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Spectrally resolved picosecond photon tagging for ultrathin clinical endoscopes

Motivation

Endoscopic Raman spectroscopy → intraoperative tissue analsysis.
An ultrathin probe can remove the need for tissue excision (biopsy free).

Example application: assessment of surgical margin during tumor resections to improve prognosis.

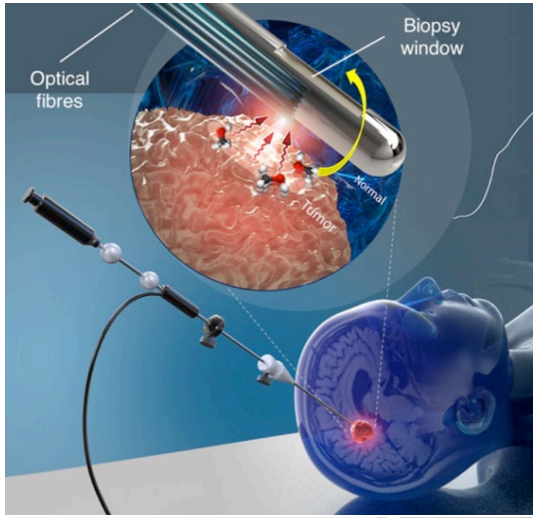
Challenge

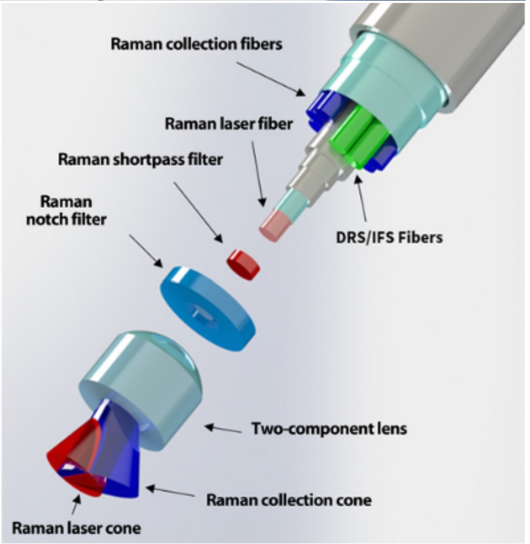
Raman signal is intrinsically weak.
Background from the probes masks relevant information in the *fingerprint* region (DNA, collagen, cytochromes)

State of the art solutions

1- Probes with complex multi-fiber arrangements and integrated optical filters.
Limitation Large probes (diam 1-2 mm), no insertion before the resection

2- Limiting the spectral range to where the background is lower
Limitation loss of information in the fingerprint region





Jermyn et al, Sci Trasl Med 2015
Desroches et al., Sci Rep 2018
Desroches et al., Biomed Opt Expr 2016

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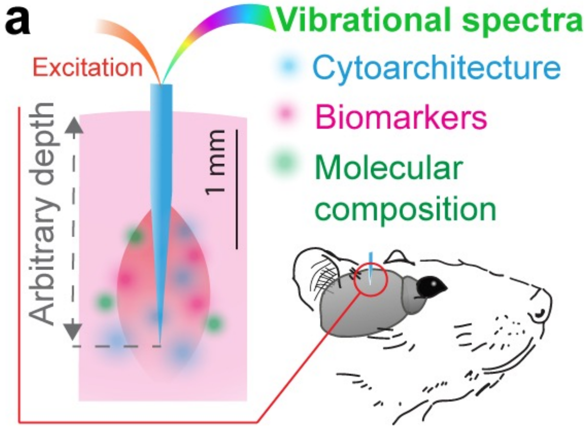
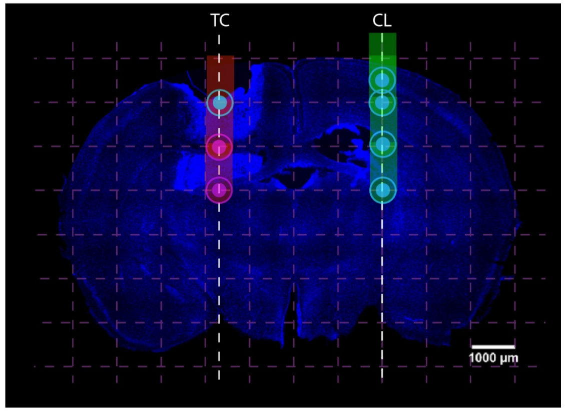
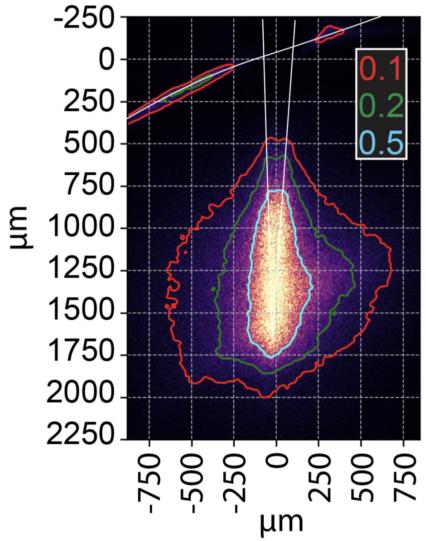
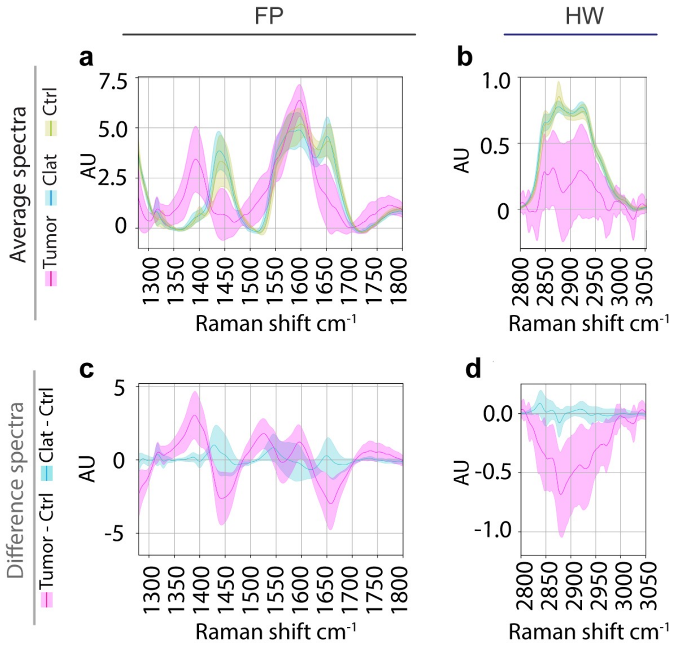
Preliminary evidence (approach 2)

A single thin probe with bulk detection can detect cancer formations at any depth.









Pisano et al, Nature Methods, accepted

Limitations

- Only a portion of the fingerprint range is detected
- The probe is short (4 cm), hard to use for clinical application

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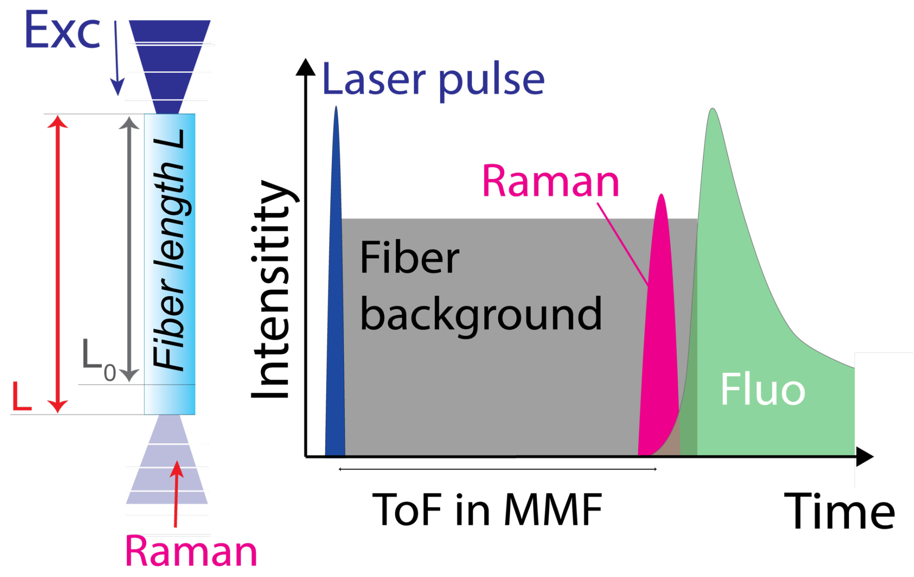
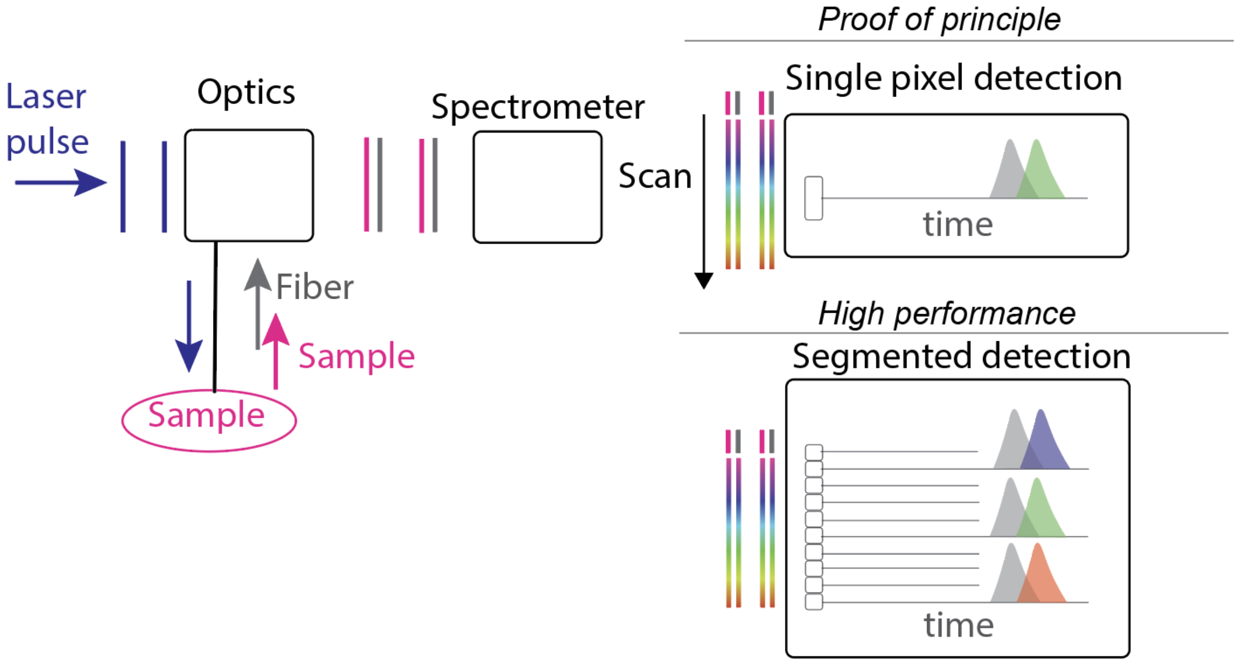
Main idea

Isolate the signal generated in the tissue from the one generated in the fiber using a photon time-of-flight detection.
The approach relies on the instantaneous Raman scattering (ps) vs the finite time of propagation in the fiber.
Together with background suppression, it offers an opportunity for endoscopic fluorescence lifetime spectroscopy

Objective

Develop and validate a system for background-suppressed endoscopic Raman spectroscopy for clinical applications using time-of-flight detection at high-temporal resolution





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Methodology

WP1 Numerical modelling

Task 1.1 Numerical modelling of temporal and spectral response of fiber + tissue system (RT + MC)

WP2 Development of the optical system

Task 2.1 Design of the optical system

Task 2.2 Construction and benchmarking of the optical system

WP3 Application in biological samples

Task 3.1 Validation in biological specimens

Task 3.2 Data analysis strategies for signal to noise improvement (denoising) and spectral classification

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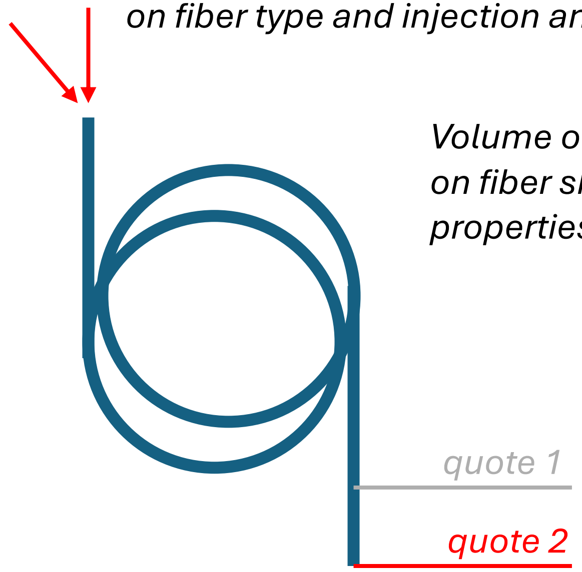
Spectrally resolved picosecond photon tagging for ultrathin clinical endoscopes

Methodology

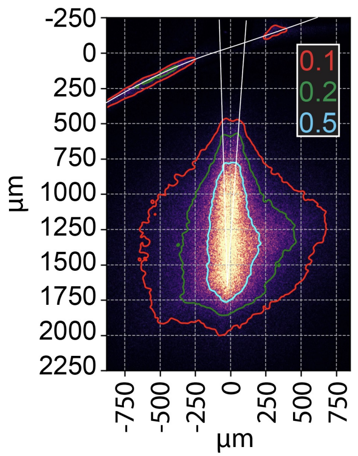
WP1 Numerical modelling

Task 1.1 Numerical modelling of temporal and spectral response of fiber + tissue system (RT + MC)

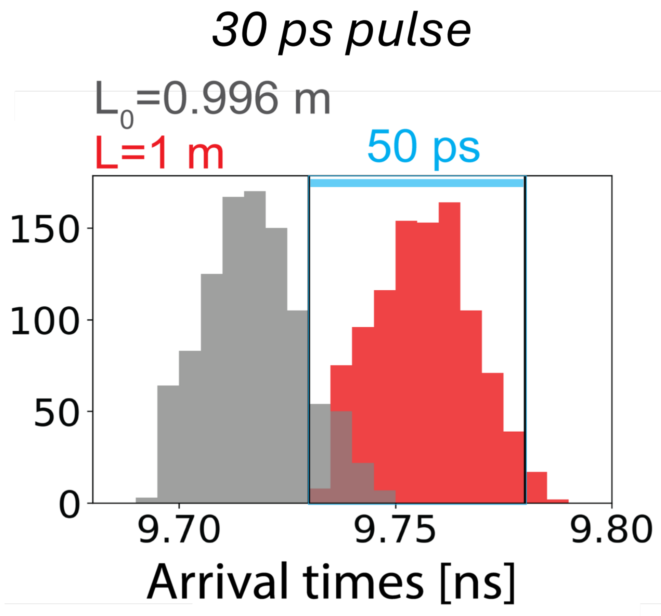
Distribution of time of flight depends on fiber type and injection angle (k_t)

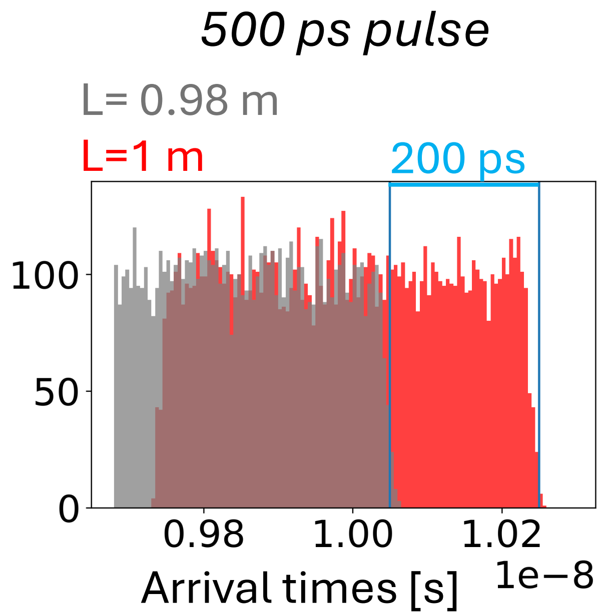


Volume of sampling depends on fiber shape and tissue optical properties



Preliminary results





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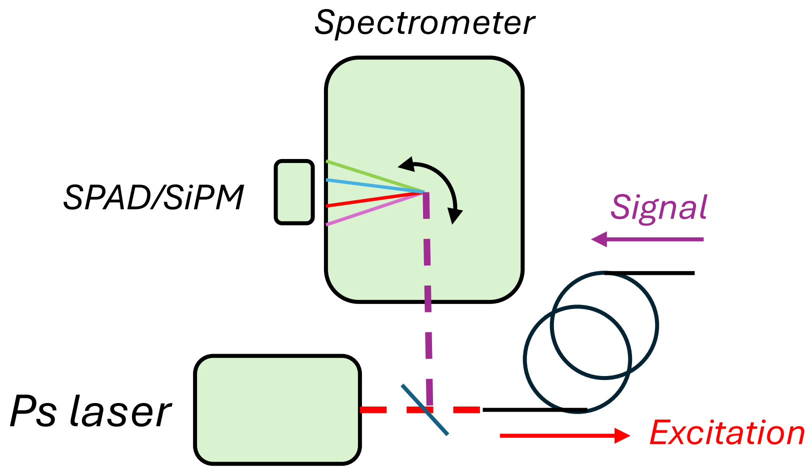
Methodology

WP2 Development of the optical system

Task 2.1 Design of the optical system (Zemax, CAD)

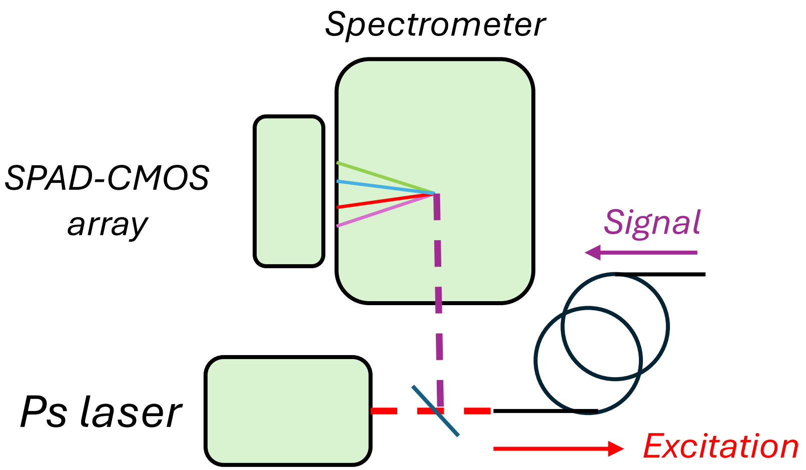
Task 2.2 Construction and benchmarking of the optical system

Proof of principle system



Ps pulsed laser 500 ps [*available*]
Spectrometer *10 keuro*
SPAD/ SiPM *2-5 keuro* [available ?]
Optics and filters *3 keuro*

High performance system



Ps pulsed laser < 100 ps *15 keuro*
Spectrometer *10 keuro*
SPAD-CMOS 320x1, 17 ps tagging, 2 ns gate *27.5 keuro*
Optics and filters *3 keuro*

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Methodology

WP3 Application in biological samples

Task 3.1 Validation in biological specimens

Detection of spectral signatures in healthy and pathological tissue (e.g. lipid and protein bands in samples from melanoma brain metastasis), detection of signatures in the region covered by the fiber background (e.g collagen or melanin band at 980 cm^{-1}).

Task 3.2 Data analysis strategies for spectral processing and classification

Spectral classification via ratiometrics, PCA or deep learning strategies; exploration of deep learning denoising for signal improvement; architecture towards real time operation (seconds)

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GANTT

	Year 1				Year 2				Year 3			
T1.1			M1									
T2.1					M2							
T2.2							M3					
T3.1									M4			
T3.2											M5	

Milestones

M1 Implementation of parametric study of effect of pulse width and fiber NA on distribution of photon time of flight

M2 Design of optical system, identification of performance benchmarks

M3 Operation of optical system and first evidence of time-resolved signal collection

M4 Detection of spectral signatures within the fiber background

M5 First evidence of spectral classification based on ratiometric and/or PC analysis

Partecipants

- F. Pisano
- Assegno di ricerca, 1 year, funded by DFA under PARD 2024 starting January - March 2025

Other funding

- PARD 2024, Deep Light, DFA-UniPD
- Waiting on ERC 2024 results, 30% success rate

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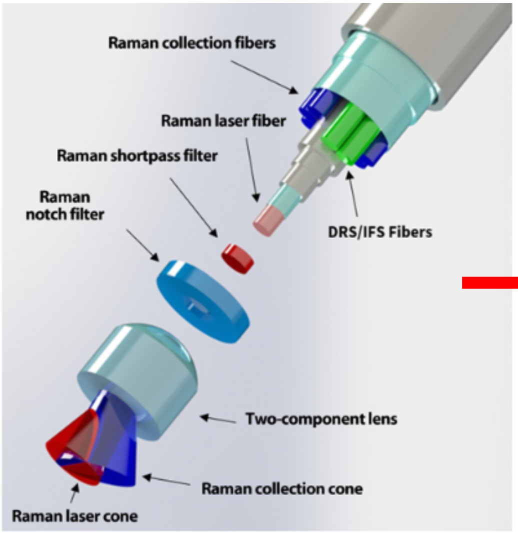
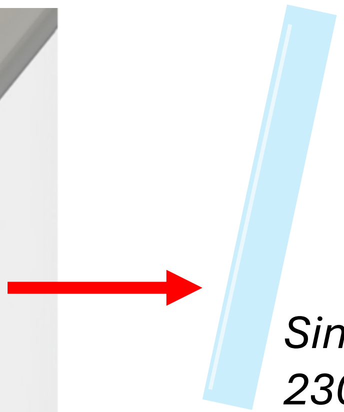
Ricadute e impatto

- *Applications of ultrafast detectors (G. Simi)*
- *Advanced data analysis and deep learning approaches (A. Zucchetta)*
- *Impact on basic research: label-free optical characterization of biormarkers in deep living tissue (DFA, DSB)*
- *Impact on translational research: minimally invasive approach for tissue analysis*
- *Opportunities for fluorescence and autofluorescence lifetime spectroscopy*

Technology transfer





Single fiber
230 um diameter

Factor 10 miniaturization

- *Potential for spin-off, targeting research and clinical market*
- *IP protection needs to be assessment against prior art*