Developing a Prognostic Deep-Learner for Chronic Obstructive Pulmonary Disease Endpoint

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Disclaimer

- All slides containing data and analysis steps have been removed in accordance with Roche Data Regulatory Requirements
- This presentation only includes open source material (data, methods and images)

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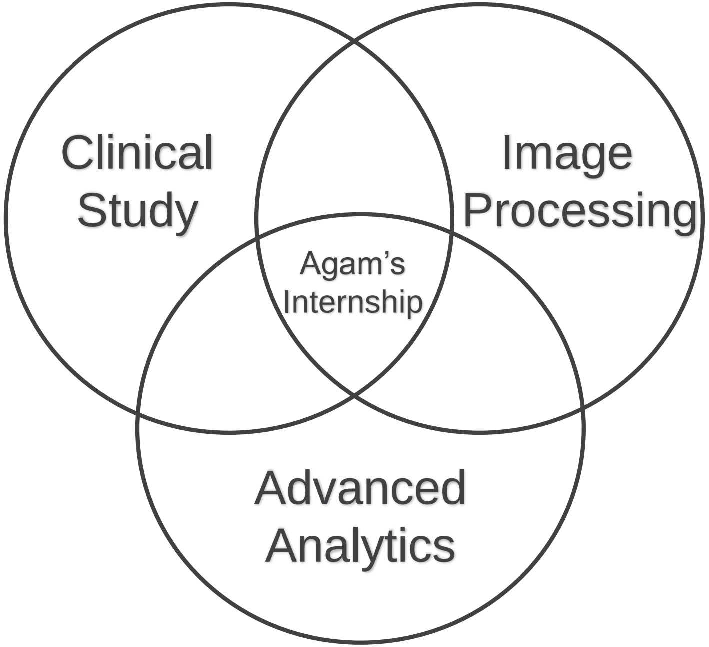

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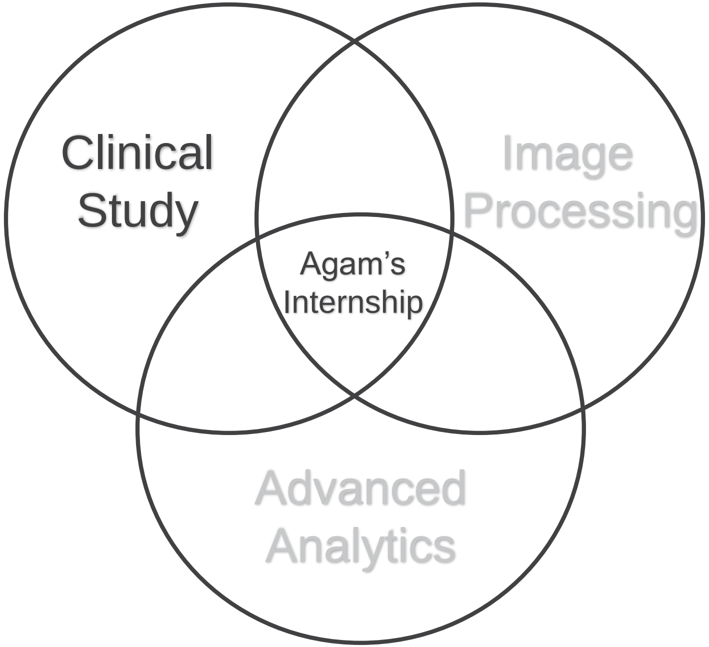
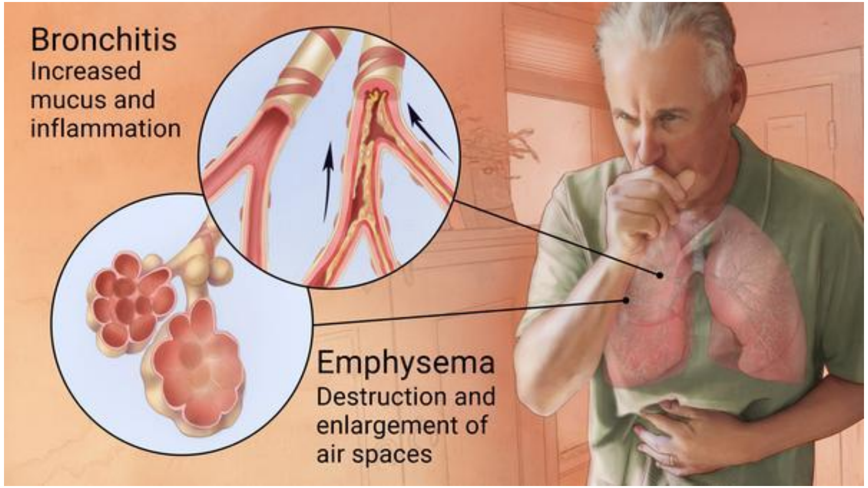


What is Chronic Obstructive Pulmonary Disease (COPD)?

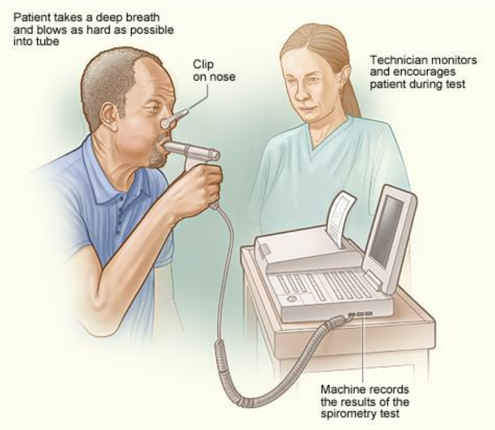
- Umbrella term used to describe progressive lung diseases characterized by increasing breathlessness
- **Emphysema** and **Chronic Bronchitis** are the two most common conditions that contribute to COPD
- 4th leading cause of death in the US affecting approximately 16 million people (source: National Heart, Lung, and Blood Institute)

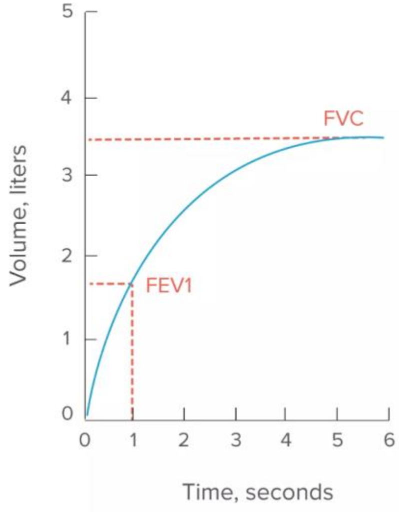


COPD Diagnosis: Pulmonary Function Test

Spirometry

- It measures lung function (the amount and speed of air that can be inhaled and exhaled)
- Helps in assessing breathing patterns that identify conditions such as asthma, pulmonary fibrosis and COPD
- Forced Expiration Volume in 1 second (FEV_1)
- Forced Vital Capacity (FVC)
- $FEV_1/FVC < 0.7$ confirms presence of persistent airflow limitation





TESRA Study and Dataset Description

- TESRA: (Treatment of Emphysema With a Gamma-Selective Retinoid Agonist)
- A Double-blind, Placebo-controlled Efficacy (as Assessed by Post-bronchodilator FEV1) and Safety Study of RAR Gamma in Subjects With Smoking-related, Moderate to Severe COPD With Emphysema Receiving Concurrent Optimised COPD Drug Therapy.

The study collected the following information

- Imaging Data
- Spirometry Data
- Patient Demographics

Source: https://clinicaltrials.gov/ct2/show/record/NCT00413205

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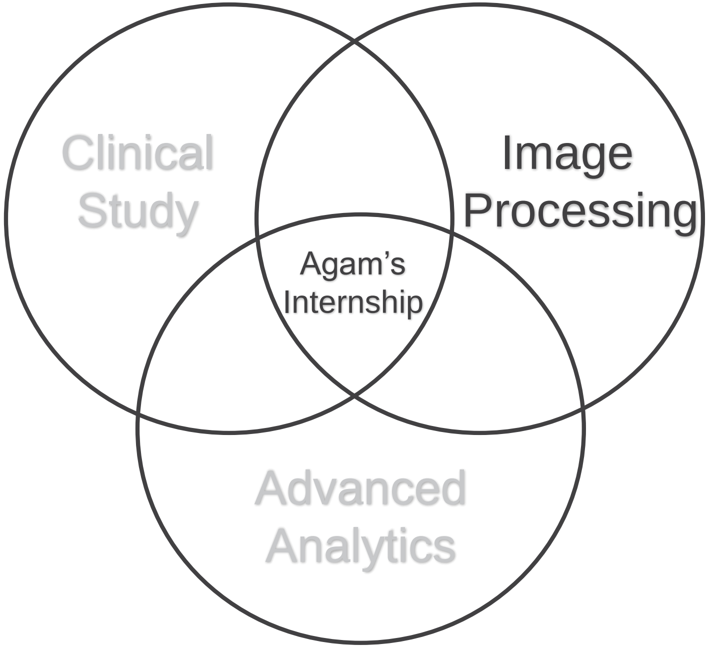
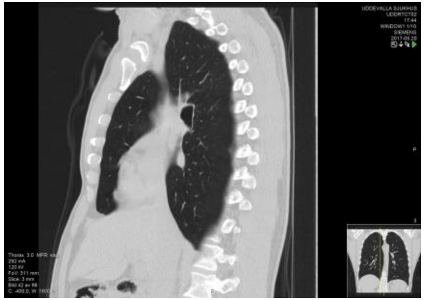


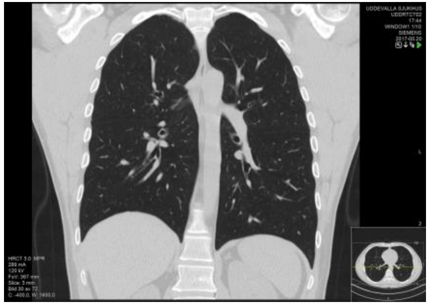
Computed Tomography (CT) Scan

- A computerized tomography (CT) scan combines a series of X-ray images taken from different angles around your body and uses computer processing to create cross-sectional images (slices) of the bones, blood vessels and soft tissues inside your body
- Hounsfield unit (HU) is a quantitative scale for describing radiodensity

Region	HU range
Bone	1000
Liver	40-60
White Matter	46
Grey matter	43
Blood	40
Muscle	10-40
Kidney	30
Cerebrospinal Fluid	15
Water	0
Fat	-50 to -1000
Air	-1000



Sagittal Plane



Coronal Plane

Axial Plane

PRM-fSAD is Prognostic for Annualized Rate of Change in FEV_1

- COPDGene (Bhatt, 2016)
- 1508 current + former smokers, followed for five years

Table 2. Association between PRM Emphysema and fSAD on Change in FEV_1 ml/Year by Baseline GOLD Grade (Estimate, 95% CI, *P* Value)

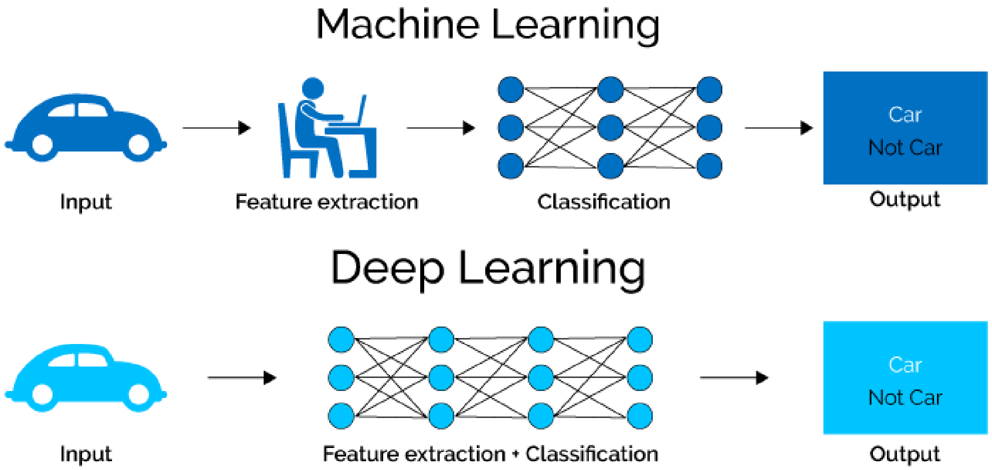
	PRM^{fSAD}	PRM^{emph}
GOLD 0 (n = 751)		
Parameter estimate per 5% (ml/yr)	−2.2 (95% CI, −4.2 to −0.1; *P* = 0.04)	5.5 (95% CI, −8.0 to 19.1; *P* = 0.42)
Mean value CT metric (%)	12.4 (9.7)	0.6 (1.4)
GOLD 1–4 (n = 757)		
Parameter estimate per 5% (ml/yr)	−4.5 (95% CI, −6.3 to −2.6; *P* < 0.001)	−3.5 (95% CI, −5.6 to −1.4; *P* = 0.001)
Mean value CT metric (%)	29.2 (12.3)	9.1 (11.4)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; fSAD = functional small airways disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRM = parametric response mapping; PRM^{emph} = emphysema on parametric response mapping; PRM^{fSAD} = functional small airways disease on parametric response mapping.
Two separate models are shown in rows for the groups GOLD 0 and GOLD 1–4 subjects. Parameter estimates and mean values for respective CT metrics are shown. All models adjusted for age, race, sex, height, current smoking, smoking history in pack-years, baseline FEV_1, baseline FVC, bronchodilator reversibility, and scanner type.

Motivation

Hypothesis: There was information in PRM-fSAD. Is there more information in the images?

- If there is more information in the images, how can we extract it?
- Can we use the extracted information to enrich our clinical trials?



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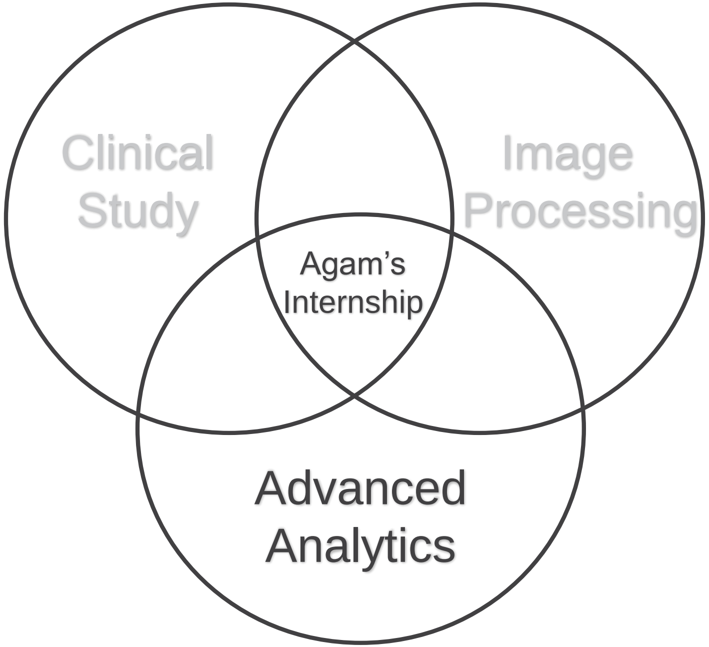
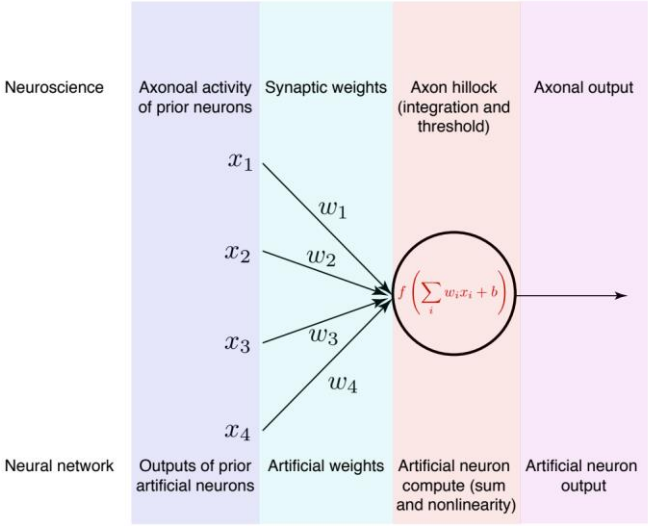
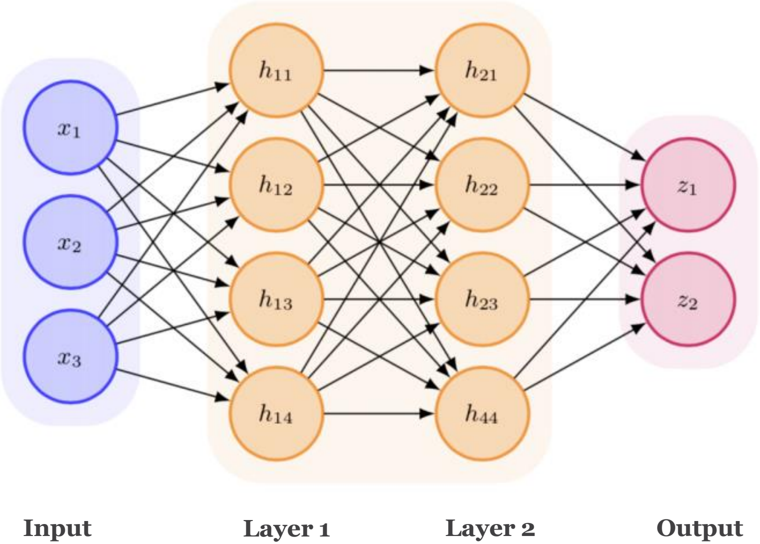


Neural Networks

Neural networks are a set of algorithms, modeled loosely after the human brain, that are designed to recognize patterns





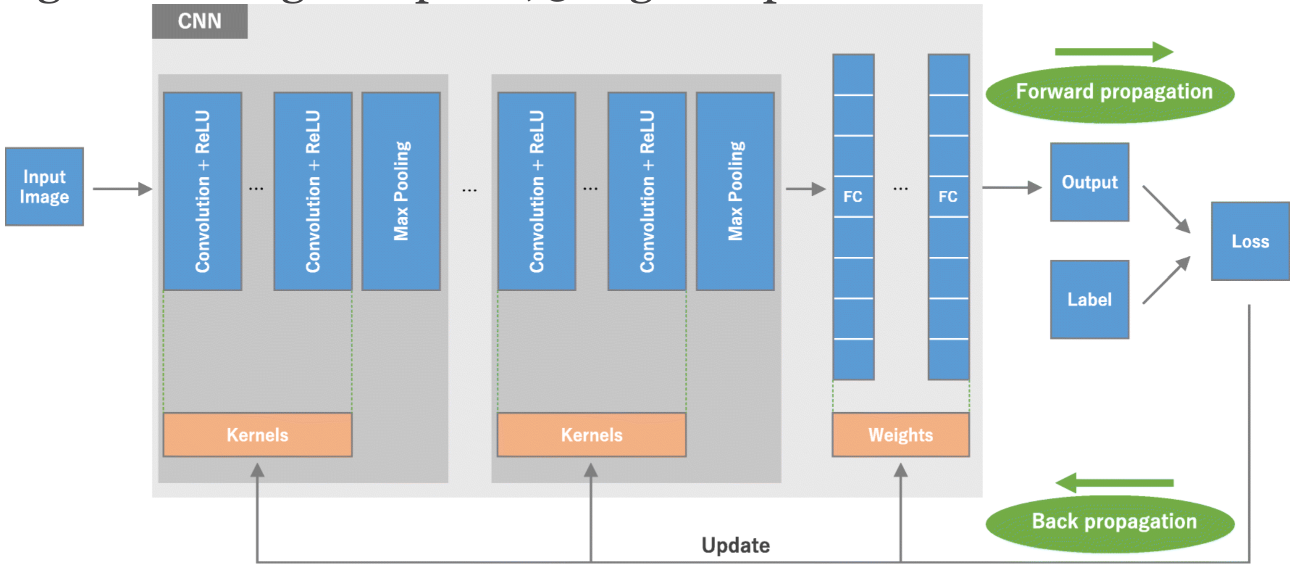
- This network has 10 neurons
- (3X4)+(4X4)+(4X2) = 36 weights, and 4+4+2=10 biases
- 46 learnable parameters

Prof. J. C. Kao, UCLA ECE

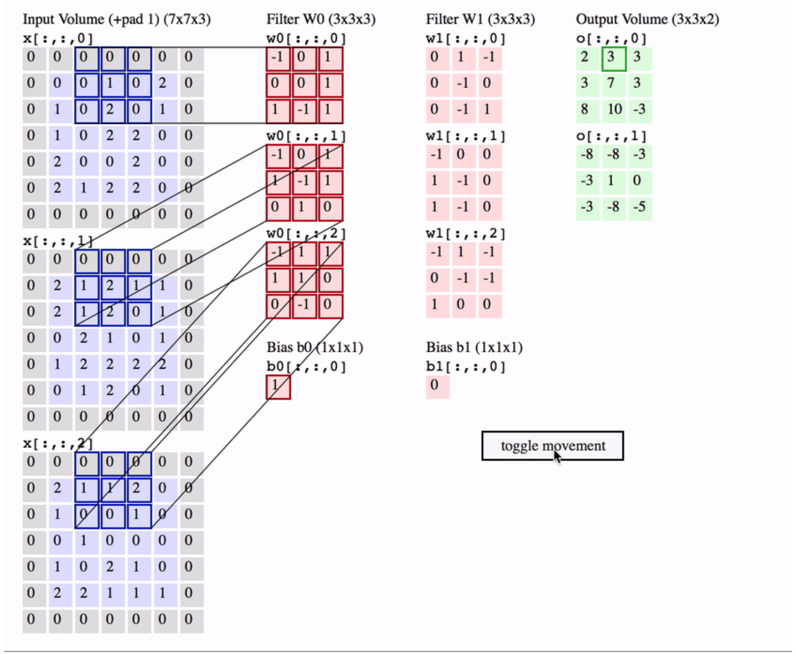
Convolutional Neural Networks (CNN)

Convolutional Neural Networks are simply neural networks that use convolution in place of general matrix multiplication in at least one of their layers.

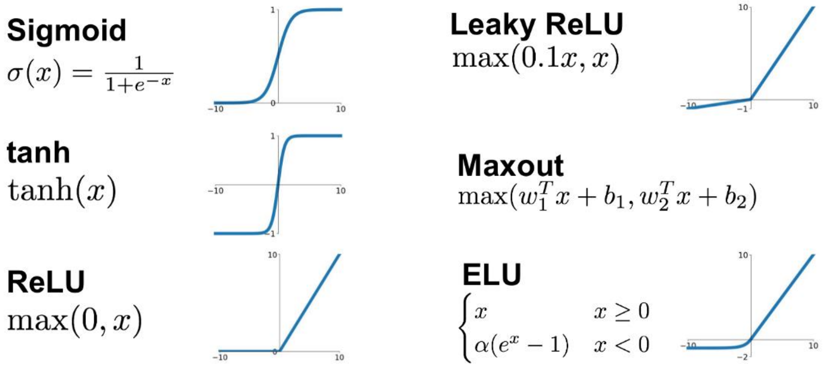
- time series data: 1-D grid taking samples at regular time intervals
- image data: 2-D grid of pixels, 3-D grid of pixels



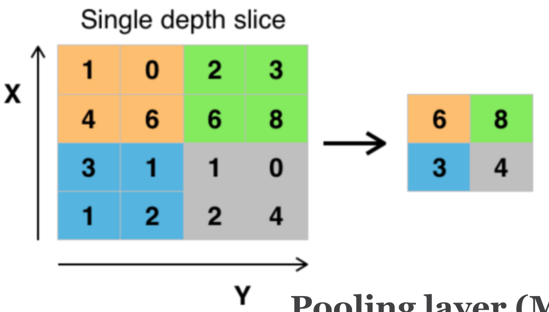
CNN Layers



Convolution layer

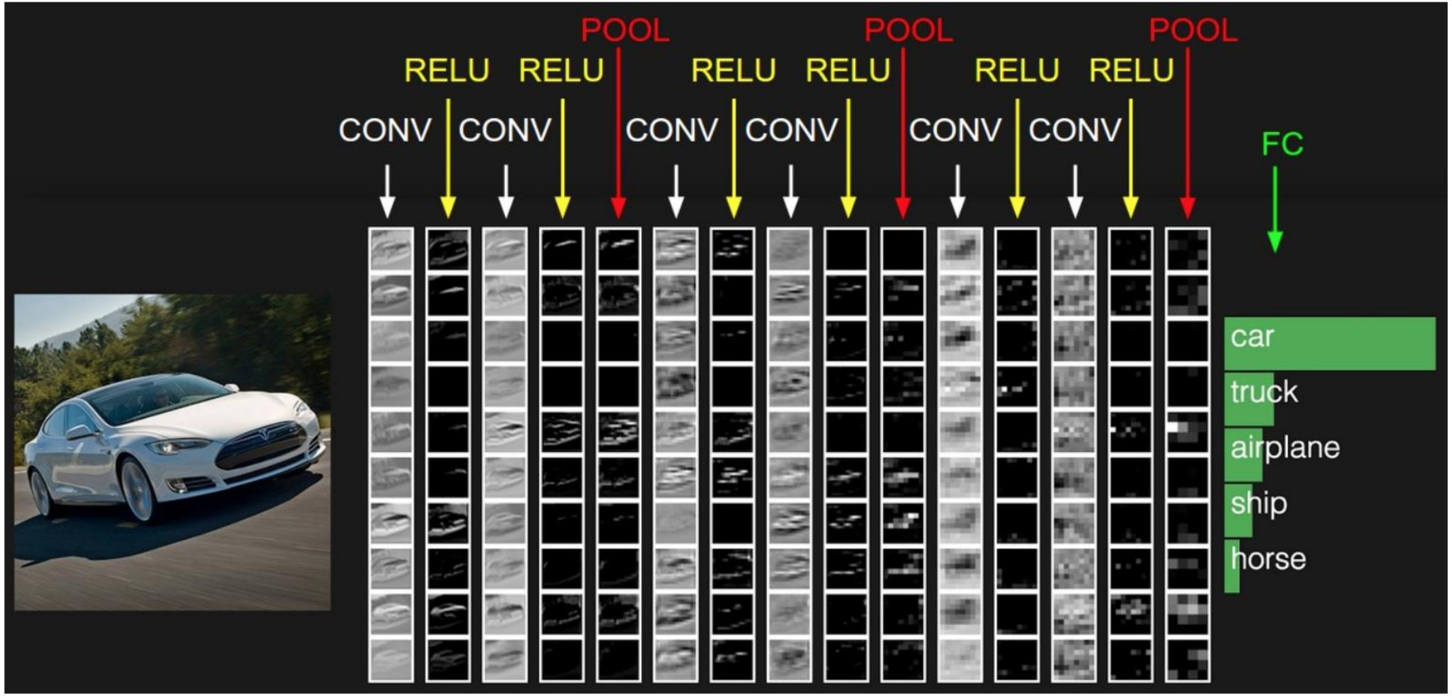


Nonlinearity layer



Pooling layer (Max Pooling)

Deep Learning in action with layer visualization



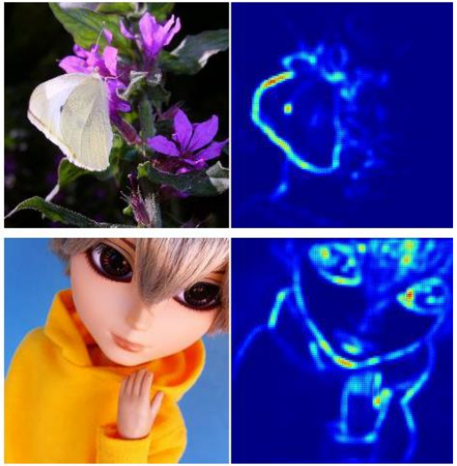
http://scs.ryerson.ca/~aharley/vis/conv/flat.html

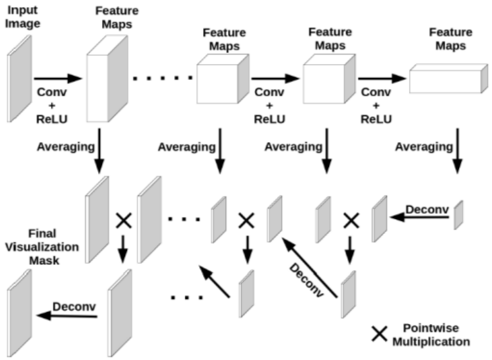
VGG19 Architecture, CS231n.github.io

Visualization of CNNs

VanillaGradient by Karen Simonyan et al. (2014) from VGG Group is a method to compute the gradient of output category to input image. We can use these gradients to highlight input regions that cause the most change in the output

- **VisualBackProp** by Marius Bojarski et al. (2017) from NVIDIA Corp. is a method for visualizing which sets of pixels of the input image contribute most to the predictions made by the CNN





Deep Learning methods for Small Data Sets

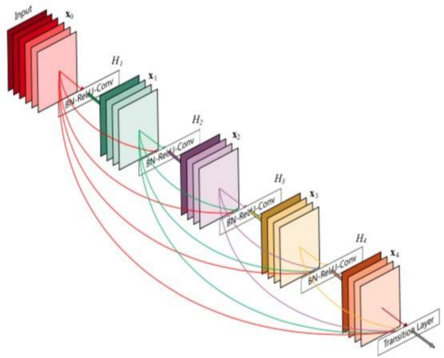


Figure 1: A 5-layer dense block with a growth rate of $k = 4$. Each layer takes all preceding feature-maps as input.

Transfer Learning from DenseNet121

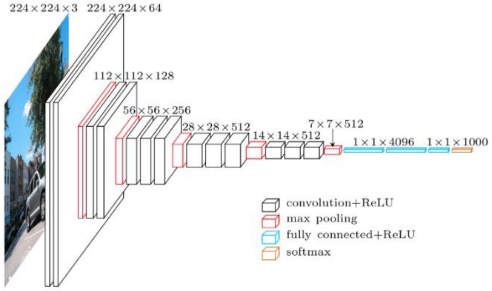


Figure 2. VGG16 Architecture (ref)

Feature Extraction from VGG16

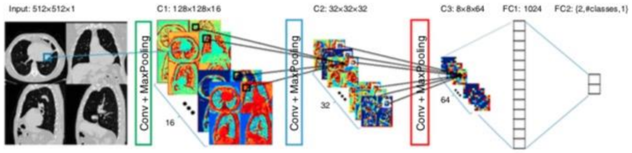
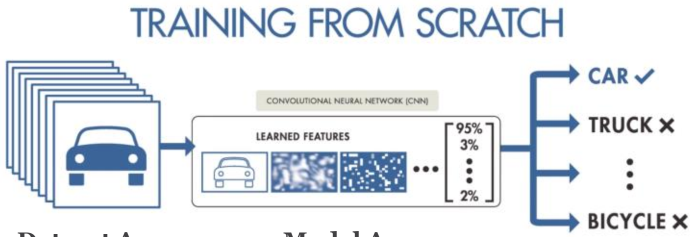


Figure 1. The input of the convolutional neural network is a composite image of four canonical views of the computed tomography scan: an axial slice at the level of the mitral valve, a coronal slice taken at the level of the ascending aorta, and two sagittal slices at the level of the right and left hila. The image is analyzed with a convolutional neural network consisting of three convolutional layers (Conv) followed by max-pooling operations, each reducing the image size fourfold in each direction. At the end of the convolutional layers are two fully connected networks, the first one of 1,024 neurons and the second one of variable size depending on the problem at hand: classification, multiclass classification, or regression.

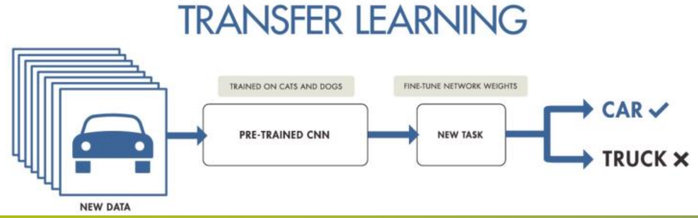
Lightweight Architecture (Gonzalez, 2018)

Transfer Learning

- In practice, training an entire Convolutional Network from scratch is rare since they need large dataset for training
- It is common to pretrain a ConvNet on a very large dataset, and then fine-tune some higher-level portion of the network



Dataset A Model A

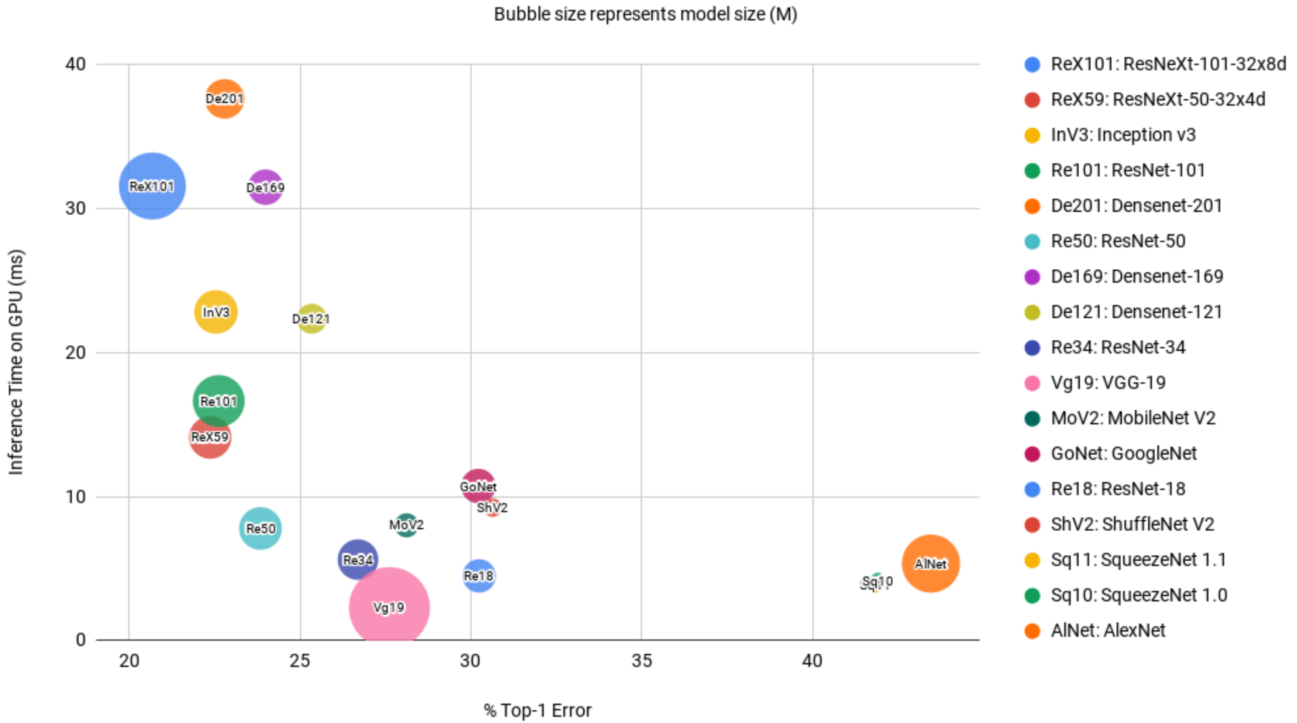


Dataset B Model B

Dataset Size	Dataset Similarity	Recommendation
Large	Very Different	Train model B from scratch, initialize weights from model A
Large	Similar	OK to fine-tune (less likely to overfit)
Small	Very different	Train classifier using the earlier layers (later layers won't help much)
Small	Similar	Don't fine-tune (Overfitting). Train a linear classifier

Source: CS231n.github.io

Pre-Trained Models Comparison



Training done on ImageNet (1.4 M Labeled Images, 1000 different classes)

Results

- COPD Progression Classification Accuracy: ~95%

Summary and Conclusion

- Deep Learning have powerful capabilities to detect patterns in data
- TESRA image dataset is very small for training a neural net for regression problem
- Pre-trained architectures are robust for classification problems but not for regression problems
- Pre-trained architectures are not trained on medical images, implementing transfer learning even for simple problems requires a lot of effort in tuning the network

Acknowledgement

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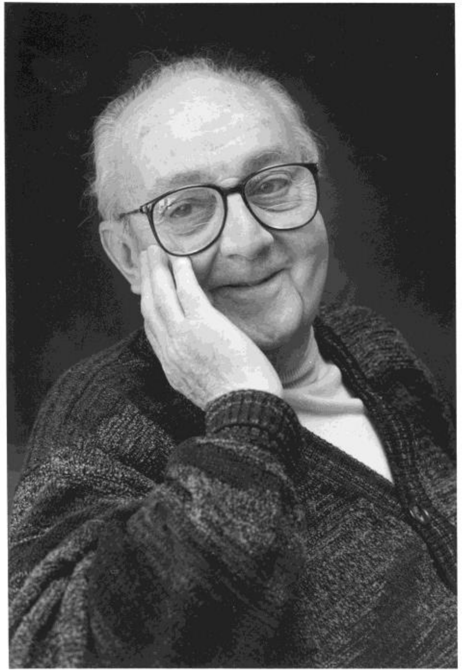

"All models are wrong, but some are useful."

– George Edward Pelham Box

Doing now what patients need next