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Deep Learning Methods for Medical Image Analysis

Junyu Chen

Mar. 2022

About Me

- Ph.D. candidate at Johns Hopkins University (5th year + M.Sc.)
- Research assistant in the Radiological Physics Division
- Research interest:
  - Image analysis and deep learning applied to nuclear medicine imaging
- Personal website:
  - https://junyuchen245.github.io/

Johns Hopkins Whiting School of Engineering
Johns Hopkins Medicine

Outline

- Image registration
  - Current methods
  - Instance-specific optimization
  - Transformers
- Image segmentation
  - Current methods
  - Supervised, unsupervised, and semi-supervised learning
- Image denoising
  - Network fine-tuning and incremental learning

Outline

- **Image registration**
  - Current methods
  - Instance-specific optimization
  - Transformers
- Image segmentation
  - Current methods
  - Supervised, unsupervised, and semi-supervised methods
- Image denoising
  - Network fine-tuning and incremental learning

Image Registration

- Affine transformation or rigid registration
  - Estimates an optimal geometric transformation that aligns the coordinates of two images
- Deformable image registration
  - Establishes spatial correspondence to minimize the differences between a pair of images

[1] Sadik et al., 2009

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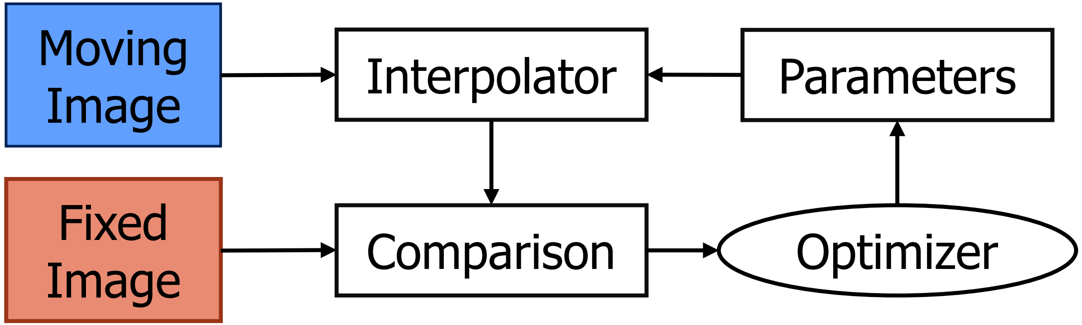

Classical Methods

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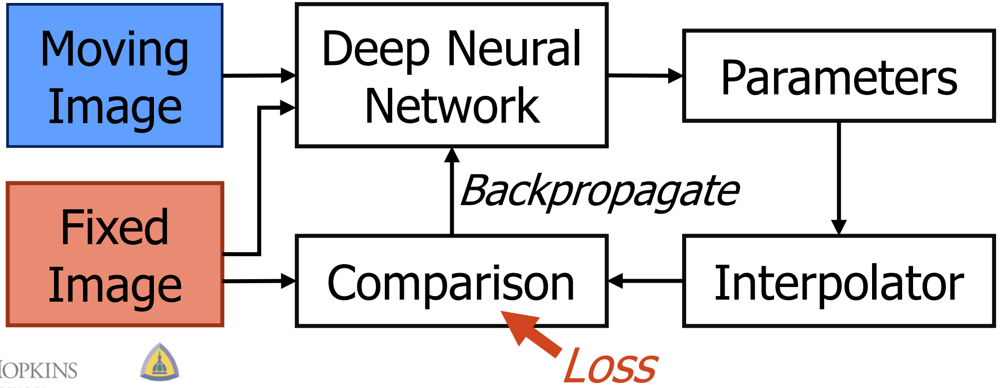

Deep Learning

Image Registration

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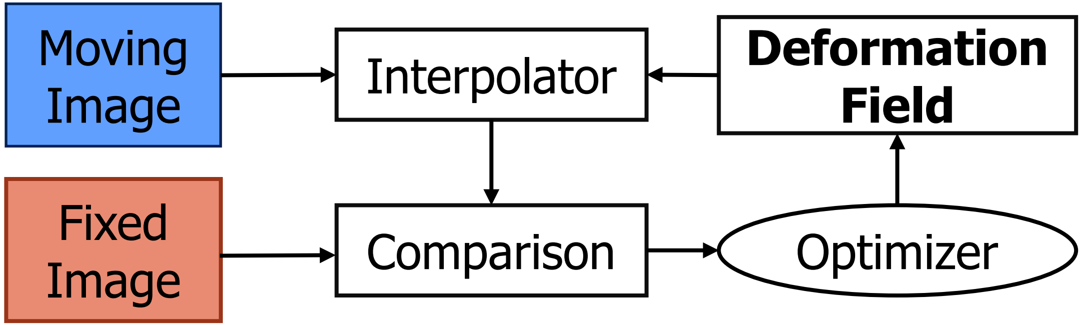

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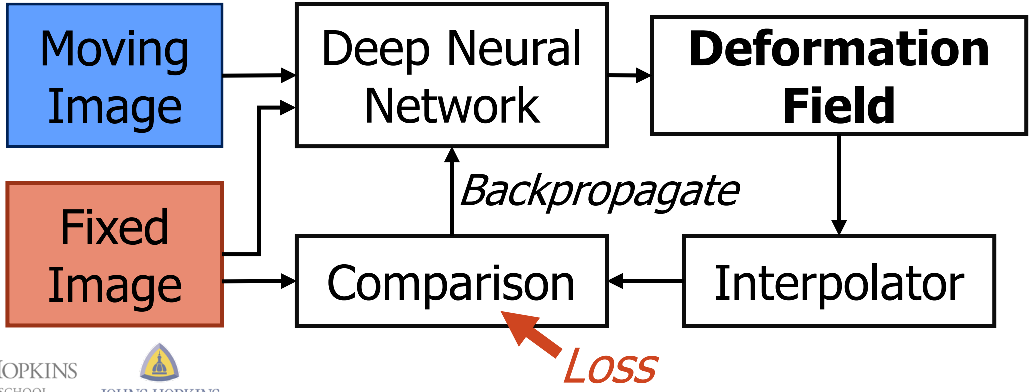


Deep Learning

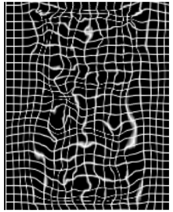
Deformable Image Registration

- DIR energy function (or loss function):
  - $E(I_f, I_m, \phi) = E_{sim}(I_f, I_m \circ \phi) + \lambda R(\phi)$
  - I_f – Fixed Image
  - I_m – Moving Image
  - ϕ – Deformation field
  - $E_{sim}(I_f, I_m \circ \phi)$ – Image similarity measurement
  - $R(\phi)$ – Deformation field regularization

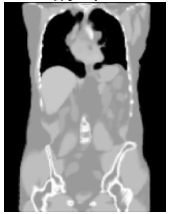
XCAT, I_m

CT, I_f

Deformation Field ϕ



Deformed XCAT, $I_m \circ \phi$



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  - $E_{sim}(I_f, I_m \circ \phi)$ – **Image similarity measurement**
  - $R(\phi)$ – Deformation field regularization

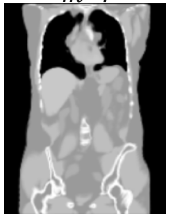
Determines the visual difference between the fixed image and the deformed moving image

$MSE: |I_f - I_m \circ \phi|^2$

CT, I_f

$-$

Deformed XCAT, $I_m \circ \phi$



$|\ \ |^2$

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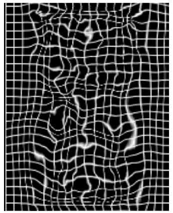
Deformable Image Registration

- DIR energy function (or loss function):
  - $E(I_f, I_m, \phi) = E_{sim}(I_f, I_m \circ \phi) + \lambda R(\phi)$
  - $E_{sim}(I_f, I_m \circ \phi)$ – Image similarity measurement
  - $R(\phi)$ – **Deformation field regularization**
    - Controlled by λ

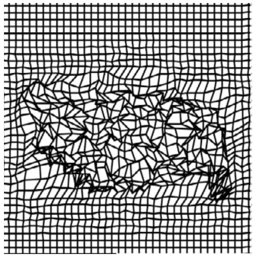
Enforces a smooth deformation field

Diffusion: $|\nabla \phi|^2$

$\Big| \nabla$ Deformation field, ϕ



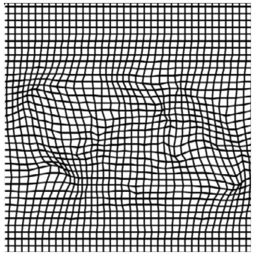
$\Big|^2$



No regularization

$\lambda = 0$

vs



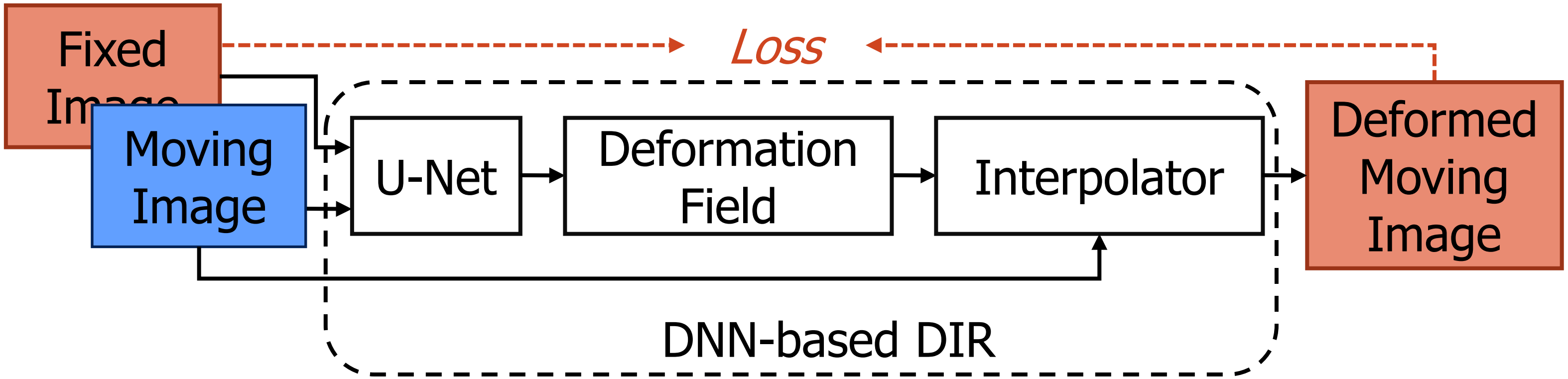
$\lambda \neq 0$

Deformable Image Registration

- Traditional DIR algorithms optimize the energy function $E\left(I_f, I_m, \phi\right)$ iteratively
  - Requires an optimization for each given image pair
    - Slow in practice, especially for 3D images
  - Operates in a small parameter space
- DNN-based models
  - Minimize a global loss function for a training dataset
  - Fast during testing
  - Accurate
  - Operate in a large parameter space (typically > 1 million parameters)

Current Learning-Based DIR Methods

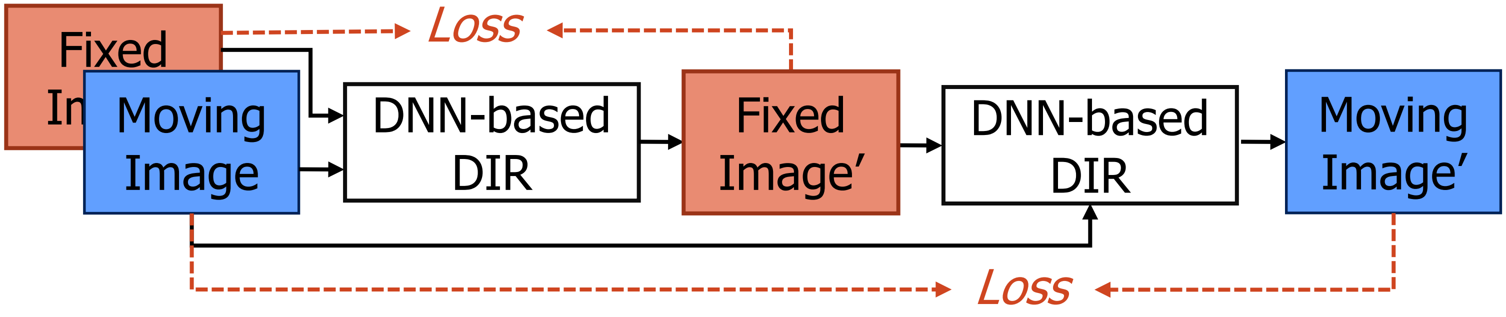
- VoxelMorph [1]:
  - U-Net
  - End-to-end unsupervised training



[1] Balakrishnan et al., 2019

Current Learning-Based DIR Methods

- CycleMorph [1]:
    - Two U-Nets
    - Cycle-consistent training
    - End-to-end unsupervised



[1] Kim et al., 2021

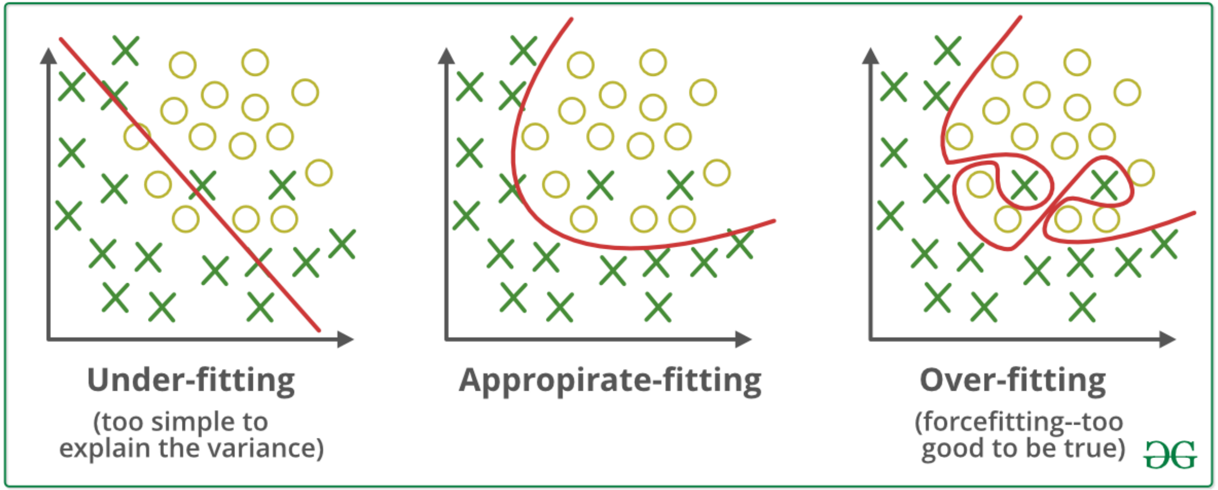
Proposed Methods

- Instance-specific optimization
  - **Chen, Junyu**, et al. "Generating anthropomorphic phantoms using fully unsupervised deformable image registration with convolutional neural networks." *Medical physics* 47.12 (2020): 6366-6380.
- Self-supervised learning via Transformers
  - **Chen, Junyu**, et al. "ViT-V-Net: Vision Transformer for Unsupervised Volumetric Medical Image Registration." *Medical Imaging with Deep Learning*. 2021.
  - **Chen, Junyu**, et al. "TransMorph: Transformer for unsupervised medical image registration." arXiv preprint arXiv:2111.10480 (2021).

[1] Kim et al., 2021

Instance-specific Optimization via DNN

- Training a DNN requires a large training dataset
  - Vast number of trainable parameters
  - Easily overfits a small dataset



Instance-specific Optimization via DNN

- Training a DNN requires a large training dataset
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- However, in image registration
  - Training is unsupervised (we know the ground truth – fixed image!)
  - Overfitting may aid in improving registration performance

XCAT, I_m

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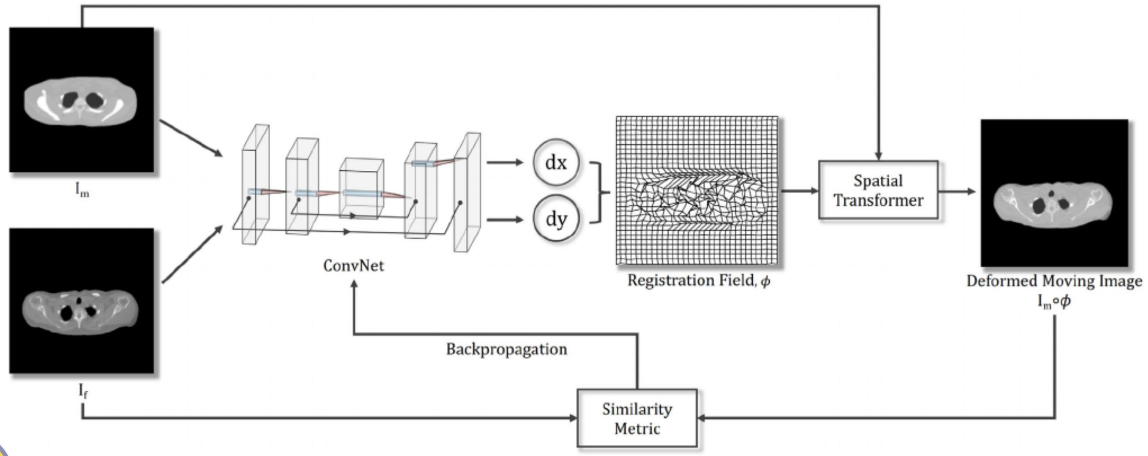
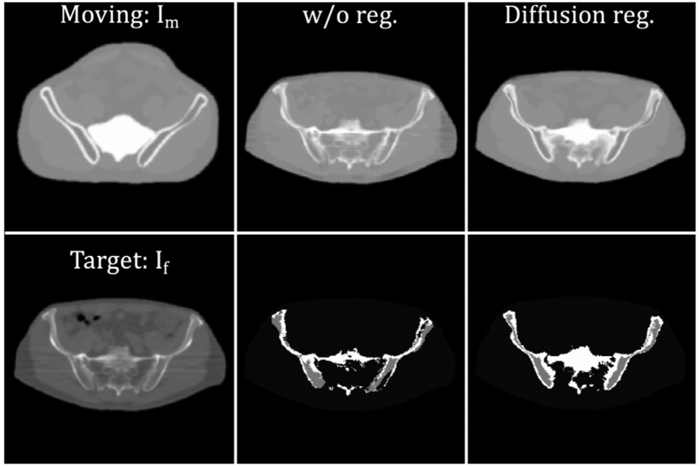
  - Vast number of trainable parameters
  - Easily overfits a small dataset
- However, in image registration
  - Training is unsupervised (we know the ground truth – fixed image!)
  - Overfitting may aid in improving registration performance
- We propose to “train” a DNN on a single image pair
  - Minimize a pair-wise loss function
  - **Instance-specific optimization**

Instance-specific Optimization via DNN

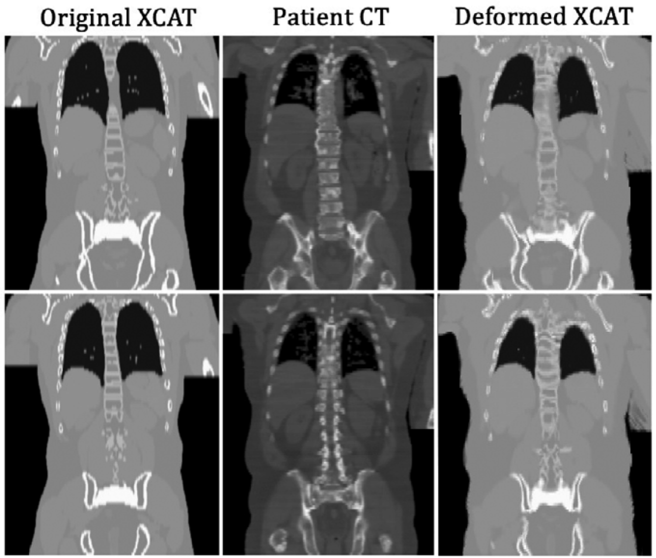
- We treat a convolutional neural net (ConvNet) as an optimization tool:
  - Initialize a new ConvNet for each image pair
  - Minimize a pair-wise loss function → $E(I_f, I_m, \phi) = E_{sim}(I_f, I_m \circ \phi) + \lambda R(\phi)$
  - Update ConvNet's parameters in each iteration



Instance-specific Optimization via DNN



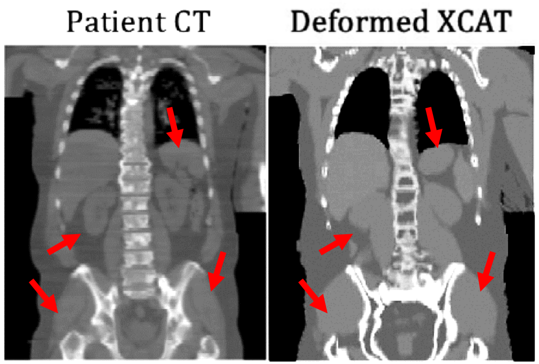
Regularization vs without regularization



Two example coronal slices of the original XCAT, clinical CT, and the deformed XCAT

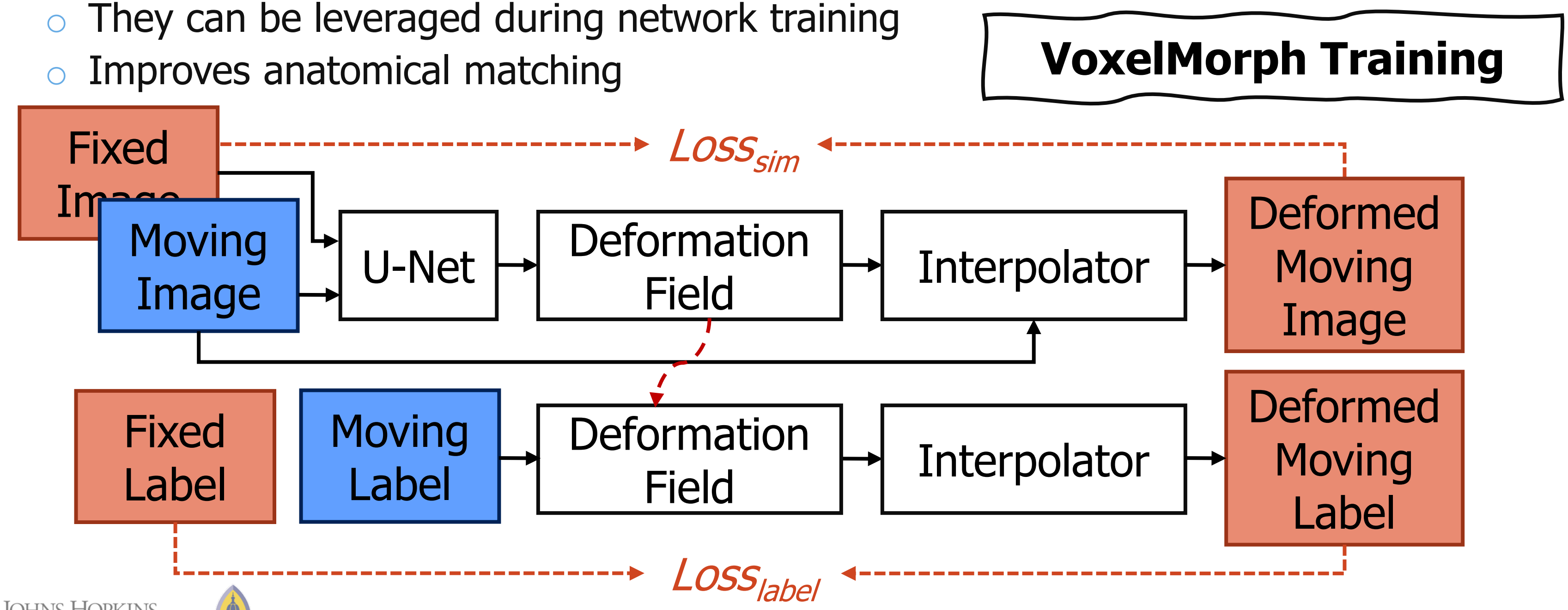
Instance-specific Optimization via DNN

- **Advantage**:
  - Can be used when dataset is small
  - No training is needed
  - Good registration accuracy
- **Disadvantage:**
  - Slow in practice
    - An optimization is needed for each pair
  - Cannot ensure a precise anatomical matching
    - Especially, in regions with low contrast



Self-supervised learning via DNN

- If the anatomical labels are available
  - They can be leveraged during network training
  - Improves anatomical matching

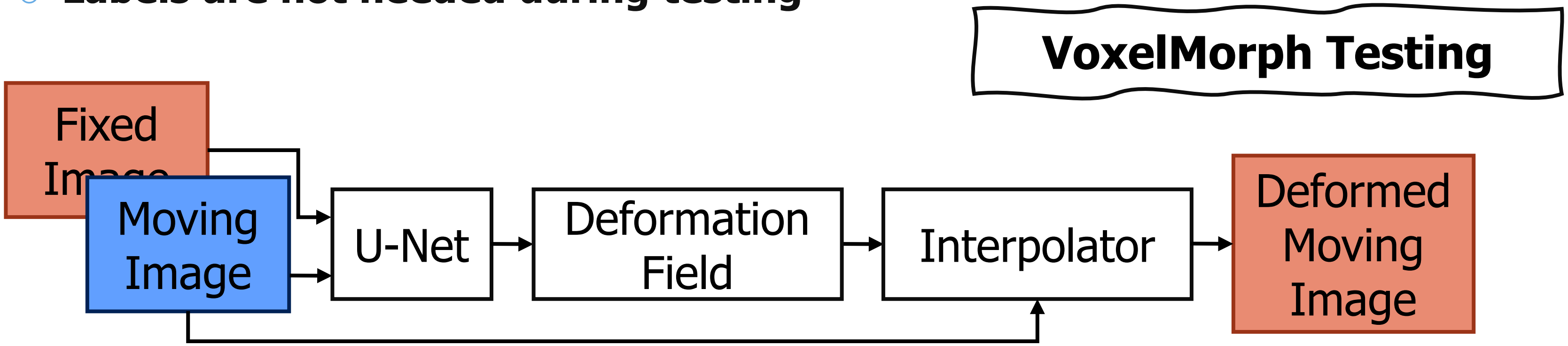


Self-supervised learning via DNN

- If the anatomical labels are available
  - They can be leveraged during network training
  - Improves anatomical matching
- Overall loss function:
  - $\mathcal{L}\left(I_f, I_m, \phi\right) = \mathcal{L}_{sim}\left(I_f, I_m \circ \phi\right) + \mathcal{L}_{seg}\left(S_f, S_m \circ \phi\right) + \lambda R(\phi)$
  - S_f, S_m: Anatomical labels of fixed and moving images
  - $\mathcal{L}_{seg}$: Dice loss

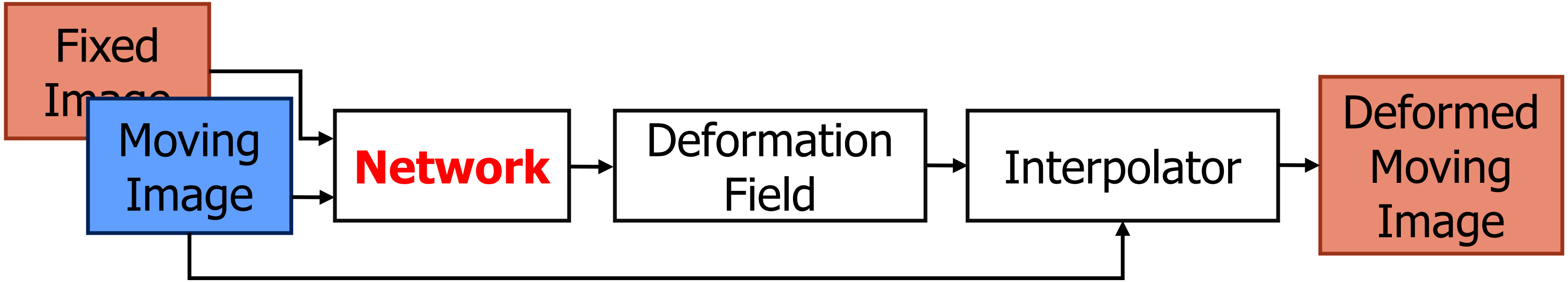
Self-supervised learning via DNN

- If the anatomical labels are available
  - They can be leveraged during network training
  - Improves anatomical matching
  - **Labels are not needed during testing**



ConvNet vs Transformers

- For details, please refer to:
  - **Chen, Junyu**, et al. "ViT-V-Net: Vision Transformer for Unsupervised Volumetric Medical Image Registration." *Medical Imaging with Deep Learning*. 2021.
  - **Chen, Junyu**, et al. "TransMorph: Transformer for unsupervised medical image registration." arXiv preprint arXiv:2111.10480 (2021).



ConvNet vs Transformers

- Most of the existing DNN-based registration methods use U-Net
- Problems with U-Net (or ConvNets in general)
  - Limited receptive field
  - The sizes of the receptive fields increase with the number of layers

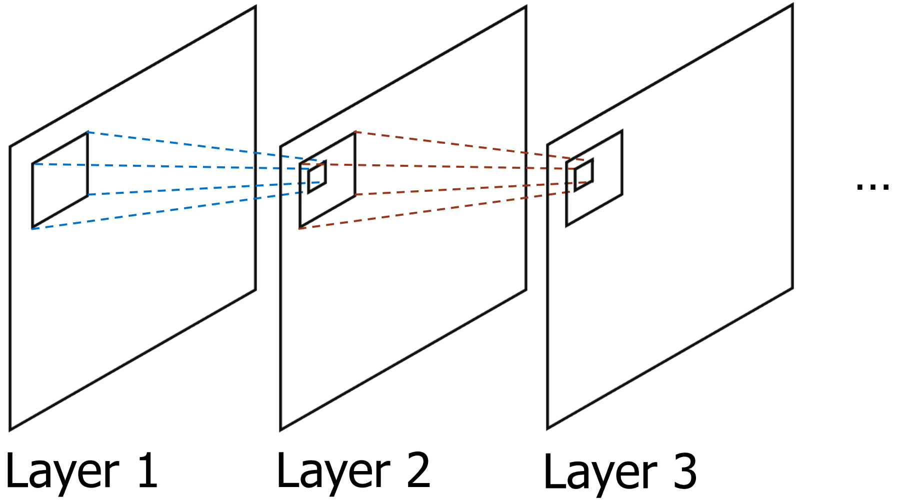


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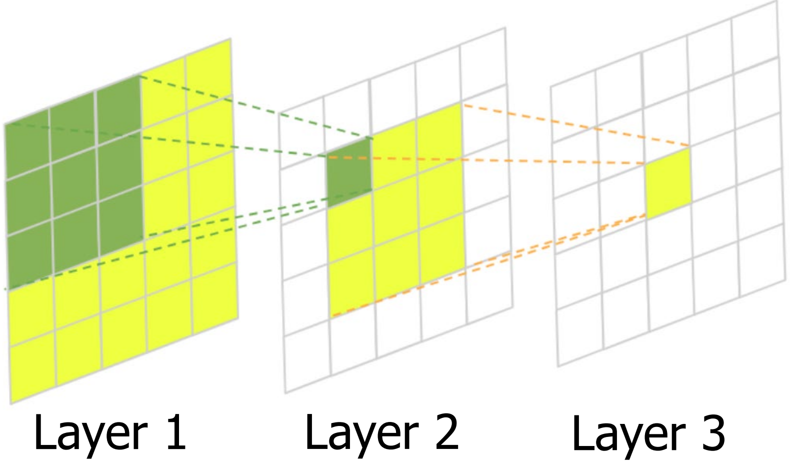
Image credit: https://www.baeldung.com/cs/cnn-receptive-field-size

Theoretical Receptive Field:

$$\sum_{i=1}^{L}\left((k_i - 1)\prod_{j=1}^{l-1} s_j\right) + 1$$

Layer 1: 3
Layer 2: (3-1)+(3-1)+1=5
Layer 3: (3-1)+(3-1)+(3-1)+1=7



ConvNet vs Transformers

- U-Net

Small receptive fields

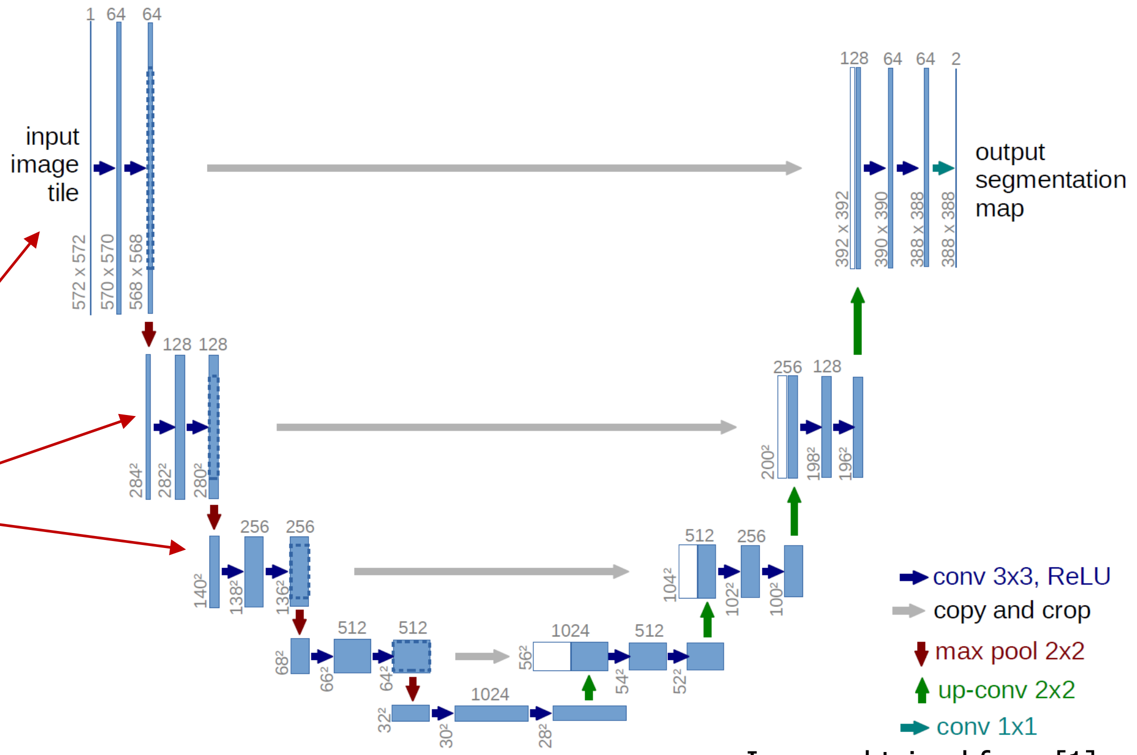
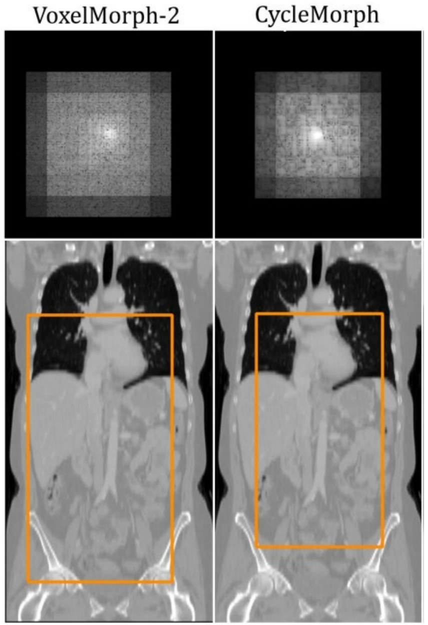


Image obtained from [1]

[1] Ronneberger et al., 2015

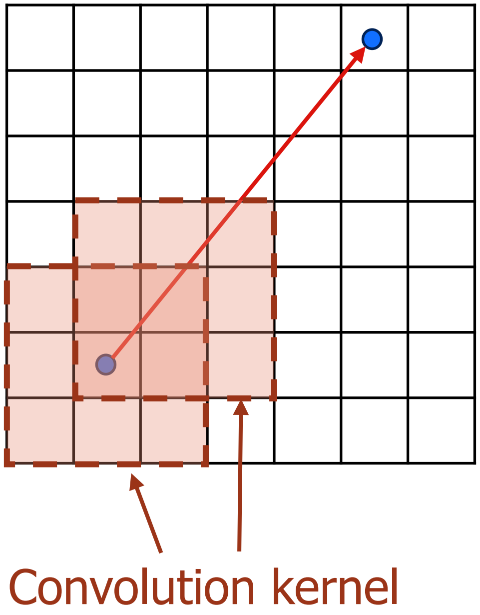
ConvNet vs Transformers

- U-Net
  - Effective receptive field of the entire network is still smaller than the image



ConvNet vs Transformers

- U-Net
  - Difficult to model long-range spatial relationship (at least in the first several layers)



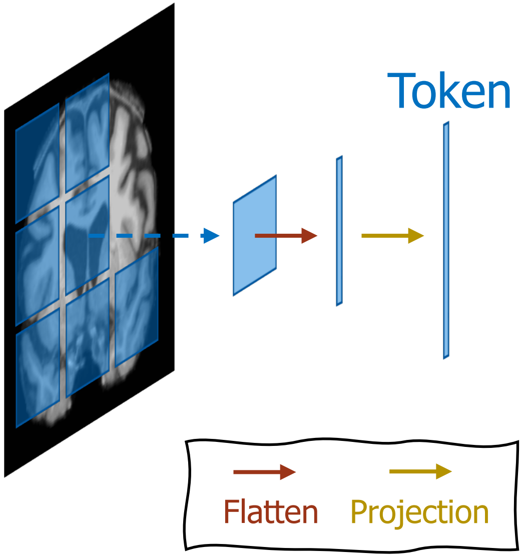
ConvNet vs Transformers

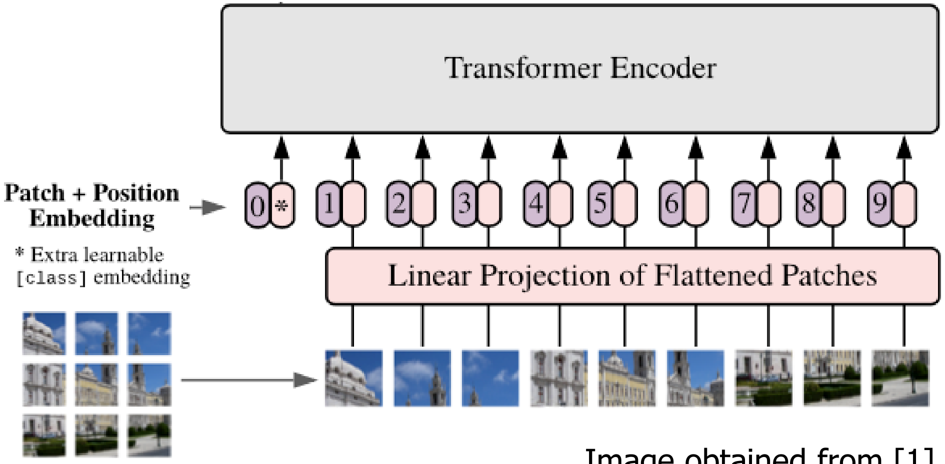
- Transformers
  - Originated from NLP
  - Adapted to computer vision tasks by Google:
    - Vision Transformer [1]
  - Have shown promising performances for medical imaging tasks:
    - https://github.com/junyuchen245/Transformer_for_medical_image_analysis
  - Self-attention mechanism
    - Large receptive field (spans over the entire image) for each layer

[1] Dosovitskiy et al., 2020

ConvNet vs Transformers

- Transformers





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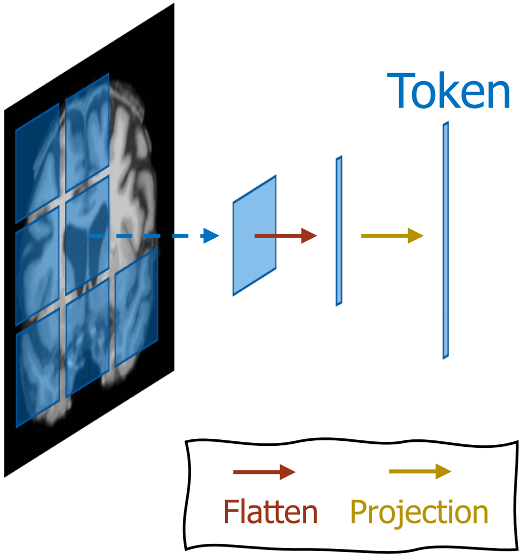
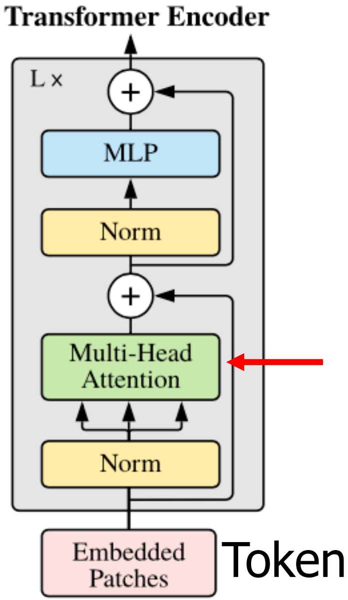
[1] Dosovitskiy et al., 2020

ConvNet vs Transformers

- Transformers





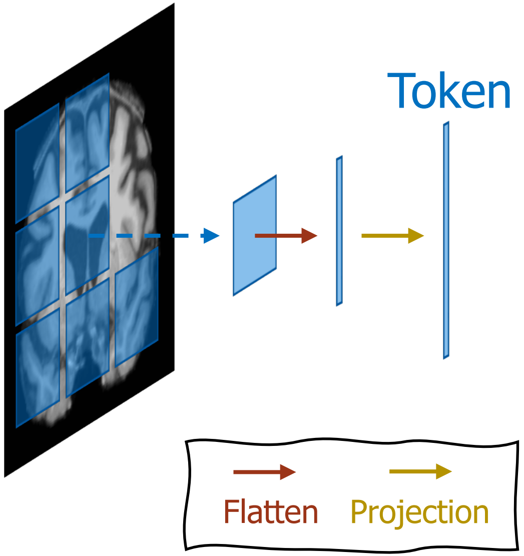
Tokens

Image obtained from [1]

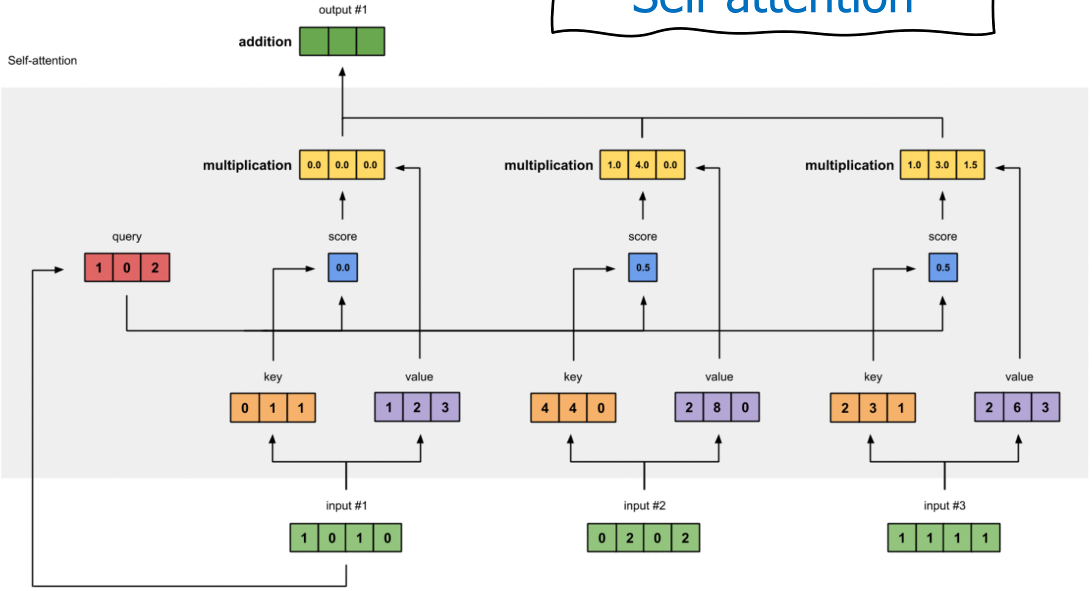
[1] Dosovitskiy et al., 2020

ConvNet vs Transformers

- Transformers



Self-attention



Token 1 Token 2 Token 3

Image credit: https://towardsdatascience.com/illustrated-self-attention-2d627e33b20a

ConvNet vs Transformers

- Transformers

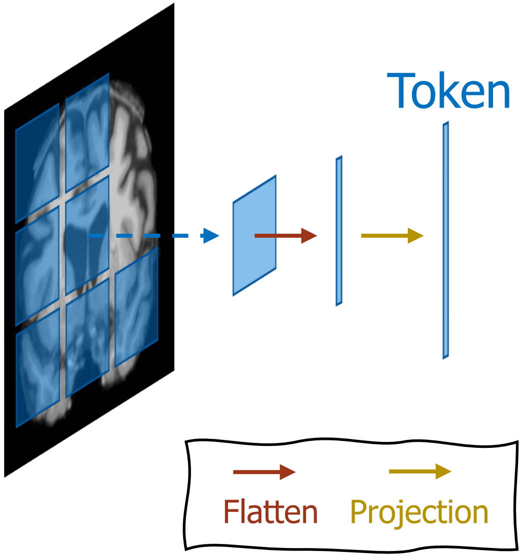
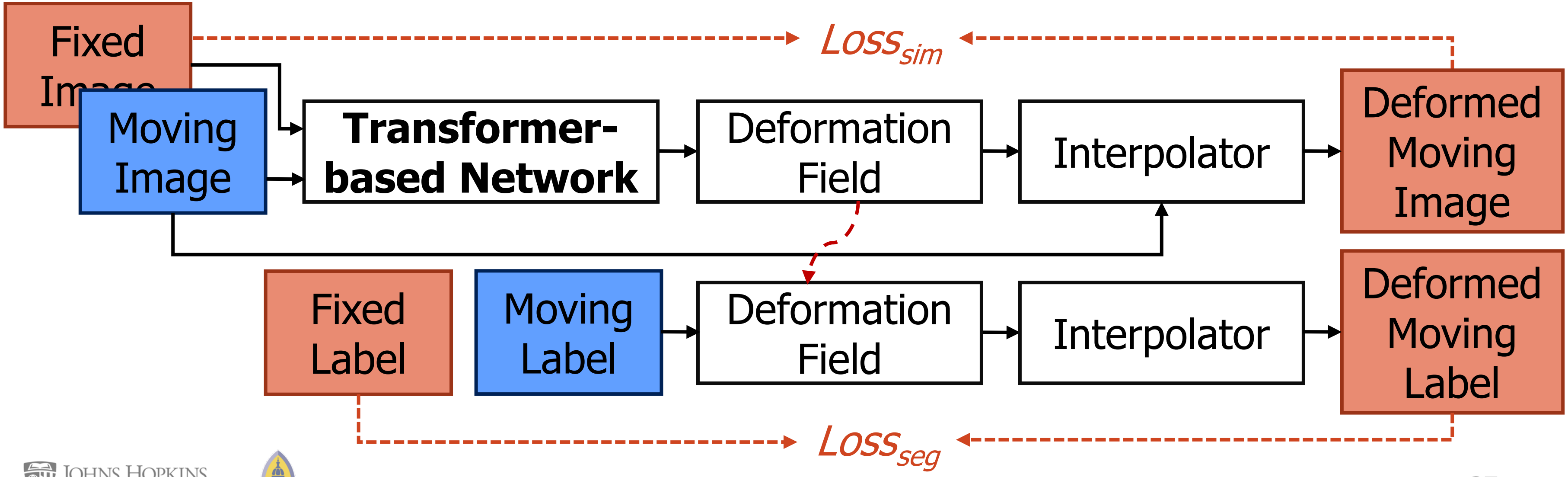


Image credit: https://towardsdatascience.com/self-attention-in-computer-vision-2782727021f6

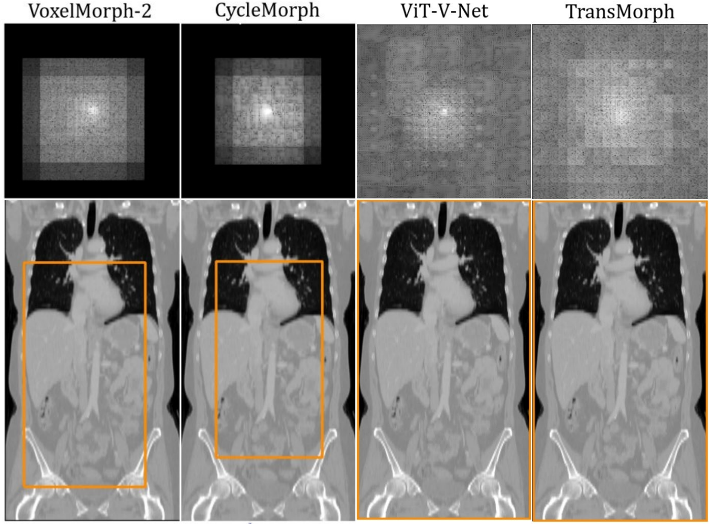
Tranformer for medical image registration

- We proposed two network architectures for image registration:
  - ViT-V-Net [1]
  - TransMorph [2]



Tranformer for medical image registration

- We proposed two network architectures for image registration:
  - Large receptive field
  - State-of-the-art performance



Model	DSC	% of $\lvert J_\phi \rvert \leq 0$
Affine	0.386±0.195	-
SyN	0.639±0.151	<0.0001
NiftyReg	0.640±0.166	<0.0001
LDDMM	0.675±0.135	<0.0001
deedsBCV	0.733±0.126	0.147±0.050
VoxelMoprh-1	0.723±0.130	1.590±0.339
VoxelMoprh-2	0.726±0.123	1.522±0.336
VoxelMorph-diff	0.577±0.165	<0.0001
CycleMorph	0.730±0.124	1.719±0.382
MIDIR	0.736±0.129	<0.0001
ViT-V-Net	0.728±0.124	1.609±0.319
PVT	0.721±0.128	1.858±0.314
CoTr	0.729±0.135	1.292±0.342
nnFormer	0.740±0.134	1.595±0.358
TransMorph-Bayes	*0.746±0.123*	1.560±0.333
TransMorph-diff	0.599±0.156	<0.0001
TransMorph-bspl	**0.752±0.128**	<0.0001
TransMorph	0.746±0.128	1.579±0.328

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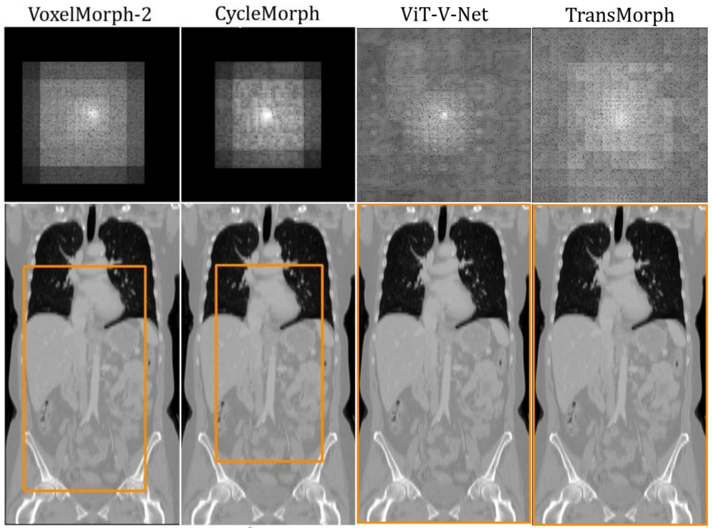

Task 3 Validation Leaderboard

Search:

Additional metrics Show all metrics

#	User (Team)	Created	--Task 3--- DICE	Comment	Publication	Algorithm Description
1st	jchen245	18 Feb. 2022	0.8623 ± 0.0144	TransMorph-Large		
2nd	cwmokab	19 Sept. 2021	0.8610 ± 0.0148	Docker_submission		
3rd	han-sie (Challenge Organizers)	13 Nov. 2021	0.8464 ± 0.0159	task03 convexAdam nnUNet3_01		
4th	hanluyi4869 (3idiots)	12 Sept. 2021	0.8410 ± 0.0139	final simple submission		
5th	ericchan000	3 Feb. 2022	0.8381 ± 0.0127	test_5		
6th	mattiaspaul (Challenge Organizers)	12 Nov. 2021	0.8368 ± 0.0167	ConvexAdam nnUNet		
7th	IWM	13 Sept. 2021	0.8282 ± 0.0141	Exp6		
8th	neighbor_wang (Driver)	20 Aug. 2021	0.8271 ± 0.0131	PCNet_v2		
9th	VIDAR (VIDAR)	21 Aug. 2021	0.8133 ± 0.0203	I am so vegetable		
10th	svesal (PIMed)	6 Sept. 2021	0.8102 ± 0.0157	PD_Baseline		

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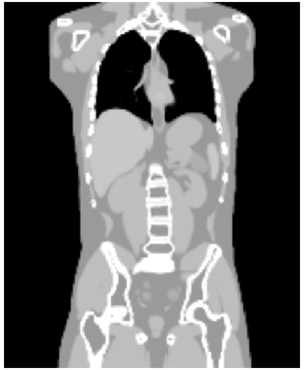
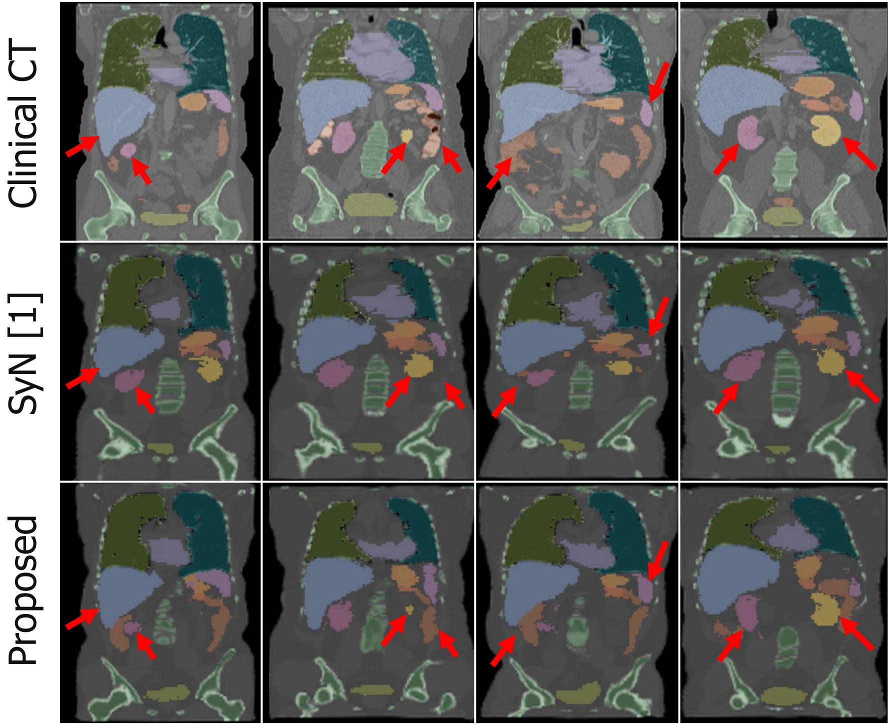
Tranformer for medical image registration

- Qualitative results:
  - Anatomical segmentation superimposed over the input CT and the registration results
  - Input XCAT:





[1] Avants et al., 2008

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- **Image segmentation**
  - Current methods
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Current DNN-based Methods

- **U-Net [1]**
  - Hour-glass shaped encoder and decoder network
- U-Net++ [2]
- nnU-Net [3]

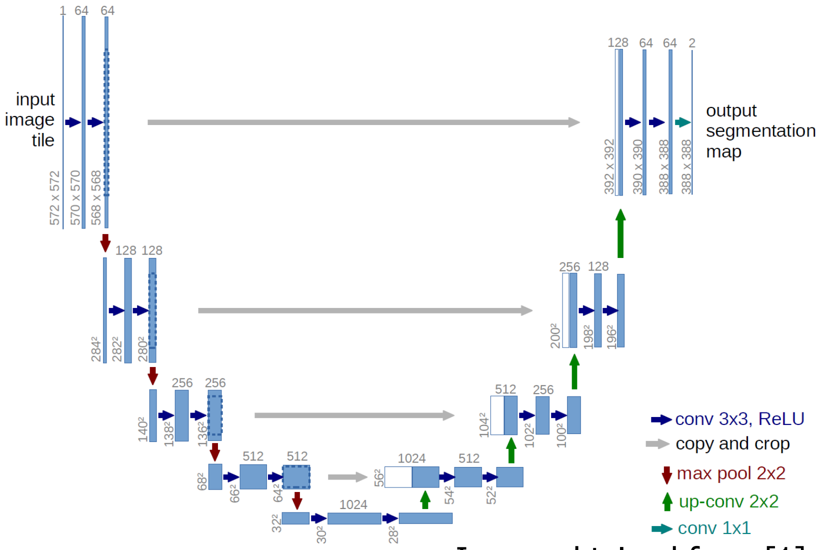


Image obtained from [1]

Current DNN-based Methods

- U-Net [1]
- **U-Net++ [2]**
  - Introduced more skip connections
  - Deep supervision
- nnU-Net [3]

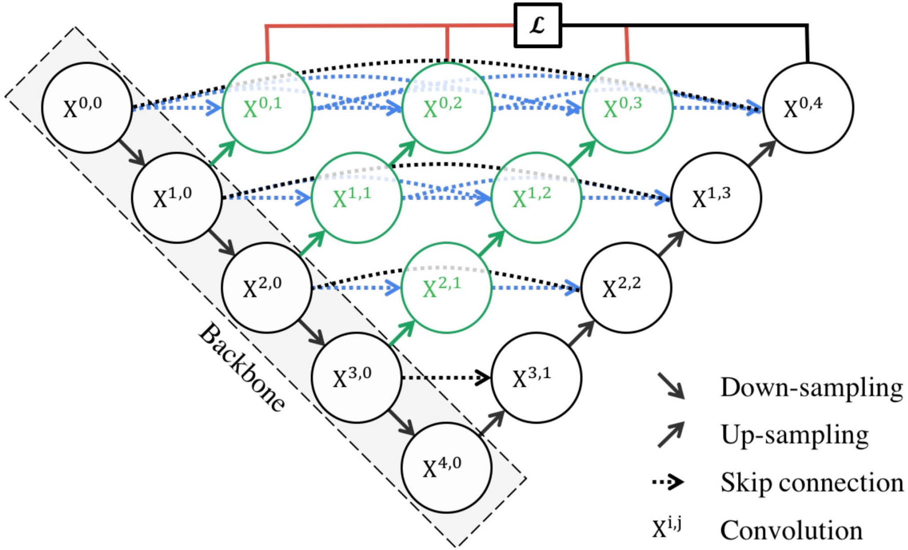


Image obtained from [2]

[1] Ronneberger et al., 2015; [2] Zhou et al., 2018; [3] Isensee et al., 2021

Current DNN-based Methods

- U-Net
- U-Net++
- **nnU-Net [3]**
  - “no new” U-Net
  - Refine preprocessing steps and training hyper-parameters
  - State-of-the-art performances on several publicly available datasets

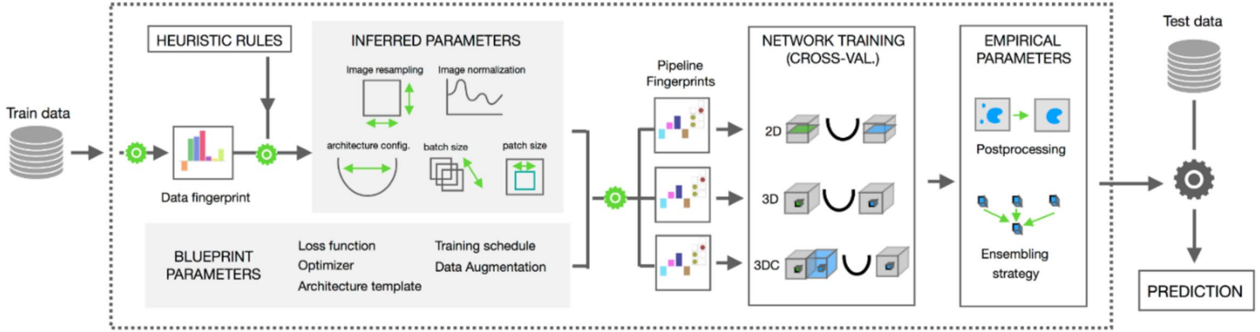


Image obtained from [3]

[1] Ronneberger et al., 2015; [2] Zhou et al., 2018; [3] Isensee et al., 2021

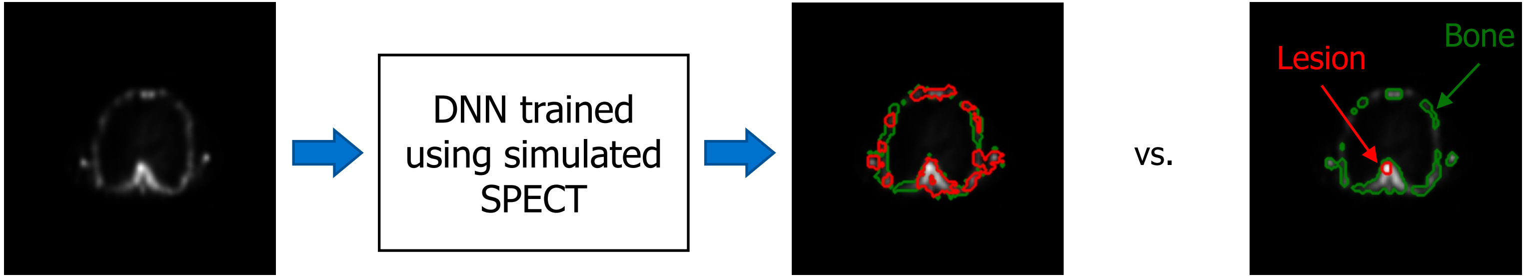
Insufficient Training Data

- Existing supervised DNN-methods
  - Focus on how to improve performance when the amount of training data is large
- There are a lot of publicly available manually annotated datasets for other modalities
  - Brain MRI (BraTS [1])
  - Liver CT, Kindey CT… (LiTS [2], KiTS [3])
- In our application, the training data we have is very limited
  - No public dataset available for NMI

[1] https://www.med.upenn.edu/cbica/brats2020/data.html
[2] https://competitions.codalab.org/competitions/17094
[3] https://kits21.kits-challenge.org/

Insufficient Training Data

- Realistic simulations based on computerized phantoms
  - DNNs trained using simulations did not generalize well on clinical images
  - Known as "domain-shift": clinical and simulated SPECT came from two different (but related) distributions



Clinical SPECT

Output segmentation

Gold-standard segmentation

Domain Adaptation Methods

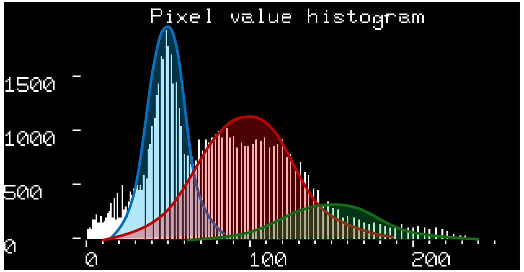
- Domain-shift problem could be alleviated using:
  - Fine-tuning
  - Adversarial domain adaptation
  - …
- These methods usually require a small dataset of images from the new domain (i.e., clinical SPECT)
  - Quantitative bone SPECT is not the standard of care image
  - The clinical images was just enough for evaluation purposes
- **How can we make DNNs more robust?**

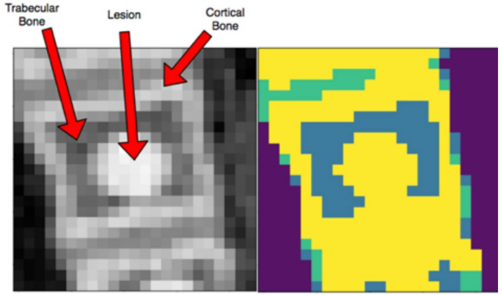
Making DNNs More Robust

- For details, please refer to:
  - **Chen, Junyu**, and Eric C. Frey. "Medical Image Segmentation via Unsupervised Convolutional Neural Network." *Medical Imaging with Deep Learning*. 2020.
  - **Chen, Junyu**, et al. "Learning fuzzy clustering for SPECT/CT segmentation via convolutional neural networks." *Medical physics* 48.7 (2021): 3860-3877.

Rethinking Unsupervised Segmentation

- Clustering methods (**domain insensitive**):
  - They model statistical distributions in intensity values of each given image
  - Difficult to incorporate supervised information (shapes, patterns, etc.)
- Conventional DNN training scheme:
  - Learns shapes and patterns from training dataset
  - Does not carefully consider intensity distributions in images
- Bridging unsupervised methods with deep learning





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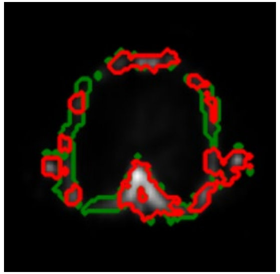
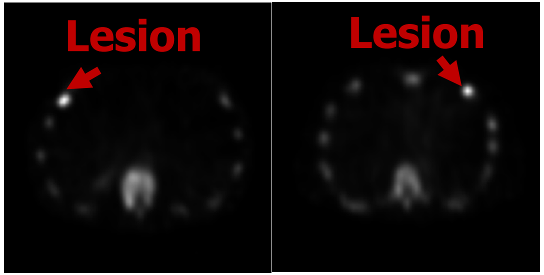
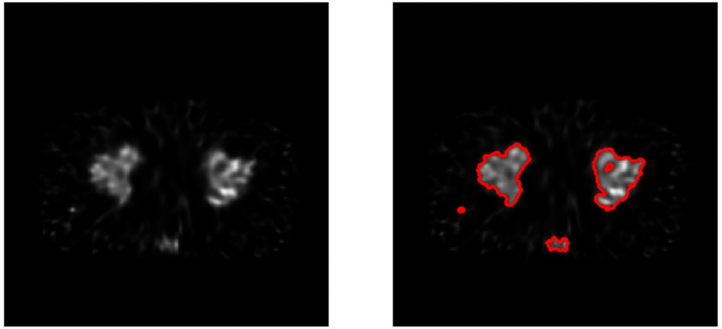




Traditional Unsupervised Methods

- **Active Contour without Edges [1]:**
  - $J_{ACWE} = \mu\text{Length}(C) + \nu\text{Area}\big(inside(C)\big) + \sum_{j\in\boldsymbol{inside}(C)} |y_j - c_1| + \sum_{j\in\boldsymbol{outside}(C)} |y_j - c_2|$
  - μ, ν: Hyper-parameters
  - C: Segmentation contour
  - c_1, c_2: Mean intensity inside and outside the contour
- Classical FCM [2]

Binary segmentation

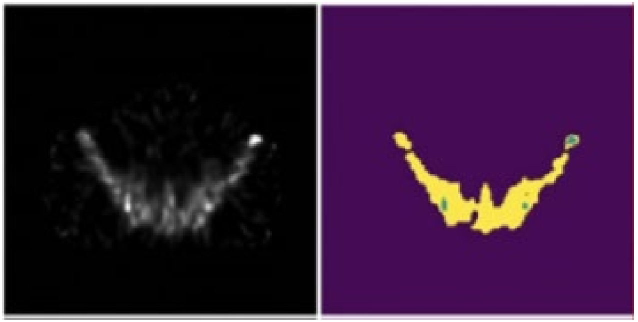


[1] Chan et al., 2001; [2] Bezdek et al., 1984

Traditional Unsupervised Methods

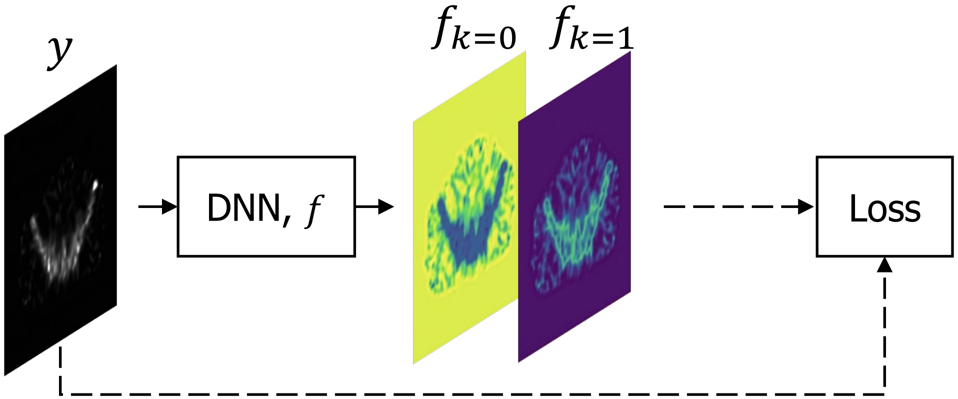
- Active Contour without Edges [1]
- **Classical FCM [2]:**
  - $J_{FCM} = \sum_{j \in \Omega} \sum_{k=1}^{C} u_{jk}^{q} \left\| y_j - v_k \right\|^2$
    - u: membership function
    - q: parameter for controlling fuzzy overlap
    - v_k: class mean
  - Assigning voxels with intensity values close to the class mean v_k with a greater membership value u

Multi-class segmentation



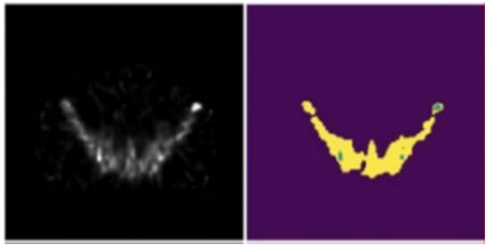
Unsupervised DNN Training

- Apply deep neural networks to solve the objective functions
  - $\mathcal{L}_{ACWE} = \nu \text{Area}(f(\boldsymbol{y};\boldsymbol{\theta}) > 0) + \sum_{j \in f(\boldsymbol{y};\boldsymbol{\theta})>0} |y_j - c_1| + \sum_{j \in f(\boldsymbol{y};\boldsymbol{\theta})<0} |y_j - c_2|$
  - $\mathcal{L}_{FCM} = \sum_{j \in \Omega} \sum_{k=1}^{C} f_{jk}^{q}(\boldsymbol{y};\boldsymbol{\theta}) \left\| y_j - v_k \right\|^2$
  - $f(\boldsymbol{y};\boldsymbol{\theta})$: the output of a network f with parameters $\boldsymbol{\theta}$ and input images $\boldsymbol{y}$

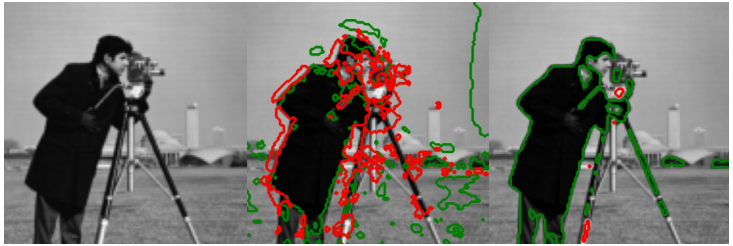


Unsupervised DNN Training

- The unsupervised loss functions are not dependent on ground truth labels (i.e., gold-standard delineations from physicians)
  - Enforces DNNs to learn intensity distributions within the training images
- A simple proof of concept:
  - We trained a DNN with the proposed loss function using the SPECT simulations



The trained DNN applied to a SPECT simulation

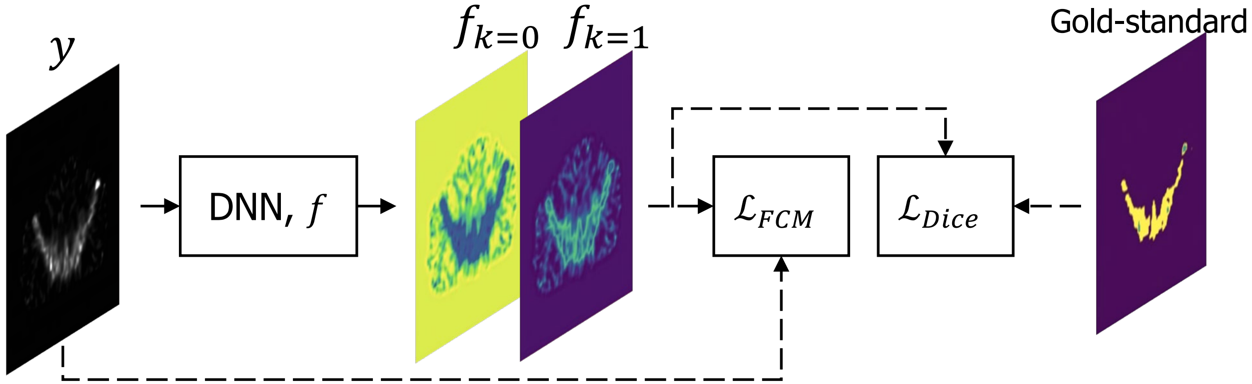


The trained DNN applied to a natural image – a domain that is entirely different from the training dataset

Different domain
Still works!!

Semi-supervised DNN Training

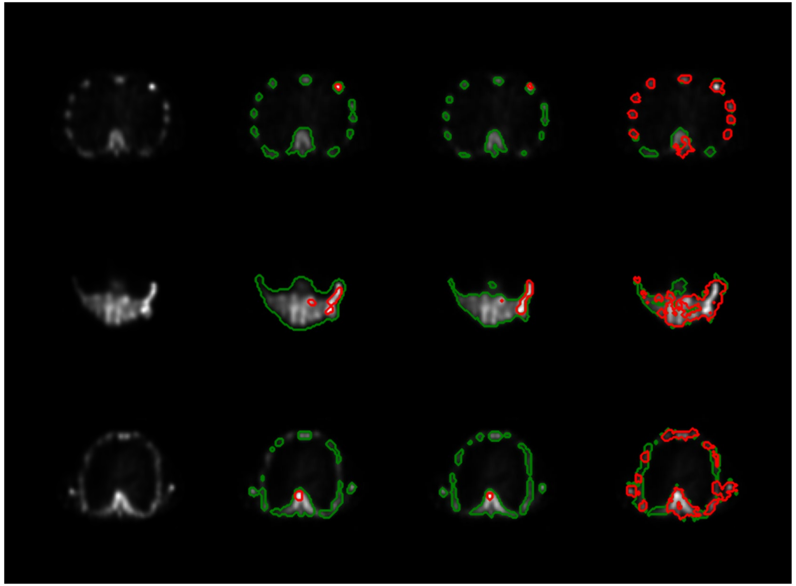
- One step further:
  - Combine the unsupervised loss with a supervised loss to embrace the supervised information from the anatomical labels
  - $\mathcal{L}_{semi-supervised}(\boldsymbol{y};\boldsymbol{\theta}) = \mathcal{L}_{unsupervised}(\boldsymbol{y};\boldsymbol{\theta}) + \alpha\mathcal{L}_{supervised}(\boldsymbol{y};\boldsymbol{\theta})$
  - $\mathcal{L}_{supervised}$ can be any supervised loss functions:
    - Dice, cross-entropy, etc.
  - α: a parameter that controls the degree of supervision



Semi-supervised DNN Training

- Qualitative results:

Input Image | Gold Standard | $\mathcal{L}_{semi-supervised}$ | $\mathcal{L}_{Dice}$



Outline

- Image registration
  - Current methods
  - Instance-specific optimization
  - Transformers
- Image segmentation
  - Current methods
  - Supervised, unsupervised, and semi-supervised methods
- **Image denoising**
  - Network fine-tuning and incremental learning

Image Denoising

- Traditional PET image denoising methods:
    - Post-filtering: Gaussian filters, non-local means with anatomical prior [1]
    - Iterative reconstruction with prior [2]
    - Good performance but computational expensive
        - Energy optimization for each given image

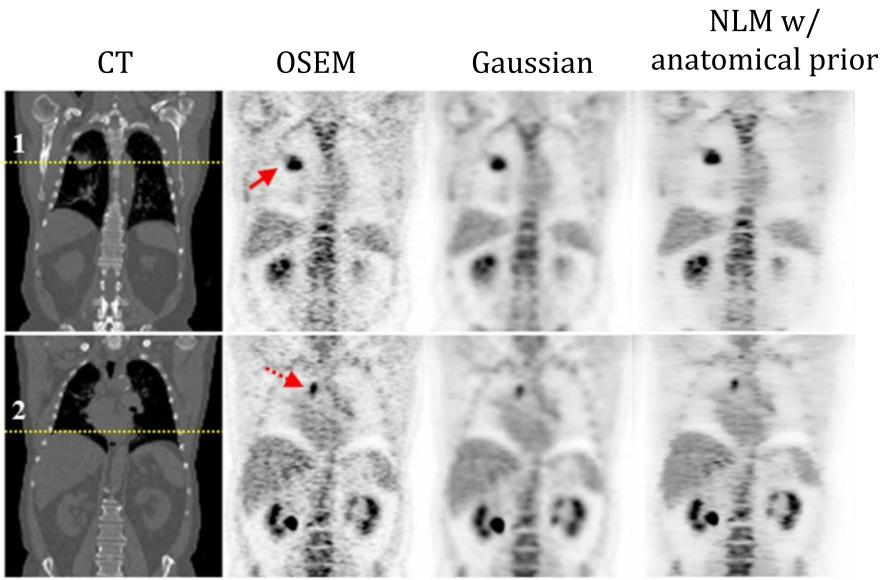
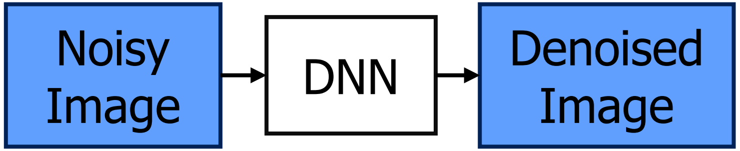


Image obtained from [1]

[1, 2] Chan et al., 2014, 2009

DNN-based Image Denoising

- Deep image prior [1,2]:
  - Unsupervised reconstruction of low-noise image
  - Similar to instance-specific optimization, but early stopping to prevent overfitting
- Denoising convolutional neural networks (DnCNN) [3,4]



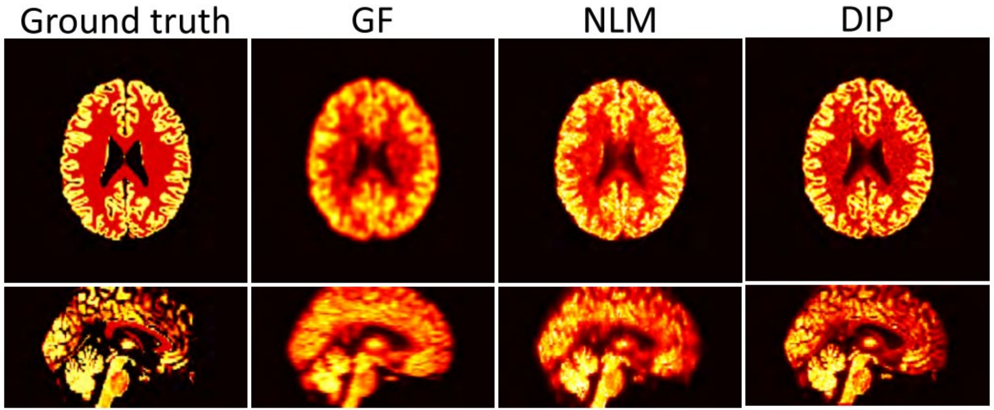


Image obtained from [2]

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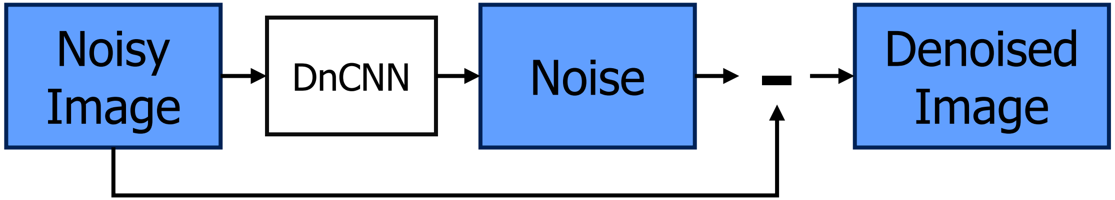
DNN-based Image Denoising

Image obtained from [2]

- Deep image prior [1,2]:
- Denoising convolutional neural networks (DnCNN) [3,4]
  - Predicts noise instead of reconstructing a low-noise image



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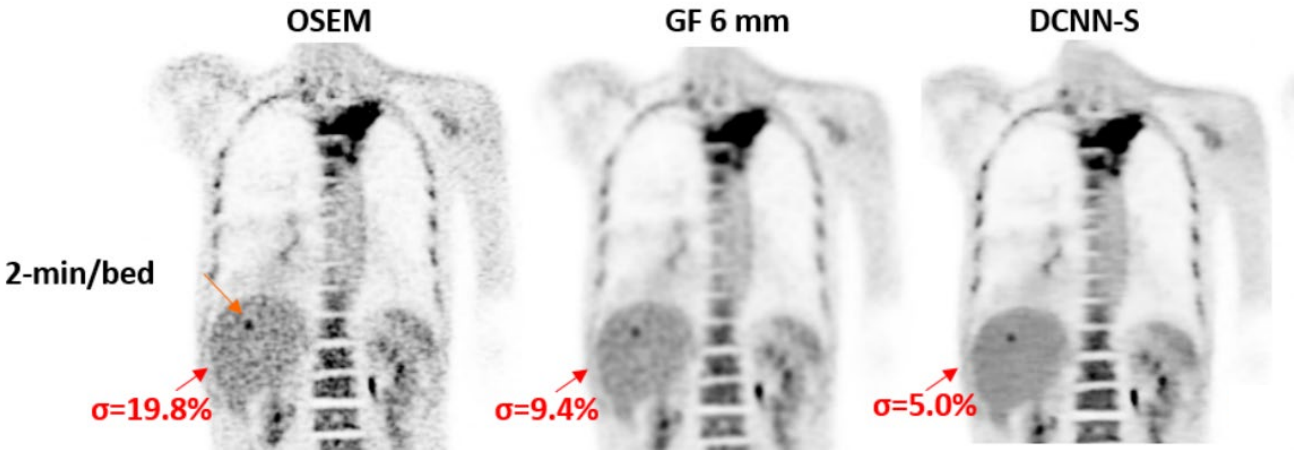
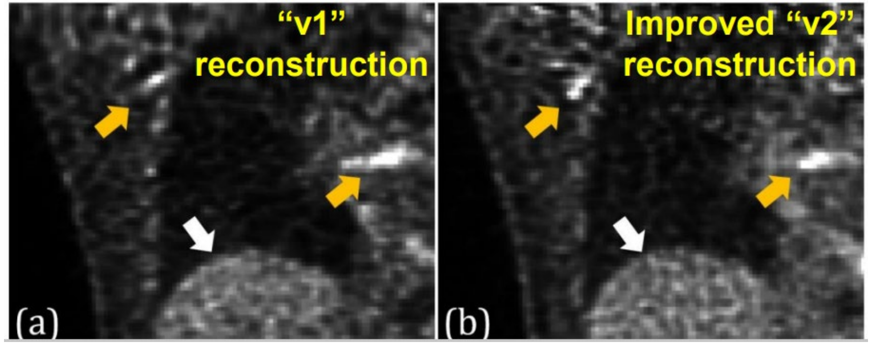


Image obtained from [4]

[1] Ulyanov et al., 2018; [2] Hashimoto et al., 2019; [3] Zhang et al., 2017; [4] Chan et al., 2018

Challenges in Medical Image Denoising

- Change in imaging protocols
  - In product development, there is often a need to improve the imaging protocols (i.e., scan or reconstruction protocol) during a product development phase
  - This requires regenerating the training datasets with the updated protocol followed by **retraining the denoising network**
- A trained DNN often produces suboptimal predictions on unseen features



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- Change in imaging protocols
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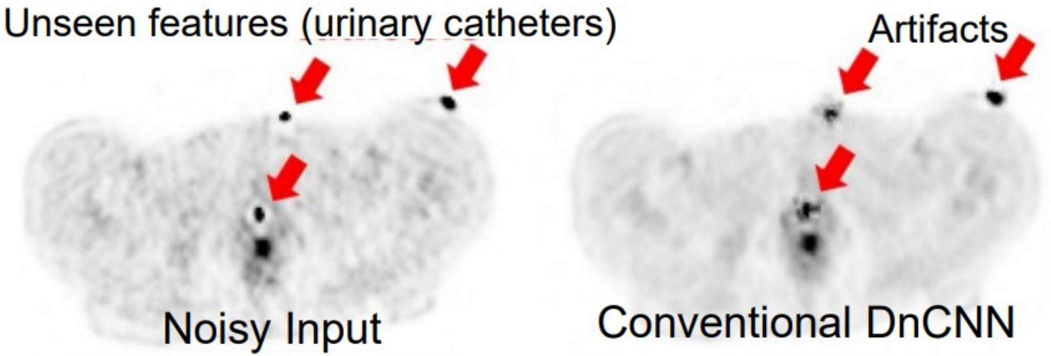


Challenges in Medical Image Denoising

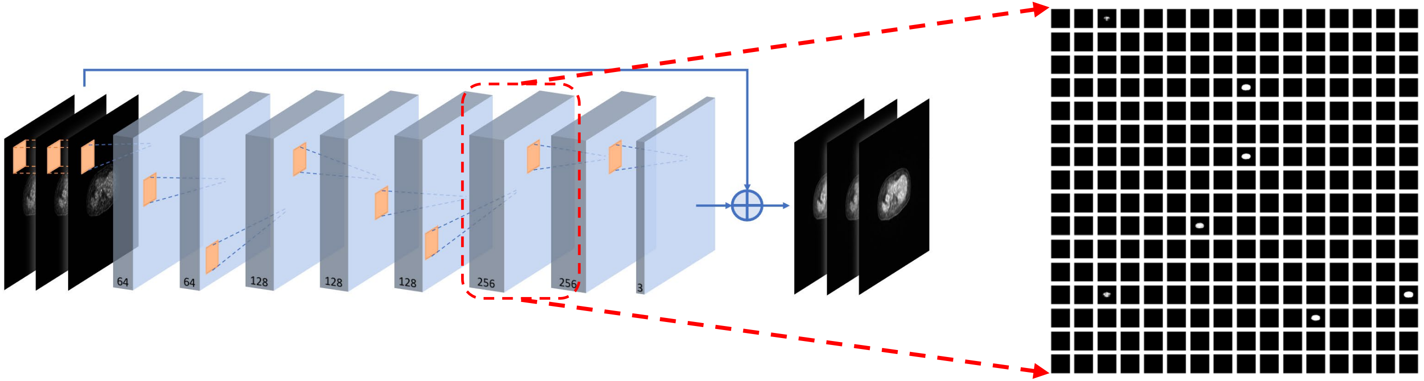
- Existing methods that can be used to avoid retraining a pretrained DNN from scratch
  - Fine-tuning, joint training, and continual learning
  - They either suffer from catastrophic forgetting or they require revisiting data from the previous tasks

Targeted Gradient Descent

- We proposed a network fine-tuning and online-learning scheme that
  - Adapts a pretrained DCNN to new imaging protocols with the minimum need for additional training data
  - Adapts a pretrained DCNN to individual testing image to avoid producing artifacts on unseen features
- This work was done during my internship at Canon Medical Research USA
- For details, please refer to:
  - **Chen, Junyu**, Evren Asma, and Chung Chan. "Targeted Gradient Descent: A Novel Method for Convolutional Neural Networks Fine-tuning and Online-learning." *International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI)*. Springer, Cham, 2021.

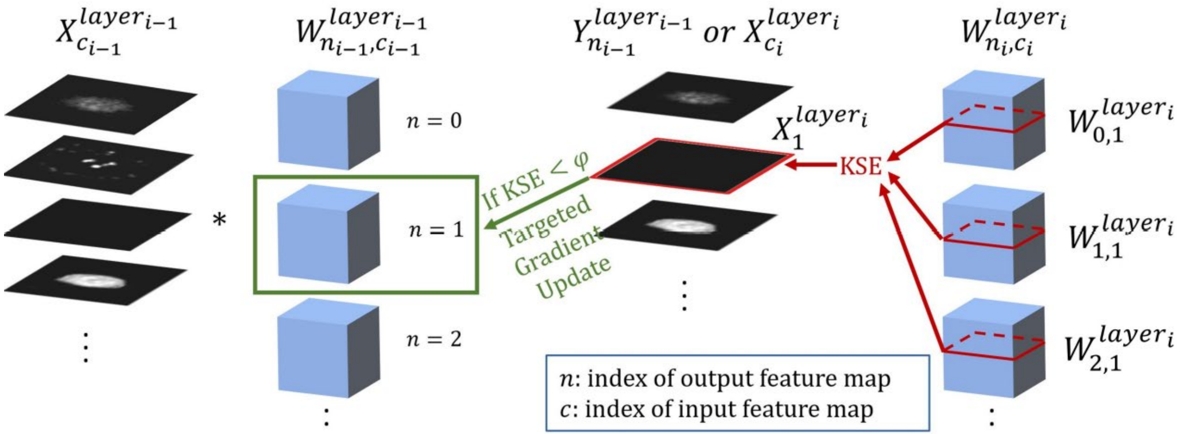
Targeted Gradient Descent

- "Useless/redundant" feature maps exist in a pretrained ConvNet:
  - ConvNet did not effectively use all of its kernels
  - Some of the kernels generates useless/redundant feature maps



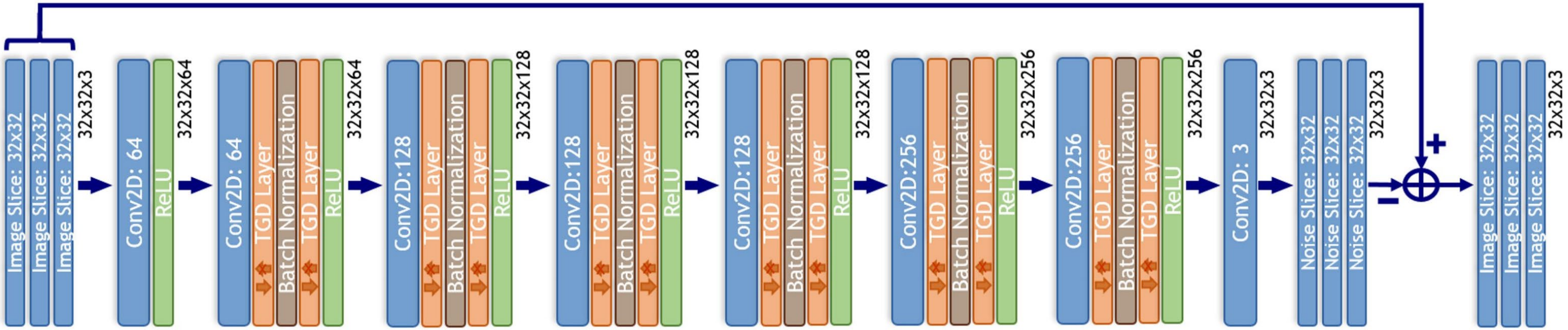
Targeted Gradient Descent

- We specifically retrain the kernels that generates these feature maps using a small dataset
- Realized via a "Targeted Gradient Descent (TGD)" layer



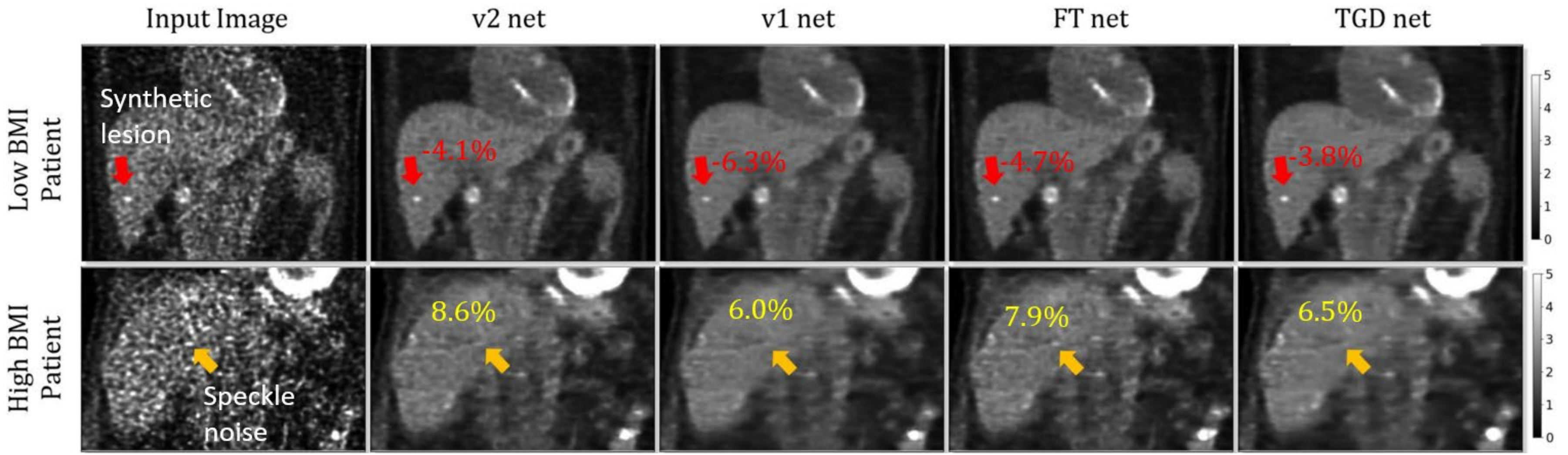
Targeted Gradient Descent

- We specifically retrain the kernels that generates these feature maps using a small dataset from a new imaging protocol
    - Realized via a “Targeted Gradient Descent (TGD)” layer



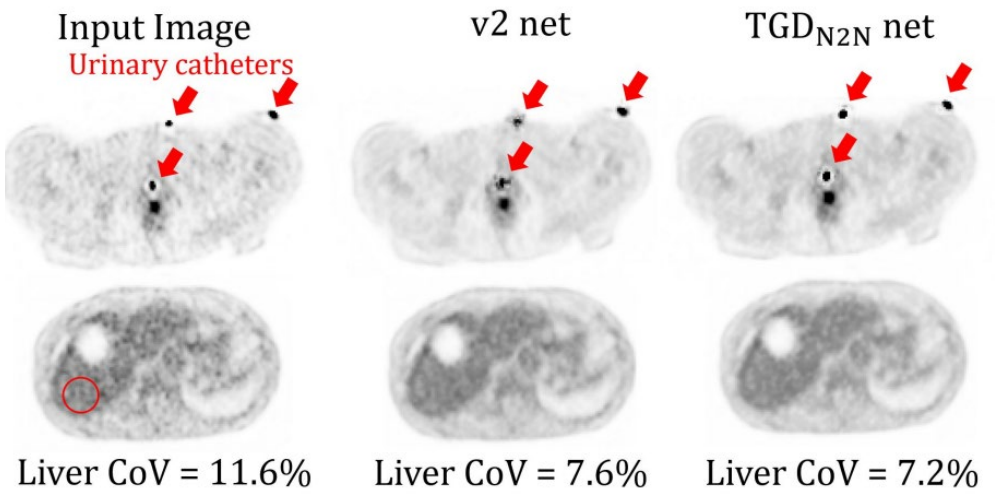
Targeted Gradient Descent

- The red numbers indicate the ensemble bias (%) comparing to the ground truth
- The yellow numbers denote the liver CoV (%)



Targeted Gradient Descent

- The red arrows indicate the urinary catheters
- TGD training successfully removed those artifacts



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