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Deep learning Learning for Extracting Clinically Useful Information from Medical Images

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Machine Learning in Medical Imaging: Opportunities



- Machine learning techniques are starting to reach levels of human performance in challenging visual tasks
- Big data is slowly arriving in medical imaging

UK Biobank will provide large-scale imaging data from 100,000 subjects

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Machine Learning in Medical Imaging: Challenges



- Images are often 3D or 4D:
 - # of voxels and # of extracted features is very large
- Number of images is limited:
 - large data set means typically 100 to 1000 images
 - "small sample size problem"
- Training data is expensive:
 - annotation of images is resource intensive (manpower, cost, time)
 - crowdsourcing not possible
- Training data is imperfect:
 - training data may be wrongly labelled, e.g. for diseases such as Alzheimer's confirmation requires pathology (difficult and costly to obtain)

Machine Learning in Medical Imaging: Challenges



- Images are highly variable
 - Different scanner hardware
 - Different imaging sequences
 - Images have artefacts



Presence or absence of pathologies





Overview









MR image acquisition: Challenges

- Magnetic Resonance Imaging (MRI)
 - MRI acquisition is inherently a slow process
 - Slow acquisition is
 - ok for static objects (e.g. brain, bones, etc)
 - problematic for moving objects (e.g. heart, liver, fetus)
 - Options for MRI acquisition:
 - real-time MRI: fast, but 2D and relatively poor image quality
 - gated MRI: fine for period motion, e.g. respiration or cardiac motion but requires gating (ECG or navigators) leading to long acquisition times (30-90 min).



Example: Cardiac imaging







 MRI acquisition is performed in k-space by sequentitraversing sampling trajectories.





• MRI acquisition is performed in k-space by sequentially traversing sampling trajectories.



K-space



Signal space





• MRI acquisition is performed in k-space by sequentially traversing sampling trajectories.

 $\mathcal{F}^{-1}\{.\}$



K-space

Signal space





 MRI acquisition is performed in k-space by sequential There is significant spatio-temporal redundancy traversing sampling trajectories.

t = T

K-space



K-space undersampling

 Acquiring a fraction of k-space <u>accelerates</u> the process but introduces <u>aliasing</u> in signal space.



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Deep Cascade of CNNs for MRI Reconstruction





Deep Cascade of CNNs for MRI Reconstruction





Deep Cascade of CNNs for MRI Reconstruction





Magnitude reconstruction (6-fold)



(a) 6x Undersampled

(b) DLTG

(c) CNN

(d) Ground Truth



Magnitude reconstruction (11-fold)



(a) 11x Undersampled

(b) DLTG

(c) CNN

(d) Ground Truth



Deep Cascade of CNNs for MRI Reconstruction: Results

• Test error across 10 subjects:

2D, PSNR: mean (sd)

Model	R=4 (dB)	R=8 (dB)
DLTG	27.5 (1.31)	22.6 (0.95)
CNN	31.0 (1.08)	25.2 (1.00)

2D+t (vs. DLTG)





Deep Cascade of CNNs for MRI Reconstruction: Results

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2D, PSNR: mean (sd)

Model	R=4 (dB)	R=8 (dB)
DLTG	27.5 (1.31)	22.6 (0.95)
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Reconstruction speed

Model	Time
DLMRI/DLTG	~6 hr (CPU)
CNN (2D)	0.69 s (GPU)
CNN (2D+t)	10 s (GPU)

2D+t (vs. DLTG)





Still, cardiac imaging is challenging

- Acquisition of cardiac MRI typically consists of 2D multislice data due to
 - constraints on SNR
 - breath-hold time
 - total acquisition time
- This leads to thick slice data (thickness 8-10 mm per slice)







Still, cardiac imaging is challenging

- Acquisition of cardiac MRI typically consists of 2D multislice data due to
 - constraints on SNR
 - breath-hold time
 - total acquisition time
- This leads to thick slice data (thickness 8-10 mm per slice)
- Images are acquired in different orientations:
 - short-axis
 - long-axis, i.e.
 - 2CH or 4CH views





Still, cardiac imaging is challenging: Low and High Resolution Images







O. Oktay et al. MICCAI 2016

Proposed 3D-SR Model (Multi-Image)



- Siamese model is used to combine information from multiple stacks

- The learned kernels can be easily integrated in this multi-model

O. Oktay et al. MICCAI 2016



Image Quality Assessment



Upsampling x5

Inference Time: 6-8 Seconds for image size (140x140x10)

O. Oktay et al. MICCAI 2016

Motion Tracking Experiments ((SR is used as a preprocessing method)





Linear Interp Img Linear Interp



CNN-SR Img CNN-SR



High Resolution Img Linear Interp CNN-SR

Surface to Surface Distance (Linear vs HR) 5.50 mm Surface to Surface Distance (Proposed vs HR) 4.73 mm

Overview











- Aim: Better fetal screening with US
 - Use multiple US probes to acquire more comprehensive imaging data
 - Use robotic control of US probes to ensure wider field of view
 - Use machine learning for automated US image acquisition and interpretation
- Partners:



HILIPS





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Goal: Do this in real-time on images straight from US machine



- Potential applications:
 - Guidance: Assist inexperienced sonographers





- Potential applications:
 - Guidance: Assist inexperienced sonographers
 - Convenience: Automatically make a check list of visited planes





- Potential applications:
 - Guidance: Assist inexperienced sonographers
 - Convenience: Automatically make a check list of visited planes
 - Reproducibility: Reduce
 variability between operators







- Very fast
- Very accurate

C. Baumgartner et al. MICCAI 2016, IEEE-TMI 2017
Automatic Standard Scan Plane Detection: Data



 We use very large 2D ultrasound dataset consisting of *images* of standard views and *videos*

> > Annotated "freeze frames" saved by operator (typically 30 images)

- Data from
 - 2700 patients
 - Between 1200 and 4800 images for each standard plane

Demo



Automatic Standard Scan Plane Detection: Localisation



Localisation is (almost) for free in this framework!

C. Baumgartner et al. MICCAI 2016, IEEE-TMI 2017



Automatic Standard Scan Plane Detection: Localisation



 Can also identify which regions of a frame caused it to make a particular prediction



 This can be used for localisation of the fetal anatomy without having bounding boxes for training

C. Baumgartner et al. MICCAI 2016, IEEE-TMI 2017

Demo



Standard Plane Detection from 3D Ultrasound



- Motivation
 - 3D ultrasound data is hard to interpret directly on the US scanner
 - We aim for a system that can automatically extract standard 2D views from a 3D view at any probe position
- Eventually, we would like this to work in real-time



Overview









Convolutional Neural Networks







Convolutional Neural Networks







Convolutional Neural Networks for Image Segmentation

- Different architectures:
 - Fully convolutional networks (Long et al., 2015)
 - U-Net (Ronneberger et al., 2015)
 - DeepMedic (Kamnitsas et al., 2016)







Convolutional Neural Networks for Image Segmentation

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Image segmentation as a machine learning problem



- Fully connected networks (Long et al., 2015)
- Manual annotations of <u>4,872 subjects</u> (QMUL/Oxford) with <u>93,128 pixelwise annotated 2D images</u> slices
- Divided into training/validation/test: 3,972/300/600





SA, basal

SA, mid-ventricular

SA, apical



LA, 2 chamber

LA, 4 chamber



Evaluation of segmentation accuracy Comparison to expert observers

(a) Absolute difference								
	Auto vs Man	O1 vs O2	O2 vs O3	O3 vs O1				
	(n = 600)	(n = 50)	(n = 50)	(n = 50)				
LVEDV (mL)	$6.1_{\pm 5.3}$	$6.1_{\pm 4.4}$	$8.8_{\pm 4.8}$	$4.8_{\pm 3.1}$				
LVESV (mL)	$5.3_{\pm 4.9}$	$4.1_{\pm 4.2}$	$6.7_{\pm 4.2}$	$7.1_{\pm 3.8}$				
LVM (gram)	$6.9_{\pm 5.5}$	$4.2_{\pm 3.2}$	$6.6_{\pm 4.9}$	$6.5_{\pm 4.8}$				
RVEDV (mL)	$8.5_{\pm 7.1}$	$11.1_{\pm 7.2}$	$6.2_{\pm 4.6}$	$8.7_{\pm 5.8}$				
RVESV (mL)	$7.2_{\pm 6.8}$	$15.6_{\pm 7.8}$	$6.6_{\pm 5.5}$	$11.7_{\pm 6.9}$				
	(b) Relative difference							
	Auto vs Man	O1 vs O2	O2 vs O3	O3 vs O1				
	(n = 600)	(n = 50)	(n = 50)	(n = 50)				
LVEDV $(\%)$	$4.1_{\pm 3.5}$	$4.2_{\pm 3.1}$	$6.3_{\pm 3.3}$	$3.4_{\pm 2.2}$				
LVESV $(\%)$	$9.5_{\pm 9.5}$	$6.8_{\pm 7.5}$	$12.5_{\pm 8.5}$	$11.7_{\pm 5.1}$				
LVM $(\%)$	$8.3_{\pm 7.6}$	$4.4_{\pm 3.3}$	$6.0_{\pm 3.7}$	$6.7_{\pm 4.6}$				
RVEDV (%)	$5.6_{\pm 4.6}$	$8.0_{\pm 5.0}$	$4.2_{\pm 3.1}$	$5.7_{\pm 3.6}$				
RVESV $(\%)$	$11.8_{\pm 12.2}$	$30.6_{\pm 15.5}$	$10.9_{\pm 8.3}$	$16.9_{\pm 9.2}$				
	Automated		Manual					



Challenges for image segmentation: Pathologies



DeepMedic: Overview



- Baseline CNN architecture:
 - Four layers with 5³ kernels for feature extraction, leading to a receptive field of size 17³.
 - The classification layer is implemented as convolutional with 1³ kernels, which enables efficient dense inference.
 - Cross-entropy as loss function

$$\mathcal{L}_{seg} = -\frac{1}{m} \sum_{i=1}^{m} [f(x_i) = y_i] log(f(x_i))$$



DeepMedic: Overview



- The size of receptive field of CNNs is important:
 - Large receptive increases computation and memory requirements
 - Pooling leads to loss of the spatial information
- Solution: Use multi-scale approach





DeepMedic: Results



Patients with severe TBI



DeepMedic in Action



DeepMedic: Results



- 66 patients with moderate-to-severe Traumatic Brain Injury (TBI)
- Imaging at Addenbrooke's Hospital, Cambridge, with 3T Siemens Trio within the first week of injury.
- MRI sequences include
 - MPRAGE
 - FLAIR, T2, Proton Density (PD) and Gradient-Echo (GE)





Challenges for image segmentation: Deployment in the clinic

ML-based segmentation often

Unsupervised domain adaptation using adversarial neural networks can be used to train a CNN-based segmentation

- which is more invariant to differences in the input data
- which does not require any annotations on the test domain
- Manually annotating new data for each test domain is not a feasible solution

Deploying machine learning into clinical practice: What is the problem?



Solution: Unsupervised domain adaptation with adversarial networks







DeepMedic: Unsupervised domain adaptation with adversarial networks



K. Kamnitsas et al. IPMI 2017, arXiv:1612.08894



DeepMedic: Unsupervised domain adaptation with adversarial networks



K. Kamnitsas et al. IPMI 2017, arXiv:1612.08894

DeepMedic: Unsupervised domain adaptation with adversarial networks



K. Kamnitsas et al. IPMI 2017, arXiv:1612.08894



DeepMedic, FCN & U-Net

• The good: There are some good/promising CNN-based segmentation Ensemble of Multiple Models & Architectures (EMMA) Performance **insensitive** to suboptimal configuration Behaviour **unbiased** by architecture & configuration

Chosen model & config may be suboptimal for other data/task
Results and conclusions of analysis are strongly biased



Ensemble of Multiple Models and Architectures (EMMA)

Need to learn: P(Y|X)

Approximate it by model: $P(Y|X; \theta_m, m)$

with learnt parameters $\theta_m = \min_{\theta_m} d\left(P\left(Y|X; \theta_m, m\right), P(Y|X)\right)$, d the loss.

Model is defined by chosen meta-parameters m.

Commonly m is neglected, but it biases the results!

We define stochastic variable *M*, over configurations of interest.

Need to marginalise out influence of *M*: $P(Y|X) = \sum_{\forall m \in M} P(Y, M = m|X) = \sum_{\forall m \in M} P(Y|X, M = m) P(M = m)$ EMMA approximate the joint by ensembling individual models: $\sim P_{EMMA}(Y|X) = \sum_{\forall m \in M} P(Y|X; \theta_m, m) \frac{1}{|M|}$



M: Network architectures





M: Network configurations

- Architecture configuration:
 - depth, width, scales, residuals, etc.
- Training Loss:
 - Cross-Entropy, IoU, DSC, etc.
- Sampling strategy:
 - equally per class, foreground/background, etc.
- Optimisation:
 - optimizer, learning rate, momentum, regulariser...
- Data normalisation:
 - z-score, bias field correction, histogram matching

Multimodal Brain Tumor Segmentation Challenge

Led by CBICA

1st Place

2017 MICCAI BraTS Challenge (Segmentation Task) K. Kamnitsas, et al. "Ensembles of Multiple Models and

Architectures for Robust Brain Tumour Segmentation"

BRATS'17 Challenge: Quantitative validation



• EMMA: 2 x DeepMedic, 3 x FCNs, 1 x U-Net

- Different training losses, sampling strategies, widths, depths, configurations
- No config was heavily optimised for the task (3/6 nets were quite suboptimal)

	DSC		Se	Sensitivity		Specificity		$Hausdorff_{95}$				
	Enh.	Whole	Core	Enh.	Whole	Core	Enh	Whole	Core	Enh.	Whole	Core
EMMA	75.7	90.2	82.0	79.0	90.9	78.3	99.8	99.5	99.9	4.22	4.56	6.11
MIC_DKFZ	73.2	89.6	82.3 79.7	79.0	91.2 89.6	65.9 78.1	99.8 99.8	99.4 99.6	99.1 99.9	4.78	5.91 6.97	1.00 9.48

• Robustness:

- EMMA of all 6 was better than individuals.
- Ensemble of 3 best nets was only marginally better than EMMA of all 6 nets.



Conventional CNNs: Do not use prior knowledge explicitly

Analysis of Neural Networks

- Model parameterization
- Model capacity / receptive field
- Loss function / objective

Standard Loss Functions

– X-Entropy loss function

$$L_x = -\sum_{i \in \mathcal{S}} \sum_{c=1}^C \log\left(\frac{e^{f_{(c,i)}}}{\sum_j e^{f_{(j,i)}}}\right)$$

– L2 or Smooth L1 loss function

$$\sum_{i \in \mathcal{S}} \left\| \Phi(oldsymbol{x}_i, heta_r) - oldsymbol{y}_i
ight\|^2$$



Conventional CNNs: Problem





Conventional CNNs: What we want





Learn anatomical priors using a stacked convolutional autoencoder

 Provides a non-linear compact representation of the underlying anatomy



O. Oktay, in press, IEEE TMI 2017


Anatomically constrained CNN: T-L networks for representing priors





Anatomically constrained CNN: Segmentation framework



Anatomically constrained CNN: Segmentation results



	Method	Mean Dist. (mm)	Hausdorff Dist. (mm)	Dice Score (%)	# Trainable Parameters
Endo-cardium	2D-FCN [264] 3D-Seg 3D-UNet [50] AE-Seg [217] 3D-Seg-MAug AE-Seg-M	2.07 ± 0.61 1.77 ± 0.84 1.66 ± 0.74 1.75 ± 0.58 1.59 ± 0.74 1.59 ± 0.74 1.59 ± 0.48	$ \begin{array}{r} 11.37 \pm 7.15 \\ 10.28 \pm 8.25 \\ 9.94 \pm 9.22 \\ 8.42 \pm 3.64 \\ 8.52 \pm 8.13 \\ 7.52 \pm 3.78 \\ \end{array} $	$\begin{array}{c} .908 \pm .021 \\ .923 \pm .019 \\ .923 \pm .019 \\ .926 \pm .019 \\ .928 \pm .019 \\ .927 \pm .017 \end{array}$	$\begin{array}{c} 1.39 \times 10^{6} \\ 1.60 \times 10^{6} \\ 1.64 \times 10^{6} \\ 1.68 \times 10^{6} \\ 1.60 \times 10^{6} \\ 1.91 \times 10^{6} \end{array}$
	$\operatorname{ACNN-Seg}$	$1.37{\pm}0.42$	7.89 ± 3.83	$.939{\pm}.017$	1.60×10^6
	p-values	$p \ll 0.001$	p pprox 0.890	$p \ll 0.001$	-
Myo-cardium	p-values 2D-FCN [264] 3D-Seg 3D-UNet [50] AE-Seg [217] 3D-Seg-MAug AE-Seg M ACNN-Seg	$p \ll 0.001$ 1.58 ± 0.44 1.48 ± 0.51 1.45 ± 0.47 1.51 ± 0.29 1.37 ± 0.41 1.32 ± 0.26 1.14 ± 0.22	$p \approx 0.890$ 9.19 ± 7.22 10.15 ± 10.58 9.81 ± 11.77 8.52 ± 2.72 9.41 ± 9.17 7 12+2 79 7.31 ± 3.59	$p \ll 0.001$.727±.046 .773±.038 .764±.045 .779±.033 .785±.041 .791±.036 .811±.027	$-$ 1.39×10^{6} 1.60×10^{6} 1.64×10^{6} 1.68×10^{6} 1.60×10^{6} 1.91×10^{6} 1.60×10^{6}
Myo-cardium	p-values 2D-FCN [264] 3D-Seg 3D-UNet [50] AE-Seg [217] 3D-Seg-MAug AE-Seg M ACNN-Seg p-values	$p \ll 0.001$ 1.58 ± 0.44 1.48 ± 0.51 1.45 ± 0.47 1.51 ± 0.29 1.37 ± 0.41 1.32 ± 0.26 1.14 ± 0.22 $p \ll 0.001$	$p \approx 0.890$ 9.19 ± 7.22 10.15 ± 10.58 9.81 ± 11.77 8.52 ± 2.72 9.41 ± 9.17 7 12+2 70 7.31 ± 3.59 $p \approx 0.071$	$p \ll 0.001$.727±.046 .773±.038 .764±.045 .779±.033 .785±.041 701±.036 .811±.027 $p \ll 0.001$	$-$ 1.39×10^{6} 1.60×10^{6} 1.64×10^{6} 1.68×10^{6} 1.60×10^{6} 1.01×10^{6} 1.60×10^{6}



Anatomically constrained CNN: Segmentation results





Anatomically constrained CNN: Super-resolution framework





Anatomically constrained CNN: Super-resolution results



Original LR image

Baseline SR approach

Anatomically constrained SR model

Ground-truth HR image

Anatomically constrained CNN: Learnt Hidden Representations



• Histogram of the learnt low-dimensional latent representations (randomly selected 16 components are shown).







Summary and Conclusions





Current state-of-the-art









Big data (population data)

Multi-modal data

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Interested in join us? We have several opportunities in deep learning research: <u>https://biomedic.doc.ic.ac.uk</u>