Università degli Studi di Padova

Dipartimento di Ingegneria dell'Informazione

Lymphoma Subtype Classification Using Neural Networks To Support Human Hematopathologist decisions

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Human Data Analytics
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Introduction

Background

- **Lymphoma** is a type of cancer that begins in lymphocytes.
- The delivered **treatment** depends on the type of the lymphoma.
- **Lymphoma subtype classification** is a **complex task** even for expert hematopathologists.
- Implementation of algorithms for the **automated classification** of Lymphoma subtypes could be helpful to support physicians' decisions.
- Deep learning models struggles to show impact in medical domain due to a **lack of transparency**.

Aim of the study

- Perform **lymphoma subtype classification** using neural networks.
- Provide **visual explanations** for machine’s decisions.

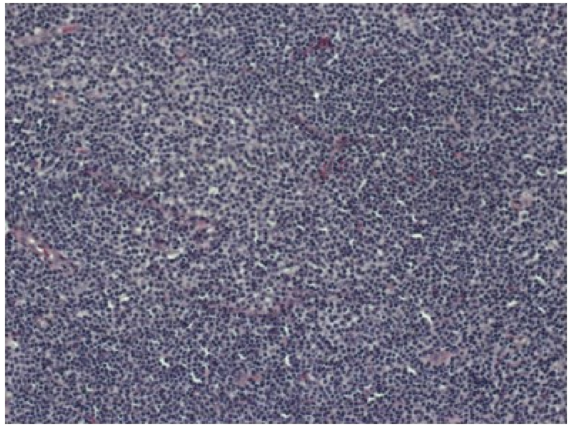
Dataset

- 374 images of size 1388x1040
  - 113 images for Chronic Lymphocytic Leukemia (CLL)
  - 139 images for Follicular Lymphoma (FL)
  - 122 images Mantle Cell Lymphoma (MCL)

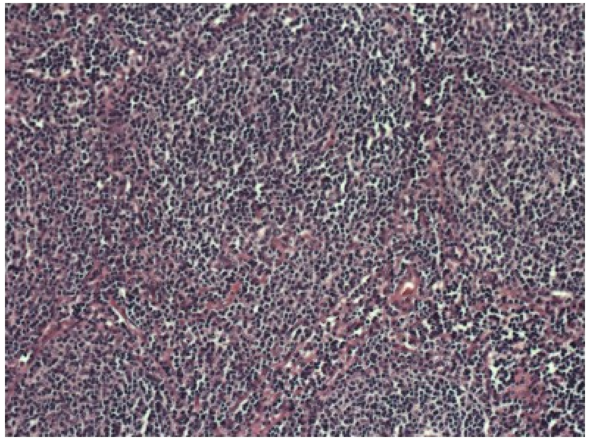
- Large degree of staining and sectioning **variation**.

- Randomly divided into **training, validation, and test set** according to **6:2:2**.

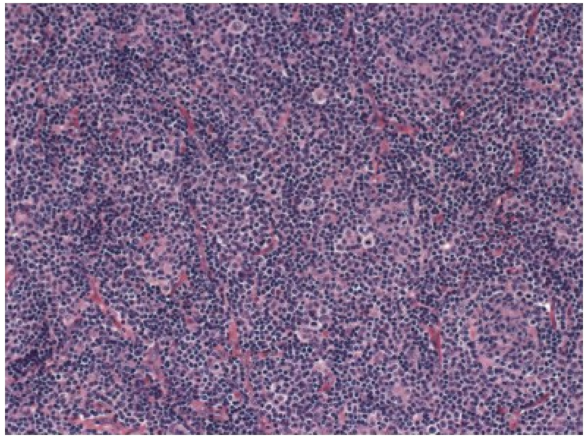
CLL



FL



MCL

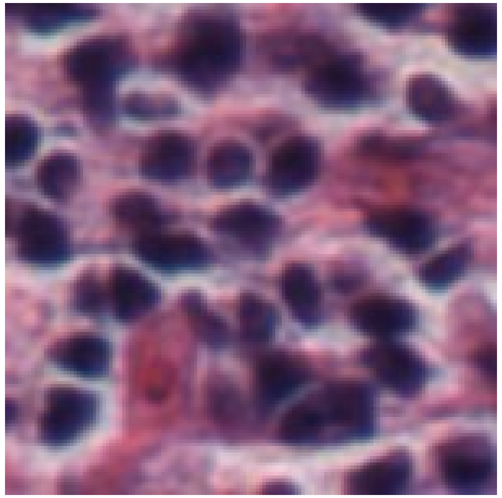


Pre-processing (1)

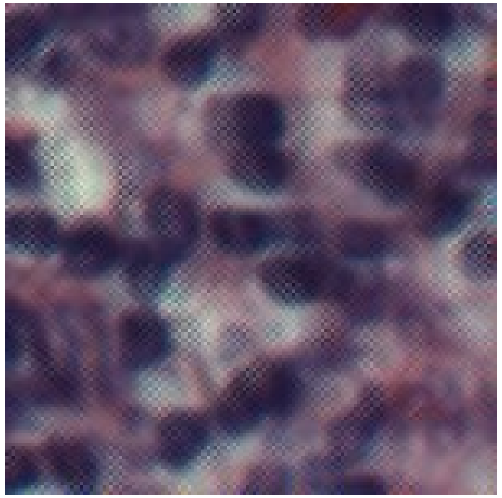
Artifact management

- 3x3 **gaussian filter**.
- Images affected by artifacts **detected automatically**.
  - **Variance** of image filtered using a **Laplacian filter** greater than 700 → Presence of artifacts

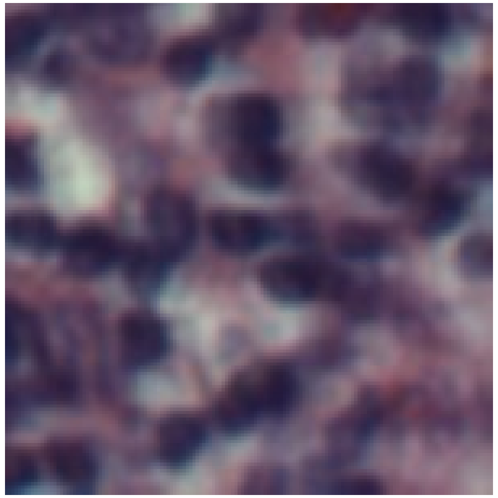
No artifacts



Artifacts



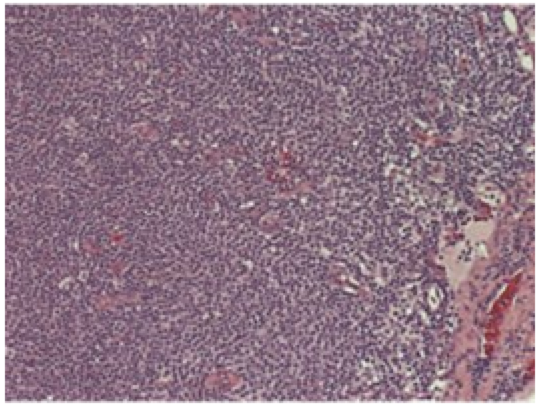
Filtered



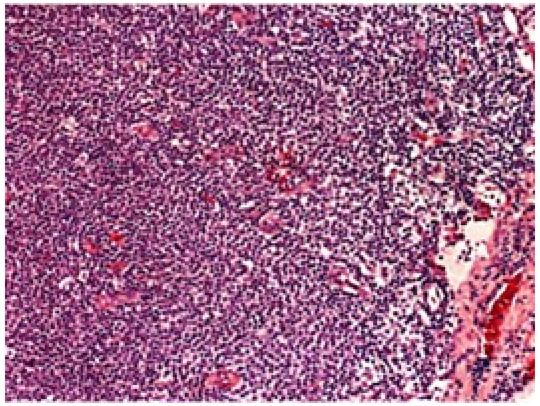
Pre-processing (2)

- **Histogram equalization →** improve image contrast
- **Macenko normalization →** reduce the staining variation in histological slides

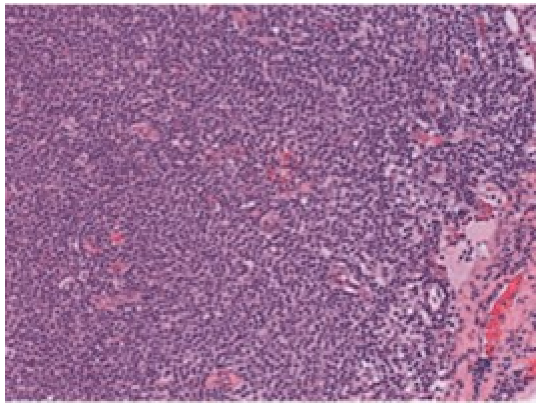
Original



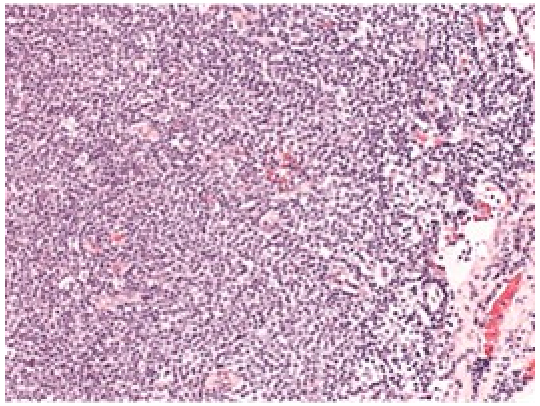
Histogram eq.



Macenko norm.



Hist eq. + M. norm.

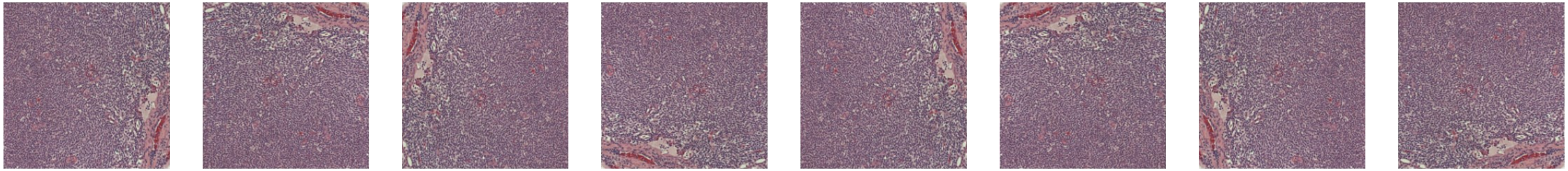


Pre-processing (3)

Data Augmentation

- Split images into **patches**
  - Resize images from 1388x1040 to 1300x1040 and split into 20 non-overlapping patches of 260x260 with a stride of 260
  - Resize images from 1388x1040 to 1300x1040 and split into 63 overlapping patches of 260x260 with a stride of 130
  - Probability of belonging to a class is obtained by summing the output probabilities of each patch

- **Rotate and/or flip** images (after **resize** from 1388x1040 to 224x224): 8 rotated and flipped versions of each image were retrieved



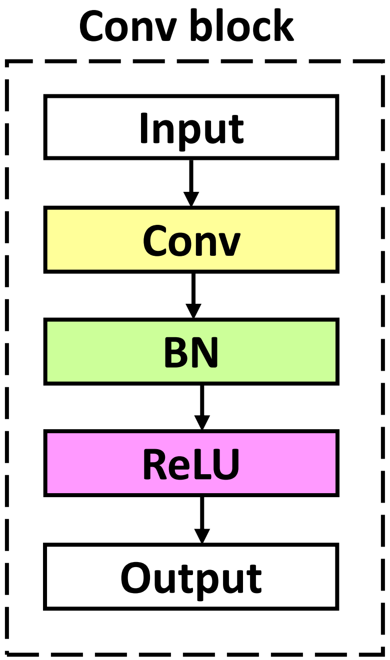
ResNets

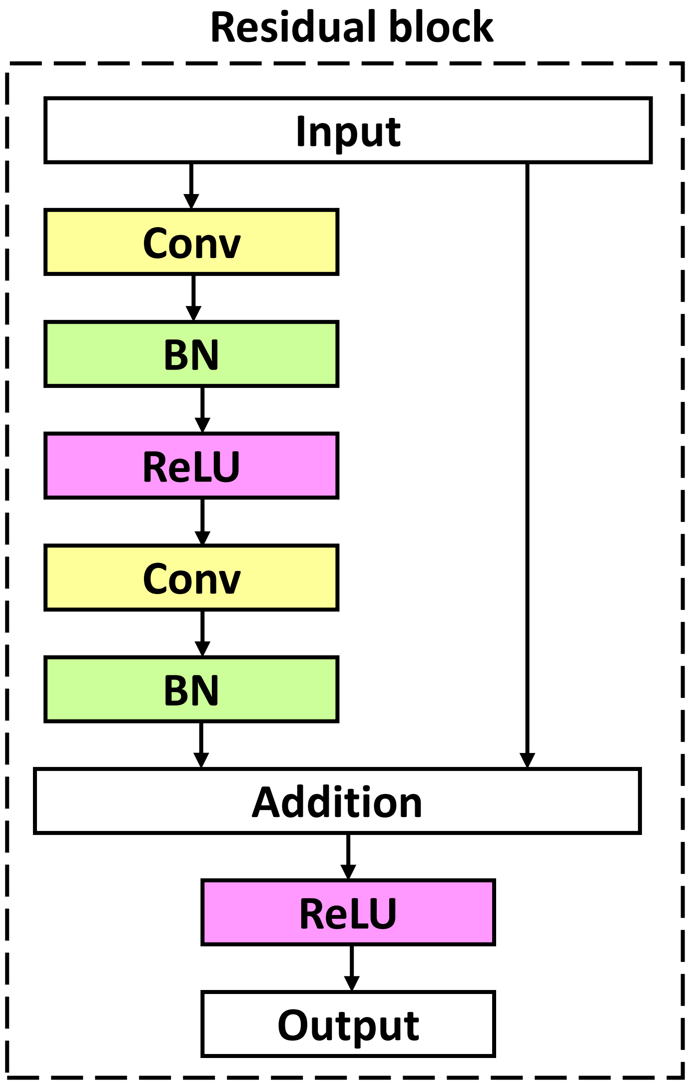
Basic elements of ResNets:

- Convolutional block
- Residual block

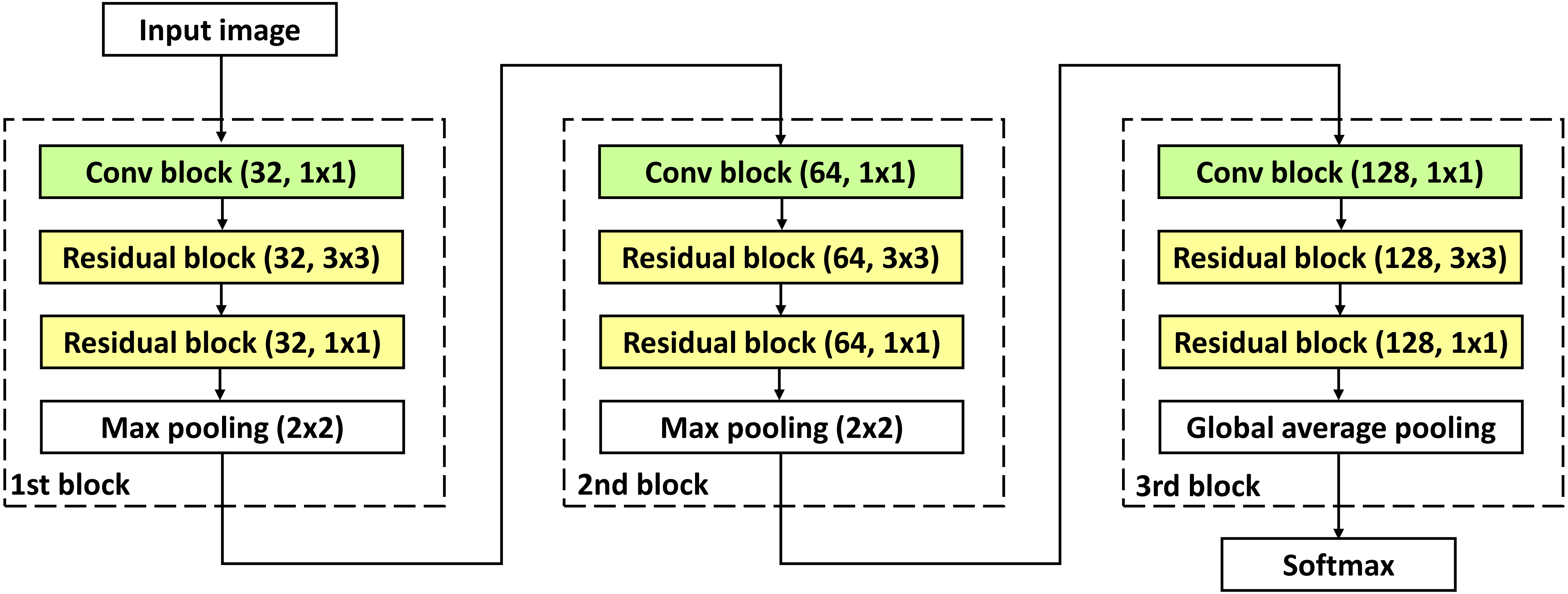
ResNet50

Transfer learning: weights initialized weights computed on ImageNet and then adapted to our dataset.





Proposed ResNet Architecture

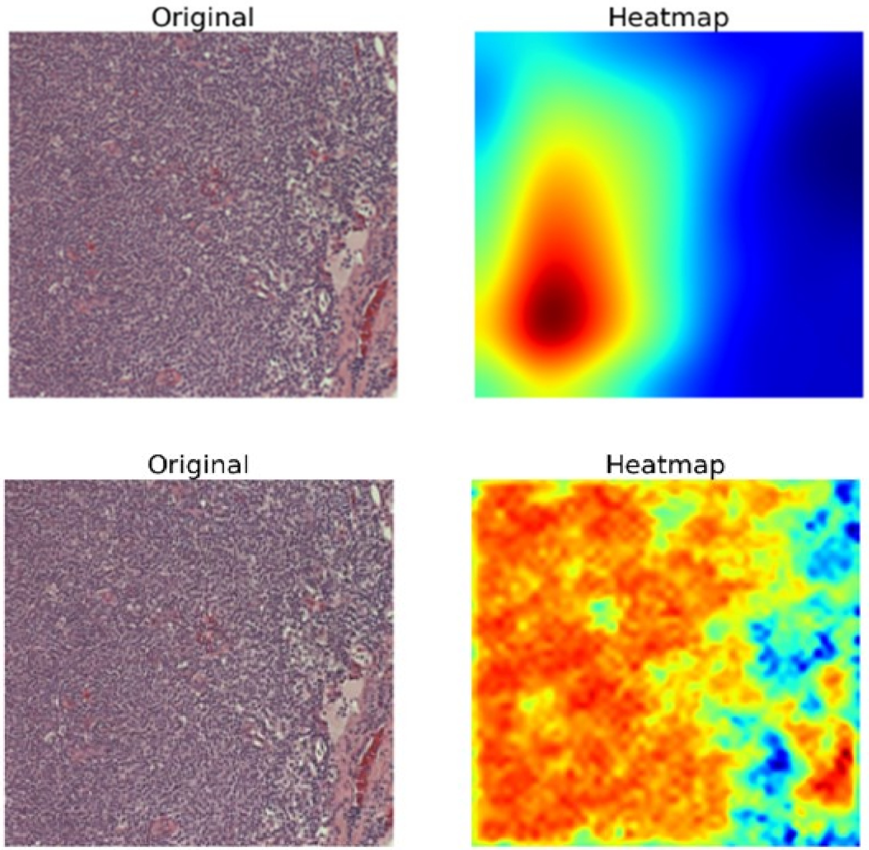


Heatmaps

- **Idea:** Provide visual explanation for machine's decisions.

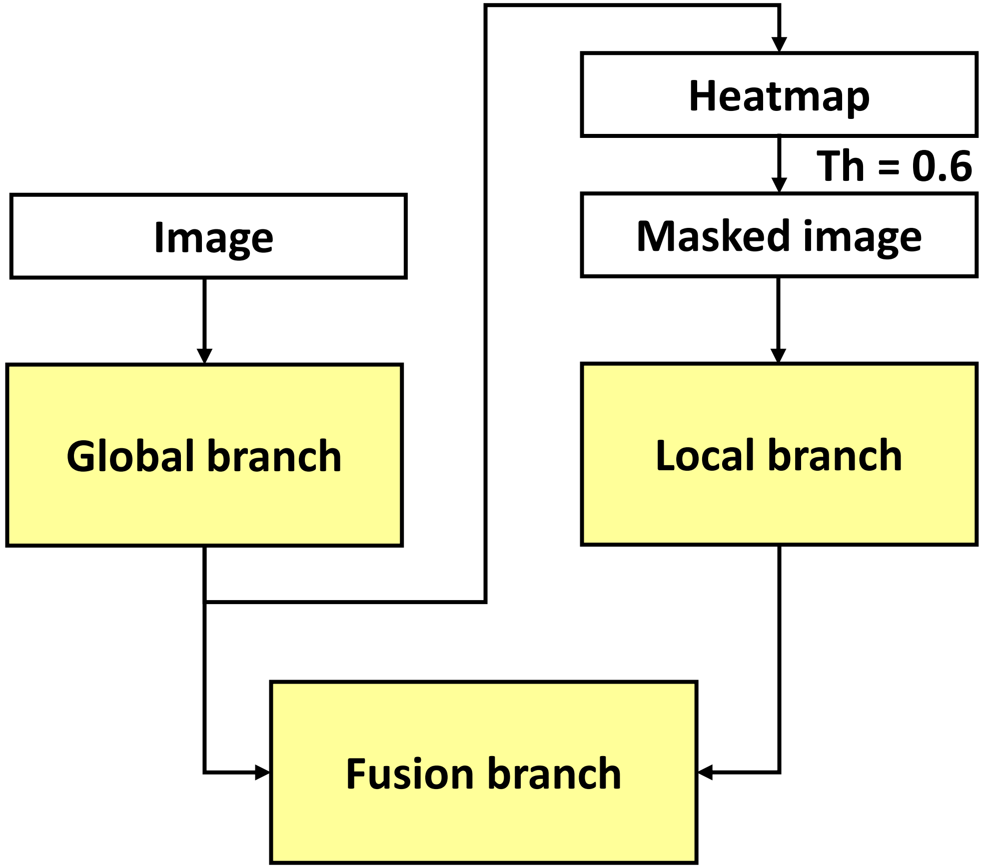
- **Heatmaps:** Weighted average of the last convolution layers using as weights the parameters the last dense layer.

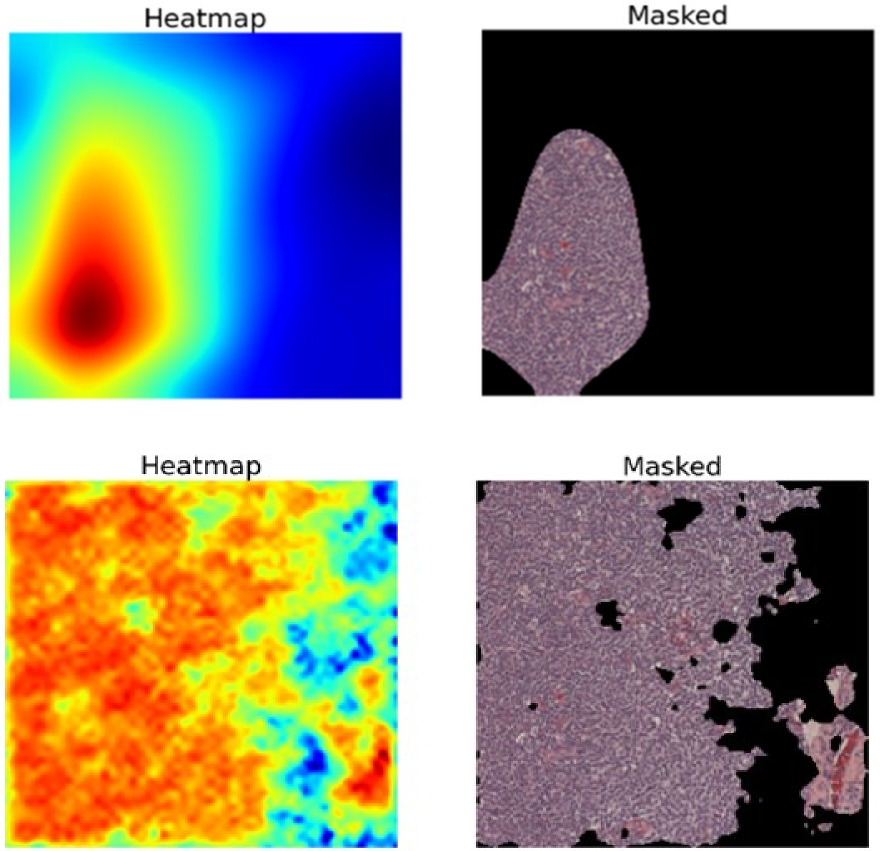
- **Validity of heatmaps:**
    - Mean of the ratios between
        - Number of non-zero pixels in the intersection image
        - Number of non-zero pixels in the image obtained by summing all the masked images related to that image
    - Number of images without intersection



Visual attention meachanism

Idea: Histological lymphoma features could be focused on a restricted area of the slide.





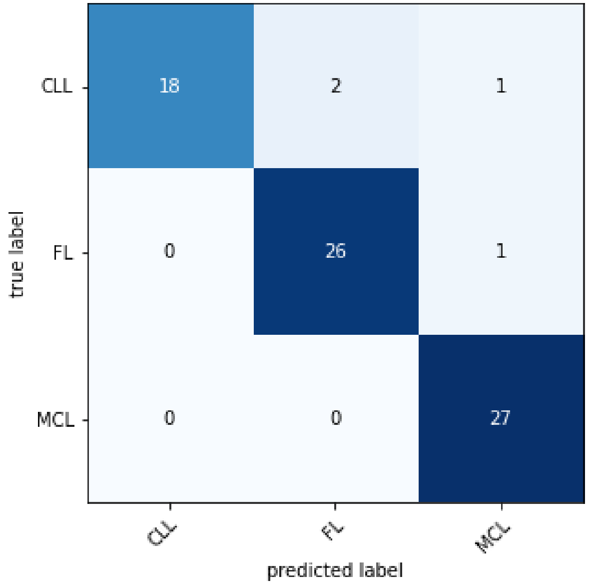
Results (1)

- **ResNet50:** 10 epochs, 32 batch size, AdaMax optimizer, variable learning rate from 0.001 to 0.0001
- **Proposed ResNet:** 15 epochs, 32 batch size, AdaMax optimizer, variable learning rate from 0.001 to 0.0001
- **Best pre-processing:** gaussian filter to remove artifacts, non-overlapping patches data augmentation (histogram equalization an Macenko normalization are not useful)

Model	Test accuracy [%]
Orlov et al. [2]	98.00
Andrew Janowczyk and Anant Madabhushi [4]	96.58
Tambe et al. [5]	97.33
Zhang et al. [6]	98.63
Hathem et al. [7]	98.70
ResNet50	98.67
Proposed ResNet	94.67

Results (2)

- Our ResNet misclassifies 4 images out of 75 in the test set.
- $\mathrm{TPR}_{\mathrm{MCL}}$ = 1: All MCL images have been correctly classified.
- $\mathrm{FPR}_{\mathrm{CLL}}$ = 0 and $\mathrm{precision}_{\mathrm{CLL}} = 1$: All CLL images predicted as CLL are correctly classified
- F-measure = 0.946



Class	TPR	TNR	FPR	Precision
CLL	0.857	1	0	1
FL	0.963	0.957	0.043	0.929
MCL	1	0.957	0.043	0.931

Results (3)

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Validity of heatmaps

Validity of heatmaps seems to be higher for the proposed ResNet.

Model	Mean [%]	Images without intersection
ResNet50	40	10
Proposed ResNet	60	0

Visual attention mechanism

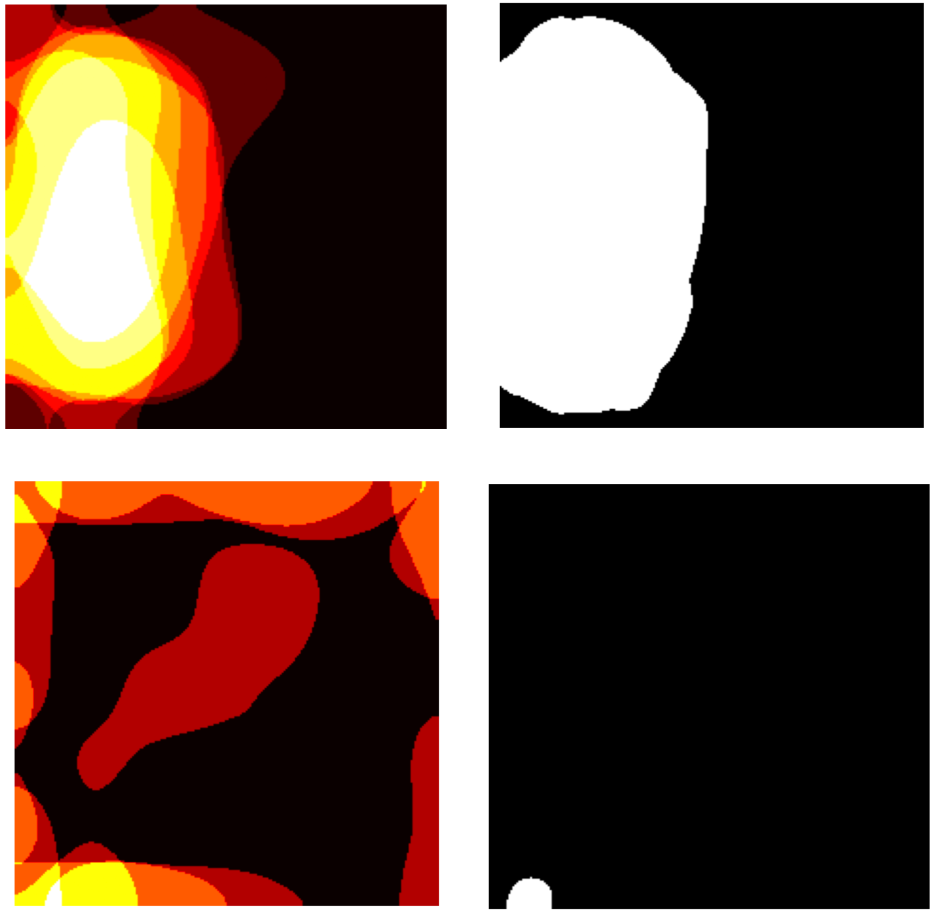
Accuracy decrease by adding to the model a local branch which focused on a restricted area of the images.

Model	Branch	Training accuracy [%]	Validation accuracy [%]
ResNet50	Global	99.72%	98.67%
	Local	100%	98.67%
	Fusion	100%	98.67%
Proposed ResNet	Global	98.00%	97.33%
	Local	99.00%	83.00%
	Fusion	99.83%	93.33%

Results (4)

Visual attention mechanism

Feeding the local branch with masked images obtained from both good (top) and bad (bottom) intersections → Accuracy decrease



Concluding remarks

- **Artifacts** management improve classification performances.
- High degree of **staining variation** is not a limit for automated lymphoma subtypes classification.
- Splitting images into **patches** is the winning strategy.
- Decreasing **model complexity** leads to slightly lower but comparable classification performances.
- Inclusion of **visual attention mechanism** in the processing pipeline worsen classification performances.
- **Explainable deep learning** could be the meeting point between machine learning and physicians.

Limitations of the study

- Based on a limited dataset including only **3 lymphoma subtypes** and **histological data** (e.g., no molecular data).
- **No clinical confirmation** of the areas of interest indicated by the heatmaps.
  - **Further step:** Ask human hematopathologist to annotate regions of interest in images.

Thanks for your attention!