Applications of deep learning in medical imaging research

FH University of Applied Sciences TECHNIKUM WIEN

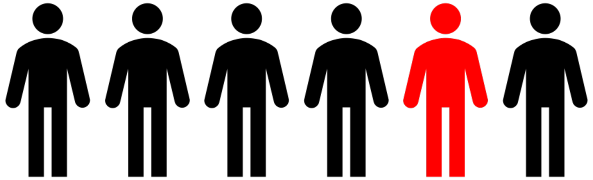
KING'S College LONDON

KING'S HEALTH PARTNERS
Pioneering better health for all

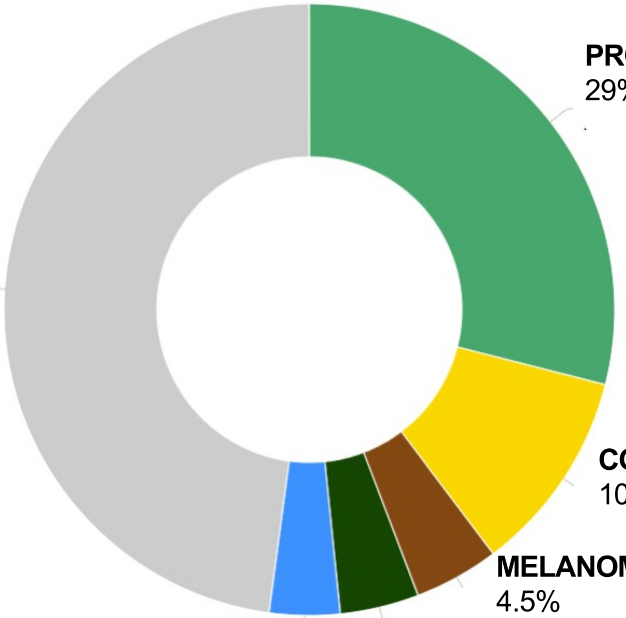
Objective of this talk

- Give insights into applications of deep learning in medical imaging
- Not attempt a comprehensive overview, but answering the following questions:
  - What is the role of imaging in healthcare, patient management
  - Where are we now with imaging? (before DL)
  - What are the challenges? Where can DL help to address these challenges and maybe even open new opportunities to improve patient outcome?
- Two examples: DL in the imaging-based diagnosis of myeloma and DL in image-guided radiotherapy

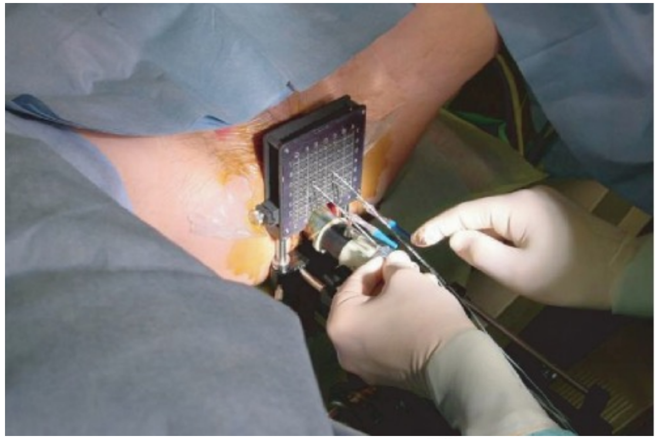
Prostate cancer

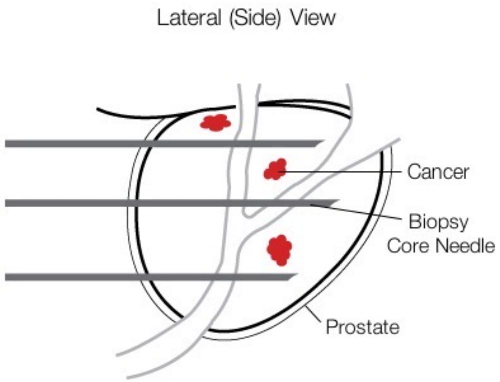


Cancer prevalence in UK (2018)



Current diagnosis: needle biopsy





https://mdxhealth.com/confirmmdx-prostate-cancer

Clinical challenge

- > 50k biopsies per year in UK[1]
- Errors of overdiagnosis (up to 67% cases[2]), missed diagnoses (15%[3])

Major **clinical challenge** is to **distinguish clinically significant cancers**.

[1] nice.org
[2]Loeb et al. *Euro Urol* 2014
[3]www.nhs.uk

The role of imaging in the management of cancer

Cancer remains a global killer alongside cardiovascular disease.

Better understanding of cancer biology

Targeted therapies – ‘Precision Cancer Medicine’

Imaging has a key role to play in the management of cancer patients and to assist drug development

- Detection and characterization of cancer
- Staging
- Monitoring therapy
- Detecting disease recurrence
- Surveillance

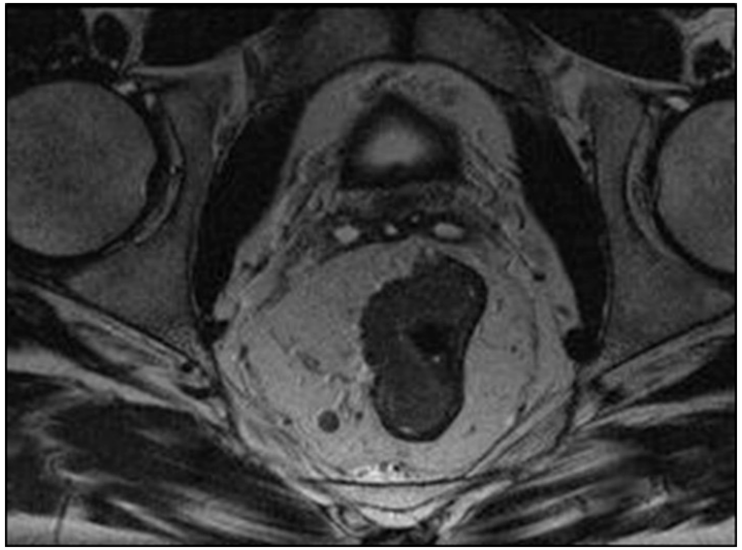
How can imaging achieve impact?

Dregely et al. J. Magn. Reson. Imaging 48: 13–26 (2018)

Imaging biomarker

- ... is a feature of an image relevant to a patient's diagnosis; can reliably distinguish healthy from pathologic tissue

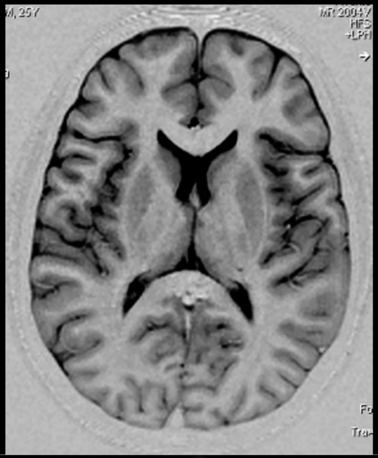
- Wishlist for a good imaging biomarker:
  - Sensitive
  - Specific & biologically relevant
  - Robust
  - Quantifiable & reproducible
  - Cost effective

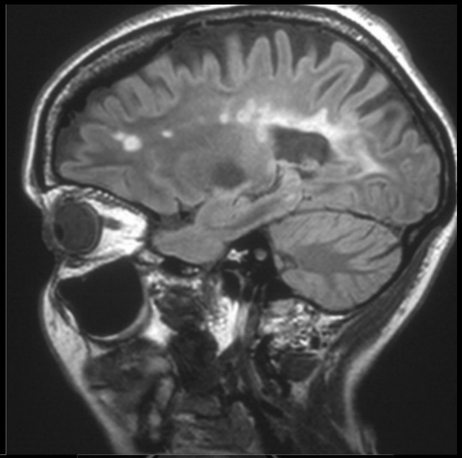


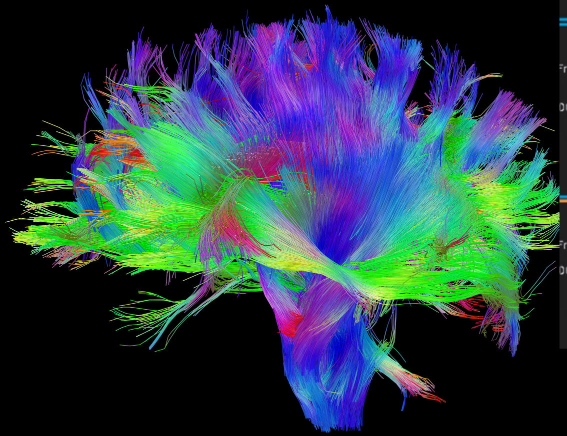
T2-weighted axial image demonstrates a T3N1 rectal cancer extending beyond the rectal wall but not involving the potential resection margin

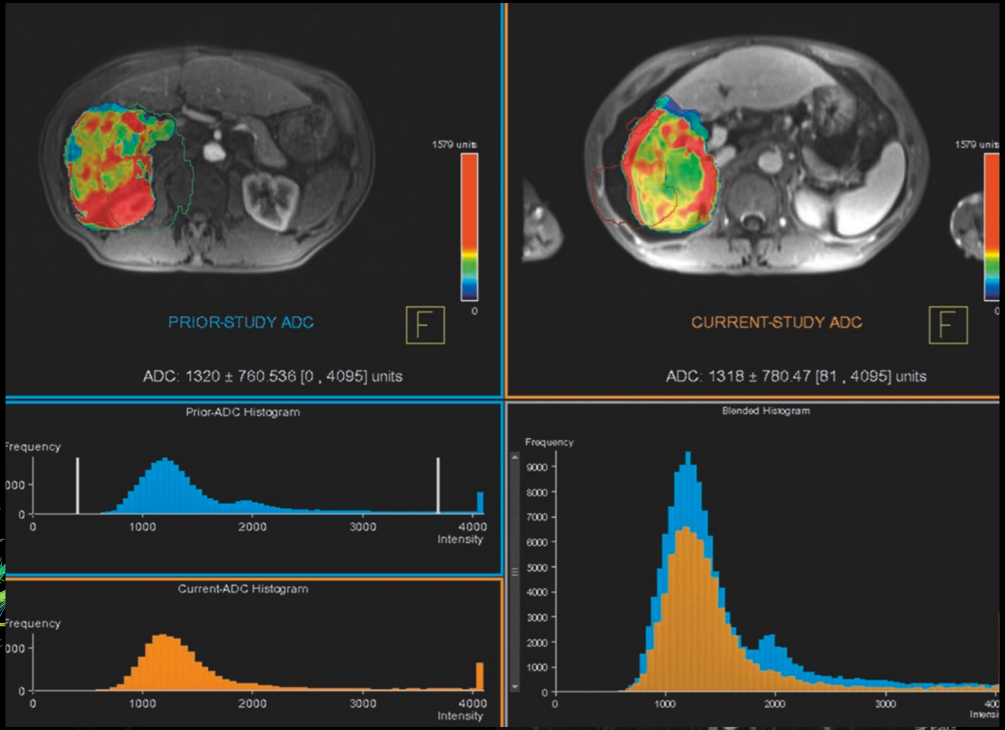
- Example: Risk of cancer; lesion detection in the image;

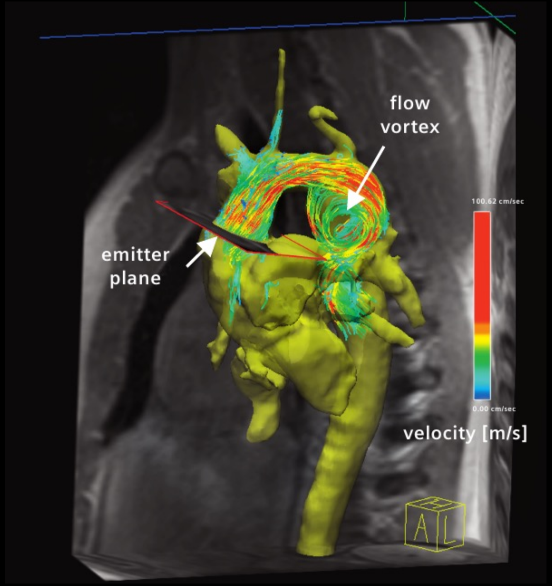
The lesion itself serves as a biomarker, but also the details of the lesion serve as biomarkers, and can collectively be used to assess the risk / aggressiveness: e.g. size, location, rate of growth, rate of metabolism... Each piece of information from the image represents a probability.

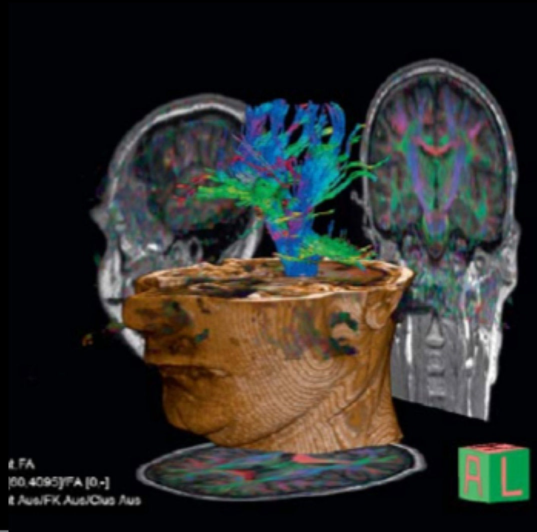






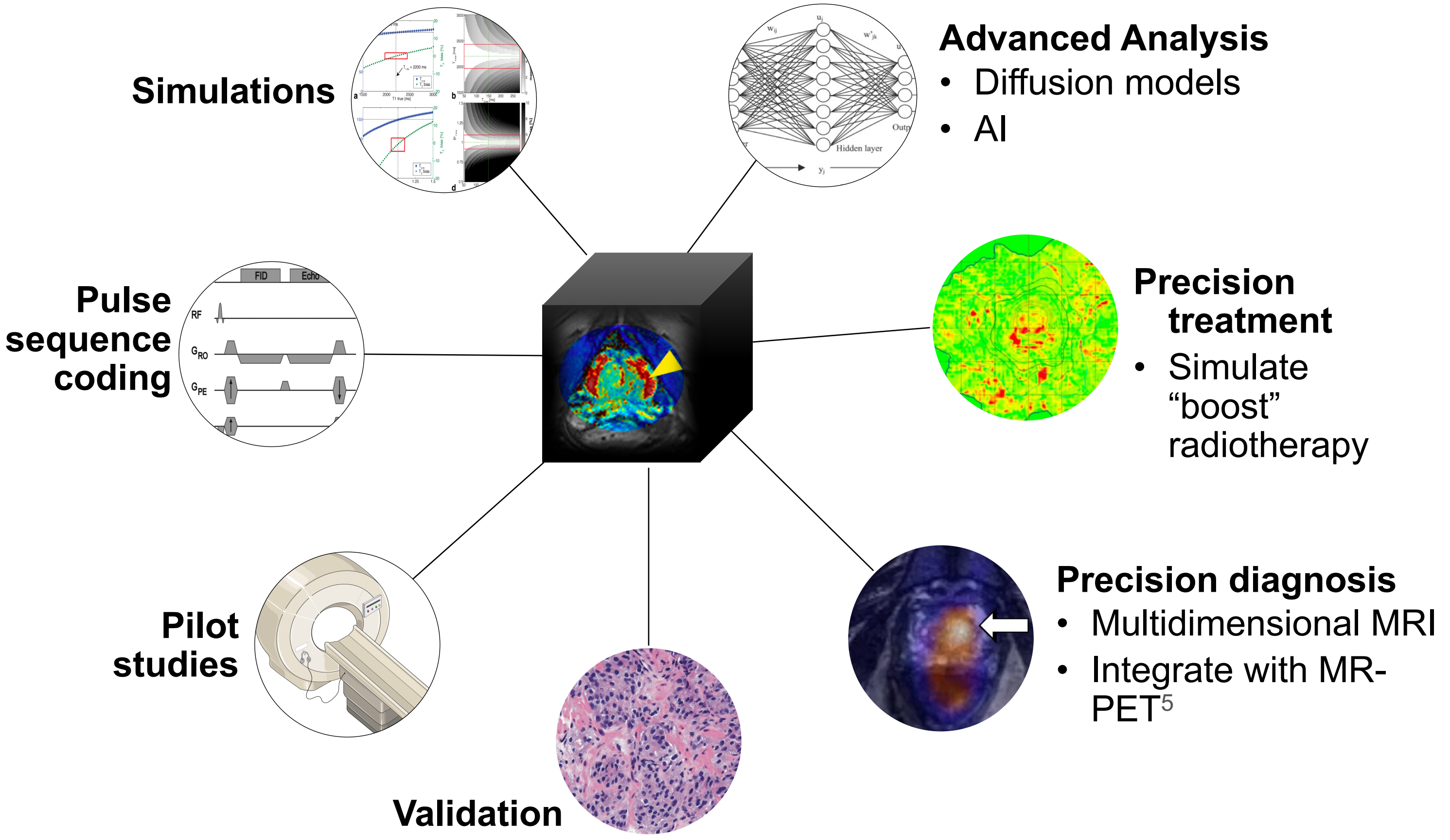






MRI is a very versatile imaging modality → multi-parametric data of morphology and function

Using MR physics to turn imaging into a precision tool for cancer diagnostics and therapy guidance



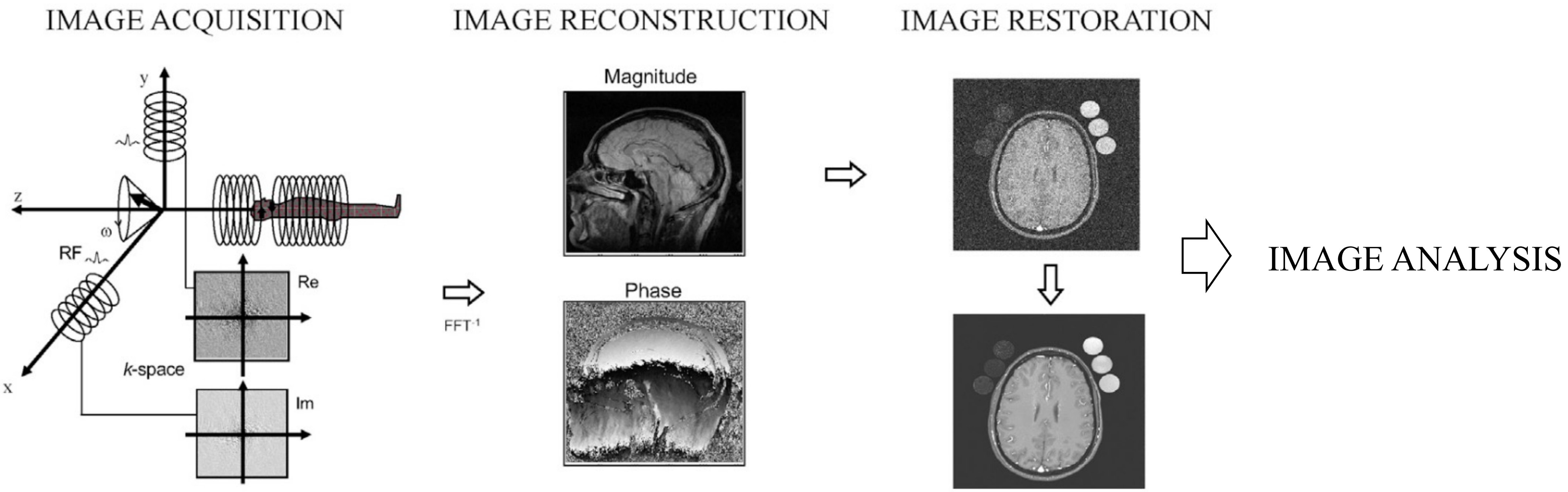
Research goals:

- faster
- more robust (motion!)
- quantitative
- multi-parametric (imaging beyond morphology)

Quantitative, co-registered, multi-parametric ***data*** as a prerequisite for deep learning applications

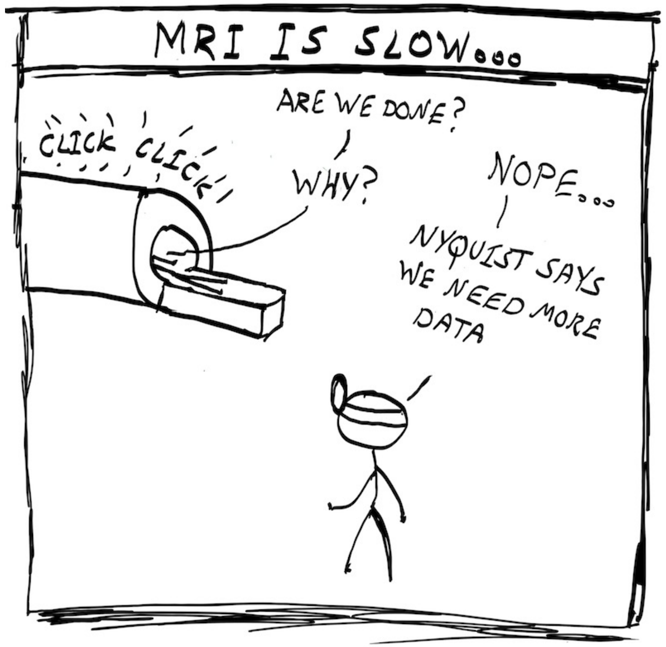
- Integrate with clinical biomarkers; radiogenomics
- Integrate with MR-guided interventions
- Clinical and industry translation

MR imaging pipeline



adapted from A.S. Lundervold, A. Lundervold / Z Med Phys 29 (2019) 102–127

MRI is too slow...

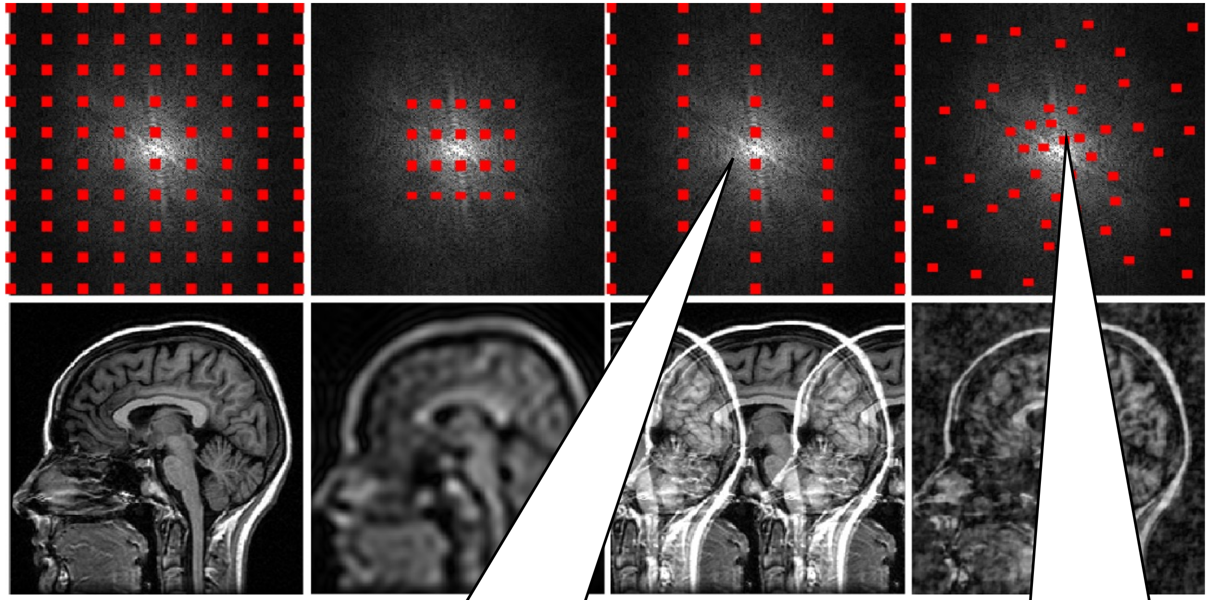


(c) Miki Lustig

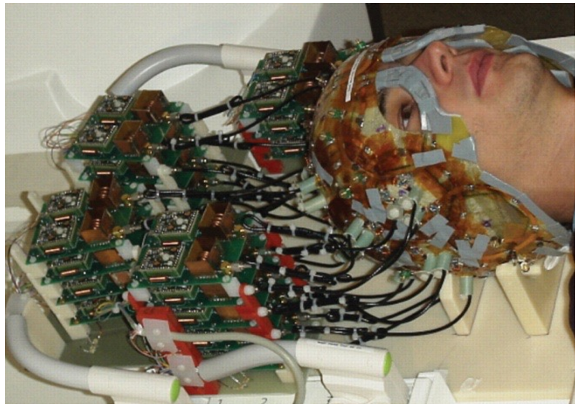
solution?

acquire less data
→ undersampling

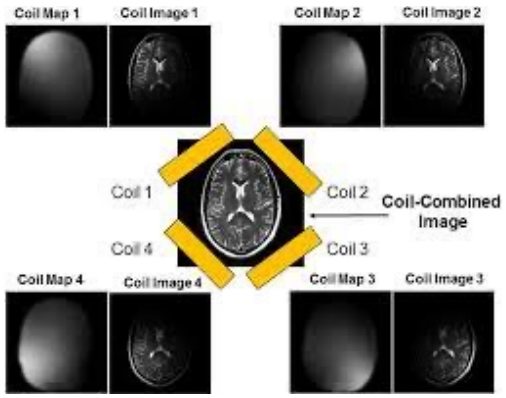
regular undersampling incoherent



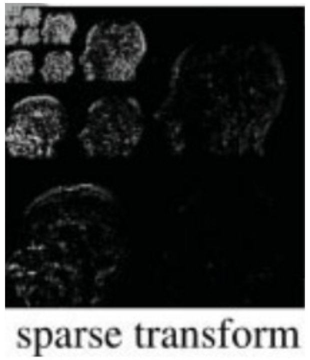
“a priori knowledge”



Wiggins et al. MRM 62(3):754-62 (2009)

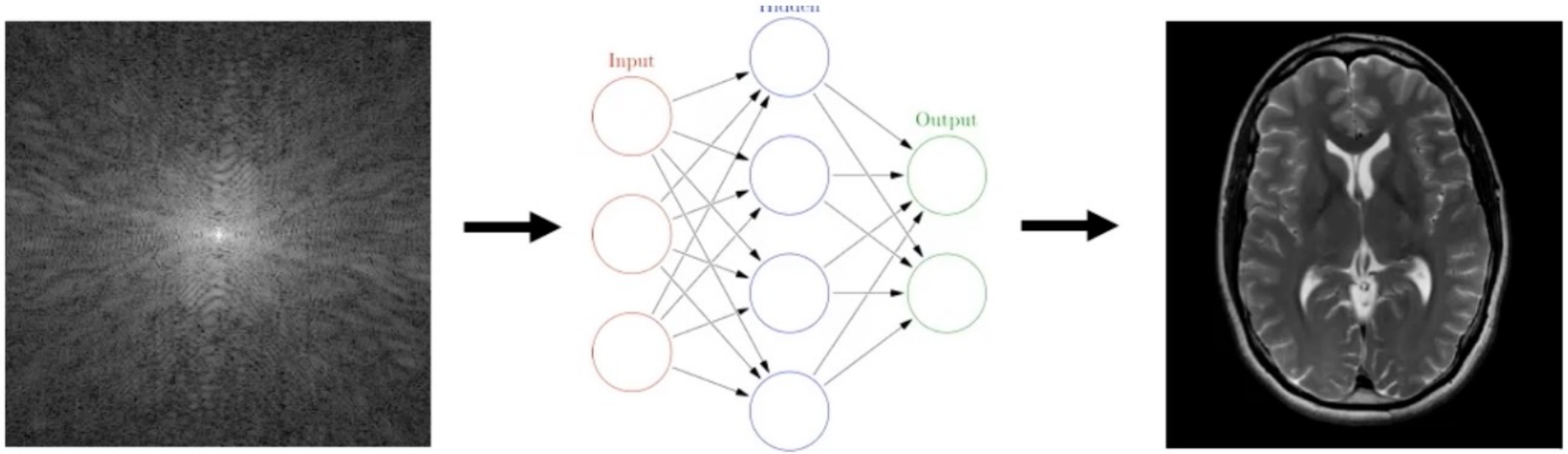


parallel imaging



compressed sensing

Can DL help?



YES

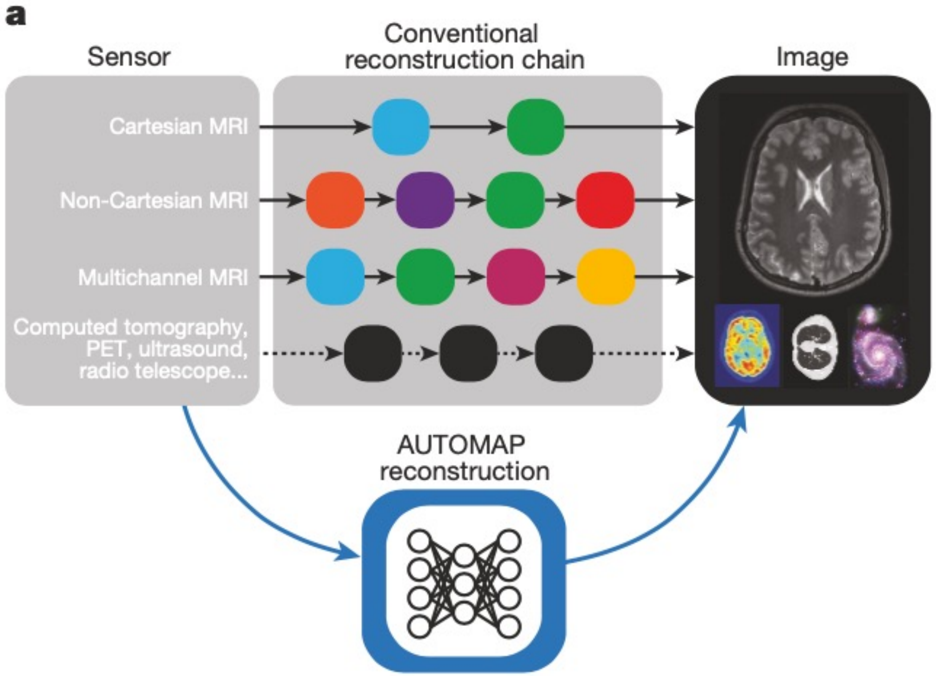
pioneered 2016 by Yang et al [1] and Wang et al [2]

since then, multiple solutions for MR image reconstruction:

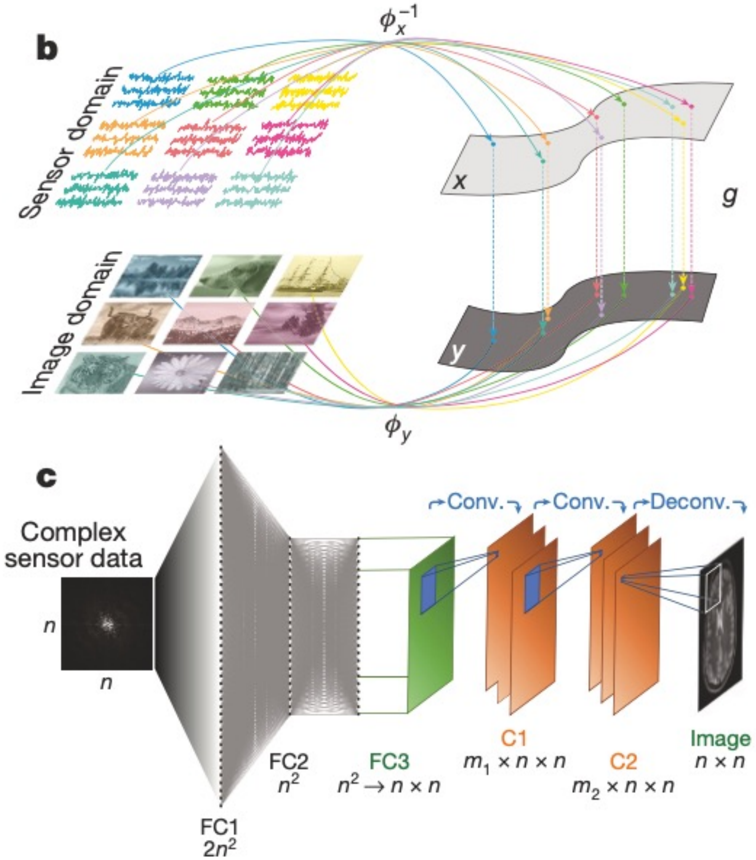
- using concatenated CNNs for highly undersampled dynamic data [e.g. 3,4]
- using a variational network for real time processing [5]
- looking into generalizability exploiting transfer learning [6]
- GANs for noise suppression [7]
- unified framework automap [8]

1. Yang Y, et al. In Advances in NIPS 2016. p. 10–8.
2. Wang S, et al In:2016 , 13th ISBI IEEE. 2016. p. 514–7.
3. Qin C. IEEE Trans Med Imaging 2018.
4. Schlemper J et al. IEEE TMI 2018;37:491–503.
5. Chen F, et al Radiology 2018:180445.
6. Knoll F, et al . Magn Reson Med 2018.
7. Mardani M, et al. IEEE Trans Med Imaging 2018.
8. Zhu B, et al. Nature 2018;555:487–92.

Unified framework for image recon - automated transform by manifold approximation (AUTOMAP)



formulate image reconstruction generically as a data-driven supervised learning task that generates a mapping between the sensor and image domain



feedforward deep NN with fully connected layers followed by a sparse convolutional autoencoder

Zhu, B., et al. *Nature* **555,** 487–492 (2018)

MR imaging pipeline

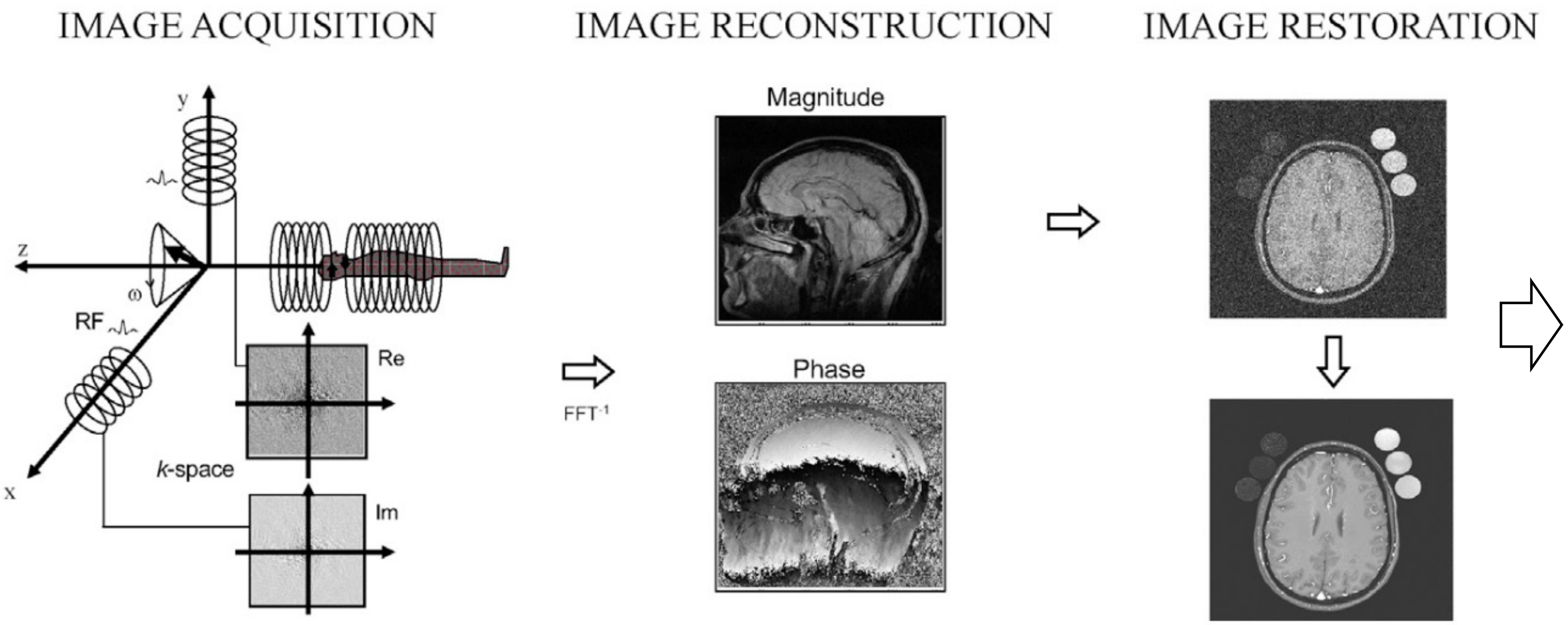
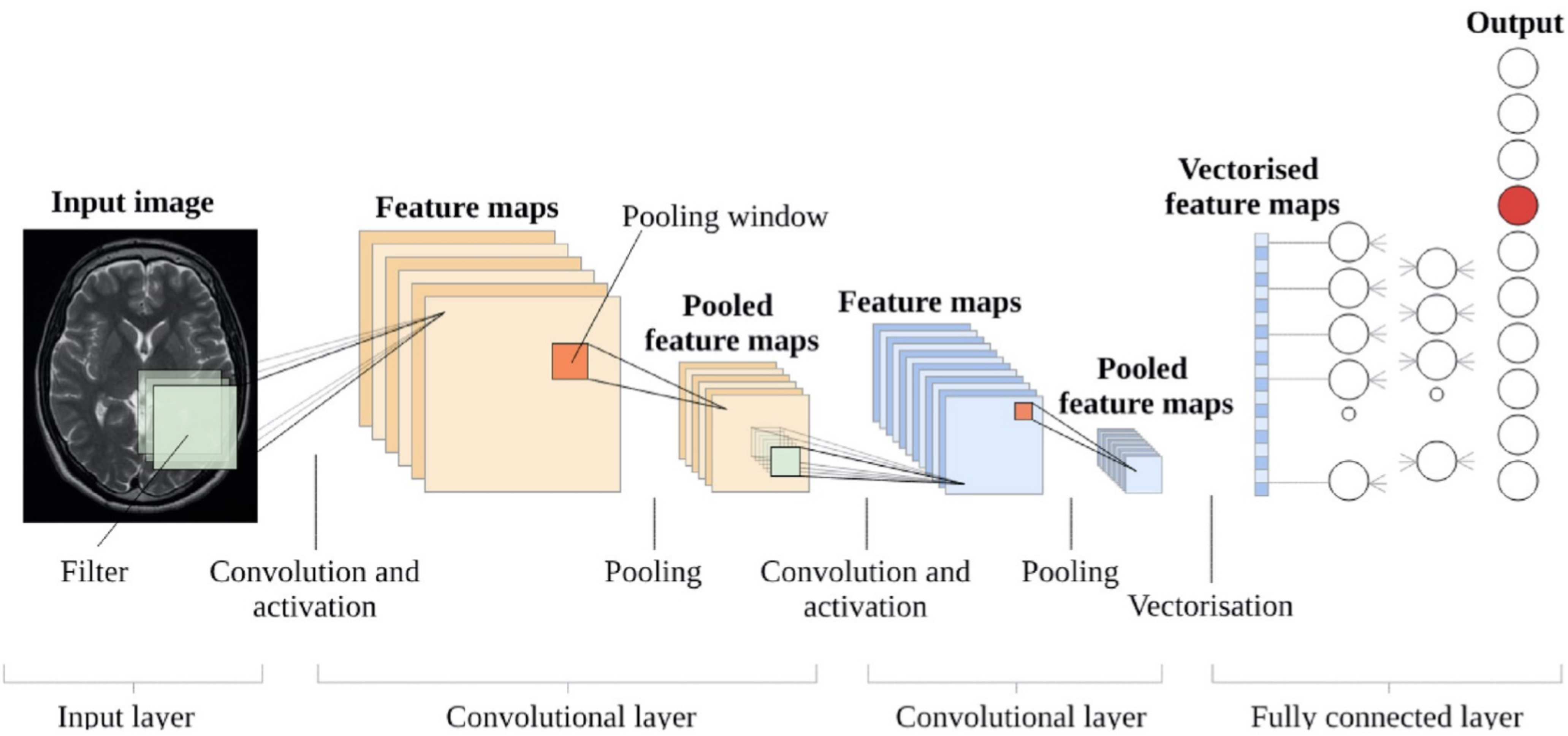


IMAGE ANALYSIS

- object segmentation
- disease detection
- disease prediction
- image registration of multiparametric or multimodal image data
- image synthesis
- ...

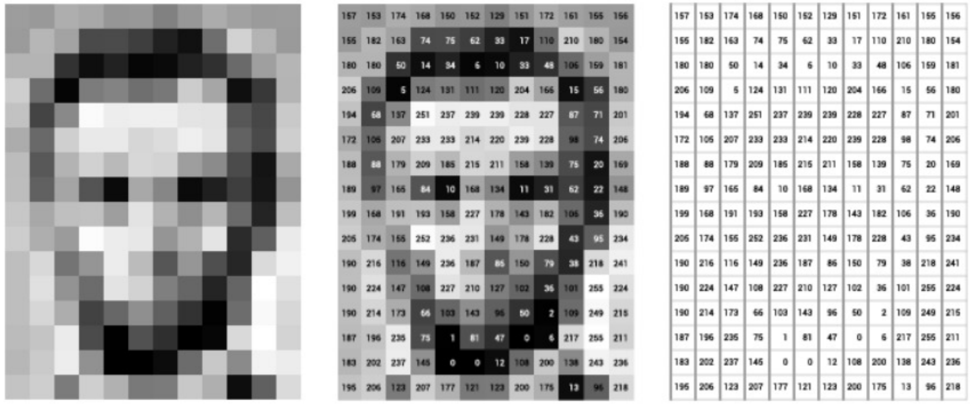
adapted from A.S. Lundervold, A. Lundervold / Z Med Phys 29 (2019) 102–127

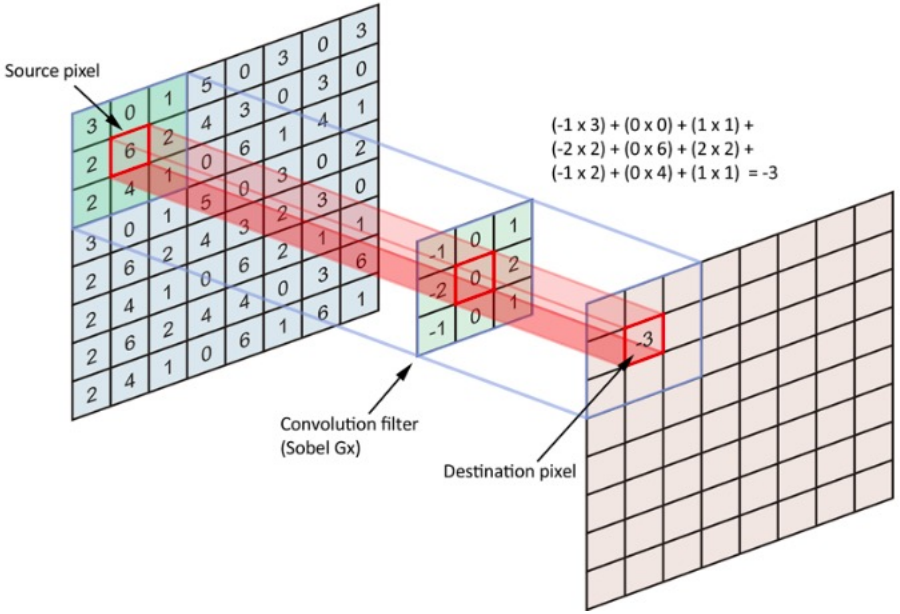
Building blocks of a CNN



A.S. Lundervold, A. Lundervold / Z Med Phys 29 (2019) 102–127

Convolution





Conv kernel “filter”:

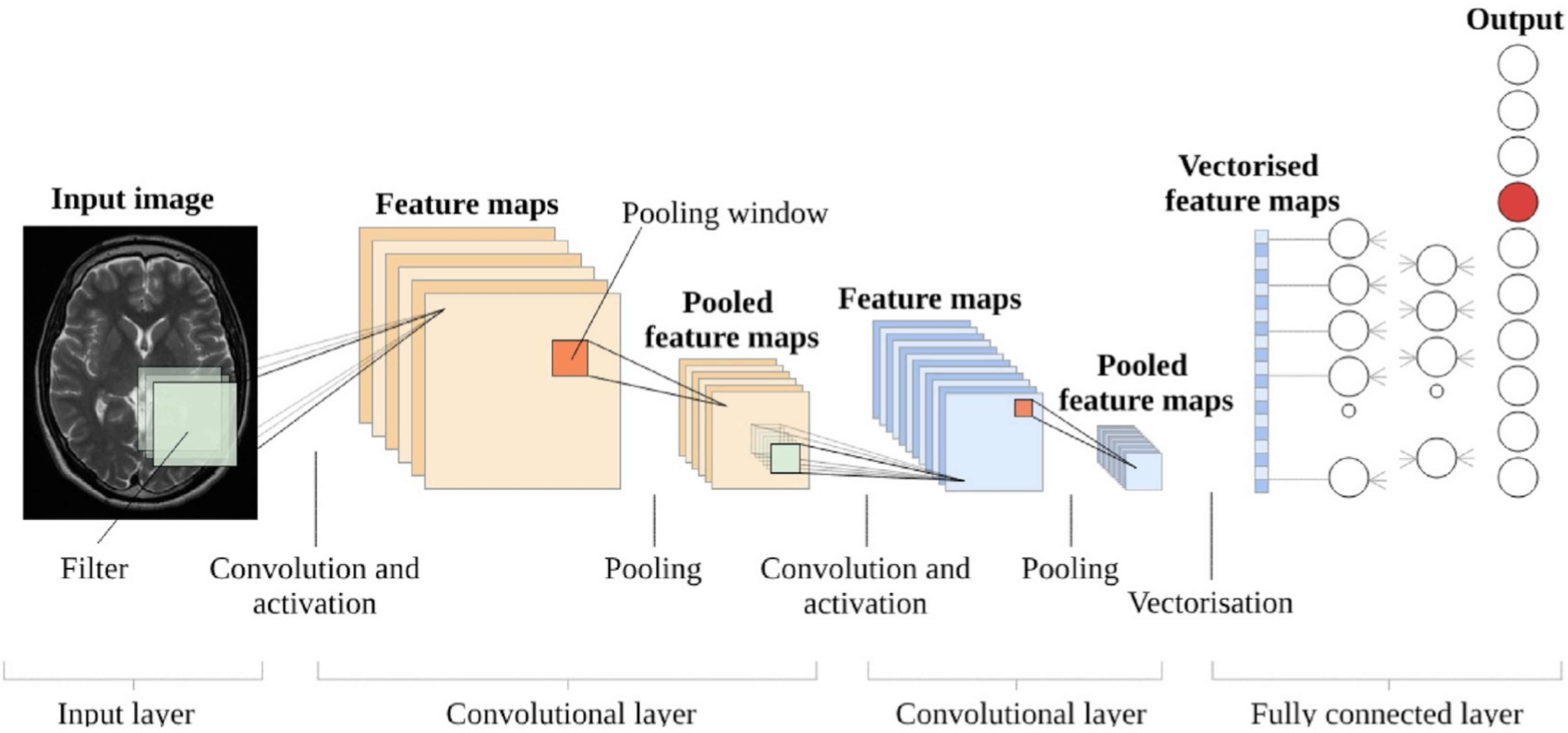
blurring (averaging)

1/9	1/9	1/9
1/9	1/9	1/9
1/9	1/9	1/9

edge detection (gradient filter)

$$\begin{bmatrix} -1 & -1 & -1 \\ -1 & 8 & -1 \\ -1 & -1 & -1 \end{bmatrix}$$

Building blocks of a CNN



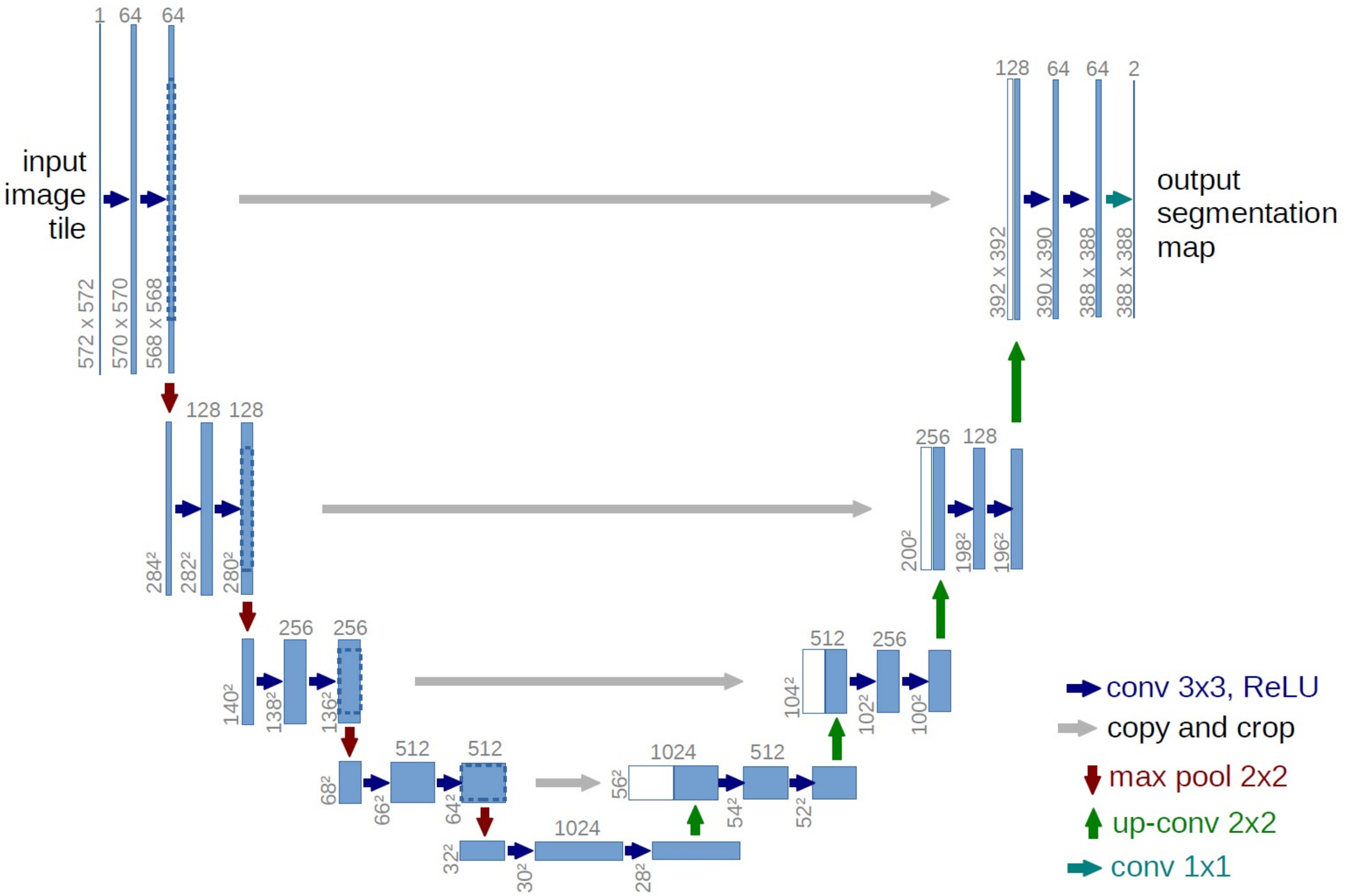
A.S. Lundervold, A. Lundervold / Z Med Phys 29 (2019) 102–127

U-Net (Ronneberger et al., 2015)

- U-Net learns segmentation in an end-to-end setting

Challenges addressed:

- very few annotated images (only approx 30) → augment training data e.g. with elastic deformations
- (relatively) fast training time
- can segment despite shape variations, variation in contrast, touching/overlapping structures



Ronneberger O., et al. (2015) U-Net: Convolutional Networks for Biomedical Image Segmentation. MICCAI 2015. https://doi.org/10.1007/978-3-319-24574-4_28

5-min teaser video on https://lmb.informatik.uni-freiburg.de/people/ronneber/u-net/

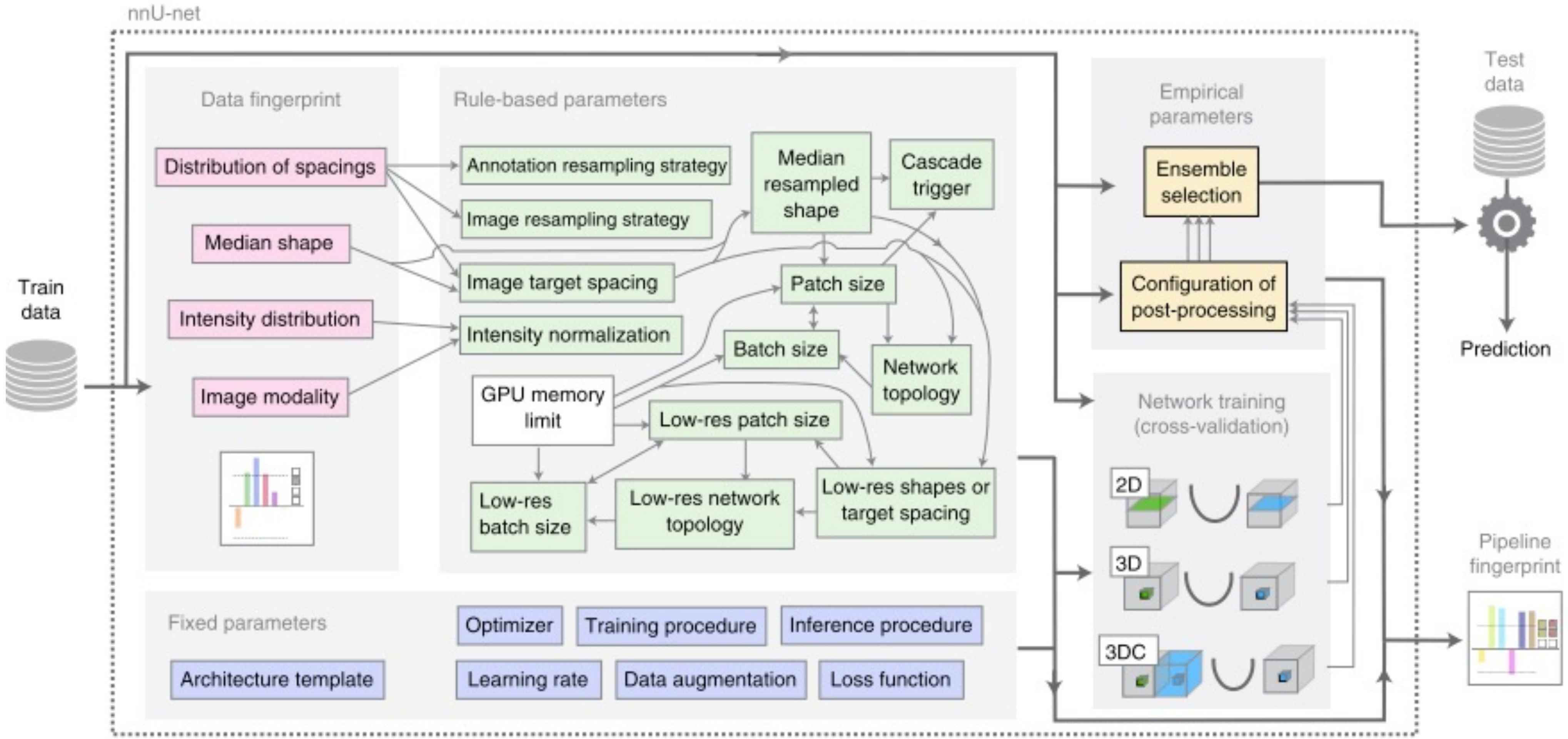
From U-Net to “no new” U-Net

- U-Net:
  - many different application-specific problems
  - task-specific design and configuration of a method requires high levels of expertise and experience, with small errors leading to large drops in performance
  - lead to many different publications promoting “new” architecture / pipelines for segmentation tasks
- nnU-Net: **automates the key decisions for designing a successful segmentation pipeline for any given dataset**
- Inexperienced users can use nnU-Net out of the box
- nnU-Net outperforms most specialized deep learning pipelines → benchmark and baseline for further development

Isensee, F., et al. (2020). nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nature Methods, 1-9.

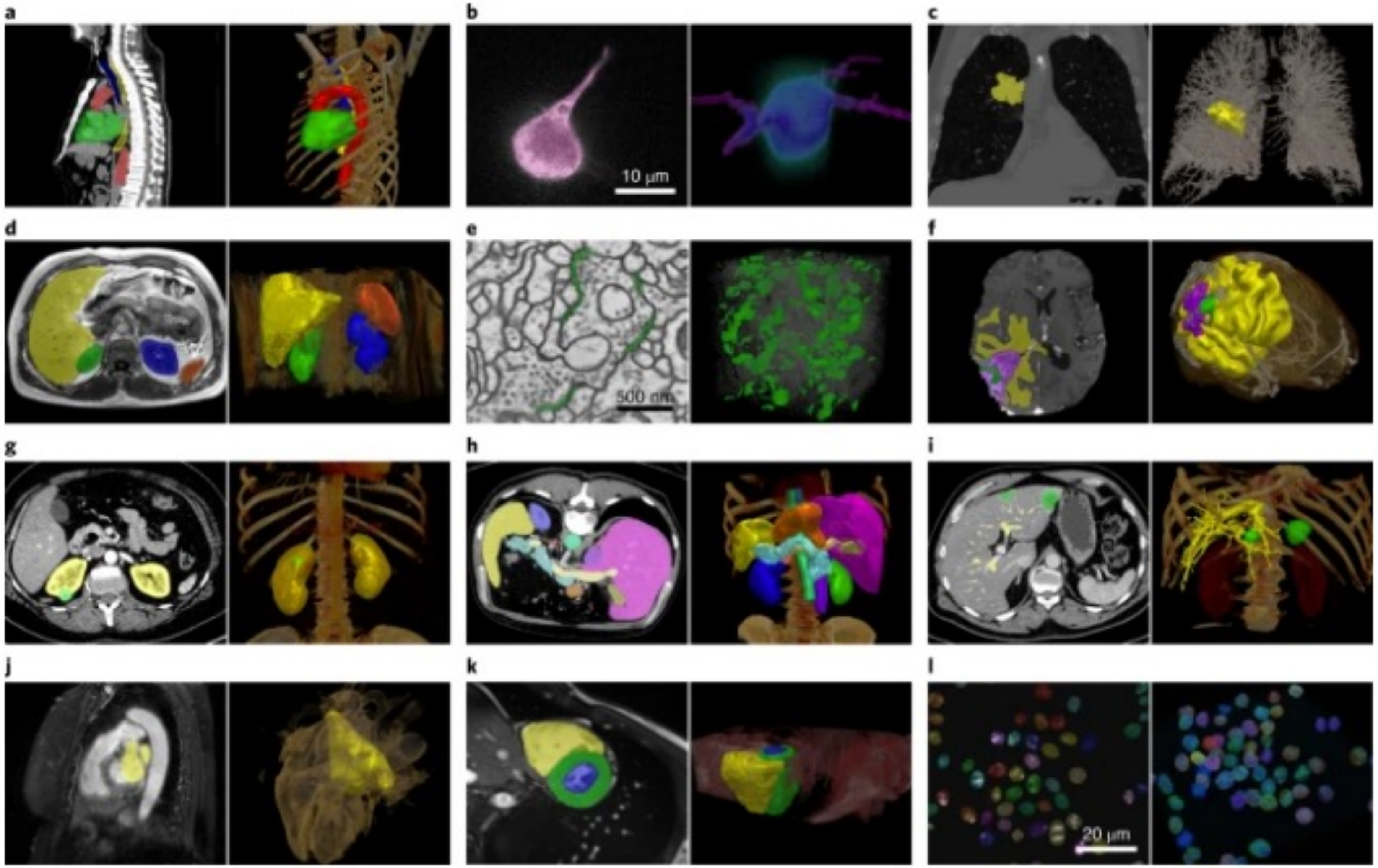
https://github.com/MIC-DKFZ/nnUNet

nnU-Net automated method configuration



Isensee, F., et al. (2020). nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nature Methods, 1-9.

Image segmentation examples



Isensee, F., et al. (2020). nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nature Methods, 1-9.

Research example #1

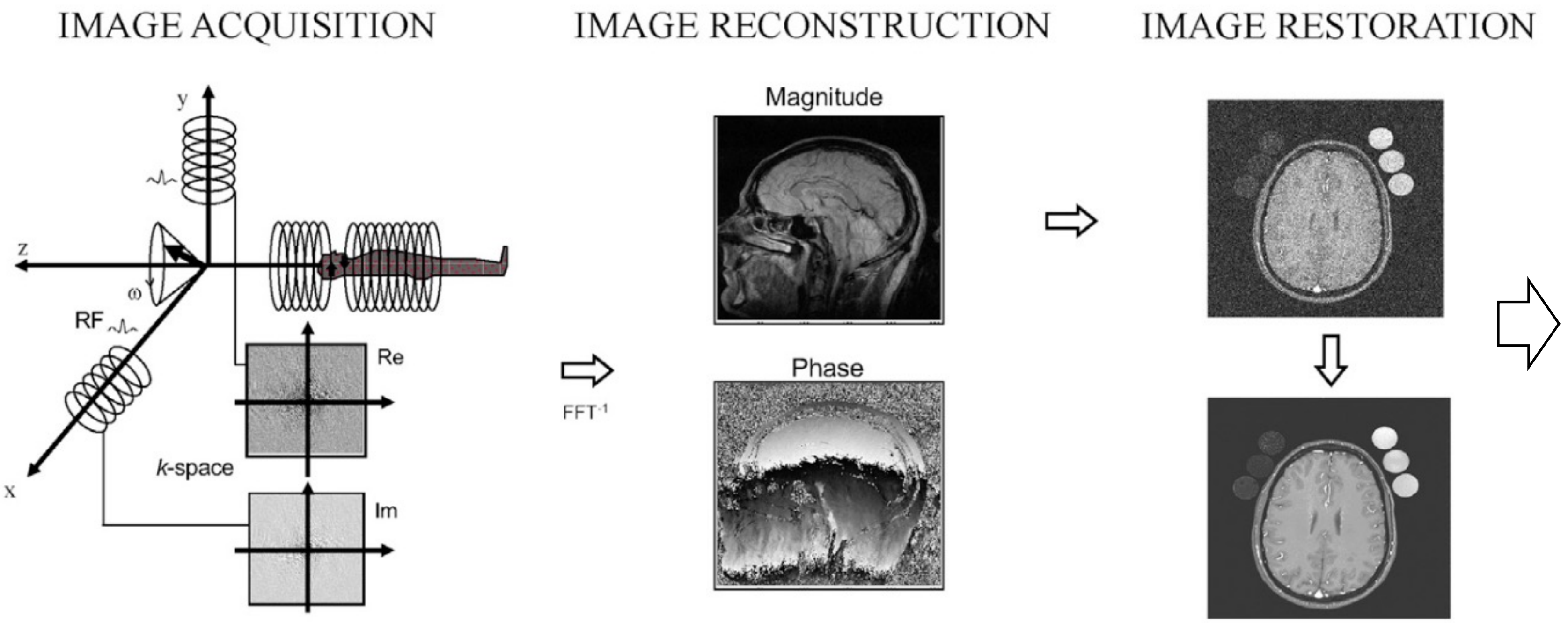


IMAGE ANALYSIS

- object segmentation
- disease detection
- disease prediction
- image registration of multiparametric or multimodal image data
- image synthesis
- ...

adapted from A.S. Lundervold, A. Lundervold / Z Med Phys 29 (2019) 102–127

Automatic segmentation of whole body MRI using uncertainty-aware nnU-Net

Renyang Gu,
KCL

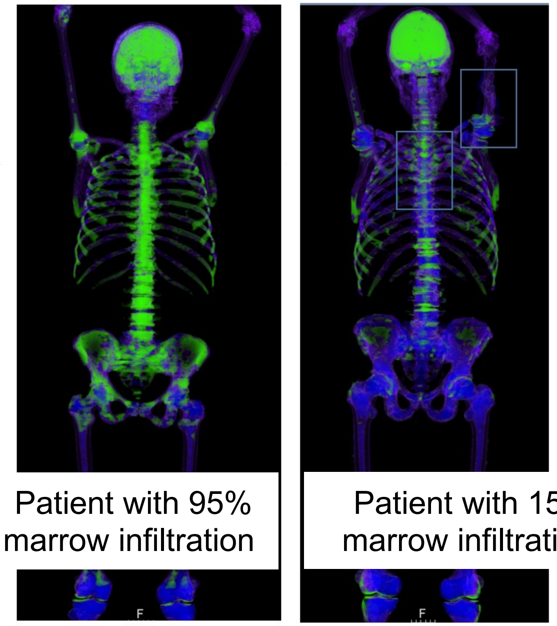
Imaging myeloma

- Myeloma is a bone marrow (whole-body) cancer with poor outcome
  - Most commonly diagnosed ≥ 50 yrs
  - 140,000 new cases each year [1,2]
  - 5-year survival rate: 48%
  - Average healthcare cost per year per patient ~65K€[3]

- Imaging diagnosis is based on focal bone lesions & ignores diffuse bone marrow infiltration

- Whole skeletal segmentation required for quantifying skeletal bone marrow infiltration may allow earlier diagnosis

CT



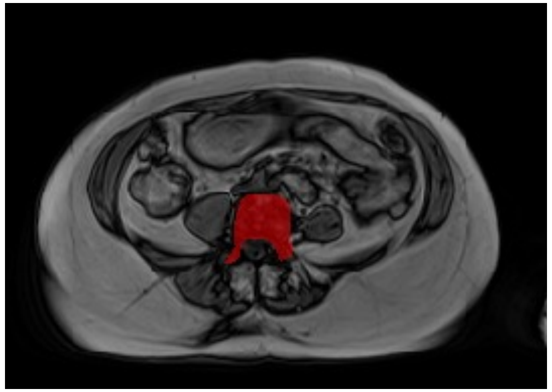
MR: bone is "invisible"

[1] Cowan et al. JAMA Oncol 2018
[2] Cancer Research UK
[3] Corso et al. Blood 2014

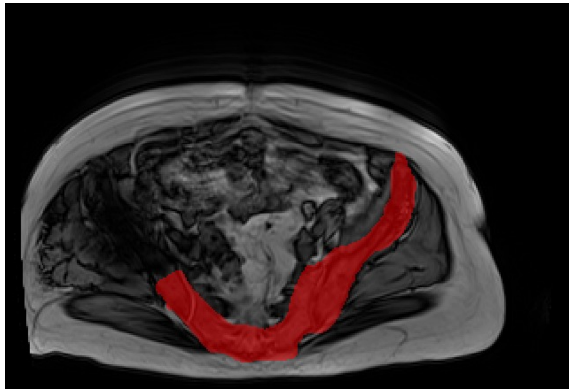
Challenges

- Manual segmentation of the entire skeleton **~ 5 hrs**
- **Low accuracy and high inter-observer variation** in ground truth, due to low image quality
- Inherent artefact of T1w Dixon images; e.g., fat water swap artefact and metal artefacts

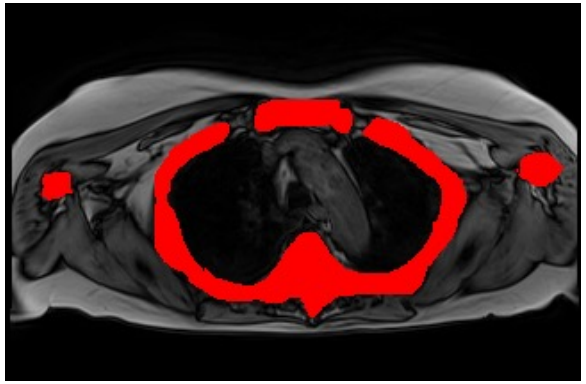
Under-segmentation of the vertebrae



Artefact



Over segmentation of the ribs & spinal canal



→ (Semi-) automatic segmentation pipeline required for WB MR biomarker quantification, correlation with clinical parameters, representation of MM cellularity

→ Uncertainty estimation to account for uncertainty in the ”ground truth” labels

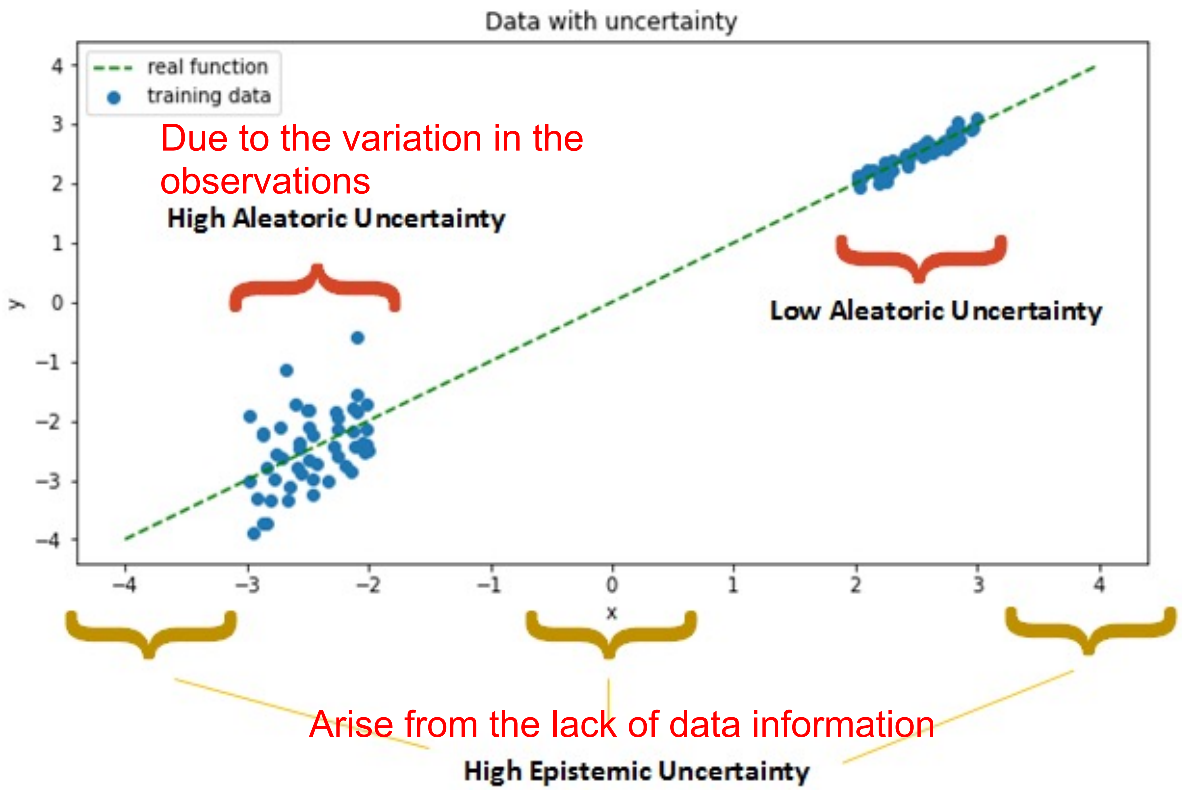
Uncertainty Estimation

Epistemic Uncertainty

- Model-parameter-dependent due to the lack of data knowledge
- Can be reduced with sufficient training samples

Aleatoric Uncertainty

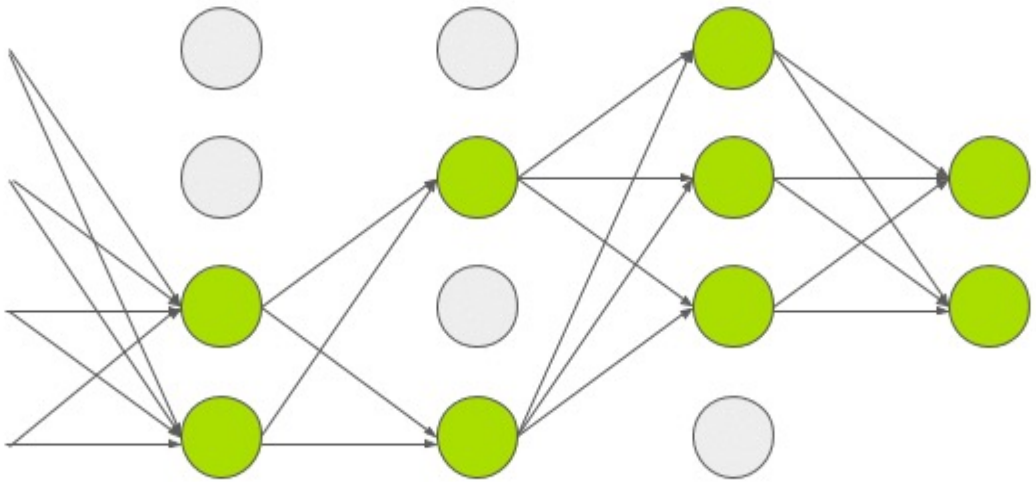
- Input-dependent
- arise from the natural stochasticity of observations
- Can be differentiated into task-specific (**homoscedastic** uncertainty) and noise-dependent (**heteroscedastic** uncertainty)
- **Homoscedastic** uncertainty is constant for all samples



Kendall & Gal, 2017

Epistemic Uncertainty

- Dropout as a Bayesian Approximation
- Dropout changes model architecture at different forward passes allowing Bayesian approximation
- Apply **dropout at both training and testing time**
- repeating prediction **T** times with random dropout = > epistemic uncertainty as variance/entropy of **T** predictions



Gal & Ghahramani, 2017

Aleatoric Uncertainty

- Uncertainty can be learned during training, modelled in the loss function
  - Model predicts both a mean $\hat{Y}$ and **variance σ²**
  - Variance (***σ²*****,** heteroscedastic uncertainty) output from the model, learned by replacing the loss with:

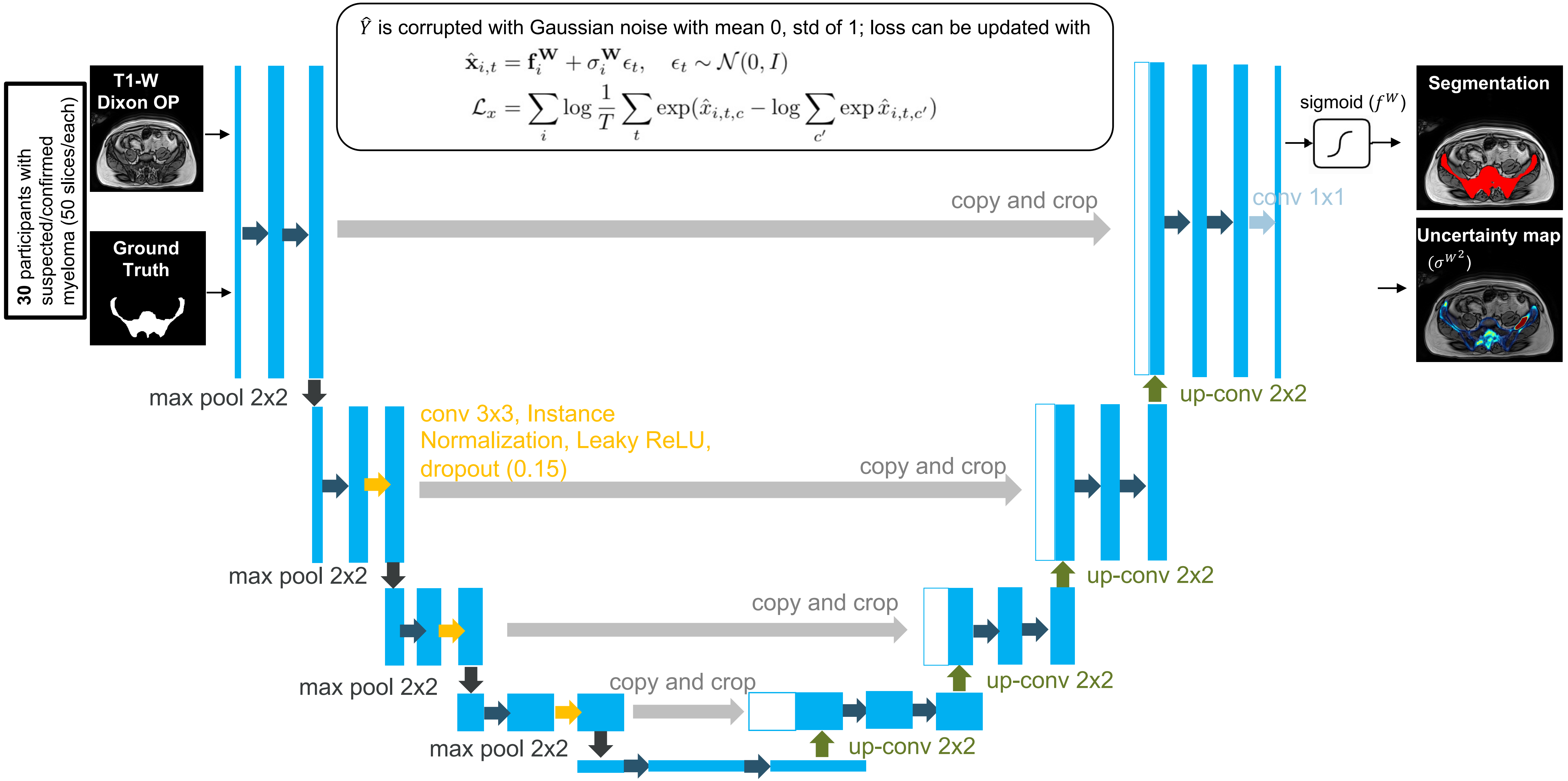
    → $\hat{Y}$ is corrupted with Gaussian noise with mean 0, std of 1

$$\hat{\mathbf{x}}_{i,t} = \mathbf{f}_i^{\mathbf{W}} + \sigma_i^{\mathbf{W}} \epsilon_t, \quad \epsilon_t \sim \mathcal{N}(0, I)$$

$$\mathcal{L}_x = \sum_i \log \frac{1}{T} \sum_t \exp(\hat{x}_{i,t,c} - \log \sum_{c'} \exp \hat{x}_{i,t,c'})$$

[1] Kendall et al., 2018
[2] Kendall & Gal, 2017

Methods – 2D nnU-Net architecture with uncertainty

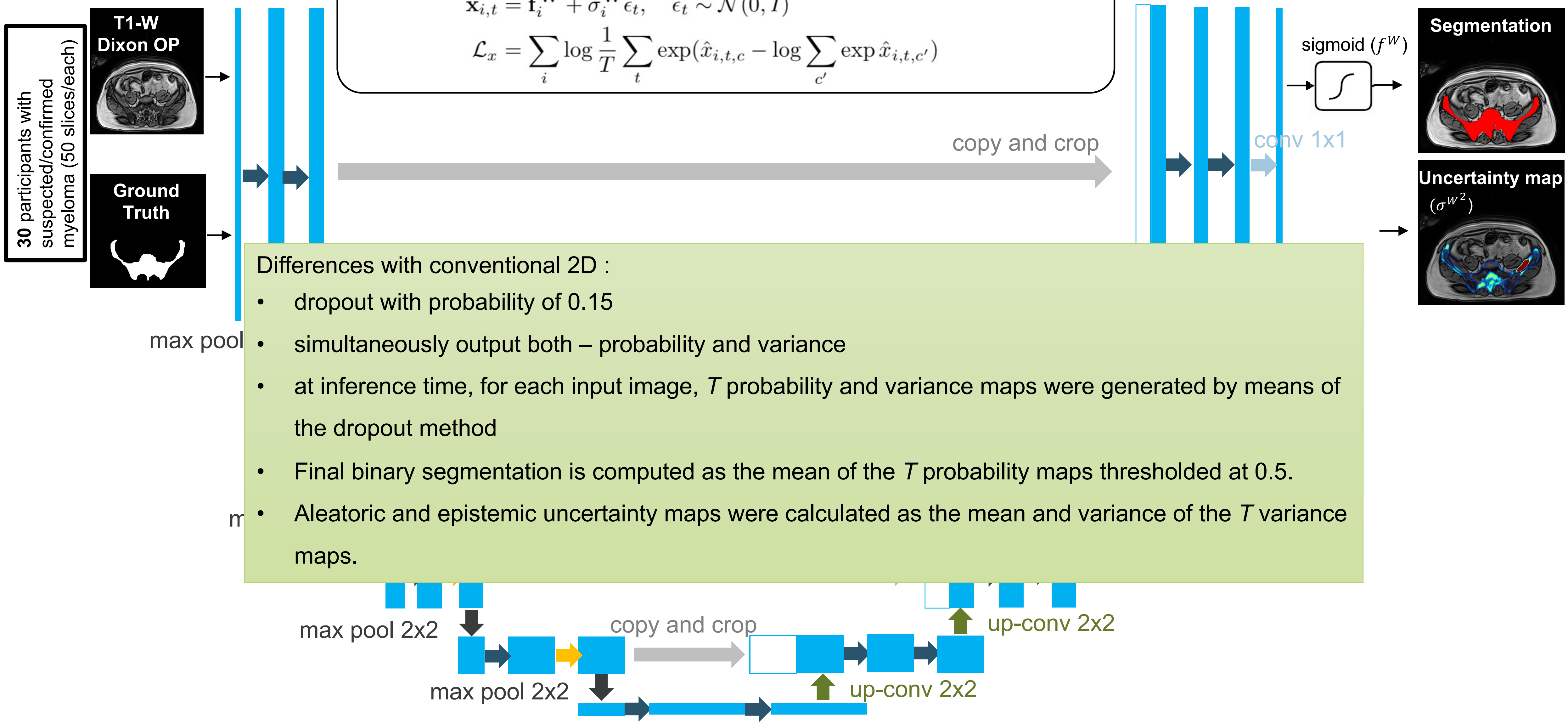


Methods – 2D nnU-Net architecture with uncertainty

$\hat{Y}$ is corrupted with Gaussian noise with mean 0, std of 1; loss can be updated with

$$\hat{\mathbf{x}}_{i,t} = \mathbf{f}_i^{\mathbf{W}} + \sigma_i^{\mathbf{W}} \epsilon_t, \quad \epsilon_t \sim \mathcal{N}(0, I)$$

$$\mathcal{L}_x = \sum_i \log \frac{1}{T} \sum_t \exp(\hat{x}_{i,t,c} - \log \sum_{c'} \exp \hat{x}_{i,t,c'})$$



Differences with conventional 2D :

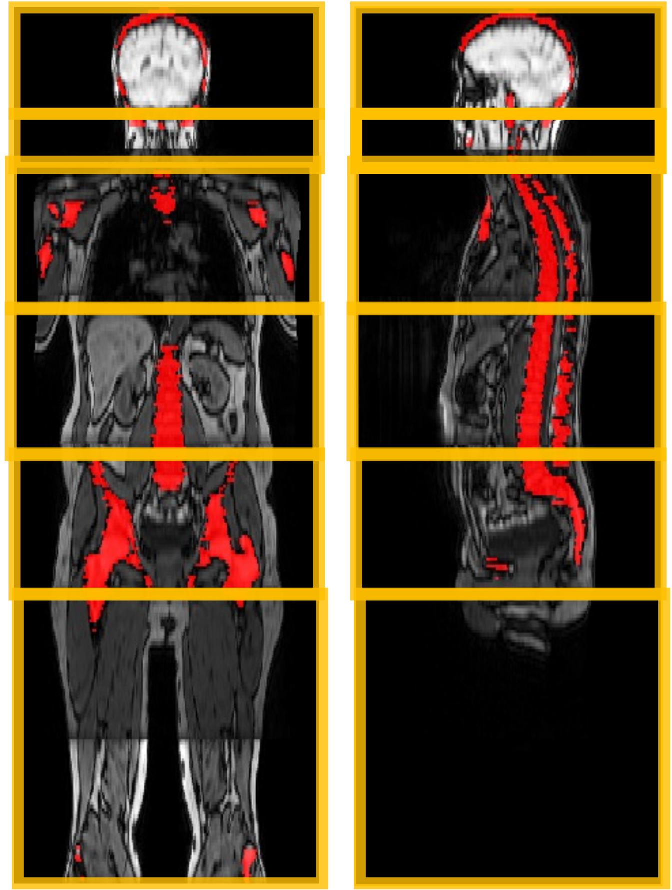
- dropout with probability of 0.15
- simultaneously output both – probability and variance
- at inference time, for each input image, *T* probability and variance maps were generated by means of the dropout method
- Final binary segmentation is computed as the mean of the *T* probability maps thresholded at 0.5.
- Aleatoric and epistemic uncertainty maps were calculated as the mean and variance of the *T* variance maps.

Methods – experiment pipeline

T1w Dixon OP & corresponding marrow GT segmentation (whole-body, 3D)

→

Manually selected station according to anatomical landmarks (3D)



→

nnU-Net (2D)
Single station

UnnU-Net (2D)
- Single station
- Sliding station
- Whole-body

→

Evaluation of segmentation
- Dice Coefficient
- Likert score

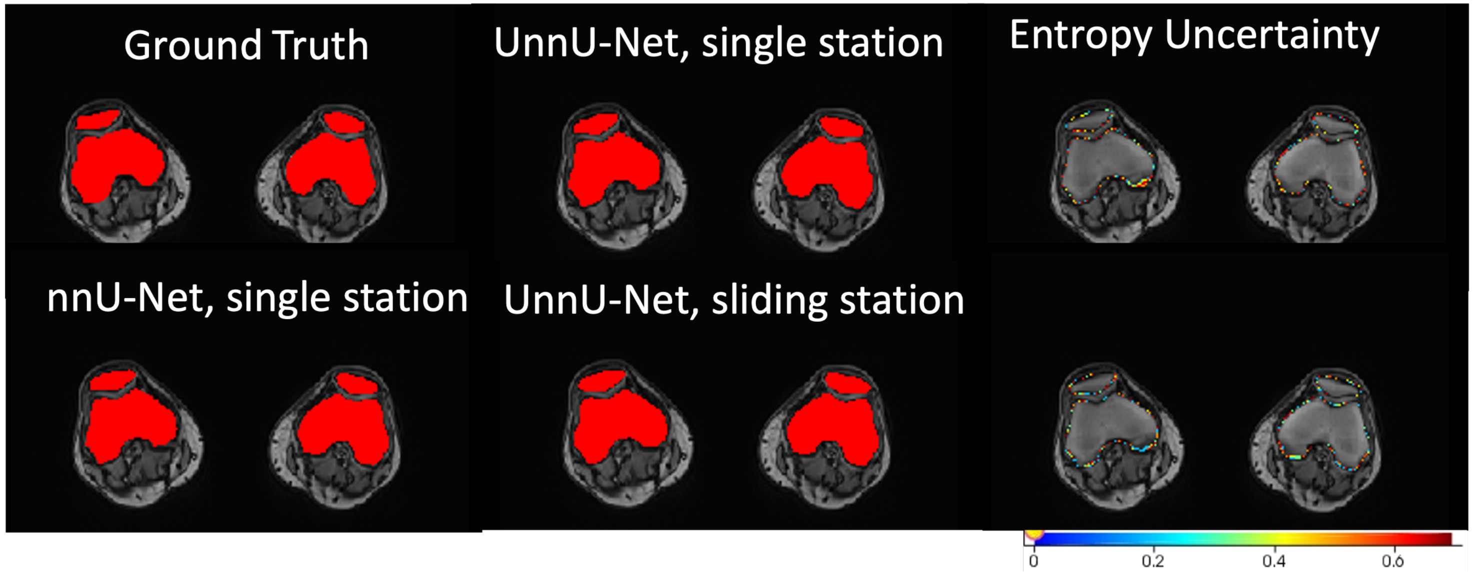
Evaluation of uncertainty map

Methods - 4-point Radiologist-Assisted Scoring System

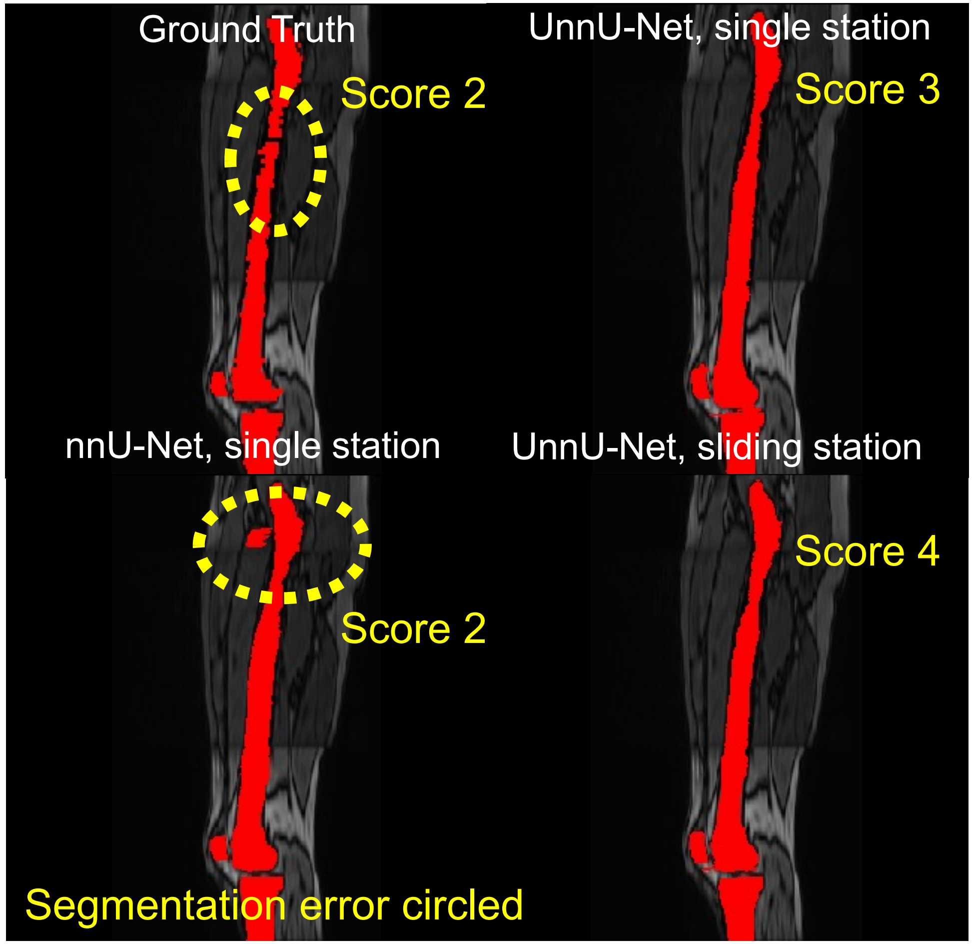
- Problem: Problem uncertainty in GT – cannot use Dice score as a metric for network performance
- → thus using Radiologist assisted scoring
- Likert 4-point score:

<table>
<tr><th>Score</th><th>Definition</th><th>Further categories</th></tr>
<tr><td>1</td><td>Completely unacceptable</td><td rowspan="3">• Under-segmentation
• Over-segmentation
• Partial overlap</td></tr>
<tr><td>2</td><td>Acceptable with major changes (the contours need significant revision)</td></tr>
<tr><td>3</td><td>Acceptable with minor changes (segmentation needs a few minor stylistic edits but does not miss important pathology)</td></tr>
<tr><td>4</td><td>Acceptable without changes</td><td></td></tr>
</table>

Example Leg Station

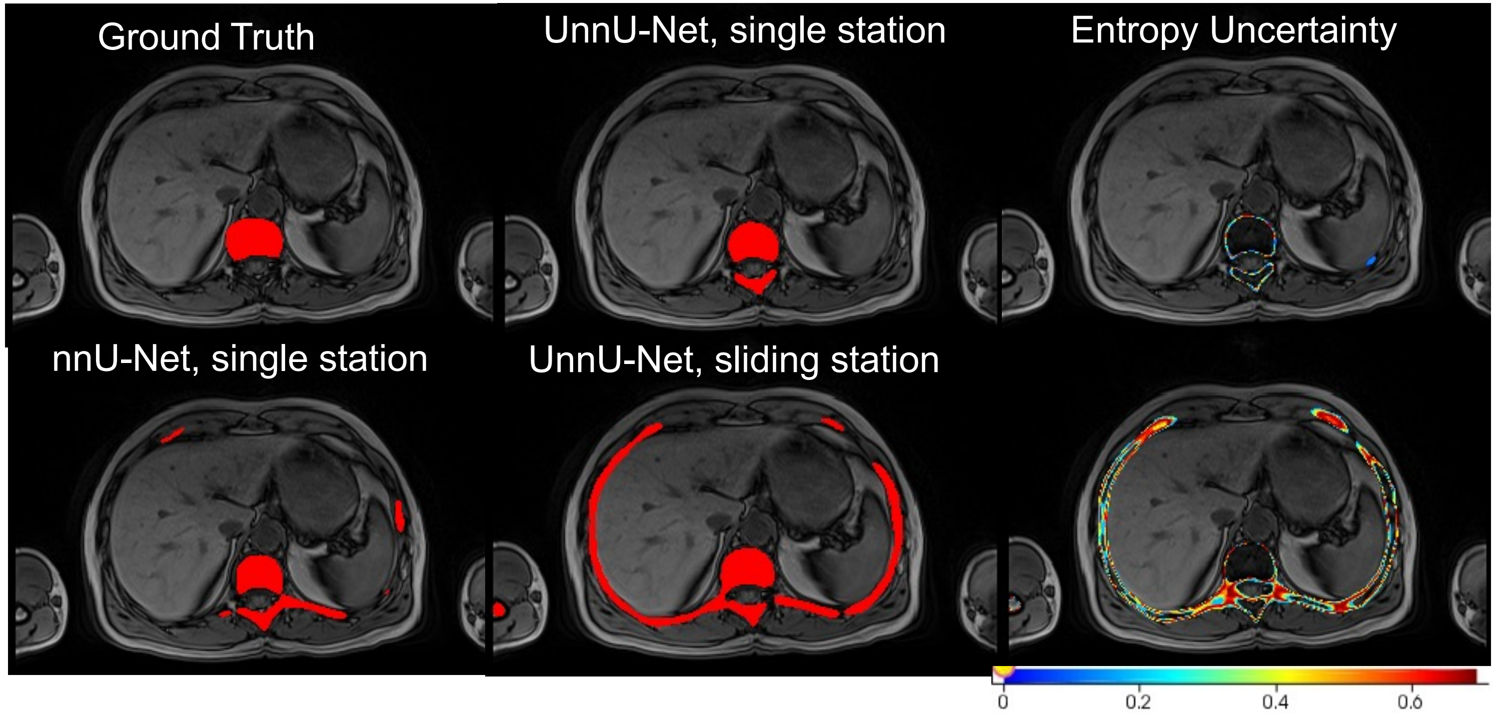


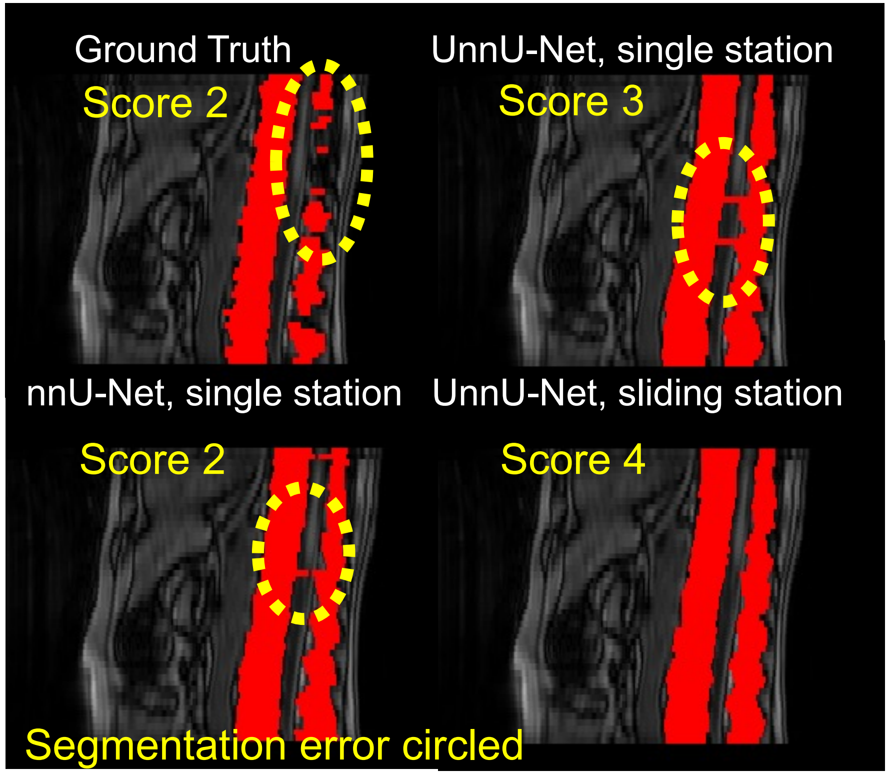
Axial & sagittal T1w Dixon images with segmentation overlay



UnnU-Net with **sliding** station images generates the most representative prediction
Likert score = **4**

Example Abdominal Station

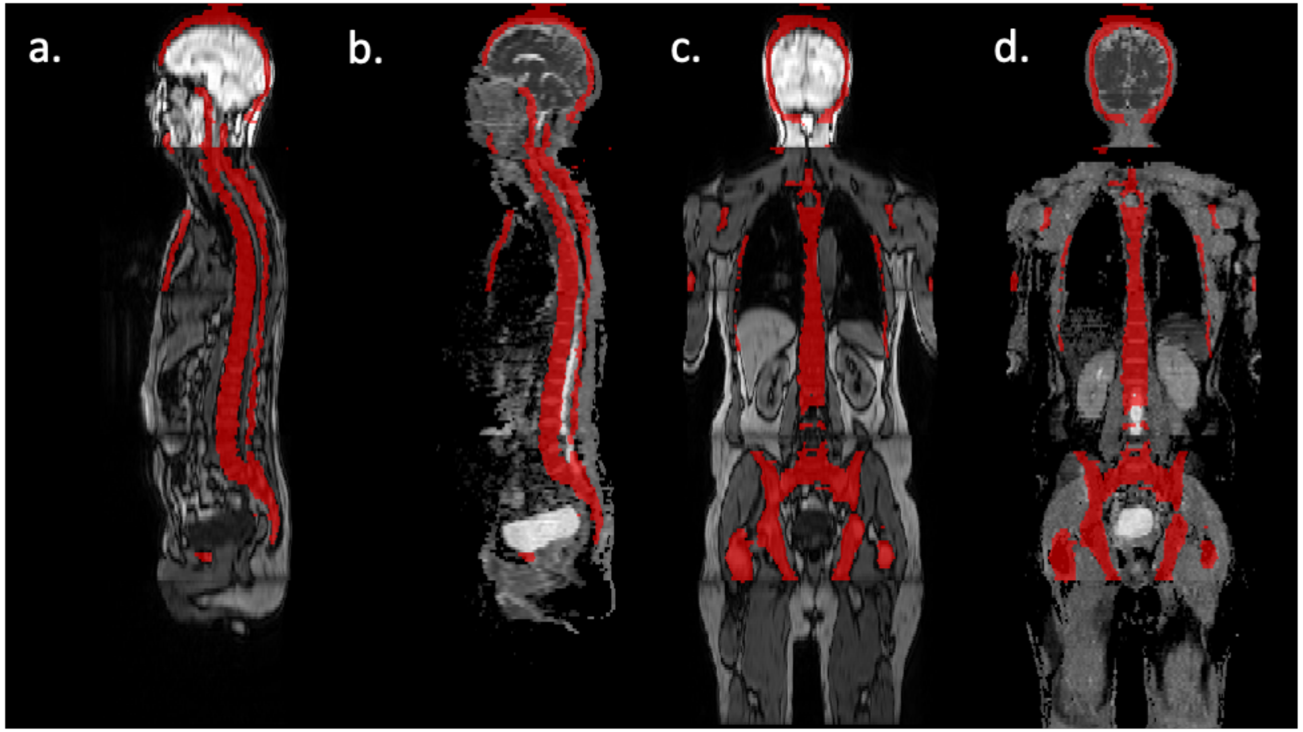


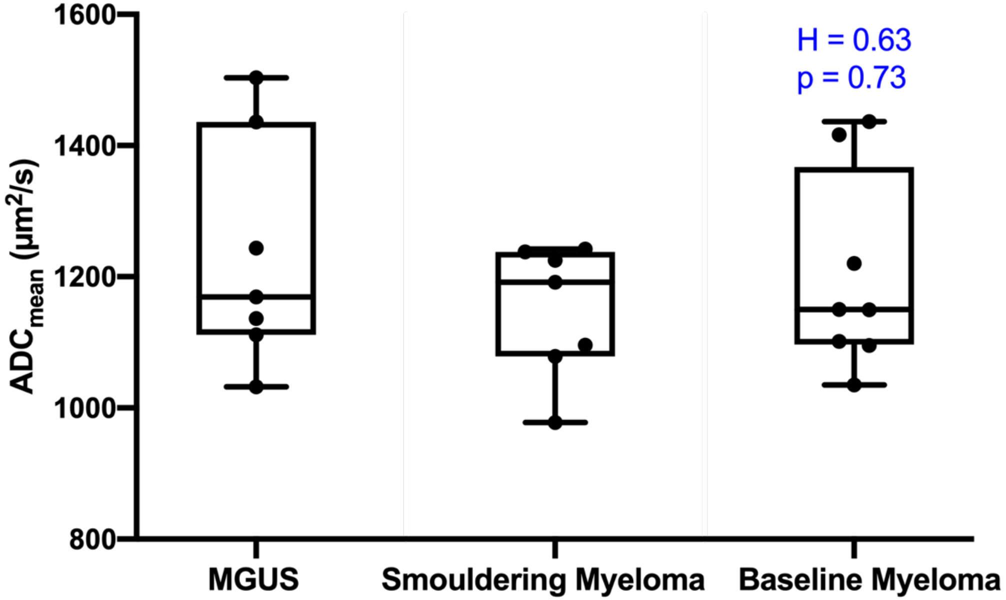


Axial & sagittal T1w Dixon images with segmentation overlay

- **UnnU-Net** with **sliding** station images generates the most representative prediction
- Prediction of the **ribs** is suboptimal

Automatic segmentation of whole body MRI using uncertainty-aware nnU-Net : Feasibility of whole skeletal ADC evaluation in plasma cell disorders





UnnU-Net segmentation of T1-weighted Dixon GRE images (in the sagittal (a) and coronal plane (c)), then overlaid onto the ADC maps (in the sagittal (b) and coronal plane (d) for whole skeleton ADC extraction.

Research example #2

IMAGE ACQUISITION   IMAGE RECONSTRUCTION   IMAGE RESTORATION

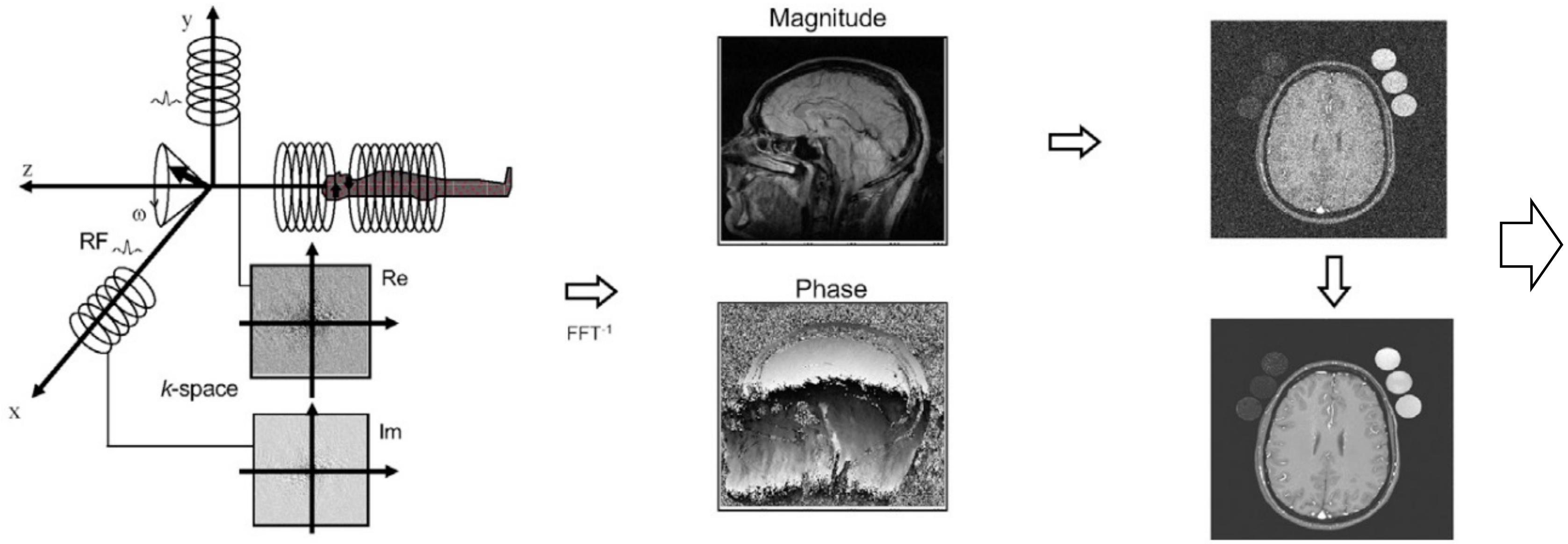


IMAGE ANALYSIS

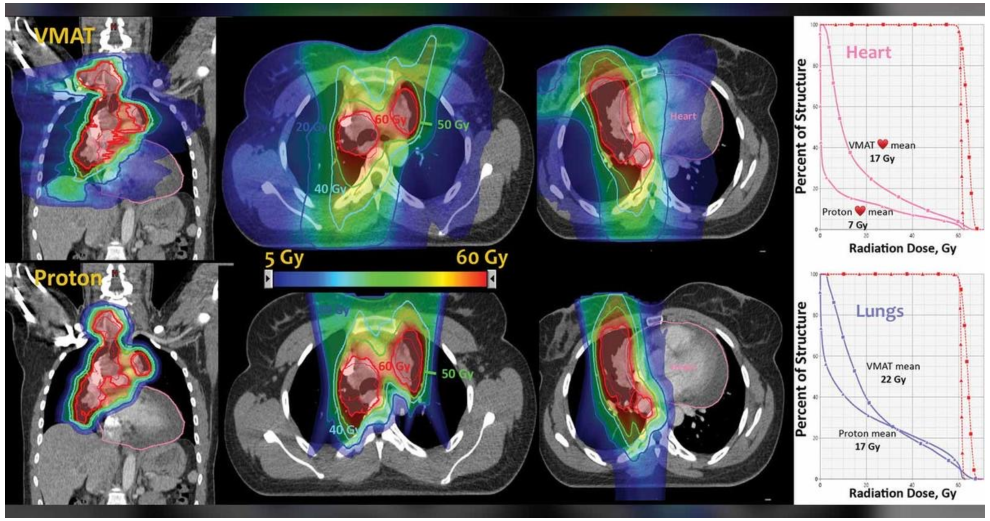
- object segmentation
- disease detection
- disease prediction
- image registration of multiparametric or multimodal image data
- image synthesis
- ...

WORKFLOW OPTIMIZATIONS

- radiotherapy dose estimation

Image-guided radiotherapy

- Radiotherapy: kill the tumour cells using (external beam) radiation
- Radiation is toxic → long term side effects
- Goal is to **maximize the therapeutic r**atio: maximize the radiation to the tumour, and save the surrounding structures
- **Key to success: image guidance to delineate target and organs at risk**



MR+DL-guided radiotherapy

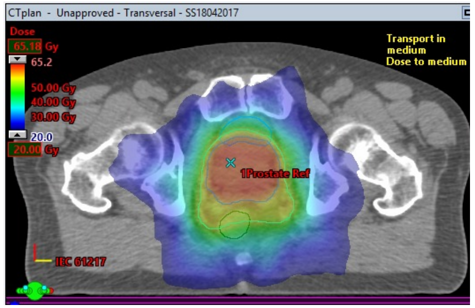
Chris Thomas, KCL

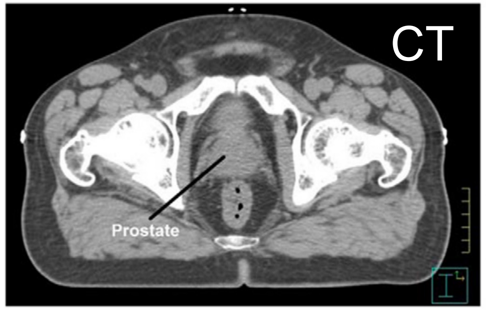
current image-guided radiotherapy:

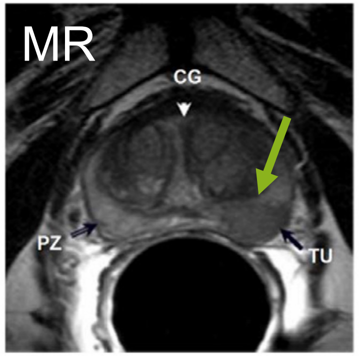
Imaging
- CT

Planning
- One-size fits all

Treatment
- Same plan







MR: much better soft tissue contrast than CT (can delineate much better!)

Promise of MR-based RT: **maximize therapeutic ratio**
- Toxicity reduction: minimize margin
- Dose escalation to tumor
- Adaption to individual patient (biology, response)

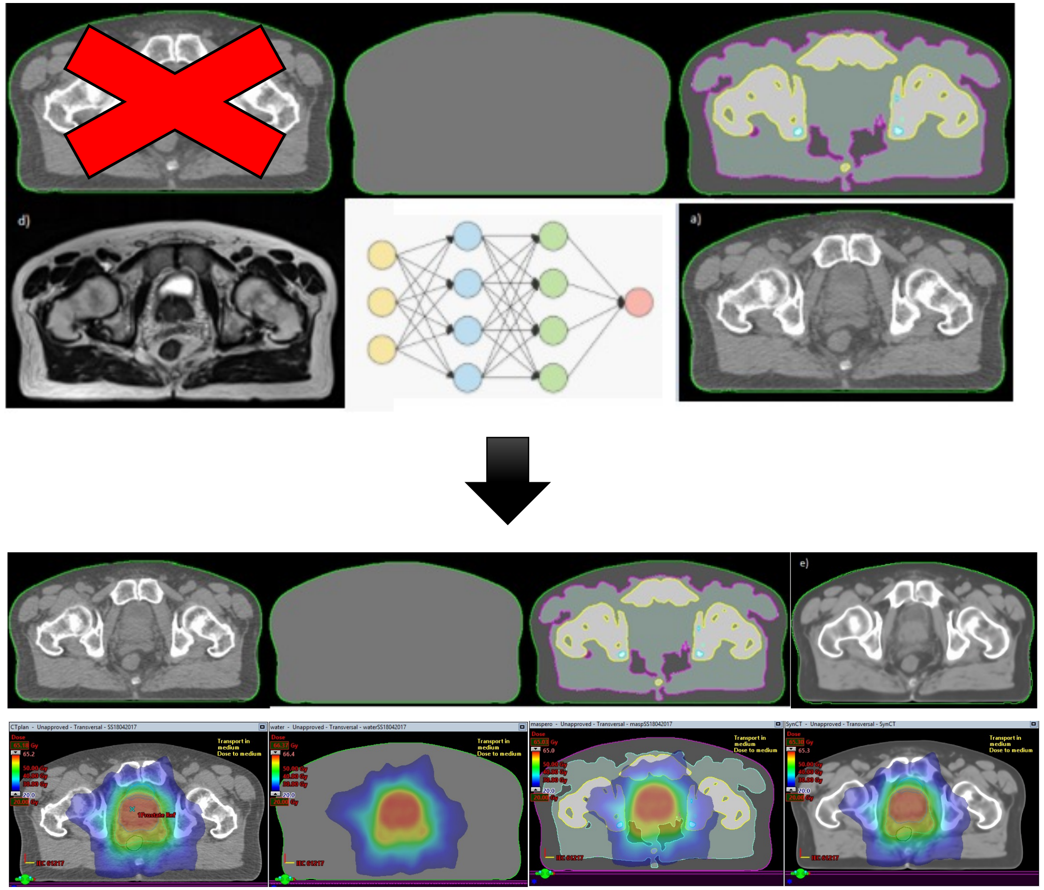
Limitations of MR-based planning
need "synCT"

Promise of DL-based RT planning:
planning usually takes several iterations, hours (!) of physicist / clinical oncologist time → DL based planning enables real-time risk assessment

Synthetic CT effect on toxicity risk prediction

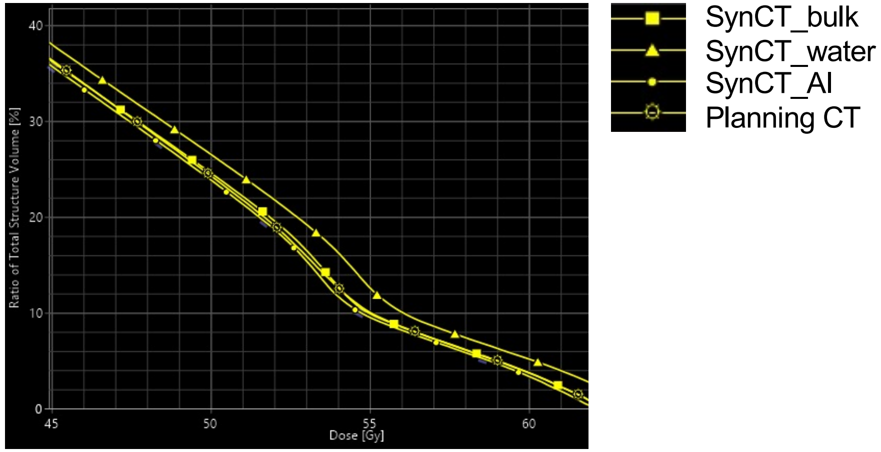
Methods:

- Image synthesis (CT from MR) using DL: “synthetic CT”
- Compare to ”standard” methods
- Perform dose calculation through all methods



Results

- CT0, CTpop, CTstrat and SynCT introduced ***maximum absolute errors of <1%*** into DVH-based rectal bleeding risk prediction.
- ***Rectal dose toxicity risk predictions were unaffected in all cases***.



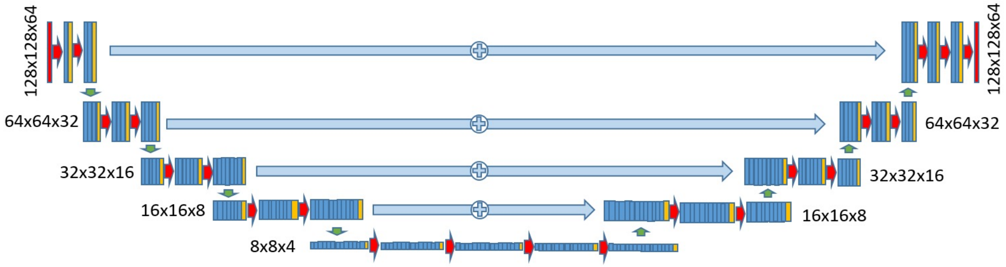
Implication:

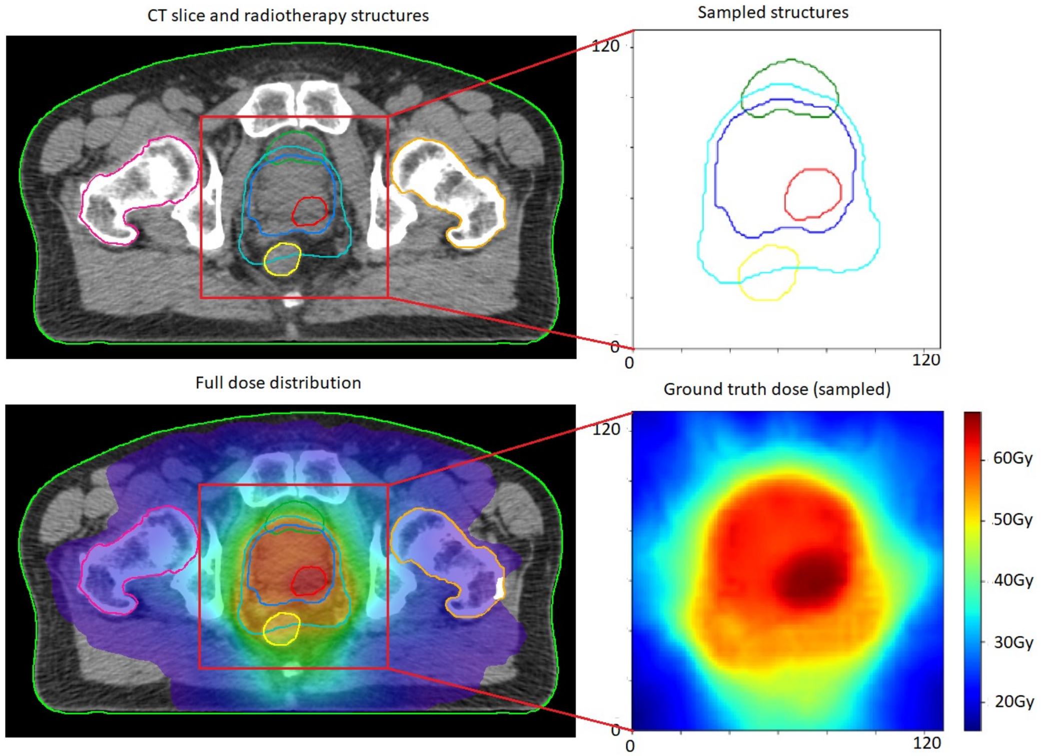
- Can use either SynCT methods to predict toxicity from DVHs
- DL-based method much faster, automatic

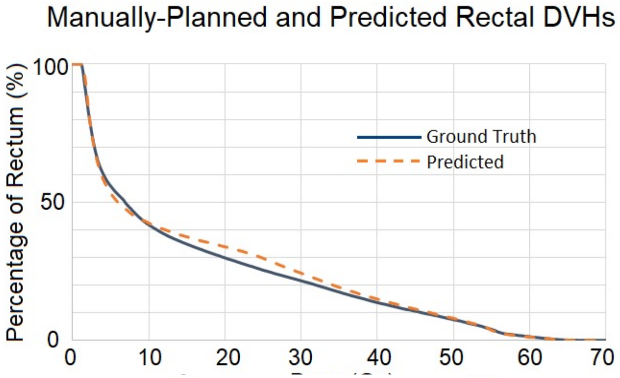
MR+DL guided radiotherapy in prostate cancer

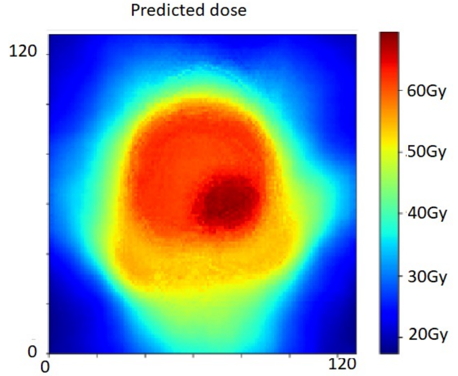
Precision radiotherapy requires precision image guidance

Simulation study:
“Boost”-radiotherapy to tumours – minimize dose to organs at risk (rectal wall)
Complicated planning -> use AI









MR imaging pipeline

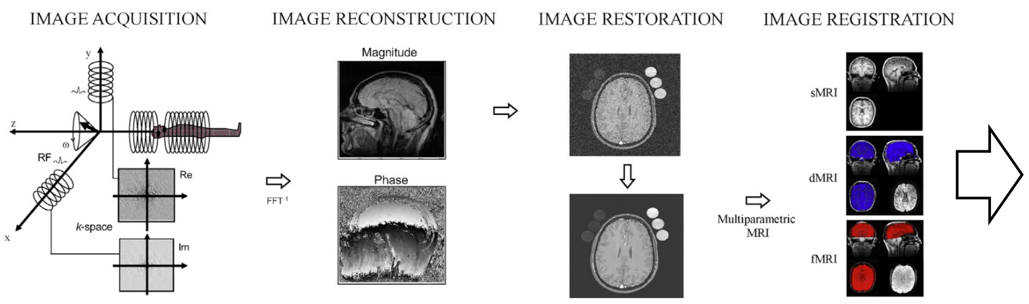


IMAGE ANALYSIS

- object segmentation
- disease detection,
- disease prediction
- image registration
- image synthesis
- ...

MR imaging pipeline

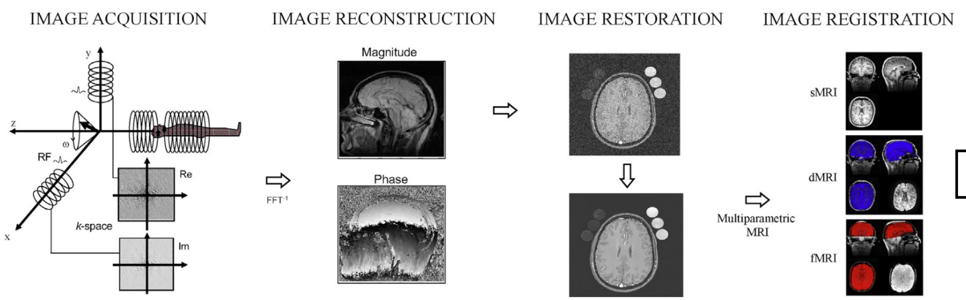


IMAGE ANALYSIS

- object segmentation
- disease detection,
- disease prediction
- image registration
- image synthesis
- ...

IMAGE INFORMATION INTEGRATION

- systems based on images and text data
- radpath
- ...

MORE IMAGE PROCESSING

- image registration
- motion correction
- artifact detection
- extracting quantitative biomarkers
- ....

WORKFLOW OPTIMIZATIONS

- protocol optimization
- Gd dose reduction
- radiotherapy
- PET/MR attenuation correction

NEW BIOMARKERS / THERAPY APPROACHES

- radiomics
- theranostics
- ....

Challenges, limitations and future perspectives

- Deep learning may yield unstable methods for image reconstruction
  - Tiny perturbations in the sampling domain may result in severe artefacts in the reconstruction;
  - a small structural change, for example, a tumor, may not be captured in the reconstructed image
  - ...
- data (Most current work on deep learning for medical data analysis use either open, or local (and thus very small number) anonymized data sets)
  - → (federated learning, transfer learning, augmenting, data synthesis, more data efficient networks, attention mechanisms)
- lack of mathematical and theoretical underpinnings, issues of trust, interpretability → Bayesian Deep Learning
- still behind on workflow integration, and regulations
- hype around DL: chance to strengthen the general computational mindset among medical researchers and practitioners, mainstreaming the field of *computational medicine*
- facilitate the transition towards **p**redictive, **p**reventive, **p**ersonalized, and **p**articipatory – P4 medicine

References

Imaging biomarkers
- Dregely I, et al. Imaging biomarkers in oncology: Basics and application to MRI. J. Magn. Reson. Imaging 2018;48:13–26. doi: 10.1002/jmri.26058.

DL in Medical imaging overview:
- A.S. Lundervold, A. Lundervold / Z Med Phys 29 (2019) 102–127
- Litjens G, et al. A survey on deep learning in medical image analysis. Med. Image Anal. 2017;42:60–88. doi: 10.1016/j.media.2017.07.005.
- Rueckert D, Glocker B, Kainz B. Learning clinically useful information from images: Past, present and future. Med. Image Anal. 2016;33:1339–1351. doi: 10.1016/j.media.2016.06.009.

DL in image reconstruction
- Zhu B, et al. Image reconstruction by domain-transform manifold learning. Nature 2018;555:487–492. doi: 10.1038/nature25988.
- Chen F, et al. Variable-Density Single-Shot Fast Spin-Echo MRI with Deep Learning Reconstruction by Using Variational Networks. Radiology 2018;289. doi: 10.1148/radiol.2018180445.
- Knoll F, et al Assessment of the generalization of learned image reconstruction and the potential for transfer learning. Magn. Reson. Med. 2018:1–13. doi: 10.1002/mrm.27355.
- Hammernik K, et al. Learning a Variational Network for Reconstruction of Accelerated MRI Data. 2017;3071:3055–3071. doi: 10.1002/mrm.26977.

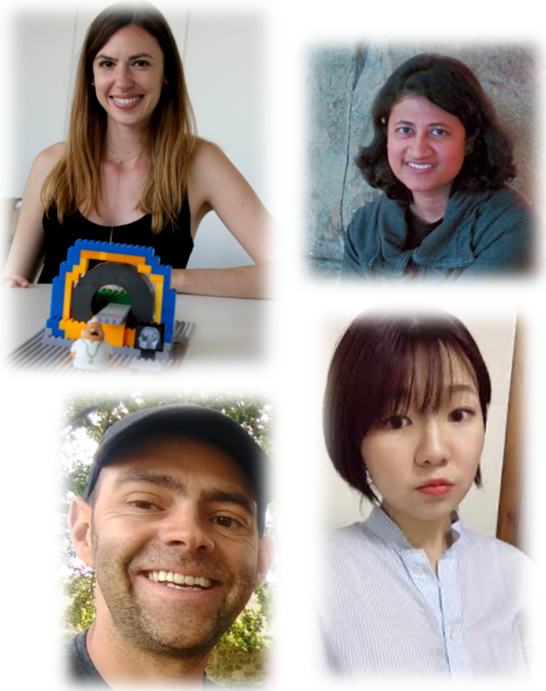
U-Net
- Ronneberger O., et al. U-Net: Convolutional Networks for Biomedical Image Segmentation. MICCAI 2015. Lecture Notes in Computer Science, vol 9351 https://doi.org/10.1007/978-3-319-24574-4_28
- 5-minute teaser video on U-Net https://lmb.informatik.uni-freiburg.de/people/ronneber/u-net/

nnU-Net
- Isensee F, et al. nnU-Net: a self-configuring method for deep learning-based biomedical image segmentation. Nat. Methods 2021;18:203–211. doi: 10.1038/s41592-020-01008-z.
- nnU-Net’s source code is available on GitHub (https://github. com/MIC-DKFZ/nnUNet).

Research Examples
- Gu R, ,... Dregely I, Goh V. Dual Energy CT Assessment of Skeletal Bone Marrow Involvement in Multiple Myeloma. Oral presentation, European Congress of Radiology Conf. Proc. 2021
- Gu R, ..., Dregely I, Goh V. Using Uncertainty Estimation to Increase the Robustness of Bone Marrow Segmentation in T1-weighted Dixon MRI for Multiple Myeloma. ISMRM Conf Proc. 2021
- Thomas C, Dregely I, et al. Deep Learning For Rectal Spacer Stratification In Prostate Boost Radiotherapy. Radiother Oncol. 2020;152:S188
- Thomas C, Dregely I, et al. Effect Of Pseudoct Methods On Dose-Derived Rectal Toxicity Prediction In Mr-Only Prostate Rt. Radiother Oncol. 2020;152:S973– 4

Thank you:

@ King's biomedical engineering Dept:
Elisa Roccia
Rohini Shankar
Christopher Thomas
Renyang Gu



@ King's Cancer Imaging Dept:
Vicky Goh
Sally Barrington
Gary Cook

@ Siemens:
Radhouene Neji

Funding by:

KING'S College LONDON

KING'S HEALTH PARTNERS
Pioneering better health for all

EPSRC
Pioneering research and skills

SIEMENS Healthineers

UK Research and Innovation

Contact details for more information:

isabel.dregely@technikum-wien.at

FH University of Applied Sciences TECHNIKUM WIEN