lorenzo.cortese@icfo.eu

Non-invasive microvascular monitoring technologies based on diffuse optics

Lorenzo CORTESE

ICFO – The Institute of Photonic Sciences @ Medical Optics group

ICFO Medical Optics group (PI: T. Durduran)

ICFO

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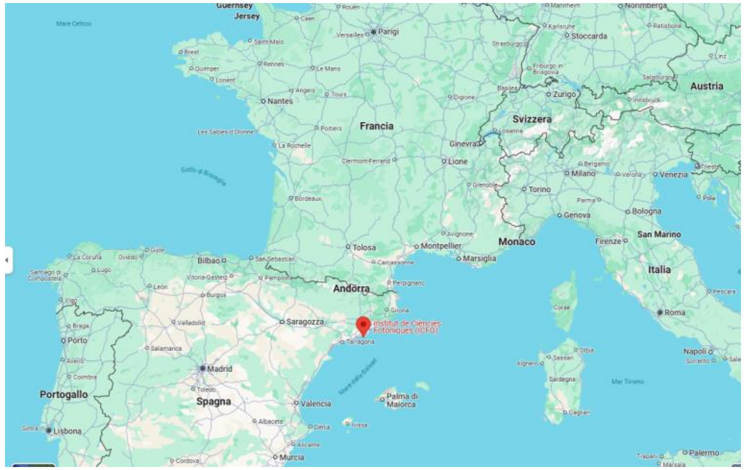
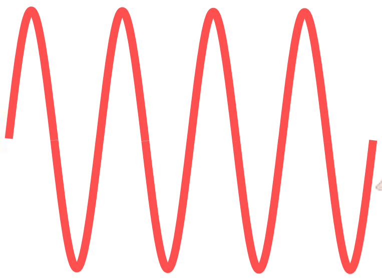


Positions open: https://jobs.icfo.eu

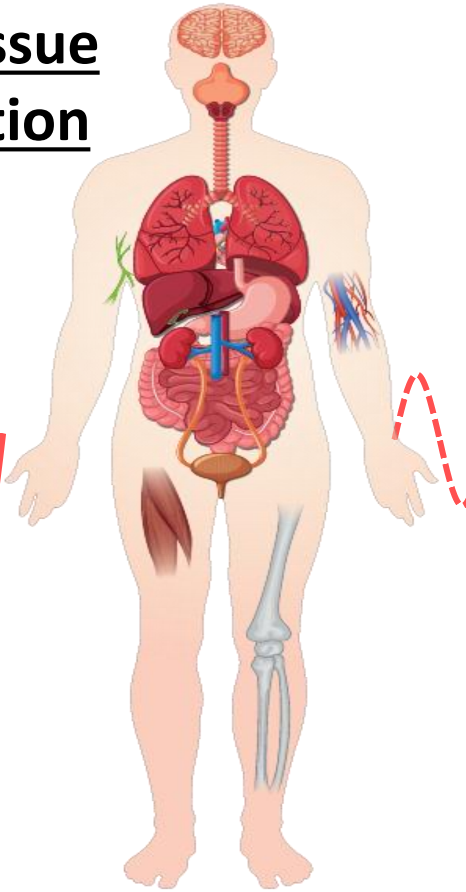
Translational research: bench-to-bedside

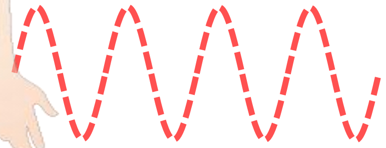
What is medical optics

Light source
- Lasers
- LEDs
- …

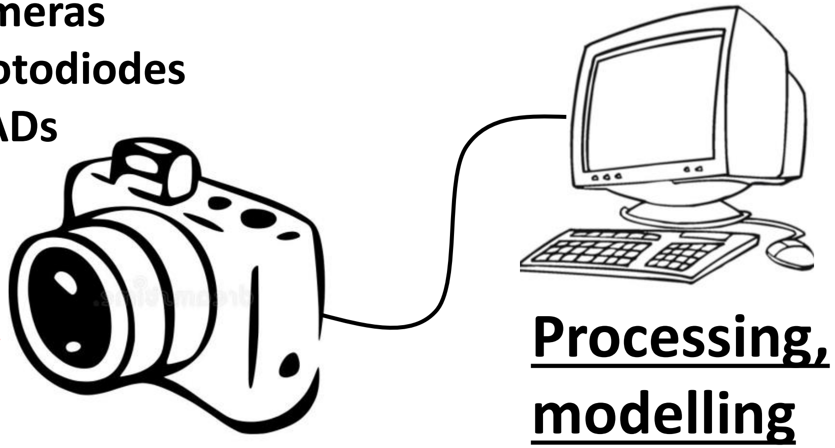


Light tissue interaction





Detector
- Cameras
- Photodiodes
- SPADs
- …



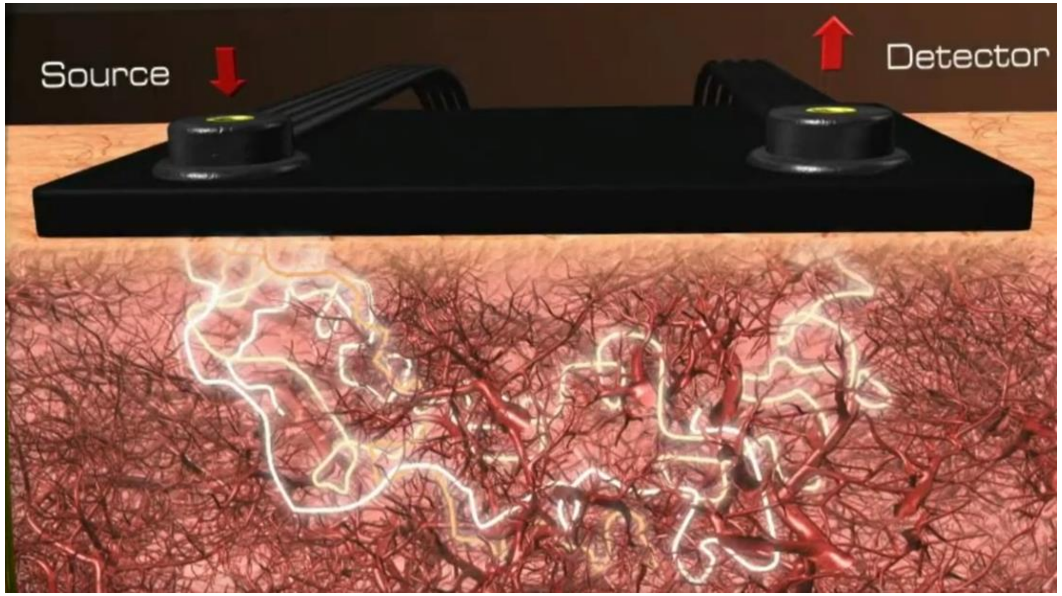
Processing, modelling

Main questions:
1. Does light penetrate deep into the tissue?
2. Does it have any clinical relevance?
3. Can we build devices that are usable in clinics?

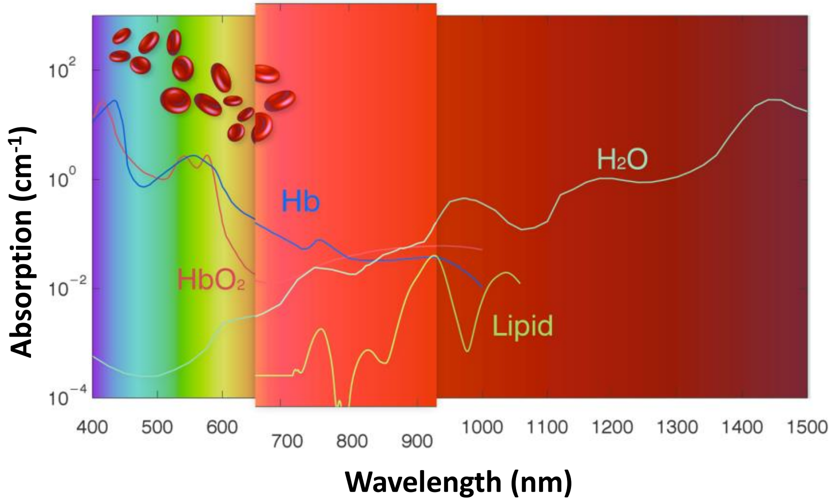
Diffuse optical near-infrared spectroscopies

Durduran et al., Rep. Progr. Phys. 72, 2010

Diffuse optical near-infrared spectroscopies



Spectroscopic techniques (CW-NIRS, TD-NIRS, FD-NIRS)



Hemoglobin concentrations, Tissue oxygen saturation

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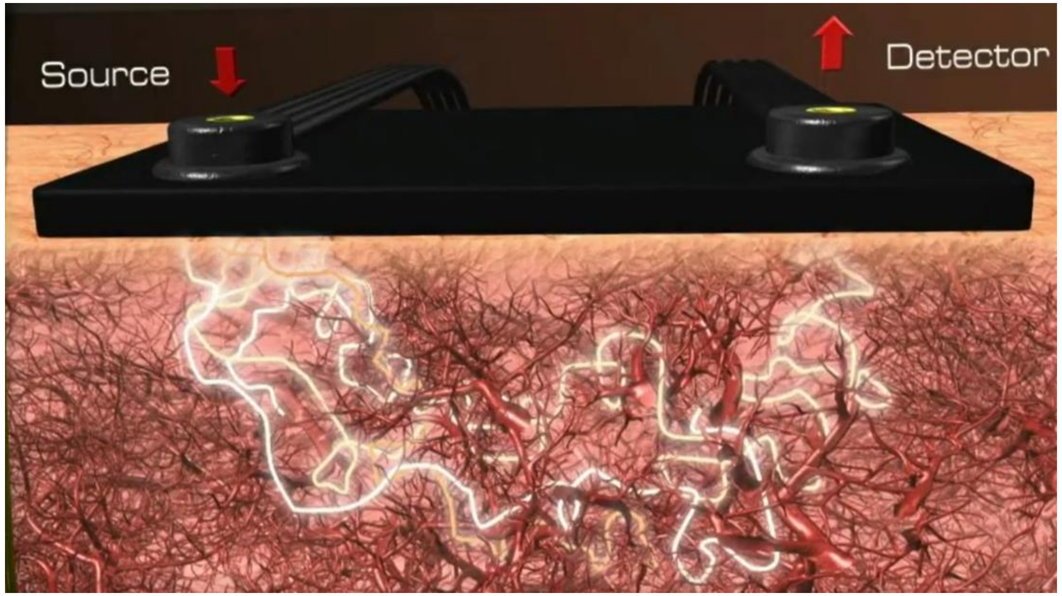
Durduran et al., Rep. Progr. Phys. 72, 2010

Diffuse optical near-infrared spectroscopies



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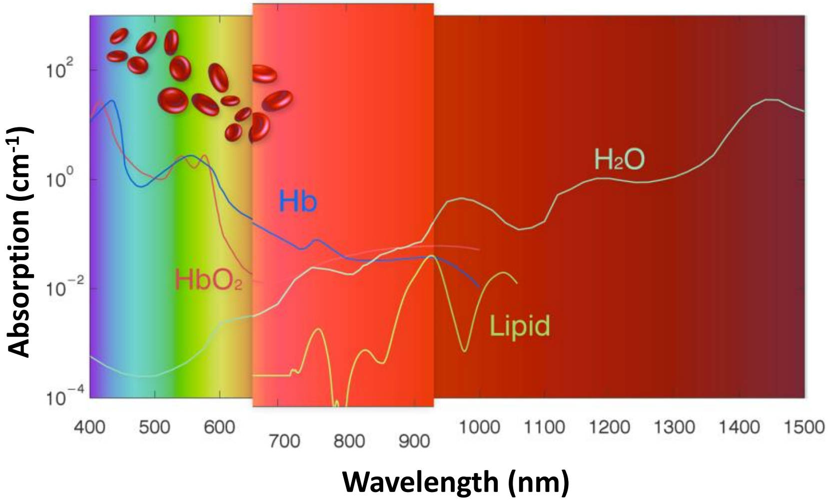
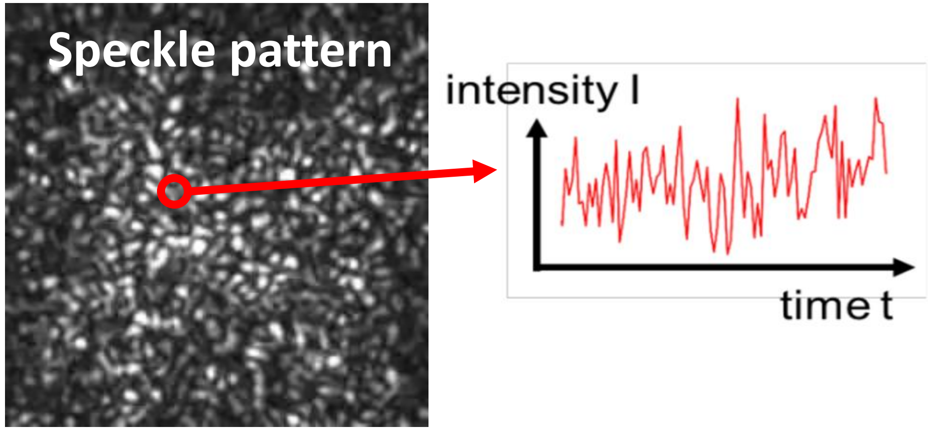


Hemoglobin concentrations, Tissue oxygen saturation

Laser speckle-based techniques (DCS, SCOS,…)

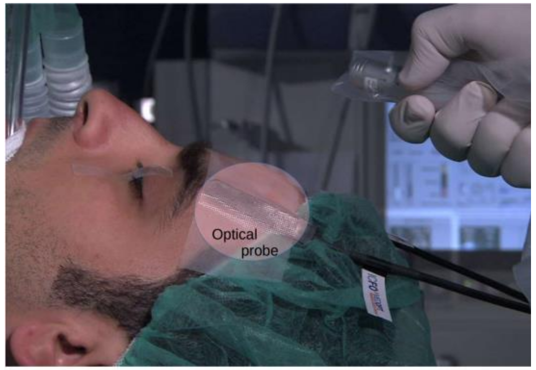


Blood flow

Durduran et al., Rep. Progr. Phys. 72, 2010

From the lab to the clinic: examples of different applications

Adult brain monitoring
(stroke, trauma, aging, sleep,…)



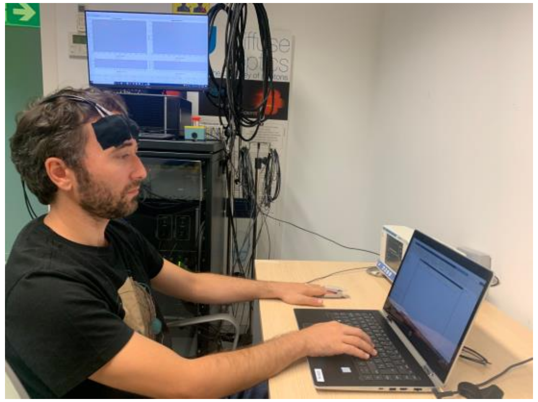
Infant brain
(preterm babies, brain development, injury)

Cancer diagnosis
& therapy follow-up
(Breast, thyroid, head and neck, prostate, …)

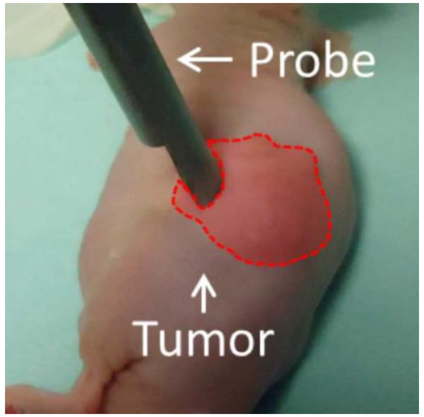
Exercise/sport, physiotherapy
(muscle metabolism)

Intensive care
(brain injury, sepsis, COVID, trauma, …)

Brain functional studies
(cognition, language, …)



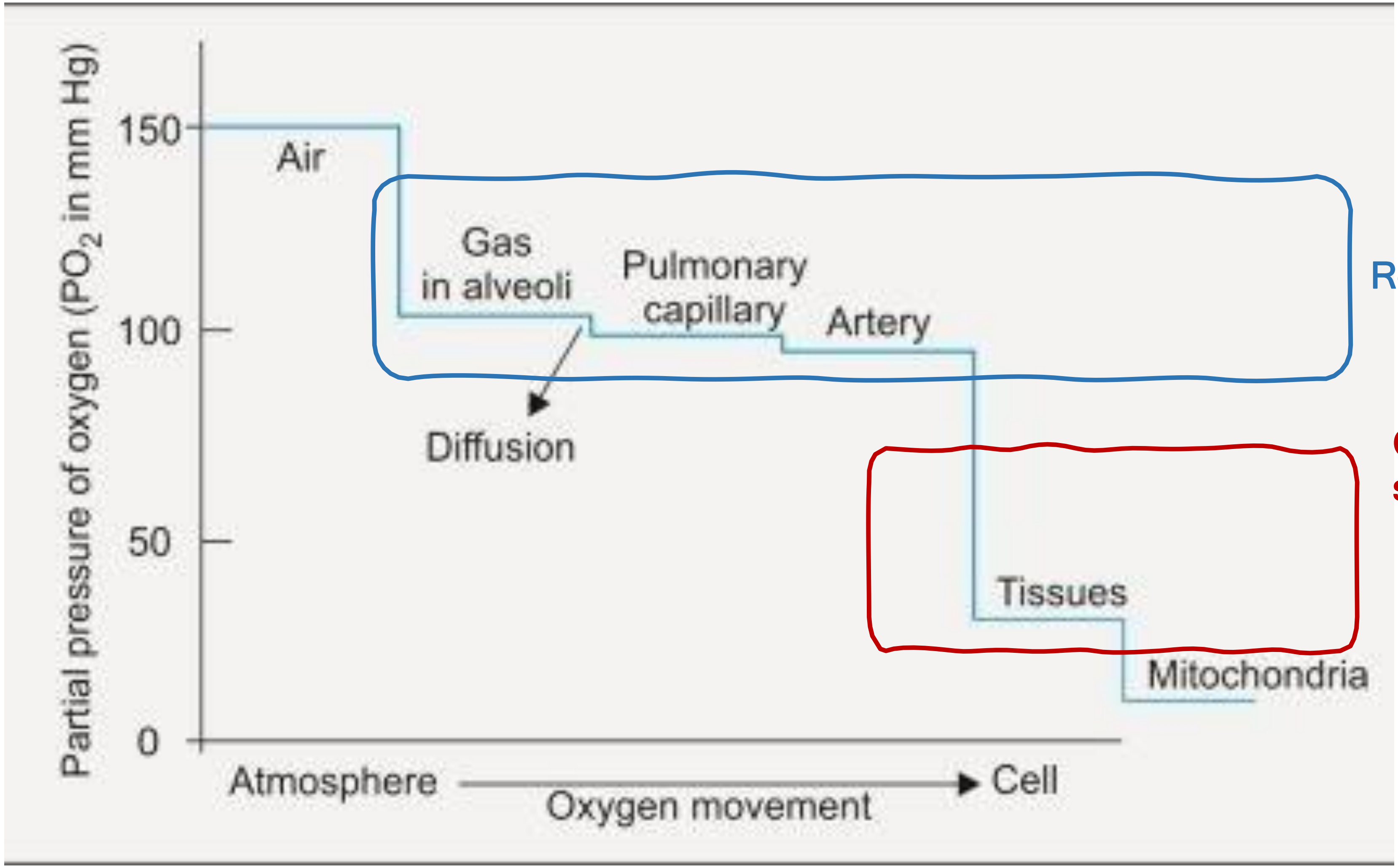
Animal studies
(cancer, plasmonic photothermal therapy, …)



Monitoring tissue oxygenation and perfusion

How oxygen is delivered to the tissue

The oxygen trail



Respiratory system

[SpO_2]

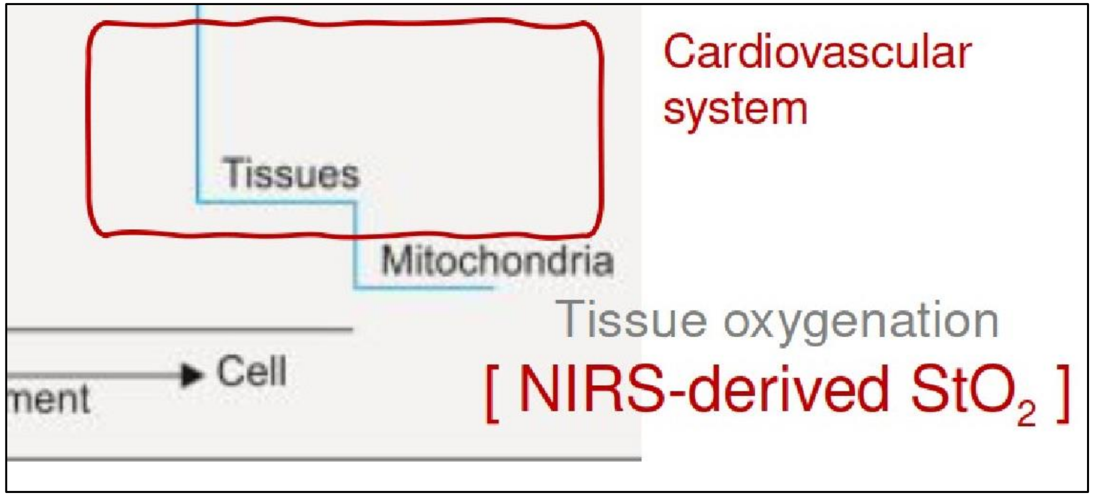
Cardiovascular system

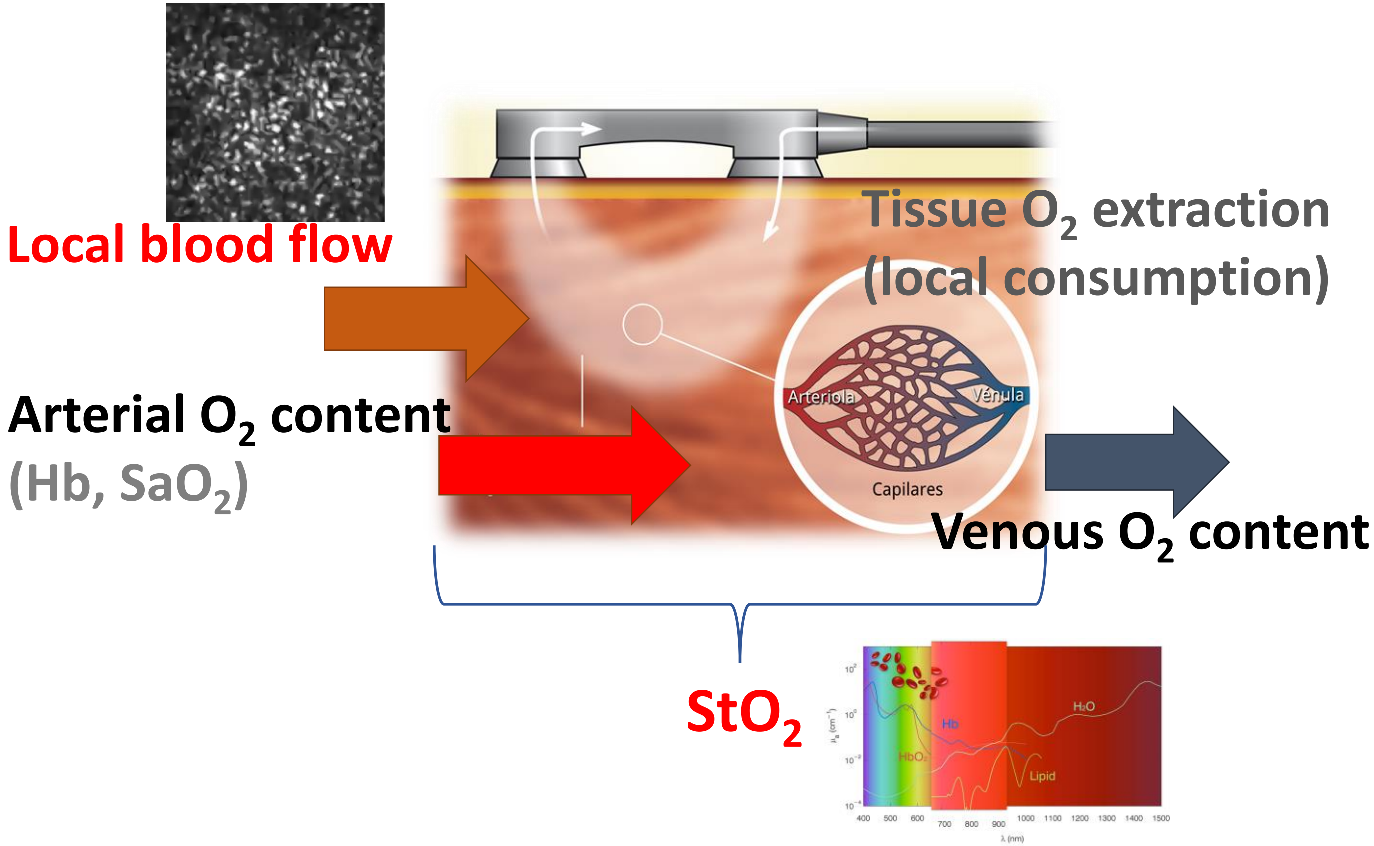
Tissue oxygenation

[NIRS-derived StO_2]

Thanks to: J. Mesquida

What we measure – Need for multimodal devices





Only NIRS: **StO2** → Integration of **blood perfusion**, **arterial oxygenation**, and the **metabolic rate** of the tissue.

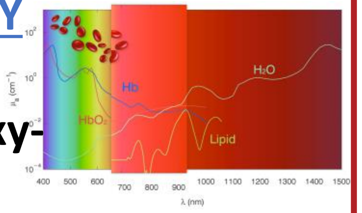
NIRS + "speckle" (DCS/SCOS): Oxygenation + blood flow → tissue oxygen metabolism, i.e. effective oxygen delivery and consumption

Thanks to: J. Mesquida

Multi-modal diffuse optical monitoring

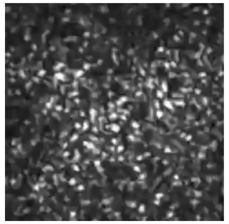
TECHNOLOGY

- NEAR INFRARED SPECTROSCOPY (CW-NIRS, FD-NIRS, TD-NIRS)



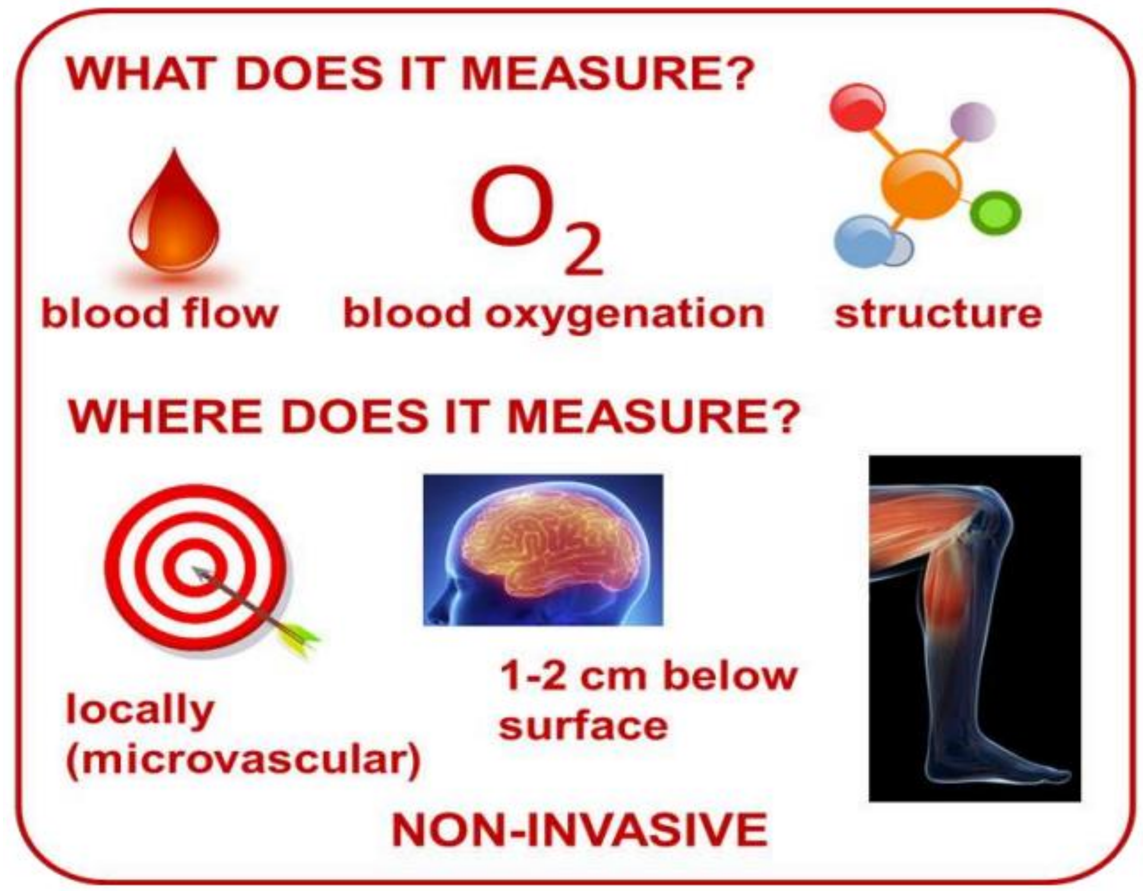
Blood oxygen saturation (StO2), oxy- & deoxy-hemoglobin (HbO2, Hb), total hemoglobin concentration (HbT)

- Speckle-based techniques (DCS, SCOS,…)



Blood flow (BF)

METABOLIC RATE OF OXYGEN EXTRACTION
MRO2 (Cerebral CMRO2, muscle MMRO2)



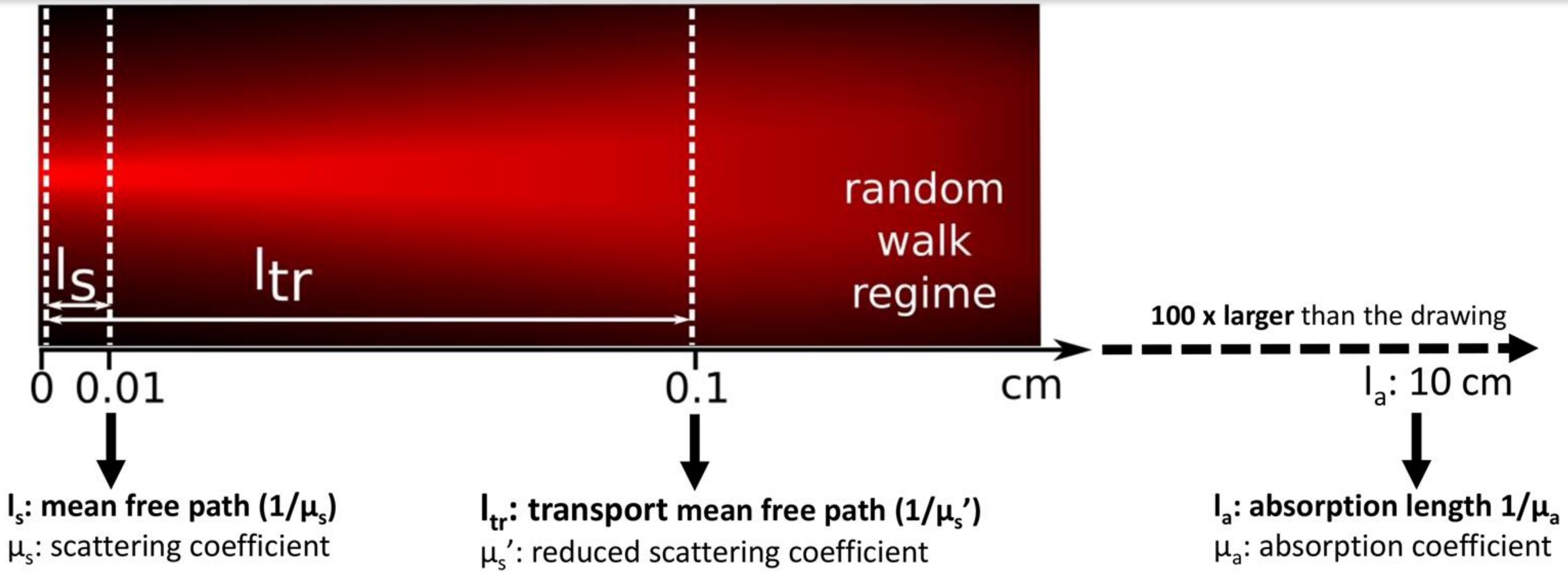
Local tissue hemodynamic and metabolic monitoring

Durduran et al., Rep. Progr. Phys. 72, 2010

Technology:

- Spectroscopy
- Laser speckle

Basic quantities

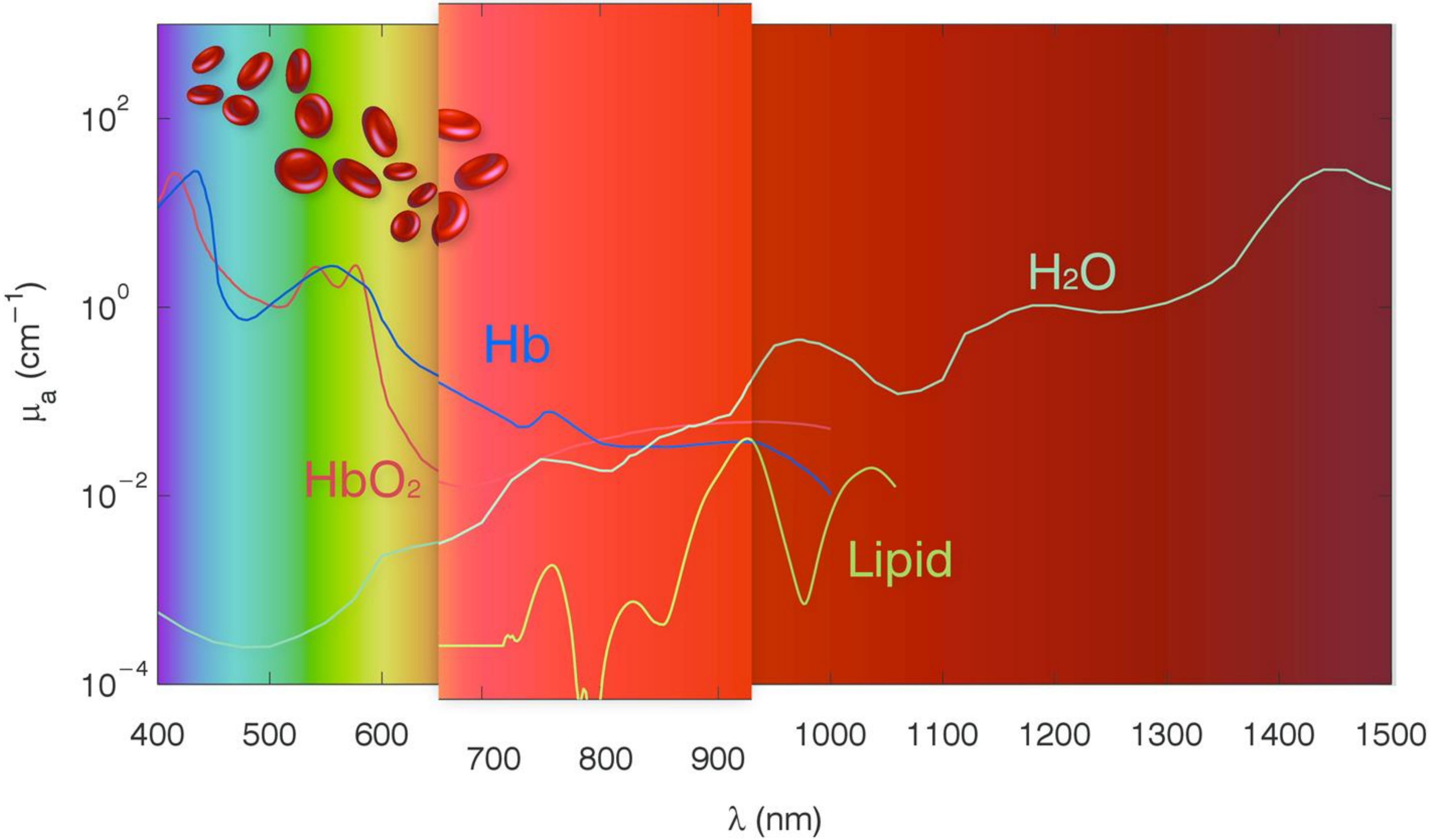


Absorbers	Scatterers
•Blood •Water •Lipids •Collagen •…..	•Membranes < 0.01μm. •Aggregations, layers < 0.1μm. •Vesicles, lysosomes <1μm. •Mitochondria, nuclei <10μm. •Cells >10μm.

Ntziachristos V. Nature Methods, 7(8):603, 2010;
Wang L V et al. Biomedical Optics: Principles & Imaging. Wiley-Interscience, 2007

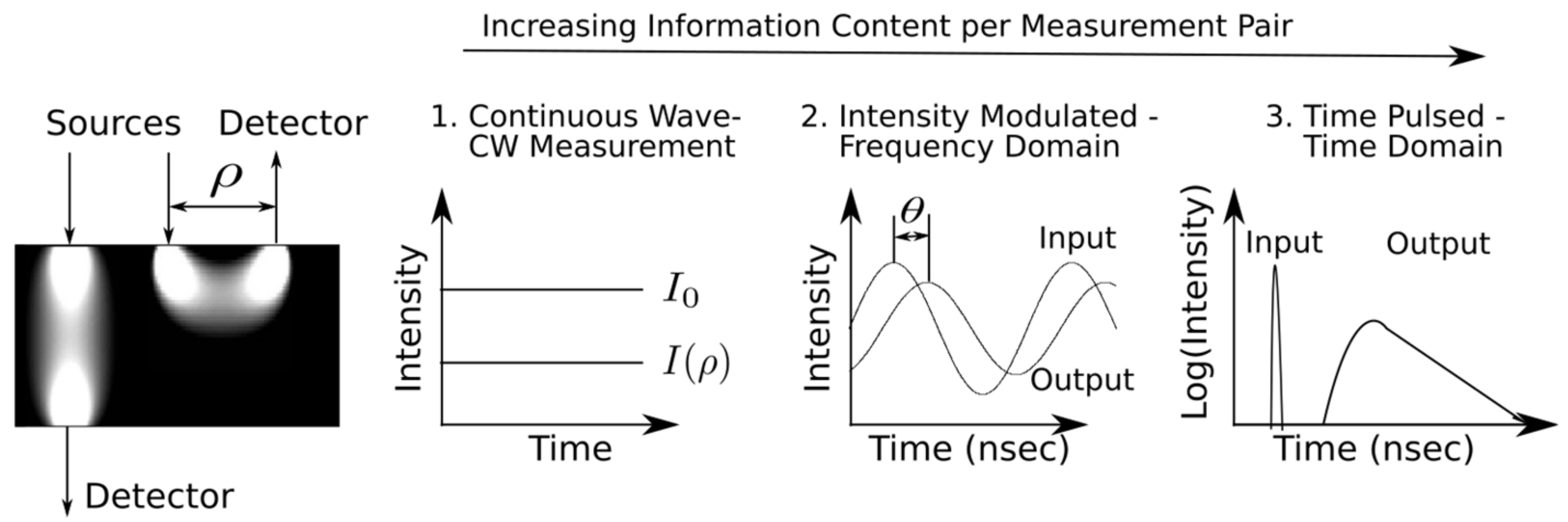
Deep tissue (>1cm) absorption spectroscopy

Wavelength dependence of absorption (μ_a (λ, r)), 1/μ_a ~ 10 cm



Measure: oxy- and deoxy-hemoglobin concentrations (HbO_2, Hb)
other chromophores, e.g. water and lipids.

Near-infrared spectroscopy: different modalities



"Banana"	Continuous wave	Amplitude Modulated	Pulsed
•Visitation probability •Transmission •Re-emission	•Amplitude only •Easy/simple •Inexpensive •Common	•"Frequency domain" •Amplitude & phase (!) •Radio freq.	•"Time domain" •Fast timing •Single-photon •Emerging

Durduran et al., Rep. Progr. Phys. 72, 2010

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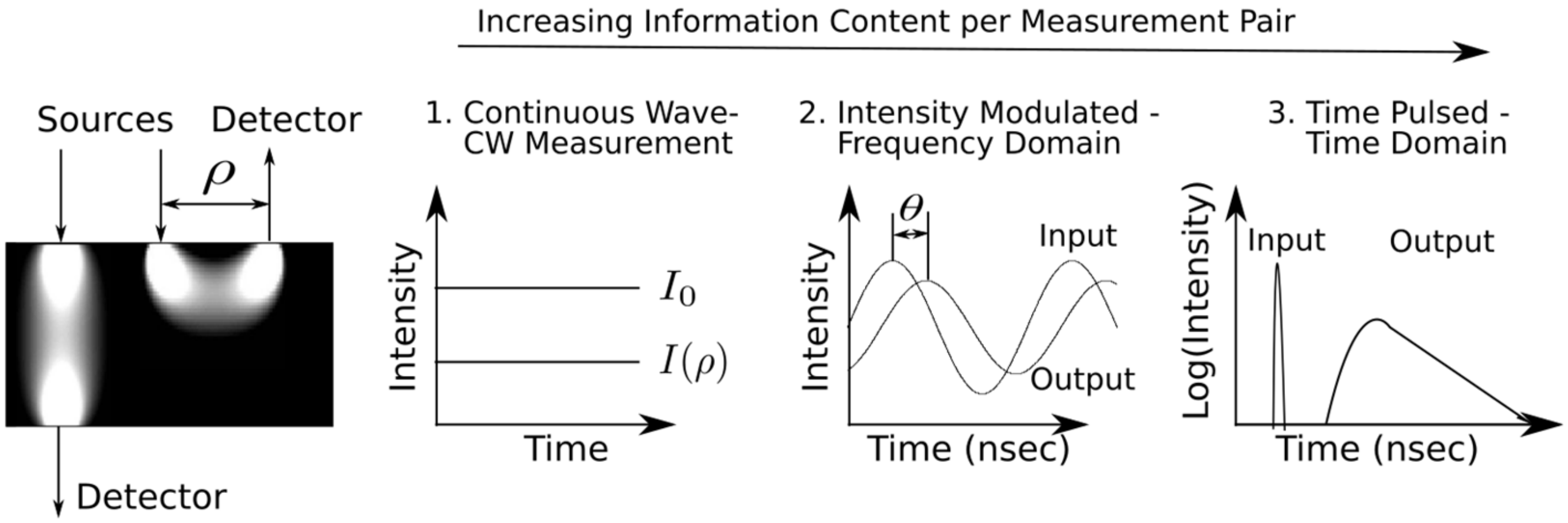

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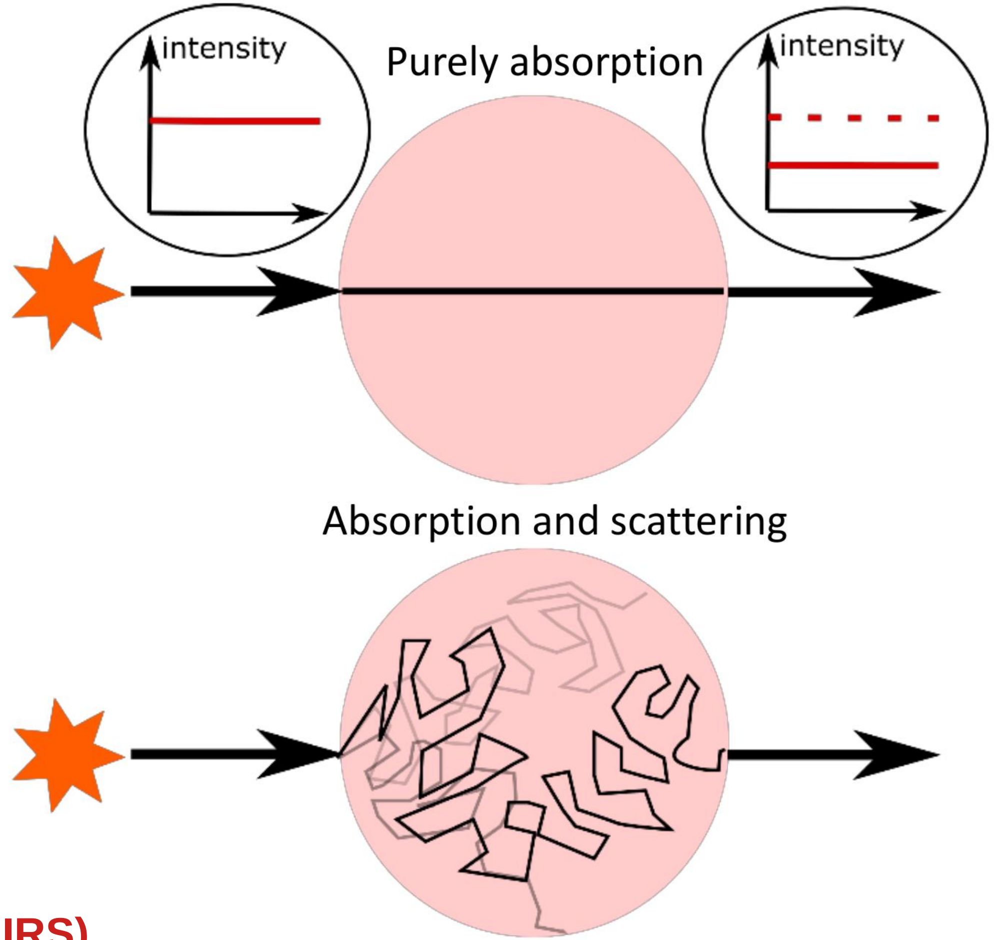
Clinical CW-NIRS based oximeters have provided mixed results.

Problematic due to the physics of the problem.

- Tissue heterogeneity is a major problem.
- Measures only oxygenation.
- Good as trend monitors.
- Well-validated in some settings.
- But a failure in others.

Clinical CW-NIRS based oximeters have provided mixed results.

Problematic due to the physics of the problem.



major problem.
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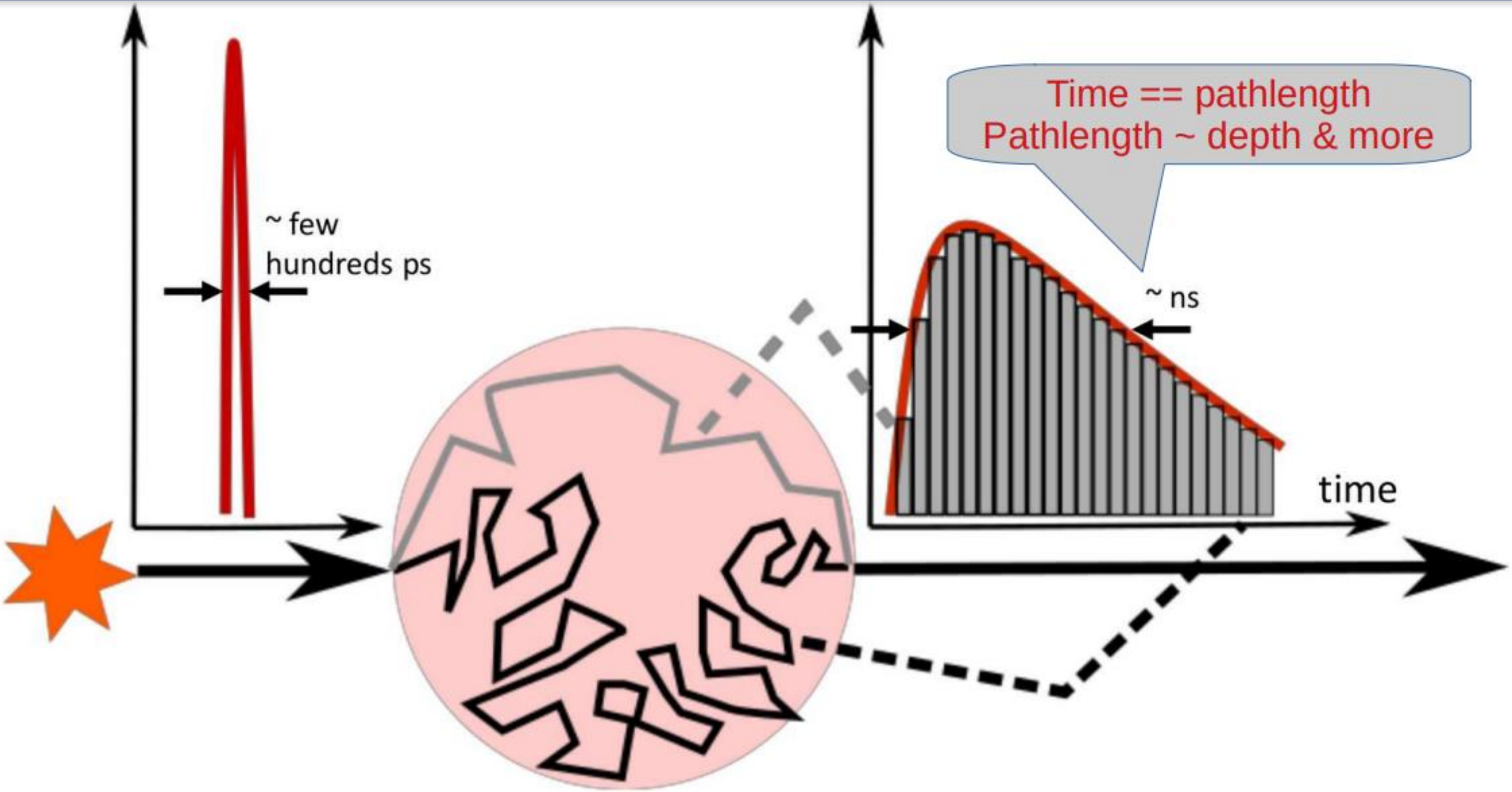
ttings.

Solutions:
Broadband NIRS (bNIRS)
Frequency domain NIRS (FD-NIRS)
Time-resolved spectroscopy (TRS, TD-NIRS)

Time-domain near-infrared spectroscopy (TD-NIRS)



Wavelength-dependent scattering (μ'_s) and absorption (μ_a) coefficients → tissue constituents

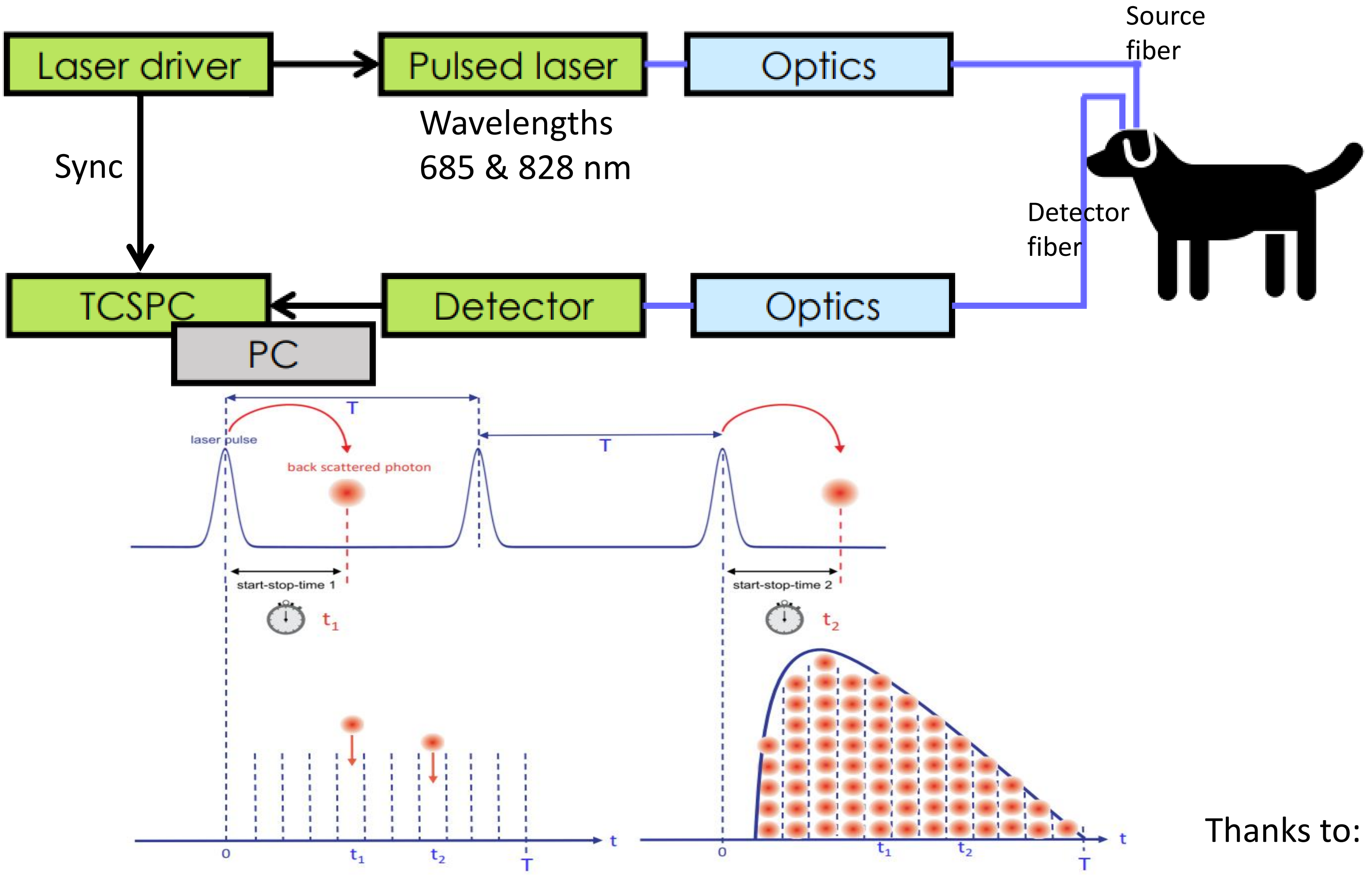
$$\mu_a(\lambda) = \sum_i \varepsilon_i(\lambda)\, c_i$$

$\varepsilon_i(\lambda)$ Molar extinction coeff. of the tissue component -i

c_i Concentration of the tissue component -i

Time-domain near-infrared spectroscopy (TD-NIRS)

Common TD-NIRS experimental configuration & components



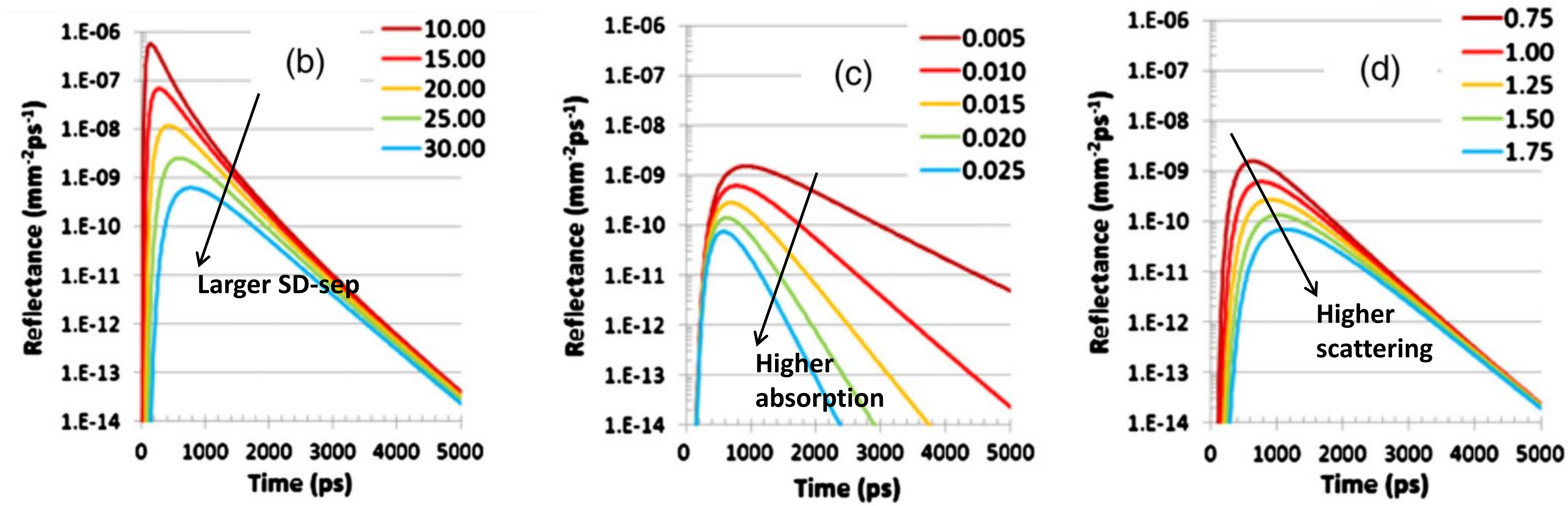
Thanks to: M. Zanoletti

TD-NIRS: Diffusion theory expectations

R: Reflectance from a semi-infinite homogeneous medium

$$R(\rho, t, \mu_a, \mu_s') = -\frac{exp(-\frac{\rho^2}{4Dvt} - \mu_a vt)}{2(4\pi Dv)^{3/2} t^{5/2}} \cdot \sum_{m=-\infty}^{+\infty} [z_{3m} exp(-\frac{-z_{3m}^2}{4Dvt}) - z_{4m} exp(-\frac{-z_{4m}^2}{4Dvt})]$$

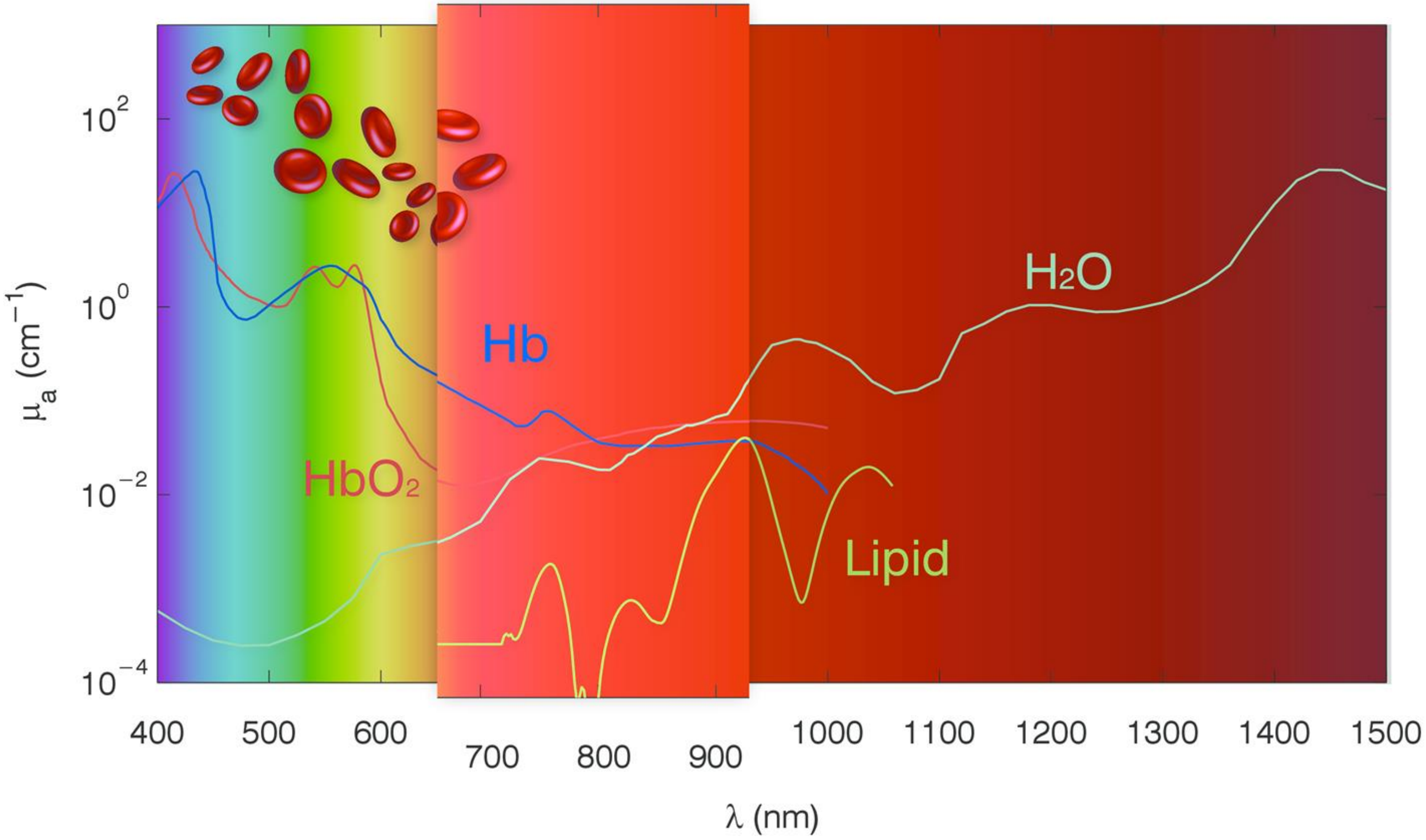
R depends on scattering and absorption



Torricelli et al., Neuroimage 85, 15, 2014

Components' concentrations

Measure: oxy- and deoxy-hemoglobin concentrations (HbO_2, Hb)
other chromophores, e.g. water and lipids.



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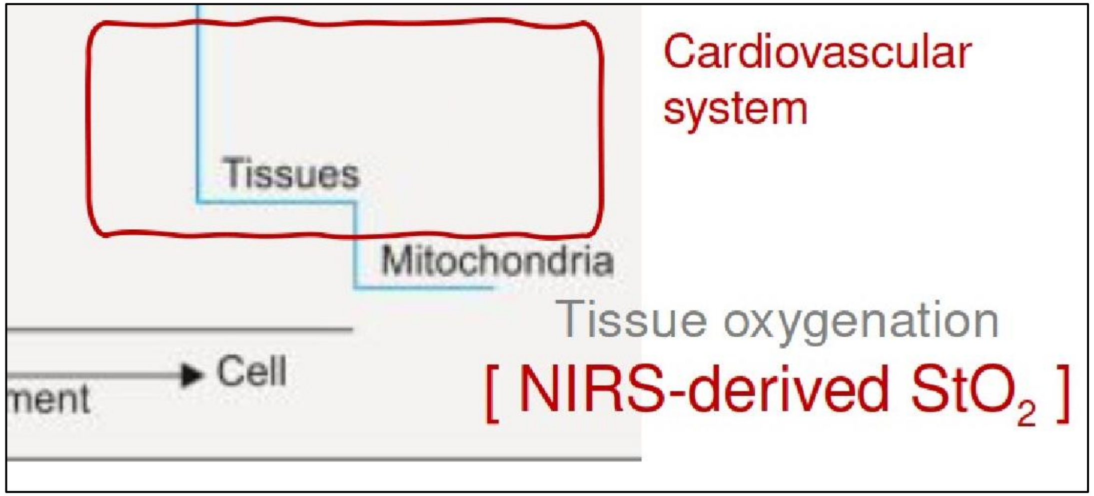
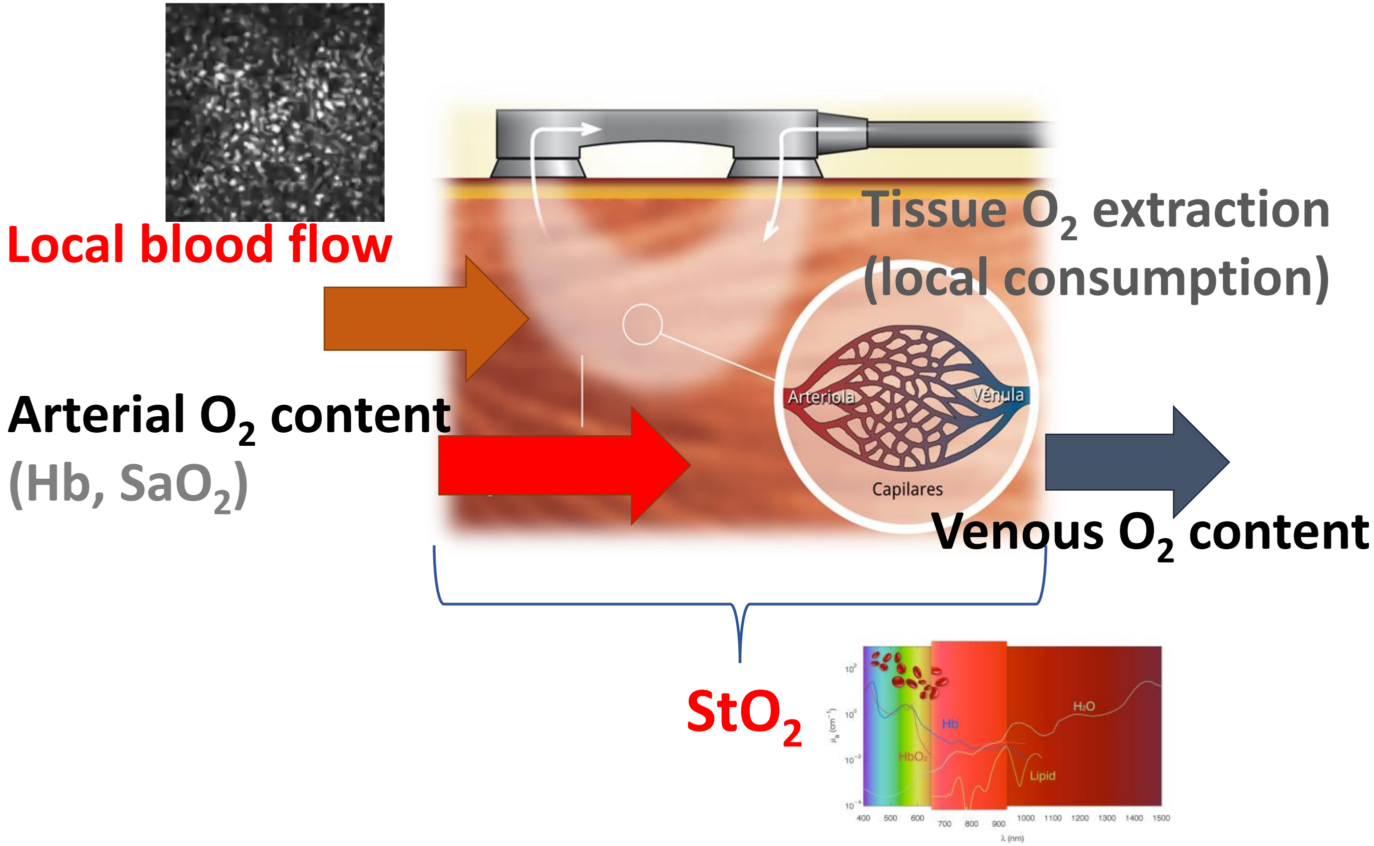
Technology:

- Spectroscopy
- Laser speckle

What we measure – Need for multimodal devices





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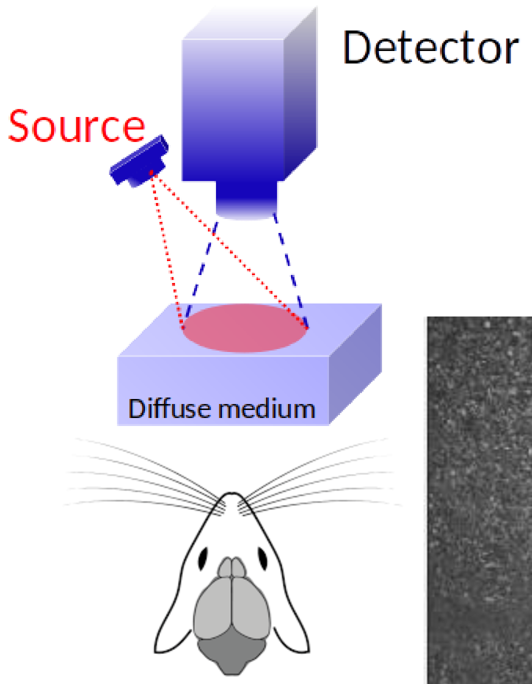
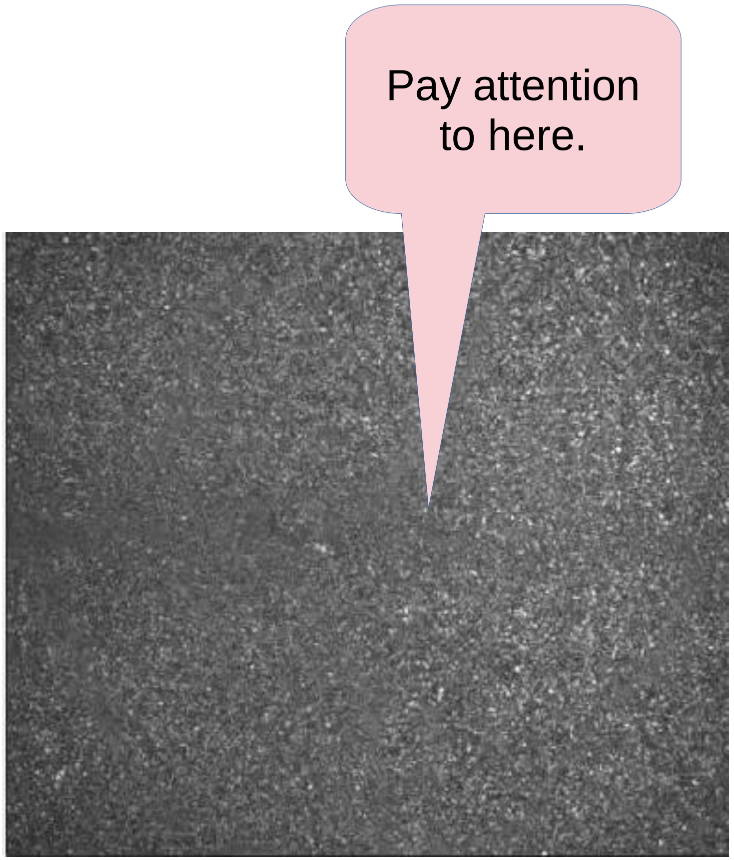
Thanks to: J. Mesquida

What about blood flow: laser speckle fluctuations





Laser speckle fluctuations observed on a mouse brain.

T. Dragojevic PhD thesis, 2019

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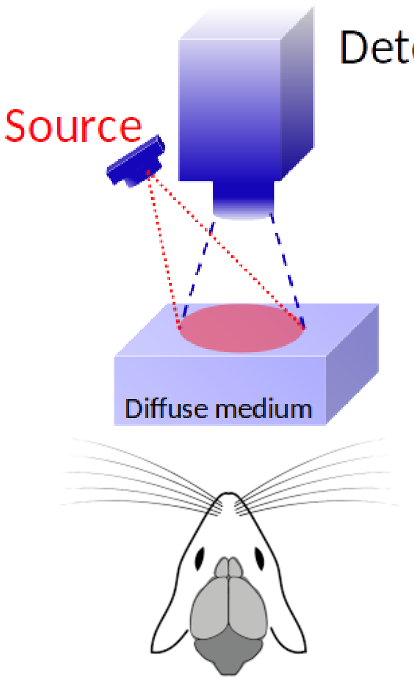

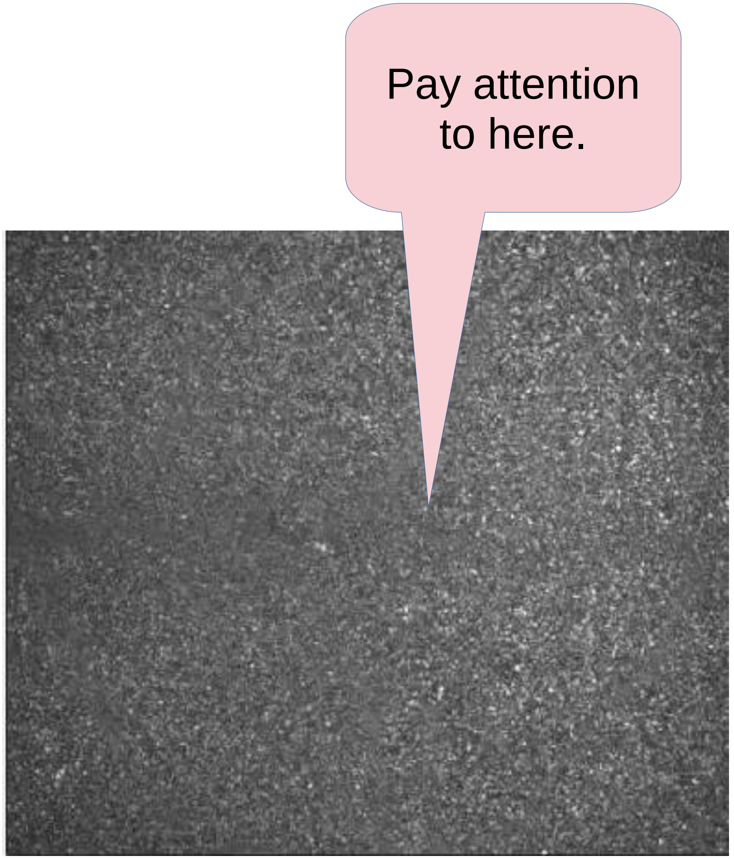

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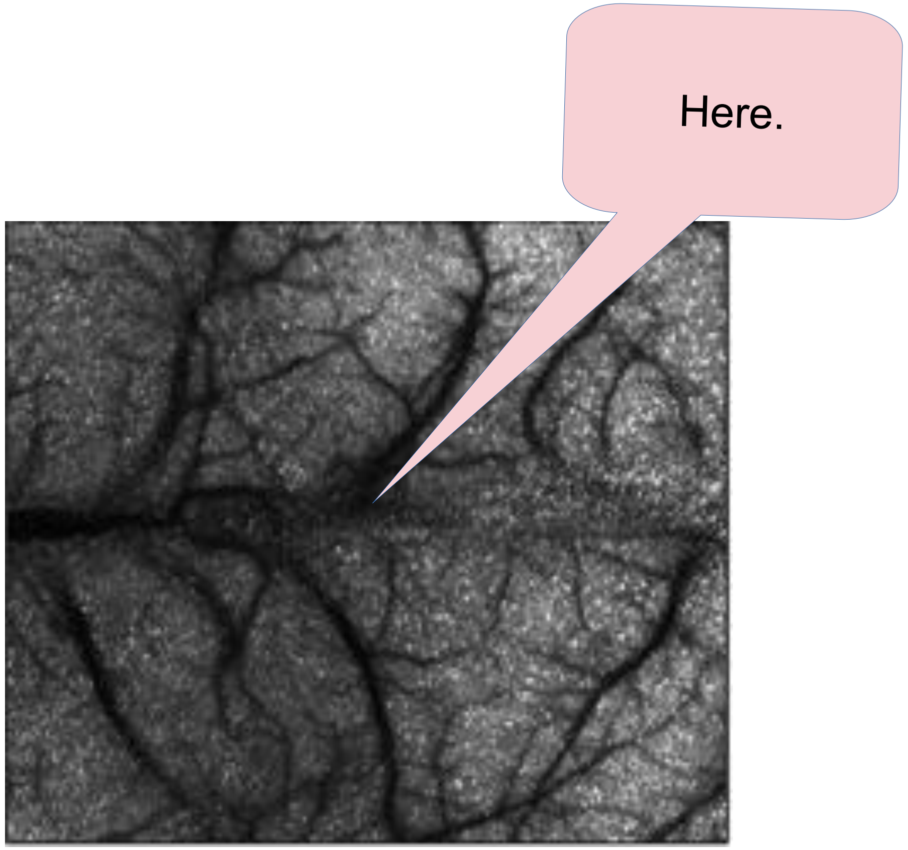

Physical model →
Map of blood flow

T. Dragojevic PhD thesis, 2019

Several methods based on speckle fluctuations

- Laser Doppler flowmetry (LDF)
- Laser speckle contrast imaging (LSCI)
- Diffuse correlation spectroscopy (DCS)
- Speckle contrast optical spectroscopy (SCOS)

. . .

and others

Several methods based on speckle fluctuations

Laser Doppler flowmetry (LDF)

Laser speckle contrast imaging (LSCI)

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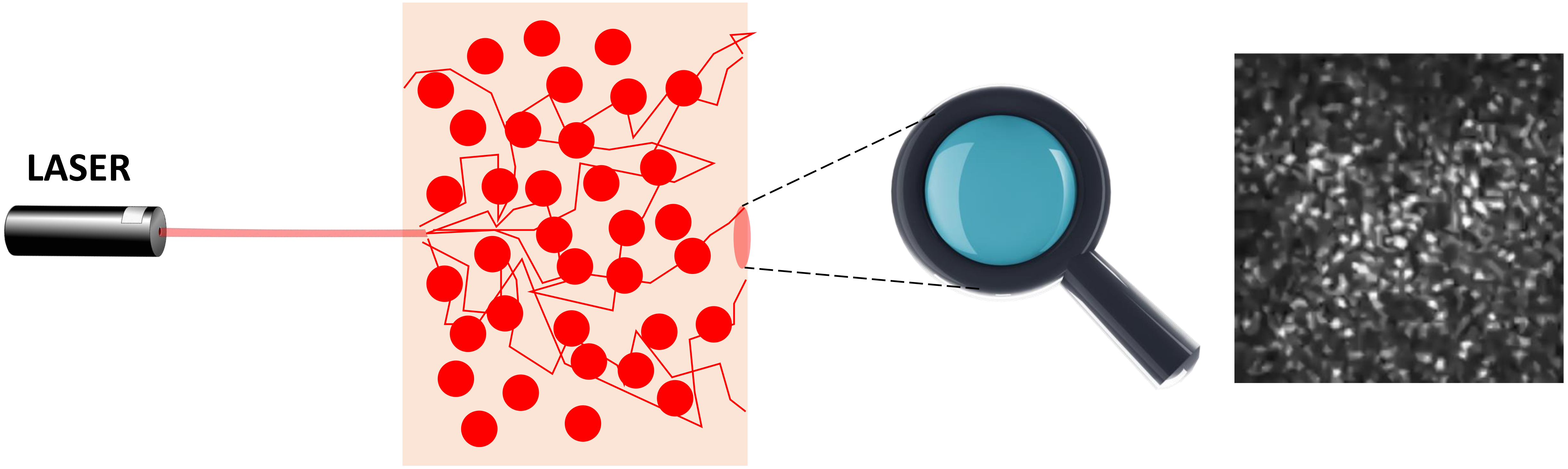
Speckle contrast optical spectroscopy (SCOS)

...

and others

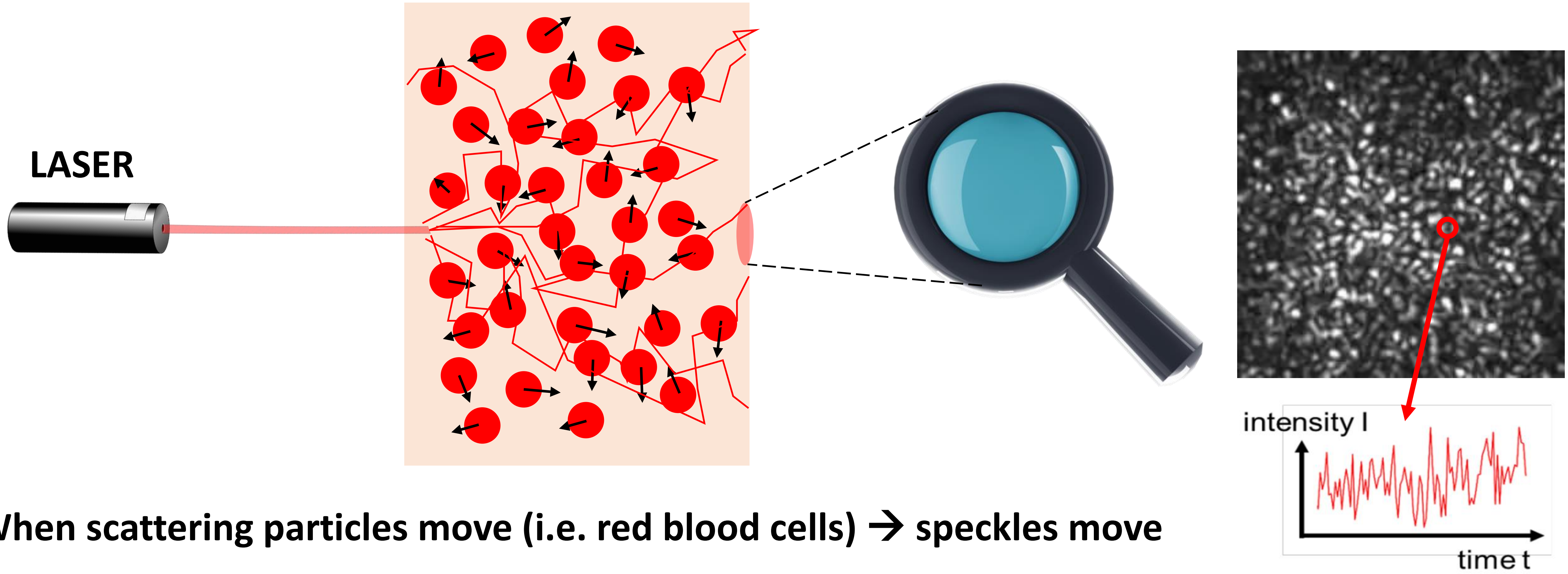
Diffuse correlation spectroscopy (DCS)

Light scattering by turbid material: speckle pattern → depends on scattering particle disposition



Diffuse correlation spectroscopy (DCS)

Light scattering by turbid material: speckle pattern → depends on scattering particle disposition

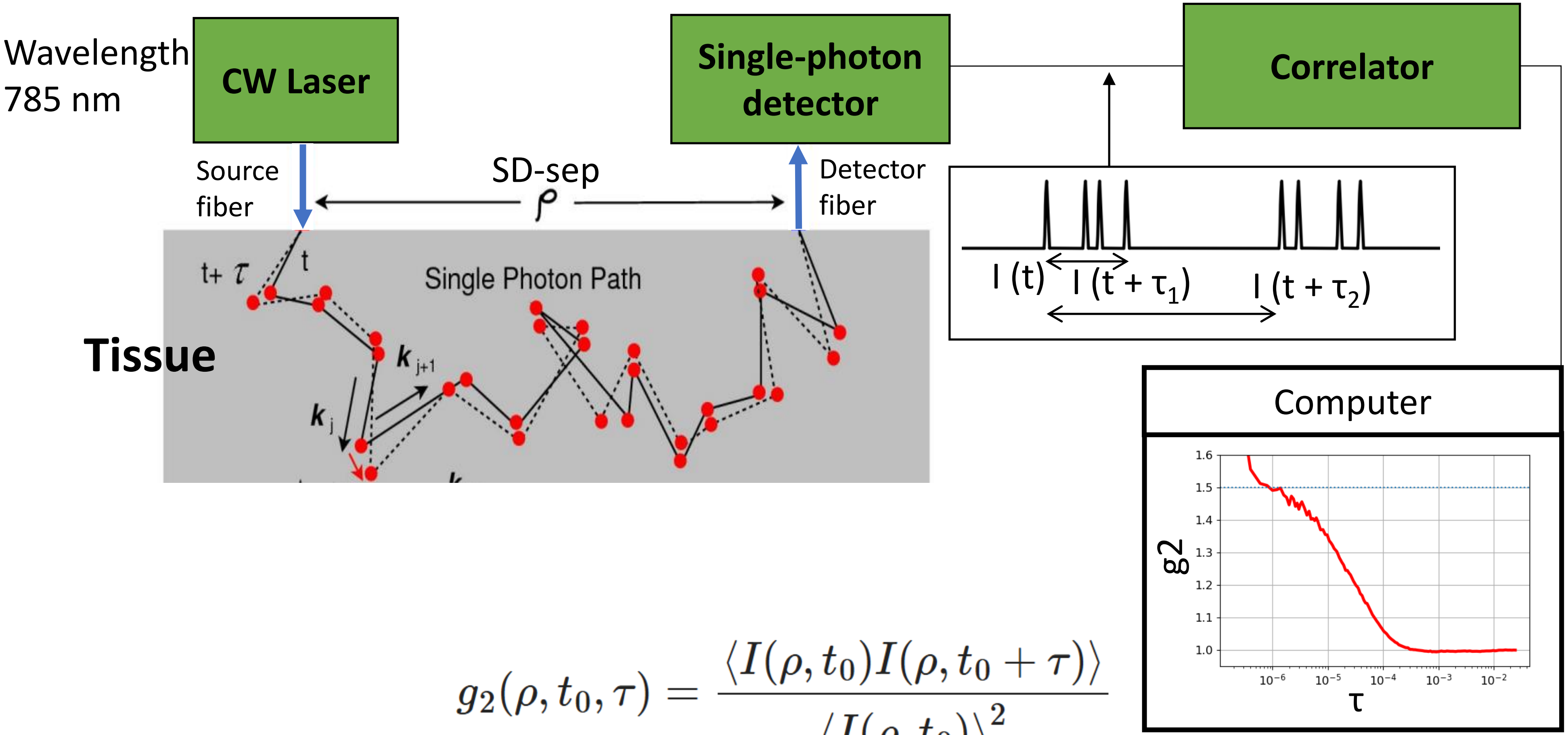


When scattering particles move (i.e. red blood cells) → speckles move

DCS: single speckle temporal fluctuation analysis → Information on blood flow

Diffuse correlation spectroscopy (DCS)

Common DCS experimental configuration & components



$$g_2(\rho, t_0, \tau) = \frac{\langle I(\rho, t_0) I(\rho, t_0 + \tau) \rangle}{\langle I(\rho, t_0) \rangle^2}$$

DCS: Diffusion theory expectations

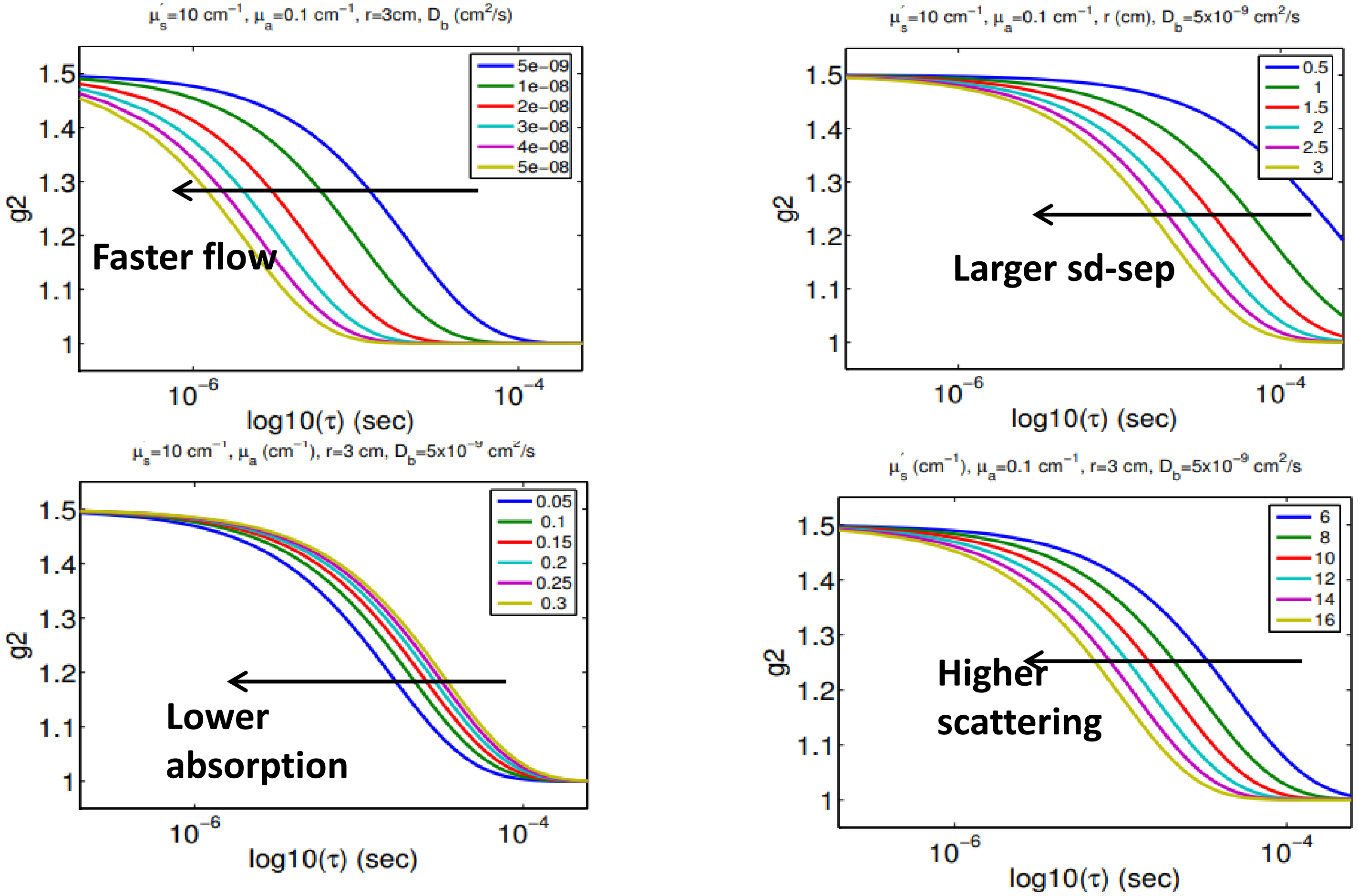
G1: electric field autocorr. function (g1 – norm.)

$$G_1(\rho, t_0, \tau) = \langle \mathbf{E}(\rho, t_0)\mathbf{E}^*(\rho, t_0 + \tau)\rangle = \frac{v}{4\pi D}\left[\frac{exp^{-K(\tau)r_+}}{r_+} - \frac{exp^{-K(\tau)r_-}}{r_-}\right]$$

g2: intensity autocorr. function

$$g_2(\rho, t_0, \tau) = 1 + \beta\,|g_1(\rho, t_0, \tau)|^2$$

g1 & g2 depend on scatterer movement (i.e. blood flow), scattering and absorption



T. Durduran PhD thesis, 2004

DCS: Validation against standard modalities

Table 1. All *in vivo* DCS validation studies published to date. ASL-MRI, arterial spin-labelled MRI; PDT, photodynamic therapy.

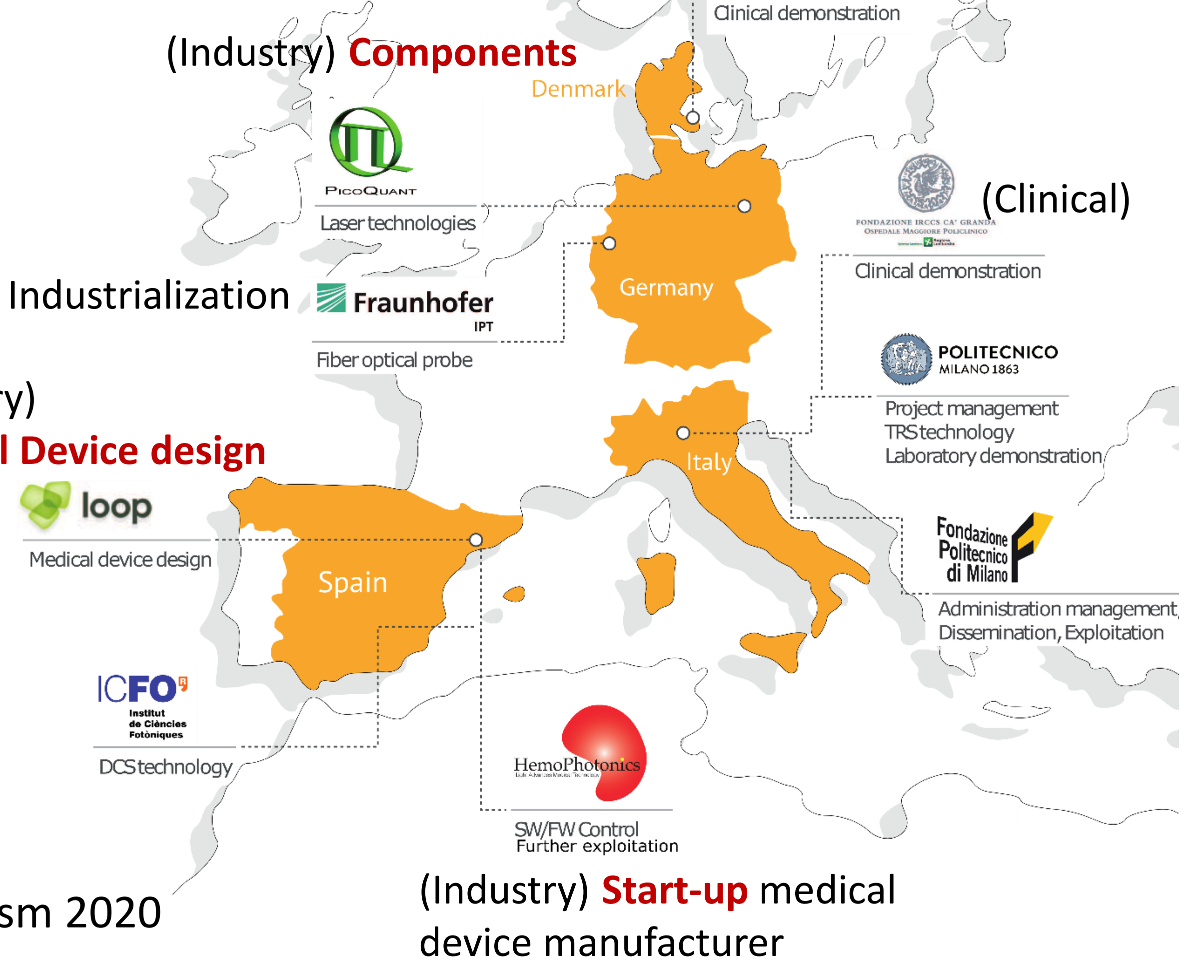
sample	perturbation	modality	correlation coefficient	slope DCS/mod	references
mouse	femoral artery occlusion	laser Doppler	>0.8	0.96–1.07	[50]
mouse tumour	antivascular therapy	contrast-enhanced ultrasound	n.a.	agreement	[24]
mouse tumour	PDT	Doppler ultrasound	n.a.	agreement	[25]
mouse tumour	PDT	power Doppler ultrasound	n.a.	0.97	[26]
rat	hypercapnia	ASL-MRI	0.81–0.86	0.75	[22]
rat	hypocapnia	laser Doppler	0.94	1.3	[51]
neonatal piglet	traumatic brain injury	fluorescent microspheres	0.63	0.4	[27]
premature neonates	absolute baseline	transcranial Doppler	0.53	n.a.	[48]
term neonate	hypercapnia	ASL-MRI	0.7	0.85	[52]
premature infant	absolute baseline	transcranial Doppler	0.91	0.9	[53]
human muscle	cuff inflation/deflation	ASL-MRI	>0.77	1.5–1.7	[29]
adult human	pressors and hyperventilation	xenon-CT	0.73	1.1	[54]
adult human	acetazolamide	transcranial	n.a.	agreement	[46]

Mesquita, Rickson C., et al. "Direct measurement of tissue blood flow and metabolism with diffuse optics." *Phil. Trans. Roy Soc. A* (2011)

BabyLux a unique opportunity for validation

BabyLux

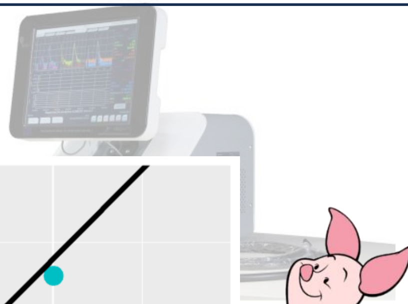
An optical neuro-monitor of cerebral oxygen metabolism and blood flow for neonatology

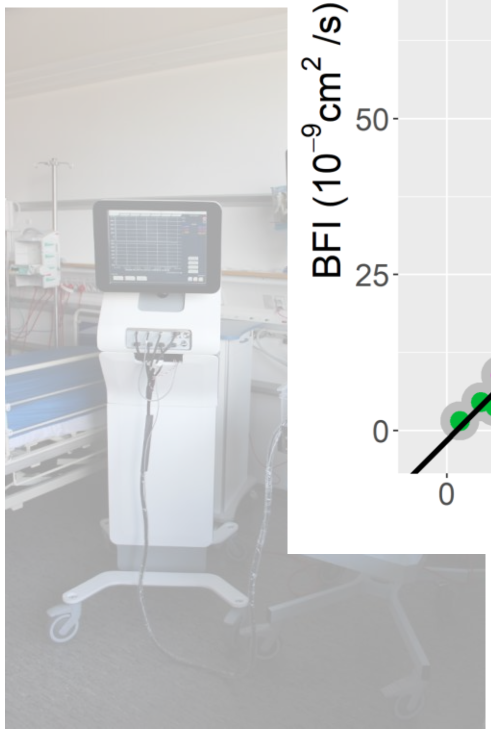


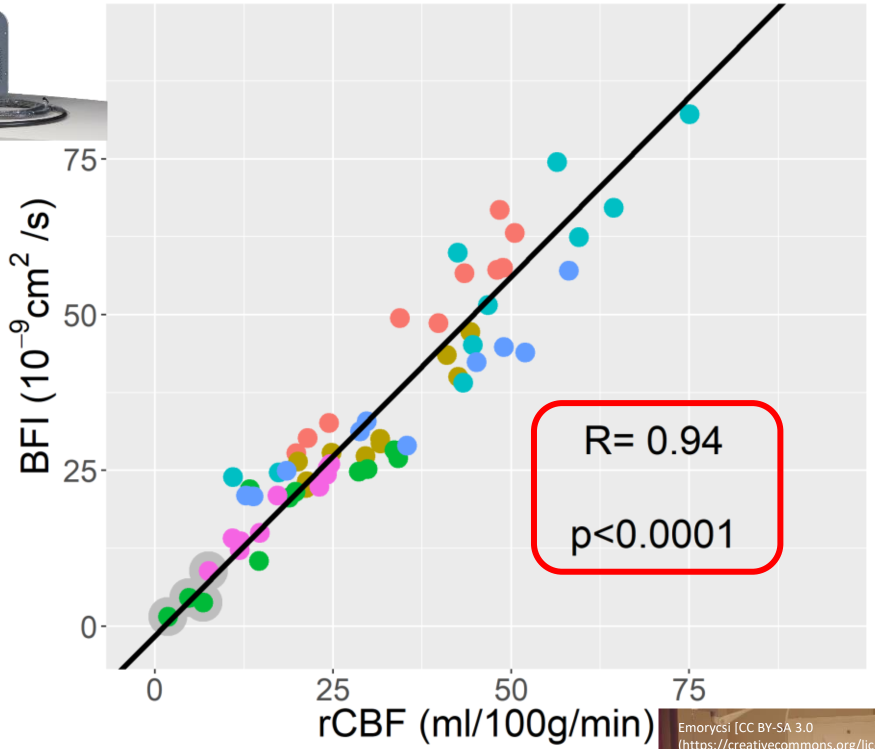
M. Giovannella, J. Cerebral Blood Flow & Metabolism 2020

Validation against ^{15}O PET

An optical neuro-monitor of cerebral oxygen metabolism and blood flow for neonatology





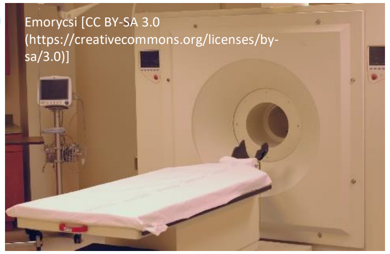


Regional CBF

PET versus Optics Validation

Error associated to the two methods:

- DCS 7%
- PET 18%



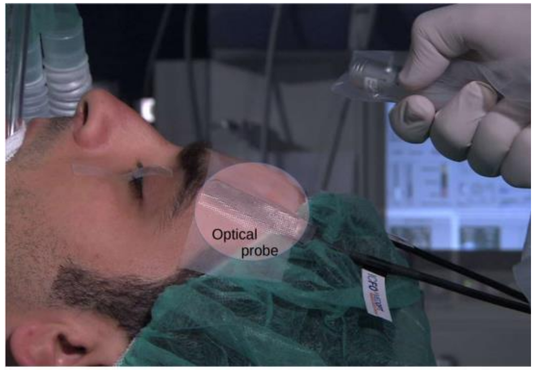
M. Giovannella, J. Cerebral Blood Flow & Metabolism 2020

(Industry) **Start-up** medical device manufacturer

Examples of clinical applications:
Devices

Many applications, many different devices

Adult brain monitoring
(stroke, trauma, aging, sleep,…)



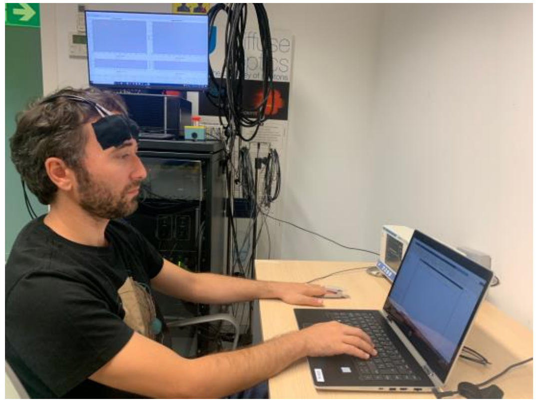
Infant brain
(preterm babies, brain development, injury)

Cancer diagnosis & therapy follow-up
(Breast, thyroid, head and neck, prostate, …)

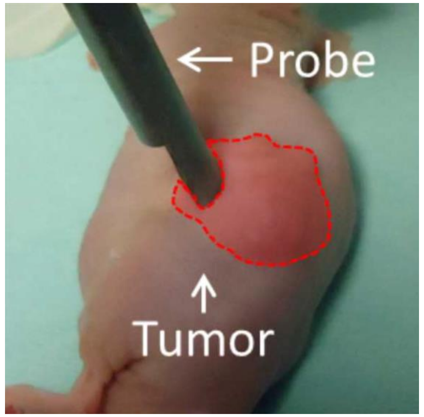
Exercise/sport, physiotherapy
(muscle metabolism)

Intensive care
(brain injury, sepsis, COVID, trauma, …)

Brain functional studies
(cognition, language, …)



Animal studies
(cancer, plasmonic photothermal therapy, …)



Our flagship device: “hDOS”

- **Battery operated** and **portable**
- **Remotely controllable**
- **DCS (blood flow monitor: BF)**
  - Acquisition rate 40 Hz
- **TD-NIRS (blood oxygen saturation, oxy-, deoxy- and total hemoglobin concentration)**
  - Acquisition rate 1 Hz
- Integrated automatized vascular occlusion test (**VOT)** protocols (**endothelial function**)
- **Blood pressure** monitor and **pulse oximeter**

Thanks to: M. Zanoletti & M. Atif Yaqub

Different technology readiness levels

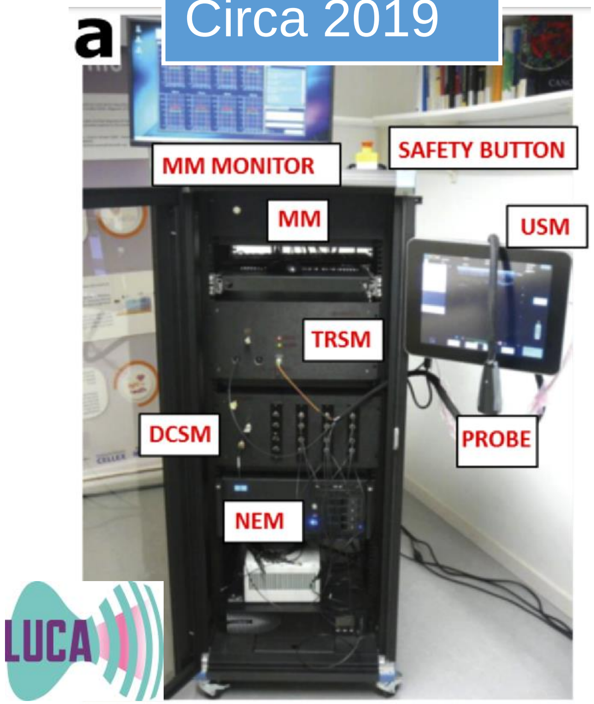
Circa 2004

Circa 2021

Circa 2017

BabyLux

Circa 2019



Circa 2024

Circa 2019

HemoPhotonics

Examples of clinical applications:

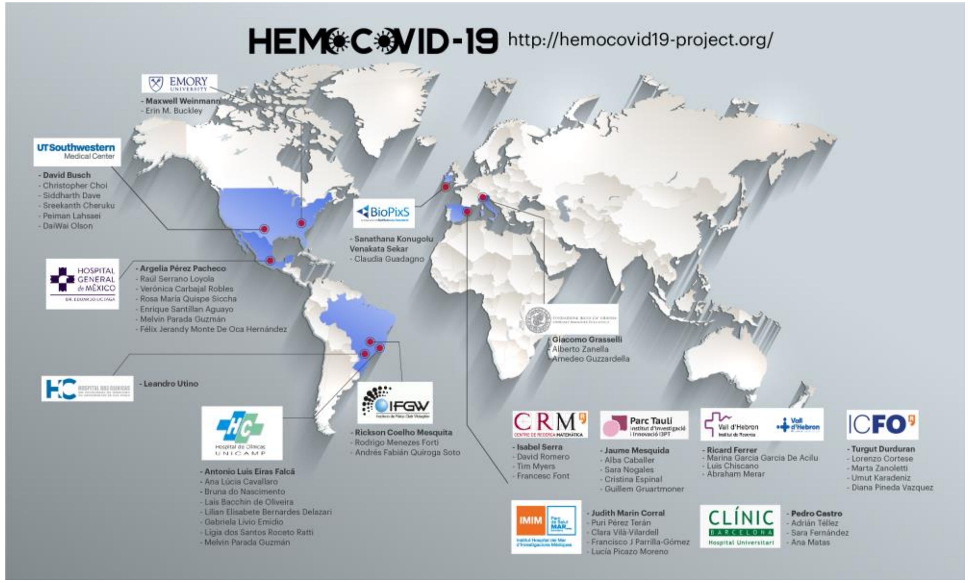
1- Intensive care: COVID patients

2- Intracranial pressure monitoring

3- Oncology: thyroid cancer

Intensive care: COVID19 patients

HEMOCOVID PROJECT



<u>Commercial devices</u>: Continuous-Wave Near-Infrared Spectroscopy (CW-NIRS)

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Mesquida, Caballer, Cortese et al., Critical Care 2021

Cortese et al., Sensors 2021

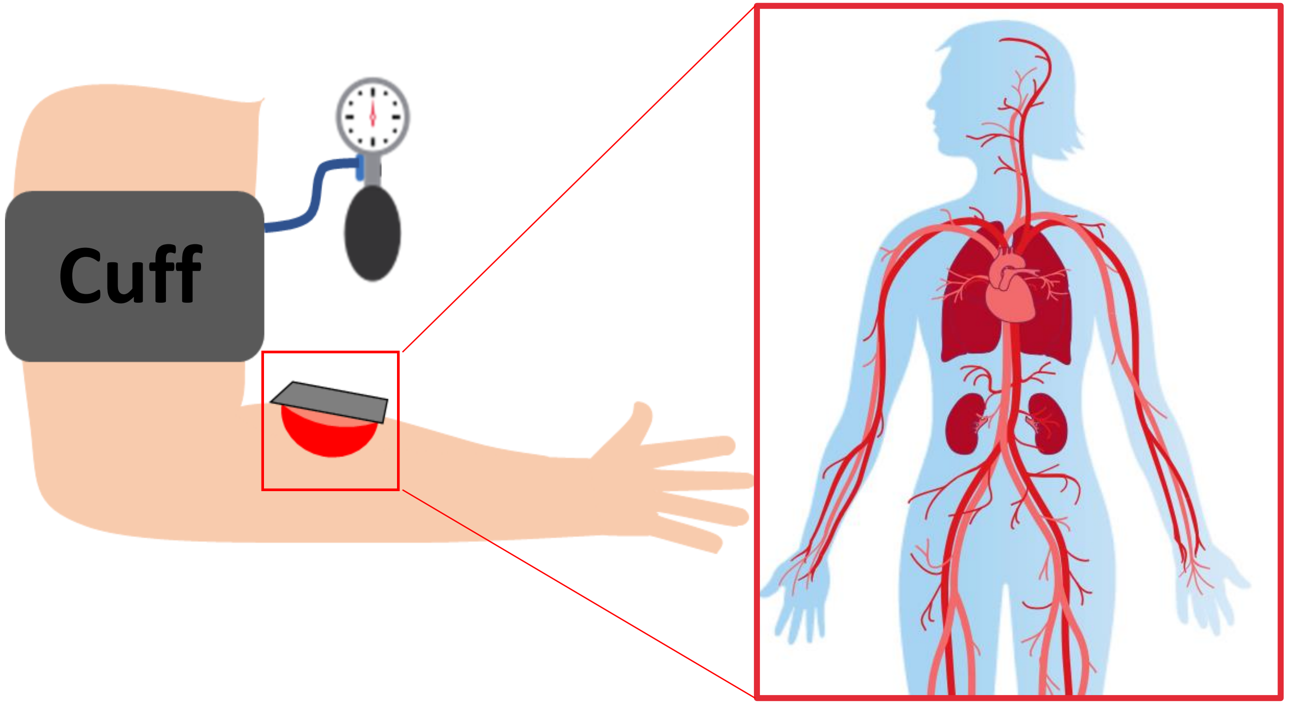
VASCOVID PROJECT

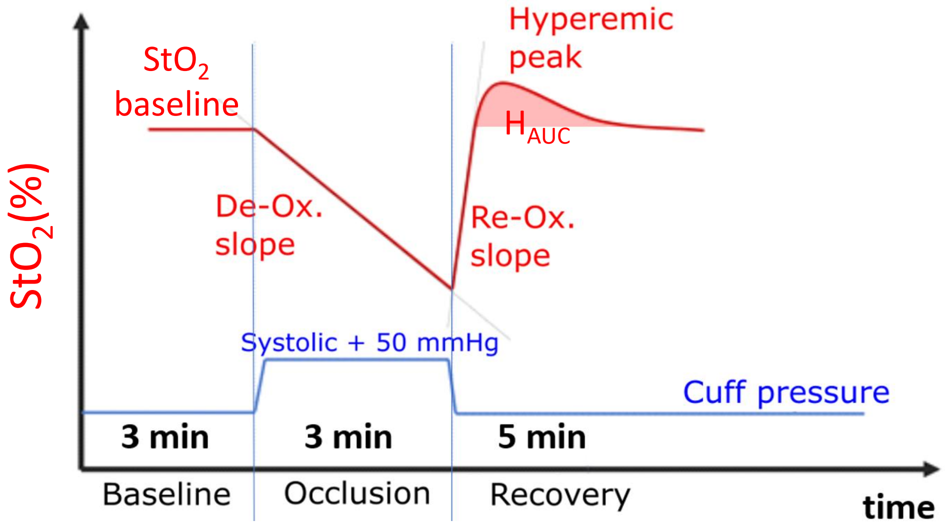
VASCOVID PROJECT

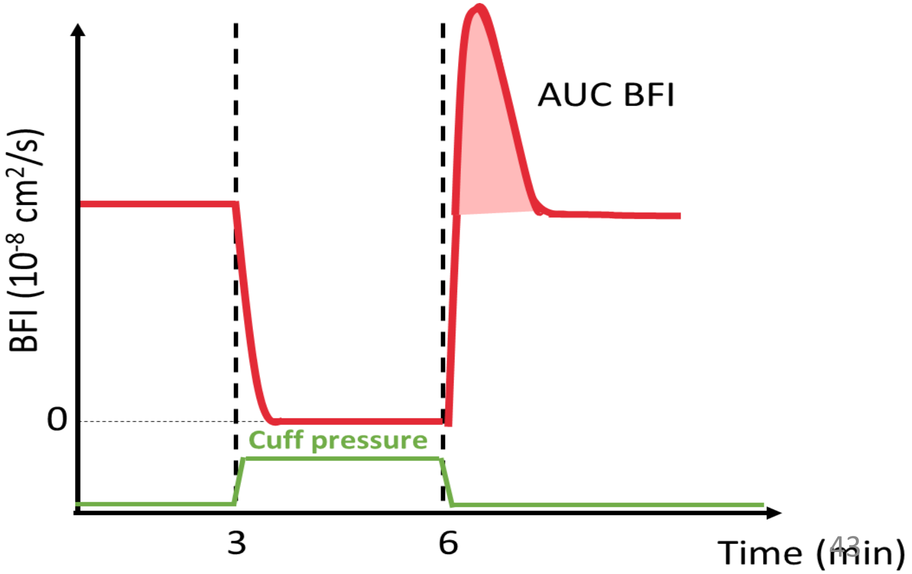
- EU funded
- Technology driven – “next-generation” NIRS
- Public/private consortium
- Roadmap to CE certification and industrialization

Vascular occlusion & NIRS

A LOCAL MEASUREMENT FOR GLOBAL HEMODYNAMIC STATUS MONITORING







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Vascular occlusion & NIRS

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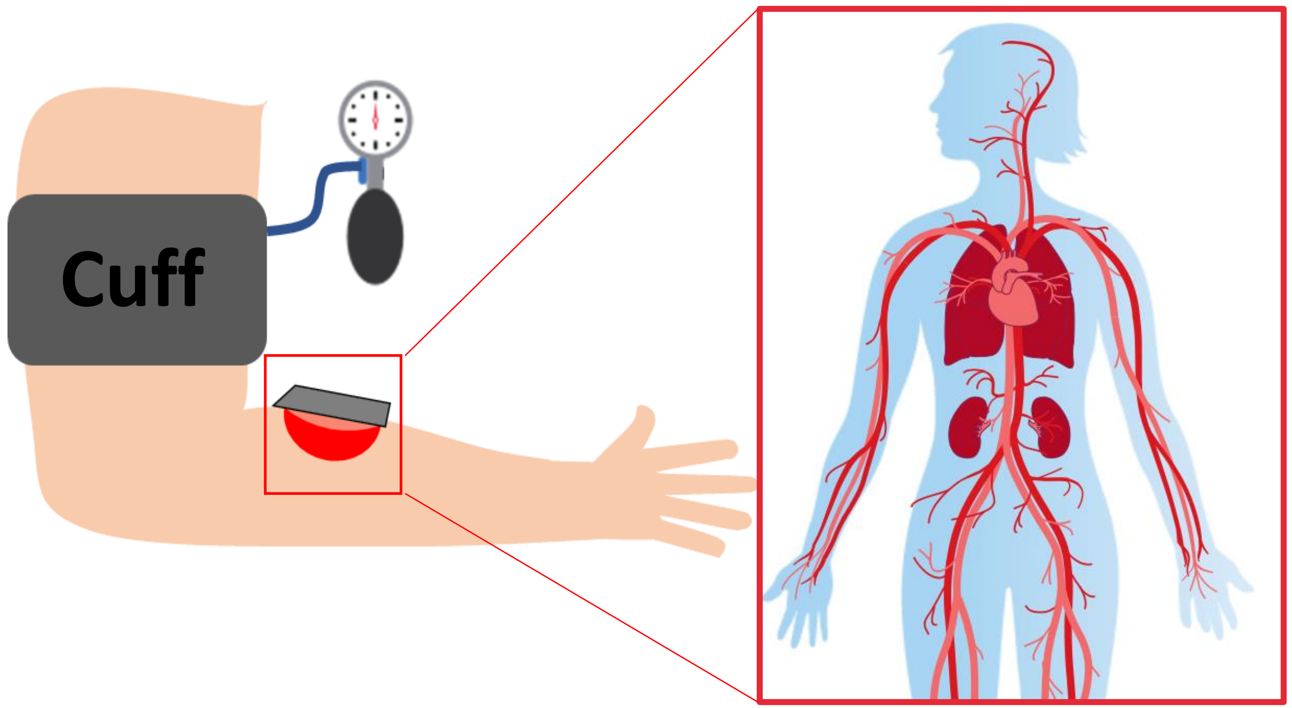

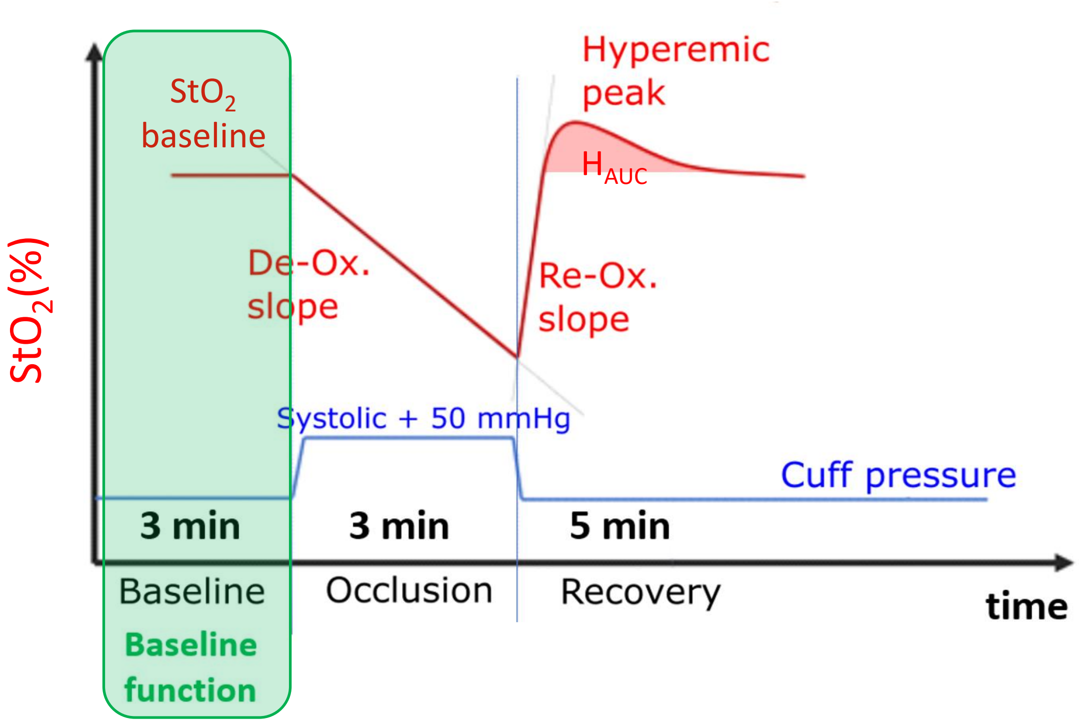

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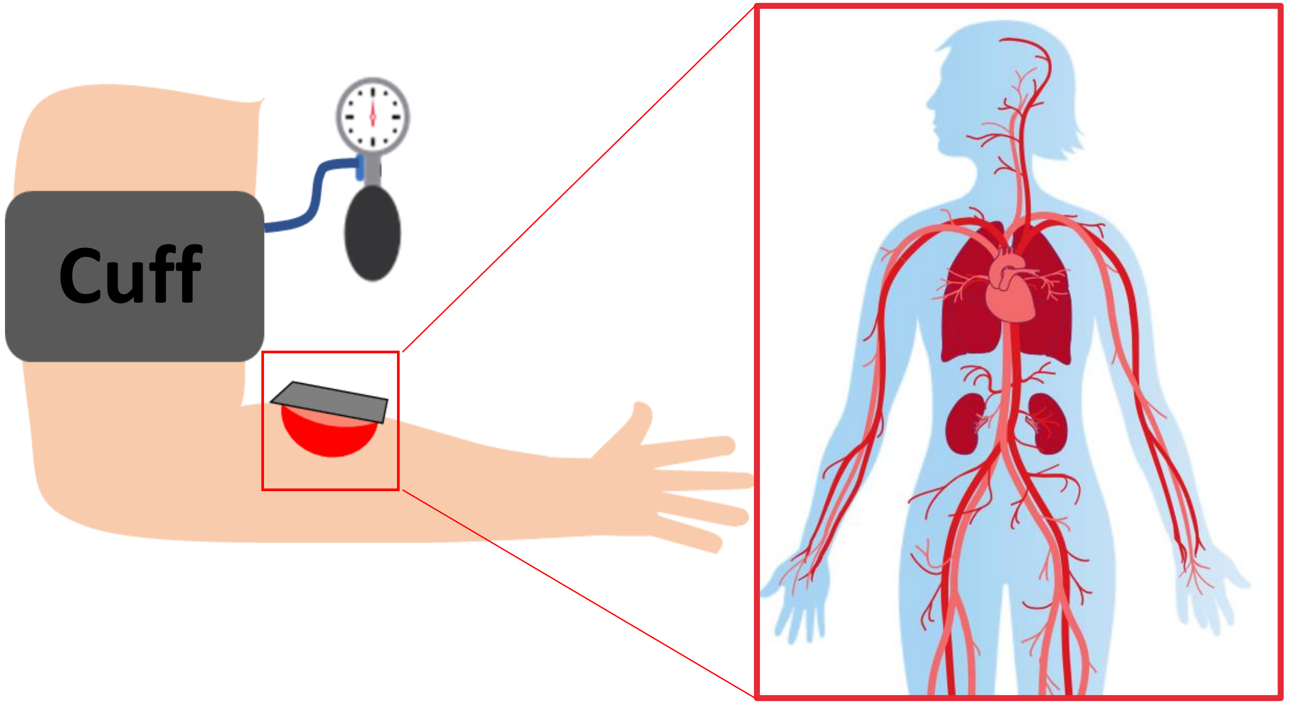

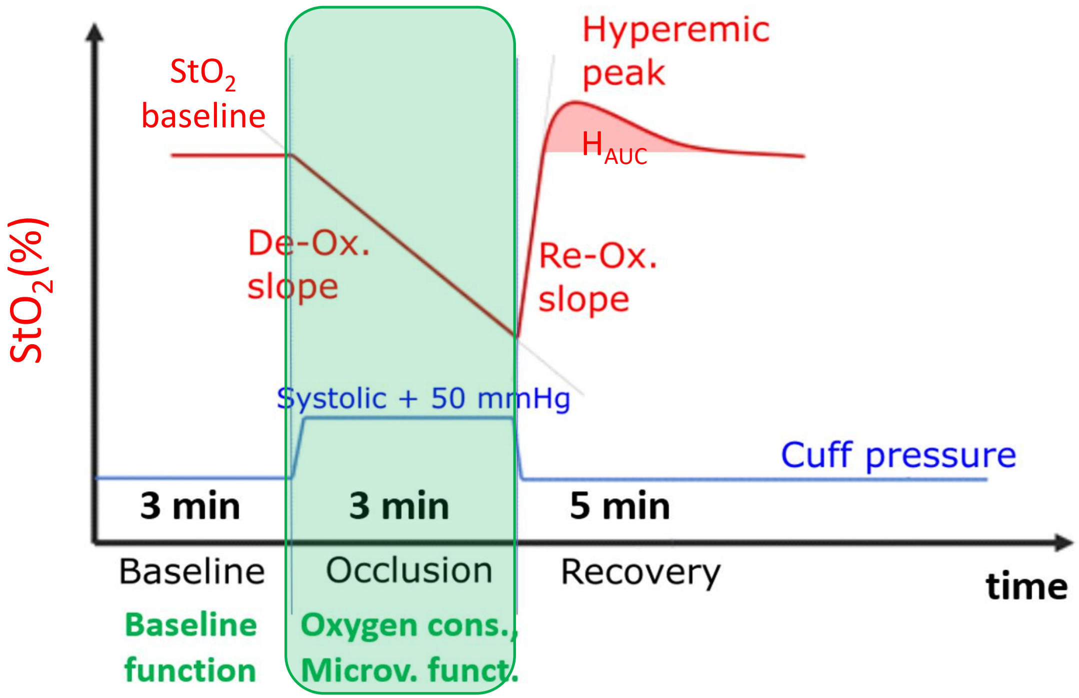

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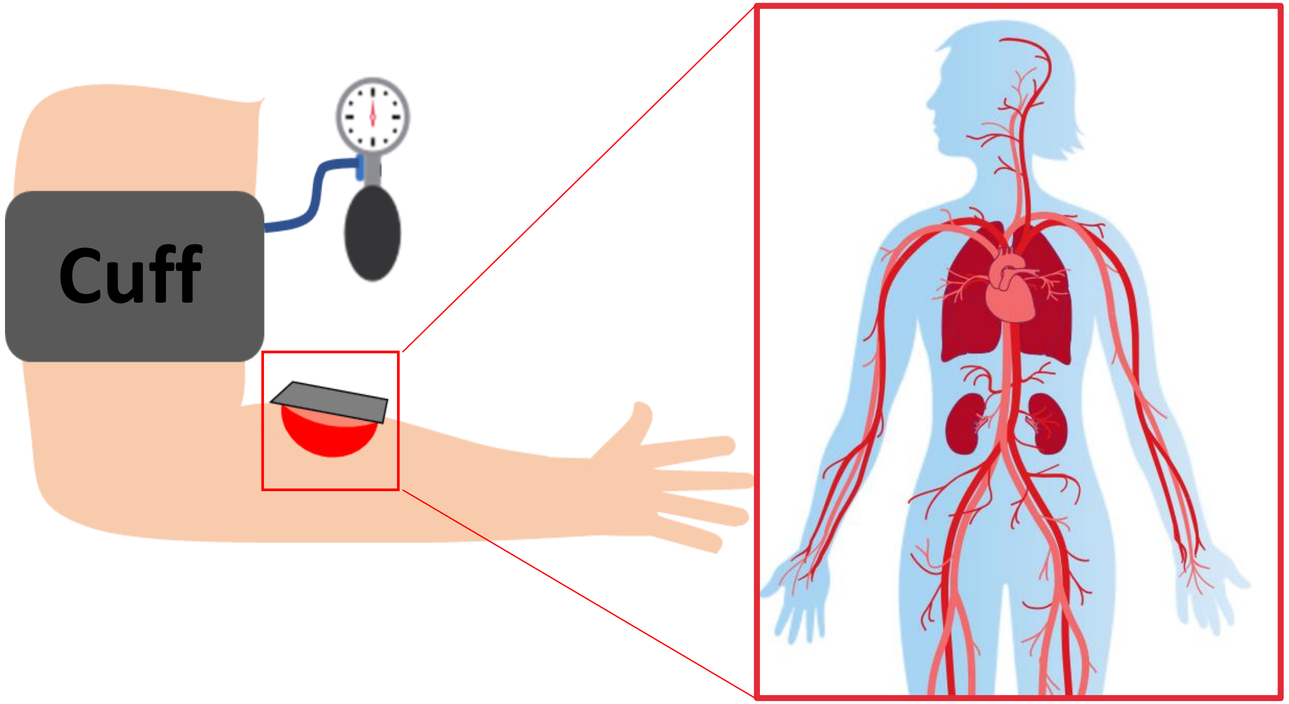

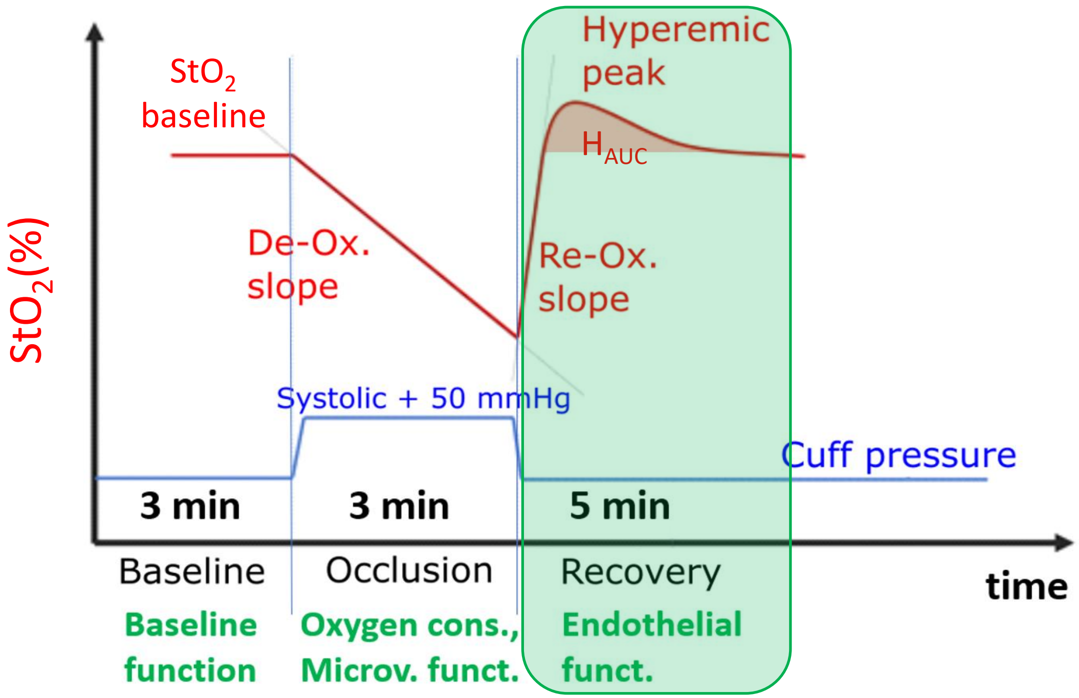

Creteur et al., Current Opinion in Critical Care (2008)
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Mesquida et al., Intensive Care Medicine (2013)

Clinical applications of VOT/NIRS in critical care

- **Monitoring global hemodynamic status** in **resuscitation**
  - Early detection of tissue hypoperfusion
  - Evaluation of persistence of tissue hypoperfusion

    - Mixed ICU-patients
    - **Septic shock**
    - **Trauma/hemorrhagic shock**

- **Cardiovascular challenges: Weaning from mechanical ventilation**
  - Unmask poor cardiovascular performance

- **Endothelial function**

  Monitoring microvascular reactivity: COVID-19, ARDS, septic and non-septic.

Creteur et al., Current Opinion in Critical Care (2008)
Lipcsey et al., Annals of Intensive Care (2012)
Mesquida et al., Intensive Care Medicine (2013)

Thanks to: J. Mesquida

Clinical applications of VOT/NIRS in critical care

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  Early detecti
  Evaluation o
  - Mixed
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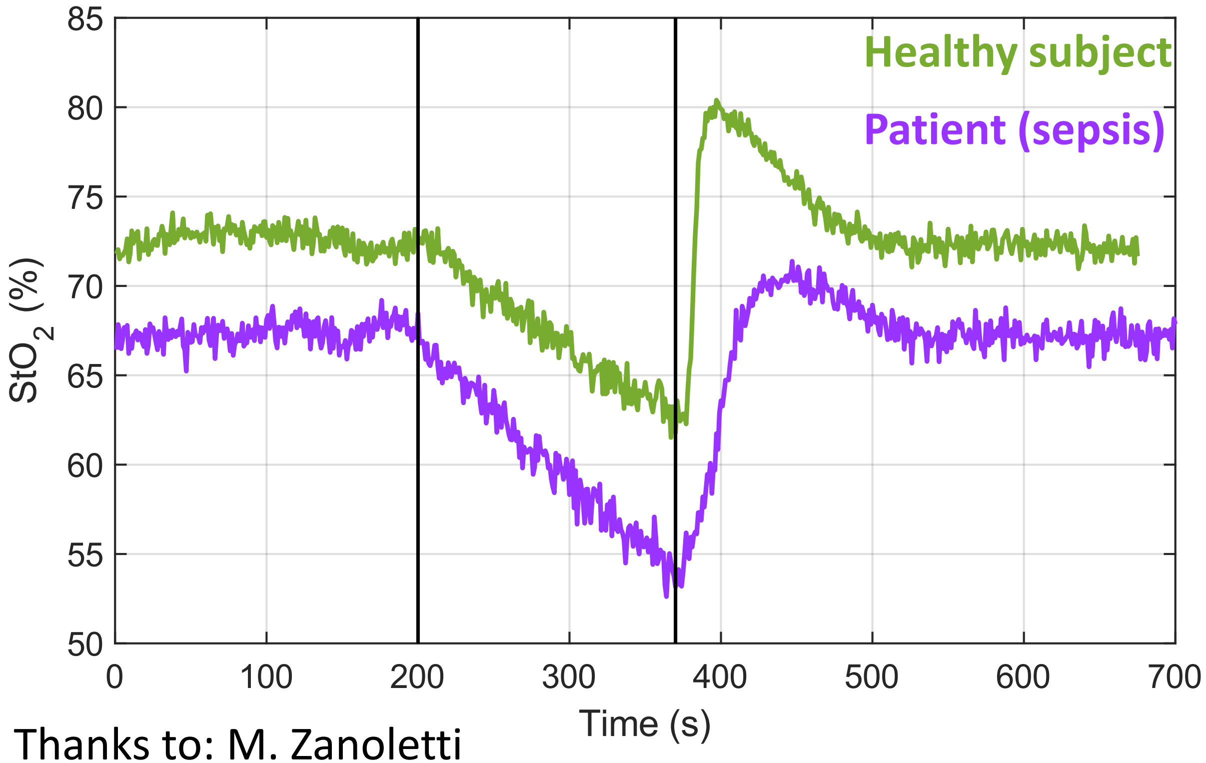

Thanks to: M. Zanoletti

Thanks to: J. Mesquida

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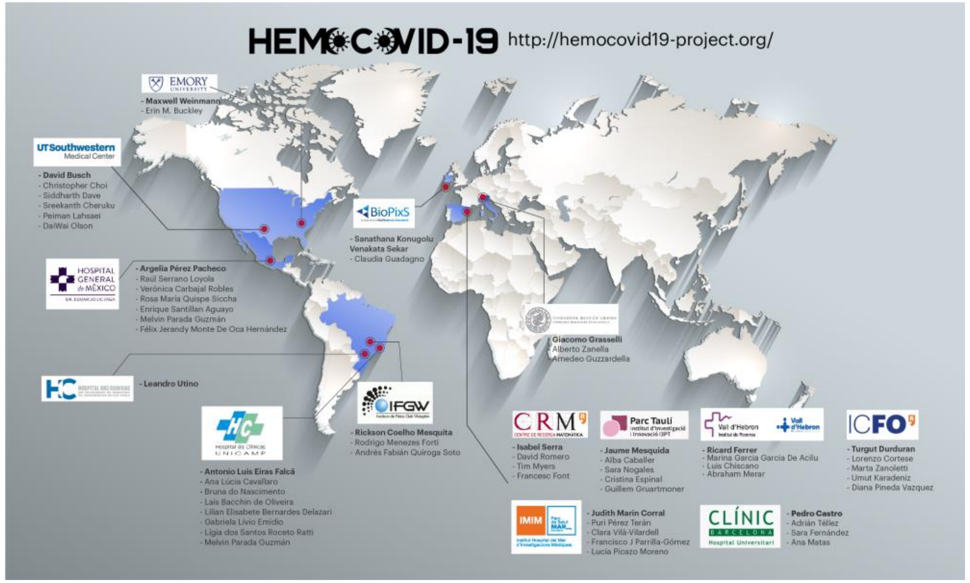
Intensive care: COVID19 patients

HEMOCOVID PROJECT



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VASCOVID PROJECT

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- EU funded
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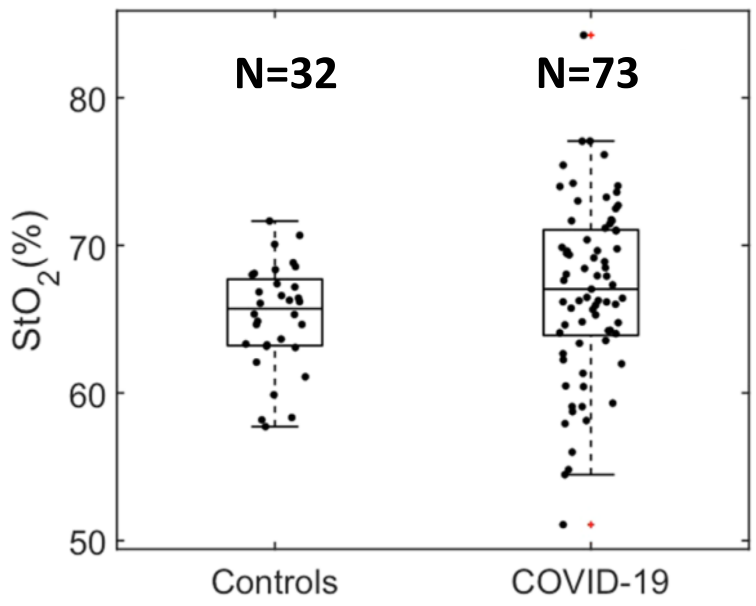
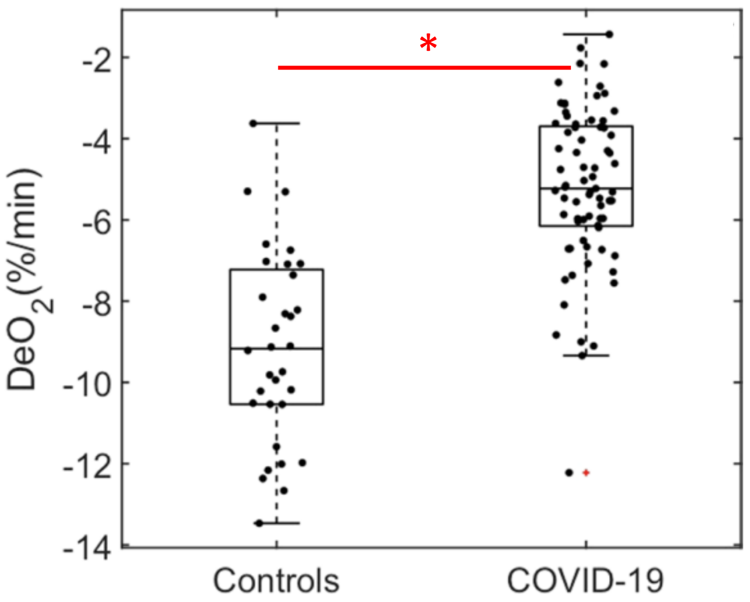
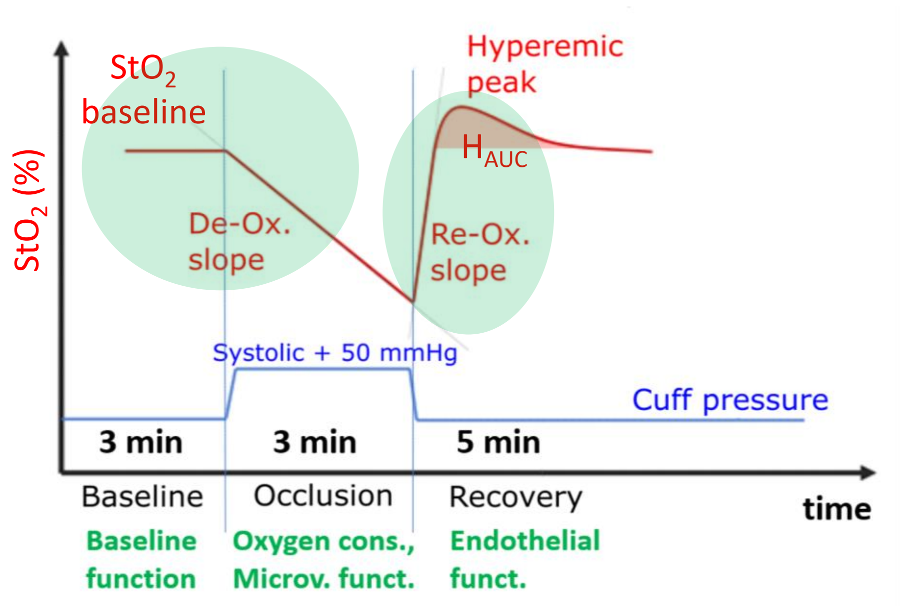
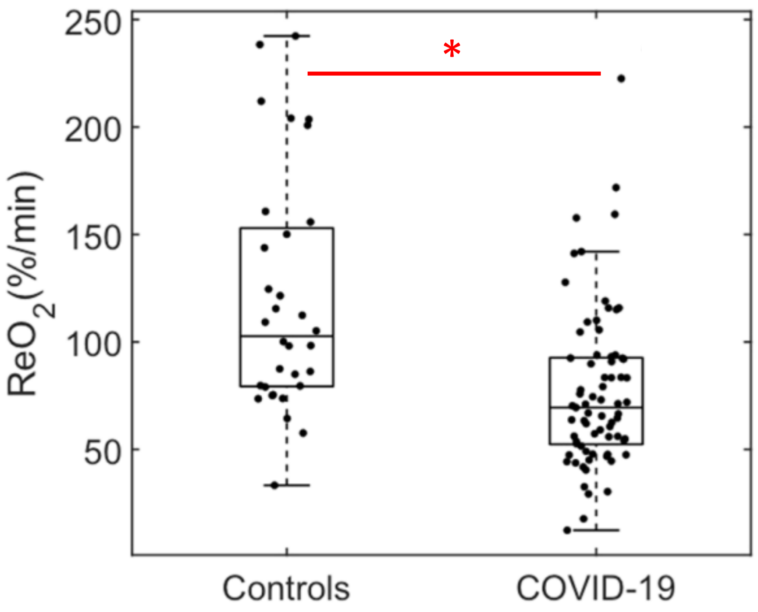
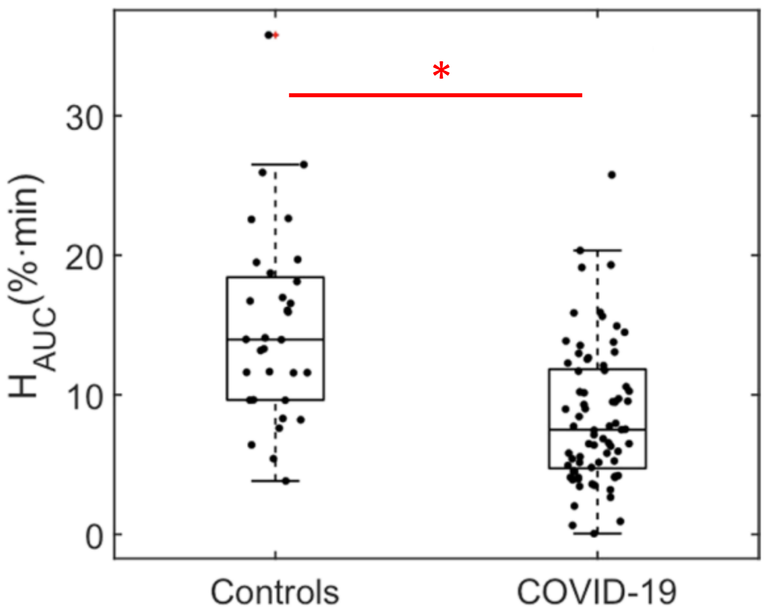
Healthy Vs. COVID-19











COVID-19 patients:

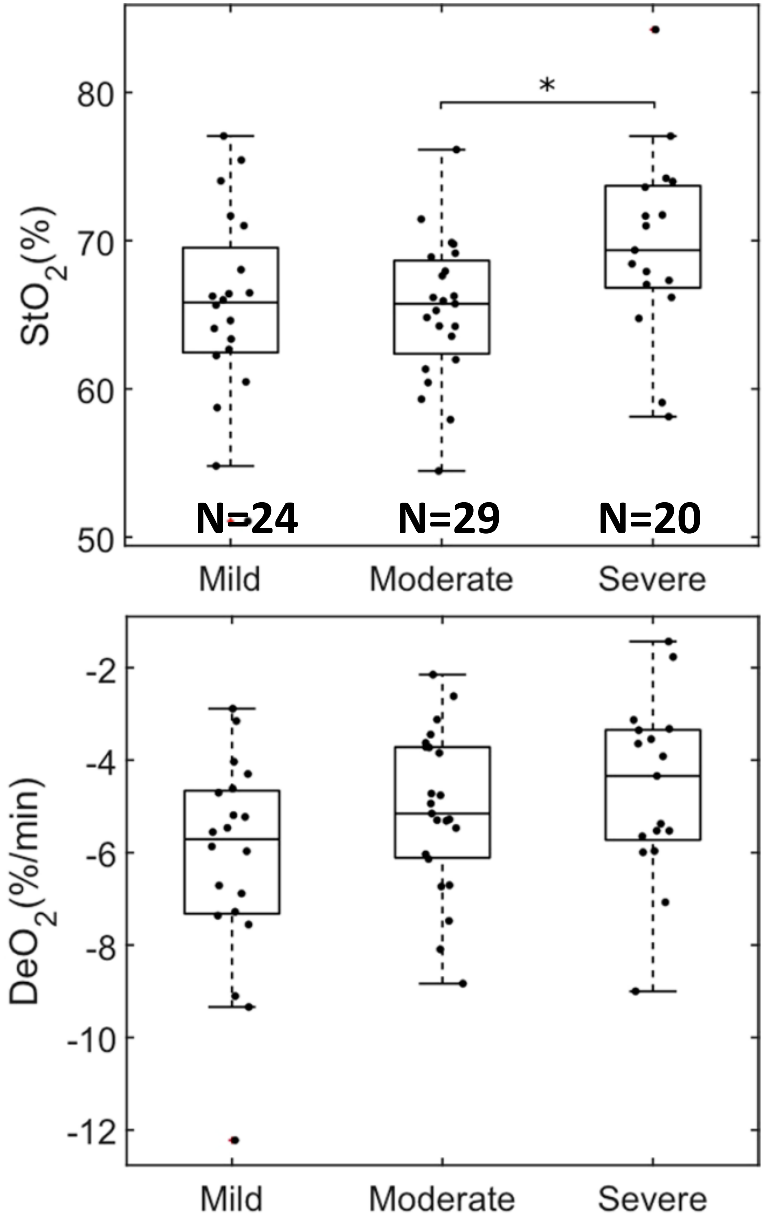
- **Consume less oxygen**

Impaired metabolism

- **Slower recovery and lower hyperemia**

Impaired endothelial function

ARDS severity Vs. endothelial impairment



ARDS: Acute Respiratory Distress Syndrome

ARDS severity defined by the SF ratio (SpO_2/FiO_2)

SpO_2: Oxygen saturation

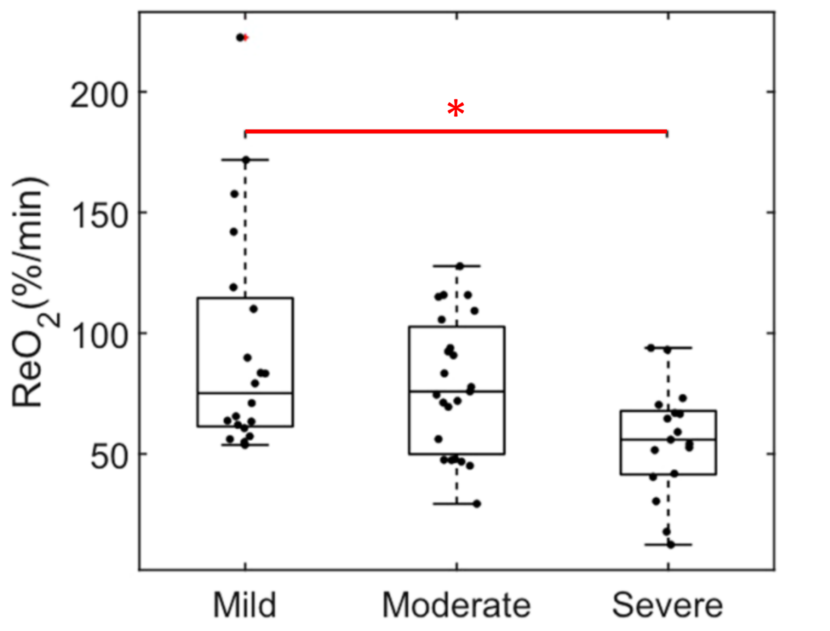
FiO_2: Fraction of inspired oxygen administered

Severe: SF < 144

Moderate: 144 < SF < 235

Mild: 235 < SF < 315

Rice et al., Chest. 2007; 132(2):410-417.

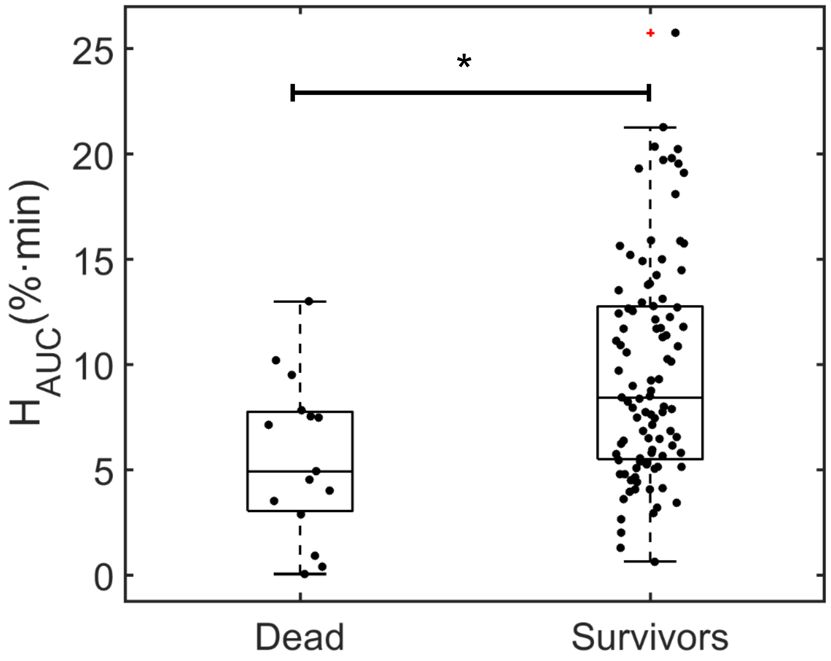


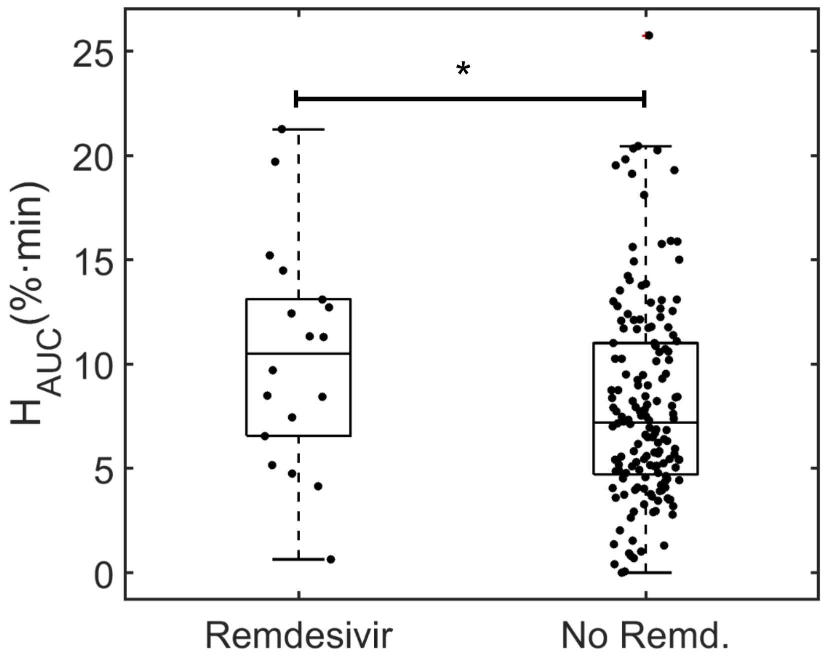
Reoxygenation slope changes for changing SF ratio

Endothelial impairment correlates with severity of ARDS

J. Mesquida, A. Caballer, L. Cortese et al., Critical Care 25, 381 (2021)

Mortality & antivirals





Endothelial impairments correlates with mortality

Remdesivir treatment is associated with a better microvascular health

Second stage: non COVID ICU patients

Thanks to: M. Zanoletti & M. Atif Yaqub

Examples of clinical applications:

1- Intensive care: COVID patients

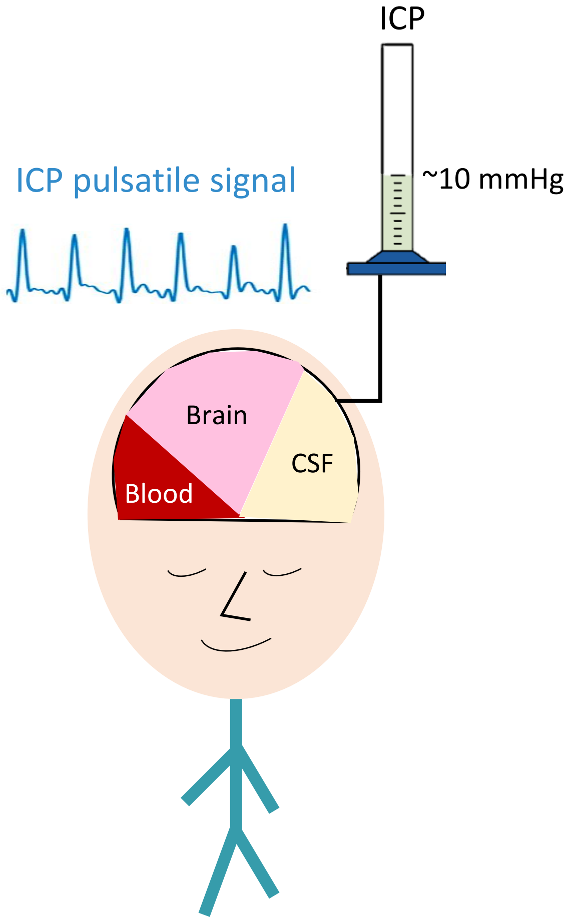
2- Intracranial pressure monitoring

3- Oncology: thyroid cancer

Intracranial pressure (ICP) monitoring

ICFO Vall d'Hebron Institut de Recerca upf. Universitat Pompeu Fabra Barcelona

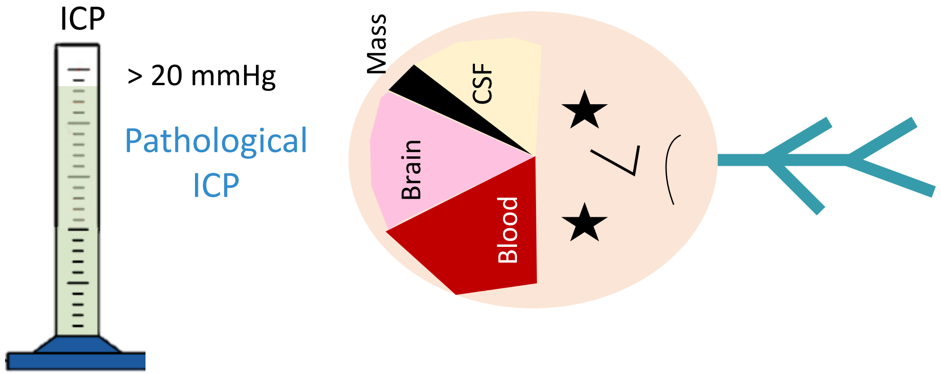
Intracranial pressure (**ICP**)



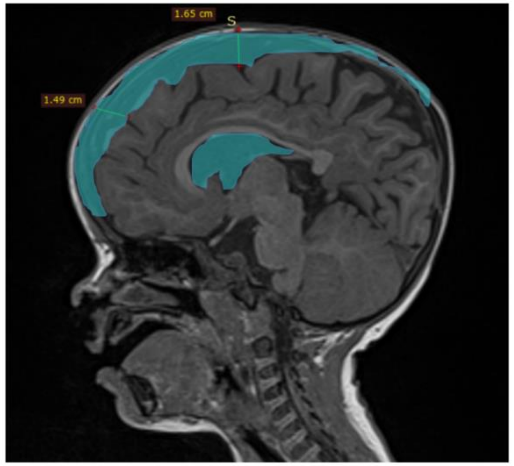
CSF= cerebrospinal fluid

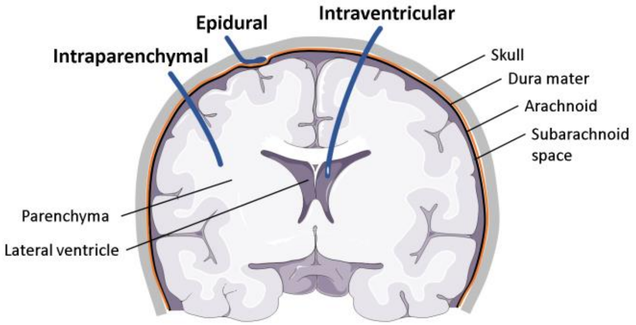
Pathological alterations of ICP present in i.e.:

- Traumatic brain injury (**TBI**) → hypertension



- Hydrocephalus → ICP with distinct pattern (i.e. B-waves)





Need for ICP monitoring

- invasive
- done when benefits outweigh risks

Possible non-invasively?

Work from: S. Tagliabue, J. Fischer, F. Maruccia, M. Torrecilla, C. Fajardo. Collaboration: M.A. Poca

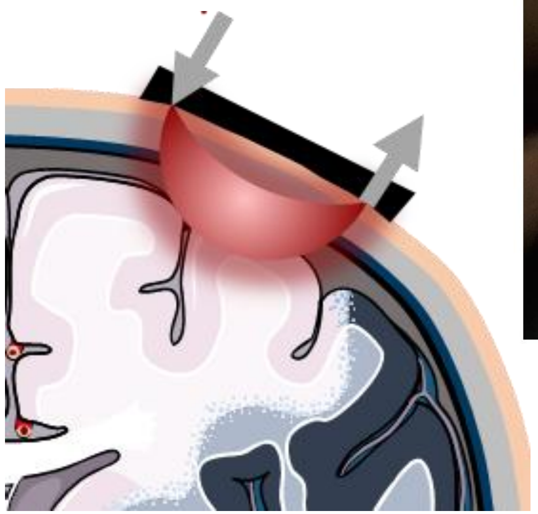
Background: proposed non-invasive methods

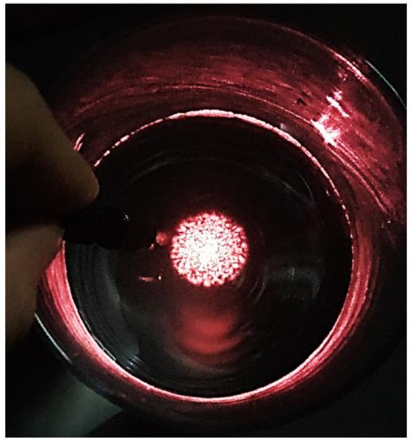
Proposed techniques using transcranial doppler ultrasound (**TCD**), near-infrared spectroscopy (**NIRS**): **not accurate** enough so far

Bellner et al., Surg. Neurol. 2004
Relander et al., Neurophot. 2022

What about using diffuse correlation spectroscopy ?

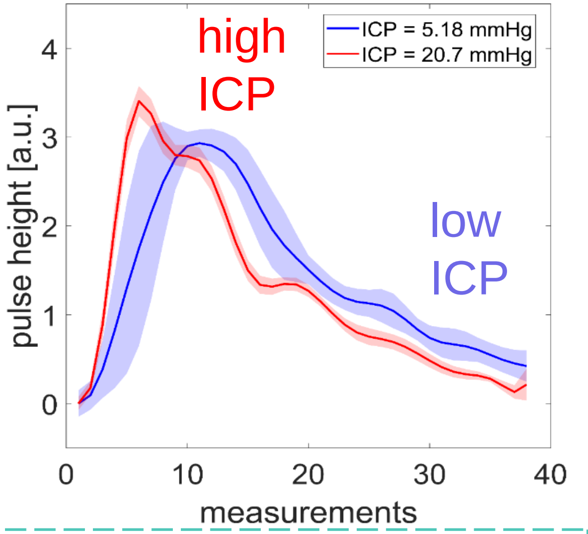
Ruesch et al, JCBFM 2020
Fischer et al, Journal of Neurotrauma 2020





Diffuse correlation spectroscopy (**DCS**):

- Non-invasive, continuous, bedside
- Based on **NIRS**
- Measures blood flow index (**BFI**) waveforms related to the microvasculature



- ICP effect on the BFI waveform
- Complex relationship

BFI pulse morphology is altered depending on the ICP

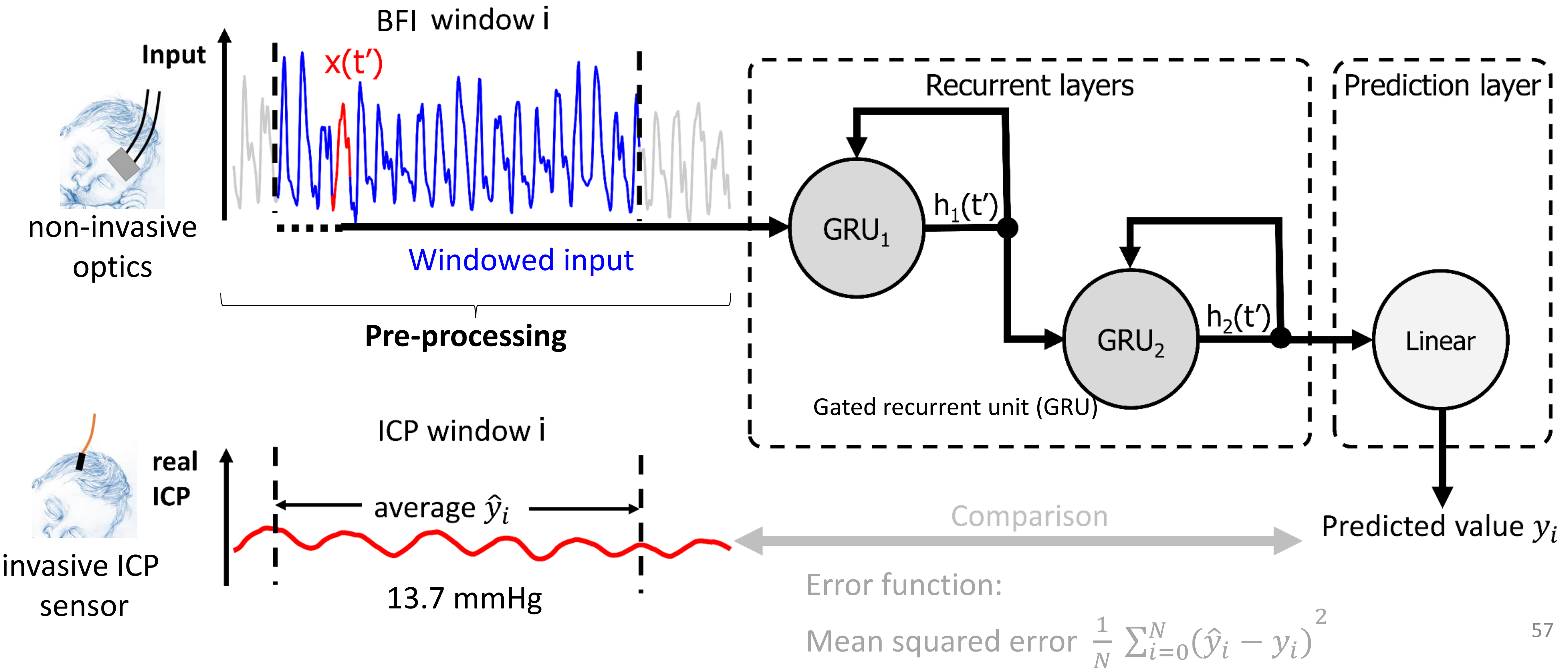
Is it possible to evaluate ICP from BFI?

Pulsatile microvascular BFI mapped to ICP by **machine learning (ML)**

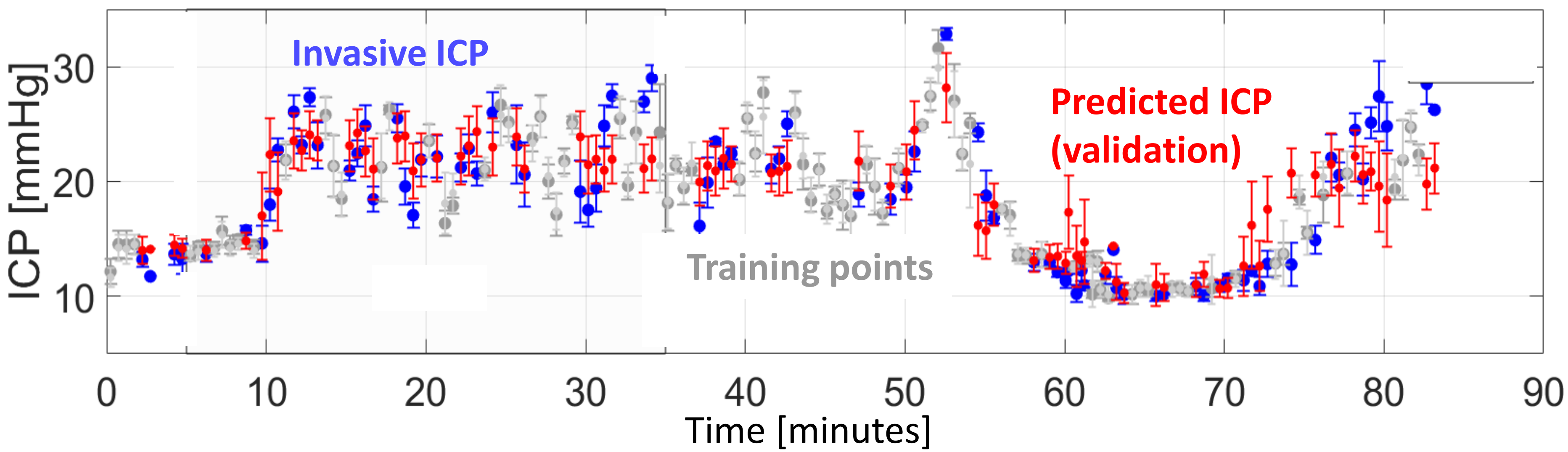
Methods: ICP prediction

- Recurrent neural network (**RNN**) with BFI as input
- Modelling of sequential data without feature engineering
- Training and validation based on a 50% hold out method

Fischer et al, Journal of Neurotrauma 2020



Results: ICP predition

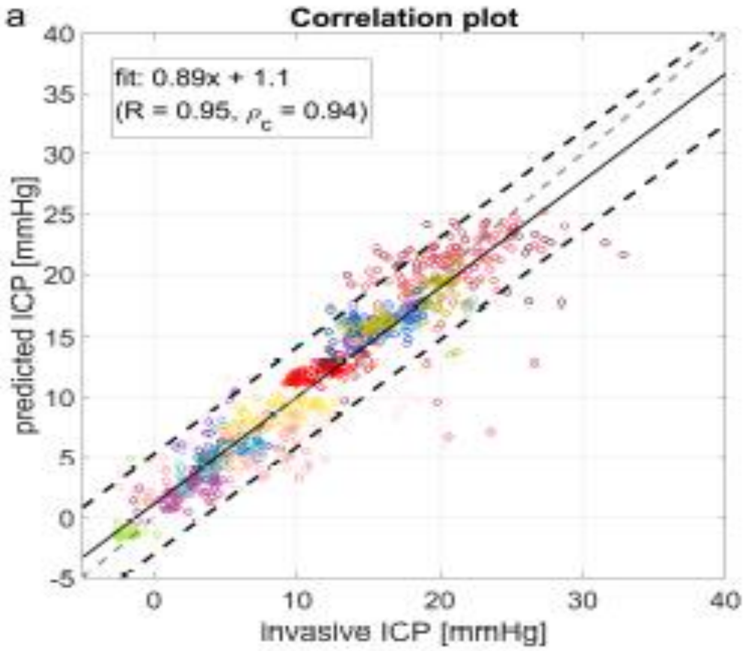


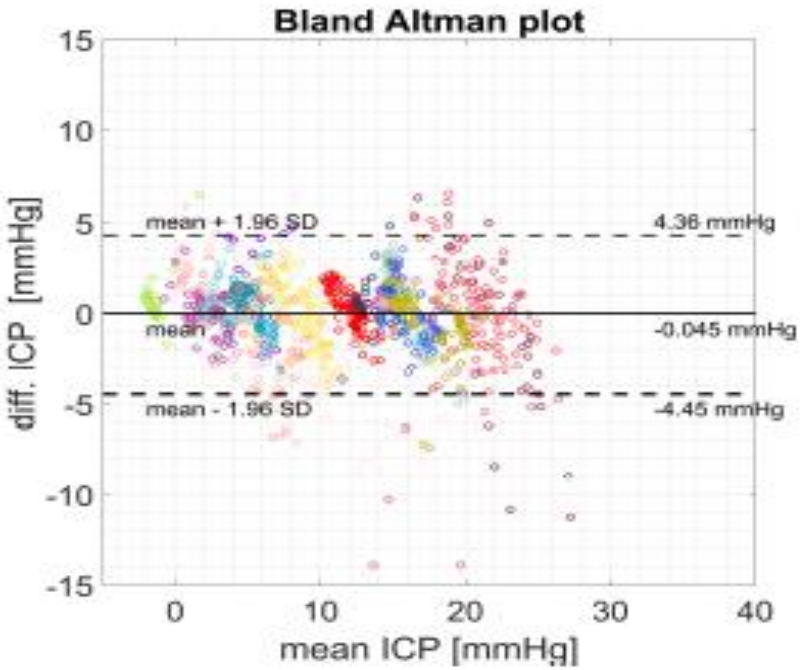
Fischer et al, J of Neurotrauma 2020

Time-trace example

30 second bins with standard deviation

Predicted VS measured ICP on TBI (N=15)





- **Accuracy ±4 mmHg; bias ~0 mmHg**
- **Similar results obtained for BEH cohort**

Can this be improved?

Examples of clinical applications:

1- Intensive care: COVID patients

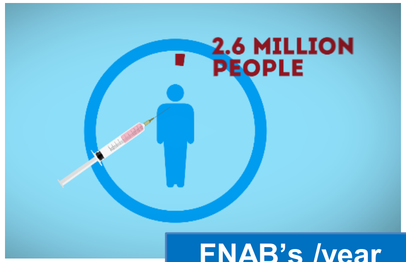
2- Intracranial pressure monitoring

3- Oncology: thyroid cancer

Thyroid cancer screening: clinical needs

Thyroid cancer is a major and growing health challenge. Chances of survival and full recovery heavily depend on an early and fast diagnosis and an effective treatment.

people with thyroid nodules



FNAB's /year

SCREENING TECHNIQUES

- Ultrasound
- Fine Needle Aspiration Biopsy

Benign vs **Malignant**

750.000 false positives or non-diagnosis in EU

3.000€ / surgery

150.000 unnecessary surgeries

LUCA

SOCIAL IMPACT

- Psychological complications
- Work-day absences
- Further healthcare

COST IMPACT

448.5 Millions €/y

CHARACTERISTICS

- Low cost
- Non-invasive device
- Enhanced information

Better and more specific results in thyroid nodule screening

Better diagnosis

Socio-economical impact: reduced number of thyroidectomies, associated comorbidities and improved quality of life of the patients

€€€ could be saved!

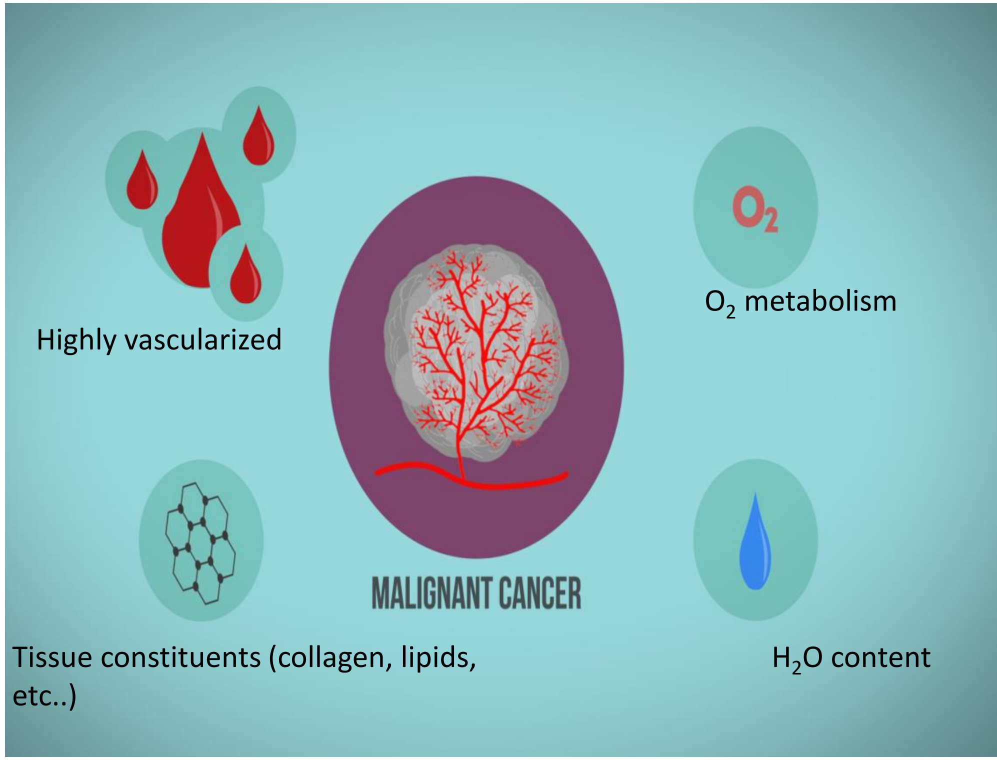
This project has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 688303.

www.luca-project.eu www.photonics21.org

Thanks to: P. Fernández Esteberena, M. Zanoletti, G. Lo Presti

Thyroid cancer screening: H2020 LUCA project

Goal: To develop a **low-cost tool** for the **screening of thyroid nodules** for malignant cancers, combining ultrasound and diffuse optics



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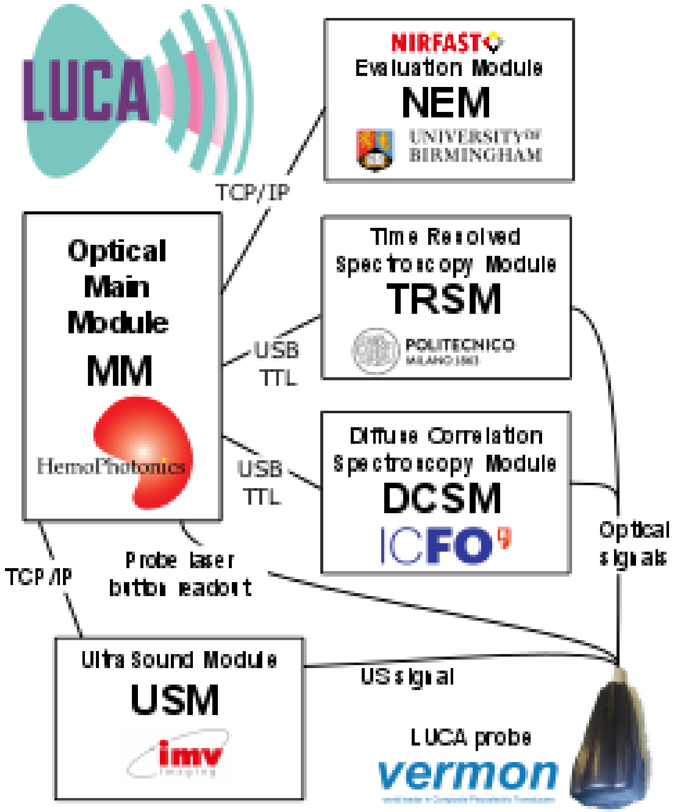
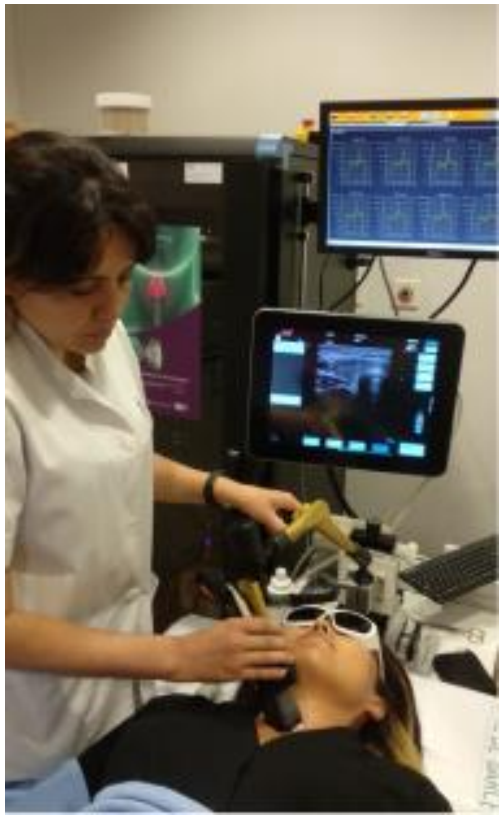
www.luca-project.eu www.photonics21.org

Thanks to: P. Fernández Esteberena, M. Zanoletti, G. Lo Presti

Thyroid cancer screening: multi-modal device

Follow standard clinical workflow of US examination but include an optical measurement (DCS-TRS) to evaluate physiological values of thyroid nodules.





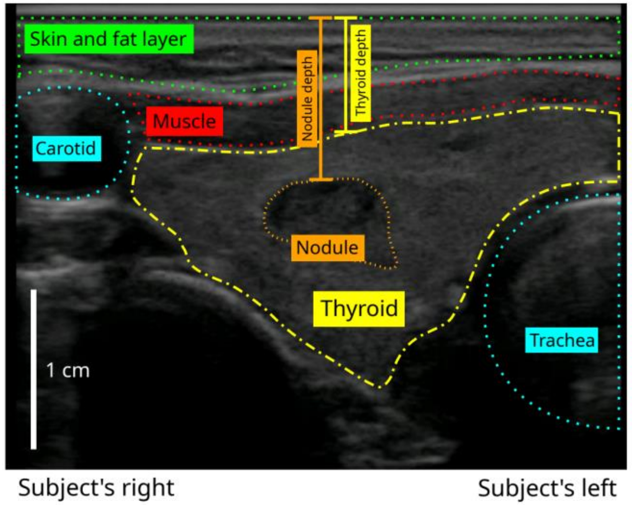
<u>TRS: 8-wavelength system</u>

-Wavelengths: 635, 670, 730, 830, 852, 915, 980, 1040 nm

<u>DCS: 16 detection channels system</u>

L. Cortese et. al, Biomedical Optics Express 2021

Thyroid cancer screening: preliminary results

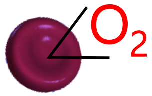


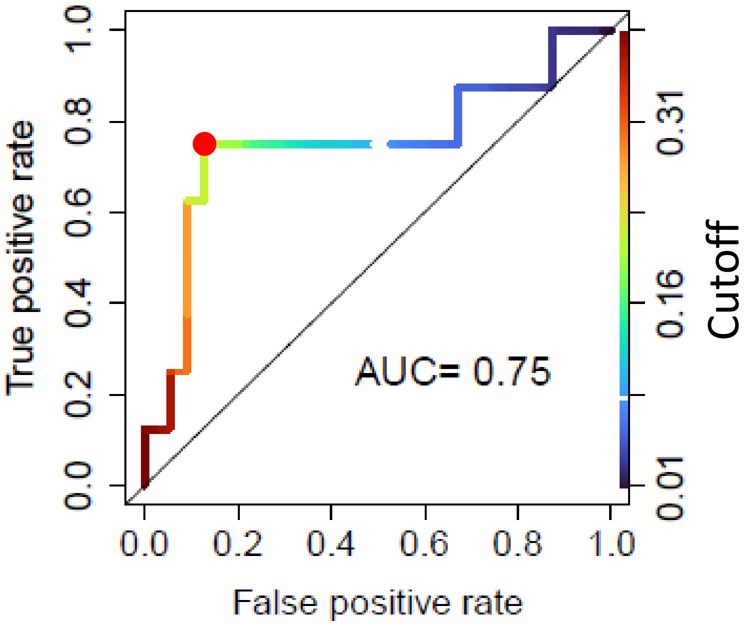
Measured TIRADS 4 nodules

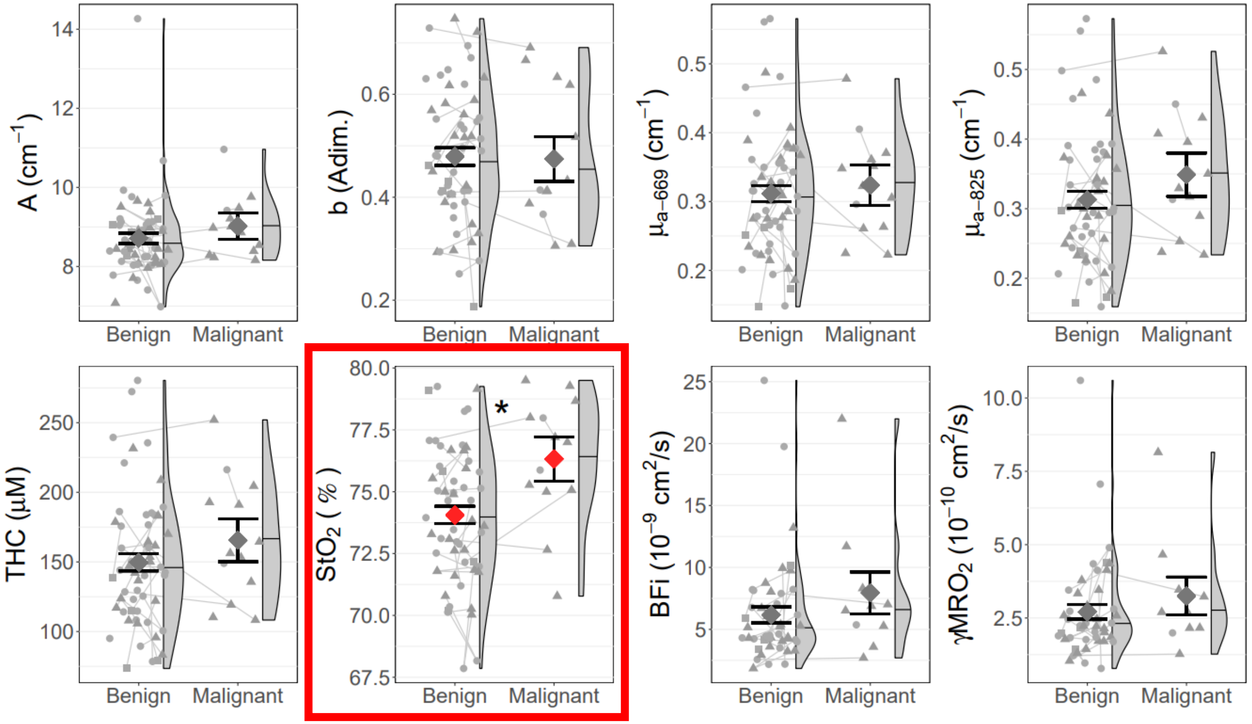
55 benign

8 malignant

StO_2







TPR=75%, FPR=11%

StO_2 holds as most promising classification parameter

Ultrasound: TPR=10-87%, FPR=4-42%

P. Fernández et. al, Biomedical Optics Express 2024

To conclude

Translational research: bench-to-bedside

It takes loooo(…..)ng time to mature (some) technologies

15 years

~1992

Physical Models

in-vivo tests

Lab Size

2004

1st in human

2009

ICFO Med Optics

2011

2013

2017

2024

HemoPhotonics

BabyLux

LUCA

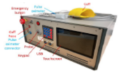
VASCOVID

SPIN-OFFs

TRL 7+

TRL 7

TRL 7+



Lines of Research and Development

1 Technology

(2011)
Off-the-shelf components
Hybrid devices - O_2 + Bf

2 Ultra-portables

(2011)
Measurement of Bf only

TRL 7

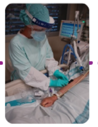
Wearables

3

(2023)
TRL 2

Proof of Concept in the Healthy Brain	Clinical translation Stroke Congenital Heart	Sleep Apnea Stenosis Premature Birth	ICU Critical Care Peripheral Circulation	+1500 people measured in brain +100 papers	+300 people measured in arm in ICU 2 papers
2004	2010	2014	2021		2024

APPLICATIONS



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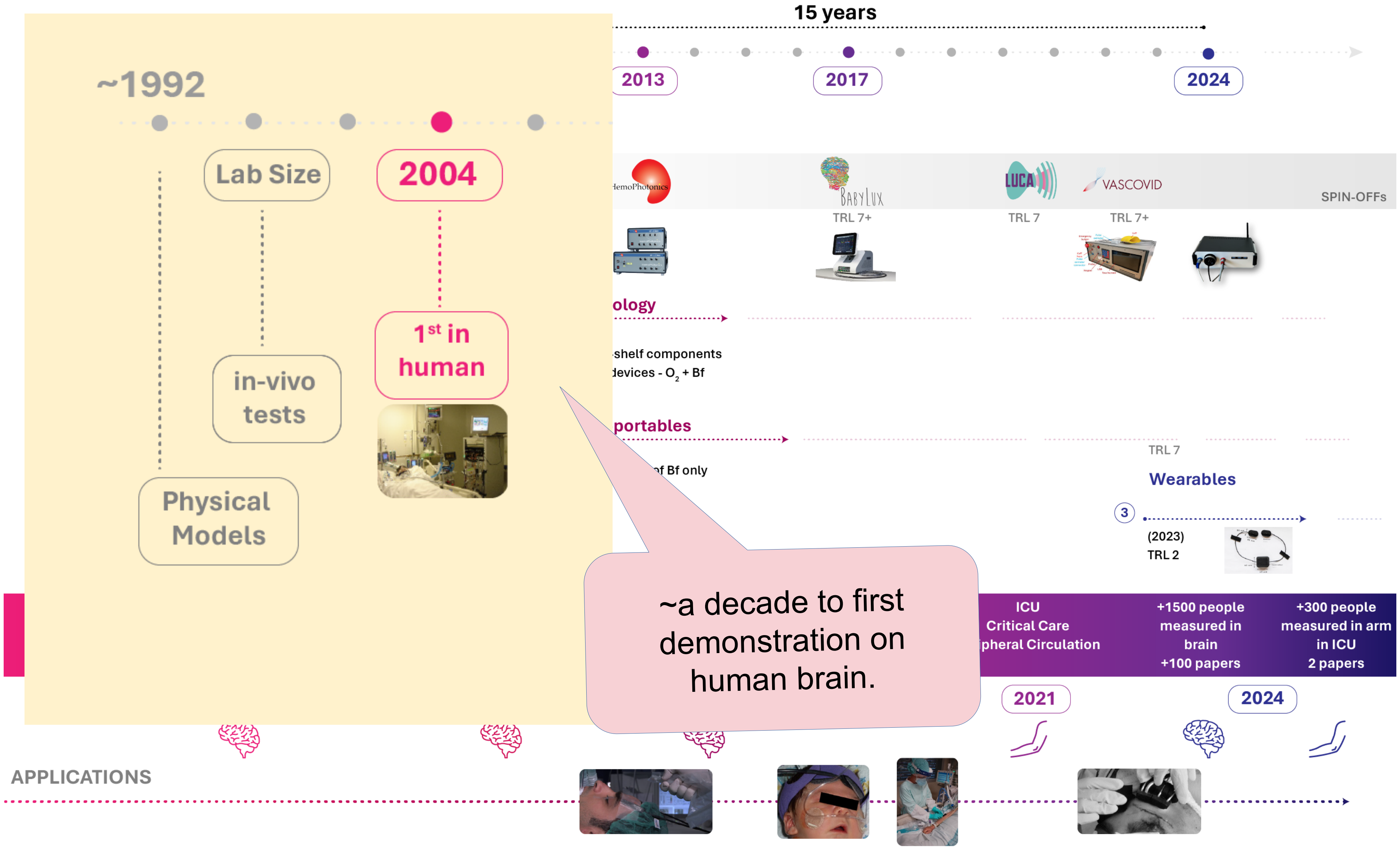

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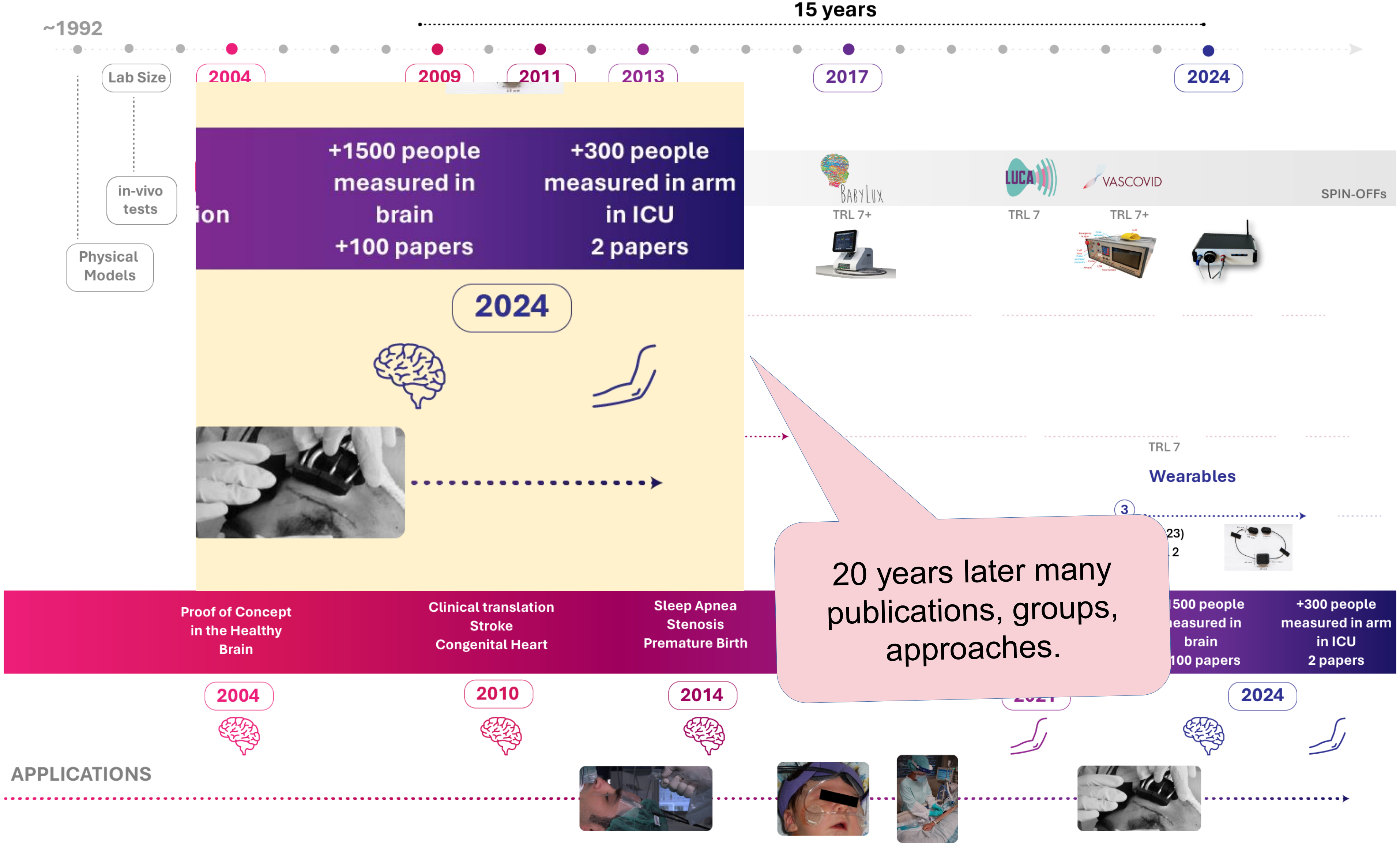

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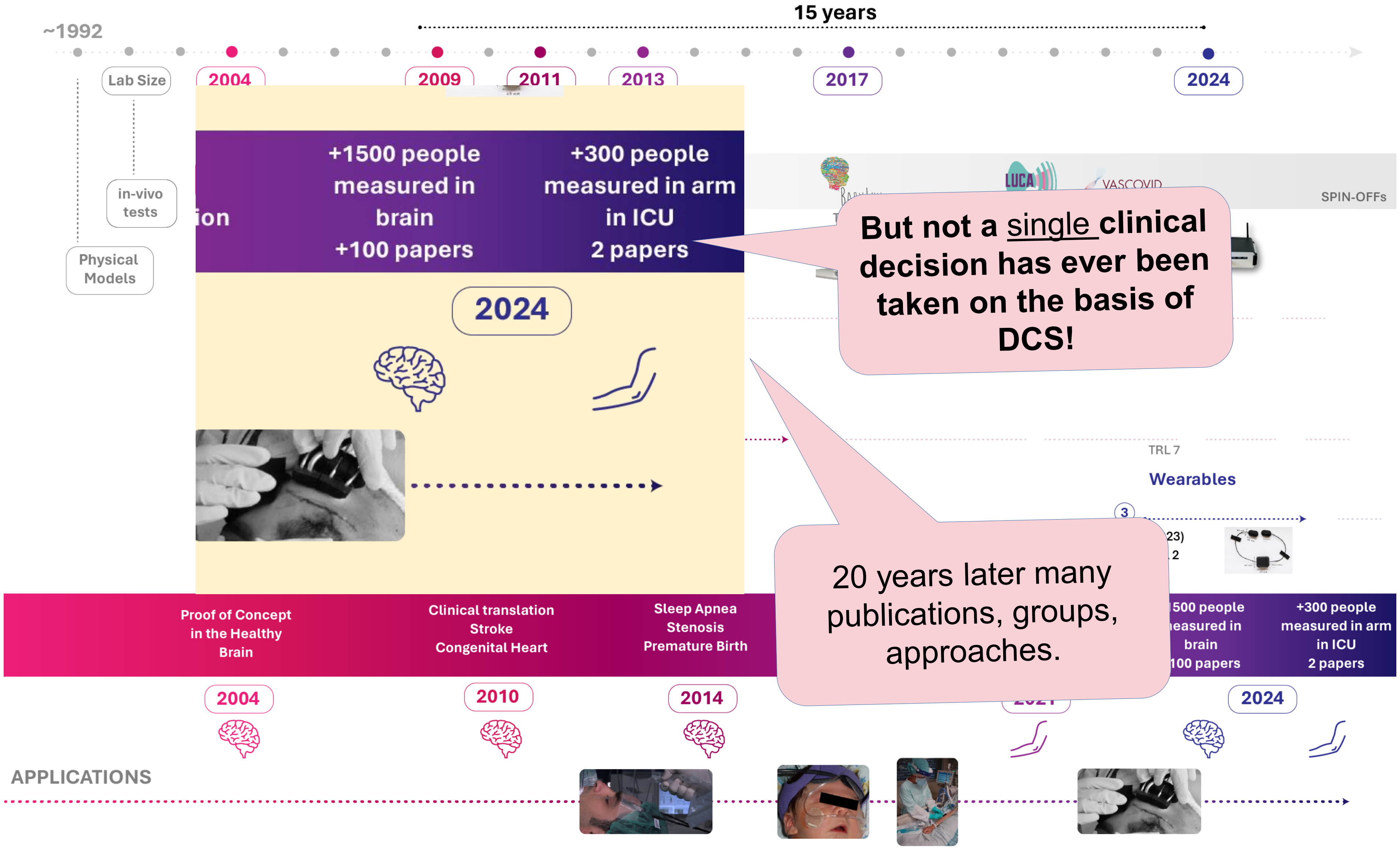

Support

ICFO
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Obra Social "la Caixa"

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European Commission

HORIZON 2020
THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION

SEVENTH FRAMEWORK PROGRAMME

BabyLux

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LUCA

neuron

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de Salud
Carlos III

Tiny Brains

Laserlab
Europe

EUROPEAN UNION
European Regional Development Fund

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Ajuntament de
Barcelona

VASCOVID

PHOTONICS21

Educational & fun series to learn about other works

Full playlist on ICFO youtube channel

https://youtube.com/playlist?list=PLLnA8B3ZULyHIUC0_eDGefWO_pdQbfkdW