Machine Learning Formulations for Histopathology Images

C. V. Jawahar

IIIT Hyderabad

www.iiit.ac.in/~jawahar

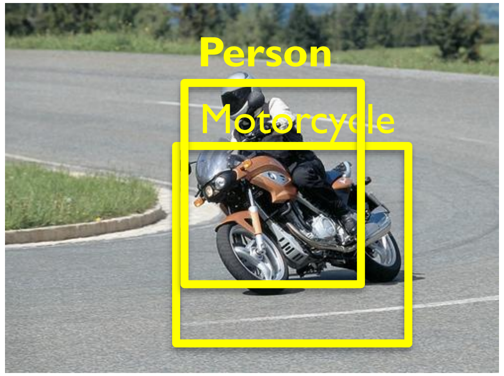
1: **Introduction**

Let us recap what happened in the "AI Wave" for the Image Understanding.

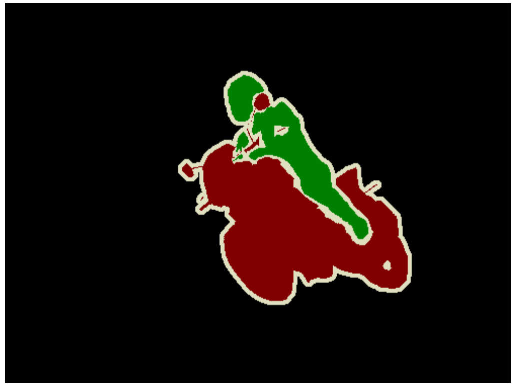
Evolution of the Space

Classification

Detection



Semantic Segmentation



Generation

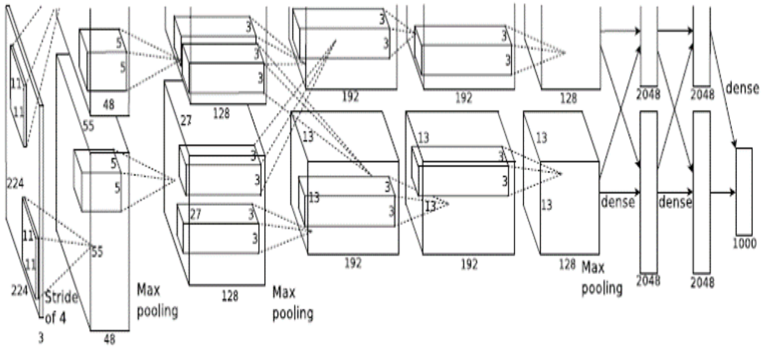
Caltech (2003)
Simple isolated objects

PASCAL (2005-2012)
20 classes.

IMAGENET

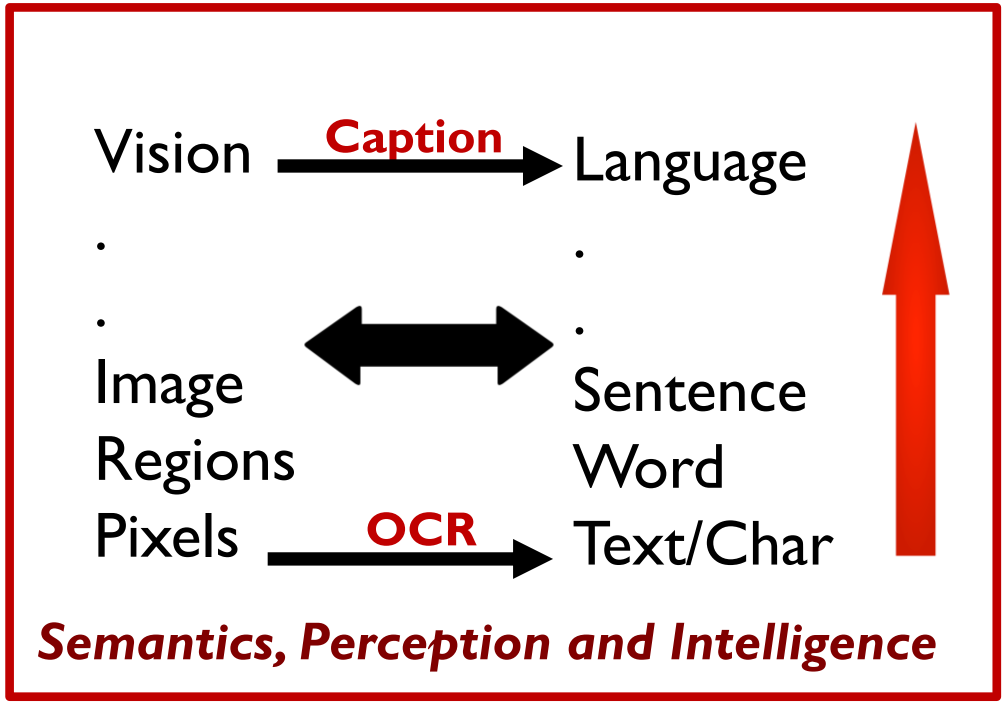
2010 - ?

1000 classes
> 1M images



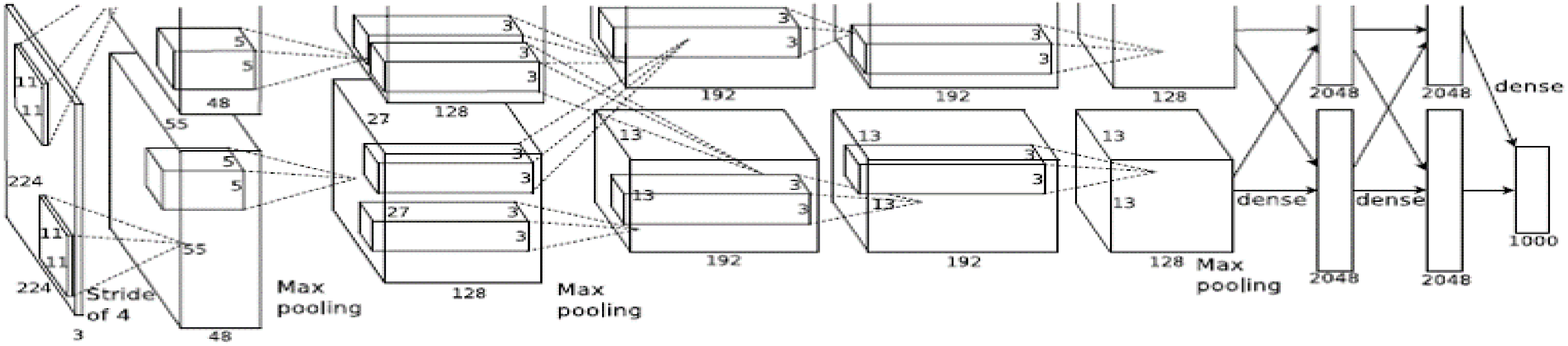
CNNs, RNNs, Deep Learning

“Understanding” Images



SEMANTIC GAP IN IMAGE UNDERSTANDING ?

AlexNet (NIPS 2012)



ImageNet Classification with Deep Convolutional Neural Networks

Alex Krizhevsky
University of Toronto
kriz@cs.utoronto.ca

Ilya Sutskever
University of Toronto
ilya@cs.utoronto.ca

Geoffrey E. Hinton
University of Toronto
hinton@cs.utoronto.ca

ImageNet Classification Task:

Previous Best : ~25% (CVPR-2011)
AlexNet : ~15 % (NIPS-2012)

What changed over time?

	LeNet(1989)	LeNet(1998)	AlexNet(2012)
Task	Digit	Digit	Objects
# Classes	10	10	1000
image size	16×16	28×28	$256 \times 256 \times 3$
# examples	7291	60,000	1.2 M
units	1256	8084	658,000
parameters	9760	60K	60 M
connections	65K	344K	652M
Operations	11 billion	412 billion	200 quadrillion

Indeed, Many Changes

Regularization

- DropOut, DropConnect, Batch Normalization, Data Augmentation, Noise in Data/Label/Gradient

Weight Initialization

- Xavier’s initialization, He’s initialization

Choosing Gradient Descent Parameters

- Adagrad, RMSProp, Adam, Momentum, Nesterov Momentum

Activation Functions

- ReLU, PReLU, Leaky ReLU, ELU

Loss Functions

- Cross-Entropy, Embedding Loss, Mean-Squared Error, Absolute Error, KLDivergence, Max-Margin Loss

Little Pieces that have made the Whole

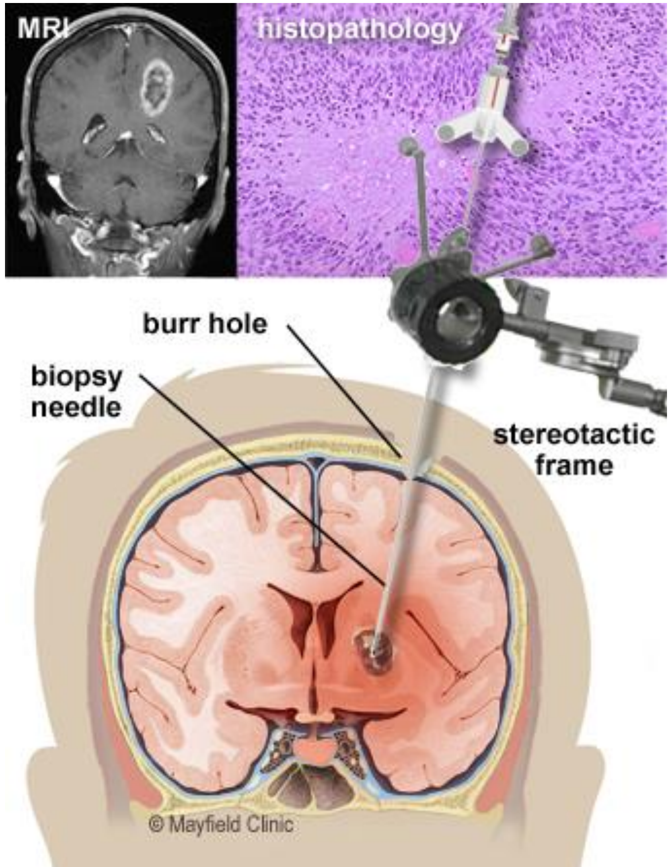
2. Cancer and Histopathology

Cancer: A disease in which abnormal cells divide uncontrollably and destroy body tissue.

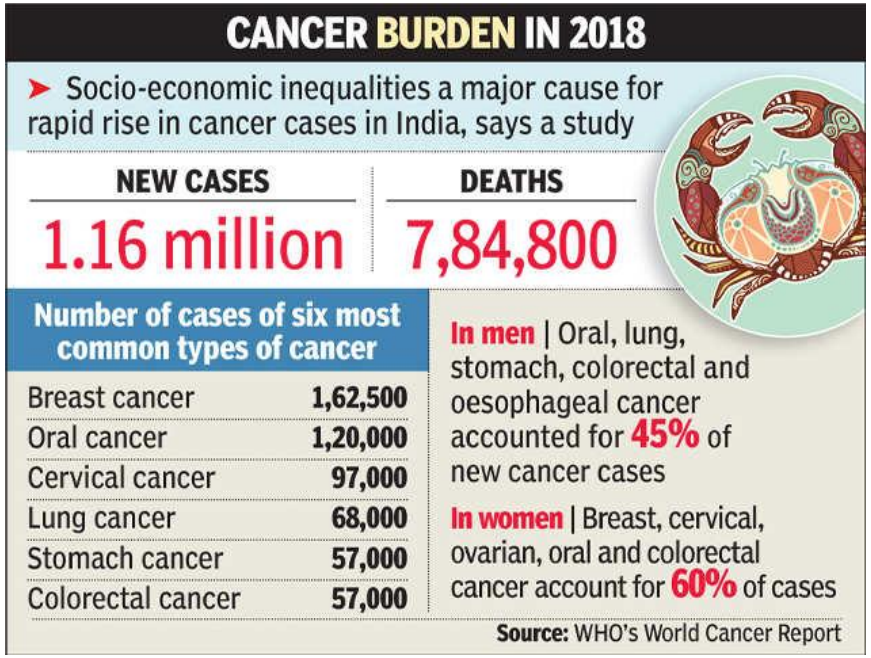
Histopathology: Histopathology refers to the microscopic examination of tissue in order to study the manifestations of disease.

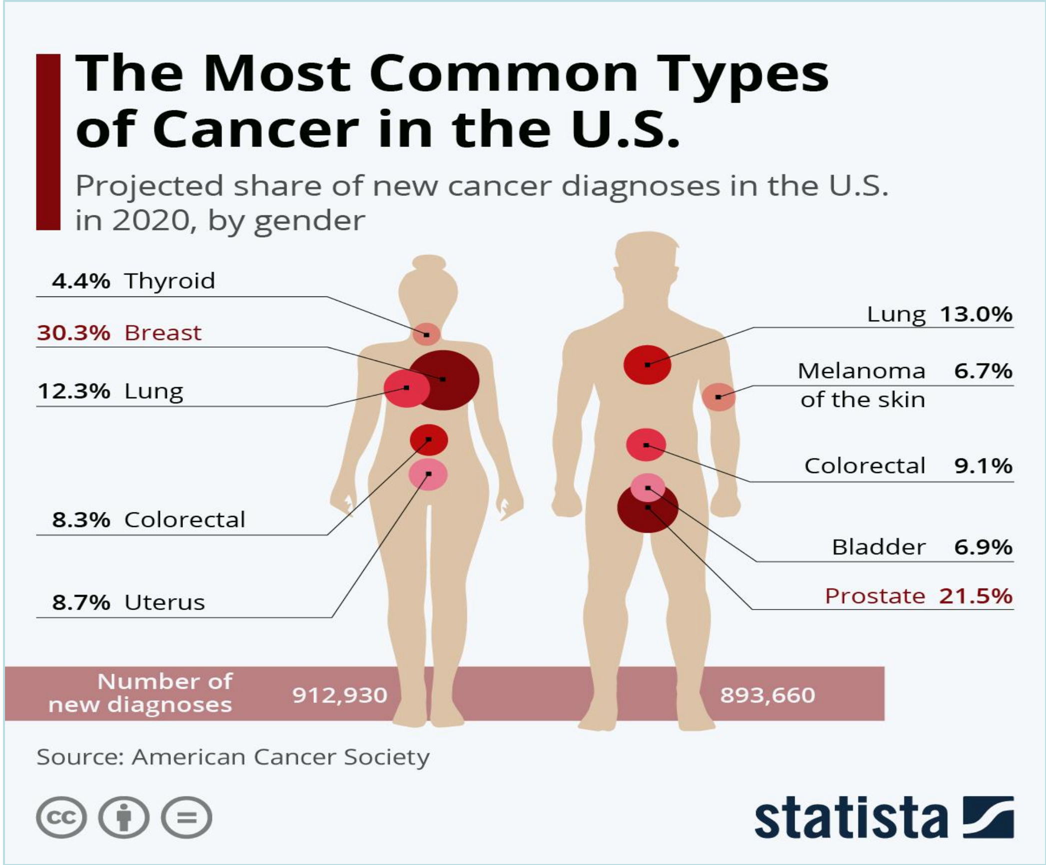
Tissue Imaging

- Invasive Imaging
- Used to study the disease symptoms through microscopic examination of a biopsy or surgical specimen.
- Hematoxylin-Eosin (H&E) staining performed to reveal different cellular parts
  - Hematoxylin stains cell nuclei as blue
  - Eosin stains cytoplasm and connective tissue pink.

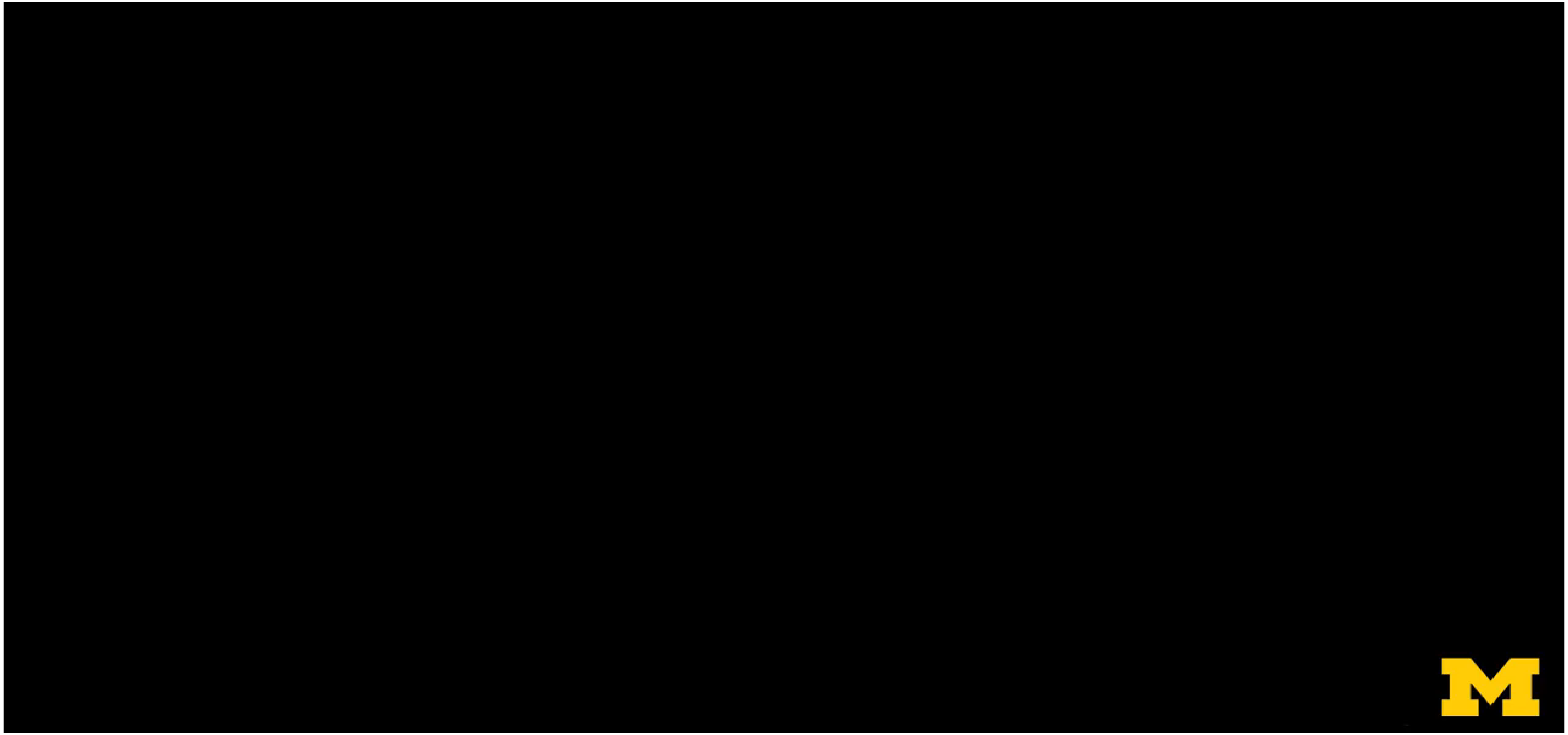



Cancer Cases In
India
Estimated To Be
13.9 Lakh In 2020
May Rise To
15.7 Lakh
By 2025
National Cancer Registry Programme
Report 2020
CANCER
AffairsCloud


CANCER BURDEN IN 2018
Socio-economic inequalities a major cause for rapid rise in cancer cases in India, says a study
NEW CASES
1.16 million
DEATHS
7,84,800
Number of cases of six most common types of cancer
Breast cancer 1,62,500
Oral cancer 1,20,000
Cervical cancer 97,000
Lung cancer 68,000
Stomach cancer 57,000
Colorectal cancer 57,000
In men | Oral, lung, stomach, colorectal and oesophageal cancer accounted for 45% of new cancer cases
In women | Breast, cervical, ovarian, oral and colorectal cancer account for 60% of cases
Source: WHO's World Cancer Report


The Most Common Types of Cancer in the U.S.
Projected share of new cancer diagnoses in the U.S. in 2020, by gender
4.4% Thyroid
30.3% Breast
12.3% Lung
8.3% Colorectal
8.7% Uterus
Lung 13.0%
Melanoma of the skin 6.7%
Colorectal 9.1%
Bladder 6.9%
Prostate 21.5%
Number of new diagnoses
912,930
893,660
Source: American Cancer Society
statista

Biopsy to Diagnosis



Courtesy : University of Michigan

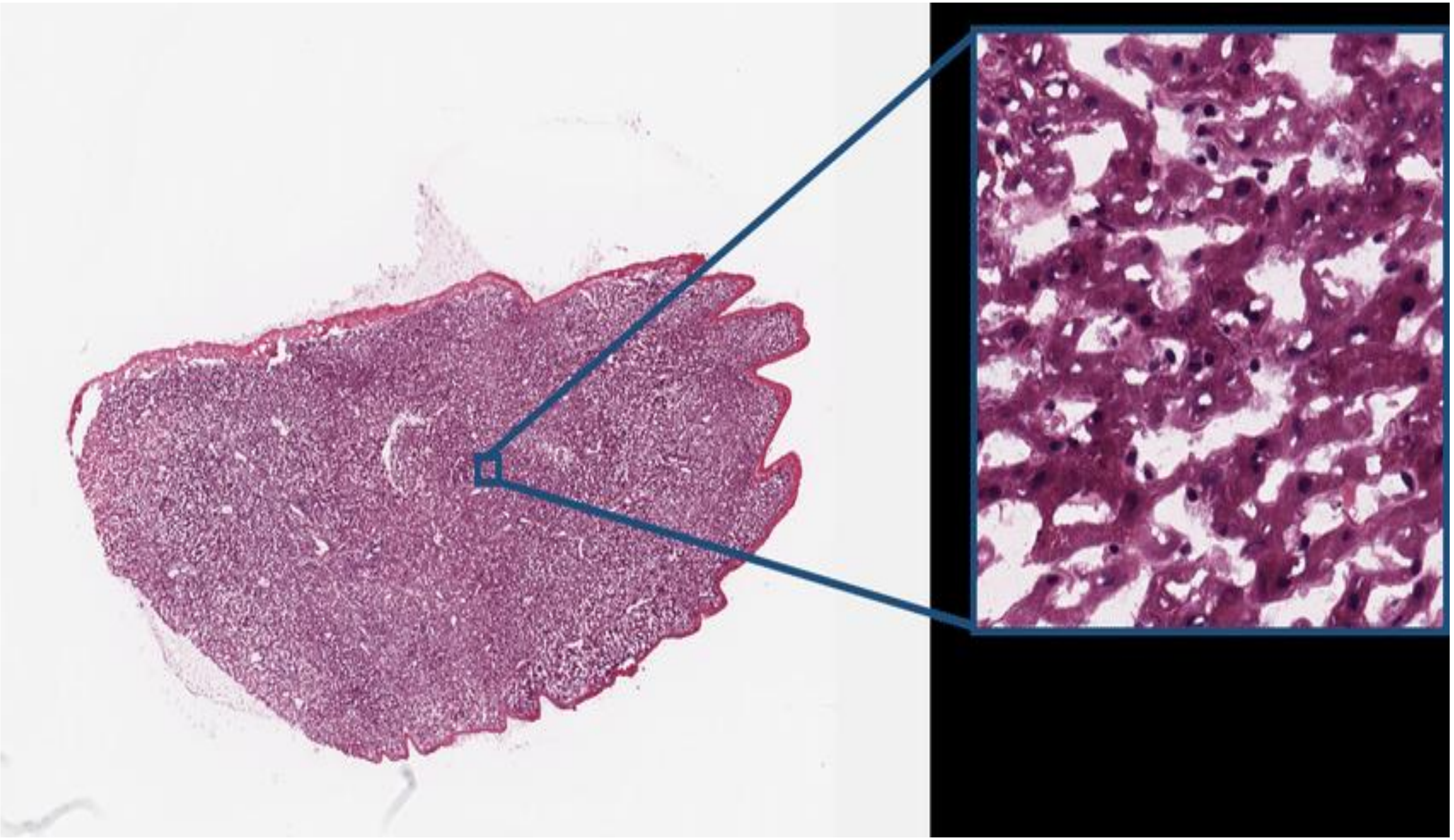
Digital Pathology

Courtesy : National Science and Media Museum

Digital Pathology

In digital pathology, thin slices of biological tissue are scanned using optical microscopy to produce whole-slide images.

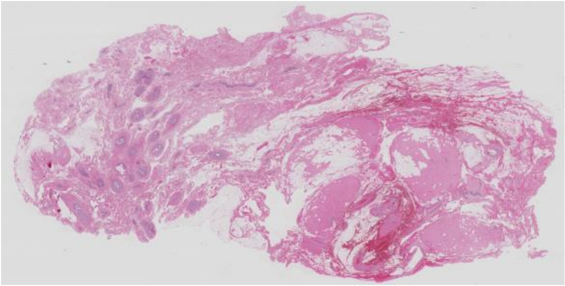
As a result of the high spatial resolution employed in digital pathology, whole-slide images exhibit very large dimensions.

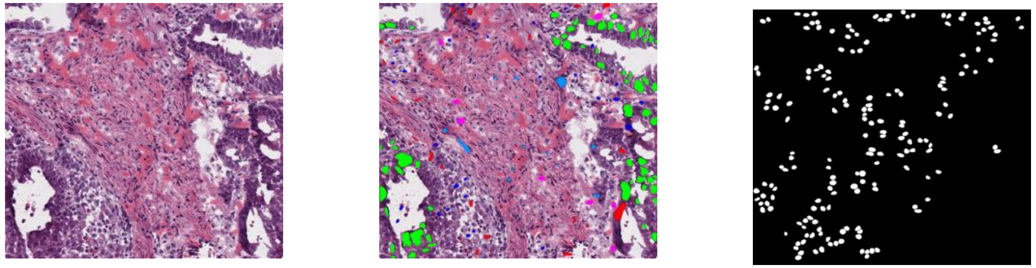


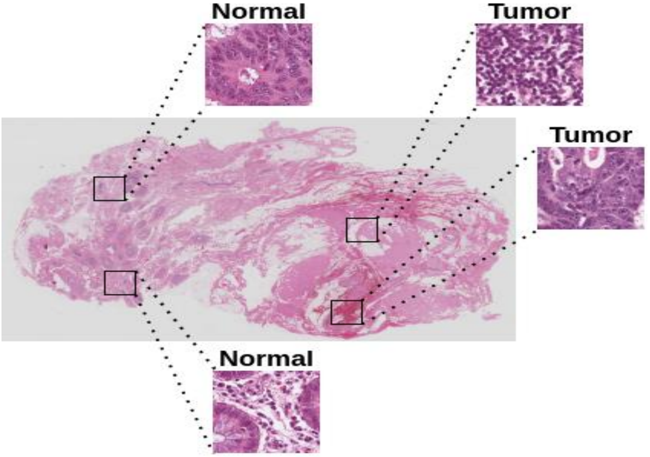
https://www.researchgate.net/publication/320511493_The_Current_Role_of_Image_Compression_Standards_in_Medical_Imaging

Whole Slide Images

- **<u>WSI:</u>** Whole Slide Image (WSI) or Histopathology WSI is digitized image of a tissue sample (biopsy).
- **<u>Need:</u>** Such images are central to Histopathology and microscopic study of diseased cells and tissues.
- **<u>Cancer:</u>** They are considered the gold standard for cancer diagnosis.
- **<u>Experts:</u>** Pathologists view biopsy under the microscope and investigate for tumor, cancerous, anomalous patterns.



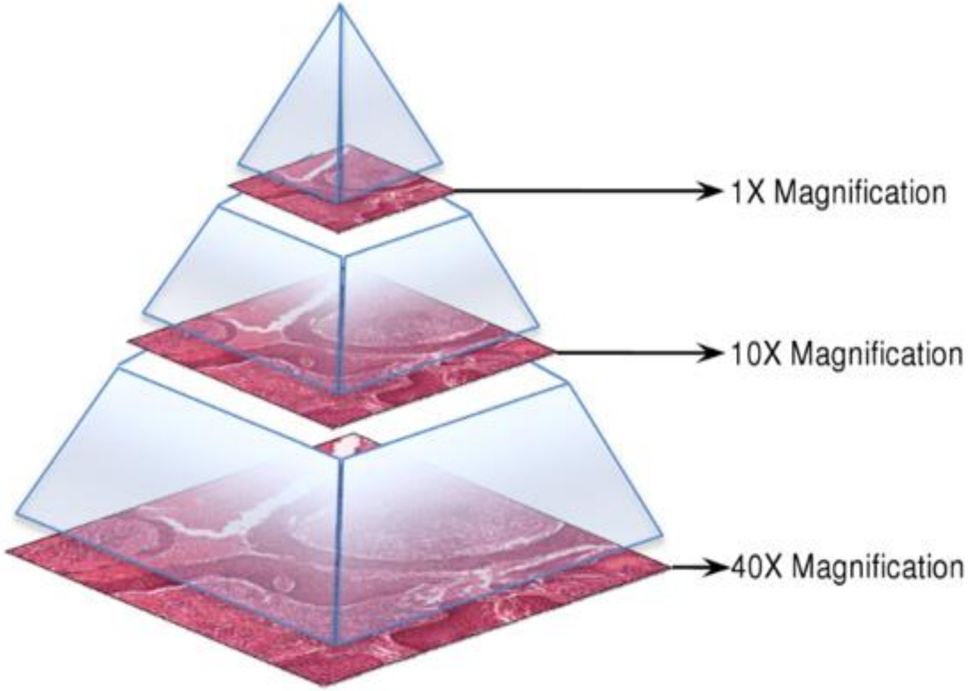




Properties of Tissue Images

- Tissues in the form of SVS (Scanscope Virtual Slides) are scans of microscope slides at 20X, 40X or 64X using an Aperio slide scanner.

- The highest resolution image can have image sizes ranging **<u>60000 - 100000 pixels (RGB) or $O(10^9)$ or Giga Pixels</u>**



<u>Scanscope Virtual slide (SVS)</u>

Deep Learning in Histopathology

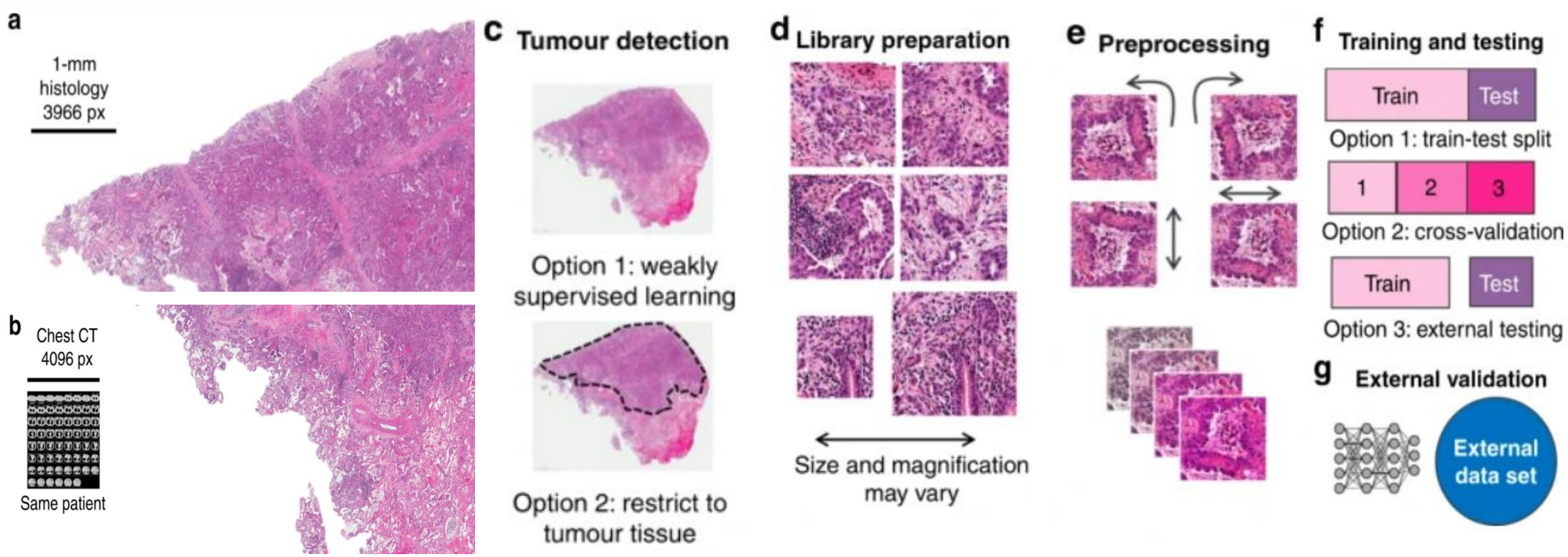
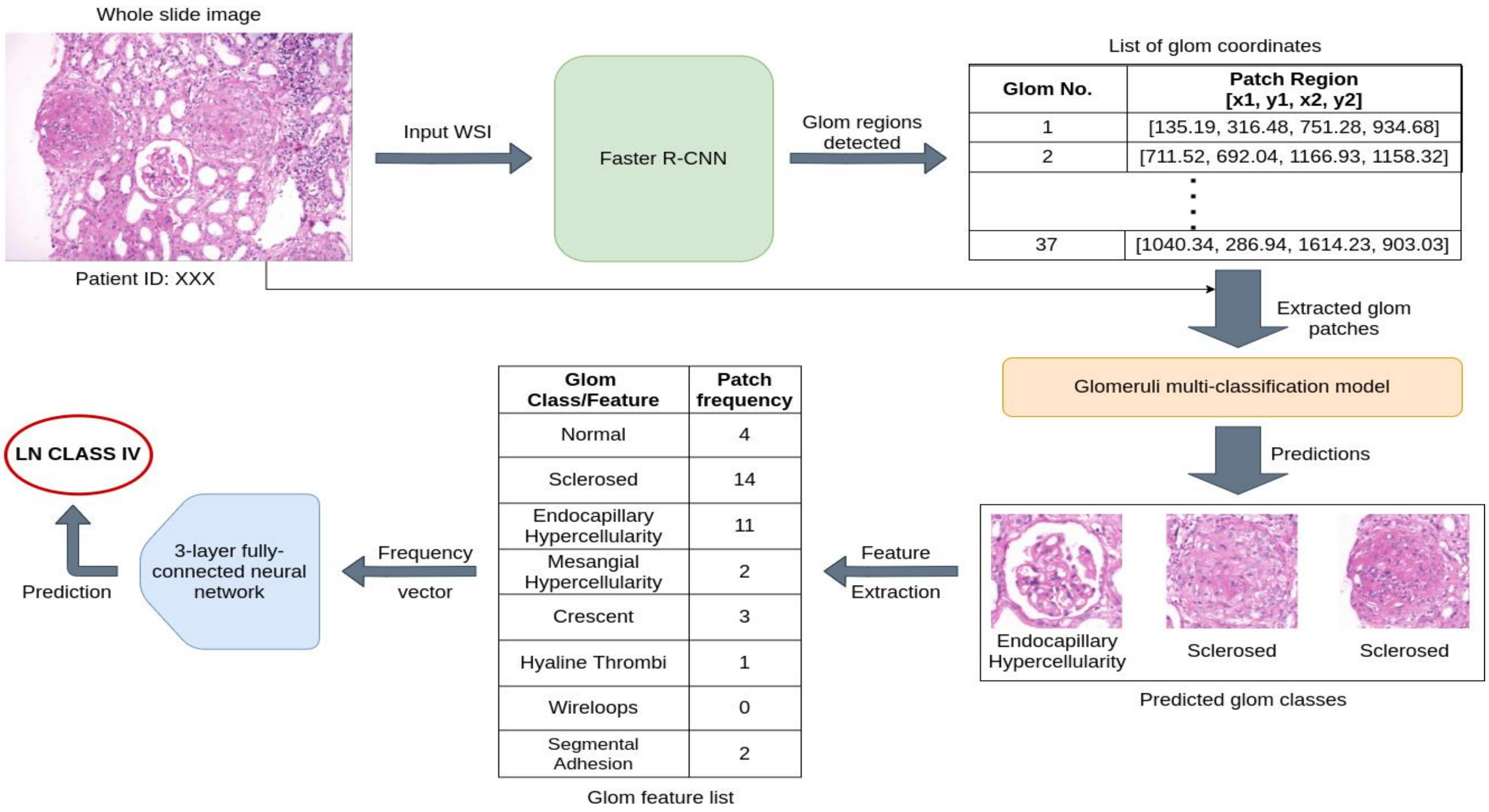


Fig. 1 Consensus pipeline of deep learning in pathology. a Routine histology image of lung cancer (from The Cancer Genome Atlas (TCGA) and The Cancer Imaging Archive (TCIA)). **b** Size comparison (in terms of pixels) of a chest CT scan of the same patient. **c** Consensus image-processing pipeline. First, either the whole slide or just the tumour region is tessellated into smaller image tiles. **d** These tiles comprise an image library, similar to the library preparation (prep.) in genome sequencing. **e** Tiles are preprocessed to achieve rotational constancy and augment the dataset. **f** Deep- learning classifiers are developed and deployed by splitting the patient cohort into a training and testing set, by using cross-validation or by having multiple cohorts available for training and testing. **g** Ideally, an additional external dataset is used for validation of the resulting classifier.

Deep learning in cancer pathology: a new generation of clinical biomarkers- Amelie Echle, Niklas Timon Rindtorff, Titus Josef Brinker, Tom Luedde, Alexander Thomas Pearson & Jakob Nikolas Kather *British Journal of Cancer, 2021*

Eg. Classification of histopathology images



Classification of histopathology images using ConvNets to detect Lupus Nephritis – Akash Gupta, Anirudh Reddy, CV Jawahar, PK Vinod

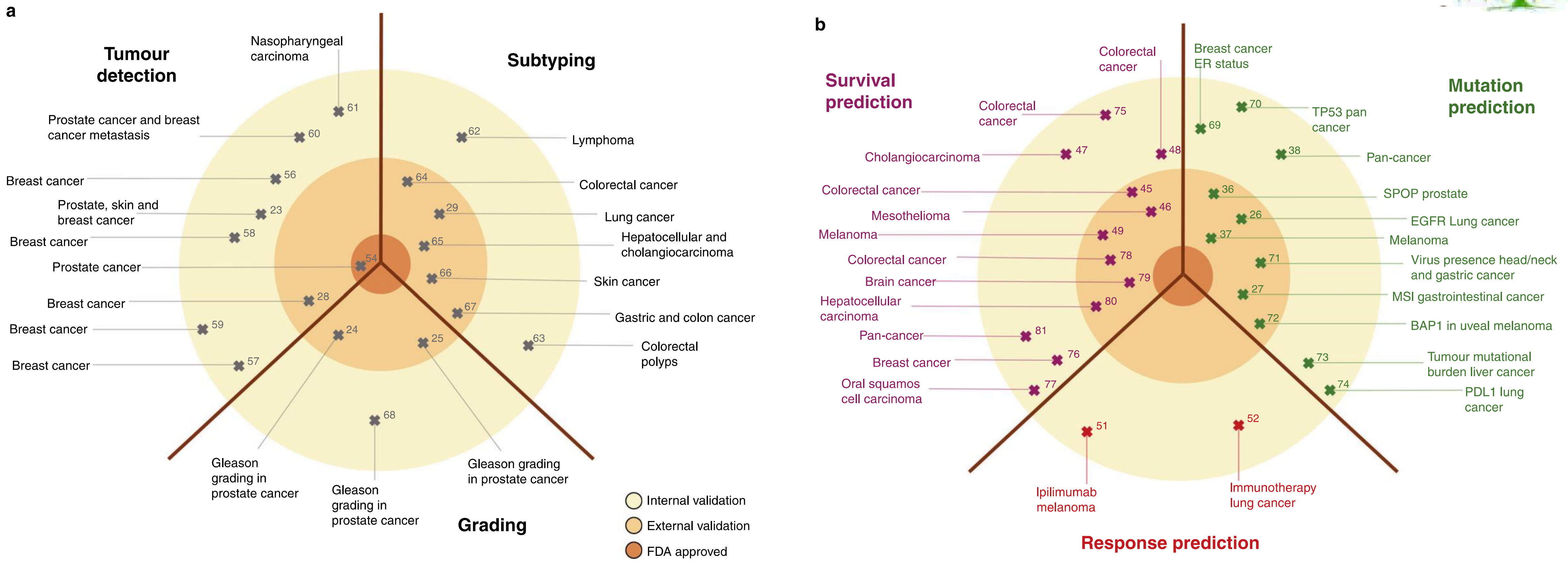


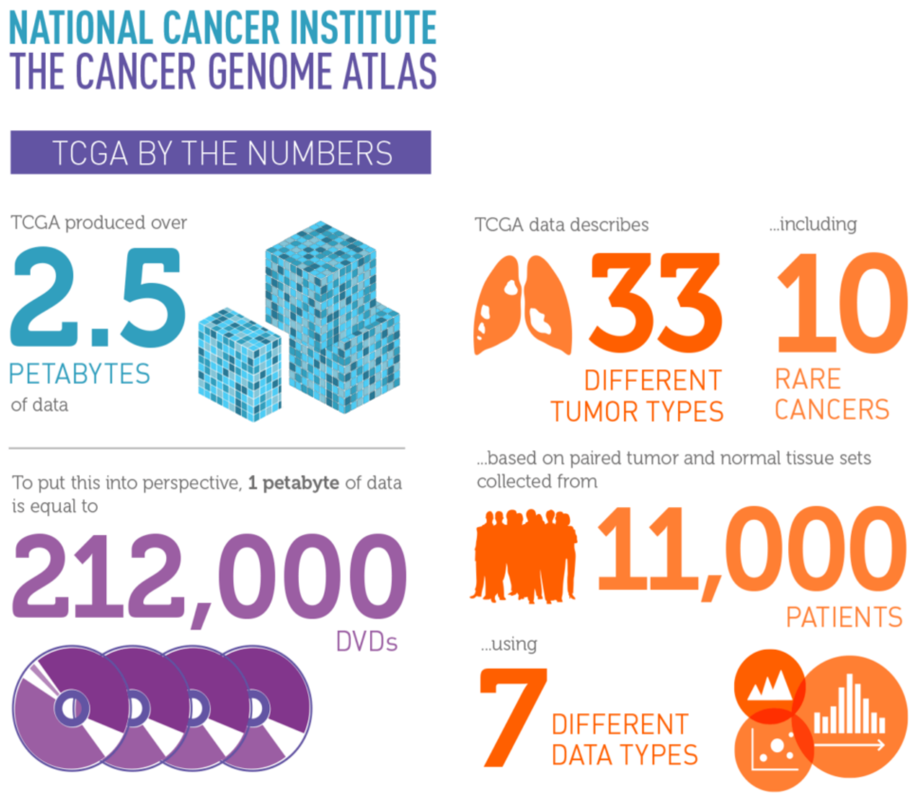
Fig. 2 Clinical applications of basic and advanced deep-learning (DL) image analysis in histopathology. DL pathology can be applied to tumour detection and identification of subtype (basic applications) or to predict clinical features of interest (advanced application). Published studies (indicated by reference number) are classified according to the level of evidence (monocentric (internally approved), multicentric (externally approved) or FDA approved). **a** Basic image analysis tasks, including tumour detection, grading and subtyping. **b** Advanced image analysis tasks, including those that exceed pathologists' routine capacities, such as prediction of mutation, prognosis and response. AI artificial intelligence, NSCLC non-small-cell lung cancer, WSI whole-slide image, ER oestrogen receptor, MSI microsatellite instability, GI gastrointestinal, SPOP speckle-type BTB/POZ protein, BAP1 BRCA-associated protein 1, HNSCC head and neck squamous cell carcinoma, CCA cholangiocarcinoma.

Deep learning in cancer pathology: a new generation of clinical biomarkers- Amelie Echle, Niklas Timon Rindtorff, Titus Josef Brinker, Tom Luedde, Alexander Thomas Pearson & Jakob Nikolas Kather *British Journal of Cancer, 2021*

3. Data and Annotated Data

Popular Datasets

Title	Tissue Source	Annotations	Size	Publisher
TCGA	33 organs	Slide level cancer/non cancer + Genomics + Patient Metadata	2500 TB	NIH (US gov)
CAMELYON	Lymph nodes	Pixel level metastasis mask	2.95 TB	Litjens et.al, Radboud Univ
ICIAR	Breast	Patch level 4 classes normal, benign, in-situ, invasive	13 GB	Araujo et. al, FEUP Portugal
NCT-CRC	Colorectal	Patch level 8 classes TUM, ADI, LYM, MUC etc.	12 GB	NCT Germany
BreaCaCHAD	Breast	Patch level 7 classes	982 MB	Aksak et.al
Kaggle	Breast	Patch level invasive / non-invasive	1.6 GB	Case Univ



Many Tasks

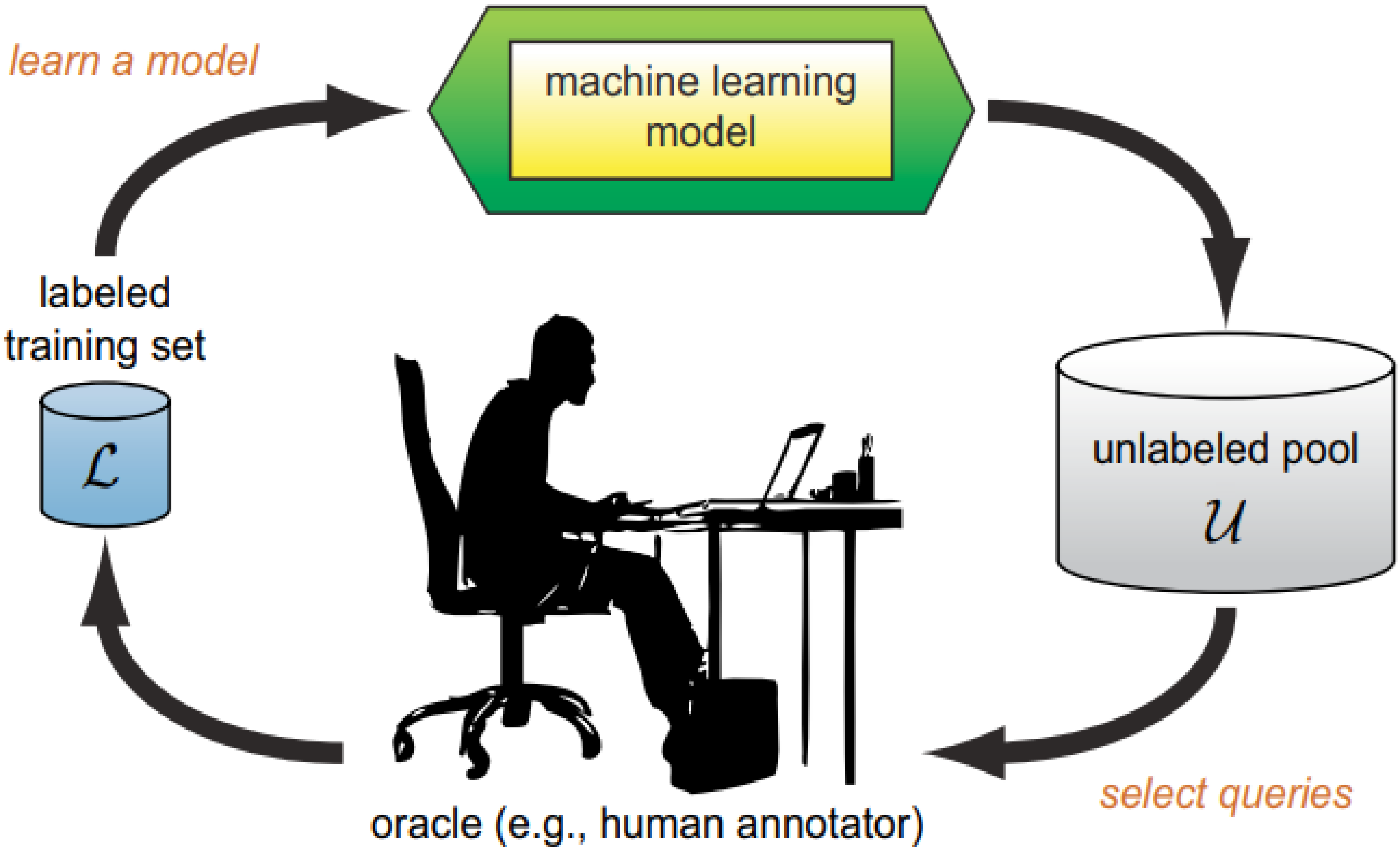
- **Annotation**
  - Slide
  - Patch
  - Regions
- **Prediction Models**
  - Disease, Subtyping
  - Survival
  - Severity, Grading
  - Localization
- **Discovery**
  - Novel patterns
  - New trends
  - Biological insights (eg. origin of cancer)
- **Applications**
  - Telemedicine
  - Effective Storage
  - Community centric solutions

Challenges

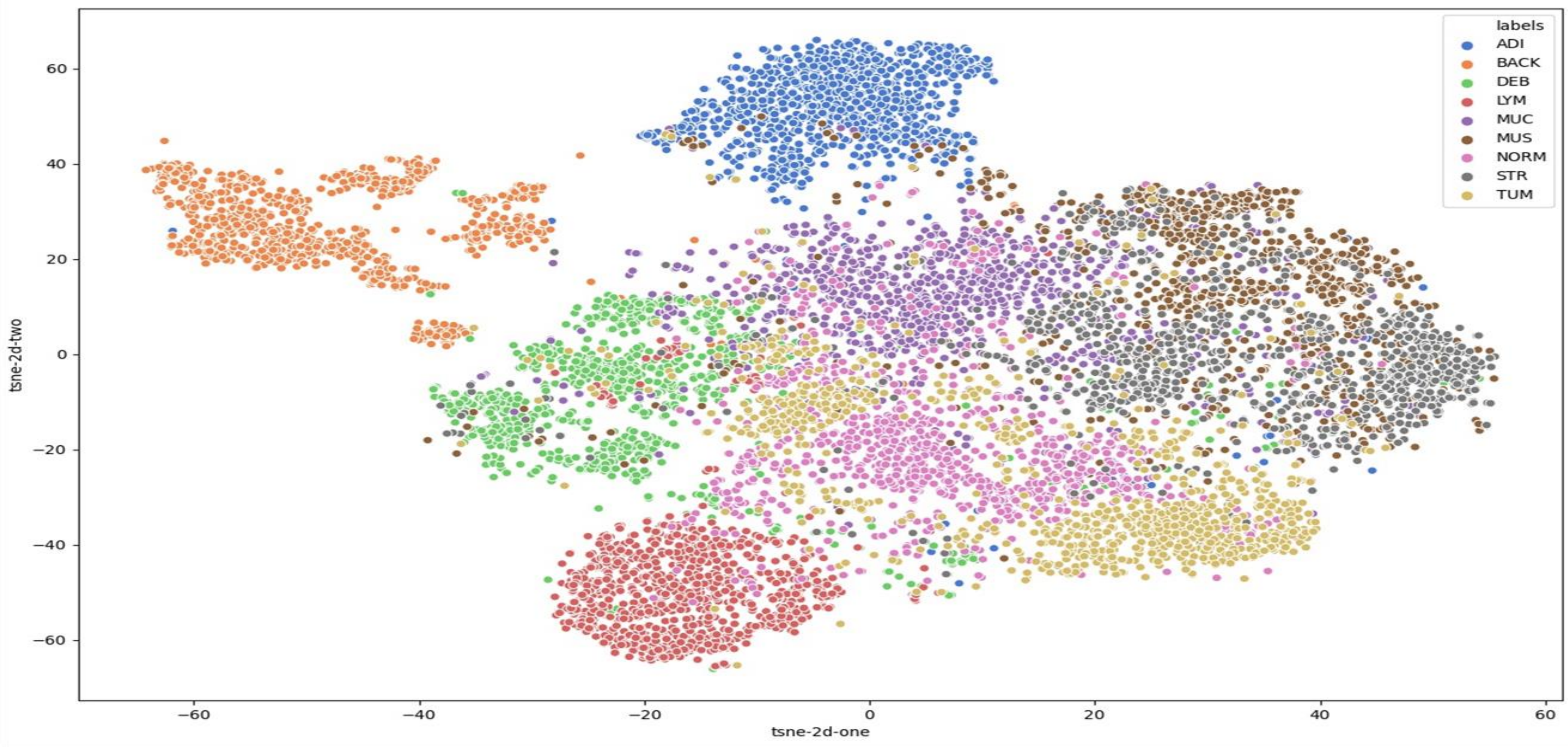
- Large image sizes
  - Patch based methods popular (spatial relationship lost)
  - Patch wise aggregation on the basis of probability score
- Data
  - Lack of data and annotated data
  - Different regions
- Variability
  - Challenges due to stain differences, quality,
  - initra-class variability, sensor/scanner changes
- Laborious for Human experts
  - Annotation, Resolution; Shortage of experts.

Jeroen A. van der Laak, Geert J. S. Litjens, and Francesco Ciompi. "Deeplearning in histopathology: the path to the clinic." In:Nature medicine 275 (2021), pp. 775–784
Daisuke Komura and Shumpei Ishikawa. "Machine Learning Methods forHistopathological Image Analysis". In:Computational and Structural Biotech-nology Journal 16 (2018), pp. 34–42

Human in the loop Labelling

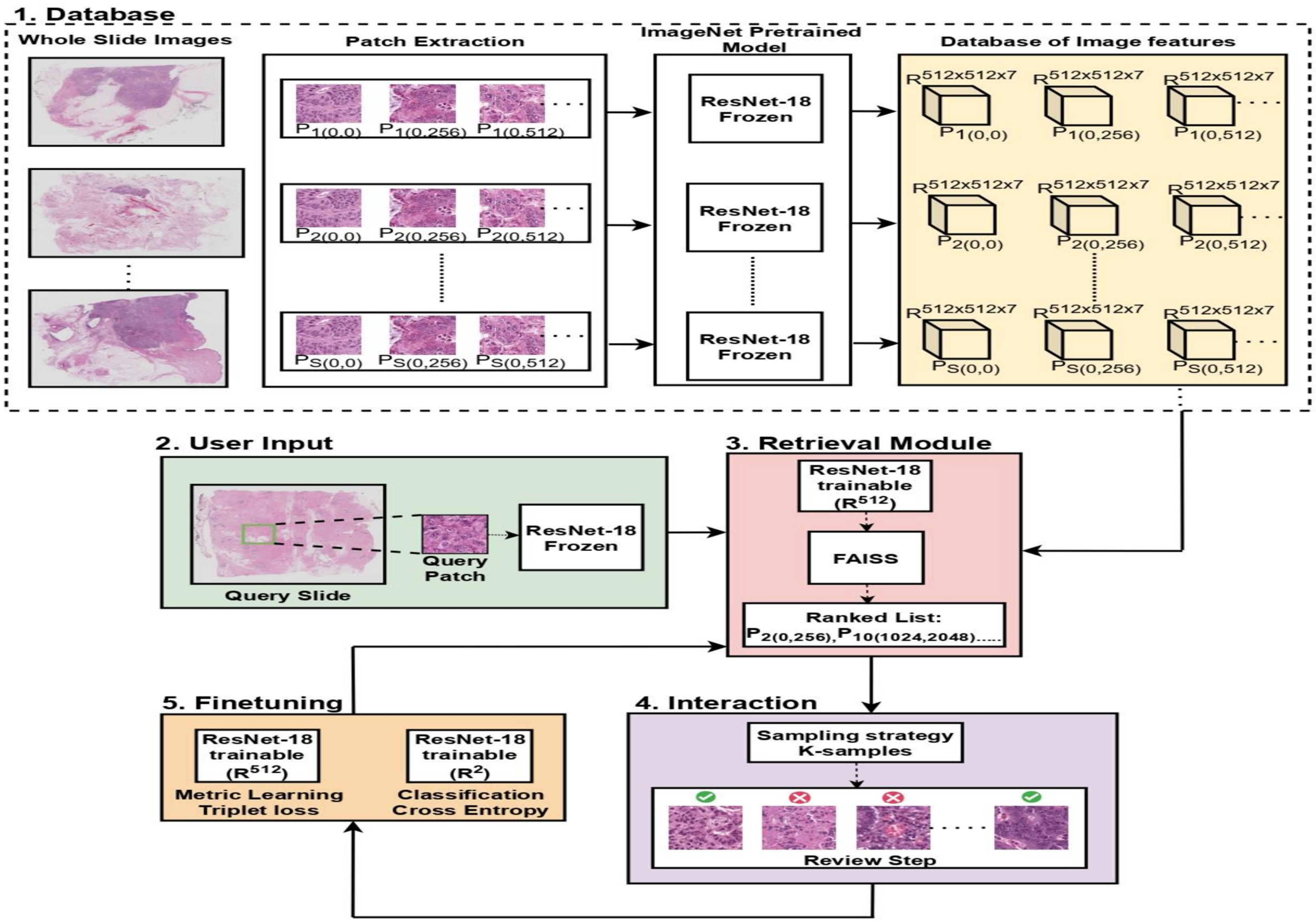


Deep Feature Representations



TSNE-visualization of ImageNet pre trained ResNet-18 embeddings for patches (CRC dataset.)

Efficient Annotation

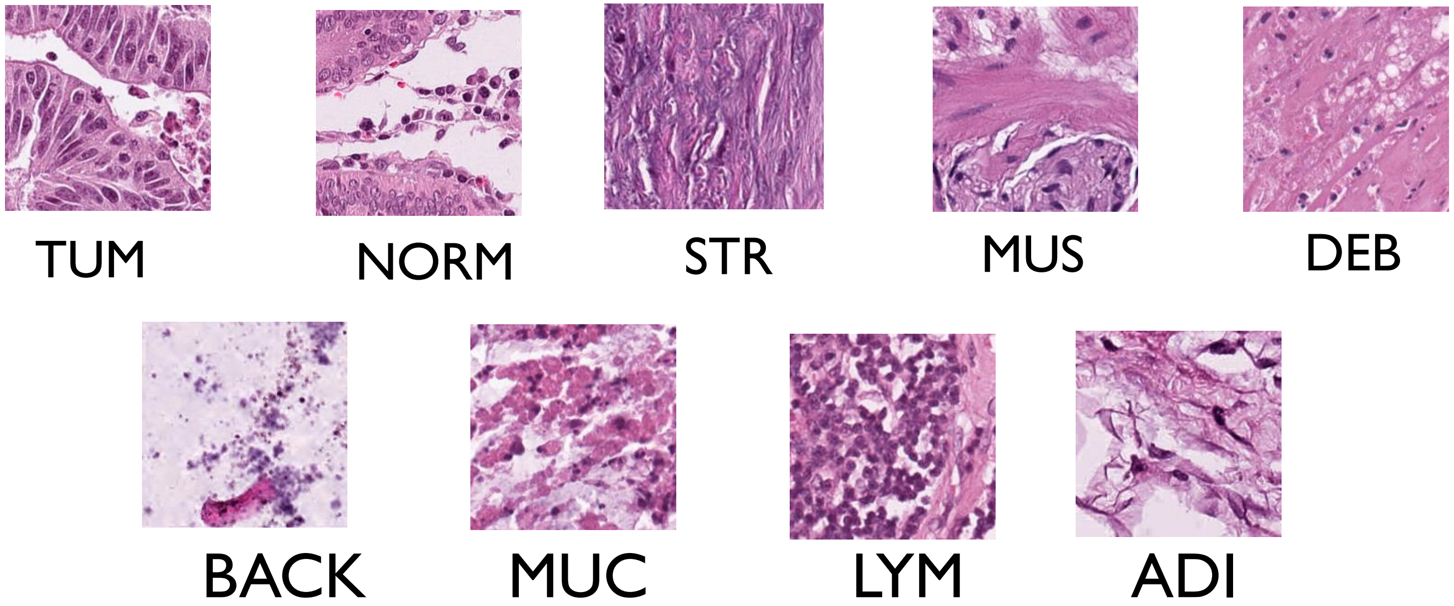


Ashish Menon, Piyush Singh, P. K. Vinod, and C.V. Jawahar Interactive Learning for Assisting WSI Annotation, ACPR, 2021

Examples and Datasets

Class Labels	MUC	MUS	NORM	STR	TUM	ADI	BACK	DEB	LYM
Search DB	8886	13526	8753	10436	14307	10397	10556	11502	11547
Held out test set	1035	592	741	421	1233	1338	847	339	634
Query DB	10	10	10	10	10	10	10	10	10

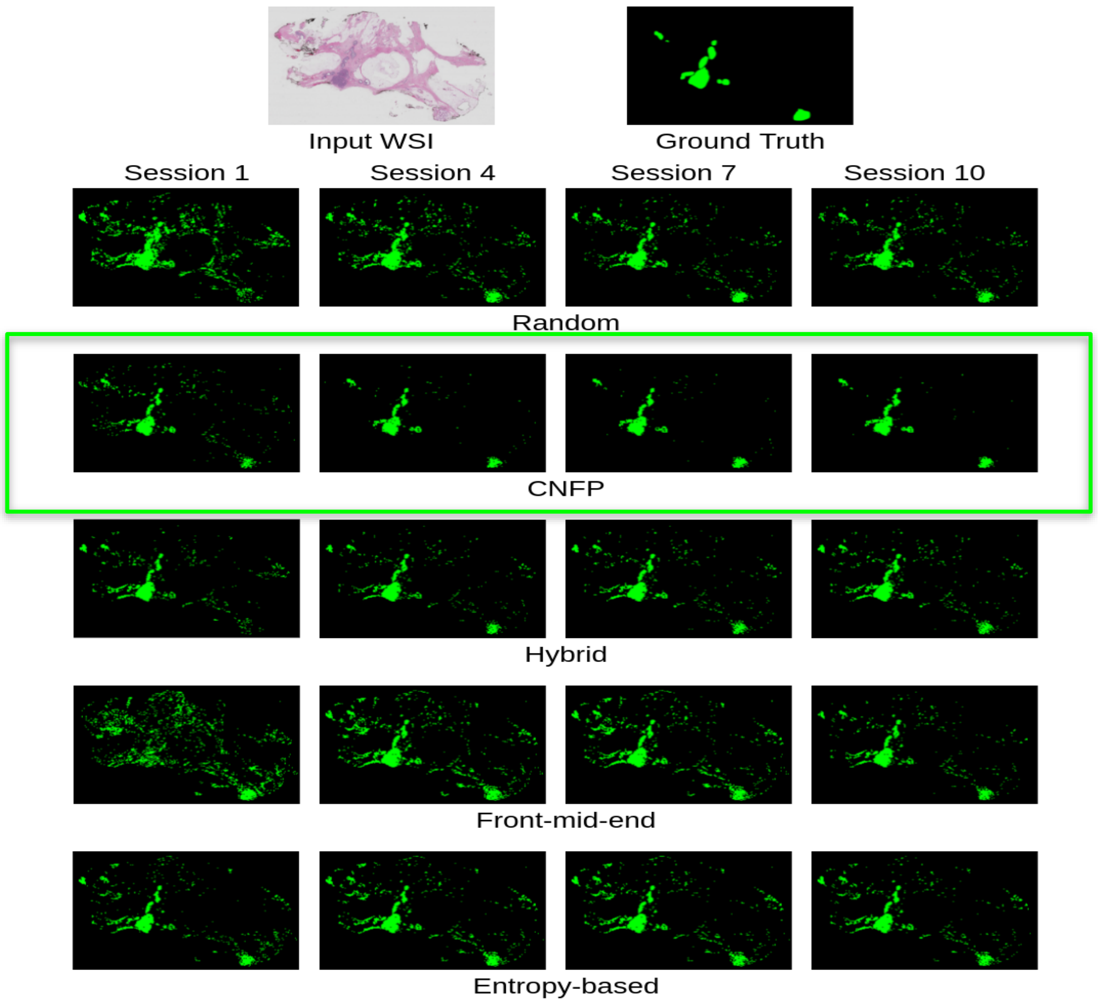
Number of images present in each class



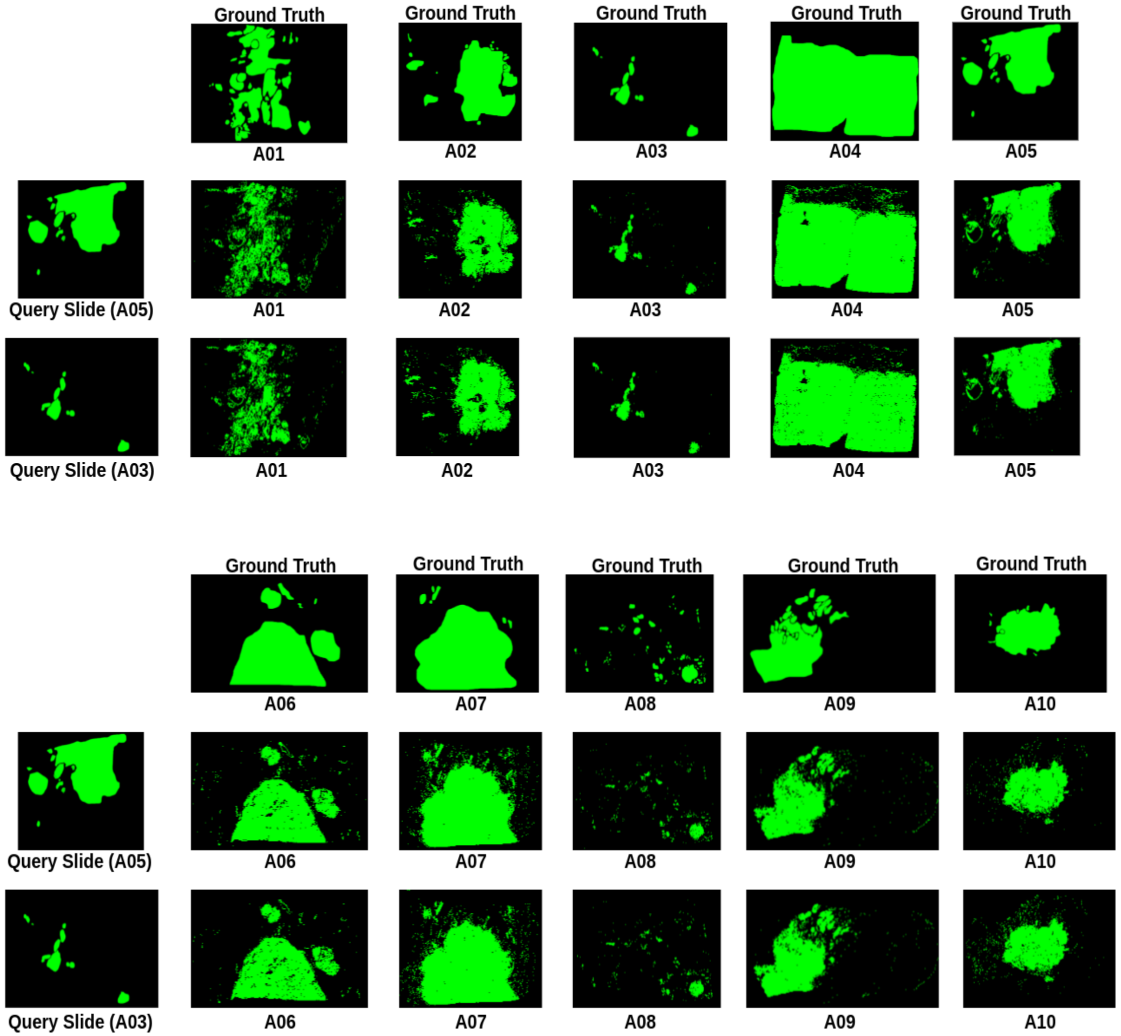
Sample Images of each class

NCT-CRC Data set

Qualitative Results (ICIAR dataset)



Annotation output of a sample slide across feedback sessions



Annotation outputs using multiple query slides with the CNFP strategy

Ashish Menon, Piyush Singh, P. K. Vinod, and C.V. Jawahar Interactive Learning for Assisting WSI Annotation, ACPR, 2021

Comparison

Work	Sampling Method	Type of Interaction	Reduction (↑)	Patch Annotations	Slide Annotations	Prior Annotations?
[1]	Variational drop-out based uncertainty sampling	160 patches per round.	**45%**	✓	×	×
[2]	Conditional random fields in a spatially adaptive manner.	Grid based method, 9 patches per grid.	**38%**	✓	✓	×
[3]	Novel FCN representation with uncertainty and similarity estimates.	Larger regions of Slide Images, 8 per round.	**50%**	×	✓	✓
[4]	Attention gated FCN (ag-FCN) with a distribution-discrepancy measure.	Larger regions of Slide Images, 16 per round.	**54%**	×	✓	✓
ACPR2021	Sampling from a ranked list using a distance metric learning based approach	10 Patches per round.	**>95%**	✓	✓	×

[1] Lukasz Raczkowski et al. "ARA: accurate, reliable and active histopathological image classification framework with Bayesian deep learning". In: Scientific Reports 9 (2019)

[2] Yiqing Shen and Jing Ke. "Representative Region Based Active Learning For Histological Classification Of Colorectal Cancer". In:2021 IEEE 18th International Symposium on Biomedical Imaging (ISBI)(2021), pp. 1730–1733

[3] L. Yang et al. "Suggestive Annotation: A Deep Active Learning Framework for Biomedical Image Segmentation". In:MICCAI. 2017.

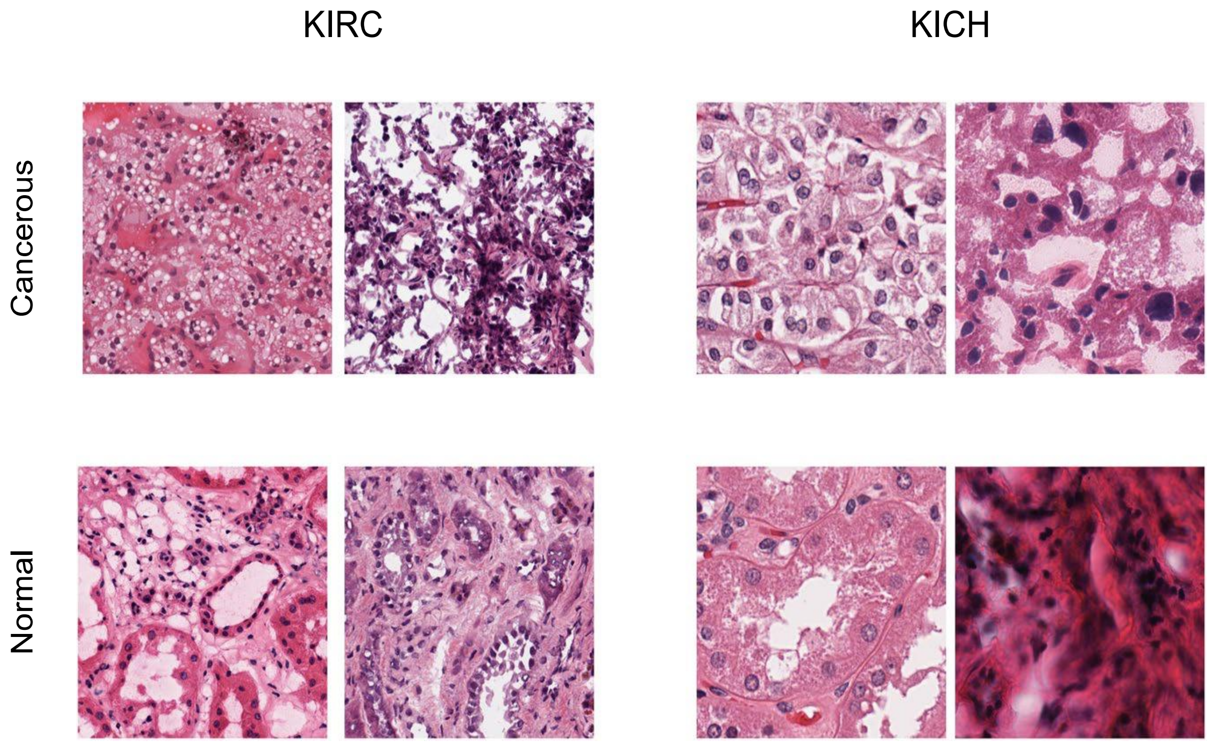
[4] Haohan Li and Zhaozheng Yin. "Attention, Suggestion and Annotation:A Deep Active Learning Framework for Biomedical Image Segmentation".In: MICCAI. 2020

Realities

- Costly
  - Fully supervised DL models are often data hungry.
  - Creating labelled data could be very costly.
    - Eg. Need of Experts even for Annotation. Laborious.
- Availability
  - For many tasks/domains, even the availability of samples/images may be a challenge
- Assumption
  - Both training and testing data are sampled from the same distribution. When they differ, performance degrades significantly.
    - In practice, they could differ or drift.

4: Supervised Formulation

Example: Kidney Cancer



Cancerous Vs Normal at 40 X resolution

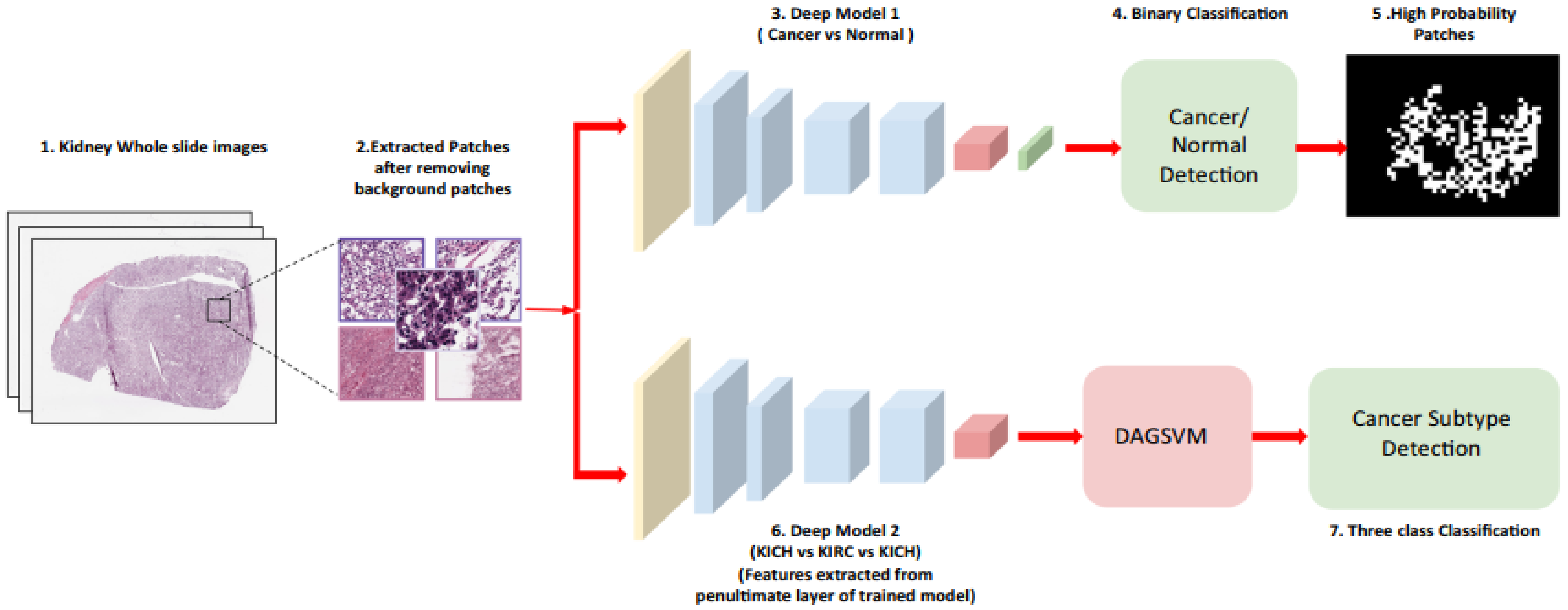
- Among the top-10 cancers
- Renal Cell Carcinoma (RCC)
  - most common malignancy
- Sub-Types
  - Clear cell RCC (KIRC)
  - Papilary RCC (KIRP)
  - Chromophobe RCC (KICH)

Challenges

- Visual appearance
- Class imbalance
- Localized appearance

Sairam Tabibu, P. K. Vinod, C.V. Jawahar, Pan-Renal Cell Carcinoma classification and survival prediction from histopathology images using deep learning, Nature Scientific Reports, 2019

Patch Classification

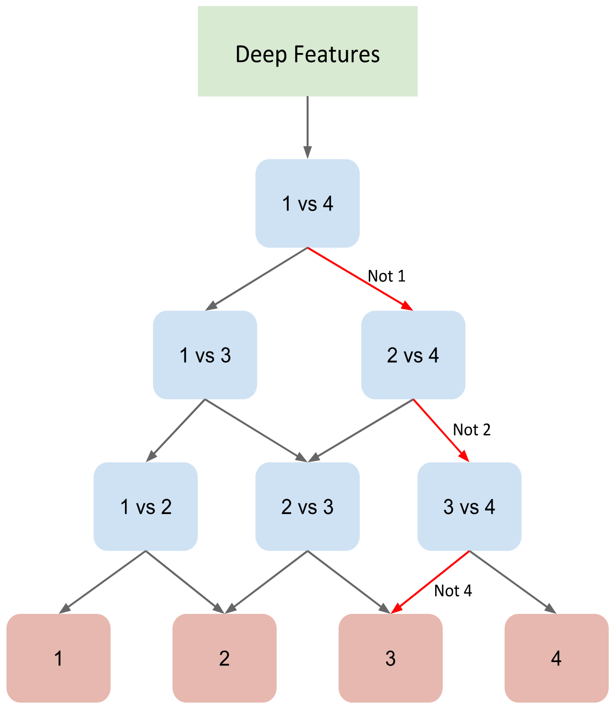


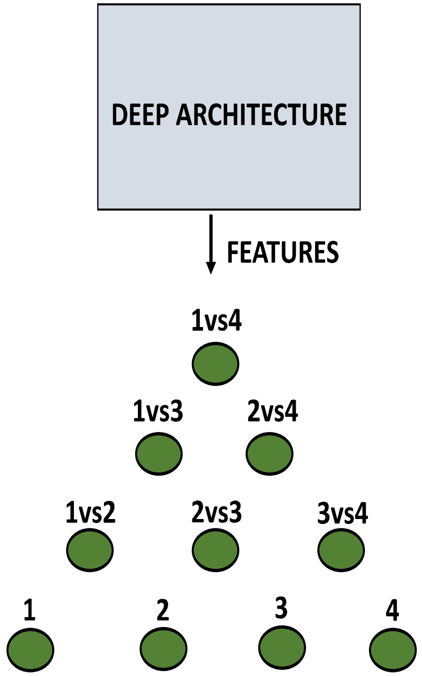
Classification of kidney patches: Cancer/Normal(Top) and subtype classification (Bottom)

Patch Classification

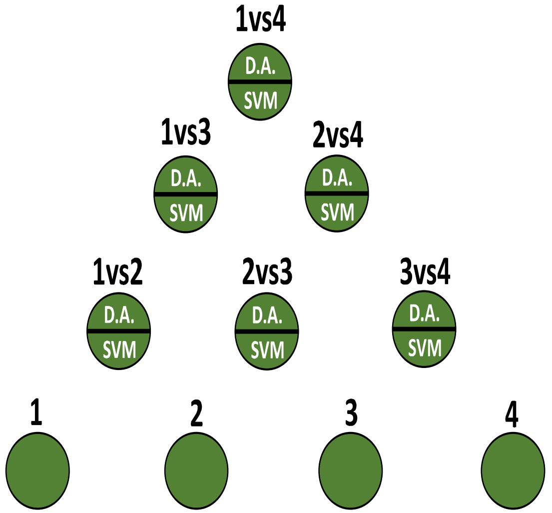
- Patch Extraction
  - Important part of pipeline to ensure data quality
  - Reject patches with less tissue region
- Cancer vs Normal Classification
  - Use Transfer Learning to extract features and replace the original classifier with a trainable classifier with required number of classes (2)
- Subtype classification (KIRC vs KIRP vs KICH)
  - Mixture of deep learning and SVM.
  - Extract features using a pre-trained model and use binary classifiers (SVMs) in a tree fashion for multi-class classification.

Fine Grained Multi-Class Classification





(a)



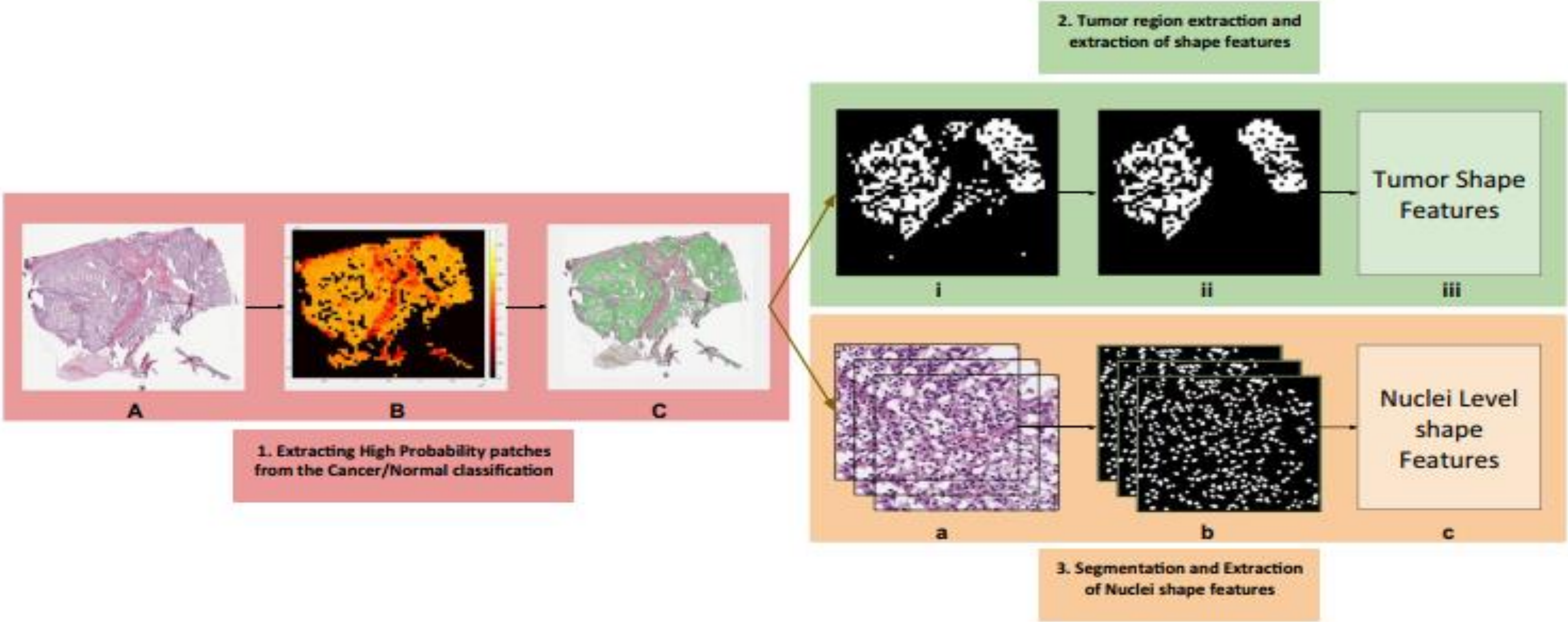
(b)

Performance of the different models on CIFAR-10 dataset. Base model* indicates model after being fine-tuned with triplet loss.

Base model	Method	Accuracy (%)
A	A + Softmax	89.07
	A + DAGSVM	90.76
	A* + DAGSVM	92.50
B	B + Softmax	87.97
	B + DAGSVM	90.17
	B* + DAGSVM	90.95
C	C + Softmax	90.98
	C + DAGSVM	92.52
	C* + DAGSVM	93.69

[1] Nakul Aggarwal, V. N. Balasubramanian, C.V. Jawahar, Improving multiclass classification by deep networks using DAGSVM and Triplet Loss, PRL, 2018
[2] Sairam Tabibu, P. K. Vinod, C.V. Jawahar, Pan-Renal Cell Carcinoma classification and survival prediction from histopathology images using deep learning, Nature Scientific Reports, 2019

Survival Analysis



Survival analysis: Nuclei segmentation using watershed method on high probability patches

Sairam Tabibu, P. K. Vinod, C.V. Jawahar, Pan-Renal Cell Carcinoma classification and survival prediction from histopathology images using deep learning, Nature Scientific Reports, 2019

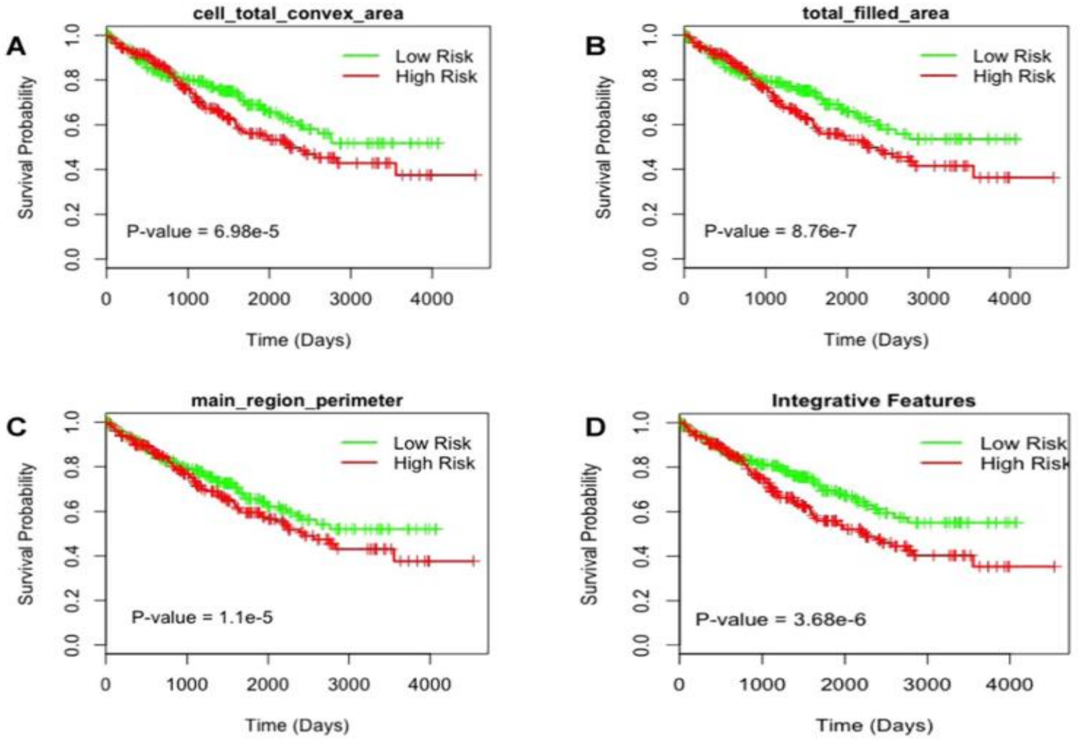
Empirical Results

Model	Patch-wise Accuracy	Precision	Recall	Slide-wise AUC
Resnet-18 (KIRC)	**93.39**	93.41	92.95	0.99
Resnet-34 (KIRC)	93.62	93.47	93.37	0.99
Resnet-18 (KICH)	79.09	79.61	80.06	0.95
Resnet-34 (KICH)	**80.57**	80.65	81.17	0.95

Cancer Vs Normal (40X)

Model	Patch-wise Accuracy	Precision	Recall	Slide-wise AUC
Resnet-18	87.69	88.82	83.66	0.88
Resnet-34	86.19	88.30	83.18	0.88
Resnet-18 + DAG-SVM	**92.62**	90.78	89.07	**0.93**
Resnet-34 + DAG-SVM	**91.96**	88.94	87.92	**0.93**

Cancer Subtype Classification



Geometrical features of nuclei are able to distinguish between high and low-risk patients on a K-M plot

Sairam Tabibu, P. K. Vinod, C.V. Jawahar, Pan-Renal Cell Carcinoma classification and survival prediction from histopathology images using deep learning, Nature Scientific Reports, 2019

5: Pan Cancer Similarities

Cancer similarities using DL

- The Cancer Genome Atlas (TCGA) contains H&E stained histopathology whole-slide images spanning across several organs and subtypes
- Significant work has been done in analysis of individual organs and subtypes using CNNs
- However, not much work has been done towards comparisons and cross-analysis of various organs and subtypes using deep learning
- We did this analysis for most common cancer subtypes as per WHO: breast, colorectal, kidney, liver, lung, prostate, stomach

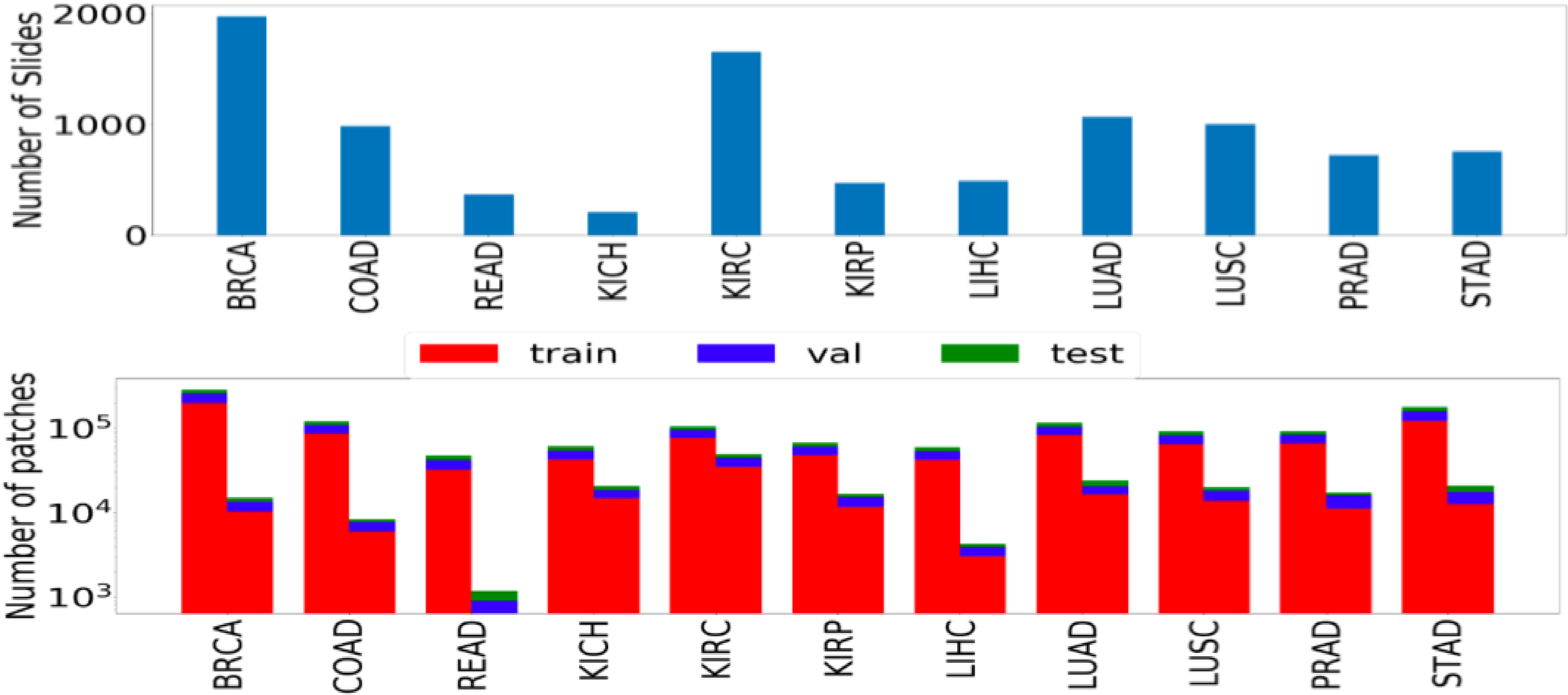


Figure 1: The number of slides and patches used in the study.

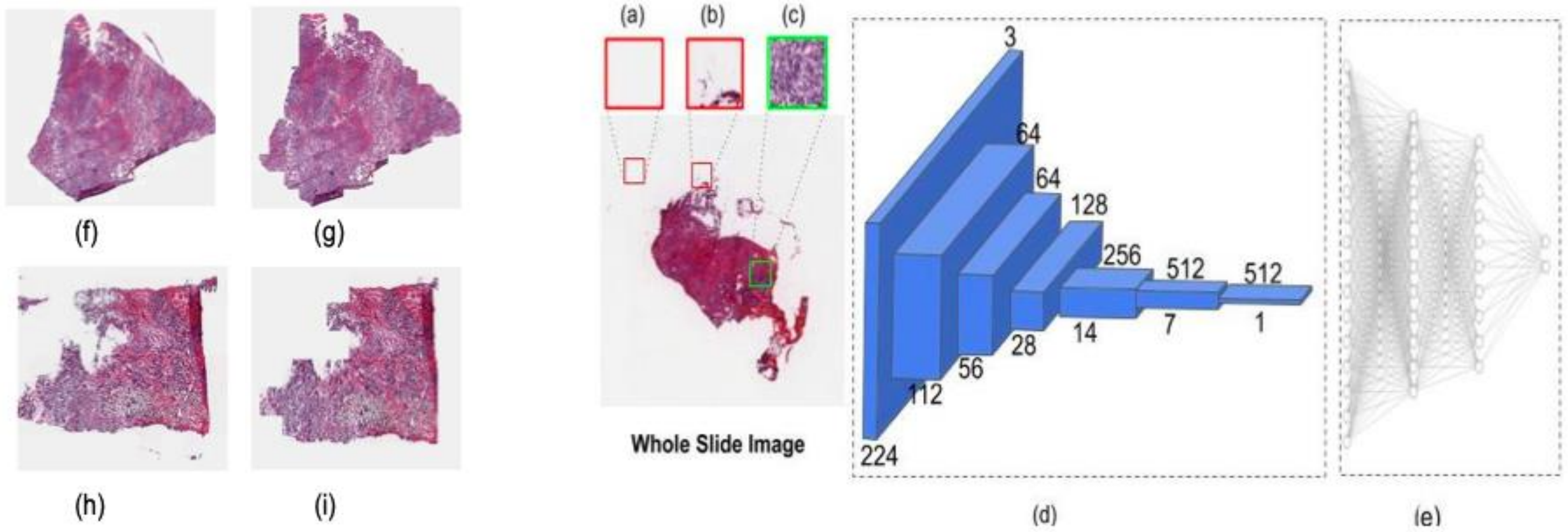


Figure 2: Overview of architecture used in our work: (a), (b) show rejected patches due to background and insufficient tissue material, respectively (c) example of a patch used to train a classifier (d) ResNet-18 architecture. Numbers at the bottom indicate size of feature map and those at the top indicate number of channels (e) Fully connected network(FCN) on top of the 512-dim feature vector. The optimum number of layers and neurons in each layer in FCN is found using a hyperparameter search. (f),(h) sample slide image before patch extraction, (g),(i) slide image reconstructed using patches after extraction

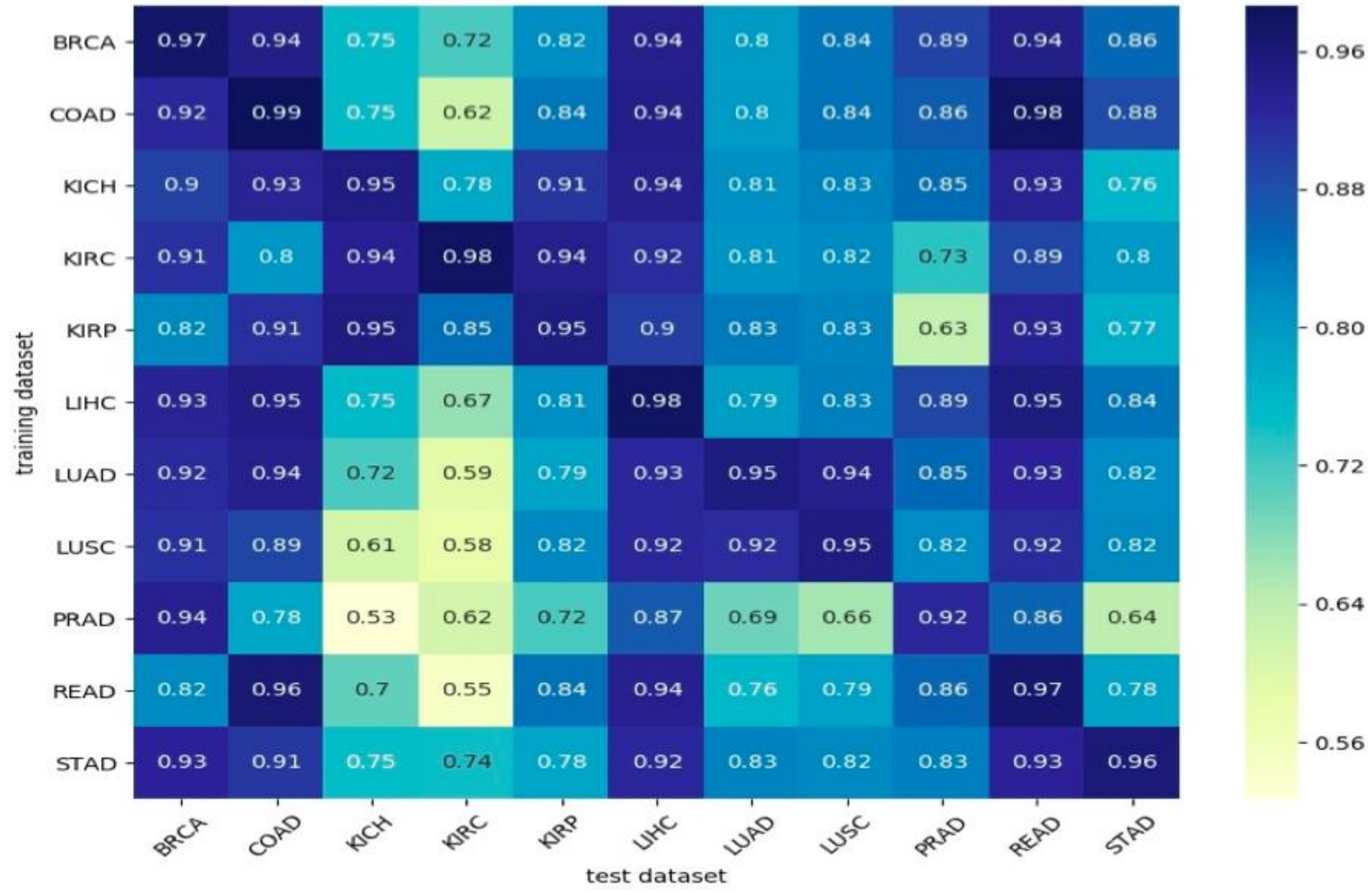
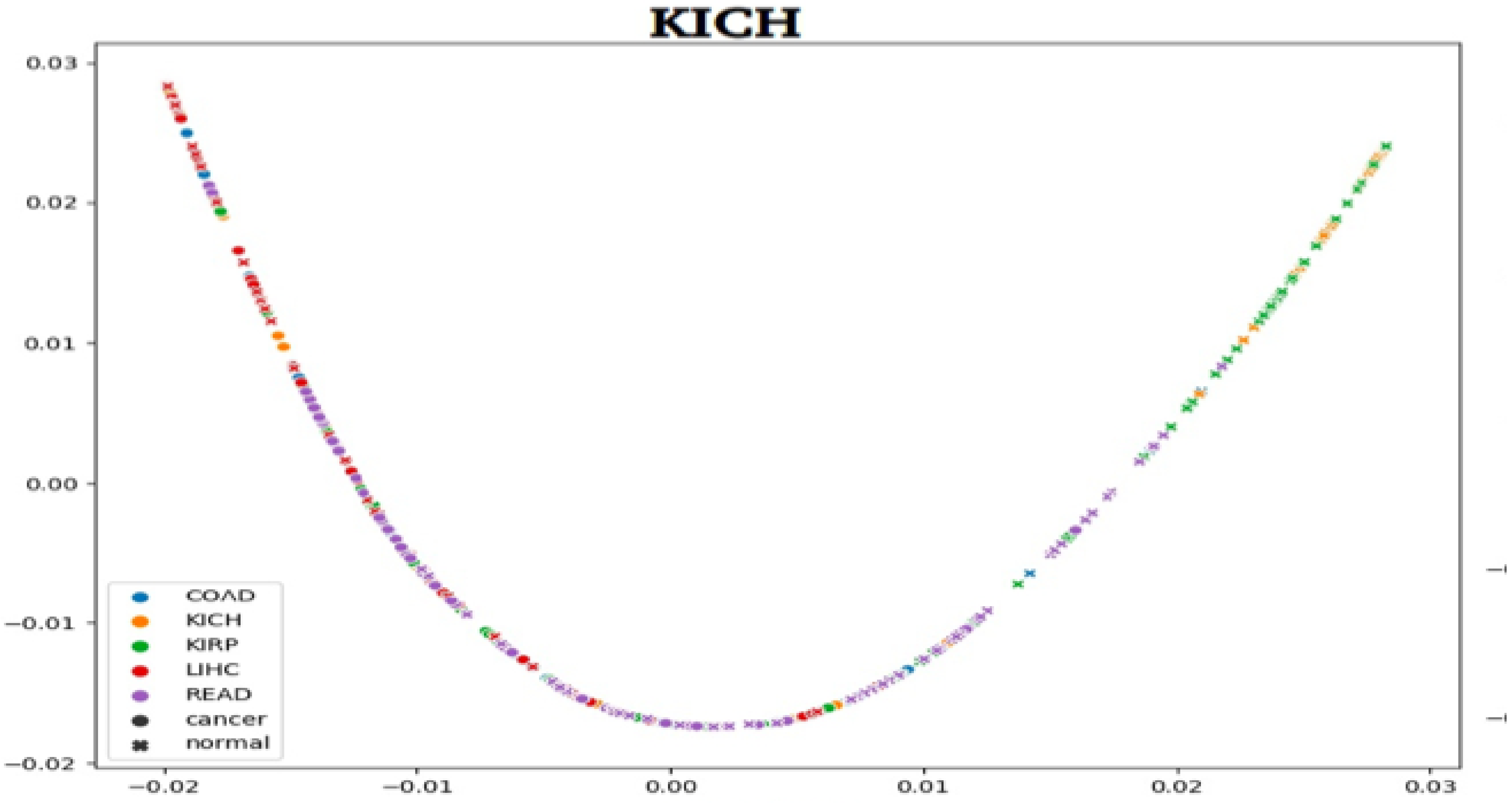
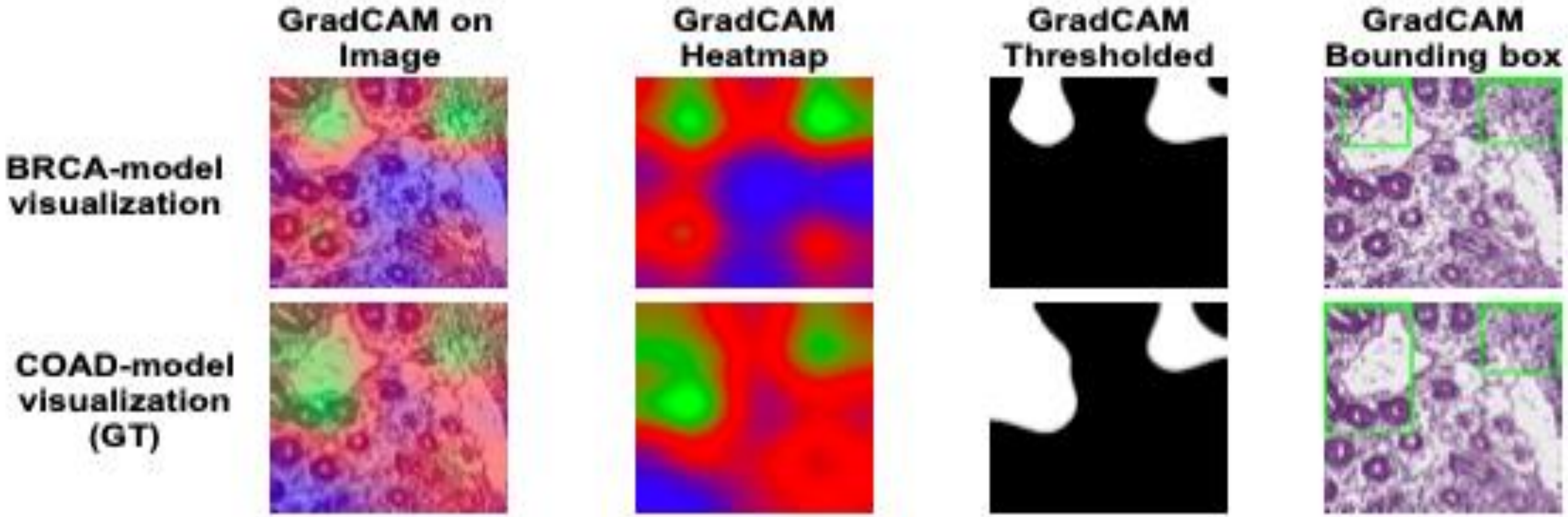


Figure 5: Cross Organ inference results: The table indicates the accuracies obtained using models trained on the organs along the rows and tested on the organs along the column

Demonstrating features separability as per unseen model



GradCAM visualization



Models with high cross-accuracy are also focusing their attention on overlapping regions

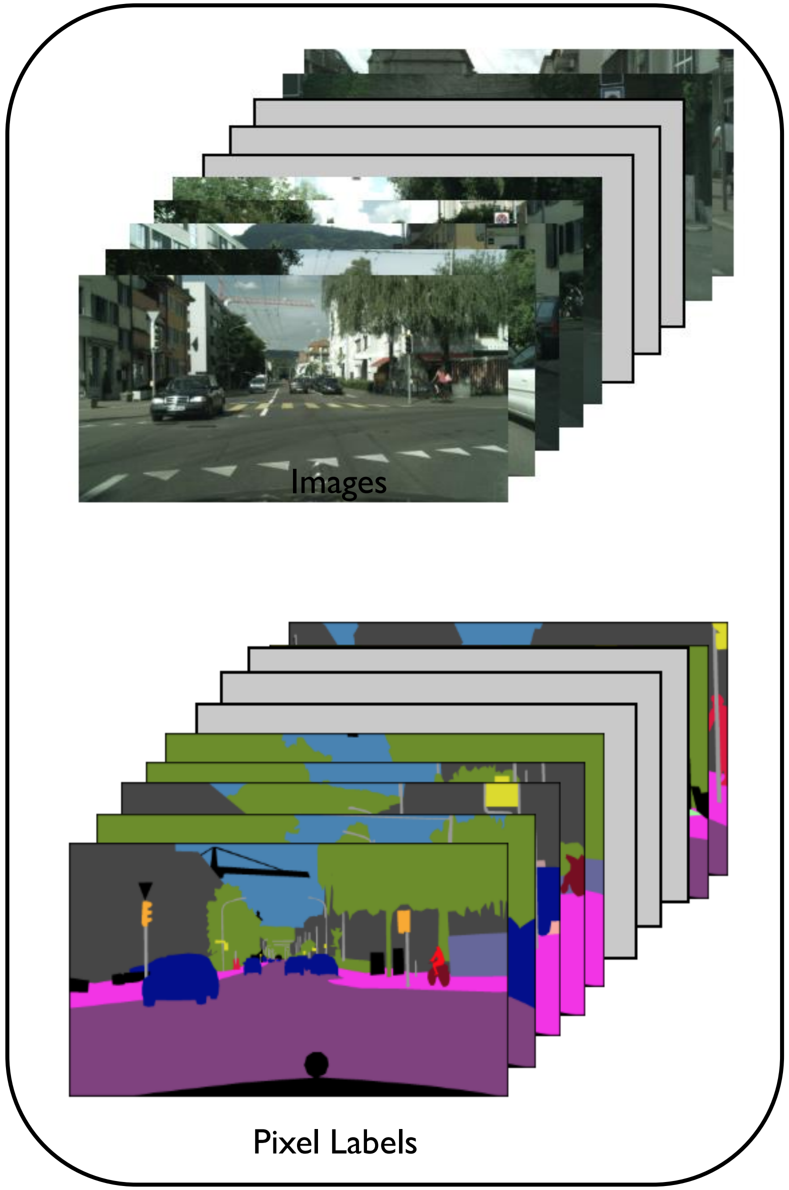
Observations

- DL based methods are emerging as a defacto standard in digital histopathology
  - Excellent results
  - Correlated with the human expert views
  - Many applications getting into practice
- Methods also show relationships across
  - Cancers, organs
  - Cell types, abnormalities; many insights
- Challenges ahead
  - ”Brute force” data driven solutions have many practical limitations

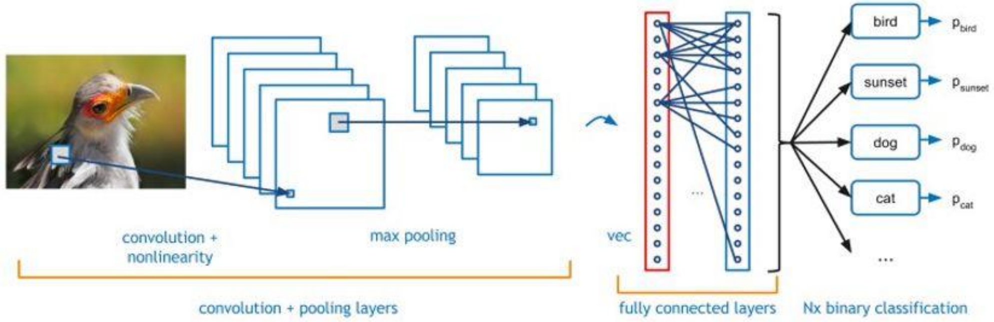
6: Advances in ML Formulations

Supervised Learning

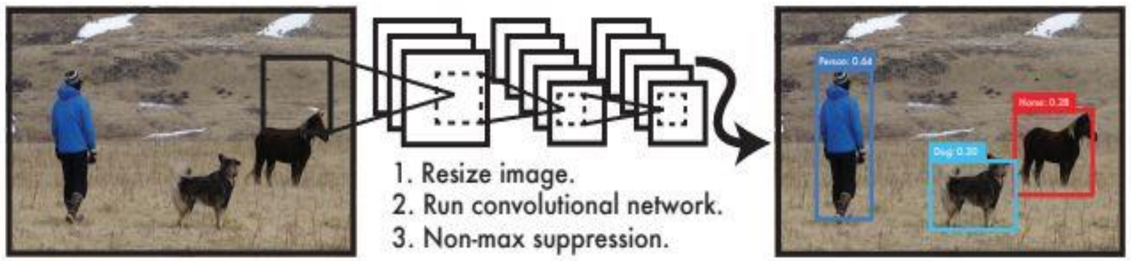
- Input space: $\mathcal{X}$
- Label space: $\mathcal{Y}$
- Input set: $X = (x_1, x_2, \cdots, x_n)$
- Label set: $Y = (y_1, y_2, \cdots, y_n)$
- Function: $f : \mathcal{X} \longrightarrow \mathcal{Y}$
- Loss function: $l : \underbrace{\mathcal{Y}}_{\text{Predicted Label Space}} \times \underbrace{\mathcal{Y}}_{\text{True Label Space}} \longrightarrow \underbrace{\mathbb{R}^{\geq 0}}_{\text{Loss Value}}$
  - Associates the value of predicted and true label with a cost
  - Used to estimate parameters of the model



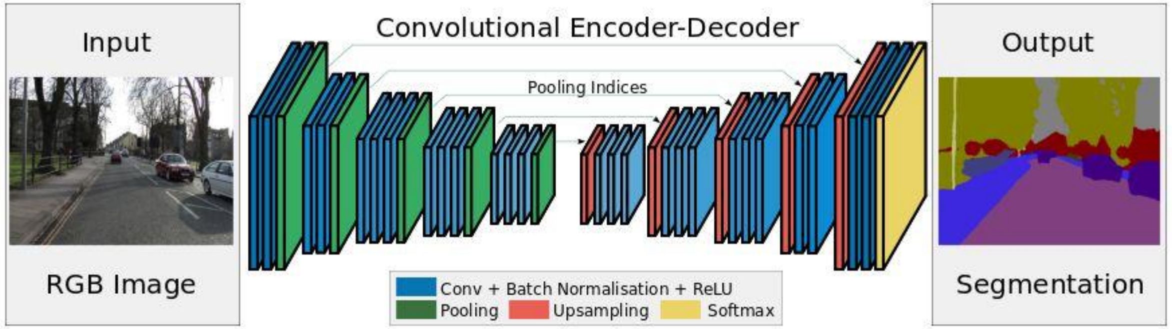
Success Stories of Supervised Models



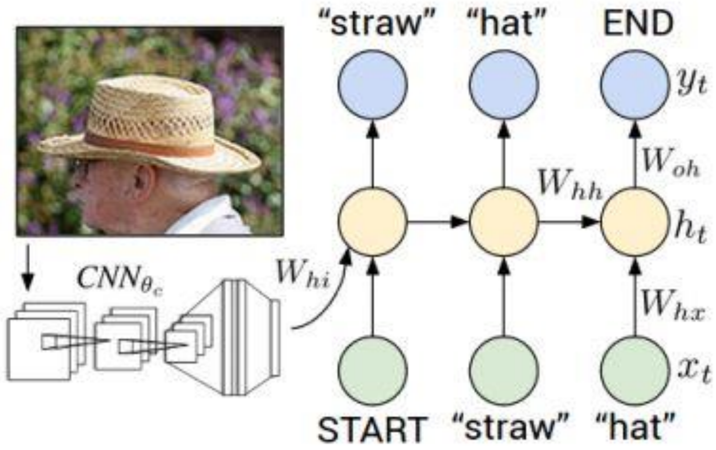
(a) Image Classification



(b) Object Detection



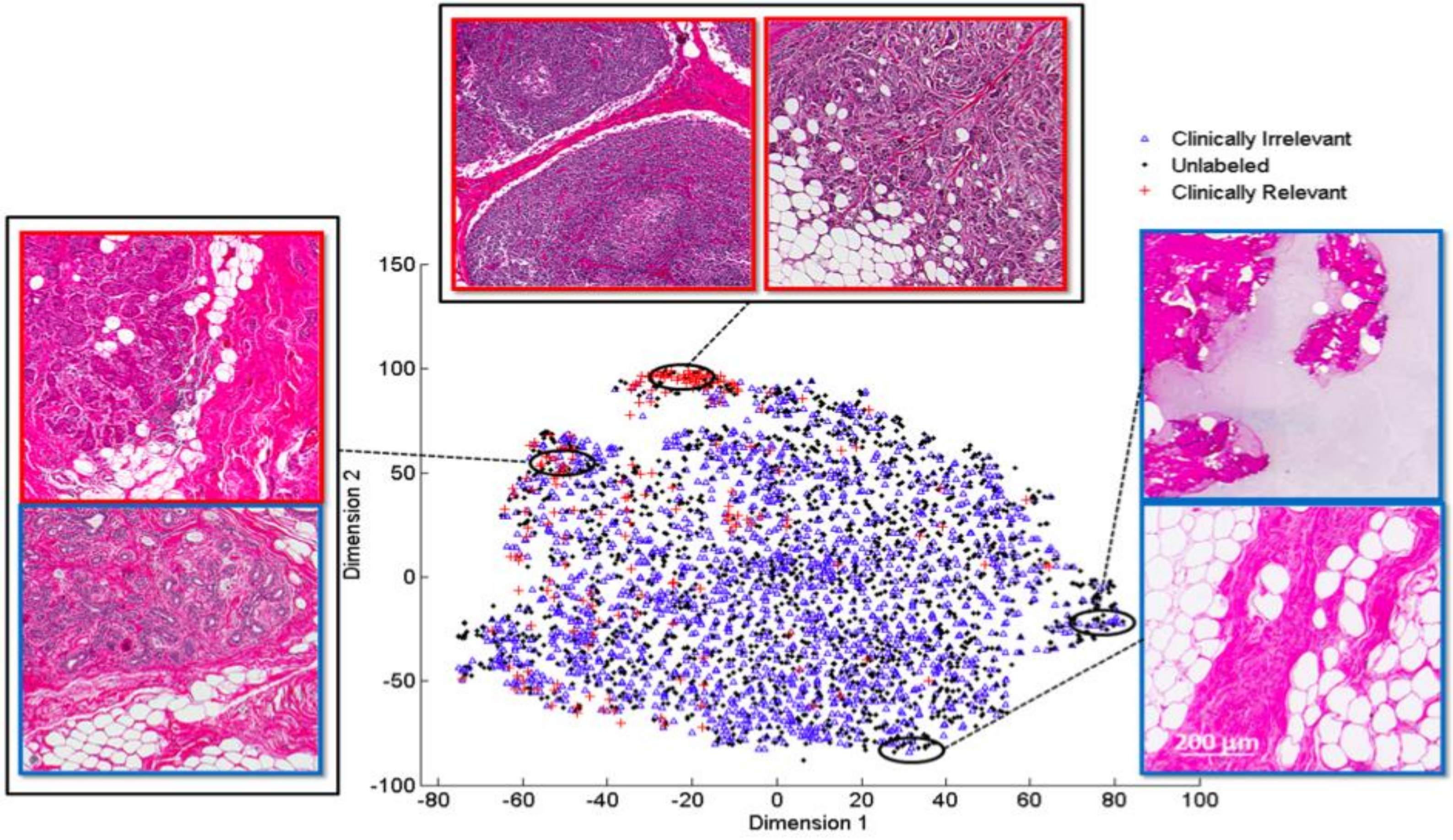
(c) Semantic Segmentation



(d) Image Captioning

SSL in Histopathology

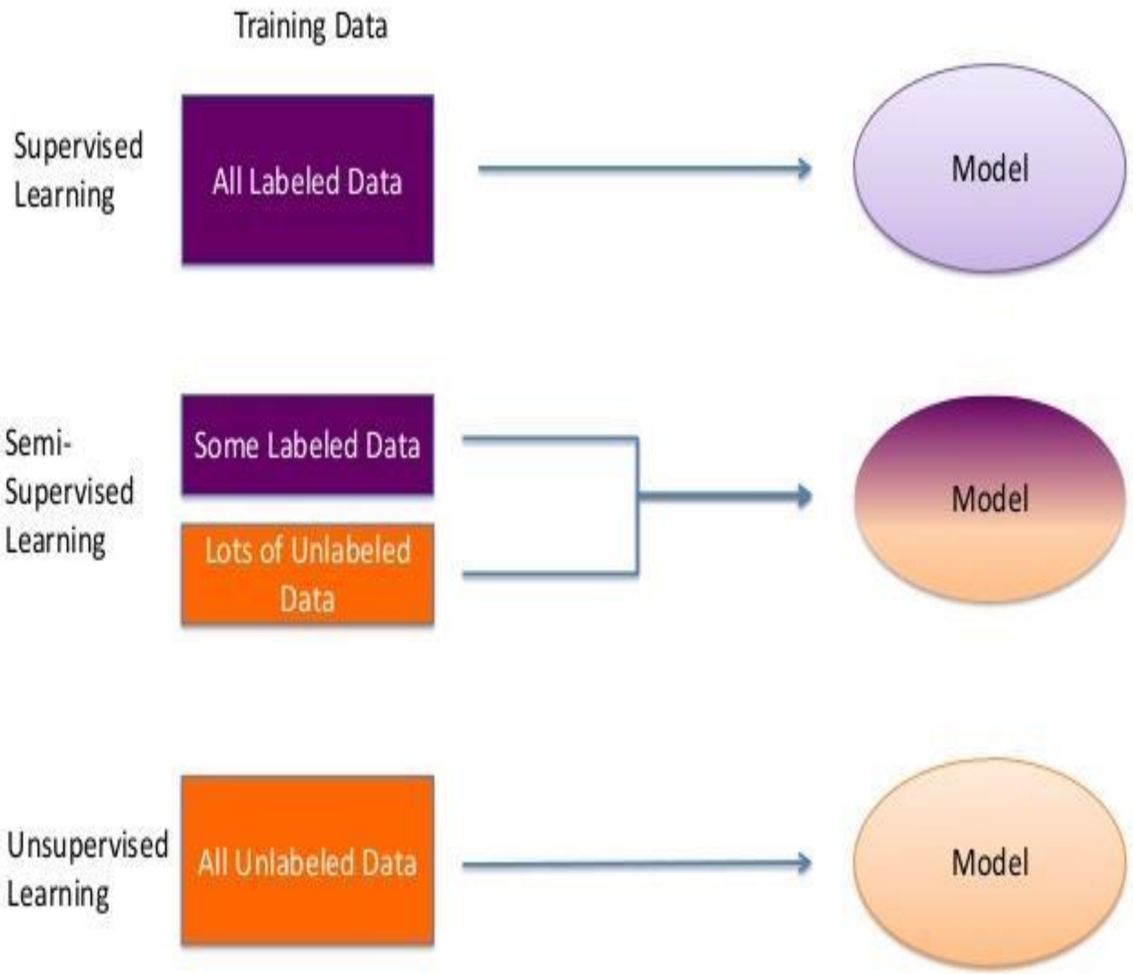
- Cluster-then-Label SSL
  - A variant of SSL
  – Use "ImageNet features of patches
  – Cluster the patches and label closest labelled sample.
  – SVM+RBF classifier

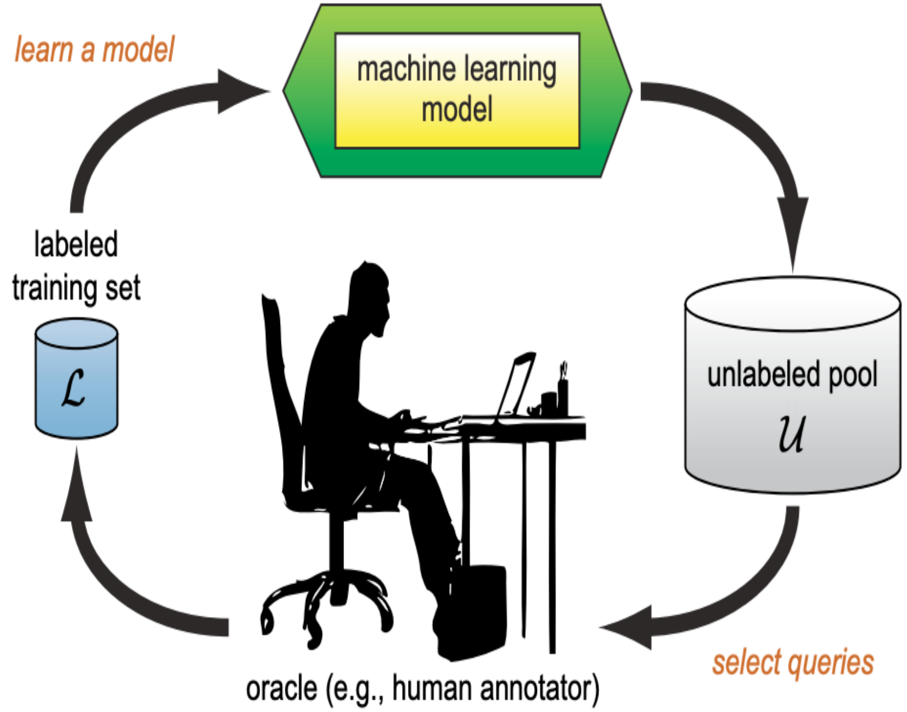


SSL Learns from Fewer Labeled Examples

A Cluster-then-label Semi- supervised Learning Approach for Pathology Image Classification, Peikari e.al, Nature Scientific Reports, 2018

SSL and Active Learning

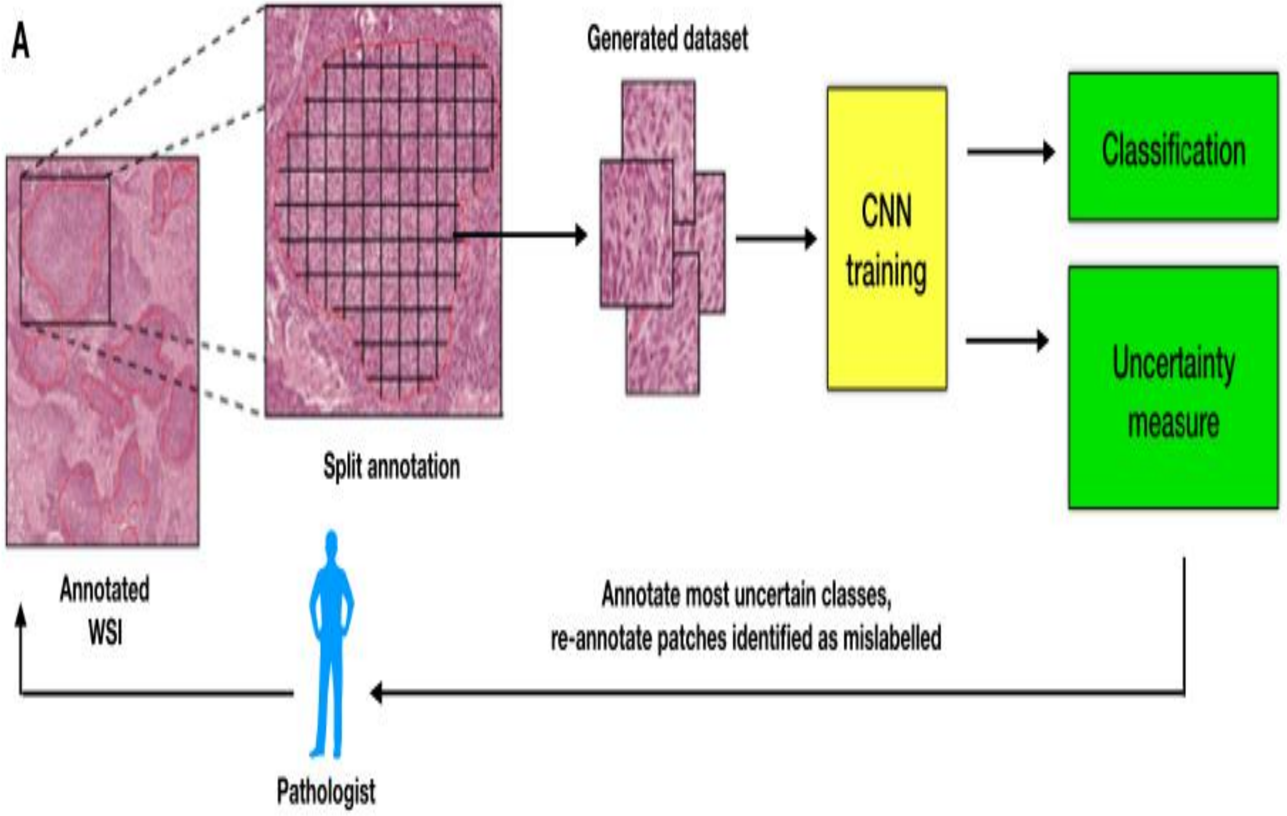




Left: SL vs Semi-SL vs USL. Bottom: Active Learning (top)

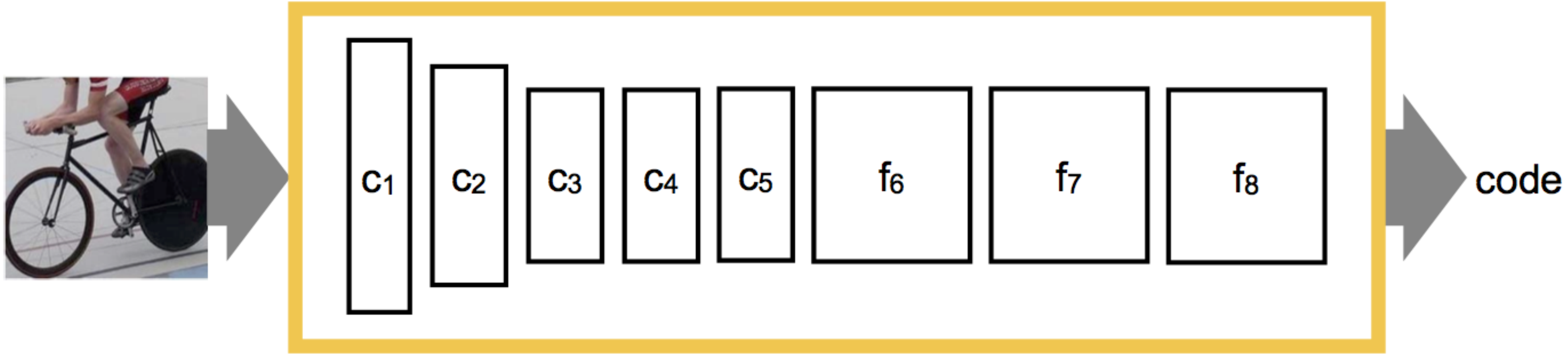
Active Learning

- ARA
  - Active Learning using Variational dropout
  - Here dropout is used to infer and measure certainty of model on specific sample
  - Can have other measures of uncertainty as well such as entropy of classification
  - Can use to annotate WSIs in a progressive manner



ARA: accurate, reliable and active histopathological image classification framework with Bayesian deep learning, Rączkowski et.al, Nature Scientific Reports, 2019

Transfer Learning

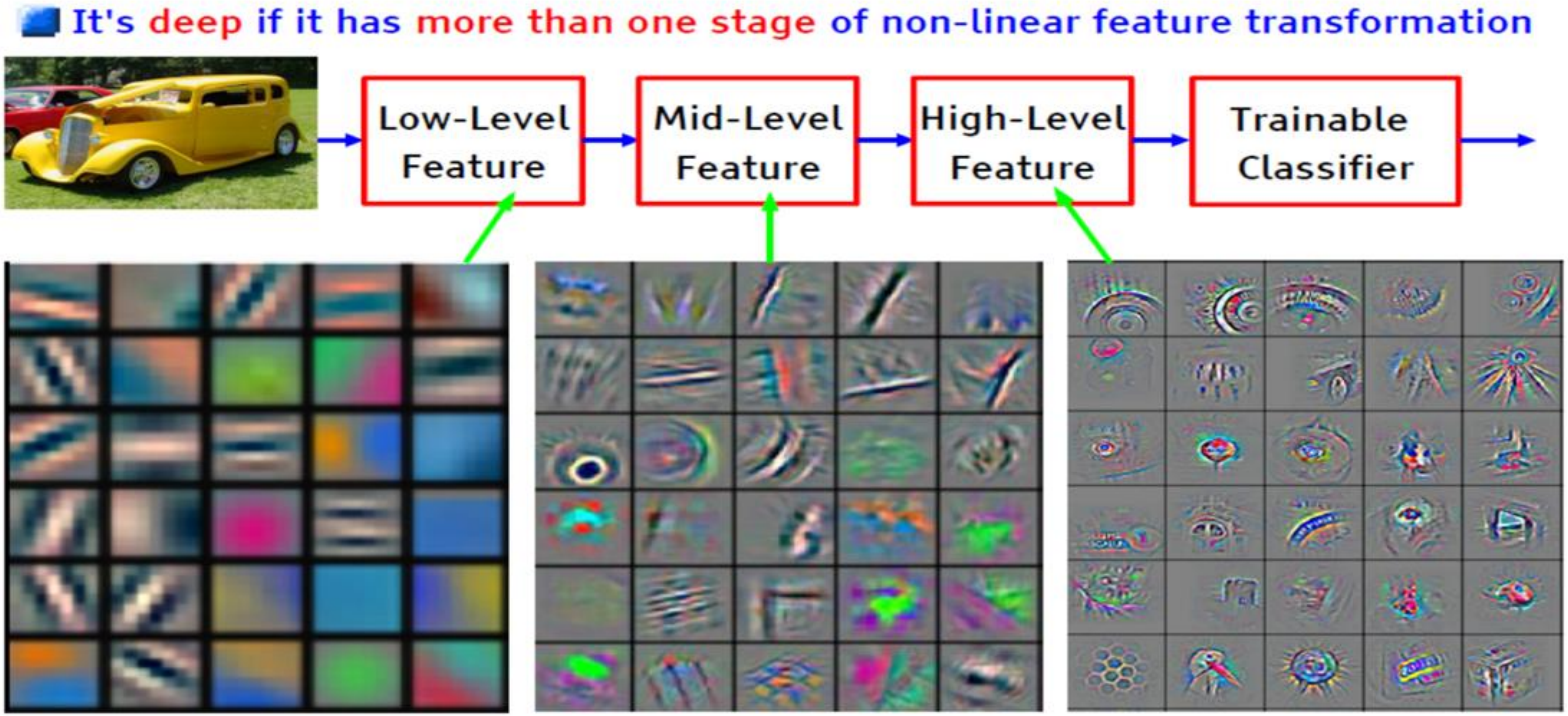


CNN Features can be used for wider applications:

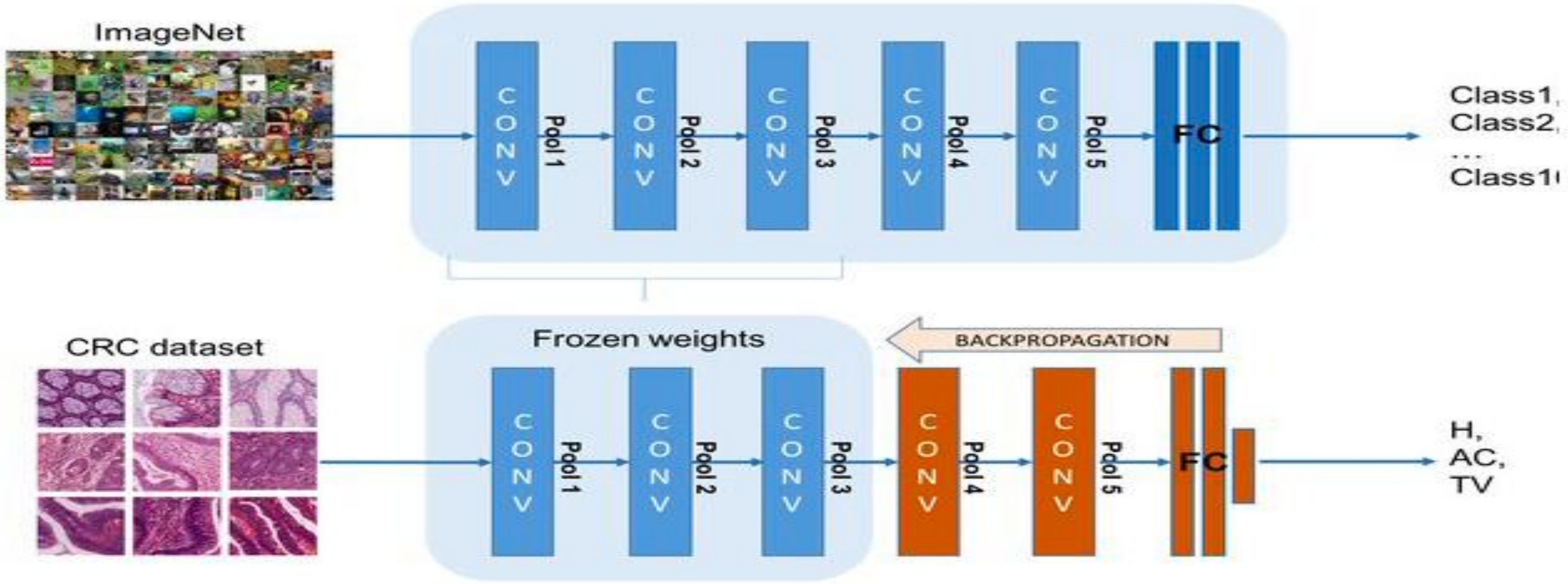
1. **Train the CNN (deep network) on a very large database such as imagenet.**

2. **Reuse CNN to solve smaller problems**
   1. **Remove the last layer (classification layer)**
   2. **Output is the code/feature representation**

Deep Learnt Features



Transfer Learning in Histopathology



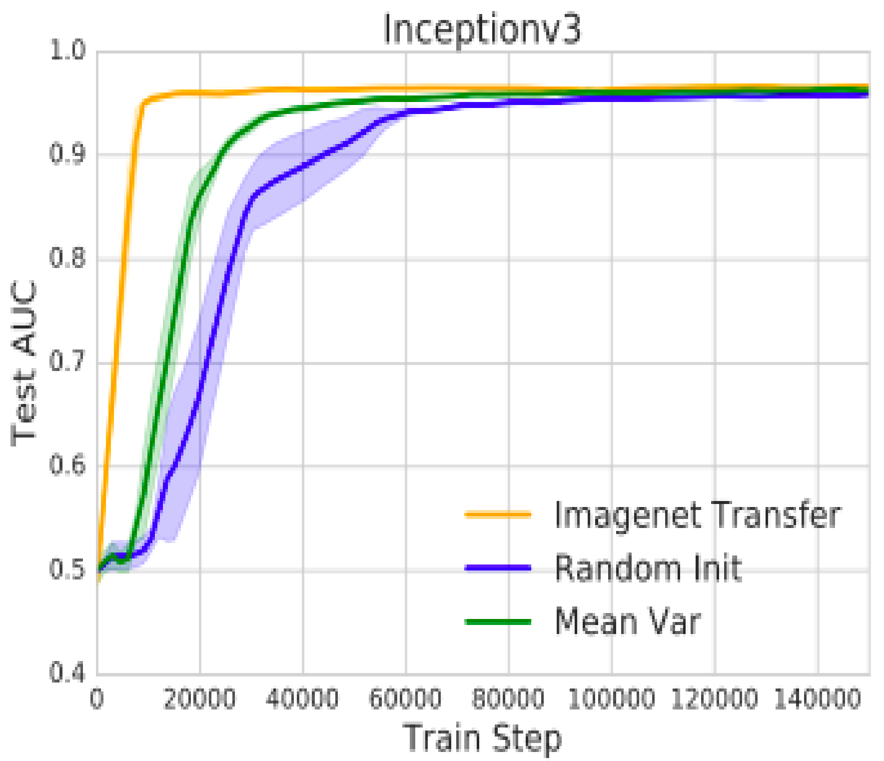
- Approach
  - Train a model f_s or borrow f_s
  - Use f_s to initialize f_t Finetune f_t
  - # layers to finetune is a design choice

A model trained on ImageNet dataset is re-used in a histopathology dataset.

Ref: "Colorectal Cancer Classification using Deep Convolutional Networks - An Experimental Study", 5th International Conference on Bioimaging 2018

TL in histopathology

- Practically useful
  - Works decently well even with small training data because image descriptors learnt from X_s are useful
  - Relatively easy to implement, works decently well even without much design experiments
- Speed
  - Converges to a local minima faster.



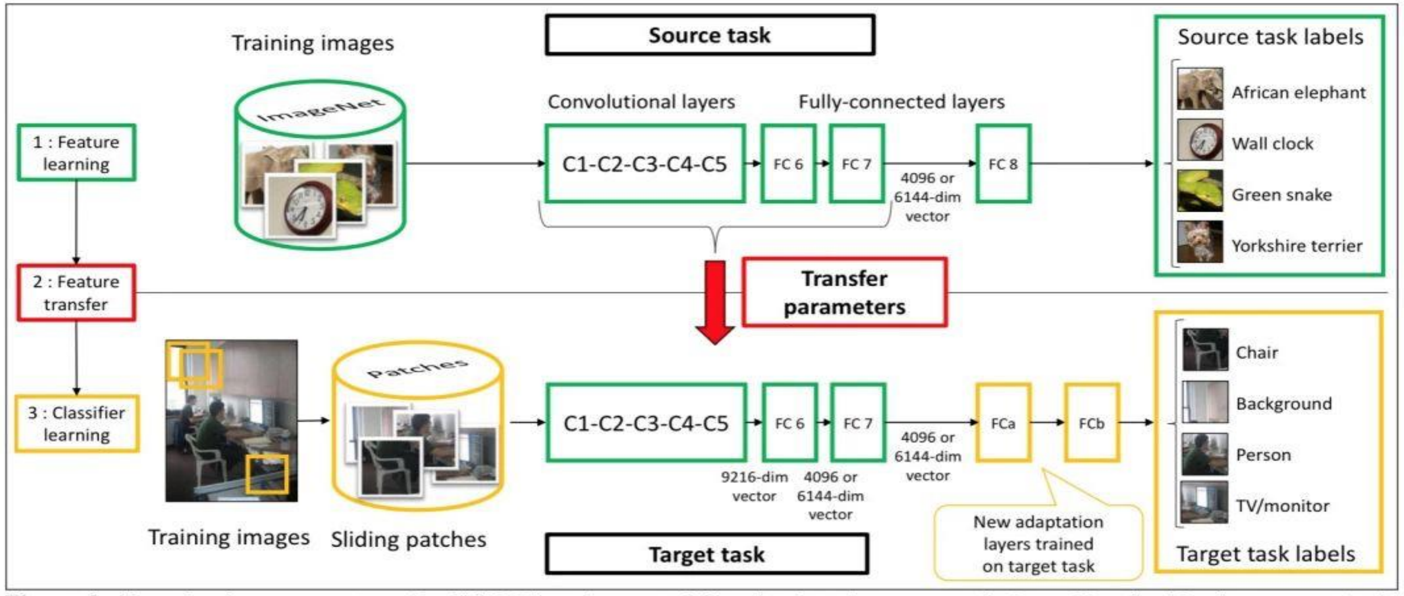
TL converges in fewer train steps

Ref: Transfusion, Raghu et.al, NeurIPS 2019

Transfer Learning Models

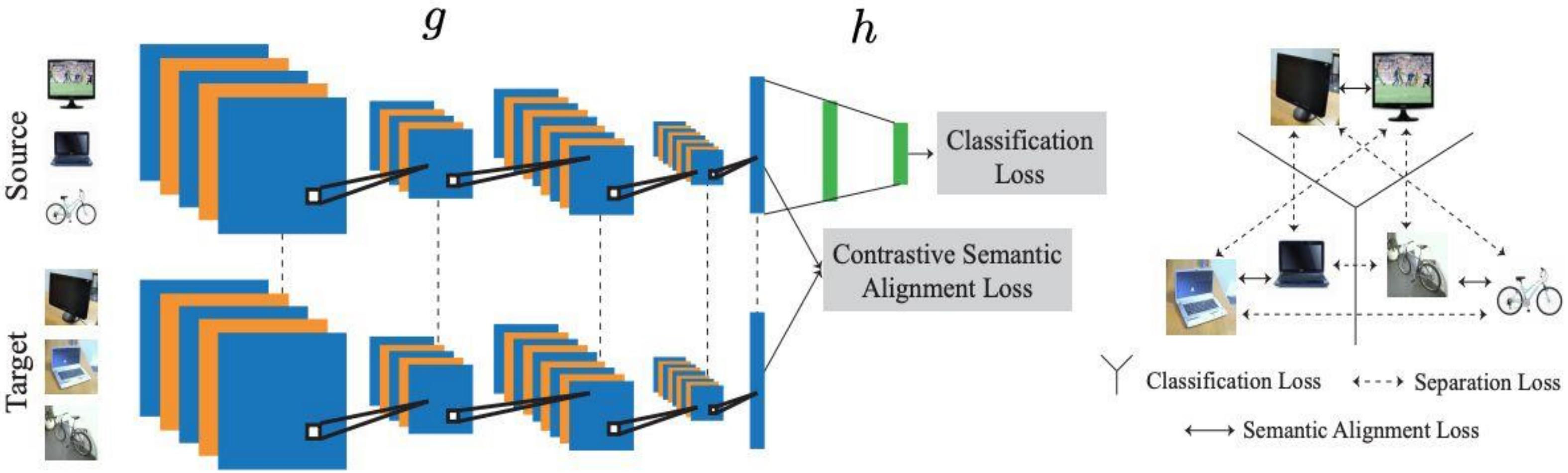
Different label space

$$\mathcal{Y}_s \neq \mathcal{Y}_t$$



Different input space

$$\mathcal{X}_s \neq \mathcal{X}_t$$



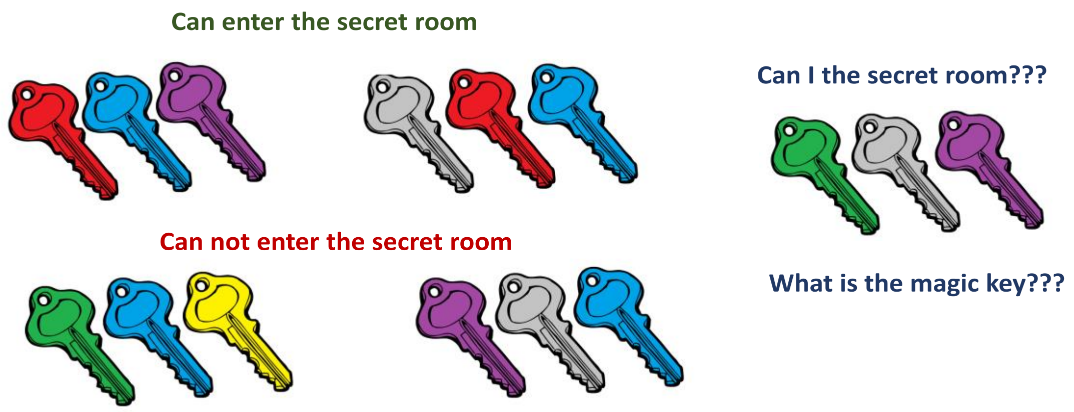
Multiple Instance Learning

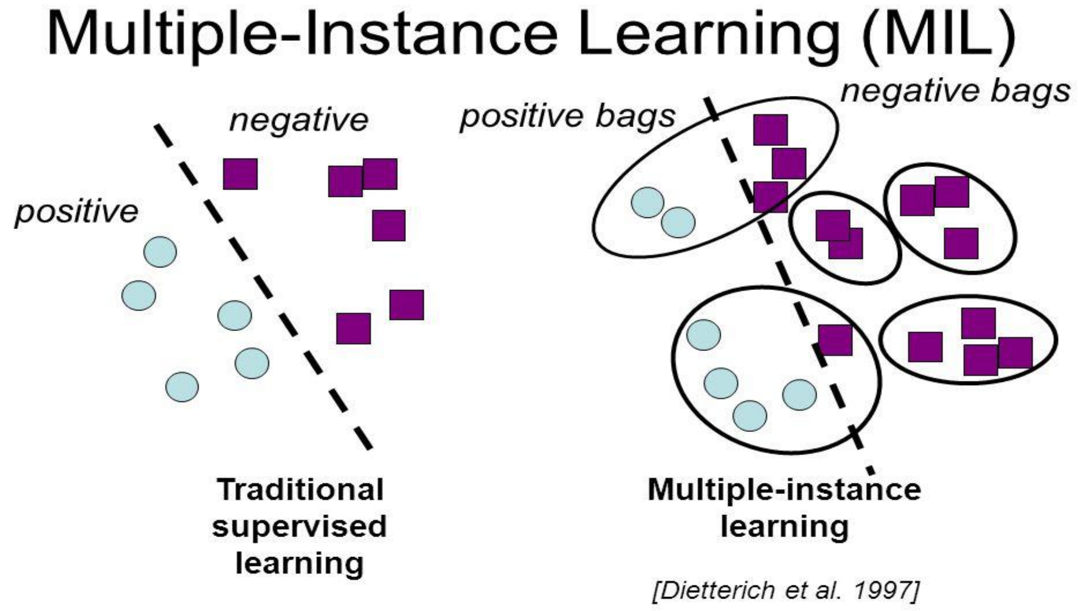
What it is:

- It is a form of **weakly** supervised learning.
- Training instances are arranged in **sets**, called bags.
- A label is provided for entire bags **but not for instances**.

What it is not:

- Supervised learning
- Unsupervised learning
- Semi-supervised learning





Formulation in Diagnosis

Objective: Predict if a subject is diseased or healthy.

Bags: Collection segments or patches extracted from a medical image.

Instances: Image segments or patches.

Justification: A large quantity of images can be used to train. Only a diagnosis is required per image. Expert local annotation are no longer required.

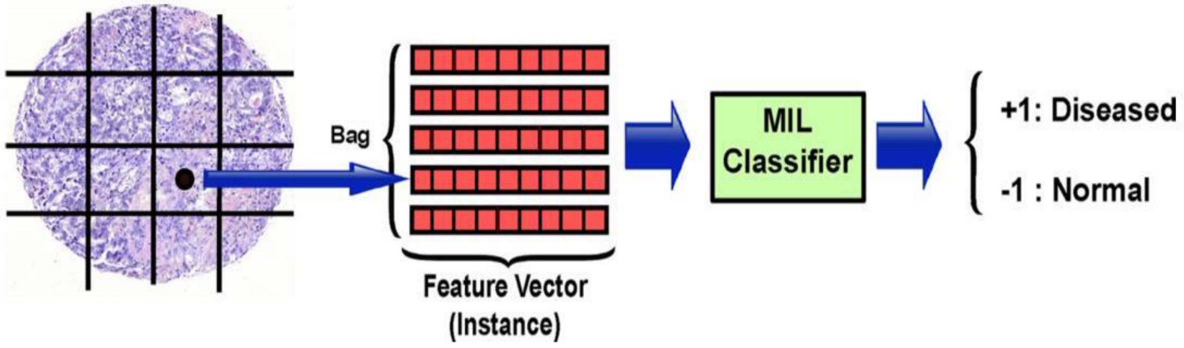


Image from: M. Kandemir and F. A. Hamprecht, "Computer-aided diagnosis from weak supervision: a benchmarking study.," *Comput. Med. Imaging Graph.*, vol. 42, pp. 44–50, Jun. 2015.

Multi Instance Learning

- Relevance of MIL to histopathology
  - We often do not have patch labels, we have only slide labels
  - The MIL assumption fits very well into how a pathologist works
- Methods
  - Perform instance prediction and pool prob.s to predict for bag. For eg.
    - $P = \max_{k=1..K} (p_k)$
    - $P = 1/K \Sigma_{k=1..K}(p_k)$
    - $P = 1/K \log \Sigma_{k=1..K}(\exp(p_k))$
  - Feature aggregation
    - AvgFeat: $z_i = \mathrm{avg}_{k=1..K}(h_{ik})$
    - Attention MIL

Multi Instance Learning

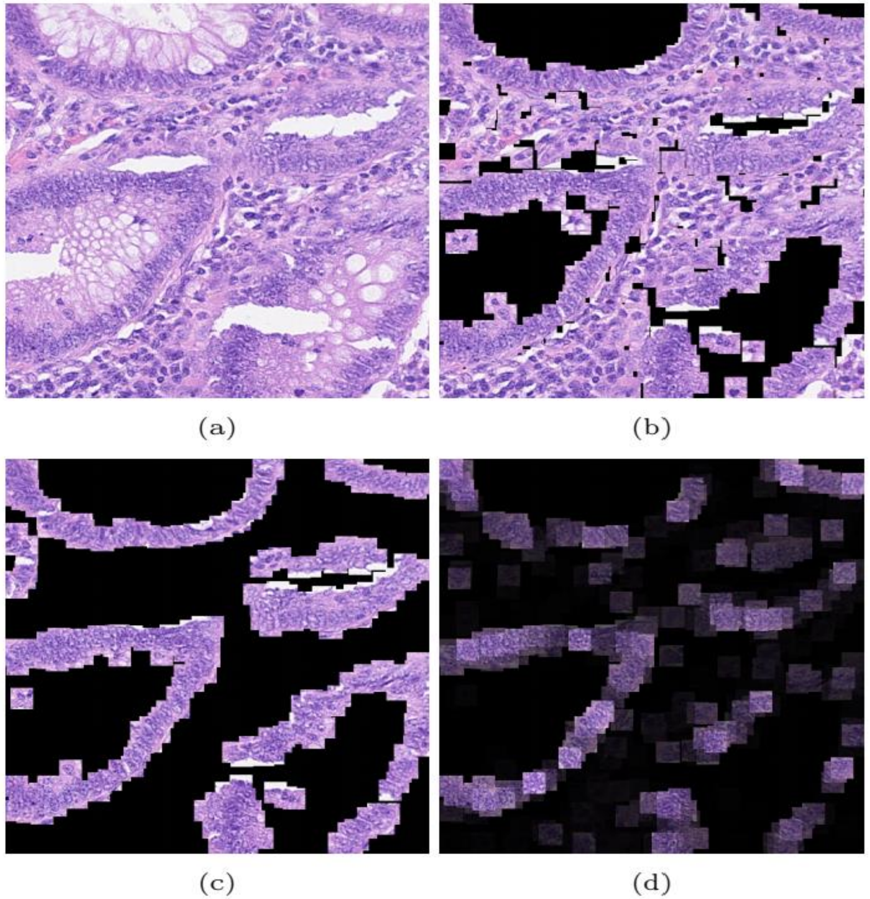
- Attention-based MIL
  - We want to learn slide representation z from patch embeddings h_k

$$\mathbf{z} = \sum_{k=1}^{K} a_k \mathbf{h}_k,$$

where:

$$a_k = \frac{\exp\{\mathbf{w}^\top \tanh\left(\mathbf{V}\mathbf{h}_k^\top\right)\}}{\sum_{j=1}^{K} \exp\{\mathbf{w}^\top \tanh\left(\mathbf{V}\mathbf{h}_j^\top\right)\}},$$

  - We train our classification model on z and we can plot a_k as attention map

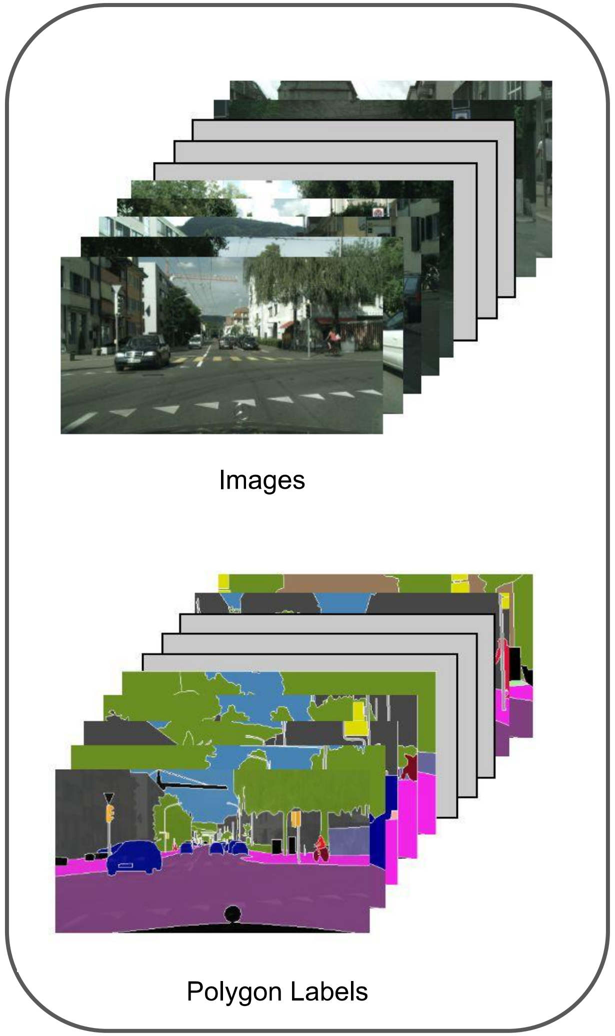


(a) WSI sample (b) Patch extraction (c) GT positives (d) Attention map from MIL model.

Results from Attention-based MIL, Ilse et.al, ICML 2018

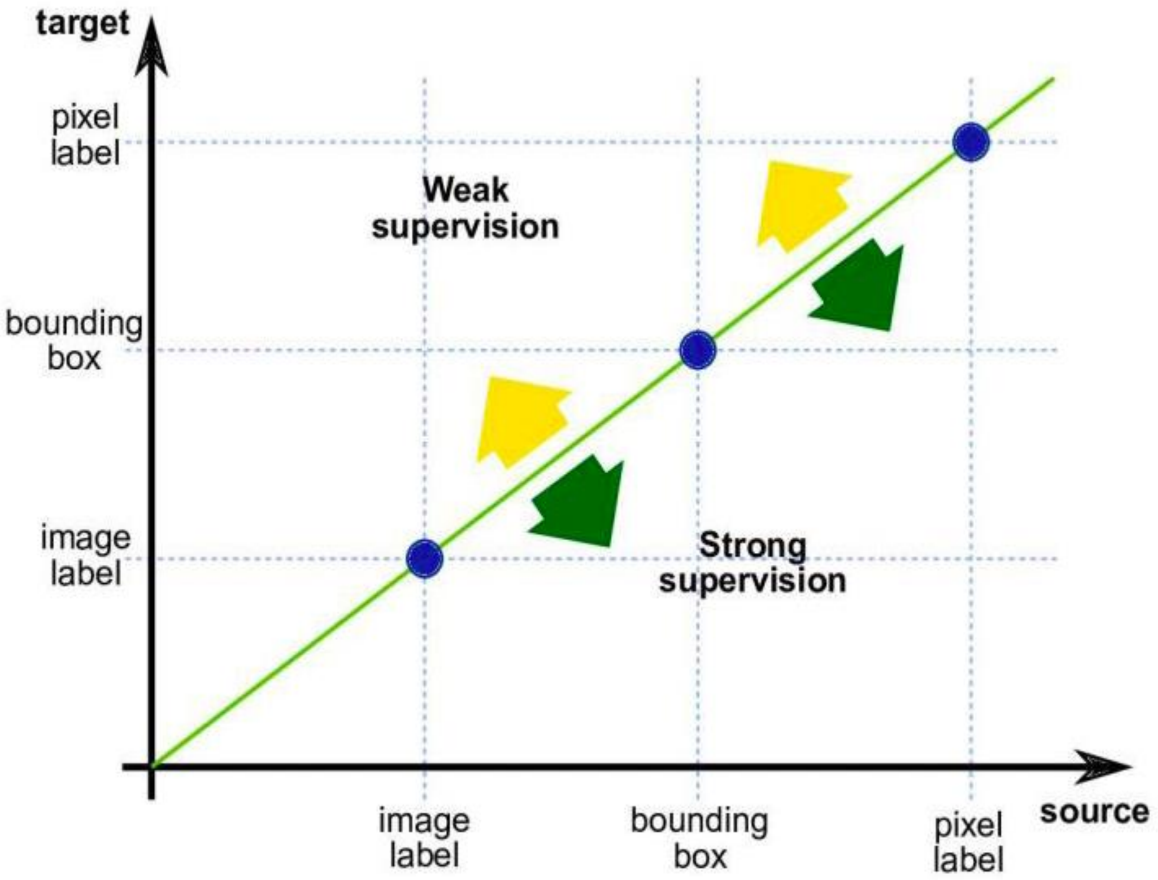
Weak Supervision

- Labels
  - Inaccurate/Noisy
    - Webly-supervised
  - Inexact
    - Heuristics
    - Distant supervision
  - Incomplete
    - A small subset of labels
- Multiple Instance Learning (MIL)
  - Bags: Images
  - Instances: Windows

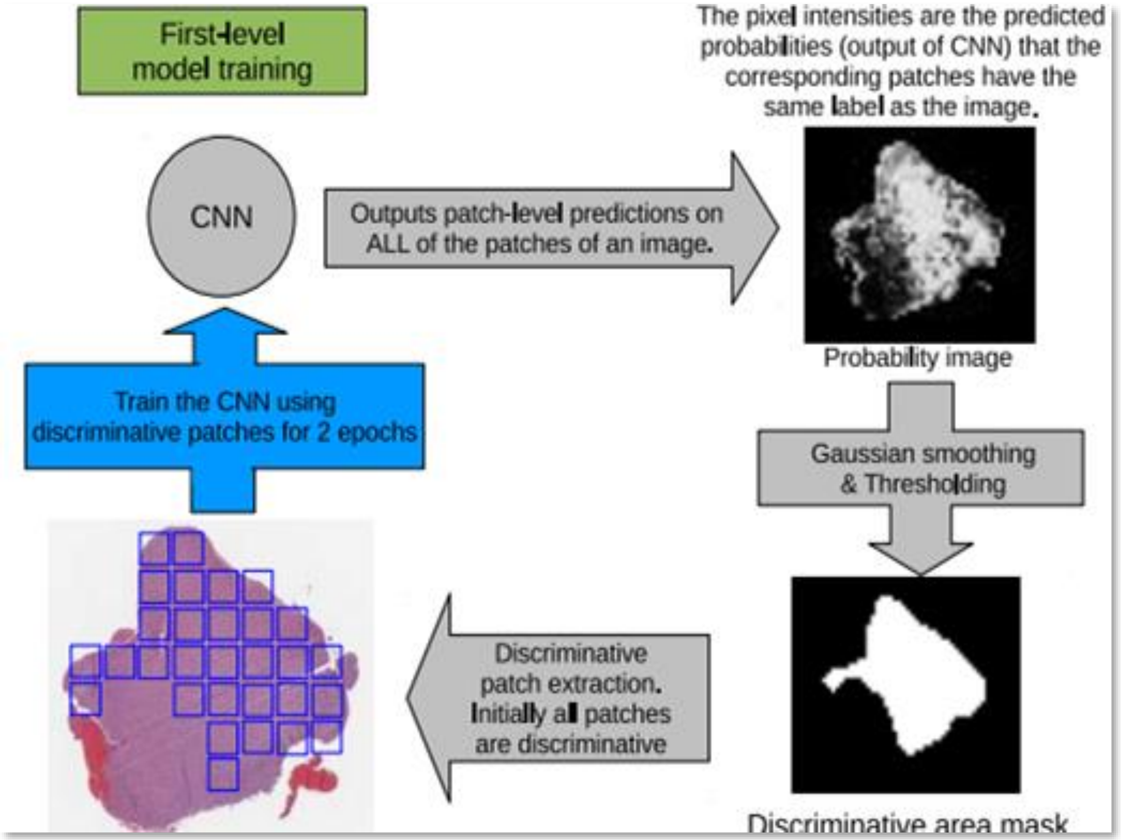


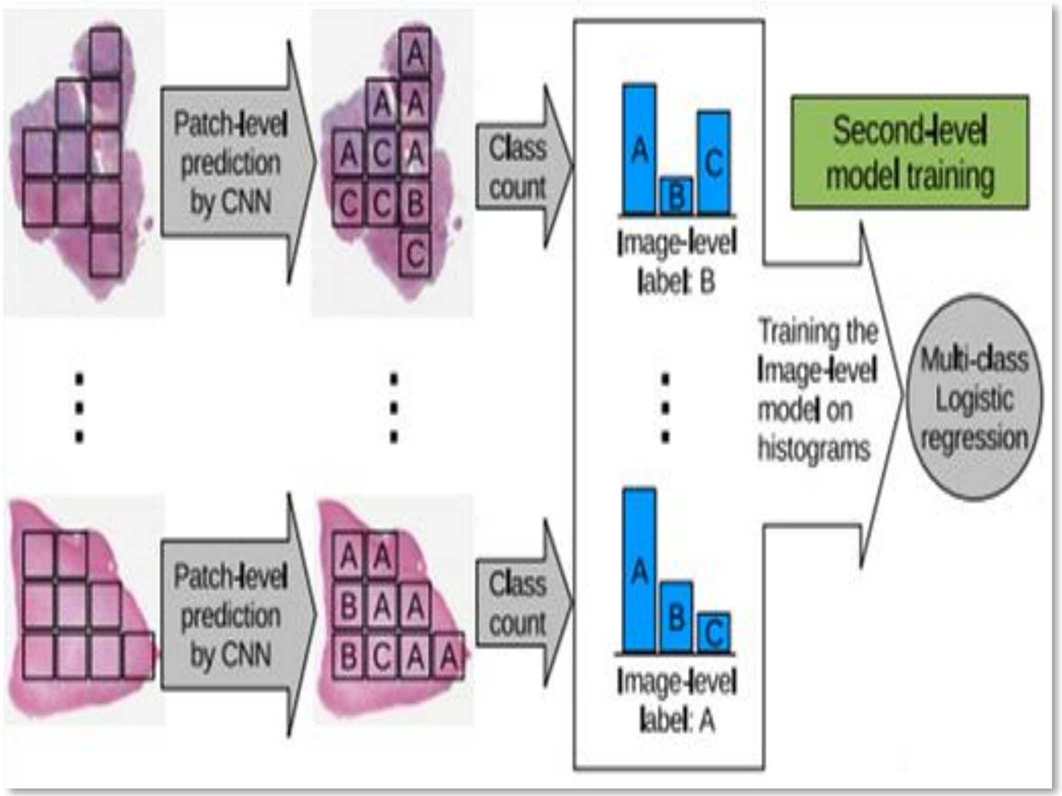
Weakly supervised learning

- Types of WSL
  - We have labels at patch level but want to predict pixel level
  - We have labels at slide level but want to predict patch or region or bounding box or mask
  - MIL is an example of WSL



Feature aggregation - EM





A CNN is trained on patches. An EM-based method iteratively eliminates non-discriminative patches.

An image-level decision fusion model is trained on histograms of patch-level predictions, to predict the image-level label

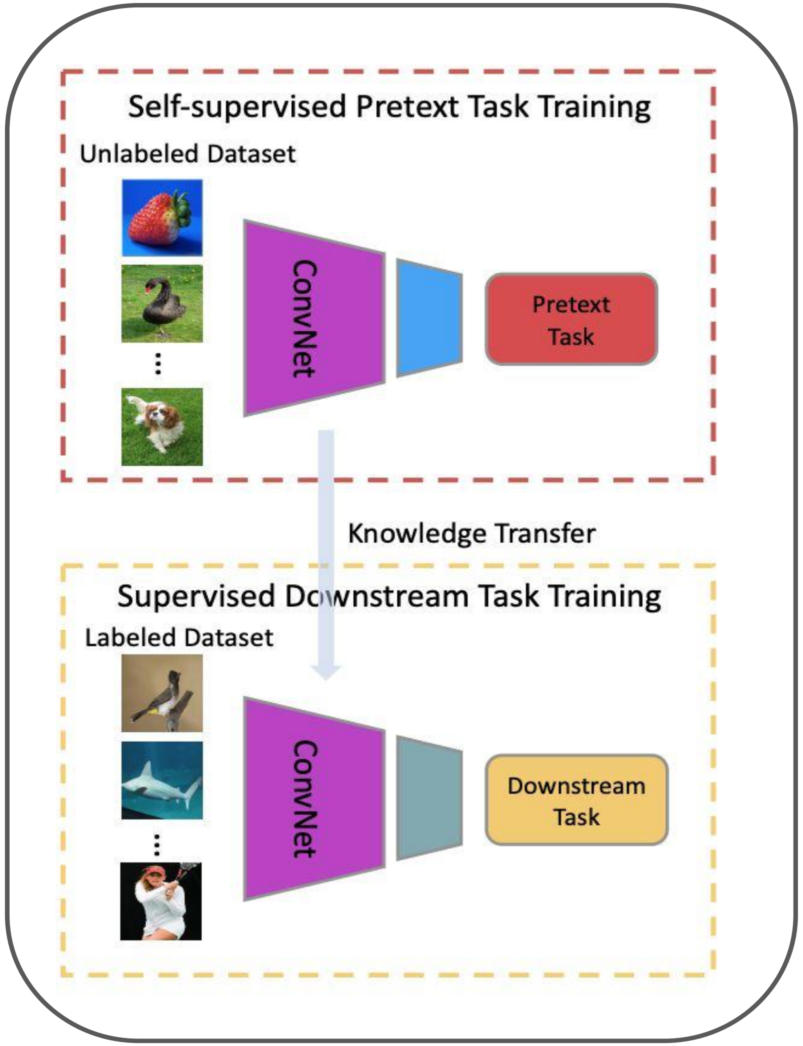
Feature aggregation - EM

- CNN + Logistic Regression + EM
  - (M step) CNN is trained only on discriminative patches. Initially all patches are discriminative
  - CNN predicts P(cancer) for all patches giving us a grayscale pixel map
  - Smooth and threshold this pixel map
  - (E step) Out of all the remaining patches in the mask, all above a threshold (say >T percentile confidence) are taken as discriminative
  - Feed the predictions of CNN to a (separate) logistic regression for slide level prediction

Le Haou et al, Patch-based Convolutional Neural Network for Whole Slide Tissue Image Classification, CVPR 2016

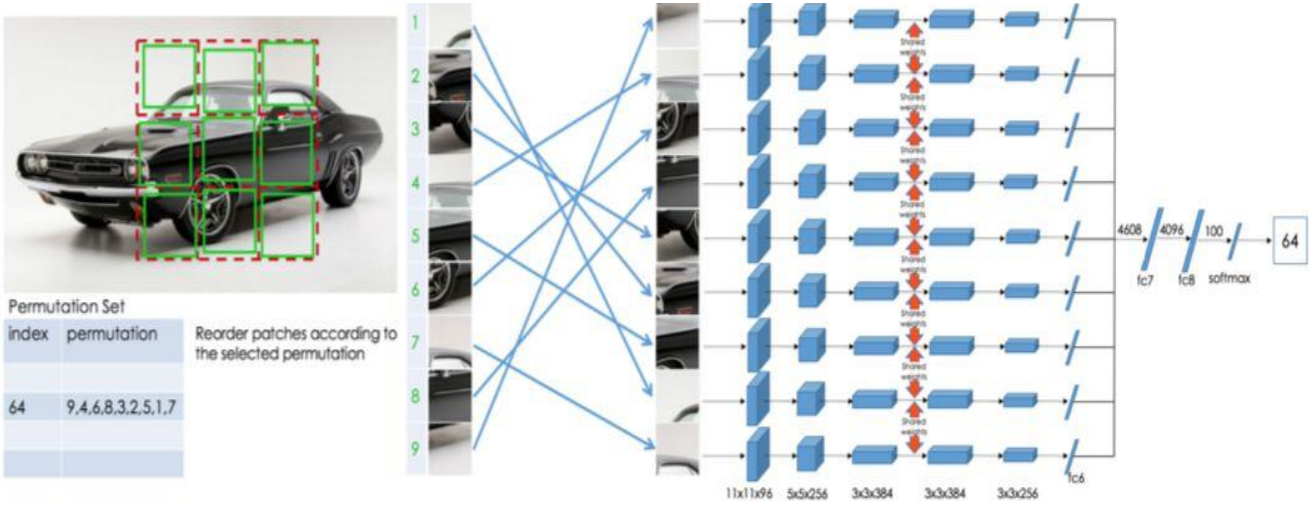
Self Supervised Learning

- Utilize naturally occuring “free” information contained within the data
- No need of explicit labels pertinent to the task
- Pretext tasks:
  - Color
  - Spatial order
  - Temporal order
  - Sound
  - Motion

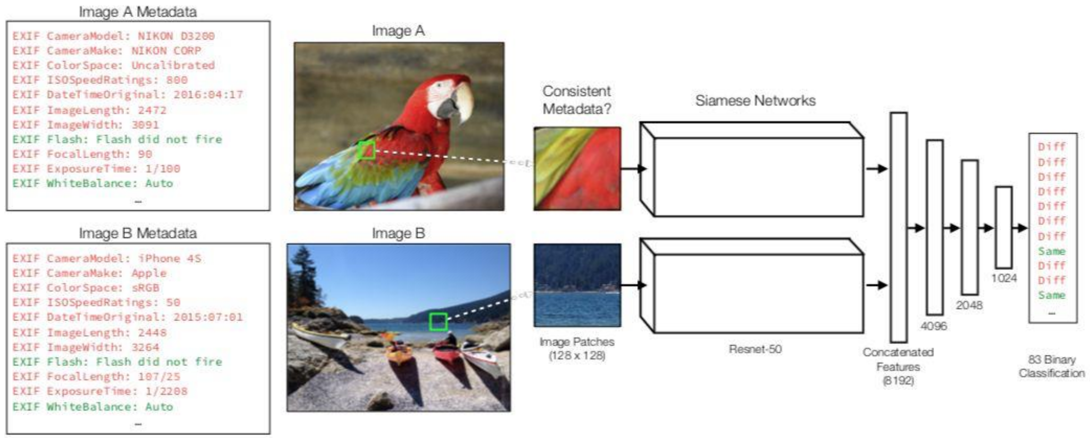


Self Supervised Models

- Spatial Context as a pretext task for feature learning
  - Learn a function to solve jigsaw puzzle
- EXIF information as a pretext task to detect image tampering
  - Each image has EXIF information
    - Camera model, ISO, shutter speed etc
  - Patches from same image → Similar EXIF
  - Patches from different images → Dissimilar EXIF
  - Training conducted using patches from untampered images
  - At test time, tampered image patches → Dissimilar EXIF values



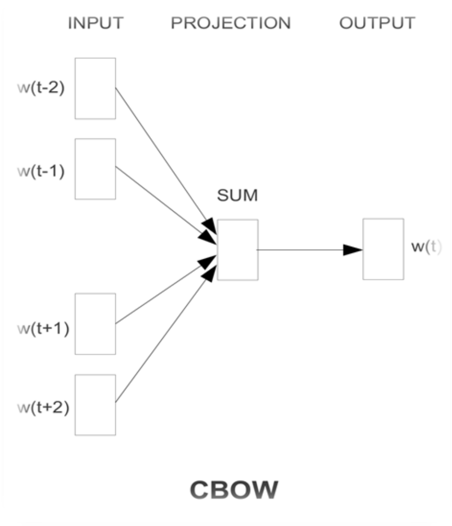
(a) Spatial Context Prediction as proxy task for feature learning

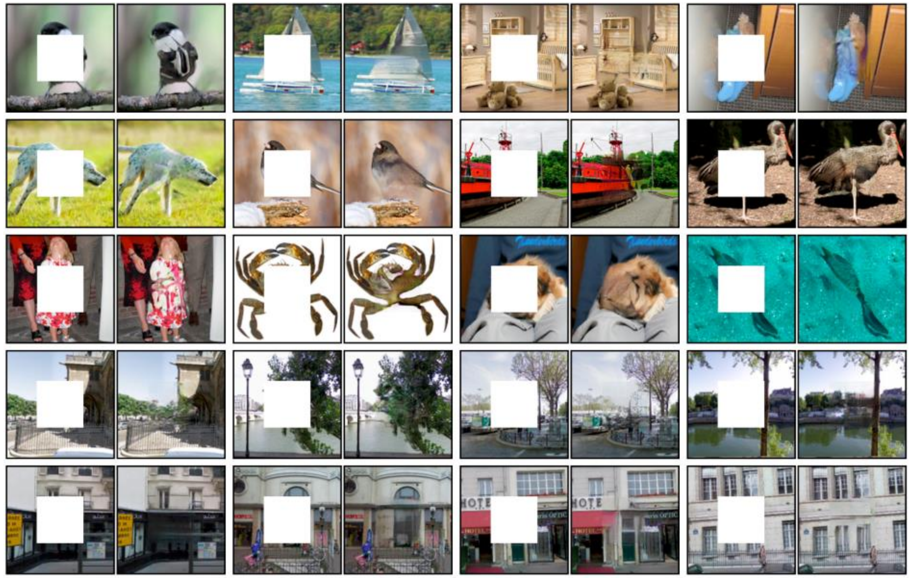


(b) EXIF information consistency as a proxy task for image tampering

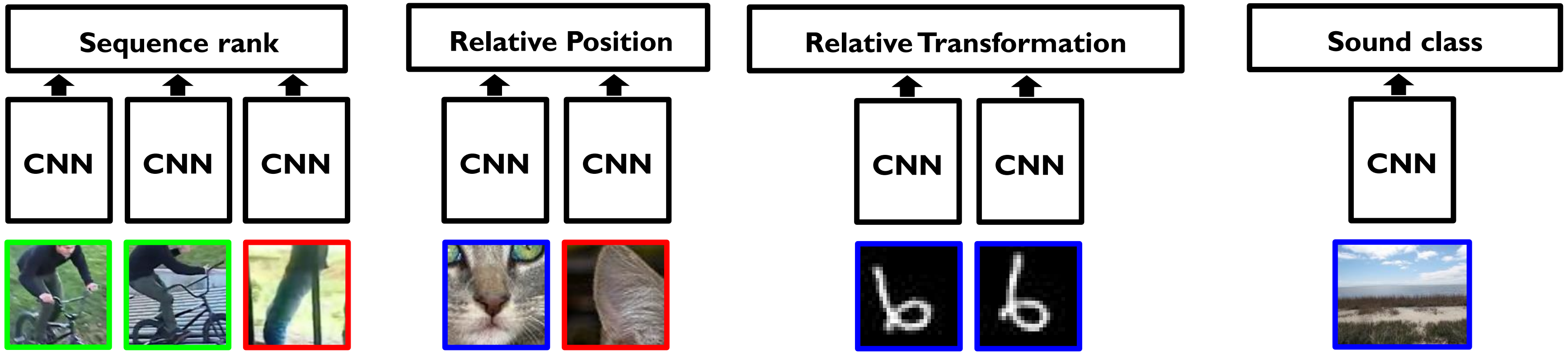
Self Supervised Learning

Word2Vec
Mikolov 2013



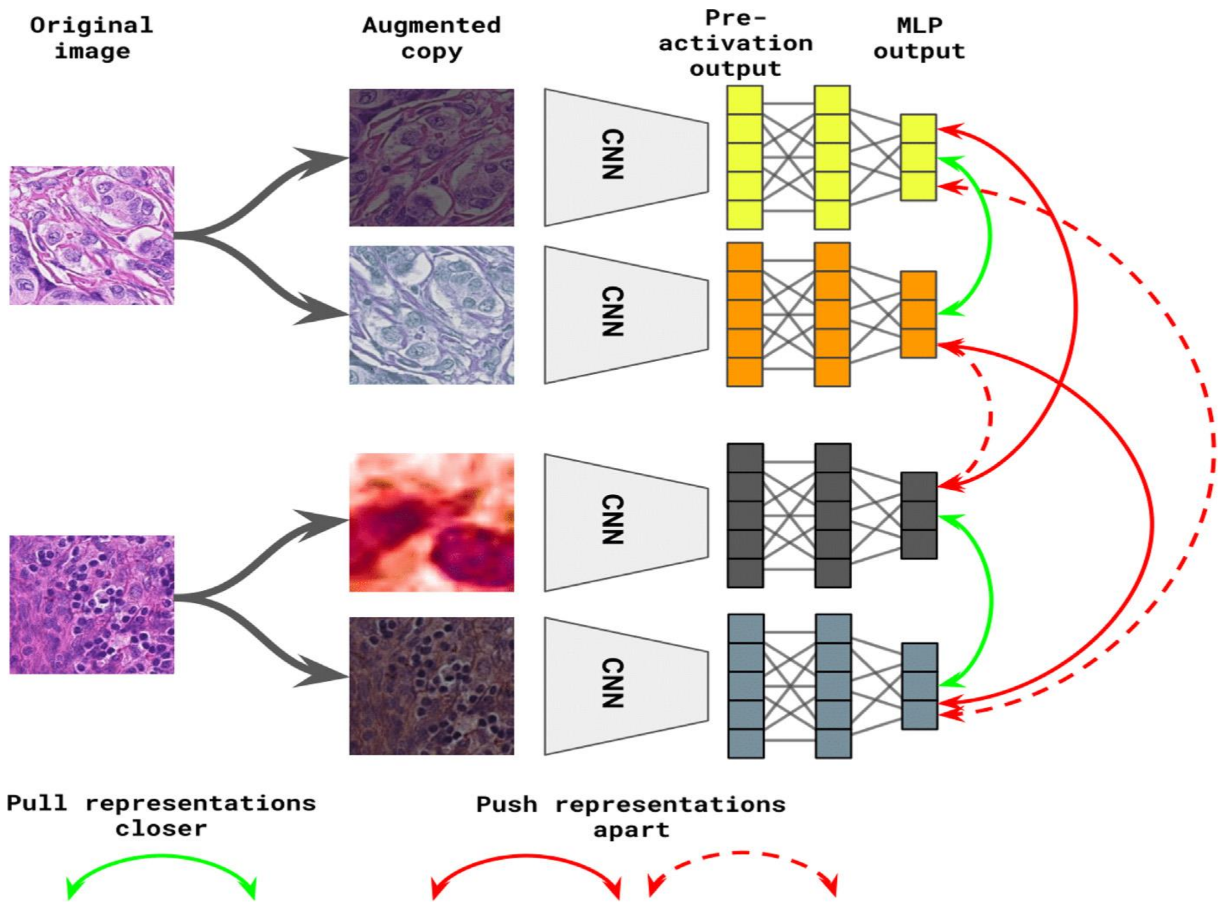


Pathak et al, 2016



(Wang et al. 2015) (Doersch et al. 2015) (Agrawal et al. 2015) (Owens et al. 2016)

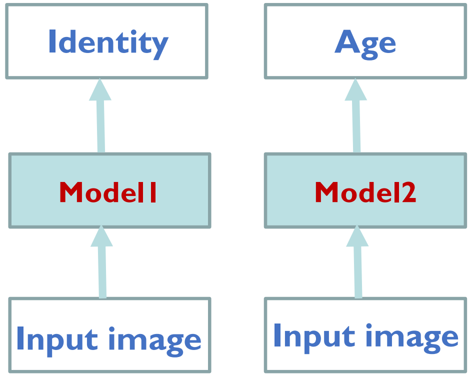
Self Supervised Learning



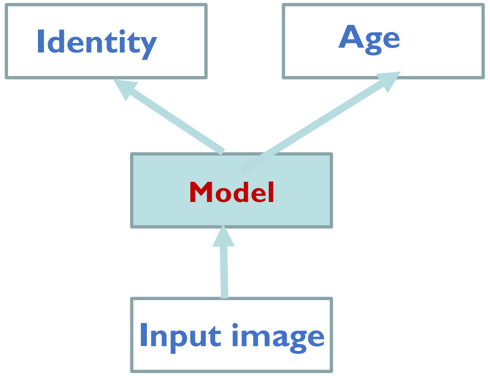
Self Supervised contrastive Learning for Digital Histopathology, machine Learning with Applications, 2022

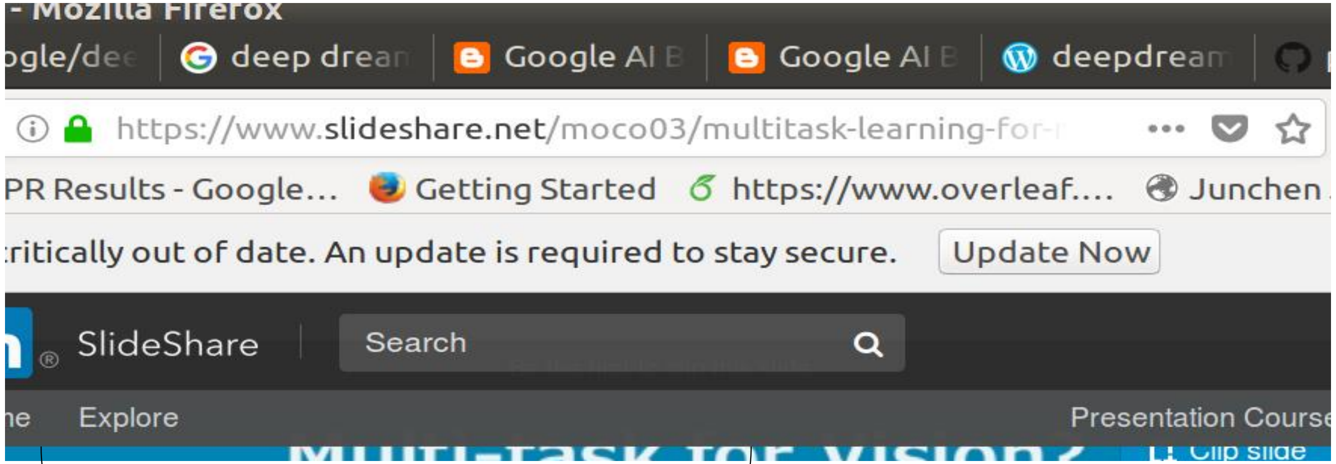
Multi Task Learning

Single Task Learning



Multi Task Learning





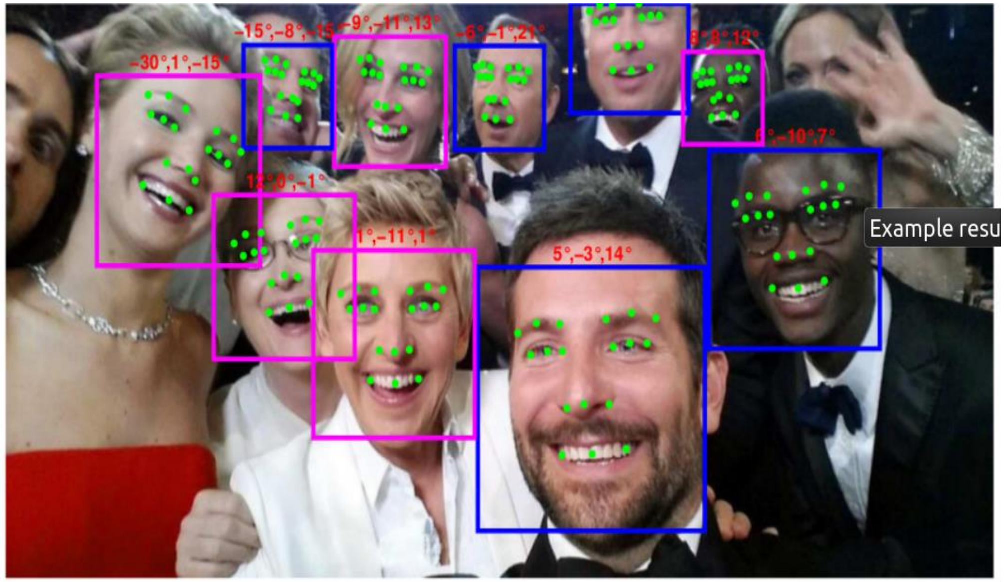
Shared hidden layers
Shared representation

Example: Hyperface

- A Deep Multi-task Learning Framework for Face Detection, Landmark Localization, Pose Estimation, and Gender Recognition.

Single architecture

- **Face/No face**
- **Landmark points**
- **Visibility Factor**
- **Roll, pitch, yaw**
- **Male/Female**



How it works?

- Pretraining the base model like Alex Net.
- Locating bounding boxes of face candidates
- Feature extraction per face candidate
- Classification and regression
  - Detection: BCE (binary cross-entropy).
  - Landmark localization: Roughly MSE (mean squared error), with some weighting for visibility.
  - Landmark visibility: MSE (predicted visibility factor vs. expected visibility factor).
  - Pose estimation: MSE.
  - Gender estimation: BCE.

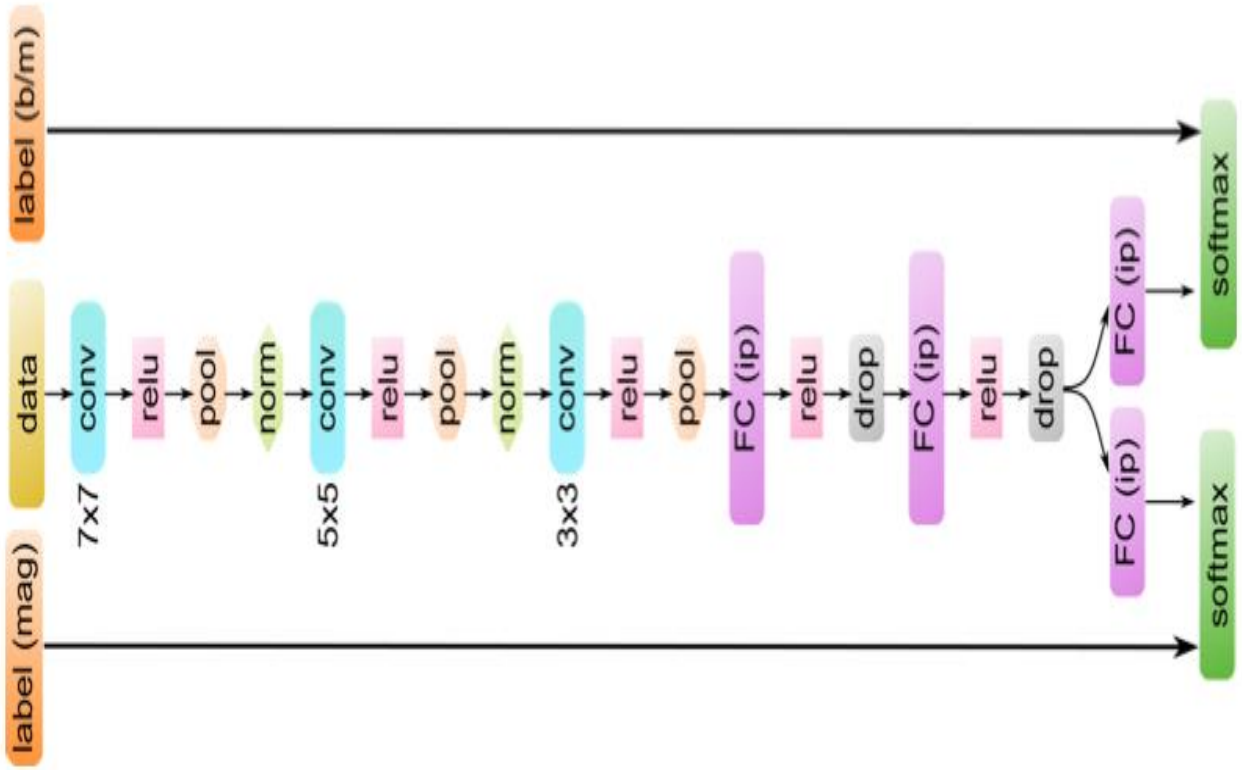
Multi-task learning in Histopathology

- **Formulation**
  – Predict multiple outputs with a single input
- **Common techniques**

  - Use a common feature extractor but separate classifier for each task

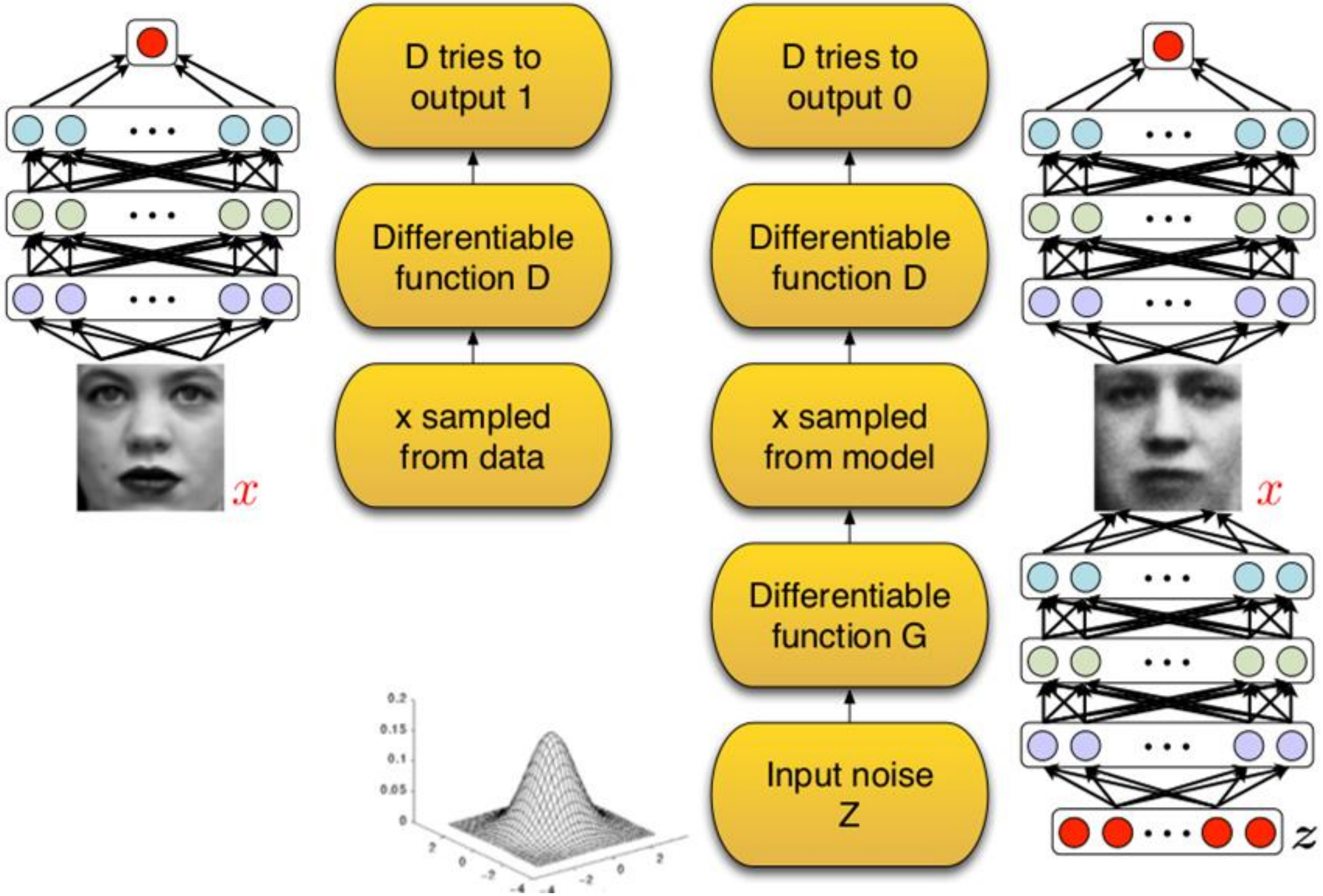
  - Create a weighted loss function where each term corresponds to an individual task

$$L_{total} = \sum_{t}^{|T|} \lambda_t L_t$$



Model has two classifiers from the same features. One for prediction of magnification and other for tumor. Ref: Deep learning for magnification independent breast cancer histopathology image classification, ICPR 2016

GANs (NIPS 2014)

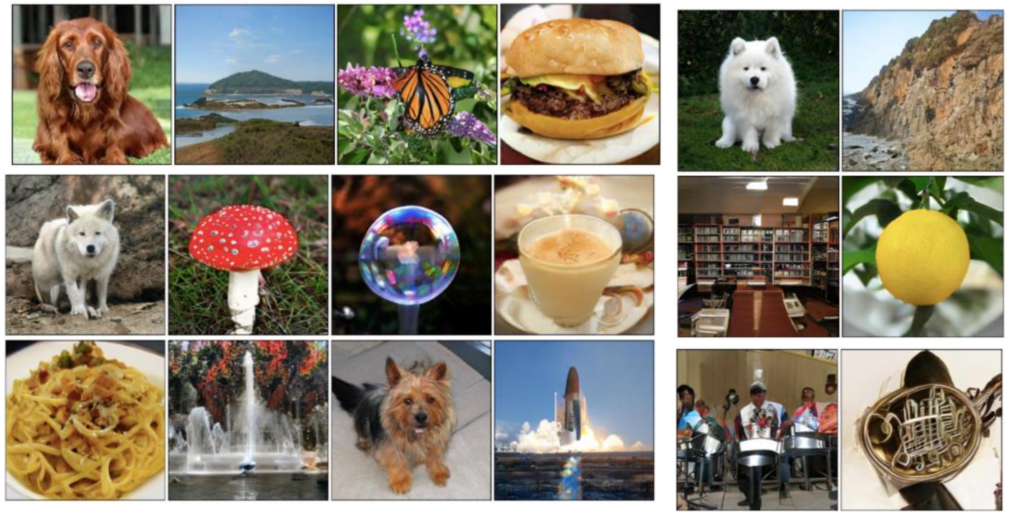


Slide credit: Ian Goodfellow

GANs: Generating Images or Labels

PROGRESSIVE GAN ICLR 2018

BIG GAN (ICLR 2019)



Pathology GAN

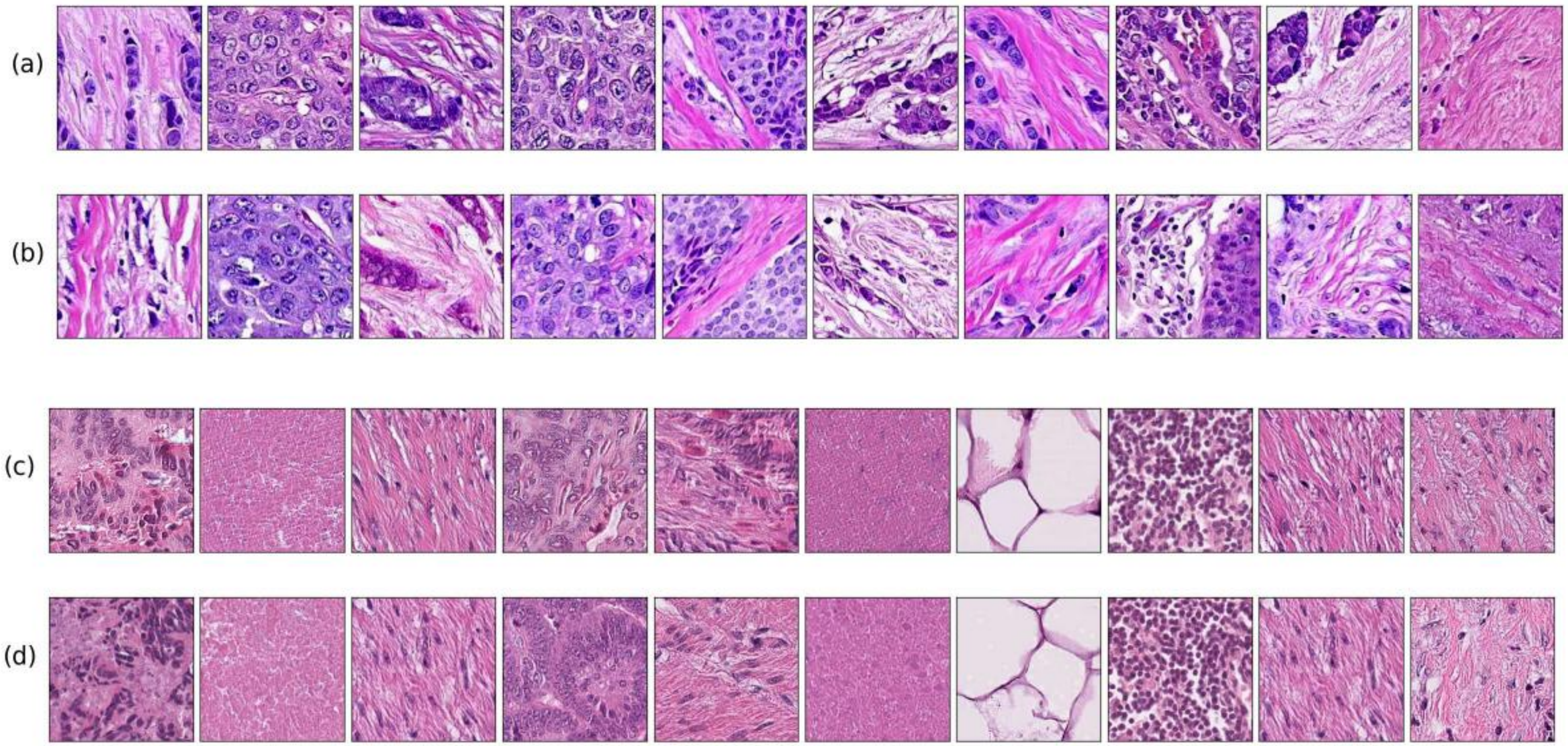
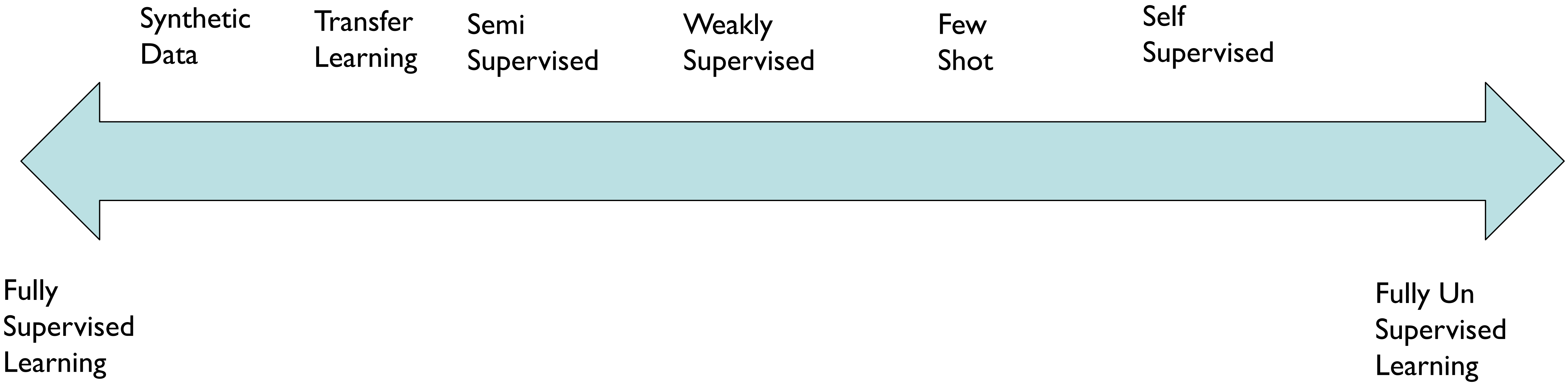


Figure 1: (a): Images (224×224) from PathologyGAN trained on H&E breast cancer tissue. (b): Real images, Inception-V1 closest neighbor to the generated above in (a). (c): Images (224×224) from PathologyGAN trained on H&E colorectal cancer tissue. (d) Real images, Inception-V1 closest neighbor to the generated above in (c).

PathologyGAN: Learning deep representations of cancer tissue, J. Machine Learning for Biomedical Imaging, 2021

7: Summary and Discussions


Synthetic Data
Transfer Learning
Semi Supervised
Weakly Supervised
Few Shot
Self Supervised
Fully Supervised Learning
Fully Un Supervised Learning

Summary and Discussions

- Supervised Learning is Working and Practical !!
  - Reasonably well understood.
- Many problems are not amenable for fully supervised learning
  - Lack of data
  - Lack of annotations
  - Noisy and higher-level annotations
  - Drift in domains. New domains. Knowledge Transfer
- "Beyond Supervised" Many ideas:
  - Practical
  - Theoretically elegant
  - Direction for the next decade

Thank You!!

Comments/Questions?