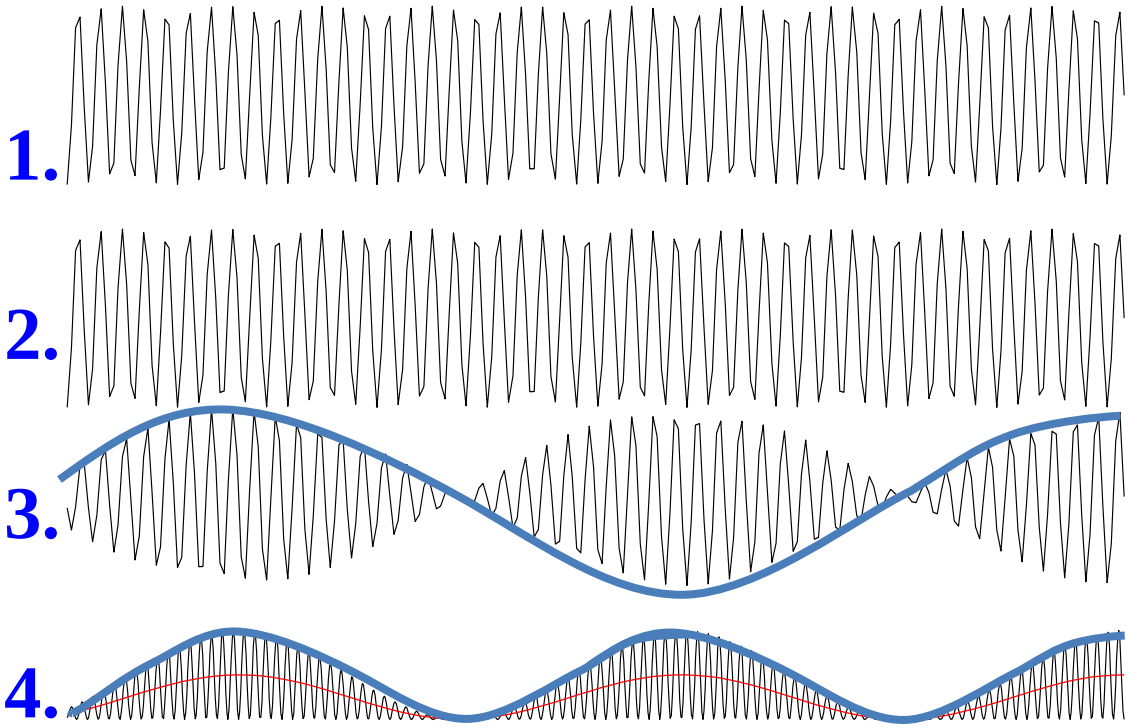
Detection preferentially in forward direction

Doppler frequency

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

LDV: Types of Instruments (2)

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



1. Original frequency
ω [$\approx 10^{14}$ Hz]

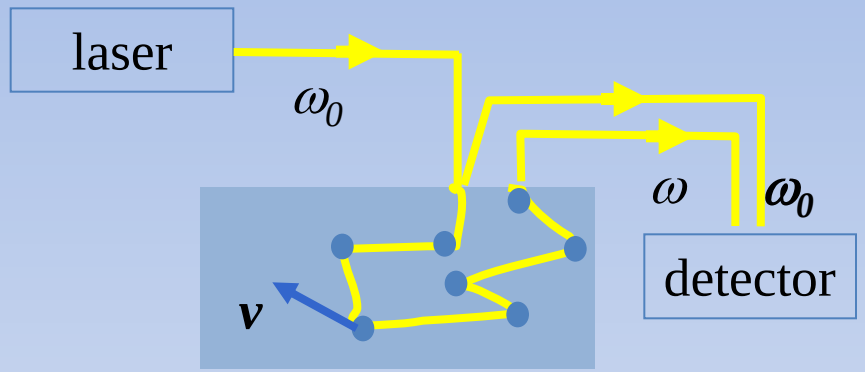
2. Doppler-shifted frequency
$\omega + \omega_D$ [$\approx 10^{14}$ Hz]

3. Doppler frequency
ω_D [$<\approx$ 20 kHz]

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

LDV: Types of Instruments (3)

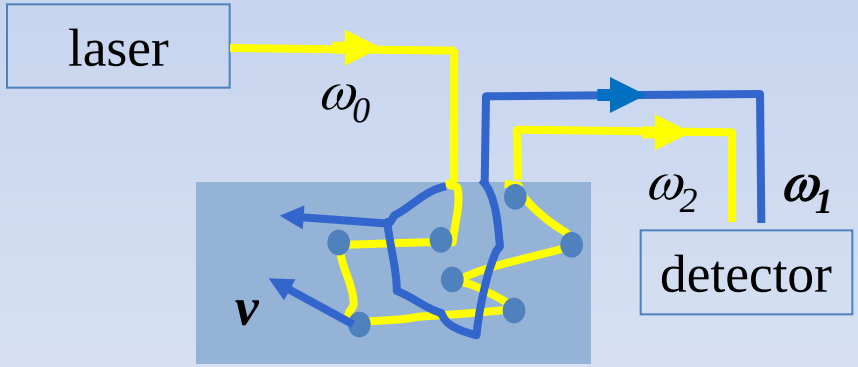
(B) Laser Doppler Perfusion Velocimetry



Averaged Doppler frequency: $\Delta\omega$

Heterodyne mixing

$\Delta\omega = \omega - \omega_0$



Homodyne mixing

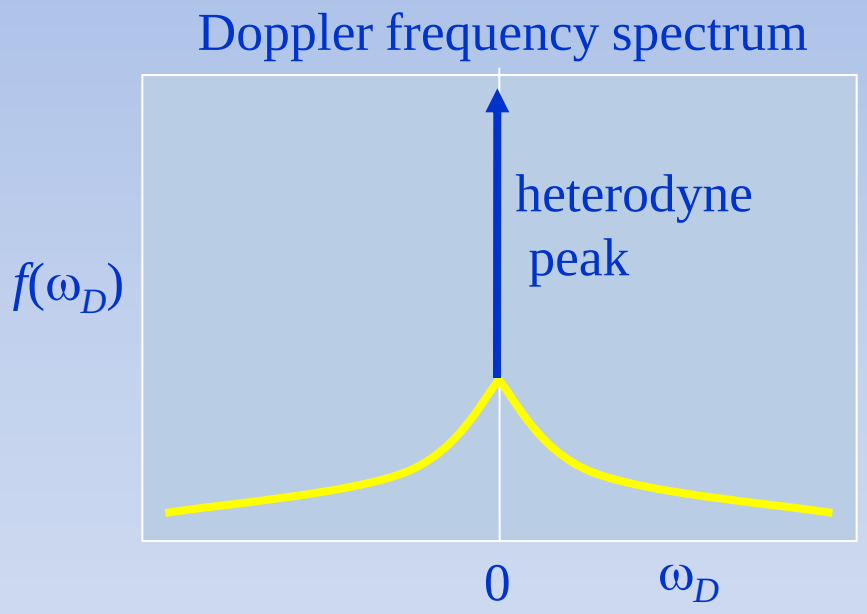
$\Delta\omega = \omega_1 - \omega_2$

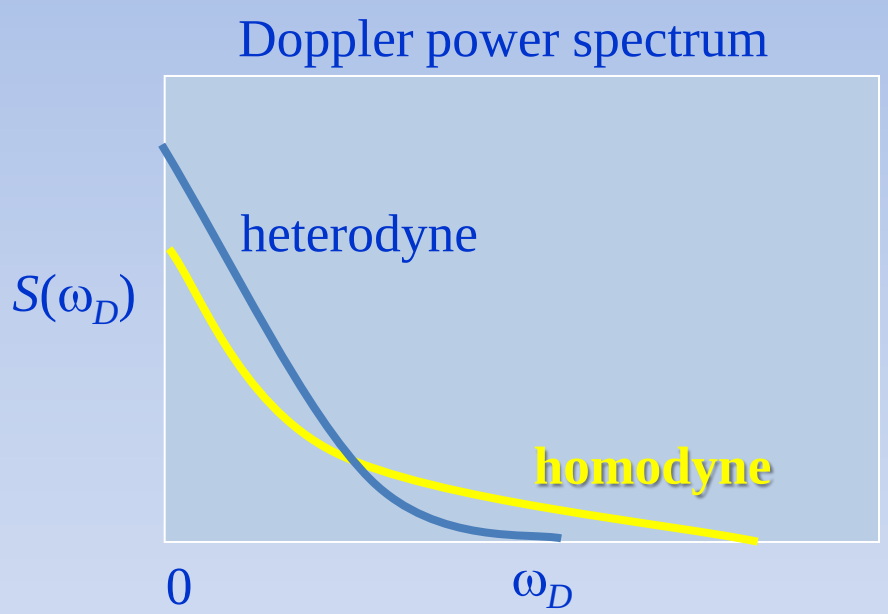
Averaging by: - random velocities

- (multiple) scattering in random directions

LDPV: Spectra (1)

(B) Laser Doppler Perfusion Velocimetry

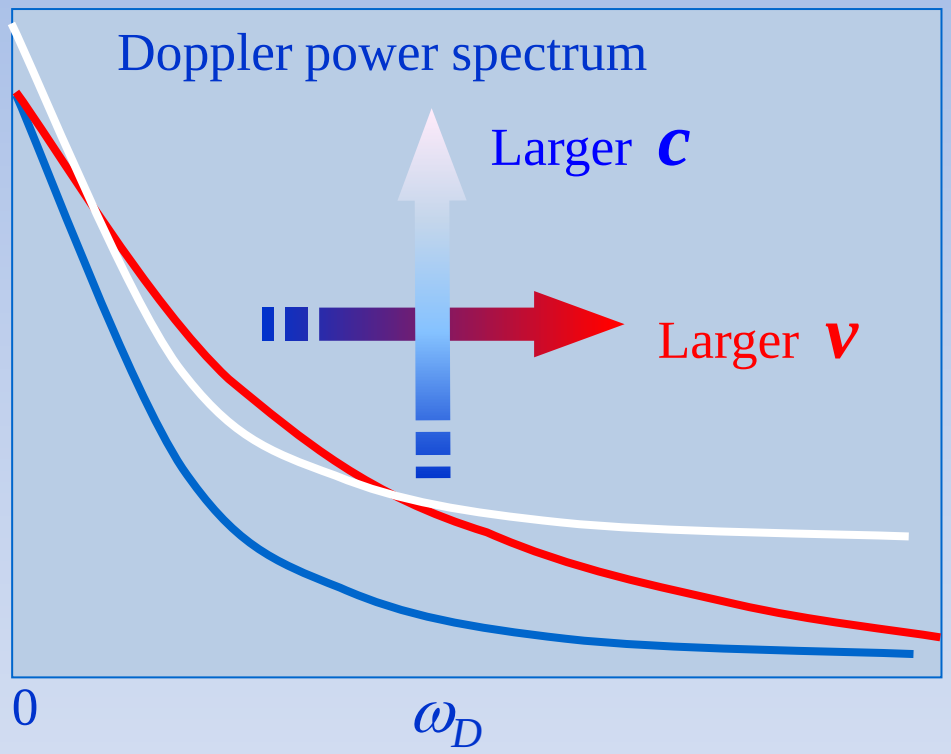




Heterodyne peak: due to large amount of non-Doppler shifted scattered photons.

LDPV: Spectra (2)

(B) Laser Doppler Perfusion Velocimetry



Power spectrum depends on:

- concentration c
- velocity v

Moments of Power spectrum :

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

$$(n = 0,1,2,\ldots)$$

Moments:

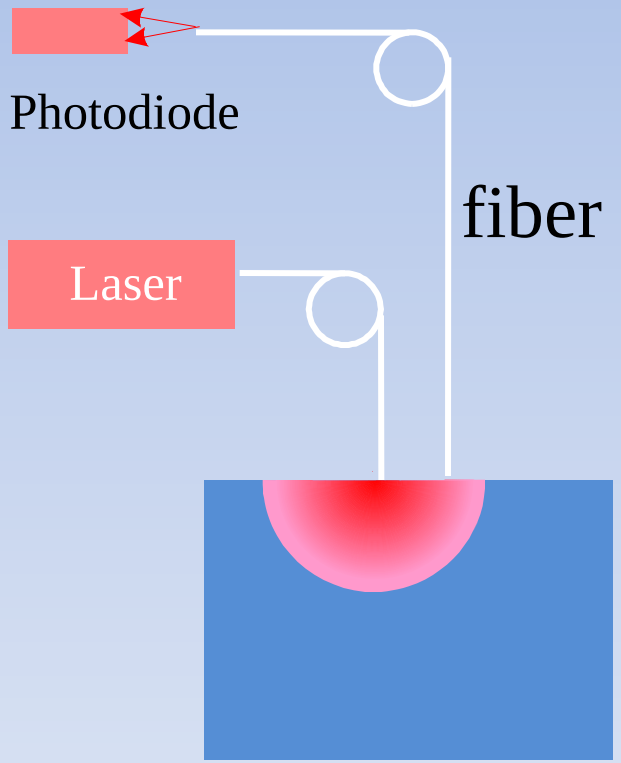
M_0 : ~ concentration of moving scatterers

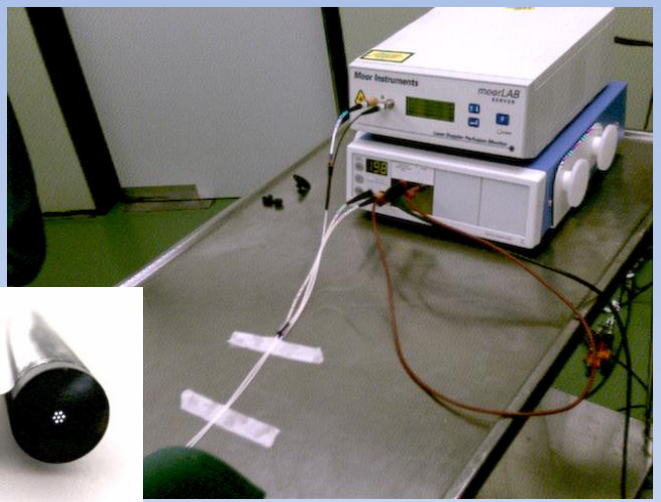
M_1: ~ flux of moving scatterers

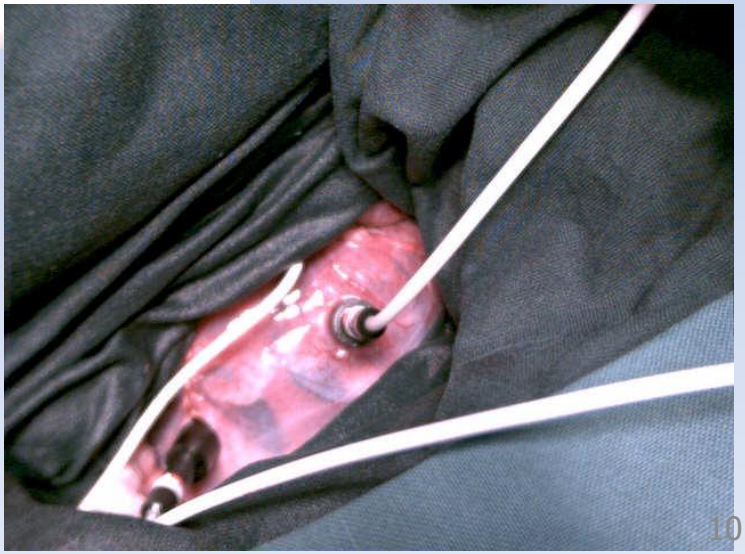
M_1 / M_0 : ~ velocity

LDPV

(B) Laser Doppler Perfusion Velocimetry

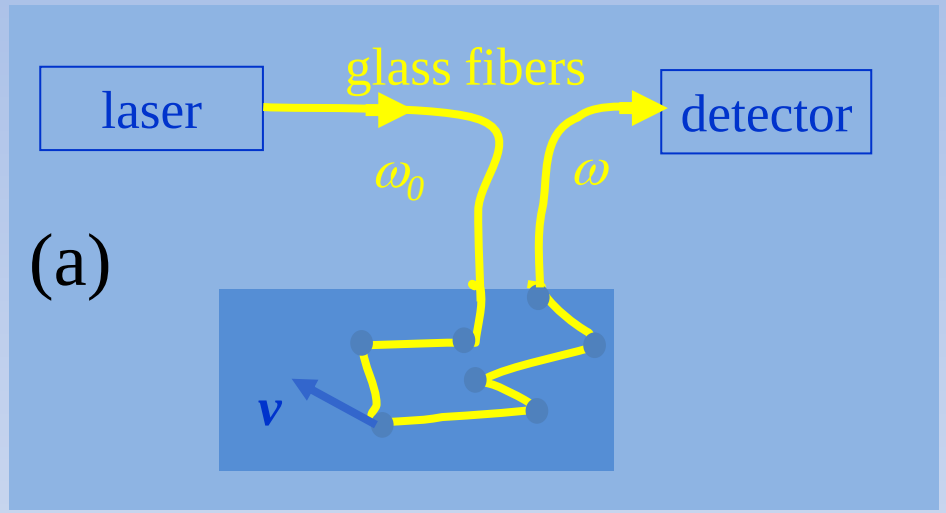


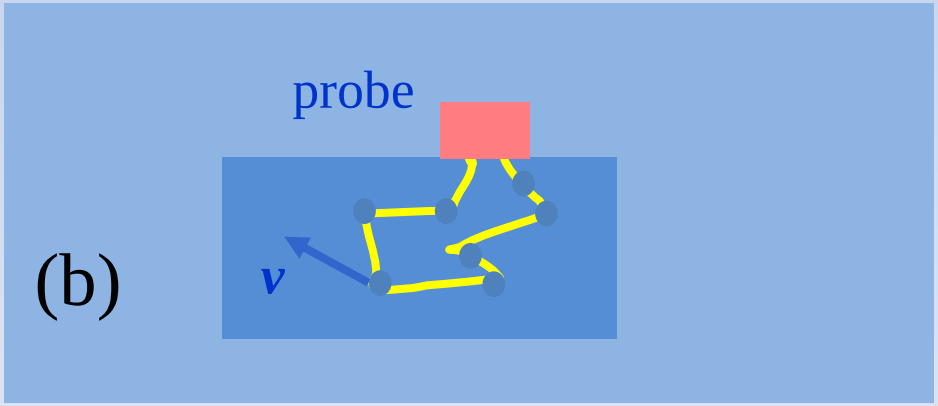




LDPV: Instruments

(B) Laser Doppler Perfusion Velocimetry: Instrument design



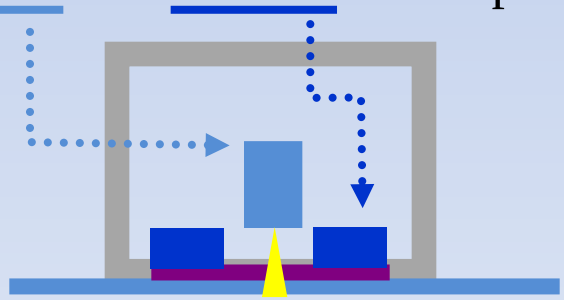


(a) Glass fibers for light transport

Disadvantages:

- motional artefacts
- sensitive for local variations

(b) Direct-contact velocimetry: Laser and detector in one probe

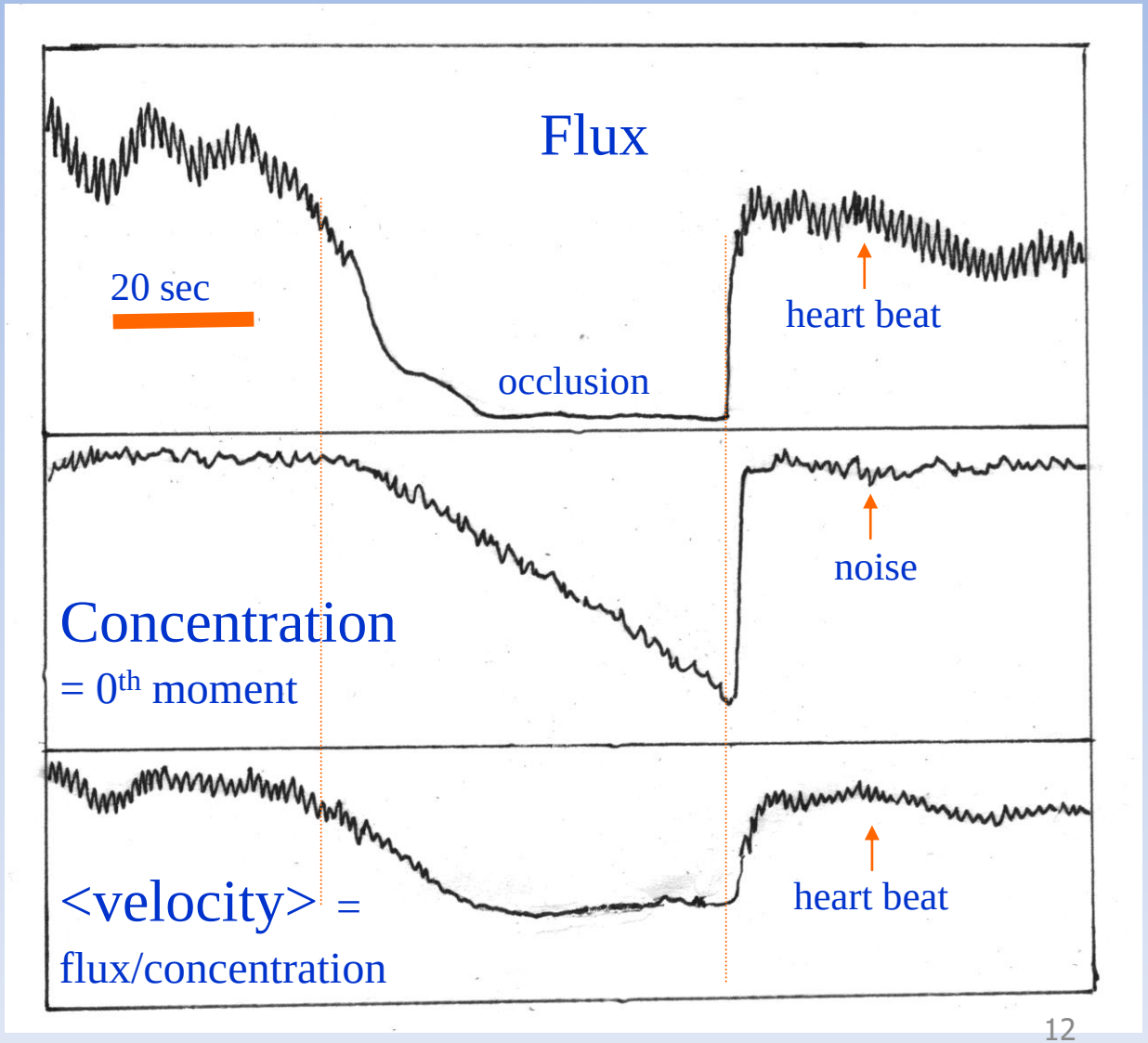


- no motional artefacts
- local averaging

LDPV: Signals

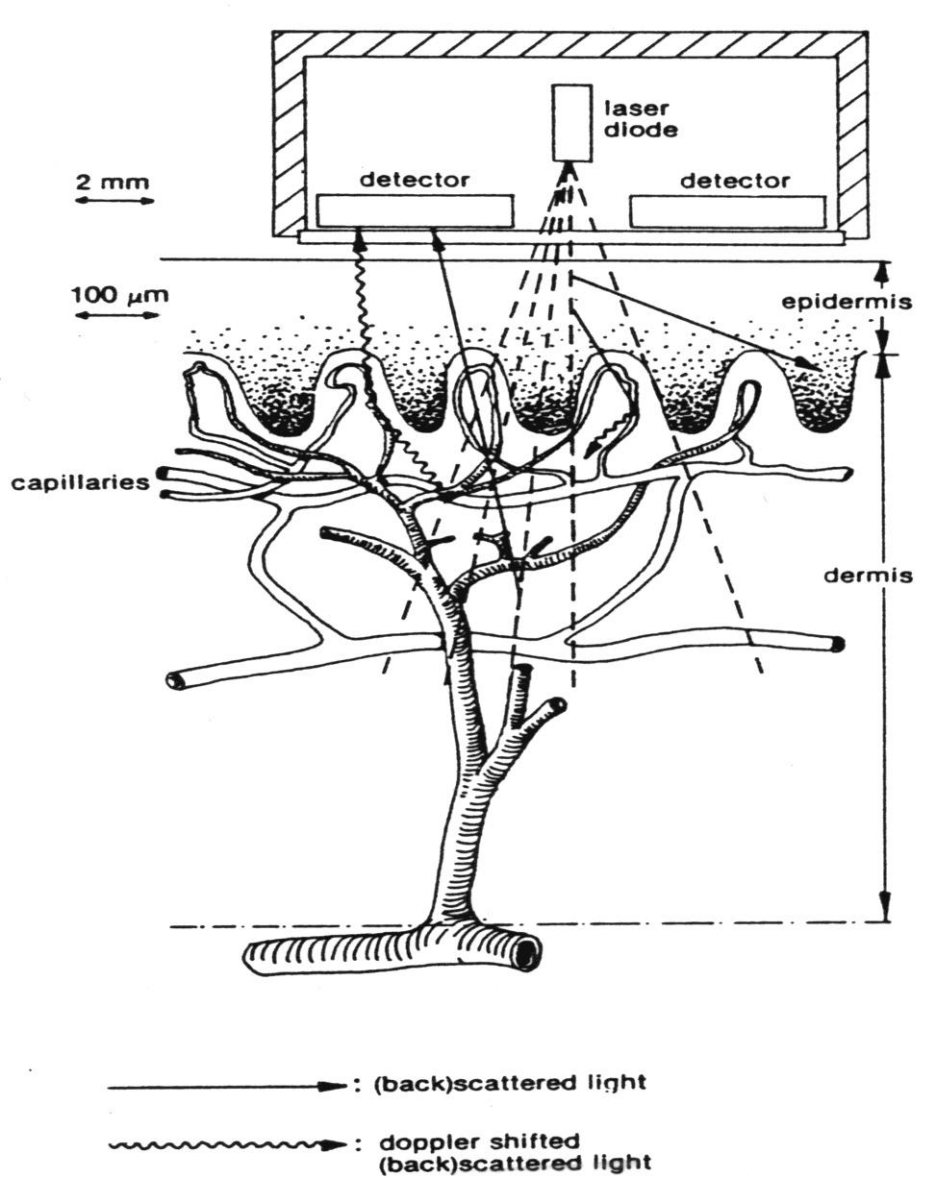
(B) Laser Doppler Perfusion Velocimetry

LD spectra of finger tip upon occlusion of upper arm



See software package LASDOPP

LDPV: Skin Tissue



(B) Laser Doppler Perfusion Velocimetry

Schematic cross section of Skin tissue

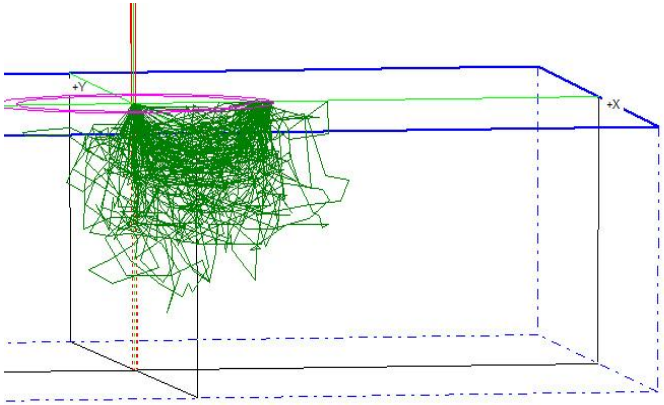
Needed:
Data about perfusion of different layers
at different depths

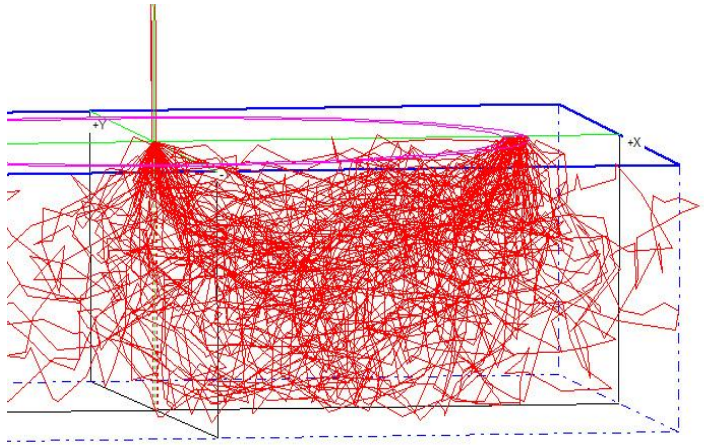
LDPV: Instruments

(B) Laser Doppler Perfusion Velocimetry: Instrument design

Depth sensitive sensor

- use detectors at different distances from the light source (see fig.)
- use different colors (**red** light probes deeper than **green**)





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A model for PORH (Post-Occlusion Reactive Hyperemia), as measured with Laser-Doppler Perfusion Monitoring

Frits F.M. de Mul

Fernando Morales Ruiz

Andries J. Smit

Reindert Graaff

Jan Aarnoudse

PORH-model

- **Microcirculation:**

  blood flow through **microvasculature** (< 1 mm diameter)

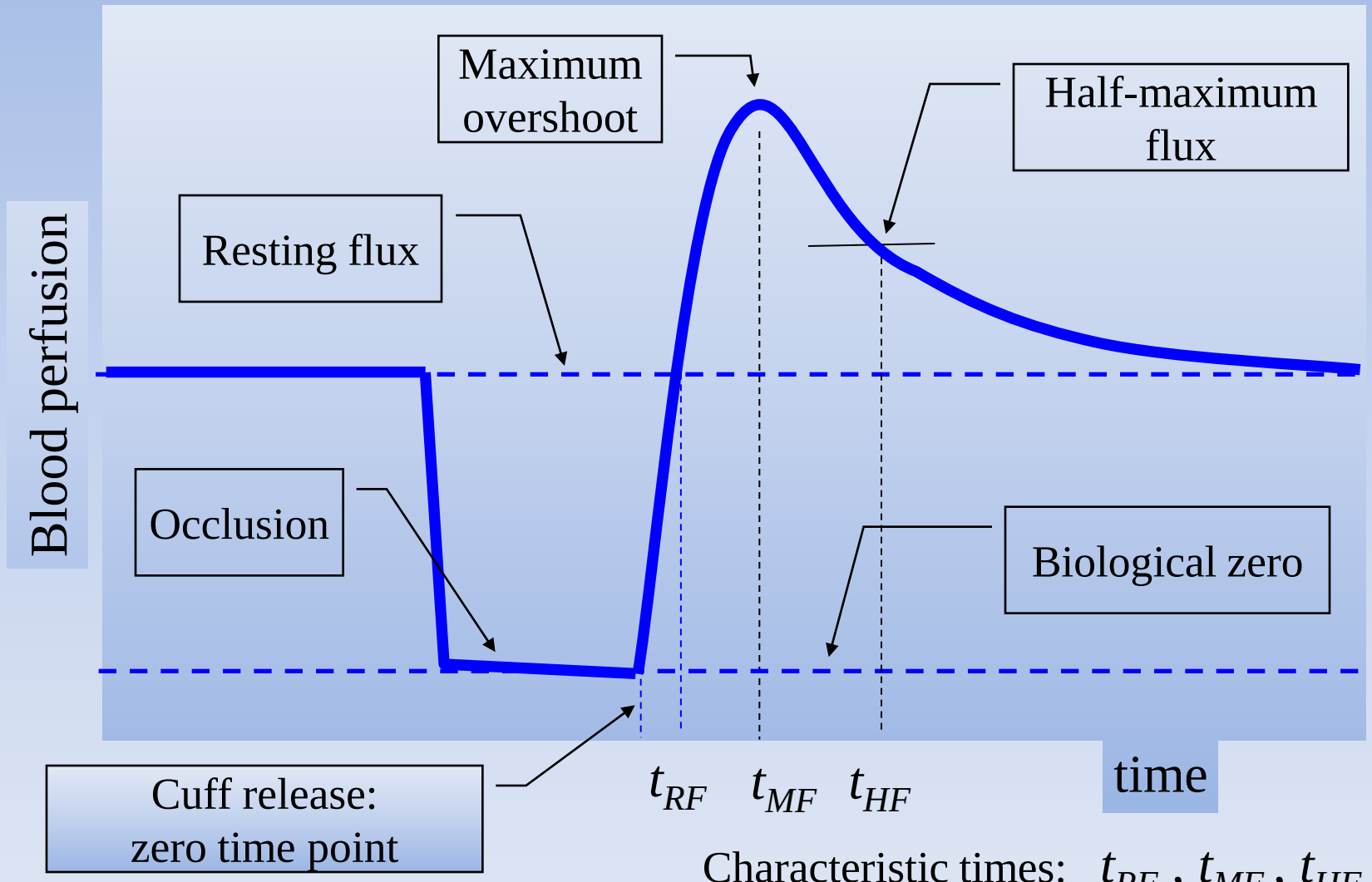
- **Regulation of microcirculation:**
  - controlled by **musculature** of the arterioles
  - based on ambient **temperature** and/or **concentration** of metabolism-related substances (O_2, CO_2, NO…)
  - operating through **vasodilatation**
- **Peripheral Arterial Occlusive Disease (PAOD):**
  - **stenoses** in proximal arteries.
  - decrease of available **pressure level** in arterioles
  - **vasodilatation** impaired or delayed

PORH-model

- **Post-Occlusive Reactive Hyperemia (PORH)-test:**
  - to assess microvascular functioning
- **Procedure of PORH:**
  - **arterial occlusion** upstream in artery to extremity
  - before, during and after **arterial occlusion:**
    - local blood perfusion measured at **distal extremity**
    - **as function of time**

PORH-model

- PORH-test procedure

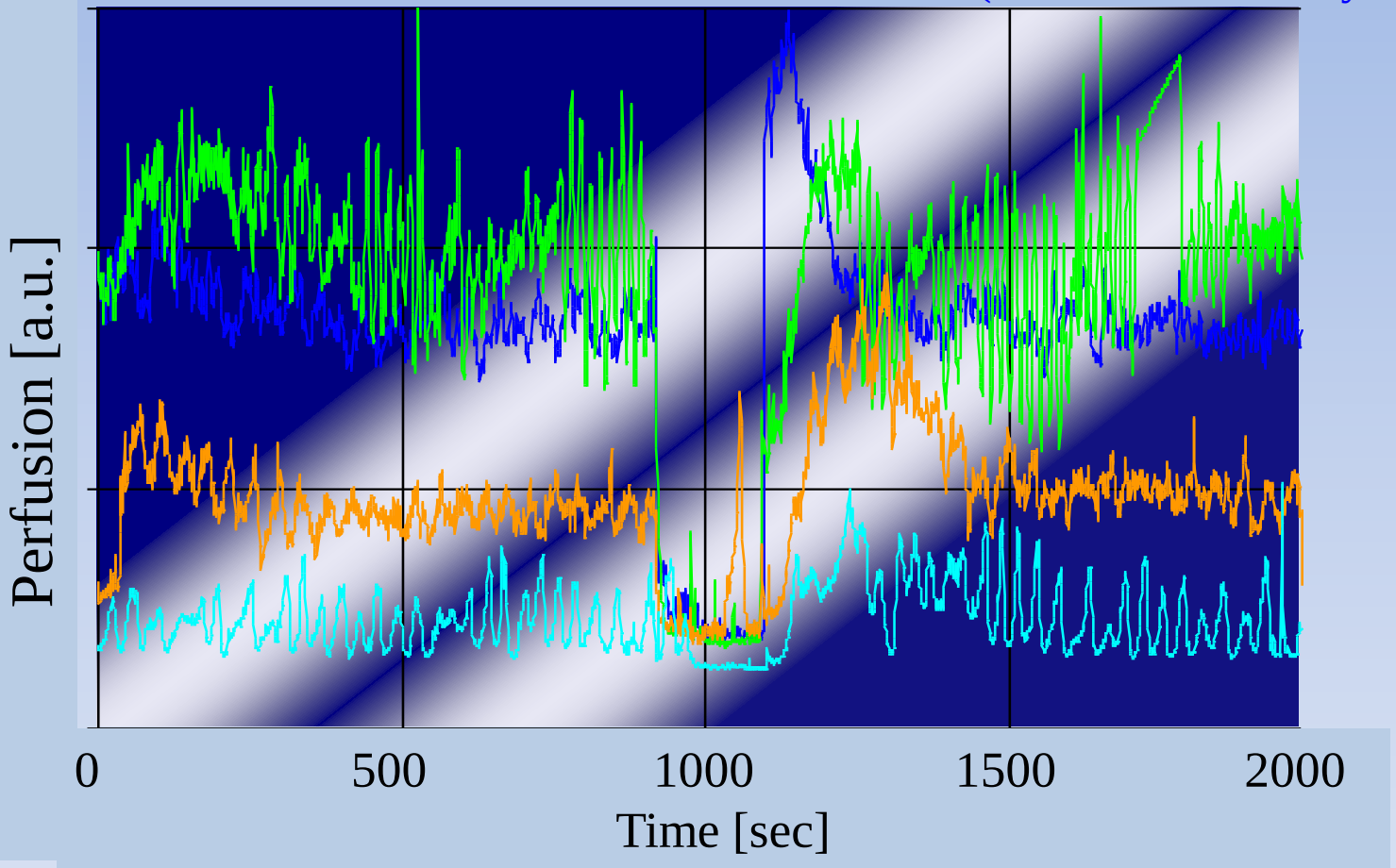


Characteristic times: t_{RF} , t_{MF} , t_{HF}

PORH-model

Measured data (typical)

(all measurements by F. Morales)



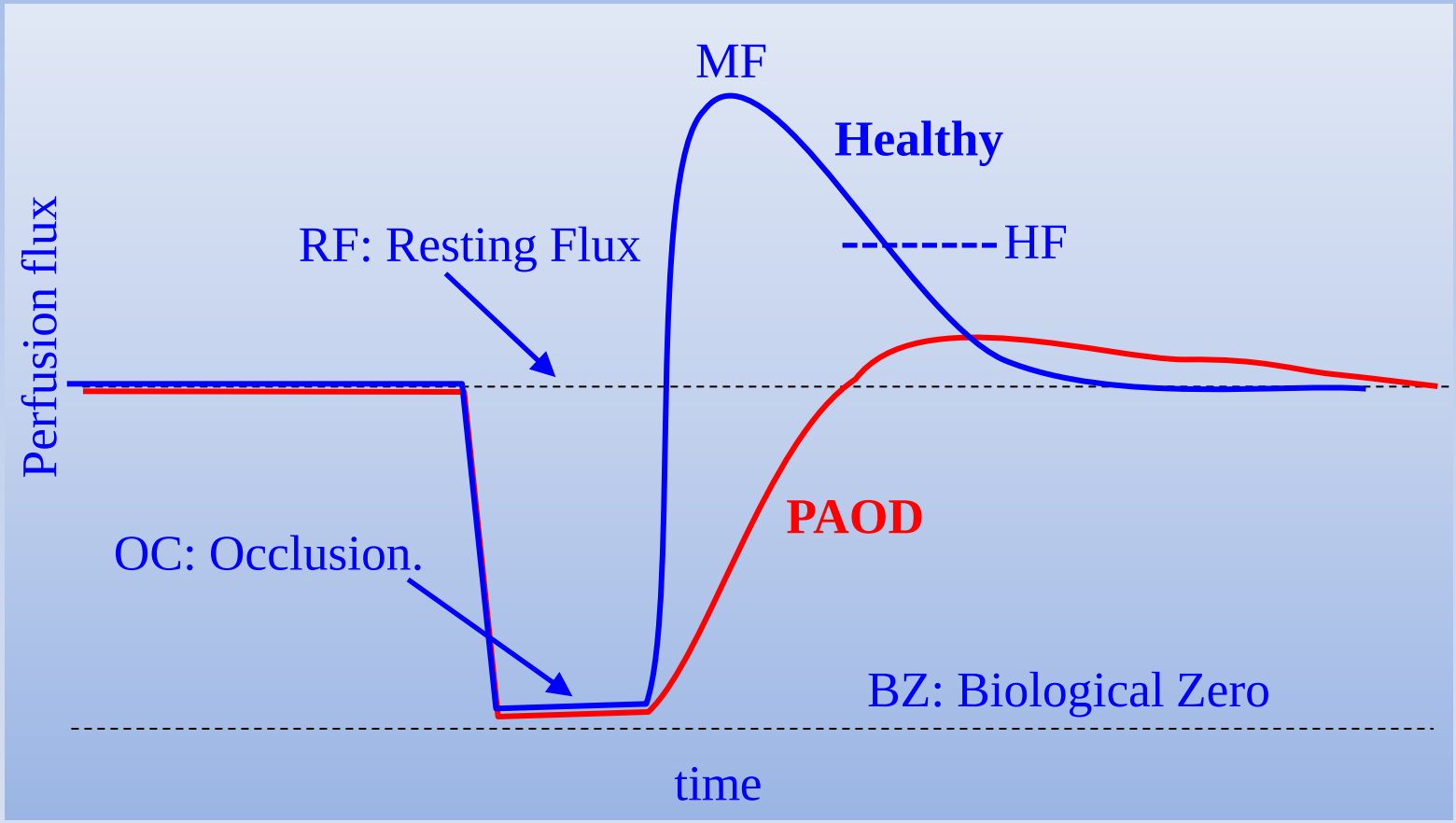
healthy

PAOD

Healthy → PAOD:

Response to occlusion: Slower and lower

PORH-model



MF = maximum, **HF** = half decrease time between maximum and resting flux, t_{RF} = time of cross point with **RF.**

PORH-model

PAOD vs. Healthy:

- Longer time scales
- Rise time and Decrease time tend to become equal
- Decreased overshoot maximum

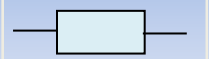
Similar behaviour for Diabetes patients

PORH-model

- **Building blocks for the flow model:**

I : Flow [m^3/s]
V : Pressure [Pa = N/m^2 = J/m^3]

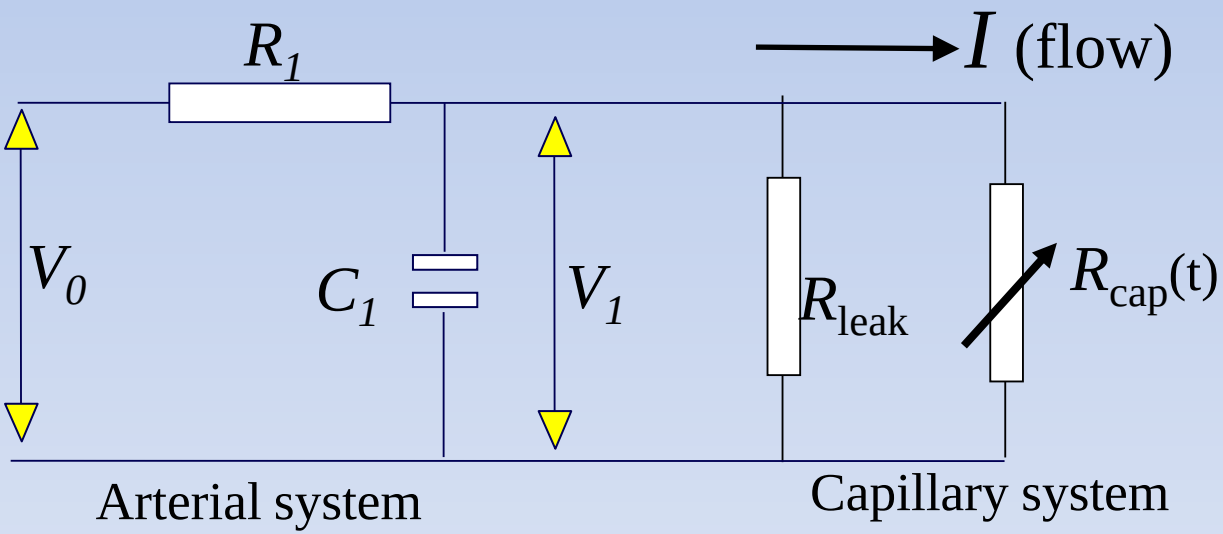
Electrical analogon
I : Current [C/s = A]
V : Voltage [V = J/C]

Block	Symbol	Units	Electrical analogon	Expression
Flow resistance R		$Pa.s/m^3$	V/A = Vs/C	$R = \frac{8\mu l}{\pi R_0^4}$
Compliance C		m^3/Pa	C/V	$C = \frac{3\pi R_0^3 l}{2Eh}$
Inertance L		$Pa.s / (m^3/s)$	V.s / A	$L = \frac{9\rho l}{4\pi R_0^2}$

μ = viscosity [Ns/m^2]
l = tube length [m]
R_0 = tube radius [m]
E = Young's elasticity modulus [N/m^2]
h = tube wall thickness [m]
ρ = density [kg/m^3]

PORH-model

- **Model:**
- Two sub-models: “arterial” and “capillary”
- **“Arterial”** part: flow resistance + compliance
- **“Capillary” part**: time-dependent flow resistance



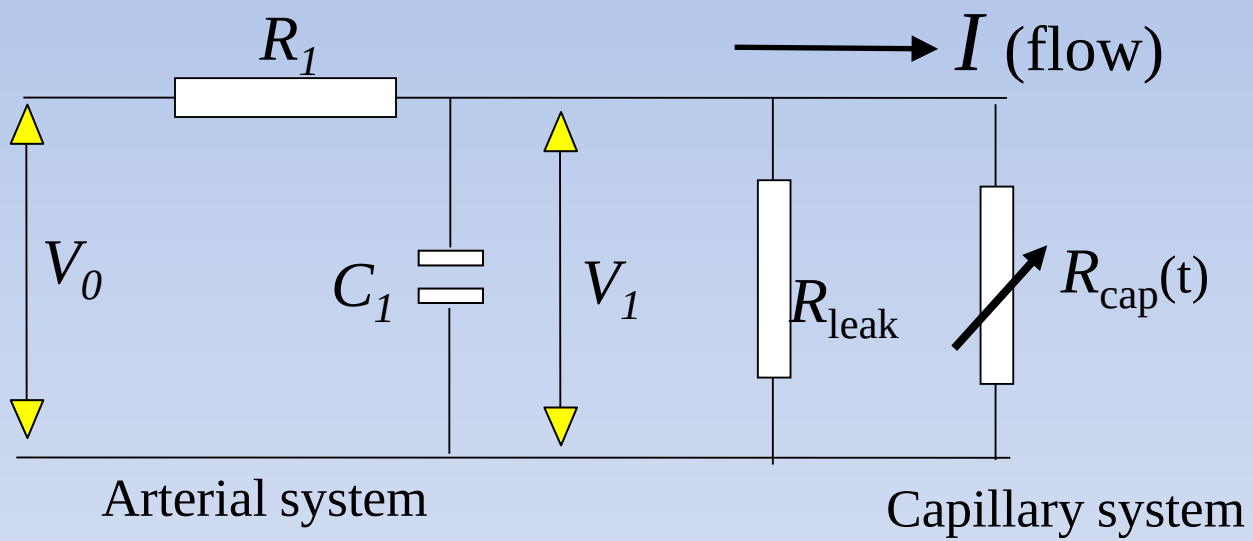
V_0 = driving pressure (battery)
supply tank
R = resistance
narrow tube
C = compliance (capacitor)
storage vessel

I is the flow measured by LDF

R_{leak} accounts for possible flow leakage passing capillary system

PORH-model

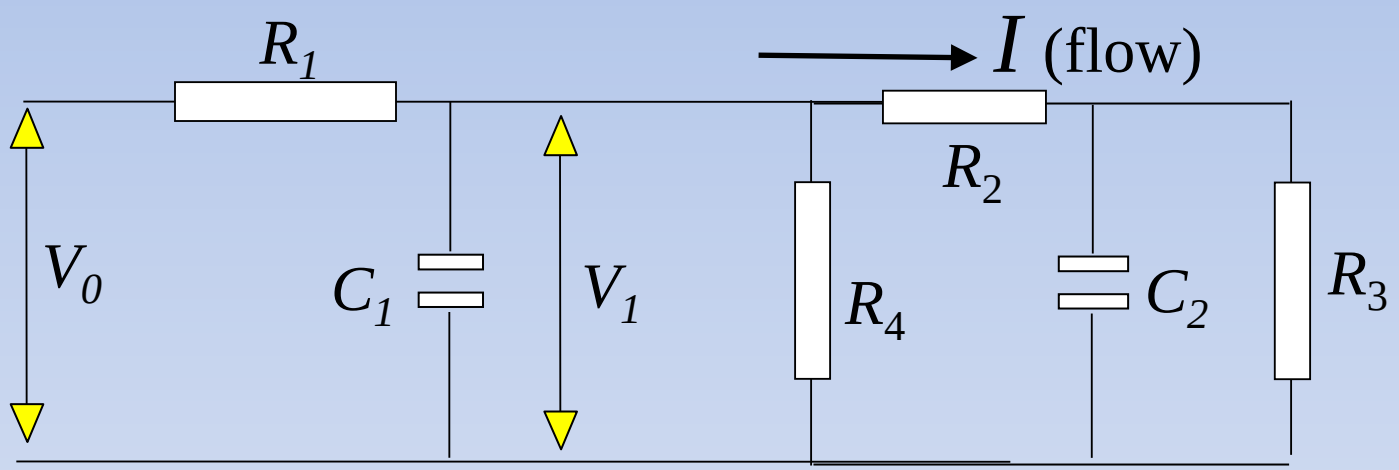
- **Model with details:**
- Two sub-models: “arterial” and “capillary”



R’s are resistances (narrow tubes)
C’s are compliances (storage vessels)

PORH-model

- **Model with details:**
- Two sub-models: “arterial” and “capillary”



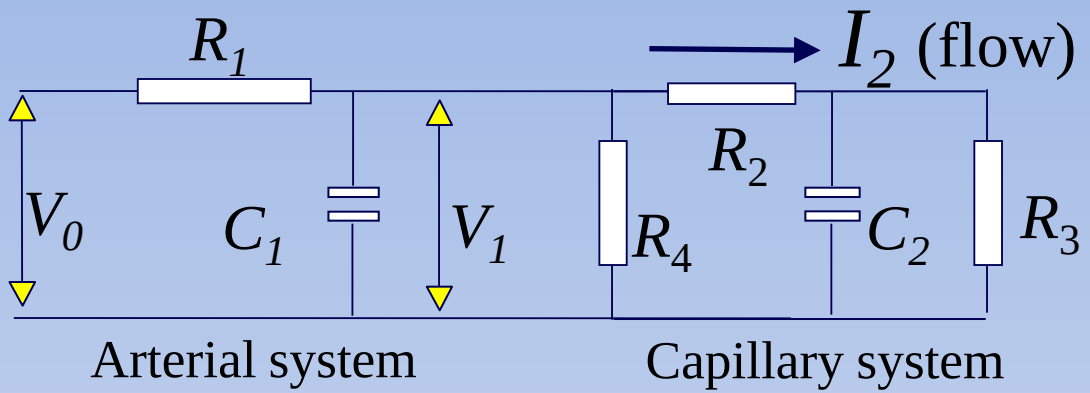
Normally $R_4 >> R_2 , R_3$.

Small times: C_2 small impedance $\rightarrow R_{cap} \approx R_2 \rightarrow$ flow I large

Large times: C_2 large impedance $\rightarrow R_{cap} \approx R_2 + R_3 \rightarrow$ flow I small

PORH-model

- **Model:**



Jump response after pressure return
upon cuff release after occlusion:

(Electrical: sudden voltage V_0)

$$I_2 = a_0\left[1 - a_1 \exp(-p_1 t) - (1 - a_1)\exp(-p_2 t)\right]$$

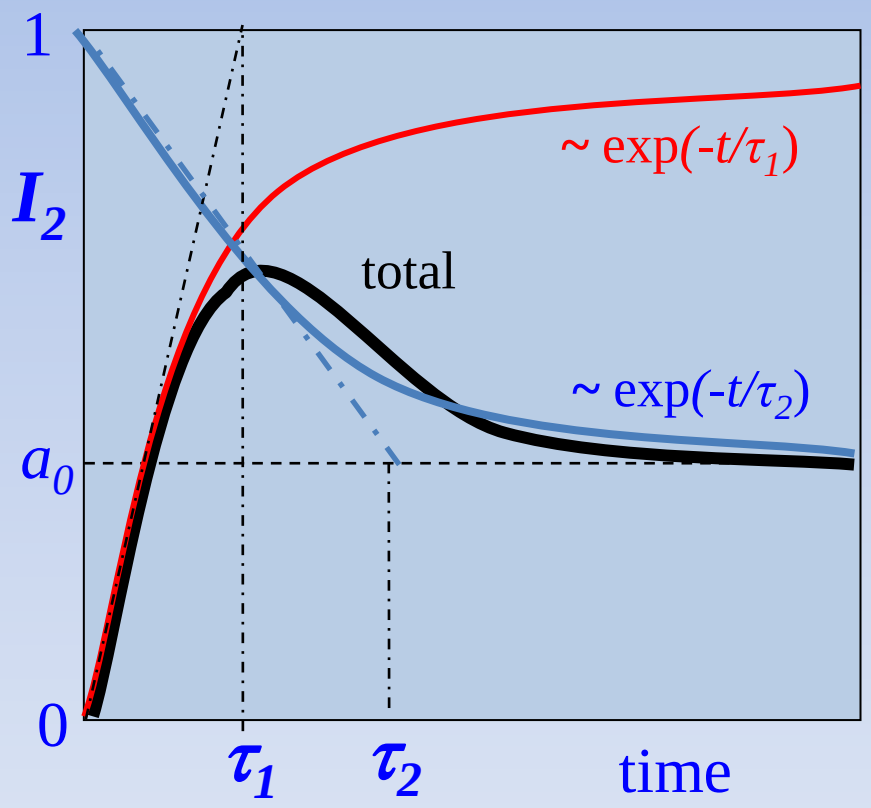
with $a_0, a_1, p_1, p_2 = f\left(R_1, R_2, R_3, R_4, C_1, C_2\right)$

NB. Two exponentials, both decreasing in time.

PORH-model

$$I_2 = a_0\left[1 - a_1 \exp(-p_1 t) - (1 - a_1)\exp(-p_2 t)\right]$$

- at time $t = 0$:
  $I_2 = a_0\,[1 - a_1 - (1 - a_1)] = 0$
- at time $t \to \infty$:
  $I_2 \to a_0\,[1 - 0 - 0] = a_0$



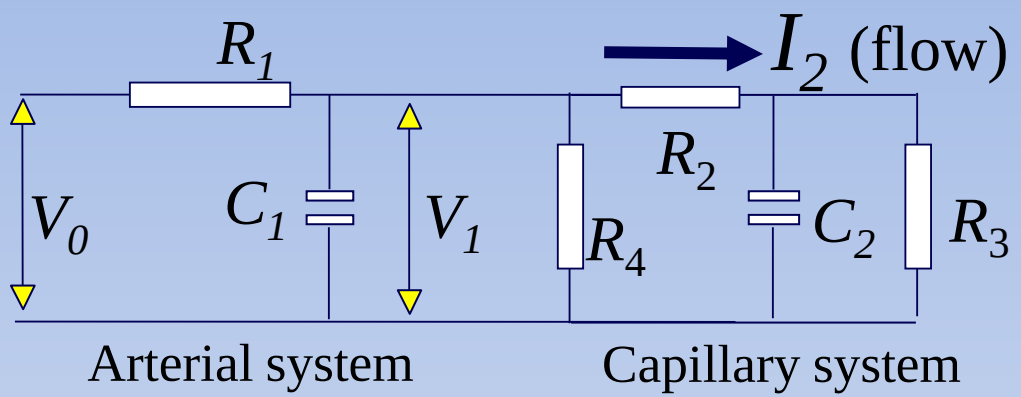
With $p_1 = 1/\tau_1$ and $p_2 = 1/\tau_2$:

- τ_1 and τ_2 : characteristic times
- If $\tau_1 < \tau_2$: see figure →

PORH-model

Approximation:

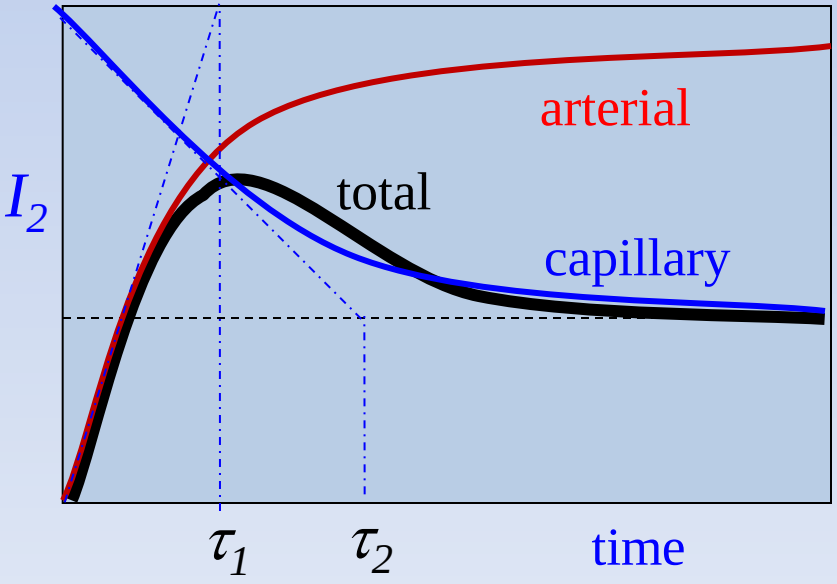
- "Arterial" much faster than "capillary" →
- Two separate submodels: "arterial" and "capillary"
- $R_4 \to \infty$



$$V_1 = V_0\left(1 - e^{-t/\tau_1}\right) \qquad \tau_1 = R_1 C_1$$

$$I_2 = \frac{V_1}{R_2 + R_3}\left(1 + \frac{R_3}{R_2}\, e^{-t/\tau_2}\right)$$

$$\tau_2 = C_2 \frac{R_2 R_3}{R_2 + R_3}$$

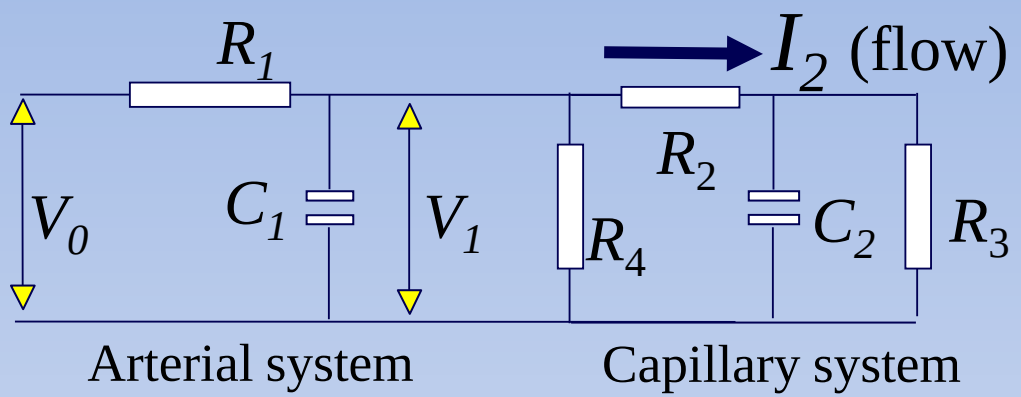


PORH-model

Approximation:

$$\tau_1 = R_1 C_1$$

$$\tau_2 = C_2 \frac{R_2 R_3}{R_2 + R_3}$$



From flow physics:

$$\tau = RC = \frac{8\mu l}{\pi R_0^{\,4}} \cdot \frac{3\pi R_0^{\,3} l}{2Eh} = \frac{12\mu l^2}{EhR_0}$$

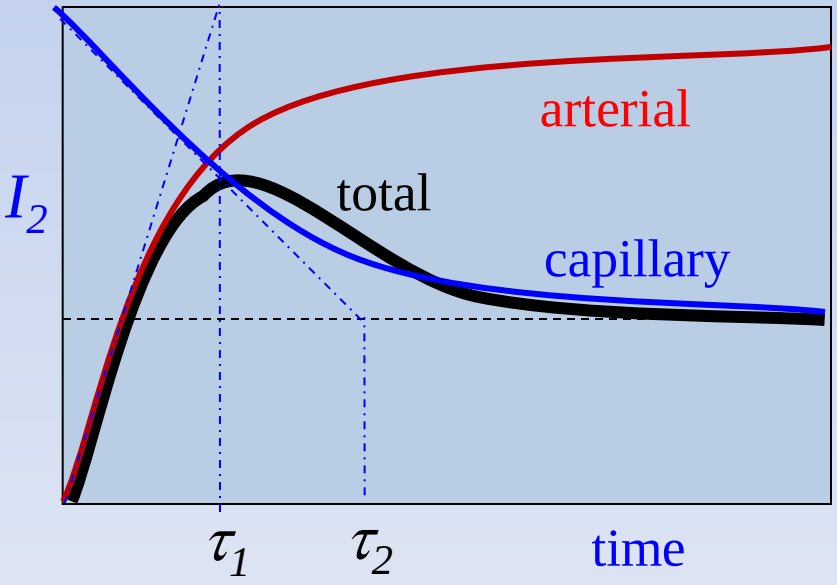
$\tau \uparrow$ if $\mu \uparrow$ (viscosity)

or $l^2 \uparrow$ (tube length)

or $E \downarrow$ (wall elasticity)

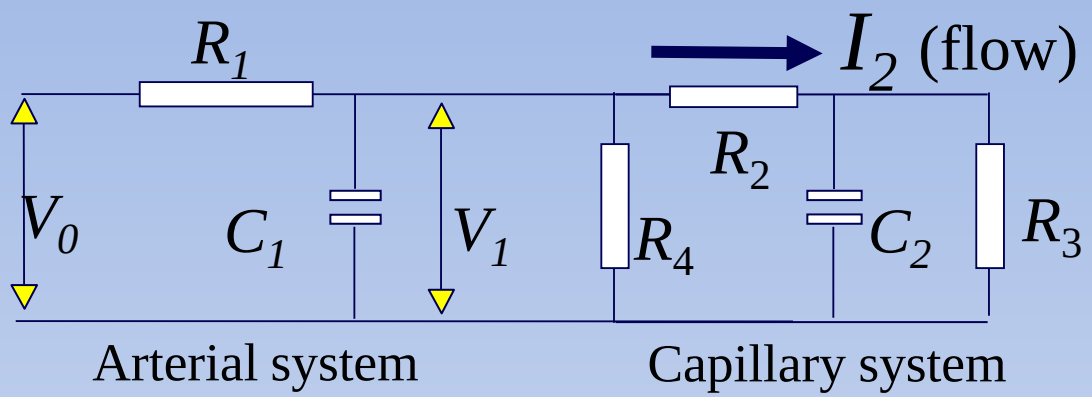
or $h \downarrow$ (wall thickness)

or $R_0 \downarrow$ (tube radius)



PORH-model

- **Model**
- **approximation:**

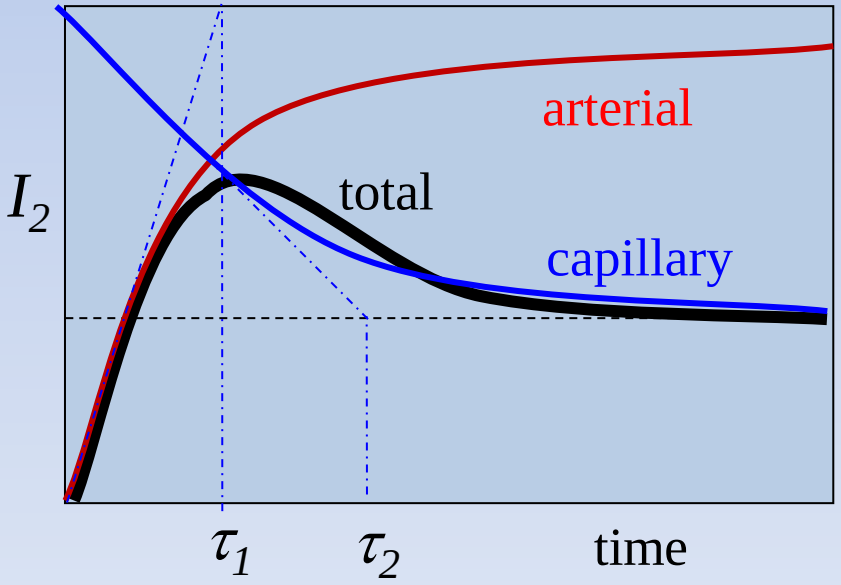


$$V_1 = V_0\left(1 - e^{-t/\tau_1}\right)$$

$$I_2 = \frac{V_1}{R_2 + R_3}\left(1 + \frac{R_3}{R_2}\, e^{-t/\tau_2}\right)$$

Even better approx.:

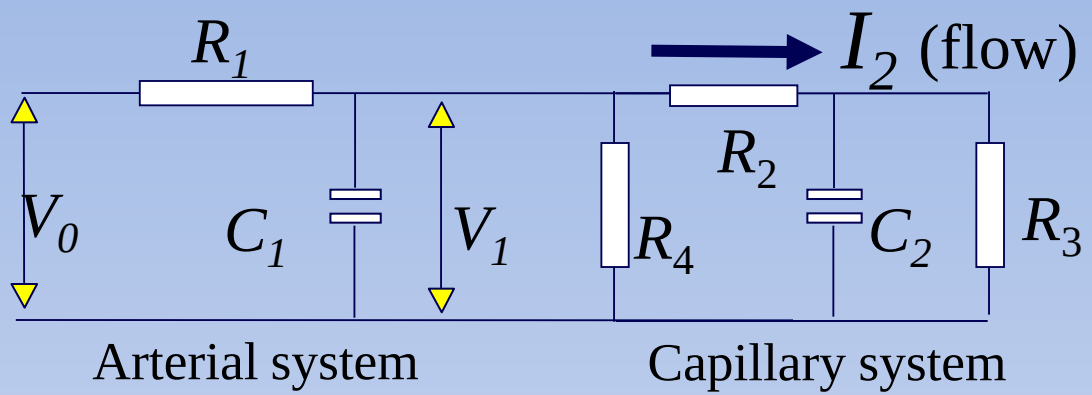
$$I_2 = \frac{V_1}{R_1 + R_2 + R_3}\left(1 + \frac{R_3}{R_2}\, e^{-t/\tau_2}\right)$$

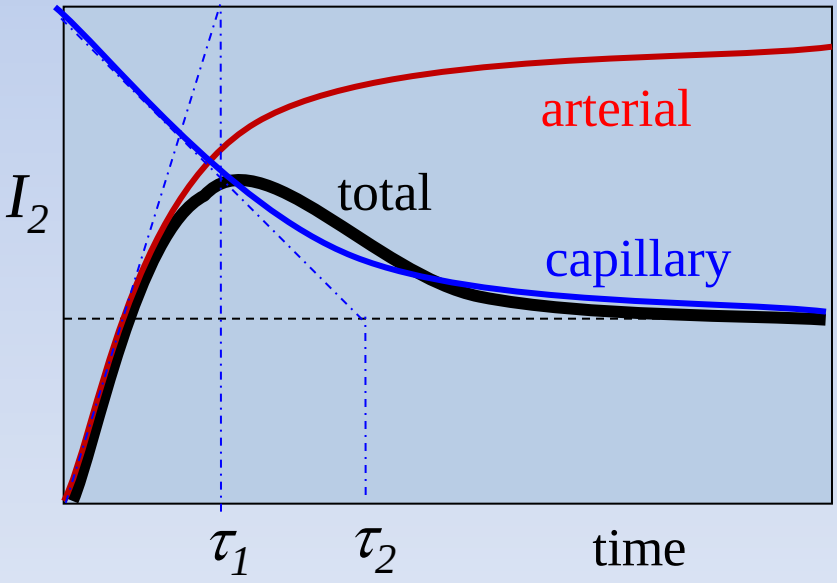


Question: when can we use the approximation ?

PORH-model

- **Model:**



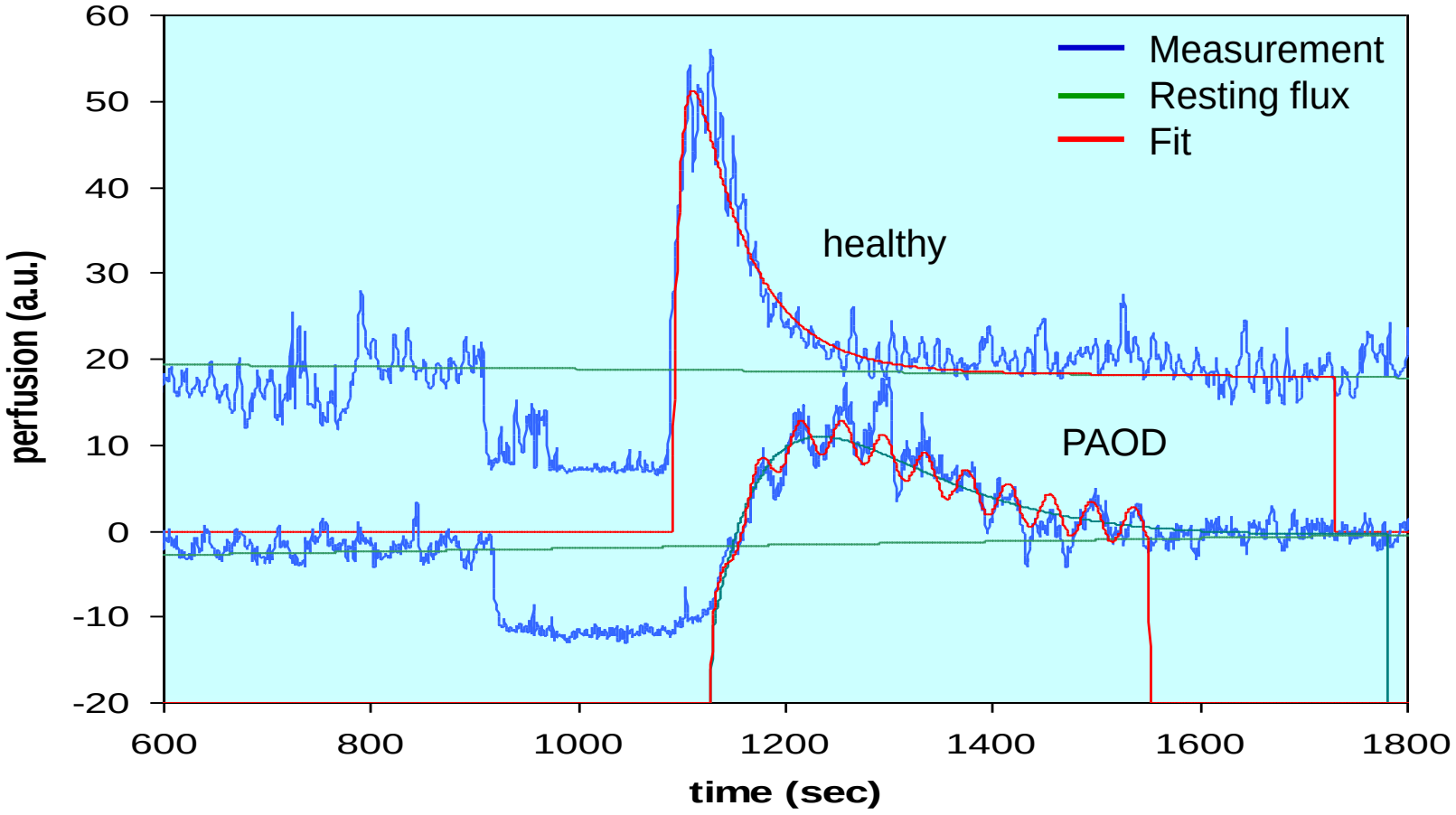


Examples of fitting:
program LASDOP:

PORH-model

- **Model fitting : two examples:**

  Healthy person (upper) and PAOD-patient (lower; down shifted -20)

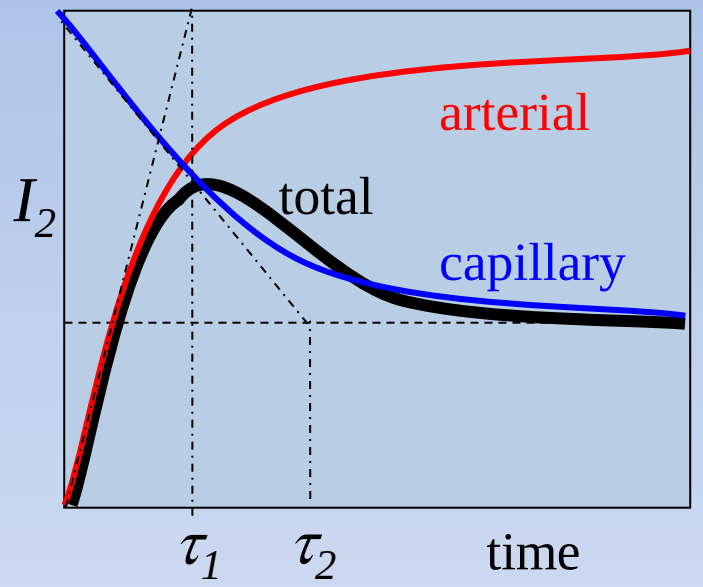


Lower figure includes sine-approx. of vasomotion

PORH-model

- **Model fits:**
- Model parameters for recordings of a typical healthy person and a typical PAOD-patient

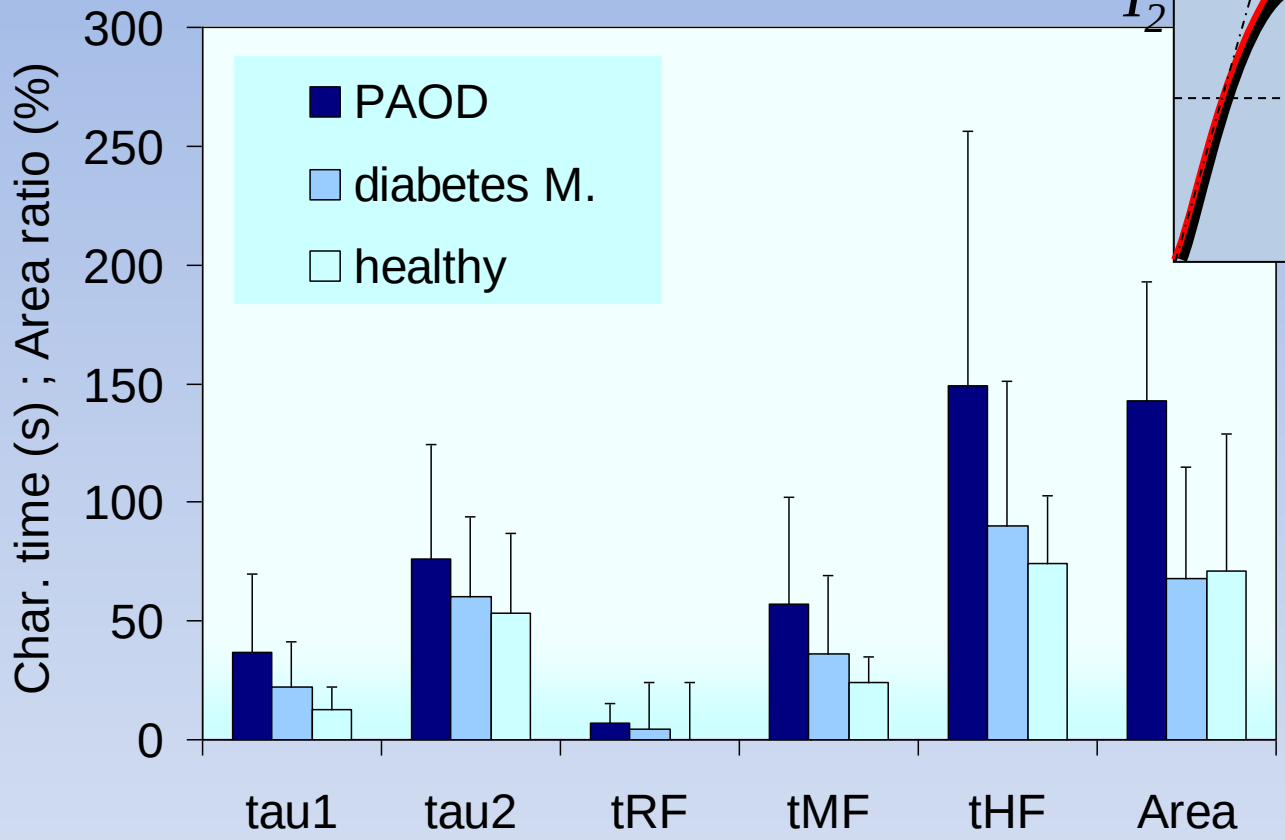
Person	*Model*	τ_1 (sec)	τ_2 (sec)
Healthy	Exact	4.6	81.2
	Approx	4.7	81.2
PAOD	Exact	80	86
	Approx	314	114

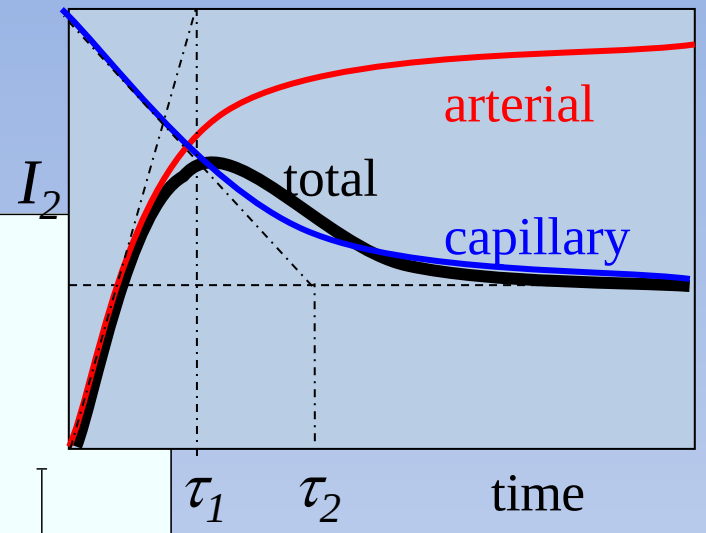


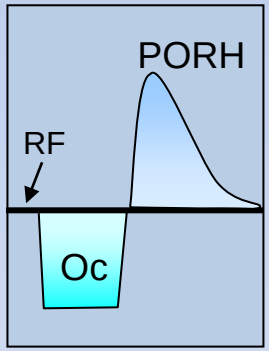
Healthy persons: exact model and approximation coincide;
and render similar parameter values:
indication for: “arterial part” faster than “capillary part”.

PAOD-persons: models have very different parameters;
Both “arterial part” and “capillary part” are slow.

PORH-model







"Area": Ratio of areas between measured data and extrapolated resting flux RF, for Reactive Hyperemia period (PORH) vs. Occlusion period (Oc).

Indicates compensation of oxygen debt from Occlusion period in the PORH period.

PORH-model

- **Model fits:** Signal strengths

Ratio of maximum flux vs. resting flux:
no significant differences between healthy,
Diabetes M. and PAOD:

3.1 ± 0.6 for PAOD-group (N=7)
5.8 ± 4.8 for Diabetes M.-group (N=9)
3.2 ± 2.7 for healthy group (N=8)

Overall signal strength:
No significant differences

PORH-model

- Conclusions from model fitting:

1. Exact model fits all measurements
2. Approximate model fits healthy group only
3. Response time:
   a. "Arterial part": Healthy group faster than Diabetes-M.-group and much faster than PAOD-group
   b. "Capillary part": ≈ similar response time for all
4. Signal strengths (resting flux and maximum flux) :

   no significant differences between groups
5. Area ratio between (PORH-RF) and (Occl.-RF) signals

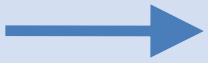
   < 1 (aver. 0.6; healthy pers.) and >1 (aver. 1.5; POAD

   (Indicates compensation of oxygen debt from occlusion period)

Contents:

1. Principles of Laser-Doppler Blood Perfusion Monitoring

2. Model for Post-Occlusion Reactive Hyperaemia (PORH) to study
   Peripheral Arterial Occlusive Disease (PAOD)



3. Model for Drug Administration using Iontophoresis

A Diffusion Model for Drug Administration by Iontophoresis, as measured with Laser-Doppler Perfusion Flowmetry

Frits F.M. de Mul,

Judith Blaauw,

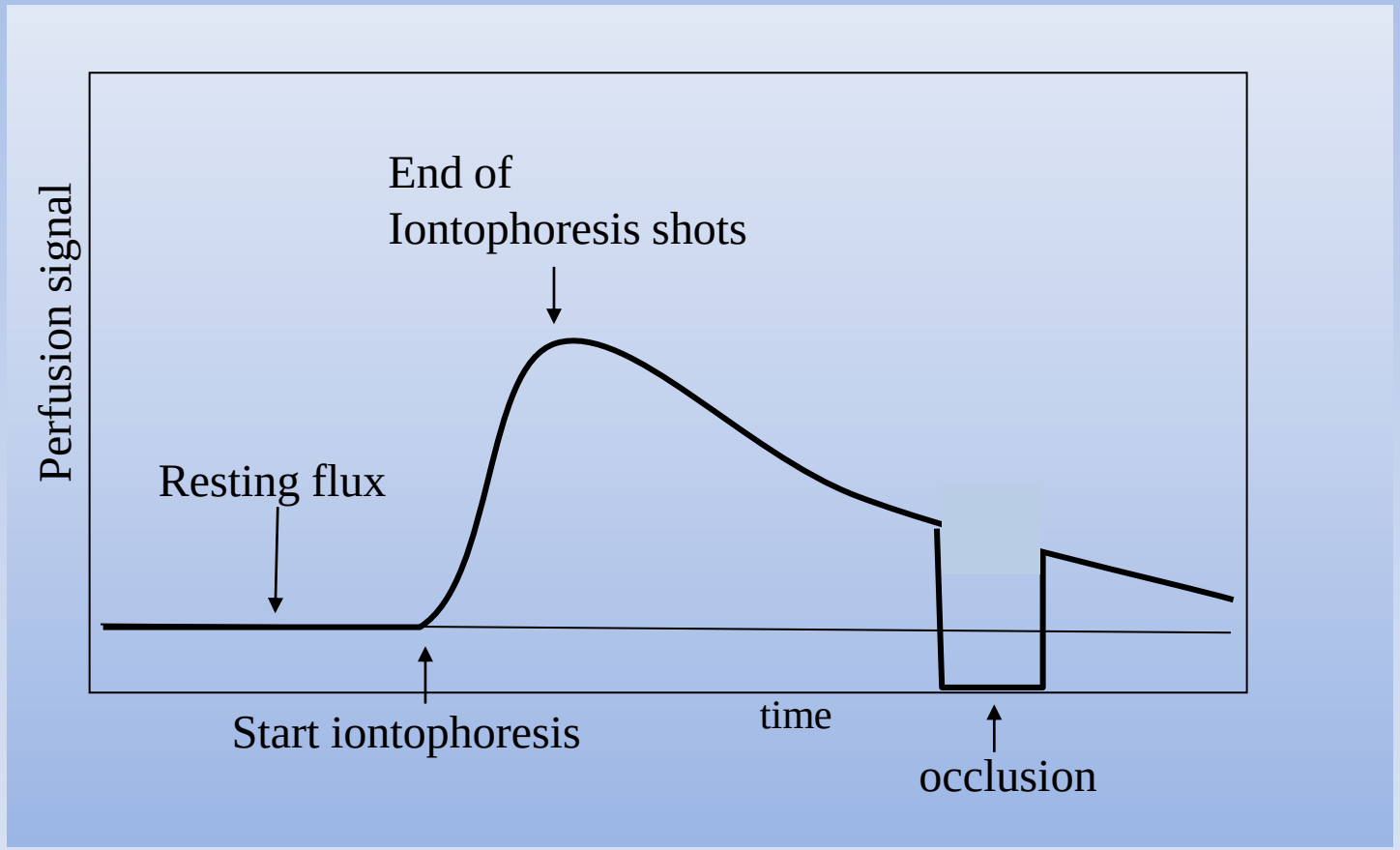
Jan Aarnoudse

LD - Diffusion model for Iontophoresis

- Goal of the project:
  - Model to characterise Iontophoresis,
  - As measured with Laser-Doppler blood perfusion flowmetry in capillaries in extremities,
  - Application: preeclampsia,
  - Characteristics:
    - 1-dim. Diffusion of concentration
    - Decay term (removal)
    - Saturation with subsequent iontophoretic shots.

LD - Diffusion model for Iontophoresis

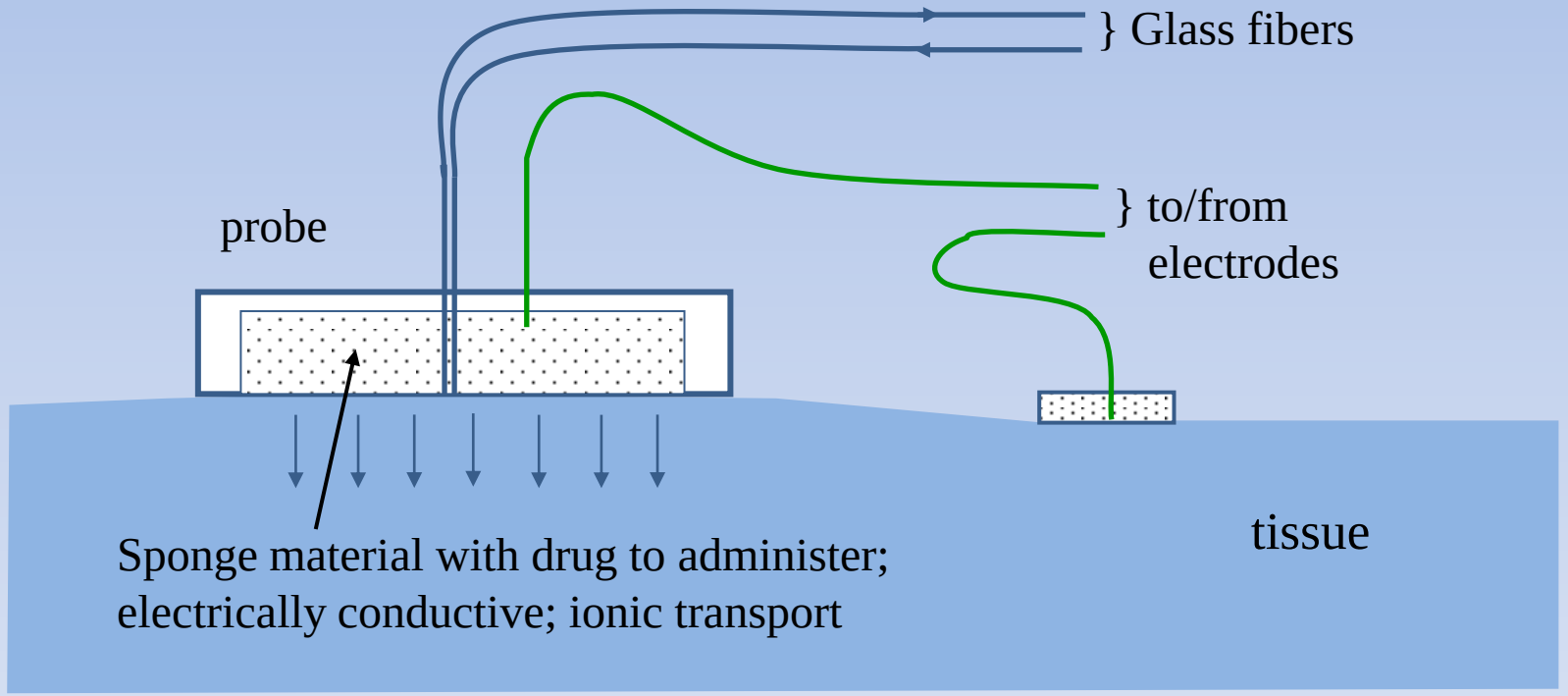
Typical iontophoresis recording



("occlusion" performed to measure biological zero level)

LD - Diffusion model for Iontophoresis

Laser-Doppler probe for Iontophoresis



Typical dimensions: probe: diameter 10-20 mm, height 5-10 mm;
fiber separation 250 μm.

The diffusion can be considered as mono-dimensional (in depth direction).

LD - Diffusion model for Iontophoresis

- The model:

1. 1-Dimensional diffusion
2. Decay (removal)
3. Saturation with subsequent shots.

LD - Diffusion model for Iontophoresis

- The model:
1. 1-Dimensional diffusion
2. Decay
3. Saturation by subsequent shots.

1. 1-Dimensional diffusion

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

t = time [s]
z = depth [m]
c = concentration [kg/m^3]
D = diffusion coefficient [m^2/s]

$$\boldsymbol{c = f\,(z\,,\,t)}$$

Start (boundary condition) for $c\,(z,t)$:
concentration "pulse" at z=0 and t=0.

$c(0,0) = c_0$, with $\int_0^\infty c(z,t)dz = Q$ for all t, including $t = 0$.

Q ~ total amount of administered molecules

LD - Diffusion model for Iontophoresis

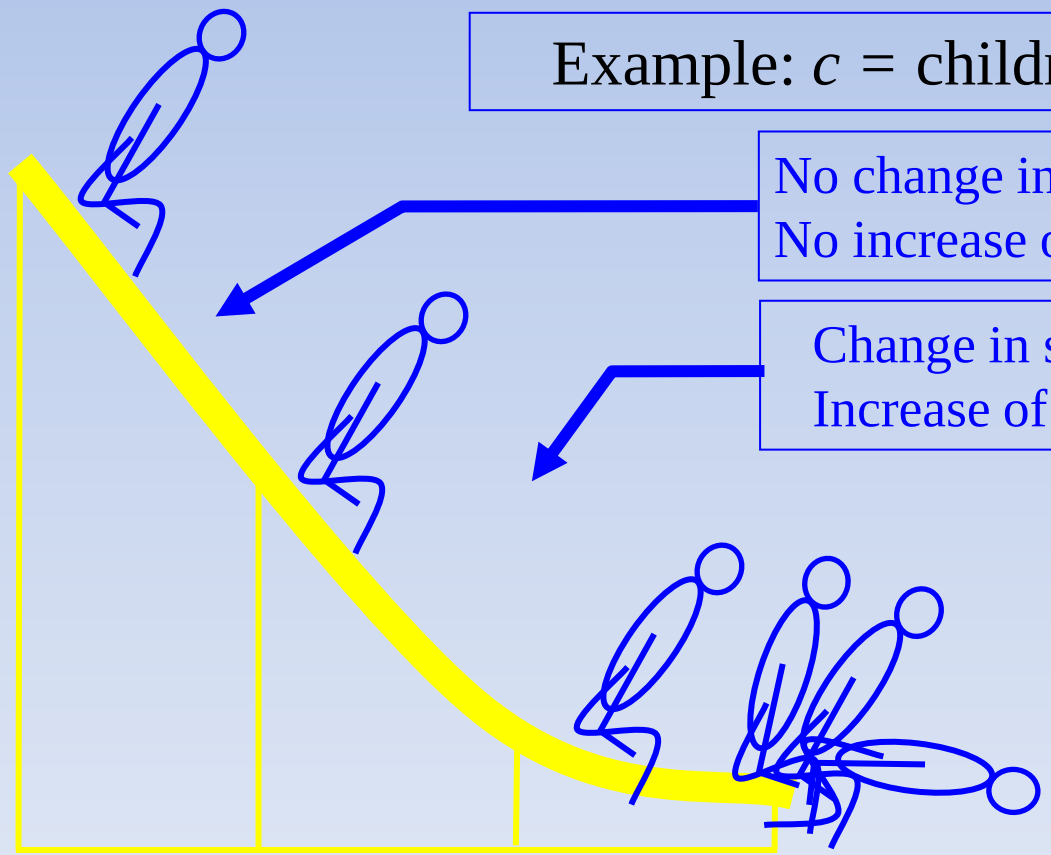
$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial z^2}$$

$\partial c / \partial t$ = increase of c in time

$\partial c / \partial z$ = increase of c in space (slope)

$\partial^2 c / \partial z^2 = \partial / \partial z \, (\partial c / \partial z)$ = change in slope

Example: c = children on a slide:



No change in slope →
No increase of # children in time

Change in slope present. →
Increase of # children in time

D is proportionality constant

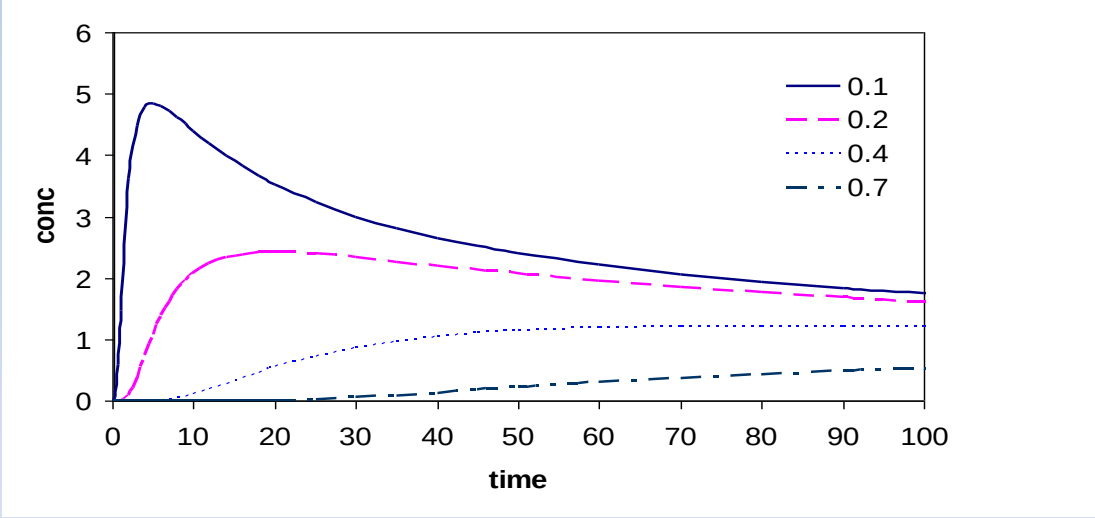
LD - Diffusion model for Iontophoresis

The model:
1. 1-Dimensional diffusion
2. Decay
3. Saturation by subsequent shots.

1-Dimensional diffusion : solution

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

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



Q = amount of injected molecules

Parameter in fig.:
depth z
Constants in fig.:
D = 0.001
Q = 1

Drawback: decrease by diffusion only is too slow

But : decrease by leakage (sideways) will also be present

LD - Diffusion model for Iontophoresis

The model:
1. 1-Dimensional diffusion
2. Decay
3. Saturation by subsequent shots.

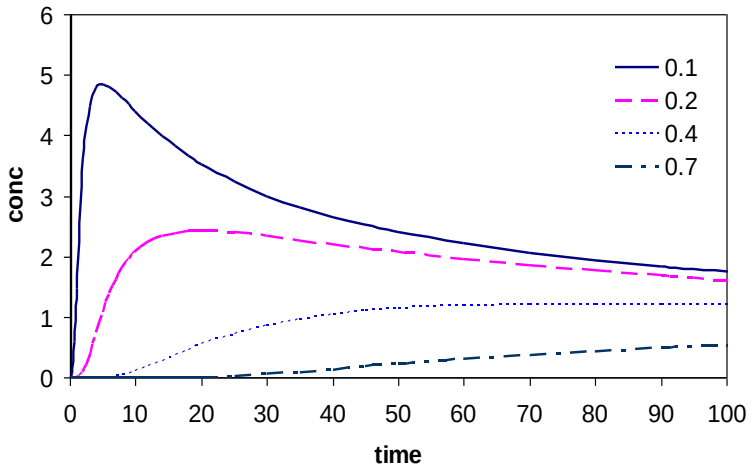
2. Experiments show:
Decrease in time too slow:
Add decay term: $-\lambda c$

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

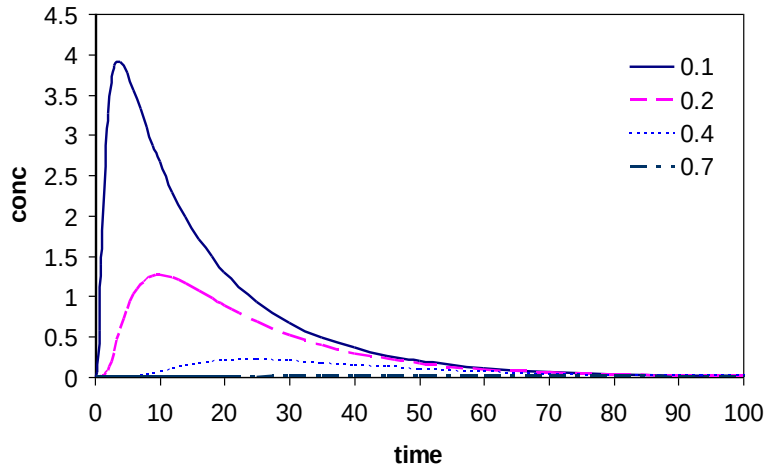
$$\text{if } D = 0: \quad c(t) = c(0).\exp(-\lambda t)$$

,

Without decay



With decay



LD - Diffusion model for Iontophoresis

The model:
1. 1-Dimensional diffusion
2. Decay
3. Saturation by subsequent shots.

Assume:

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

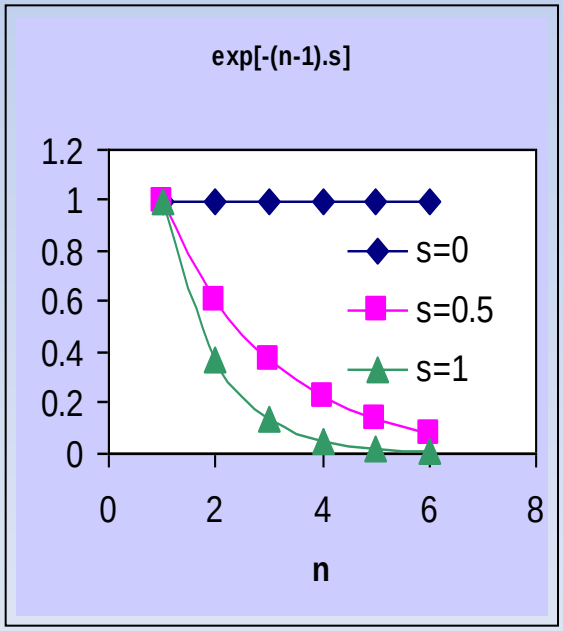
(*) = above resting flux level.

$$c(z,t) = \frac{Q}{\sqrt{\pi D t}} \exp\{-\frac{z^2}{4Dt} - \lambda t\} \Rightarrow \Delta F(t) = \frac{Q_0}{\sqrt{\pi D t}} \exp\left(-\frac{z^2}{4Dt} - \lambda t\right)$$

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 (exp=1)

if $s >> 1$: only first shot contributes (n=1 only)

LD - Diffusion model for Iontophoresis

The model:
1. 1-Dimensional diffusion
2. Decay
3. Saturation by subsequent shots.

Final model:

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

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

Notation in program:

$$\Delta F = \sum_{n=1}^{N} \exp\left[-(n-1)s\right] \frac{C}{\sqrt{t_n}} \exp\left(-\frac{\tau_1}{t_n} - \frac{t_n}{\tau_2}\right);$$

$$C \sim \frac{Q_0}{\sqrt{\pi D}};\ \tau_1 = \frac{z^2}{4D};\ \tau_2 = \frac{1}{\lambda}$$

τ_1 = diffusion time constant

τ_2 = decay time constant

(both: if larger, then process slower)

LD - Diffusion model for Iontophoresis

Experiments: (by J. Blaauw)

- Periflux 4000 laser Doppler system (Perimed),
- Periflux tissue heater set to 31°C (PF4005, Peritemp),
- Perfusion probe: Laser beam (wavelength 780 nm),
- Iontophoresis probe (PF481-2, Perimed, Sweden) containing a thermostatic probeholder,
- Iontophoresis controller (PeriIont 382, Perimed),
- Position: dorsal side of middle phalanx of third finger,
- Subjects sitting, forearms on soft pillow at heart level,
- Temperature-controlled room (T=23.4 ± 0,5°C)

LD - Diffusion model for Iontophoresis

Laser-Doppler perfusion monitor:

measures 0th and 1st moment of power spectrum of Doppler signal

$$M_n = \int_{\omega 1}^{\omega 2} \omega^n . S(\omega) . d\omega \quad ; \quad n = 0,1$$

,

M_0 ~ concentration of moving (red) blood cells
M_1 ~ perfusion flux (flow)
M_1 / M_0 ~ averaged velocity of blood cells

Practical limits: ω_1 = 20 Hz ; ω_2 = 12 kHz

LD - Diffusion model for Iontophoresis

Experiments:

Administered drugs:

1. ACh: acetylcholine
2. SNP: sodium nitroprusside

Expected: SNP has dilatation effect on vessels and capillaries; this will lead to a higher perfusion.

LD - Diffusion model for Iontophoresis

Subjects for experiments, using in testing the model:

	code	ACh	SNP
Subjects: - Pre-eclampsia patients (Post partum) - Controls (healthy) (Post partum)	 PPP PPC	 N=22 18	 N=21 20
Experimental settings: • Resting flow measurement, duration (s) ([1]) • Shot duration (s) • Current (mA), anodal (A) or cathodal (C) • Nr. of shots • Shot interval (s)		 600 20 0.1 A 7 60	 600 20 0.2 C 9 90

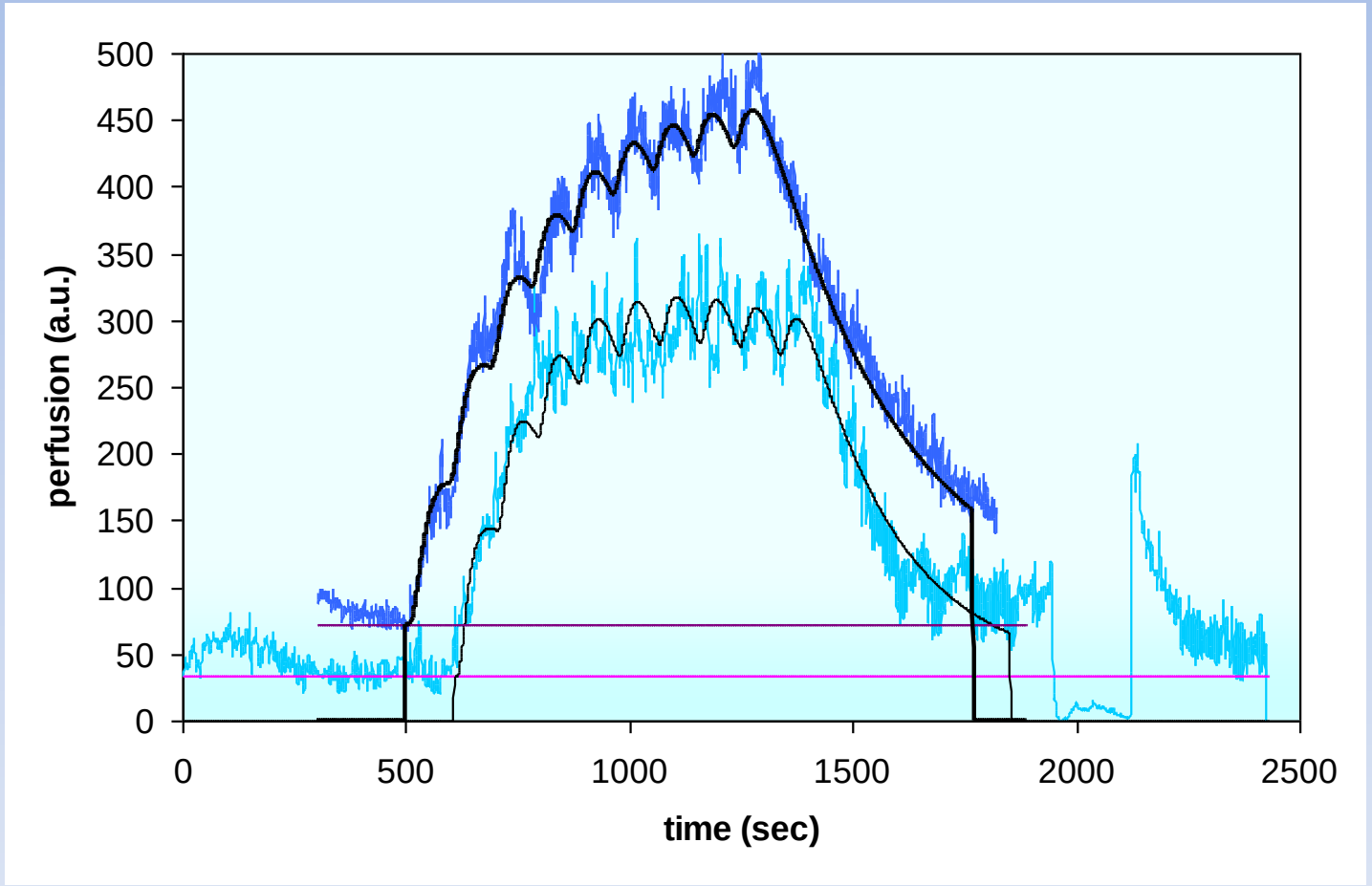
([1]): in some cases 100 or 200 s

See LASDOP program

LD - Diffusion model for Iontophoresis

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

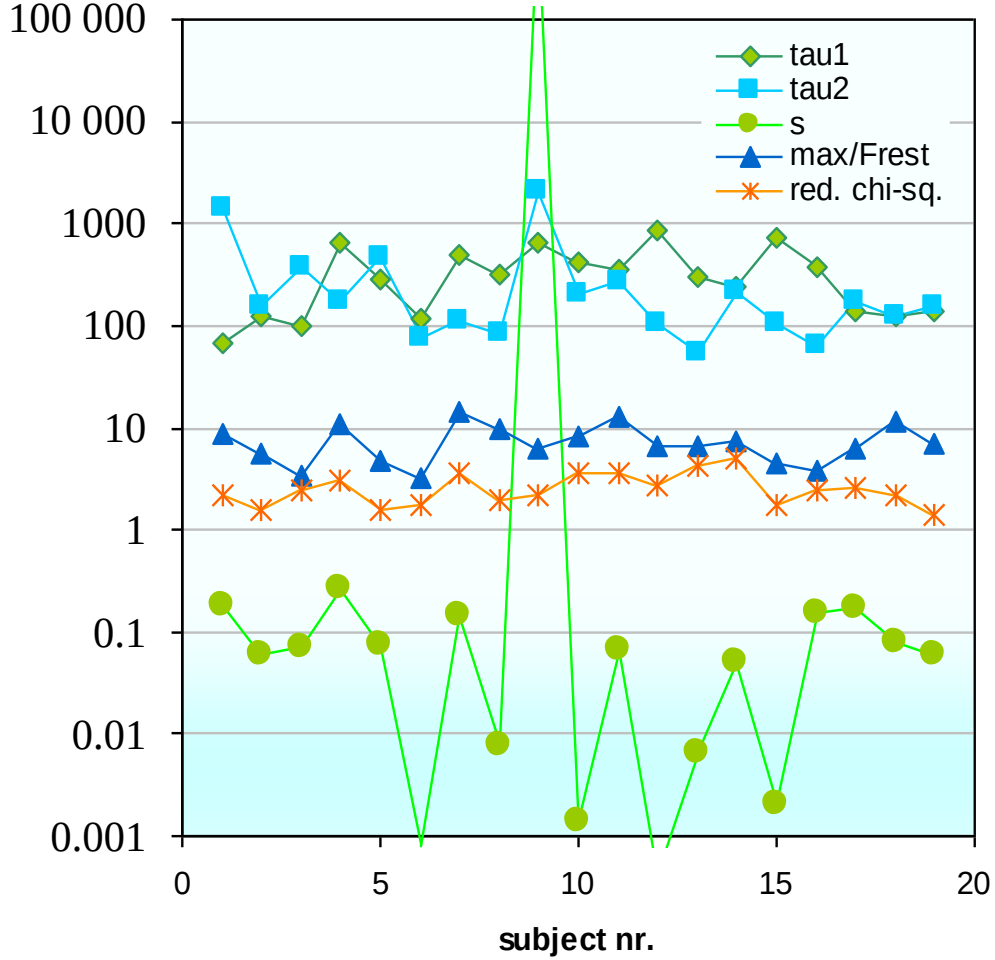
9 shots; 90 sec. apart.



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

LD - Diffusion model for Iontophoresis



Group:
Pre-eclampsia patients;
Post-partum;
SNP-administration

Time constants:
τ_1 : diffusion
τ_2 : decay

Shot saturation constant: ***s***
$s = 0$: all shots contribute;
$s \rightarrow \infty$: first shot only

Reduced χ^2 :
= 1 for optimum fit.

LD - Diffusion model for Iontophoresis

Overall results for post-partum patients (PPP)
and post-partum controls (PPC)

4 groups: PPC-ACh, PPC-SNP, PPP-ACh, PPP-SNP

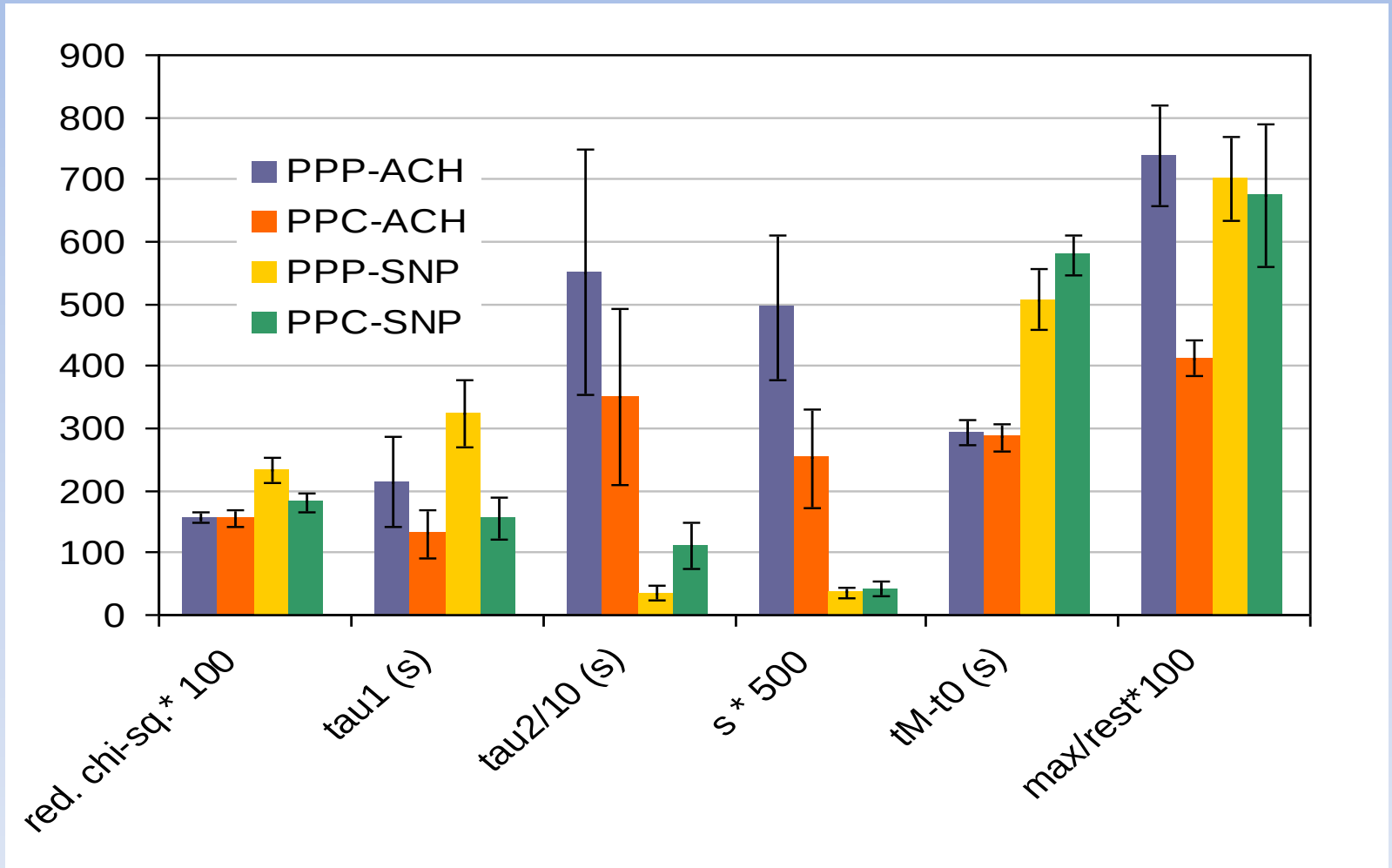
Excluded subjects from calculations, due to off-limit values
($s >= 10^6$ or $\tau_2 >= 10^5$ s):
6 of 80 ; max. 3 of 22.

$\tau_2 \rightarrow \infty$: decay negligible

$s = 0$: all shots contribute equally
$s \rightarrow \infty$: first shot contributes only

LD - Diffusion model for Iontophoresis

Overall results for post-partum patients (PPP) and controls (PPC)

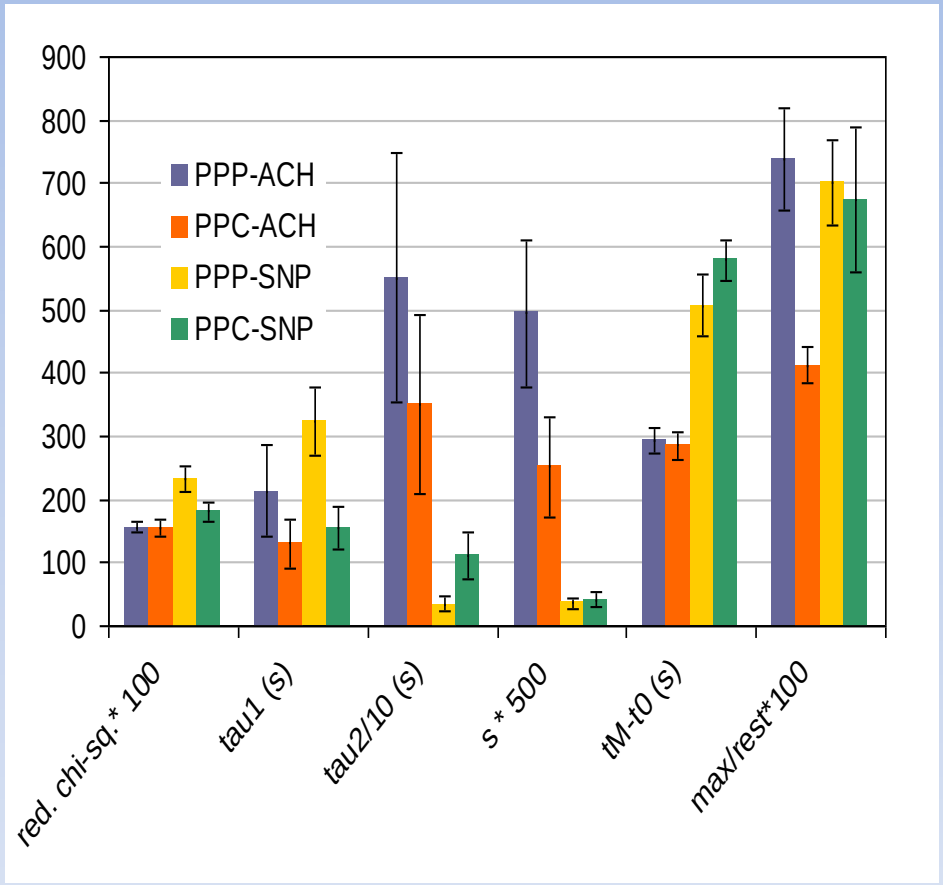


LD - Diffusion model for Iontophoresis

PPP = post-partum patients
PPC = post-partum controls

Conclusions:

- $\tau_1 \sim 1/D$: sign. higher in PPP's (ACh and SNP); slower **diffusion**
- $\tau_2 \sim T_{1/2}$: sign. higher in ACh's (PPP and PPC); slower **decay**
- s : shot saturation constant: sign. higher in ACh's (PPC and PPP); **first shot(s)** dominate(s)
- t_M : sign. higher in SNP's (PPC and PPP); see τ_2
- max / resting flux : sign lower in PPC-ACh.
- diffusion coefficients (with z = 1 mm resp. 10 µm): $\approx 10^4$ resp. 1 x not-electrically sustained values.



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Publications: see website:
www.demul.net/frits, scroll to “Laser Doppler”.

the end