UNIVERSITÄT ZU LÜBECK
INSTITUT FÜR MEDIZINTECHNIK

Detektion von Plaque in Gefäßen mit KI

Analyse von Arteriosklerose in histologischen Schnittbildern

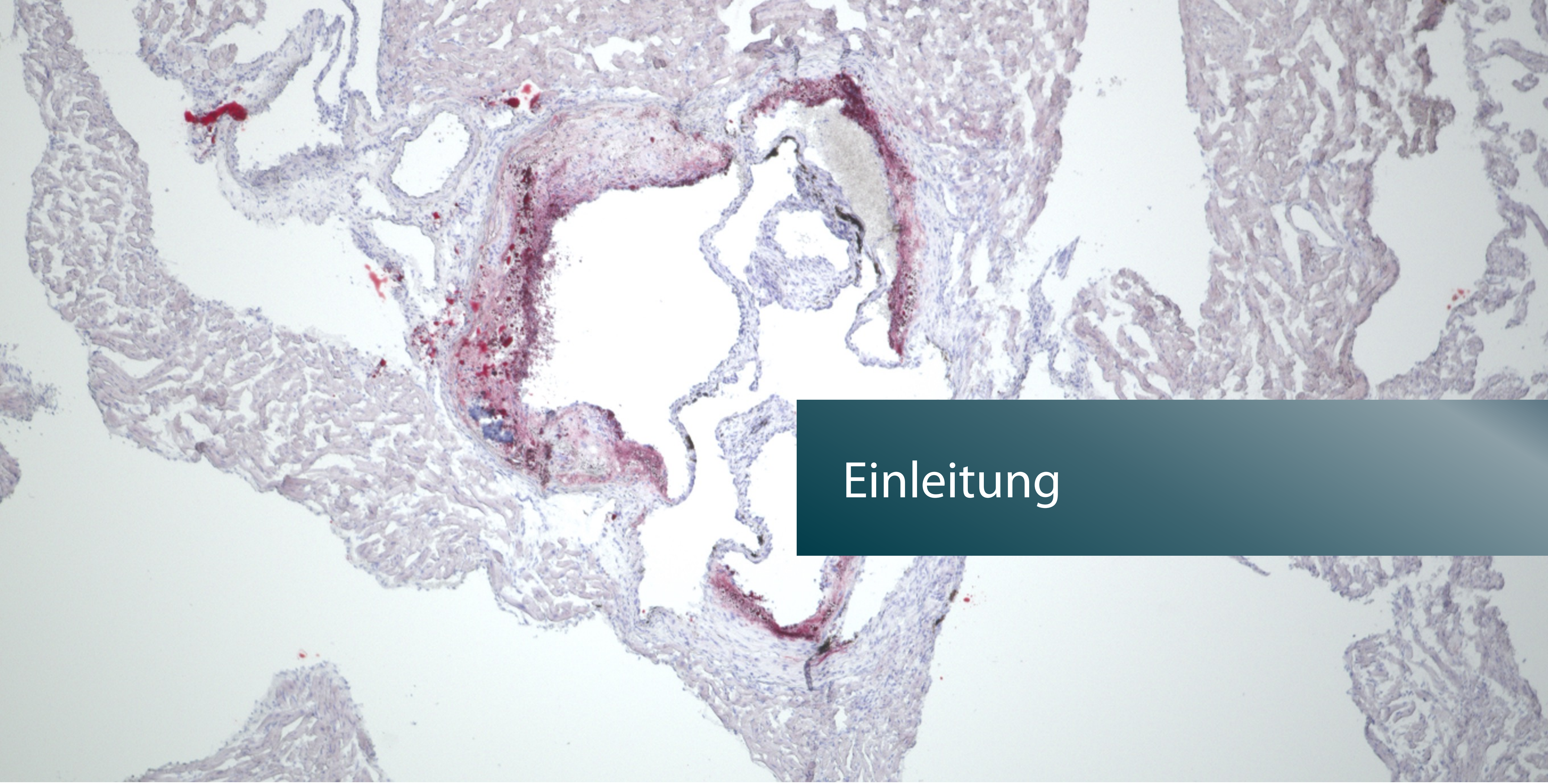
von Johann Christopher Engster

Gliederung

Einleitung
- Teamvorstellung
- Motivation

Methoden
- Datensatz
- Arterien Segmentierung
  - Single-Network Approach
  - Multi-Network Approach
  - Ensembles
- Plaque Segmentierung
  - Erstellen eines Datensatzes
  - Unüberwachtes Lernen mit W-Net

Ausblick



Einleitung

Einleitung

Teamvorstellung

Johann Engster
Student

Nele Blum
IMT/IMTE

Pascal Stagge
IMT/IMTE

Tobias Reinberger
Institut für Kardiogenetik

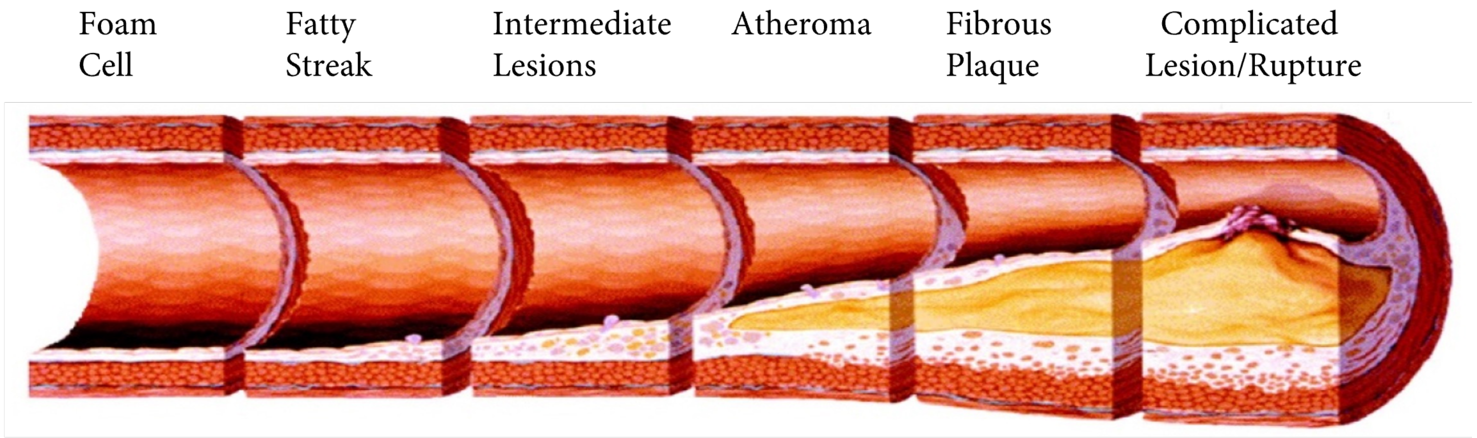
Maik Stille
IMT/IMTE

Einleitung

Motivation — Westlicher Lebensstil

Wenig Bewegung, fettlastige Ernährung oder Rauchen
- Steigende Übergewichtigkeit und Bluthochdruck
- Reduktion der Lebenserwartung

Hauptursache: Atherosklerose
- Multifaktorielle degenerative Erkrankung der Arterien
- Bilden von Ablagerungen (Plaques) in den Arterien
  - Ischämischen Herzerkrankungen, Thrombosen oder Schlaganfällen
- Haupttodesursache in Industriestaaten


Foam Cell
Fatty Streak
Intermediate Lesions
Atheroma
Fibrous Plaque
Complicated Lesion/Rupture

W. Koenig and N. Arnold. Biomarkers of Atherosclerotic Plaque Instability and Rupture. Arteriosclerosis, Thrombosis, and Vascular Biology, 27:15–26, 2007.

Einleitung

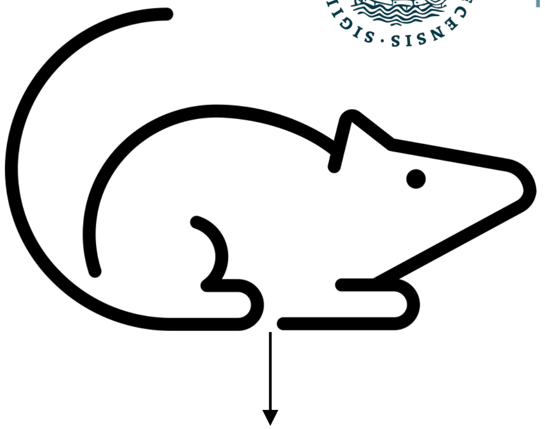
Motivation — Forschung an Mäusen

Mäuse für Atherosklerose Forschung

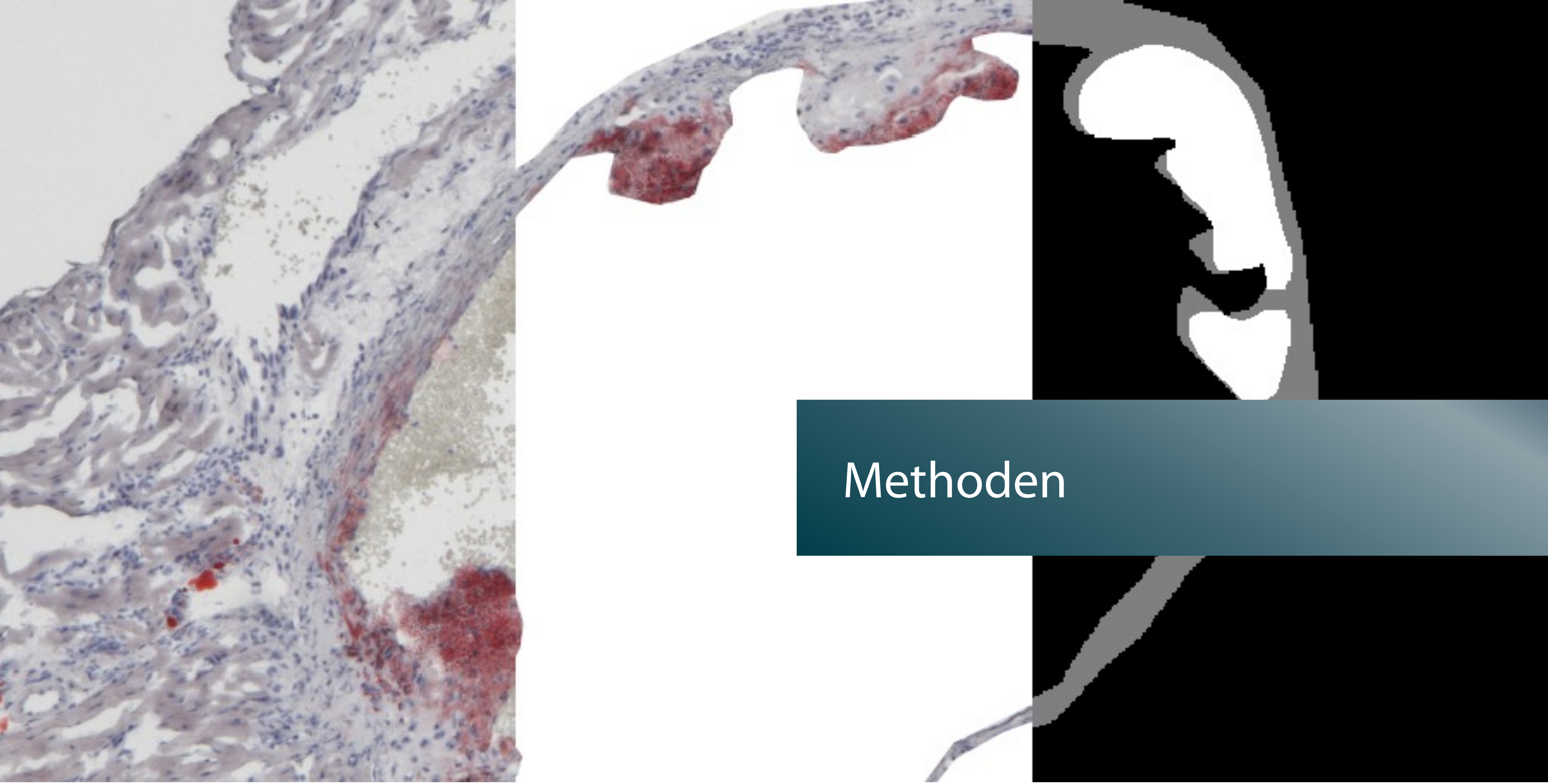
- Mäuse werden seziert
- Histologische Schnitte von der Aortenwurzel
- Färbung mit OilRedO (ORO)

Bestimmung der Arterien und Plaques

- Arterien werden per Hand am PC „ausgeschnitten“
- Zeitintensiver und teurer Prozess
- Plaquebestimmung durch Threshold-basierte Segmentierung



Gliederung



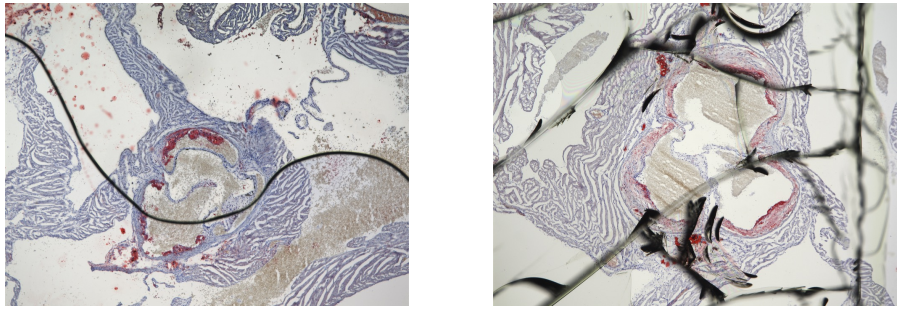
Methoden

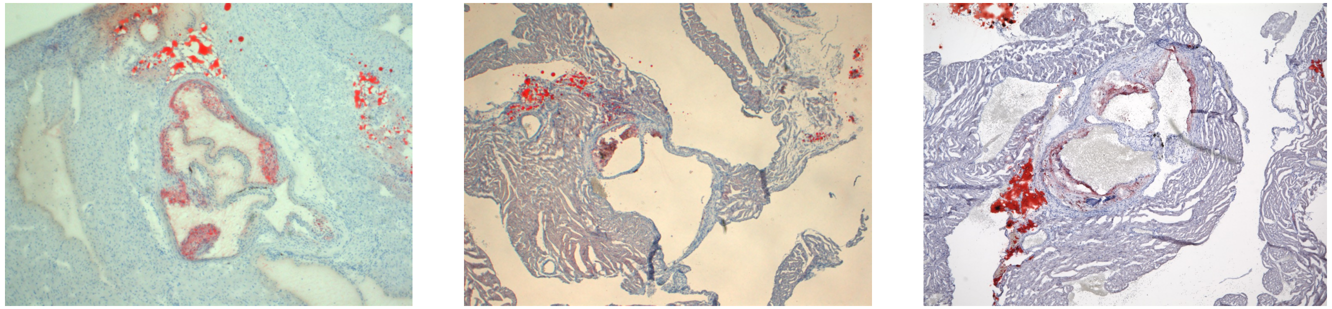
Methoden

Datensatz

Datensatz

- Bereitgestellt vom Institut für Kardiogenetik (vielen Dank!)
- 7357 Schnittbilder, 731 Maus IDs
- Daten vorbereitet mit Skripten
  - Rausfiltern von beschädigten Bildern
  - Teils große visuelle Unterschiede

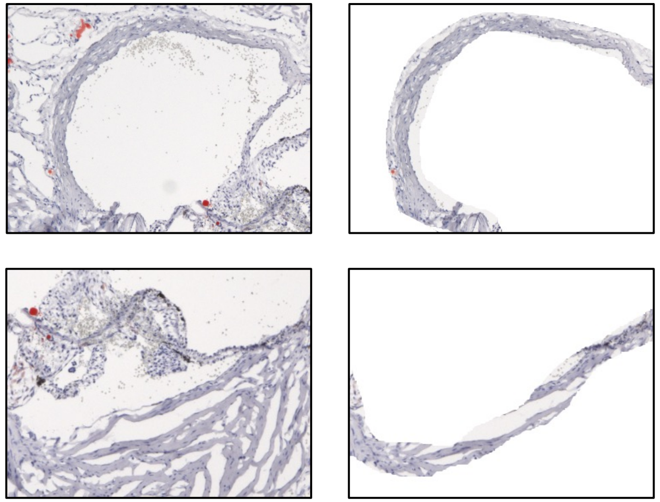




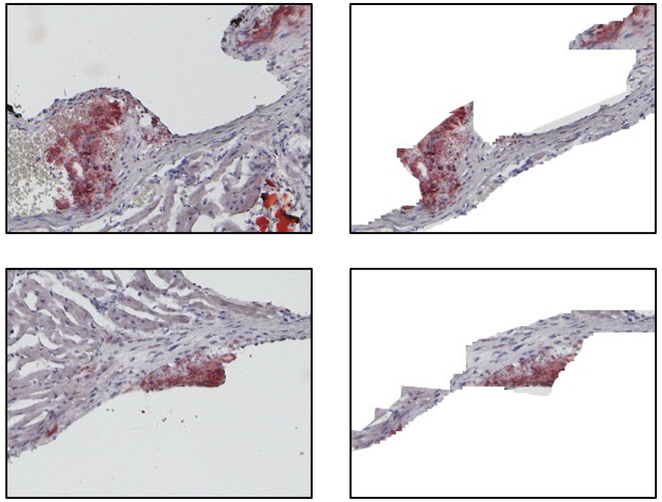
Methoden

Datensatz — Fehler in den Daten

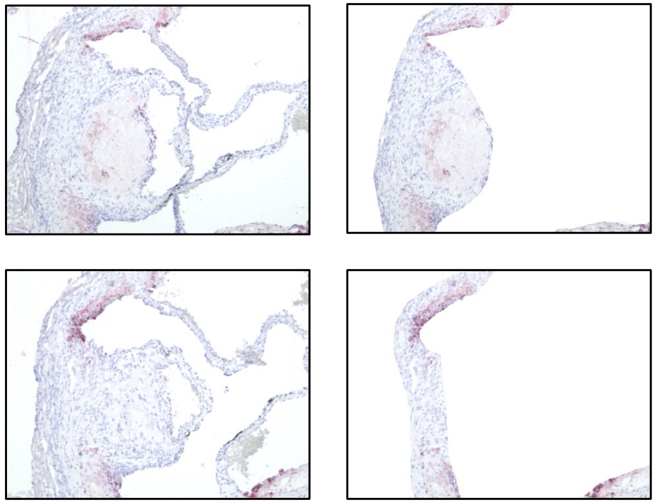
Übersegmentierte Masken



Untersegmentierte Masken

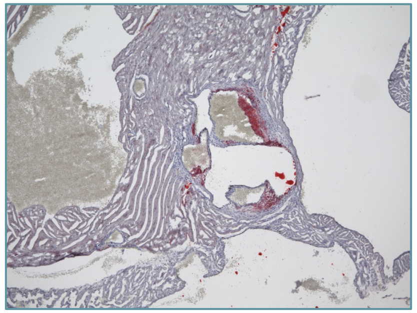


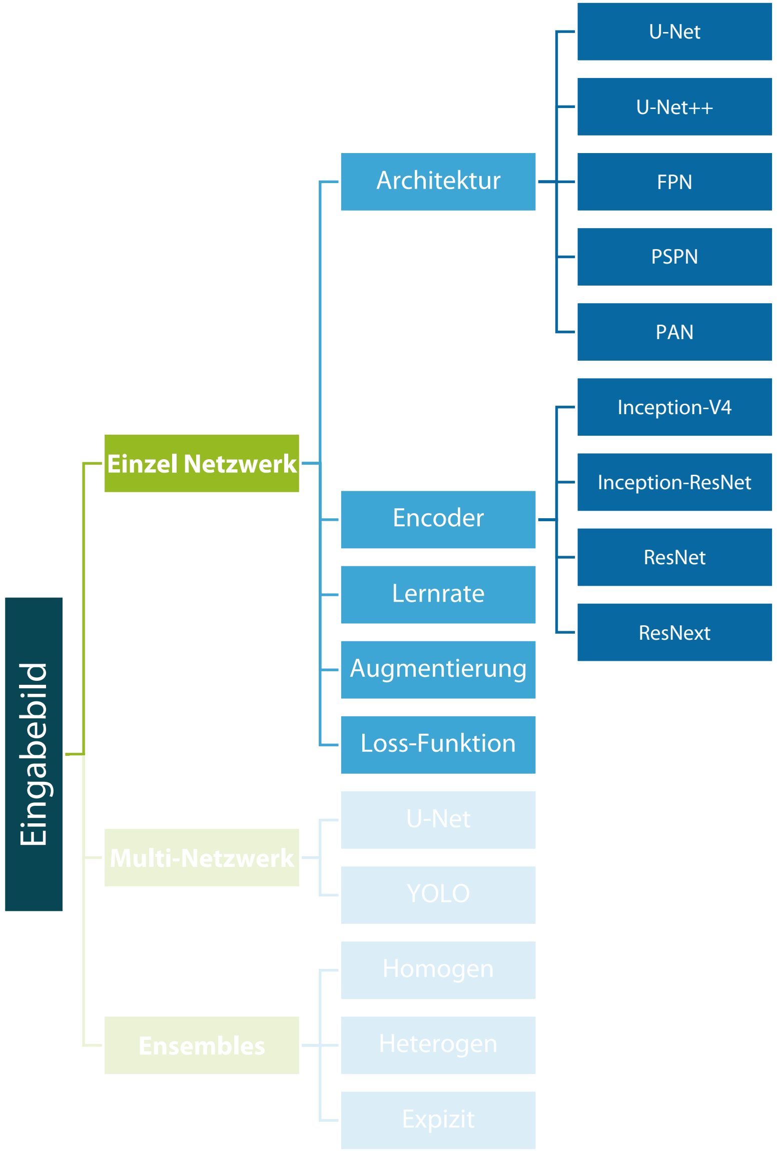
Inkonsistente Masken



Gliederung

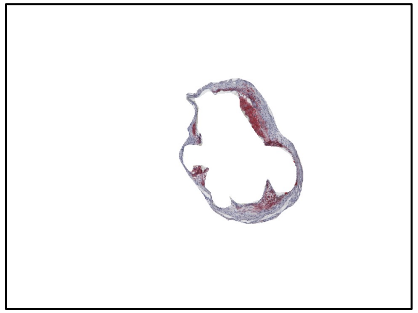
Histologischer Schnitt





- Eingabebild
  - Einzel Netzwerk
    - Architektur
      - U-Net
      - U-Net++
      - FPN
      - PSPN
      - PAN
    - Encoder
      - Inception-V4
      - Inception-ResNet
      - ResNet
      - ResNext
    - Lernrate
    - Augmentierung
    - Loss-Funktion
  - Multi-Netzwerk
    - U-Net
    - YOLO
  - Ensembles
    - Homogen
    - Heterogen
    - Expizit

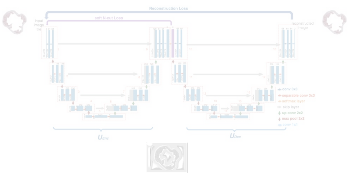
Segmentierung der Arterien



Morph. K-NN

- Eingabebild
  - Supervised
  - Unsupervised

W-Net

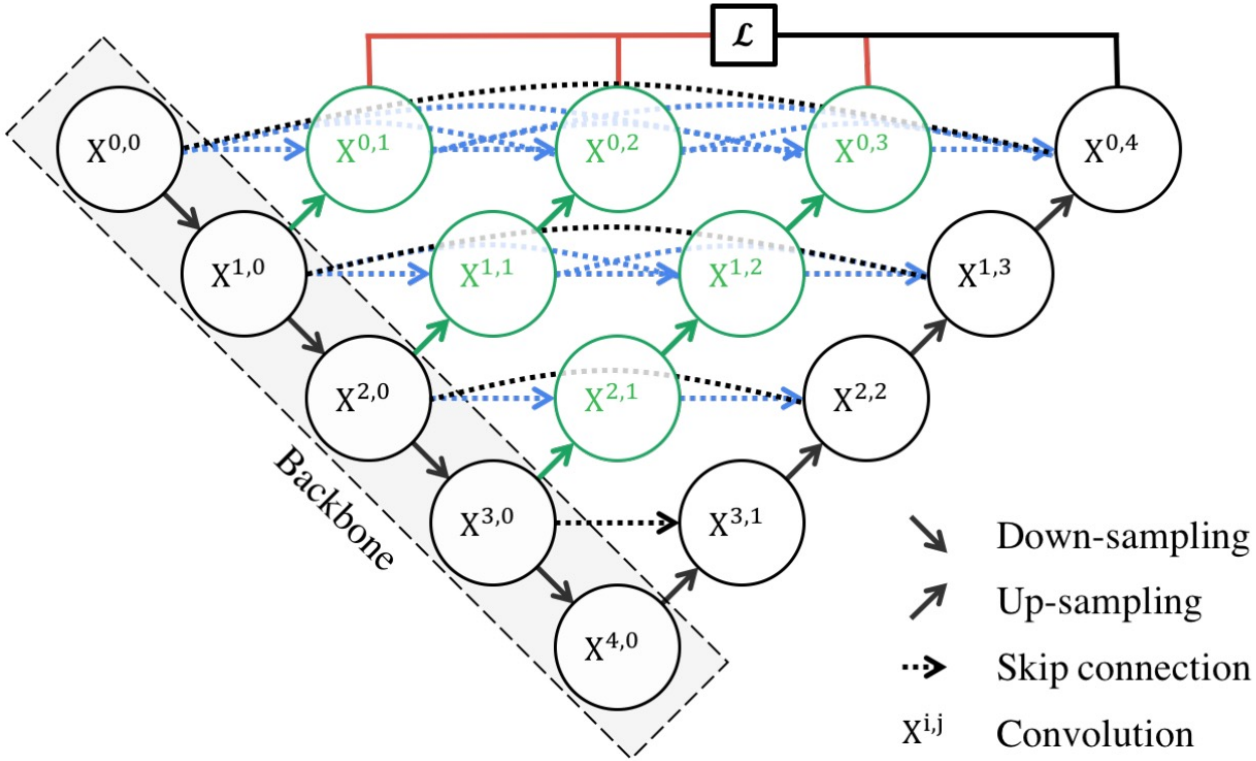


Segmentierung der Plaques

Methoden

Arterien Segmentierung — Encoder-Decoder basierte Netzwerke

U-Net++

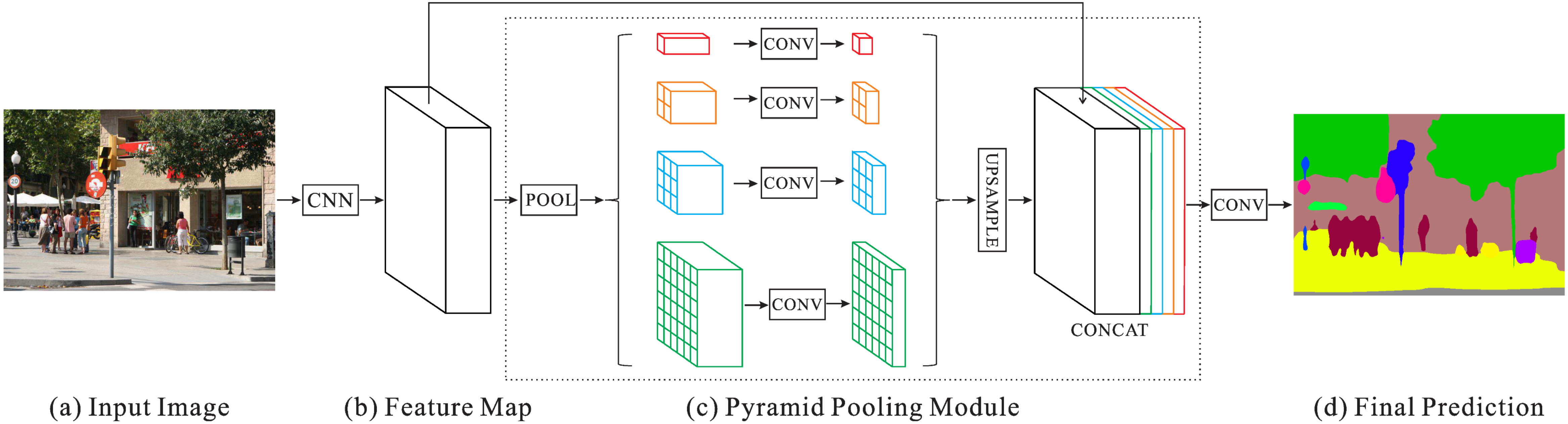

$\mathcal{L}$
$X^{0,0}$
$X^{0,1}$
$X^{0,2}$
$X^{0,3}$
$X^{0,4}$
$X^{1,0}$
$X^{1,1}$
$X^{1,2}$
$X^{1,3}$
$X^{2,0}$
$X^{2,1}$
$X^{2,2}$
$X^{3,0}$
$X^{3,1}$
$X^{4,0}$
Backbone
Down-sampling
Up-sampling
Skip connection
$X^{i,j}$ Convolution

O. Ronneberger, P. Fischer, and T. Brox. U-Net: Convolutional Networks for Biomedical Image Segmentation. Medical Image Computing and ComputerAssisted Intervention – MICCAI 2015, :234–241, 2015.
Z. Zhou, M. Rahman Siddiquee, N. Tajbakhsh, and J. Liang. UNet++: A Nested U-Net Architecture for Medical Image Segmentation. Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support, :3–11, 2018.

Methoden

Arterien Segmentierung — Multi-Auflösung / Pyramiden Netzwerke

Pyramid Scene Parsing Network

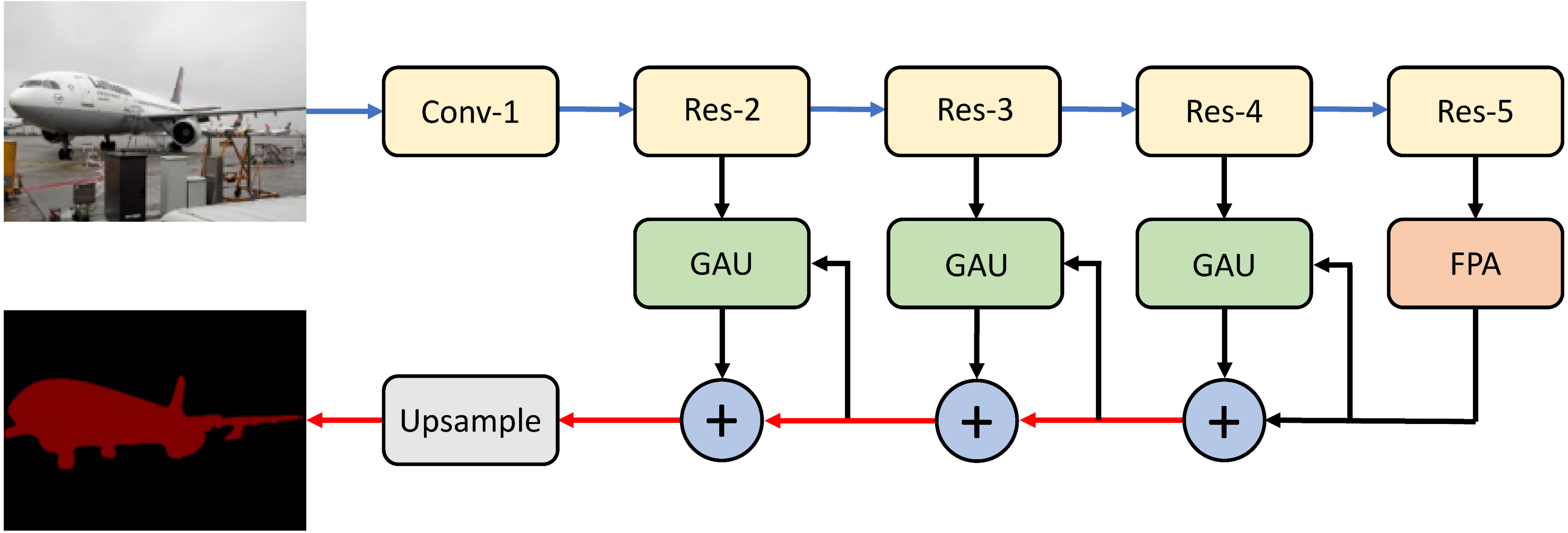

CNN
POOL
CONV
CONV
CONV
CONV
UPSAMPLE
CONCAT
CONV
(a) Input Image
(b) Feature Map
(c) Pyramid Pooling Module
(d) Final Prediction

T.-Y. Lin, P. Dollár, R. Girshick, K. He, B. Hariharan, and S. Belongie. Feature Pyramid Networks for Object Detection. 2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), :936–944, 2017.
H. Zhao, J. Shi, X. Qi, X. Wang, and J. Jia. Pyramid Scene Parsing Network. 2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), :6230–6239, 2017.

Methoden

Arterien Segmentierung — Attention-basierte Netzwerke

Pyramid Attention Network


Conv-1
Res-2
Res-3
Res-4
Res-5
GAU
GAU
GAU
FPA
Upsample
+
+
+

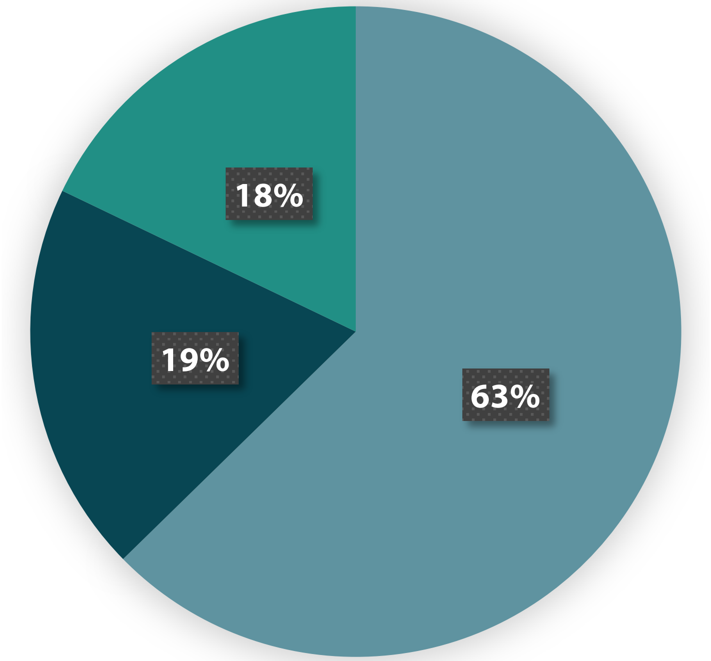
H. Li, P. Xiong, J. An, and L. Wang. Pyramid Attention Network for Semantic Segmentation, 2018.

Methoden

Arterien Segmentierung — Netzwerk Training

Bilder nach Maus IDs gemischt

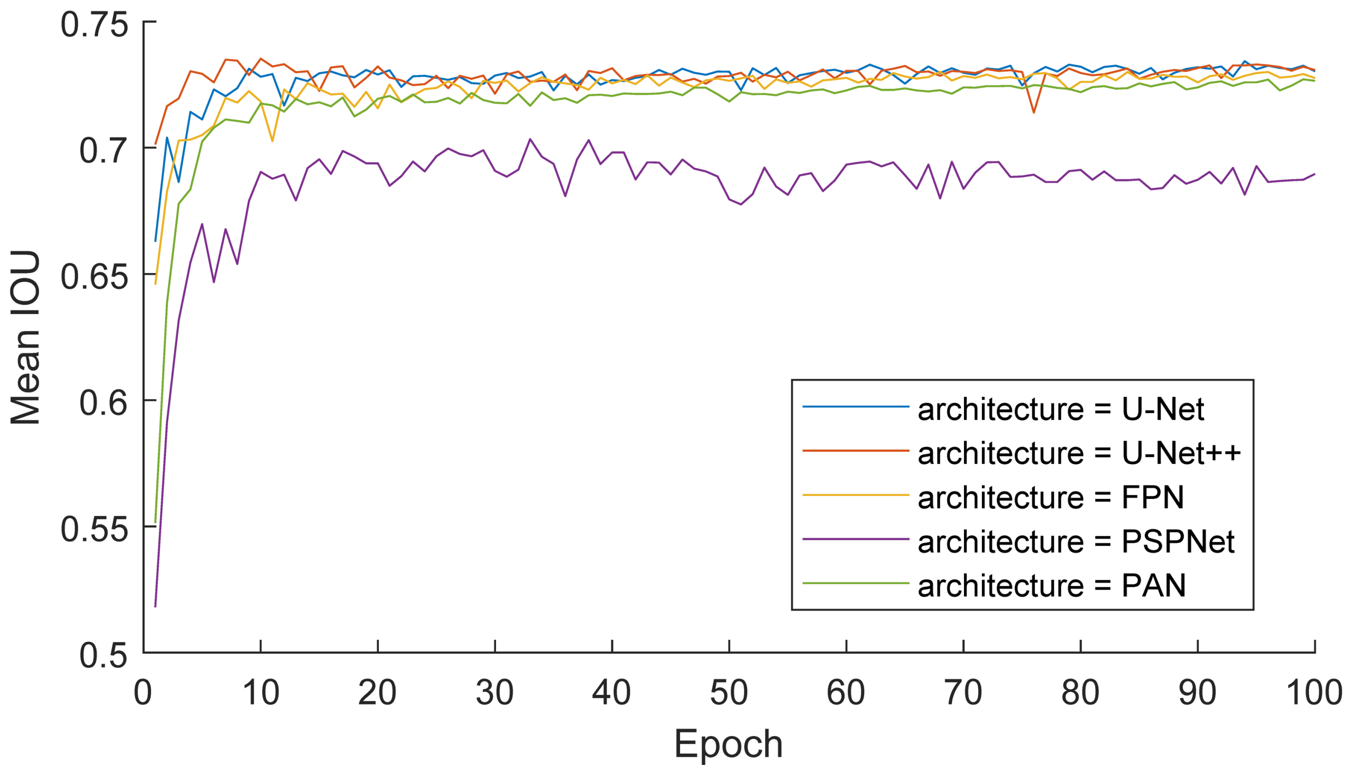
- keine konsekutiven Bilder in z.B. Training und Validation Data Set



Training → Netz lernt mit diesen Bildern
Validierung → Bestimmen des besten Netzes
Test → Zum Finalen Testen

Methoden

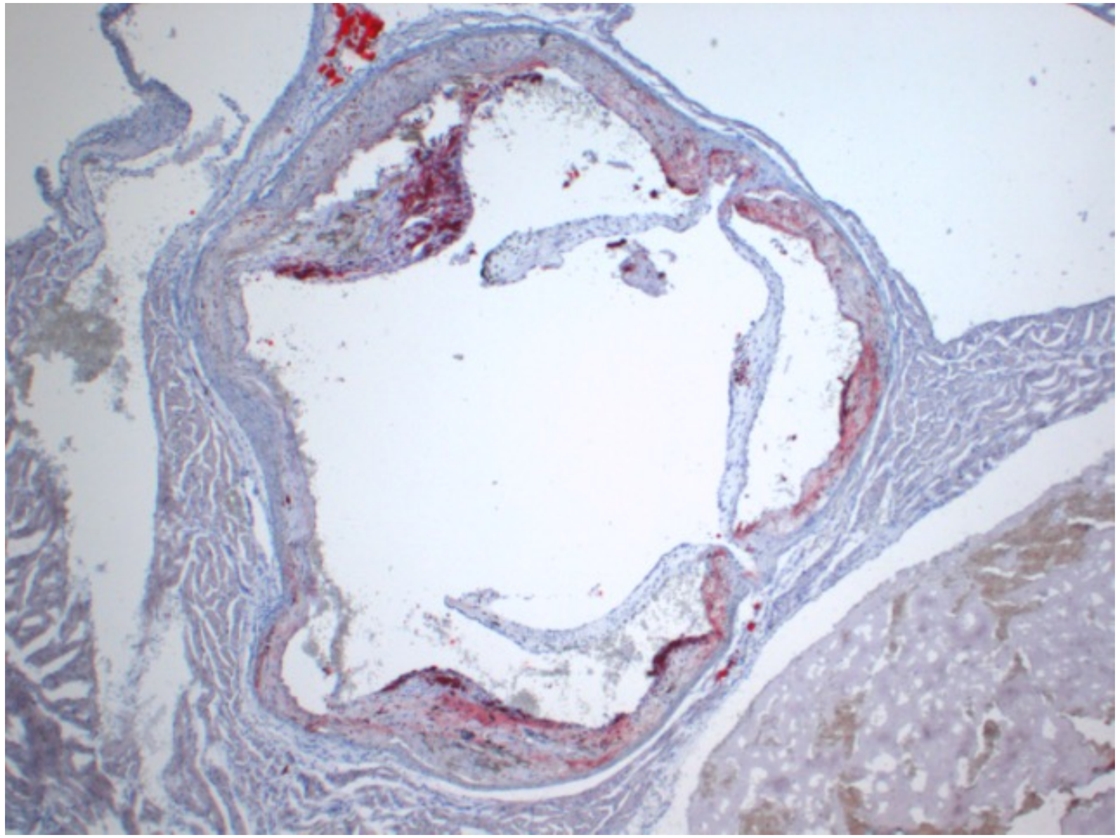
Arterien Segmentierung — Single-Network Approach Architecture

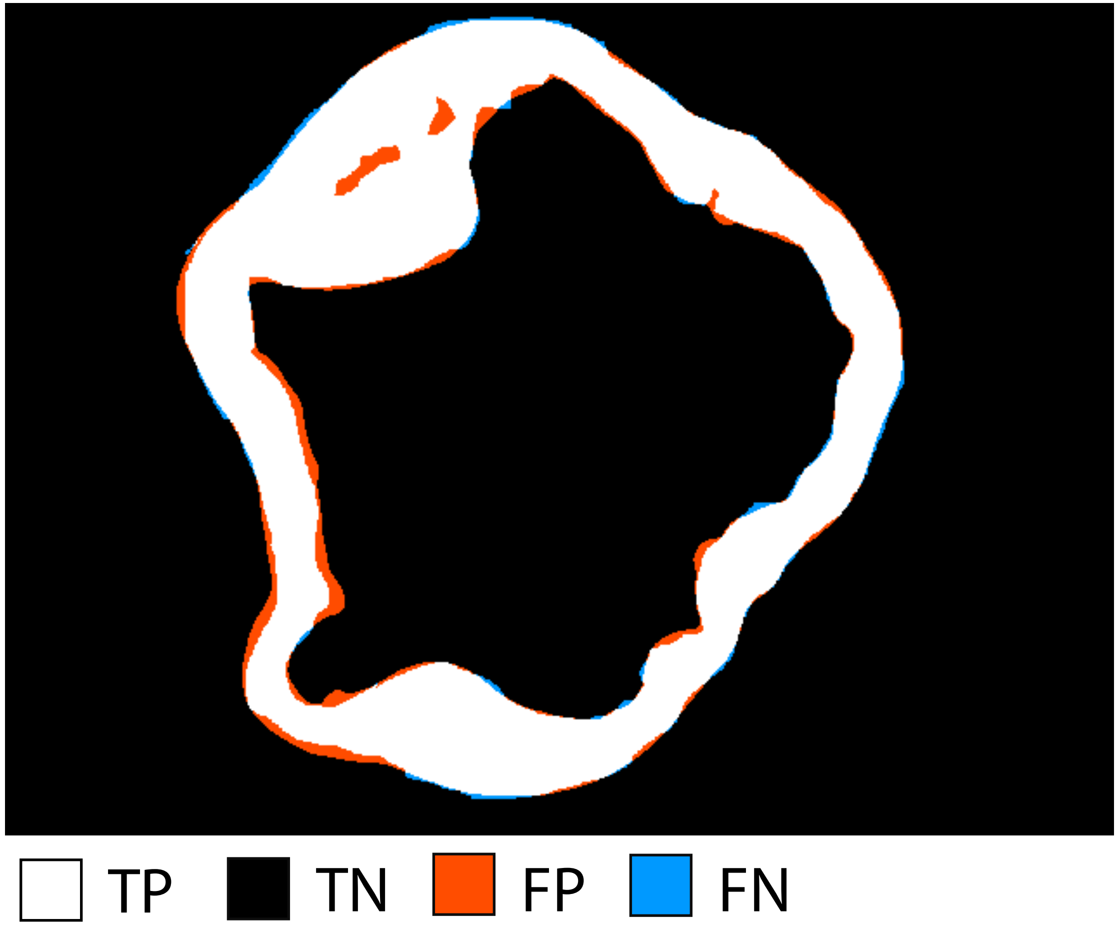


→ Anschließende Feinjustierung

Methoden

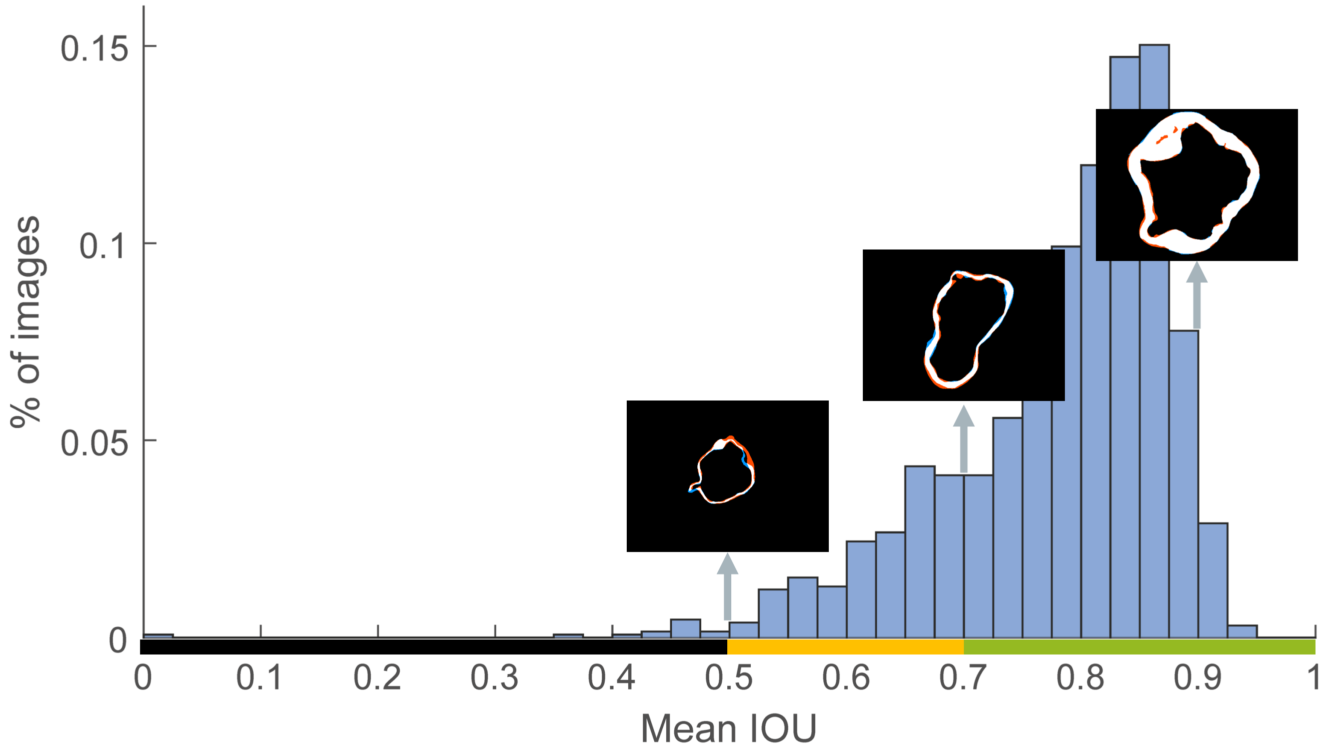
Arterien Segmentierung — Mean IOU = 0.9029





Methoden

Arterien Segmentierung — Single-Network Approach



Methoden

Arterien Segmentierung — Single-Network Approach Retrain

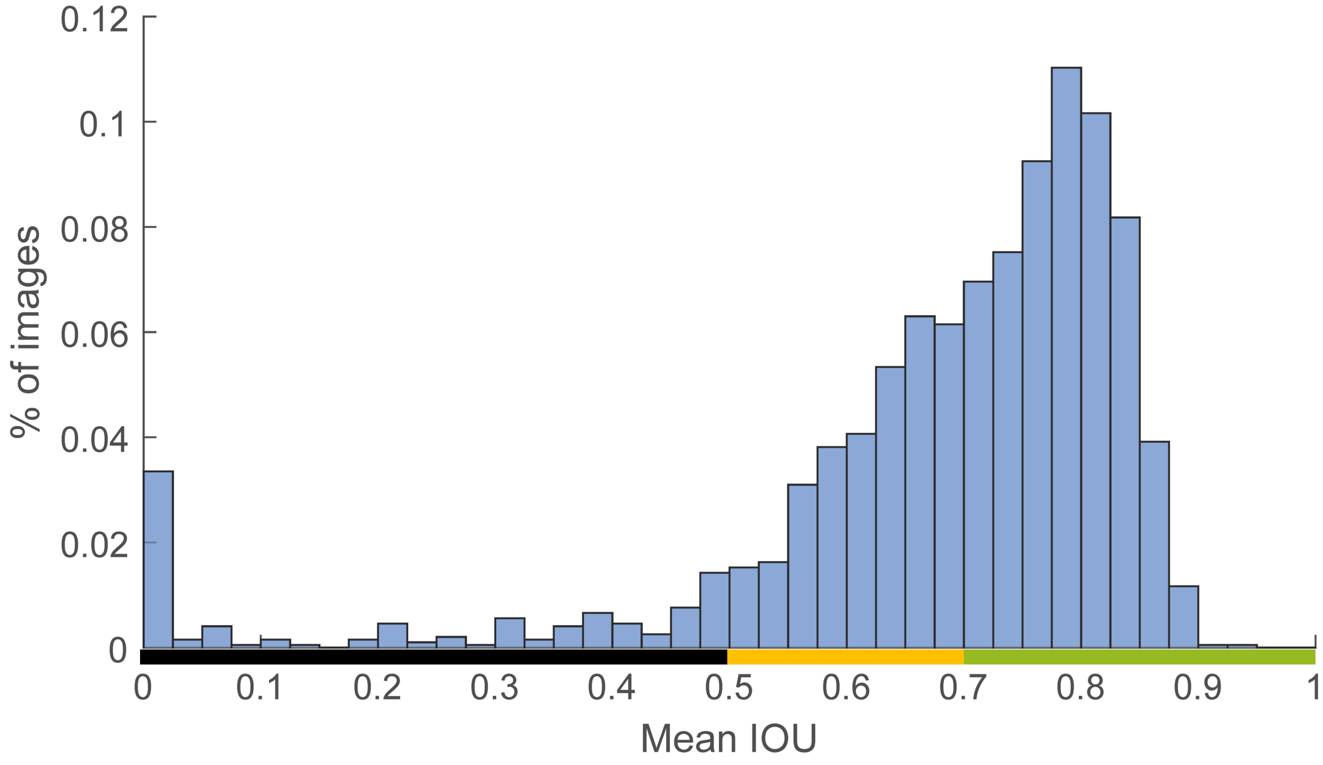
Folder ID	Number of images	Number of IDs	Microscope(s)	Acquisition date(s)	Resolution(s)
1	353	35	Keyence BZ-9000	06.03.2020	2720 × 2048
2	165	16		09.10.2020	
3	391	34		01.07.2020	1040 × 772
4	1075	63	Olympus IX70	26.01.2015	
5	278	16	Keyence BZ-X800	13.06.2020	4080 × 2048
6	271	25	Keyence BZ-9000	10.04.2020	1040 × 772
7	216	3		12.05.2020	2720 × 2048
8	322	29			1040 × 772
9	396	32	Olympus IX70	05.02.2014	
10	483	44	Keyence BZ-9000 Keyence BZ-X800	20.05.2020 07.07.2020	1920 × 1440 2720 × 2048
11	232	23	Keyence BZ-X800	17.12.2020	1920 × 1440
12	565	50		24.11.2021	
13	642	179		18.11.2020	960 × 720 1920 × 1440 2720 × 2048
14	569	48		01.07.2022	1920 × 1440
15	1103	104		15.02.2022	960 × 720 1920 × 1440
16	296	30	Keyence BZ-9000	01.09.2020	2720 × 2048
16 total	7357 total	731 total	3 different microscopes	8+ years	5 different resolutions

Training und Validation

Tests

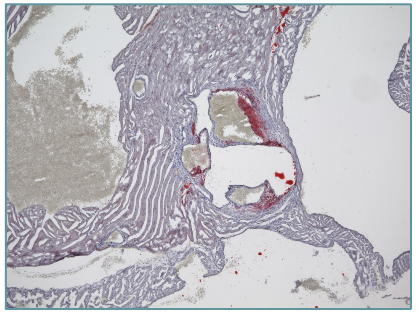
Methoden

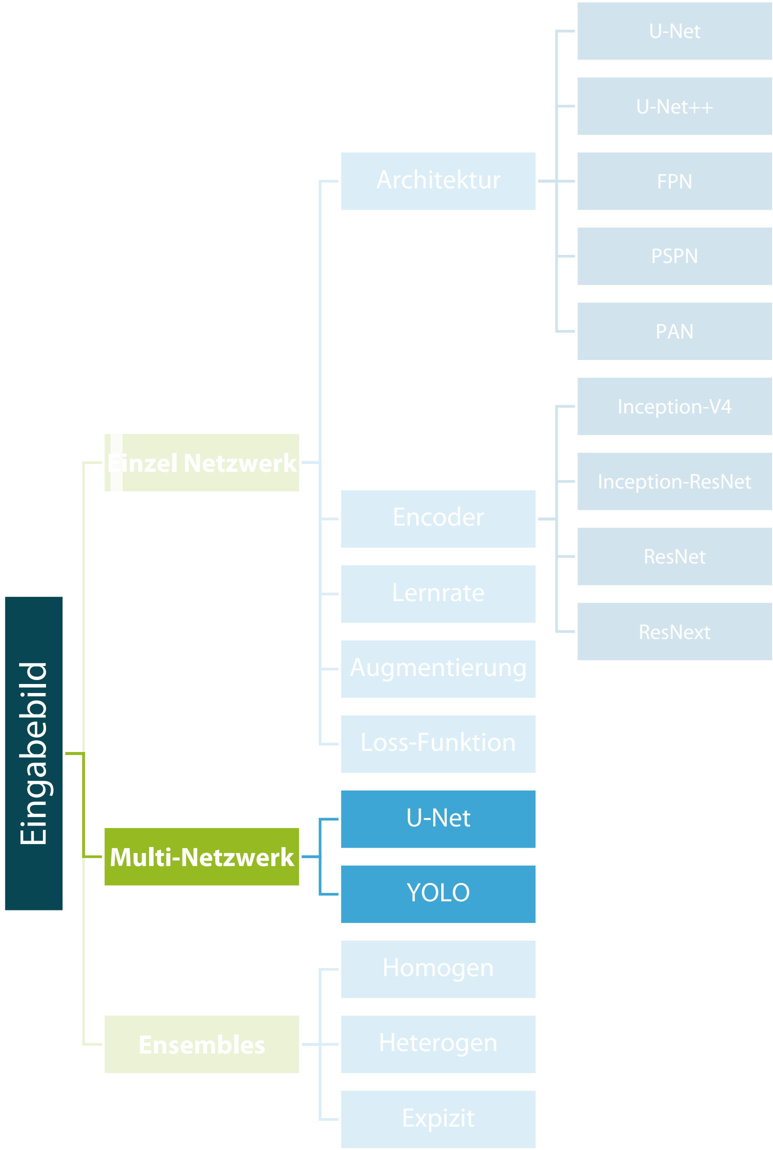
Arterien Segmentierung — Single-Network Approach



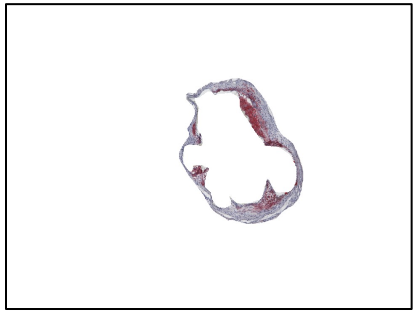
Gliederung

Histologischer Schnitt

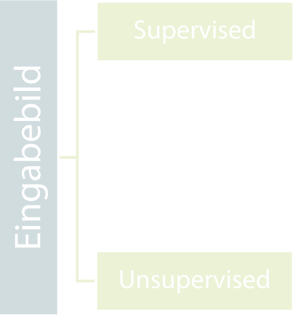



Eingabebild
Einzel Netzwerk
Architektur
U-Net
U-Net++
FPN
PSPN
PAN
Encoder
Inception-V4
Inception-ResNet
ResNet
ResNext
Lernrate
Augmentierung
Loss-Funktion
Multi-Netzwerk
U-Net
YOLO
Ensembles
Homogen
Heterogen
Expizit

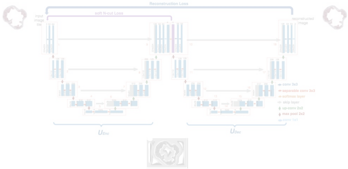
Segmentierung der Arterien



Morph. K-NN


Eingabebild
Supervised
Unsupervised

W-Net



Segmentierung der Plaques

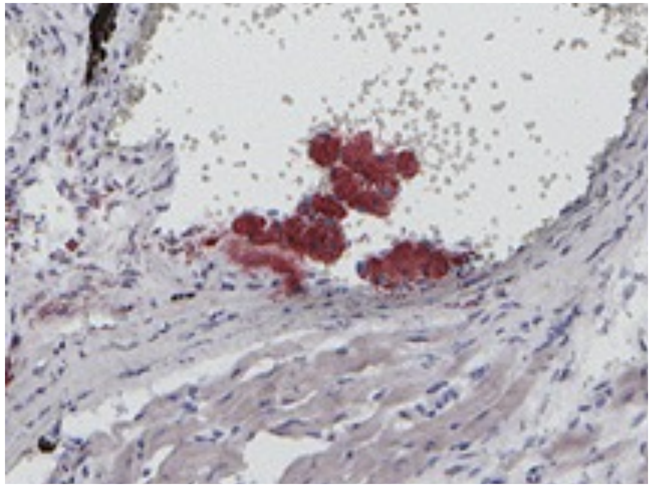
Methoden

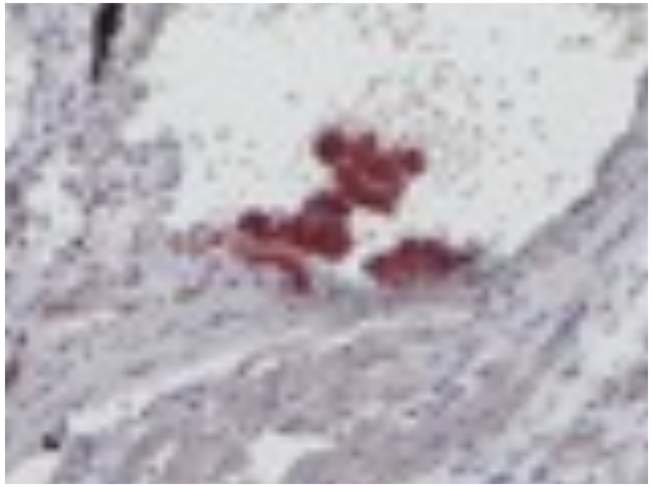
Arterien Segmentierung — Multi-Network Approach

Motivation:
- Großteil der Bilder (>75% im Schnitt) ist Hintergrund
- Bilder haben sehr hohe Auflösung

Idee:
- Region of Interest (ROI) bestimmen
- ROI ausschneiden und Größe ändern
- Netzwerk auf der ROI trainieren

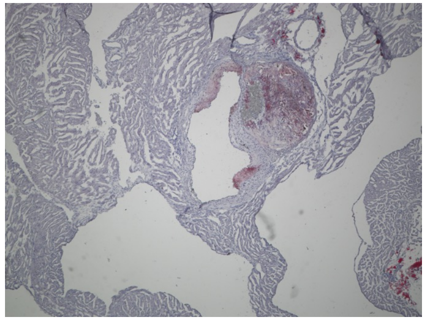
Zwei Ansätze zum Erhalten der ROI:
  - Segmentierungsnetz liefert ROI
  - YOLOv5 Object Detector liefert ROI


Ausschneiden und dann resizen

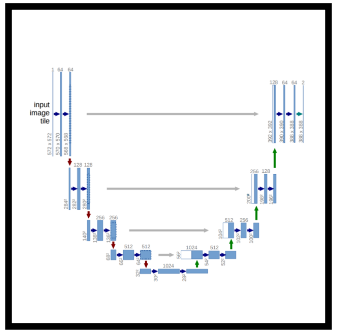

Resizen und dann ausschneiden

Methoden

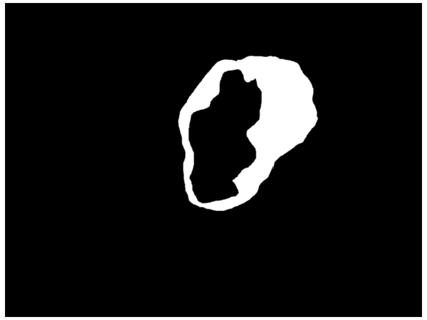
Arterien Segmentierung — Multi-Network Approach mit U-Net



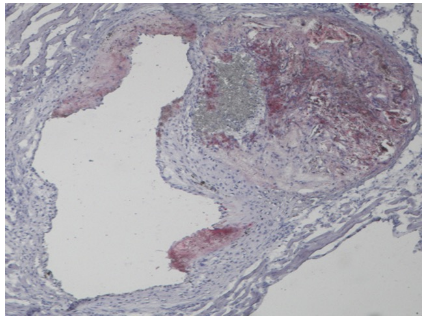
RGB Image (resized)


input image tile

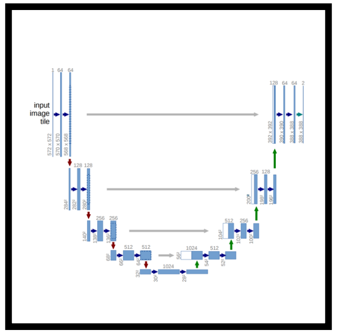
Netzwerk 1



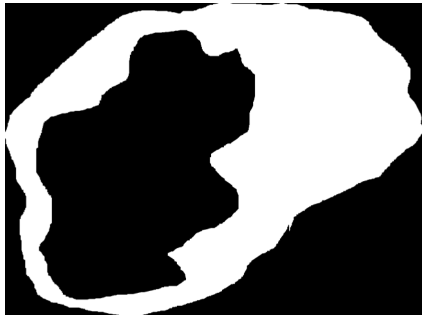
Output Mask for ROI



RGB Image (cropped and resized)


input image tile

Netzwerk 2



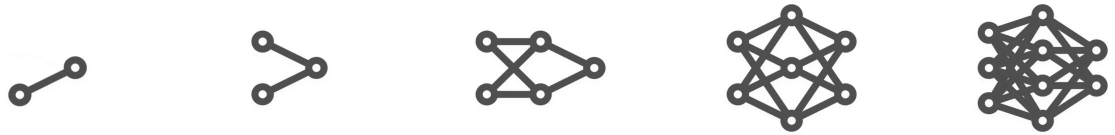
Final Output Mask

Methoden

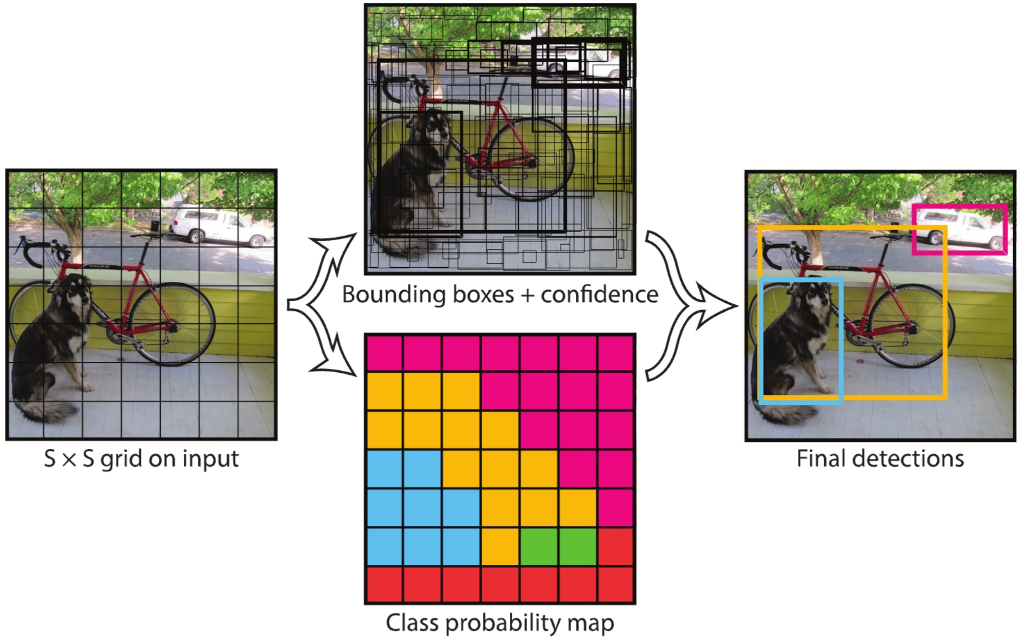
Objekterkennung

Bestimmung der ROI

- You Only Look Once (YOLO) als Object Detector
- Eine der neusten Versionen: YOLOv5
  - Verschiedene vorgefertigte Modellarchitekturen



Nano	Small	Medium	Large	XLarge
YOLOv5n	YOLOv5s	YOLOv5m	YOLOv5l	YOLOv5x
4 MB$_{\text{FP16}}$	14 MB$_{\text{FP16}}$	41 MB$_{\text{FP16}}$	89 MB$_{\text{FP16}}$	166 MB$_{\text{FP16}}$
6.3 ms$_{\text{V100}}$	6.4 ms$_{\text{V100}}$	8.2 ms$_{\text{V100}}$	10.1 ms$_{\text{V100}}$	12.1 ms$_{\text{V100}}$
28.4 mAP$_{\text{COCO}}$	37.2 mAP$_{\text{COCO}}$	45.2 mAP$_{\text{COCO}}$	48.8 mAP$_{\text{COCO}}$	50.7 mAP$_{\text{COCO}}$

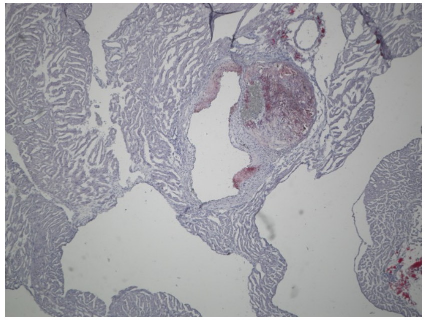


J. Redmon, S. K. Divvala, R. B. Girshick, and A. Farhadi. You Only Look Once: Unified, Real-Time Object Detection. 2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), :779–788, 2016.

G. Jocher et al. Ultralytics/Yolov5: v6.2 - YOLOv5 Classification Models, Apple M1, Reproducibility, ClearML and Deci.ai Integrations. https://github. com/ultralytics/yolov5, 2022. [Online; Accessed on 07.11.2022].

Methoden

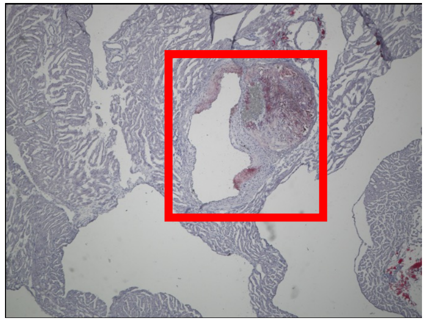
Arterien Segmentierung — Multi-Network Approach mit YOLOv5



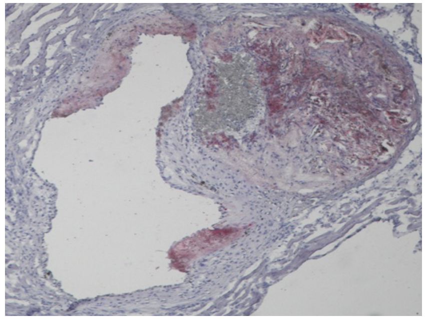
RGB Image (resized)

YOLOv5

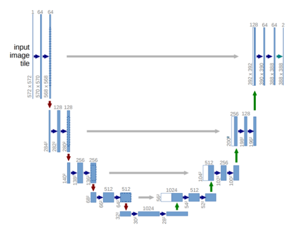
Netzwerk 1



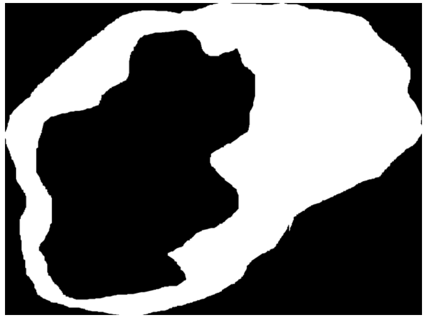
Bounding Box
for ROI



RGB Image (cropped
and resized)



Netzwerk 2

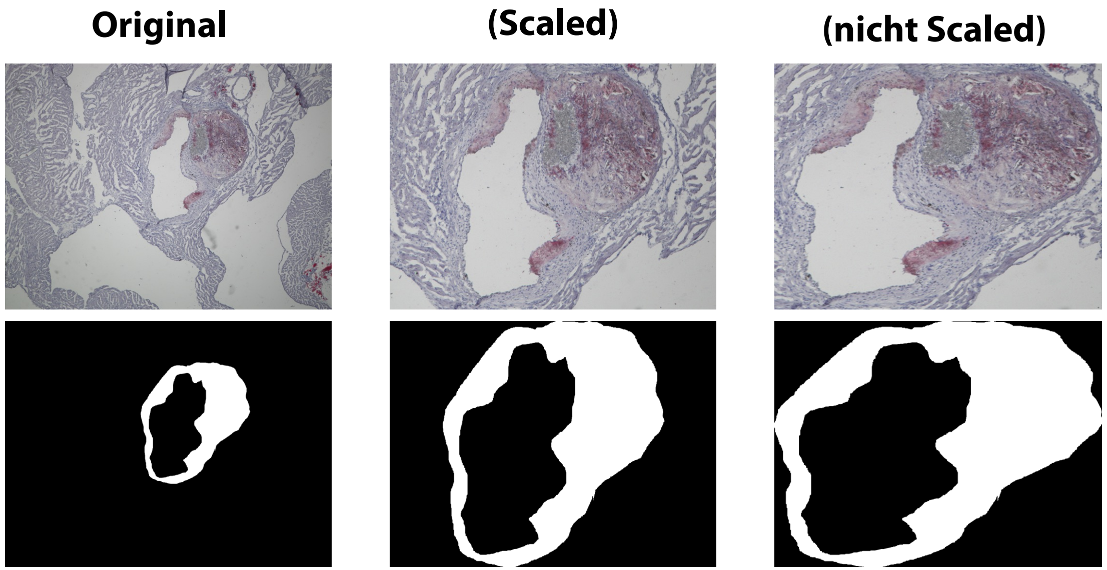


Final Output
Mask

Methoden

Arterien Segmentierung — Multi-Network Approach

Method	Mean IOU	SD	Mean IOU < 0.5 in %	Mean IOU < 0.7 in %
single-network approach	0.7793	0.1042	1.3	19.2
GT ROI	**0.7884**	**0.0896**	**0.8**	**17.4**
GT ROI scaled	0.7859	0.0904	0.9	17.9



Original

(Scaled)

(nicht Scaled)

Methoden

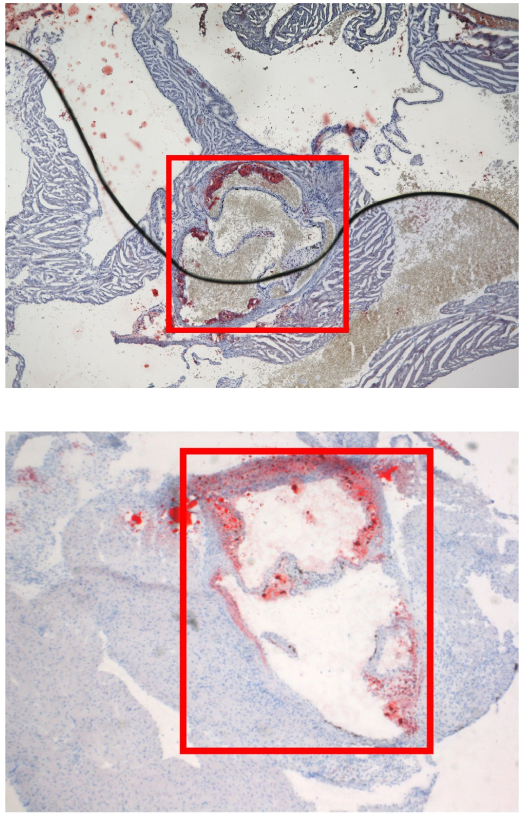
Arterien Segmentierung — Multi-Network Approach

Method	Mean IOU	SD	Mean IOU < 0.5 in %	Mean IOU < 0.7 in %
single-network approach	0.7793	0.1042	1.3	19.2
single-network approach ROI	0.7835	0.1009	1.4	17.9
YOLOv5n ROI	**0.7906**	**0.0892**	**0.7**	**16.1**

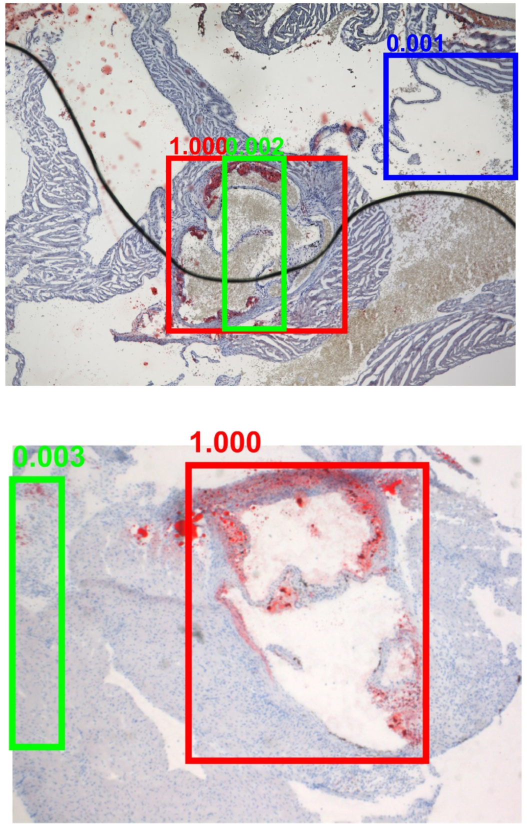
Methoden

Arterien Segmentierung — Multi-Network Approach

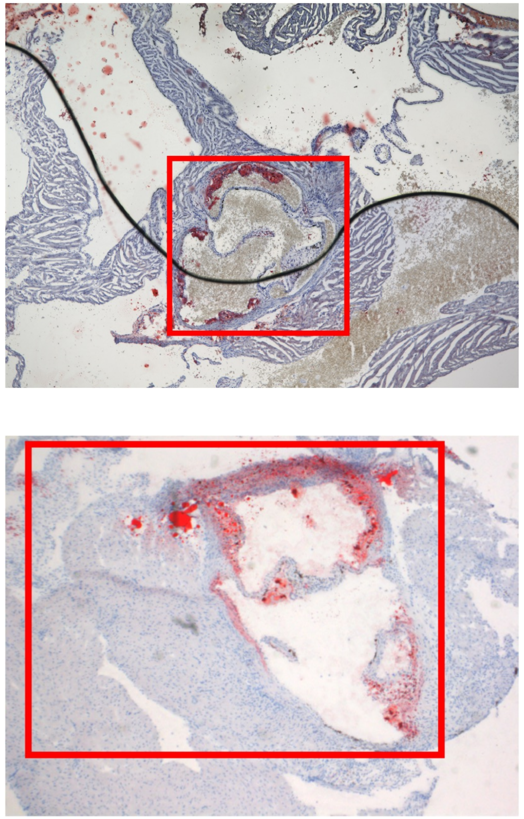
GT Bounding Box



YOLOv5 Bounding Box

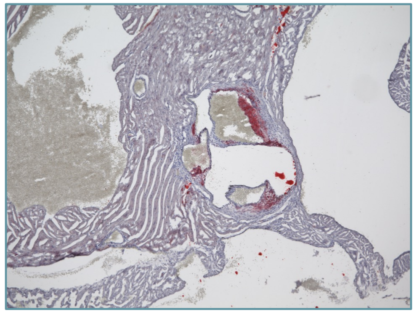

0.001
1.000
0.002
0.003
1.000

U-Net Bounding Box



Gliederung

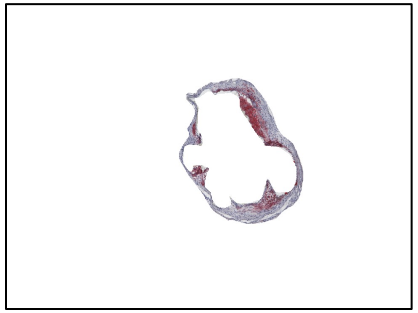
Histologischer Schnitt



Eingabebild

- Einzel Netzwerk
  - Architektur
    - U-Net
    - U-Net++
    - FPN
    - PSPN
    - PAN
  - Encoder
    - Inception-V4
    - Inception-ResNet
    - ResNet
    - ResNext
  - Lernrate
  - Augmentierung
  - Loss-Funktion
- Multi-Netzwerk
  - U-Net
  - YOLO
- **Ensembles**
  - Homogen
  - Heterogen
  - Expizit

Segmentierung der Arterien

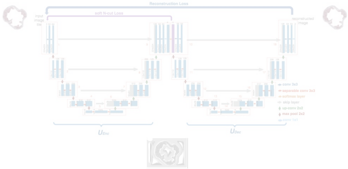


Eingabebild

- Supervised
- Unsupervised

Morph. K-NN

W-Net



Segmentierung der Plaques

Methoden

Arterien Segmentierung — Ensemble Kombination

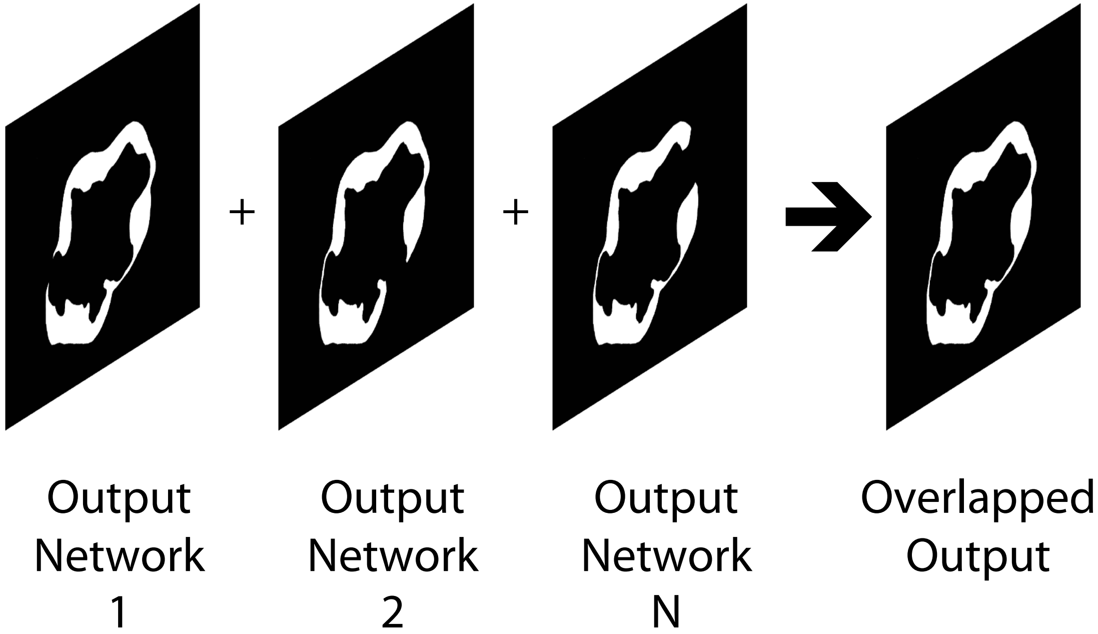
Kombination mehrerer Netzwerkausgaben

- Robustheit und Fehlertoleranz
- Überwinden lokaler Optima
- Mehrere Netzwerktrainings
  - Homogenes und Heterogenes Ensemble
- Einzelnes Netzwerktraining
  - Implicites und Explicites Ensemble

Output Maske durch Average

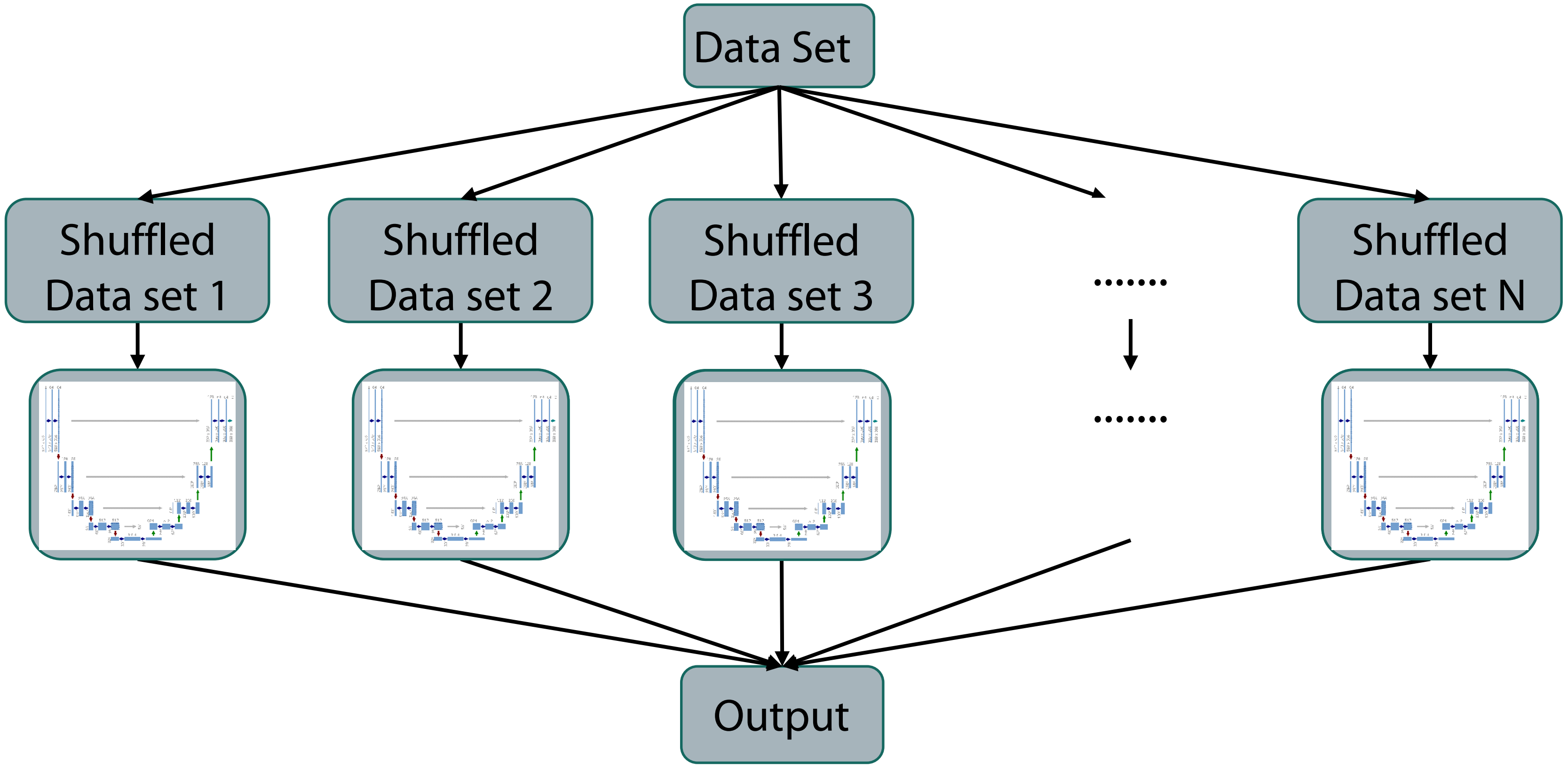
Output Maske durch Überlappen

- Konsens von $n \geq \alpha$ Outputs
  - Klassifikation des Pixels als Arterie
  - α Hyperparameter zum Feinjustieren


+
+
Output Network 1
Output Network 2
Output Network N
Overlapped Output

Methoden

Arterien Segmentierung — Homogenes Ensemble



Data Set

Shuffled Data set 1

Shuffled Data set 2

Shuffled Data set 3

....

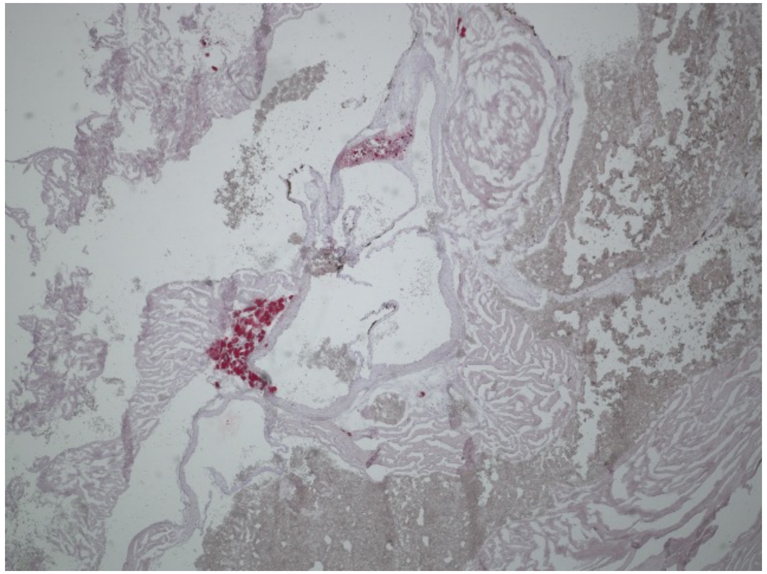
....

Shuffled Data set N

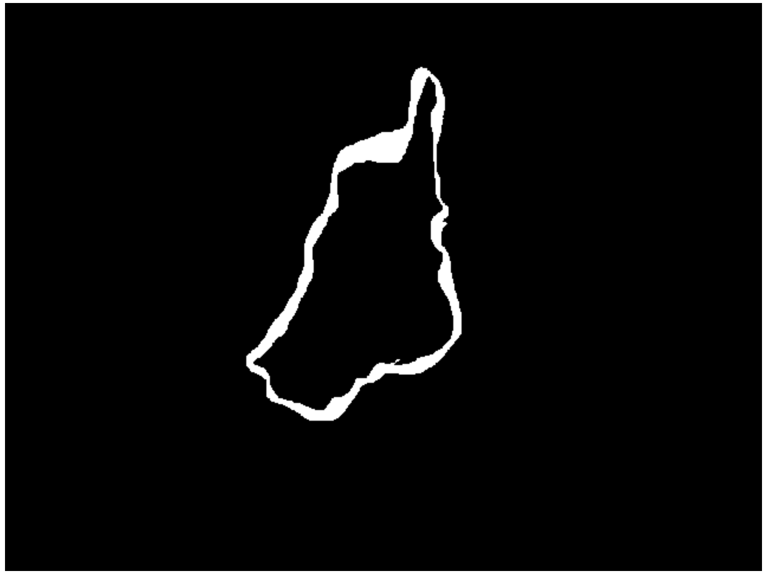
Output

Methoden

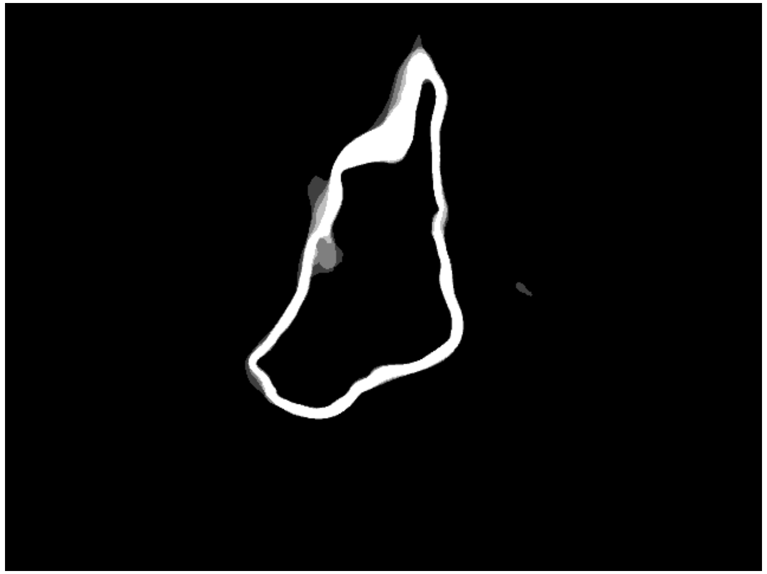
Arterien Segmentierung — Ensemble (Homogen)



RGB Input



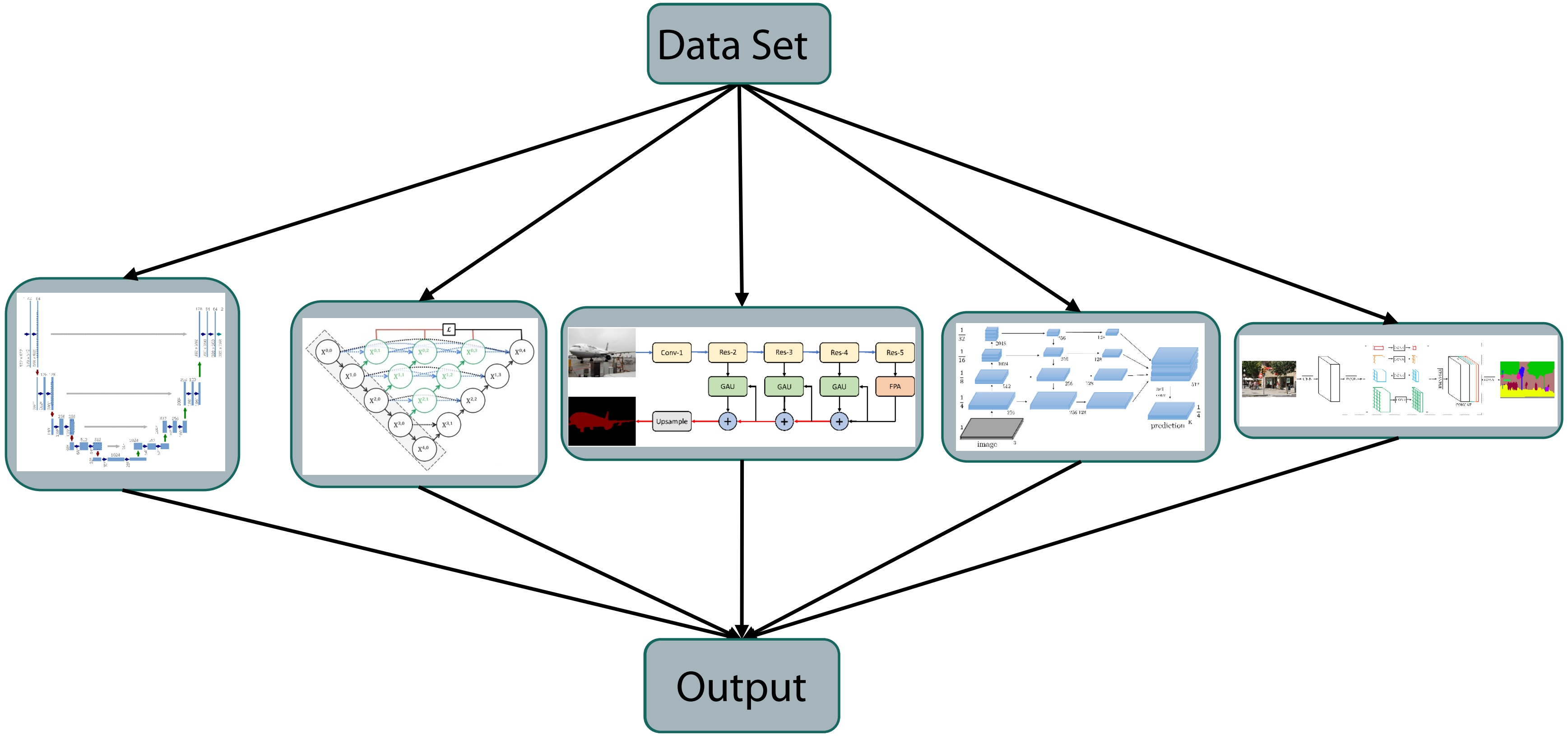
GT Mask



Overlap Pred

Methoden

Arterien Segmentierung — Heterogenes Ensemble

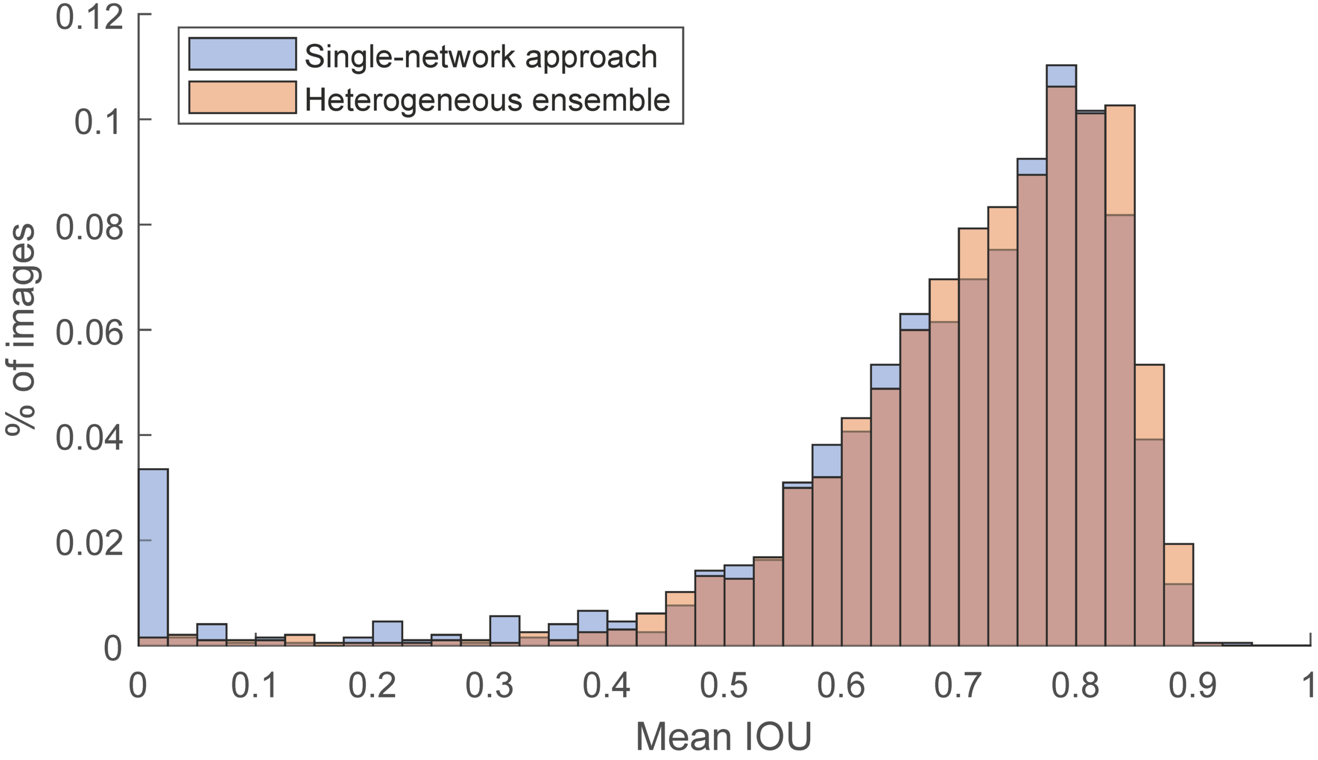

Conv-1
Res-2
Res-3
Res-4
Res-5
GAU
GAU
GAU
FPA
Upsample
image
prediction

Data Set

Output

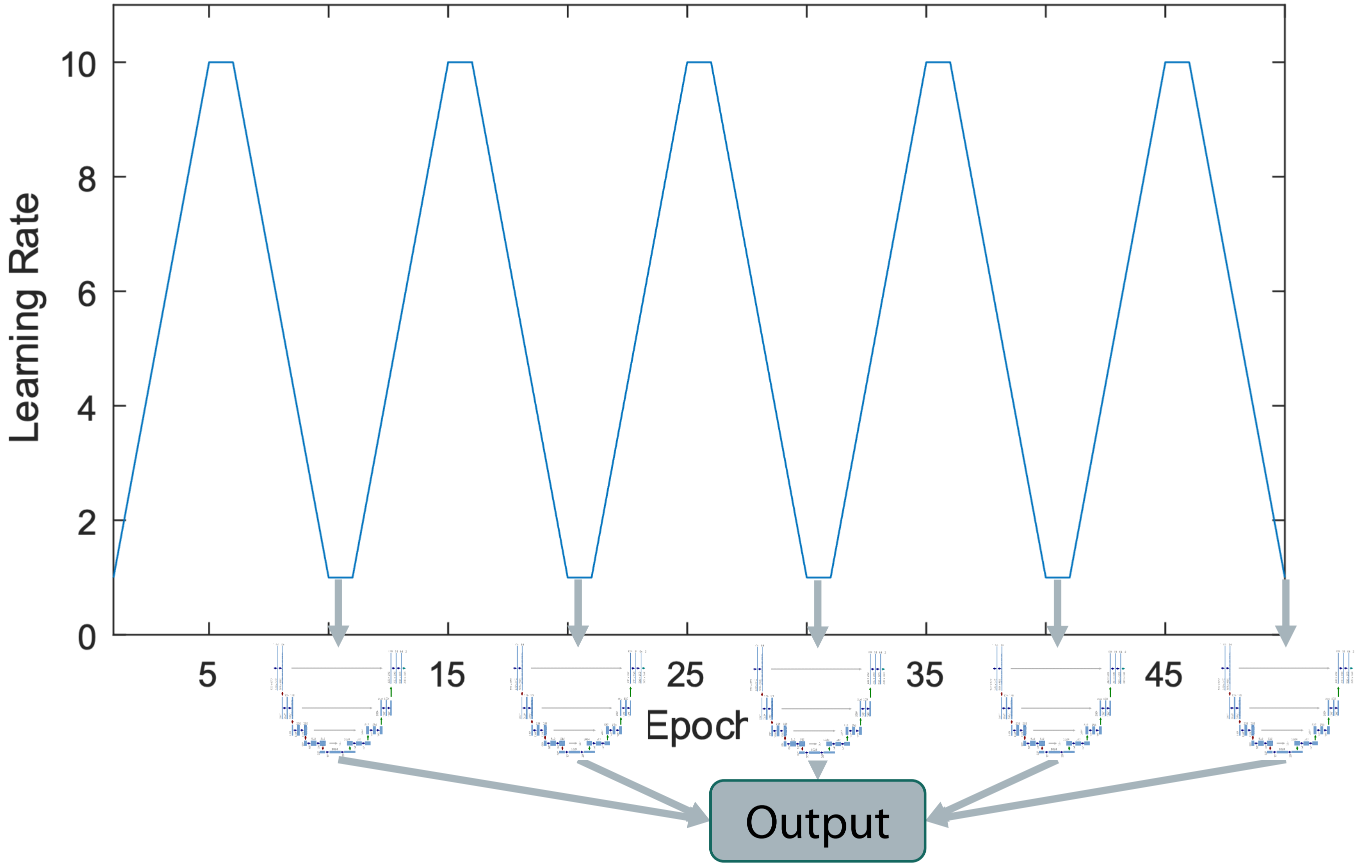
Methoden

Arterien Segmentierung — Ensemble (Heterogen)



Methoden

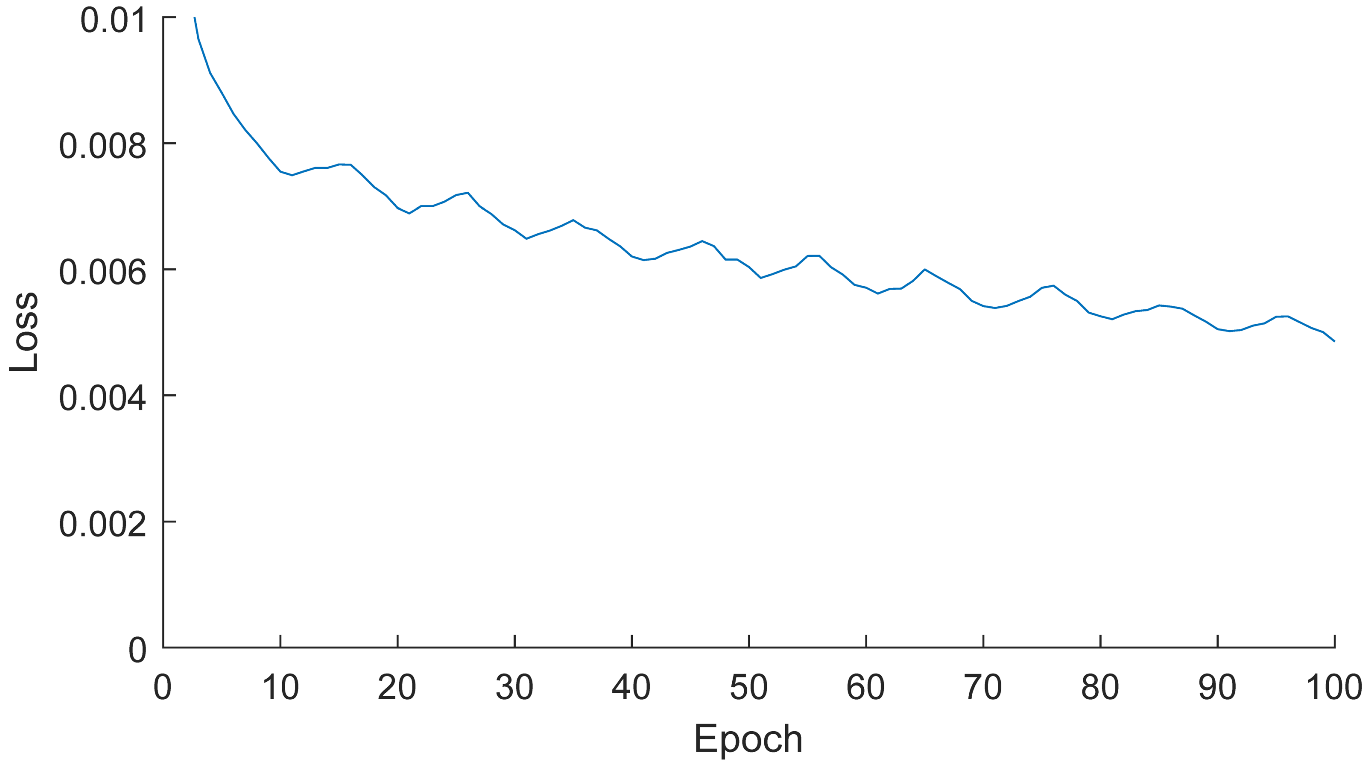
Arterien Segmentierung — Snapshot Ensemble



G. Huang, Y. Li, G. Pleiss, Z. Liu, J. E. Hopcroft, and K. Q. Weinberger. Snapshot Ensembles: Train 1, get M for Free. International Conference on Learning Representations, 2017.

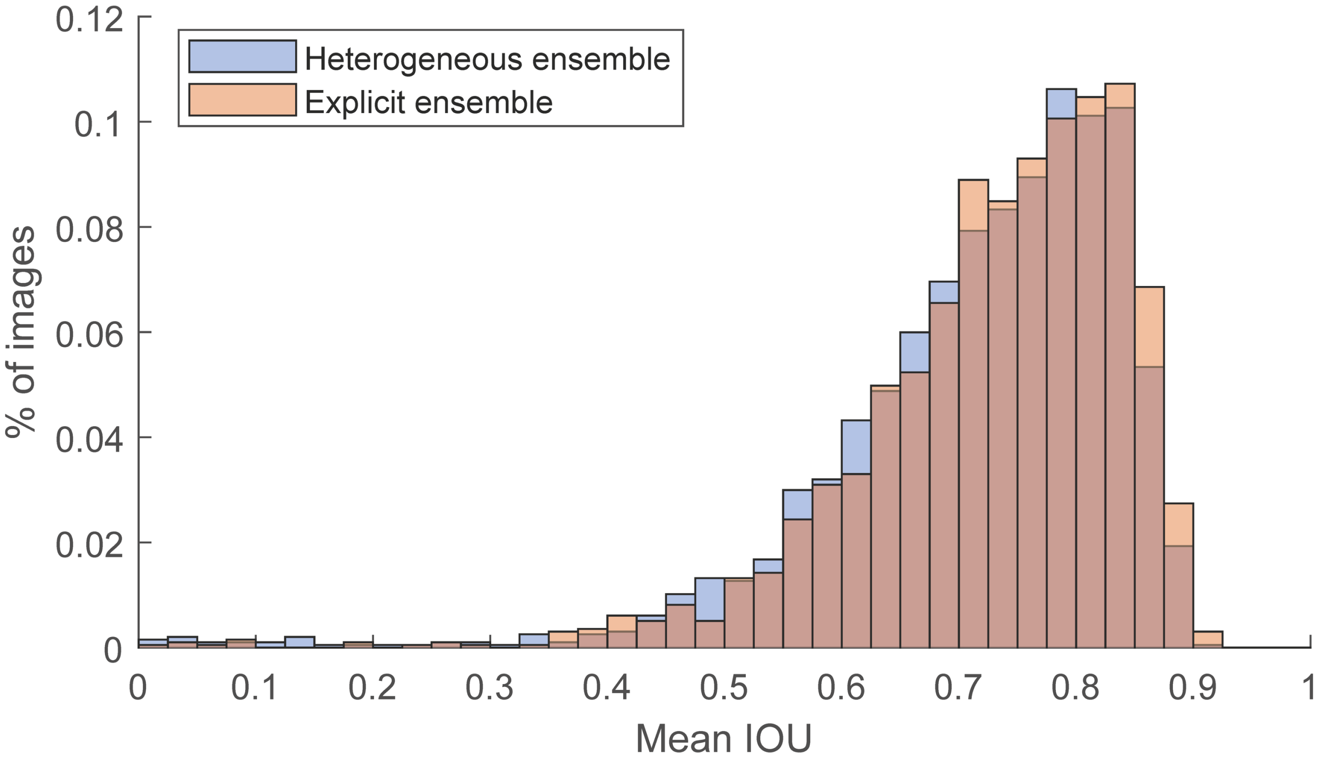
Methoden

Arterien Segmentierung — Ensemble (Explicit)



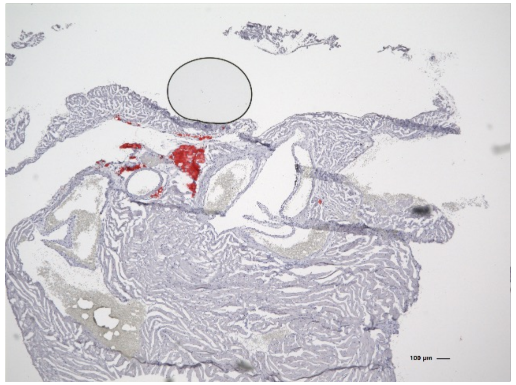
Methoden

Arterien Segmentierung — Ensemble (Explicit)

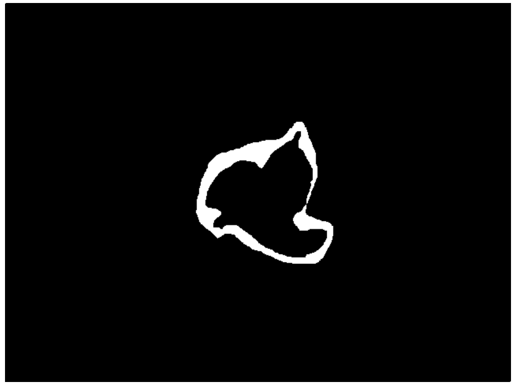


Methoden

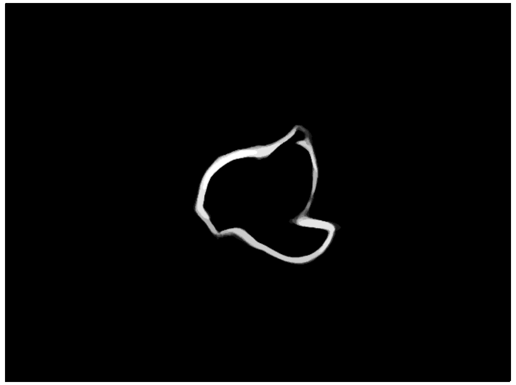
Arterien Segmentierung — Ensemble (Explicit)



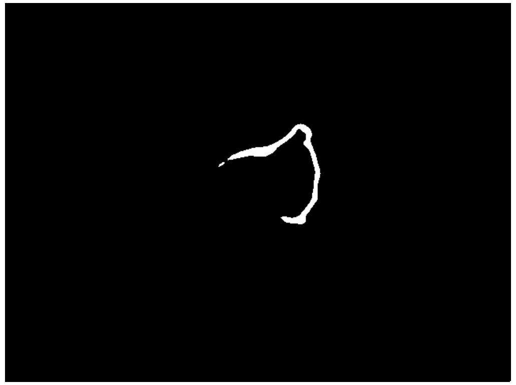
RGB Input



GT Mask



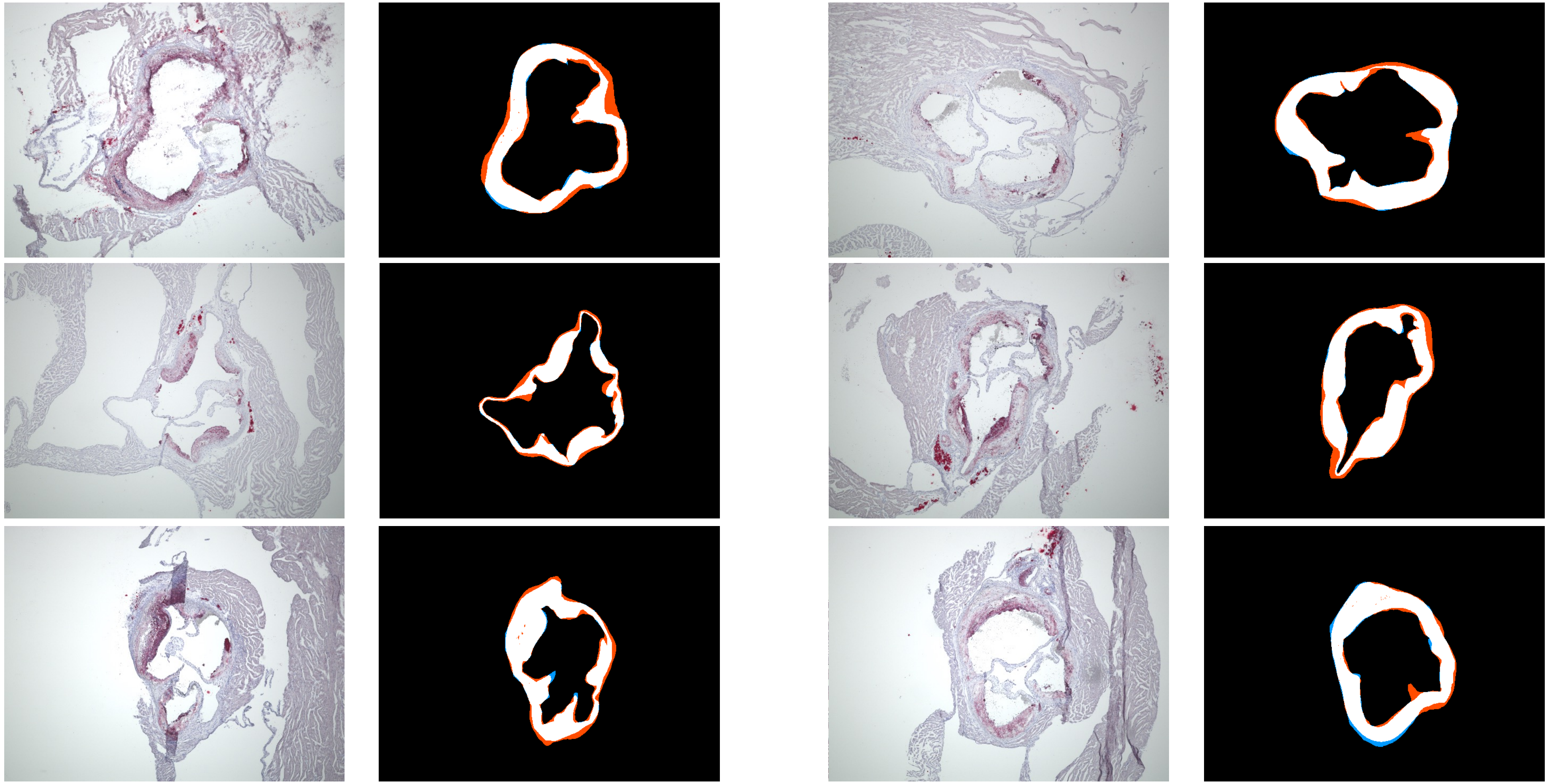
Overlap Pred



Single-Network Output

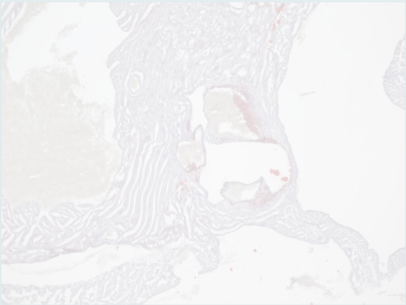
Evaluation

Arterien Segmentierung — Ensemble (Explicit)



Gliederung

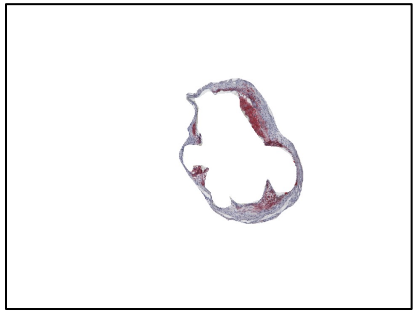
Histologischer Schnitt



Eingabebild

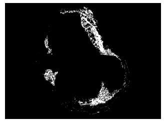
- **Einzel Netzwerk**
  - Architektur
    - U-Net
    - U-Net++
    - FPN
    - PSPN
    - PAN
  - Encoder
    - Inception-V4
    - Inception-ResNet
    - ResNet
    - ResNext
  - Lernrate
  - Augmentierung
  - Loss-Funktion
- **Multi-Netzwerk**
  - U-Net
  - YOLO
- **Ensembles**
  - Homogen
  - Heterogen
  - Expizit

Segmentierung der Arterien



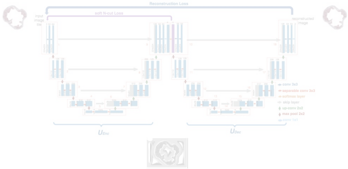
Eingabebild

Morph. K-NN

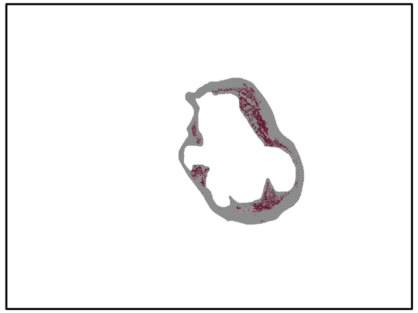


- Supervised
- Unsupervised

W-Net



Segmentierung der Plaques



Methoden

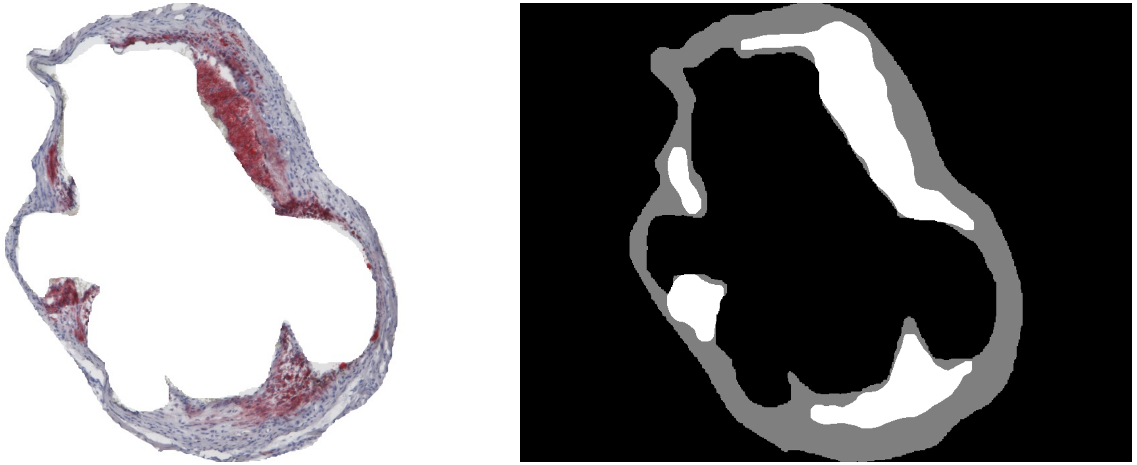
Erstellen eines Datensatzes — Motivation

Nach der Arteriensegmentierung

- Plaque Segmentierung aufbauend auf der Maske
- Aktuelles Verfahren nutzt Threshold-basierte Segmentierung

Idee: Datensatz erstellen

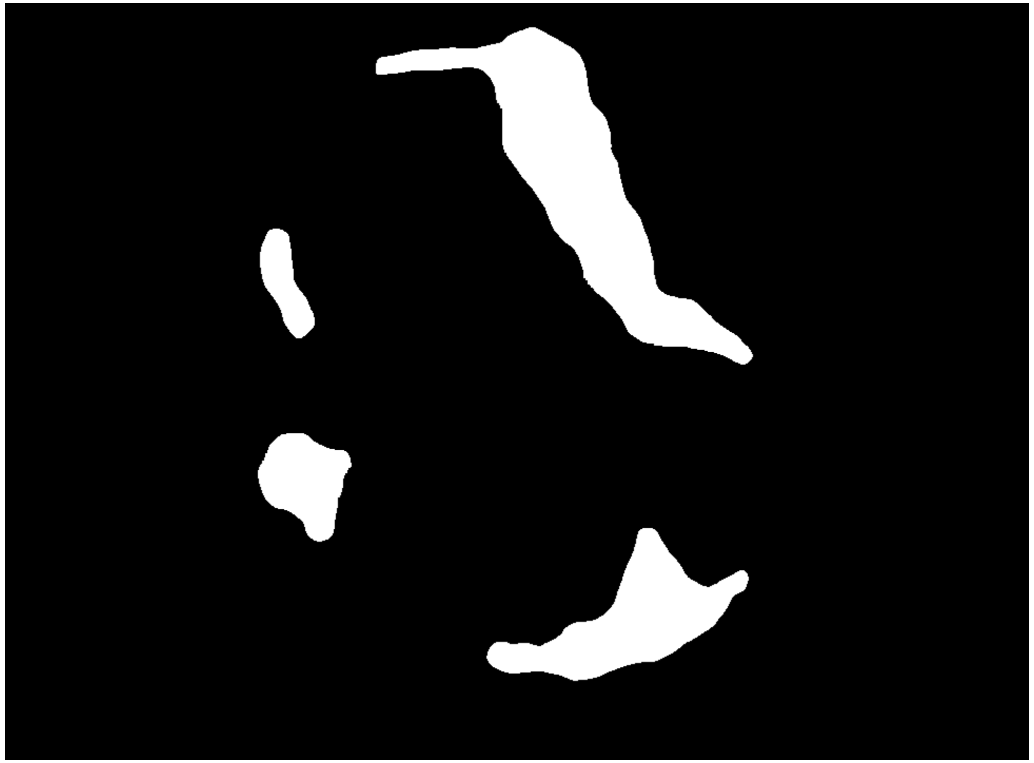
- Augmentation der automatischen Masken
  - K-Nearest neighboring
  - Morphologische Operationen
- Vorladen der Masken in ein Labeling Tool
  - MTAs des Institut für Kardiogenetik überprüfen die Daten
  - Fehler werden behoben
  - Anschließender Datensatz für überwachtes Lernen



Methoden

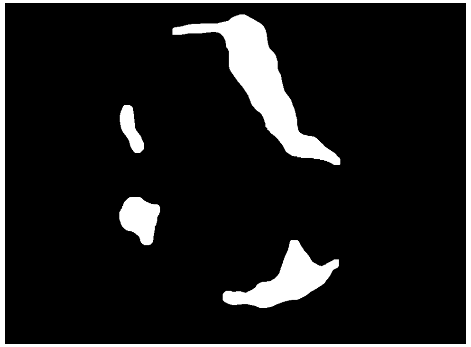
Erstellen eines Datensatzes — Augmentierung

Finale Artefakte und Fragmente werden durch eine weitere Erosion entfernt

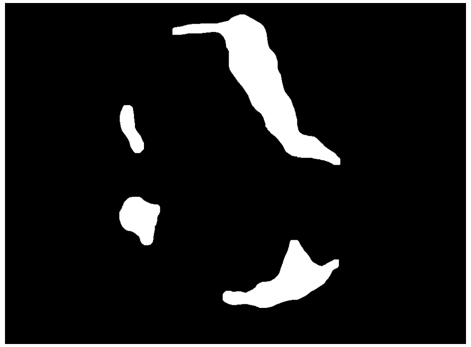


Methoden

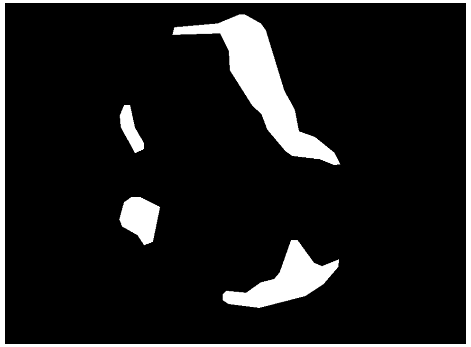
Erstellen eines Datensatzes — Ramer-Douglas-Peuker (RDP)



RDP, $\epsilon = 0$, 814 Vertices

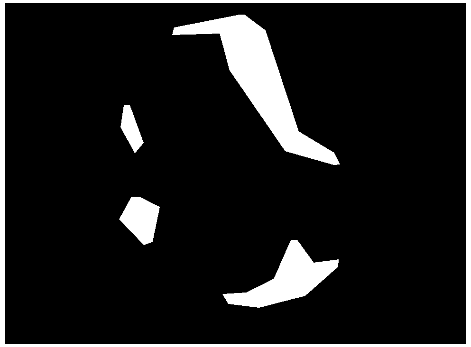


RDP, $\epsilon = 1$, 142 Vertices

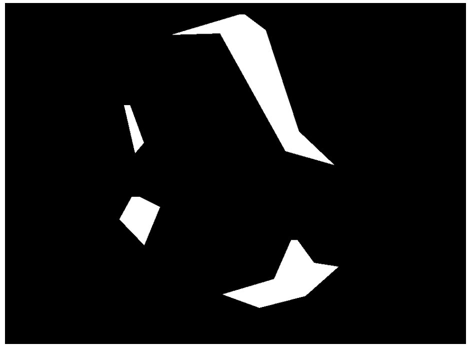


RDP, $\epsilon = 5$, 47 Vertices

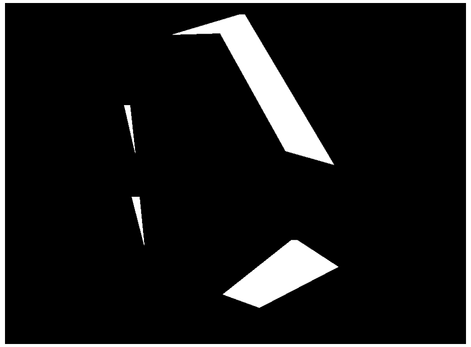
→ **93% weniger Vertices bei 1.8% Area Change**



RDP, $\epsilon = 10$, 30 Vertices



RDP, $\epsilon = 20$, 22 Vertices



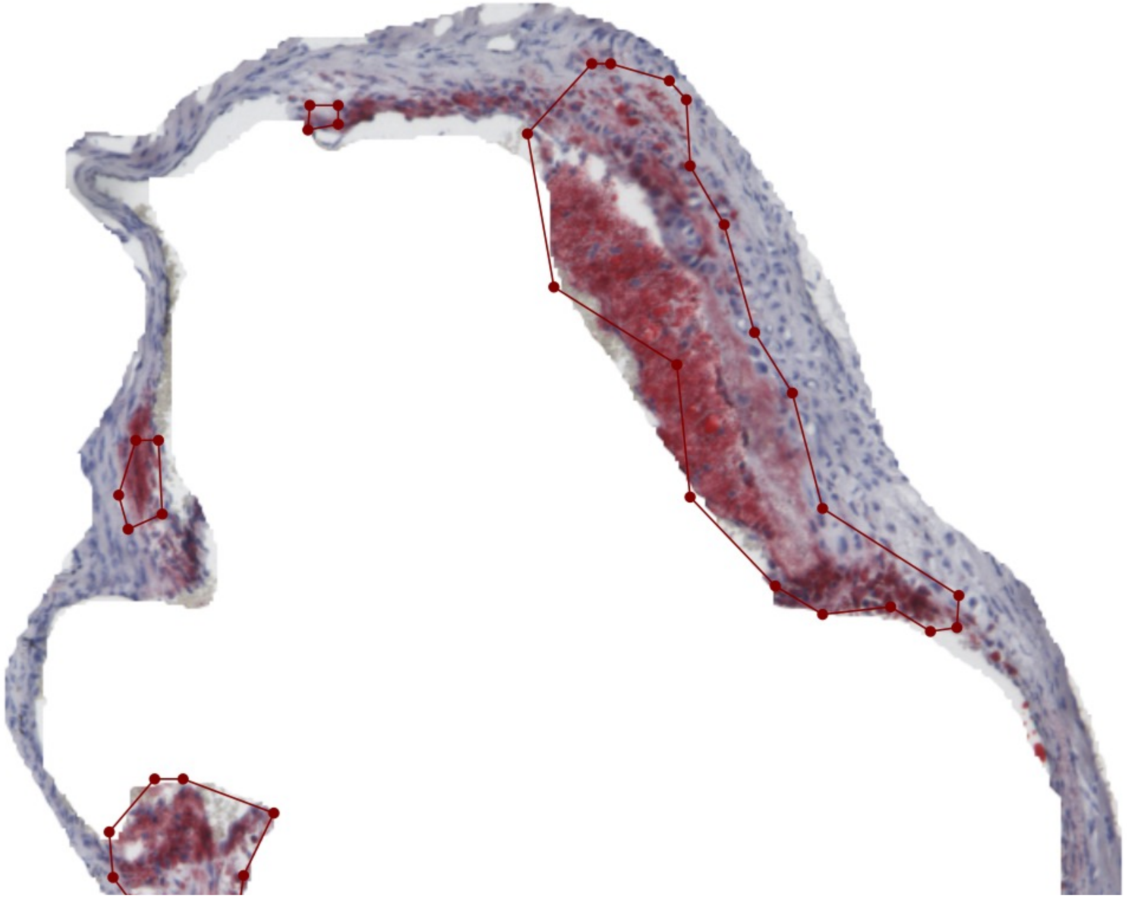
RDP, $\epsilon = 50$, 15 Vertices

U. Ramer. An Iterative Procedure for the Polygonal Approximation of Plane Curves. Computer Graphics and Image Processing, 1:244–256, 1972.

D. H. Douglas and T. K. Peucker. Algorithms for the Reduction of the Number of Points Required to Represent a Digitized Line or its Caricature. Cartographica: The International Journal for Geographic Information and Geovisualization, 10:112–122, 1973.

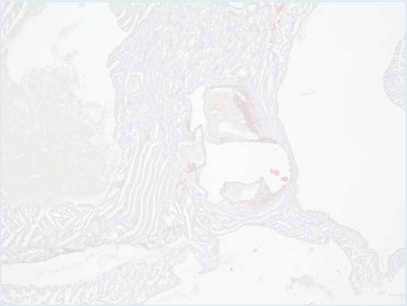
Methoden

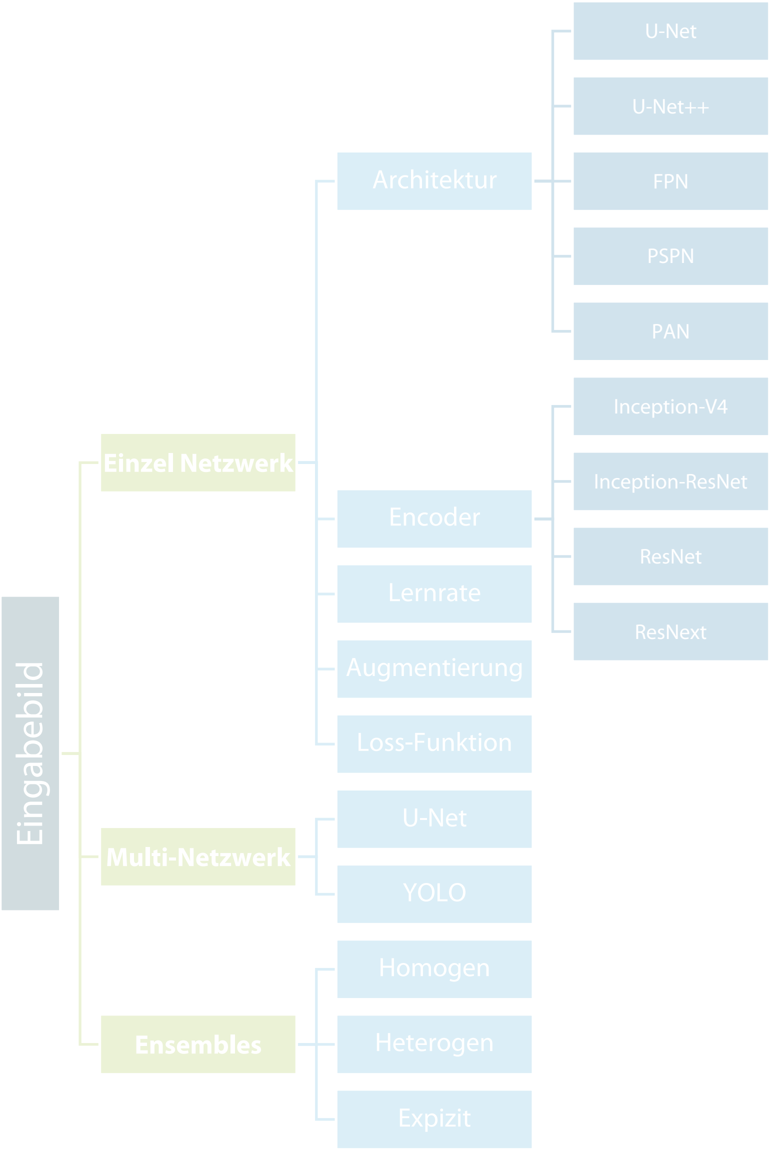
Erstellen eines Datensatzes — LabelMe



Gliederung

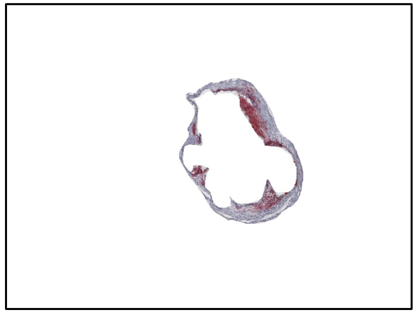
Histologischer Schnitt



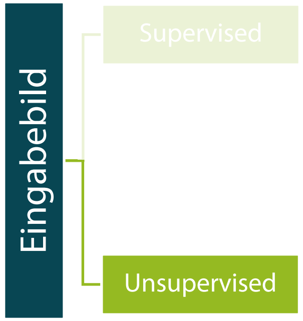


- Eingabebild
  - Einzel Netzwerk
    - Architektur
      - U-Net
      - U-Net++
      - FPN
      - PSPN
      - PAN
    - Encoder
      - Inception-V4
      - Inception-ResNet
      - ResNet
      - ResNext
    - Lernrate
    - Augmentierung
    - Loss-Funktion
  - Multi-Netzwerk
    - U-Net
    - YOLO
  - Ensembles
    - Homogen
    - Heterogen
    - Expizit

Segmentierung der Arterien

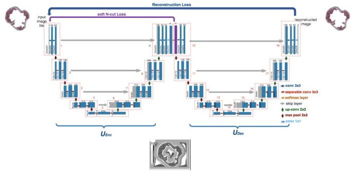


Morph. K-NN

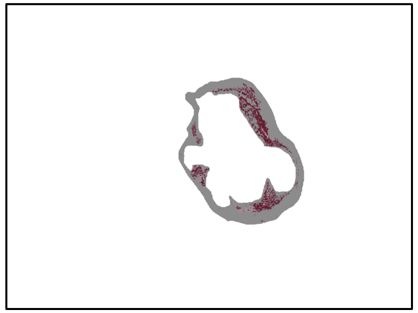


- Eingabebild
  - Supervised
  - Unsupervised

W-Net

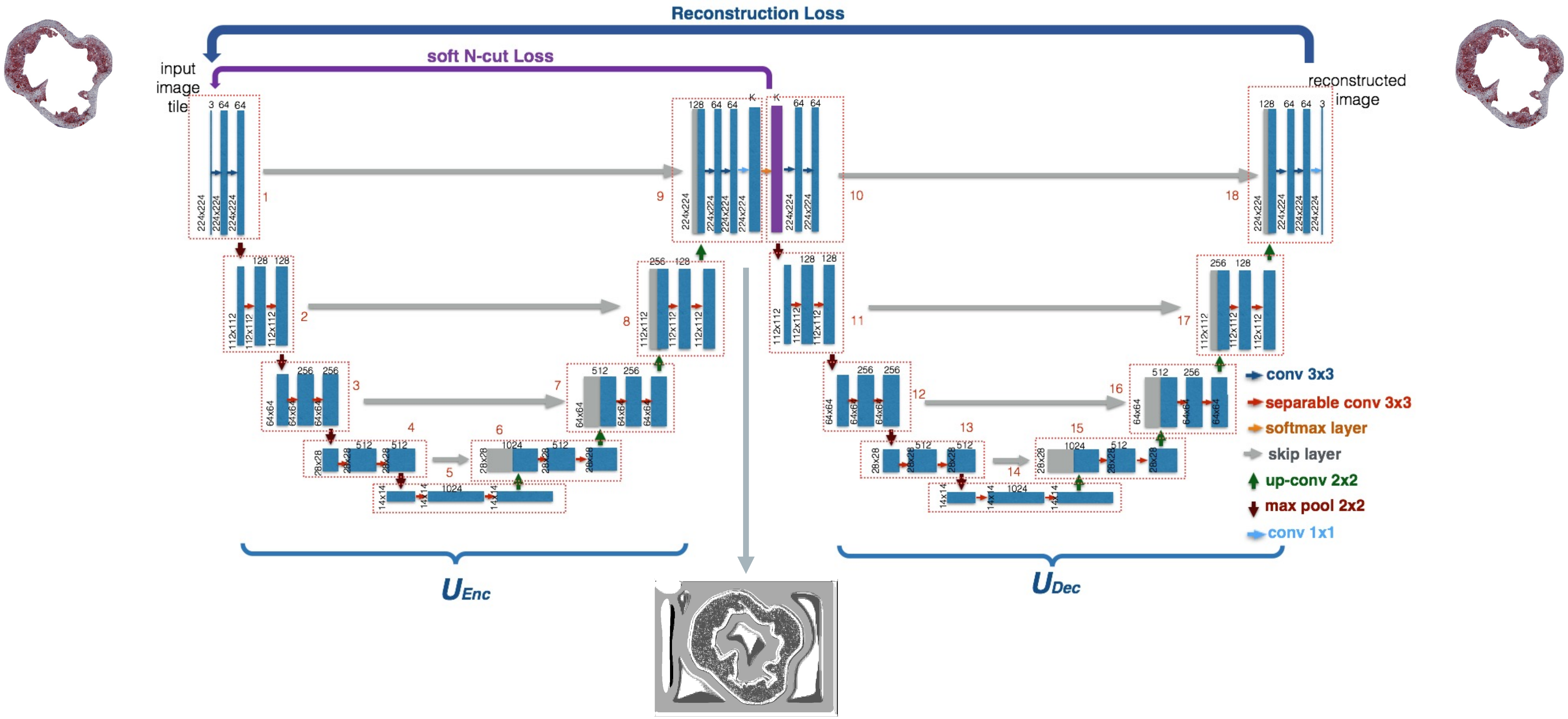


Segmentierung der Plaques



Methoden

Plaque Segmentierung — Unüberwachtes Lernen mit W-Net


Reconstruction Loss
soft N-cut Loss
input image tile
reconstructed image
3 64 64
224x224
128 64 64 K
K 64 64
128 64 64 3
128 128
112x112
256 128
256 256
64x64
512 256
512 512
28x28
1024
14x14
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
conv 3x3
separable conv 3x3
softmax layer
skip layer
up-conv 2x2
max pool 2x2
conv 1x1
UEnc
UDec

X. Xia and B. Kulis. W-Net: A Deep Model for Fully Unsupervised Image Segmentation, 2017.

Grundlagen

Segmentierung — Unüberwachtes Lernen mit W-Net

UNIVERSITÄT ZU LÜBECK
INSTITUT FÜR MEDIZINTECHNIK

Reconstruction Loss

- $J_{\text{reconstruction}} = \|\mathbf{X} - U_{Dec}\left(U_{Enc}\left(\mathbf{X}; W_{Enc}\right); W_{Dec}\right)\|_2^2$

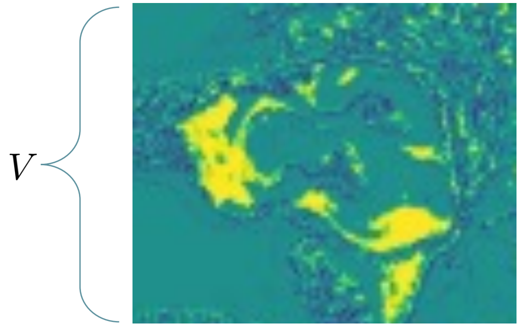
Eingabe

Parameter
Encoder und Decoder

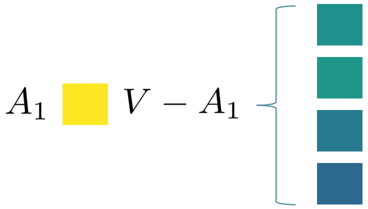
Soft N-Cut Loss basiert auf dem N-Cut Loss

- $J_{\text{Soft N-Cut}} = K - \sum_{k=1}^{K} \frac{\sum_{u \in V, v \in V} w(u,v) p\left(u = A_k\right) p\left(v = A_k\right)}{\sum_{u \in A_k, t \in V} w(u,t) p\left(u = A_k\right)}$

A_k	Set of pixels in segment k
V	Set of all pixels
w	Weight between two pixels
$p\left(u = A_k\right)$	Probability of node u belongs to class A_k



Example: $k = 1, \ldots, 5$



X. Xia and B. Kulis. W-Net: A Deep Model for Fully Unsupervised Image Segmentation, 2017.
J. Shi and J. Malik. Normalized Cuts and Image Segmentation. IEEE Transactions on Pattern Analysis and Machine Intelligence, :888–905, 2000.

Methoden

Unüberwachtes Lernen mit W-Net — Weightings

Default

- $$w_{ij} = e^{\frac{-\|F(i)-F(j)\|_2^2}{\sigma_I^2}} * \begin{cases} e^{\frac{-\|X(i)-X(j)\|_2^2}{\sigma_X^2}} & \text{if } \|X(i)-X(j)\|_2 < r_1 \\ 0 & \text{otherwise} \end{cases}$$

Linear

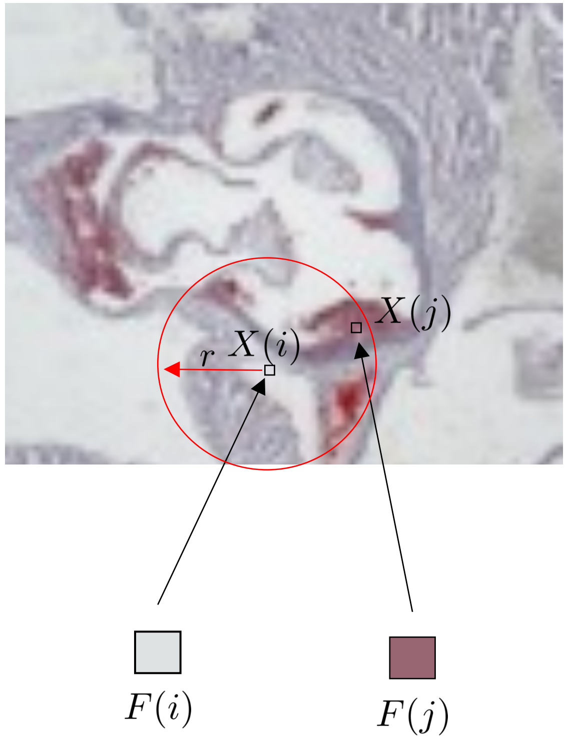
- $$w_{ij} = e^{\frac{-\|F(i)-F(j)\|_2^2}{\sigma_I^2}} * \begin{cases} 1 & \text{if } \|X(i)-X(j)\|_2 = 0 \\ \frac{1}{\|X(i)-X(j)\|_2^2} & \text{else if } \|X(i)-X(j)\|_2 < r_1 \\ 0 & \text{otherwise} \end{cases}$$

Intensity

- $$w_{ij} = e^{\frac{-\|F(i)-F(j)\|_2^2}{\sigma_I^2}} * \begin{cases} 1 & \text{if } \|X(i)-X(j)\|_2 < r_1 \\ 0 & \text{otherwise} \end{cases}$$

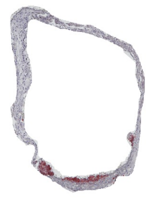
Two Radii

- $$w_{ij} = e^{\frac{-\|F(i)-F(j)\|_2^2}{\sigma_I^2}} * \begin{cases} e^{\frac{-\|X(i)-X(j)\|_2^2}{\sigma_X^2}} & \text{if } \|X(i)-X(j)\|_2 < r_1 \\ 1 & \text{if } r_1 < \|X(i)-X(j)\|_2 < r_2 \\ 0 & \text{otherwise} \end{cases} , r_1 < r_2$$

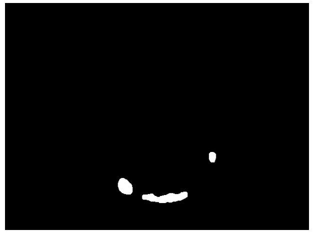


Evaluation

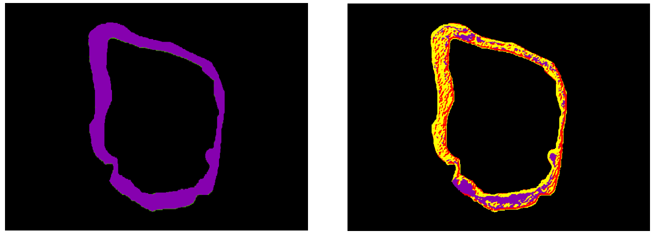
Plaque Segmentierung — W-Net



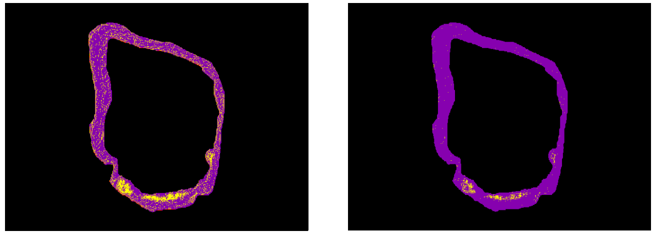
RGB Input



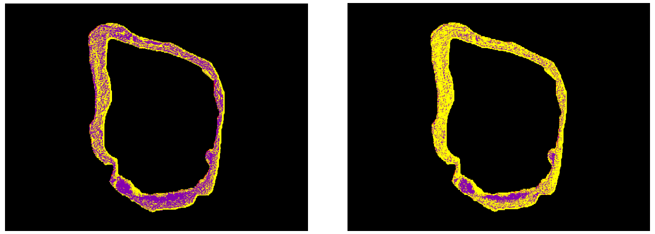
Plaque Maske



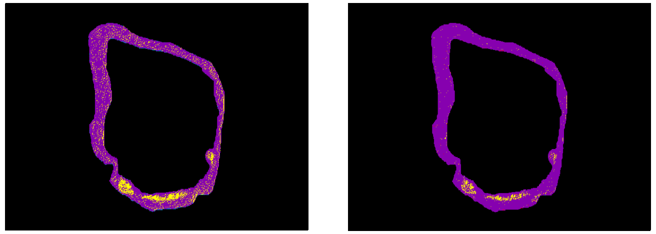
Paper Update, Default Weighting
Epoche 250 und 1000



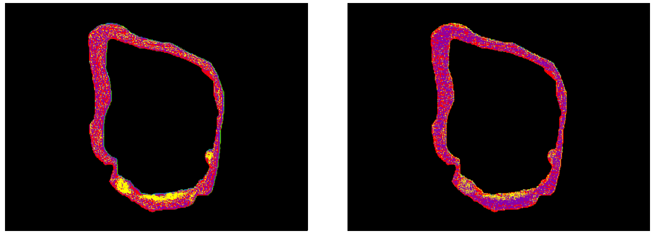
Combined Update, Default Weighting
Epoche 250 und 1000



Combined Update, Linear Weighting
Epoche 250 und 1000



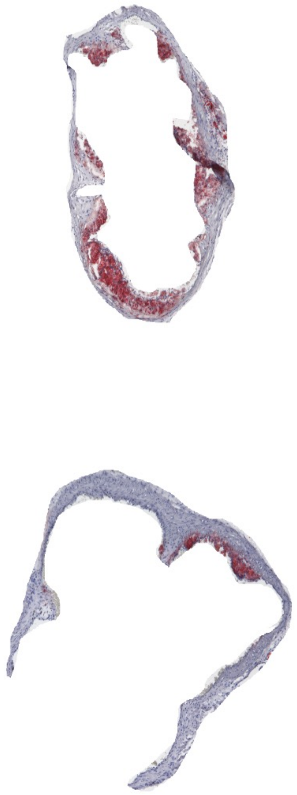
Combined Update, Intensity Weighting
Epoche 250 und 1000



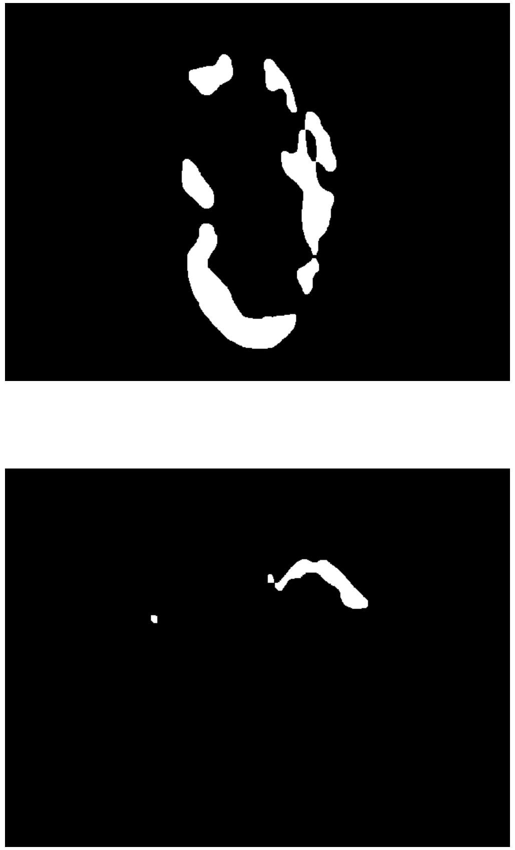
Combined Update, Two Radii Weighting
Epoche 250 und 1000

Methoden

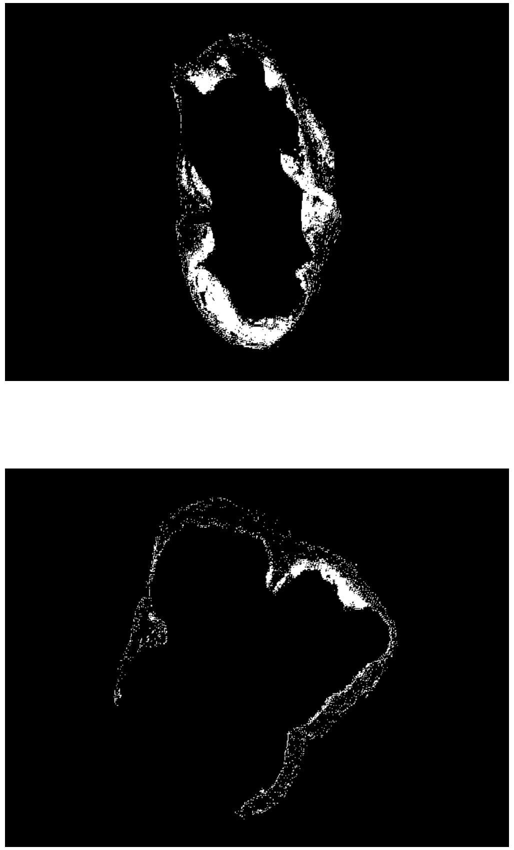
Plaque Segmentierung — W-Net



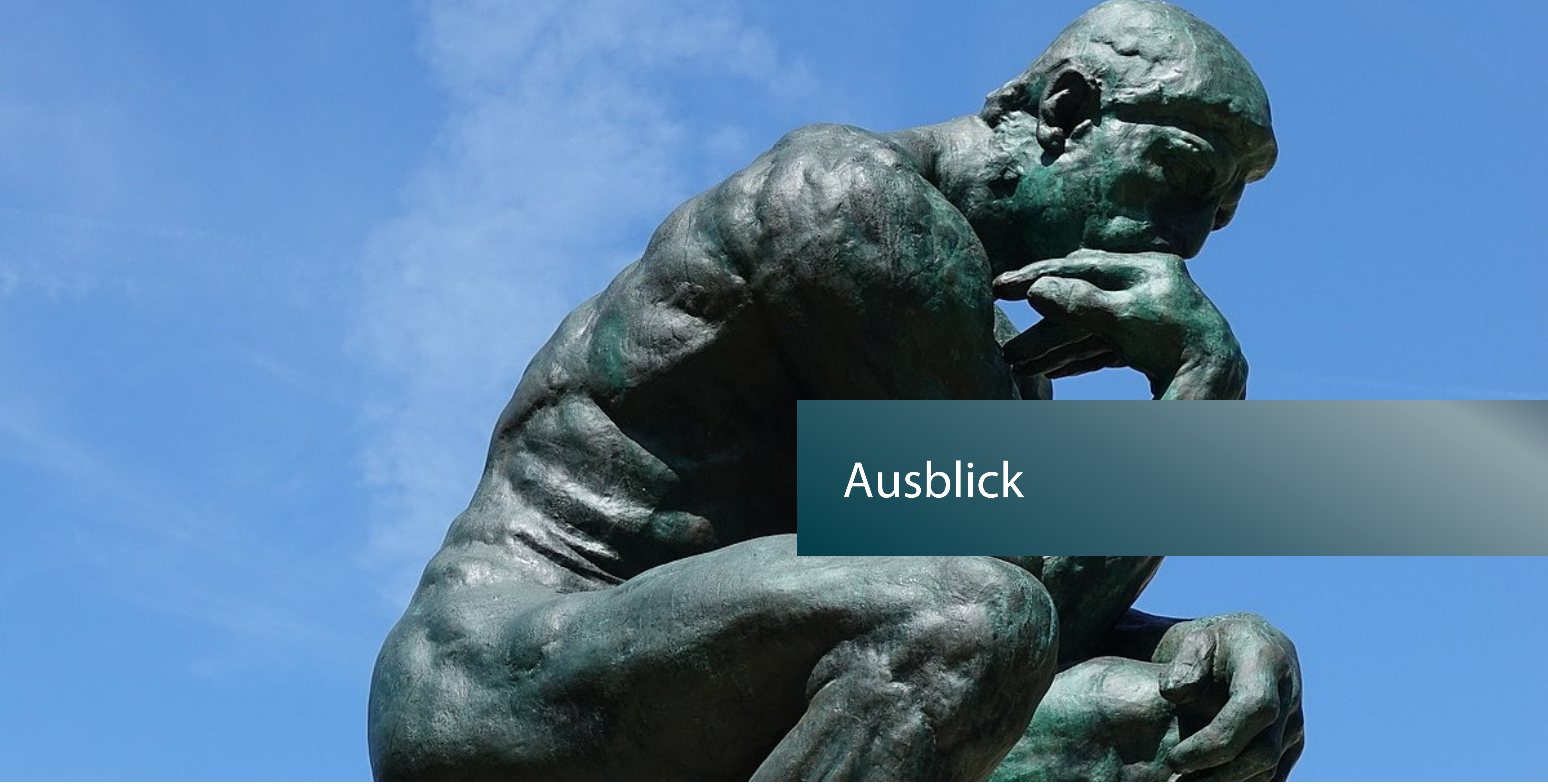
RGB Input



Plaque Maske



Combined Update, Linear Weighting
Epoche 1000



Ausblick

https://de.wikipedia.org/wiki/Datei:Mus%C3%A9e_Rodin_1.jpg#globalusage

Diskussion und Ausblick

Zusammenfassung und Ausblick

Segmentierung der Arterien und Plaques

- Wichtig für die Atherosklerose Forschung
- Manuelle Segmentierung von Mäusearterien
  - Teurer und zeitintensiver Prozess
- Lösung mit KI untersucht

Arterien Segmentierung

- Single-Network Approach gibt gute Grundlage
  - Verbessert durch Multi-Network Approach und Ensembles

Plaque Segmentierung

- Datensatz aufbauend auf Threshold-basierter Segmentierung
- W-Net erkennt Plaques

Future Work

- 3D Convolutions

Vielen Dank für Ihre Aufmerksamkeit