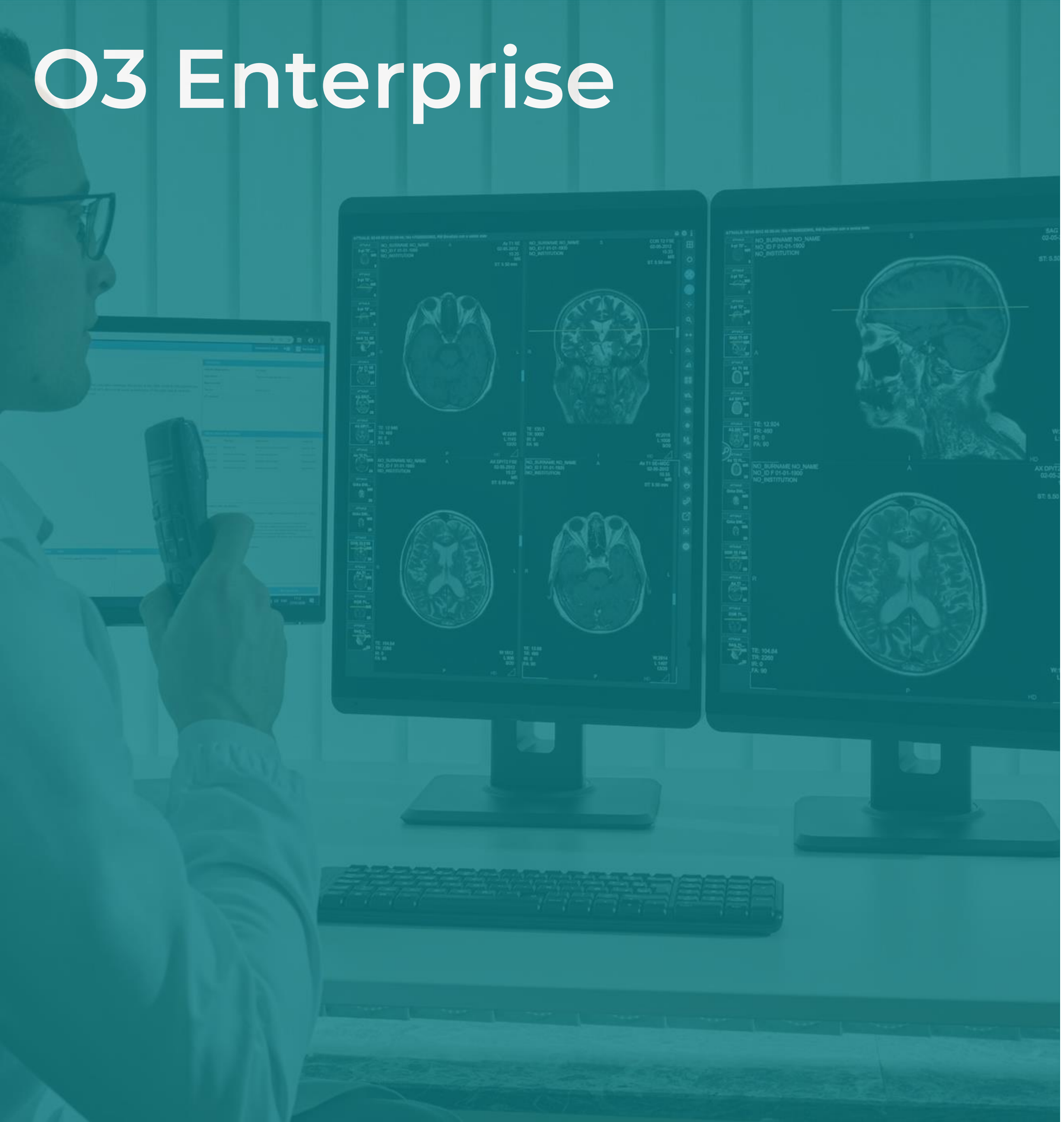
AI IN MEDICAL IMAGING

XI SPRING SCHOOL

7th June 2023

Dr. Teresa Pace

O3 Enterprise



ZEEROmed

O3 enterprise
ZUCCHETTI

OUR STORY

- **2008** — Spin-off University of Trieste
- **2011** — ISO 13485 certification
- **2015** — First global project (Latin America)
- **2016** — Launch of the brand ZEEROmed
- **2017** — First project on Google Cloud
- **2018** — Google Cloud Partner; First Foreign National Project (Messico)
- **2019** — Acquisition of FUTURAD
- **2020** — FDA
- **2022** — Entry into ZUCCHETTI group

WHERE WE ARE

More than
165 installations
supporting the work of
70 clients
around the world

OUR SOLUTIONS

Medical **imaging** suite developed using the latest medical **software paradigms** to provide a **smooth experience** for our users.

ZEEROmed imaging
VIEW .PACS

A STATE OF ART IMAGING DIAGNOSTIC SOLUTION

ZEEROmed screening
.MIS .VIEW .PACS

A NEW ERA FOR MAMMOGRAPHY SCREENING

ZEEROmed

ZEEROmed imaging

A STATE-OF-ART IMAGING DIAGNOSTIC SOLUTION

The perfect scalable solution for any type of healthcare facility. The web-based platform uses the latest technologies to guarantee usability, security and functionality, allowing the creation of a connected network between different sites from the same healthcare establishment.

- MULTI MONITOR AND MULTI DEVICE
- MANY IMAGES, ONE PATIENT
- HUB-SPOKE SUPPORT
- SMART IMPLEMENTATION
- UNIVERSAL (MULTISPECIALTY)
- REMOTE REPORT/TELERADIOLOGY

O3 enterprise
ZUCCHETTI

ZEEROmed screening

A NEW ERA FOR MAMMOGRAPHY SCREENING

The perfect suite for distributed management of mammography screening activity: it covers all stages of the process, from acquisition to reporting and archiving, allowing the implementation of a totally paperless workflow. The web-based platform uses the latest technologies to guarantee usability, security and functionality.

- MULTI MONITOR AND MULTI DEVICE
- FIRST AND SECOND LEVEL
- UNIVERSAL (MULTISPECIALTY)
- MANY IMAGES, ONE PATIENT
- SMART IMPLEMENTATION
- ADVANCED HANGING PROTOCOLS

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ZEEROmed

UNIVERSAL VIEWER

FDA CLEARED 510(K)

CE

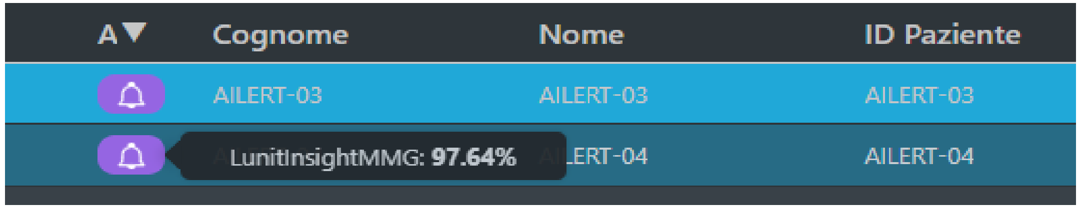
ANVISA N°81460810002

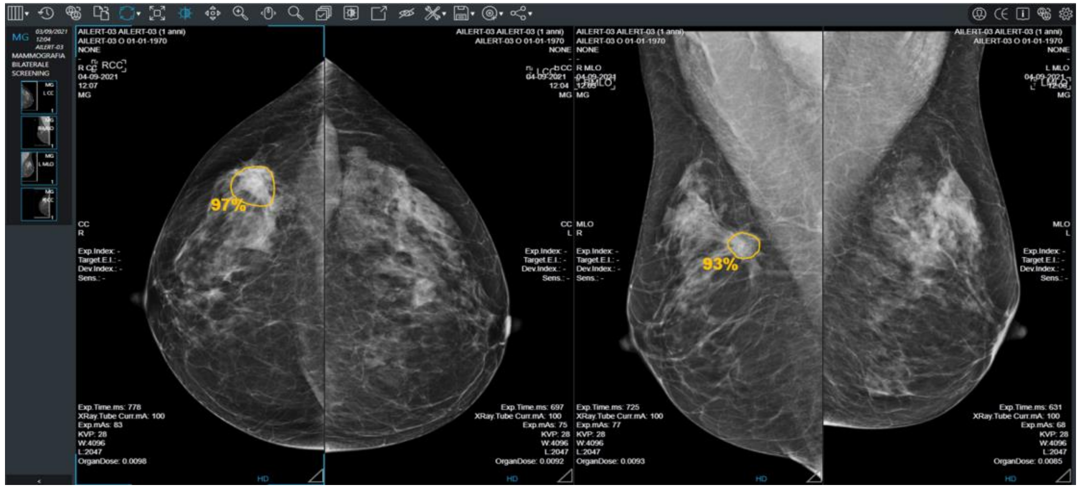
Maximum Performance and Diagnostic Reliability

Universal Diagnostic Viewer with **high-performance streaming technology** and **Artificial Intelligence Hub** that allows interactive reading of **very large exams** and **multi-specialty exam comparison** in a seamless and quickly way, **anytime, anywhere**

- MULTI MONITOR AND MULTI DEVICE
- USER-FRIENDLY WEB-BASED INTERFACE
- SMART IMPLEMENTATION
- REMOTE REPORT/TELERADIOLOGY
- REAL-TIME REMOTE COLLABORATION
- UNIVERSAL (MULTISPECIALTY)
- AI ENABLER: INTEGRATION WITH DIFFERENT & SPECIALIZED ARTIFICIAL INTELLIGENCE ALGORITHMS

UNIVERSAL VIEWER





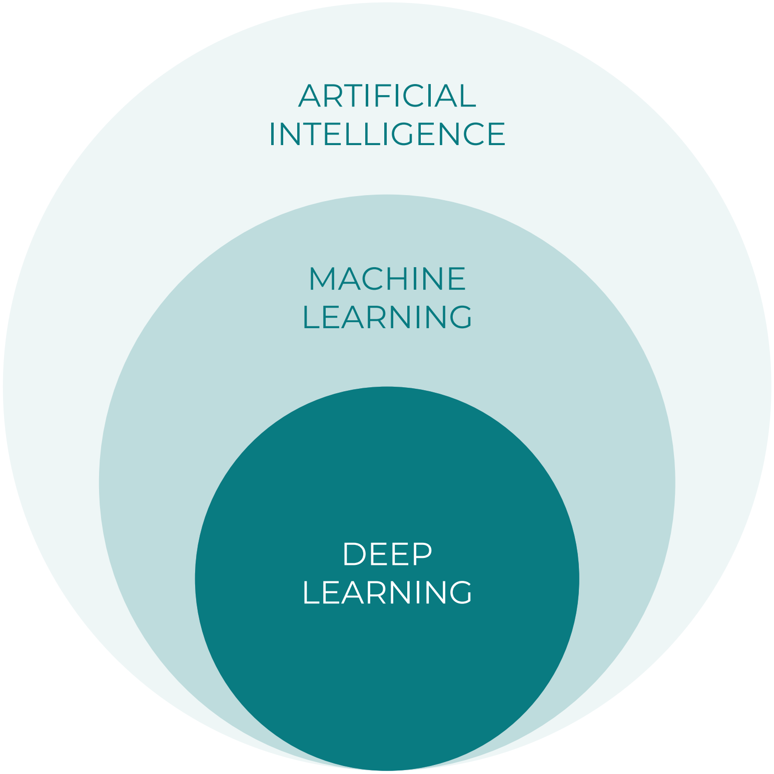
MultiSpecialty and Automatic AI post processing

ZEEROmed Universal Viewer includes features not only for the radiology department, but also for the cardiology department, senology, operating room, pathological anatomy, and ophthalmology

Integrated with several **artificial intelligence algorithms** and ready to easily integrate with many others, ZEEROmed Universal Viewer becomes a hub for multi specialty centers without major changes or additions

Convolutional Neural Networks

Convolutional Neural Networks
What is AI?



Artificial Intelligence

Effort to automate intellectual tasks normally performed by humans

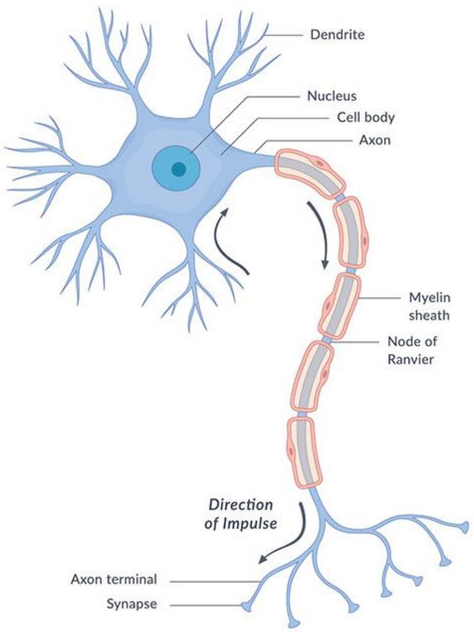
Machine Learning

Algorithms which use statistical methods to enable machines to improve at tasks with experience

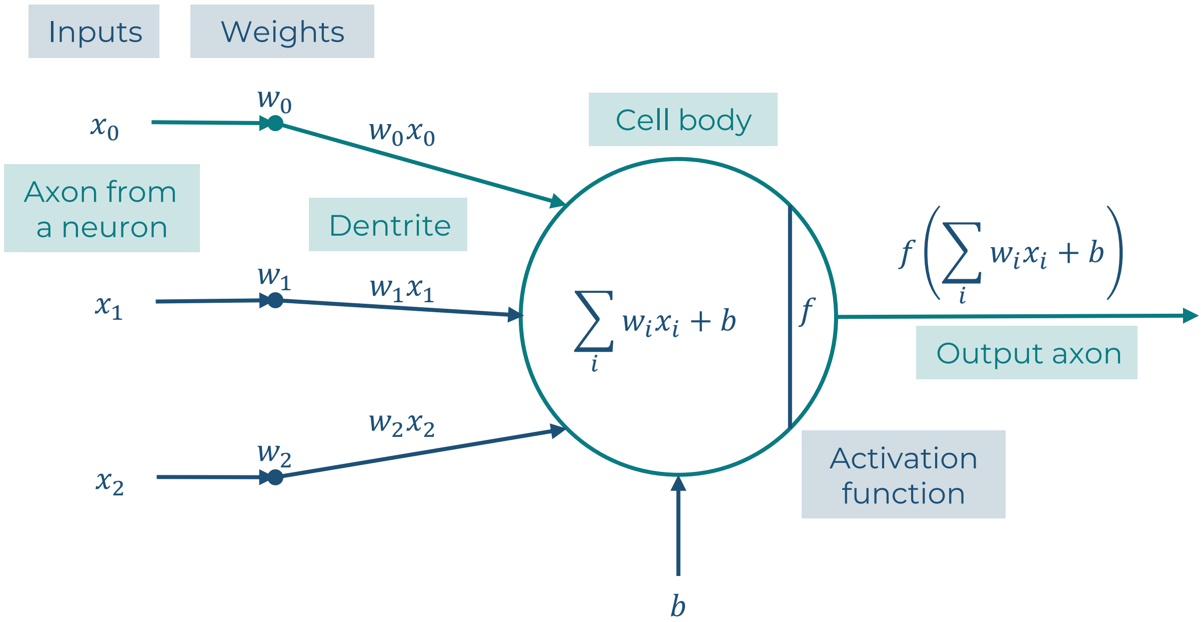
Deep Learning

Subset of machine learning in which algorithms with brain-like logical structure adapt and learn from vast amounts of data

Artificial Neurons



Biological Neuron



Artificial Neuron

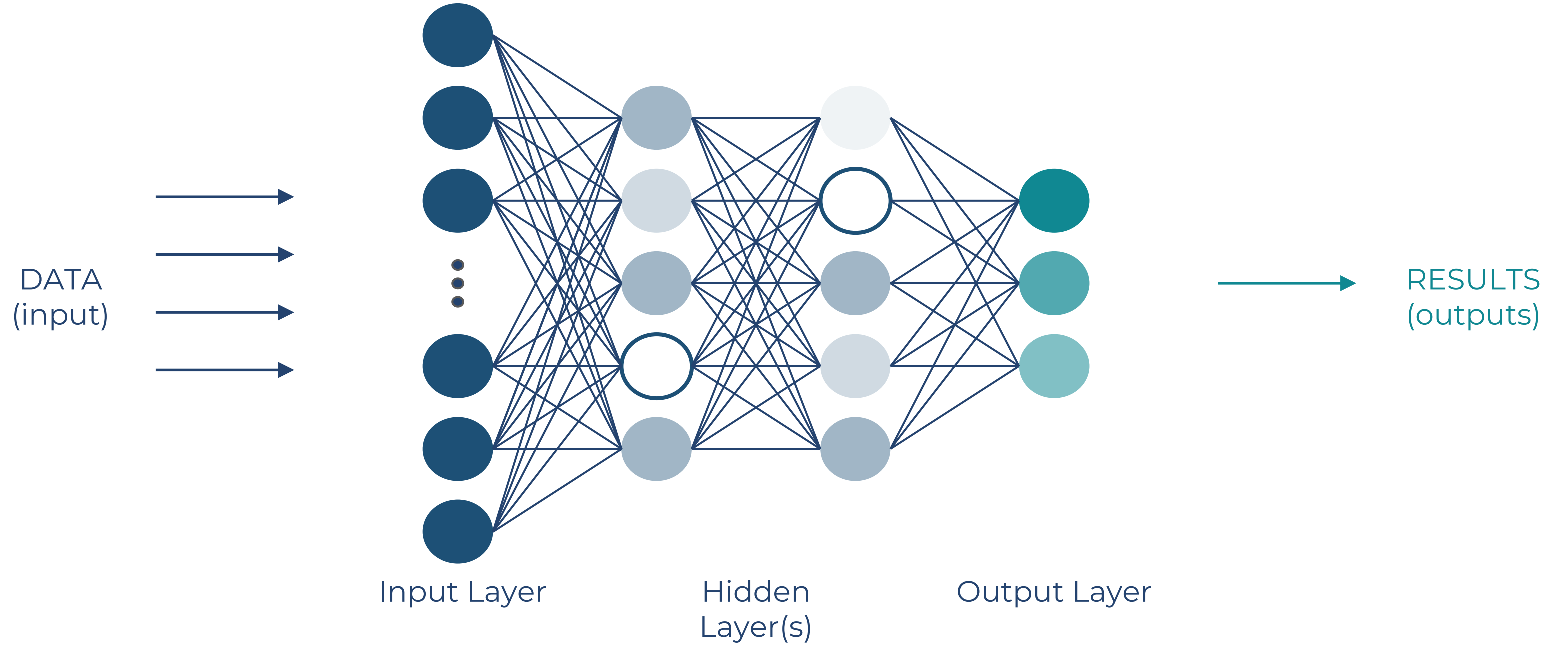
- In a biological neuron, the **dendrites** receive input signals, the **cell body** perform a summation function and, if the final sum is above a certain threshold, the neurons output an action potential sending a spike along their **axon**

- An artificial neuron receives one or more inputs and computes its output by a **non-linear function of the weighted sum of its inputs**

- Each input has a **weight** that adjusts during learning, increasing or decreasing the strength of a connection

Convolutional Neural Networks

Artificial Neural Networks (ANNs)



- In an ANN, artificial neurons are aggregated into layers: the signal goes from the **input layer** to the **output layer**, after traversing one or more **hidden layers**
- Different layers may perform different kind of transformation on their inputs

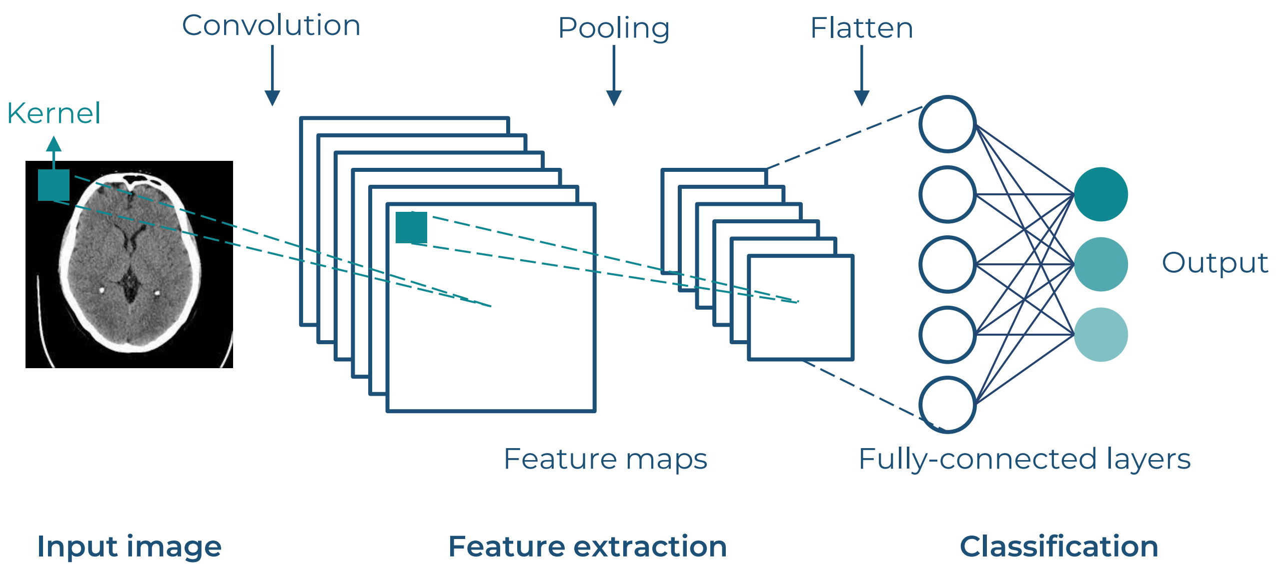
Convolutional Neural Networks (CNNs)

- **Convolutional Neural Networks (CNNs)** are artificial neural networks inspired by the organization of animal visual cortex which are specifically designed to learn representations of relevant features from images automatically and adaptively
- In 2012 the Convolutional Neural Network (CNN) proposed by Krizhevsky et al. [1] won the 2012 ImageNet Large Scale Visual Recognition Challenge (ILSVRC)
- CNNs became dominant in computer vision tasks forming the basis for some of the most influential innovations in this field
- In medical imaging, CNNs obtained or exceeded expert-level performances in various applications
- **CNNs are considered the state of the art in image analysis**

[1] Krizhevsky, A., Sutskever, I., & Hinton, G .E. (2012). ImageNet Classification with Deep Convolutional Neural Networks. In F. Pereira, C. J. C. Burges, L. Bottou & K. Q. Weinberger (ed.), *Advances in Neural Information Processing Systems 25* (pp. 1097--1105). Curran Associates, Inc..

Convolutional Neural Networks

Convolutional Neural Networks (CNNs)

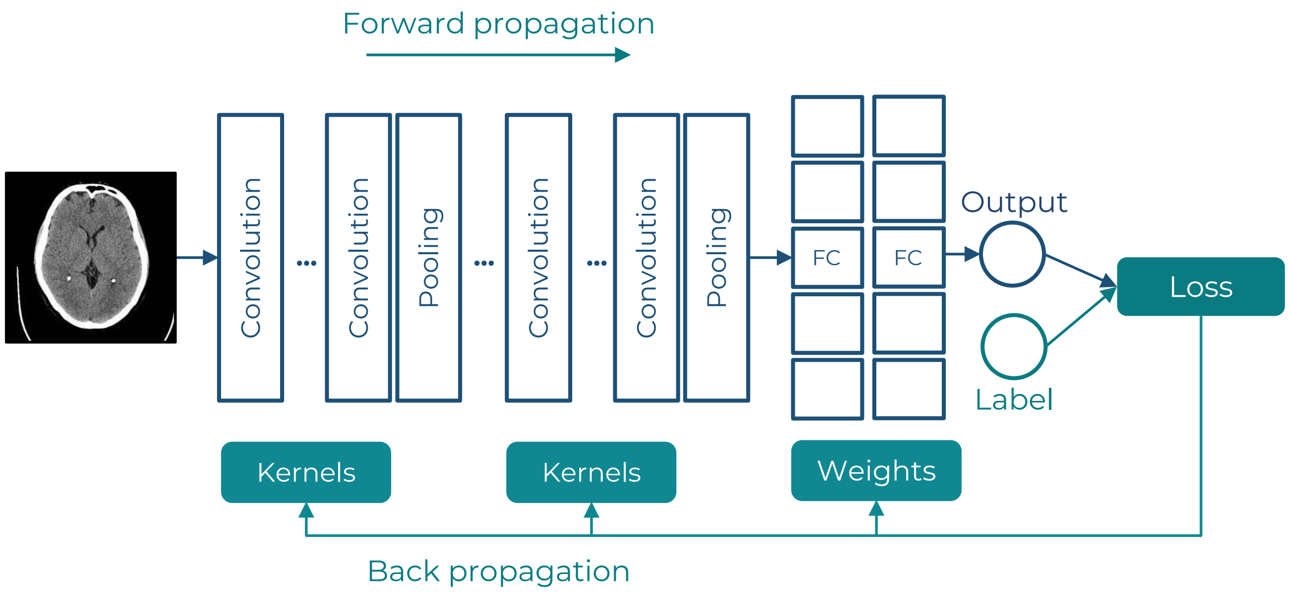


- The **convolution layer** computes the convolutional operation of the input images using kernel filters to extract fundamental features. The output of a convolutional layer is then passed through a non-linear activation function, generating a **feature map**

- The **pooling layer** reduces the number of parameters and computation by down-sampling the representation

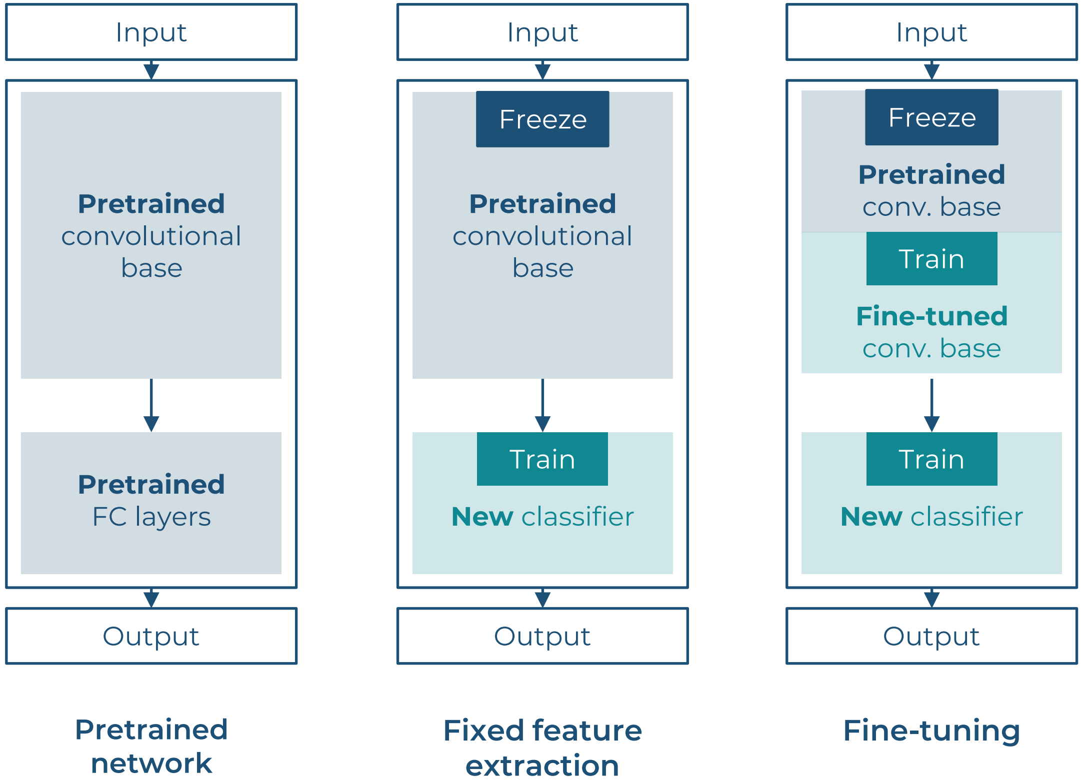
- Feature maps of the final convolutional or pooling layer are flattened and connected to one or more **fully-connected layers.** The final fully connected layer typically has the same number of output nodes as the number of classes

Convolutional Neural Networks
Training a Network



- Training a network is a process of finding kernels in convolutional layers and weights in fully connected layers which **minimize differences between output predictions and given true labels on a training set**
- A model's performance under certain kernels and weights is calculated with a **loss function** through forward-propagation on a training dataset
- Learning parameters are updated according to the loss value through backpropagation with an **optimization algorithm**

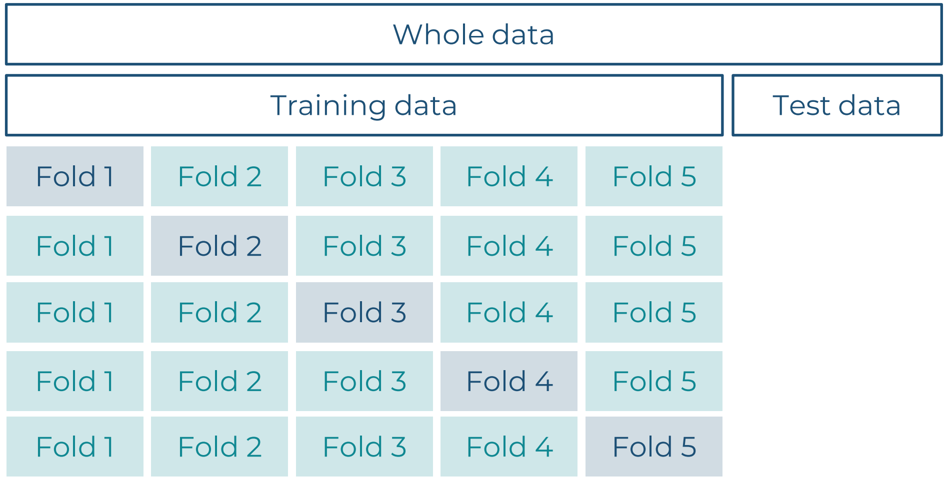
Convolutional Neural Networks
Transfer Learning



- **Transfer Learning** involves the application of a model pre-trained on an extremely large dataset to address the lack of training data
- **Fixed feature extraction**: the fully connected layers from the pre-trained model are replaced with a new set of fully connected layers and retrained while its convolutional base is maintained
- **Fine-tuning**: the fully connected layers from the pre-trained model are replaced with a new set of fully connected layers but during the training process also all the layers (or the last) in the convolutional base will be trained on the new dataset

Convolutional Neural Networks
Dataset Splitting

- Available data are typically split into a **training set**, used to train the network, a **validation set**, used to evaluate the model during the training process, and a **test set**, used only once in order to evaluate the performance of the model



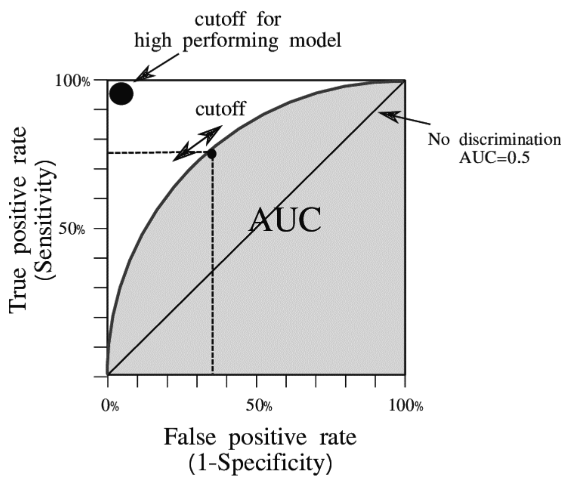
- In **k-fold cross-validation** the dataset is split in a training and a test sets, and the training set is partitioned into k subsets. The model is trained using k-1 subsets as training data and validated on the remaining one. The process is iterated k times by rotating the training and validation subsets

Cross-validation (CV) is the approach commonly used to overcome to the reduction of training samples that arises when the available data are split into three sets

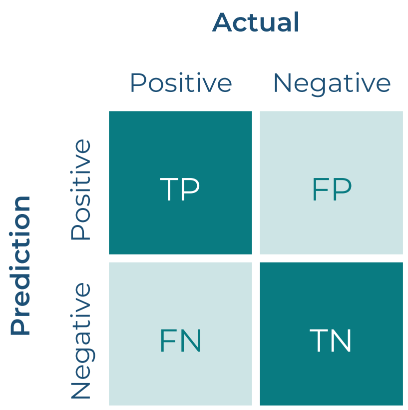
Convolutional Neural Networks
CNN Architectures

Model	Main finding	Depth	Dataset	Error rate	Input size	Year
AlexNet	Utilizes Dropout and ReLU	8	ImageNet	16.4	227×227×3	2012
VGG	Increased depth, small filter size	16, 19	ImageNet	7.3	224×224×3	2014
GoogLeNet	Increased depth, block concept, different filter size, concatenation concept	22	ImageNet	6.7	224×224×3	2015
Inception-v3	Utilizes small filter size, better feature representation	48	ImageNet	3.5	229×229×3	2015
Inception-v4	Divided transform and integration concepts	70	ImageNet	3.08	229×229×3	2016
ResNet	Robust against overfitting due to symmetry mapping-based skip links	152	ImageNet	3.57	224×224×3	2016
Inception-ResNetv2	Introduced the concept of residual links	164	ImageNet	3.52	229×229×3	2016

Convolutional Neural Networks
Model evaluation



AUC



Confusion Matrix

- The **receiver operating characteristic curve (ROC curve)** plots the **true positive rate (TPR)** against the **false positive rate (FPR)** at different classification thresholds
- The area under the ROC curve measures the two-dimensional area underneath the ROC curve. It ranges from 0.0 (**all predictions wrong**) to 1.0 (**all predictions correct**)
- A confusion matrix compares the actual target values (*ground truth*) with those predicted by the model, making easy to see whether the system is confusing the classes
- Each row represents the instances in a **predicted class** while each column represents the instances in an **actual class**

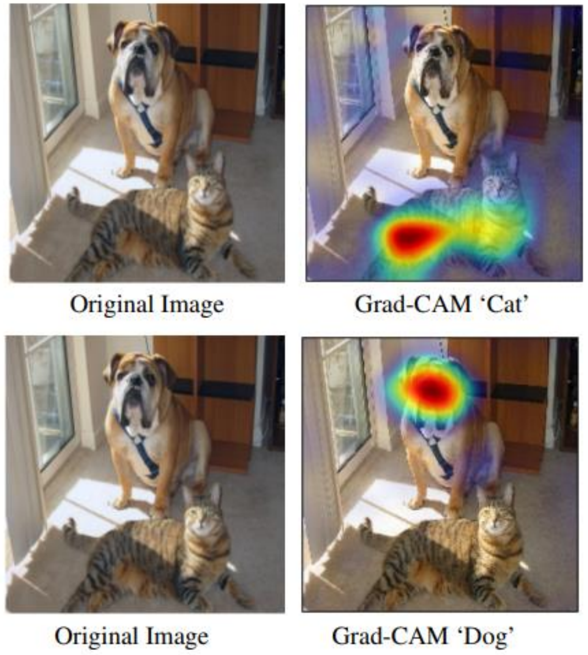
Convolutional Neural Networks
Explainable AI

- AI systems are often perceived by physicians as **black boxes**

- **Explainable artificial intelligence (XAI)** is a technique that has been introduced to explain how the AI model derived its prediction, helping the user to understand the prediction process

- **Gradient-weighted Class Activation Mapping (Grad-CAM)** aims to generate visual explanations for a large class of CNN-based network

- GradCAM output is a coarse **localization heatmap** that highlights the regions of the input image considered important for the final prediction



The MTM AI project

In collaboration with

- **Dr. Barbara Parolini**, Director of the Vitreoretinal Service at Eyecare Clinic in Brescia

The MTM AI project
Background and objectives

- **Myopic Traction Maculopathy (MTM)** is a complex disease characterized by a wide spectrum of clinical pictures that affects 9% to 34% of eyes with high myopia

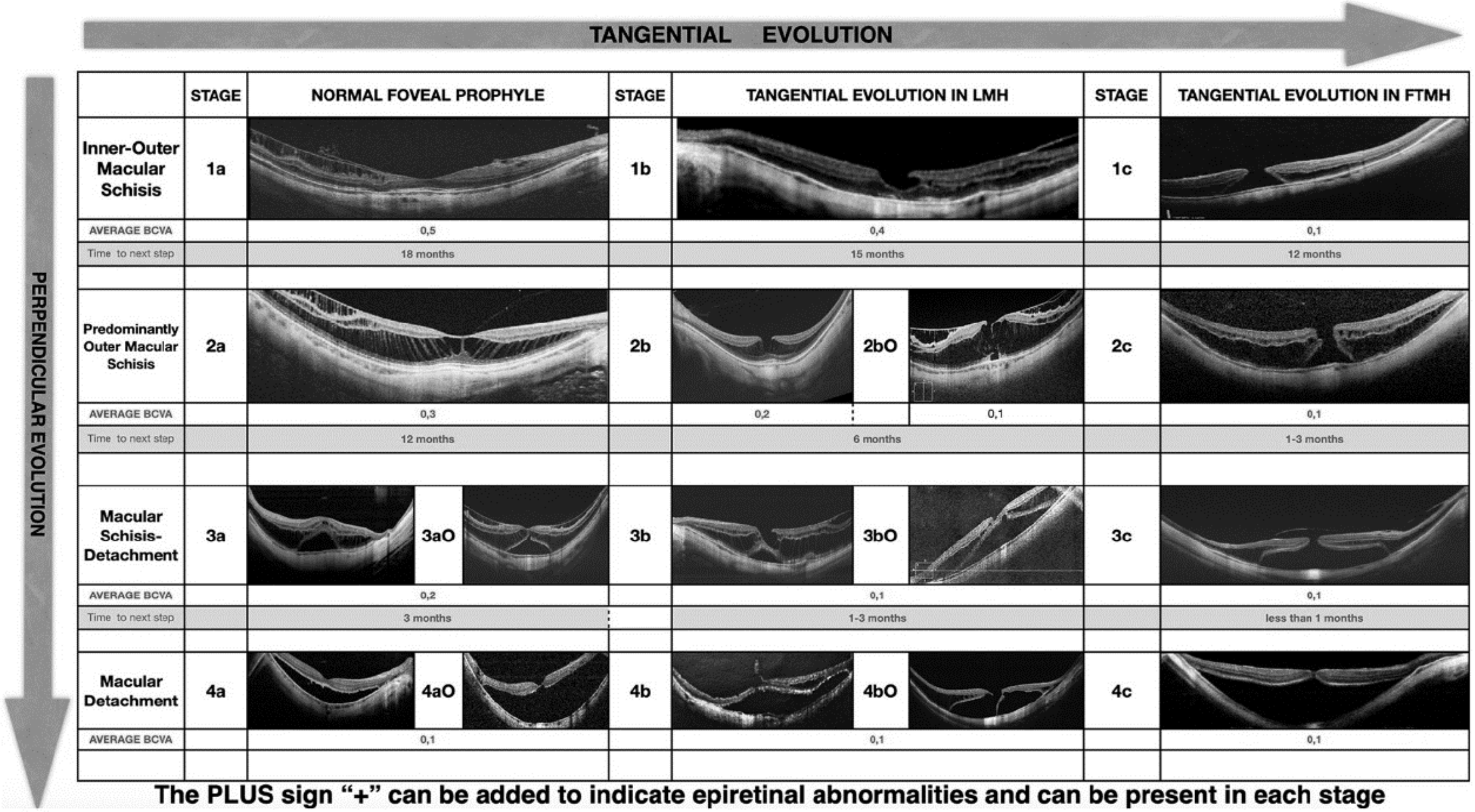
- MTM still represents a diagnostic challenge, and its pathogenesis, natural evolution and prognosis is not fully known

- In 2021, Parolini *et al.* [5] introduced the new OCT-based **MTM staging system (MSS)**

- MSS defines all the distinct types of MTM and their prognosis and proposes guidelines for treatment

[5] Parolini, B., Palmieri, M., Finzi, A., Besozzi, G., Lucente, A., Nava, U., ... & Frisina, R. (2021). The new myopic traction maculopathy staging system. *European journal of ophthalmology, 31*(3), 1299-1312.

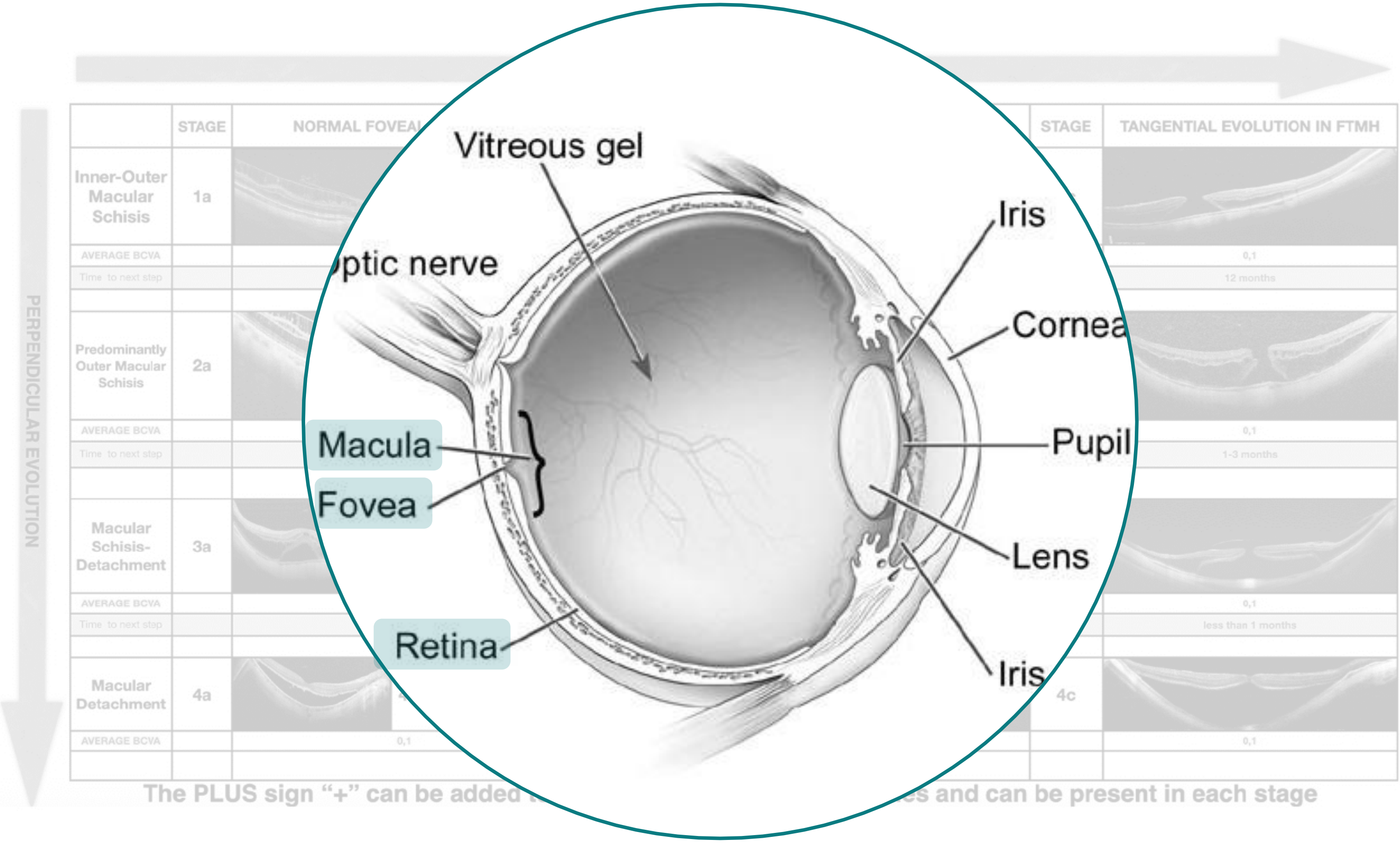
The MTM AI project
Background and objectives



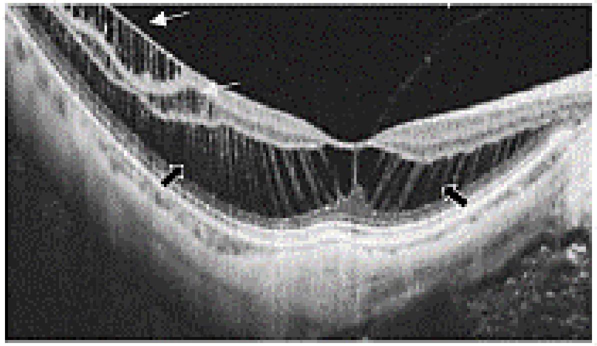
	STAGE	NORMAL FOVEAL PROPHYLE	STAGE	TANGENTIAL EVOLUTION IN LMH	STAGE	TANGENTIAL EVOLUTION IN FTMH
Inner-Outer Macular Schisis	1a		1b		1c	
AVERAGE BCVA		0,5		0,4		0,1
Time to next step		18 months		15 months		12 months
Predominantly Outer Macular Schisis	2a		2b	2bO	2c	
AVERAGE BCVA		0,3		0,2 / 0,1		0,1
Time to next step		12 months		6 months		1-3 months
Macular Schisis-Detachment	3a	3aO	3b	3bO	3c	
AVERAGE BCVA		0,2		0,1		0,1
Time to next step		3 months		1-3 months		less than 1 months
Macular Detachment	4a	4aO	4b	4bO	4c	
AVERAGE BCVA		0,1		0,1		0,1

The PLUS sign "+" can be added to indicate epiretinal abnormalities and can be present in each stage

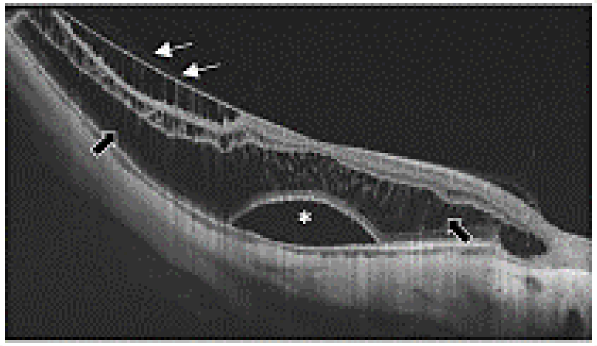
The MTM AI project
Background and objectives



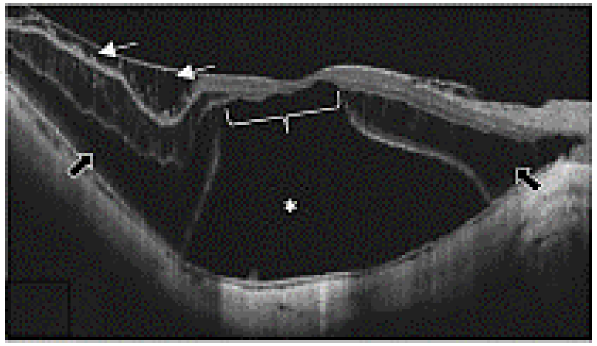
The MTM AI project
Background and objectives



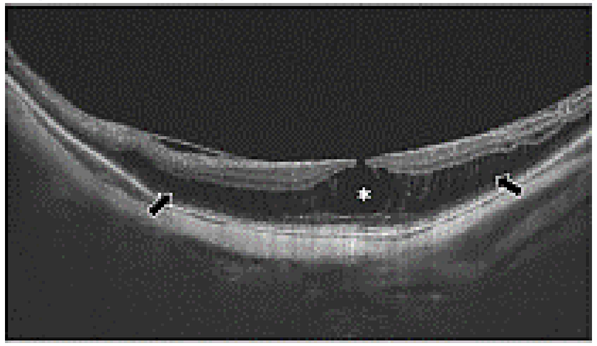
Macular schisis (MS). A separation of retinal layers, which remain connected by cells stretched in multiple columnar structures. It appears in both inner layers (white arrows, I-MS) and outer layers (black arrows, O-MS)



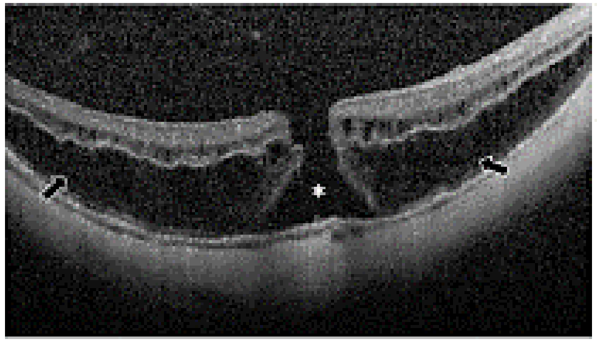
Macular detachment (MD) highlighted by an asterisk. White arrows show I-MS, black arrows show O-MS



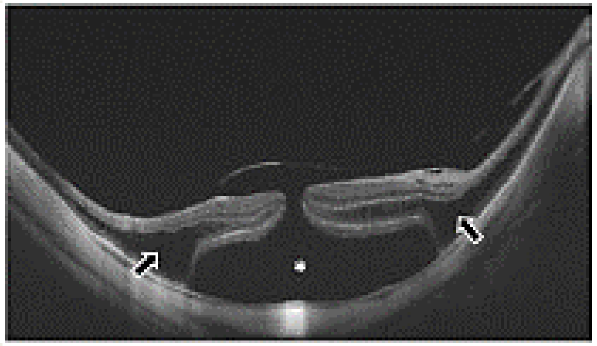
MD (asterisk) associated with I-MS (white arrows) and O-MS (black arrows). White line indicates **outer lamellar macular hole (O-LMH)**



Lamellar macular hole (LMH), highlighted by an asterisk, associated with O-MS (black arrows)



Full-thickness macular hole (FTMH), highlighted by an asterisk, associated with O-MS (black arrows)



FTMH associated with MD (asterisk) and O-MS (black arrows)

The MTM AI project
Objectives

MTM AI PROJECT (2022)

Development of an AI system that can automatically process OCT scans of an MTM eye to provide its stage according to the new MSS in order to support ophthalmologists in the assessment of eyes with MTM

- Not yet covered in literature
- Educational value
- Encourage the use of the MSS as a universally accepted classification system

The MTM AI project
Related works

Study	Task	Method	Dataset	Results (AUCs)
[6] Lee *et al.* (2017)	Classification: Age-related Macular Degeneration (AMD)	Modified VGG-16	Train: 80,839 Val: 20,163	92.78% (image level), 97.45% (patient level)
[7] Lu *et al.* (2018)	Classification: Cystoid Macular Edema, Serous Macular Detachment (MD), Epiretinal Membrane, Macular Hole (MH)	ResNet -101 4 binary classifiers	10-fold CV: 22,017 Test: 3,317	[97.7% (Serous MD), 99,9% (MH)]
[8] Kermany *et al.* (2018)	Classification: Drusen, Choroidal Neovascularization (CNV), Diabetic Macular Edema (DME)	Inception-v3	Train: 198,312 Val: 1,000	[99.87% (Drusen), 100.0% (CNV)]
[9] Li *et al.* (2020)	Classification: Retinoschisis, Macular Hole (MH), Retinal Detachment, Pathological Myopic Choroidal Neovascularization (PMCNV)	Inception-ResNet-v2 4 binary classifiers	Train: 4,338 Val: 1,167 Test: 412	[96.1% (Retinoschisis), 99.9% (MH)]
[10] Choi *et al.* (2021)	Classification: High myopia, Other retinal diseases	VGG-16 ResNet-50 Inception-v3	5-fold CV: 1,200 Test: 180	86.19% (VGG-16) 99.99% (ResNet-50) 97.28% (Inception-v3)
[11] Ye *et al.* (2021)	Classification: Macular Choroidal Thinning (MCT), Macular Bruch Membrane (BM) Defects, Subretinal Hyper-Reflective Material (SHRM), Myopic Traction Maculopathy, Dome-Shaped Macula (DSM)	ResNet-101 5 binary classifiers	Train: 1874 Val: 468 Test: 450	[92.7% (MTC), 97.4% (MTM)]

[6] Lee, C. S., Baughman, D. M., & Lee, A. Y. (2017). Deep Learning Is Effective for the Classification of OCT Images of Normal Versus Age-Related Macular Degeneration. Ophthalmology Retina, 1, 322-327.
[7] Lu, W., Tong, Y., Yu, Y., Xing, Y., Chen, C., & Shen, Y. (2018). Deep learning-based automated classification of multi-categorical abnormalities from optical coherence tomography images. *Translational vision science & technology, 7*(6), 41-41.
[8] Kermany, D. S., Goldbaum, M., Cai, W., Valentim, C. C., Liang, H., Baxter, S. L., ... & Zhang, K. (2018). Identifying medical diagnoses and treatable diseases by image-based deep learning. *Cell, 172*(5), 1122-1131.
[9] Li, Y., Feng, W., Zhao, X., Liu, B., Zhang, Y., Chi, W., ... & Lin, H. (2022). Development and validation of a deep learning system to screen vision-threatening conditions in high myopia using optical coherence tomography images. *British Journal of Ophthalmology, 106*(5), 633-639.
[10] Choi, K. J., Choi, J. E., Roh, H. C., Eun, J. S., Kim, J. M., Shin, Y. K., ... & Kim, S. J. (2021). Deep learning models for screening of high myopia using optical coherence tomography. *Scientific reports, 11*(1), 1-11.
[11] Ye, X., Wang, J., Chen, Y., Lv, Z., He, S., Mao, J., ... & Shen, L. (2021). Automatic screening and identifying myopic maculopathy on optical coherence tomography images using deep learning. *Translational vision science & technology, 10*(13), 10-10.

The MTM AI project
Dataset

- **1,668 OCT images from 139 eyes of 88 patients affected by MTM** seen between July 2020 and September 2022 - 466 images excluded for poor acquisition quality

- Scan protocol: **12 radial slices** of the posterior pole centered on the fovea with scan length from 6 mm to 23 mm acquired using Canon Xephilio OCT-A1 and Canon Xephilio OCT-S1 instruments

- Images stored in DICOM format and converted in JPEG Lossless format before feeding to the AI system

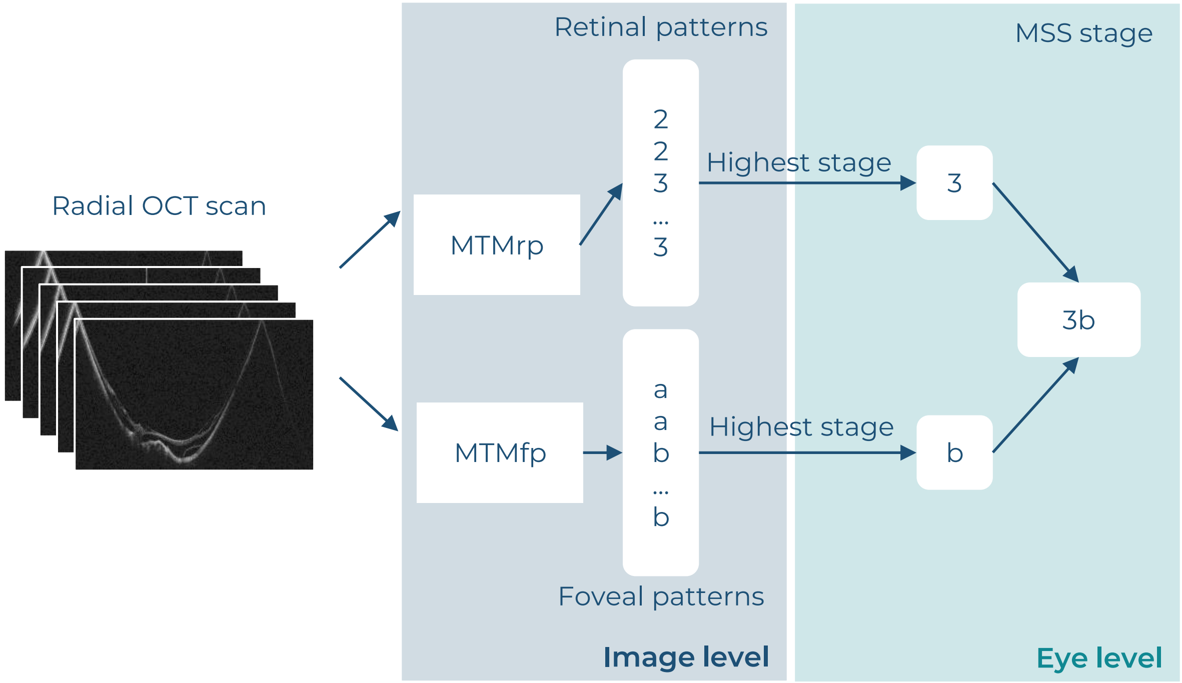
The MTM AI project
Dataset

› Images labeled by two clinical experts according to the **MSS table**

Retinal pattern	Foveal pattern (O-LMH/+)			Total (O-LMH/+)
	a	b	c	
1	211 (0/26)	115 (0/16)	12 (0/0)	338 (0/42)
2	408 (0/82)	139 (0/56)	8 (0/0)	555 (0/132)
3	211 (56/53)	34 (0/3)	9 (0/0)	254 (56/56)
4	12 (0/2)	8 (0/2)	35 (0/0)	55 (0/4)
Total	**842 (56/163)**	**296 (0/71)**	**64 (0/0)**	**1202 (56/234)**

Characteristics of the collected dataset

The MTM AI project
CNN models



Overview of the AI system for staging MTM

MTMrp: classification of retinal patterns (stages 1-4)

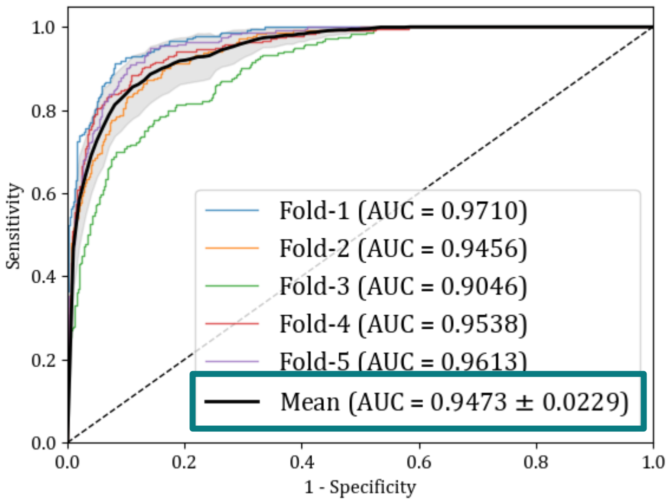
MTMfp: classification of foveal patterns (stages a-c)

- Images from a radial OCT scan are processed individually by each model (*image level classification*)
- The highest stage provided by each model is selected (*eye level classification*)
- The final MSS stage is given by the association of the eye level classification for retinal and foveal patterns

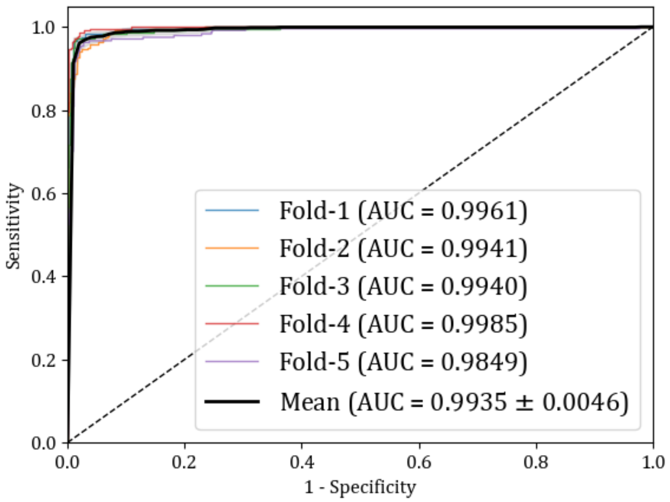
The MTM AI project
CNN models

- **Backbones**
  - VGG-16
  - ResNet-50
  - ResNet-101
  - Inception-v3
  - InceptionResNet-v2
- **Transfer learning**
  - ImageNet dataset (fine-tuning)
  - New classifier: 1 fully-connected layer with Softmax activation function
- **Pre-processing**
  - Resizing (512 x 512 pixels)
  - Zero-centering (VGG-16, ResNet-50, ResNet-101)
  - Normalization (Inception-v3, InceptionResNet-v2)
- **Data augmentation**
  - Horizontal flipping
  - Random rotation
- **Hyperparameters**
  - Epochs: 25
  - Batch size: 8
  - Optimizer: Adam
  - Learning rate: 10^{-4}
  - Loss function: categorical cross-entropy
- **Dataset splitting**
  - 5-fold cross-validation, test set
- **Framework**
  - TensorFlow (Python)
  - NVIDIA GeForce GTX 1070 GPU

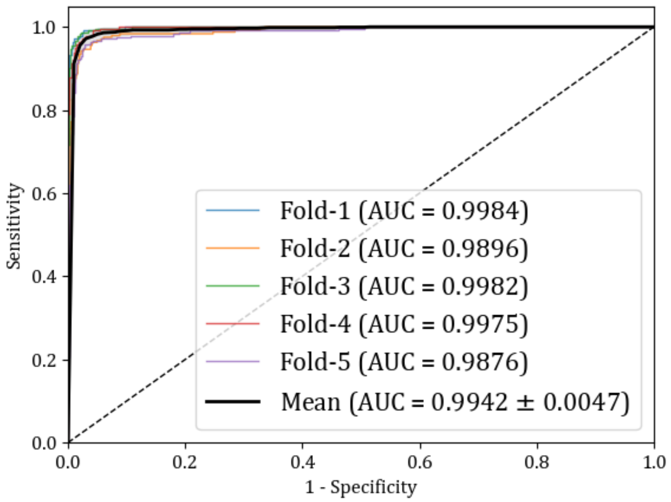
The MTM AI project
Results



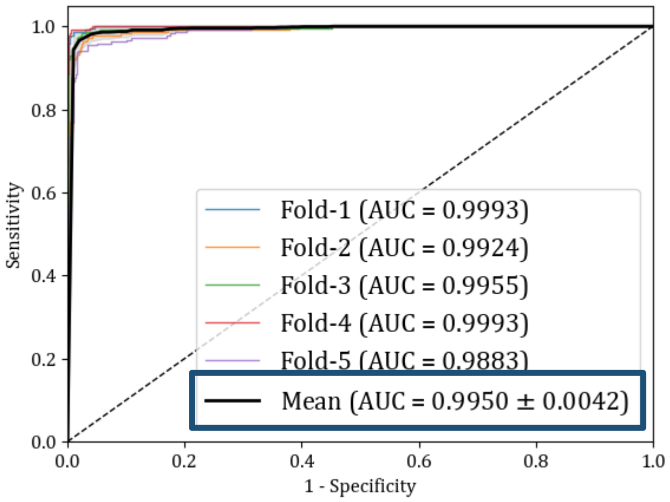
(a)



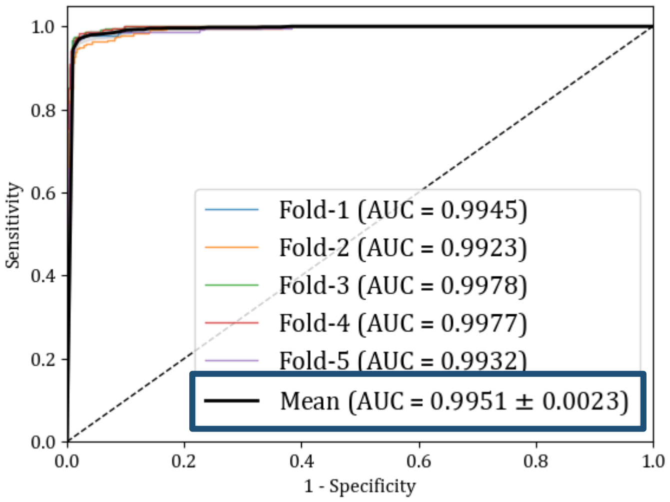
(b)



(c)



(d)



(e)

Micro-Average ROC curves for the *MTMrp* model (stages 1-4)

(a) VGG-16, (b) ResNet-50, (c) ResNet-101, (d) Inception-v3, (e) InceptionResNet-v2

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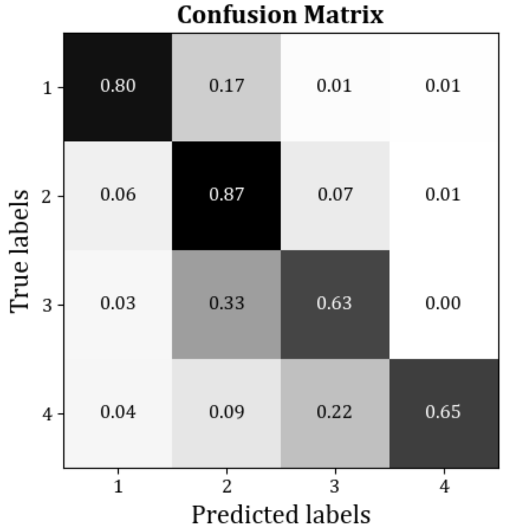
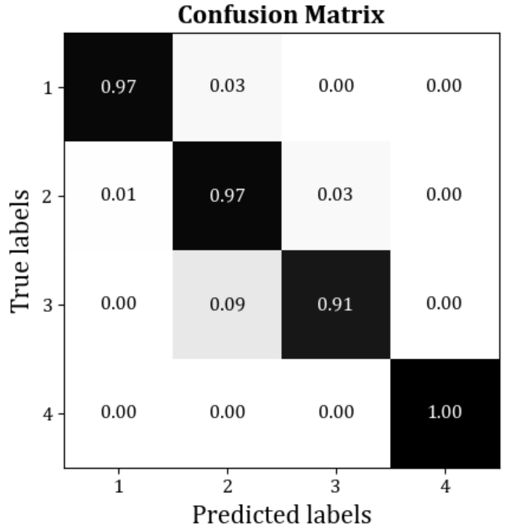
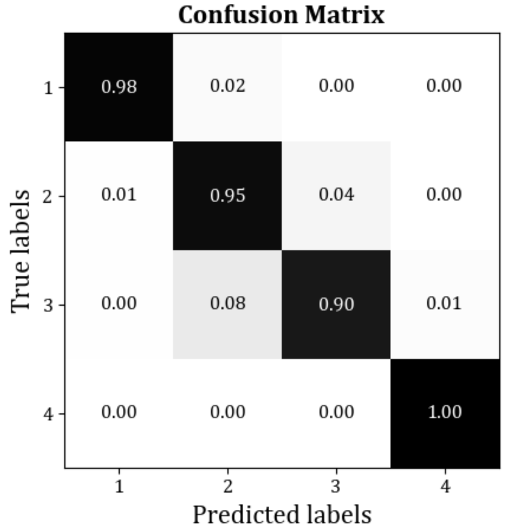
Results



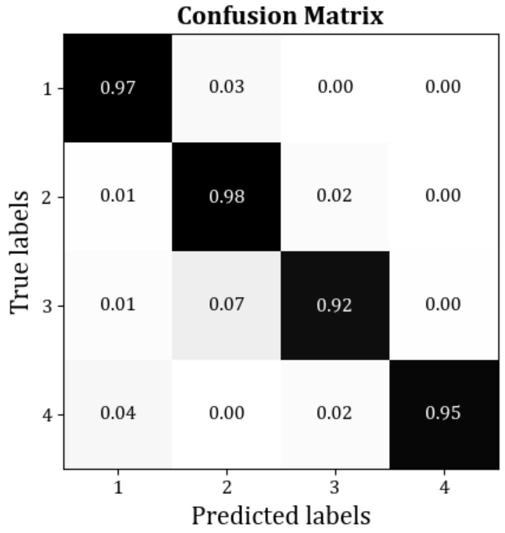
(a)



(b)



(c)



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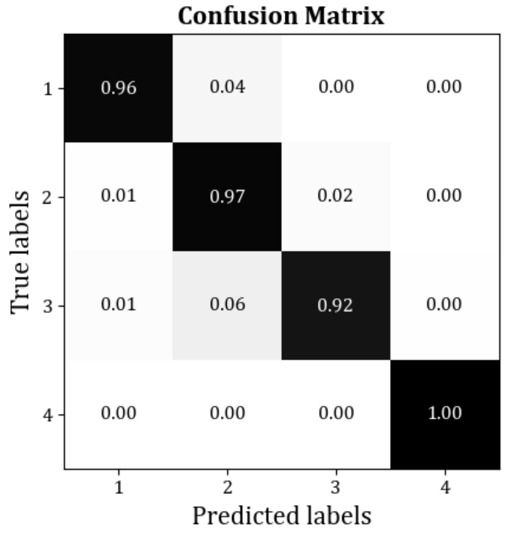

(e)

Confusion matrices for the *MTMrp* model (stages 1-4)

(a) VGG-16, (b) ResNet-50, (c) ResNet-101, (d) Inception-v3, (e) InceptionResNet-v2

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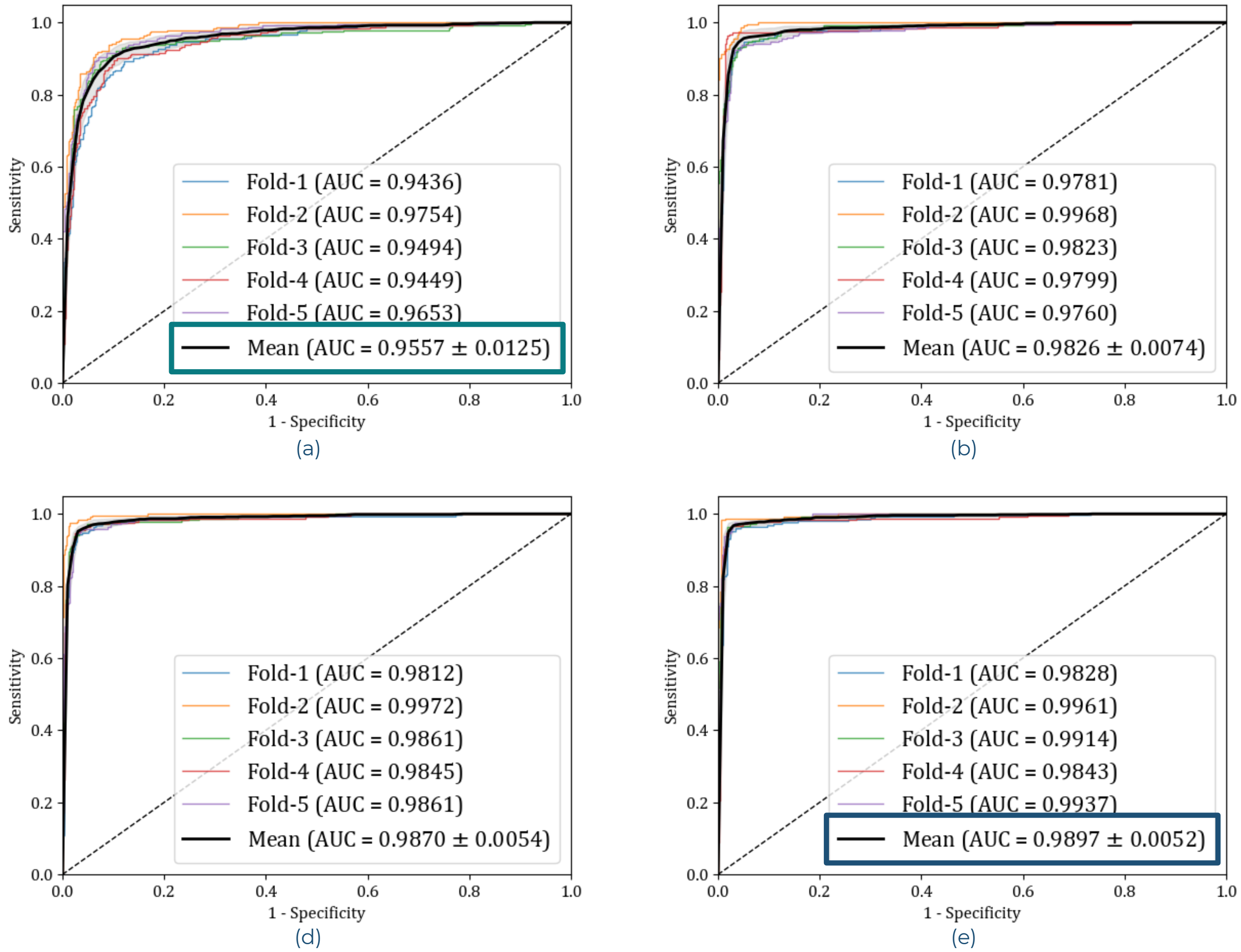

Micro-Average ROC curves for the *MTMfp* model (stages a-c)

(a) VGG-16, (b) ResNet-50, (c) ResNet-101, (d) Inception-v3, (e) InceptionResNet-v2

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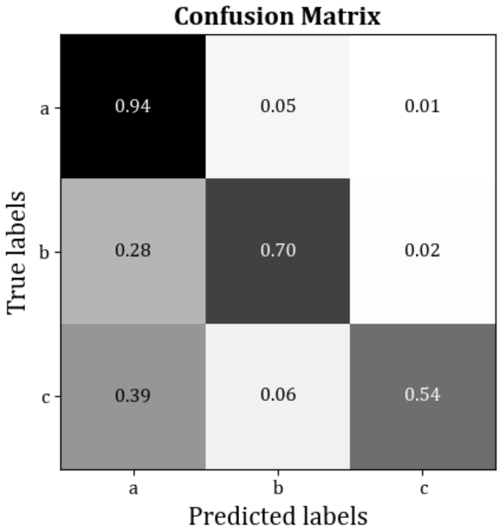
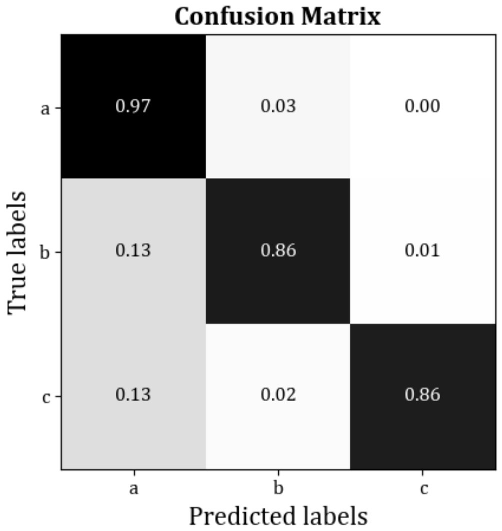
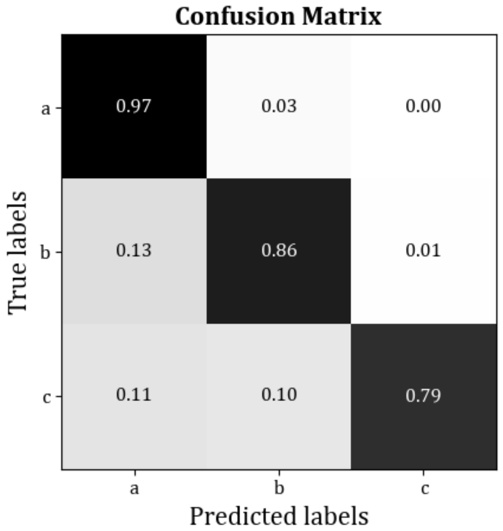
Results



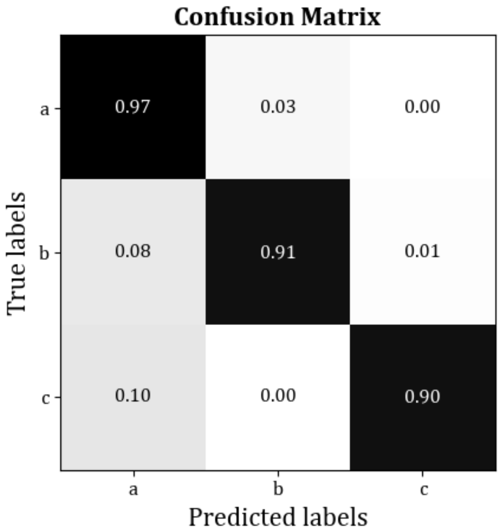
(a)



(b)



(c)



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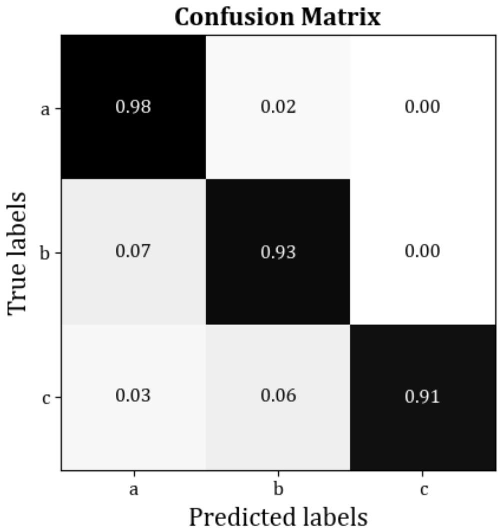

(e)

Confusion matrices for the *MTMfp* model (stages a-c)

(a) VGG-16, (b) ResNet-50, (c) ResNet-101, (d) Inception-v3, (e) InceptionResNet-v2

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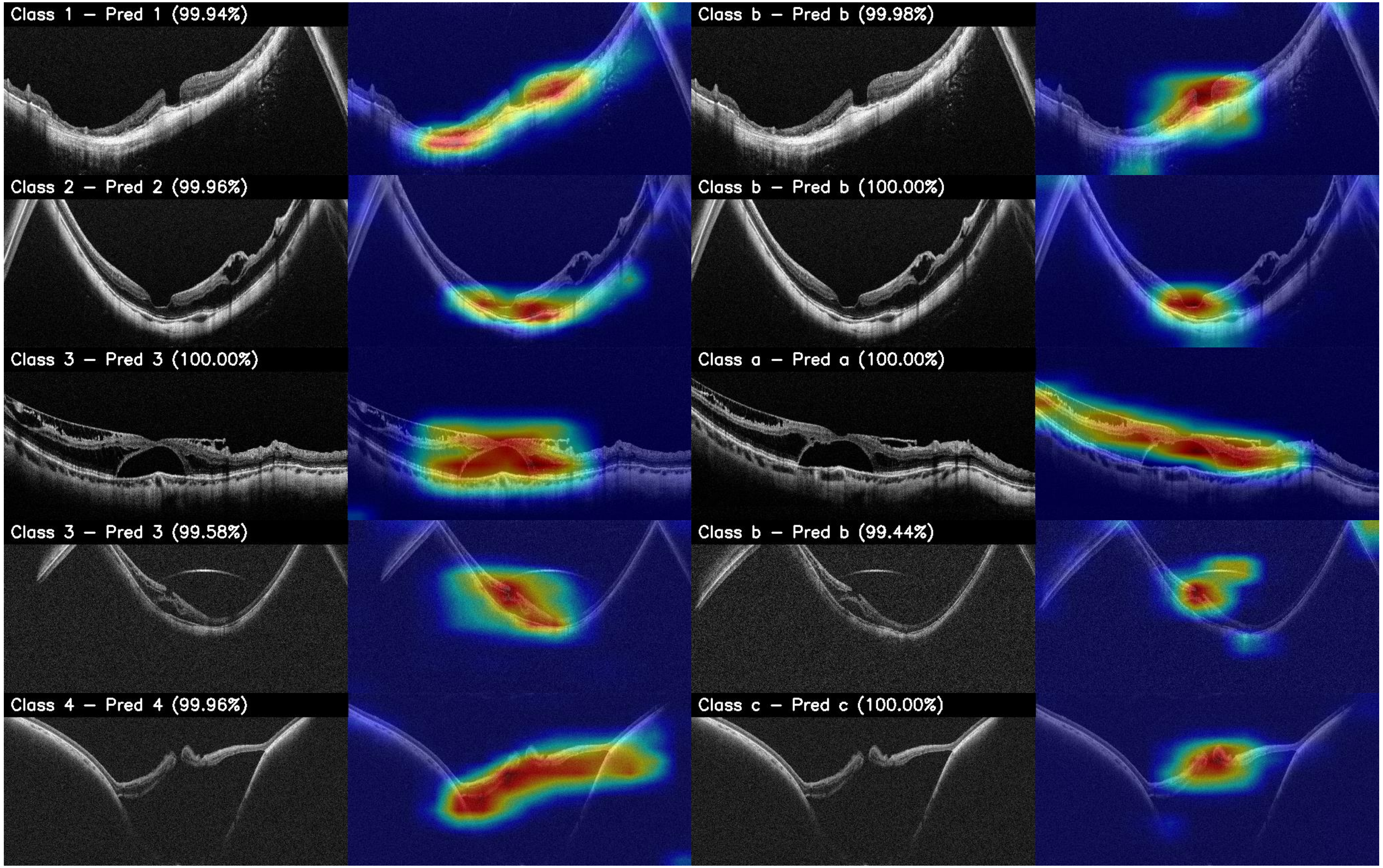
Results



Examples of visual explanation heatmaps generated by Grad-CAM on OCT images (Inception-ResNet-v2)

Red areas of heatmaps reflect image regions where the final model searched for retinal (left) and foveal (right) patterns

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Conclusion

The models proposed could be considered to have the requirements to form the basis for the development of an AI system with high clinical and educational utility

- Inception-ResNet-v2 architecture achive greater performance in identifying both retinal and foveal patterns
- GradCAM heatmaps allow the visualization of both retinal and foveal patterns, distinguishing among them

- **Next steps**
  - Training and testing the models on a larger dataset with images from other OCT instruments
  - Considering also O-LMHs and epiretinal abnormalities

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www.zeeromed.com

+39-040-9828200
info@o3enterprise.com
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