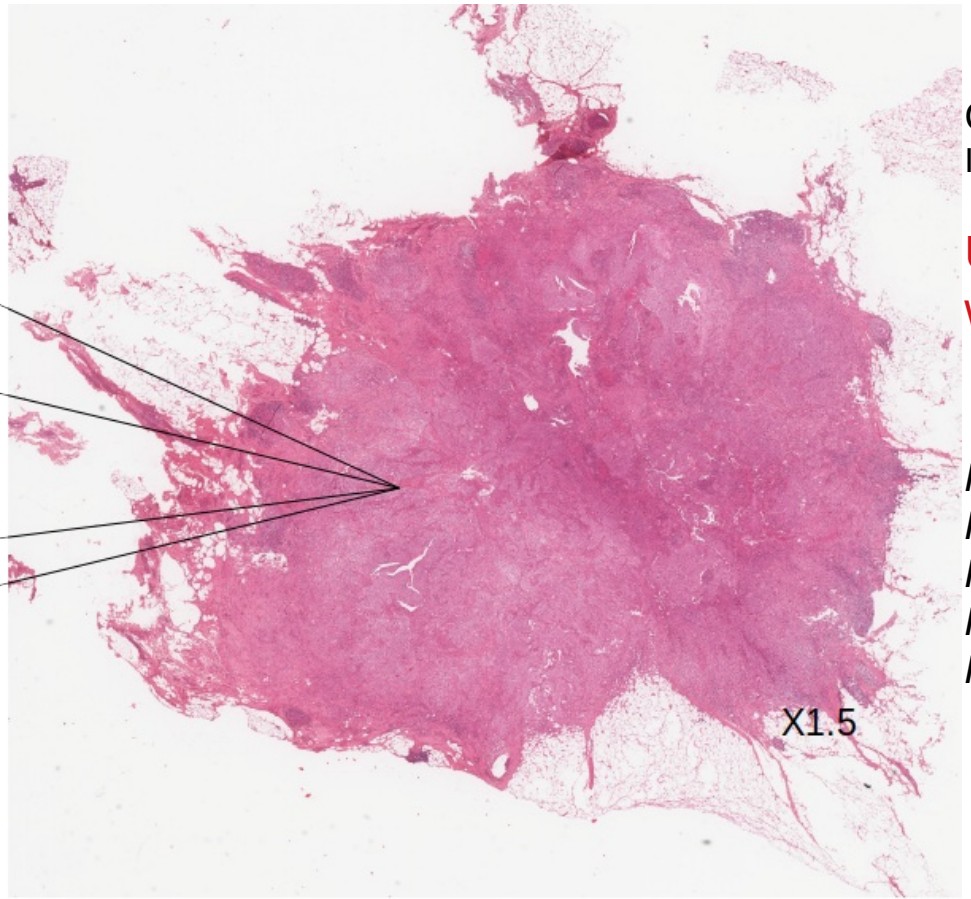
When AI meets Histopathology

Figure 1. This image is a WSI. At a low magnification (x1.5).
At the highest resolution for instance 40x it weights between 5 and 10 GB of data just for one single patient examination.

Figure 1. (follow.) By automatic analysis of thousands of them we can build up efficient models for immuno-oncology treatments for instance. Deep learning is a core mechanism to achieve this goal.



Computer Sciences Lab (LIPADE)
Intelligent Systems of Perception team (SIP)

Université Paris Cité
with the DIIP

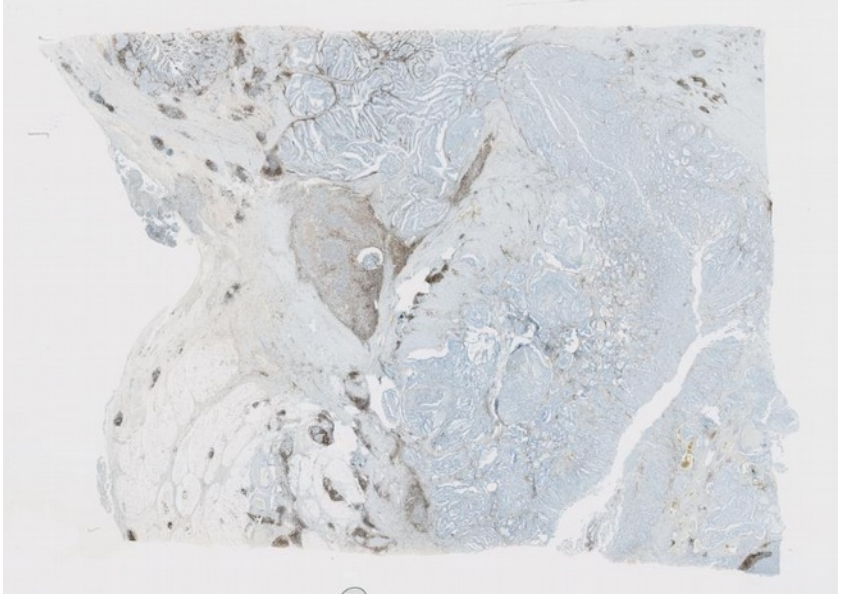
Prof. ***Nicolas Loménie****,*
PhD. ***Qinghe Zeng***
PhD. ***Zhuxian Guo***
Research Engineer ***Amine Marzouki***
Prof. ***Camille Kurtz***

Clinical Context

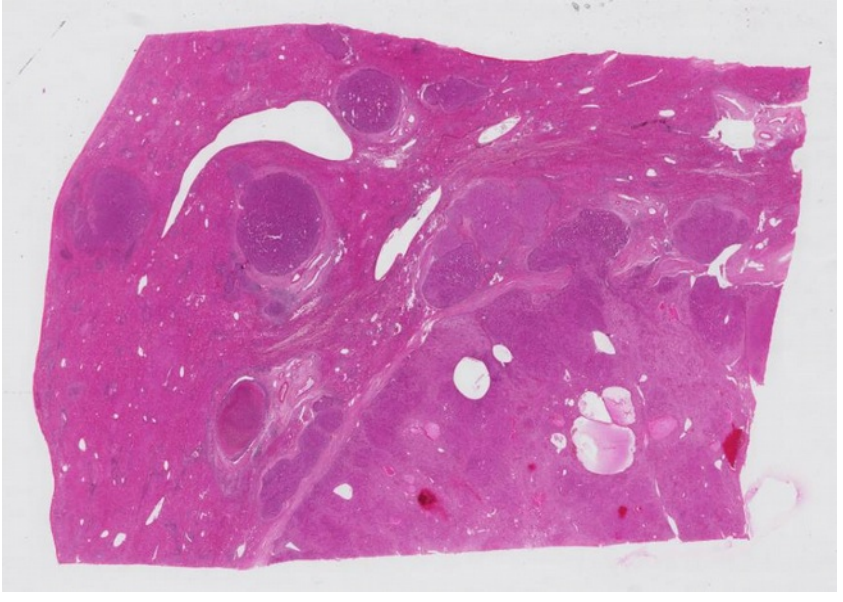
What is a Whole Slide Image (WSI)?

A digital representation of a microscopic slide, at multi-scale level of magnification such as 20x or 40x

https://cloud.cytomine.com/#/project/8596634/image/8612979/slice/16107736?viewer=q2lafymrl



Immunohistochemistry staining
69632pixels x 48384pixels, 9.41 GB uncompressed

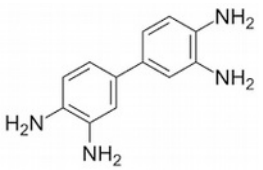


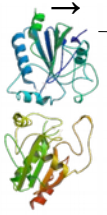
Stained with hematoxylin and eosin (H&E)
59520pixels x 41216pixels, 6.85 GB uncompressed

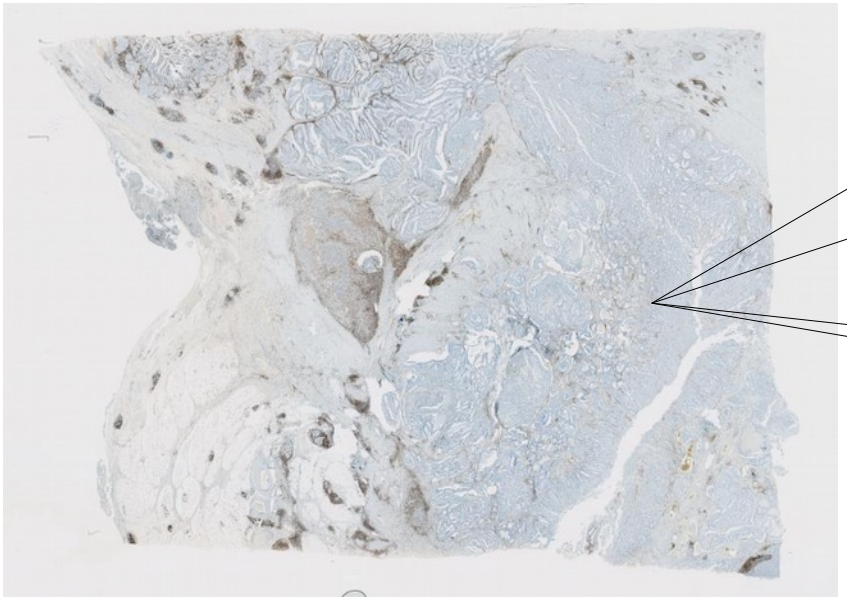
Chemistry Context → ImmunoHistoChemistry

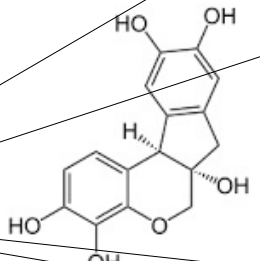
How to spot proteins like ki67, CD3 in bright-field microscopy ?

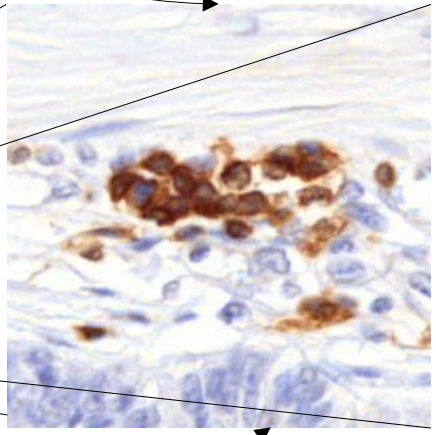
H_2O_2 + **DAB** → color → **Brownish** :-(





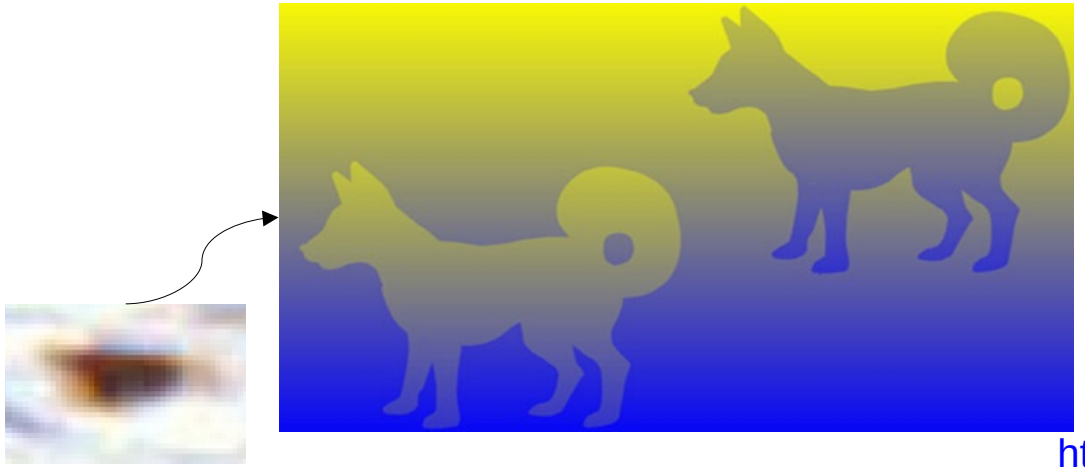






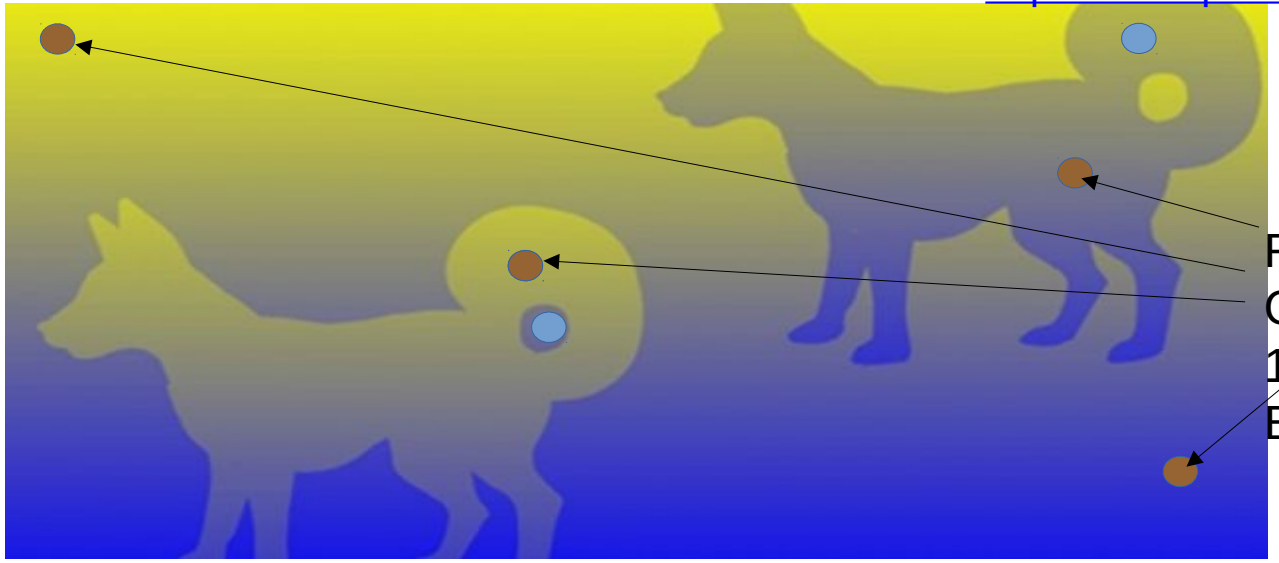
Hematoxylin → color → **Bluish** : nucleic acids

WHAT IS BROWNISH → Human perception / interpretation vs. Machine perception



Human perception is complex
Evolution → Brain + Eyes

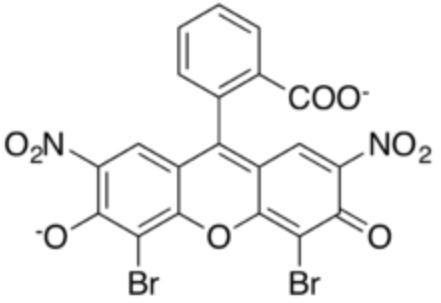
https://www.peko-step.com/fr/tool/hsvrgb.html



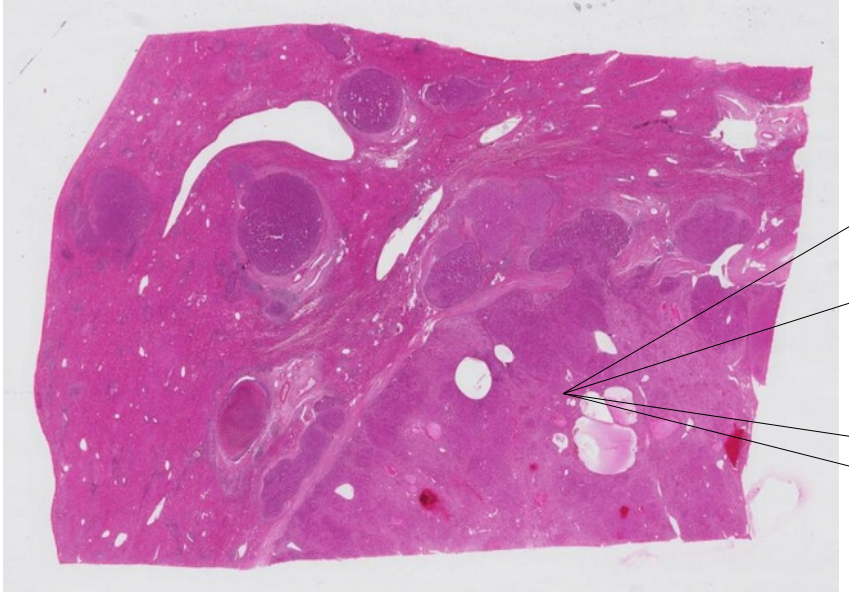
Red : 150
Green : 100
Blue : 50

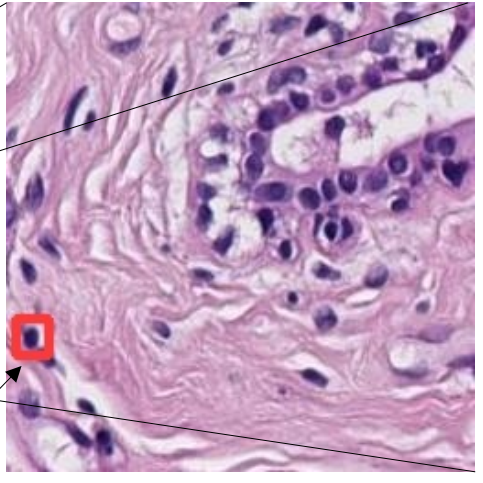
Chemistry Context → clinical routine H&E

H&E Coloration (+Safran sometimes)



Eosin (basophile) stains the cytoplasm (acidophile)
→ redish or pinkish

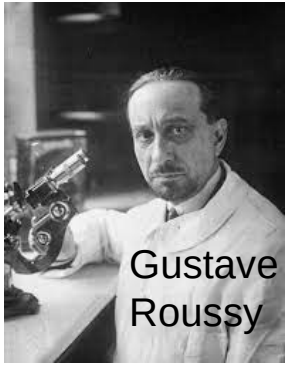




Bright Field Microscopy (vs. Fluorescence) :

- **Basophile** nuclei (H) : **purple**
- Nuclei : **blue/violet**
- **Acidophile** cytoplasm (E) : red
- (Muscle : **dark pink,** Erythrocytes : cherry-red, Collagen : **light pink)**

How to detect lymphocyte ? “Specific color” + shape + texture
Color analysis (Computer Vision) or Machine Learning ?
→ Deep Learning https://tiger.grand-challenge.org/

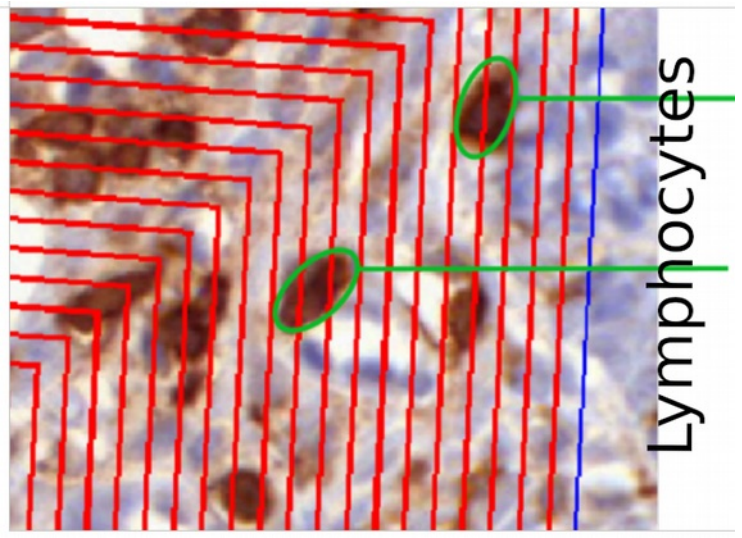

Gustave Roussy

Medical Context

XIXth → ? → XXIth

Traceability
Quantification
Large scale screening

IHC : Immuno Histo-Chemistry
→ the lymphocytes appear in brownish

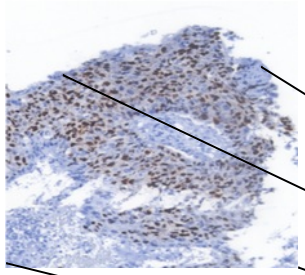


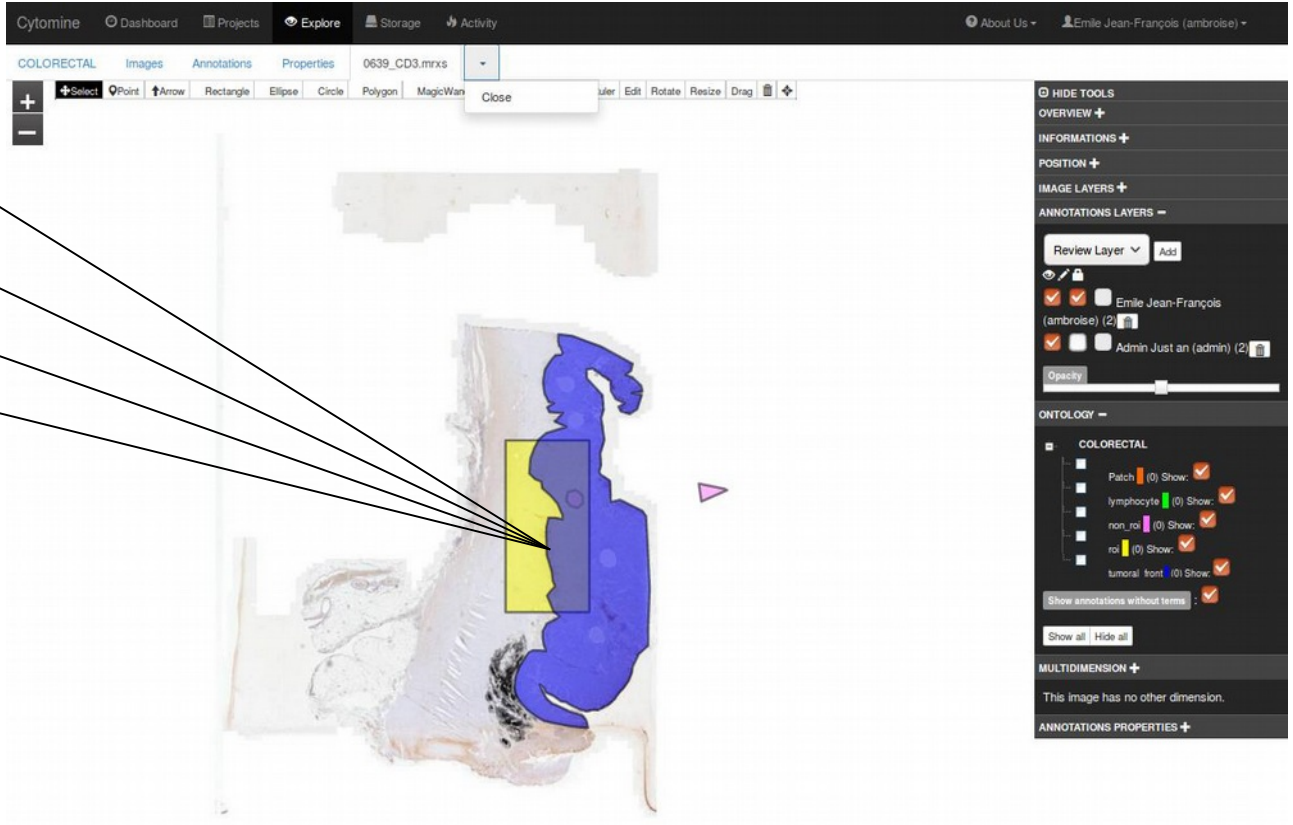
Computer Vision to
Ease quantify and scale up
assessment
+ IVD for immunotherapy
(In Vitro Diagnosis, Companion test)

Medical Context

A Companion Test

POCHI Project - Collaboration with PUPH JF. Emile – Hôpital Ambroise Paré.





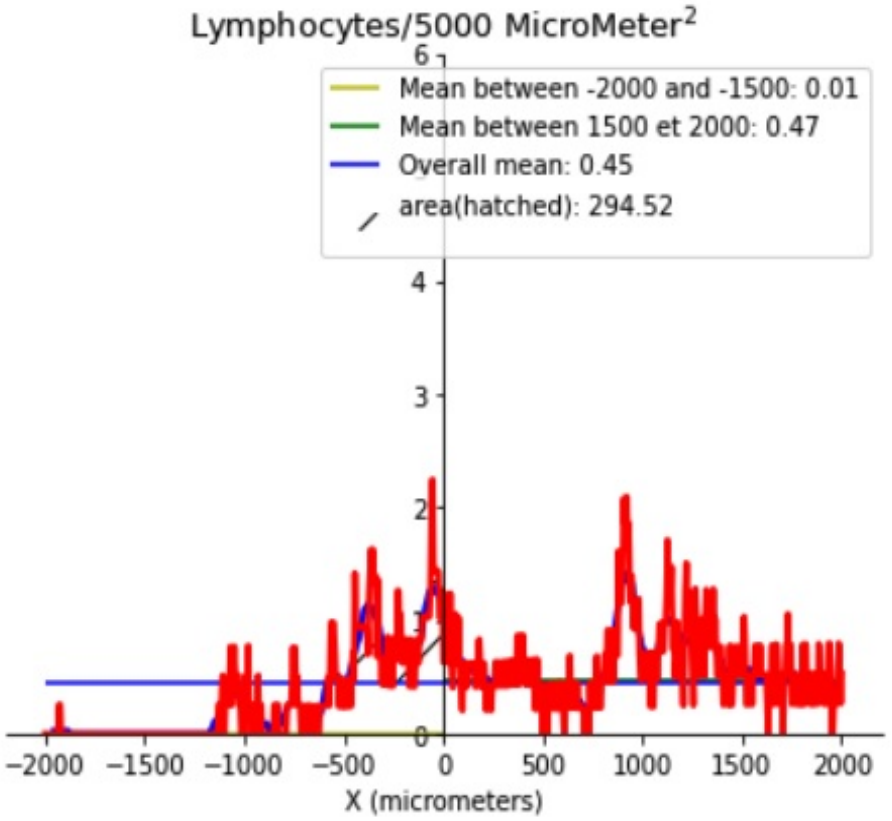
Colorectal Cancer

IHC Staining

Cytomine

Semi-Automatic
(IVD certification)

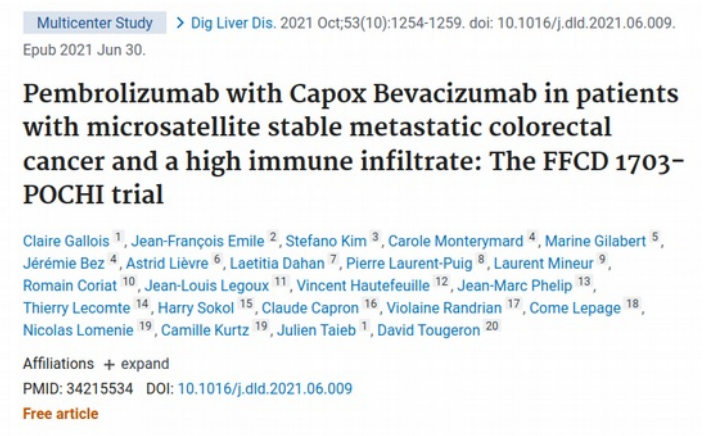
Medical Context



Classify infiltration curve to detect patients benefiting from immunotherapy

- using rules provided pathologist
- automatically through ML/AI

Currently, Phase 2 clinical trial IVD



Multicenter Study > Dig Liver Dis. 2021 Oct;53(10):1254-1259. doi: 10.1016/j.dld.2021.06.009. Epub 2021 Jun 30.

Pembrolizumab with Capox Bevacizumab in patients with microsatellite stable metastatic colorectal cancer and a high immune infiltrate: The FFCD 1703-POCHI trial

Claire Gallois [1], Jean-François Emile [2], Stefano Kim [3], Carole Monterymard [4], Marine Gilabert [5], Jérémie Bez [4], Astrid Lièvre [6], Laetitia Dahan [7], Pierre Laurent-Puig [8], Laurent Mineur [9], Romain Coriat [10], Jean-Louis Legoux [11], Vincent Hautefeuille [12], Jean-Marc Phelip [13], Thierry Lecomte [14], Harry Sokol [15], Claude Capron [16], Violaine Randrian [17], Come Lepage [18], Nicolas Lomenie [19], Camille Kurtz [19], Julien Taieb [1], David Tougeron [20]

Affiliations + expand

PMID: 34215534 DOI: 10.1016/j.dld.2021.06.009

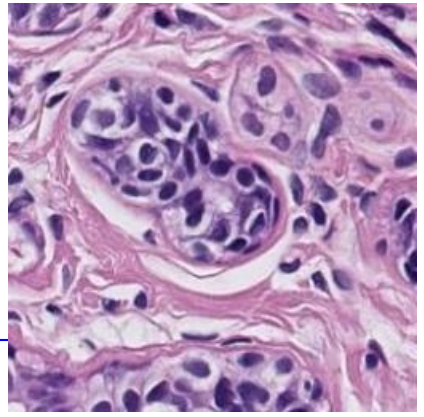
Free article

Chemical staining & Computer Vision Context

Some math and computer vision reading :-)

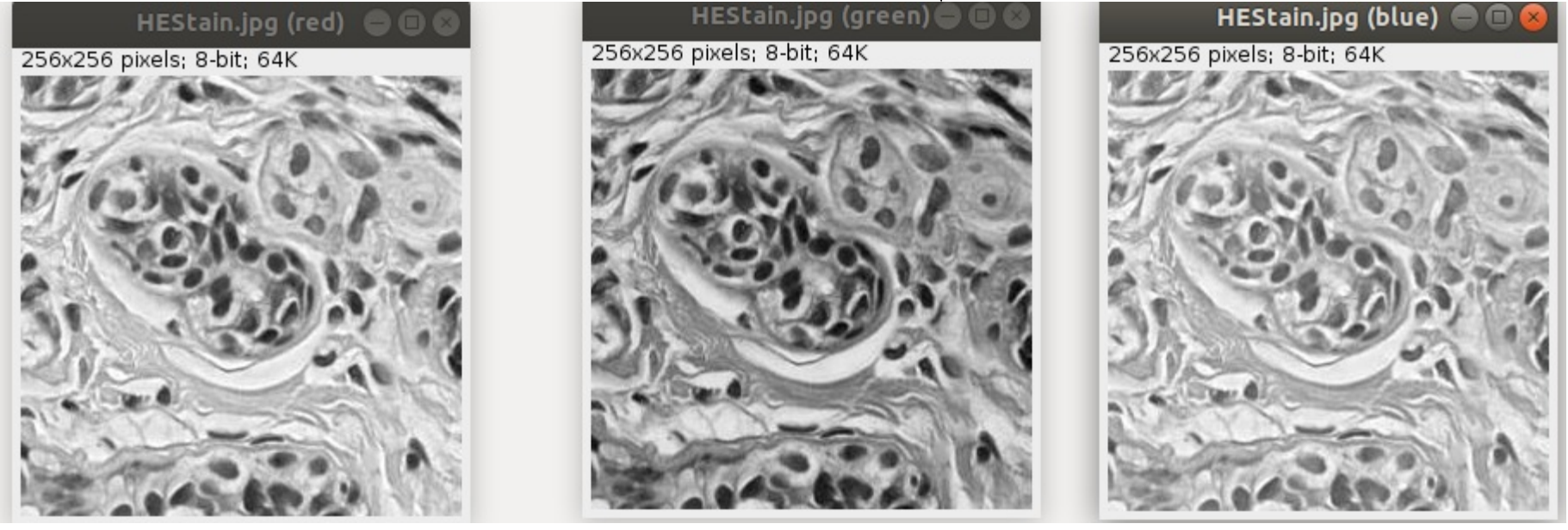
A paper by Ruifrok AC, Johnston DA.

[Quantification of histological staining by color deconvolution. Anal Quant Cytol Histol 23: 291-299, 2001.]



Human physiological vision (RGB) to a kind of Chemical Display (HES)

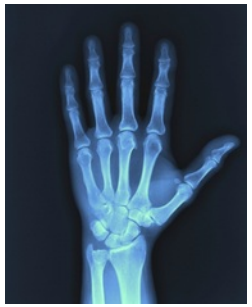
Red Green Blue

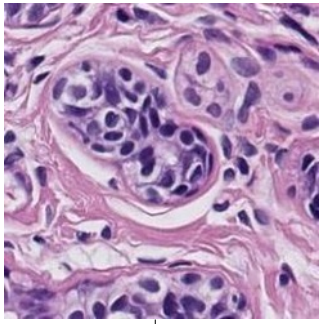


,

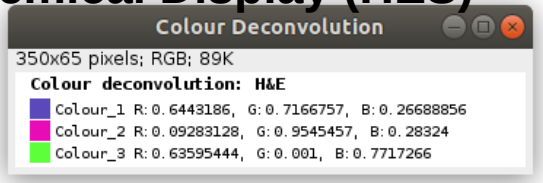
Computer Vision Context → Color Deconvolution for Chemical Staining

Beer-Lambert Law of absorbance
$A = \varepsilon lc$





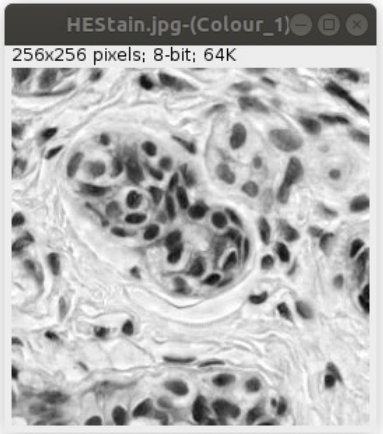
Human physiological vision (RGB) to a kind of **Chemical Display (HES)**

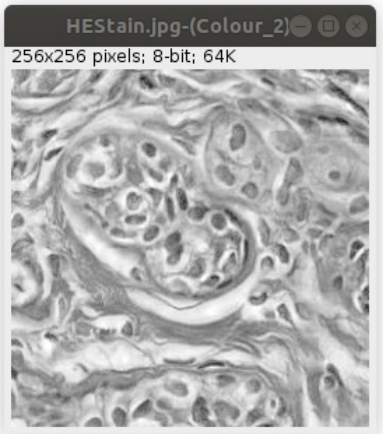


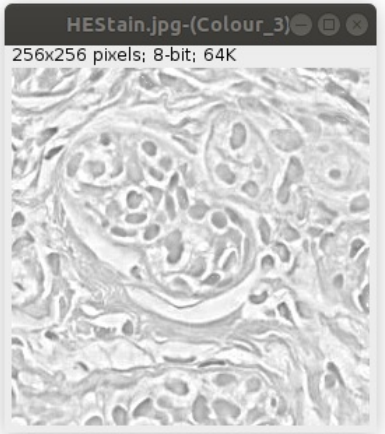
The trick :
The H stain in the displayed Red channel

The E stain in the displayed Green channel

Safran or orthogonal channel

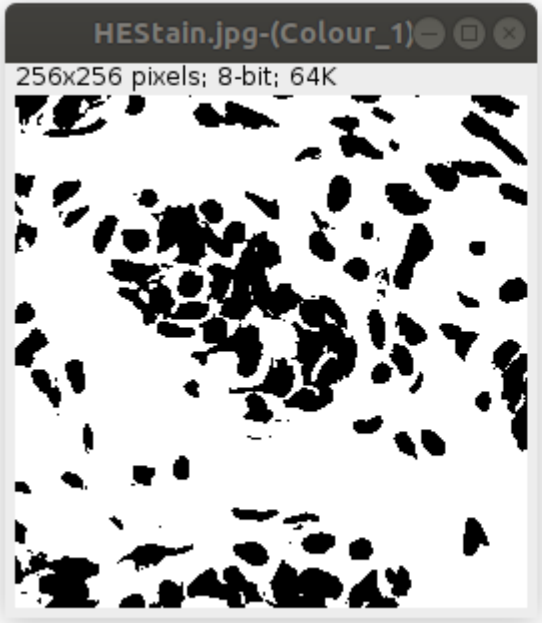


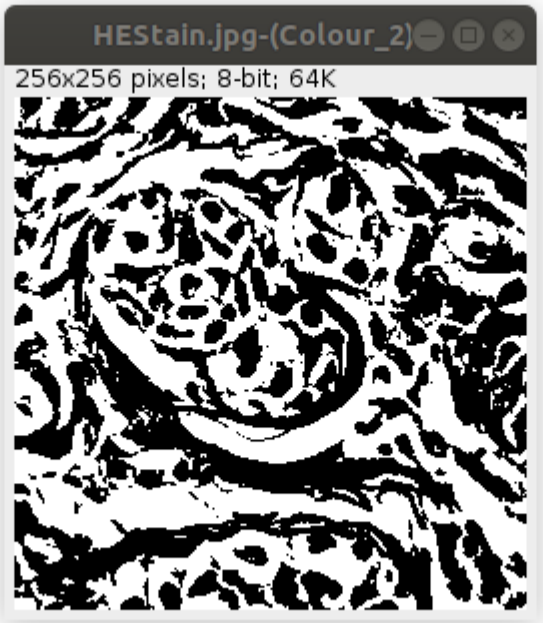


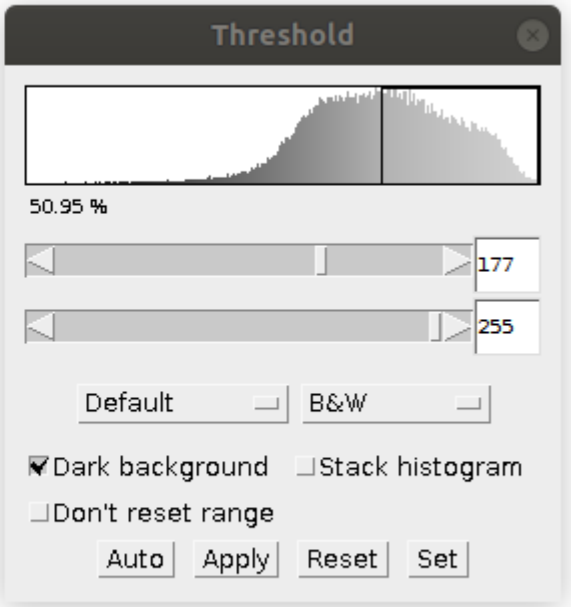


An explanation of this article and the ***colour_deconvolution*** plugin in ImageJ/Fiji (Menu Image/Color) can be read up here : https://biii.eu/colour-deconvolution
Python Material inhere : https://helios2.mi.parisdescartes.fr/~lomn/Cours/CV/BME/HistoPatho/Color/PythonColorDeconv/

Computer Vision & Machine learning





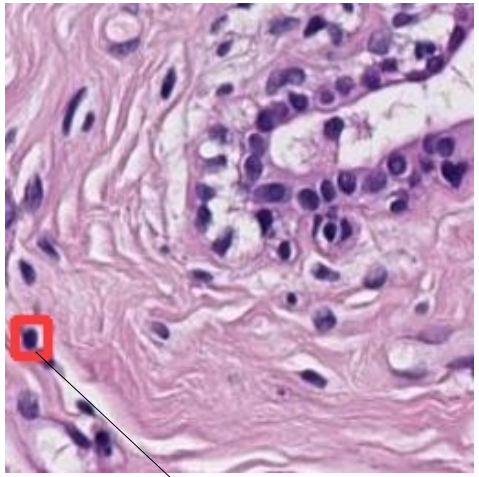


$$\begin{bmatrix} H \\ E \\ Comp \end{bmatrix} = \begin{bmatrix} 0{,}64 & 0{,}71 & 0{,}26 \\ 0{,}09 & 0{,}95 & 0{,}28 \\ 0{,}63 & 0 & 0{,}77 \end{bmatrix} \begin{bmatrix} R \\ G \\ B \end{bmatrix}$$

Learning the matrix coef ?
But more to come…. :
texture,
shape, organization etc.

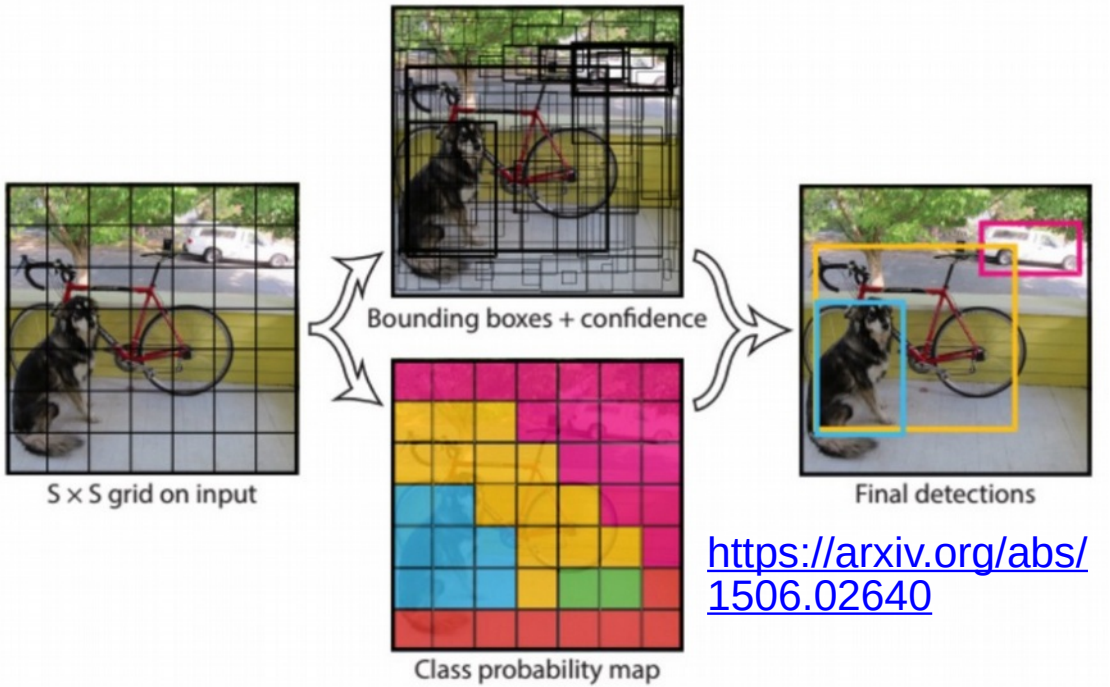
What’s the promise of deep learning or AI ?

Open question but a new way to explore micro-tumoral environment



YOLO Architecture

You Only Look Once
For **object detection**



https://arxiv.org/abs/1506.02640

Fine tuned for lymphocyte detection

https://towardsdatascience.com/yolo-you-only-look-once-real-time-object-detection-explained-492dc9230006

What Deep Learning revolution can bring ?

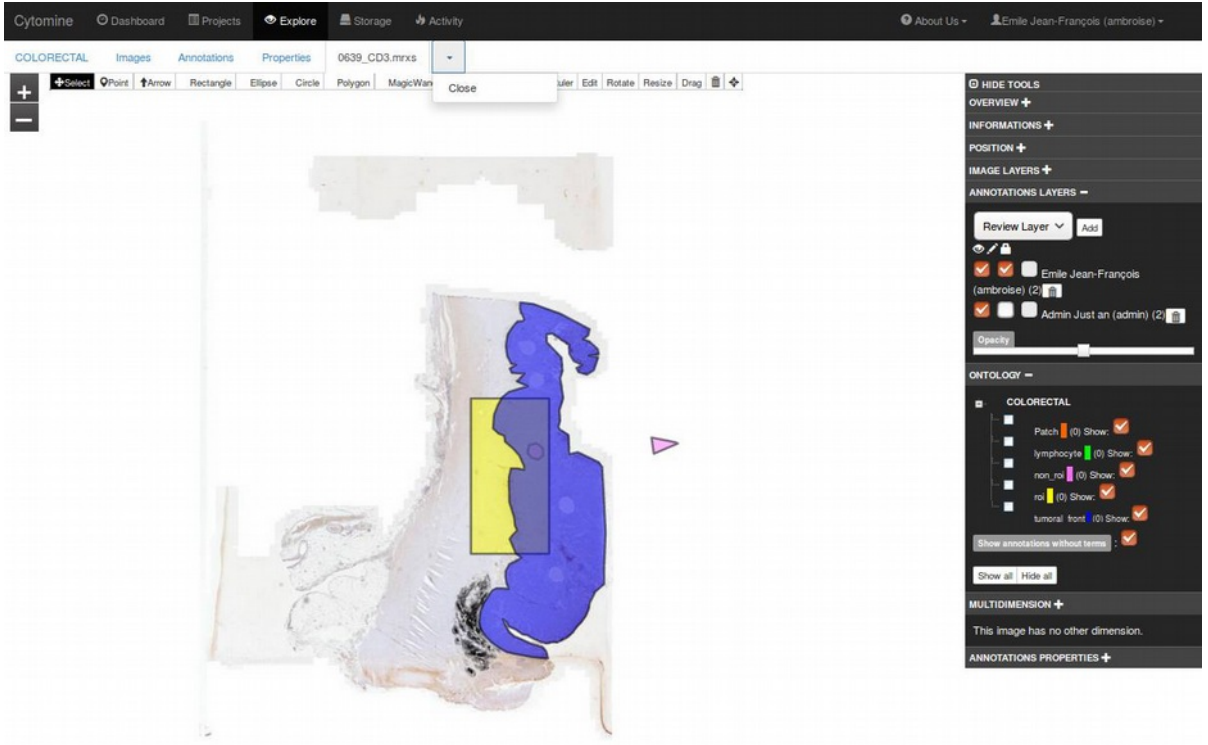
Open question but a new way to explore micro-tumoral environment

Automatic recognition of tumoral tissue ?

Classification for diagnostic ?

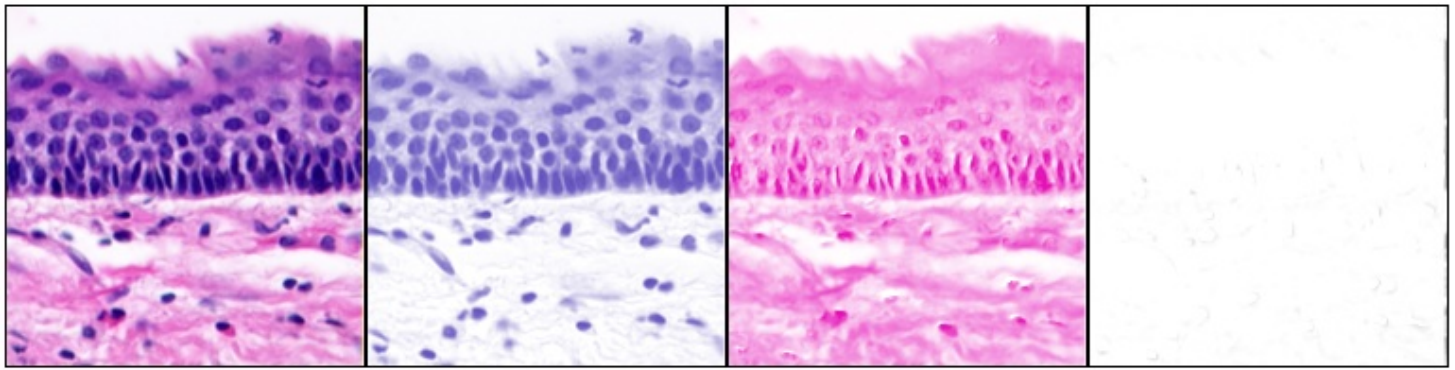
Improved care ?

A new ecosystem : https://tissuepathology.com/ (like https://owkin.com/)



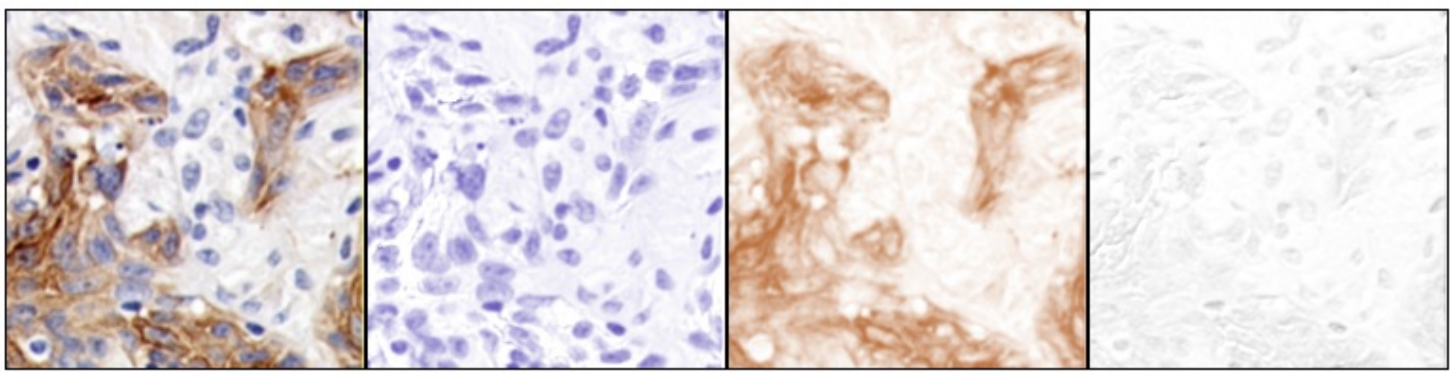
Annex 1

Examples



Haematoxylin and Eosin unmixing (using the built-in H&E vectors).

From left to right: original, Haematoxylin, Eosin, virtually empty 3rd (complementary) component (showing that the vectors match the image quite well, except a column of corrupted pixels at the right border of the image).



Haematoxylin and DAB unmixing (using the H DAB built-in vectors).

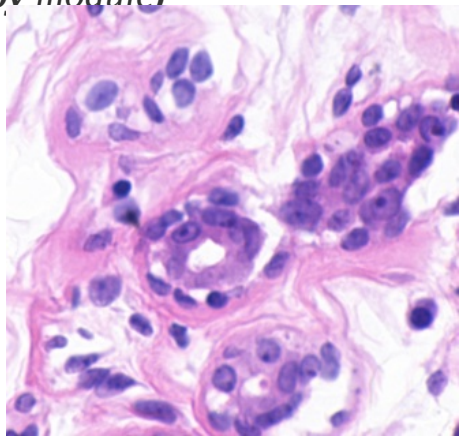
From left to right: original, Haematoxylin, DAB, 3rd component (the vectors did not perfectly matched the stains in this image, so they should be determined again from single-stained samples).

Annex 2

Staining Deconvolution

Demo
Material here : https://helios2.mi.parisdescartes.fr/~lomn/Cours/CV/BME/HistoPatho/Color/PythonColorDeconv/

A corresponding python code to the FiJi plugin is given in **color.py** *(using **color_decon.py** module)*



First, with a python command line, reproduce the code step by step using the instructions in ***color.py***.

Then, you can run the color.py over another image like RNA1.tif

$python color.py RNA1.tif

This image takes much more time to be processed in python and is IHC staining then the deconvolution matrix will not work.

Annex 3

- https://tissuepathology.com/2022/06/30/visiopharm-supports-umc-utrecht-to-improve-patient-care-with-the-launch-of-an-automated-and-ivdr-certified-ai-driven-digital-pathology-workflow/
- https://bci.grand-challenge.org/
- https://tiger.grand-challenge.org/
- Watch the video on TILs https://rumc-gcorg-p-public.s3.amazonaws.com/i/2021/10/20/TILs+Education+What+They+Are+and+What+They+Do.mp4