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Rafael Nozal Cañadas - 31/March/2023

/:Health / Data / Lab /

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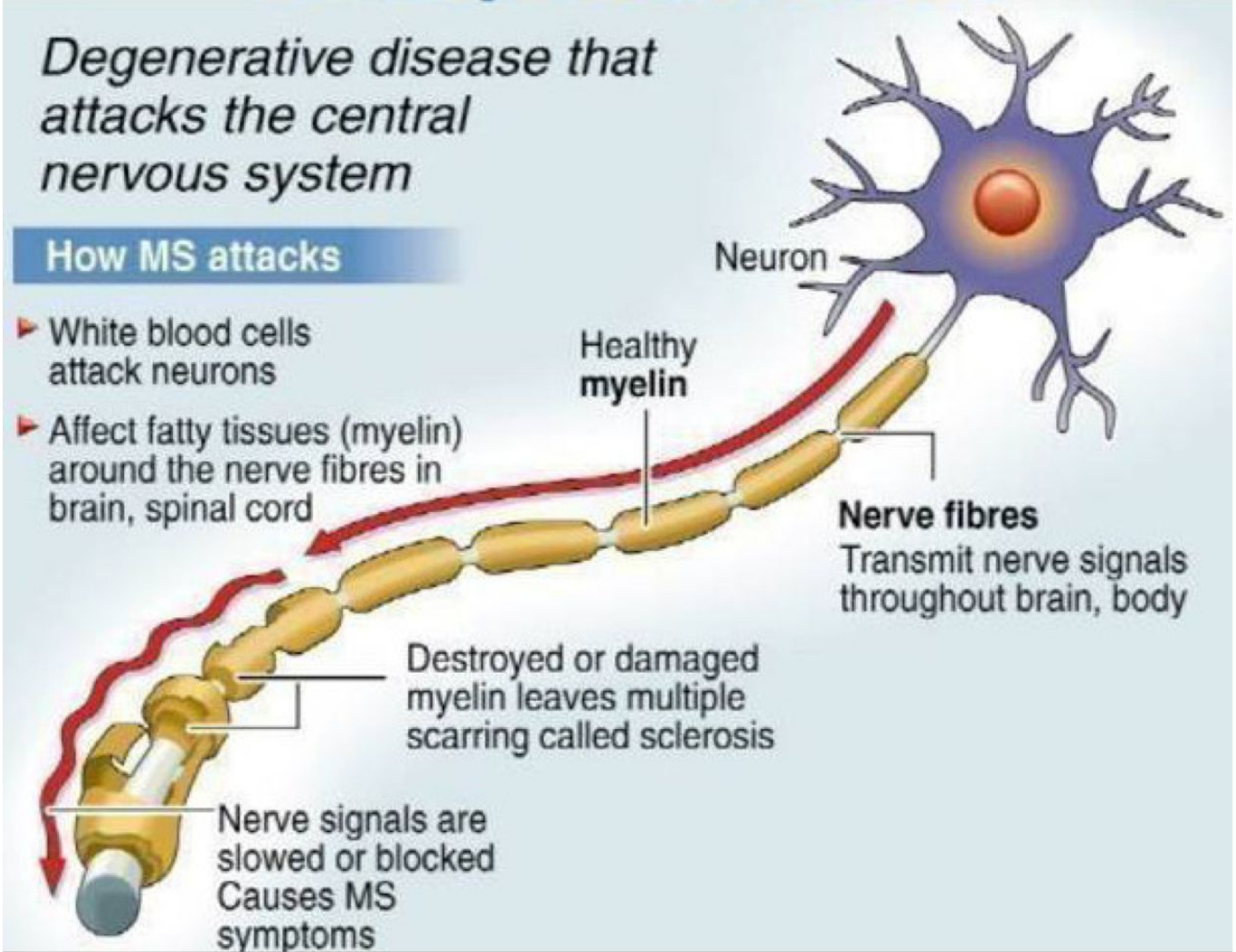
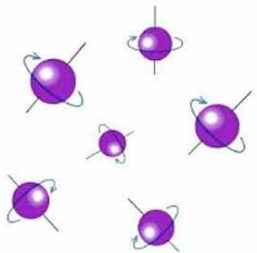
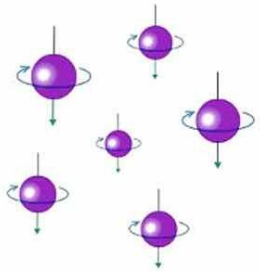
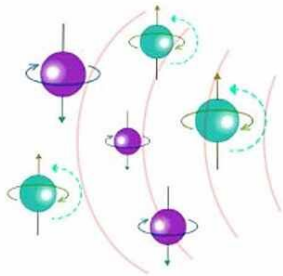
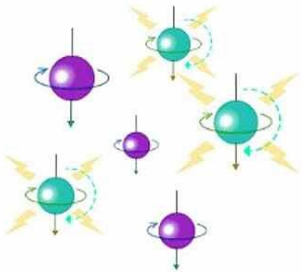
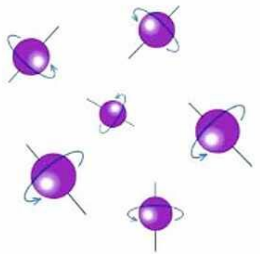
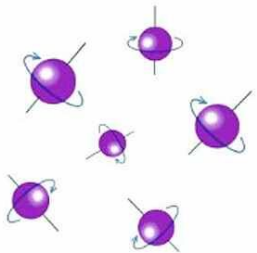
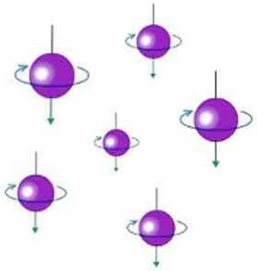
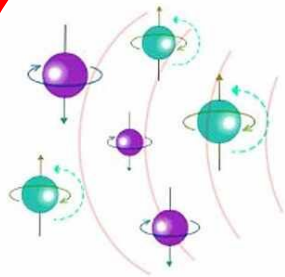
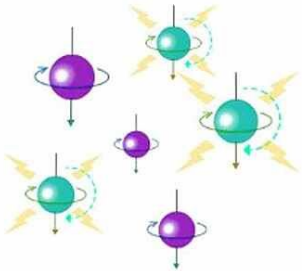
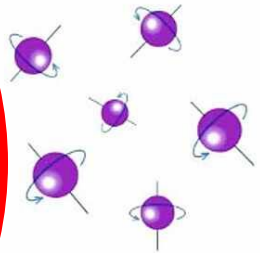

Degenerative disease that attacks the central nervous system
How MS attacks
White blood cells attack neurons
Affect fatty tissues (myelin) around the nerve fibres in brain, spinal cord
Neuron
Healthy myelin
Nerve fibres
Transmit nerve signals throughout brain, body
Destroyed or damaged myelin leaves multiple scarring called sclerosis
Nerve signals are slowed or blocked
Causes MS symptoms


SIGNA
Explorer
100 GAUSS

MRI-generated magnetic field OFF	MRI-generated magnetic field ON	MRI-generated radio wave frequency pulse ON	MRI-generated radio wave frequency pulse OFF	MRI-generated magnetic field OFF
1 	2 	3 	4 	5 
Under normal circumstances, hydrogen protons in the body spin along their individual axes in random alignment.	When the body is placed in a strong magnetic field, such as that generated by MRI, the protons' axes all line up.	Radio wave frequency (RF) pulses are then transmitted to the area of examination, causing deflection of the magnetic vector of unmatched protons.	RF pulses are terminated, causing the magnetic vector of deflected protons to realign with the MRI-generated magnetic field. This emits a radio wave signal that can be captured by receiver coils in the MRI scanner and transformed into images.	Removing the body from the MRI-generated magnetic field allows the magnetic vectors of the hydrogen protons to return to their resting state.

MRI-generated magnetic field OFF	MRI-generated magnetic field ON	MRI-generated radio wave frequency pulse ON	MRI-generated radio wave frequency pulse OFF	MRI-generated magnetic field OFF
1 	2 	3 	4 	5 
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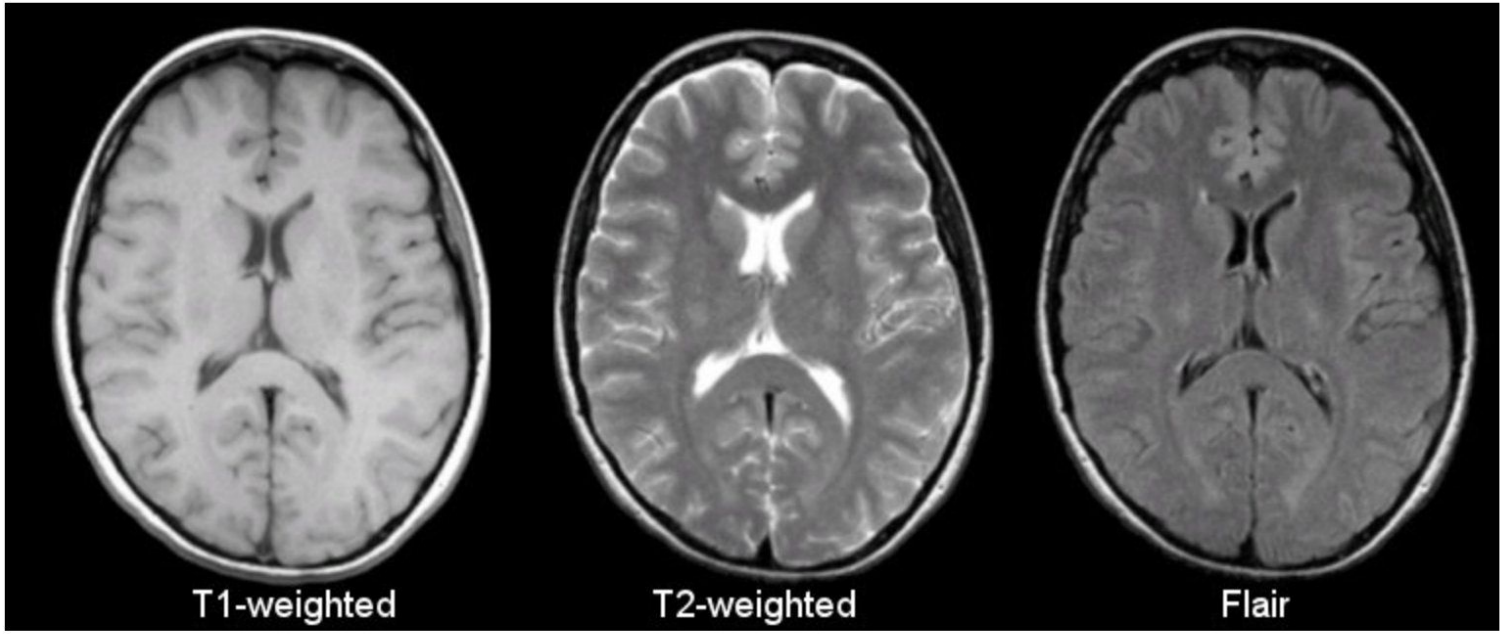

Tissue	T1-Weighted	T2-Weighted	Flair
CSF	Dark	Bright	Dark
White Matter	Light	Dark Gray	Dark Gray
Cortex	Gray	Light Gray	Light Gray
Fat (within bone marrow)	Bright	Light	Light
Inflammation (infection, demyelination)	Dark	Bright	Bright

THE MS LESION CHECKLIST

Description of Lesion Types	Present = yes Absent = no (Circle)	Note Number of Lesions
Nerve root entry zone. The lesions that track along nerve roots, especially the trigeminal nerve root, favor an inflammatory over vascular etiology. In an active MS lesion, enhancement may extend from parenchyma into nerve proper.[16]	Yes No	
Middle cerebellar peduncle. Middle cerebellar peduncle (MCP) involvement in MS is seen frequently, but less than in the body of the pons.[17,18]	Yes No	
Medial longitudinal fasciculus. This tract is commonly affected in MS both clinically (internuclear ophthalmoplegia [INO]) and on MRI, however, vascular etiology is more common. Bilateral internuclear ophthalmoplegia may be somewhat more common in MS compared to stroke but is seen in many conditions.[19]	Yes No	
Other brainstem lesions adjacent to cerebrospinal fluid border. "With remarkable regularity the brainstem lesions [are] contiguous with the inner and outer cerebrospinal fluid (CSF) borders."[4]	Yes No	
Cerebellar hemisphere. Demyelinating cerebellar lesions are not contiguous with the CSF border, but appear within the deep cerebellar white matter. The cerebellum is often spared in vascular disease, but is commonly affected in MS, especially when the brainstem is involved.[4,16]	Yes No	
Inferior temporal lobe. Another area of white matter that is preferentially affected in MS compared to vascular disease.[2]	Yes No	
Lesions adjacent to lateral ventricle—*Dawson's fingers*. "Wedge-shaped areas with broad base to the [lateral] ventricle, and extensions into adjoining tissue in the form of finger-like processes or ampullae, in each of which a central vessel could usually be found."[3] Frontal caps and bands along ventricular surface are normal signs of aging and should be not be confused with periventricular demyelinating lesions.[10]	Yes No	
Corpus callosum. Demyelination at the callosal-septal interface may take the form of discrete lesions or more diffuse lumpy-bumpy appearance (ie, dot-dash sign), which is seen on multiple sagittal FLAIR images, in contrast to the smooth appearance of the subcallosal vein that is usually only seen on a single sagittal image.[20,21]	Yes No	
U-fibers (arcuate fibers). U-fiber lesions that track along arcuate fibers are particularly characteristic of demyelination and are not seen in normal aging or vascular disease.[22]	Yes No	
Other cortical/juxtacortical lesions. Plaques in cortex and at junction of cortex and white matter are very common in MS. A recent study recommended combining cortical and juxtacortical lesions for purposes of MS diagnosis.[23] Cortical lesions may be better appreciated on double inversion recovery (DIR) sequence, which is not routinely available.	Yes No	

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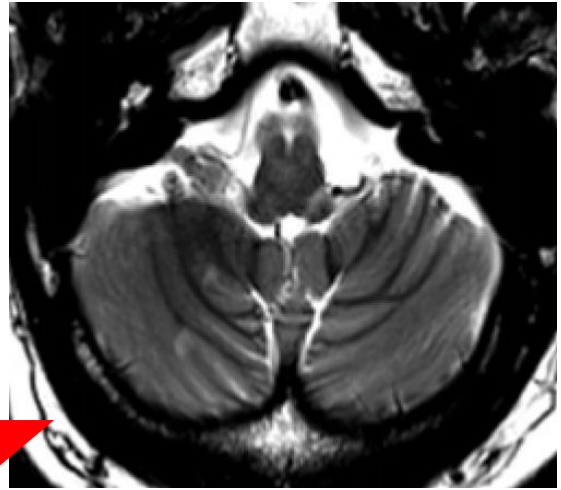

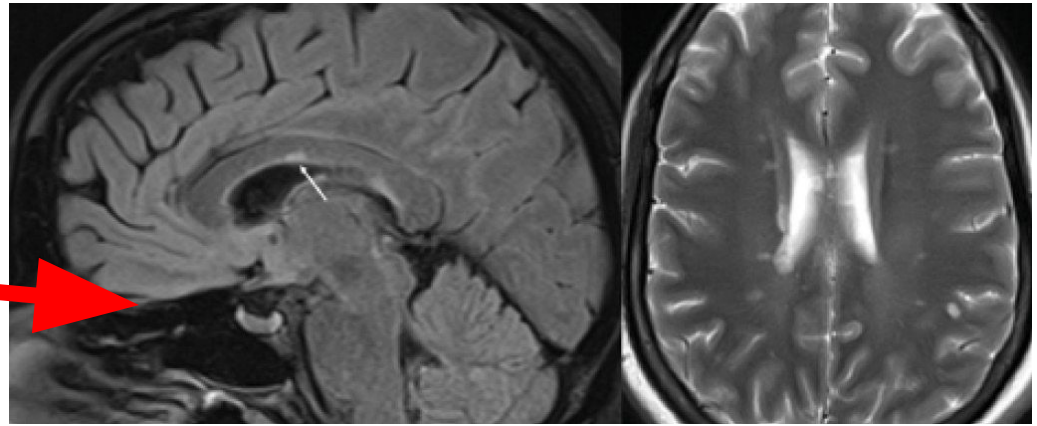

THE RED FLAG LIST

Look for another diagnosis instead of multiple sclerosis (MS) when these findings are present.

Normal MRI (No T2W lesions)
However, patients with neurologic signs and normal brain MRI findings may have spinal cord lesions.[6]

Multiple white matter hyperintensities (WMH) with very few (<20%) MS-typical lesions
(See The MS Checklist.)

No T1W hypointense lesions on T1W sequence
Approximately half of MS lesions will show T1 hypointensity a year after their genesis, making absence of T1 hypointense lesions a red flag.[24]

Diffusion restriction is a hallmark of acute ischemia and very rare in MS
Ischemic lesions are bright on diffusion-weighted images (DWI) and dark on apparent diffusion coefficient (ADC) images.

Lesions enhancing for >3 months
Acute phase of gadolinium positivity in MS lesions lasts on average 3 weeks (range, 2-12 wk).[25] Large tumefactive lesions occasionally enhance longer.

All lesions enhancing
MS typically shows both acute and chronic lesions.

Signs of hemorrhage
Chronic hemorrhage appears as a blooming artifact on susceptibility weighted imaging (SWI) sequence, if intraparenchymal, or dark band around cortex (siderosis). Neither is seen in MS.

Edema/mass effect around lesions
A caveat is tumefactive lesions of MS, which have a highly variable appearance. Often, more typical MS lesions are seen alongside tumefactive lesions.

Diffuse meningeal enhancement
Although focal leptomeningeal-meningeal enhancement has been reported in MS, diffuse meningeal enhancement is not consistent with MS.

Symmetrical abnormalities
Symmetrical lesions are more typical of genetic and metabolic disorders, but may be seen in advanced MS.

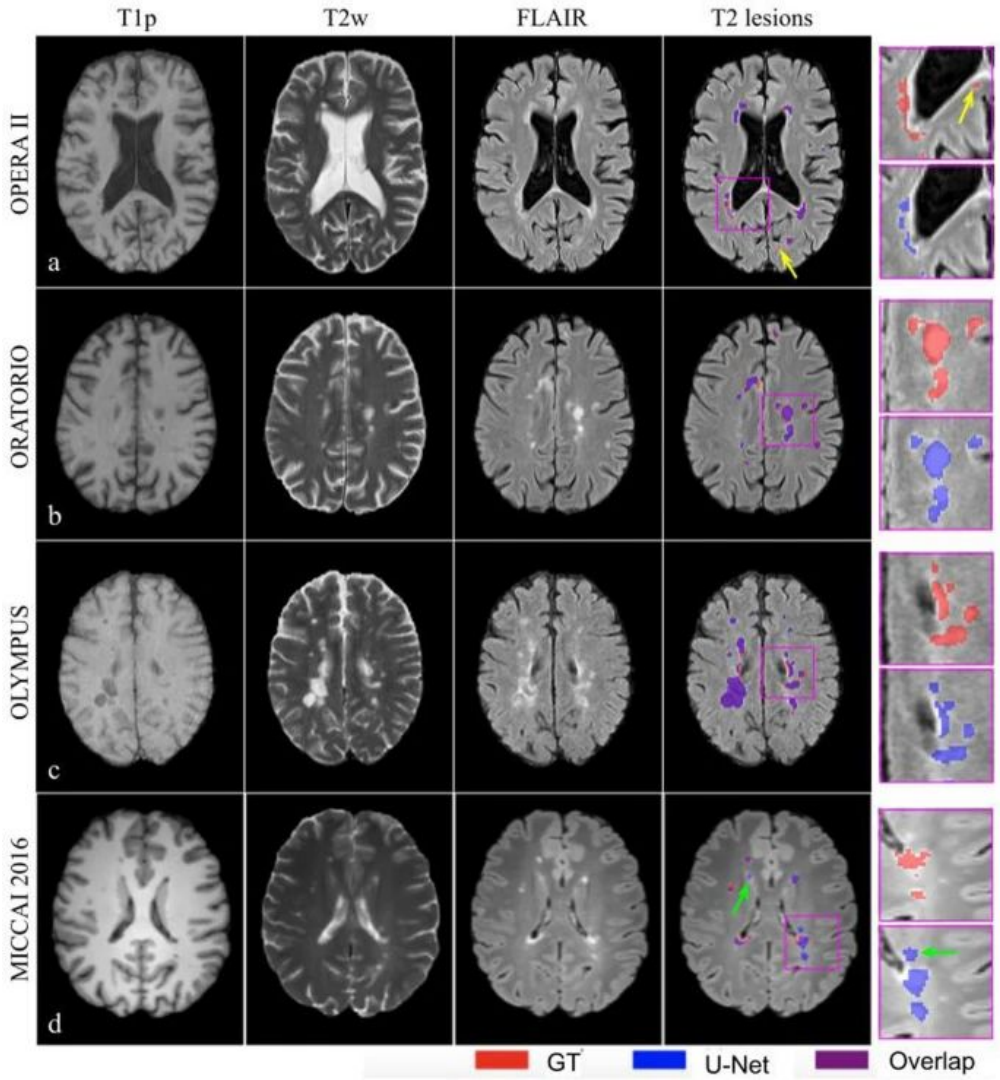

Figure 2

*Illustrative examples of T2 lesion segmentations from GT and multi-arm U-Net predicted masks. The inputs to the model: T1p, T2w, and FLAIR MRI, are shown in columns 1–3. Column 4 shows the overlay of T2 lesions on FLAIR MRI, with GT shown in red, model predictions in blue, and their overlap shown in purple. Magnified insets are shown in column 5 for a better visualization of the segmentation agreement between model predictions and GT annotations. Yellow arrows point to false negative lesions and green arrows point to false positive lesions. Rows (**a**–**c**) are examples of T2 lesion segmentations from internal test sets of a patient with relapsing MS in the OPERA II trial (**a**) and patients with PPMS in the ORATORIO (**b**) and OLYMPUS (**c**) trials. Row d corresponds to an illustrative patient with MS in the MICCAI 2016 dataset used as the external test set here. The examples highlight the good agreement of model predictions with GT masks and have high sensitivity to detect a majority of small lesions across various test sets. GT ground truth.*

Introduction

- Human experts have too high variability diagnosing MS lesions. And they can do it at about 70% true positive rate.

- Other machine learning models exist that perform similarly to human expertise. This models have been tested with open data in a multitude of challenges.

- What is new here is a combination of models that seems to perform better for 3D images coming from T2

Materials and methods

Training dataset:

- MRI datasets and GT lesion annotations from the OPERA I trial (NCT01247324, *n* = 821)

Test dataset:

- OPERA II (NCT01412333, *n* = 835, RMS)
- ORATORIO (NCT01194570, *n* = 732, primary progressive MS [PPMS]) trials of ocrelizumab
- OLYMPUS (NCT00087529, *n* = 439, PPMS) trial of rituximab as the internal test sets.

Request data at: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx.

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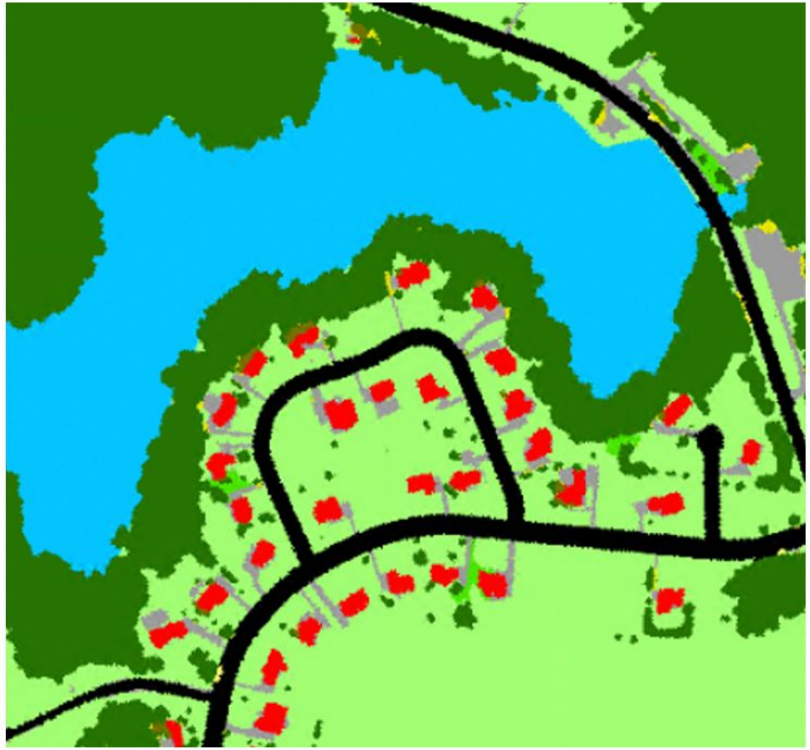

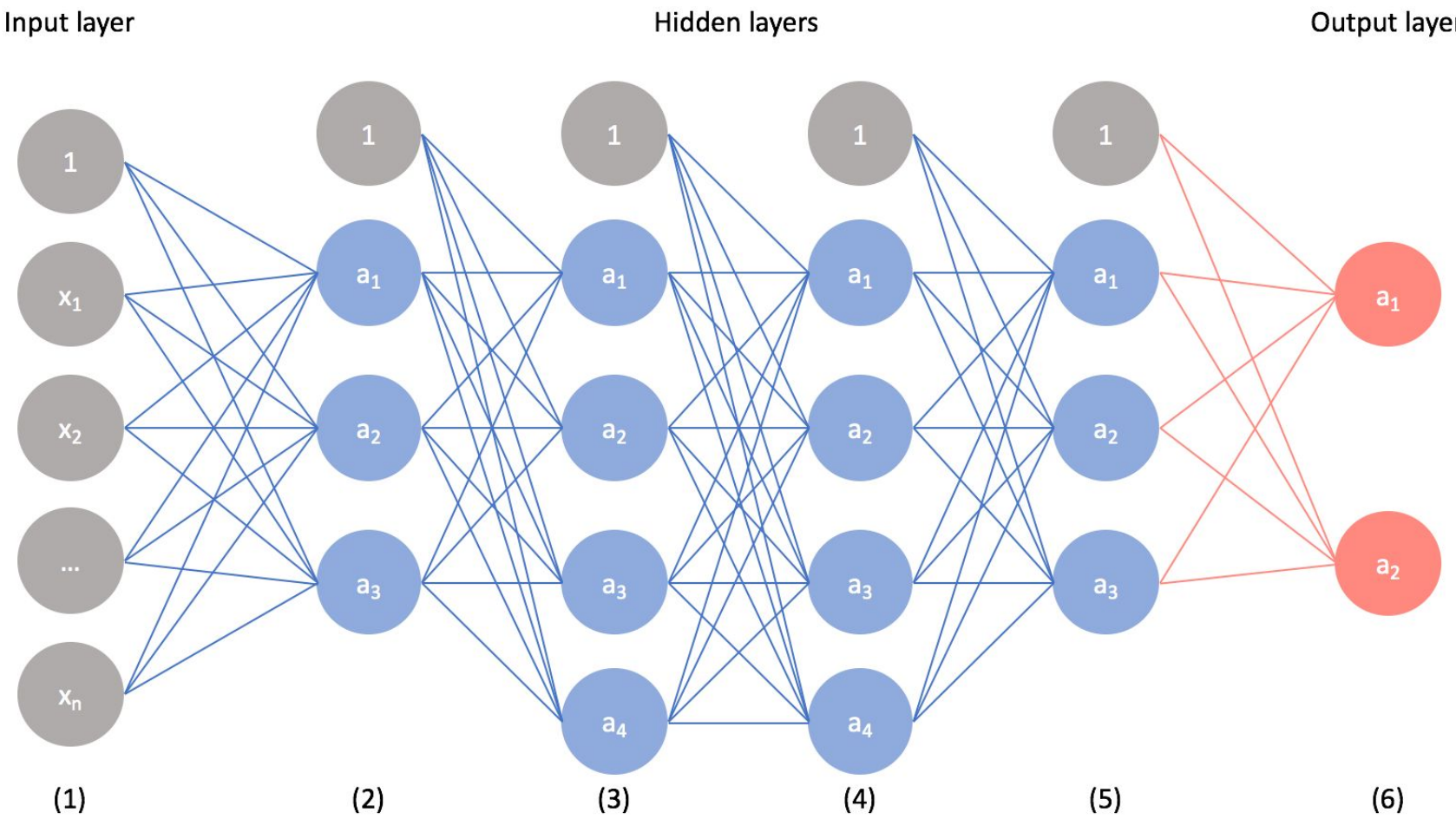
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Hidden layers
Output layer
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x_2
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x_n
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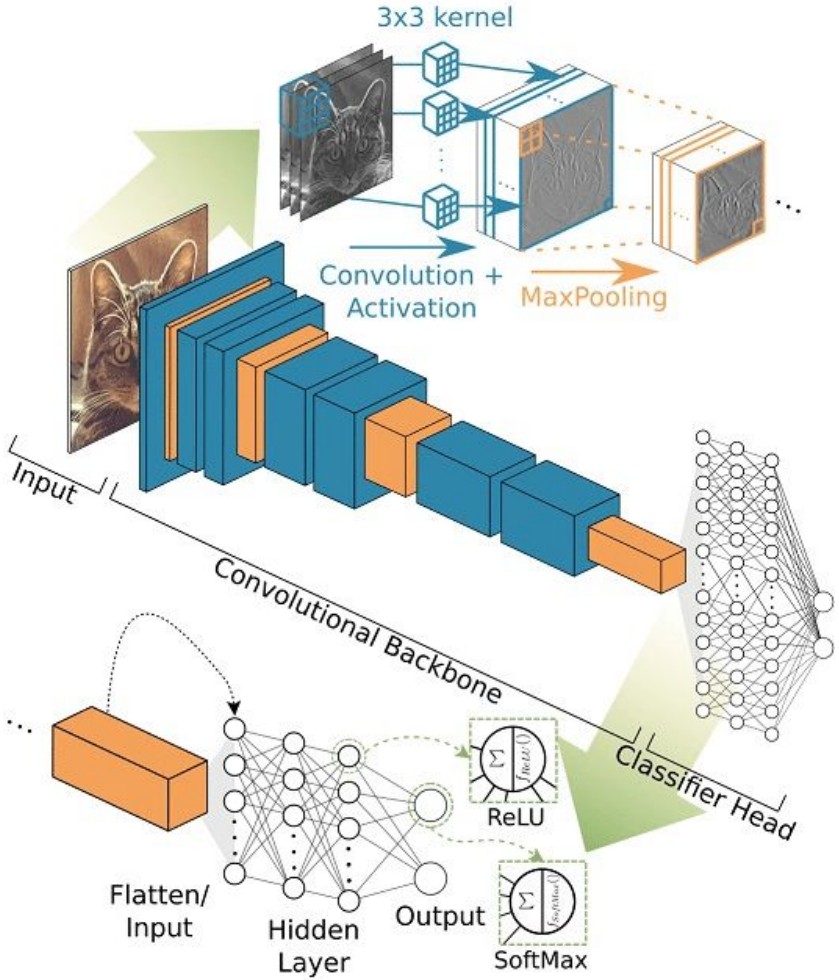
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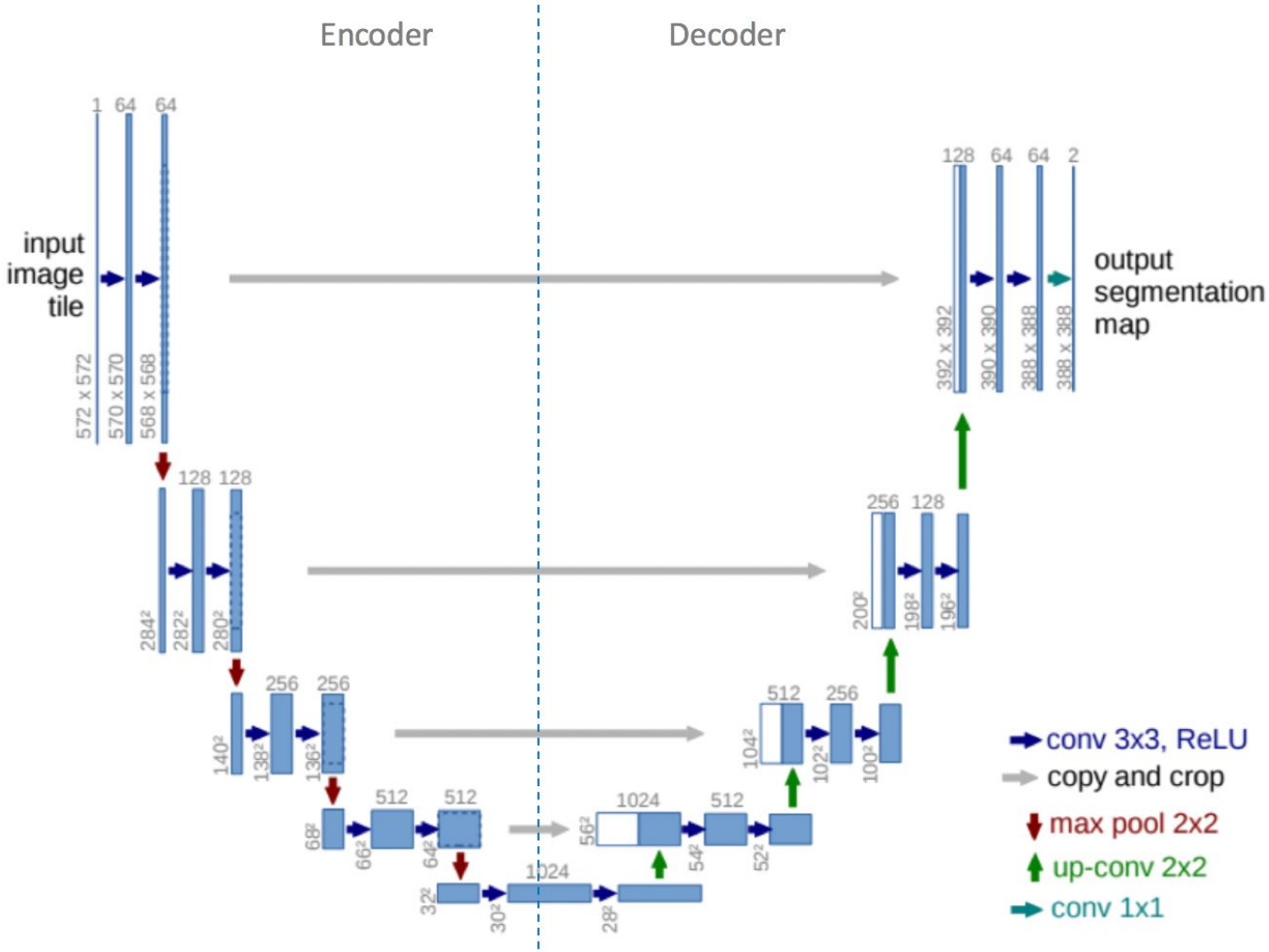
Convolution +
Activation
MaxPooling
Input
Convolutional Backbone
Classifier Head
ReLU
Flatten/
Input
Hidden
Layer
Output
SoftMax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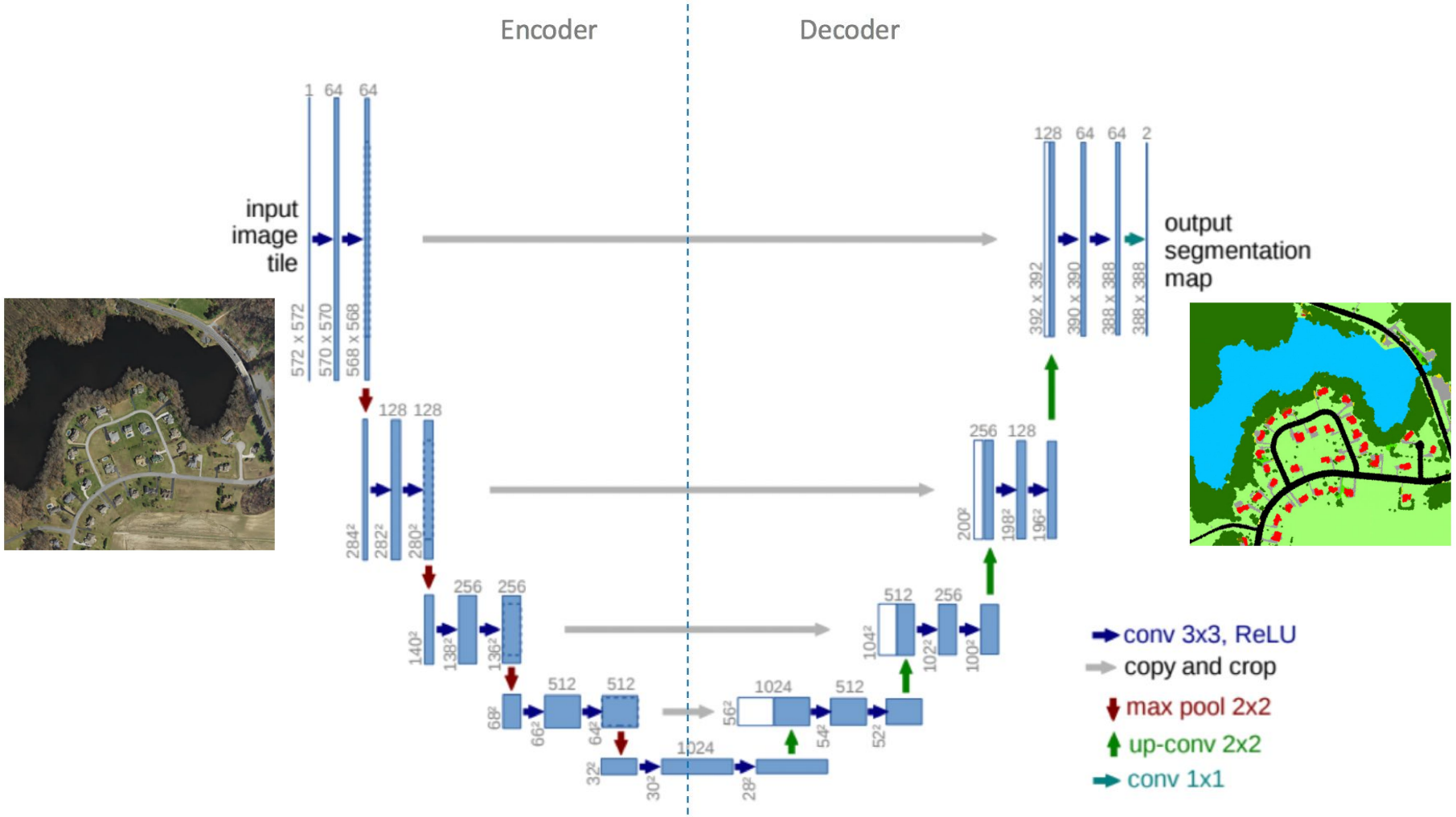
Decoder
input image tile
output segmentation map
conv 3x3, ReLU
copy and crop
max pool 2x2
up-conv 2x2
conv 1x1


Encoder
Decoder
input image tile
output segmentation map
1
64
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572 x 572
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280²
256
256
140²
138²
136²
512
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68²
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64²
1024
32²
30²
28²
512
1024
56²
54²
52²
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512
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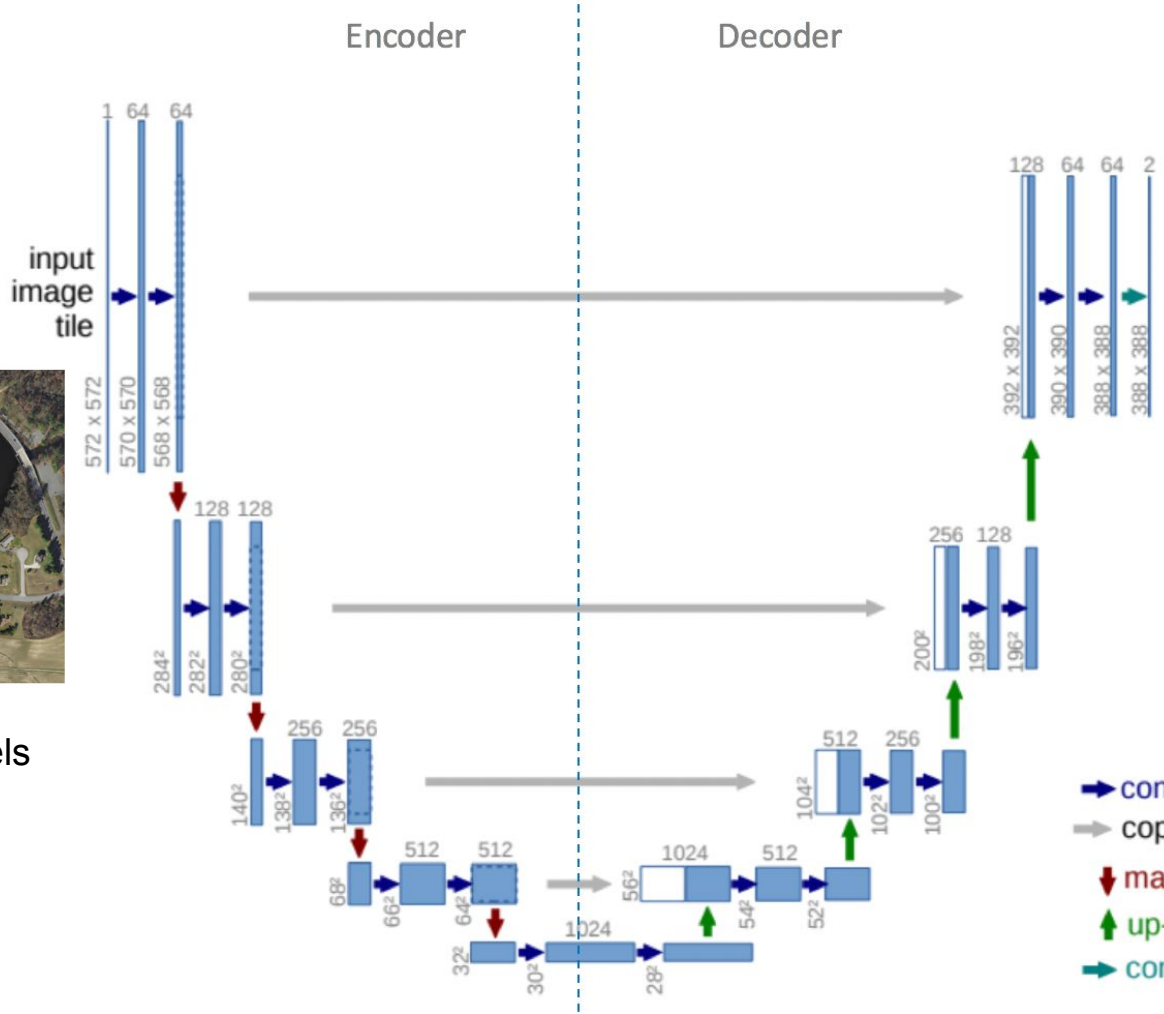
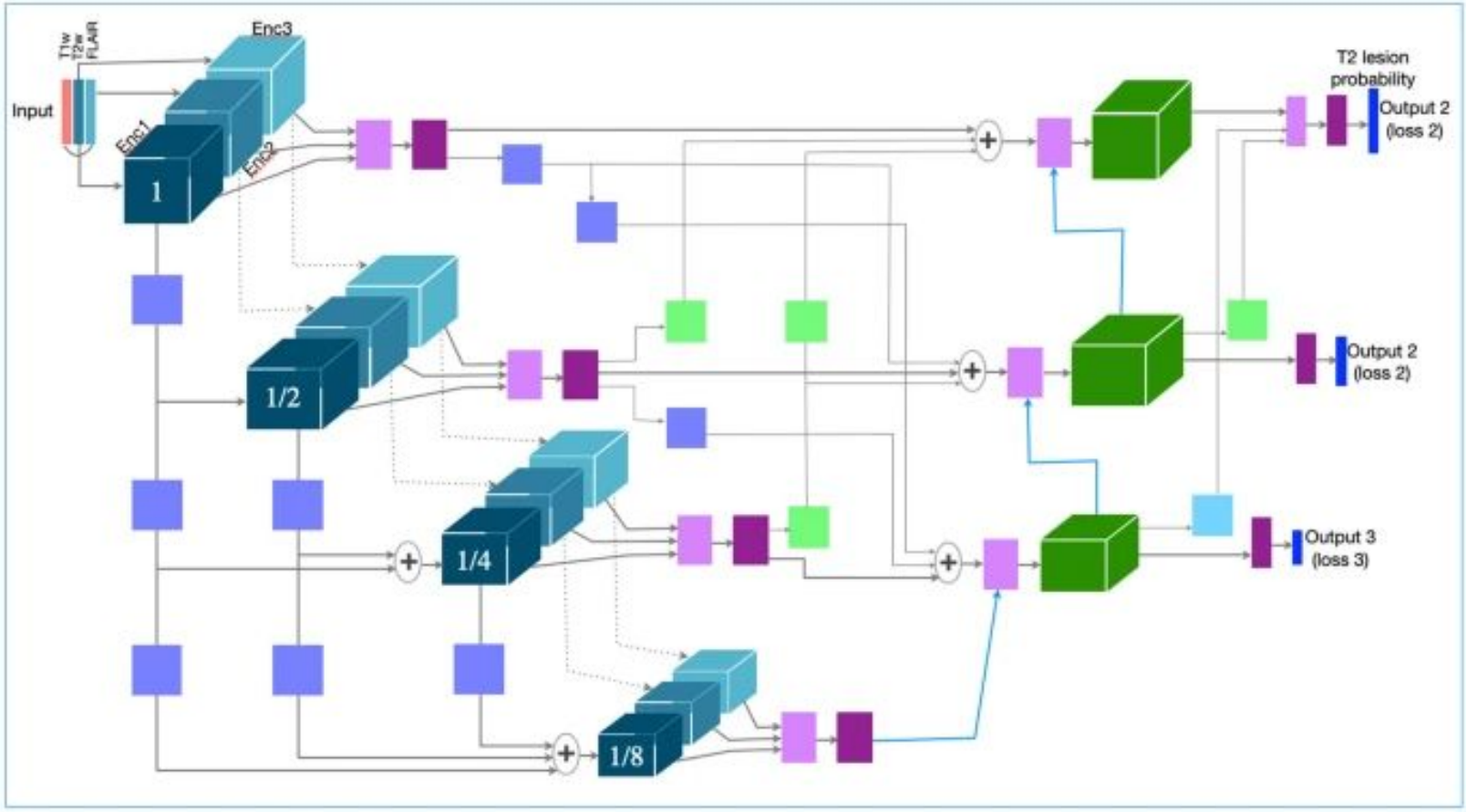
102²
100²
256
128
200²
198²
196²
128
64
64
2
392 x 392
390 x 390
388 x 388
388 x 388
conv 3x3, ReLU
copy and crop
max pool 2x2
up-conv 2x2
conv 1x1

H x W x Channels



H x W x Classes



Residual block: Enc1 - encoder 1, Enc2- encoder2, Enc3 - encoder 3
1x3x3 conv, ReLu, Batch Norm (BN)
3x3x3 conv, ReLu, BN

Residual block:
3x3x3 conv, ReLu, BN
3x3x3 conv, ReLu, BN

Upsample by 2, project

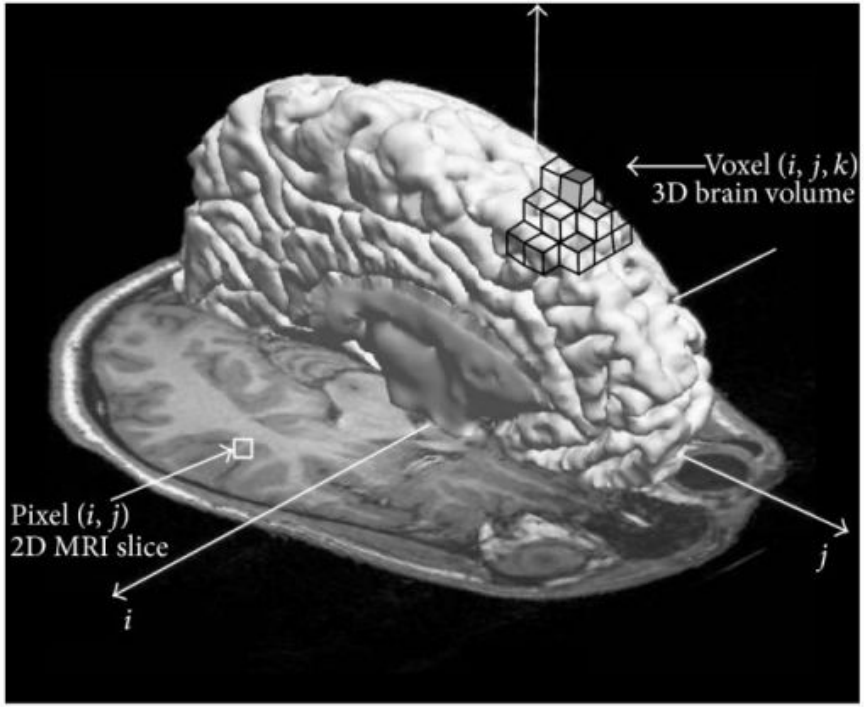
Upsample by 4, project

Upsample by 2

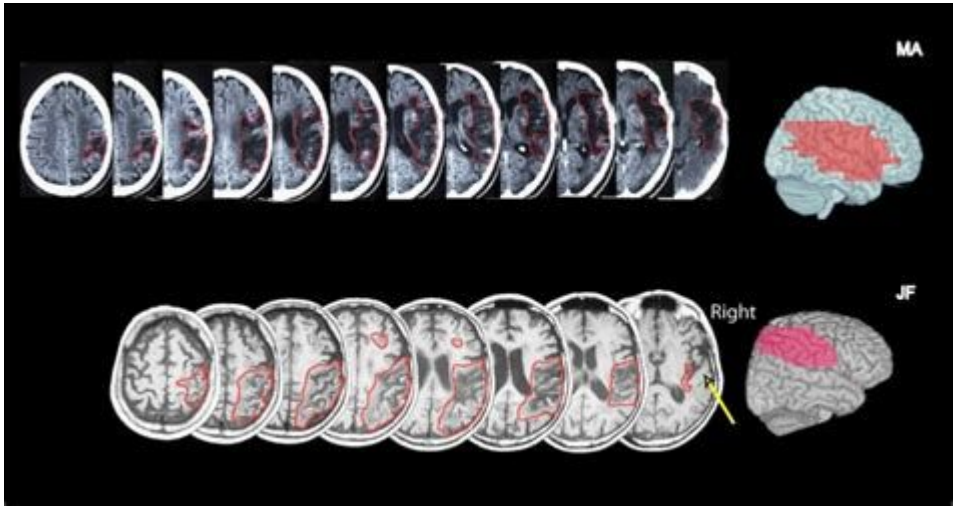
Down sample by 2:
3x3x3, stride 2 conv, ReLu, BN

Concatenate

Project: 1x1x1conv, ReLu, BN



3D voxel
(≤ 30 µL, 3–10 voxels)



2.5D stack

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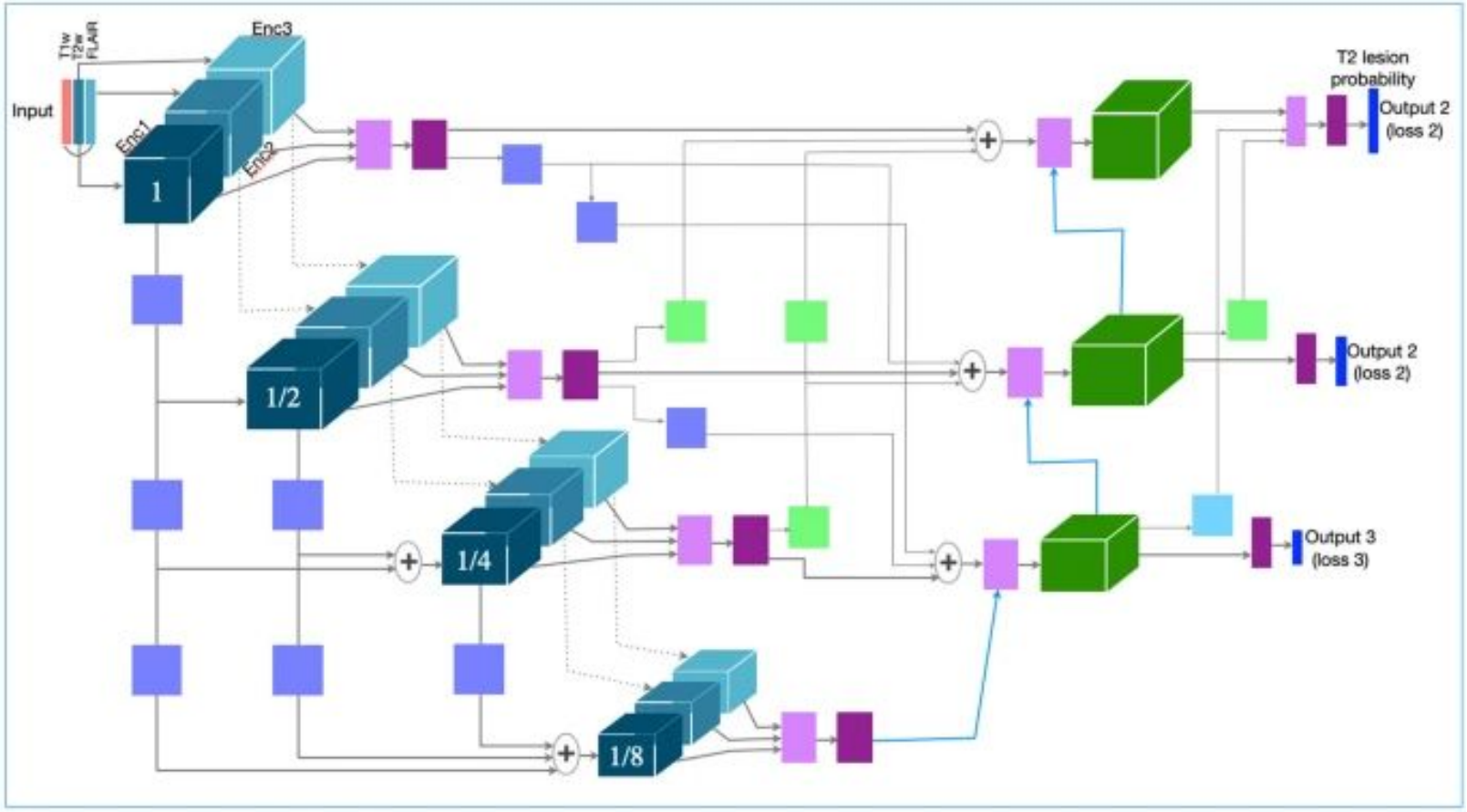

Residual block: Enc1 - encoder 1, Enc2- encoder2, Enc3 - encoder 3
1x3x3 conv, ReLu, Batch Norm (BN)
3x3x3 conv, ReLu, BN

Residual block:
3x3x3 conv, ReLu, BN
3x3x3 conv, ReLu, BN

Upsample by 2, project

Upsample by 4, project

Upsample by 2

Down sample by 2:
3x3x3, stride 2 conv, ReLu, BN

Concatenate

Project: 1x1x1conv, ReLu, BN

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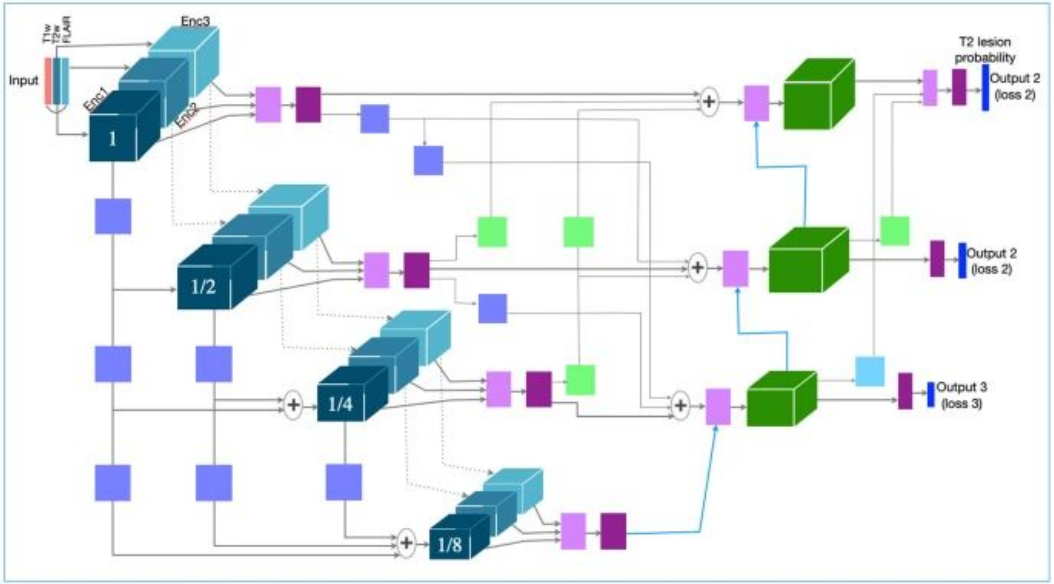


The lession got bigger?

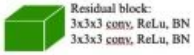
The lession remain the same?

The lession get smaller?

Residual block: Enc1 - encoder 1, Enc2- encoder2, Enc3 - encoder 3
1x3x3 conv, ReLu, Batch Norm (BN)
3x3x3 conv, ReLu, BN

Control groups

MS group



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Upsample by 4, project

Upsample by 2

Down sample by 2:
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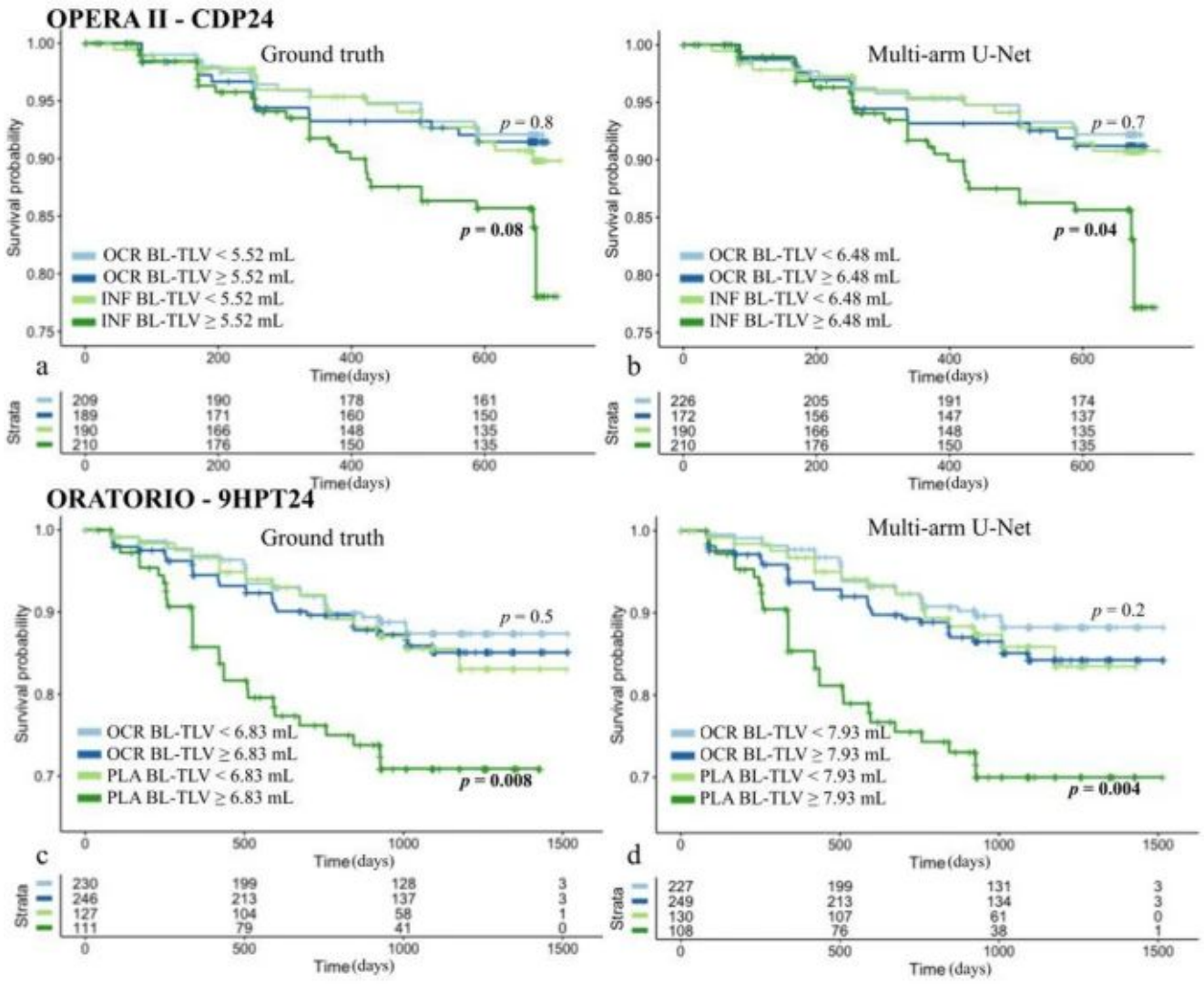
Concatenate

Project: 1x1x1conv, ReLu, BN

Performance

The trained model achieved a mean dice coefficient of ≥ 0.66 and a lesion detection sensitivity of ≥ 0.72 across the internal test datasets. On the external test dataset, the model achieved a mean dice coefficient of 0.62, which is comparable to 0.59 from the best model in the challenge, and a lesion detection sensitivity of 0.68.


OPERA II - CDP24
Ground truth
Survival probability
p = 0.8
p = 0.08
OCR BL-TLV < 5.52 mL
OCR BL-TLV ≥ 5.52 mL
INF BL-TLV < 5.52 mL
INF BL-TLV ≥ 5.52 mL
a
Time(days)
Strata
209 190 178 161
189 171 160 150
190 166 148 135
210 176 150 135
Multi-arm U-Net
p = 0.7
p = 0.04
OCR BL-TLV < 6.48 mL
OCR BL-TLV ≥ 6.48 mL
INF BL-TLV < 6.48 mL
INF BL-TLV ≥ 6.48 mL
b
226 205 191 174
172 156 147 137
190 166 148 135
210 176 150 135
ORATORIO - 9HPT24
Ground truth
p = 0.5
p = 0.008
OCR BL-TLV < 6.83 mL
OCR BL-TLV ≥ 6.83 mL
PLA BL-TLV < 6.83 mL
PLA BL-TLV ≥ 6.83 mL
c
230 199 128 3
246 213 137 3
127 104 58 1
111 79 41 0
Multi-arm U-Net
p = 0.2
p = 0.004
OCR BL-TLV < 7.93 mL
OCR BL-TLV ≥ 7.93 mL
PLA BL-TLV < 7.93 mL
PLA BL-TLV ≥ 7.93 mL
d
227 199 131 3
249 213 134 3
130 107 61 0
108 76 38 1

Other works

Similar performance to other product but with smaller input

Other competitor is a NN-Unet, that generate U-nets depending on your input data, and adjust the models until the data fit well

Training

The model was implemented in Python using Keras in Tensorflow and was trained using three-fold cross-validation with splits at the patient level. Input MRI data were rescaled to the same intensity range, clipped to remove intensity outliers, and normalized by z-scoring using the mean and standard deviation of intensities within the 1st and 99th percentiles. 3D patches of 32 × 96 × 96 from T2w, FLAIR, and T1p sequences concatenated along the channel dimension were used as inputs. The 3D patches were created using a sliding approach with overlaps (20%) and patches containing T2 lesions were retained in the training and validation sets. As the patches were relatively large, they included a large portion that did not contain any lesions and inclusion of negative patches decreased model performance. During training, half of the input images were augmented randomly on the fly with affine transformations and elastic deformations. The models were trained on NVIDIA V100 GPUs for 30 epochs using an Adam optimizer with an initial learning rate of 0.0001 and a batch size of 10. The training took 9 to 12 days.

The end!