Physikalisch-Technische Bundesanstalt
Braunschweig und Berlin
Nationales Metrologieinstitut

Phantoms and performance assessment for fNIRS: IEC/ ISO standard draft and experience of the nEUROPt project

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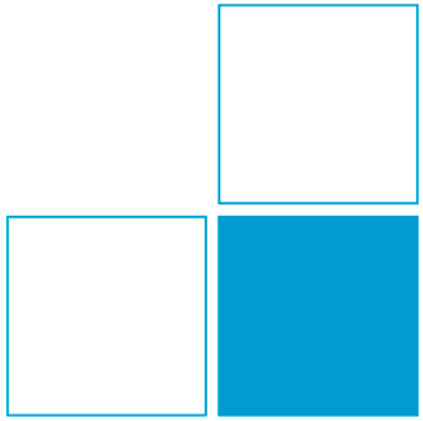
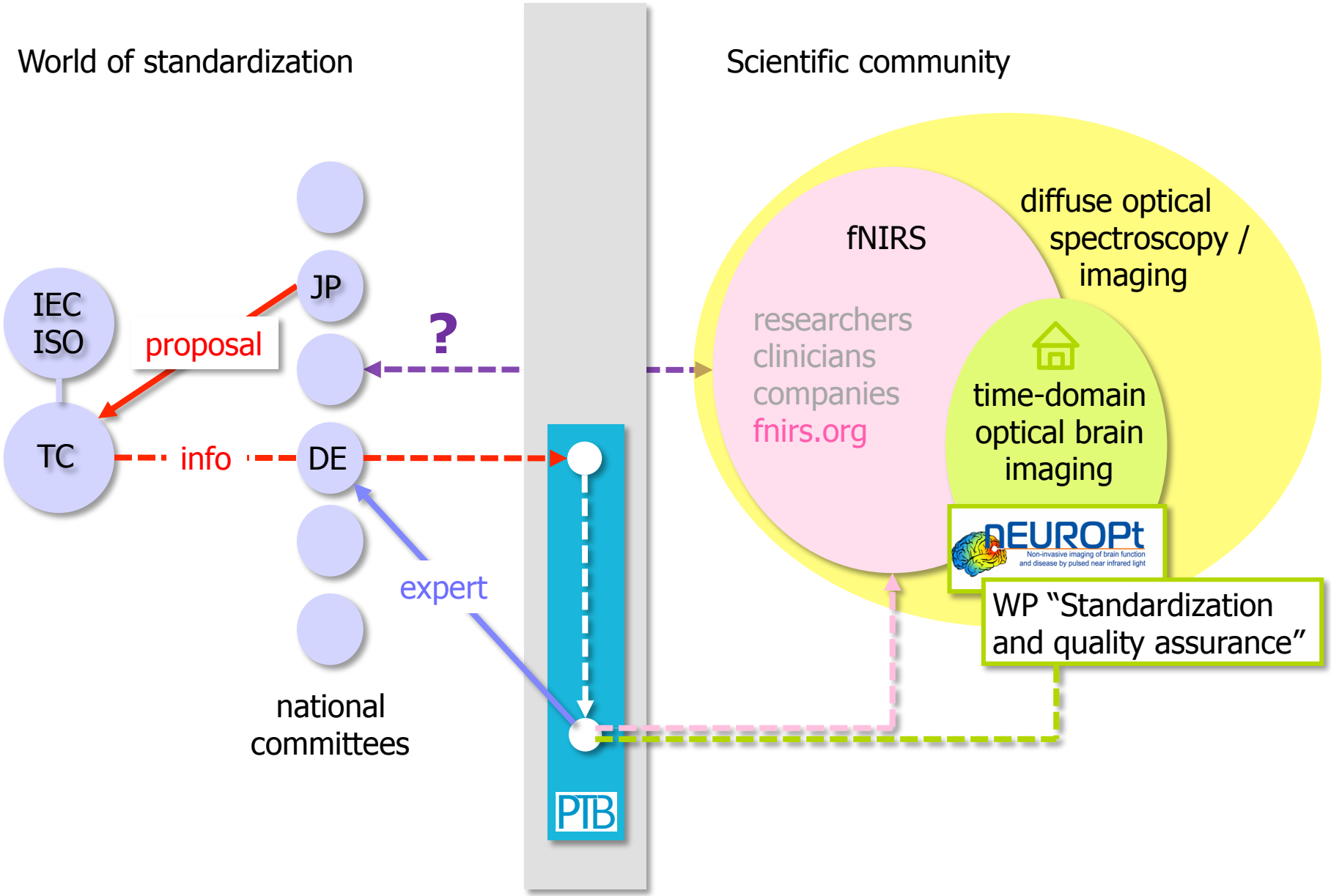


Introductory remarks



Part I: Phantoms and performance tests in IEC/ISO 80601-2-71 draft (functional NIRS)

Part II: Performance assessment of time-domain brain imagers in the nEUROPt project

Medical electrical equipment —

Part 2-71:
Particular requirements for the basic safety and essential performance of functional Near-Infrared Spectroscopy (NIRS) equipment

230 **201.4.3 ESSENTIAL PERFORMANCE**

231 Amendment (add to 4.3):

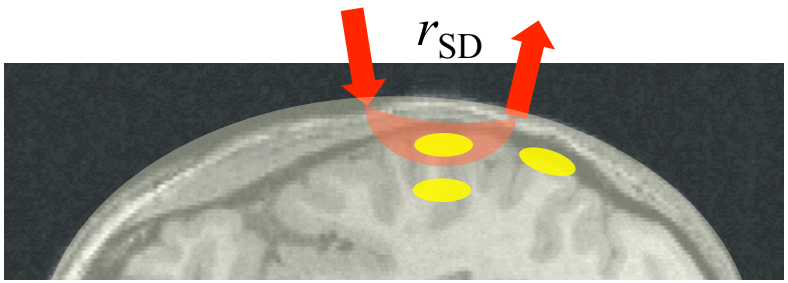
232 For the purposes of this standard, FUNCTIONAL NIRS EQUIPMENT is considered to not have
233 ESSENTIAL PERFORMANCE. ...

What does that mean?
General Standard **IEC 60601-1** (Medical electrical equipment …) defines

3.27
* **ESSENTIAL PERFORMANCE**
performance necessary to achieve freedom from unacceptable RISK

NOTE ESSENTIAL PERFORMANCE is most easily understood by considering whether its absence or degradation would result in an unacceptable RISK.

Signals in functional NIRS



brain activation:
change in detected light intensity

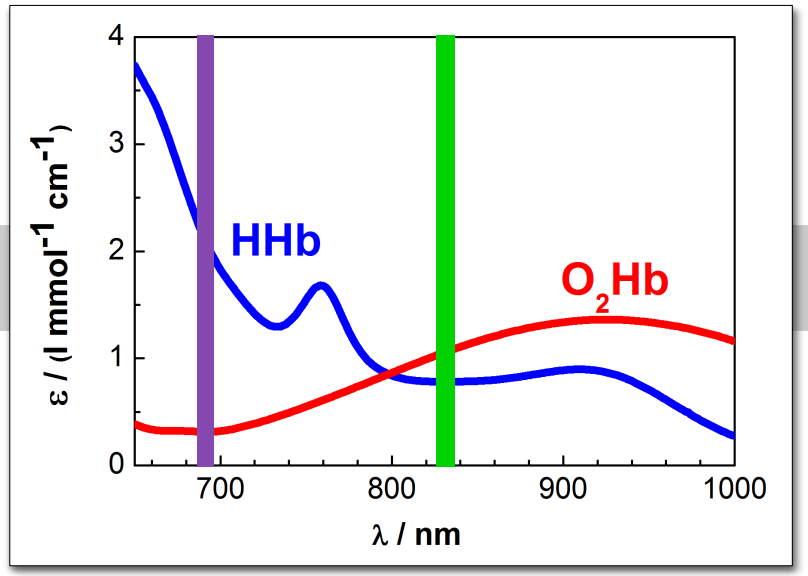
modified Beer-Lambert law:

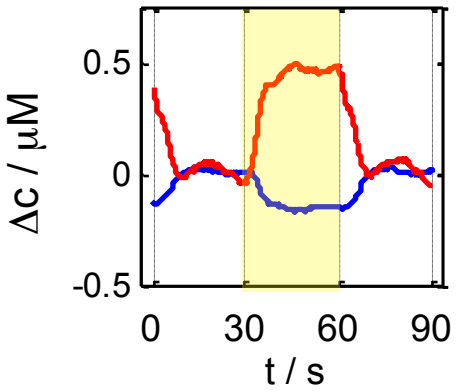
$$I_B / I_A = \exp(-\Delta\mu_a L)$$

(L – mean optical pathlength)

$\Delta\mu_a(\lambda_1)$

$\Delta\mu_a(\lambda_2)$





"Pathlength-dependent haemoglobin change"

$$-\Delta A(\lambda_i) = \log_{10}(I_B / I_A) = \Delta\mu_a L / \log_e 10$$
$$= \varepsilon_{O_2Hb}(\lambda_i)\Delta C_{O_2Hb} L + \varepsilon_{HHb}(\lambda_i)\Delta C_{HHb} L$$

L – mean optical pathlength, assumption: $L = L(\lambda_1) = L(\lambda_2)$

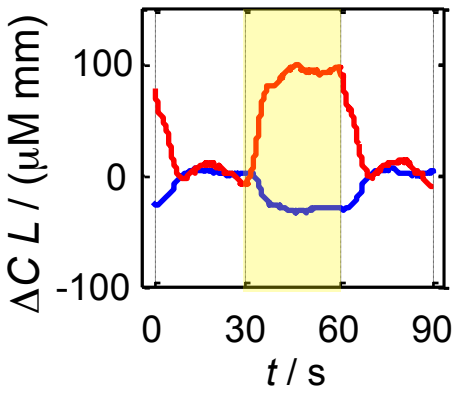
Note:

- this approach (manufacturer-specific) does not make use of the differential pathlength factor DPF = L / r_{SD} (λ-dependent, ~6 for head)
- L remains part of the signal

$$\Delta C_{O_2Hb} L = \frac{\varepsilon_{HHb}(\lambda_2)\Delta A(\lambda_1) - \varepsilon_{HHb}(\lambda_1)\Delta A(\lambda_2)}{\varepsilon_{O_2Hb}(\lambda_1)\varepsilon_{HHb}(\lambda_2) - \varepsilon_{O_2Hb}(\lambda_2)\varepsilon_{HHb}(\lambda_1)}$$

$$\Delta C_{HHb} L = \ldots$$

fNIRS signals:
$\Delta C_{O2Hb}L$(t), $\Delta C_{HHb}L$(t)



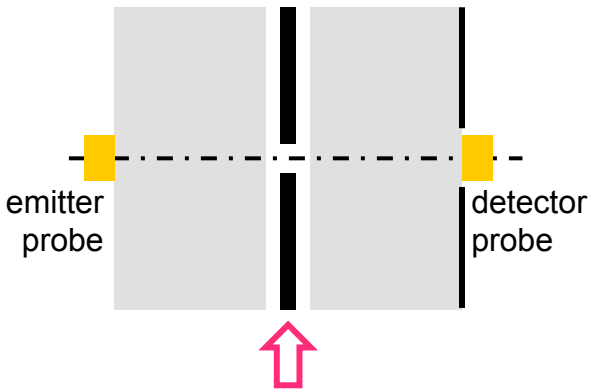
Performance tests in the IEC/ISO 80601-2-71 draft (CDV / DIS)

201.12.1.101. Performance of FUNCTIONAL NIRS EQUIPMENT

2 AVERAGE OPTICAL POWER
3 PEAK WAVELENGTH
4 FULL WIDTH AT HALF MAXIMUM of spectral distribution
5 PATHLENGTH DEPENDENT HAEMOGLOBIN CHANGE
6 Signal stability
7 RESPONSE TIME
8 *SIGNAL-TO-NOISE RATIO
9 SIGNAL CROSS-TALK

- no phantom
- large, typical attenuation between emitter and detector probe (turbid material)
- + means to generate attenuation change ΔA

Annex BB: Phantom specifications



- 2 scattering and absorbing attenuators (POM *)
  μ_s': 0.8 mm^{-1} – 1.2 mm^{-1}, μ_a: 0 – 0.05 mm^{-1}
- thickness > 30 mm, diameter > 60 mm
  (avoid edge effects)
- overall attenuation >40 dB or >60 dB (10^4, 10^6)
  (depending on test - ?)
  - valid for window diameter 8 mm (detection side)
- interchangeable circular aperture (size ? - small)
  → attenuation change 3 dB to 4 dB (factor 2 to 2.5)
  - measured by reference system (power meter - ?)

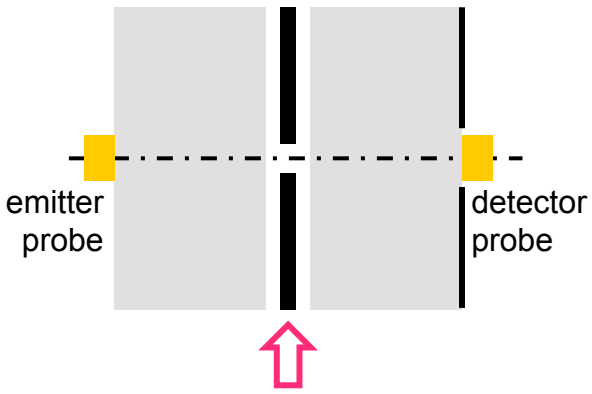
* "POM" (polyoxymethylene; also "acetal", "polyacetal"; e.g. Delrin®, Duracon®,…) not unambiguous: POM-H (e.g. Delrin®), POM-C (e.g. Hostaform®) with many different products with different composition and physical properties (Dupont: 85 Delrin® materials!)

153 **Fantini *et al.*: Frequency-domain optical mammography**
Med. Phys. 1996

TABLE I. Measured absorption and reduced scattering coefficients of the Delrin block.

λ (nm)	μ_a (cm^{-1})	μ_s' (cm^{-1})
685	0.019 ± 0.001	13.2 ± 0.5
825	0.023 ± 0.001	11.9 ± 0.5

Annex BB: Phantom specifications



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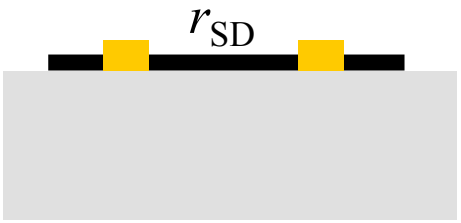
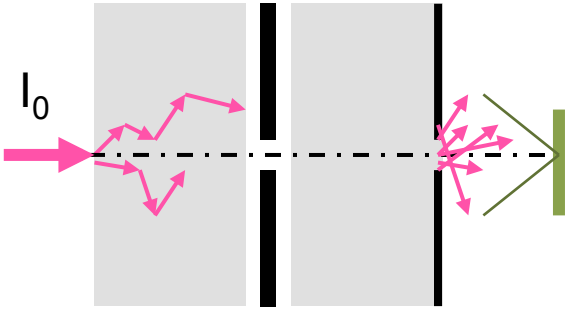


Problem:

- not applicable for all-in-one probes
- no technical solution so far

Total attenuation of the phantom

Aim: diffuse transmittance ***T*** of the phantom similar to typical diffuse reflectance ***R*** of the head at r_{SD} = 3 cm



detected amount of light depends on

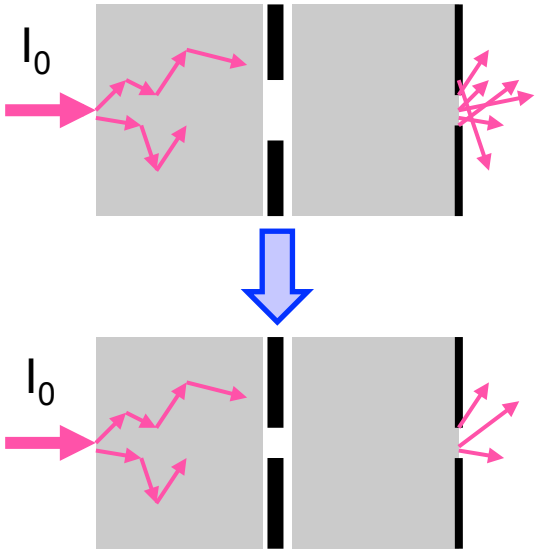
- optical properties μ_s', μ_a (→ on λ)
- size of pinhole between blocks
- size of aperture on detection side
- size and distance of detector
- acceptance angle
- size of illuminated area on input side (edge effects)

→ "optical loss" is not a property of the phantom alone, but also depends on measurement conditions

→ need to specify all relevant parameters

Performance test for signal (hemoglobin change)

Simulation of hemoglobin change by turbid phantom with interchangeable aperture
→ specific value of intensity change



measure I_B / I_A by power meter

Calculation of related signal

$$\Delta C_{O_2Hb} L = \frac{\varepsilon_{HHb}(\lambda_2)\Delta A(\lambda_1) - \varepsilon_{HHb}(\lambda_1)\Delta A(\lambda_2)}{\varepsilon_{O_2Hb}(\lambda_1)\varepsilon_{HHb}(\lambda_2) - \varepsilon_{O_2Hb}(\lambda_2)\varepsilon_{HHb}(\lambda_1)}$$

$$\Delta C_{HHb} L = \ldots$$

concrete values depend on

- I_B / I_A
- wavelengths λ_1, λ_2
- Hb spectra applied

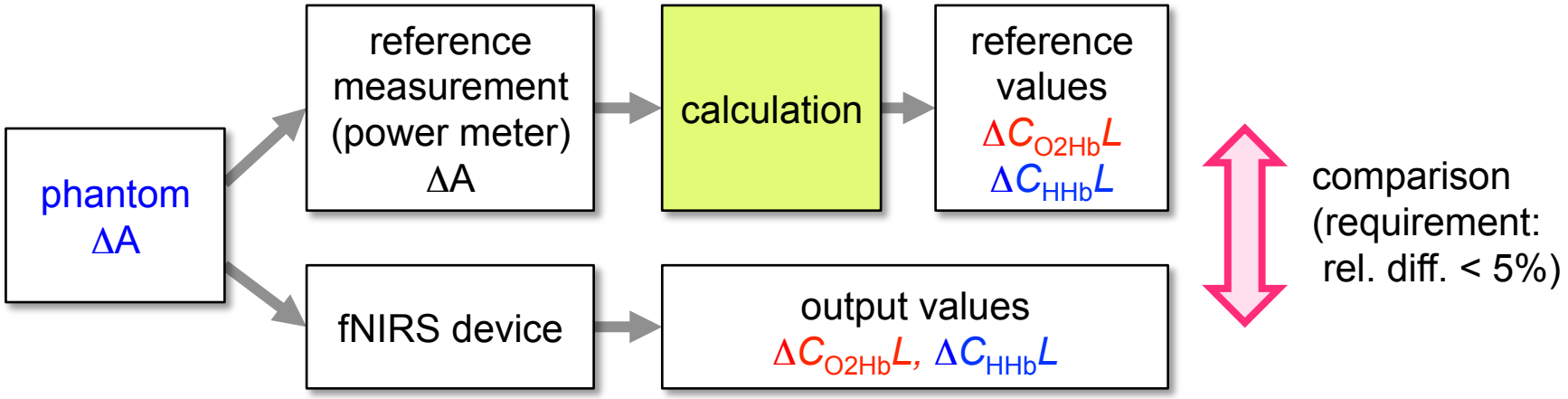
Example:

- $I_B = I_A/2$
- λ_1 = 690 nm, λ_2 = 830 nm
- spectra: M. Cope, PhD Thesis, London 1991

$$\Delta C_{O_2Hb} L = 204\ \mu\mathrm{M}\cdot\mathrm{cm}$$

$$\Delta C_{HHb} L = 111\ \mu\mathrm{M}\cdot\mathrm{cm}$$

Performance test for signal (hemoglobin change)



Criticism:

- only 1 value of ΔA realized (e.g. linearity not tested)
- this value is much larger than typical values occurring in fNIRS (ΔI / I ~ few %)
- mistakes in algorithm cannot be detected (→ disclose I_B / I_A as well)
- not applicable to all-in-one probes

→ see proposal at end of talk

Pro:

- very simple test (industrial environment), phantom easy to build
- ΔA largely independent of wavelength and optical properties

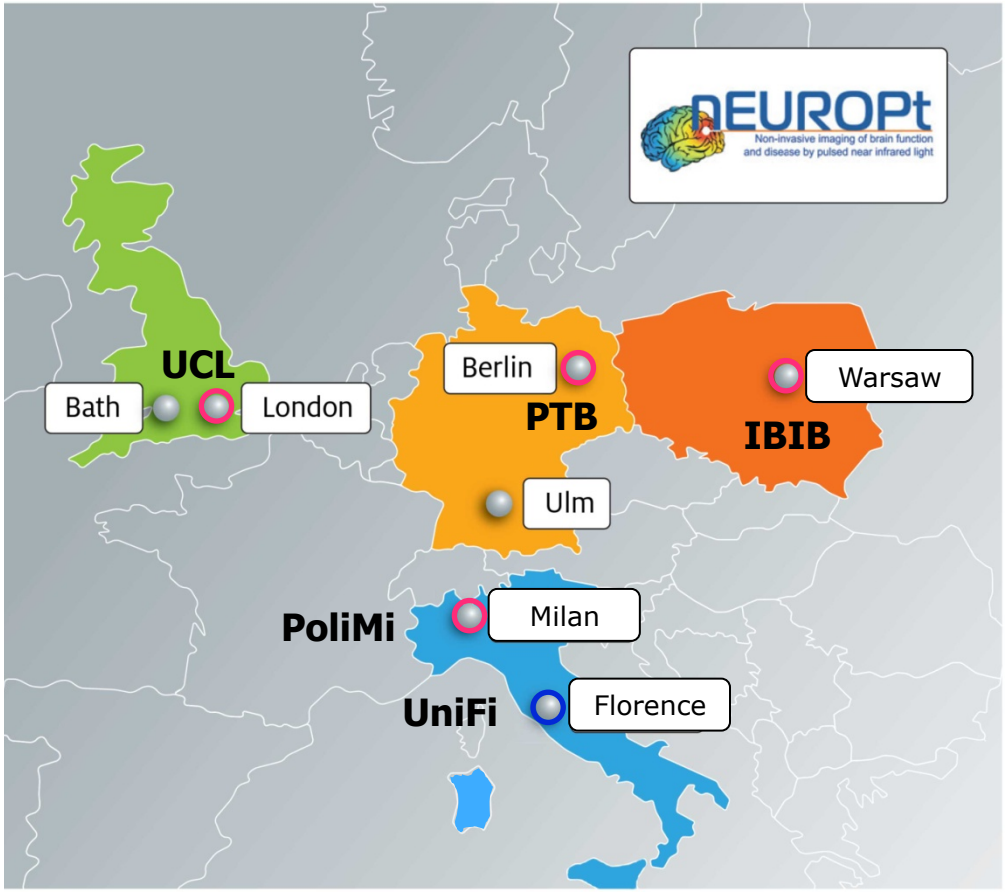
Part II: Performance assessment of time-domain optical brain imagers in the nEUROPt project

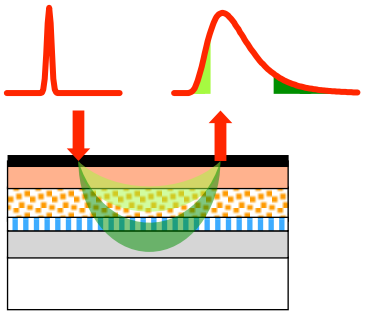
- Standardized protocols
- "Basic instrumental performance"
  - Responsivity of the detection system
- "nEUROPt protocol"
  - Liquid phantom with black inclusions: contrast
  - Two-layered phantom: depth selectivity
- Proposal for solid phantom for fNIRS test

NEUROPt
Non-invasive imaging of brain function and disease by pulsed near infrared light

2008 – 2012

Non-invasive imaging of brain function and disease by pulsed near infrared light





Partners

14 institutions, among them

- 4 physics and engineering groups + clinical partners
- 4 modeling and data analysis groups
- 3 companies (optoelectronics)

Tasks

- developments in technology and data analysis
- performance assessment
- clinical pilot studies

Motivation

Aim: standardized procedures to assess the performance of time-domain optical brain imagers

Scope: time-domain **fNIRS** ($\Delta\mu_a$ → changes in concentrations - HHb, O_2Hb; ICG) (but also applicable to cw and frequency domain techniques)

Application:

- comparison of various instruments and technical principles, estimation of impact of technological and methodological advances
- assessment of methods of data analysis
- preparatory work for test procedures in future standards

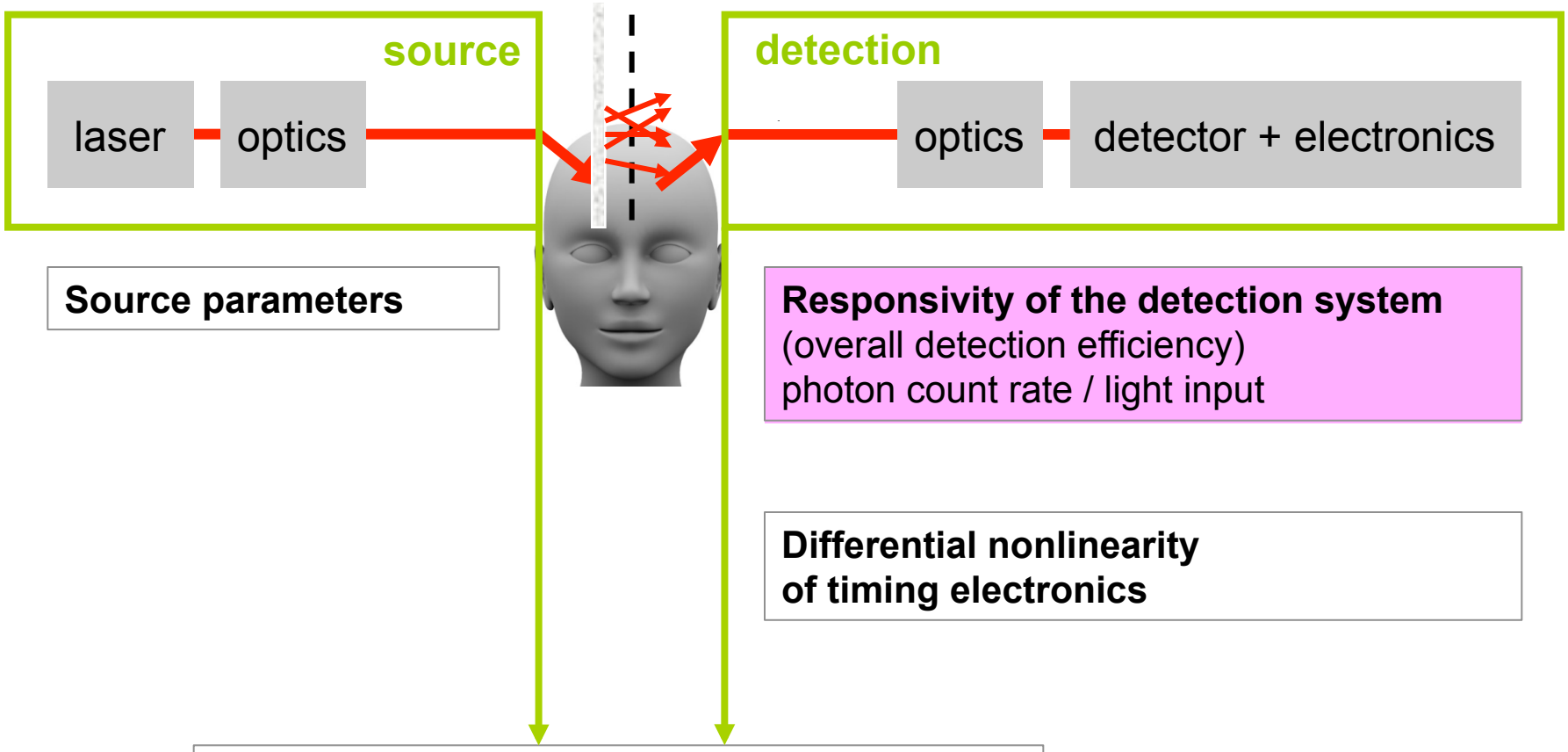
. . .

Standardized protocols

Guidelines	Sample	Data analysis
"Basic instrumental performance" protocol	no* phantoms	no data analysis
H. Wabnitz et al. SPIE 7896 2011; JBO 2014, part 1 (submitted)		
"MEDPHOT" protocol	μ_s' , μ_a	"standard" methods time-domain: fit
A. Pifferi et al. Appl. Opt. 2005	homogeneous	
"nEUROPt" protocol	$\Delta\mu_a$	various approaches of different complexity
specific needs of this project	model of brain activation	
H. Wabnitz et al. SPIE 8583 2013; JBO 2014, part 2 (submitted)		

Basic instrumental performance

Aim: record all relevant characteristics of the instrument



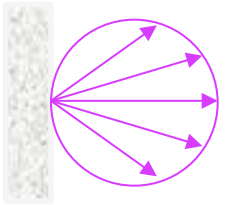
Responsivity of the detection system

Responsivity ~ overall efficiency of the detection system:

$$s_{\mathrm{det}}^{L}(\lambda) = \frac{\dot{N}_{\mathrm{det}}}{L_p(\lambda)}$$

count rate

photon radiance
(photons s^{-1} m^{-2} sr^{-1})



Required:

uniform light source with angular distribution ~ as from tissue (~ Lambertian)

Implementation:

thick slab phantom in transmission

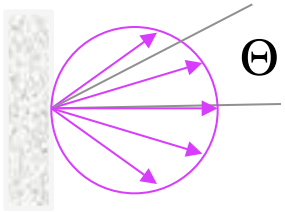
2 cm slab phantoms prepared and characterized (collaboration PoliMi – PTB)

$$L_p(\lambda) = \kappa_p(\lambda) \cdot \overline{P}_{\mathrm{in}}(\lambda)$$

transmittance factor of phantom
(photons s^{-1} m^{-2} sr^{-1} / W)

Responsivity: Contributions

Responsivity ~ overall efficiency of detection system:



$$s_{\mathrm{det}}^{L}(\lambda) = A\,\eta_{\mathrm{det}}(\lambda)\,\eta_{\mathrm{TCSPC}}\int_{0}^{2\pi} d\Phi \int_{0}^{\Theta_{\mathrm{max}}} \cos\Theta\; T_{\mathrm{optics}}(\Theta, A, \lambda)\sin\Theta d\Theta$$

unit: m^2 sr

tissue area from which light is collected, m^2

quantum yield of the detector, %

recording efficiency, % (limited time range, …)

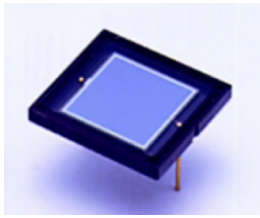
Lambertian

transmittance of bundle and relay optics, in part angle-dependent, %

- factors not exactly known, not easy to measure
- combined quantification of s_{det} by phantom measurement
- quantitative comparison of instruments

Characterization: Setup

Si photodiode
S1337-1010BQ
Hamamatsu
1 x 1 cm²



calibrated (PTB 7.3)
spectral irradiance
responsivity s_E
(A W^{-1} m^2)

SC laser
+ AOTF

reference
powermeter

collimator

$\overline{P}_{in,0}$

630 … 850 nm
in steps of 20 nm

r_1

d

r_2

pA-
meter

κ_p

$G = \pi r_1^2 / d^2$

I_{photo}

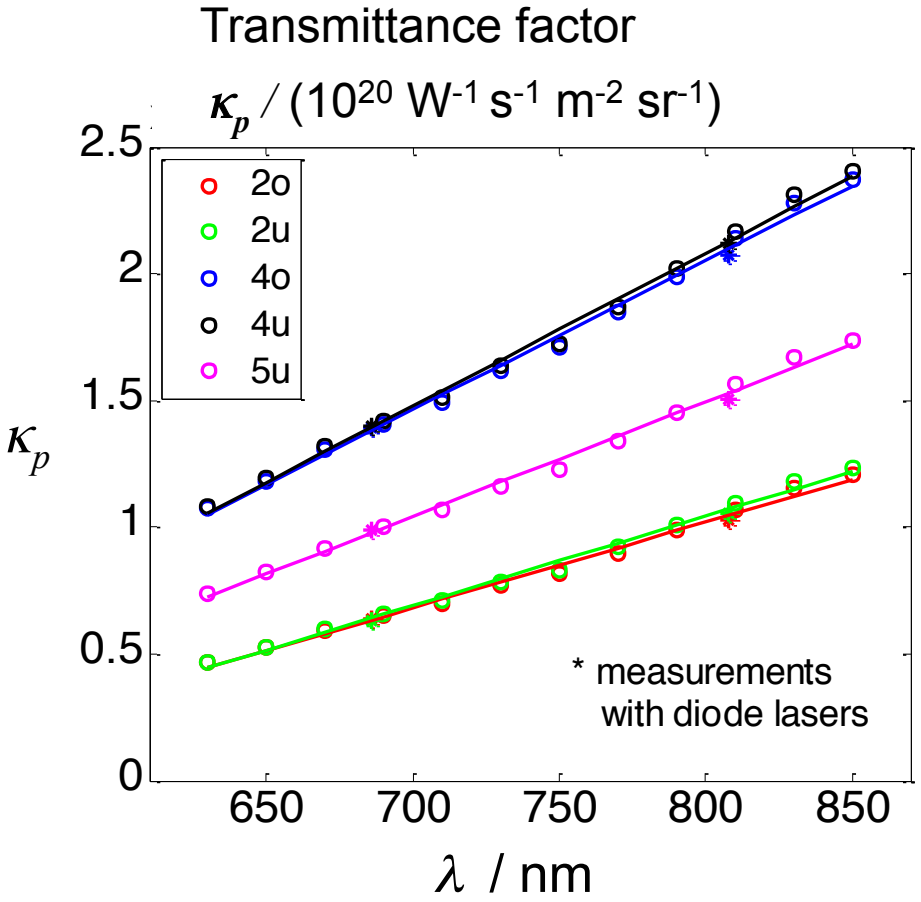
$$L_{p,0} = \frac{I_{photo}}{s_E} \frac{\lambda}{G} \frac{\lambda}{hc}$$

transmittance factor

$$\kappa_p(\lambda) = L_{p,0}(\lambda) / \overline{P}_{in,0}(\lambda)$$

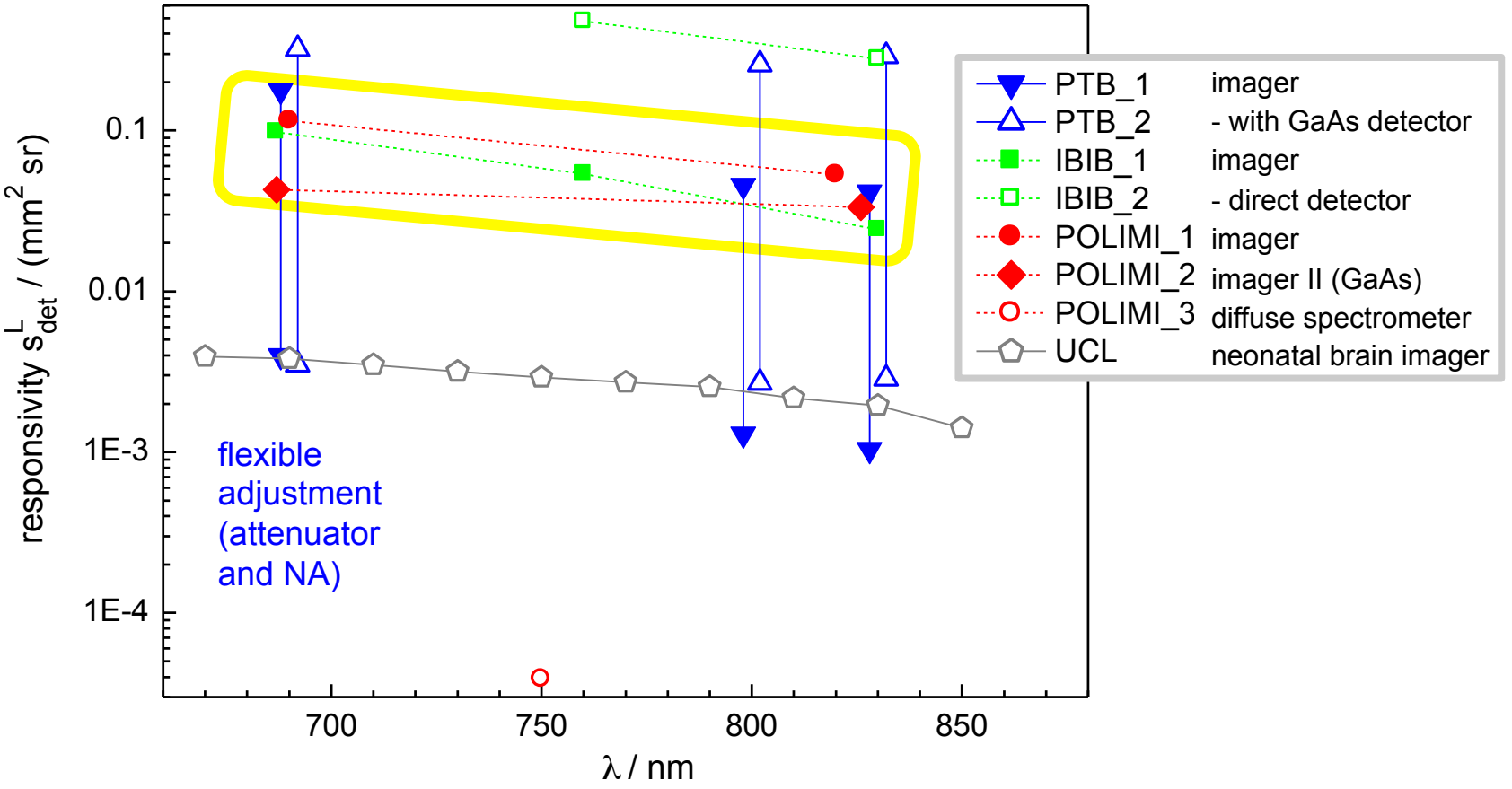
$$= \frac{T_{tot}(\lambda)}{\pi \, hc / \lambda}$$

Characterization measurement: Results



- absolute values (uncertainty < 10%)
- wavelength dependence ≈ linear
- phantoms (with data sheets) distributed to project partners

Responsivity: Results



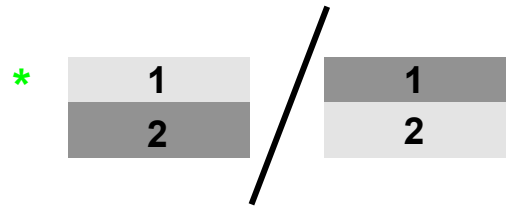
- all imagers (clinical, for adults) have very similar responsivities! (with min. attenuation in detection path)
- cathode material → wavelength dependence
- effect of technical improvements on responsivity easily checked

Tests

Sensitivity
- Contrast
- Contrast-to-noise ratio

Spatial resolution
- Lateral spatial resolution
- Depth selectivity (*)

Quantification
of absorption changes
- Accuracy
- Linearity



nEUROPt protocol

Tests

Sensitivity
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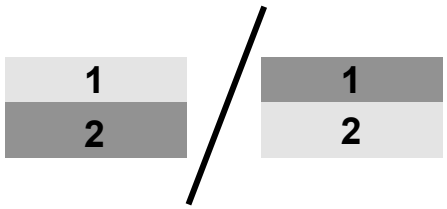
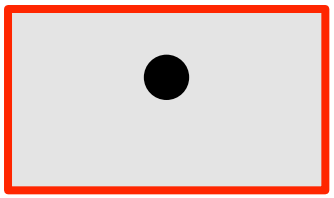
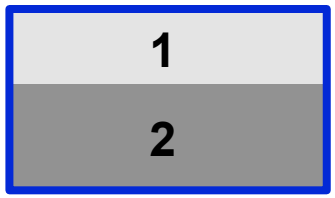
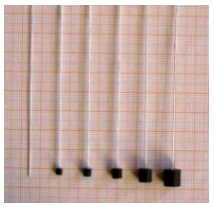
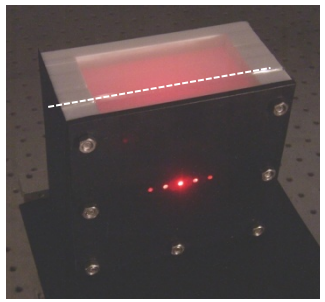
* 

Phantoms









+ Mylar foil

+ intralipid and pre-diluted ink accurately characterized (UniFi)

F. Martelli et al., Opt. Expr. 2007 (cw method)
P. Di Ninni et al., Opt. Expr. 2010 (ink)
P. Di Ninni et al., Phys. Med. Biol. 2011 (IL)

multilaboratory:

L. Spinelli et al., Biomed. Opt. Expr. 2014

nEUROPt protocol: Implementation

Tests

Sensitivity
- Contrast
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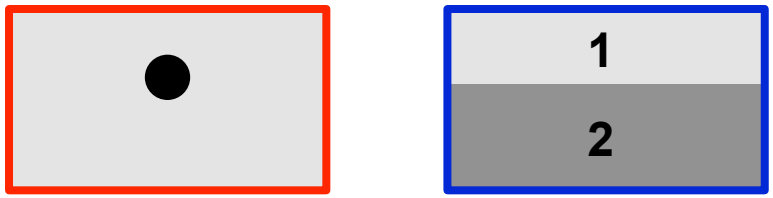
Phantoms



Why liquid phantoms?

- flexibility:
  - changing optical properties
  - varying position of inclusion
- easy replication
- parallel measurement campaigns
- accuracy of characterization of μ_s', μ_a (few %)

Requirements:

- fresh preparation
- exact weighing and mixing of components
- exact positioning of inclusions / foil

Inter-laboratory comparison of intrinsic optical properties of Intralipid and India ink

reduced scattering and absorption coefficients of
dilute mixtures of Intralipid and India ink (linear regime)

$$\mu_a = \varepsilon_{a\mathrm{ink}}\,\rho_{\mathrm{ink}} + \mu_a^{\mathrm{BKG}}, \qquad \mu_s' = \varepsilon_{s\mathrm{il}}\,\rho_{\mathrm{il}}$$

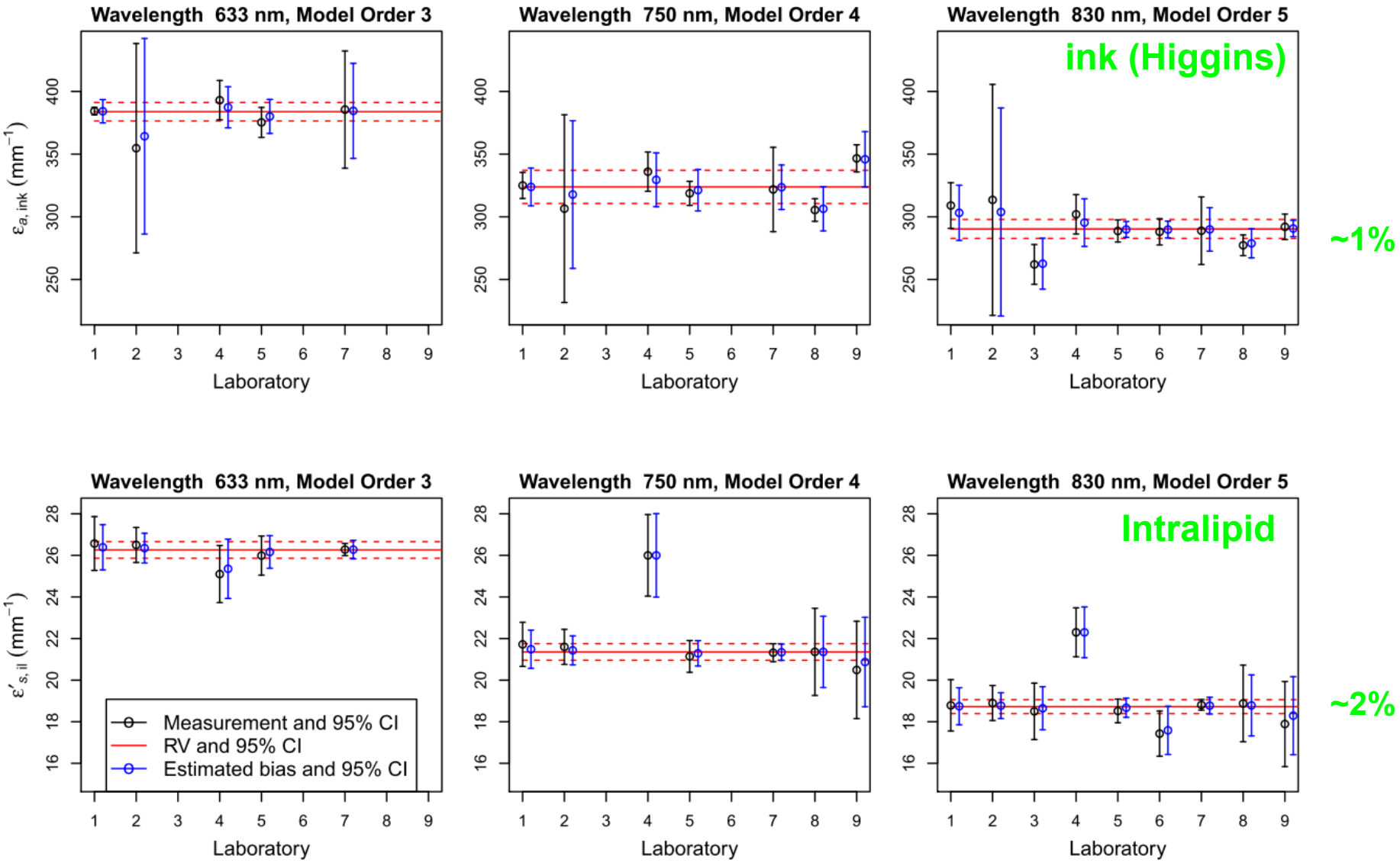
$\varepsilon...$ coefficients of the pure substance, ρ - mass concentration

Institution	Country	Measurement Tech.	Analysis Tech.	Wavelength (nm)
POLIMI	ITALY	Time Resolved	Linear method	633, 750, 830
INO	CANADA	Time Resolved	Non-linear fitting, MC RTE model	633, 750, 830
IBIB	POLAND	Time Resolved	Method of moments	830
Université de Sherbrooke	CANADA	Integrating sphere, direct method (abs only)	Inverse adding doubling, linear method (abs only)	633, 750, 830
UNIFI	ITALY	Continuous Wave	Linear method	633, 750, 830
ICFO	SPAIN	Time Resolved	Non-linear fitting, DE model	687, 785, 830
ILM	GERMANY	Spatially Resolved	Non-linear fitting, MC simulations	633, 750, 830
PTB	GERMANY	Time Resolved	Linear method	750, 830
ULUND	SWEDEN	Time Resolved	Non-linear fitting, MC simulations	750, 830, 916

L. Spinelli et al., "Determination of reference values for optical properties of liquid phantoms based on Intralipid and India ink", BOE 2014 (coming soon)

Statistical analysis of results

PTB 8.42, “fixed effects model” (accounts for inconsistency in dataset, bias)



nEUROPt protocol: Implementation

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Sensitivity
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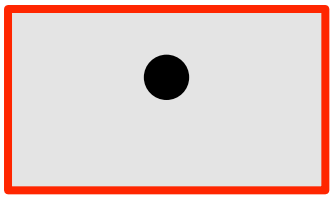
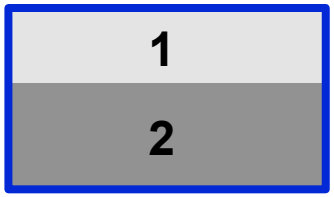
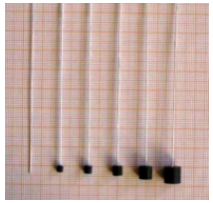
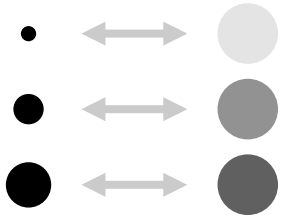
Phantoms







equivalence



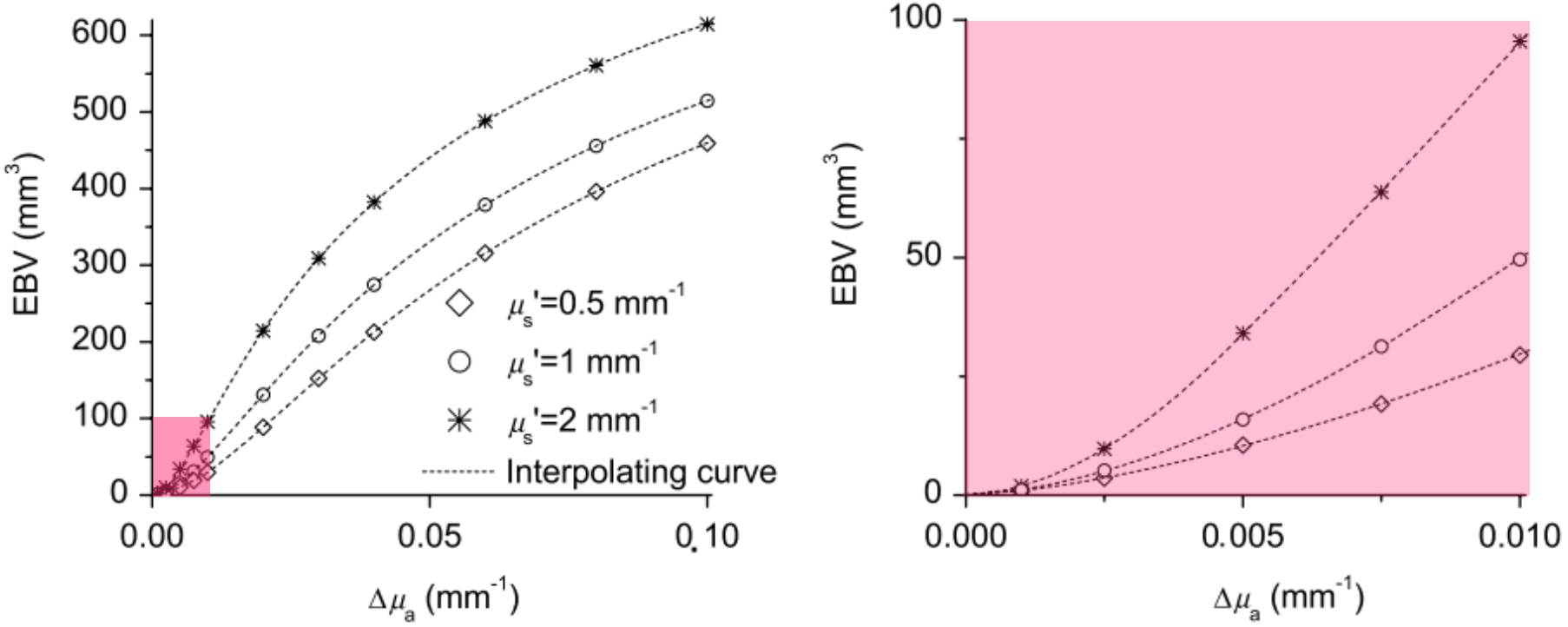
size $\Delta\mu_a$

(for deep inclusions)

F. Martelli et al., JBO 2013

F. Martelli et al., JBO 2014 (coming soon)

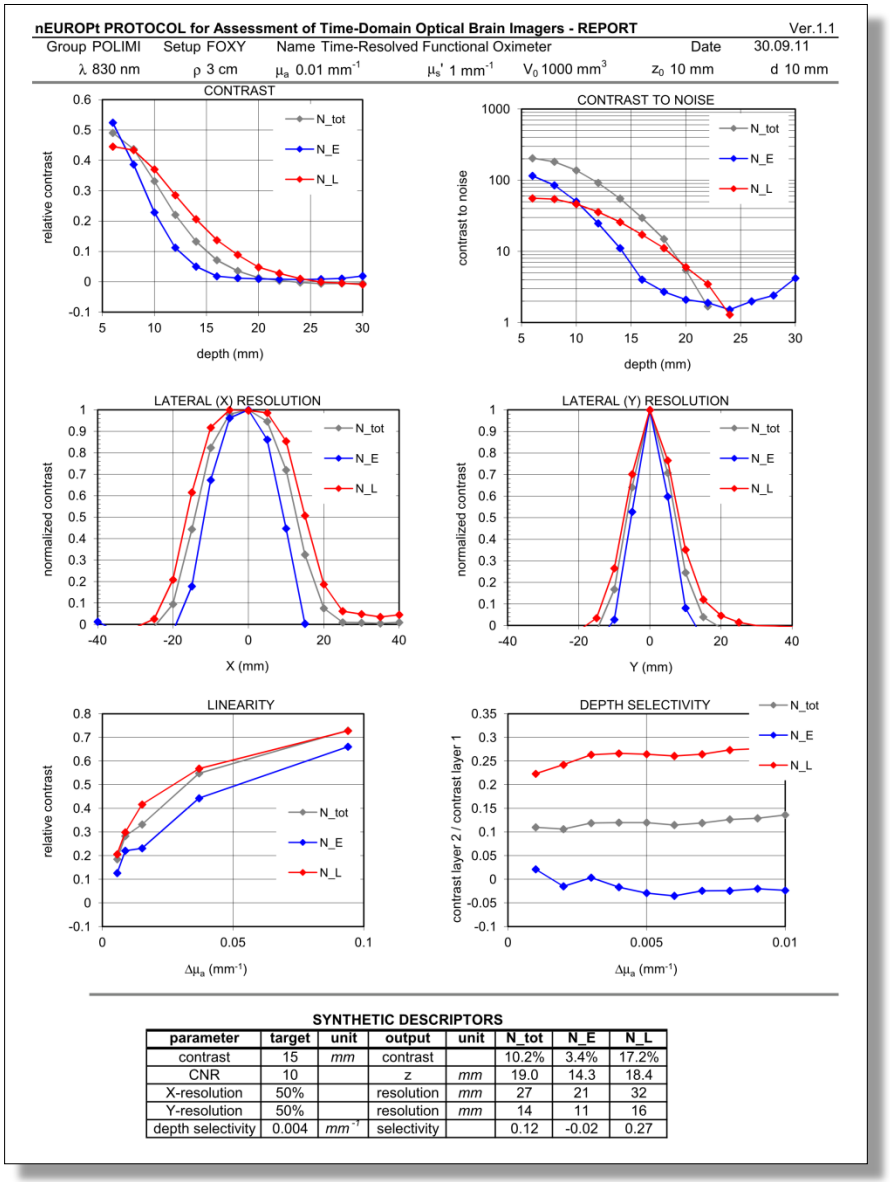
Total absorbers - equivalence relation



EBV: "equivalent black volume"
related to an absorption change $\Delta\mu_a$ in a 1000 mm^3 volume

F. Martelli et al., JBO 2013

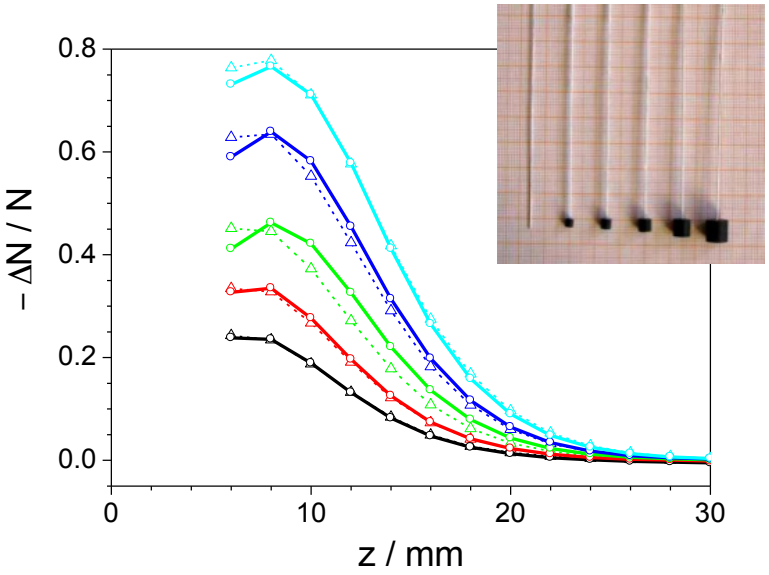
Reporting sheet

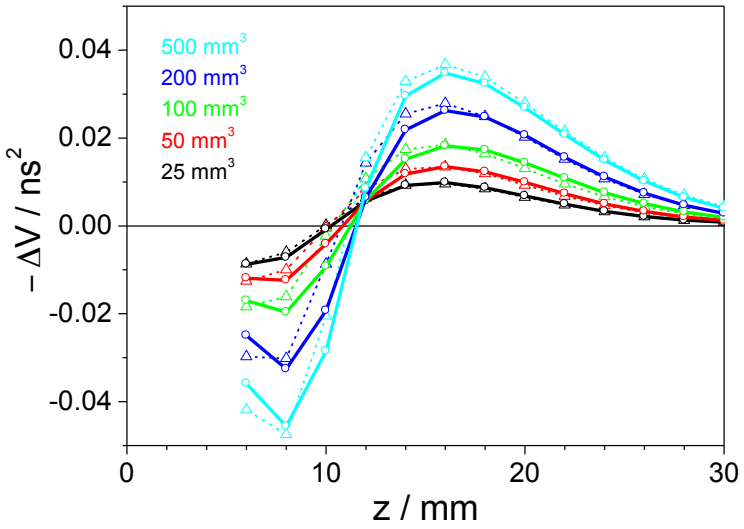


parameter	target	unit	output	unit	N_tot	N_E	N_L
contrast	15	*mm*	contrast		10.2%	3.4%	17.2%
CNR	10		z	*mm*	19.0	14.3	18.4
X-resolution	50%		resolution	*mm*	27	21	32
Y-resolution	50%		resolution	*mm*	14	11	16
depth selectivity	0.004	mm^{-1}	selectivity		0.12	-0.02	0.27

- consolidated presentation of results
  - contrast, contrast to noise ratio as function of depth
  - lateral spatial resolution
  - linearity
  - depth selectivity
- synthetic descriptors
- actual implementation of the nEUROPt protocol, definition of measurands, conditions for analysis and reporting

z scan – moments

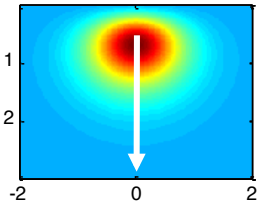




measured (PTB3)

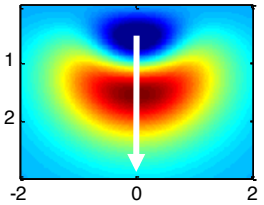
MC simulation (UniFi), black spheres of same volume

Integral

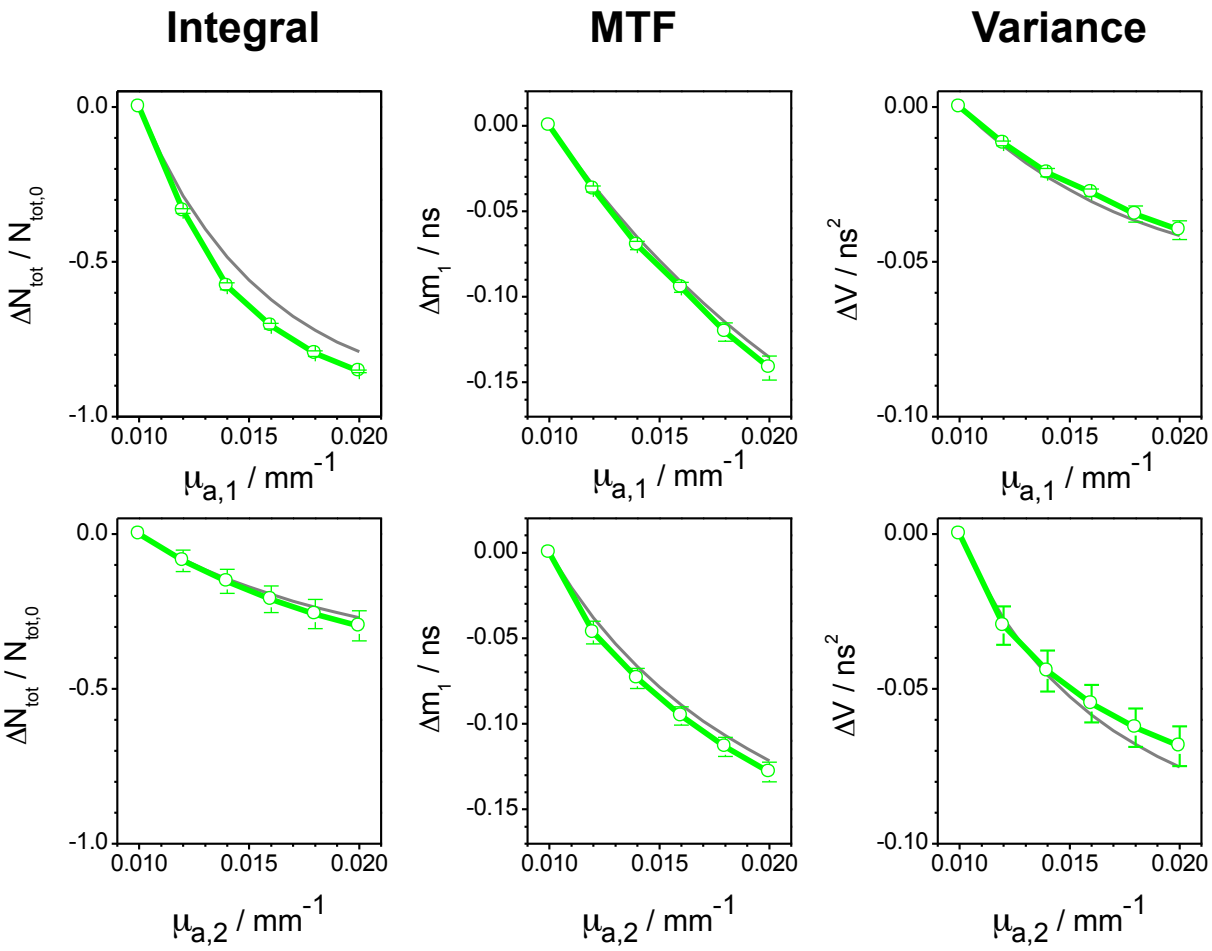


$x = 0$

Variance



2 layers - moments



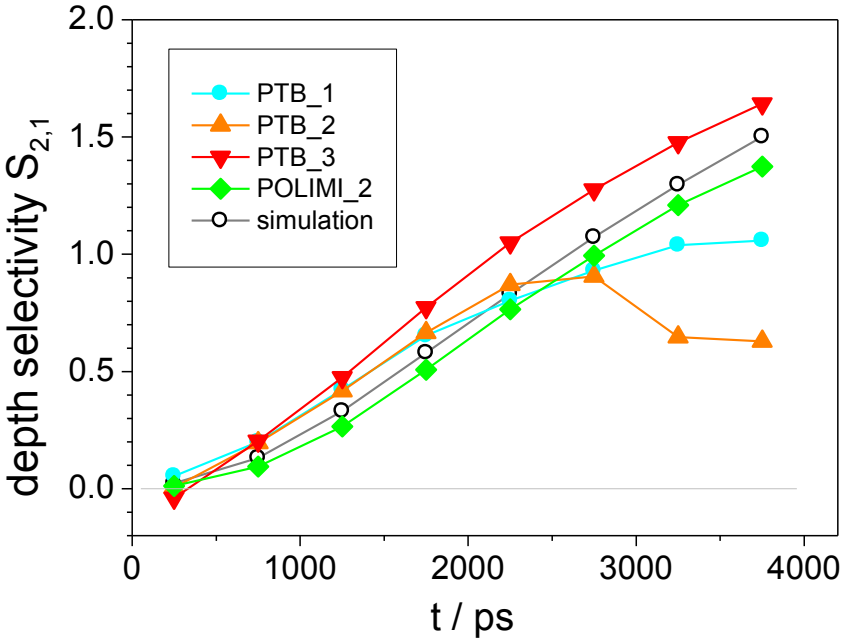
d = 10 mm
μ_s' = 1 mm^{-1}
$\mu_{a,0}$ = 0.01 mm^{-1}
t_{meas} = 1 s
N_{tot} ~ 10^6

measured (IBIB) simulation (N-layer diffusion model, Liemert, Kienle, JBO 2010; www.ilm-ulm.de)

→ derive depth selectivity $S_{2,1}$ for small $\Delta\mu_a$

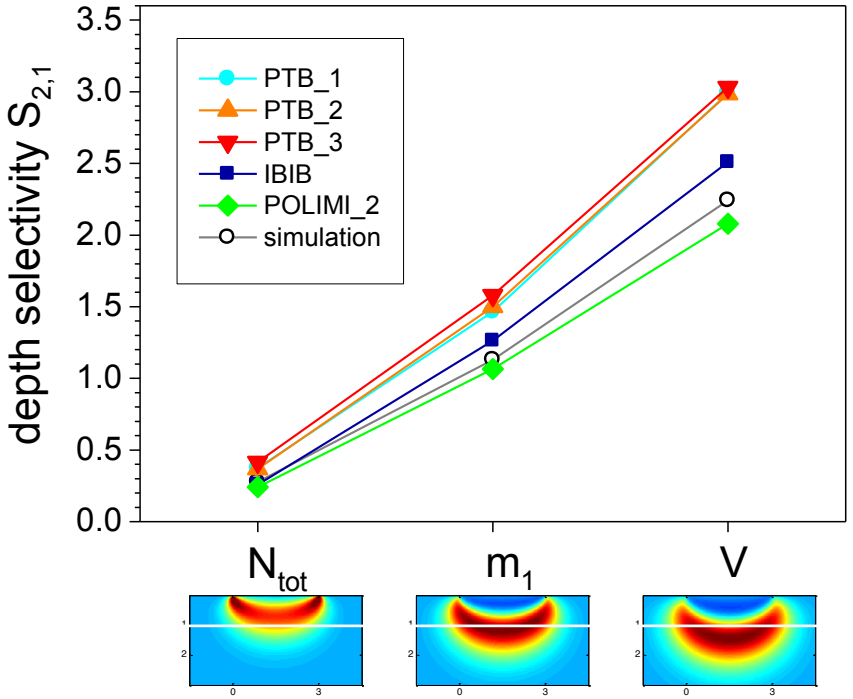
Depth selectivity (2 layers): Comparison

Time windows



- influence of IRF
- depth selectivity can be improved by taking ratios late / early

Moments

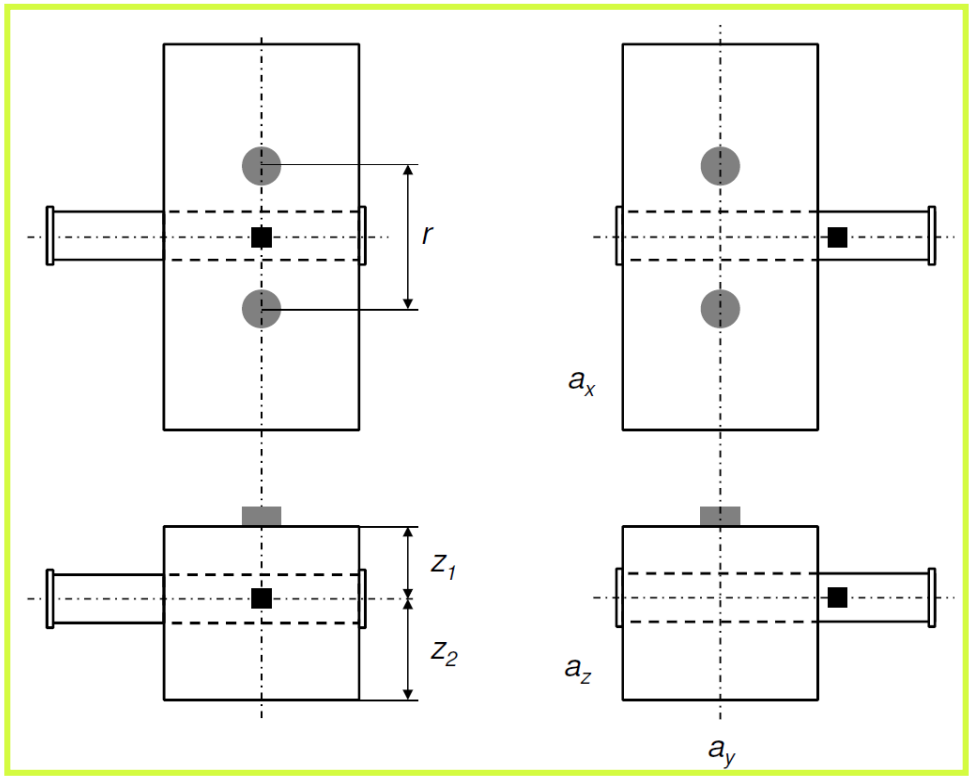


- ~ no influence of IRF (PTB)
- differences due to deviations in thickness → improved mounting
- best depth selectivity: variance

Proposal: Solid phantom

Proposed test measurements for fNIRS standard (Hb change)
based on nEUROPt experience (collaboration PTB, PoliMi, July 2012):

attenuation change ~ typical brain activation
← localized absorption change in a solid phantom, reflection geometry



$\mu_s' = 1\ mm^{-1}$, $\mu_a = 0.01\ mm^{-1}$

$a_x = 80$ mm, $a_y = 40$ mm, $a_z = 35$ mm
$d_{rod} = 10$ mm, $z_1 = 15$ mm, $z_2 = 20$ mm

$h_{cyl} = d_{cyl} = 4.0$ mm ($V_{cyl} = 50\ mm^3$)

optode position

black cylindrical inclusion

Proposal: Solid phantom

Attenuation change:

- depends on r_{SD} (as in the in-vivo situation)
  0.43 dB for r_{SD} = 3 cm and V_{cyl} = 50 mm^3
- can be modified by changing V_{cyl}
- depends on wavelength (due to $\mu_s'(\lambda)$)
- can be predicted by Monte-Carlo simulations (look-up table)

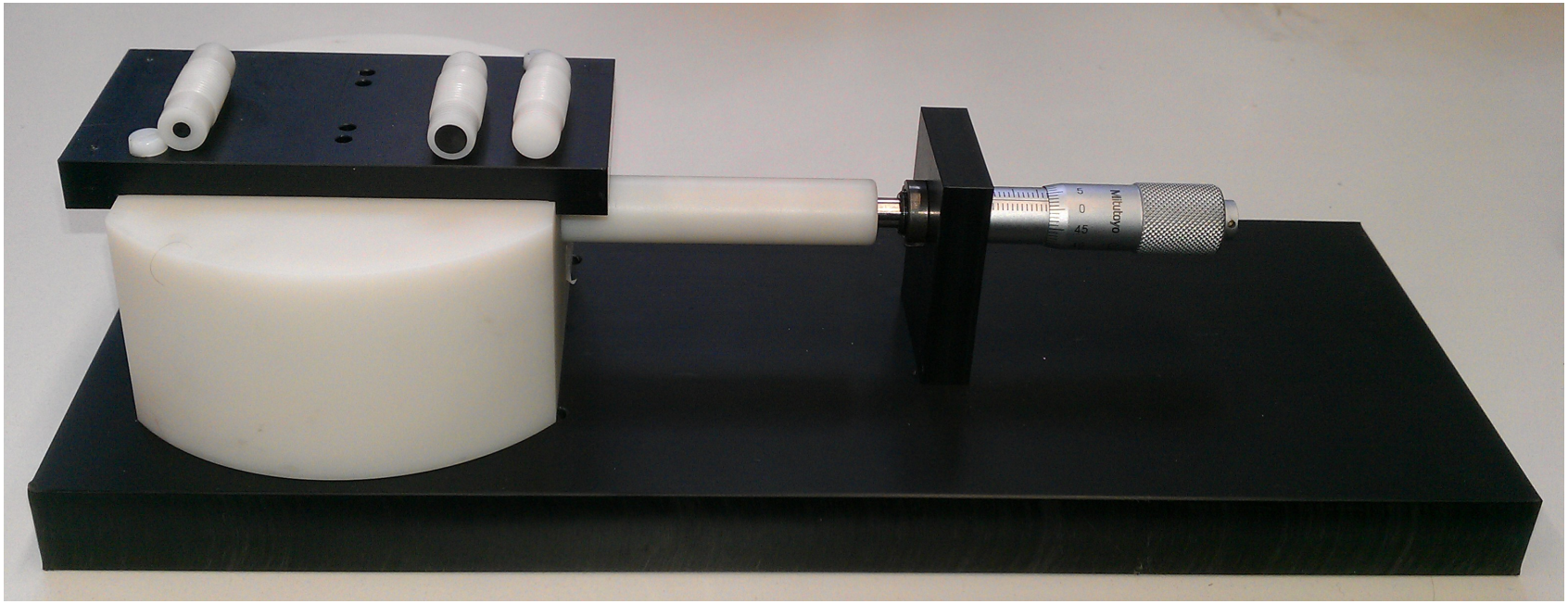
Advantages:

- applicable in reflection geometry, suitable for all-in-one probes
- more realistic absorption change

Disadvantages:

- requires material with specific, accurately characterized optical properties
- manufacturing challenging

Improved implementation



R. Cubeddu, Politecnico di Milano, May 2014

Conclusions

- fNIRS standard draft: simple, basic performance tests (improvements needed)
- Research, development of instrumentation (and analysis tools): comprehensive characterization desired
- nEUROPt: two protocols developed (for time-domain fNIRS, but transferable) implemented with two types of inhomogeneous liquid phantoms
- Solid phantom seems feasible, but further development required

Questions:

- Role of performance tests in (safety) standard (60601)?
- Better option than ISO / IEC to standardize phantom tests?
- Alternative: Separate Technical Report / Specification for phantoms?

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fNIRS standard

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Thank you!

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