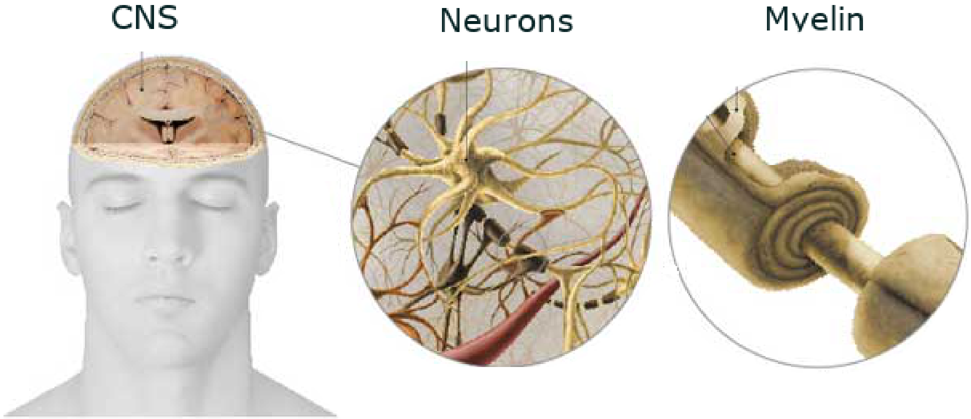
Predicting the brain lesion recovery in multiple sclerosis by MRI biomarkers

Nicolás Bonilla, Gustavo Pineda MSc., Eduardo Romero PhD.

Universidad Nacional de Colombia

Definition



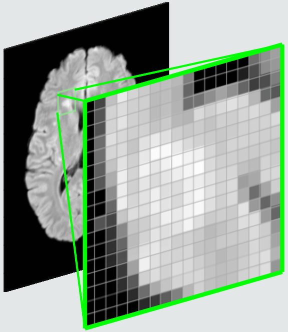
Multiple sclerosis (MS)

MS is a demyelinating disorder that is characterized by multiple inflammatory plaques (lesions) of demyelination involving the white matter of the brain and spinal cord.

MS Manifestations

Brain lesion can have different types of consequences depending on where it is.

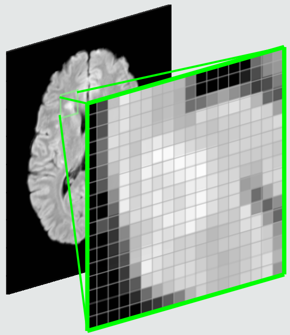
Brain



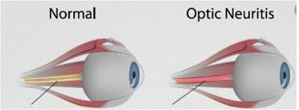
MS Manifestations

Brain lesion can have different types of consequences depending on where it is.

Brain



Optic

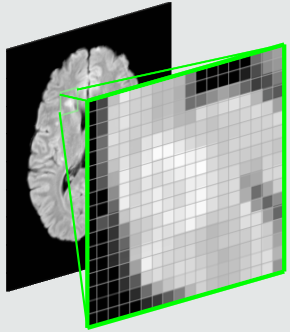


Eye problem

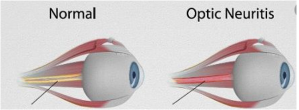
MS Manifestations

Brain lesion can have different types of consequences depending on where it is.

Brain

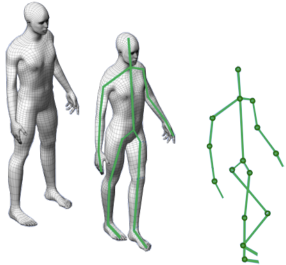


Optic



Eye problem

Motor



Body key points Dynamics

MS Diagnosis

Mc. Donald criteria

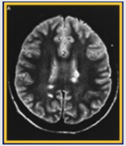
The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space and time.

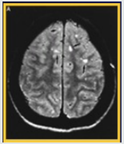
MS Diagnosis

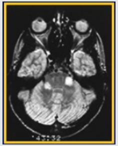
Mc. Donald criteria

The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space and time.

Dissemination in Space


a


b


c

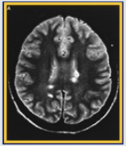
>1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord.

MS Diagnosis

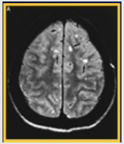
Mc. Donald criteria

The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space and time.

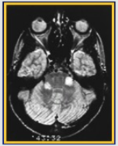
Dissemination in Space



a



b



c

$>$ 1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord.

Dissemination in Time

A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI.

MS progession

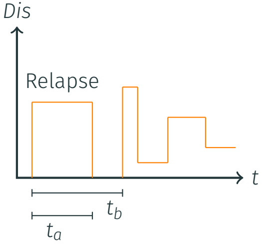
Relapse time	t_a	minimum	24 hour
Time between relapse	t_b	minimum	30 days

MS progession

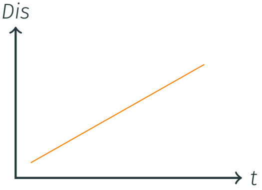
Relapse time	t_a	minimum	24 hour
Time between relapse	t_b	minimum	30 days

Depend progress of disease we have four different **types of MS**:

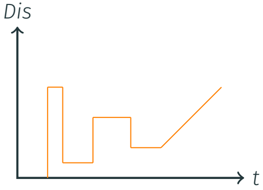
Relapse Remitting RR



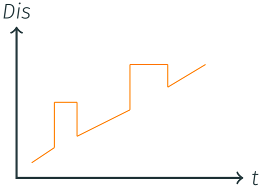
Primary progressive PP



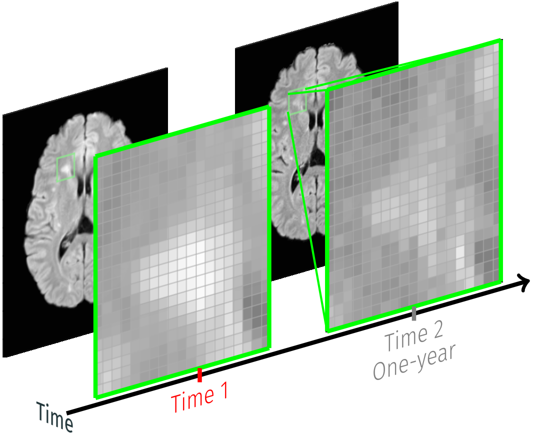
Secondary Progressive SP



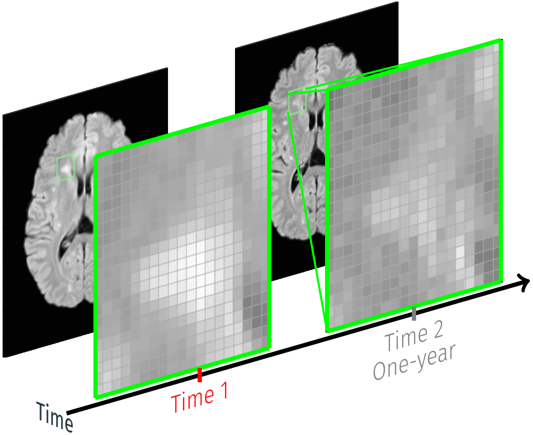
Progressive relapsing PR

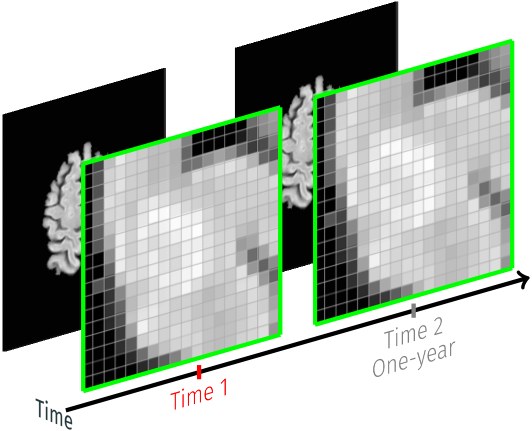


Brain lesion Progression in MRI

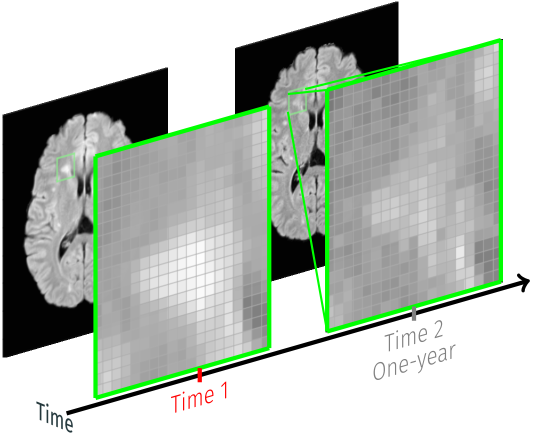


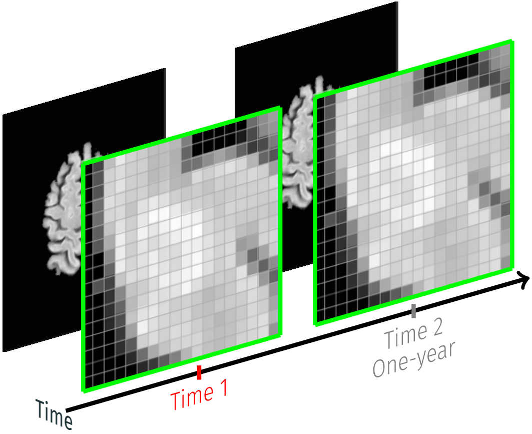
Brain lesion Progression in MRI





Brain lesion Progression in MRI





Research Question

Can the **features** of the MRI brain lesions in MS have information about their progression and **predict** their recovery?

Proposal

Hypotesis

The **low level features** of the MRI brain lesion in MS can predict brain lesion recovery since those features could be correlated with the neuro-inflammation process and cell death. [1]

[1] Zhao et al (2001). Non-invasive detection of apoptosis using magnetic resonance imaging and a targeted contrast agent. Nature medicine, 7(11), 1241

Proposal

Hypotesis

The **low level features** of the MRI brain lesion in MS can predict brain lesion recovery since those features could be correlated with the neuro-inflammation process and cell death. [1]

If the **feature** can predict whether the lesion will recovery, this feature is a **biomarker**.

[1] Zhao et al (2001). Non-invasive detection of apoptosis using magnetic resonance imaging and a targeted contrast agent. Nature medicine, 7(11), 1241

Proposal

Hypotesis

The **low level features** of the MRI brain lesion in MS can predict brain lesion recovery since those features could be correlated with the neuro-inflammation process and cell death. [1]

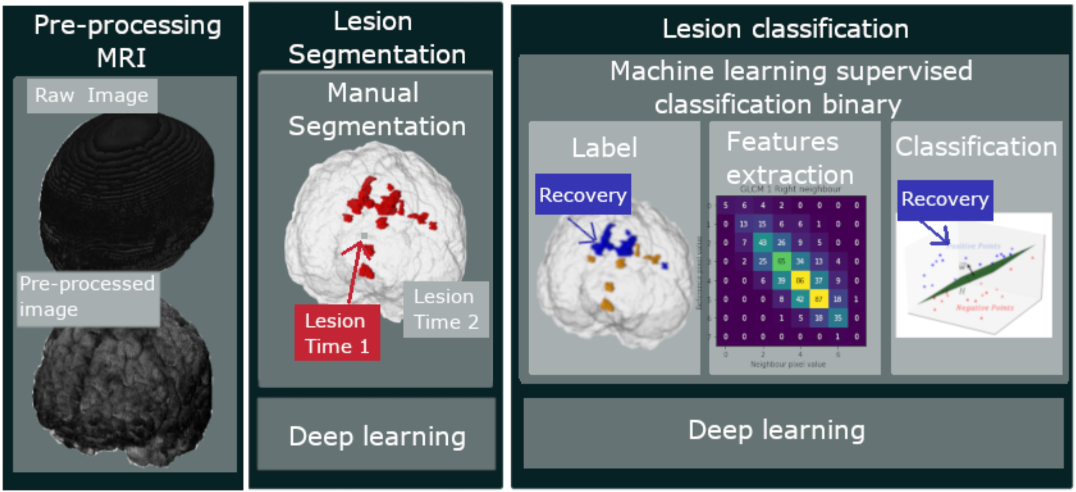
If the **feature** can predict whether the lesion will recovery, this feature is a **biomarker**.

Main Goal

To find and validate a **MRI biomarker** in the **low level features** for predict the brain lesion recovery in MS.

[1]Zhao et al (2001). Non-invasive detection of apoptosis using magnetic resonance imaging and a targeted contrast agent. Nature medicine, 7(11), 1241

Proposal Pipeline



Data set: MRI

ISBI 2015 challenge, [2] 19 patients of MS

Same patient in Five different times.

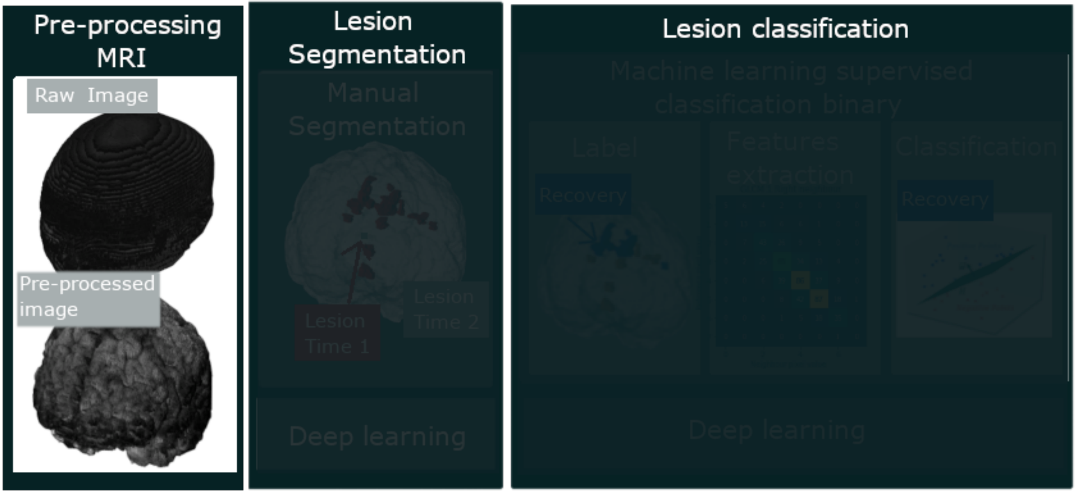
We only use the two first time:

- Time 1 (Baseline).
- Time 2 (one year later).

Data set	N(M/F)	Time points Mean(SD)	Age Mean(SD)	Follow-Up Mean(SD)
Training	5(1/4)	4.4 (±0.55)	43.5(±10.3)	1.0(±0.13)
RR	4(1/3)	4.5 (±0.5)	40.0(±7.55)	1.0(±0.14)
PP	1(0/1)	4.0	57.9	1.0(±0.04)
Test A	10 (2/8)	4.3(±0.68)	37.8(±9.18)	1.1 (±0.28)
RR	9 (2/7)	4.3(±0.71)	37.4(±9.63)	1.1(±0.29)
SP	1 (0/1)	4.0	41.7	1.0(±0.05)
Test B	4(1/3)	4.5(±0.58)	43.3(±7.64)	1.0(±0.05)
RR	3(1/2)	4.7(±0.58)	44.8(±8.65)	1.0(±0.05)
SP	1(0/1)	4.0	39	1.0(±0.04)

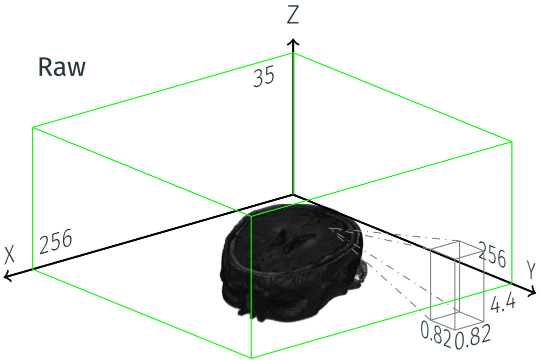
[2] Carass, A., Cardoso, M.J., 2017. Longitudinal multiple sclerosis lesion segmentation: resource and challenge. NeuroImage, 148, pp.77-102.

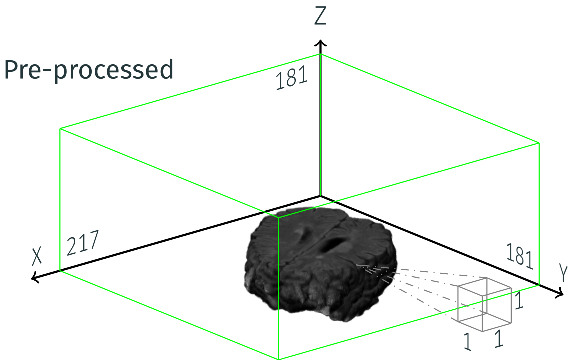
Pipeline: 1. Pre-Processing



Pre-processing

Homogenization
(N4 Correction)

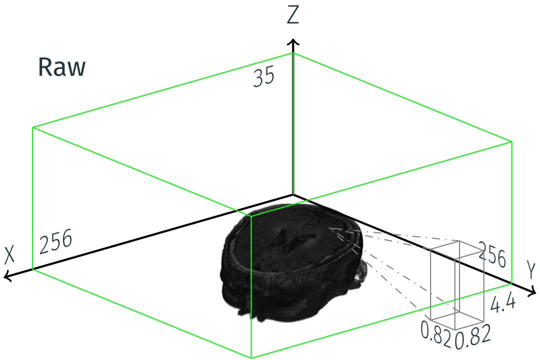


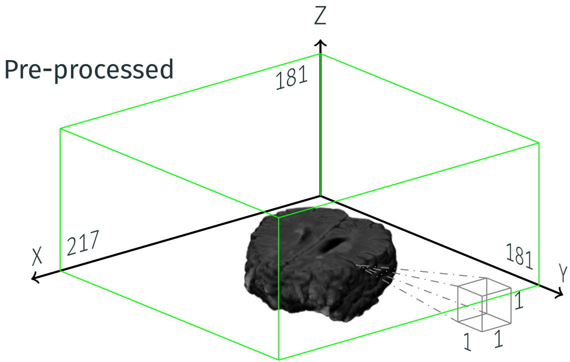


Num Vox=[256 256 35], **Dim Vox**=[0.82 0.82 4.4] mm	**Num Vox**=[181 217 181], **Dim Vox**=[1 1 1] mm
Datatype Vox: int 16, [0, 65536]	**Datatype Vox:** float 32 [0, 4.3^9]

Pre-processing

Homogenization (N4 Correction) → **Skull stripped** (Dura stripped)

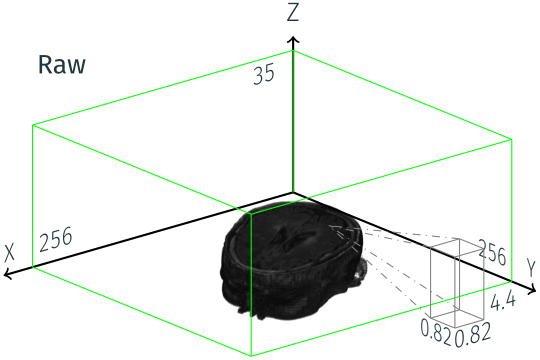


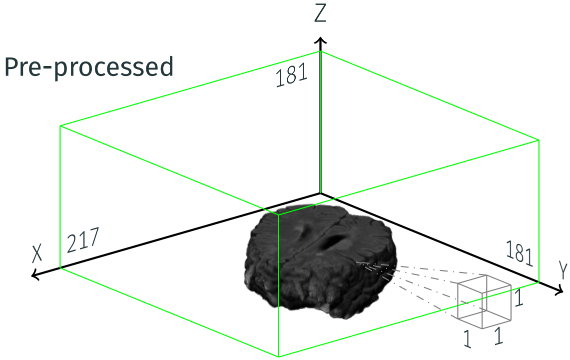


Num Vox=[256 256 35], **Dim Vox**=[0.82 0.82 4.4] mm	**Num Vox**=[181 217 181], **Dim Vox**=[1 1 1] mm
Datatype Vox: int 16, [0, 65536]	**Datatype Vox:** float 32 [0, 4.3^9]

Pre-processing

Homogenization (N4 Correction) → Skull stripped (Dura stripped) → Homogenization (N4 Correction)

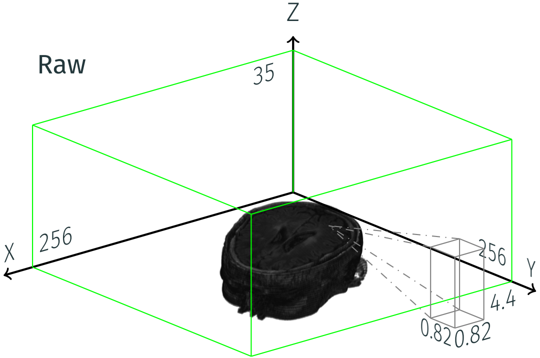


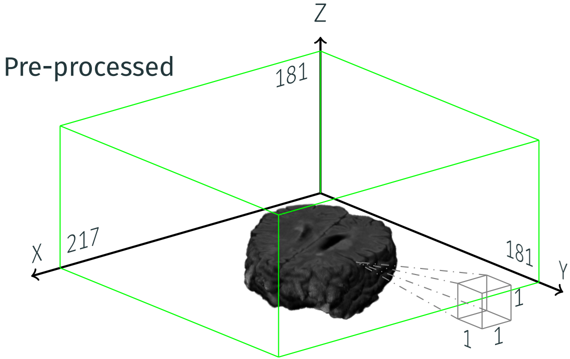


Num Vox=[256 256 35], **Dim Vox**=[0.82 0.82 4.4] mm	**Num Vox**=[181 217 181], **Dim Vox**=[1 1 1] mm
Datatype Vox: int 16, [0, 65536]	**Datatype Vox:** float 32 [0, 4.3^9]

Pre-processing

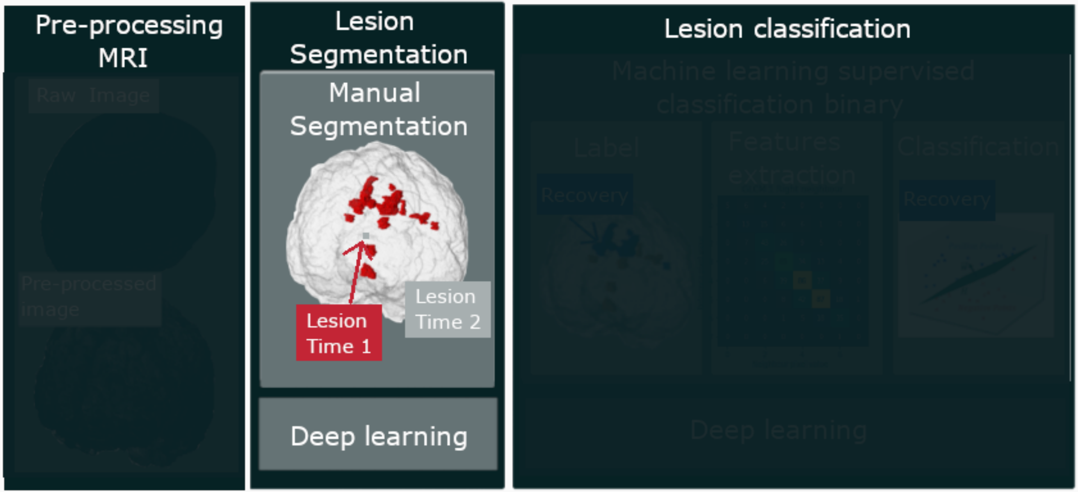
Homogenization (N4 Correction) → Skull stripped (Dura stripped) → Homogenization (N4 Correction) → Regitration (Rigid)





Num Vox=[256 256 35], **Dim Vox**=[0.82 0.82 4.4] mm	**Num Vox**=[181 217 181], **Dim Vox**=[1 1 1] mm
Datatype Vox: int 16, [0, 65536]	**Datatype Vox:** float 32 [0, 4.3^9]

Pipeline: 2. Segmentation lesion



2. Segmentation lesion: Manual segmentation

Expert

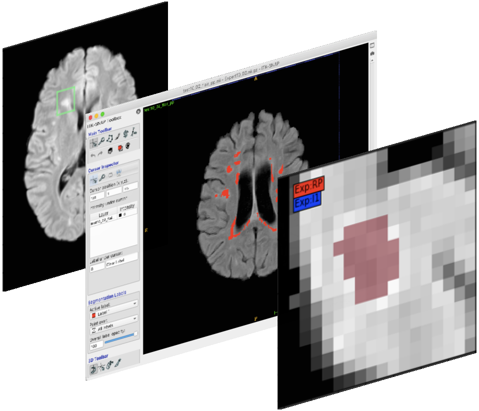
Neuroradiologist: Dr. Ricardo Pinto
Policlinico Olaya

Tool Segmentation

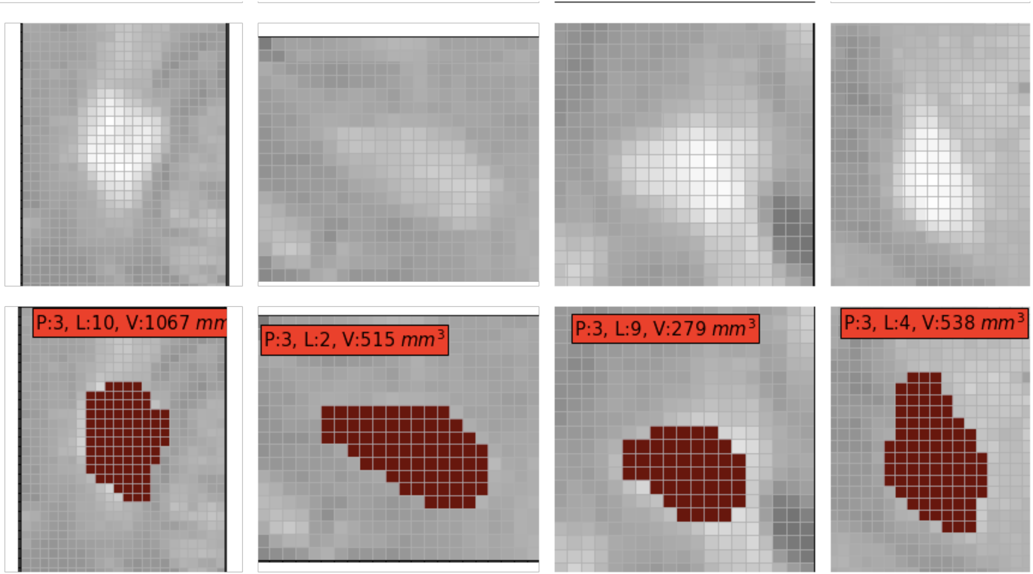
Software: ITK-Snap

Time in this activity

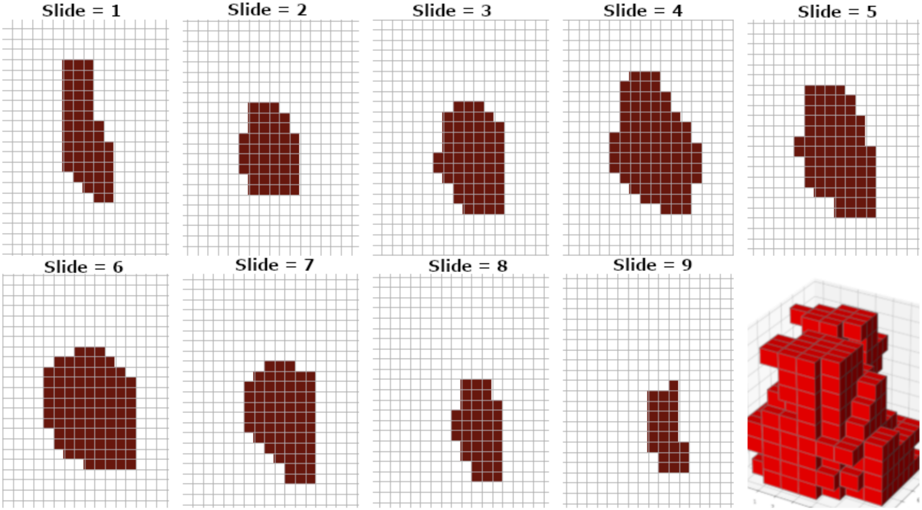
34 hour total
4 h/d, 2 d/w, total 5 weeks



Segmentation lesion



Build lesion 3D

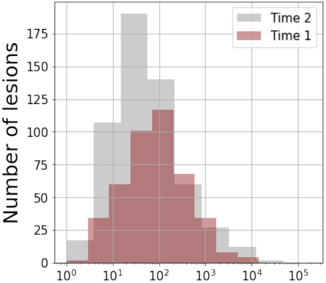


2. Segmentation lesion Result

Patient	1		2		3		4		5		6		7		8		9		10	
Time 1/Time 2	6	3	30	11	26	10	10	2	27	4	55	17	72	27	14	8	13	8	17	5

Patient	11		12		13		14		15		16		17		18		19	
Time 1/Time 2	29	13	3	0	5	2	43	21	34	24	16	10	21	15	4	2	3	2

Table 1: Number of lesions per patient in Time 1 and Time 2.

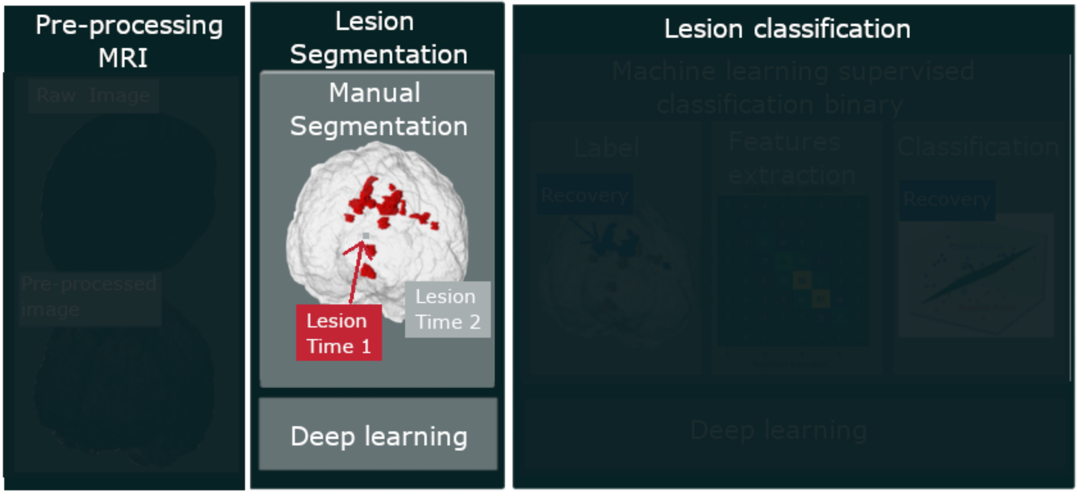


984 Lesions

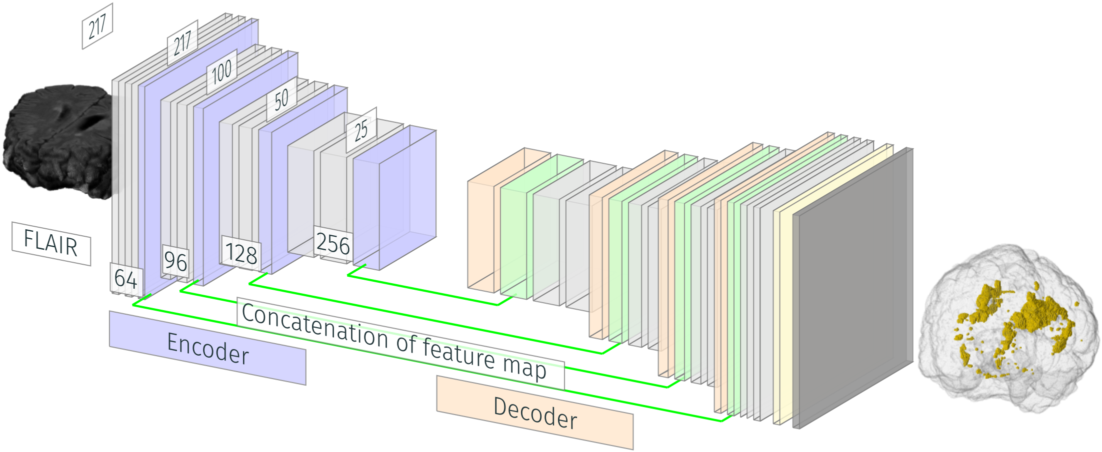
In **19** patients

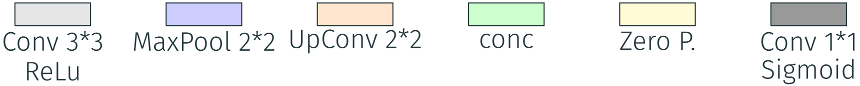
Time 1	Time 2
429	555

Pipeline: 2. Segmentation lesion

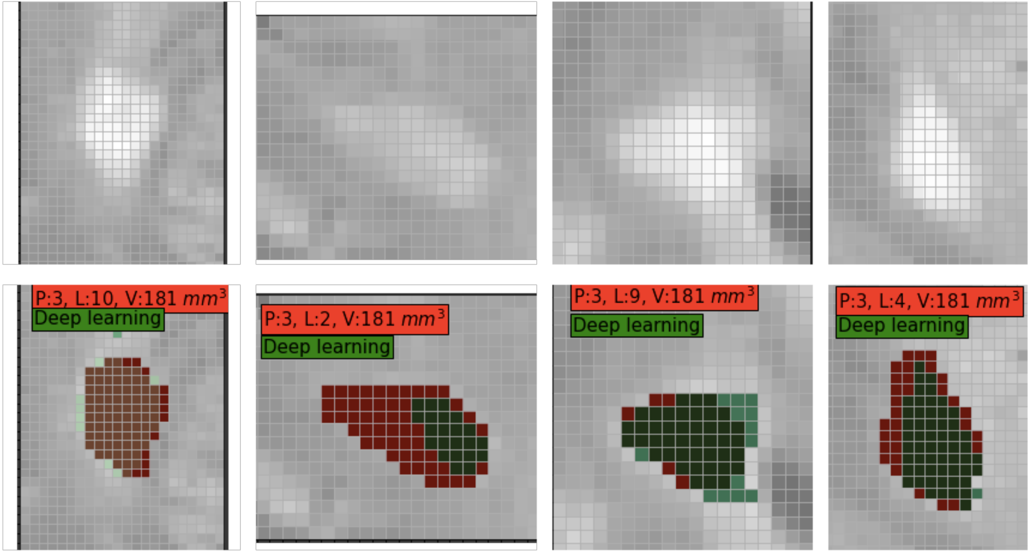


Deep learning U-Net: Segmentation





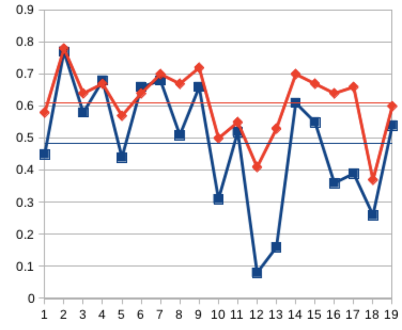
Deep learning: Segmentation lesion



DSC: Dice Score

This measures the overlap in percentage between M (Manual) and D(Deep learning).

$$DSC = \frac{2(M \cap D)}{|M| + |D|} \qquad (1)$$

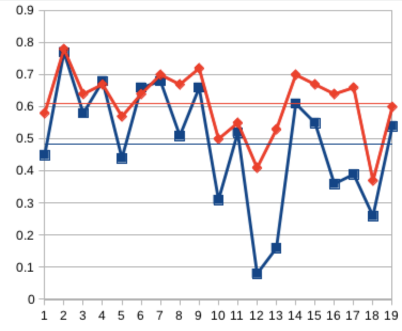


Deep learning : Metrics

DSC: Dice Score

This measures the overlap in percentage between M (Manual) and D(Deep learning).

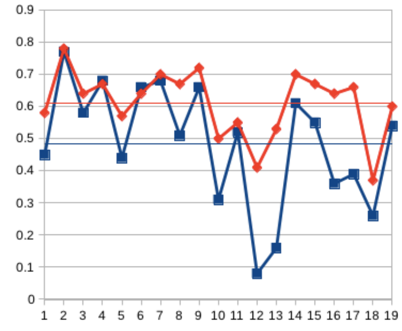
$$DSC = \frac{2(M \cap D)}{|M| + |D|} \tag{1}$$



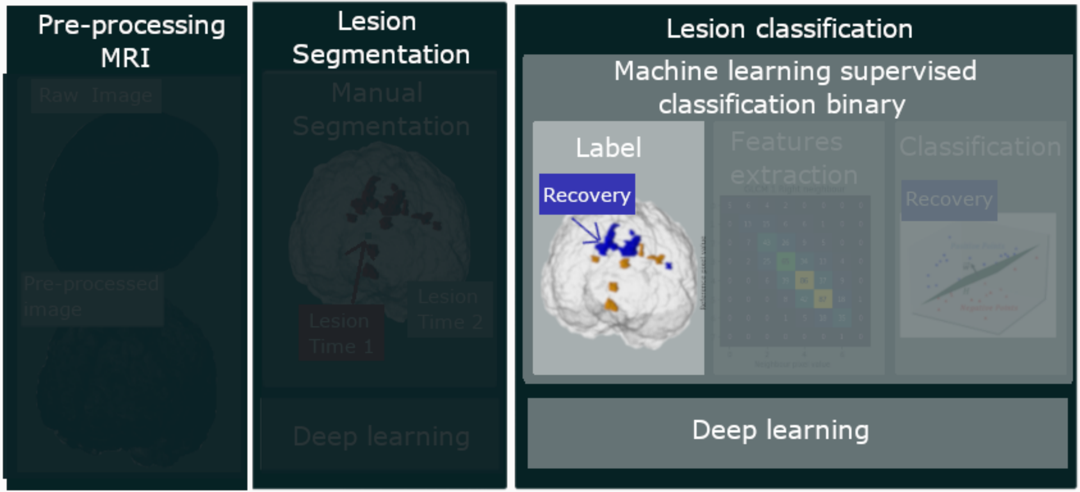
AVD: Average Difference Volume

V=volume. the Average Volume Difference (AVD) in percentage is:

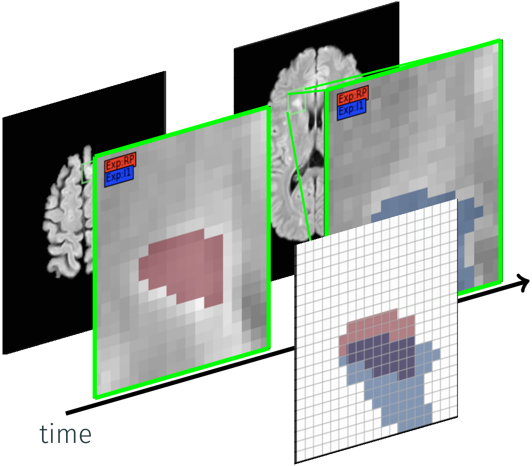
$$AVD = \frac{|V_M - V_D|}{V_M} \tag{2}$$



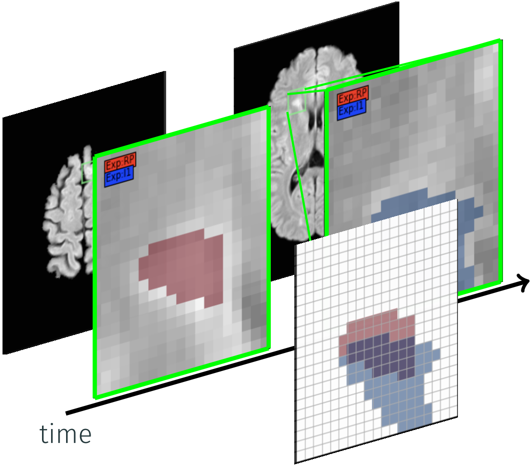
Pipeline: 3. Lesion classification



Label: Lesion recovery



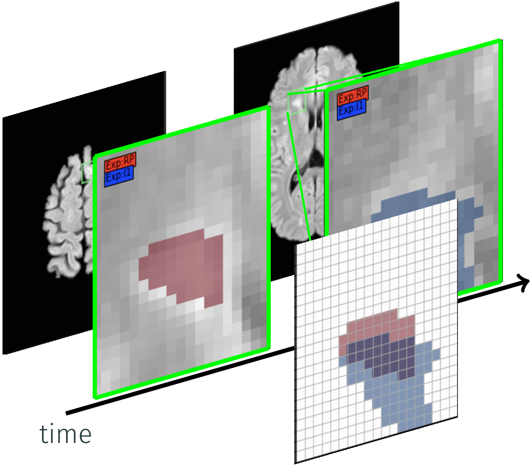
Label: Lesion recovery



Voxel recovery

If the voxel lesion in time 1 is a voxel healty in time 2, count as a **voxel recovery**.

Label: Lesion recovery

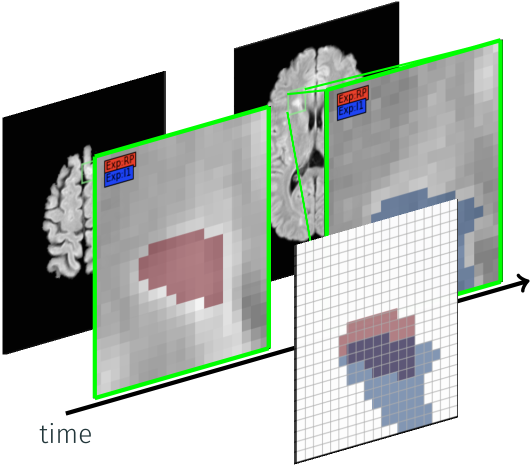


Voxel recovery

If the voxel lesion in time 1 is a voxel healty in time 2, count as a **voxel recovery**.

Run all lesion

Label: Lesion recovery



Voxel recovery

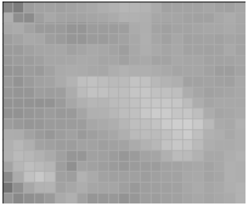
If the voxel lesion in time 1 is a voxel healty in time 2, count as a **voxel recovery**.

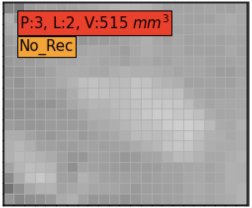
Run all lesion

Lesion recovery

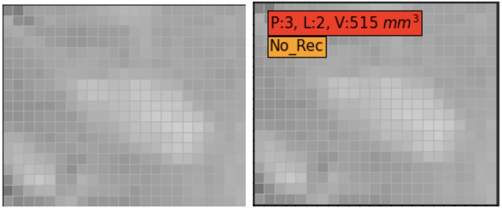
If the total of voxel recovery is bigger than 50% of the lesion in time 1, **lesion recovery**

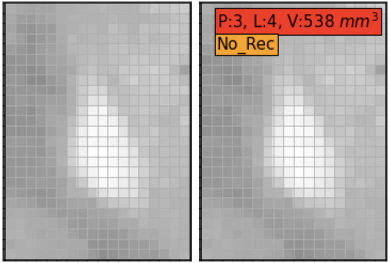
Label lesion Rec



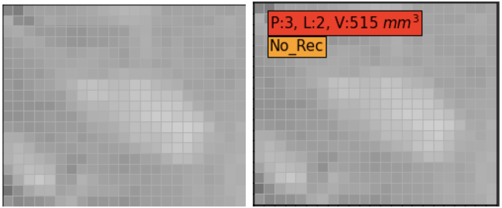


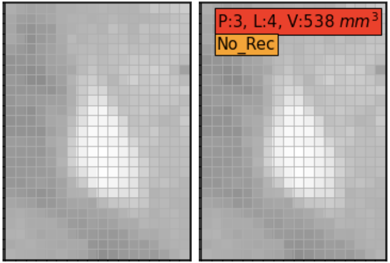
Label lesion Rec

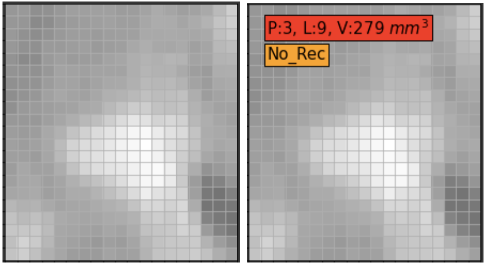




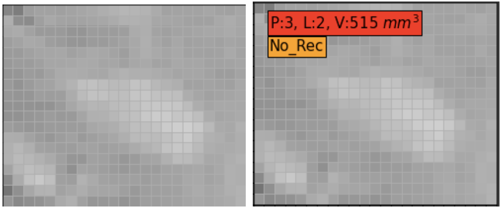
Label lesion Rec

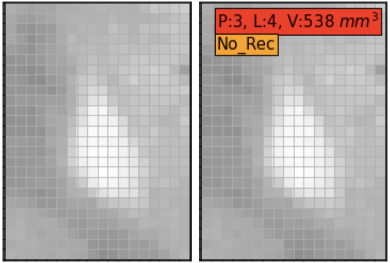


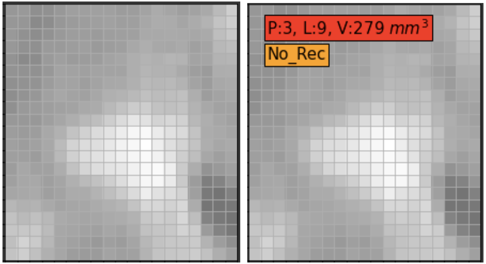


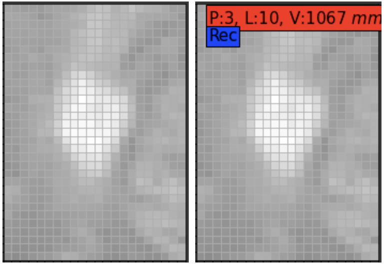


Label lesion Rec









3.1. Build Label: Rec

Patient	1		2		3		4		5		6		7		8		9		10	
Time 1/Rec	6	3	30	19	26	16	10	8	27	23	55	38	72	45	14	6	13	5	17	12

Patient	11		12		13		14		15		16		17		18		19	
Time1/Rec	29	13	3	0	5	2	43	21	34	24	16	10	21	15	4	2	3	2

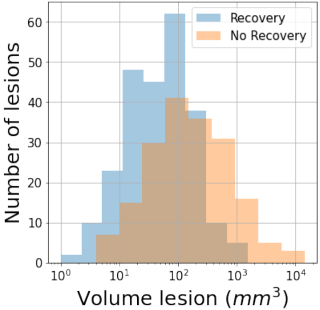
Table 2: Number of lesions per patient in Time 1 and how many will be recovered Rec.

3.1. Build Label: Rec

Patient	1		2		3		4		5		6		7		8		9		10	
Time 1/Rec	6	3	30	19	26	16	10	8	27	23	55	38	72	45	14	6	13	5	17	12

Patient	11		12		13		14		15		16		17		18		19	
Time1/Rec	29	13	3	0	5	2	43	21	34	24	16	10	21	15	4	2	3	2

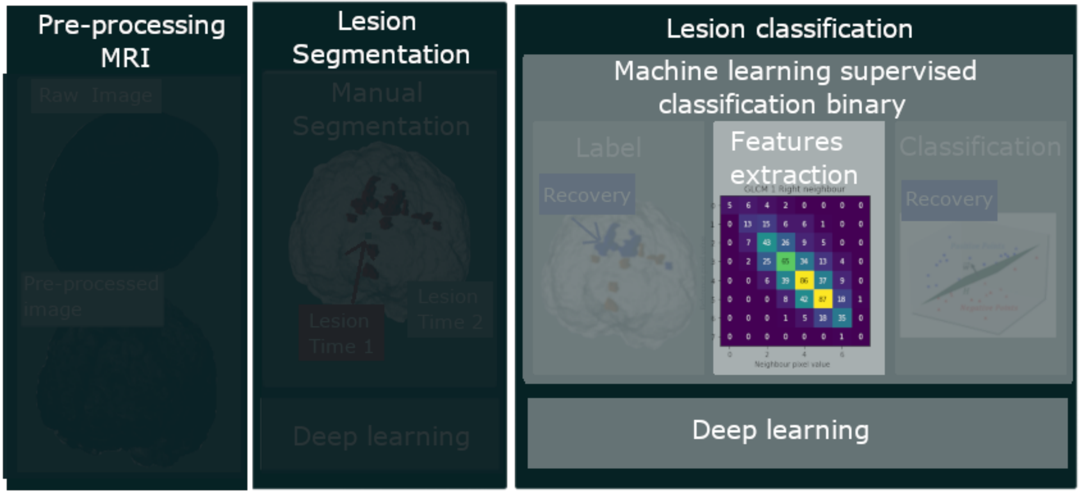
Table 2: Number of lesions per patient in Time 1 and how many will be recovered Rec.



429 Lesions in Time 1

Recovery	NO Recovery
244 (56.9%)	185 (43.1%)

Pipeline: 3. Lesion classification

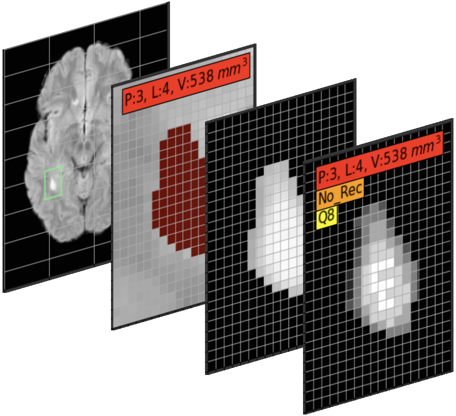


Quantization in MRI

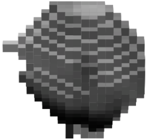
In MRI we have different graylevels (data type: float32) for image and the **quantization** is a form for standardize the same value in every image.

Quantized MRI

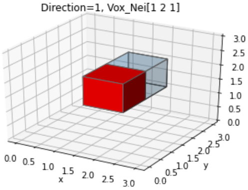
Quantized the MRI in differents levels: 8,16,32,64,128,256.



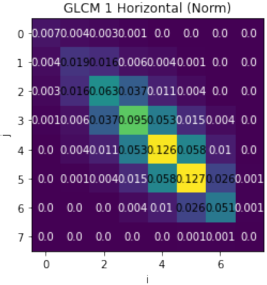
Quantized lesion



Direction, Distance.

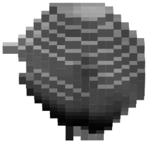


GLCM

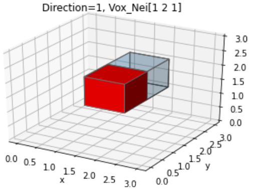


Feature Haralick 3D	
Contrast	-
Correlation	-
Entropy	-

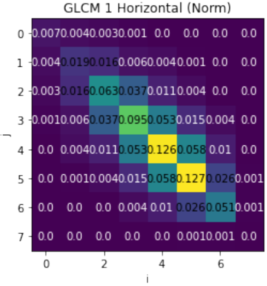
Quantized lesion



Direction, Distance.



GLCM

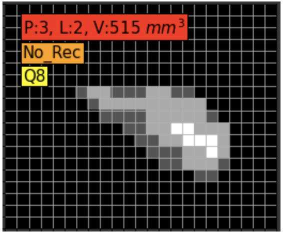


Feature Haralick 3D	
Contrast	-
Correlation	-
Entropy	-

Initial Condition		
MRI	GLCM	
Quantization	Distance	Direction
3-bit	1	1
–	2	–
8-bit	3	13

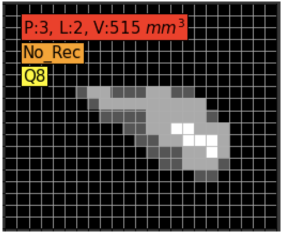
Feature
Haralick
ASM
—
Coefficient Correlation

Lesion - Features Haralick 3D

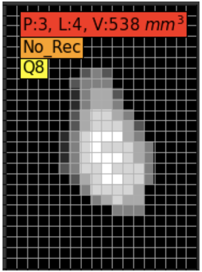


Feature Haralick 3D	
Contrast	0.201
Correlation	0.011
Entropy	5.001

Lesion - Features Haralick 3D

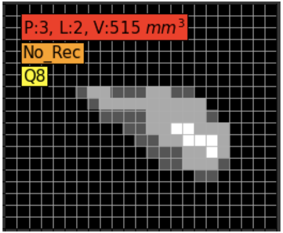


Feature Haralick 3D	
Contrast	0.201
Correlation	0.011
Entropy	5.001

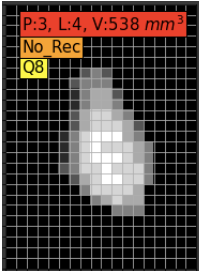


Feature Haralick 3D	
Contrast	1.057
Correlation	3.110
Entropy	2.679

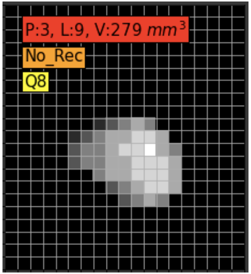
Lesion - Features Haralick 3D



Feature Haralick 3D	
Contrast	0.201
Correlation	0.011
Entropy	5.001

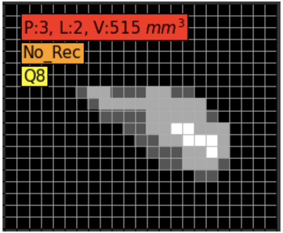


Feature Haralick 3D	
Contrast	1.057
Correlation	3.110
Entropy	2.679

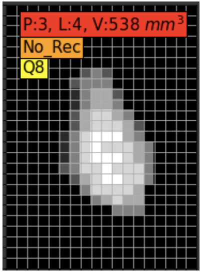


Feature Haralick 3D	
Contrast	3.100
Correlation	2.125
Entropy	4.085

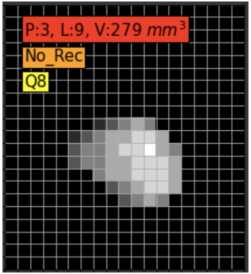
Lesion - Features Haralick 3D



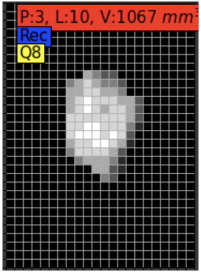
Feature Haralick 3D	
Contrast	0.201
Correlation	0.011
Entropy	5.001



Feature Haralick 3D	
Contrast	1.057
Correlation	3.110
Entropy	2.679



Feature Haralick 3D	
Contrast	3.100
Correlation	2.125
Entropy	4.085



Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

3.1.2. Feature Matrix

Feature Matrix

It contains the descriptive characteristics of the lesions, also known as the observations, it is complemented with the label and the patient to whom the lesion belongs.

3.1.2. Feature Matrix

Feature Matrix

It contains the descriptive characteristics of the lesions, also known as the observations, it is complemented with the label and the patient to whom the lesion belongs.

	Patient #	Lesion #	Feature Haralick 3D			Label	
			1	...	3042		
1	1	1					Test
..	1	n					
..	2	1				X	Train
...	2	n				X	
...	..					...	
...	19	1				X	
452	19	n				X	

Feature Matrix

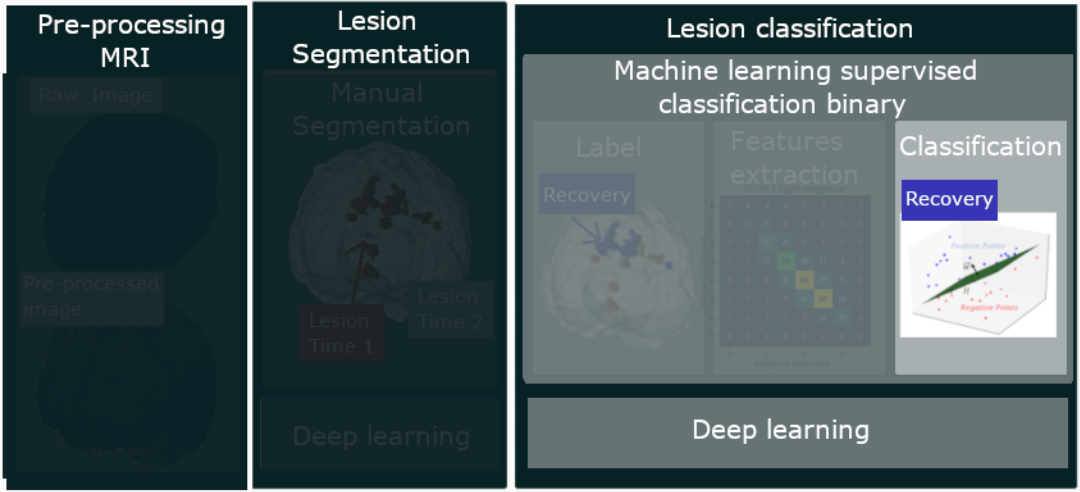
It contains the descriptive characteristics of the lesions, also known as the observations, it is complemented with the label and the patient to whom the lesion belongs.

	Patient #	Lesion #	Feature Haralick 3D			Label	
			1	...	3042		
1	1	1					Test
..	1	n					
..	2	1				X	Train
...	2	n				X	
...	..					...	
...	19	1				X	
452	19	n				X	

Pre-Processing data:

1. Use lesion with # Voxeles$>$ 50
2. standarize the feature Haralicks (μ=0, σ=1).

Pipeline: 3. Lesion classification



Leave-One-Subject-Out

Cross validation

validation technique for assessing how the results of a statistical analysis will generalize to an independent data set.

Leave-One-Subject-Out

Cross validation

validation technique for assessing how the results of a statistical analysis will generalize to an independent data set.

Leave-One-Subject-Out grouping by patient.

Experiment	1		2		3		4		5		6		7		8		9		10	
TEST/Rec	6	3	30	19	26	16	10	8	27	23	55	38	72	45	14	6	13	5	17	12

Experiment	11		12		13		14		15		16		17		18		19	
TEST/Rec	29	16	3	3	5	3	43	22	34	10	16	6	21	6	4	2	3	1

Table 3: The experiment is per patient, Test is the number of lesion and how many will be recovered Rec.

Leave-One-Subject-Out

Cross validation

validation technique for assessing how the results of a statistical analysis will generalize to an independent data set.

Leave-One-Subject-Out grouping by patient.

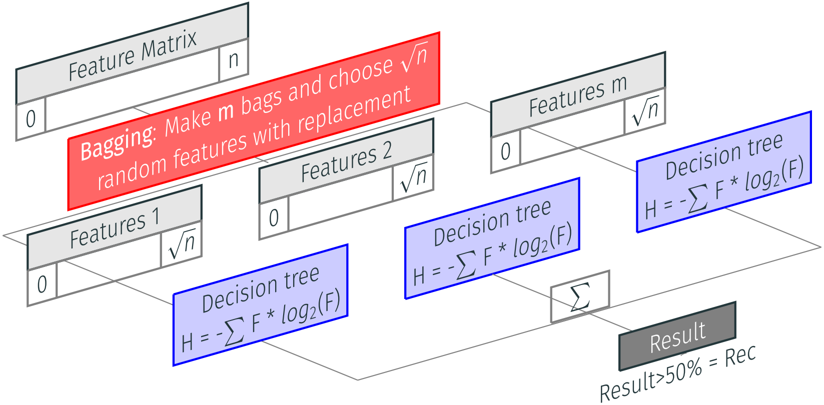
Experiment	1		2		3		4		5		6		7		8		9		10	
TEST/Rec	6	3	30	19	26	16	10	8	27	23	55	38	72	45	14	6	13	5	17	12

Experiment	11		12		13		14		15		16		17		18		19	
TEST/Rec	29	16	3	3	5	3	43	22	34	10	16	6	21	6	4	2	3	1

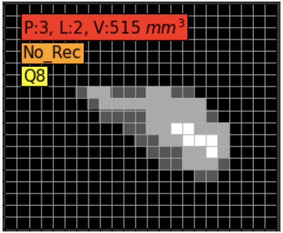
Table 3: The experiment is per patient, Test is the number of lesion and how many will be recovered Rec.

The metric is made by **the average of the metric** of each experiment.

Random forest



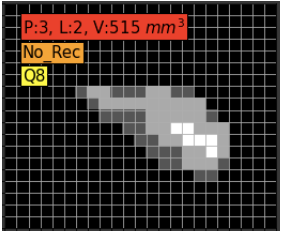
Result



Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

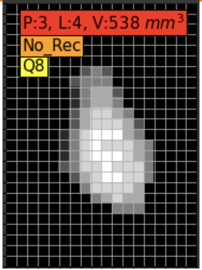
Rec	FP

Result



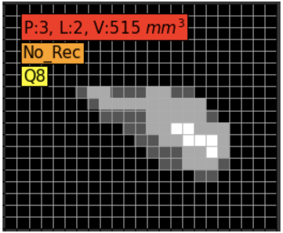
Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

Rec	FP



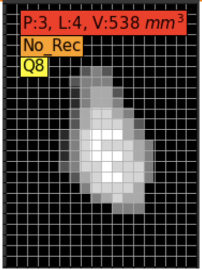
Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

No Rec	TN



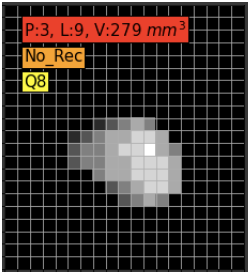
Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

Rec	FP



Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

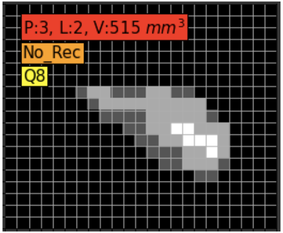
No Rec	TN



Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

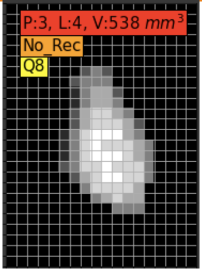
Rec	FP

Result



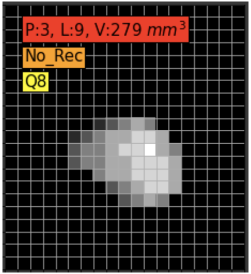
Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

Rec	FP



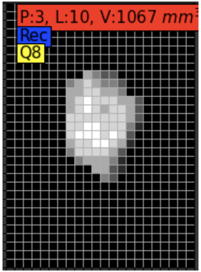
Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

No Rec	TN



Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

Rec	FP



Feature Haralick 3D	
Contrast	0.451
Correlation	1.819
Entropy	8.101

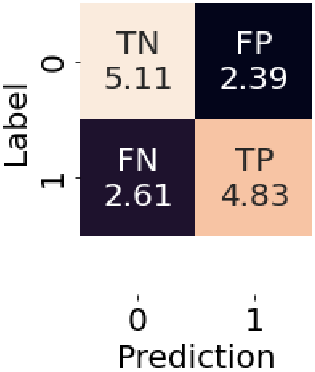
Rec	TP

Metrics: Random forest classifier

Different performance metrics are used to evaluate the Machine Learning Algorithm in the supervised classification model for predict the recovery in brain lesion of MS.

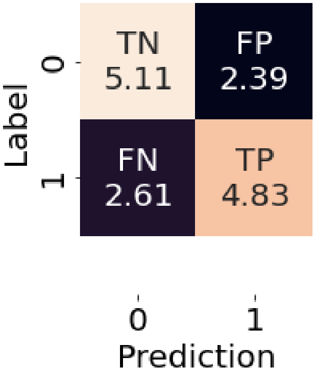
Metrics: Random forest classifier

Different performance metrics are used to evaluate the Machine Learning Algorithm in the supervised classification model for predict the recovery in brain lesion of MS.



Metrics: Random forest classifier

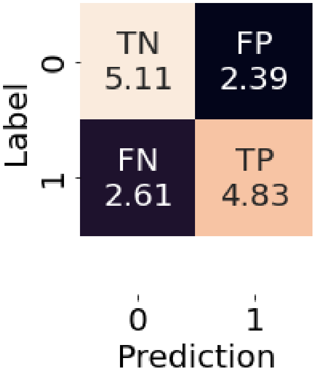
Different performance metrics are used to evaluate the Machine Learning Algorithm in the supervised classification model for predict the recovery in brain lesion of MS.



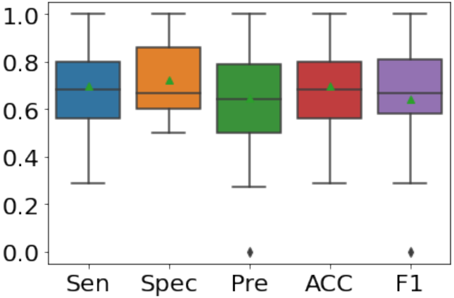
- $Sen = \frac{TP}{TP+FN}$
- $Spec = \frac{TN}{TN+FP}$
- $Pre = \frac{TP}{TP+FP}$
- $ACC = \frac{TP+TN}{TP+FP+TN+FN}$
- $F1 = 2 * \frac{Pre*Sen}{Pre+Sen}$

Metrics: Random forest classifier

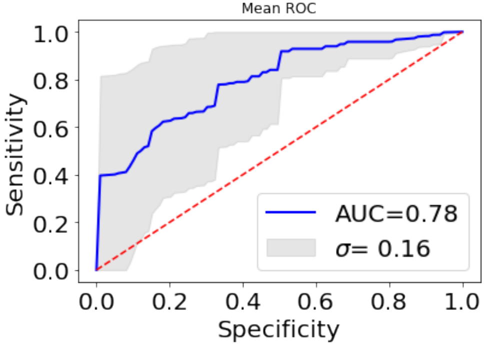
Different performance metrics are used to evaluate the Machine Learning Algorithm in the supervised classification model for predict the recovery in brain lesion of MS.



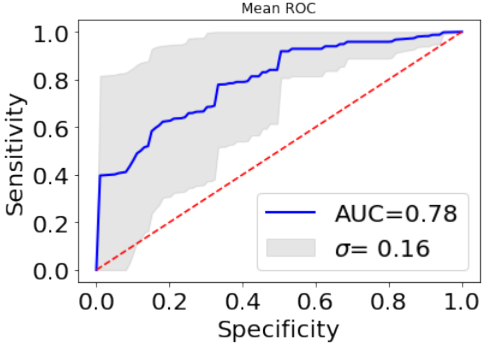
- $Sen = \frac{TP}{TP+FN}$
- $Spec = \frac{TN}{TN+FP}$
- $Pre = \frac{TP}{TP+FP}$
- $ACC = \frac{TP+TN}{TP+FP+TN+FN}$
- $F1 = 2 * \frac{Pre*Sen}{Pre+Sen}$

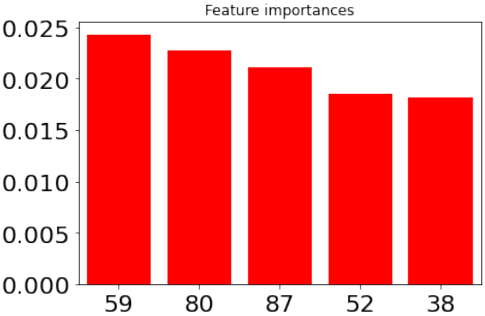


Classification Haralick: Result

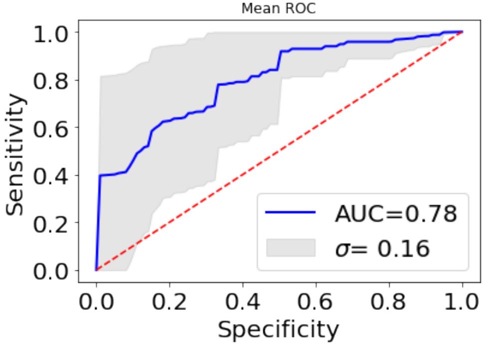


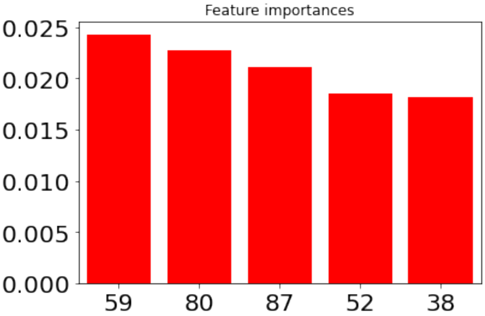
Classification Haralick: Result





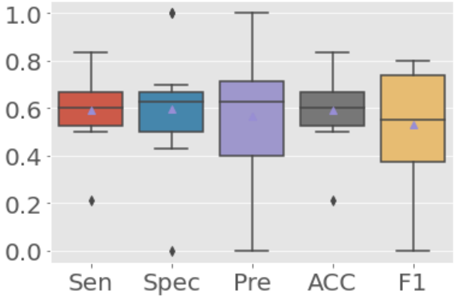
Classification Haralick: Result



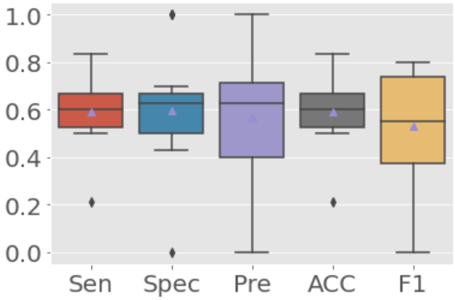


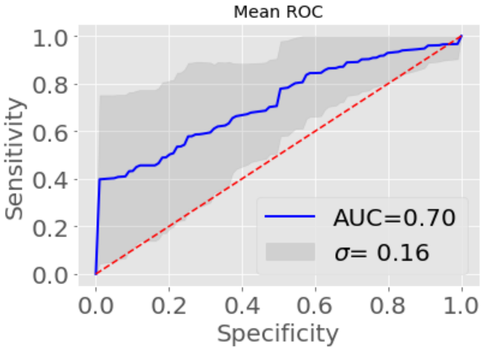
Features		Initial Condition			Feature
		MRI	GLCM		
Importance		Quantization	Distance	Direction	Haralick
1	59	3-bit	1	9	Correlation
2	80	3-bit	1	12	Correlation
3	87	3-bit	1	13	Correlation

Classification Correlation

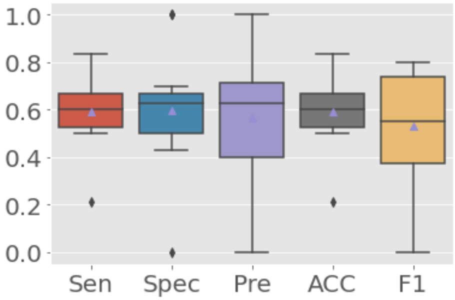


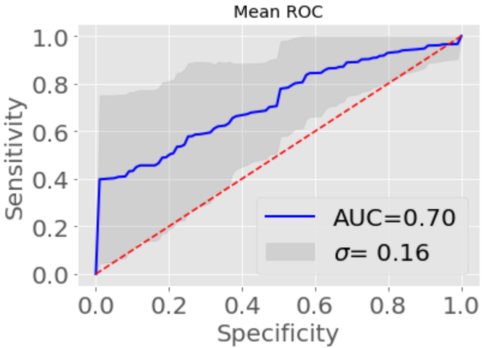
Classification Correlation





Classification Correlation

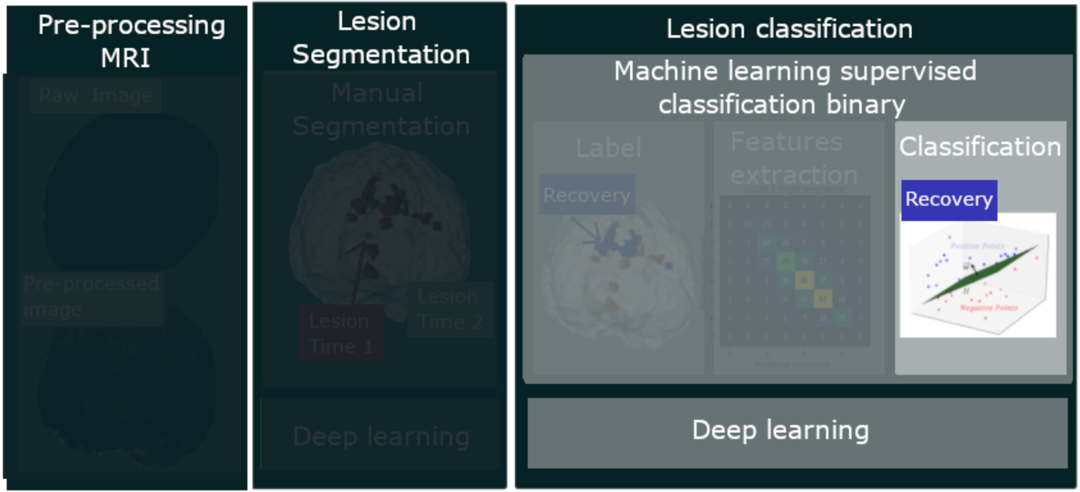




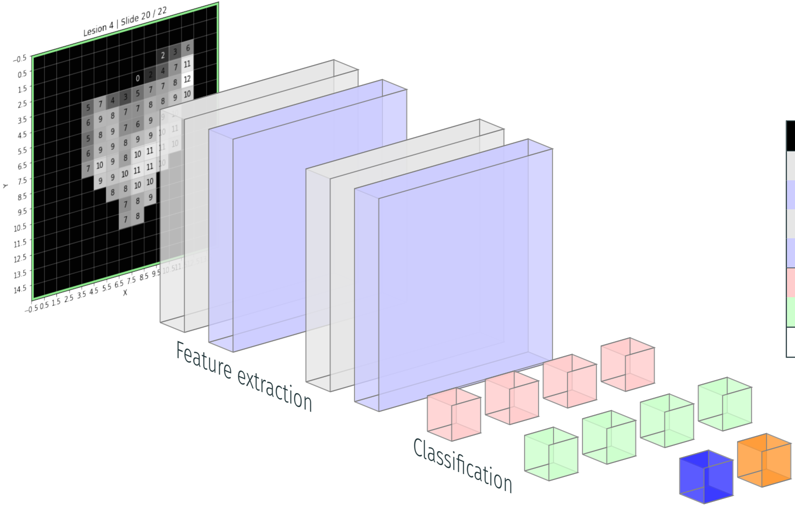
Features Haralick in MRI for prediction the brain lesion recovery in MS

Correlation see differences between recovery lesion and others lesions.

Pipeline: Deep learning Classification

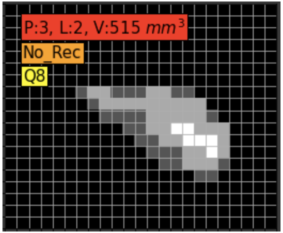


Deep learning CNN 3D: Classification



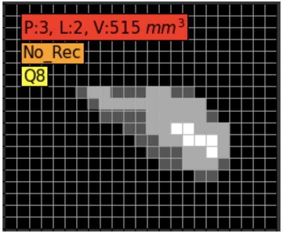
	Input	[20,20,20]
	Conv 3D	[3,3,3]
	Max. Pooling	[2,2,2]
	Conv 3D	[3,3,3]
	Max. Pooling	[2,2,2]
	Flatten	[432]
	FC layer	[32]
	Output	[2]

Result

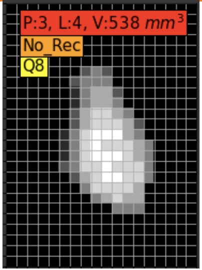


No Rec	TF

Result

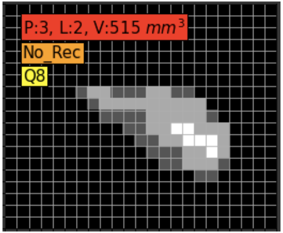


No Rec	TF

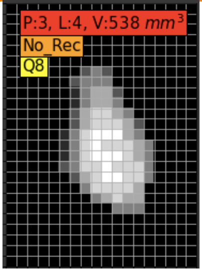


No Rec	TN

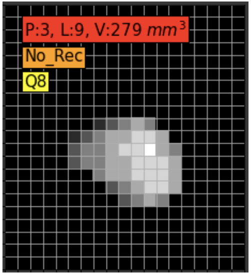
Result



No Rec	TF

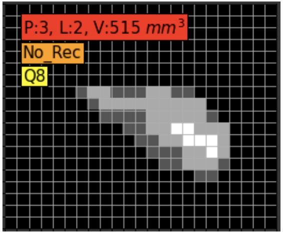


No Rec	TN

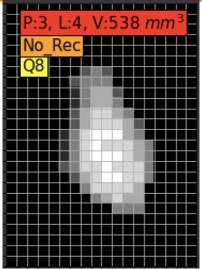


Rec	FP

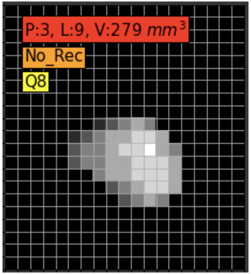
Result



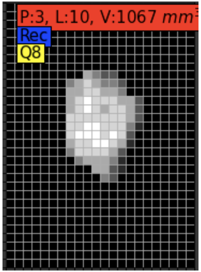
No Rec	TF



No Rec	TN

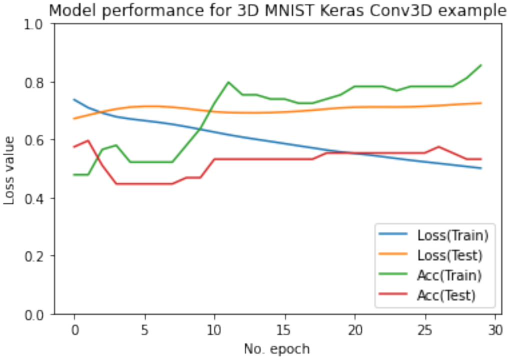


Rec	FP



Rec	TP

Deep learning: Classification



Optimizer:
Adam

Loss:
Categorical Cross-Entropy

Evaluate:
Loss
Acc

Future Work

We have different results, so we want compare

The idea is compare different result as a deep learning classification, Haralick, correlation, and others.

Whit this comparisons analyze which is the differences between the lesion recovery in one year and other lesions.

Until now the best result for classify the lesion is the Haralick: correlation we obtain 0.7 of AUC only with this parameter.

The idea is to see the results of deep learning segmentation and manual segmentation, analyze if is possible in the future no depend of the expert for the segmentation.