The whole process from clinical paradigm to industrial standards: the EU experience in Diffuse Optics

DIFFUSE OPTICS

Antonio Pifferi – Politecnico di Milano, Department of Physics, Italy
when and how standardization is useful
Biophotonics, a key technology for health: unique features of Diffuse Optics

- time-domain Diffuse Optics
- non-invasive
- chemical specificity
- quantitative operator independent
- scalable
- functional
- non-contact
- deep
- $\mu_s = \text{scattering}$
- $\mu_a = \text{absorption}$
- $Z \approx 2\div4 \text{ cm}$
- $27 \, ^\circ\text{C}$
Bridging the Valley of Death

<table>
<thead>
<tr>
<th>Performance assessment</th>
<th>Standardization</th>
</tr>
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<tbody>
<tr>
<td>Research</td>
<td>Clinics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technology Readiness Level (TRL)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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Required funding for clinical devices
- €
- €€
- €€€
Aims of Performance Assessment & Standardization

- Anticipate many technical issues from clinical trials (€€€) to laboratory validation (€)
- Benchmark research and innovation process
- Facilitate deployment of industrial standards
- Mitigate market barriers
- Facilitate use of Open Data
- Support Machine Learning by providing validated data sets
- Focus development of key clinical needs
- Improve quality of clinical prototypes
- Improve reliability of clinical studies / trials
- Improve Patient Health
- Reduce health costs by higher reliability of instruments
what is going on in Europe and outside

Specific domain
METHODOLOGY
A vision on the whole process

STEP 1
Clinics
2
Physics

STEP 2
Protocols

STEP 3
Phantoms

STEP 4
Laboratory
Comparison of
Instruments

STEP 5
Clinical
Comparison of
Instruments

STEP 6
Industrial
Standards

- Test 1
- Test 2
- ...
- Test n

>15 years coherent process, growing in scope and actors

All items developed through multi-laboratory / institutions consensus

Transverse to many EU and national projects, but growing as spontaneous, long-term and flexible network

Unique EU experience, yet with strong ties worldwide (USA, Japan)
Step 1 – CLINICS to PHYSICS
Translate Clinical problem into Physical model

Example 1 – measuring brain oxygenation

≈

- 2 layers
- absolute StO2 in deep layer

Example 2 – measuring brain function

≈

- localized inhomogeneity
- $\Delta \mu_a$ change as compared to initial reference state

strong interaction between Clinicians – Physicists/Engineers
Step 1 – CLINICS to PHYSICS
Translate Clinical problem into Physical model

characterising breast lesions

measuring brain function

- localized inhomogeneity
- $\Delta \mu_a$ change as compared to a reference state

strong interaction between Clinicians – Physicists/Engineers

EQUIVALENCE RELATION

$\cong$


Table 2: Examples of absorption perturbations expressed as equivalent black volume.

<table>
<thead>
<tr>
<th>Perturbation</th>
<th>EBV (mm$^3$)</th>
<th>Wavelength (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mm$^3$ totally absorbing sphere</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$\Delta \mu_o = 0.01$ mm$^{-1}$ V=1000 mm$^3$</td>
<td>50</td>
<td>800</td>
</tr>
<tr>
<td>nmol Hb</td>
<td>120</td>
<td>830</td>
</tr>
<tr>
<td>Motor task</td>
<td>$\approx$10</td>
<td>830</td>
</tr>
<tr>
<td>Malignant breast lesion</td>
<td>$\approx$100</td>
<td>635</td>
</tr>
</tbody>
</table>
## Step 2 – PROTOCOLS

**BIP + MEDPHOT + NEUROPT Protocols**

### BIP

**basic performances**

1. responsivity
2. instrument response function
3. noise
4. stability

### MEDPHOT

**homogeneous problems**

1. accuracy
2. linearity
3. noise
4. stability
5. reproducibility

### NEUROPT

**heterogeneous problems**

1. sensitivity
   1a. contrast
   1b. contrast-to-noise ratio
2. localization
   2a. lateral resolution
   2b. axial resolution
3. quantitation
   3a. Accuracy
   3b. Linearity

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**6 Institutions**

- Pifferi et al. *Appl Opt.*, 2005

**5 Institutions**

Step 3 – PHANTOMS
multilaboratory phantom kits

LIQUID phantom

India ink absorption
Intralipid scattering

\[ \varepsilon_{\text{ink}} \text{ (mm}^{-1}\text{)} = 324 \pm 7.0 \ (2.0 \%) \]
\[ \varepsilon_{\text{sil}} \text{ (mm}^{-1}\text{)} = 21.4 \pm 0.2 \ (0.9\%) \]

excellent agreement


MEDPHOT kit
Absorption

SWITCHABLE phantom

RESPONSIVITY phantom

LIQUID DCS-TRS phantom

Joint DOT/US phantoms

\[ \text{Absorption} \]

\[ \text{Scattering} \]

\[ \text{Switch} \]

\[ \text{Responsivity} \]

\[ \text{Joint DOT/US} \]
Step 4 – INSTRUMENT COMPARISON IN LAB - multilaboratory performance assessment

Example 1
Tissue spectrometers

Example 2
brain oximeters

Pifferi et al. Appl Opt, 2005

Step 5 – INSTRUMENT COMPARISON IN CLINICS

See for instance
SAFEBOOSC Experience talk by Gorm Greisen
Step 6 – INDUSTRIAL STANDARDS

Standards on brain oximetry

• ISO/IEC 80601-2-71:2015
  *Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment* (in force)

• In preparation by joint ISO/TC 121/SC 3-IEC/SC 62D WG
  *Particular requirements for basic safety and essential performance of cerebral tissue oximeter equipment* (in preparation)

see talk by
Heidrun Wabnitz
work in progress… the BITMAP exercise

**Action 1**
**MEASUREMENTS**
- 3 protocols
  - BIP + MEDPHOT
  - + NEUROPT
- 3 phantom kits

**Action 2**
**OPEN DATA**
- cloud based
- standardised report sheet
- ZENODO (open data)

**Action 3**
**ANALYSIS**
- model 1
- model 2
- model n
- raw data

organized by BITMAP – EU Innovative Training Network – driven by Early Stage Researchers
possible common EU strategy

Specific domain
A (naïve) vision on the future

Try to adopt also in Biophotonics the multicentre collaboration and cross-validation approach of other disciplines (e.g. high energy physics, astrophysics)
Common EU strategy: few ideas

- Push multi-laboratory studies (on protocols / phantoms / comparison)
- Favor interactions among EU projects
- Problem of fabrication of identical phantom kits
- Stronger links with EU institutions / agencies (i.e. work together)
CONCLUSIONS

PAST – PRESENT

- >15 years EU collaboration
- interactions in 8 EU projects
- 2 clinics → physics paradigms
  (brain functional imaging, breast lesions)
- 3 international protocols
  (BIP, MEDPHOT, NEUROPT)
- 4 families of shared phantoms
  (solid hom, switchable, responsivity, liquid)
- 4 laboratory instrument comparison
  (1 large exercise in progress)
- 1 clinical instrument comparison
  (brain functional imagers)
- 2 industrial standards
  (1 in force, 1 in progress)

FUTURE

- we need Biophotonics
- we need Performance Assessment and Standardization
- we need Europe
Aknowlegments (only most recent, surely missing somebody)

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Rigshospitalet, Denmark
Gorm Greisen

University Hospital of Zürich, Switzerland
Martin Wolf, Stefan Kleiser

Lund University, Sweden
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Hamid Dehghani

Supersonic Imagine
David Savery

Vermon
Bodgan Rosinko

EU Projects involved
- MEDPHOT, EU FP5
- OPTIMAMM, EU FP5
- nEUROPt, EU FP7 2009-2012 (n. 201076)
- LaserLab Europe, EU H2020 2015-2019 (n. 654148)
- BabyLux, EU CIP 2014-2016 (n. 620996)
- LUCA, H2020 2016-2019 (n. 688303)
- SOLUS, H2020 2016-2020 (n. 731877)
- BITMAP H2020 2015-2019 (n. 675332)