Kombinierte und kaskadierte neuronale Netze in der diagnostischen Pathologie

Lübeck Summer Academy, Media Docks, 9. 10. 2023

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Gemeinschaftspraxis für Pathologie, Lübeck
www.pathologen-luebeck.de

Offenlegung der Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition
   - Mitinhaber Gemeinschaftspraxis für Pathologie, Lübeck
   - Inhaber PathoPlan GbR, Lübeck

2. Beratungs- bzw. Gutachtertätigkeit

3. Besitz von Geschäftsanteilen, Aktien oder Fonds
   - Besitz KI-Fonds-Anteile

4. Patent, Urheberrecht, Verkaufslizenz

5. Honorare

6. Finanzierung wissenschaftlicher Untersuchungen
   - Sachmittelbeihilfe von Sysmex Deutschland (Stellung eines Scanners für 6 Monate)
   - Sachmittelbeihilfe von Roche Deutschland (Stellung eines Scanners für 2 Jahre)
   - Referenzzentrum für Künstliche Intelligenz i.R. des EMPAIA-Projekts, Förderung durch Bundesministerium für Wirtschaft

7. Andere finanzielle Beziehungen

8. Immaterielle Interessenkonflikte

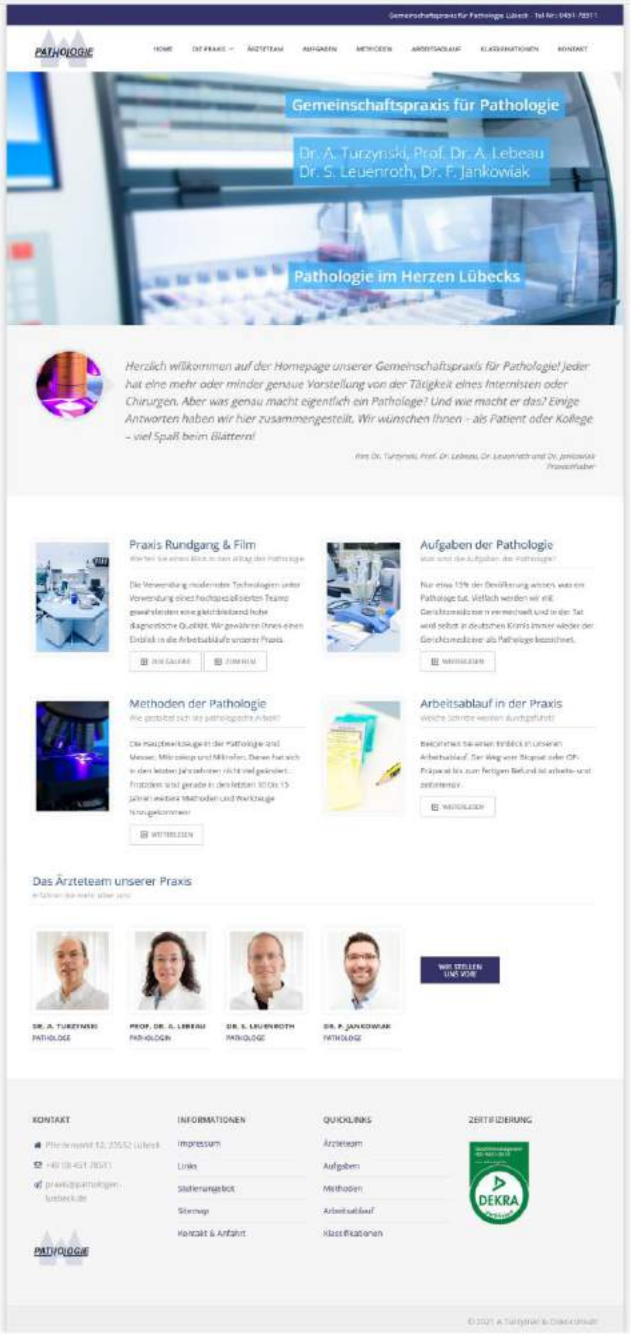
Agenda

- Pathohistological Diagnostics
- Ensemble networks → HEROHE ECDP2020
- Cascaded networks → Prostate cancer:

  Tissue segmentation and interpretation

  Breast cancer:

  Measurement of nuclear features



www.pathologen-luebeck.de

Von Der Bischof mit der E-Gitarre at de.wikipedia - Selbst fotografiert, Gemeinfrei, https://commons.wikimedia.org/w/index.php?curid=16661579

https://de.freepik.com

Vernetzung

EU/Internatl.

European Commission

Europ. Comm.
Leitlinienentwicklung
Advisory Boards
Multicenterstudien
AI-Challenges

Lokal

LÄN Lübecker Ärztenetz

Hausärzte
Fachärzte
Krankenhäuser
Organzentren
ASV

NOZ Netzwerk Onkologischer Zentren

Sana Kliniken Lübeck GmbH

HELIOS Agnes Karll Krankenhaus Bad Schwartau

Marien-Krankenhaus Lübeck

PATHOLOGIE

Bund

QuIP Qualitätssicherungs-Initiative Pathologie GmbH

DKG KREBSGESELLSCHAFT

Bundesvorstände DGP, DGS, BDP
QuIP-Board
EMPAIA
Zertifizierungskommission DKG
Fachgruppe IQTiG
S3-Leitlinienkommission AWMF
Gutachter Norddeutsche Schlichtungsstelle
Multicenter-Studien
Advisory Boards

IQTIG Institut für Qualitätssicherung und Transparenz im Gesundheitswesen

DEUTSCHE GESELLSCHAFT FÜR PATHOLOGIE E.V.
Seit 1897 – dem Leben verpflichtet

BUNDESVERBAND DEUTSCHER PATHOLOGEN e.V.

Deutsche Gesellschaft für Senologie

Land

KVSH

HA/FÄ
QuaMaDi
Krankenhäuser
Organzentren
QS-Kommissionen
Krebsregister

Sana Kliniken Ostholstein

Deutsches Rotes Kreuz
DRK-Krankenhaus Mölln-Ratzeburg
Akademisches Lehrkrankenhaus des UKSH, Campus Lübeck

IKE

PATHOLOGIE

Pathologie

- Messer
- Makroskopie

- Mikroskop
- Mikroskopie

- Mikrofon
- Diagnose

Pathologie

- Klinisch-diagnostisches Querschnittsfach
- Diagnostik an Gewebe
  - Mikroskopie
    - Konventionelle Histologie
    - Schnellschnittdiagnostik
    - Immunhistologie

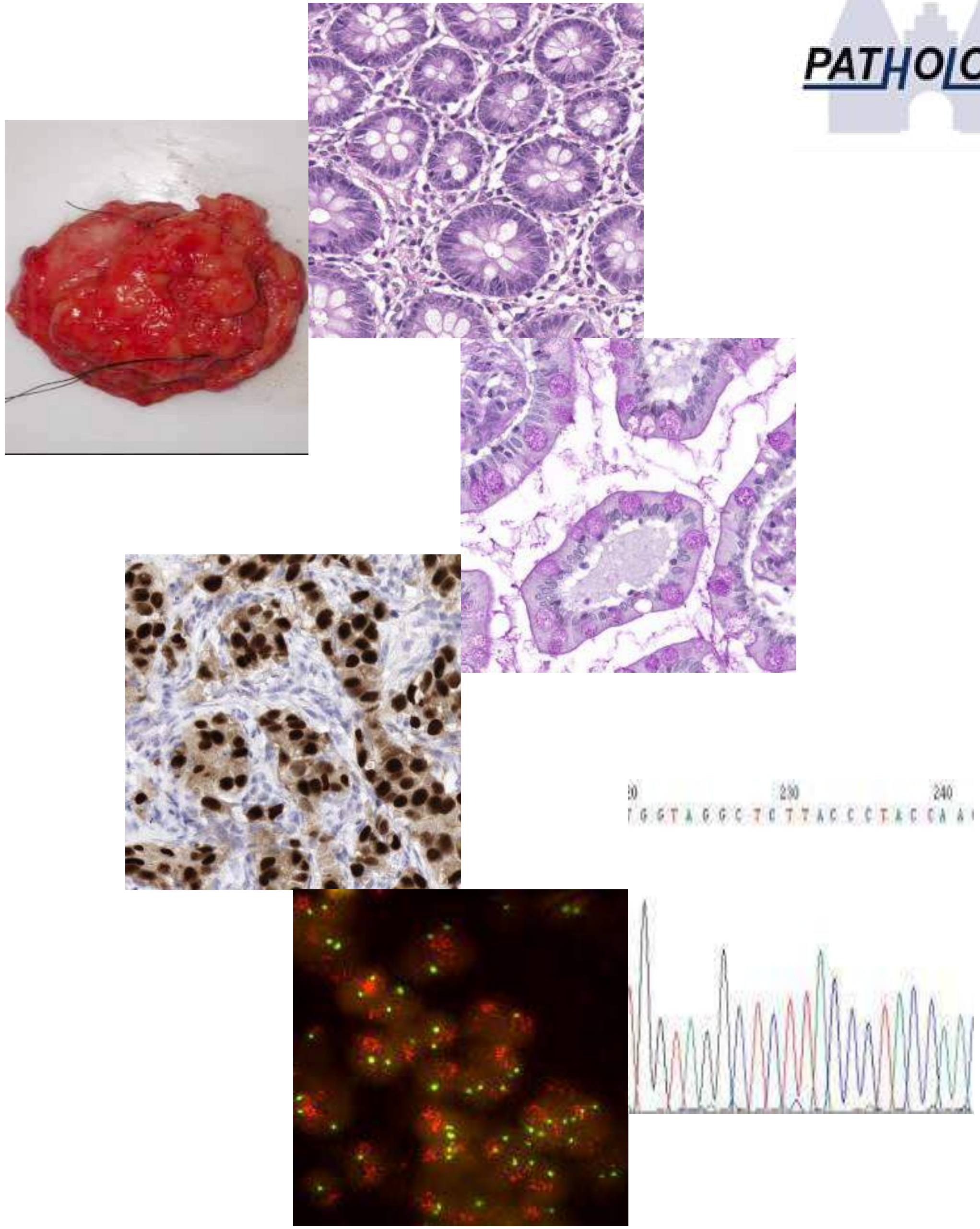
1. Revolution

  - Molekularpathologie
    - PCR,
    - In-situ-Hybridisierung
    - Sequenzierung

2. Revolution

  - AI/computational pathology

3. Revolution

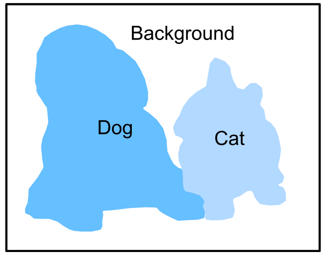


KI-Methoden in der Computervision

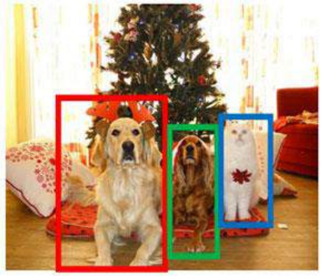
PATHOLOGIE

- Bildbearbeitung/Klassisches Maschinenlernen
  - Segmentierungsmethoden, Entscheidungsbäume

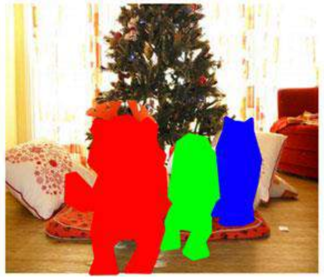
- Deep learning / neuronale Netze
  - Klassifikation: was ist zu sehen?
  - Segmentierung: wie ist die räumliche Ausdehnung?
  - Objektdetektion/
  - Instanzsegmentierung: wo und wieviele?



Object Detection



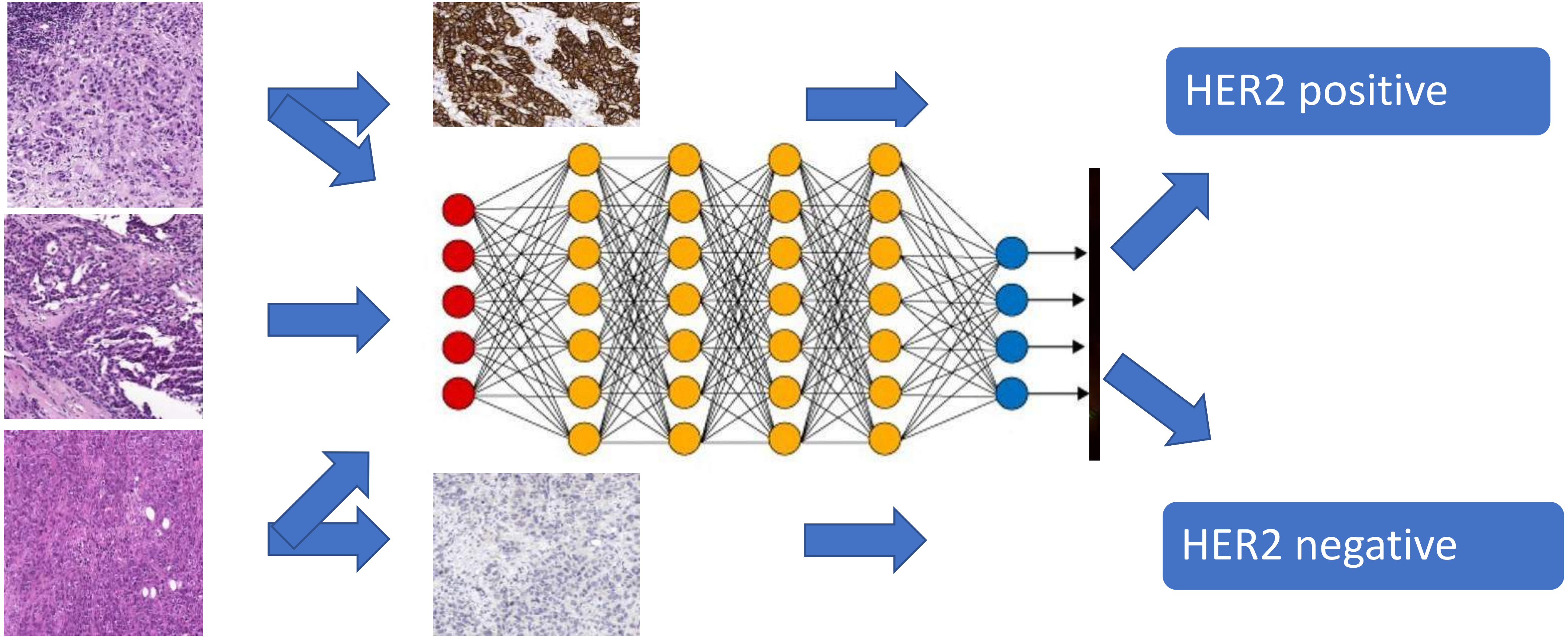
Instance Segmentation



1., 2. https://colab.research.google.com/github/d2l-ai/d2l-en-colab/blob/master/chapter_computer-vision/semantic-segmentation-and-dataset.ipynb
3. https://pyimagesearch.com/wp-content/uploads/2018/11/instance_segmentation_example.jpg

HEROHE
ECDP2020

HER2 on HE



Ensemble Networks: HEROHE-Challenge

Journal of *Imaging*

MDPI

Article

HEROHE Challenge: Predicting HER2 Status in Breast Cancer from Hematoxylin–Eosin Whole-Slide Imaging

Eduardo Conde-Sousa [1,2], João Vale [1,3], Ming Feng [4], Kele Xu [5], Yin Wang [4], Vincenzo Della Mea [6], David La Barbera [6], Ehsan Montahaei [7], Mahdieh Baghshah [7], Andreas Turzynski [8], Jacob Gildenblat [9], Eldad Klaiman [10], Yiyu Hong [11], Guilherme Aresta [12,13], Teresa Araújo [12,13], Paulo Aguiar [1,2], Catarina Eloy [1,3,14] and Antonio Polónia [1,3,*]

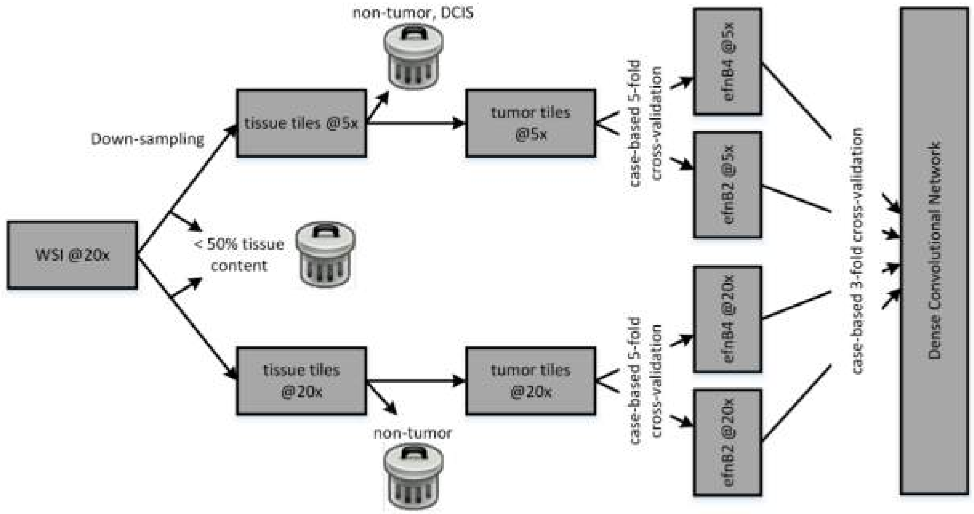
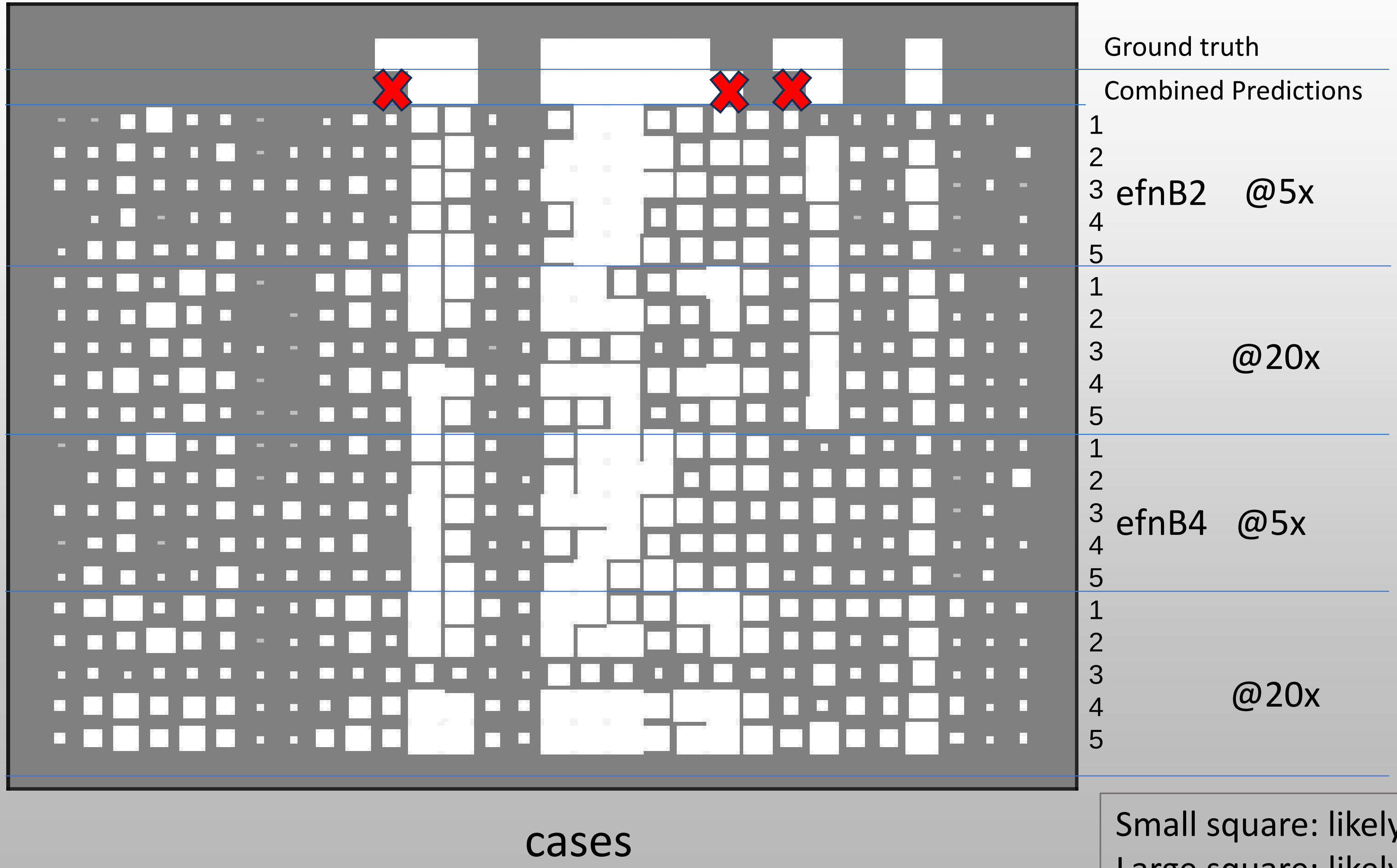


Figure 5. Overall architecture of the model developed by team Dratur.

Table 3. Final classification of the HEROHE Challenge according to F_1 score.

Rank	Team	AUC	Precision	Recall	F_1 Score
1	Macaroon	0.71	0.57	0.83	0.68
2	MITEL	0.74	0.58	0.78	0.67
3	Piaz	0.84	0.77	0.55	0.64
4	Dratur	0.75	0.57	0.70	0.63
5	IRISAI	0.67	0.58	0.67	0.62
6	Arontier_HYY	0.72	0.52	0.73	0.61
7	KDE	0.62	0.51	0.75	0.61
8	joangibert14	0.66	0.48	0.78	0.60
9	VISILAB	0.63	0.51	0.73	0.60
10	MIRL	0.50	0.40	1.00	0.57
11	aetherAI	0.66	0.49	0.67	0.57
12	NCIC	0.63	0.52	0.62	0.56
13	biocenas	0.57	0.46	0.53	0.50
14	HEROH	0.59	0.46	0.53	0.49
15	Reza Mohebbian	0.61	0.51	0.43	0.47
16	mindmork	0.63	0.53	0.38	0.45
17	Institute of Pathology Graz	0.63	0.50	0.38	0.43
18	katherandco	0.44	0.44	0.40	0.42
19	QUILL	0.63	0.50	0.33	0.40
20	HEROHE_Challenge	0.48	0.37	0.27	0.31
21	UC-CSSE	0.47	0.31	0.27	0.29

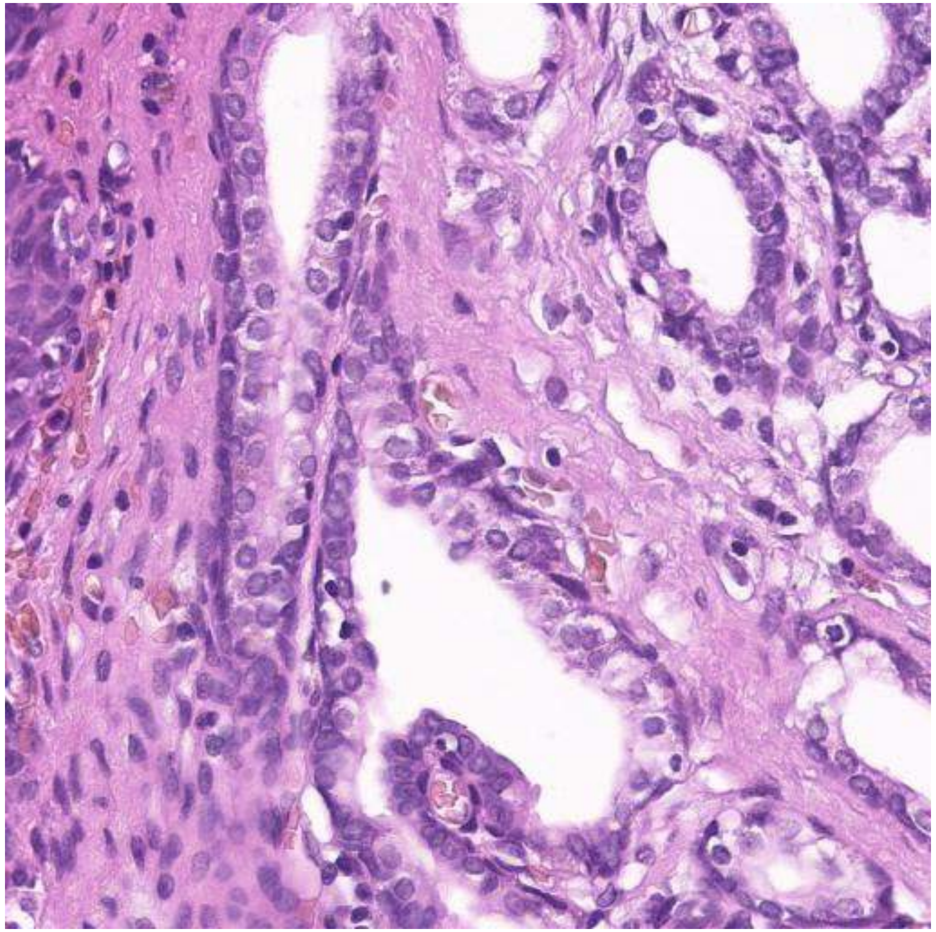
HEROHE-Challenge
Hinton-Plot: raw prediction of HER2 positivity in 30 cases



Small square: likely HER2-negative
Large square: likely HER2-positive

Prostate cancer - Criteria-based Diagnosis - Cascaded Networks

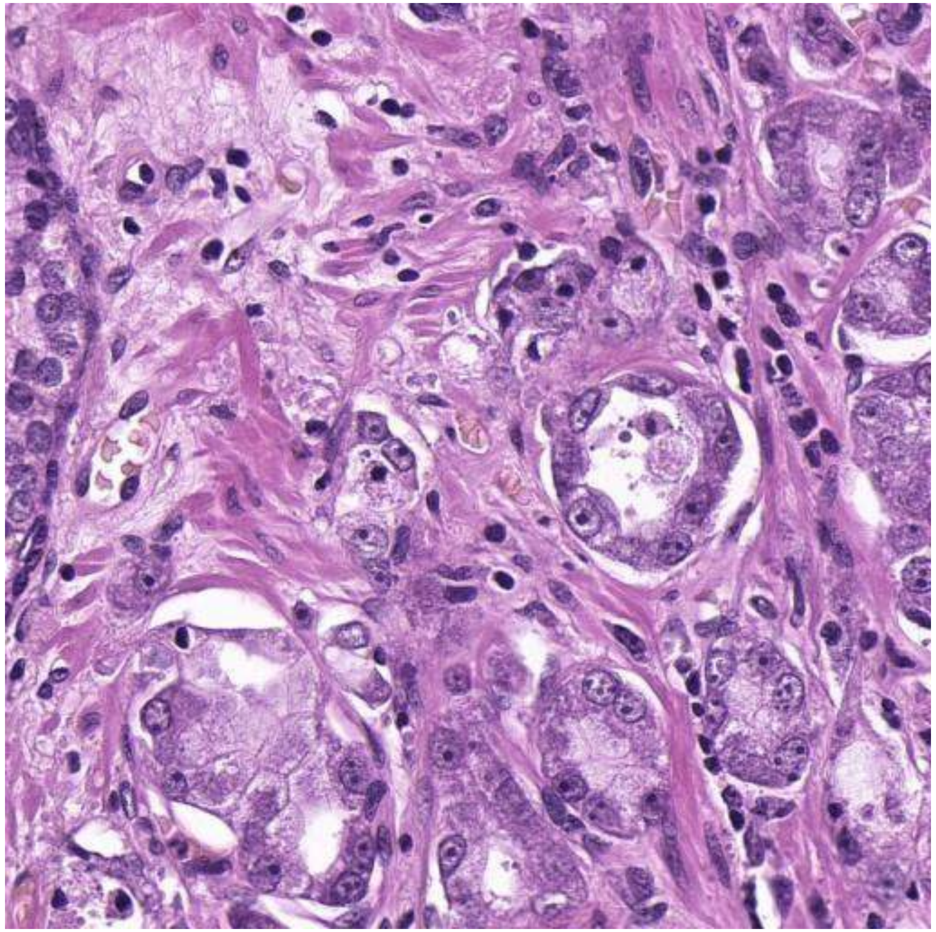
Benign

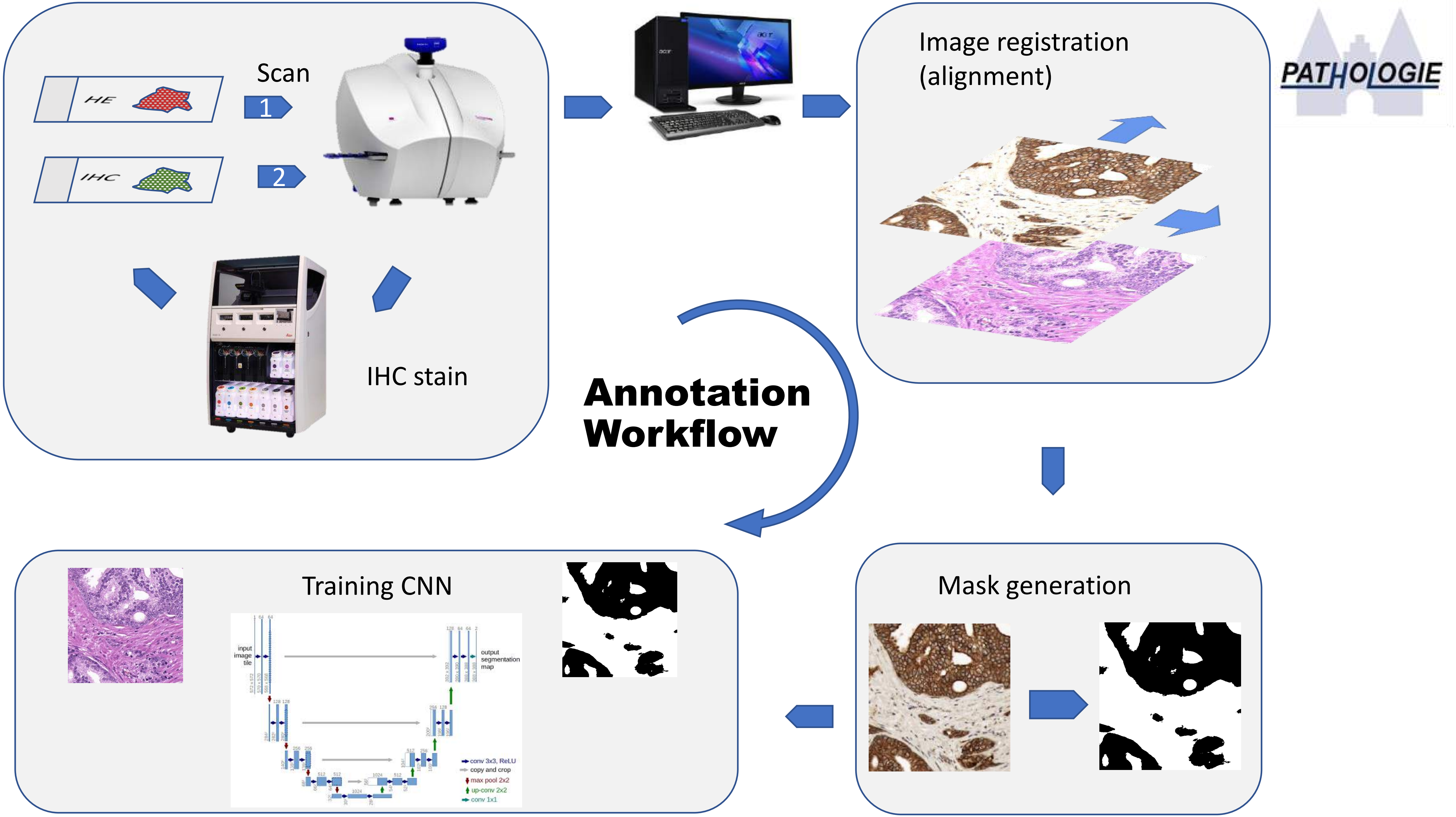


Criteria for malignancy:

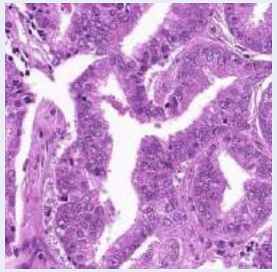
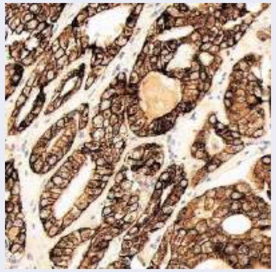
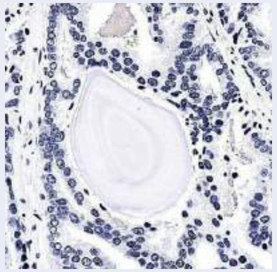
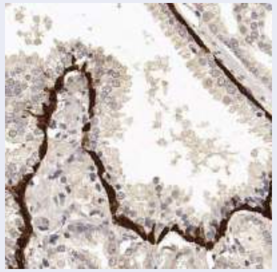
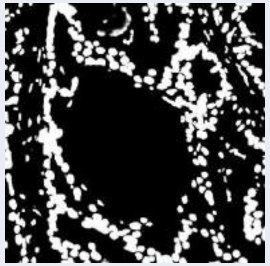
Loss of basal cells
Enlarged nuclei
Prominent nucleoli
Growth pattern
Infiltrating growth
Perineural invasion

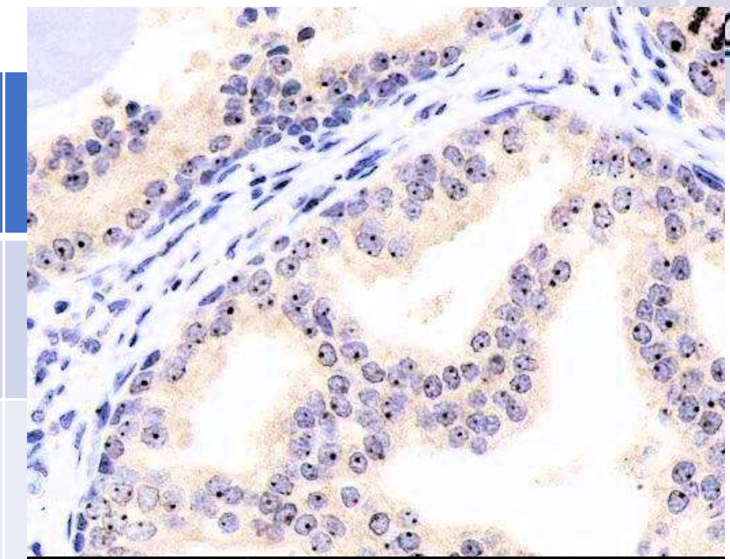
Malignant

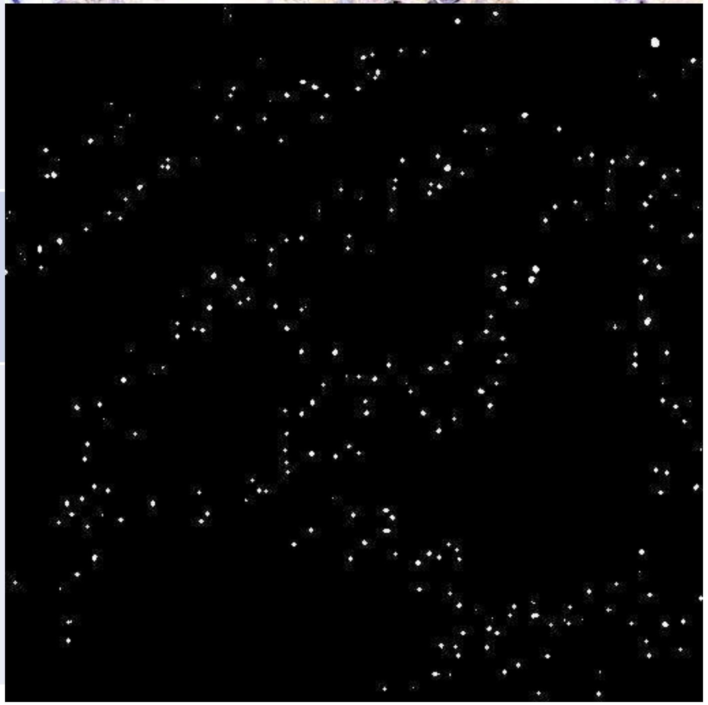



Scan
HE
IHC
1
2
IHC stain
Image registration
(alignment)
PATHOLOGIE
Annotation
Workflow
Mask generation
Training CNN
input
image
tile
output
segmentation
map
conv 3x3, ReLU
copy and crop
max pool 2x2
up-conv 2x2
conv 1x1

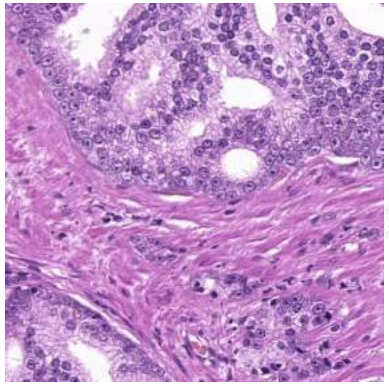
Diagnostic relevant tissue targets in prostate

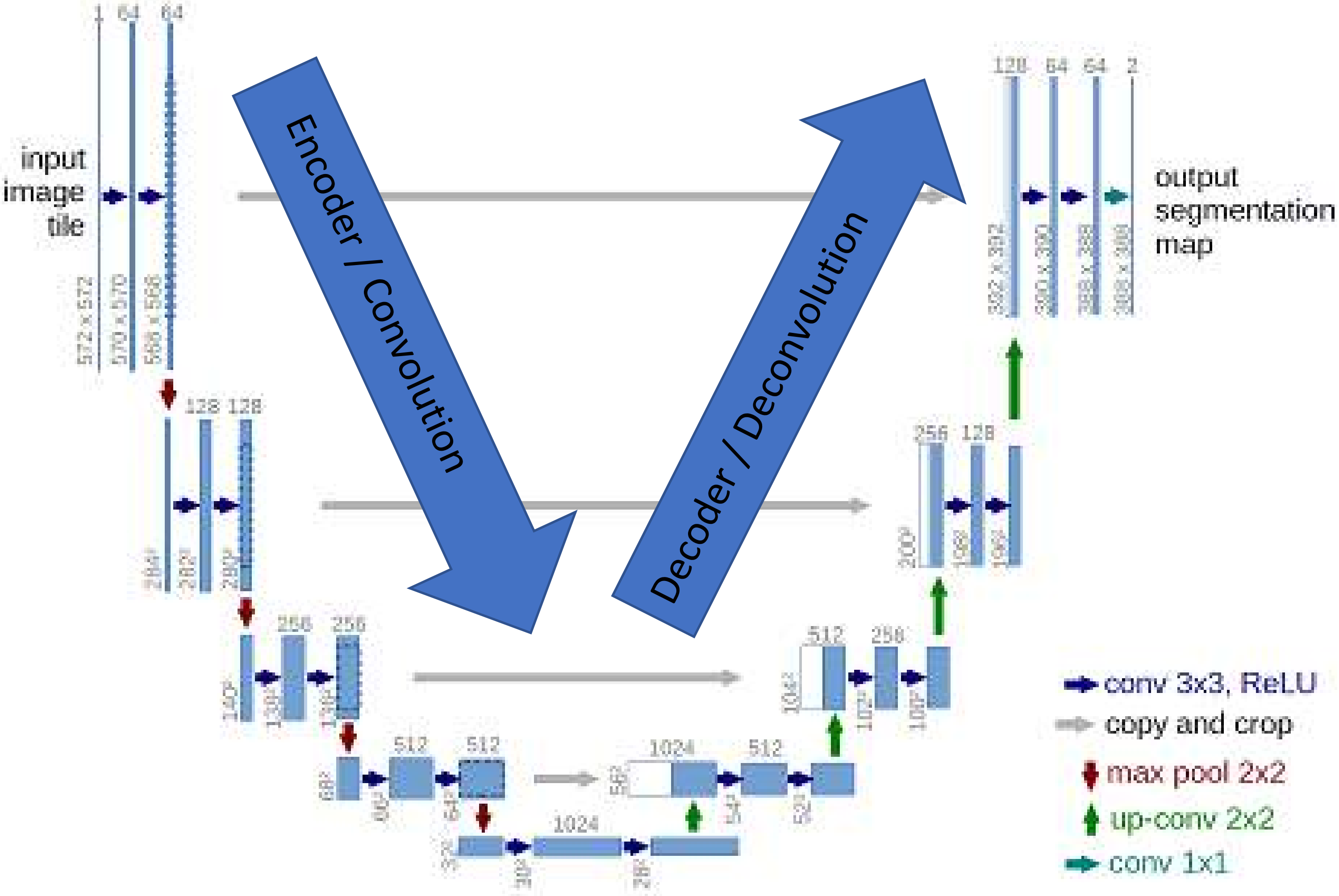
Objects	Tissue/ lumina	Epithelium	Nuclei	Basal cells
stain	H&E	AE1/AE3/ CK8/18 + ECad	Histon H3 or Hematoxilin	34ßE12 + p63
image				
Mask generation	Ilastik → U-Net	Ilastik → U-Net	Ilastik → U-Net	class. image processing
mask				





U-Net Architecture for Image Segmentation

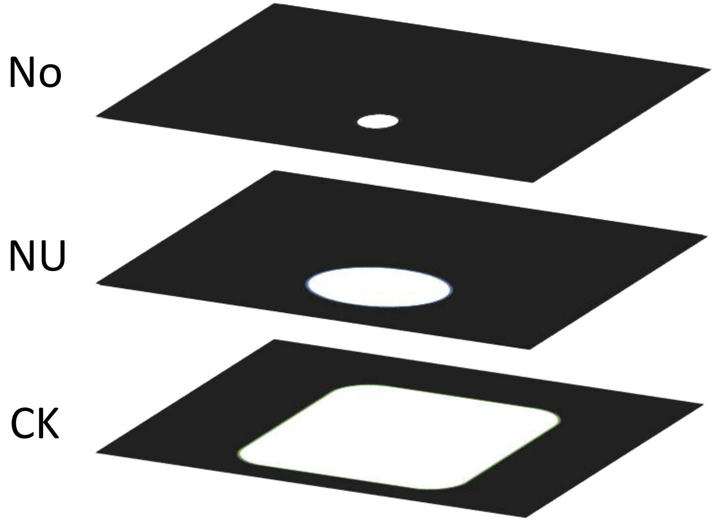


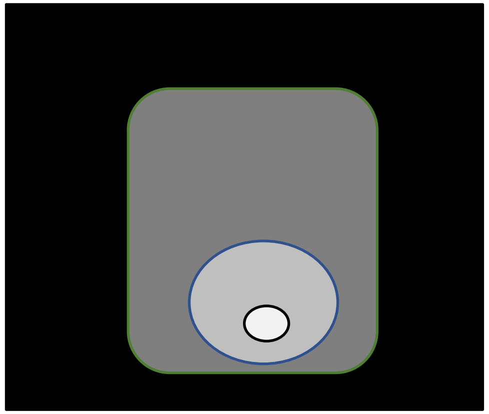


Olaf Ronneberger, Philipp Fischer, Thomas Brox: U-Net: Convolutional Networks for Biomedical Image Segmentation
Medical Image Computing and Computer-Assisted Intervention (MICCAI), Springer, LNCS, Vol.9351: 234--241, 2015

Generation of a multiclass dataset

- Binary segmentation models for
  - Luminal epithelium, basal cells, nuclei of different compartiments, nucleoli, lumina, corpora amylacea, fat vacuoles, nervs, sleletal muscle, lipofuscin, black ink, green ink, red ink, yellow ink
- Predict each class on a patchified H&E dataset (512x512px @ 20x, 0.5µm/px)
- Stack the binary prediction masks
- Generate a categorical multiclass mask (np.argmax)





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0000001111122233222111000000
0000000111111222211110000000
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Classes and Class Imbalance

PATHOLOGIE

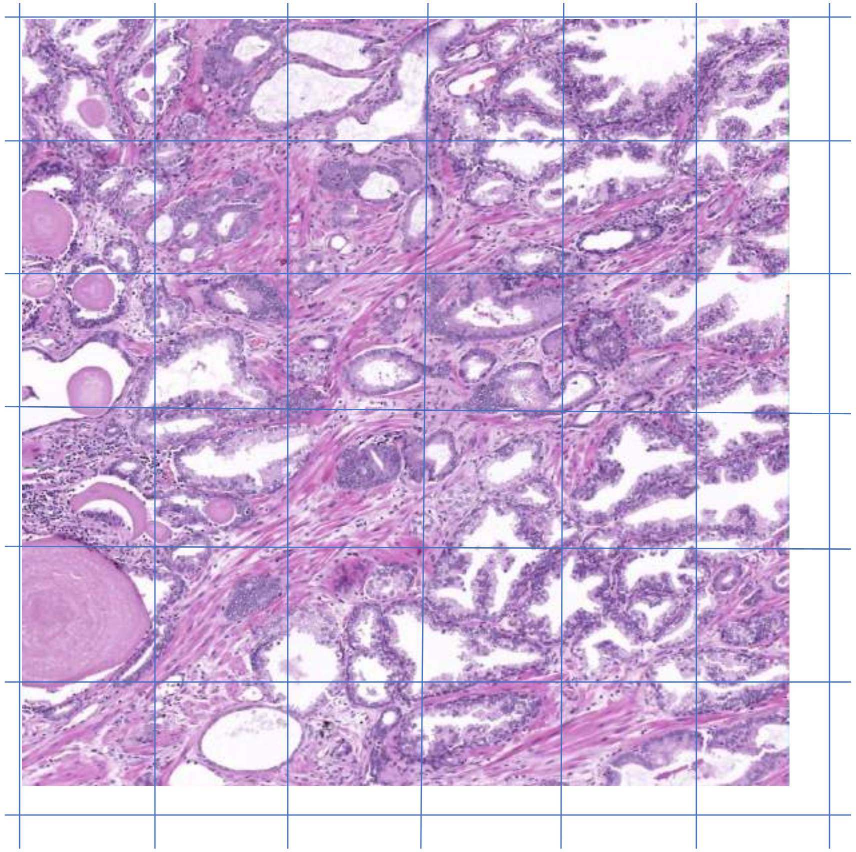
Class/Item	Abbrev.	%	Class/item	Abbrev.	%
Background	bg	4.33	Red ink	ri	0.37
Stroma	st	56.11	Green ink	gi	0.12
Striated muscle	sm	0.59	Black ink	bi	0.91
Fat	ft	0.89	Lipofuscin	lf	0.17
Lumen	lu	8.06	Stromal nuclei	nu_st	3.96
Corpora amylacea	ca	0.33	Nuclei in lumina	nu_lu	0.02
Basal cells	bc	1.78	Luminal/cancer cell nuclei	nu_ck	4.97
Luminal cells/ Cancer cells	ck	13.08	Lymphocytes	ly	1.20
Nervs	nv	0.27	Basal cell nuclei	nu_bc	2.46
Yellow ink	yi	0.32	Nucleoli	no	0.06

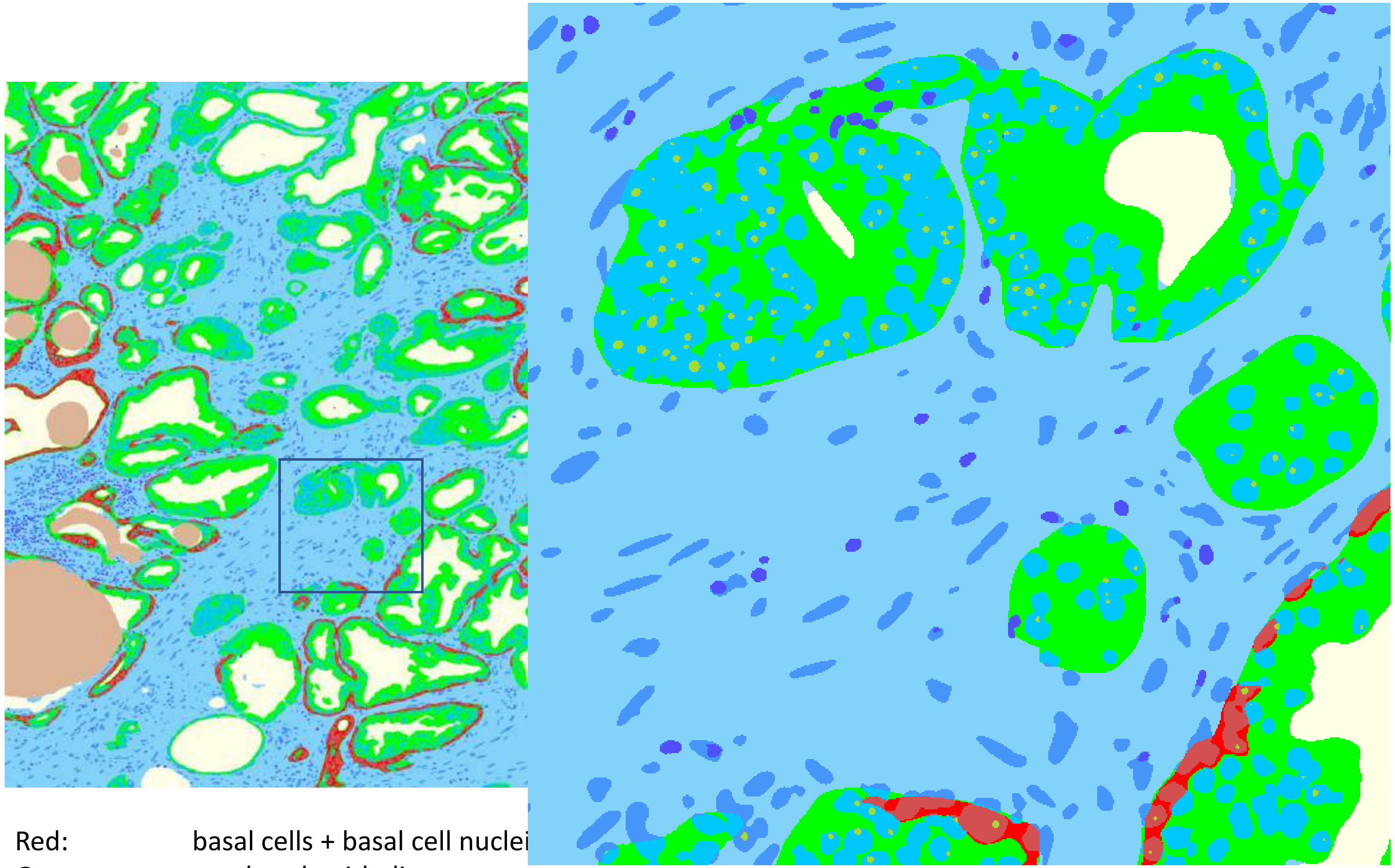
Training: 75 epochs (21 days), Unet with efficientnetB2 backbone, focal loss, lr = 0.003, callbacks

Testset results: IoU-score: 0.8609, F1-score: 0.8956

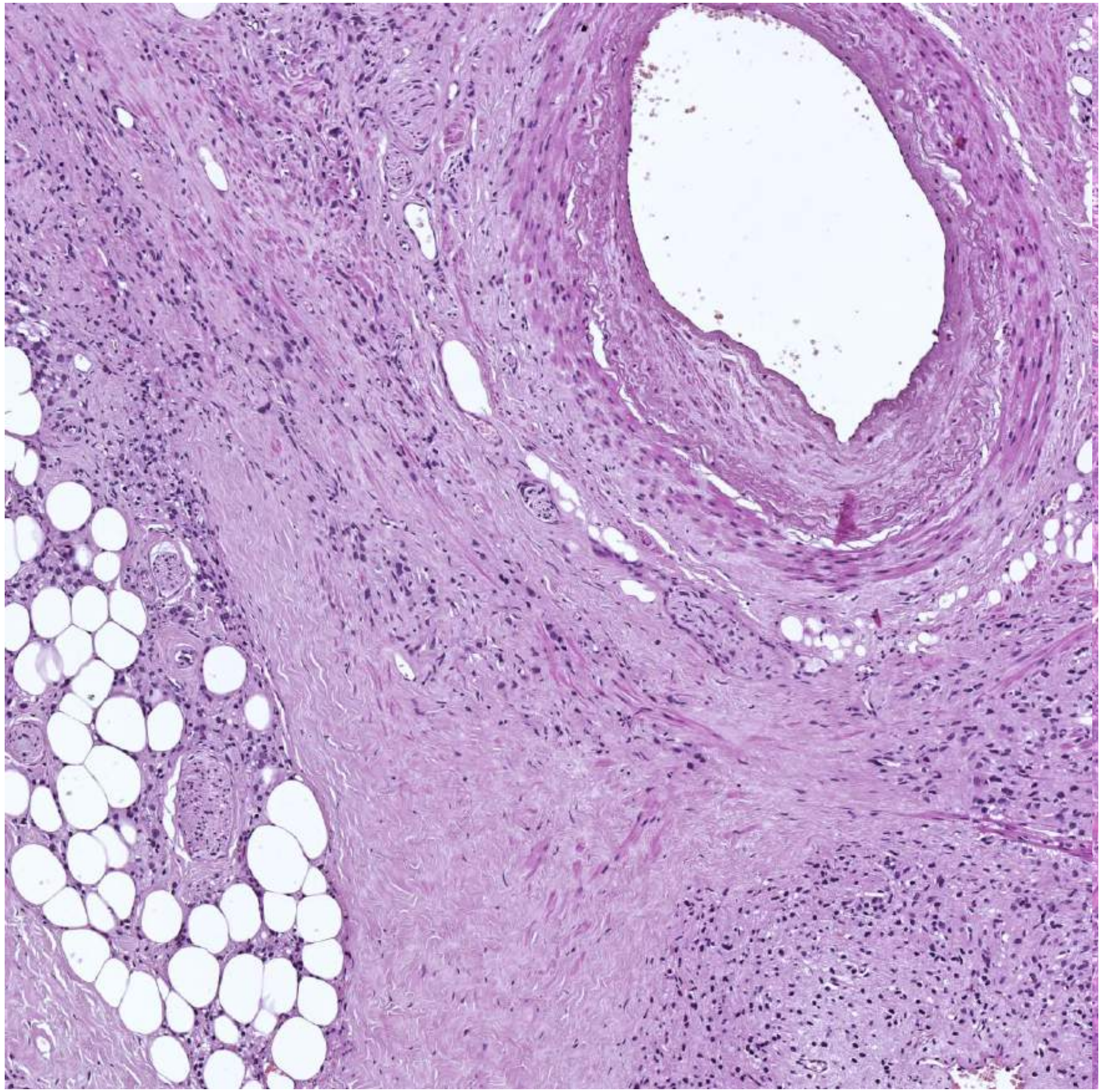
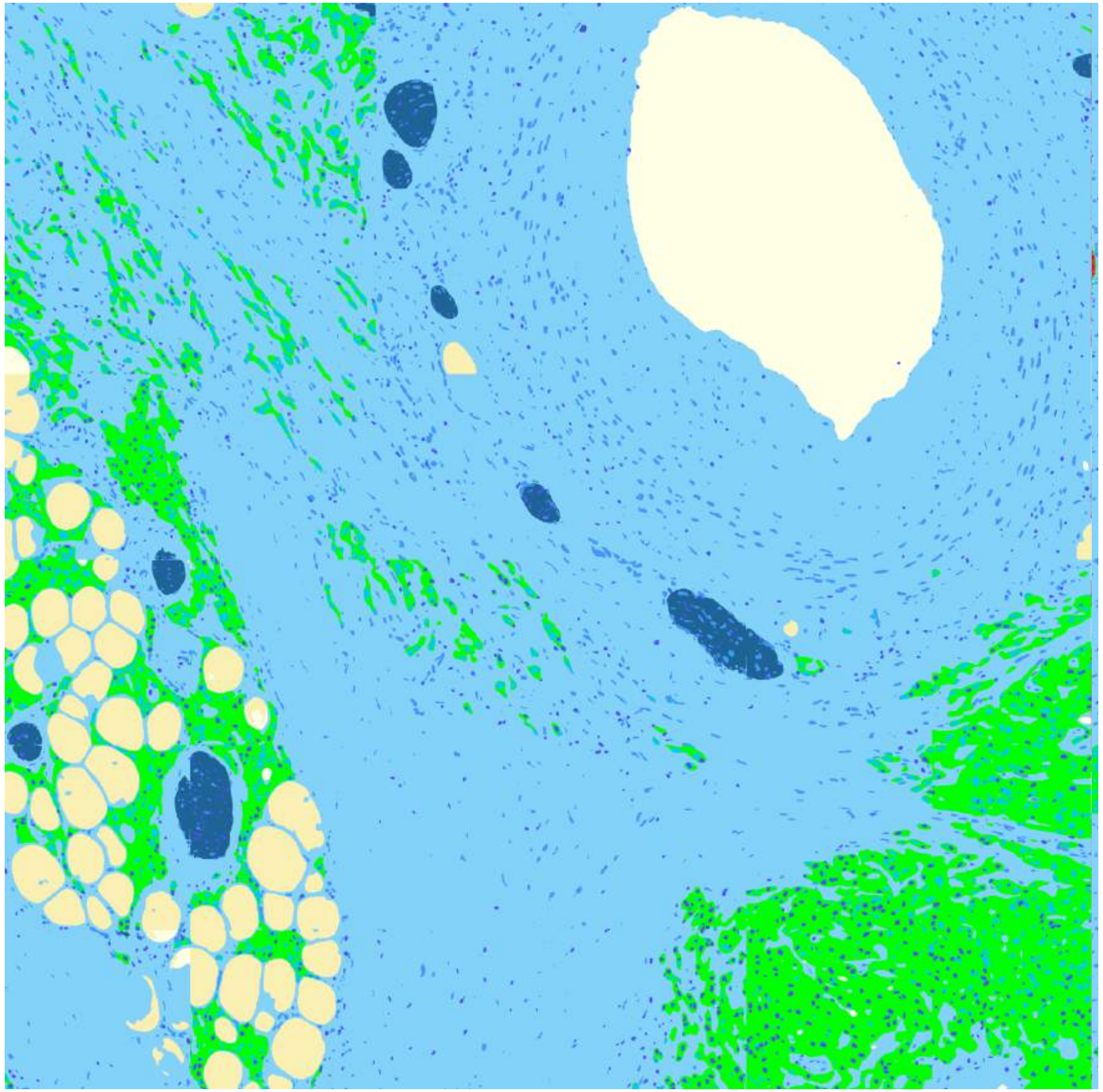
20 class tissue segmentation:

3000x3000 px (= 1.5x1.5 mm)

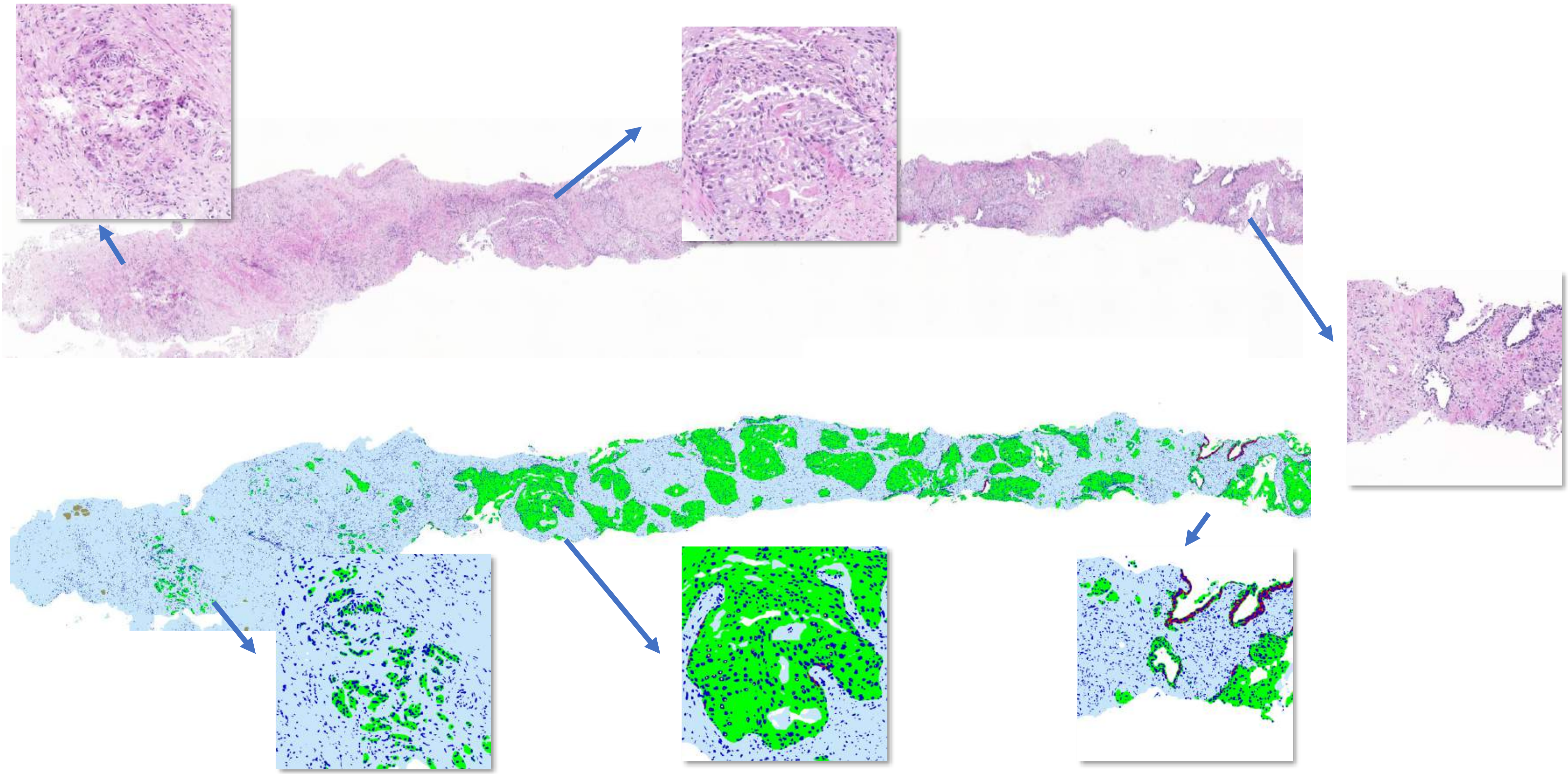




Red:	basal cells + basal cell nuclei
Green:	non basal epithelium
Blue to cyan:	nuclei (epithelial, stromal, lymphocytic)
Yellow:	nucleoli
White:	lumina
Light blue:	stroma

Segmentation in prostate core needle biopsies



Confusion matrices

focal_loss vs. dice_loss

focal_loss

Confusion Matrix (rows: Actuals; columns: Predictions)

Actuals \ Predictions	bg	st	sm	ft	lu	ca	bc	ck	nv	yi	ri	gi	bi	lf	nu_st	nu_lu	nu_ck	ly	nu_bc	no
bg	0.907	0.043	0.0	0.0	0.049	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
st	0.0	0.976	0.0	0.0	0.005	0.0	0.013	0.001	0.001	0.0	0.0	0.0	0.0	0.0	0.004	0.0	0.0	0.0	0.0	0.0
sm	0.0	0.054	0.923	0.0	0.007	0.014	0.0	0.0	0.0	0.0	0.0	0.0	0.001	0.0	0.001	0.0	0.0	0.0	0.0	0.0
ft	0.001	0.116	0.0	0.881	0.003	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
lu	0.003	0.022	0.0	0.0	0.966	0.002	0.007	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ca	0.0	0.031	0.0	0.0	0.069	0.898	0.001	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
bc	0.0	0.034	0.0	0.0	0.003	0.0	0.933	0.013	0.0	0.0	0.0	0.0	0.0	0.001	0.0	0.0	0.013	0.0	0.001	0.0
ck	0.0	0.041	0.0	0.0	0.0	0.0	0.183	0.721	0.0	0.0	0.0	0.0	0.001	0.001	0.001	0.0	0.006	0.0	0.046	0.0
nv	0.0	0.33	0.0	0.0	0.0	0.002	0.006	0.0	0.655	0.0	0.0	0.0	0.0	0.0	0.007	0.0	0.0	0.001	0.0	0.0
yi	0.0	0.056	0.0	0.0	0.0	0.0	0.001	0.0	0.0	0.943	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ri	0.0	0.044	0.0	0.0	0.022	0.001	0.008	0.002	0.0	0.0	0.921	0.0	0.0	0.0	0.001	0.0	0.0	0.0	0.0	0.0
gi	0.0	0.01	0.0	0.0	0.001	0.0	0.0	0.0	0.0	0.0	0.0	0.989	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
bi	0.0	0.023	0.0	0.0	0.0	0.0	0.008	0.002	0.0	0.0	0.0	0.0	0.955	0.0	0.002	0.0	0.006	0.002	0.002	0.0
lf	0.0	0.055	0.0	0.0	0.031	0.0	0.155	0.022	0.0	0.0	0.0	0.0	0.0	0.709	0.002	0.0	0.021	0.0	0.005	0.0
nu_st	0.0	0.042	0.0	0.0	0.0	0.0	0.001	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.909	0.001	0.026	0.015	0.006	0.0
nu_lu	0.0	0.014	0.0	0.0	0.102	0.01	0.008	0.0	0.0	0.0	0.0	0.0	0.0	0.001	0.128	0.623	0.07	0.044	0.001	0.0
nu_ck	0.0	0.001	0.0	0.0	0.0	0.0	0.021	0.001	0.0	0.0	0.0	0.0	0.0	0.0	0.022	0.0	0.91	0.009	0.033	0.003
ly	0.0	0.008	0.0	0.0	0.001	0.0	0.002	0.0	0.0	0.0	0.0	0.0	0.001	0.0	0.034	0.001	0.023	0.917	0.012	0.0
nu_bc	0.0	0.001	0.0	0.0	0.0	0.0	0.003	0.01	0.0	0.0	0.0	0.0	0.0	0.0	0.027	0.0	0.108	0.006	0.843	0.001
no	0.0	0.0	0.0	0.0	0.0	0.0	0.008	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.027	0.0	0.233	0.006	0.056	0.669

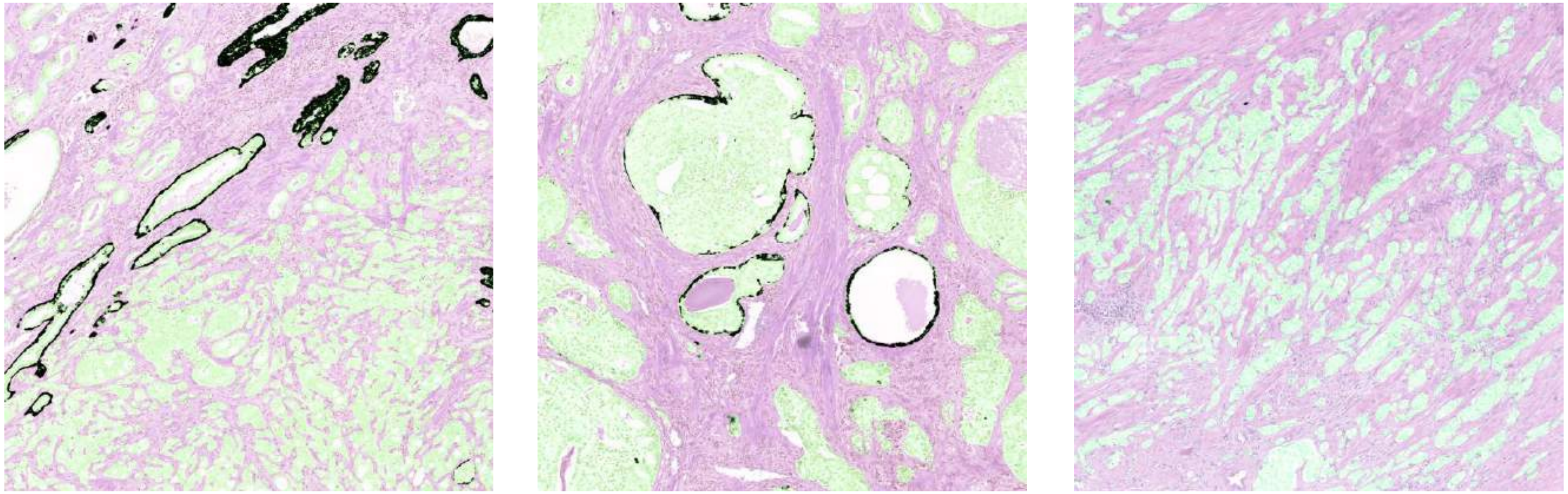
dice_loss

Confusion Matrix (rows: Actuals; columns: Predictions)

Actuals \ Predictions	bg	st	sm	ft	lu	ca	bc	ck	nv	yi	ri	gi	bi	lf	nu_st	nu_lu	nu_ck	ly	nu_bc	no	unlab
bg	0.905	0.075	0.0	0.001	0.02	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
st	0.004	0.972	0.001	0.001	0.006	0.0	0.008	0.001	0.003	0.0	0.0	0.0	0.0	0.001	0.003	0.0	0.0	0.0	0.0	0.0	
sm	0.0	0.058	0.941	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.001	0.0	0.0	0.0	0.0	0.0	
ft	0.019	0.076	0.0	0.903	0.002	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
lu	0.046	0.069	0.0	0.002	0.871	0.0	0.008	0.0	0.0	0.0	0.0	0.0	0.0	0.005	0.0	0.0	0.0	0.0	0.0	0.0	
ca	0.0	0.105	0.003	0.0	0.155	0.0	0.001	0.0	0.0	0.0	0.0	0.0	0.0	0.736	0.0	0.0	0.0	0.0	0.0	0.0	
bc	0.0	0.12	0.0	0.0	0.01	0.0	0.793	0.039	0.0	0.001	0.0	0.0	0.001	0.013	0.001	0.0	0.02	0.001	0.002	0.0	
ck	0.0	0.11	0.0	0.0	0.001	0.0	0.215	0.6	0.0	0.0	0.0	0.0	0.001	0.01	0.002	0.0	0.015	0.0	0.047	0.0	
nv	0.0	0.268	0.0	0.0	0.0	0.0	0.047	0.0	0.677	0.0	0.0	0.0	0.0	0.0	0.005	0.0	0.002	0.0	0.0	0.0	
yi	0.0	0.228	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.768	0.0	0.0	0.0	0.004	0.0	0.0	0.0	0.0	0.0	0.0	
ri	0.0	0.313	0.001	0.0	0.011	0.0	0.001	0.0	0.0	0.0	0.0	0.0	0.0	0.672	0.001	0.0	0.0	0.0	0.0	0.0	
gi	0.0	0.015	0.0	0.0	0.0	0.0	0.013	0.001	0.0	0.0	0.0	0.324	0.517	0.128	0.0	0.0	0.0	0.0	0.0	0.002	
bi	0.0	0.101	0.0	0.0	0.0	0.0	0.005	0.0	0.0	0.0	0.0	0.0	0.853	0.032	0.002	0.0	0.004	0.001	0.001	0.0	
lf	0.0	0.073	0.0	0.0	0.041	0.0	0.178	0.084	0.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.016	0.0	0.007	0.0	
nu_st	0.0	0.092	0.0	0.0	0.0	0.0	0.001	0.0	0.001	0.0	0.0	0.0	0.001	0.002	0.846	0.0	0.026	0.025	0.006	0.0	
nu_lu	0.0	0.089	0.0	0.0	0.295	0.0	0.009	0.002	0.0	0.0	0.0	0.0	0.0	0.353	0.075	0.0	0.109	0.066	0.003	0.0	
nu_ck	0.0	0.017	0.0	0.0	0.0	0.0	0.033	0.003	0.0	0.0	0.0	0.0	0.001	0.005	0.062	0.0	0.757	0.031	0.088	0.004	
ly	0.0	0.016	0.0	0.0	0.001	0.0	0.002	0.0	0.0	0.0	0.0	0.0	0.003	0.002	0.064	0.0	0.034	0.87	0.009	0.0	
nu_bc	0.0	0.015	0.0	0.0	0.0	0.0	0.007	0.018	0.0	0.0	0.0	0.0	0.001	0.001	0.045	0.0	0.195	0.035	0.682	0.001	
no	0.0	0.005	0.0	0.0	0.0	0.0	0.004	0.0	0.0	0.0	0.0	0.0	0.0	0.005	0.03	0.0	0.224	0.022	0.125	0.584	
unlab																					

Does the computer (i.e. another segmentation model) „understand“ the segmented images ?

- Manual annotion of 400 images 3000 x 3000 px on overlays of
  - HE,
  - IHC of basal cells (34ßE12, p63) and
  - epithelium prediction from a binary network
- 3 classes: benign, CIS/HGPIN, malignant (+ background)

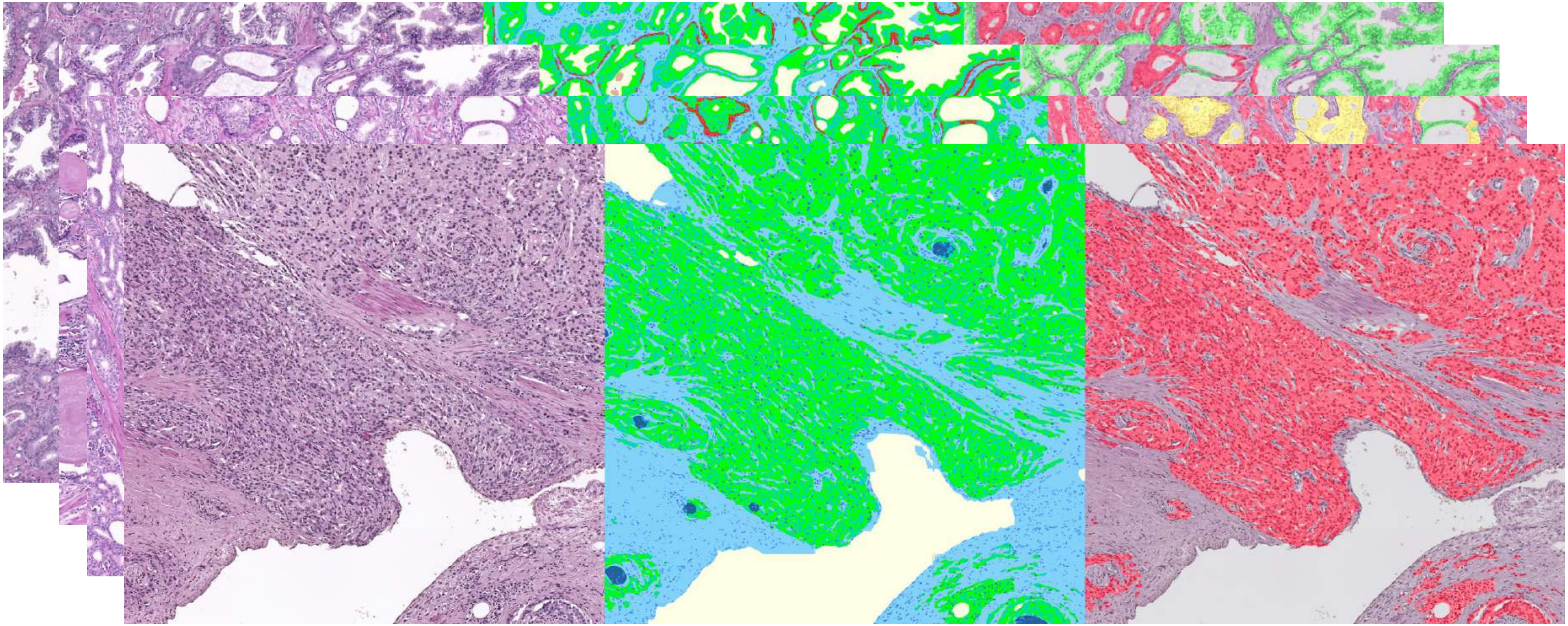


Preproc. → Analysis → Decision

HE 3000x3000 px

20 class segmentation

3 class segmentation:
benign, Ca in situ, malignant

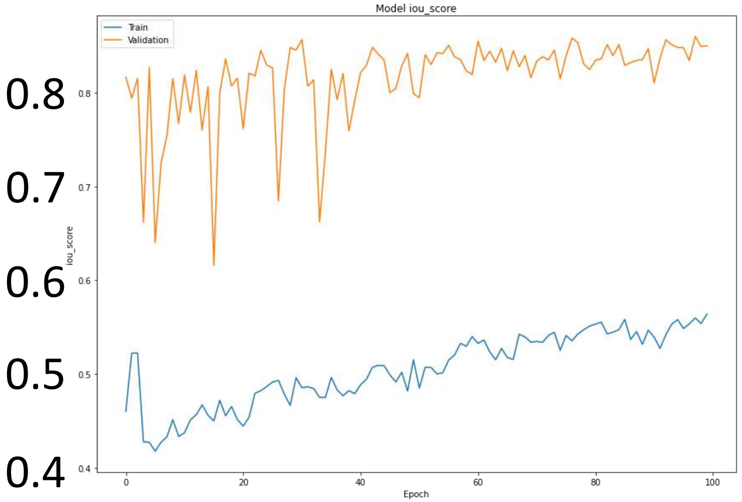


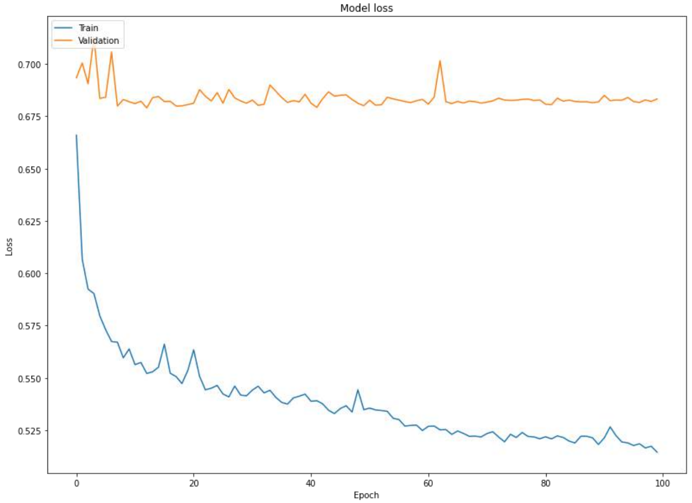
The diagnostic Path vs. Black Box Model

H&E

MC20

dignity





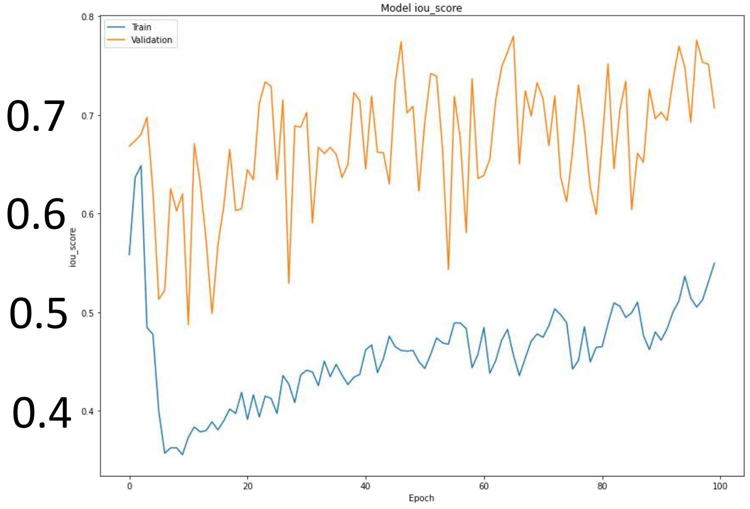
Results in test set:

Mean IoU: 0.859

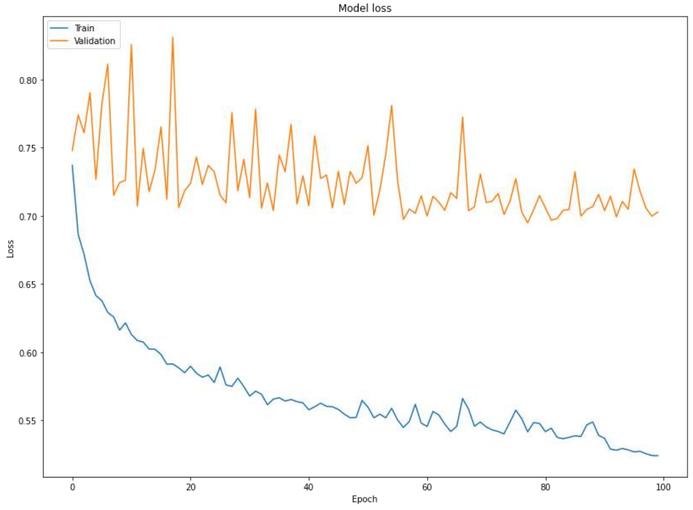
F1-score: 0.884

H&E

dignity



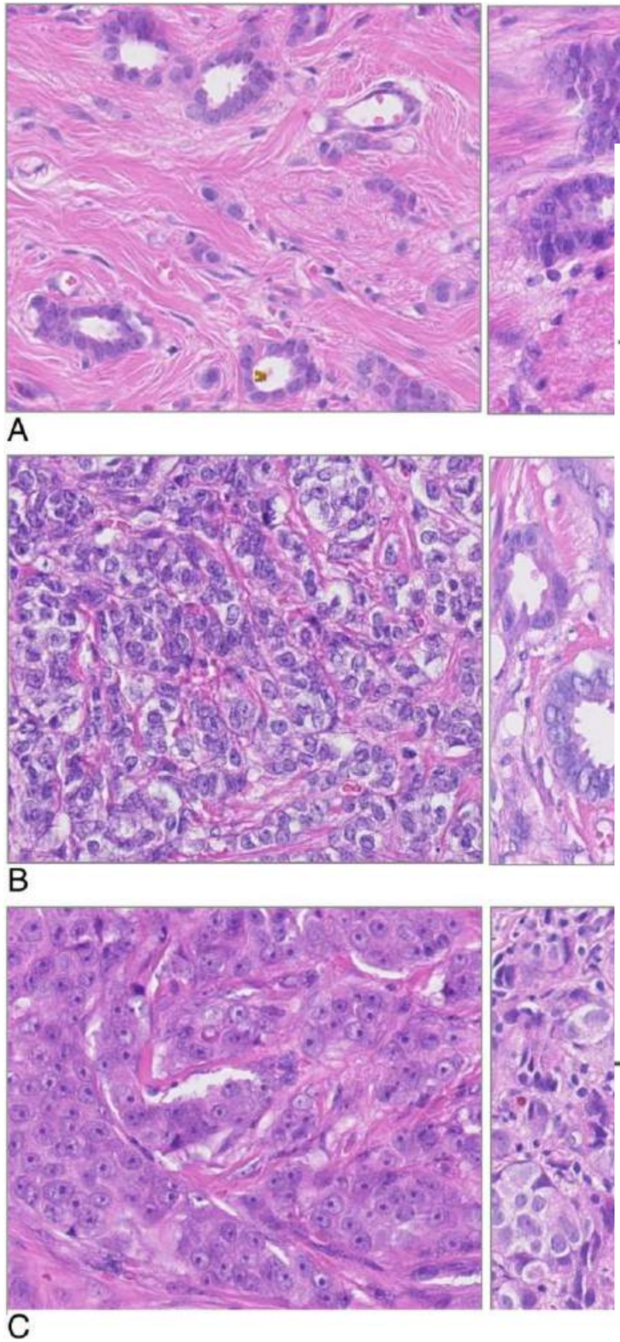
IoU score



Dice loss

Mean IoU: 0.779

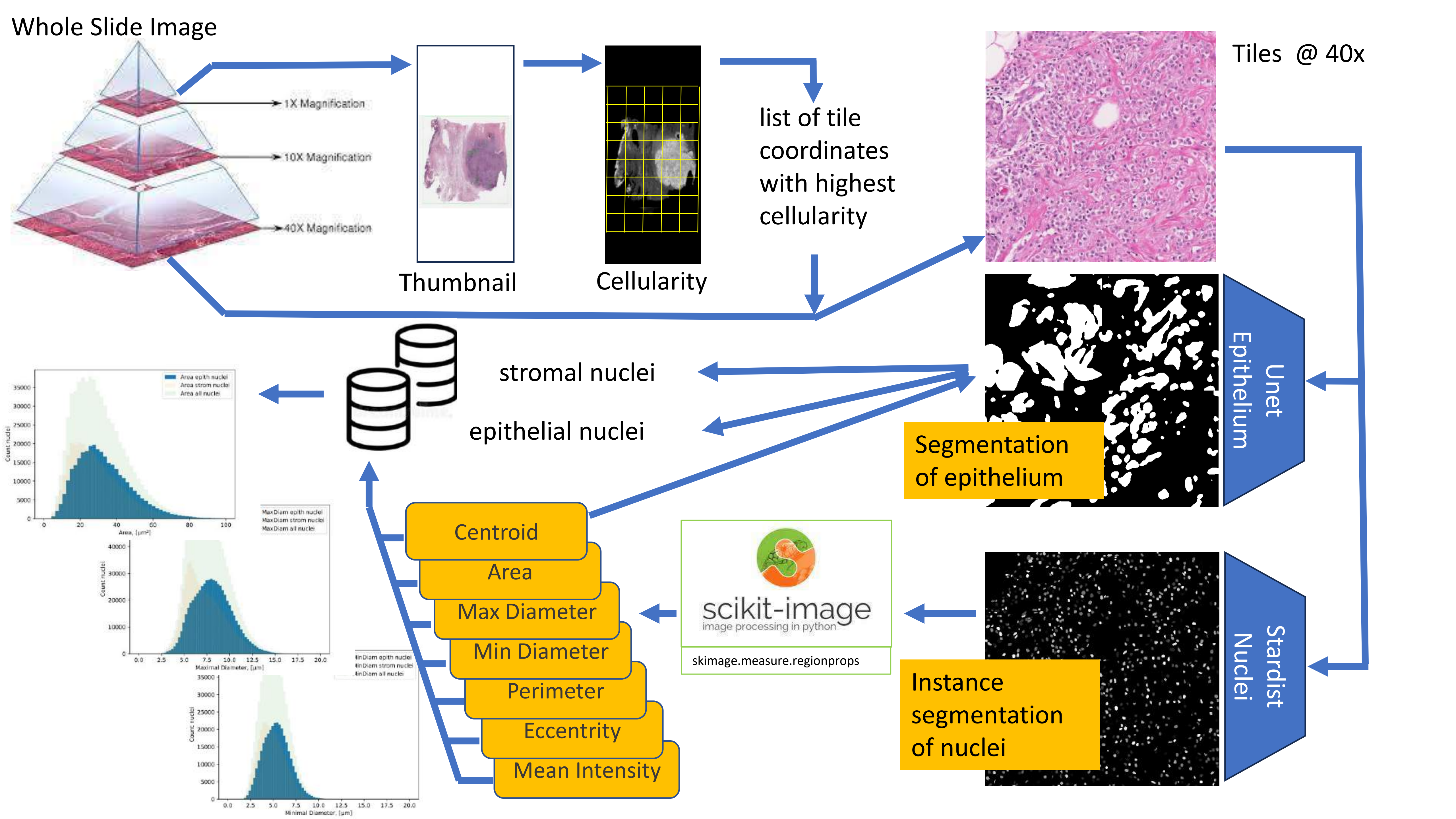
F1-score: 0.811



Grading of Breast Cancer

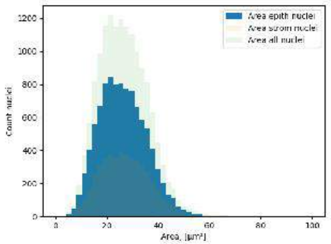
Parameter	Score 1	Score 2	Score 3
Tubule formation	>75%	10-75%	<10%
Nuclear pleomorphism	Absent*	Moderate	Marked
Mitotic count**	<9	9-17	>17

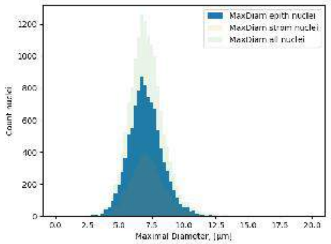
Final score	3	4	5	6	7	8	9
	Grade I			Grade II		Grade III	

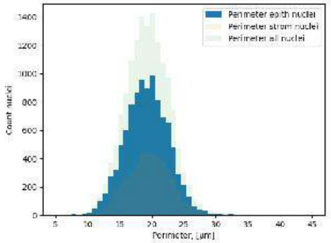


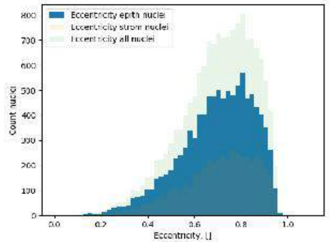
Whole Slide Image
1X Magnification
10X Magnification
40X Magnification
Thumbnail
Cellularity
list of tile coordinates with highest cellularity
Tiles @ 40x
Unet Epithelium
Segmentation of epithelium
Stardist Nuclei
Instance segmentation of nuclei
stromal nuclei
epithelial nuclei
scikit-image
image processing in python
skimage.measure.regionprops
Centroid
Area
Max Diameter
Min Diameter
Perimeter
Eccentrity
Mean Intensity
Area epith nuclei
Area strom nuclei
Area all nuclei
Area, [μm²]
Count nuclei
MaxDiam epith nuclei
MaxDiam strom nuclei
MaxDiam all nuclei
Maximal Diameter, [μm]
Minimal Diameter, [μm]

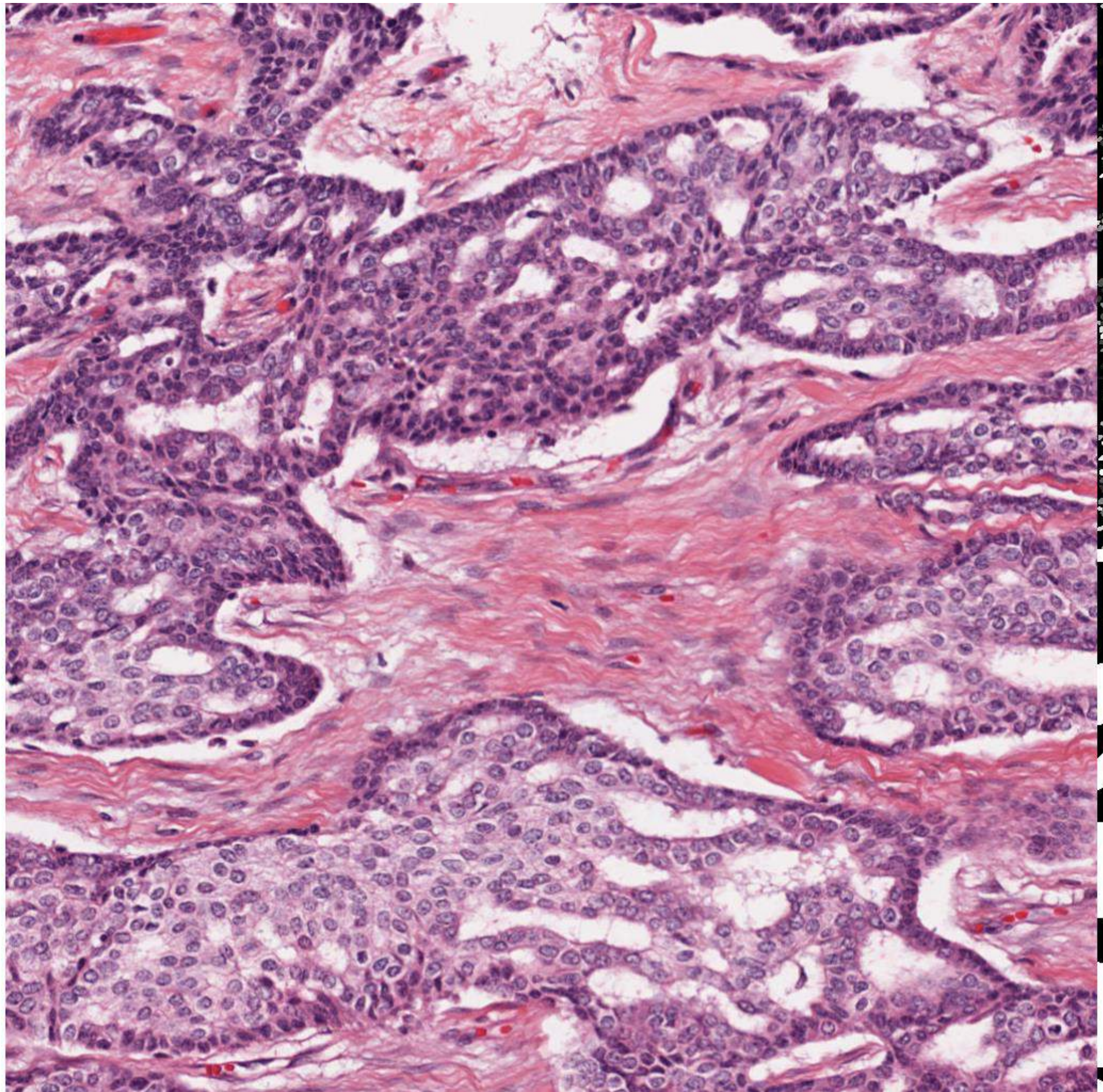
Nuclear Breast Cancer Analysis (TCGA Dataset)

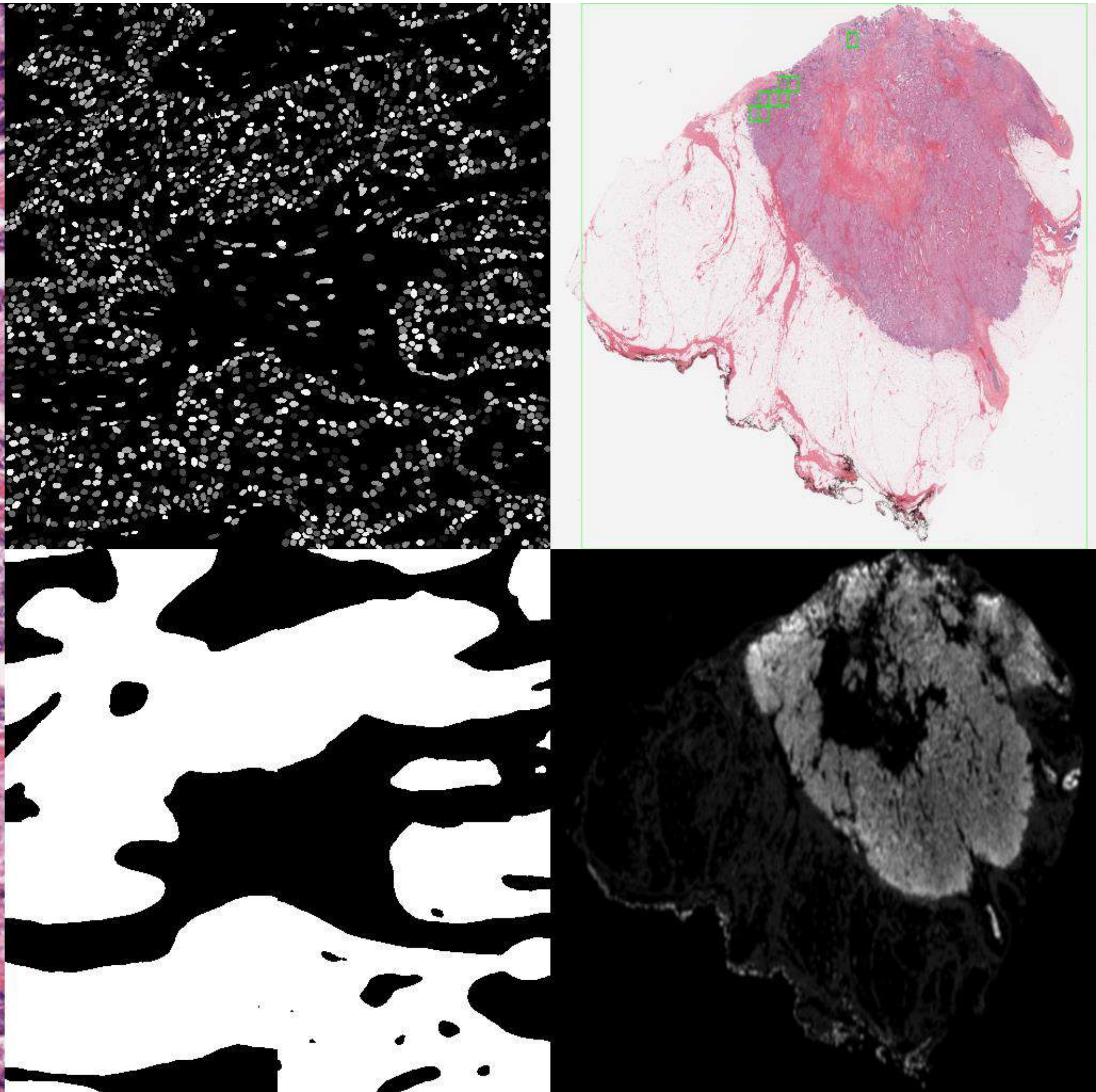












Summary

- Neural networks and specialized libraries can be **paralleled, combined and cascaded**.
- This stategy is useful to organize and **structure a task into subtasks**.
- It forces the pathway into **diagnostically established pathways**.
- Image, intermediate results and final prediction can be placed side-by-side.
- This results in explainable AI (xAI) and moreover in **self-explaining AI**.
- Diagnostical **criteria in Pathology will be refined** by the results obtained by AI.