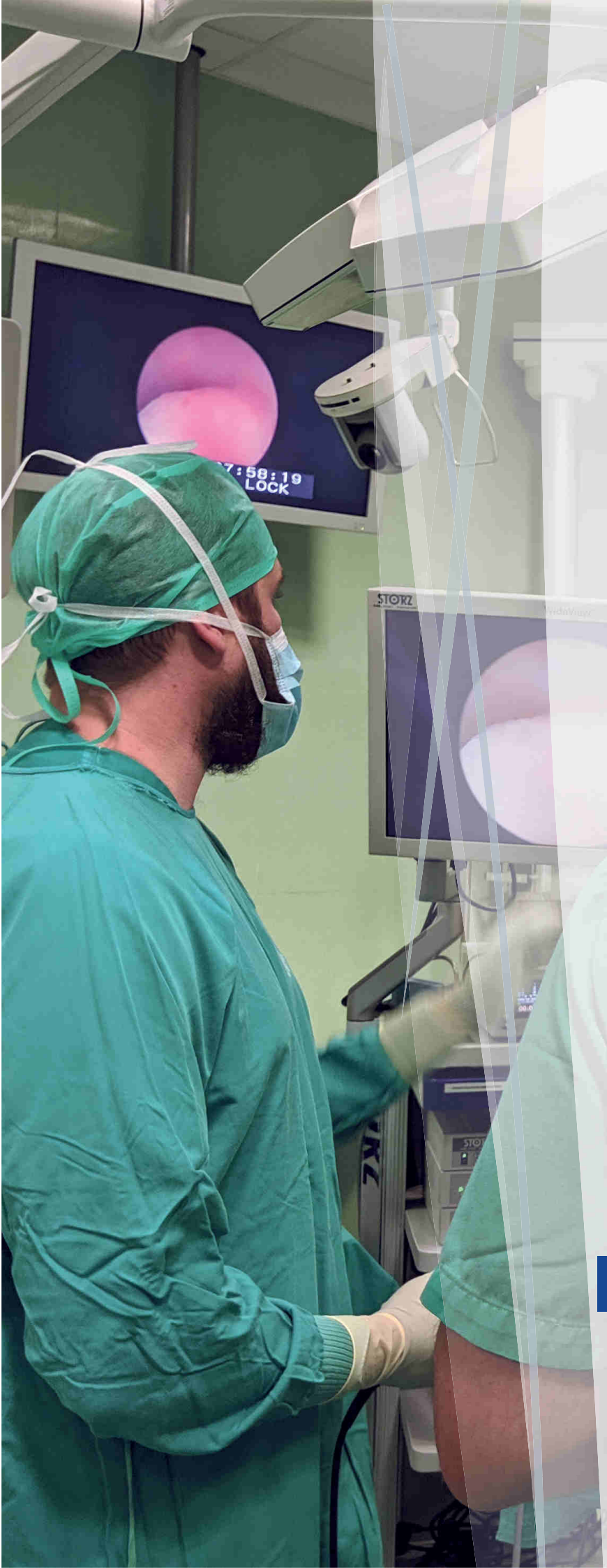


PICCOLO

Multimodal highly-sensitive PhotonICs endoscope for improved in-vivo COLOn cancer diagnosis and clinical decision support

The project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 732111

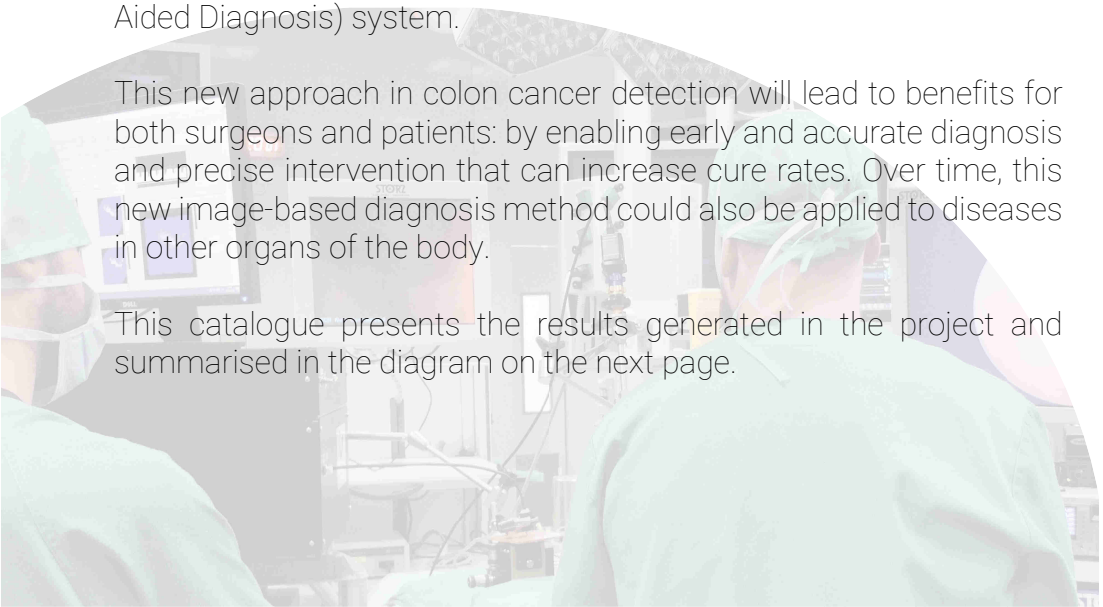
PICCOLO PAVING THE WAY TOWARDS IN-VIVO COLON OPTICAL BIOPSY

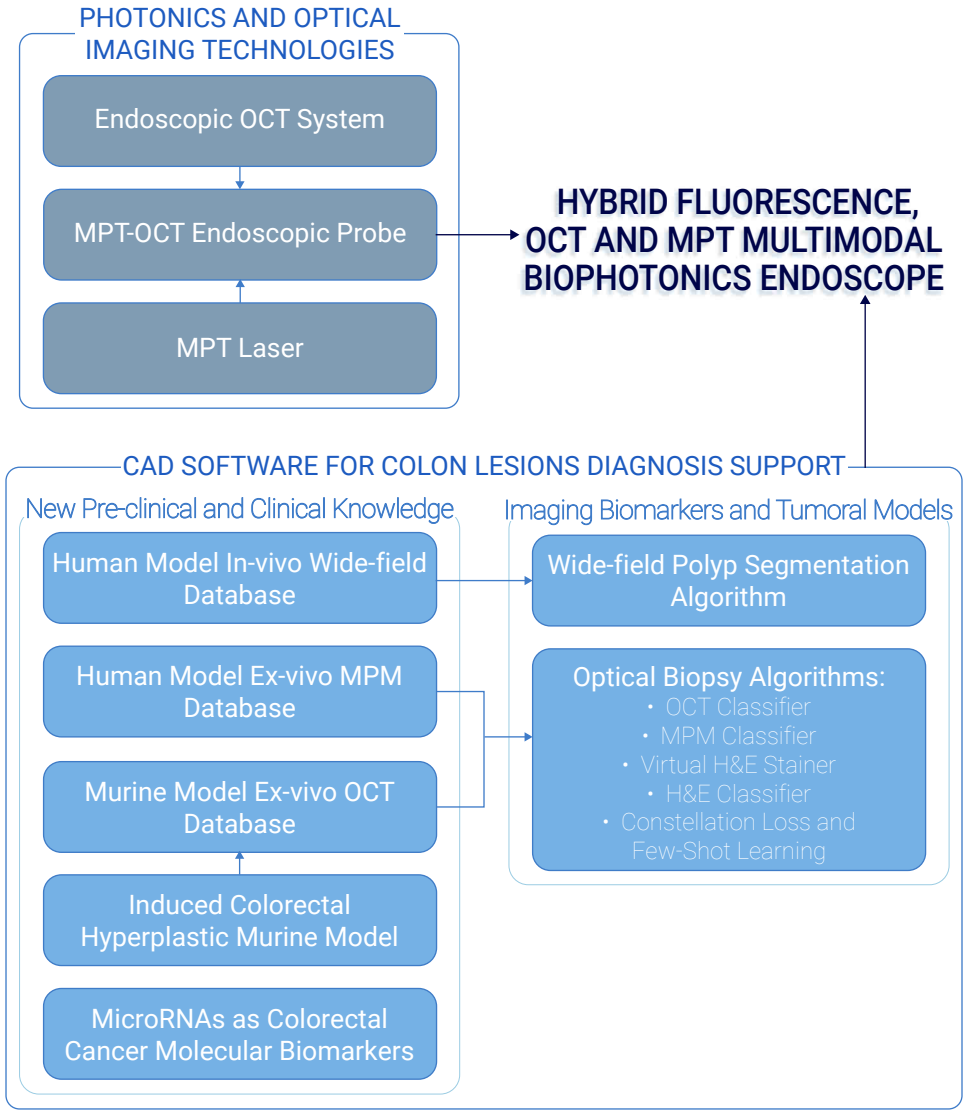
PICCOLO brings together European scientists and clinicians to create an endoscopic probe to better diagnose bowel polyps and early colon cancer run by algorithms that perform optical biopsy of the colon

By combining the outstanding structural information from OCT (Optical Coherence Tomography) with the precise structural and functional information from MPT (Multiphoton Tomography) together with novel red-flag fluorescence technology, the new endoscope will provide gastroenterologists with immediate and detailed in-situ identification of colorectal neoplastic lesions and facilitate accurate and reliable diagnosis, with additional grading capabilities for colon cancer (non-cancerous polyps, pre-cancerous polyps and early colon cancers) as well as in-situ lesion infiltration and margin assessment. This will significantly impact clinical practice allowing in-vivo real-time optical biopsy assessment via the automatic analysis of images by the newest deep learning algorithms integrated in a CAD (Computer Aided Diagnosis) system.

This new approach in colon cancer detection will lead to benefits for both surgeons and patients: by enabling early and accurate diagnosis and precise intervention that can increase cure rates. Over time, this new image-based diagnosis method could also be applied to diseases in other organs of the body.

This catalogue presents the results generated in the project and summarised in the diagram on the next page.

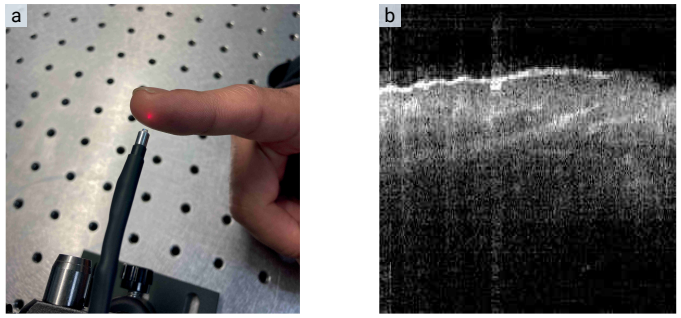




ENDOSCOPIC OCT SYSTEM

High scanning speed miniaturised Optical Coherence Tomography (OCT) for endoscopy

An optical coherence tomography system has been developed where the scanning head has been miniaturised and integrated at the end of a 2 metre fibre, so that it can be inserted down the working channel of an endoscope and take OCT images of internal human tissue. The scanning head contains piezo-electric components and a lens to scan a probe spot across the tissue, and collect the reflected light back into an optical fibre. This signal is then recorded on PC and plotted to give 2D and 3D OCT images. Cross-sectional images can be taken in 0.35 ms.



Non-destructive measurements with the biocompatible OCT system (a)
OCT B-scan of colon tissue showing surface and sub-surface structure (b)

FEATURES

- High scanning speeds.
- 0.25 ms per B-scan.
- Can be used in combination with MPT imaging.
- 2 metre fibre and probe can be inserted to endoscope working channel.
- 2D and 3D OCT images plotted in real-time.

INTENDED USE

- Discriminate between healthy tissue and pre-cancerous polyps.

ADVANTAGES

- For use on ex-vivo and in-vivo tissue.
- Insensitive to sample movement due to high speed scan.

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MPT-OCT ENDOSCOPIC PROBE

Multiphoton Tomography (MPT) and Optical Coherence Tomography (OCT) imaging probe for colonoscopic application

A very **small probe** with an integrated piezo scanner that moves a double-clad optical fibre along a **Lissajous path**. To perform optical coherence tomography or two-photon fluorescence imaging, a dedicated GRIN lens is placed in front of the distal fibre tip to focus the laser light inside the sample and to collect respectively the reflected light for OCT or the generated two-photon fluorescence, coupling it back in the fibre towards the detection system.
The system, composed of **piezo scanner**, **double-clad fibre** and **GRIN lens**, is **embedded** in a mechanical housing that covers the electrical contact of the piezo, prevents the fibre from hitting something and keeps the GRIN lens at the right distance from the distal fibre tip. The probe has the smallest possible dimensions (external diameter is 3.5 mm) to **fit the service channel of a commercial colonoscope**.

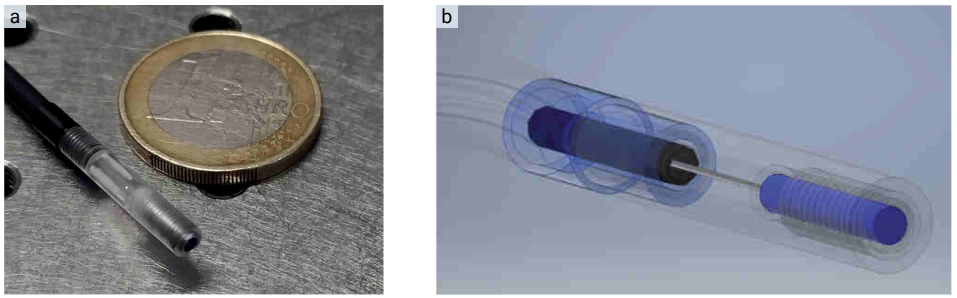

Photo of the fiber probe (a) and 3D rendering (b)

FEATURES

- Very small size.
- Suitable for endoscopy application.
- Distal scanning.
- Large field of view.

INTENDED USE

- MPT endoscopic images.
- Help in early discrimination of healthy tissue or precancerous polyps.
- Extend MPT imaging to other imaging domains.

ADVANTAGES

- User-friendly.
- High speed scan.
- Novel techniques.
- Real-time application.
- Autofluorescence imaging without labelling.

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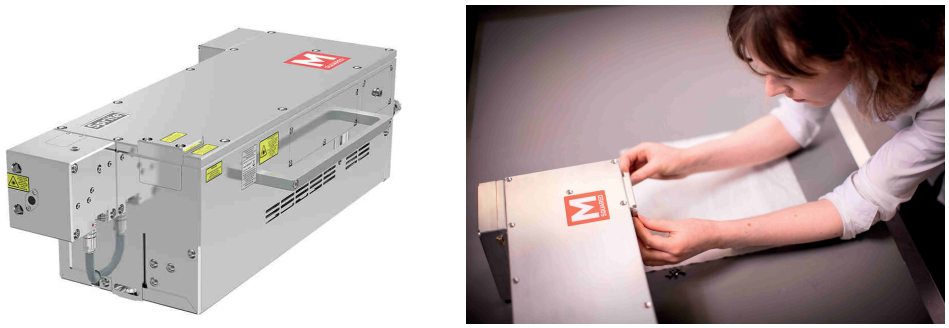
MPT LASER

Delivering tunable ultrashort pulses in a compact form factor

The MPT Laser is a **titanium sapphire** laser used as the primary source for the multiphoton tomography modality. The laser has been designed in such a way that the **pump source is integrated into the same housing as the ultrafast Ti:sapphire oscillator.** This dramatically reduces the footprint of the laser system and increases its robustness by fixing and physically isolating the beam transport element between pump and laser. The **compact system** can be made portable for future clinical deployment, whilst remote operation and on-board diagnostics enable flexible control options.



Front and top views of the MPT laser system

FEATURES

- Typical tuning range: 720-940 nm
- Output power (modelocked):
  - >0.6 W at ~725 nm
  - >1.3 W at ~800 nm
  - >0.6 W at ~935 nm
- Pulse width: <150 fs
- Amplitude noise: < 0.125%
- Power stability: <± 0.5%
- Spatial Mode: TEM_{00} (M2 < 1.1)

INTENDED USE

- Deliver ultrashort pulsed light for multiphoton tomography modality probe.
- Portable unit for future clinical deployment.

ADVANTAGES

- Smallest footprint for this type of laser.
- Hands-free operation; fully sealed laser head with factory-set optical alignment.
- Class-leading power stability and beam-pointing stability.
- Ethernet connectivity, providing remote laser control functionality.
- Browser-based control system and on-board laser diagnostics.

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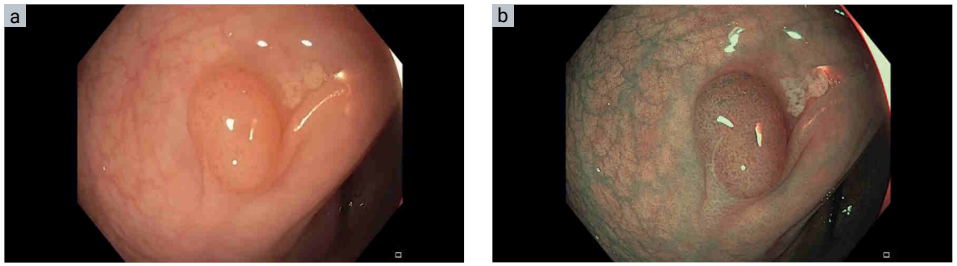
HUMAN MODEL IN-VIVO WIDE-FIELD DATABASE

RGB/NBI (Red Green Blue / Narrow Band Imaging) videos and images of human colorectal polyps for clinical applications

The human wide-field database consists of **RGB/NBI clinical colonoscopy videos**, composed of RGB and NBI images obtained from colonoscopy procedures in human patients. It includes **76 different lesions from 48 patients.** For each lesion, the following **clinical metadata** are provided: number of polyps of interest, polyp size (in mm), Paris Classification, NICE Classification, preliminary diagnosis, literal diagnosis, histological stratification. Clinical metadata are included in a plain text file, where each line corresponds to one frame.



RGB image of a colon polyp (a) and NBI image of the same polyp (b)

FEATURES

- Videos are of length equal to 70.05±59.28 s, which corresponds to 1965.49±1677.57 frames per lesion.
- Videos are provided either on .wmv or .mp4 formats and transformed into .png frames of sizes 854x480 or 1920x1080 px.
- The name of frames files follows the following structure: LesionID_videoID_frameXXX.png.
- In all, there are more than 145,000 frames.
- 3,434 polyp frames have a binary mask for the polyp area. These masks have been manually created by expert gastroenterologists.

INTENDED USE

- The openly accessible dataset is at the scientific community's disposal for the training of clinicians, or for their use in algorithms for the detection/classification of colorectal cancer.

ADVANTAGES

- Precise manual segmentation of more than 3,400 polyp frames in white light and NBI.
- This dataset includes paired images from different modalities which can help to learn how information is related between those two medical imaging domains.

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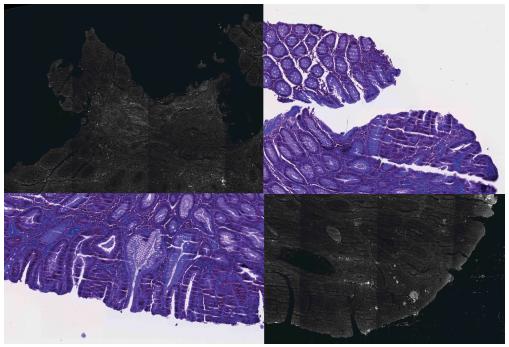
HUMAN MODEL EX-VIVO MPM DATABASE

Towards label-free digital pathology

Multiphoton Microscopy (MPM) images were acquired using a custom-made multimodal multiphoton microscope from human colon samples. Paraffin-embedded blank tissue slices obtained from ex-vivo human colon were provided by the Basque Biobank and processed following standard operation procedures with appropriate approval of the Ethical and Scientific Committees. These samples were imaged using the multiphoton microscope at a **resolution of 500 nm/px**, hence providing microscopic resolution over a macroscopic sample size. The generated database consists of **two-photon fluorescence (TPF)** and **second harmonic generation (SHG)** images from **21 benign**, **24 malignant** and **5 healthy** samples, together with the **Hematoxylin and Eosin (H&E) high resolution** images acquired from the same samples. The different multiphoton image modalities were fully co-registered against their corresponding H&E images.



Depiction of an MPM image and its corresponding co-registered H&E image

FEATURES

- Human colon MPM images fully co-registered with their corresponding H&E images.
- High resolution (down to 500 nm/px).
- Very large FOV (up to several tens of mm).

INTENDED USE

- Train and test MPM image analysis algorithms.
- Generation of virtual staining algorithms.
- Maintain the database for potential future use.
- Openly accessible for the research community.

ADVANTAGES

- 1:1 correlation with H&E images.
- Useful for knowledge transfer from H&E to MPM.

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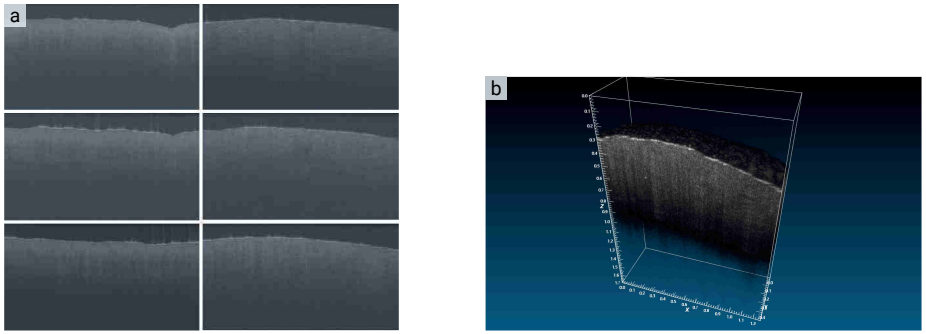
MURINE MODEL EX-VIVO OCT DATABASE

Optical biopsy: microscopical observation of structures

This database consists of OCT **3D volumes (C-scans) and 2D images (B-scans)** of murine (*Rattus norvegicus*) samples from healthy tissue, hyperplastic polyps, neoplastic polyps and unknown (polyp adjacent) tissue. **Healthy** tissue has been recorded from control animals for ground-truth comparison. **Hyperplastic** polyps have been obtained from the "Induced colorectal hyperplastic murine model". **Neoplastic** (adenomatous and adenocarcinomatous) polyps have been obtained from clinically validated Pirc F344/NTac-Apcam1137 model. Additionally, for each polyp identified in the specimen, **unknown** (lesion adjacent, presumably healthy) tissue has also been recorded with the OCT device.
The database has been **acquired with a commercial OCT system** with 930 nm centre wavelength that provides 1.2 KHz A-scan rate, 7 µm axial resolution in air, 4 µm lateral resolution, 6 mm x 6 mm FOV, 1.7 mm imaging depth in air and 107 dB sensitivity.



OCT 2D images (B-scans) from healthy and tumoral samples (a) and OCT 3D image (C-scan) from tumoral sample (b)

FEATURES

- 3D volumes (C-scans) data.
- 2D (B-scan) images.
- Extensive database: healthy tissue (18 samples; 66 C-scans; 17,478 B-scans), hyperplastic polyps (47 samples; 153 C-scans; 42,450 B-scans), neoplastic polyps (232 samples; 564 C-scans; 158,557 B-scans) and unknown tissue (98 samples; 157 C-scans; 42,070 B-scans).

INTENDED USE

- Classification/segmentation machine learning algorithm training, testing and validation.
- Study correlation between OCT features and histopathological structures.
- Develop new non-invasive in-situ methods of diagnosis of colorectal cancer.
- Openly accessible for the research community.

ADVANTAGES

- Novel database.
- Fasten development of Computer Aided Diagnosis (CAD) solutions.

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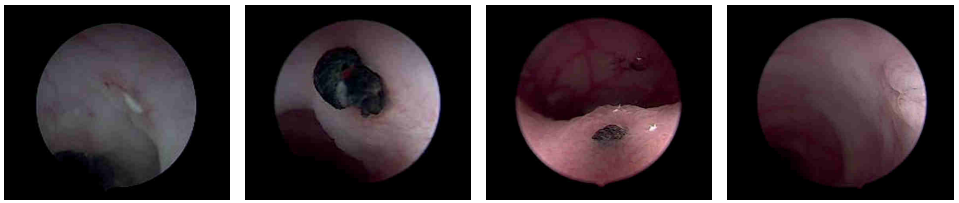
INDUCED COLORECTAL HYPERPLASTIC MURINE MODEL

New method for the creation of hyperplasia model in colon for endoscopic applications

A new surgical model of rat colonic hyperplasia has been induced after laparotomy through endoscopic procedures. According to our knowledge, this is the first induced colonic hyperplasia model in rats. In the PICCOLO project tissue samples from this model have been used in the creation of the murine model ex-vivo OCT database and in the later extraction of OCT optical biomarkers with the OCT Classifier.



Pictures of hyperplastic growth in descending colon of rat

FEATURES

- The reproducibility of the chosen model has been obtained and the optimal time determined, after induction of the model.

INTENDED USE

- Validation and development of endoscopic technology.
- Use in molecular studies.
- Improvement of optical biomarkers of colorectal cancer.
- Useful to discriminate between endoscopic findings.

ADVANTAGES

- A surgical model of colonic hyperplasia that solves limitations of other traditional models that only produce hypertrophy has been developed.
- This allows its reproducibility for subsequent studies.
- Not necessary to use external agents placed in the submucosa of the colon wall.

CONTACT

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MicroRNAs AS COLORECTAL CANCER MOLECULAR BIOMARKERS

Novel molecular biomarkers for improving the early diagnosis of colorectal cancer

Molecular biomarkers of colorectal cancer have been obtained by microRNA tests, specifically the **Next Generation Sequencing** tests, followed by tests using **qPCR** (quantitative polymerase chain reaction) through several blood extractions during **different stages** of the colorectal disease in a murine model.

Extraction of blood (a) and plasma (b) for obtaining microRNA markers

FEATURES

- The combination of a panel of plasma biomarkers that occur before the transformation of adenomatous lesions into adenocarcinomas in colorectal cancer and detect the presence of microRNAs can predict early the conversion of an adenomatous lesion of the colon into a neoplastic lesion.

INTENDED USE

- Compare the presence and concentration of certain microRNAs with other diagnostic systems such as endoscopy, histopathology and imaging biomarkers, being able to establish a correlation between them to develop an early diagnosis through the use of microRNAs.

ADVANTAGES

- It is a very novel tool to validate (or relate) the image biomarkers.
- It allows obtaining information during all the disease development, with several follow ups since first stage until the last stage of the disease.

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WIDE-FIELD POLYP SEGMENTATION ALGORITHM

Improving the detection of polyps by highlighting their contour

An automatic polyp segmentation algorithm has been implemented using a **Fully Convolutional Network** (FCN) and **transfer learning** between two publicly available medical image databases: CVC-EndoSceneStill and CVC-VideoClinicDB.
The main novelty of this work lies in the combination of an FCN (**U-Net** based) and transfer knowledge between two medical image databases, using a previously established benchmark, showing that combining a larger database with weaker ground truth to train the FCN from scratch with a smaller database with better ground truth for fine-tuning outperforms training the FCN from scratch with the latter.

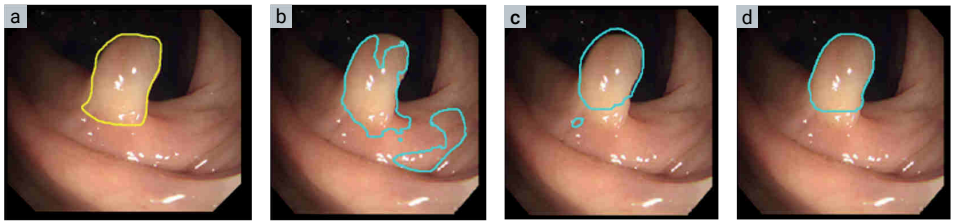

Image with the contour of the predicted polyp superimposed:
a. Ground truth
b. FCN trained from scratch with CVC-EndoSceneStill
c. FCN trained from scratch with CVC-VideoClinicDB
d. FCN fine-tuned with CVC-EndoSceneStill

FEATURES

- Network architecture is based on U-Net.
- IoU is improved from 61.17% to 69.01%.
- DICE is improved from 69.10% to 77.70%.
- Improved balance between recall and precision, thus resulting on a better segmentation of the polyp.
- Prediction takes 36 ms/image in average.

INTENDED USE

- Automatic segmentation of polyps in colonoscopic images.

ADVANTAGES

- FCNs have great success for polyp semantic segmentation.
- It is the first one that applies fine-tuning to a network previously trained on images of the same domain instead of natural images.
- It allows for its use in real-time applications.

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OPTICAL BIOPSY: OCT CLASSIFIER

Software based analysis of Optical Coherence Tomography (OCT) images for colon lesion malignancy detection

A **deep learning model** for automatic classification of images acquired with an **OCT** imaging system has been developed with the aim to support online optical biopsy. The images are classified in **benign** (healthy & hyperplastic) **vs malignant** (adenomatous & adenocarcinoma) lesions. This technique consists in a **high-level classification based on lesion architecture and structural information**. The algorithm has been trained, validated and tested with a preliminary version of the murine model ex-vivo OCT database. The evaluation over individual B-scan images reports 96.95±1.41% sensitivity and 80.94±15.24% specificity, and over C-scan volumes 98.21±1.97% sensitivity and 78.65±20.5% specificity. This algorithm is specific for OCT images, since dedicated pre-processing techniques to maximize classification success have been applied.

Model[1]		BAC[2]	Sensitivity	Specificity	PPV[2]	NPV[2]
B-scan (TTA)	mean	0.8895	0.9695	0.8094	0.9305	0.9093
	std dev	0.0792	0.0141	0.1524	0.0526	0.04
C-scan (TTA)	mean	0.8843	0.9821	0.7865	0.9212	0.9472
	std dev	0.1068	0.0197	0.205	0.0693	0.0614

OCT Classifier performance metrics

(1) Statistics (mean and standard deviation) obtained from 6 experiments
(2) BAC = Balanced Accuracy; PPV = Positive Predictive Value; NPV = Negative Predictive Value

FEATURES

- Classification of OCT images as benign (healthy & hyperplastic) vs malignant (adenomatous & adenocarcinoma).
- High-level classification based on lesion architecture and structural information.
- Complementary to MPM Classifier as initial assessment of malignancy.
- Self-reliability mechanism over its own predictions.

INTENDED USE

- Automatic diagnostics of colon polyp lesions with different imaging modalities.
- Support the development of real-time optical biopsy for novel imaging methods.
- Development of Computer Aided Diagnosis (CAD) applications based on deep learning.

ADVANTAGES

- Flexible and scalable: it can be trained with multiple classes.
- Real-time capable.
- It can be combined with algorithms of other imaging modalities.

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OPTICAL BIOPSY: MPM CLASSIFIER

Software based analysis of Multiphoton Microscopy (MPM) images for colon neoplastic lesion diagnosis

A **deep learning model** for automatic classification of images acquired with a **multiphoton microscope** has been developed with the aim to support online optical biopsy. The images are classified in **benign** (including healthy, hyperplastic and adenomatous samples) **vs malignant** (adenocarcinomas) lesions. This technique consists in a **low-level classification based on structural and functional information** of the tissue. The baseline algorithm, which has been trained, validated and tested against a preliminary version of the human model ex-vivo MPM database, gets 80.11±12.52% sensitivity and 85.76±9.54% specificity when classifying images that correspond to tissue tiles of 511x511 μm^2. The results improve with the proposed spatially coherent predictions (SCP) scheme that considers several adjacent tiles for diagnosis prediction achieving 82.28±15.75% sensitivity and 91.14±8.14% specificity.

Model[1]		BAC[2]	Sensitivity	Specificity	PPV[2]	NPV[2]
Baseline	mean	0.8293	0.8011	0.8576	0.8604	0.8084
	std dev	0.0895	0.1252	0.0954	0.0887	0.1080
SCP	mean	0.8671	0.8228	0.9114	0.9105	0.8418
	std dev	0.0966	0.1575	0.0814	0.0826	0.1314

MPM Classifier performance metrics

(1) Statistics (mean and standard deviation) obtained from 6 experiments
(2) BAC = Balanced Accuracy; PPV = Positive Predictive Value; NPV = Negative Predictive Value

FEATURES

- Classification of MPM images as benign (healthy, hyperplastic or adenomatous) vs malignant (adenocarcinoma) lesions.
- Low-level classification based on structural and functional information.
- Complementary to OCT Classifier as final assessment of neoplastic malignancy (adenomatous or adenocarcinoma).
- Self-reliability mechanism over its own predictions.

INTENDED USE

- Automatic diagnostics of colon polyp lesions with different imaging modalities.
- Support the development of real-time optical biopsy for novel imaging methods.
- Development of Computer Aided Diagnosis (CAD) applications based on deep learning.

ADVANTAGES

- Flexible and scalable: it can be trained with multiple image modalities.
- Real-time capable.
- It can be combined with algorithms of other imaging modalities.

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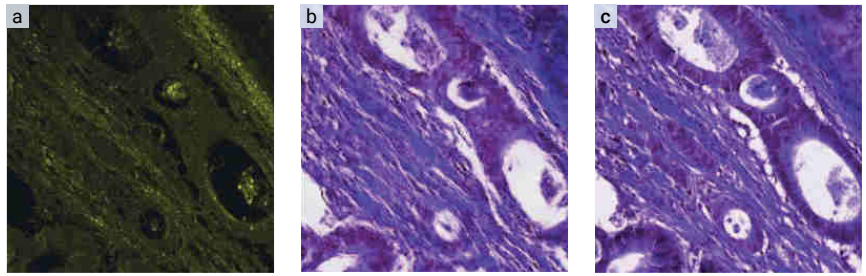
OPTICAL BIOPSY: VIRTUAL H&E STAINER

Software based staining method of autofluorescence images

A method capable of **staining** two-photon fluorescence (TPF) and second harmonic generation (SHG) images, acquired with a multimodal multiphoton microscope, **without** the need for **Hematoxilyn and Eosin (H&E) chemical stains** has been developed and patent application filed by TECNALIA. H&E images are the gold standard used by pathologists to diagnose biopsies. This method opens new horizons for optical biopsy algorithms allowing H&E images to be obtained online in real-time without the need for being chemically stained.



TPF/SHG image (a), virtually stained image (b) and chemically stained H&E image (c)

FEATURES

- Virtually stains a TPF-SHG image and generates an H&E image.
- Reduces the perception-distortion trade-off problem avoiding the staining network to invent false data.
- Multiple optical modalities can employ this technique to generate H&E images.
- The generated H&E image is compatible with the H&E classification optical biopsy algorithm.

INTENDED USE

- Convert online acquired images into clinicians' gold standard H&E images.
- Clinicians can diagnose directly over the virtually stained H&E image.

ADVANTAGES

- Flexible and scalable: it can be trained with multiple image modalities.
- Real-time capable.
- Gold standard H&E image is obtained in real-time with no need for staining.
- Clinicians know to interpret H&E images.

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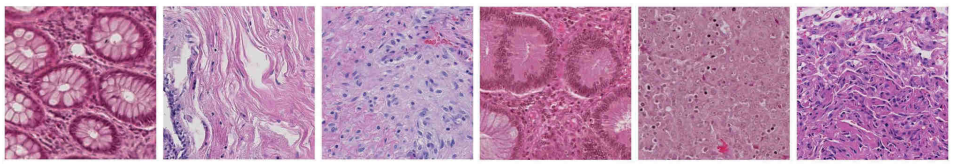
OPTICAL BIOPSY: H&E CLASSIFIER

Software based model for histology images malignancy detection

A model for **classifying Hematoxilyn and Eosin (H&E) images as tumoral or healthy** is proposed. This algorithm incorporates an internal method for estimating the reliability of its own prediction. In this way, we obtain accuracies of 100% when requiring the algorithm a high confidence on its own prediction. Furthermore, this algorithm is not only **compatible with** chemically stained H&E images, but also with the **images that have been synthetically created** from other imaging modalities by the virtual H&E stainer. This makes this method not only appropriate for histology image classification, but to support online optical biopsy.

Method	BAC	Sen	Spe	NPV	PPV
Baseline Densenet	0.88	0.87	0.90	0.87	0.90
Cycle-Network	0.91	1.00	0.84	1.00	0.86
Siamese Cycle-Network	0.95	1.00	0.90	1.00	0.91

H&E Classifier performance metrics



Examples of different tissues already stained with Hematoxylin and Eosin

FEATURES

- Classification of H&E images as tumoral/non-tumoral.
- Self-reliability mechanism over its own predictions.
- Compatible with virtually stained H&E images.

INTENDED USE

- Automatic diagnosis of H&E images.
- Support real-time optical biopsy for novel imaging methods.

ADVANTAGES

- Flexible and scalable: it can be trained with multiple classes.
- Real-time capable.

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OPTICAL BIOPSY: CONSTELLATION LOSS & FEW-SHOT LEARNING

Improving the efficiency of deep metric learning loss functions for optimal embedding

Constellation loss is a function that **optimises a deep learning classifier with very few training images.** It goes one step further than other loss functions by **simultaneously learning distances among all class combinations**. It can **attract same class image embeddings whilst pulling apart the rest of the classes**, all at the same time. This way, an optimal embedding or descriptor of the image is generated.

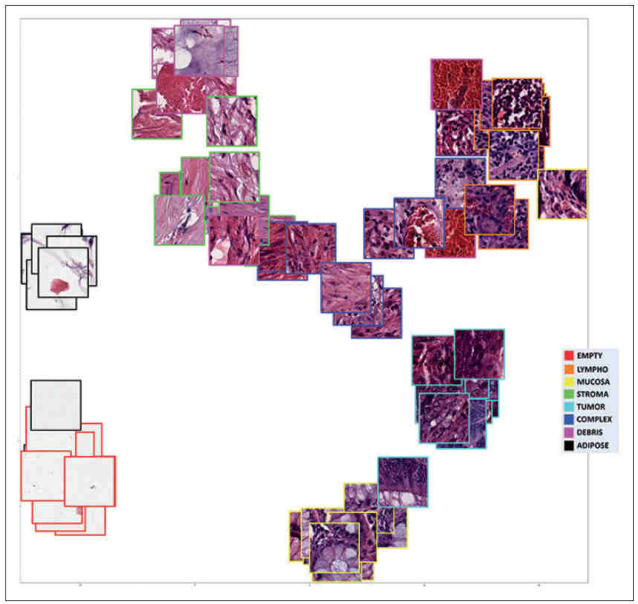

Image based t-Distributed Stochastic Neighbour Embedding visualization of test image embeddings extracted with a model trained with constellation loss

FEATURES

- Train a model with few data, also known as few-shot learning.
- More stable training.
- Useful for new image modalities, such as OCT and MPT.
- Flexible number of classes: when an embedding lies very far from all the previously learned classes, it can be considered as a new class.

INTENDED USE

- Train OCT and MPT deep classification models.
- Extend this to other medical imaging domains.

ADVANTAGES

- No need to gather much data.
- No need to label the data.
- Due to previous advantages, a more time efficient and cheap process for training deep learning models.
- It is a parameterisable function that can be adapted to many distinct problems.

CONTACT

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