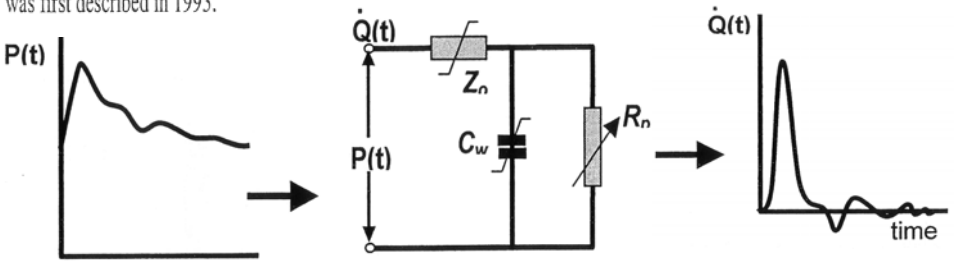
Tfy-99.269 Current methods and issues in monitoring physiological systems
Lecture 12, April 11, 2005

- More about cardiac output by Model Flow
- Cardiac output by impedance plethysmography
- Brain: Functional NIRS measurements
- Cerebral Blood Flow
- Cerebral Oxygenation
- Neurovascular coupling

Wesseling II: Modelflow method

In an effort to reduce errors associated with the assumptions in the "cZ" method and to eliminate the requirement for invasive cardiac output measurements, Dr. Wesseling went on to develop a new algorithm based on a non-linear, three-element model of aortic input impedance (Z_0) that computes aortic flow from blood pressure. The "Modelflow" algorithm was first described in 1993.[2]



Aortic Characteristic Impedance (Z_o)
Windkessel Compliance (C_w), and
Peripheral Resistance (R_p).

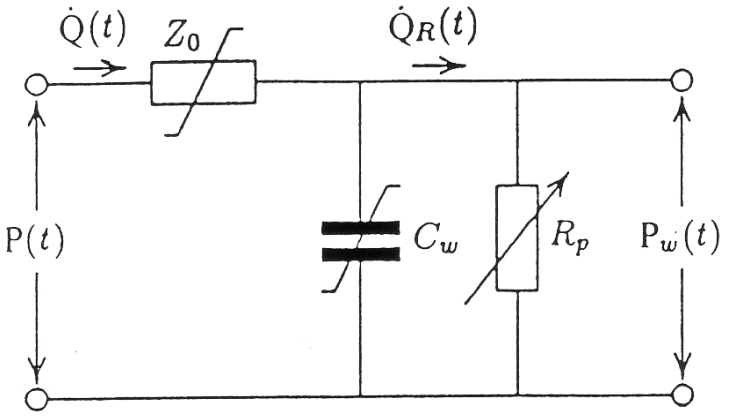


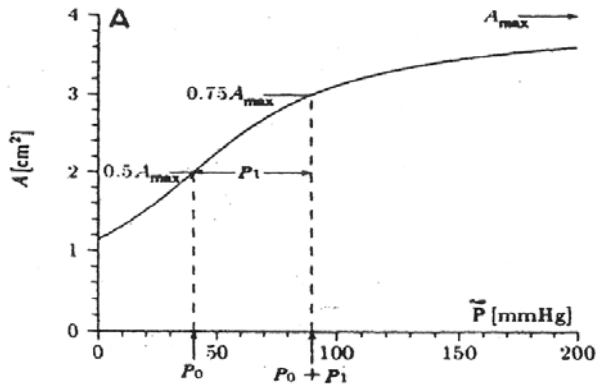
FIG. 1. Diagram of 3-element model used in this study to compute flow. Z_0, characteristic impedance of proximal aorta; C_w, windkessel compliance of arterial system; R_p, total systemic peripheral resistance. Z_0 and C_w have nonlinear, pressure-dependent properties, indicated by stylized S symbol. R_p varies with time, as symbolized by arrow. $\dot{Q}(t)$, blood flow as function of time; $P(t)$, arterial pressure waveform; $P_w(t)$, windkessel pressure.

1) Aortic Impedance (Z_0)

Aortic impedance is calculated as $Z_o = \sqrt{\rho / (AC')}$ where:

ρ = density of blood,
A = cross-sectional area of the aorta, and
C′ = aortic compliance per unit length.

C′ is the derivative of the pressure-area function with respect to pressure (P), i.e. C′ = dA/dP



The P-A curve for any particular aorta can be characterized by three parameters (See Figure 3):

a) (P_0) the pressure at which aortic compliance is maximal,

b) (P_1) the difference between the pressure at which aortic compliance is one-half of its maximum ($P_{Cmax/2}$) and P_0, i.e. $P_1 = P_{Cmax/2} - P_0$, and

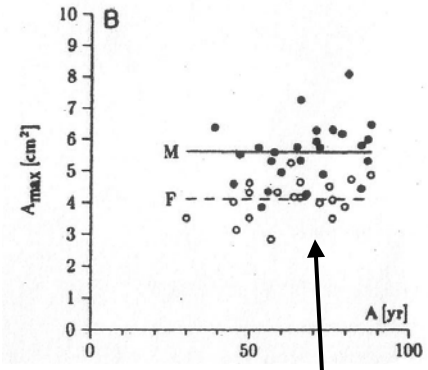
c) (A_{max}) the maximum aortic area.

Aortic area as a function of pressure (P) can be computed as:

$$A(P) = A_m\,(1/2 + \tan^{-1}((P-P_0)/P_1)/\pi).$$

C′ is the derivative of the above equation:

$$C'(p) = \frac{A_m / \pi P_1}{1 + \left(\frac{P - P_0}{P_1}\right)^2}$$



P_0 decreases strongly with age
P_1 decreases slightly with age
A_{max} is age independent, but depends on gender in a scattered way

In practice aortic pressure is not available but you need to use e.g. radial pressure from the arm as a surrogate. Requires more modeling and solution of inverse problem to calculate p_{aortic} from p_{radial}

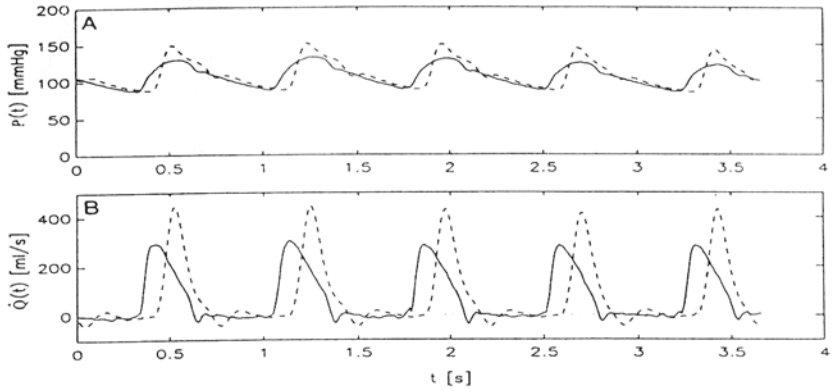
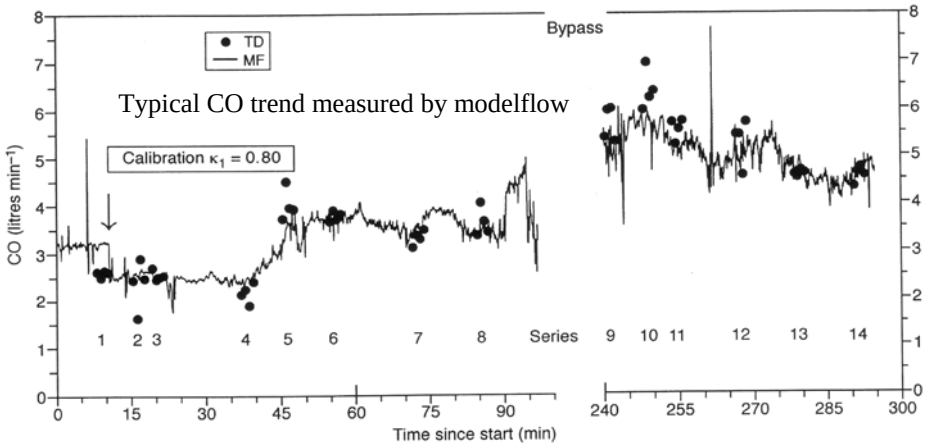
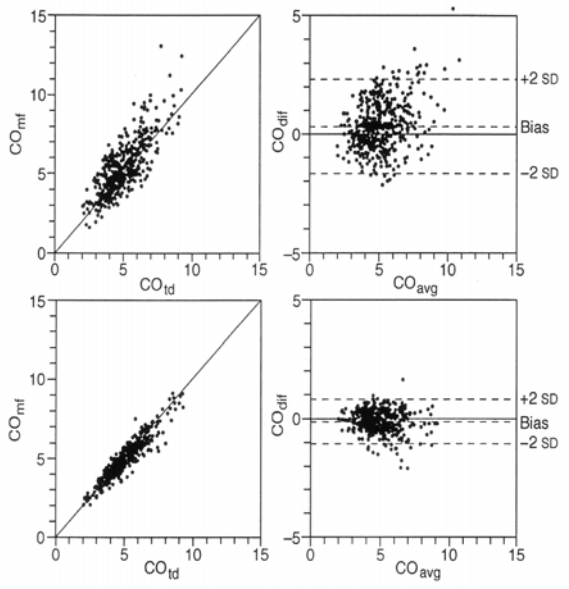


FIG. 3. *A*: simultaneous aortic (solid line) and radial pressures (dashed line). *B*: simulated model flow from aortic (solid line) and radial pressures (dashed line). Model flow computed from aortic pressure shows typical characteristics of an aortic flow pulsation: steep upslope at beginning of systole, a gradual down slope terminated in a steep final phase, and sharp dicrotic notch at end systole, followed by a period of almost zero flow in diastole. Model flow computed from radial pressure is delayed and distorted and shows typical characteristics less convincingly.



Typical CO trend measured by modelflow

Variable	Units	Mean	SD	Range
Patient characteristics, *n*=54				
Age	yr	62	9	43–78
Height	cm	169	8	153–188
Weight	kg	74	8	55–92
κ_1	Calibration factor !	0.95	0.18	0.62–1.45

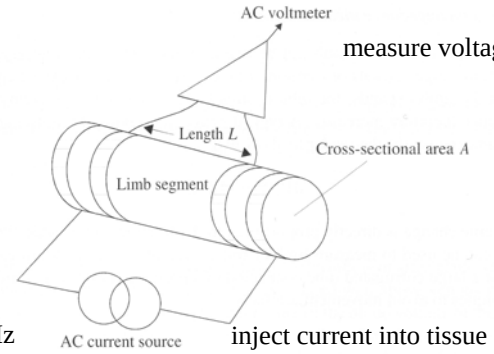


before calibration

after calibration

Fig 7 Diagrams showing the data pairs in all 54 patients before (top, *n*=490) and after (bottom, *n*=490–54=436) calibration on the first series after induction of anesthesia. In the Bland–Altmanplot CO_{dif} either CO_{mf}–CO_{td} before, or $CO_{\kappa 1}$–CO_{td} after calibration; CO_{avg} is their mean. The dashed lines indicate the bias and limits of agreement between methods.

Cardiac output by impedance plethysmography



measure voltage difference

1 mA @100 kHz

inject current into tissue

In general, it is not possible to relate impedance changes directly to volume changes. However, impedance plethysmography has been used to measure blood flow, respiration and cardiac output, with varying success. As an example: if current is passed down the leg and two electrodes are used to measure the impedance of the calf and thigh then a baseline impedance of about 200 Ω is found. The impedance will be found to decrease during systole by about 0.1 Ω (see Brown *et al* 1975). If the venous return is occluded then the impedance of the limb falls progressively by about 0.1 Ω on each cardiac cycle.

Impedance change vs. volume change

It is instructive to consider the change in impedance resulting from a change in tissue dimensions alone, as this illustrates the effect of the assumptions that are made. If we take a segment of length L and cross-sectional area A, then the impedance Z is given by

$$Z = \rho L/A = \rho L^2/V \qquad \text{where} \quad V = LA.$$

We could make three different assumptions about the expansion of this segment:

- it is radial only;
- axial only; or
- expands isotropically.

Taking the first two cases, and finding the change in impedance with volume

$$\left[\frac{\delta Z}{\delta V}\right]_L = -\frac{Z}{V} \qquad \text{and} \qquad \left[\frac{\delta Z}{\delta V}\right]_A = \frac{Z}{V}. \tag{19.15}$$

The first two assumptions give the same *magnitude* of change, but *opposite* sign! A more reasonable assumption is that the tissue expands equally in all directions, i.e. $dL/L = dR/R$, where R is the radius of the section. We now have $Z = f(L, R)$ where L and R are both functions of V.

Thus,

$$\frac{dZ}{dV} = \left[\frac{\delta Z}{\delta L}\right]_R \frac{dL}{dR} + \left[\frac{\delta Z}{\delta R}\right]_L \frac{dR}{dV}.$$

Problem: Find the printing errors in this calculation!

From $Z = \rho L/A$ we find

$$\left[\frac{\delta Z}{\delta L}\right]_R = \frac{\rho}{\pi R^2} \quad \text{and} \quad \left[\frac{\delta Z}{\delta R}\right]_L = \frac{2\rho L}{\pi R^3}.$$

From $V = \pi R^2 L$ and $dL/L = dR/R$ we can obtain

$$dL/dV = 1/3\pi R^2 \quad \text{and} \quad dR/dV = 1/3\pi RL.$$

Substituting these values into the equation for dZ/dV gives

$$dZ/dV = -\rho/3A^2 = -Z/3V. \tag{19.16}$$

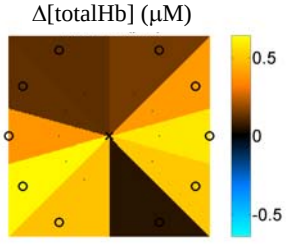
The three starting assumptions (radial expansion, axial expansion or isotropic expansion) thus give three different solutions for the change in impedance with volume.

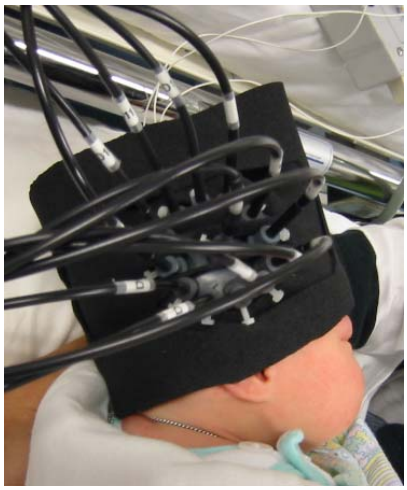
Measuring brain function optically by NIR light

IR light can propagate in brains up to 5…6 cm

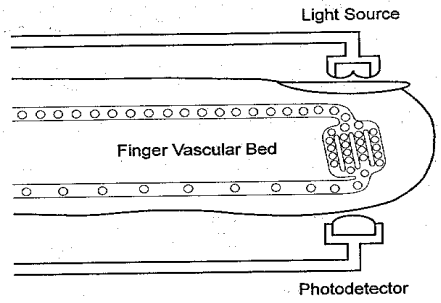
Measures changes in:

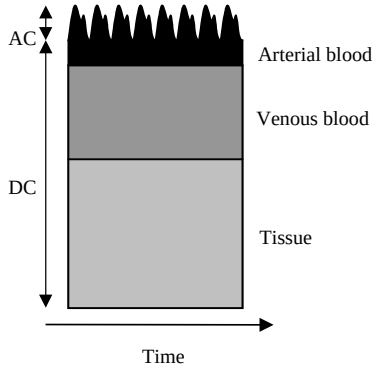
-cerebral blood flow and volume
-oxygenation of blood
-neurovascular coupling
-circulatory response to stimuli
-neuronal response to stimuli?





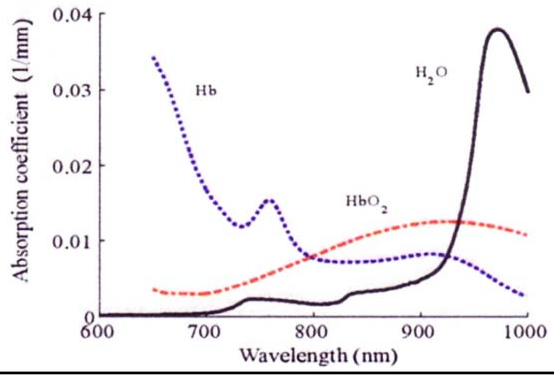
Measuring cerebral blood volume and oxygenation by NIRS (Near IR Spectroscopy)
Same principle as in pulse oximetry, BUT since pulsation in brain is weak, usually only DC component is utilized.
"High end": NIRS optical tomograpy, multi-channel devices using diode lasers, both absorption and phase measurement, photon diffusion model, solving inversion Problem. "Low-end": Functional measurements



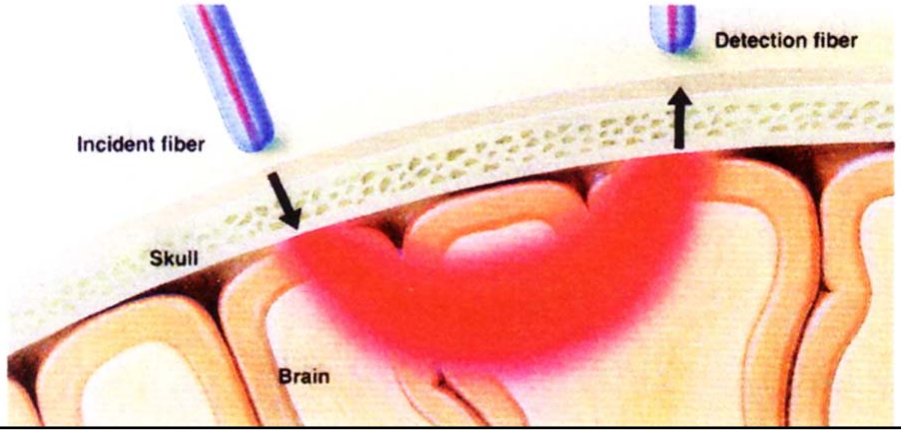


Near-infrared spectroscopy (NIRS) is an optical method for non-invasive monitoring of cerebral hemodynamics. In NIRS imaging, near-infrared (NIR) light (650–950 nm) is delivered into tissue, and the transmitted light is detected. The overall absorption of NIR light in tissue is relatively low while the differences in oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) absorption are still detectable. As a result, the local concentration changes of HbO_2 and Hb in cerebral cortex up to several centimeters of penetration depths can be detected non-invasively.

- At near-infrared (NIR) wavelengths (650-950 nm), the absorption of light in tissue is relatively low
- Absorption spectra of oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) are different in the near-infrared region
- By using at least two wavelengths, changes in the concentrations of HbO_2 and Hb can be calculated
- In non-invasive near-infrared specroscopy (NIRS), NIR light is delivered into tissue on the surface of the skin, and the light reflected from the tissue is detected at another position on the skin surface



- Source-detector (SD) distance is typically a few centimeters
- Penetration depth of NIR light is approximately one-half of the SD separation
- Tissue scatters light strongly, which significantly increases the mean photon path length in tissue and decreases the measured light intensity compared to a non-scattering medium



MODIFIED BEER-LAMBERT LAW

- Beer-Lambert law describes the exponential decay of the light intensity *I(x)* as a function of propagation distance *x* in a homogeneous absorbing medium

$$I(x) = I_0 e^{-\mu_a x}$$

μ_a = absorption coefficient
I_0 = intensity of incident light

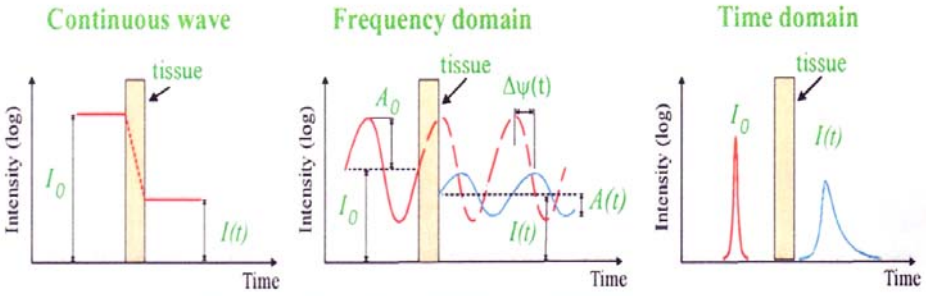
- Strongly scattering medium, such as tissue, can be handled by the modified Beer-Lambert law

$$A = \ln\left(\frac{I_0}{I}\right) = \mu_a \mathrm{DPF} \cdot d + G$$

DPF = differential path length factor
d = SD distance
G = background scattering

- The term DPF $\cdot d$ is the mean path length of the photons including the effect of scattering, and G contains the background scattering

MEASUREMENT TECHNIQUES



- In continuous wave technique, the average intensity *I(t)* is measured
- In frequency domain: the modulation amplitude *A(t)*, the phase difference $\Delta\psi(t)$ with respect to the incident light, and the average intensity *I(t)* are measured
  - The phase difference is proportional to the mean path length of the detected photons
- In time domain: picosecond light pulses are guided into the tissue, and the full time-of-flight distribution of the photons is measured
  - The mean path length is proportional to the mean time-of-flight

NEAR-INFRARED SPECTROSCOPY

In NIRS, the temporal changes in intensity are often assumed to be due to hemodynamics, and the background absorption and scattering are considered to be time-independent

Assuming N absorbers with temporarily varying concentrations, μ_a can be written as

$$\mu_a = \sum_i^N \alpha_i(\lambda) c_i + B$$

α_i = specific absorption coefficient for chromophore i at wavelength λ
c_i = concentration of chromophore i
B = constant background absorption

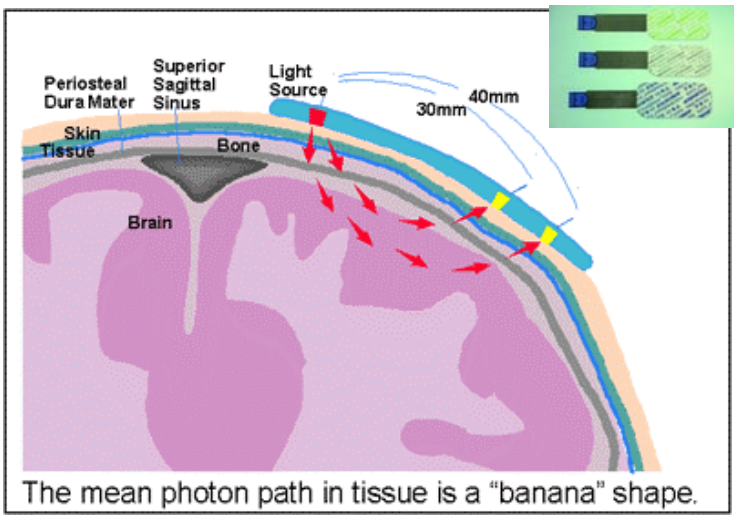
By using $M \geq N$ wavelengths, the concentration changes of the N absorbers can be solved from the intensity changes of the signal:

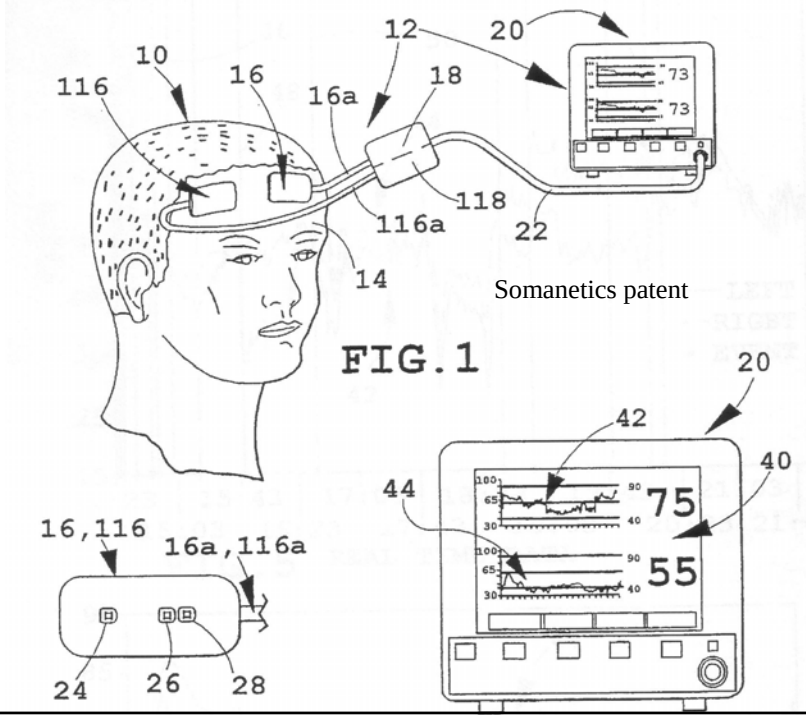
$$\Delta C = \left(\alpha^T \alpha\right)^{-1} \alpha^T \frac{\Delta A}{d \cdot \mathrm{DPF}}$$

$\Delta C_{N\times 1}$ = concentration changes of each chromophore
$\alpha_{M\times N}$ = matrix containing specific coefficients for each chromophore at each wavelength
$\Delta A_{M\times 1}$ = measured changes in A at each wavelength

In NIRS studies, changes in the concentrations of HbO_2 and Hb are usually considered as the dominant contributors to the temporarily varying part of the optical signal

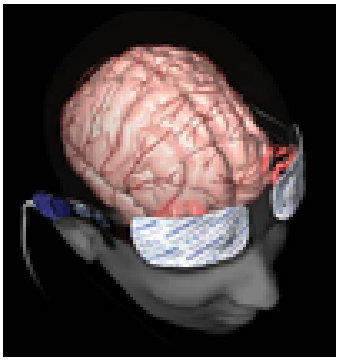
INVOS by Somanetics

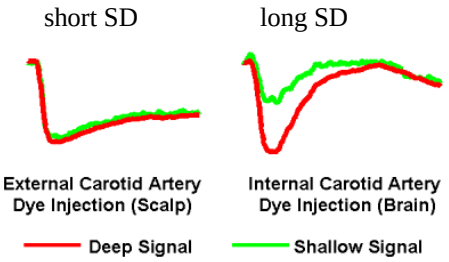




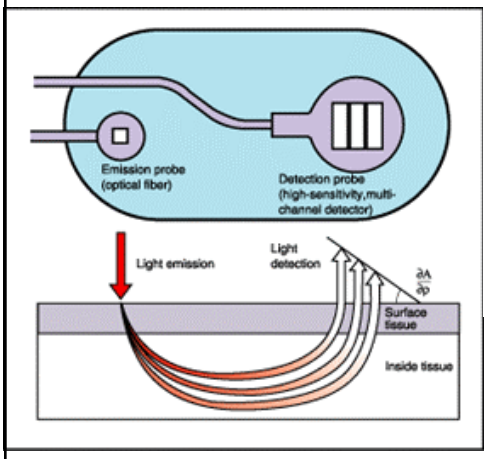
Somanetics patent

How to separate signals from surface tissue (upon scull) from those of cortical origin?





NIRO by Hamamatsu



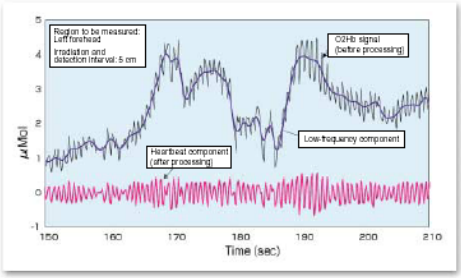
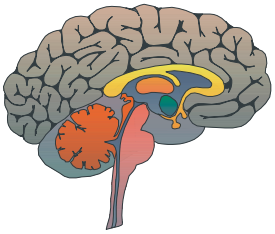


Figure 4. Data of high-speed 6-Hz measurement

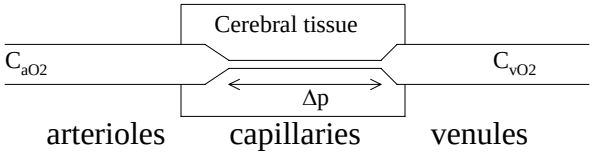
Cerebral blood flow and oxygenation



Some basic numbers about brain vs. body:

$m_{brain} \approx 0.02 \cdot m_{body}$	mass
$VO2_{brain} = 0{,}2 \cdot VO2_{body}$	oxygen consumption
$CBF = 0{,}12 \cdots 0.15 \cdot CO$	cerebral blood flow
$OEF = VO2/DO2 = VO2/(C_{aO2} \cdot CO)$	oxygen extraction fraction
$OEF_{brain} = 1.33 \cdots 1.66\ OER_{body}$	
$OEF = 1 - (C_{vO2}/C_{aO2})$	→ C_{vO2} lower in brain

Basic equation (again) Fick: $CBF = VO2_{brain}/(C_{aO2} - C_{vO2})$



For laminar flow in capillaries: $\Delta p = R \cdot Q$ or $Q = \Delta p/R$ (volumetric flow)

Resistance $R = 8\mu/\pi r^4$, where μ= viscosity, r= radius of the capillary vessel

Velocity of blood: $v = Q/A = Q/\pi r^2$

Assume Δp = constant = CPP = MAP - ICP or

Cerebral Perfusion Pressure = Mean Arterial Pressure - Intra Cranial Pressure

General rule : if r increases by x %, v will increase by 2x % and and CBF by 4x %

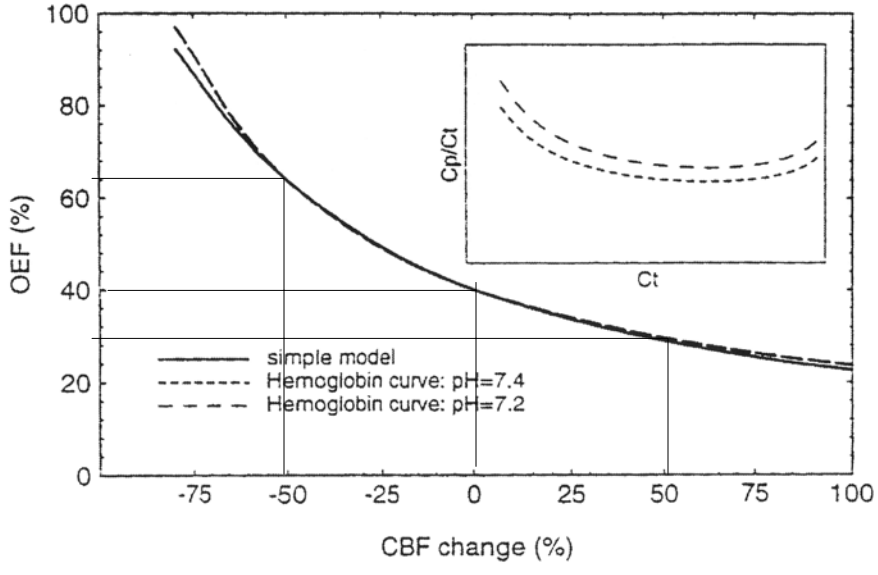
OER depends on time blood cells stay in capillaries wherefrom the diffusion to cerebral tissue takes place: OER ⇩ when v ⇧

Assume at onset of stimulus (e.g. waking up from asleep) VO2 ⇧
then if neurovascular coupling regulates r ⇧ by 5%, DO2 ⇧ by 20%

but on the other hand v ⇧ by 10%, which decreases OER and increases C_{vO2}
(because OER = 1 - (C_{vO2}/C_{aO2}))

Basic cerebral IR measurement (DC-based) cannot differentiate arterial and venous blood. According to literature around 70% of the signal comes from the venous blood and 30 from arterial. In addition cerebral S_{aO2} follows whole body S_{aO2} which can be measured by pulse oximetry. So NIRS measures basically **cerebral venous oxygenation and/or OER**

Oxygen extraction fraction vs. cerebral blood flow



Neurovascular coupling

A feedback control mechanism to regulate the balance between local cerebral oxygen delivery (DO_2) and oxygen consumption (VO_2). Increased local neural activity will e.g. release gaseous mediator NO which acts as a vasodilator for capillaries by relaxing smooth muscles of endothelium.

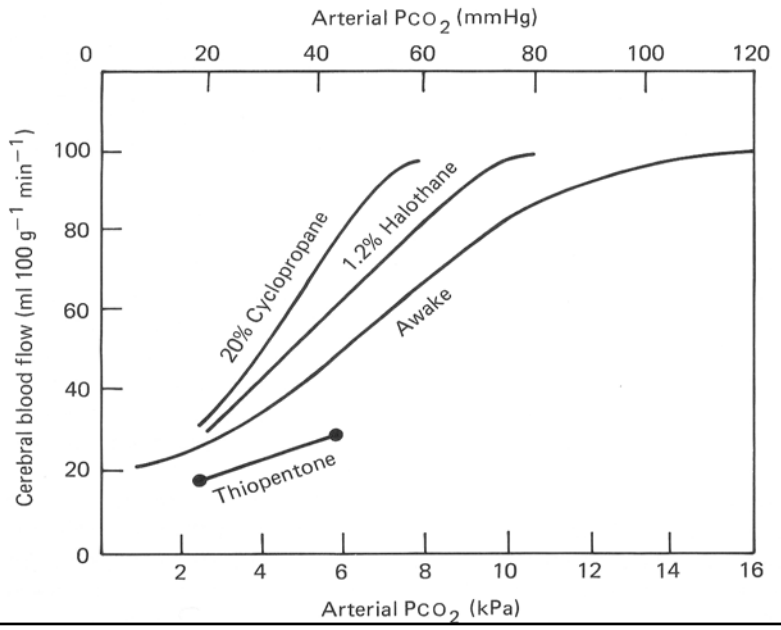
Other regulating factors

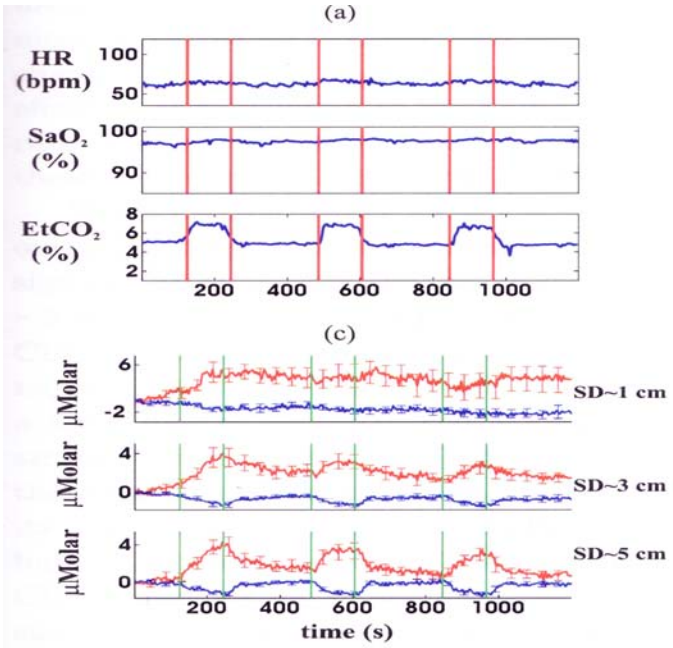
- Body temperature: CBF down by 6 ··· 7 % / ^oC decrease in T
- p_{aCO2} : Hypocapnia (p_{aCO2} low, hyperventilation, CBF ⇩)
  Hypercapnia (p_{aCO2} high, rebreathing, CBF ⇧)

ISSUES:

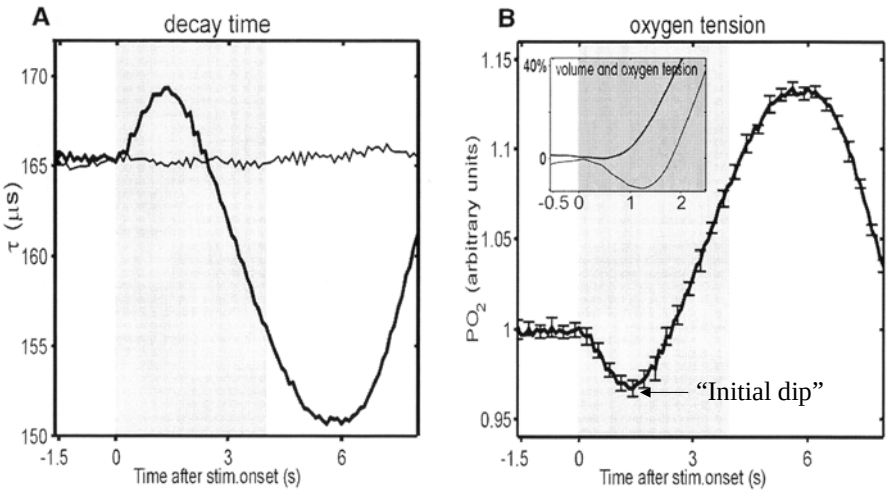
1) The coupling between neuronal activity and blood flow,
2) The link between blood flow and oxygen delivery to tissue,
3) The effect of changes in blood flow on changes in blood volume and venous outflow,
4) The effect of changes in flow, volume, and oxygen extraction fraction (OEF) on changes in the concentration of deoxyhemoglobin.

Cerebral blood flow as function of CO_2 in arterial blood





Hypercapnia experiment (CO_2 breathing)



Cerebral oxygenation changes measured by BOLD fMRI
(Brain Oxygen Level Dependent functional Magnetic Resonance Imaging)

Slow fluctuations in CBF: signal or interference/noise?

Neuroscience Letters

Neuroscience Letters 245 (1998) 147–150

Relationship between fluctuations in the cerebral hemoglobin oxygenation state and neuronal activity under resting conditions in man

Yoko Hoshi[a,*], Shinobu Kosaka[b], Yuxiao Xie[c], Shunji Kohri[a], Mamoru Tamura[a]