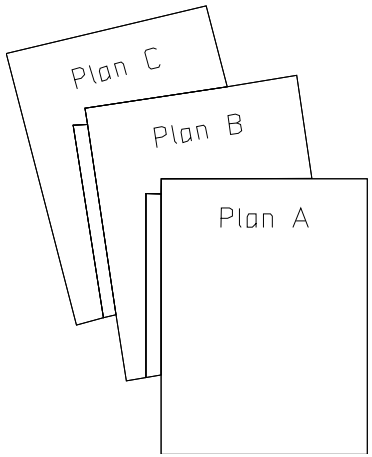
Machine Learning in Medicine

이영기
서울대학교 컴퓨터공학부

Overview

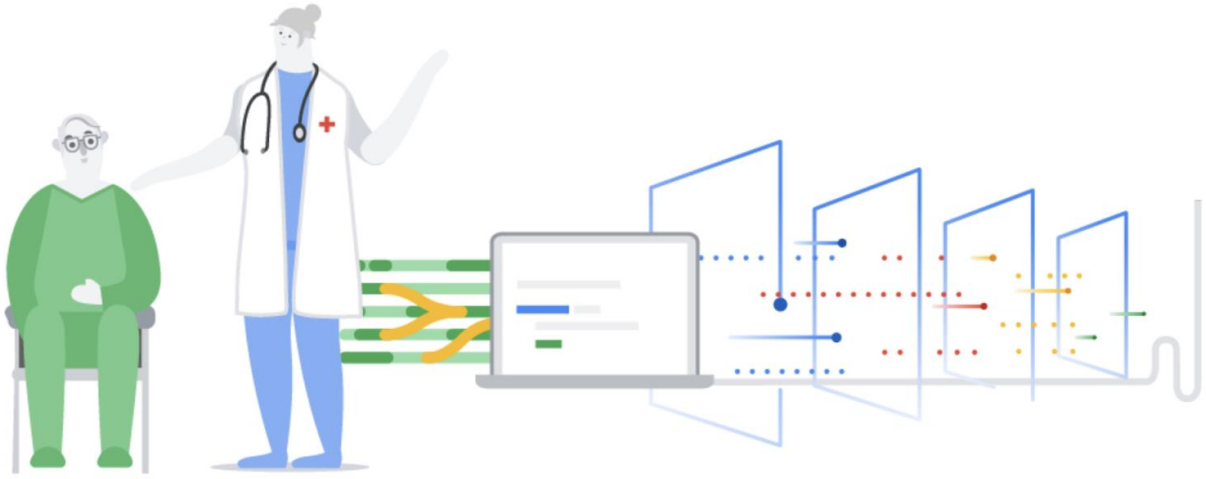
- Objective
  - To understand the current usages of machine learning in medicine and upcoming challenges



- Content
  - Medical record analysis
  - Medical imaging
  - Pervasive healthcare
  - Overcoming Obstacles

Machine learning in Medicine

- Medical record analysis
- Medical imaging
- Pervasive healthcare



Medical Record Analysis

IBM Watson

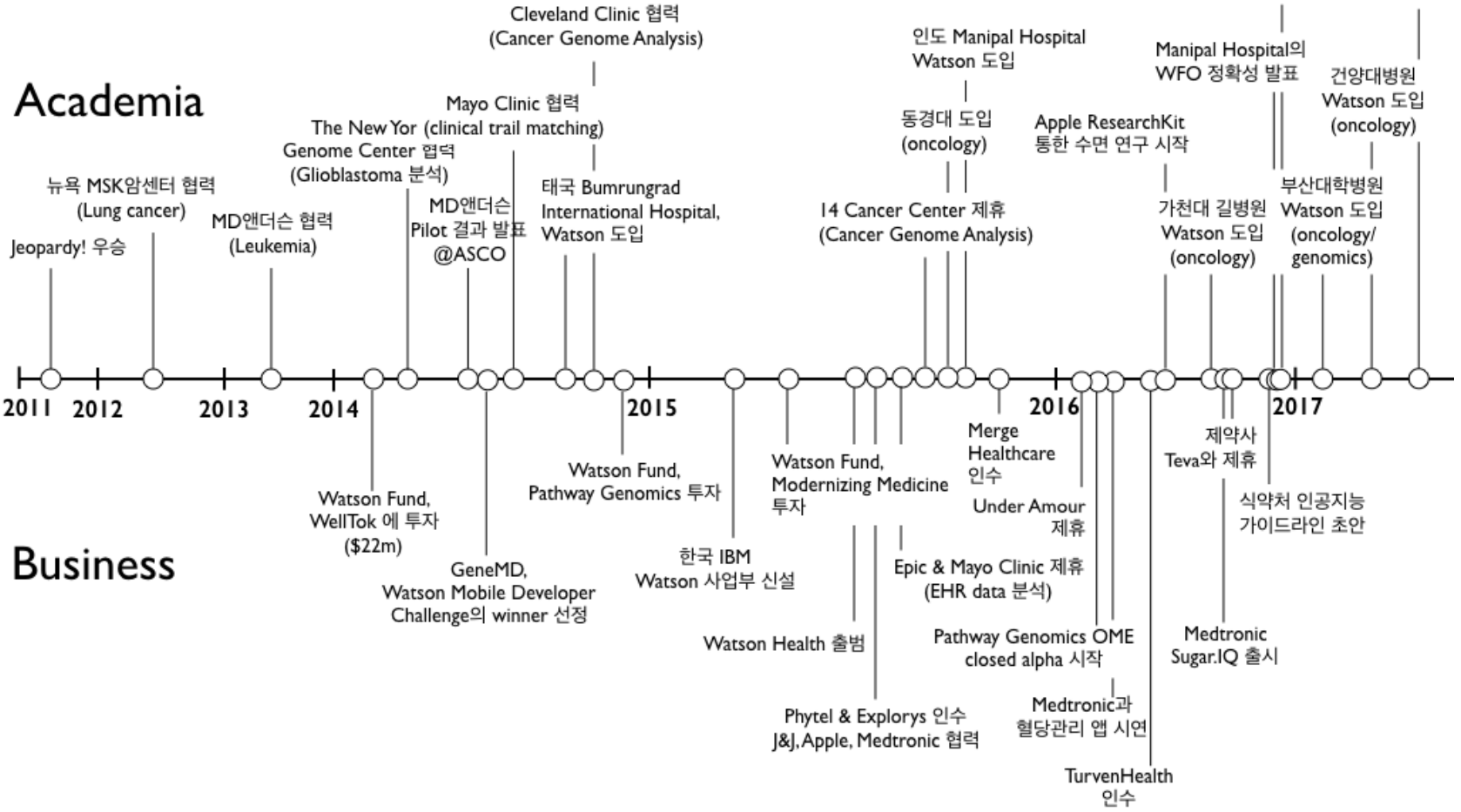
- Jeopardy challenge (2011)

IBM Watson for Oncology

Watson learned...

600,000 pieces of medical evidence
2 million pages of text from 42 medical journals and clinical trials
69 guidelines, 61,540 clinical trials
+
1,500 lung cancer cases
physician notes, lab results and clinical research
+
14,700 hours of hands-on training

IBM Watson for Oncology (cont'd)



최윤섭, "인공지능은 의료를 어떻게 혁신하는가", 2019

IBM Watson for Oncology (cont'd)

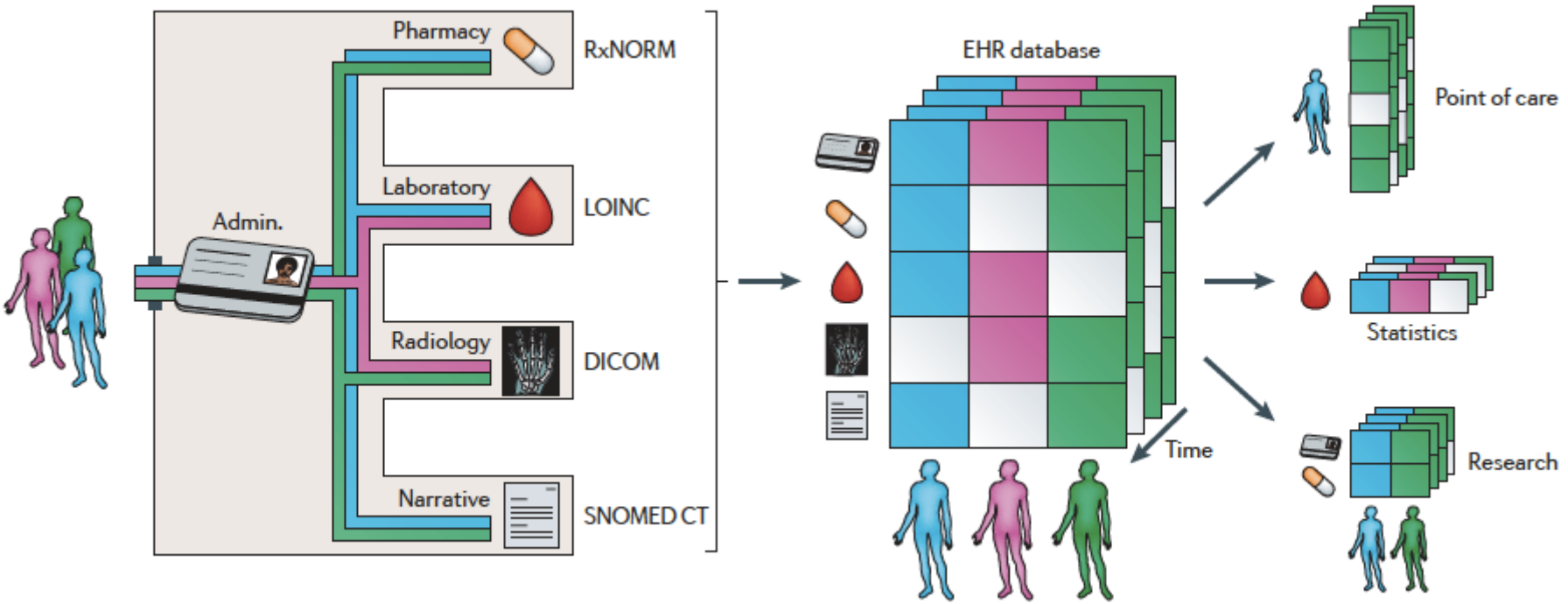
- In Denmark, oncologists at one hospital said they have dropped the project altogether after finding that local doctors agreed with Watson in only about **33 percent** of cases.
- "We had a discussion with [IBM] that they had a very limited view on the international literature, basically, putting **too much stress on American studies**, and too little stress on big, international, European, and other-part-of-the-world studies," said Dr. Leif Jensen, who directs the center at Rigshospitalet in Copenhagen that contains the oncology department.

IBM Watson for Oncology (cont'd)

- Challenges
  - ✓Localization
  - ✓Reasoning behind the decision
  - ✓Providing treatment decision support
  - ✓Multiple treatment options

Electronic Health Records Analysis

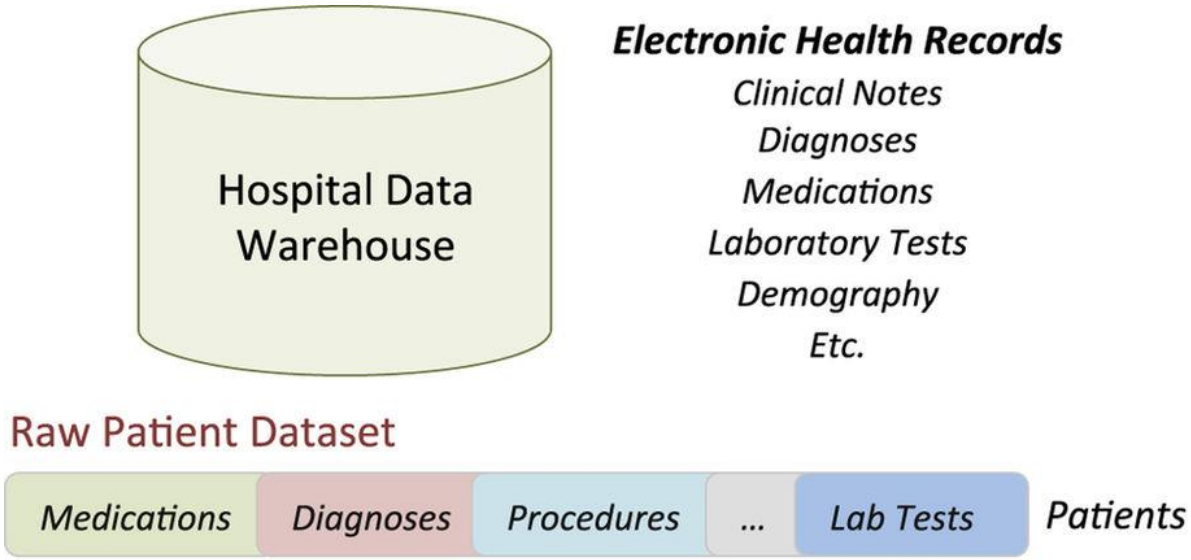
- Unsupervised EHR analysis



Miotto et el, "Deep Patient: An Unsupervised Representation to Predict the Future of Patients from the Electronic Health Records", Nature Scientific Reports 2016

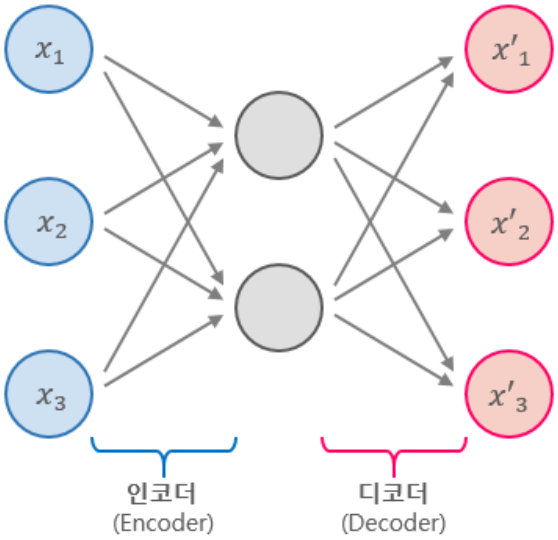
Electronic Health Records Analysis

- Raw data contains tons of data (**unlabeled**)
- Use natural language processing model to extract 300 features (Hand-crafted)

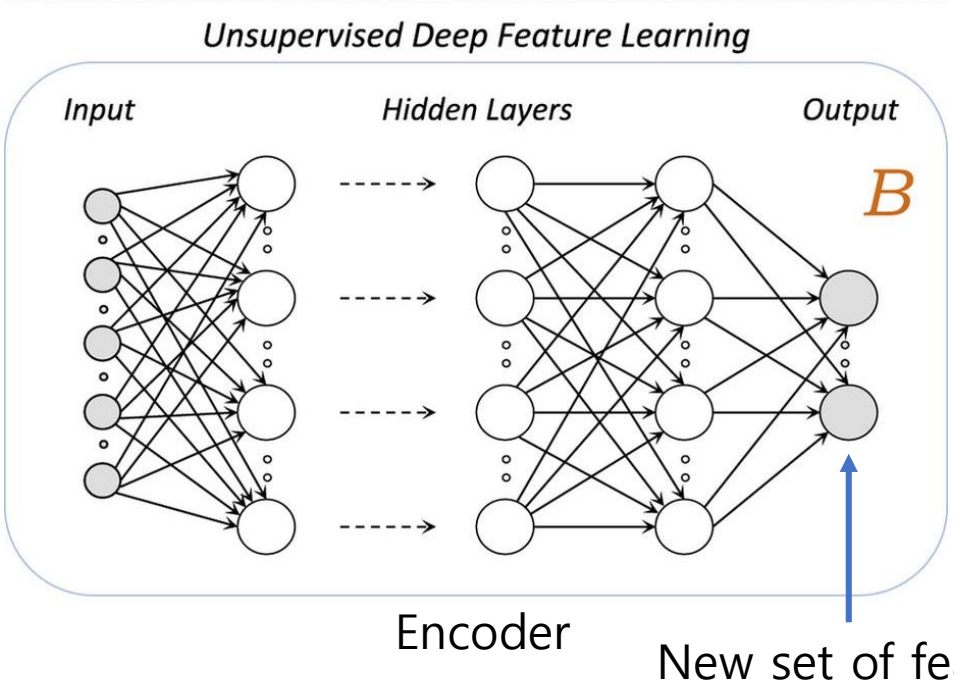


Electronic Health Records Analysis

- Use autoencoder to reduce the feature domain
  - ✓Important feature extraction in an unsupervised manner
  - ✓Computation time & memory



Autoencoder

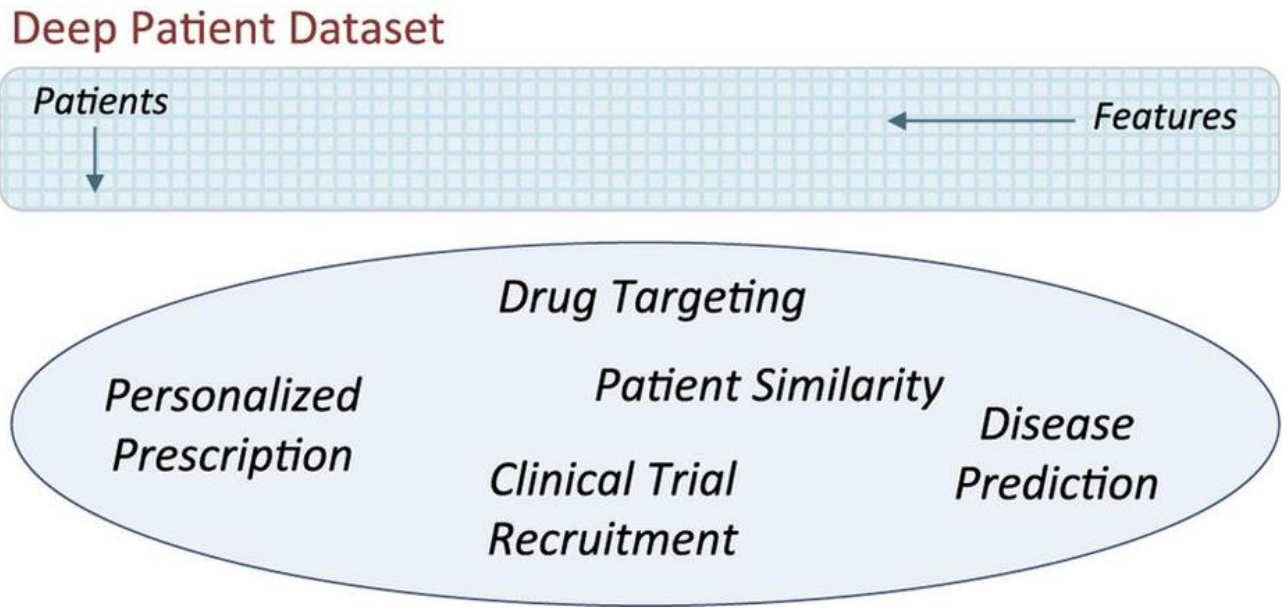


Encoder

New set of features

Electronic Health Records Analysis

- Construct a dataset with deep features for a number of clinical tasks



Electronic Health Records Analysis

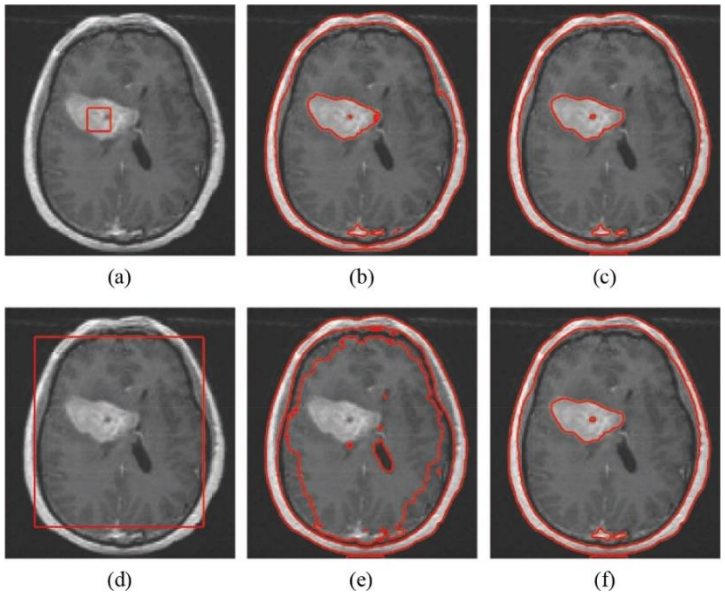
- Train random forest with 100 trees
- Proposed method was able to extract **best representation** of the patient from a data

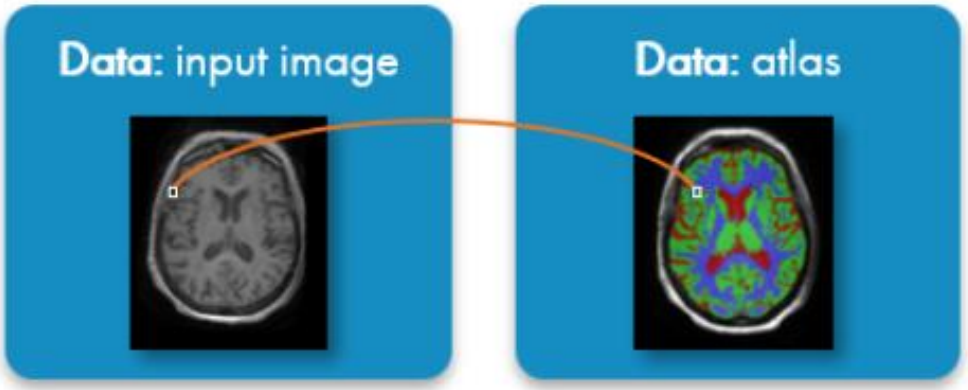
Time Interval = 1 year (76,214 patients)			
		Classification Threshold = 0.6	
Patient Representation	AUC-ROC	Accuracy	F-Score
RawFeat	0.659	0.805	0.084
PCA	0.696	0.879	0.104
GMM	0.632	0.891	0.072
K-Means	0.672	0.887	0.093
ICA	0.695	0.882	0.101
DeepPatient	**0.773***	**0.929***	**0.181***

Medical Image Analysis

Pre-Deep Learning Era

- Use training data to build a model
  - ✓Active shape models
  - ✓Atlas methods
  - ✓Feature extraction & Statistical classifiers



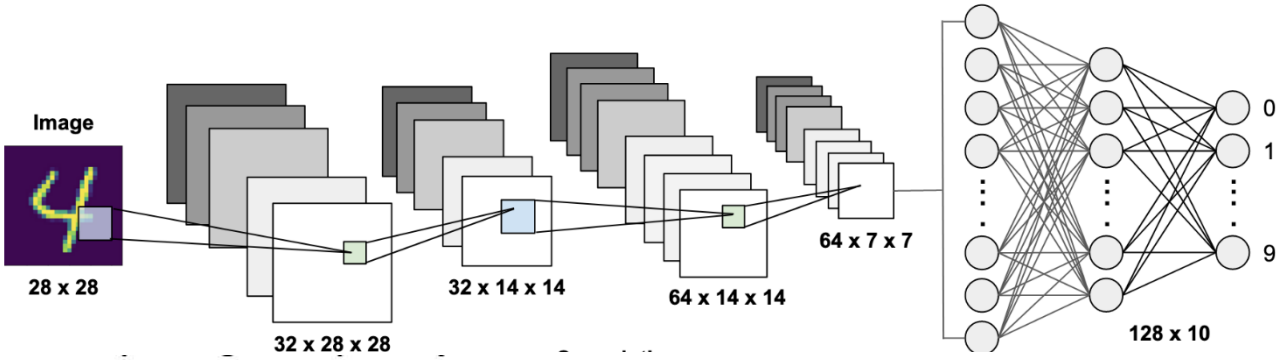


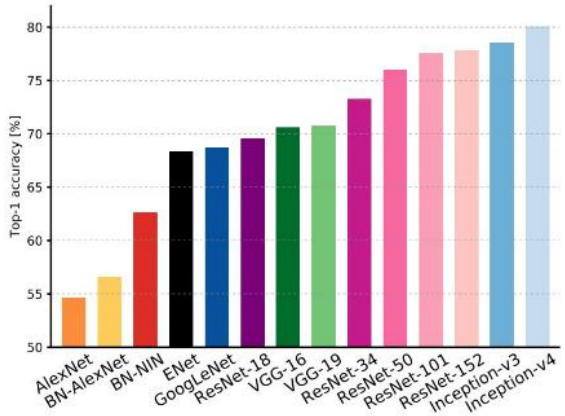
Pre-Deep Learning Era (cont'd)

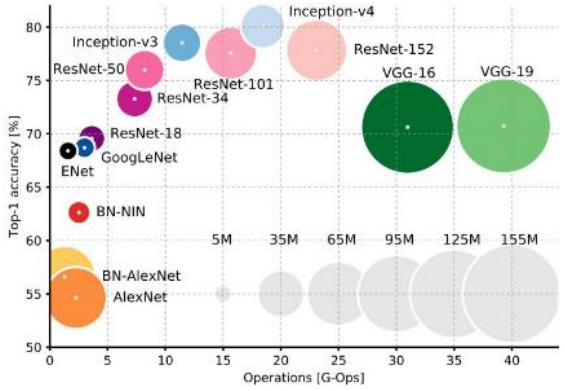
- Use training data to build a model
  - ✓Active shape models
  - ✓Atlas methods
  - ✓Feature extraction & Statistical classifiers
- Extract discriminant features
  - ✓**Hand-crafted** features
  - ✓Human experience

Medical Imaging

- Emergence of Deep Learning (CNN)







An Analysis of Deep Neural Network Models for Practical Applications, 2017.

Human vs Deep Learning

Geoffrey Hinton

"I think that if you work as a radiologist, you are like Wile E. Coyote in the cartoon. You're already over the edge of the cliff, but you haven't yet looked down. There's no ground underneath. People should stop training radiologists now. It's just completely obvious that in five years deep learning is going to do better than radiologists."

Nov 24, 2016

Deep Learning in Medical Image Analysis

- Segmentation
- Registration
- Anomaly Detection
- Structural Analysis
- …

Image Segmentation

What is Segmentation?

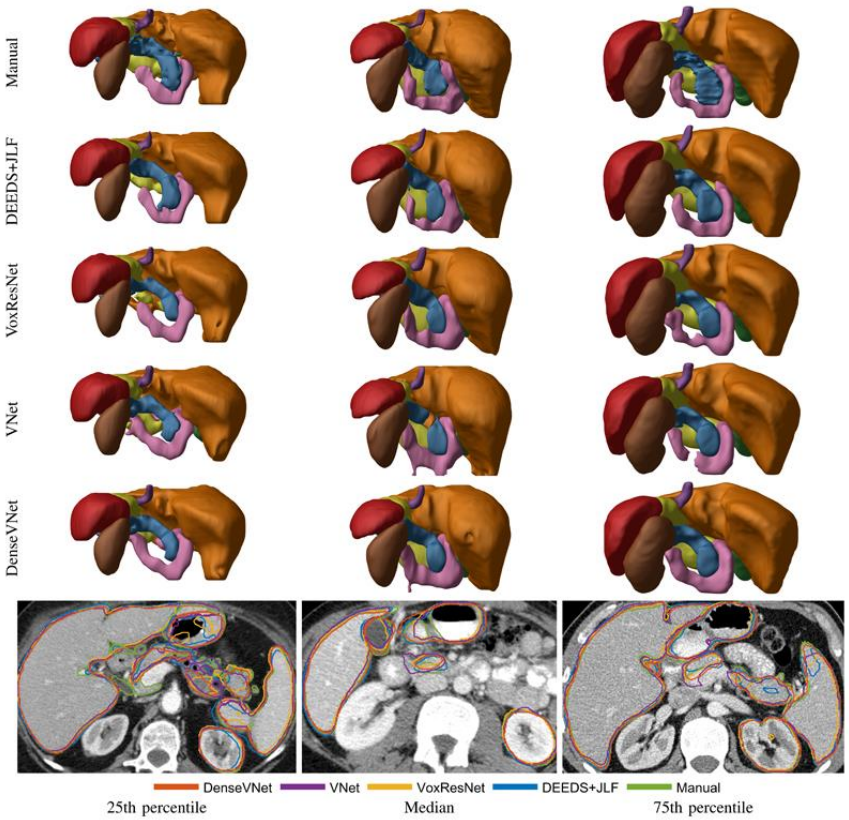
- Process of partitioning a digital image into multiple segments
- Image into something that is meaningful and easier to analyze

Image 1

Image 2

Medical Image Segmentation

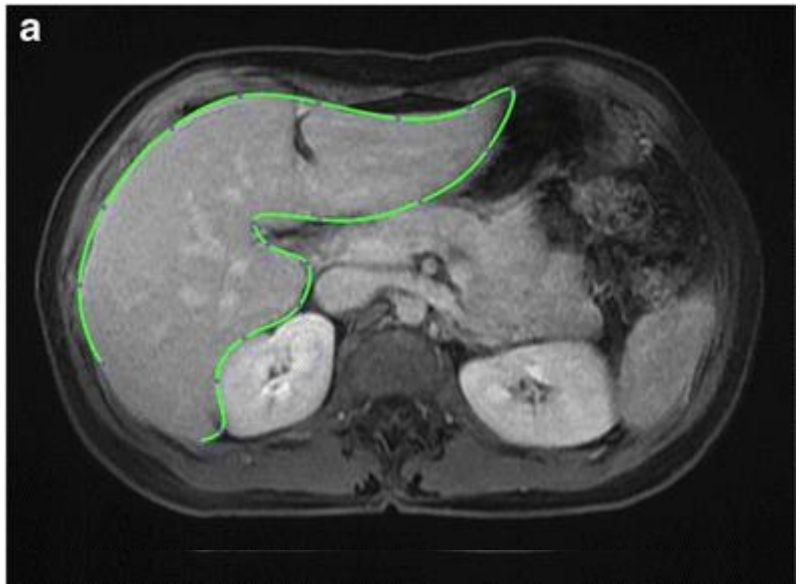
- Multi-organ segmentation

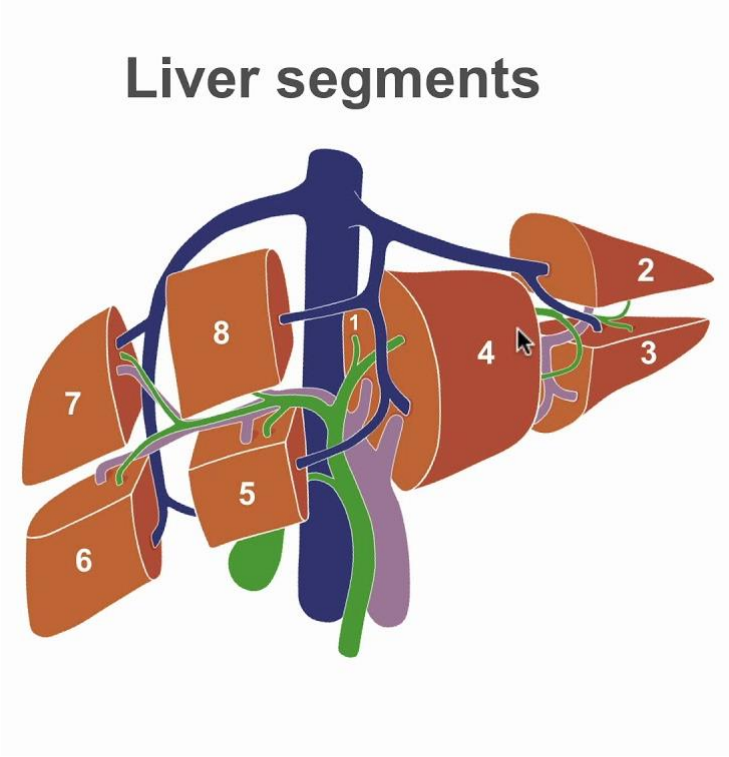


Gibson et el, “Automatic Multi-organ Segmentation on Abdominal CT with Dense V-networks”, IEEE Transactions on Medical Imaging, 2018

Use case (1/2)

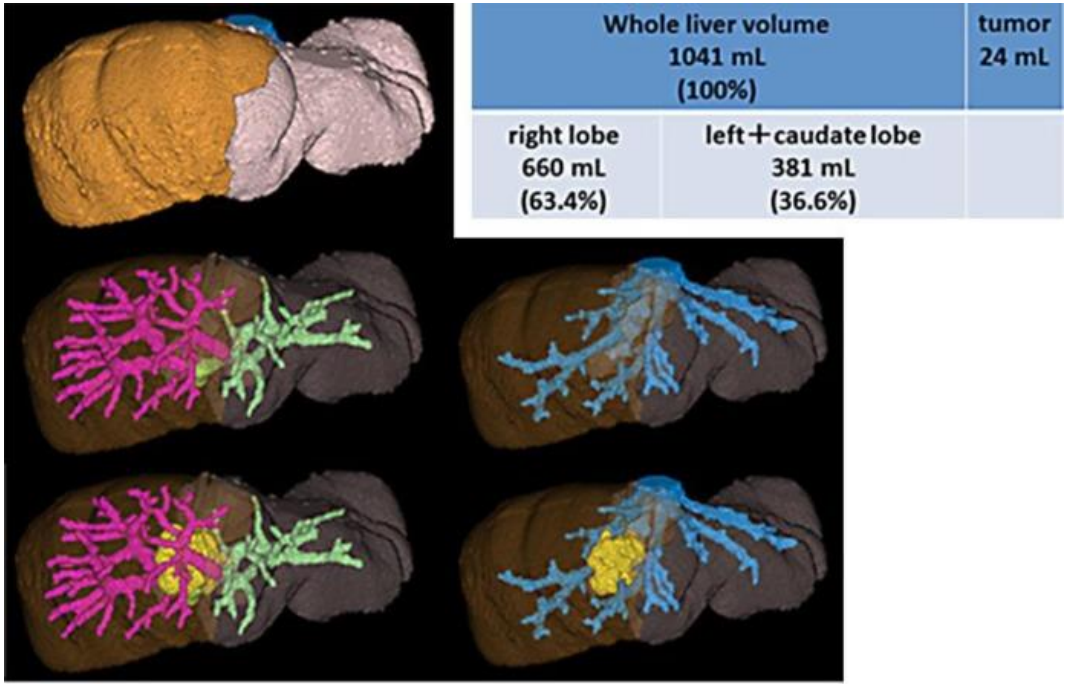
- Liver segmentation in abdominal CT





Use case (1/2)

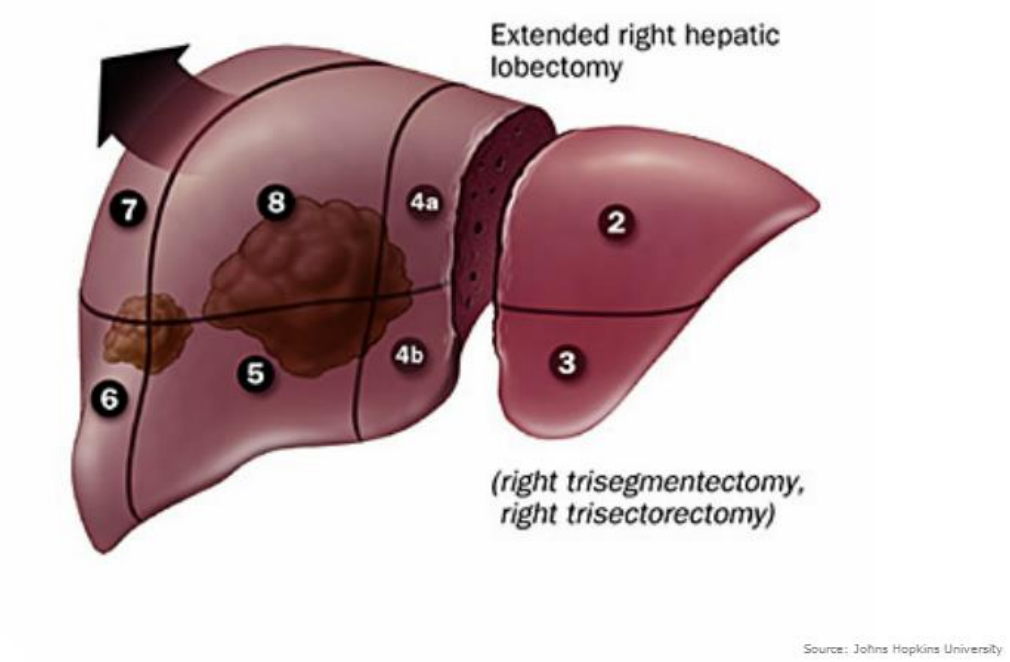
- Measurement of liver volume is important for selection of surgical procedure



Zhu et el, "Measurement of liver volume and its clinical significance in cirrhotic portal hypertensive patients" World Journal Gastroenterol 1999

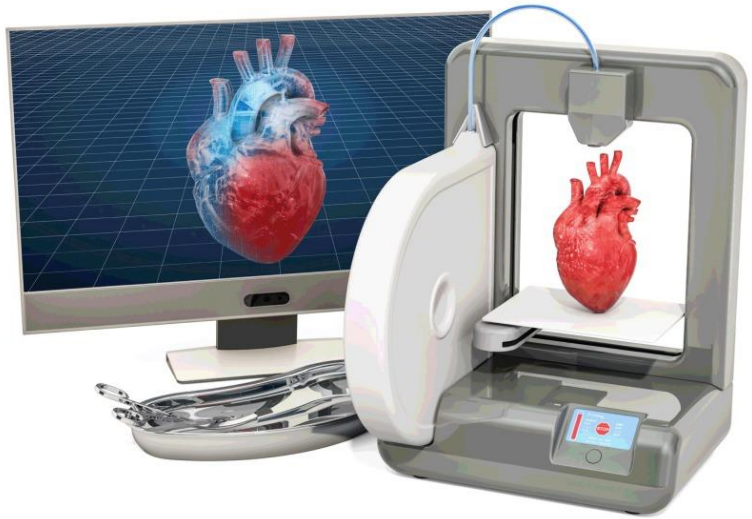
Use case (1/2)

- Liver cancer surgery
  - ✓Identify the target segments



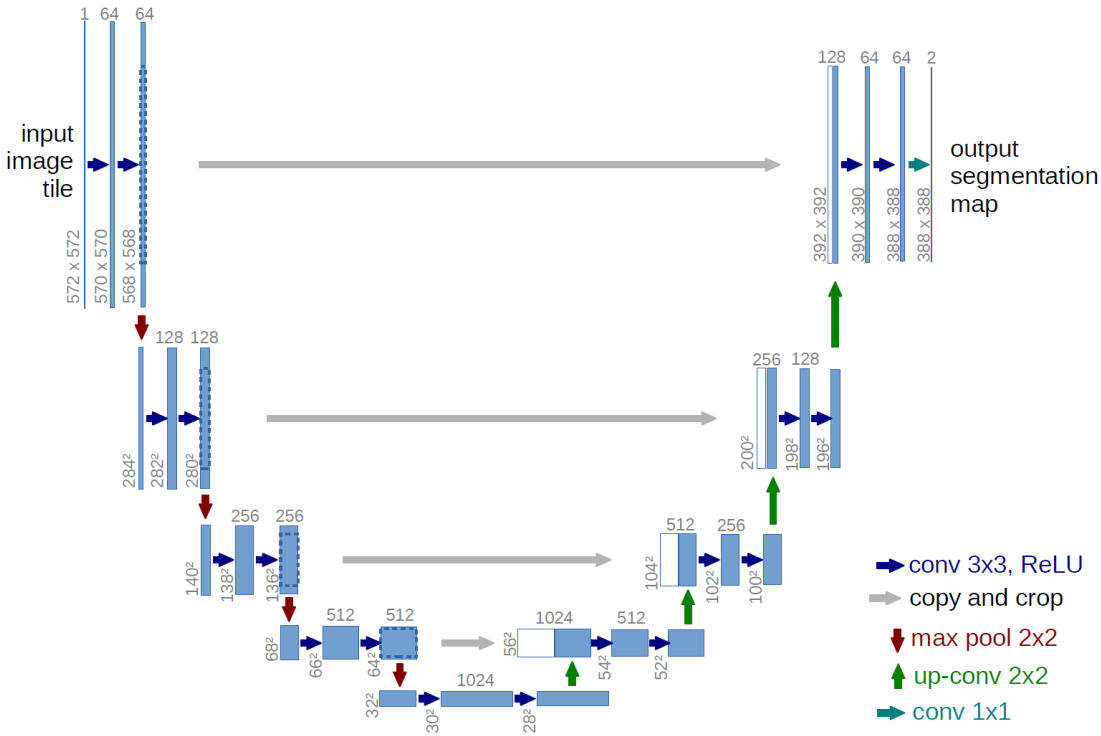
Use case (2/2)

- 3D Printing
  - ✓Surgical guide
  - ✓Education
  - ✓Artificial organ



U-net

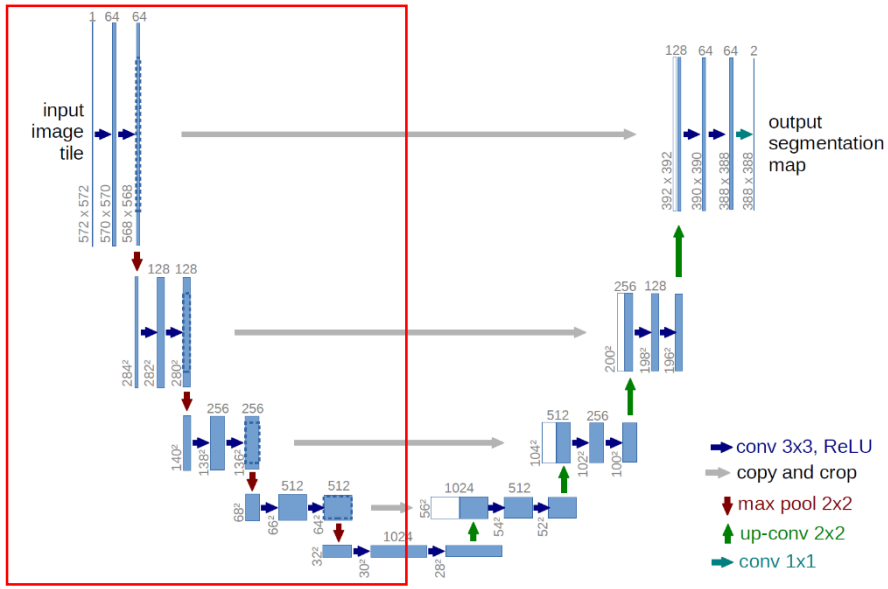
- 2 path approach



Ronneberger et el, “U-Net: Convolutional Networks for Biomedical Image Segmentation” Medical Image Computing and Computer-Assisted Intervention (MICCAI) 2015

U-net

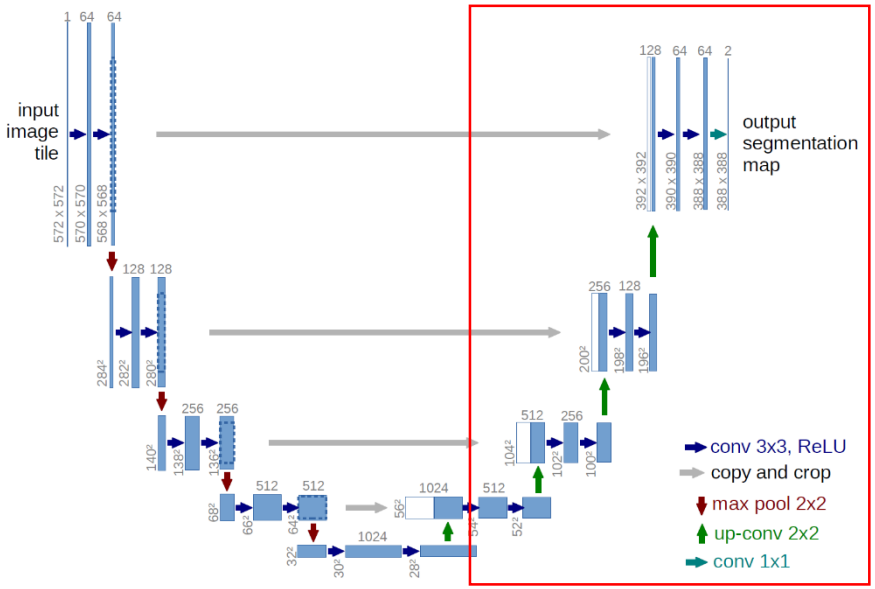
- Contraction path
  - ✓Extract more advanced features but it also reduce the size of feature maps

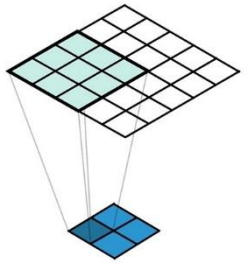


Ronneberger et el, "U-Net: Convolutional Networks for Biomedical Image Segmentation" Medical Image Computing and Computer-Assisted Intervention (MICCAI) 2015

U-net

- Expansion path
  - ✓Recover the size of segmentation map but also loss the localization information



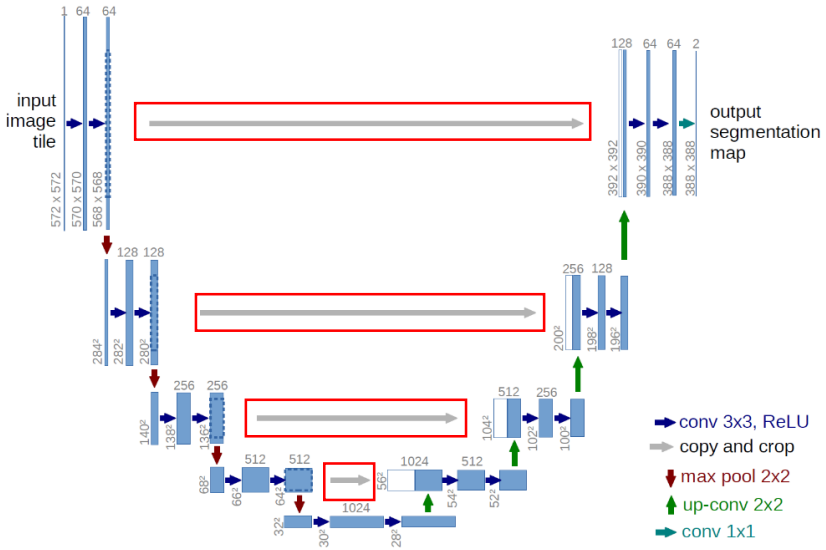


Up Convolution

Ronneberger et el, "U-Net: Convolutional Networks for Biomedical Image Segmentation" Medical Image Computing and Computer-Assisted Intervention (MICCAI) 2015

U-net

- Expansion path
  - ✓Concatenate feature maps that are with the same level
  - ✓Gives the localization information from contraction path to expansion path

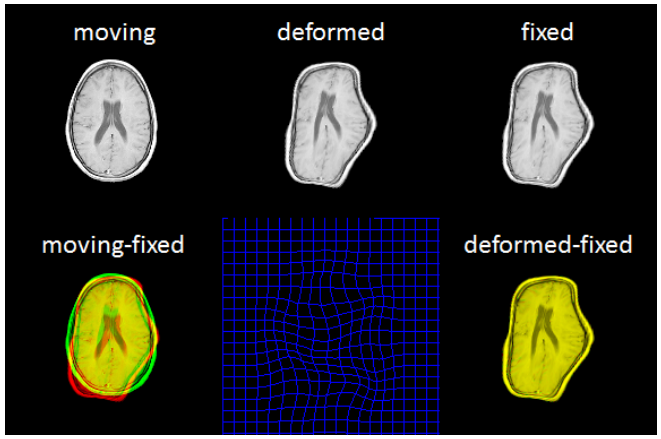


Ronneberger et el, "U-Net: Convolutional Networks for Biomedical Image Segmentation" Medical Image Computing and Computer-Assisted Intervention (MICCAI) 2015

Image Registration

What is Registration?

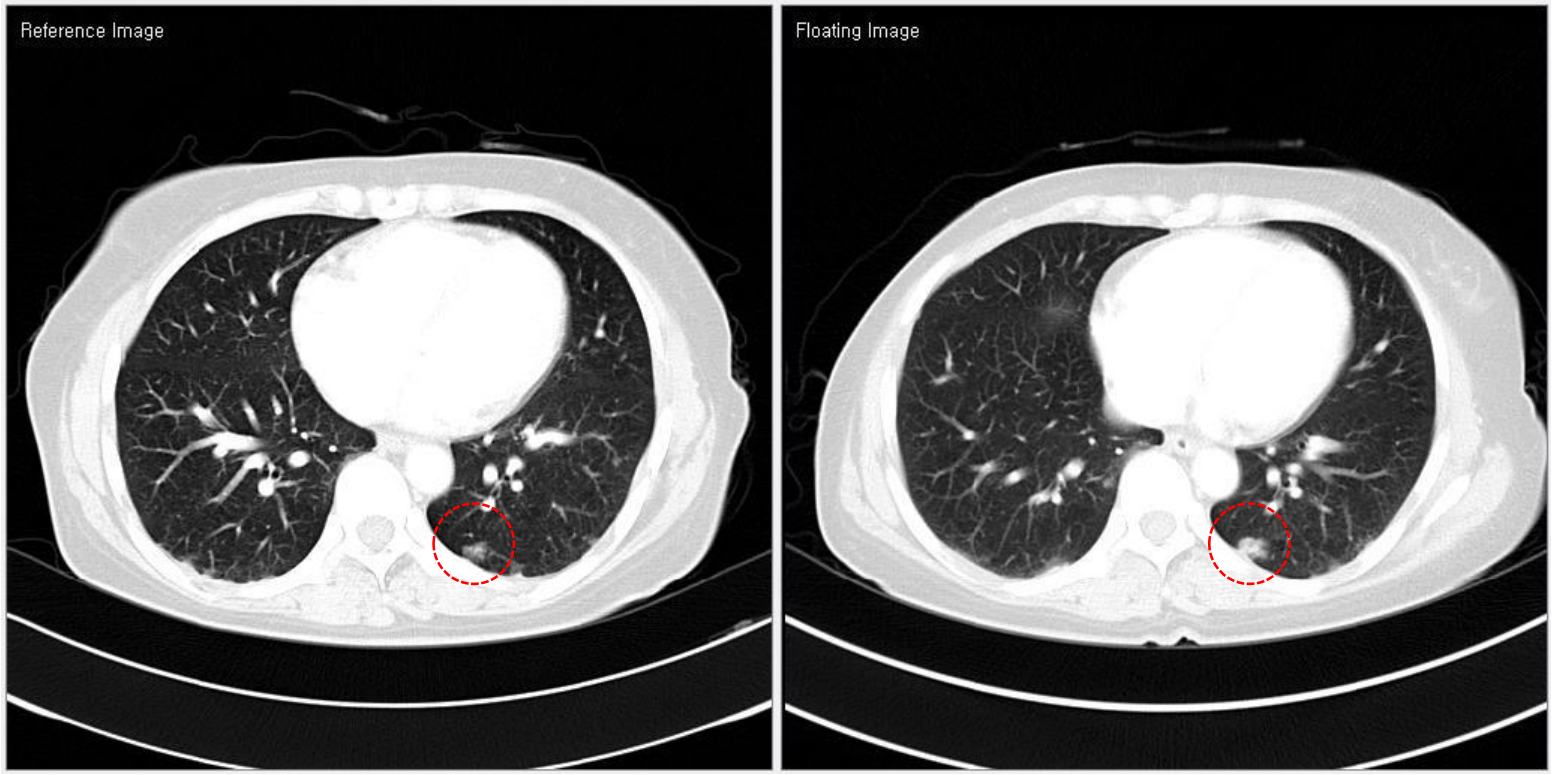
- Process of transforming different sets of data into one coordinate system
- Images from different
  - ✓Time
  - ✓Modality (X-ray, MRI, CT, and Ultrasound …)



Use case (1/2)

- Lung registration
  - ✓2 CT images from different time
  - ✓How to compare size of the nodule?

Use case (1/2)



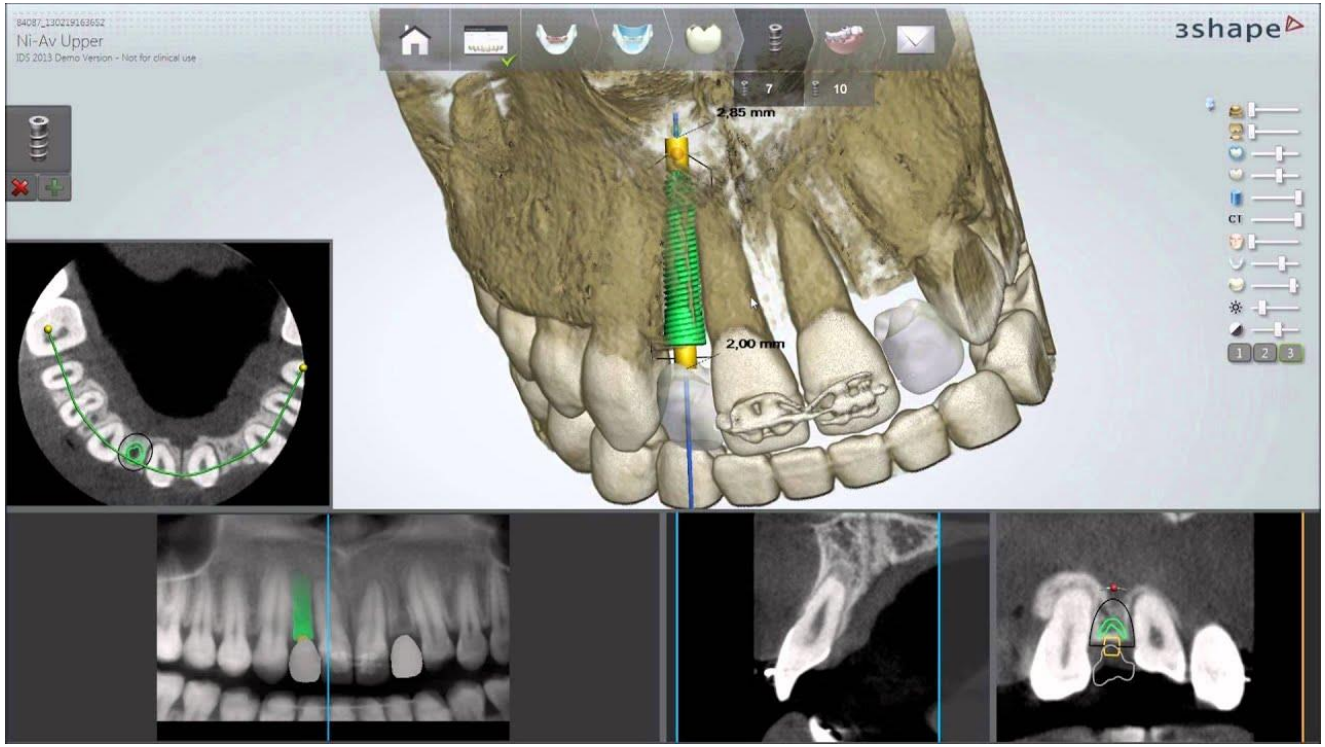
After Registration

Use case (2/2)

- Registration between CT & Dental impression
  - ✓Inter-modality registration

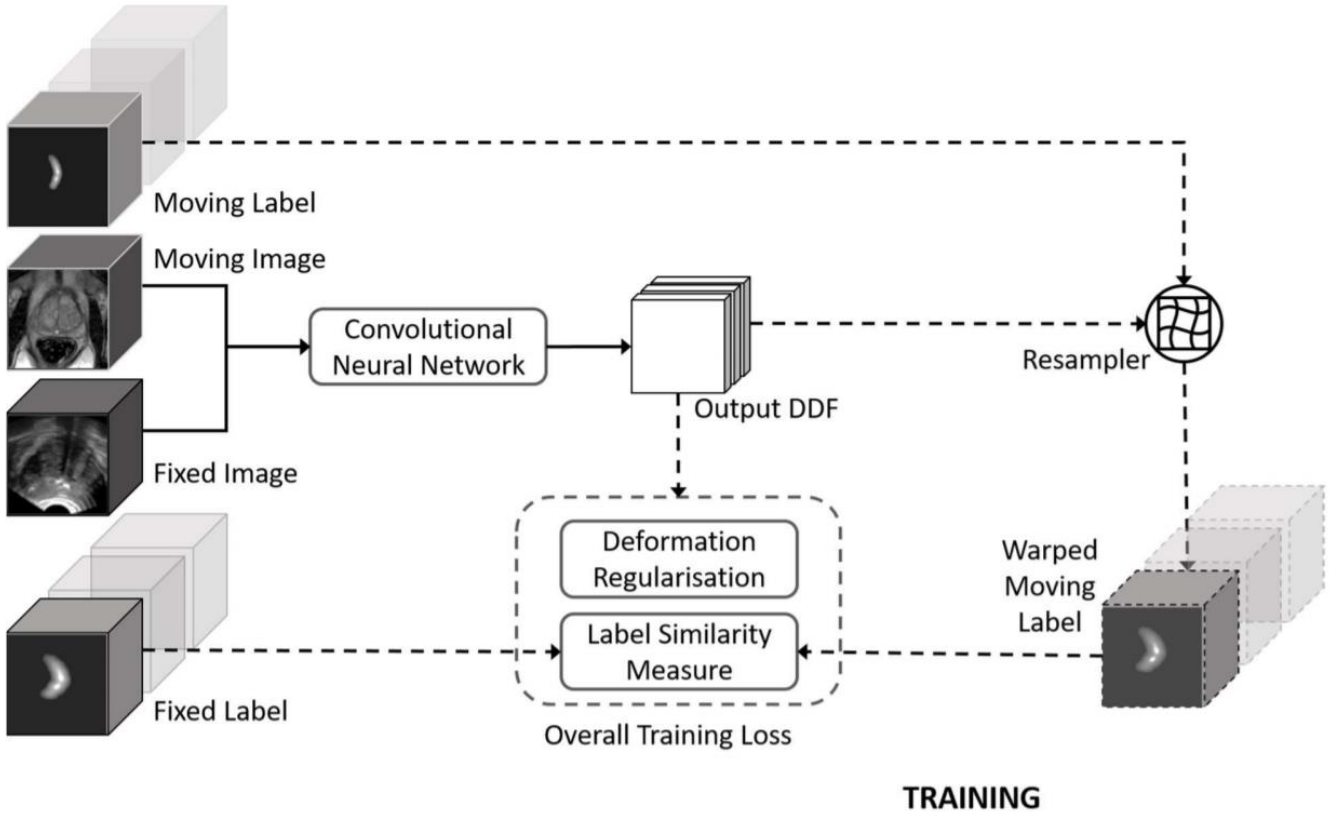
Use case (2/2)

- Surgical guide for implant
  - ✓Teeth from impression
  - ✓Root from CT



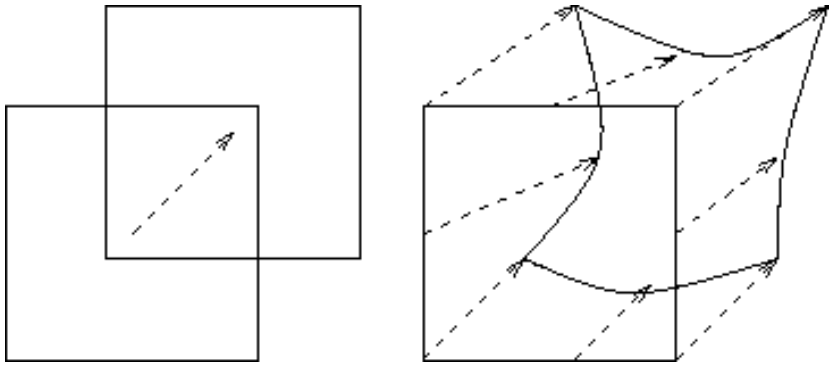
Example usage of CNN

- Goal : Registration of the multimodality image

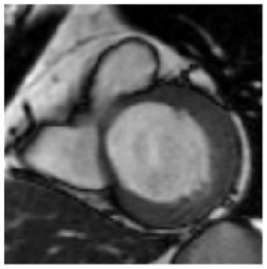


Example usage of CNN(cont'd)

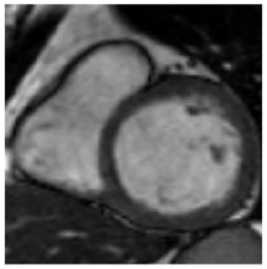
- CNN estimates Dense Displacement Field(DDF)



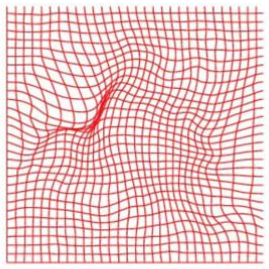
Dense Displacement Field



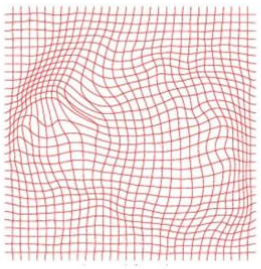
Reference image



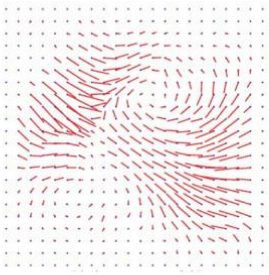
Sensed image



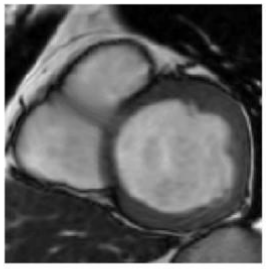
Deformation grid



Inverse deformation grid



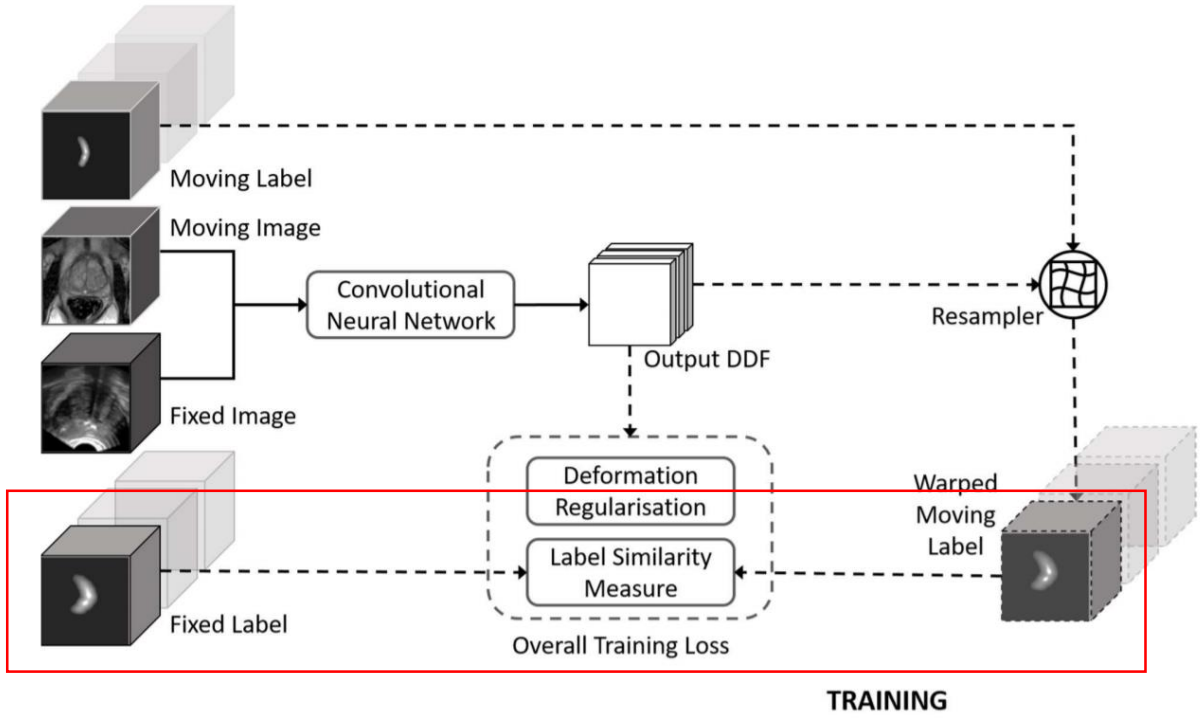
Displacement vector field



Deformed sensed image

Example usage of CNN(cont'd)

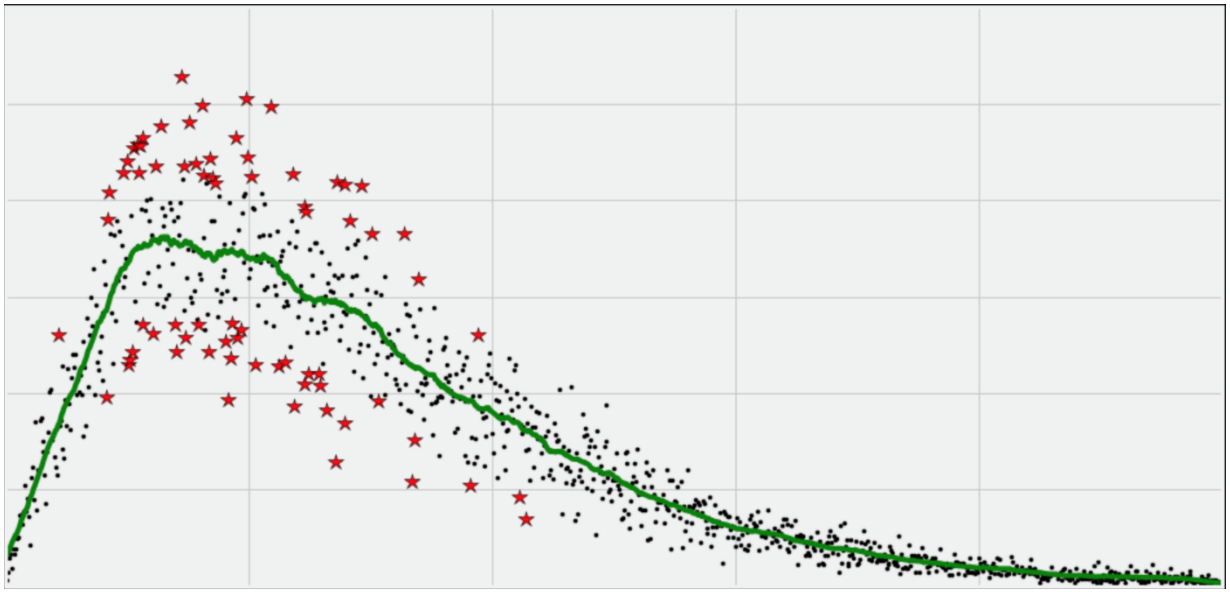
- Compute image similarity (Loss function) between **reference image** and **deformed moving image**



Anomaly Detection

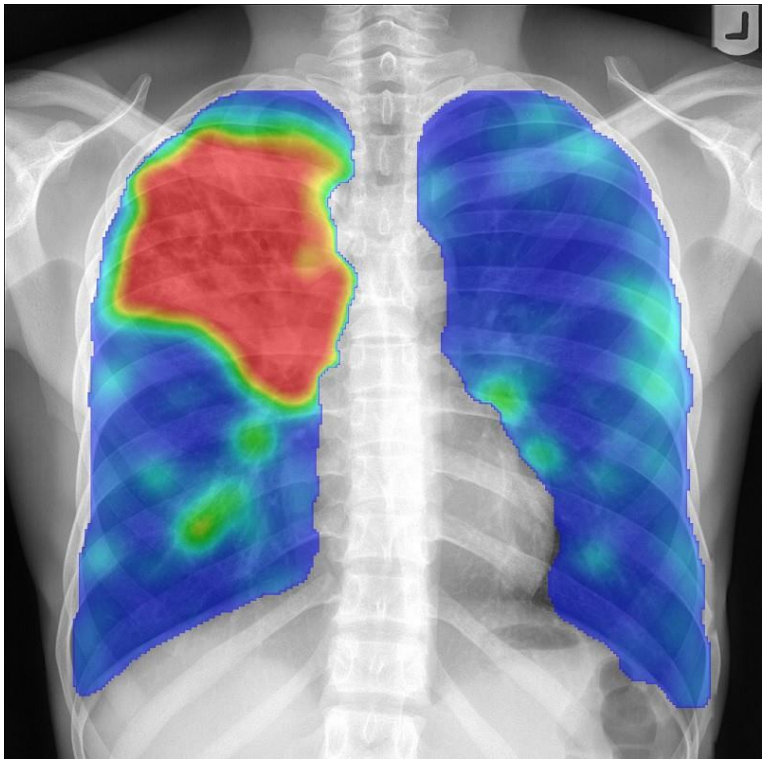
What is Anomaly Detection?

- Identification of rare items, events or observations which raise **suspicions** by **differing significantly** from the majority of the data



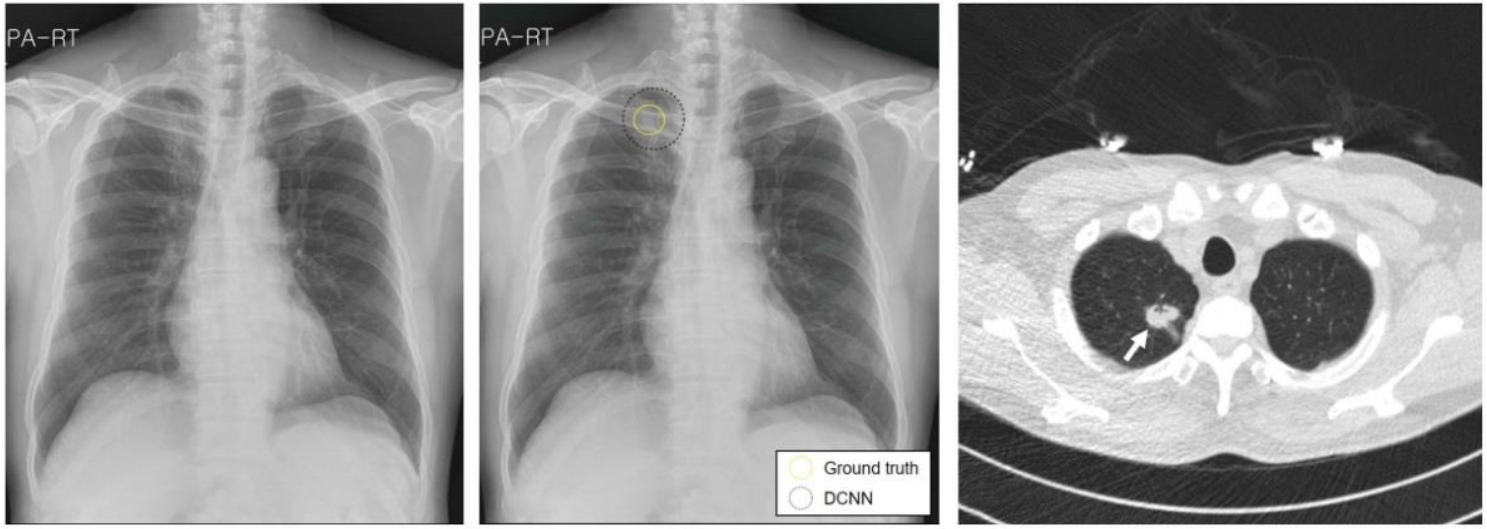
Anomaly Detection in Medical Image Analysis

- Where is the lesion?



Computer Aided Diagnosis

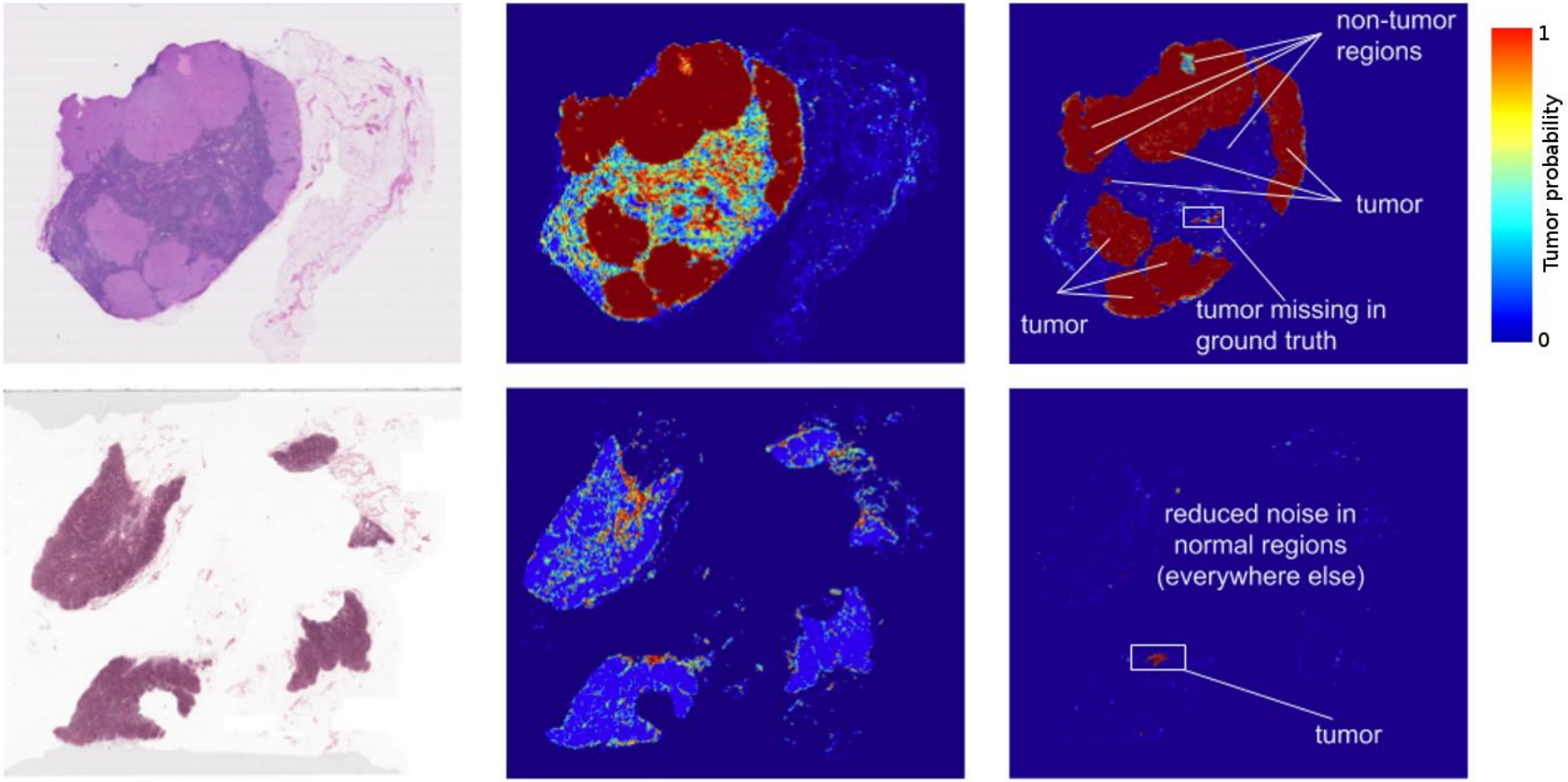
- “The average sensitivity of radiologists was improved by 5.2% when they re-reviewed X-rays with the deep-learning software,”



Byoung Wook Choi ,Yonsei University College of Medicine Seoul, Korea.

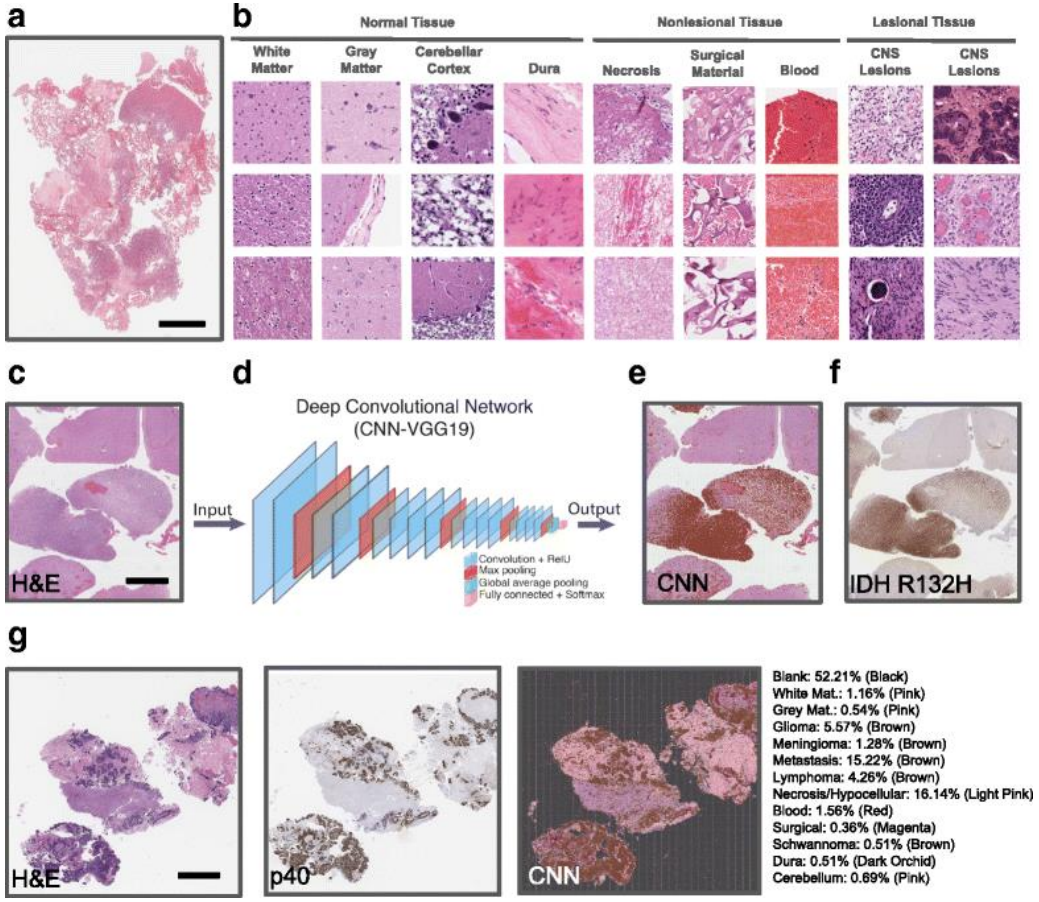
Use case (1/2)

- Breast cancer detection



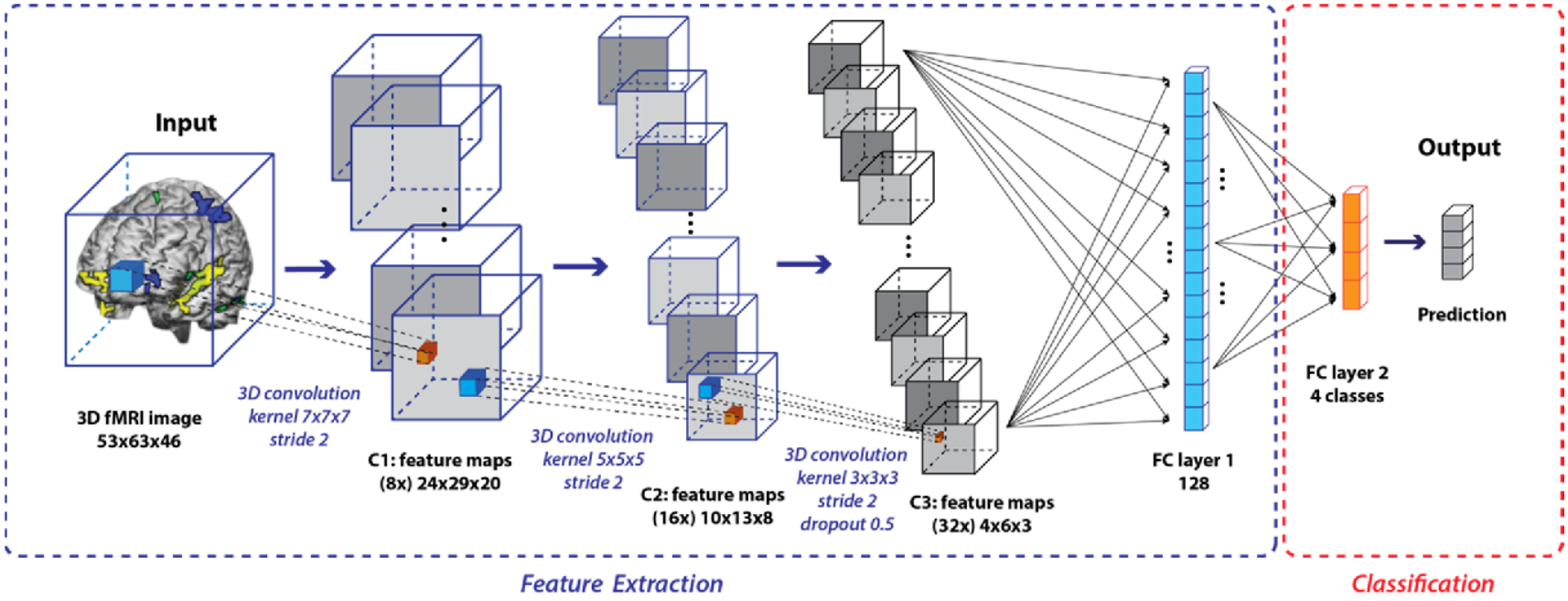
Use case (2/2)

- Analysis of central nervous system tissue



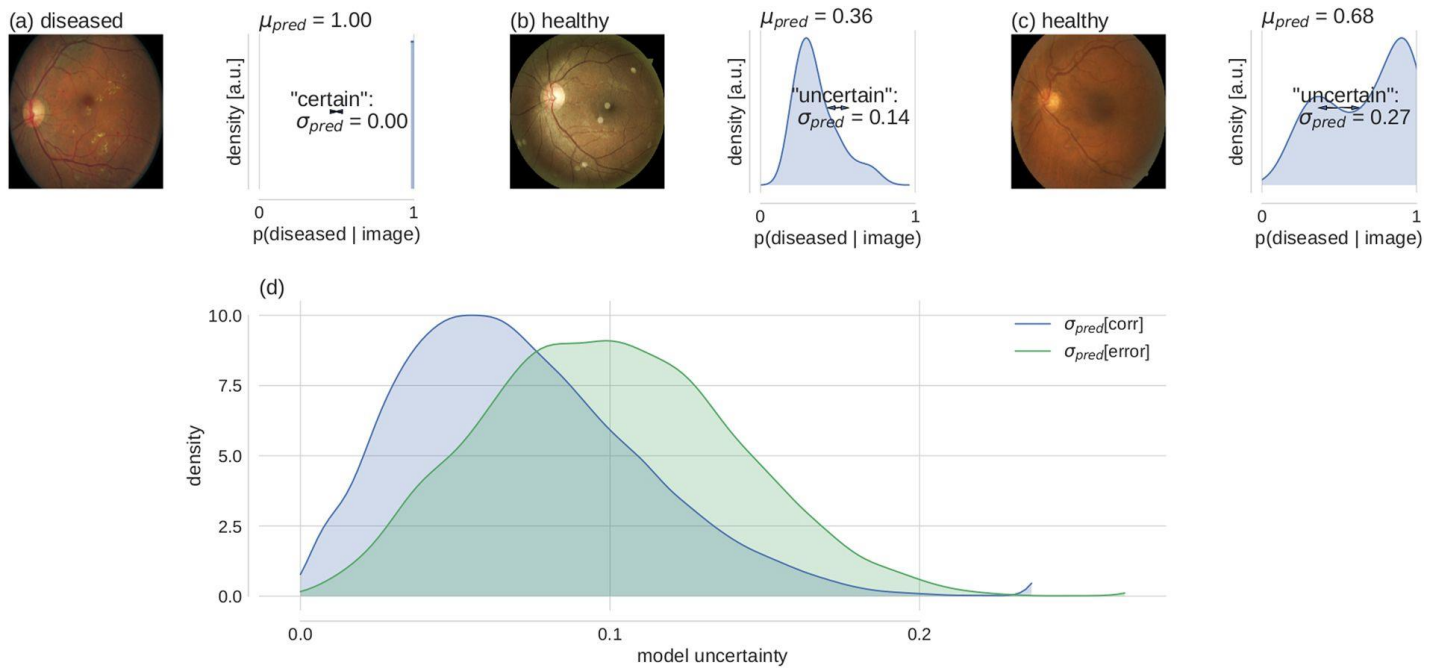
Anomaly Detection in Medical Image Analysis (cont'd)

- No big difference in a model architecture



Anomaly Detection in Medical Image Analysis (cont'd)

- How to quantify the uncertainty in a decision

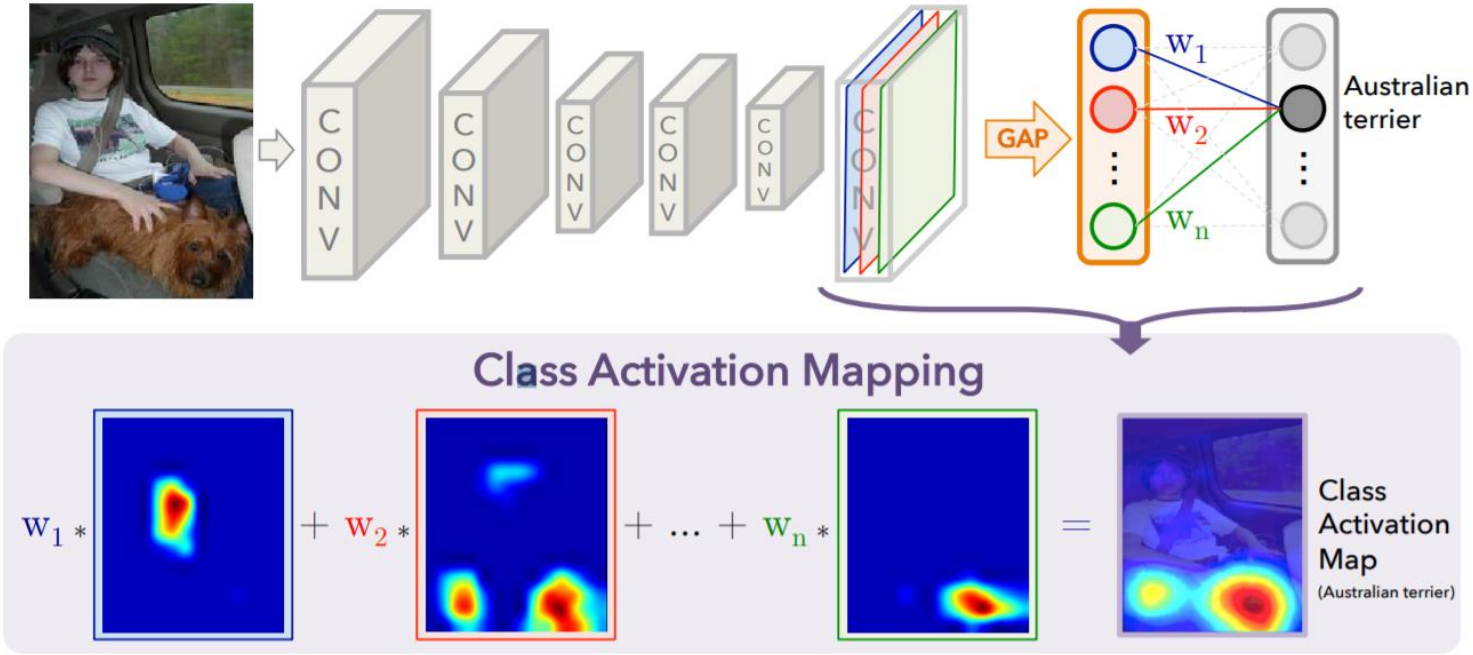


Leibig et el, "Leveraging uncertainty information from deep neural networks for disease detection" Nature Scientific Reports, 2017

Useful Techniques in Deep Learning

Class Activation Map (CAM)

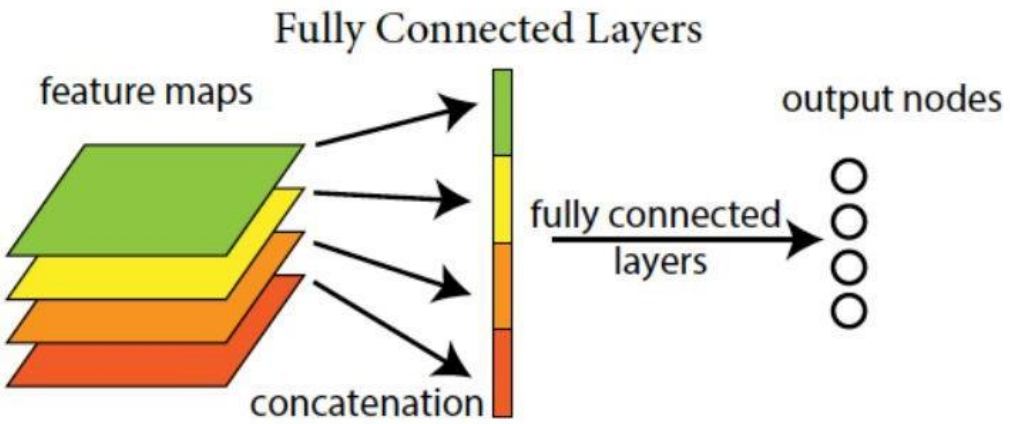
- Pixel-wise activation map to analyze the classificati on result

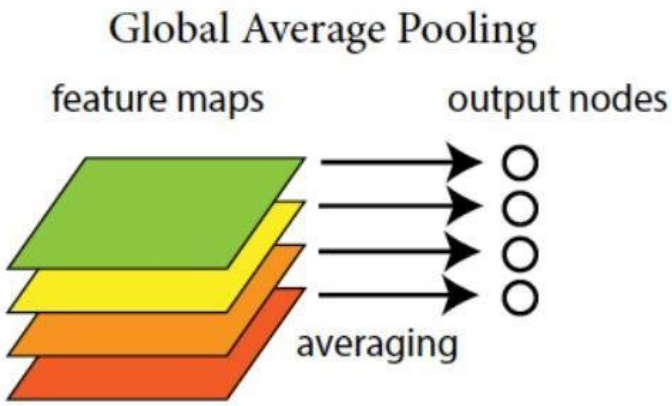


B. Zhou et el, "Learning Deep Features for Discriminative Localization" CVPR'16

Global Average Pooling

- Pass **average value** of feature map to softmax layer
- Replace fully-connected layers
- Preserves spatial information for CAM

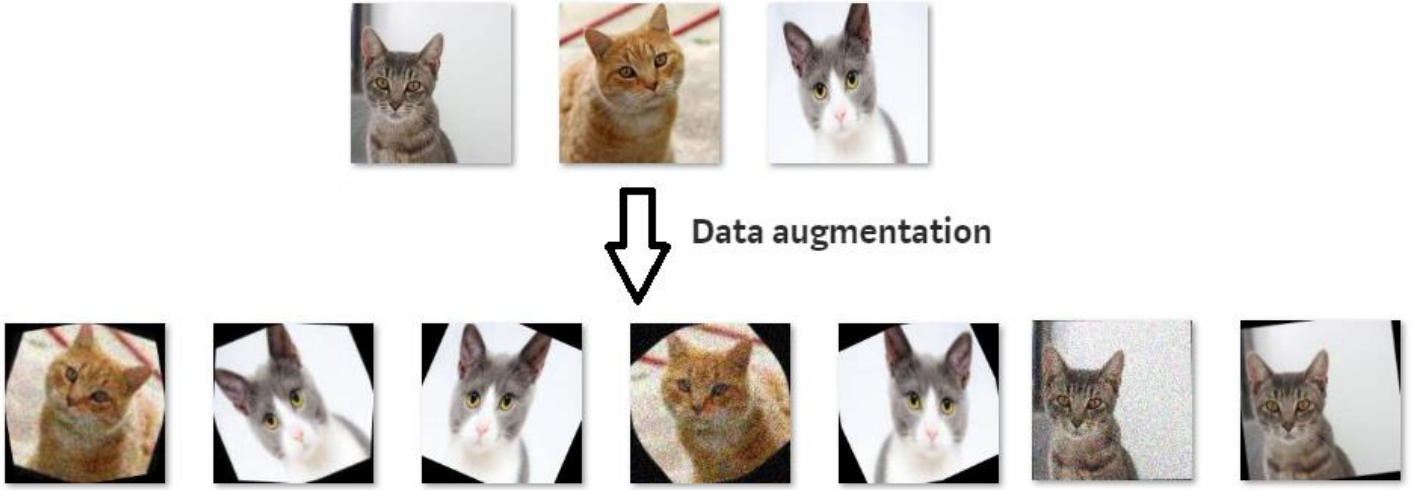




Lin et el. "Network in network." arXiv preprint 2013.

Data Augmentation

- Artificially expand the size of a training dataset by **creating modified versions of images** in the dataset
- Rotation / Scale / Shift / Sheer …



Pervasive Healthcare

Pervasive Healthcare

Making healthcare available everywhere, anytime, and to anyone

Clinical Applications (used in hospital)	Daily Wellness (used in daily life)
• RFID for patient tracking • Robot-aided surgery • DNN-aided diagnosis	• Telemedicine • Activity tracking • Stress monitor • Home language therapy

Opportunities (1/4)

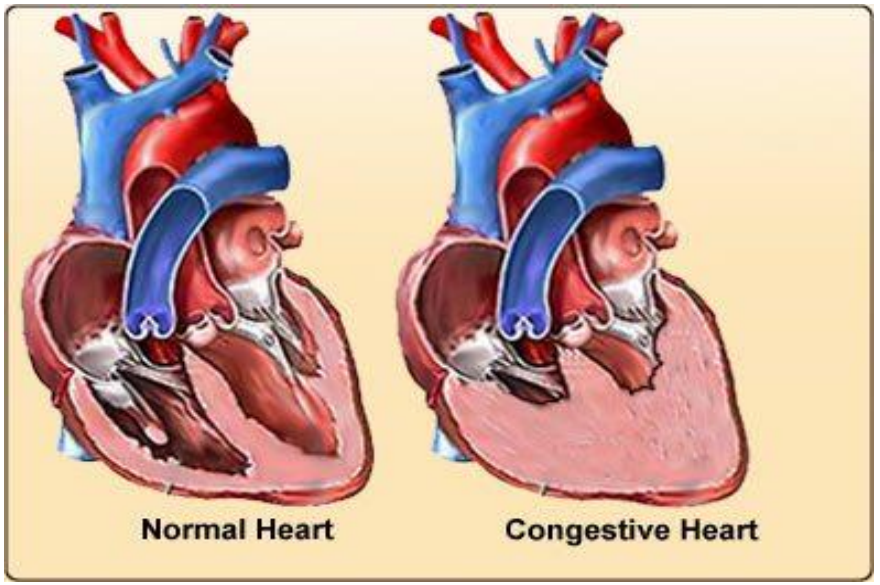
- No reach of doctors

Opportunities (2/4)

- Daily well-being and preventive healthcare

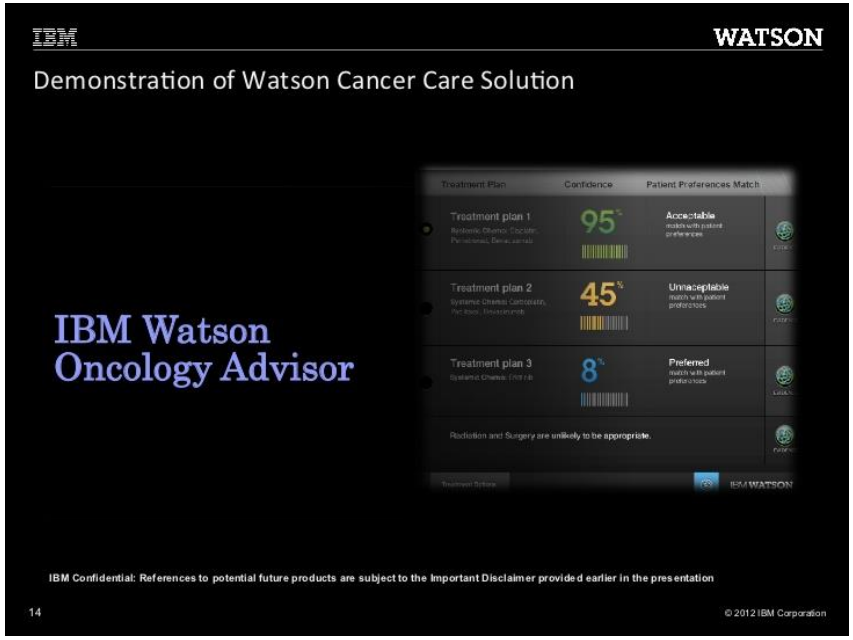
Opportunities (3/4)

- Non-life threatening but life-impacting issues
- Chronic diseases (e.g., diabetes, arrhythmia, fatty heart)
- Children with autism or ADHD (Attention deficit hyperactivity disorder)



Opportunities (4/4)

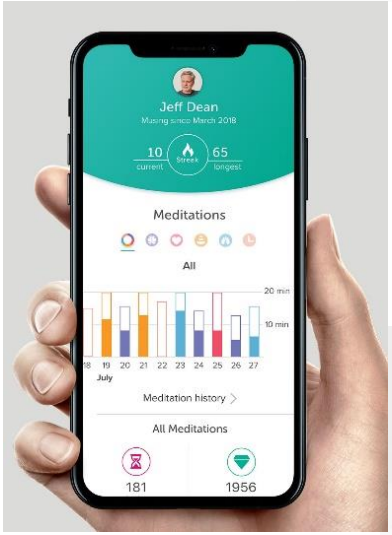
- Corner cases that doctors hardly see
- Lack of human resources and inefficient operations in hospitals



Wearable and IoT Devices

- Wearable and IoT devices are emerging to measure different physiological signals such as
  - ✓cardiac rhythms, breathing, sweat, brain waves, gestures, muscular contractions, eye movement
- Health sensors will be integrated into clothing, jewelry, and many other accessories
- Many new health-related applications are emerging using these devices

Example Devices

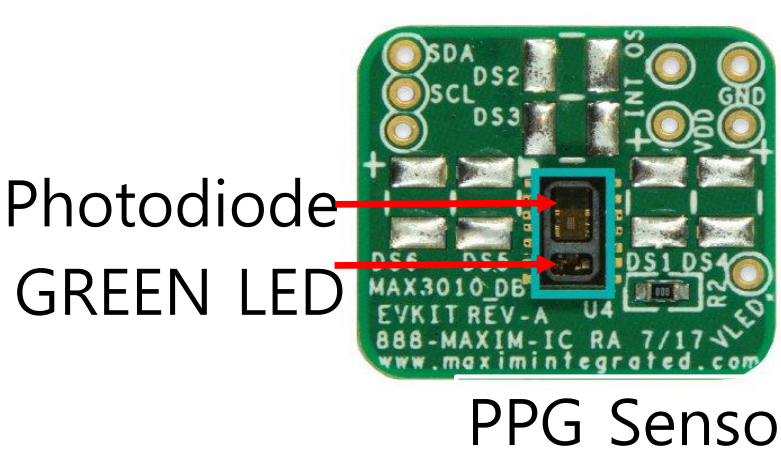


PhotoPlethysmoGraphy (PPG)

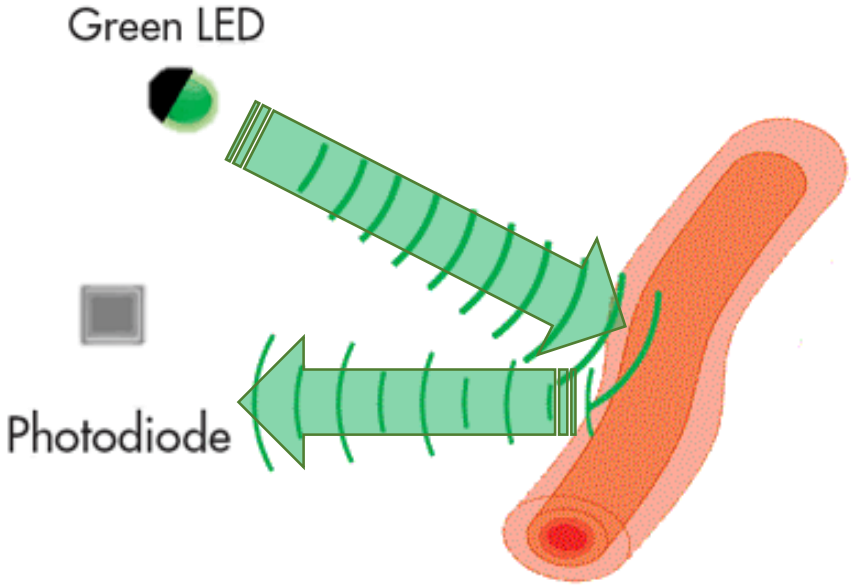
- PPG is a non-invasive technique for measuring blood volume changes in the blood vessels close to the skin
- PPG has become a popular method for extracting heart rate and oxygen saturation (left figure)
- PPG can be measured using a built-in cellphone camera without any additional hardware (right figure)

Basic Operation of PPG

- Uses green LED light emissions and a photodiode capturing reflected light levels from the skin
- Detects heartrate by measuring the differences in light absorption from the skin



PPG Sensor

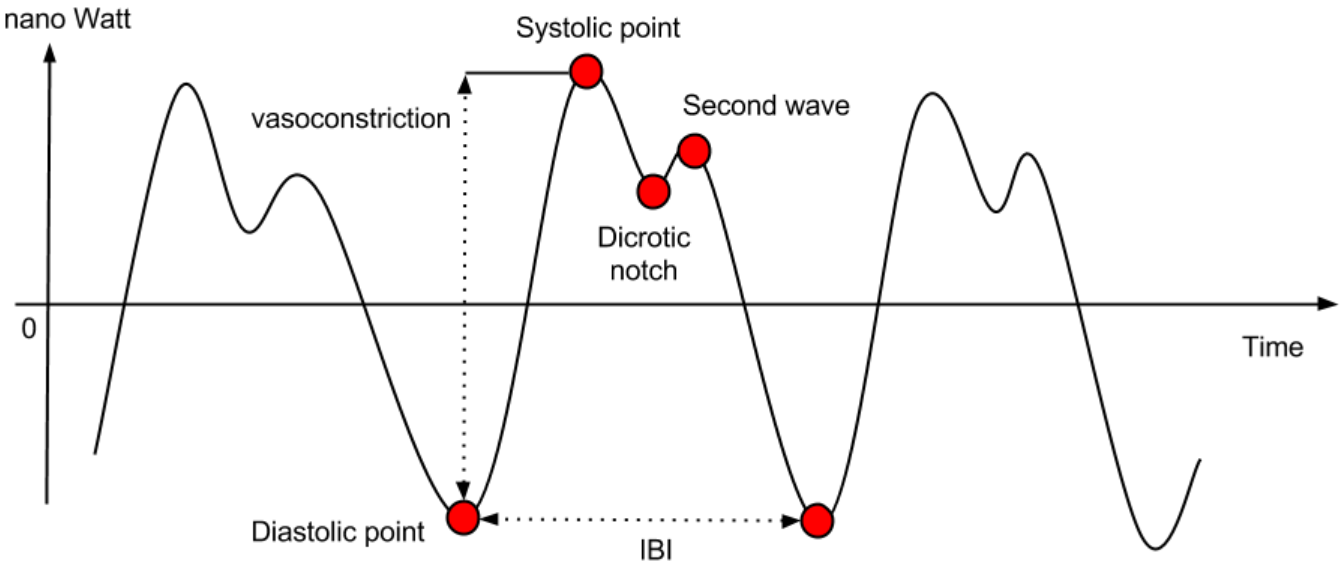


PPG with Smartwatches/bands

PPG with Smartphones

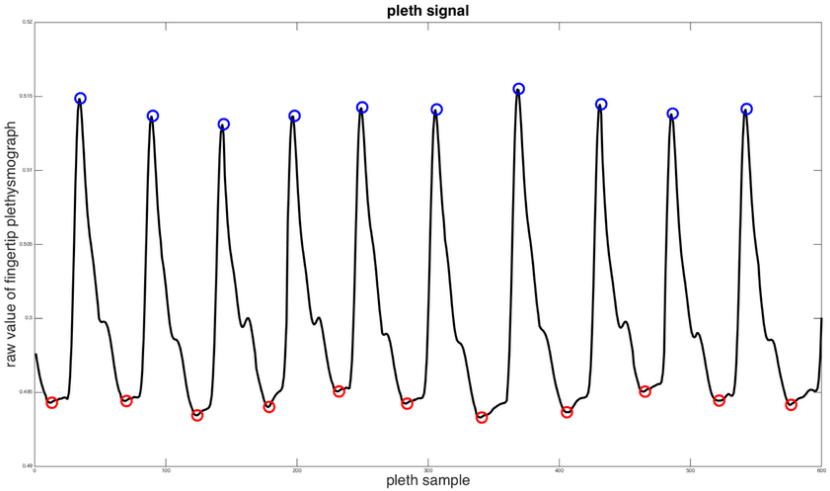
Detecting Heartrate from PPG

- The green intensity in the PPG signal forms peaks corresponding to cardiac pulse



Heartrate Calculation Method

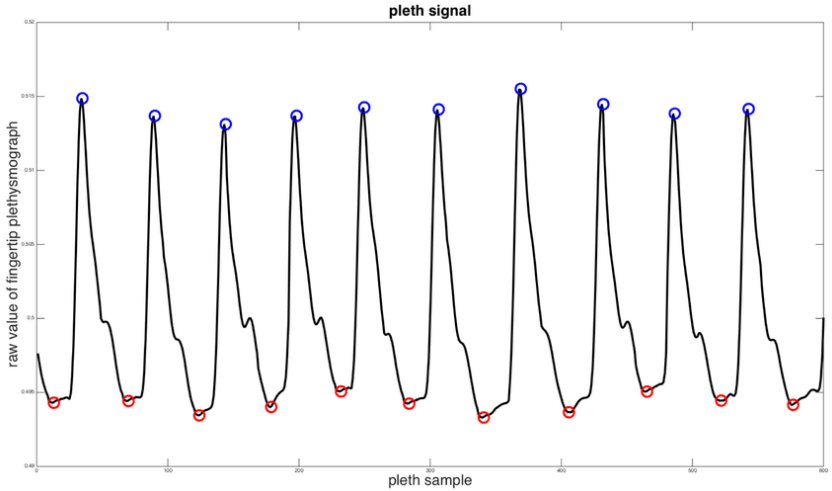
- Step 1: Get the average green intensity per frame
- Step 2: Use a peak detection algorithm to find all the cardiac peaks in the signal
  - ✓A peak: the highest average green intensity in a fixed window (~0.7 seconds).



Acknowledgement: Prof. Deepak Ganesan's Lecture Note

Heartrate Calculation Method

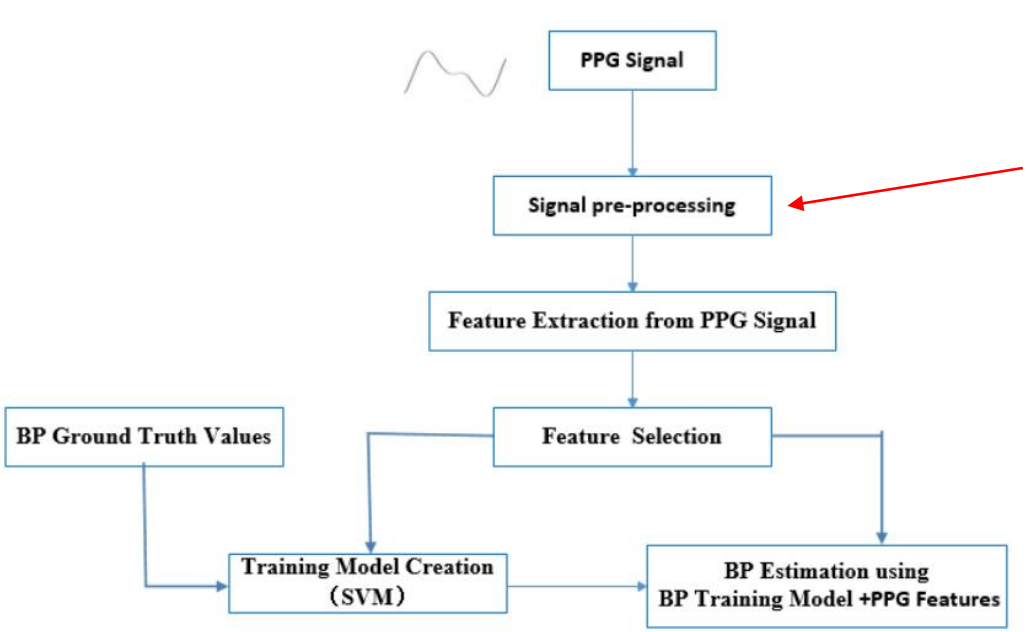
- Step 3: The time difference between consecutive peaks is computed. This time difference is known as R-R interval (RRI) or Inter-Beat Interval (IBI).
- Step 4: HR is estimated from the RR Interval: HR = 60 / RRI

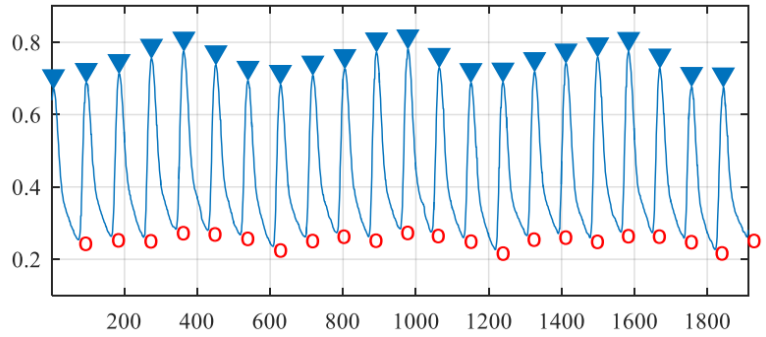


Acknowledgement: Prof. Deepak Ganesan's Lecture Note

Usage of PPG

- Blood pressure estimation using SVM

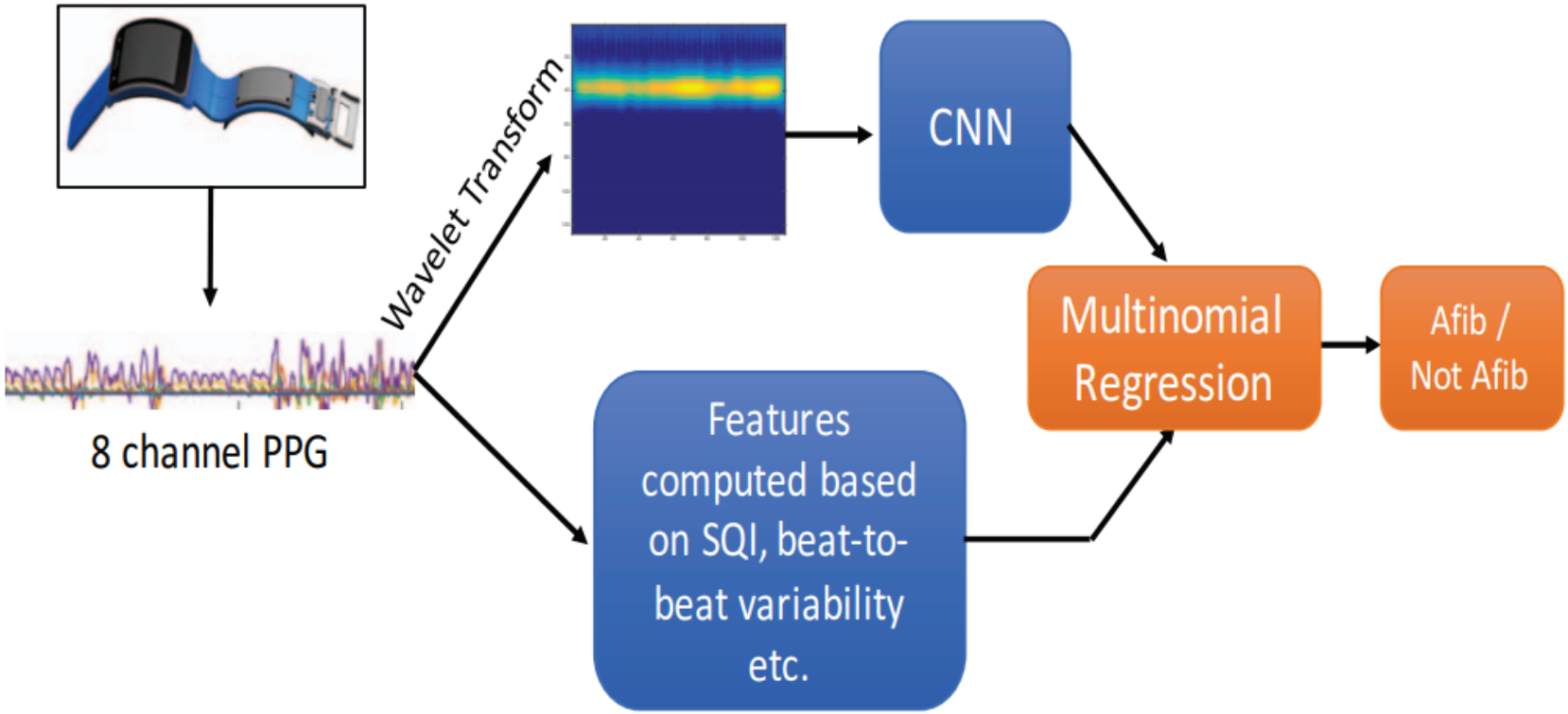




Zhang et el, "A SVM Method for Continuous Blood Pressure Estimation from a PPG Signal " Proceedings of the 9th International Conference on Machine Learning and Computing, 2017

Usage of PPG

- Atrial fibrillation detection using PPG signal
- CNN as a feature extractor



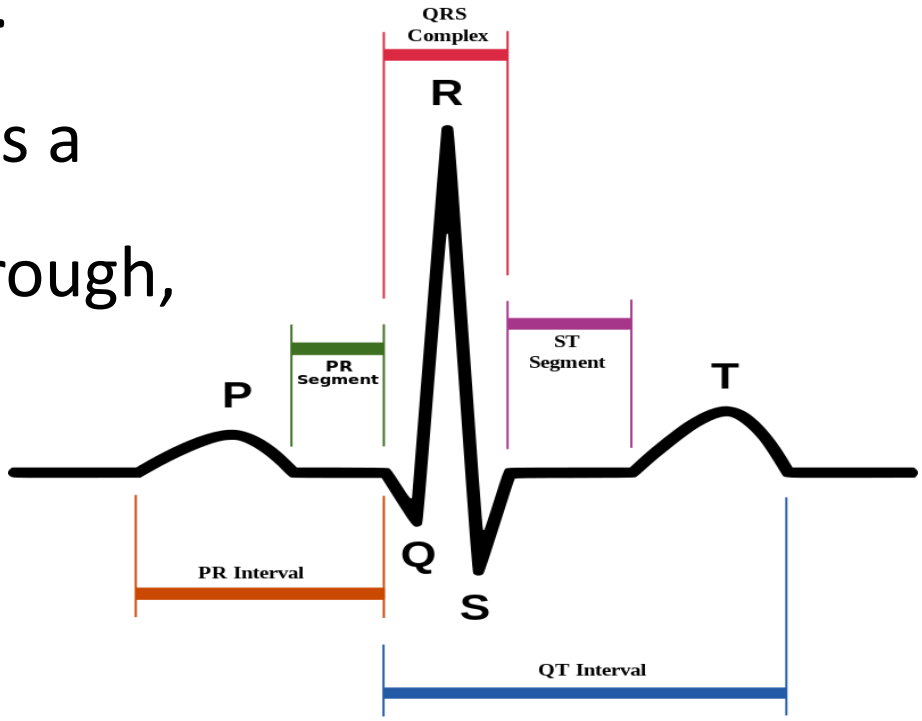
Shashikumar et el, "A deep learning approach to monitoring and detecting atrial fibrillation using wearable technology "

ElectroCardioGram (ECG)

- ECG is a recording of the electrical activity of the heart
- With each heartbeat, an electrical signal spreads from the top of the heart to the bottom.
  - ✓As it travels, the signal causes the heart to contract and pump blood. The process repeats with each new heartbeat
- ECG shows how fast your heart beats, the rhythm of your heartbeat (steady vs irregular), and the strength and timing of the electrical signals as they pass through each part of the heart

ECG Signal

- A typical ECG wave looks as shown in the right figure. Each heartbeat comprises a sequence of peaks and trough, labeled P, Q, R, S, and T



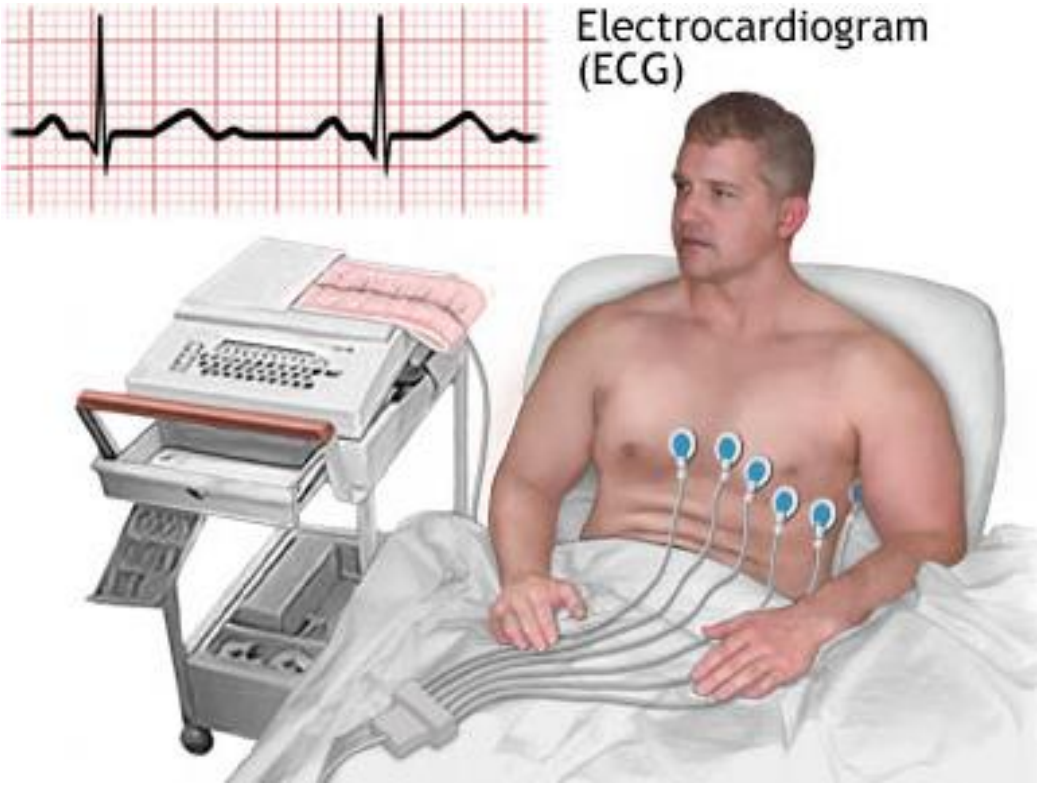
Applications of ECG

Diagnosing Cardiac Disease

- Arrhythmia
- Cardiac Malformation
- Cardiac Valve disease
- Cardiac Muscle disease

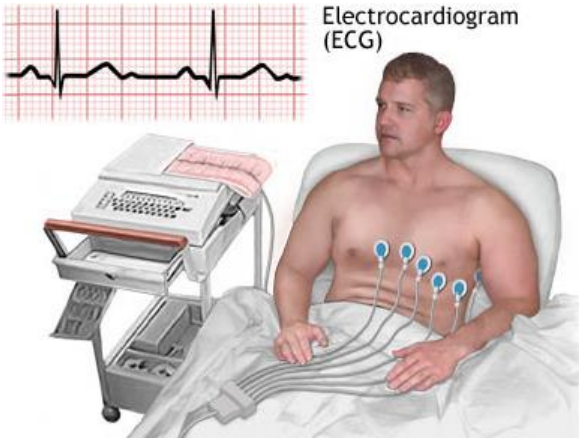
Monitoring Autonomous Nervous System (ANS)

- Stress Management
- Sleep Analysis
- Affect Recognition



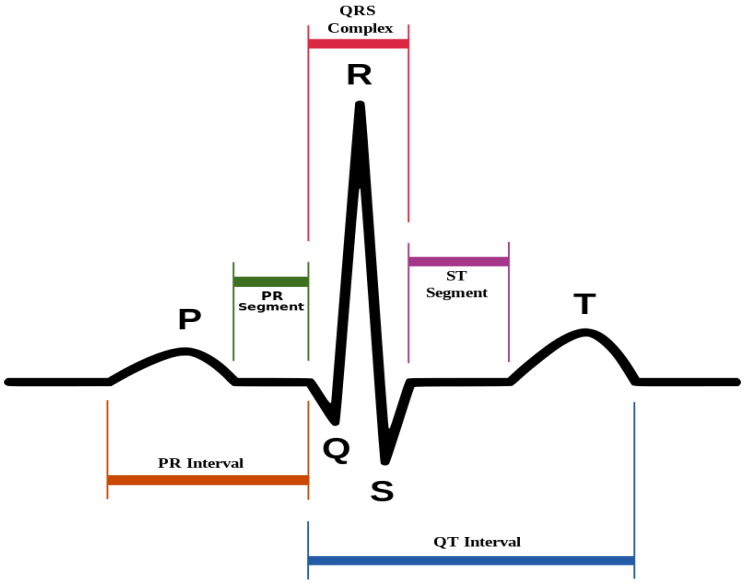
How Do We Measure ECG?

- Use two or more electrodes at different points on t he chest (or on two opposite body parts from the c hest), and measuring the electrical activity between these electrodes



Detecting Peaks from ECG

- A good starting point: A step det ector that we studied in Week 2
- As in step detection, you look for a change in the slope from positi ve to negative (peak) or negative to positive (trough)
- You then look at the sequence in formation to label the appropriat e peaks (P, Q, R, S, T)



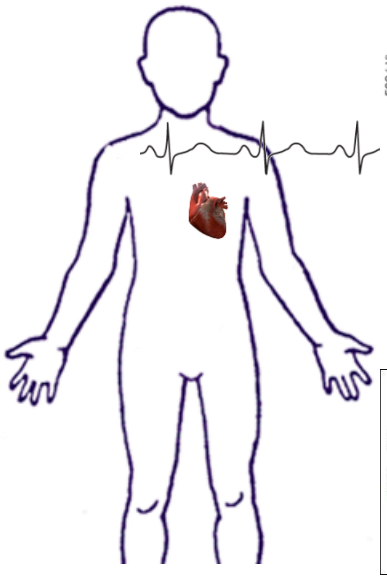
Heartrate Calculation from ECG

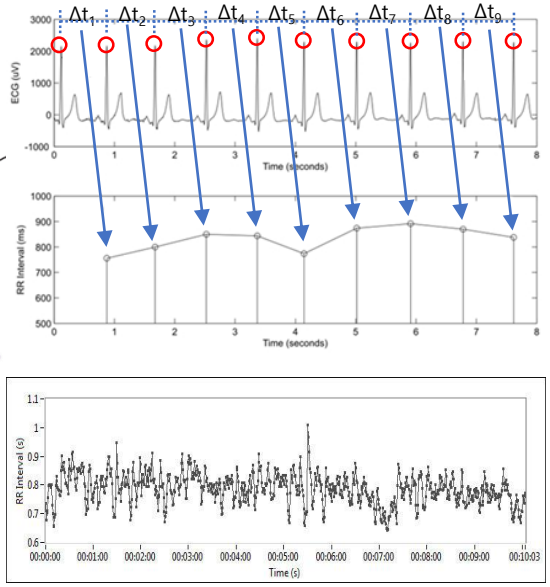
- Obtaining heart rate from ECG is straightforward
  - ✓Each RR interval corresponds to the time between two successive heartbeats
  - ✓HR = 60 / RR Interval

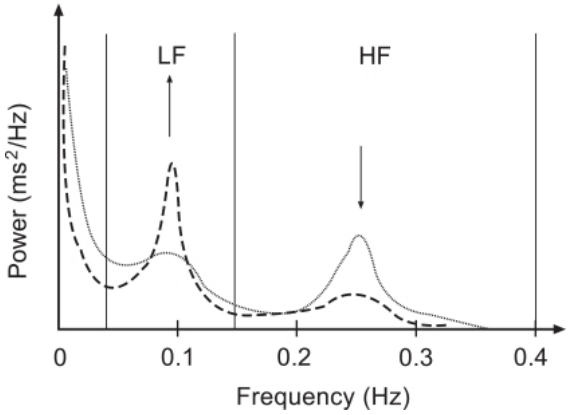
- The time differences between different peaks are known to be useful features.
  - ✓E.g.) RR interval, PR interval, the QRS interval, the QT interval, the ST interval
  - ✓Look at how these intervals vary to detect abnormalities in the heart

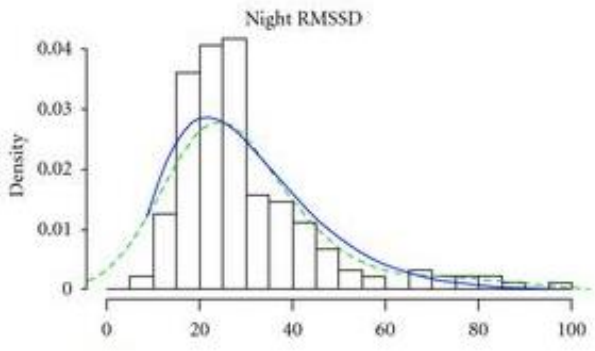
Detecting Stress from ECG

ECG Sensing → **Heartbeat Detection** → **LF / HF features** → **Stress Analytics**







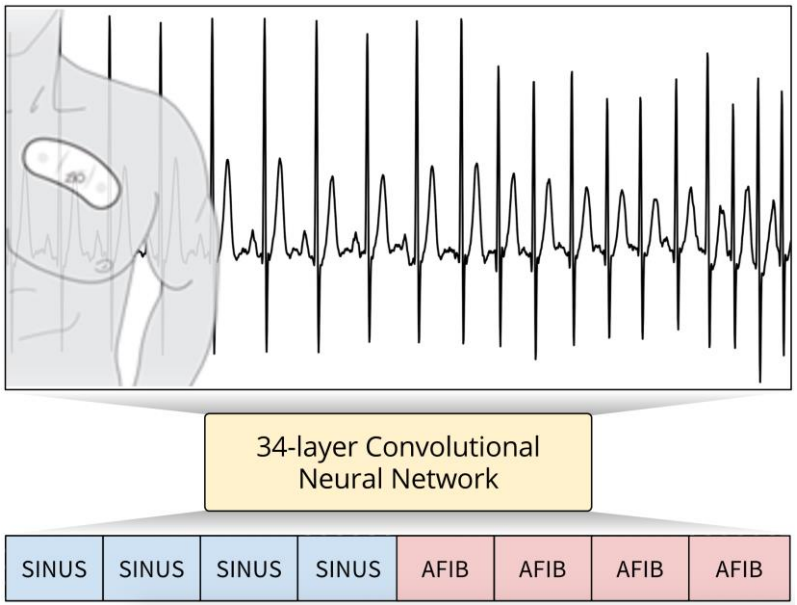


Arrhythmia Detection With Convolution al Neural Networks

- 1D CNN to detect arrhythmias in arbitrary length EC

  G time-series

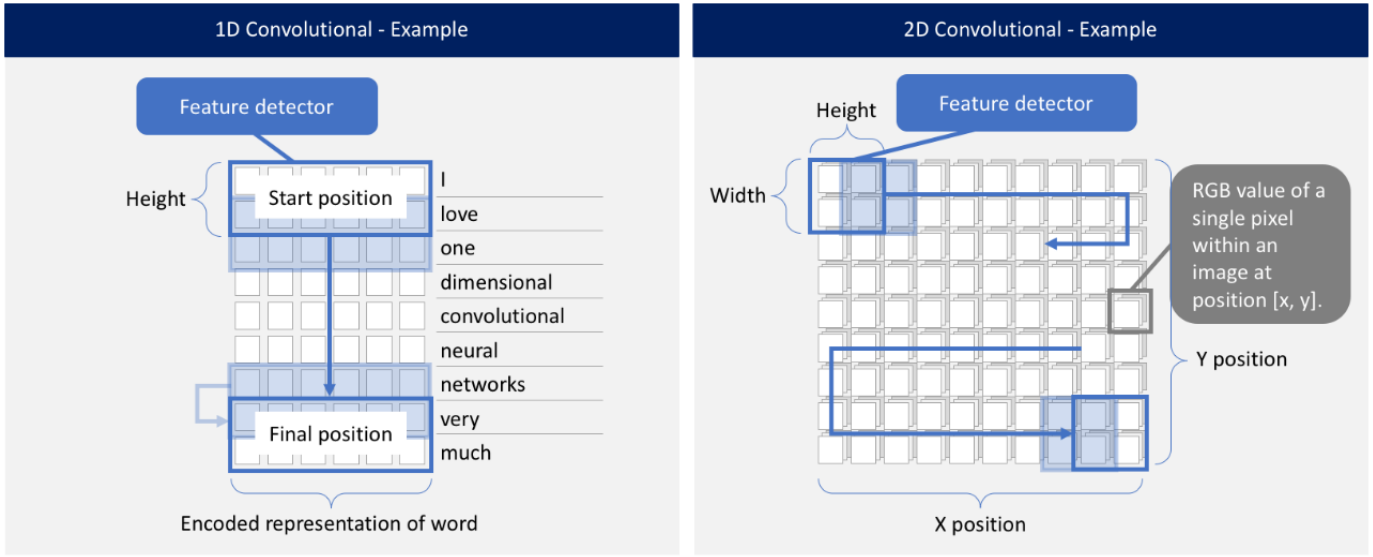
- Detect arrhythmias per 256 samples (every 1.28s)



Hannun et el, "Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network" Nature

1D Convolution vs 2D Convolution

- 1D conv. encodes **series of information**
  - ✓ECG time-series in this case
- 2D conv. encodes feature at a **certain position**

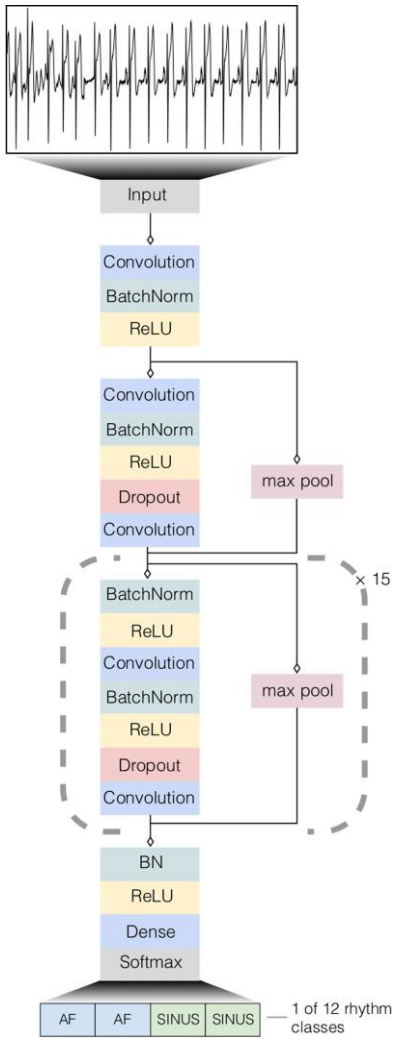


Arrhythmia Detection With Convolution al Neural Networks

- Input normalization

- **Shortcut connections** allows inform ation to **propagate well** in very deep neural networks

  ✓33 layers of convolution



Hannun et el, "Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network" Nature

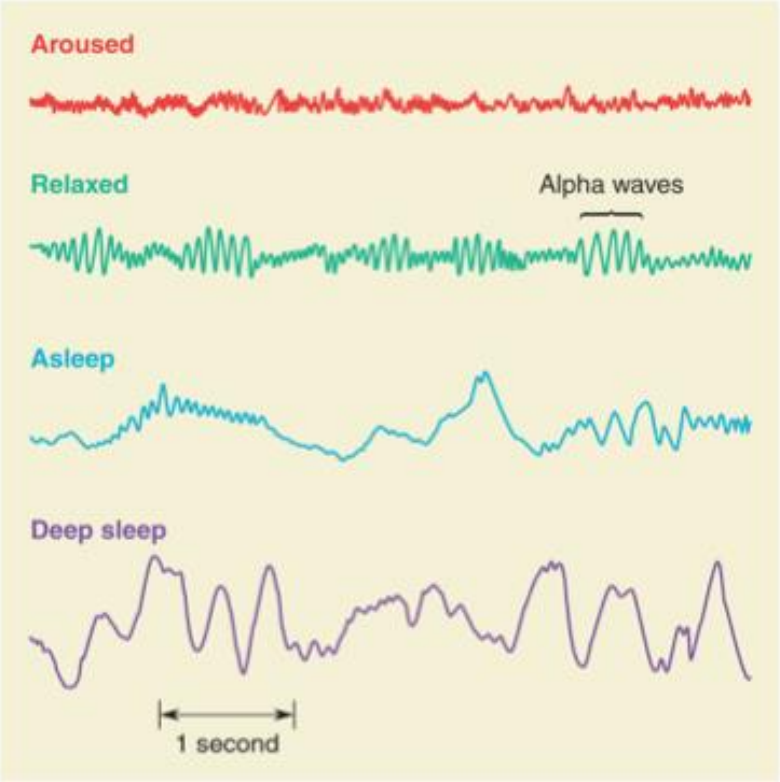
ElectroEncephaloGraphy (EEG)

- EEG signals are recordings of brain signals
- Traditionally captured by a huge array of electrodes on the scalp (head)
- Recent EEG headbands with fewer electrodes to capture a subset of EEG signal

Electroencephalography (EEG)

- Many useful EEG-driven applications are emerging

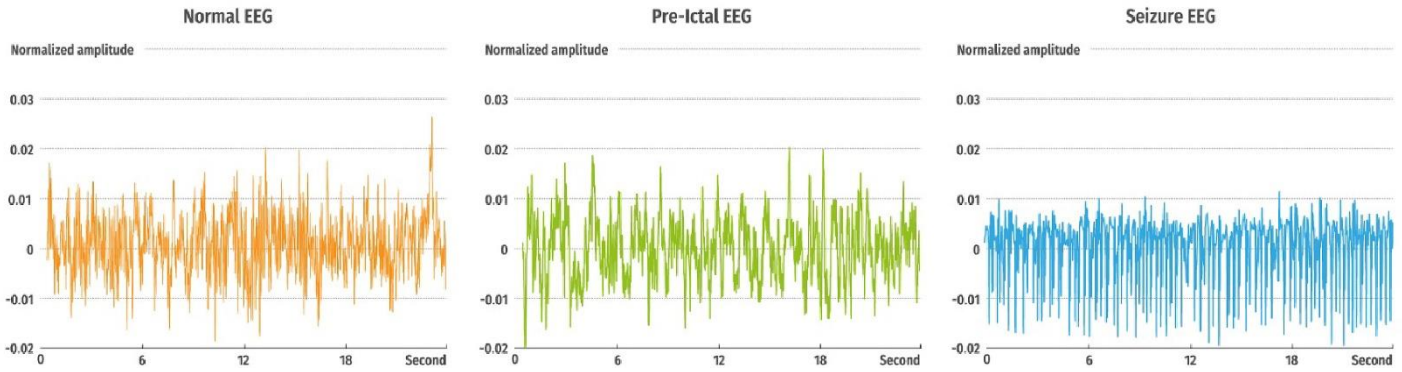
- They classify various states (e.g, aroused, relaxed, asleep, etc.) of a person using various time-domain and frequency-domain features



EEG signals when an individual is aroused, relaxed, asleep and in deep sleep state.

Deep Learning for EEG

- Use of CNN to analyze complex raw signal



- Preprocessing

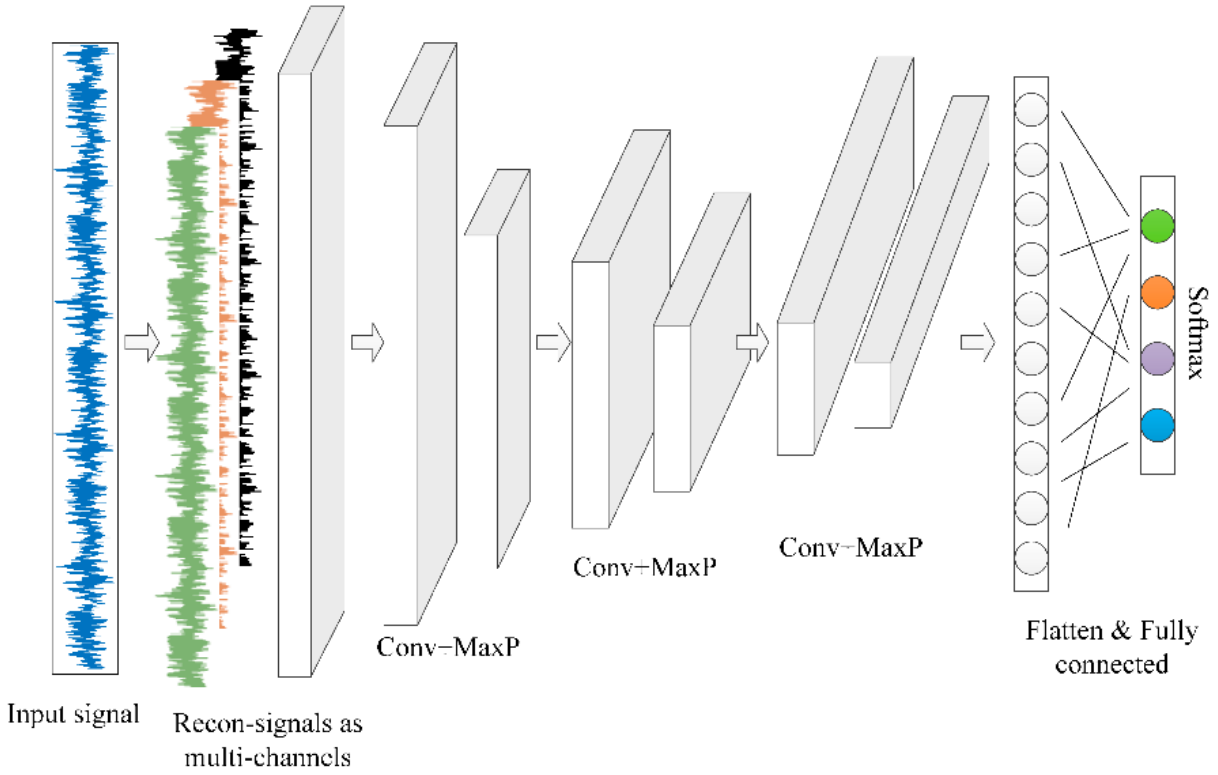
  ✓Normalized with Z-score normalization

  - Zero mean and standard deviation of 1

Acharya et el, "Deep convolutional neural network for the automated detection and diagnosis of seizure using EEG signals" Computers in Biology and Medicine, 2018

Deep Learning for EEG

- CNN based seizure detection (1D CNN)

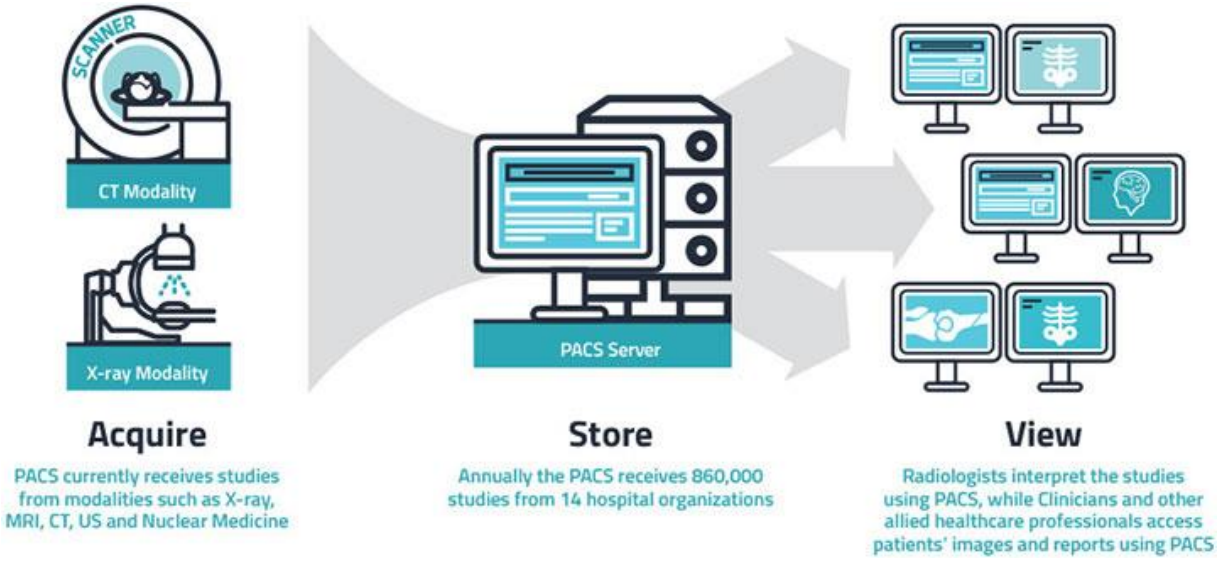


Acharya et el, "Deep convolutional neural network for the automated detection and diagnosis of seizure using EEG signals" Computers in Biology and Medicine, 2018

Upcoming Obstacles

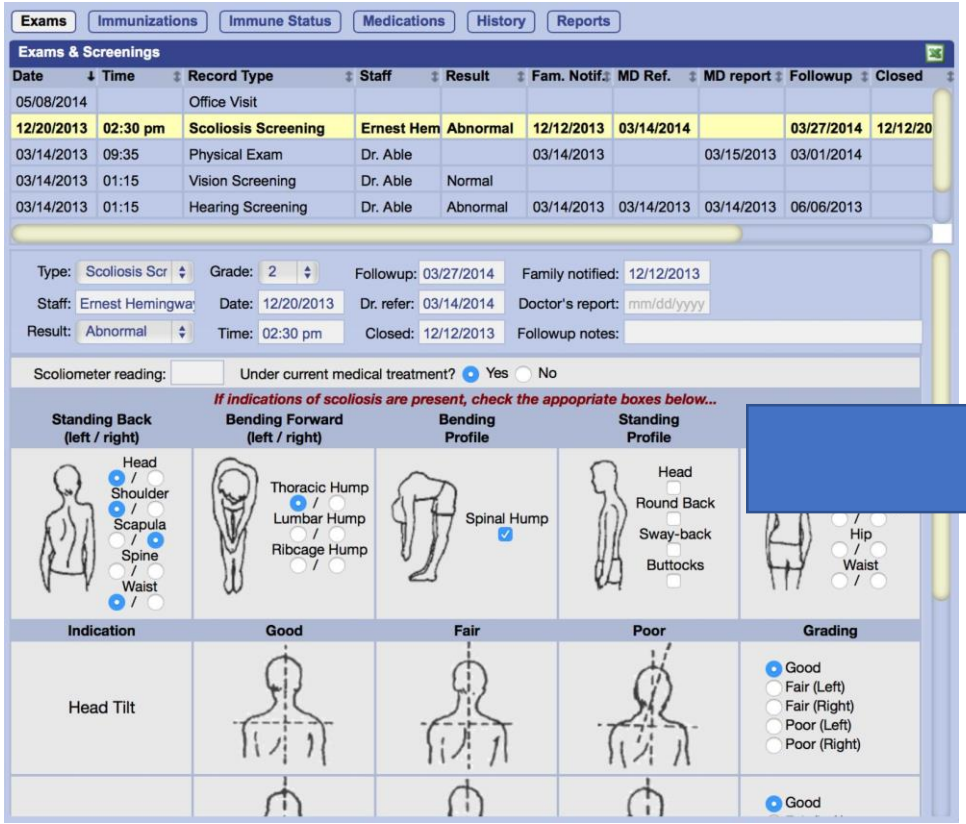
Fragmented database

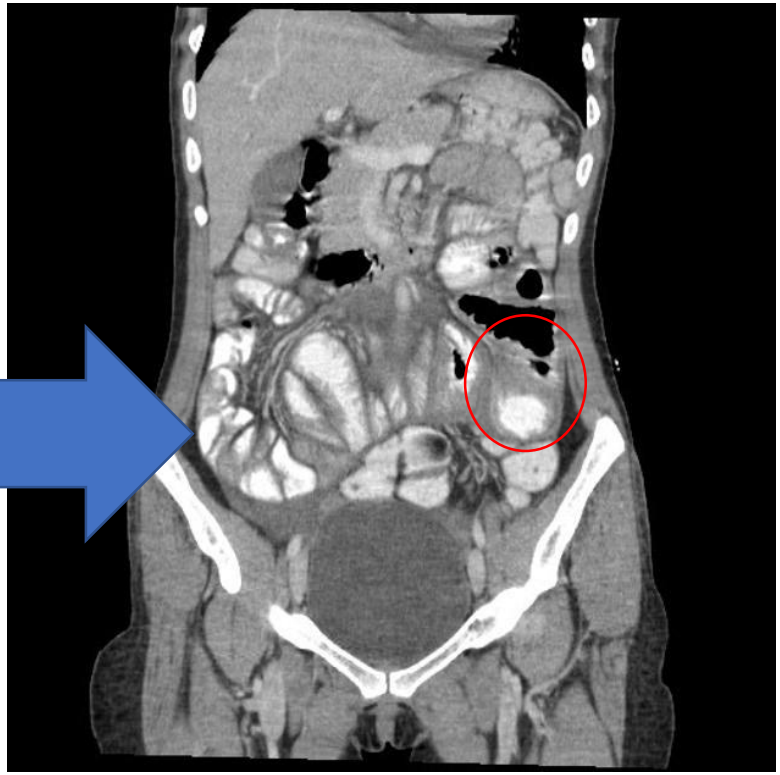
- PACS (Picture Archiving and Communication System) is not centralized
- Personal health record archive



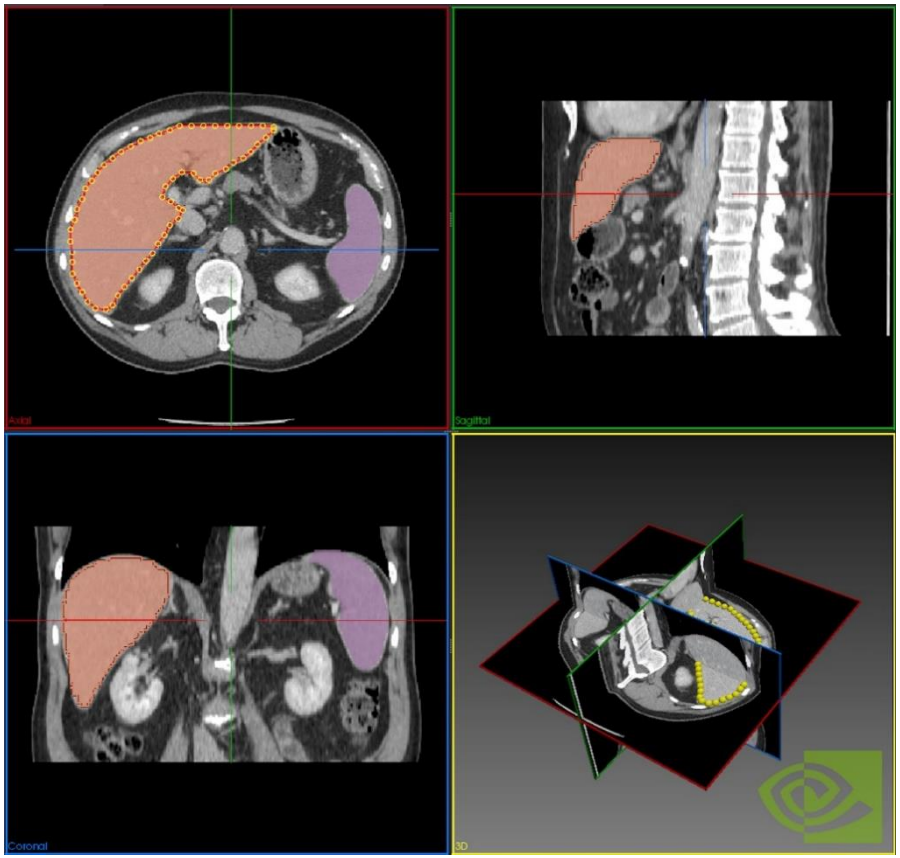
How to utilize existing data?

- Electronic health record to annotation mask





Need a unified protocol



“Clara Train SDK,” Nvidia 2019.

Privacy & Legal Issue

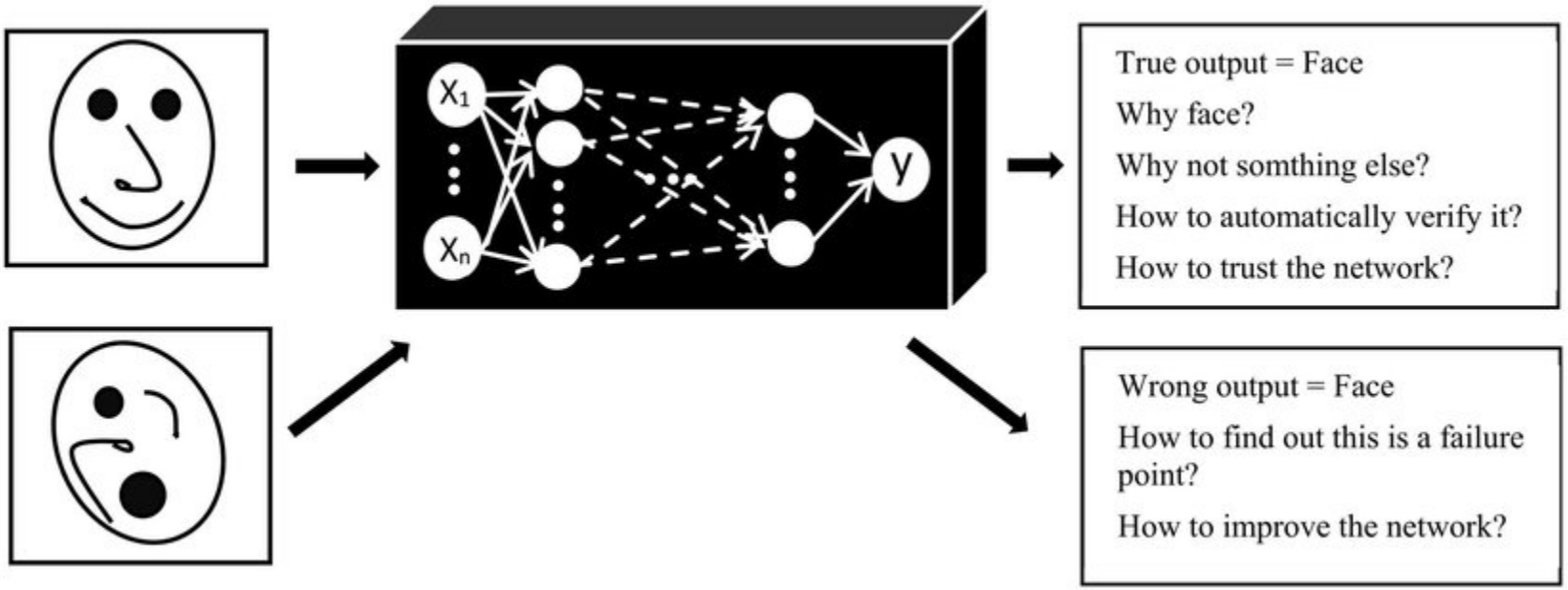
- Privacy and security risks have emerged
- Who is responsible?

There is still a core segment who cannot see any circumstances under which they would allow commercial organisations access to NHS health data. 17 per cent of people say they would not want commercial organisations to have access to health data for research under any circumstances. Of these, one-fifth (20 per cent) say commercial organisations cannot be trusted to store the data safely, and a similar proportion say that profit should not be made from health data, even if there are potential societal and health benefits as well.

"survey on public attitude," Wellcome Foundation UK 2016 .

Transparency of Machine Learning

- Hard to understand the reasoning behind the decision

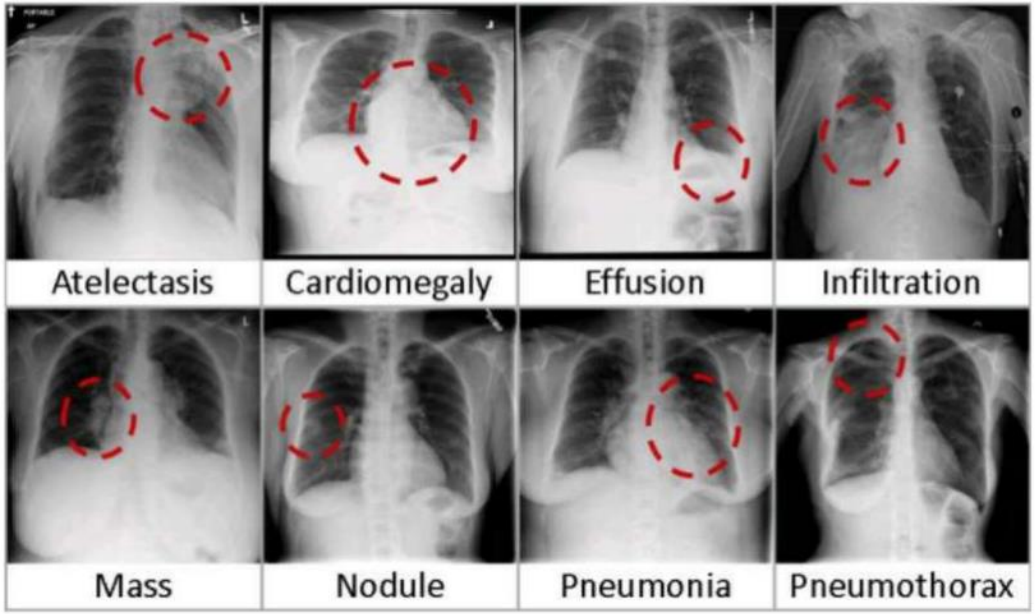


Transparency of Machine Learning (cont'd)

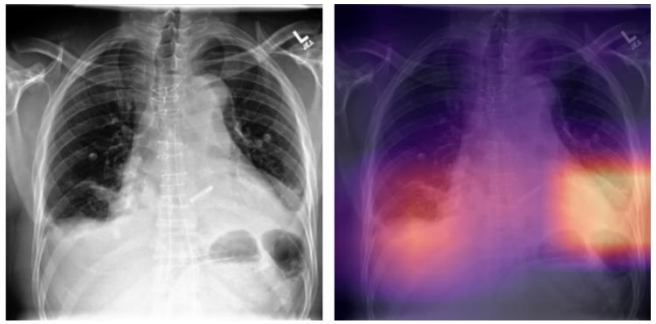
- Activation map shows where model sees

Transparency of Machine Learning (cont'd)

- How to define the correct answer with the wrong activation?



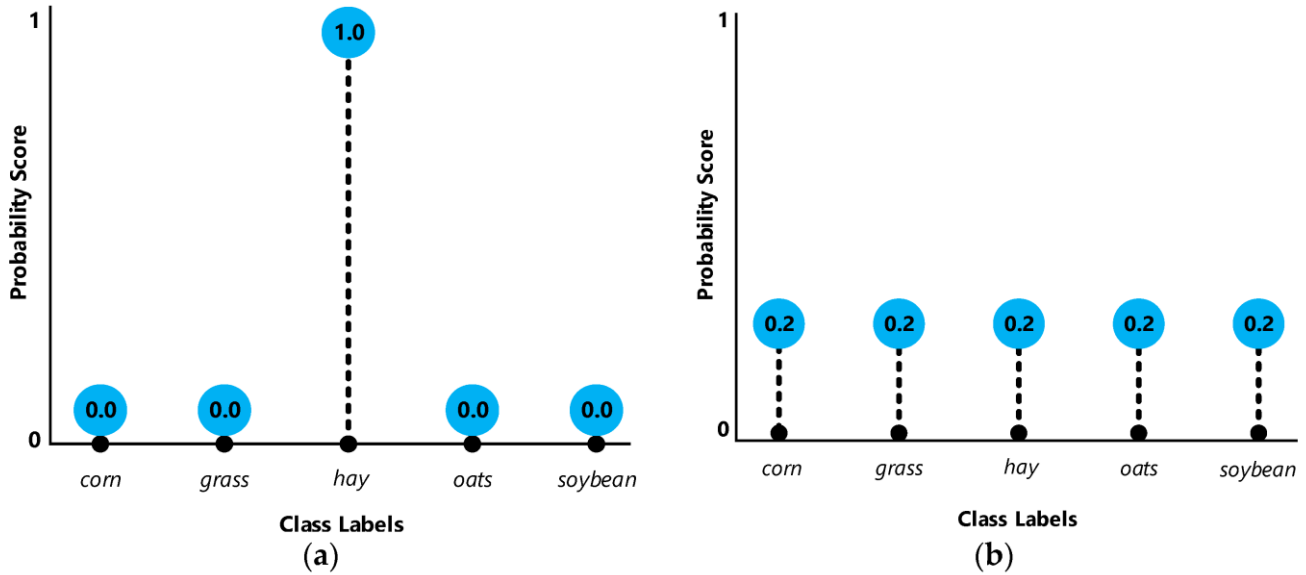
Human



Deep Learning

Uncertainty Quantification

- Model should say “I don’t know” if it’s unknown
- What is the correct response to the unseen data?



Summary

- Machine learning (especially deep learning) is widely used in medicine.
- Many works are still in an early stage, requiring more evaluations and improvements.

Thank You!