Medical Imaging with Deep Learning Tutorial

Chapter 1 - Radiology and Multi-View

Chapter 2 - Histology and Segmentation

Chapter 3 - Cell Counting

Chapter 4 - Incorrect Feature Attribution

Chapter 5 - GANs in Medical Imaging



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Chapter 1

Radiology and Multi-View

Common X-ray projections/views



(a) P-A



(b) Lateral

Most common

(e) A-P



(c) Lordotic



(d) A-P supine







(j) A-P



(h) Lordotic

(i) A-P supine

PA = PosteroAnterior = BackFront

Image: [Bustos, "PadChest: A Large Chest x-Ray Image Dataset with Multi-Label Annotated Reports." 2019]

(g) Lateral

Chest X-ray14 Dataset

Released 2017, first large scale chest X-ray dataset

>100k frontal images released as public domain

Enabled the deep learning radiology revolution



Ronald Summers NIH Clinical Center

Media Advisory Wednesday, September 27, 2017

NIH Clinical Center provides one of the largest publicly available chest x-ray datasets to scientific community

The dataset of scans is from more than 30,000 patients, including many with advanced lung disease.

What



The NIH Clinical Center recently released over 100,000 anonymized chest xray images and their corresponding data to the scientific community. The release will allow researchers across the country and around the world to freely access the datasets and increase their ability to teach computers how to detect and diagnose disease. Ultimately, this artificial intelligence mechanism can lead to clinicians making better diagnostic decisions for patients.

NIH compiled the dataset of scans from more than 30,000 patients, including



Stanford Pneumonia study

In 2017 Pranav Rajpurkar and Jeremy Irvin trained a DenseNet on NIH data scaled to 224x224 pixels

Set the benchmark performance which has not been significantly improved.

They evaluated pneumonia predictions against 4 radiologists.

"We find that the model exceeds the average radiologist performance on the pneumonia detection task."



Criticism of the Chest X-ray14 Dataset

In 2017 Luke Oakden-Rayner published a blog post discussing issues with the labels in the NIH data.

This led to more work on automatic label extraction.



DECEMBER 18, 2017 ~ LUKEOAKDENRAYNER

A couple of weeks ago, I mentioned I had some concerns about the ChestXray14 dataset I said I would come back when I had more info, and since then I have

https://lukeoakdenrayner.wordpress.com/2017/12/18/thechestxray14-dataset-problems/



In a sample of images red are said to be wrong

Exploring the ChestXray14 dataset: problems

2019: the year of chest X-ray data







PADCHEST 160k images Multiple views Almost 200 labels

27% hand labelled, others using an RNN.

License:Creative Commons Attribution-ShareAlike CheXpert 224k images PA and L views 13 labels.

Automated rule-based labeler

Non-commercial research purposes only

MIMIC-CXR 377k images PA and L views 13 labels.

Automated rule-based labeler. NIH (NegBio) and CheX labelers ran.

Non-commercial research purposes only. Confidentially training required. Many datasets exist with different methods of obtaining labels. Automatic () or hand labelled



NIH chest X-ray14 14 labels

Automated rule-based labeler (NegBio)







PADCHEST, ~200 labels

27% hand labelled, others using an RNN.

CheXpert, 13 labels

Custom rule-based labeler.

MIMIC-CXR, 13 labels

Automated rule-based labeler. NIH (NegBio) and CheX labelers used.

KSNA

RSNA Pneumonia Kaggle Relabelled NIH data



A group at Google relabelled a subset of NIH images



MeSH automatic labeller

Multi-modal/view inference (X-ray use case)



Here saliency maps are from models trained on single views.

These two tasks perform better when using lateral views.

[Bertrand, 2019]

Pleural effusion

Flattened

diaphragm

Also: Multi-modal/view inference (MRI use case)



Ischemic stroke lesion segmentation (ISLES dataset) Stroke perfusion estimation

Brain tumor segmentation (BraTS dataset)

Challenge: missing modalities/views



Integrating multiple views



Image: [Hashir, Quantifying the Value of Lateral Views in Deep Learning for Chest X-rays, 2020]

Integrating multiple views (X-ray images)



All models are about equal in performance given the right hyperparameters. Hyperparameter tuning is easier on some models but not others

Image: [Hashir, Quantifying the Value of Lateral Views in Deep Learning for Chest X-rays, 2020]

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Chapter 2

Histology and Segmentation

CAMELYON17: A large high resolution open histology dataset for cancer detection





Example of a WSI of a H&E stained section with a delineated micro-metastasis at increasing zoom levels, and the corresponding IHC (cytokeratin 8-18 stained) slide at the same location. The metastasis is outlined with black.

CAMELYON17 Dataset 1000 whole-slide images (WSIs) of sentinel lymph node. (~3GB each!) 5 medical centers. 40 patients from each center. 5 whole-slide images per patient.

> Peter Bandi, et al. From detection of individual metastases to classification of lymph node status at the patient level: the CAMELYON17 challenge. IEEE-TMI 2018

Patch wise segmentation

Use case: Invasive Ductal Carcinoma (most common subtype of all breast cancers)







Starting with a full slide image of breast tissue.

Image is labelled as IDC or not

Image is chopped into patches and labelled as IDC or not

https://colab.research.google.com/drive/13T9s3weexAw6YskKoY6c-VvoUgUvWsgf

Patch wise segmentation

Use case: Invasive Ductal Carcinoma (most common subtype of all breast cancers)



Slide design: Fei-Fei Li & Andrej Karpathy & Justin Johnson



Input size 4

Output size 1



Output size 2

Input size 5





Output size 2

Model's receptive field = 4 nodes

Multiplications saved = 4

Allows for very fast inference.

However, training this way requires a lot of memory. Need to save past outputs.

Patch wise training together with FCN inference is a good balance.



https://colab.research.google.com/drive/13T9s3weexAw6YskKoY6c-VvoUgUvWsqf

Recap: Segmentation using a bottleneck



Upsampling possible with

- Unpooling
- Transposed convolutions

Noh et al, "Learning Deconvolution Network for Semantic Segmentation", ICCV 2015 Slide design: Fei-Fei Li & Andrej Karpathy & Justin Johnson

Recap: U-NET



Difference: Skip connections (like resnet)

Dogma: skips carry spatial information, bottleneck carries high level structure.

Segmentation metrics



$$Precision = \frac{TP}{TP + FP}$$

 $IoU = Jaccard Index = \frac{TP}{TP + FN + FP} = \frac{|A \cap B|}{|A \cup B|} = \frac{|A \cap B|}{|A| + |B| - |A \cap B|}$ Dice Coefficient = $\frac{2 \cdot TP}{(2 \cdot TP) + FN + FP} = \frac{2|X \cap Y|}{|X| + |Y|}$

Training with dice

Exercise: What p maximizes this?

Using the dot product to compute the intersection allows for a differentiable loss.

For multiple classes a basic approach is to average over all classes

 $DL_{mean}(p, \hat{p}) = \frac{1}{|C|} \sum_{c \in C} \frac{2\sum_{i} p_i^c \hat{p}_i^c}{\sum_{i} (p_i^c + \hat{p}_i^c)}$

 $DL(p, \hat{p}) = \frac{2\sum_{i} p_{i} \hat{p}_{i}}{\sum_{i} (p_{i} + \hat{p}_{i})}$

Use a sigmoid or a softmax to restrict output.

Tricks: Improving edges in segmentations by predicting edges



Images provided by Konrad Wagstyl (University College London) 2020

More reading about idea: [Polzounov, WordFence: Text Detection in Natural Images with Border Awareness, 2017]

Challenge: extreme class imbalance (e.g. lung nodule)

Background classes can dominates the loss and cause learning instability do to large gradients.

Balanced sampling may not work as well because patches which could yield false positives are rarely seen to train on.



CASED importance sampling for large images

General Idea:

Store a probability for each patch.

Generate patches based on this probability.

Probability is inverse of how well your model performs on that patch.

Samples are stratified by class.



Fig. 1. Schematic diagram of CASED framework

Chapter 2 - References

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Chapter 3

Cell Counting

Use case: Proliferation/Cell growth studies



Standard 96-well plate

Treat cells with different compounds and observe proliferation over time





Bachstetter, MW151 Inhibited IL-1? Levels after Traumatic Brain Injury with No Effect on Microglia Physiological Responses, PLOS ONE, 2017

Use case: Proliferation/Cell growth studies

Use case: Counting in histology slides





Complicated cell structure



- 1. Create binary segmentation image
- 2. Watershed segmentation
- 3. Isolate and count







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- 1. Create binary segmentation image
- 2. Watershed segmentation
- 3. Isolate and count

This works well on easy tasks but doesn't scale.

"Pipelines" end up breaking on new images with different lighting or stain.

How to get labels?





Targets for regression

Sigma is typically small like a few pixels

$$F^{gt}(x,y) = \sum_{i}^{\text{\# Cells}} \mathcal{N}([x,y]; [x_i, y_i], \sigma^2)$$



Targets for regression

4 Colla

Sigma is typically small like a few pixels

$$F^{gt}(x,y) = \sum_{i}^{\# \text{ Cens}} \mathcal{N}([x,y]; [x_i, y_i], \sigma^2)$$

Train model to regress

$$L = \sum_{x,y} |F^{gt}(x,y) - F(I)(x,y)|$$



Targets for regression

// C_{alla}

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Train model to regress

$$L = \sum_{x,y} \left| F^{gt}(x,y) - F(I)(x,y) \right|$$

To recover count:

$$\operatorname{count} = \sum_{x,y} F(I)(x,y)$$

x,y



Targets for regression

// C_{alla}

Sigma is typically small like a few pixels

$$F^{gt}(x,y) = \sum_{i}^{\# \text{ Cens}} \mathcal{N}([x,y]; [x_i, y_i], \sigma^2)$$

Note: Square kernels for redundant counting work better [Cohen 2017]

To recover count:

$$\operatorname{count} = \sum_{x,y} F(I)(x,y)$$

x,y

Multiple output classes



Lymphocyte





Malignant Epithelial

Raw Image - Estimated points





Count and classify different cell types [Bidart 2018]

Counting and classifying also possible using multiple output channels.

Combine losses together

 $\lambda_1 L_{lymph} + \lambda_2 L_{norm} + \lambda_3 L_{mal}$

Max prediction over output channels for each cell identified

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BBBC021 - Human MCF7 cells - compound-profiling

RxRx1 - CellSignal: Disentangling biological signal from experimental noise

MBM - Modified Bone Marrow cell counting dataset

Chapter 4

Incorrect Feature Attribution



Goal: predict if there are two plus signs anywhere

However, an easy to spot confounder exists!

The confounding variable distracts the model causing it to fail to generalize.

[Ross, Right for the Right Reasons, 2017] [Viviano, Underwhelming Generalization Improvements From Controlling Feature Attribution, 2019]



Goal: predict if there are two plus signs anywhere

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Goal: predict if there are two plus signs anywhere

However, an easy to spot confounder exists!

The confounding variable distracts the model causing it to fail to generalize.

We can observe this by looking at the saliency map





[Ross, Right for the Right Reasons, 2017] [Viviano, Underwhelming Generalization Improvements From Controlling Feature Attribution, 2019]

Models can overfit to confounding variables in the data.

- Merging datasets with different class imbalance (confounding artifacts from each hospital)
- Labels confounding with each other
- Demographics confounding with labels

[Ross, Right for the Right Reasons, 2017] [Zeck, Confounding variables can degrade generalization performance of radiological ..., 2018] [Viviano, Underwhelming Generalization Improvements From Controlling Feature Attribution, 2019] [Simpson, GradMask: Reduce Overfitting by Regularizing Saliency, 2019]

Models can overfit to confounding variables in the data.

- Merging datasets with different class imbalance (confounding artifacts from each hospital)
- Labels confounding with each other
- Demographics confounding with labels

Example:Systematic discrepancy between average image in datasets



[Ross, Right for the Right Reasons, 2017]

Diff

[Zeck, Confounding variables can degrade generalization performance of radiological ..., 2018] [Viviano, Underwhelming Generalization Improvements From Controlling Feature Attribution, 2019] [Simpson, GradMask: Reduce Overfitting by Regularizing Saliency, 2019]

AP (NIH)

PA (NIH)





Mitigation approaches

Feature engineering

- Range normalization (/max)
- Subspace alignment (align data using their eigenbasis based on a feature) [Fernando 2014]
- **Removing the largest principle component** (joint PCA and reconstruct without largest eigenvector)

Mitigation approaches

Feature engineering

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- Subspace alignment (align data using their eigenbasis based on a feature) [Fernando 2014]
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During training

- **Reverse gradient** (make intermediate layer invariant to a label) [Ganin & Lempitsky, 2014]
- Right for the Right Reasons (regularize saliency map) [Ross, Hughes, & Finale Doshi-Velez, 2017]
- **GradMask** (regularize contrast saliency map between classes) [Simpson, 2019]
- ActivDiff (regularize representation to focus on pathology) [Viviano, 2019]

What if feature artifact is correlated with target label? Is the reason that should be used for prediction known? What if it is not known?

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Chapter 5

GANs in Medical Imaging

Medical image-to-image translation considered harmful

Many papers have proposed methods that can "translate between modalities"



Adversarial losses are very good at distribution matching (e.g. CycleGAN). But artifacts could be introduced and then used in diagnosis which can be dangerous.







But a bias in training data can lead to incorrect translation

Cohen, Distribution Matching Losses Can Hallucinate Features in Medical Image Translation, 2018



But a bias in training data can lead to incorrect translation

Cohen, Distribution Matching Losses Can Hallucinate Features in Medical Image Translation, 2018



Tumors here are a proxy to illustrate the impact of an unaccounted pathology

Example: CytoGAN learning a self-supervised representation for cell images.

- Encoder can be useful for semi-supervised learning
- Exploring representations to understand the cell biology



Semi-supervised Segmentation with GANs



Images without segmentation labels

Semi-supervised Segmentation with GANs

Predicted segmentations from images that were trained on



Match distributions

Predicted segmentations from unlabelled images



Luc et al. "Semantic Segmentation using Adversarial Networks" 2016 Zhang et al., "Deep Adversarial Networks for Biomedical Image Segmentation Utilizing Unannotated Images," 2017

Semi-supervised Segmentation with GANs

Segmentation Loss



Segmentation output should not make E predict 0

Luc et al. "Semantic Segmentation using Adversarial Networks" 2016

Zhang et al., "Deep Adversarial Networks for Biomedical Image Segmentation Utilizing Unannotated Images," 2017

Explanation by Progressive Exaggeration

Train a classifier and generative model jointly while maintaining consistency between them.

Explainer function: (c_f outputs a one hot)

$$\mathcal{I}_f(\mathbf{x}, \delta) = G(E(\mathbf{x}), c_f(\mathbf{x}, \delta))$$



- 1. **Data Consistency:** perturbed samples generated by \mathcal{I}_f should lie on the data manifold, \mathcal{M}_x , to be consistent with real data. In other words, the generated samples should look realistic when compared to other samples.
- 2. Compatibility with f: changing the second argument in $\mathcal{I}_f(\mathbf{x}, \cdot)$ should produce the desired outcome from classifier f, *i.e.*, $f(\mathcal{I}_f(\mathbf{x}, \delta)) \approx f(\mathbf{x}) + \delta$.
- 3. Self Consistency: Applying reverse perturbation should bring x back to its original form *i.e.*, $\mathcal{I}_f(\mathcal{I}_f(\mathbf{x}, \delta), -\delta) = \mathbf{x}$. Also, applying setting δ to zero should return the query, *i.e.*, $\mathcal{I}_f(\mathbf{x}, 0) = \mathbf{x}$.

Explanation by Progressive Exaggeration



Prediction (normalized heart size)

Generating images conditioned on an over and under prediction of the model helps explain what aspects of the image were important in prediction. Here we can see the heart enlarge or shrink.

[Singla et al. Explanation by Progressive Exaggeration. ICLR 2020]

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