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PASSION FOR INNOVATION

Bioresorbable multifunctional fiber-optic devices for theranostic and monitoring of tumor

Nadia G. Boetti, Jawad T. Pandayil, Sharon Russo, Davide Janner

EPIC TECHNOLOGY MEETING ON PHOTONICS TECHNOLOGIES FOR MEDICAL DIAGNOSIS AND TREATMENTS

BARCELONA, 3 – 4 DECEMBER 2024

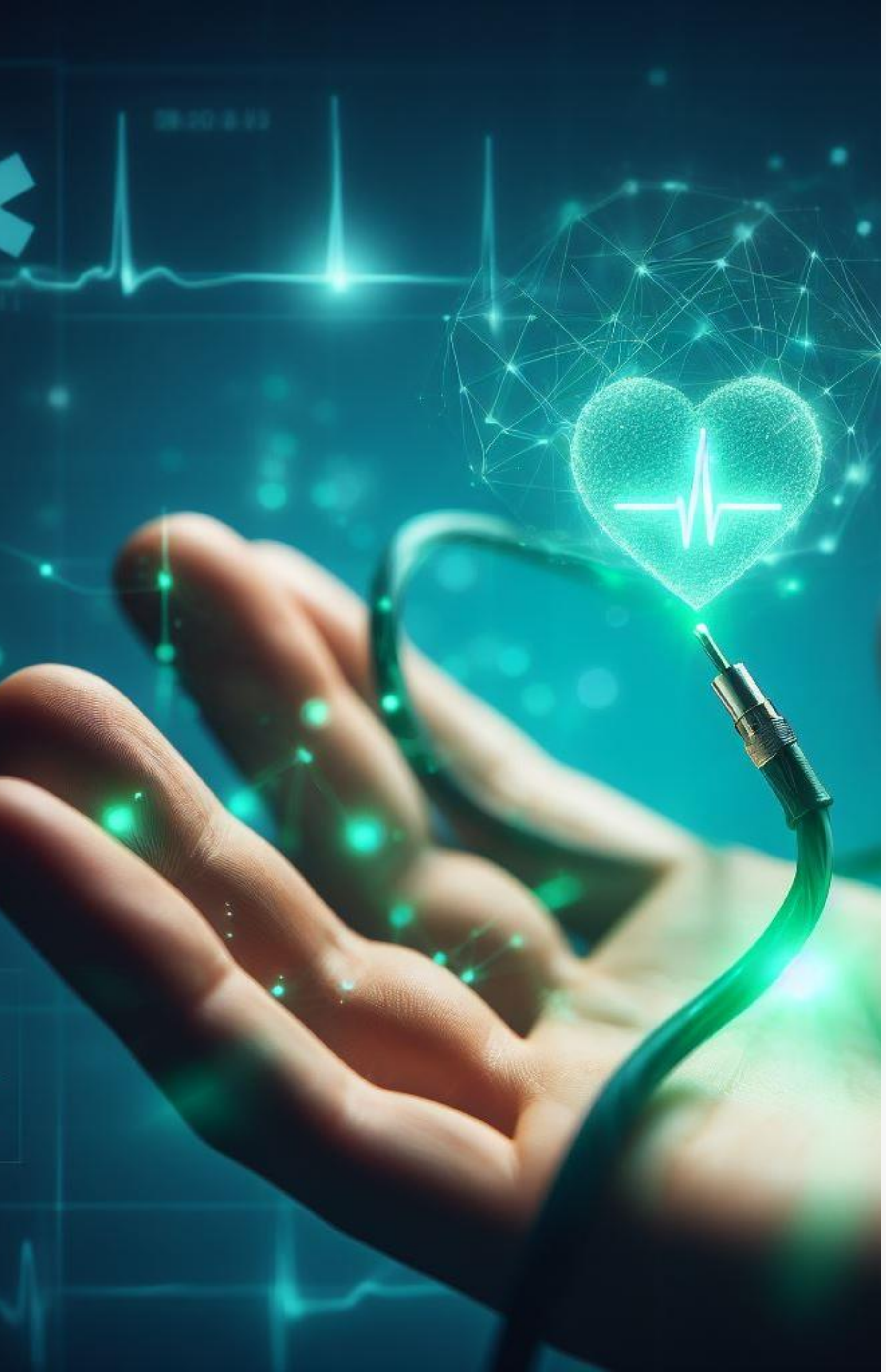
PHAST

PHOTONICS FOR HEALTHCARE: MULTISCALE CANCER DIAGNOSIS AND THERAPY

LINKS FOUNDATION

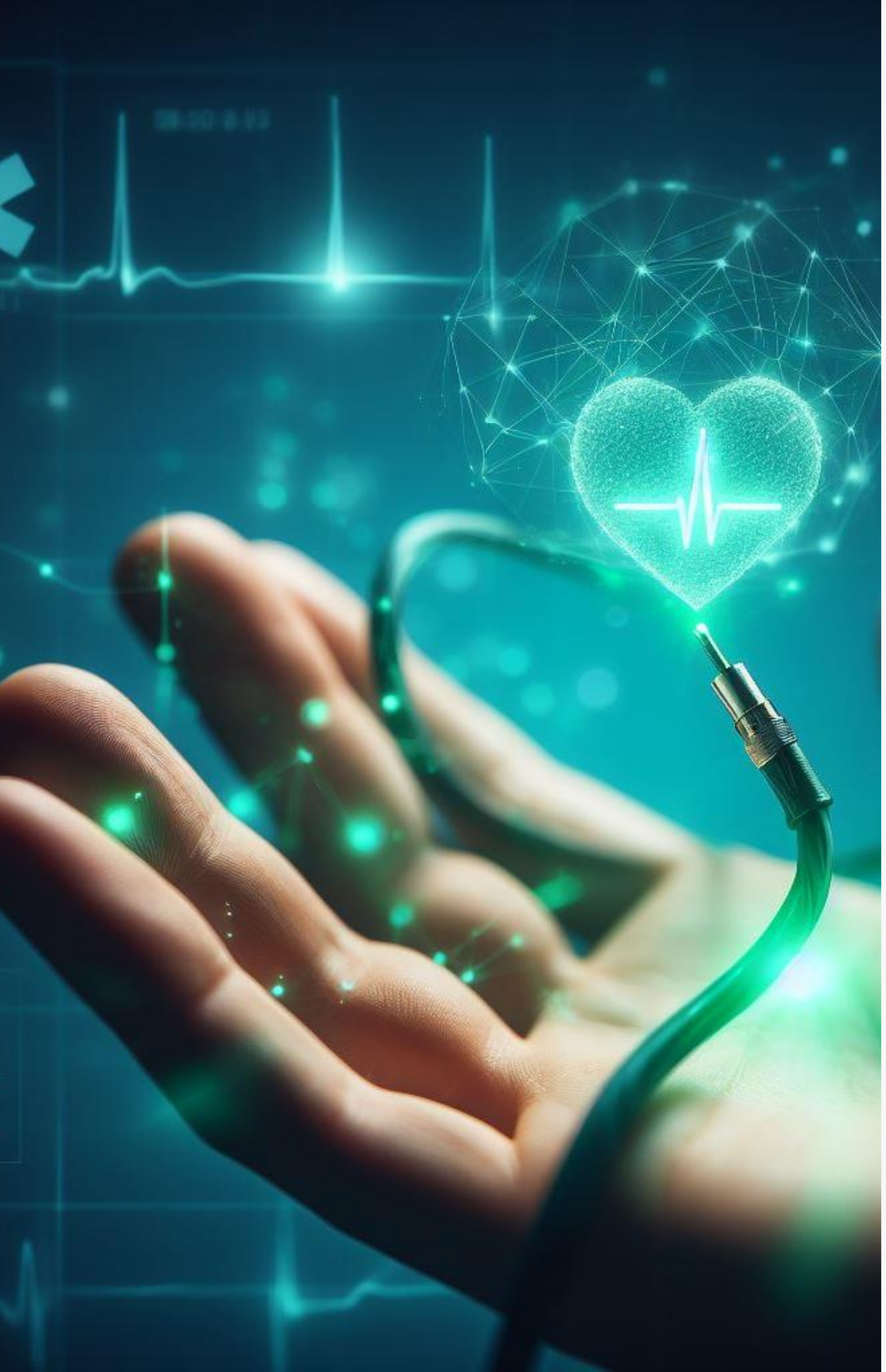
LINKS foundation is a non-profit private research centre, with more than 180 researchers, that operates at a national and international level in applied research, innovation and technology transfer.

The **Biomedical, Healthcare, Materials and Sensors Lab** brings together a multidisciplinary team focused on research in specialty optical glasses and fibers, sensors (LIG- and fiber-based), laser material processing, biomimetic phantoms, e-Health and



Outline

- Introduction to optical fibers in medicine
- Bioresorbable optical fibers
- Biomedical applications of bioresorbable fibers:
  - ❑ Drug release from hollow fibers
  - ❑ Diffuse Correlation Spectroscopy
  - ❑ Interstitial Time Domain Diffuse Optics
  - ❑ Diffuse fluorescence tomography in PDT
- Conclusions and ongoing research activities



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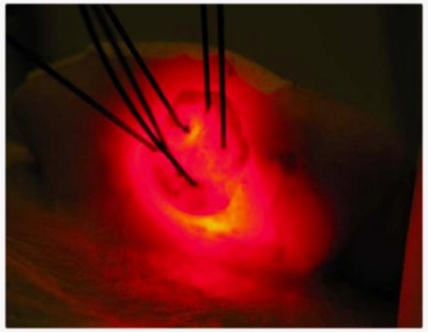
Biomedical applications of optical fibers

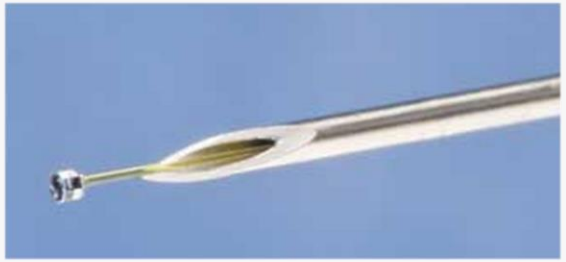


Diagnostics

illumination, imaging, OCT spectroscopy

Treatment

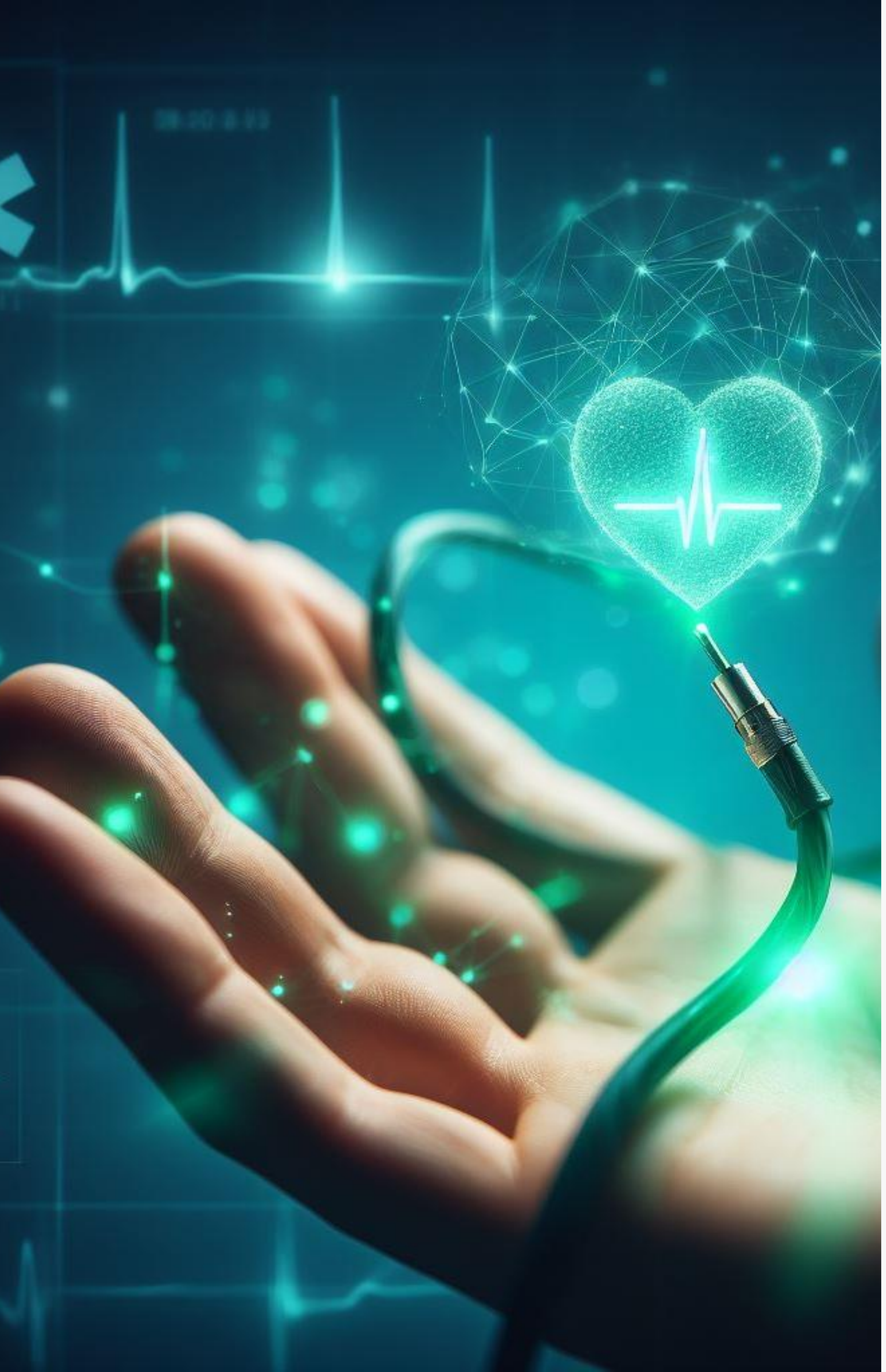
laser surgery, tissue ablation, Photodynamic therapy (PDT)



Biosensors

Chemical, biological & physiological parameters

- Minimally invasive
- Chemically inert
- Tolerant to radiations
- Transparent to magnetic field
- Immunity to EM interference



Outline

Introduction to optical fibers in medicine

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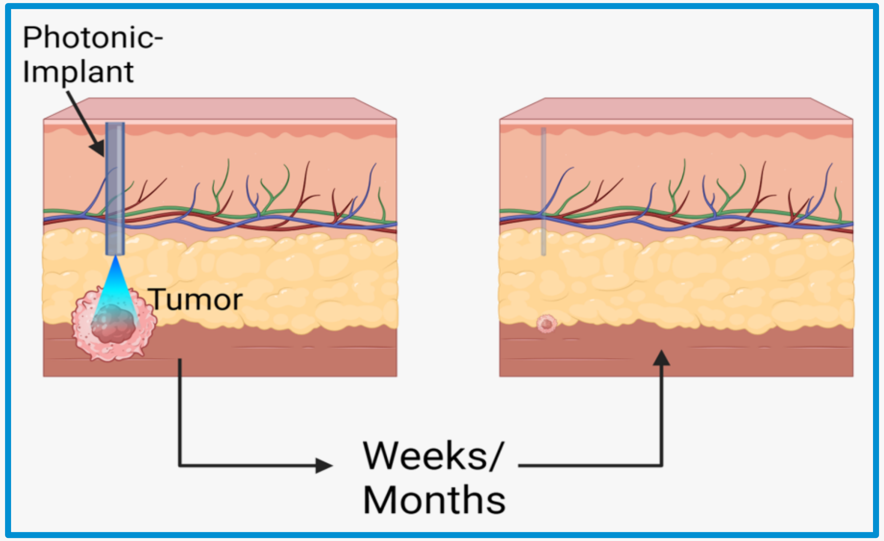
Bioresorbable optical devices



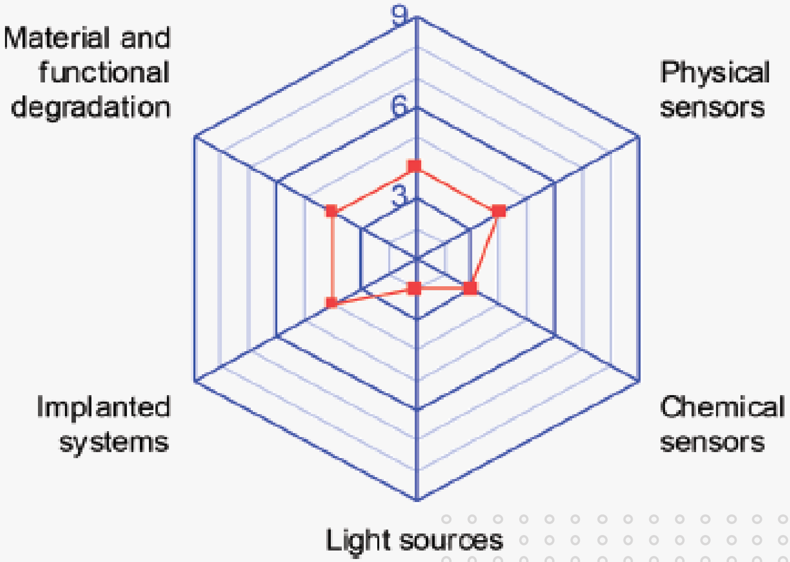
Ability to dissolve in body fluids **without harmful effects** once its function has been accomplished **over a clinically relevant time scale**.

https://www.thebusinessresearchcompany.com/report/bioresorbable-medical-material-global-market-report

Bioresorbable devices

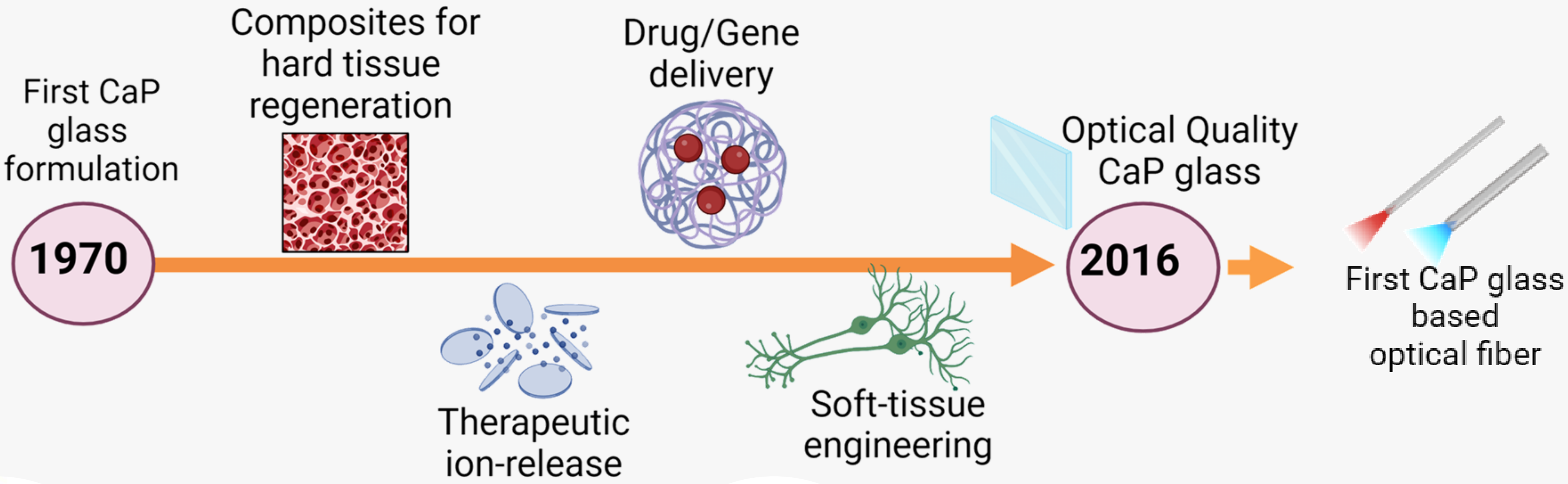
- Orthopedic Implants
- Surgical Adhesives
- Drug Delivery Systems
- Sensors

TRLs of bioresorbable optical components



Antonino A. La Mattina et al., Adv. Sci. 2020, 7, 1902872

Bioresorbable optical glass and fibers



Combine optical and biomedical functionalities in a single material

Develop glass material that is:

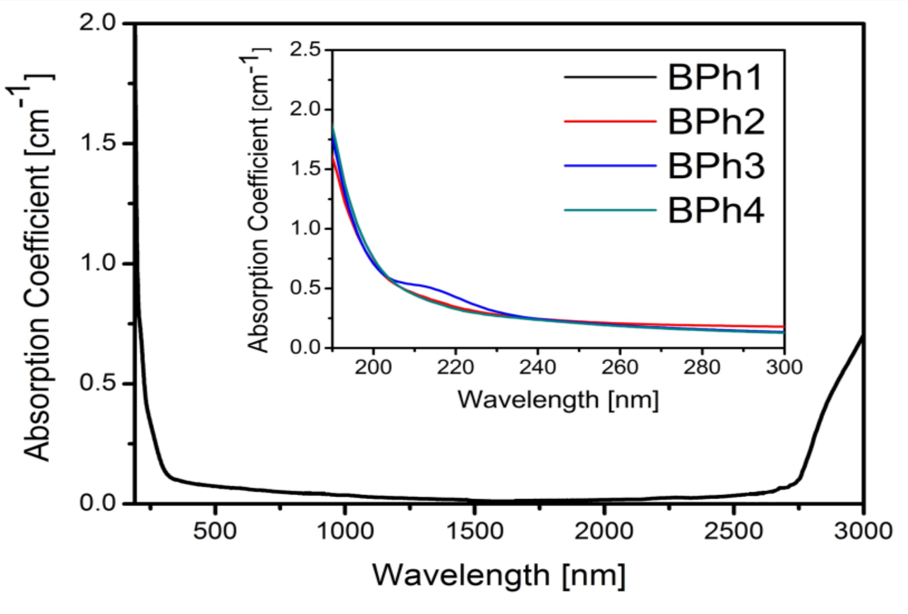
- Optically transparent (extended to UV)
- Biodegradable and soluble in biological fluids (bio-resorbable)
- Suitable for fiber drawing

Bioresorbable calcium-phosphate glasses

Glass components

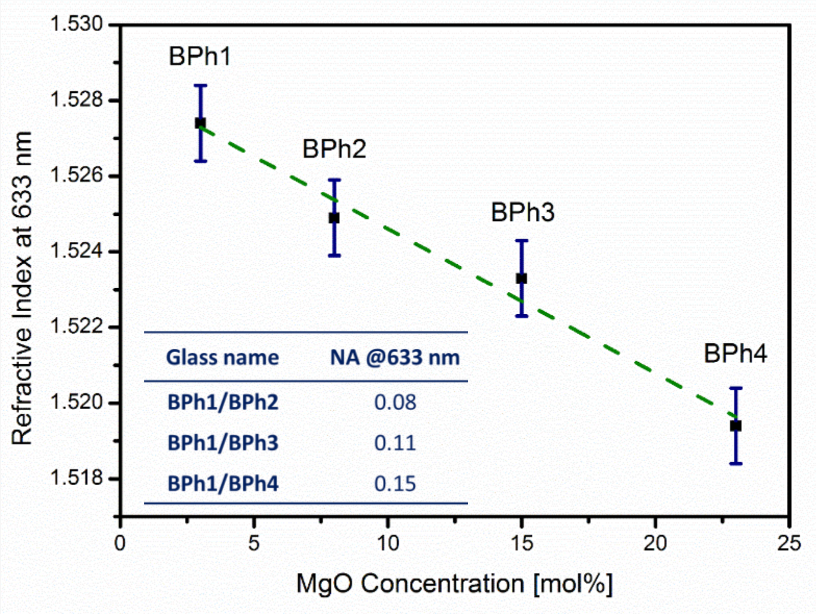
$P_2O5 – CaO – Na_2O – SiO_2 – MgO$

UV-VIS/NIR TRANSPARENCY



- Broader window of transparency vs. polymers
- Ability to transmit UV light (UV edge 240 nm)

REFRACTIVE INDEX

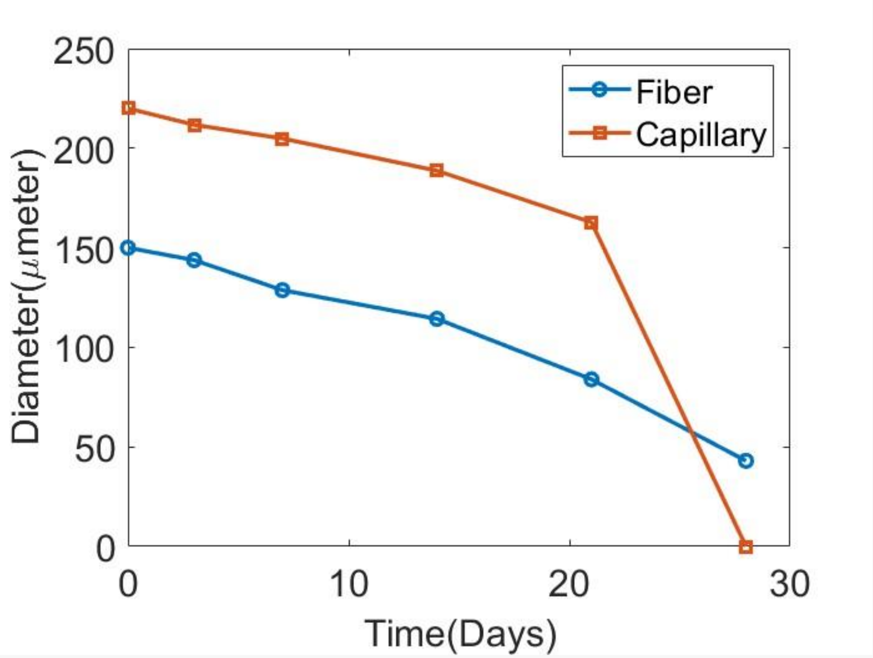


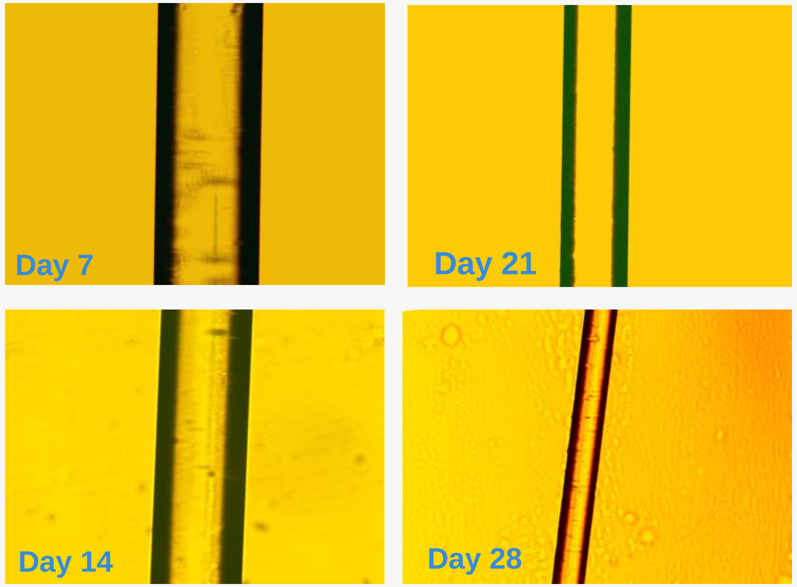
- Tailorable refractive index w/o changing in thermo-mechanical properties
- Tunable fiber NA

Ceci-Ginistrelli et al., Opt. Mater. Express 6, 2040-2051, 2016

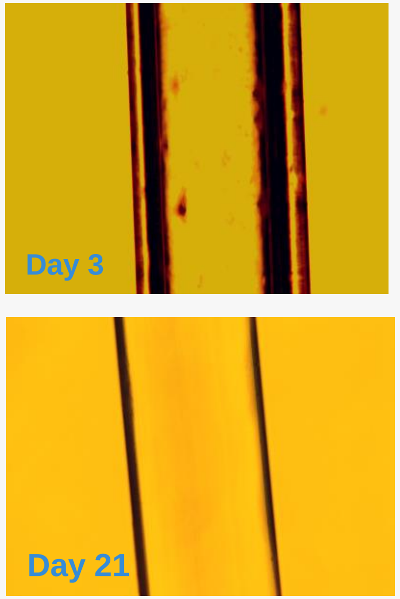
Dissolution studies in PBS

- Phosphate buffer saline (PBS) solution
- Ph = 7.4, Temperature = 37°C
- Solution/Sample area = 0.1
- Solution refresh every 3 days





Optical microscope image of dissolving fibers in PBS

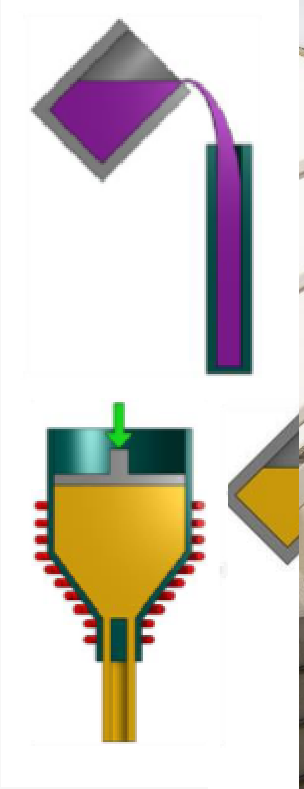


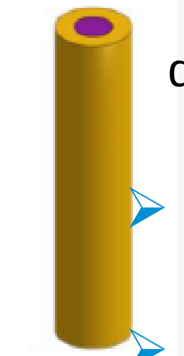
Optical microscope image of dissolving capillaries

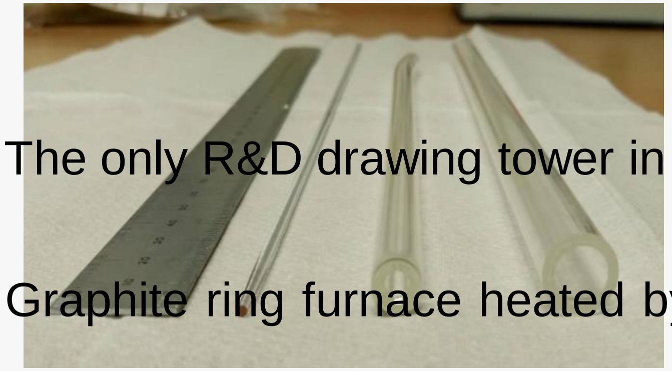
- ➢ Capillary (Ø = 220 μm) dissolves quicker due to the bulk degradation, giving a complete dissolution in 28 days
- ➢ Fiber (Ø = 150 μm) undergoes surface degradation; thus, some part is left even after 30 days of the study

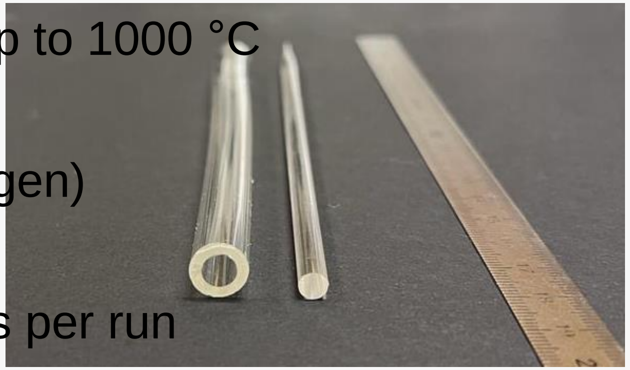
Optical fiber fabrication

- Fiber manufactured by preform drawing
- Preform was fabricated by rod-in-tube technique
  - rod of core glass – cast in a cylindrical mould
  - tube of cladding – rotational casting or extrusion



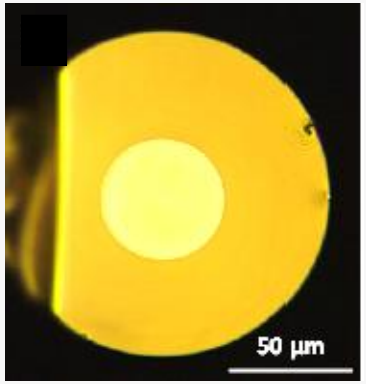
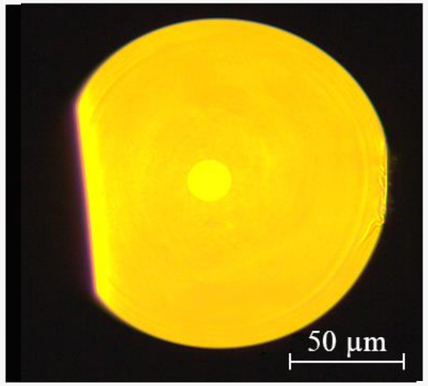
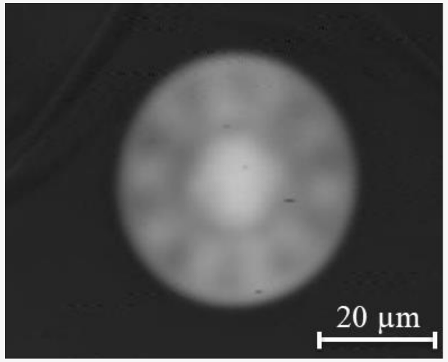
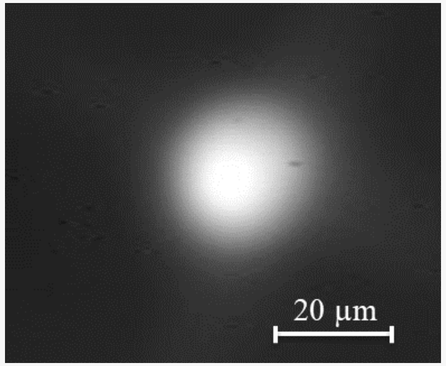




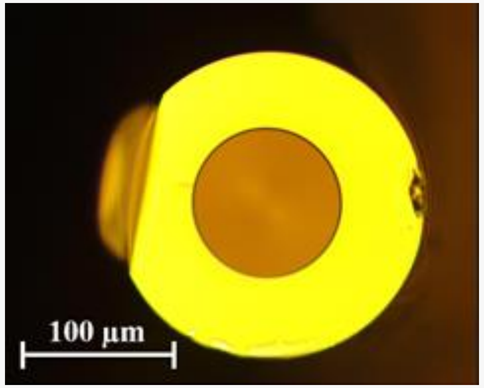


- The only R&D drawing tower in Italy
- Graphite ring furnace heated by induction: drawing temperatures up to 1000 °C
- Inert atmosphere (nitrogen)
- Drawing of 100s meters per run

Fabricated fibers and capillary

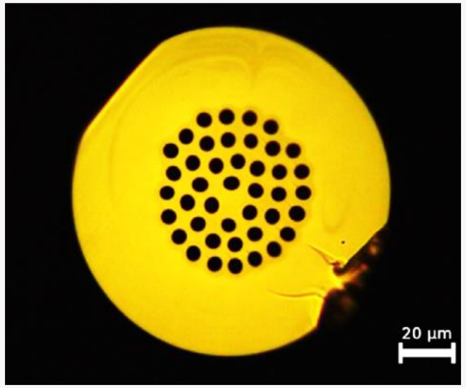
	MULTI-MODE FIBER	SINGLE-MODE FIBER
		
DIMENSIONS	45/ 125 µm	15 / 120 µm
CORE NA	0.15	0.08
LOSS AT 633 nm	4.7 dB/m	5 dB/m
LOSS @ 1300 nm	1.9 dB/m	2 dB/m
		

CAPILLARY



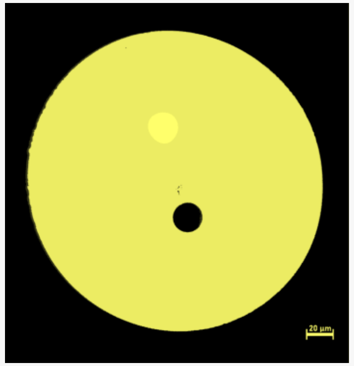
Ø = 120/ 220 µm

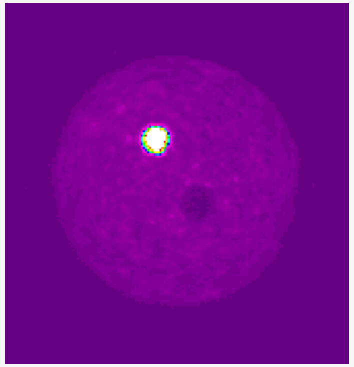
MICRO-STRUCTURED FIBER



$Ø_{ext}$= 125µm

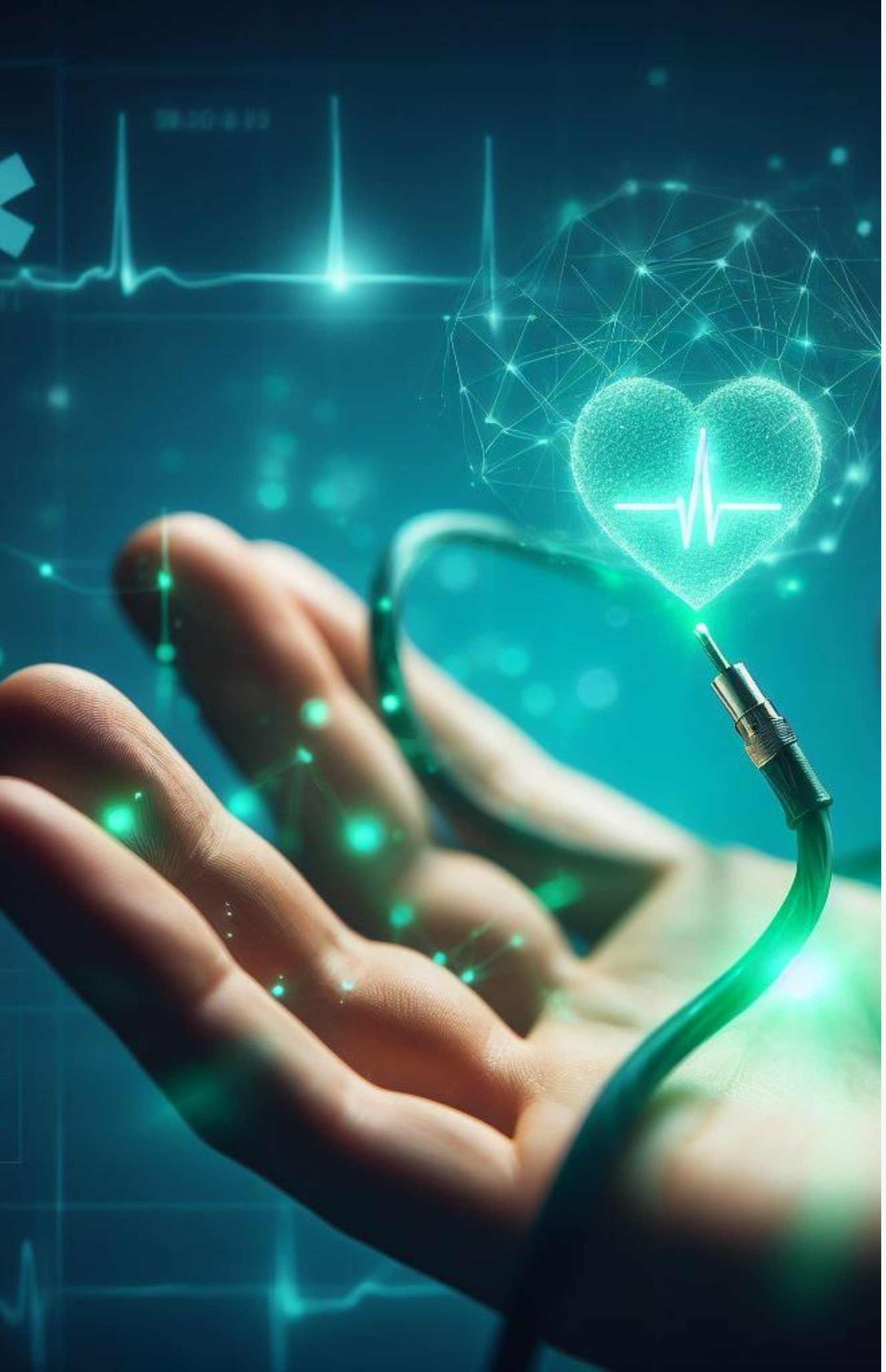
MICRO-STRUCTURED FIBER WITH HOLE AND CORE





Ø = 15 / 25 / 230 µm

Patent # 102018000021559



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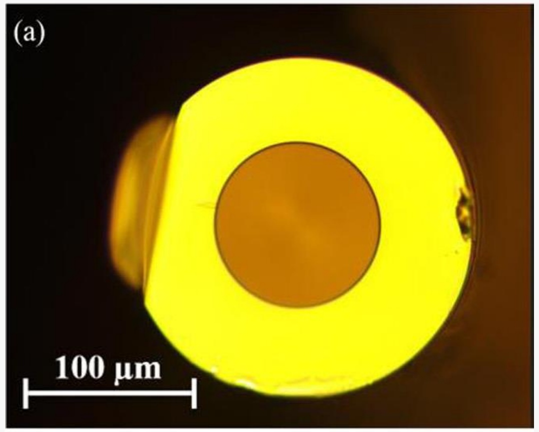
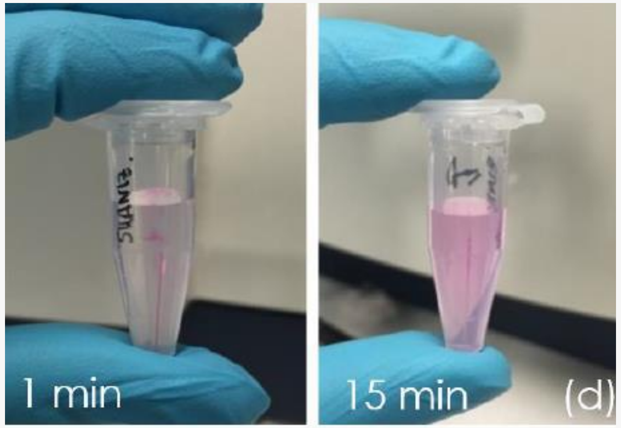
Drug release from hollow bioresorbable fibers

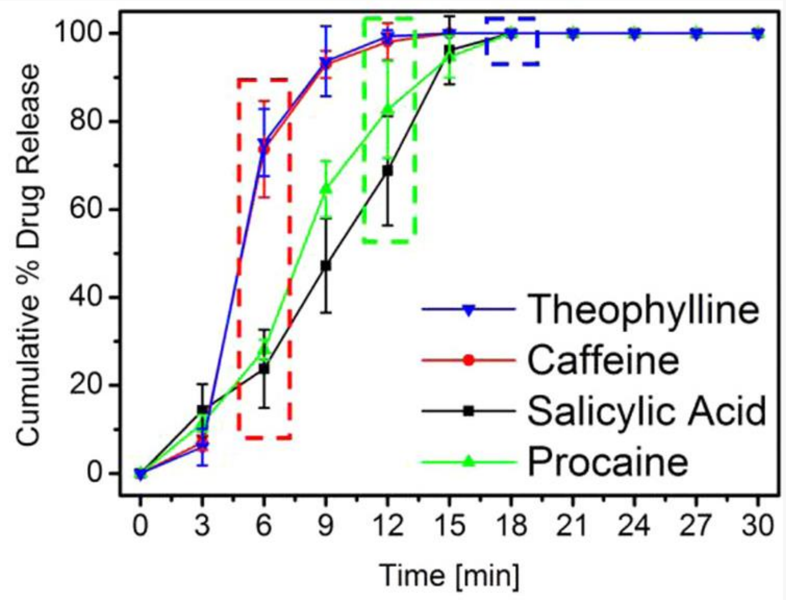
UNIVERSITÀ DEGLI STUDI DI TORINO

<u>Aim</u>: characterize the release kinetics of four drugs with different chemical behaviours.



- capillary of Ø = 110/ 220 µm
- 2 cm-long sections of hollow fiber
- drug release in PBS monitored by UV-VIS **spectroscopy**





Molecule	Absorption peak [nm]	Chemical behavior	%Release @6, 12, 18 min
Theophylline	272	Neutral	75%, 90%, 100%
Caffeine	274	Neutral	75%, 90%, 100%
Salicylic Acid	293	Anionic	25%, 65%, 100%
Procaine	290	Cationic	25%, 80%, 100%

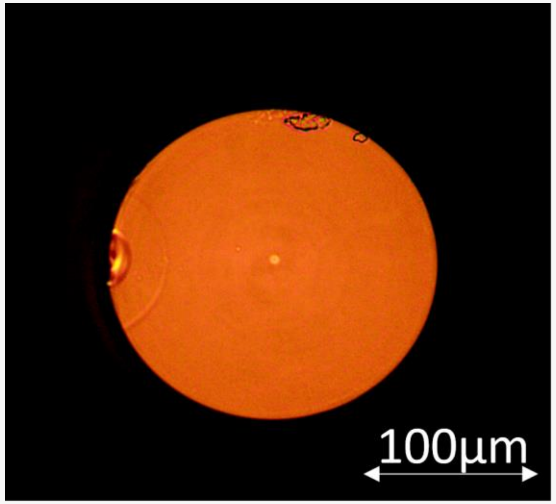
Ceci-Ginistrelli et al., Materials letters, 191, 116-118, 2017

Diffuse correlation spectroscopy (DCS)

Non-invasive technique that uses the temporal fluctuations of near-infrared light to directly measure blood flow in biological tissue.

Applications: diagnosis and therapeutic monitoring of cardio cerebral diseases, skeletal muscles, tumors, PDT therapy.

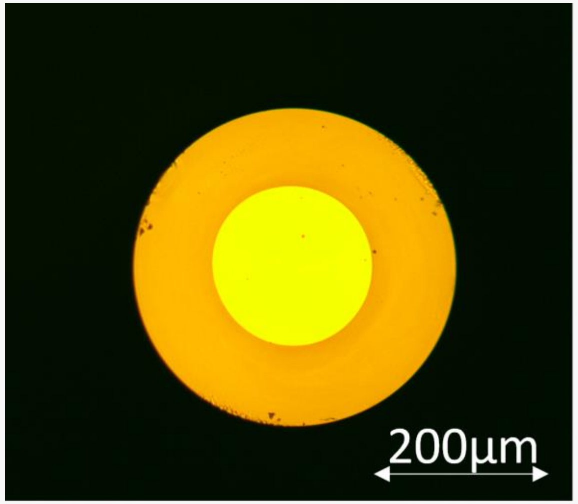
SINGLE-MODE FIBER



Ø = 4.8/ 125 µm

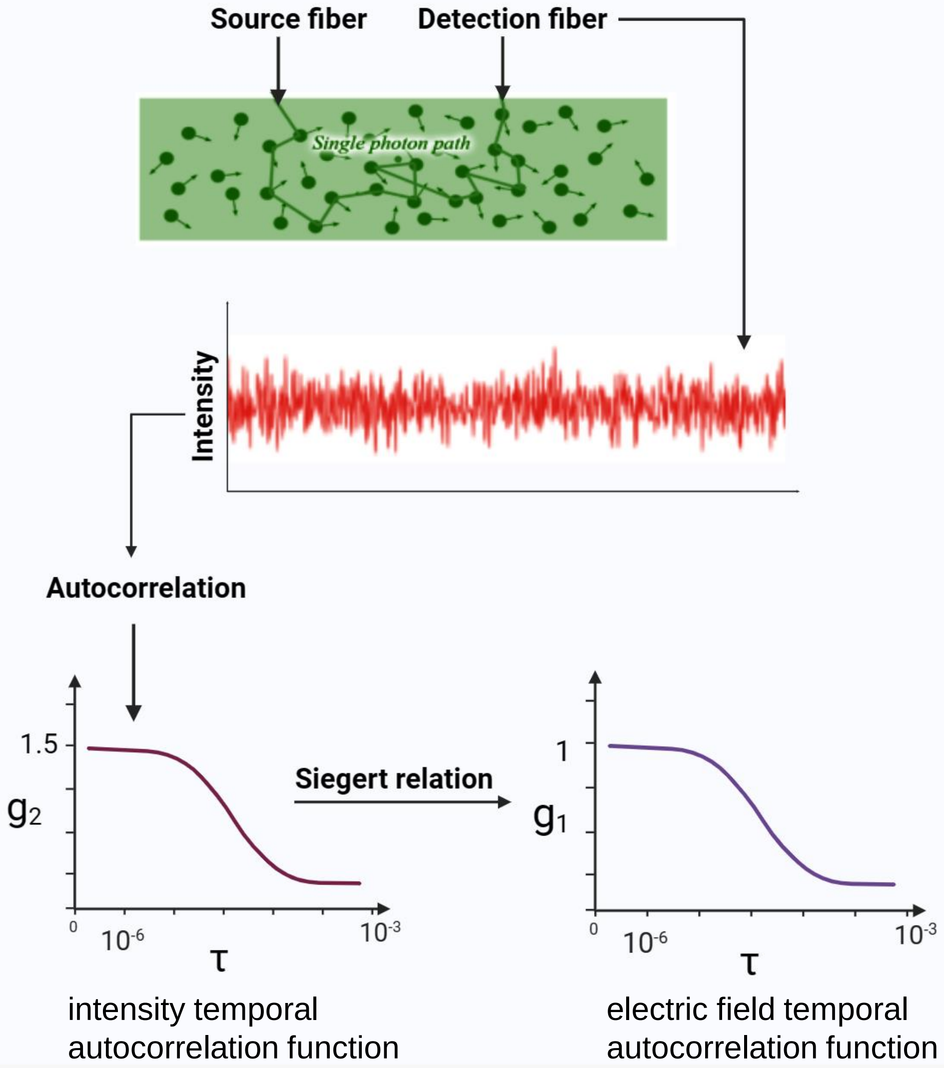
NA = 0.11

MULTI-MODE FIBER



Ø = 220/ 420 µm

NA = 0.21

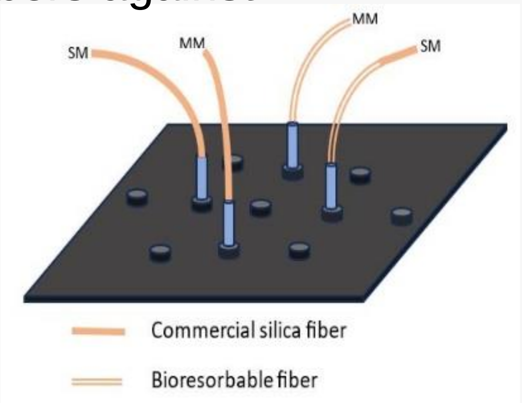


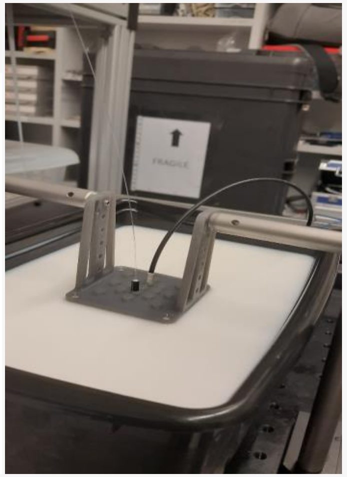
J. T. Pandayil, et al., Biomed. Opt. Express 15, 6384-6398 (2024)

DCS: Ex vivo Measurements

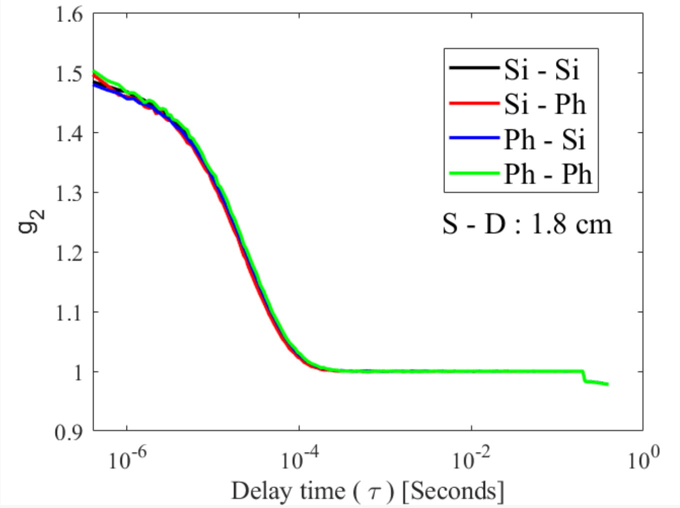
Objective: systematically compare the performance of bioresorbable fibers against standard silica fibers in terms of estimating the flow index parameter.

- Measurement on Intralipid Phantom
- Scattering coefficient: 5 cm^{-1}
- Source-Detector (S-D) separation: 1.8 cm

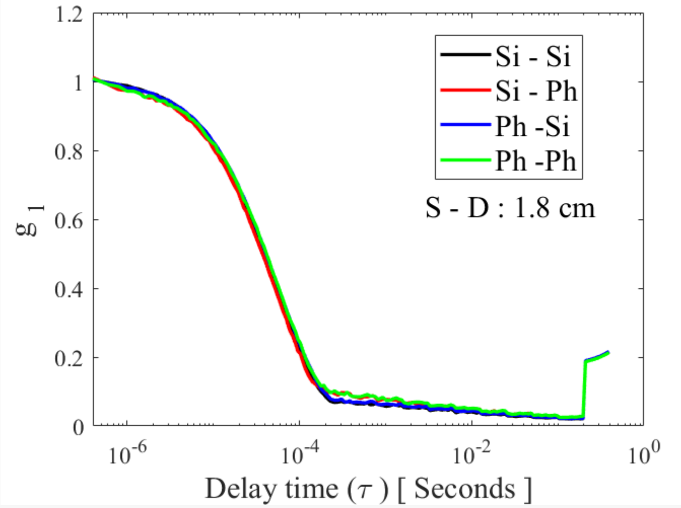


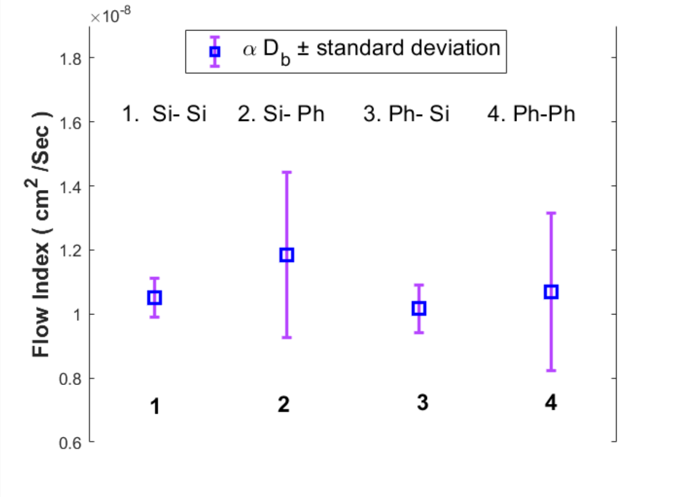


intensity temporal autocorrelation function



electric field temporal autocorrelation function

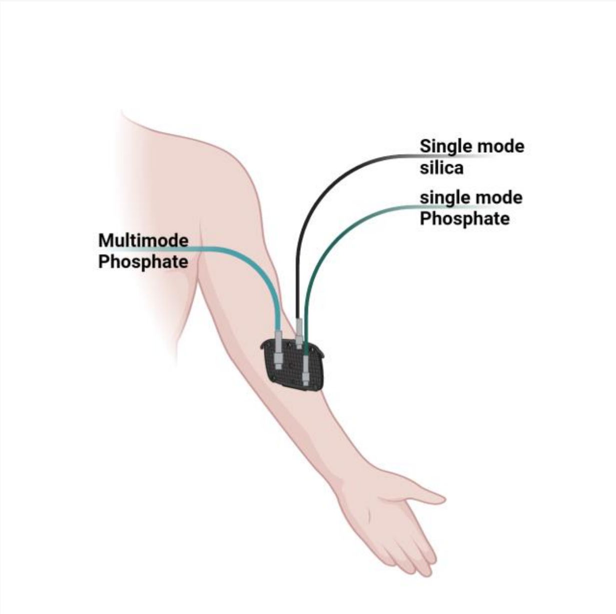


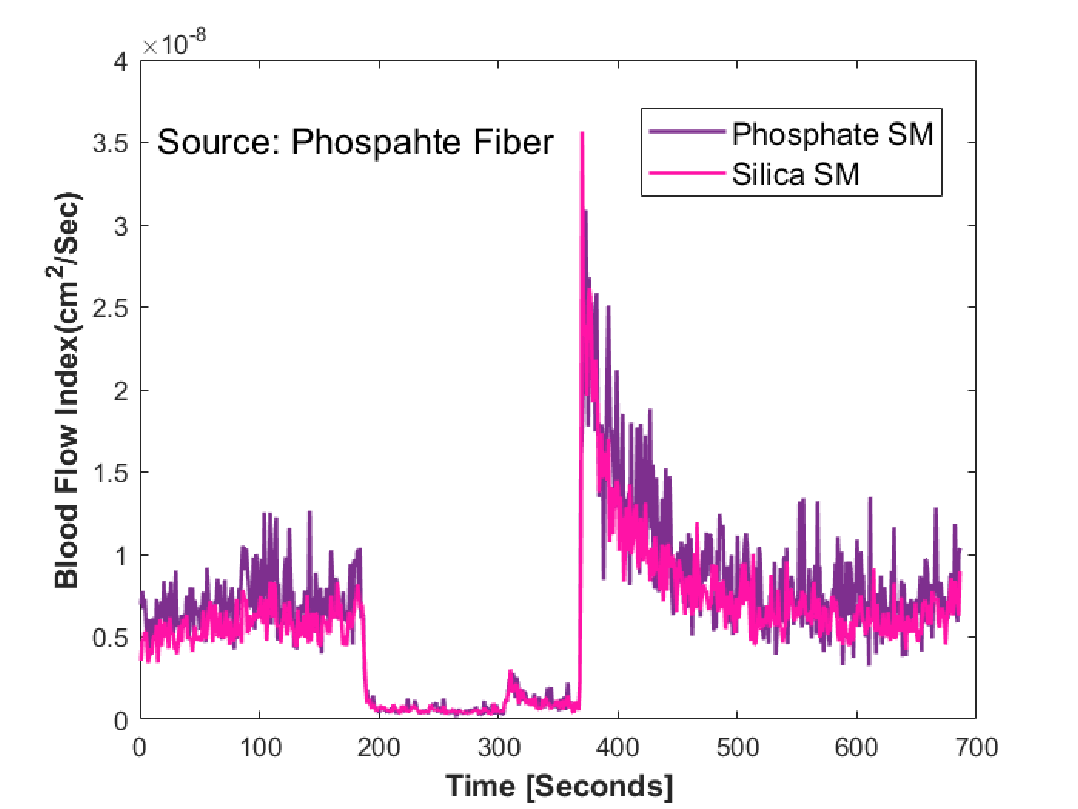


for all fiber combinations
- ➤ g_2 and g_1 posses the same decay characteristics
- ➤ estimated flow index are similar
- ➤ higher relative error due to lower photon count rate

DCS: In Vivo measurements

Cuff occlusion test: temporary restriction/occlusion of blood flow using a blood pressure cuff.



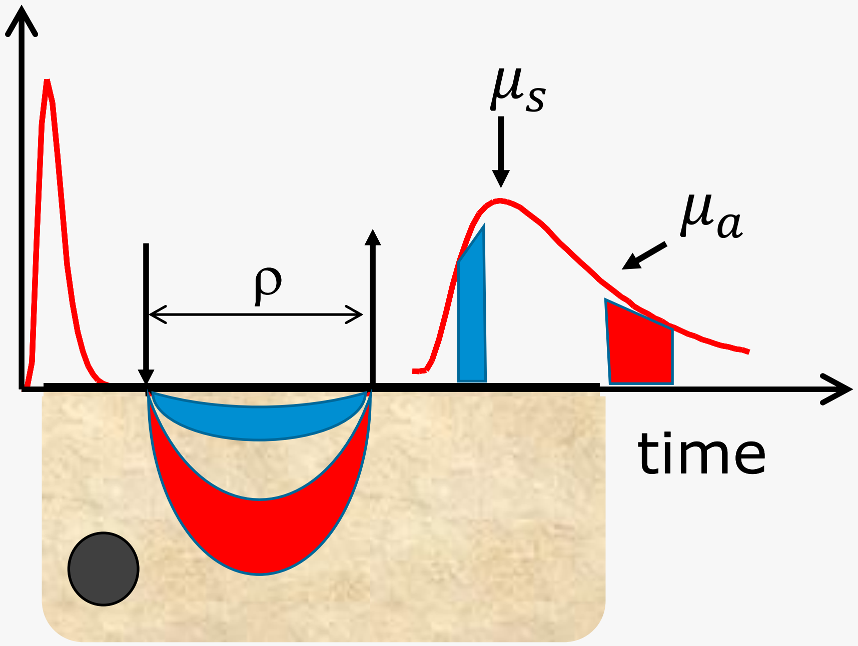


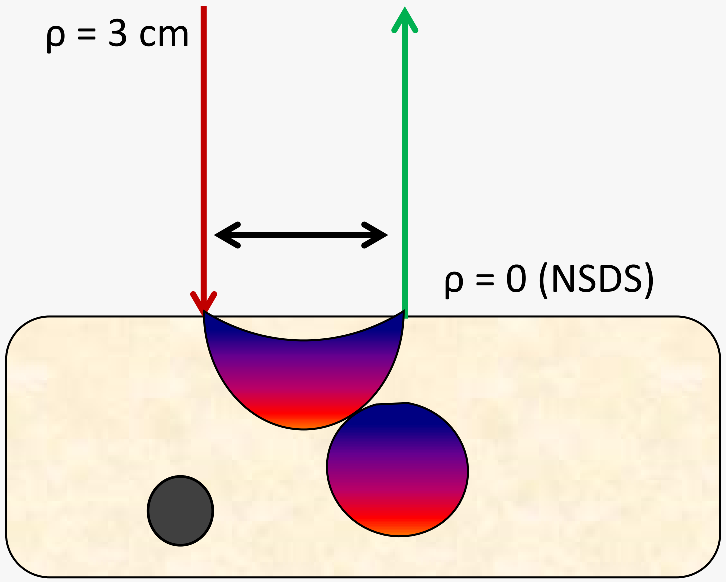
- Source - Detector separation : 1.8 cm
- Blood flow index measured using phosphate fiber is same as that of the commercial silica fiber in all phases of the measurement: baseline, inflation, deflation
- Higher variation of phosphate curve is due to lower photon count rate

Interstitial Time-Domain Diffuse Optics (TD-DOS)

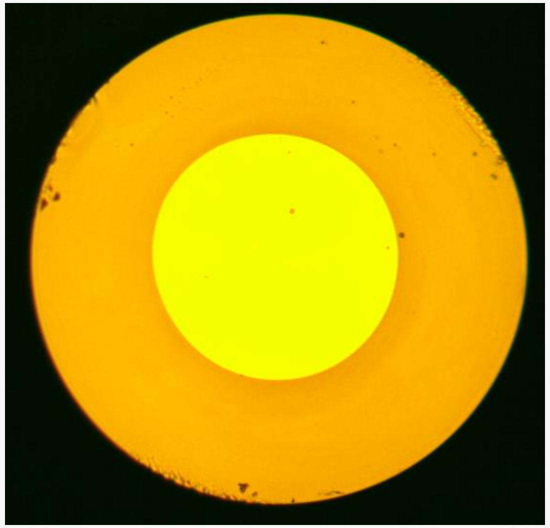
Non-invasive technique that studies the propagation of NIR light through biological tissues. By analyzing the time-related features of scattered light, it reveals details about tissue optical properties, such as scattering (tissue microstructure) and absorption (tissue constituent).

Applications: tissue oxygenation monitoring, tumor detection, monitoring of therapy, wound healing monitoring, intraoperative guidance.





Null Source-Detector Separation

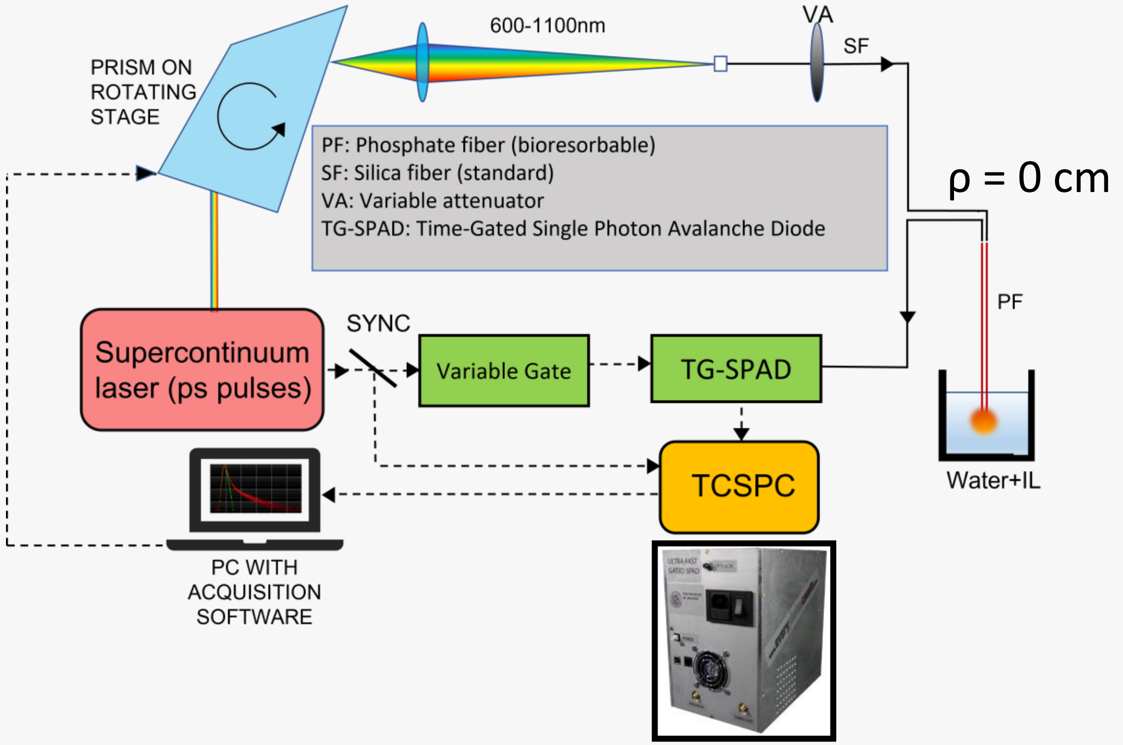


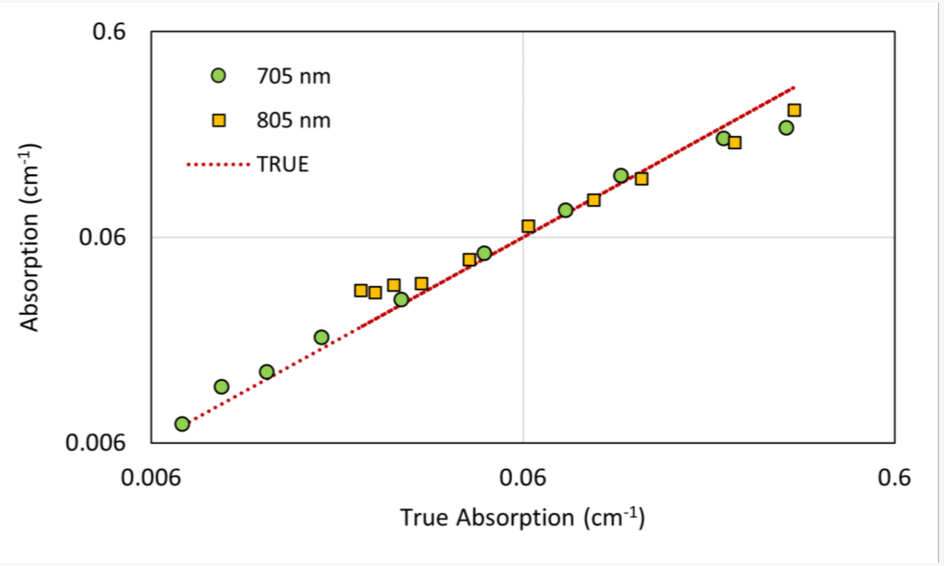
Ø = 200/ 400 μm

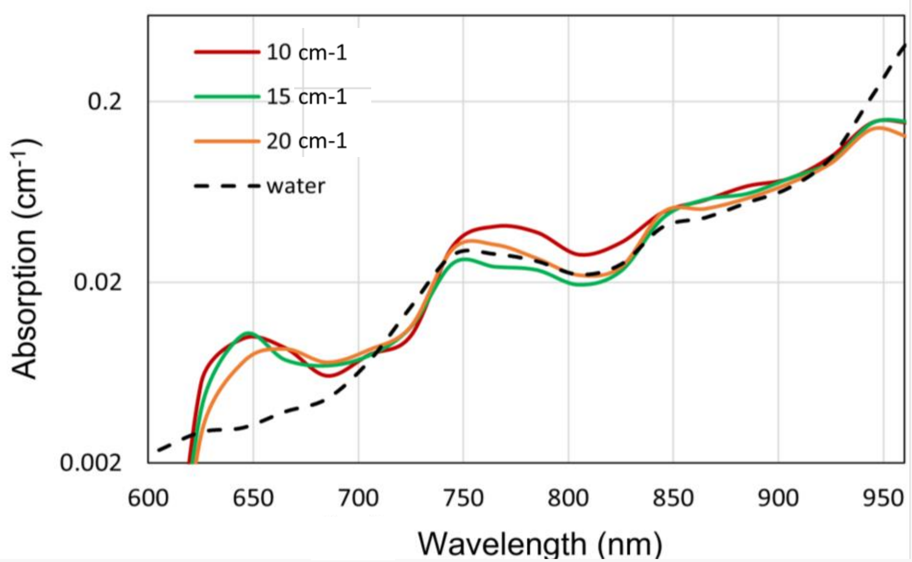
NA = 0.20

L.DiSieno et al., J.Biophotonics11(1),e201600275 (2018).

TD-DOS: Liquid Phantom Measurement



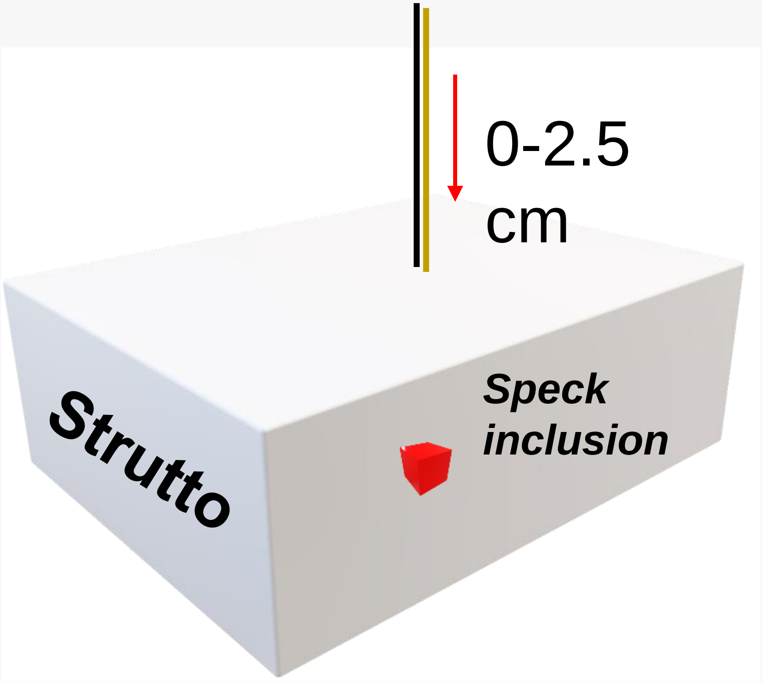




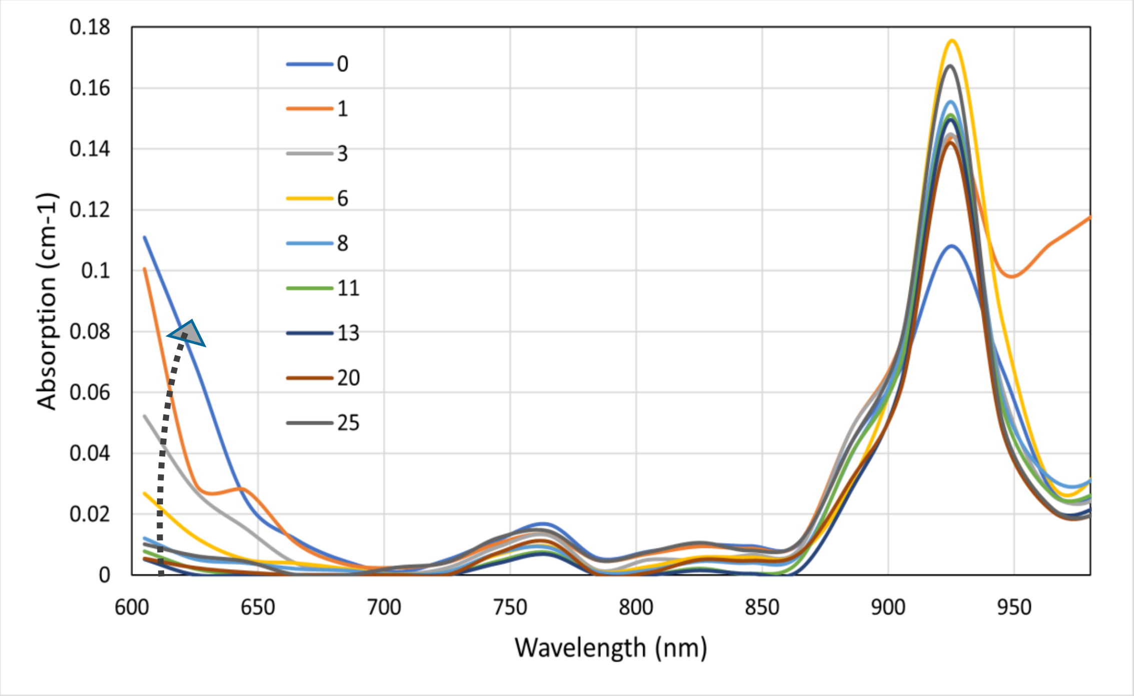
- MEDPHOT protocol
- Phantom: Water + IL (scatterers) + India ink (absorbers)
- System absorption linearity in range of 0.006 – 0.4 cm^{-1}
- Water spectrum 700 – 940 nm: < 15% relative error
- Effect of μ_s : < 10% variation for change in scattering

V. Damagatla et al., paper 1262818 in Diffuse Optical Spectroscopy and Imaging IX, Technical Digest Series

TD-DOS: solid phantom



- 2 x 2 x 2 cm speck inclusion (porcine muscle) in strutto
- Spectra recorded at different fibers distance (moving from 2.5 cm to speck surface)



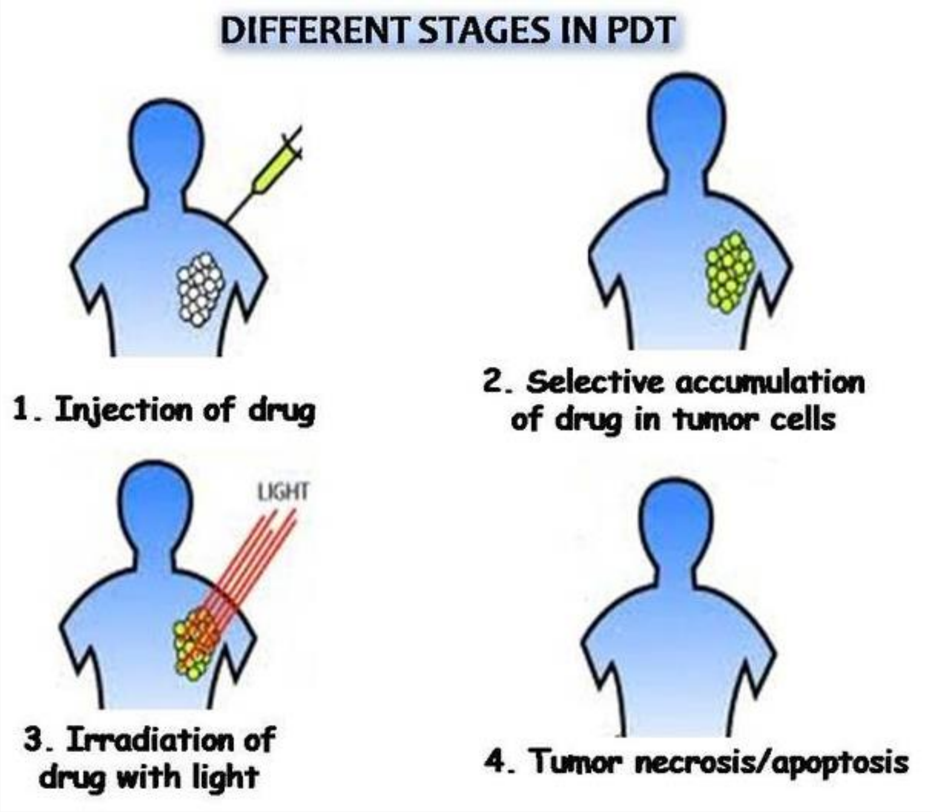
- Changes in spectral shape below 700 nm due to presence of blood components
- Increase in absorption → presence of blood components
- Can detect change from z < 10mm onwards

V. Damagatla et al., Biomed. Opt. Express 15, 5041-5052 (2024)

Photodynamic therapy (PDT)

Promising cancer treatment that involves the dynamic interactions of three components: light, a photosensitizing (PS) agent and oxygen, which together result in tissue destruction.

Applications: skin, esophageal, head and neck, lung, prostates and bladder cancers.

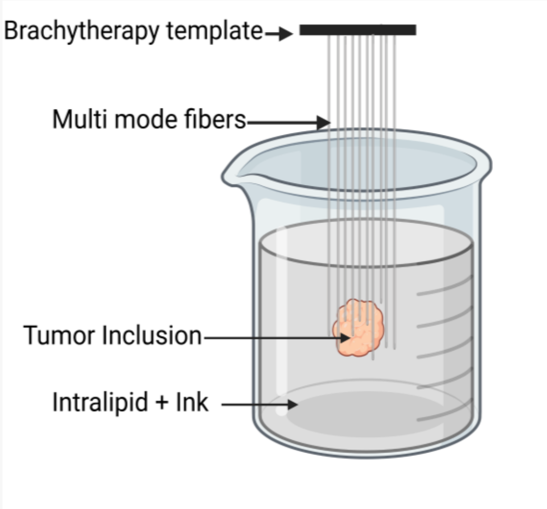


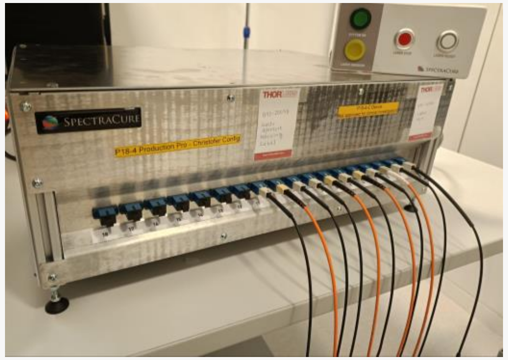
- Knowledge of spatial distribution of PS concentration would be beneficial for efficient treatment
- Monitoring of the PS distribution is not yet considered in current clinical light dosimetry planning
- Diffuse fluorescence tomography (DFT) is applied to reconstruct PS distribution in tumor site

https://neuros.net/en/photodynamic_therapy/

Drug distribution monitoring in PDT

Objective: to test the suitability of bioresorbable fibers for monitoring through DFT the spatial distribution of photosensitizing drug in PDT.

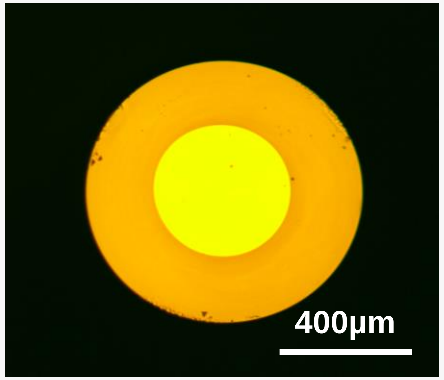




- SpectraCure's P18-4 system
- 18 photonics modules
- each with light source at 690 nm and two detectors: at 690 nm and IR (>700 nm)

Hybrid phantom:

- Intralipid phantom, mimicking prostate tissue ($\mu_a = 30\ \mathrm{m}^{-1}$, $\mu_s' = 870\ \mathrm{m}^{-1}$)
- Gelatin based solid tumor inclusion ($\mu_a = 20\ \mathrm{m}^{-1}$, $\mu_s' = 1600\ \mathrm{m}^{-1}$) with fluorescent photosensitizer Visudyne



Ø = 400/ 800 µm

NA = 0.24

11 fibers: 1 emitting at 690 nm and 10 collecting PS fluorescence

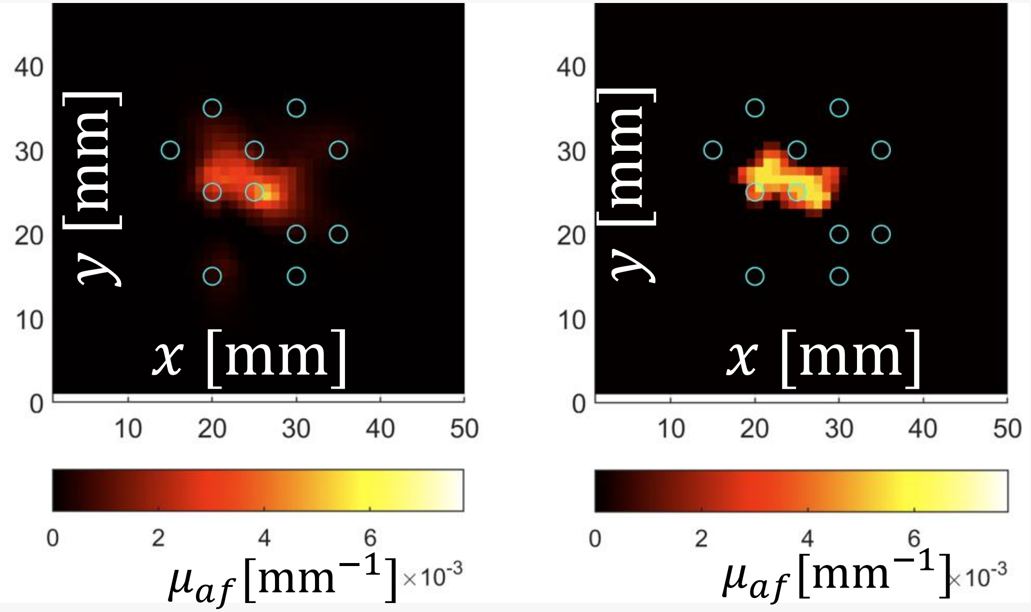
$11 \times 10 = 110$ measurement points

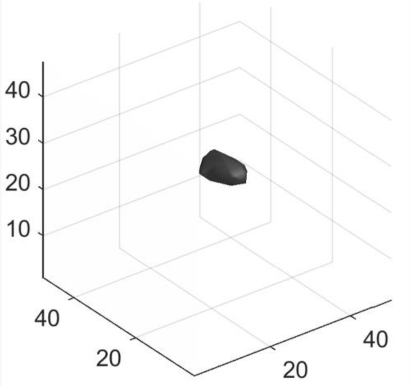
Input to DFT reconstruction of the PS absorption coefficient

Paper in preparation

Drug distribution results

Phosphate fibers

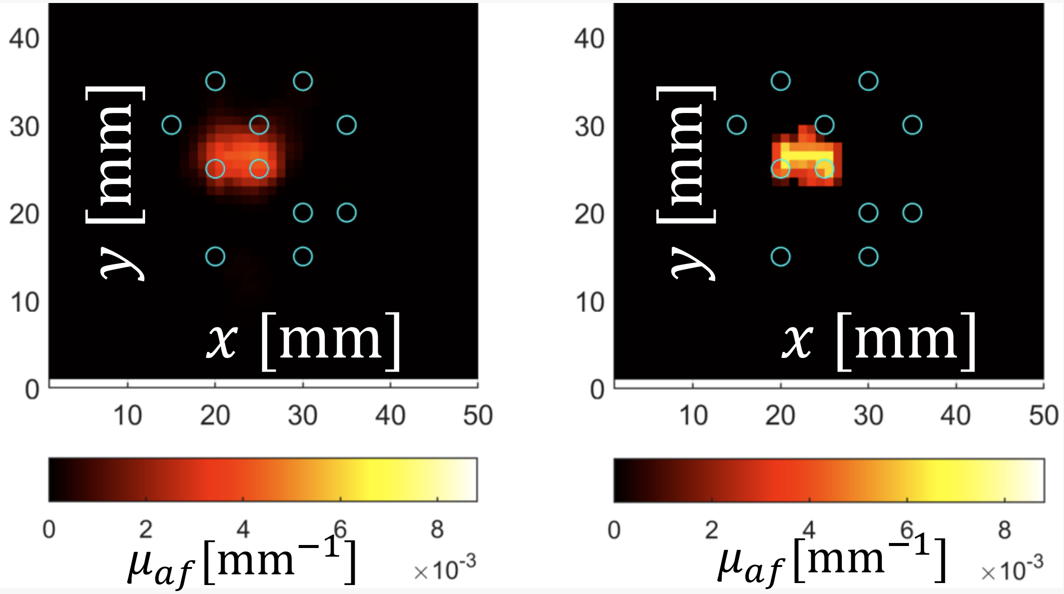


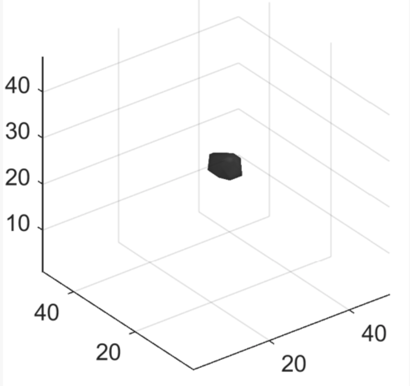


V2 = 111.6465 cm^3; μ_{af} = 0.00043 cm^{-1}

V1 = 0.1773 cm^3; μ_{af} = 0.055328 cm^{-1}

Silica fibers



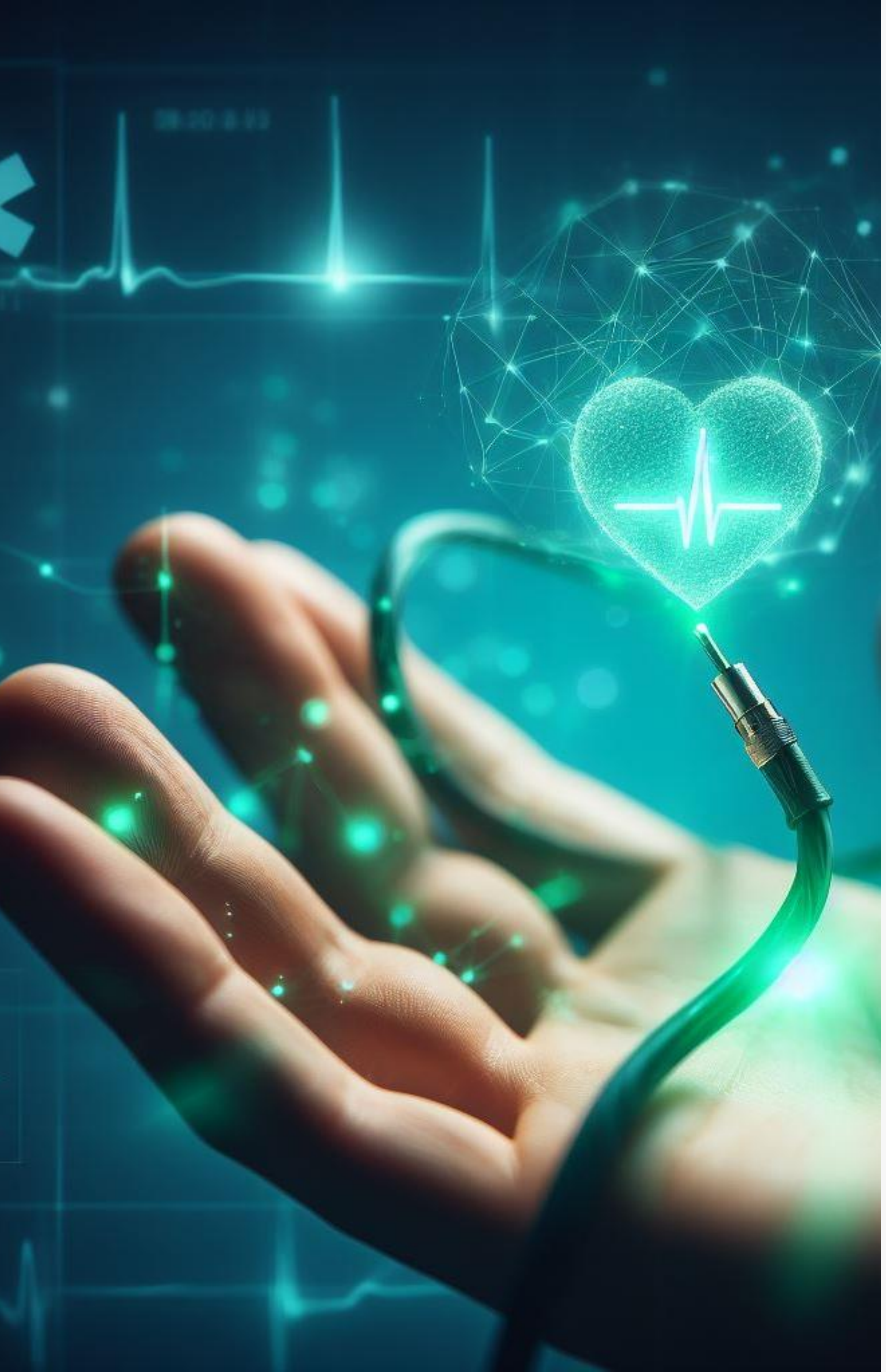


V2 = 111.6465 cm^3; μ_{af} = 0 cm^{-1}

V1 = 0.12305 cm^3; μ_{af} = 0.064877 cm^{-1}

smooth boundaries

sharp boundaries



Outline

- Introduction to optical fibers in medicine
- Bioresorbable optical fibers
- Biomedical applications of bioresorbable fibers:
  - Drug release from hollow fibers
  - Diffuse Correlation Spectroscopy
  - Interstitial Time Domain Diffuse Optics
  - Diffuse fluorescence tomography in PDT
- Conclusions and ongoing research activities

Conclusions

- Successful fabrication of bioresorbable optical fibers using calcium phosphate glass compositions.
- In vitro dissolution studies indicate that these fibers can be cleared from the body within a controlled timeframe, offering clinically relevant data.
- Demonstrated suitability for spectroscopy applications such as DCS, interstitial TD-DOS, DFT in the context of PDT therapy (ex vivo tests and in vivo tests for DCS).

Future Works

- Development of multifunctional bioresorbable optical fibers for diagnosis and therapy.
- Further in-vivo studies and integration with medical instrumentation are required to advance towards clinical applications.

Politecnico di Torino

FONDAZIONE links

PASSION FOR INNOVATION

Thank you for your attention

PHAST

PHOTONICS FOR HEALTHCARE: MULTISCALE CANCER DIAGNOSIS AND THERAPY

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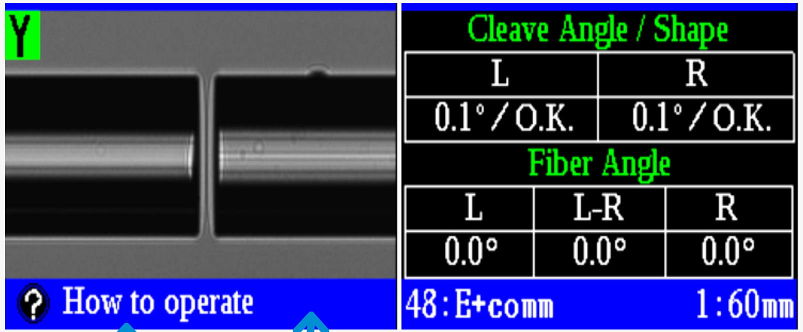
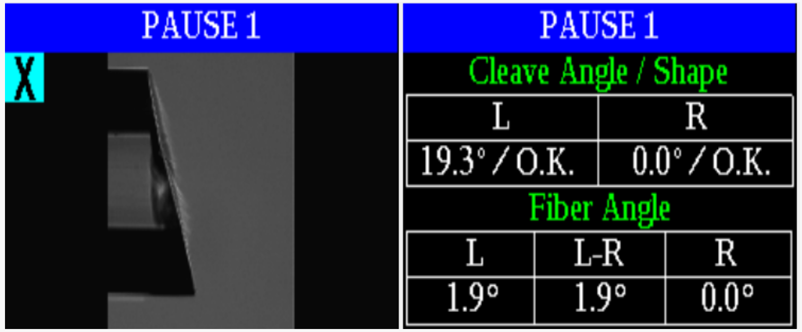
Phosphate Fibers integration

Cleaving

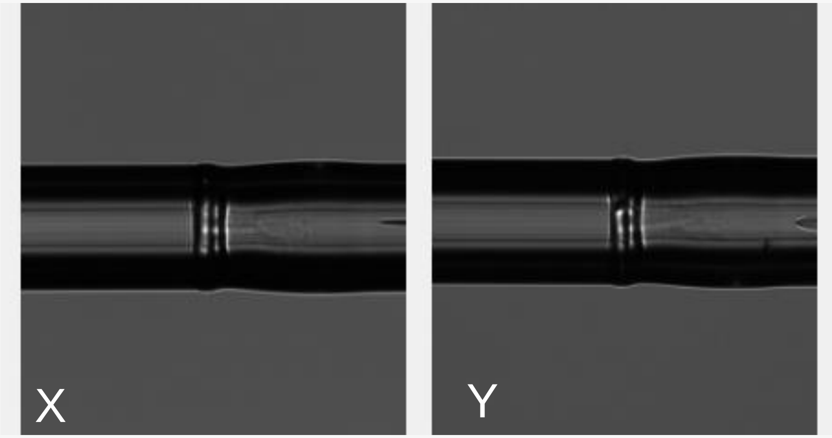


Silica fiber

Phosphate fiber



Splicing



Loss measured

@1310 nm

< 1 dB