School on Medical Physics for Radiation Therapy: Dosimetry, Treatment Planning and Delivery for Advanced Applications

ICTP

11 - 22 September 2023
An ICTP Meeting
Trieste, Italy

Further information:
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CRO
AVIANO

Introduction to Artificial Intelligence

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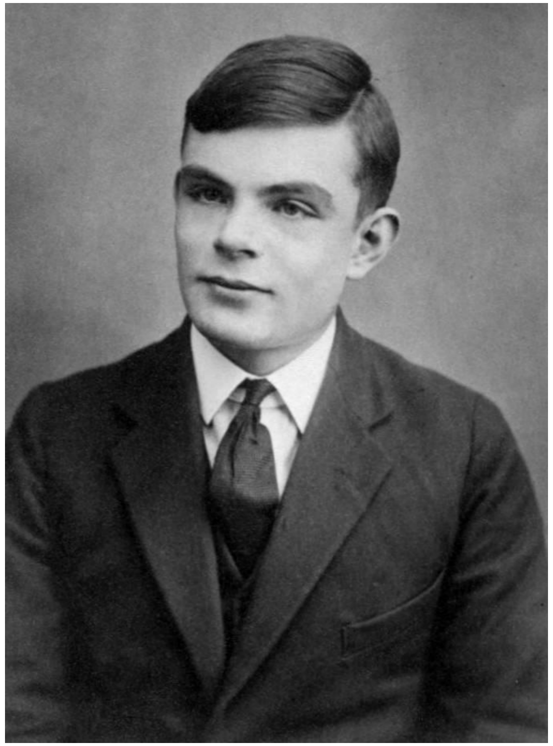
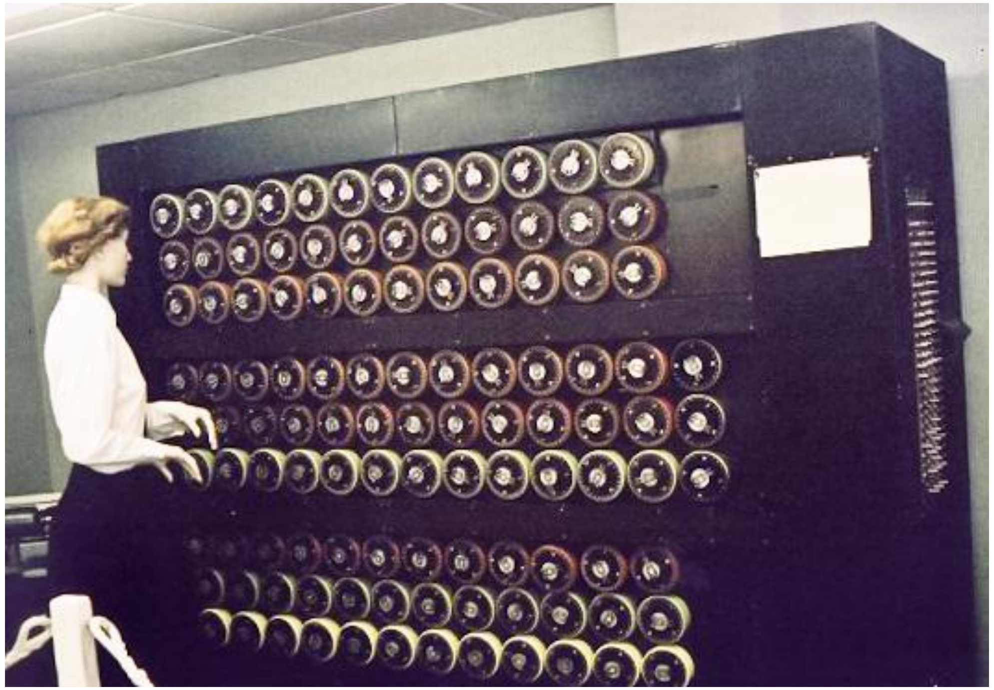
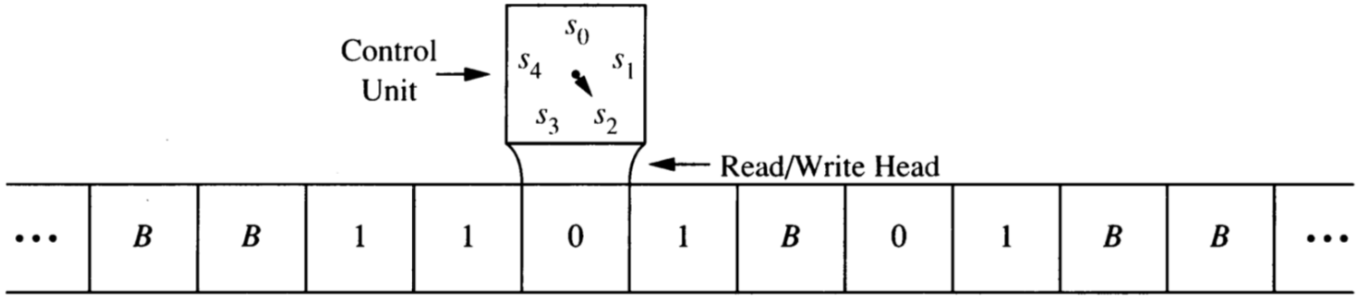
Historical background

- Alan Turing (London, 1912 – Manchester, 1954)





Historical background



Tape is infinite in both directions.
Only finitely many nonblank cells at any time.

Turing machine

VOL. LIX. No. 236.] [October, 1950

MIND
A QUARTERLY REVIEW
OF
PSYCHOLOGY AND PHILOSOPHY

I.—COMPUTING MACHINERY AND INTELLIGENCE

BY A. M. TURING

1. *The Imitation Game.*

I PROPOSE to consider the question, 'Can machines think?' This should begin with definitions of the meaning of the terms 'machine' and 'think'. The definitions might be framed so as to reflect so far as possible the normal use of the words, but this attitude is dangerous. If the meaning of the words 'machine' and 'think' are to be found by examining how they are commonly used it is difficult to escape the conclusion that the meaning and the answer to the question, 'Can machines think?' is to be sought in a statistical survey such as a Gallup poll. But this is absurd. Instead of attempting such a definition I shall replace the question by another, which is closely related to it and is expressed in relatively unambiguous words.

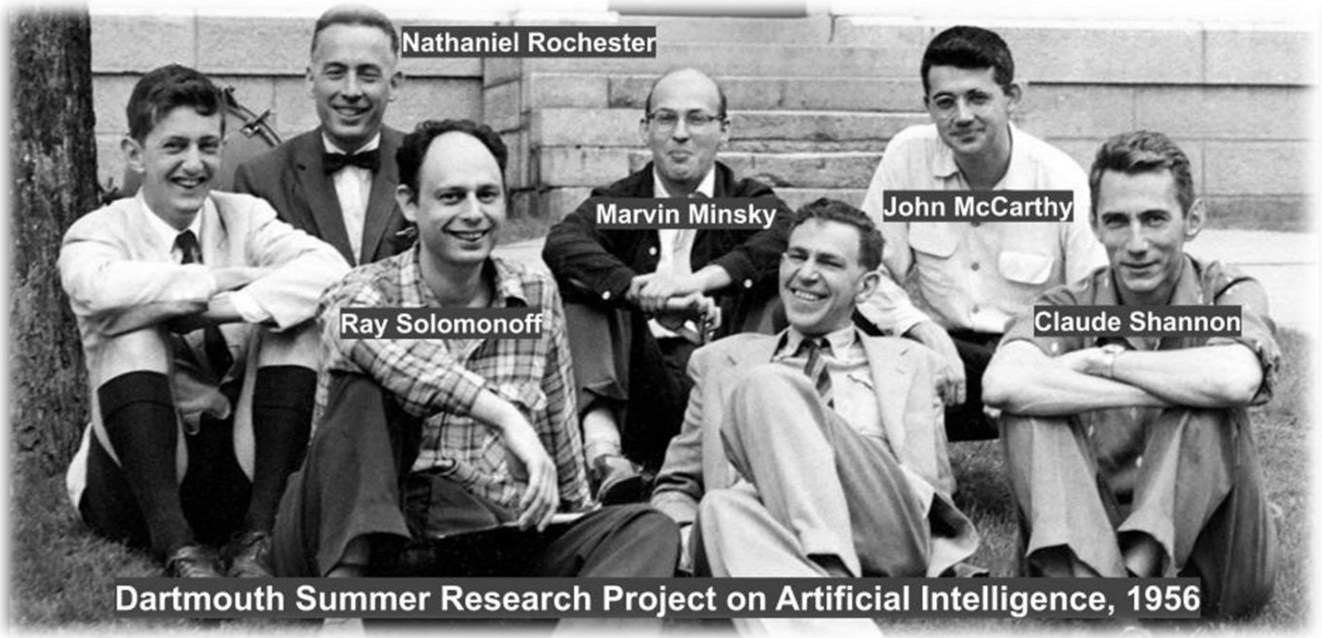
The new form of the problem can be described in terms of a game which we call the 'imitation game'. It is played with three people, a man (A), a woman (B), and an interrogator (C) who may be of either sex. The interrogator stays in a room apart from the other two. The object of the game for the interrogator is to determine which of the other two is the man and which is the woman. He knows them by labels X and Y, and at the end of the game he says either 'X is A and Y is B' or 'X is B and Y is A'. The interrogator is allowed to put questions to A and B thus:

C: Will X please tell me the length of his or her hair?

Now suppose X is actually A, then A must answer. It is A's

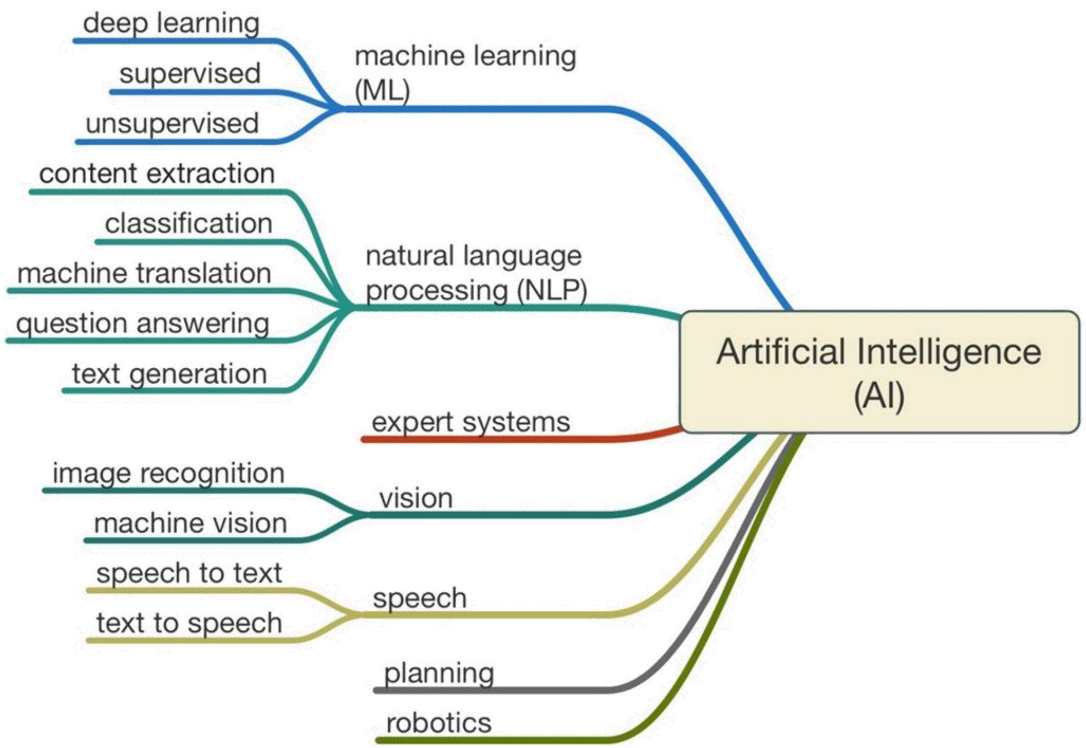
Historical background

- L'AI was born at the conference at Dartmouth College (Hanover, NH, USA) in 1956 where the the term "artificial intelligence" was coined



Artificial Intelligence

- Artificial Intelligence (AI) is a group of technologies aiming at giving to machines abilities requiring human intelligence

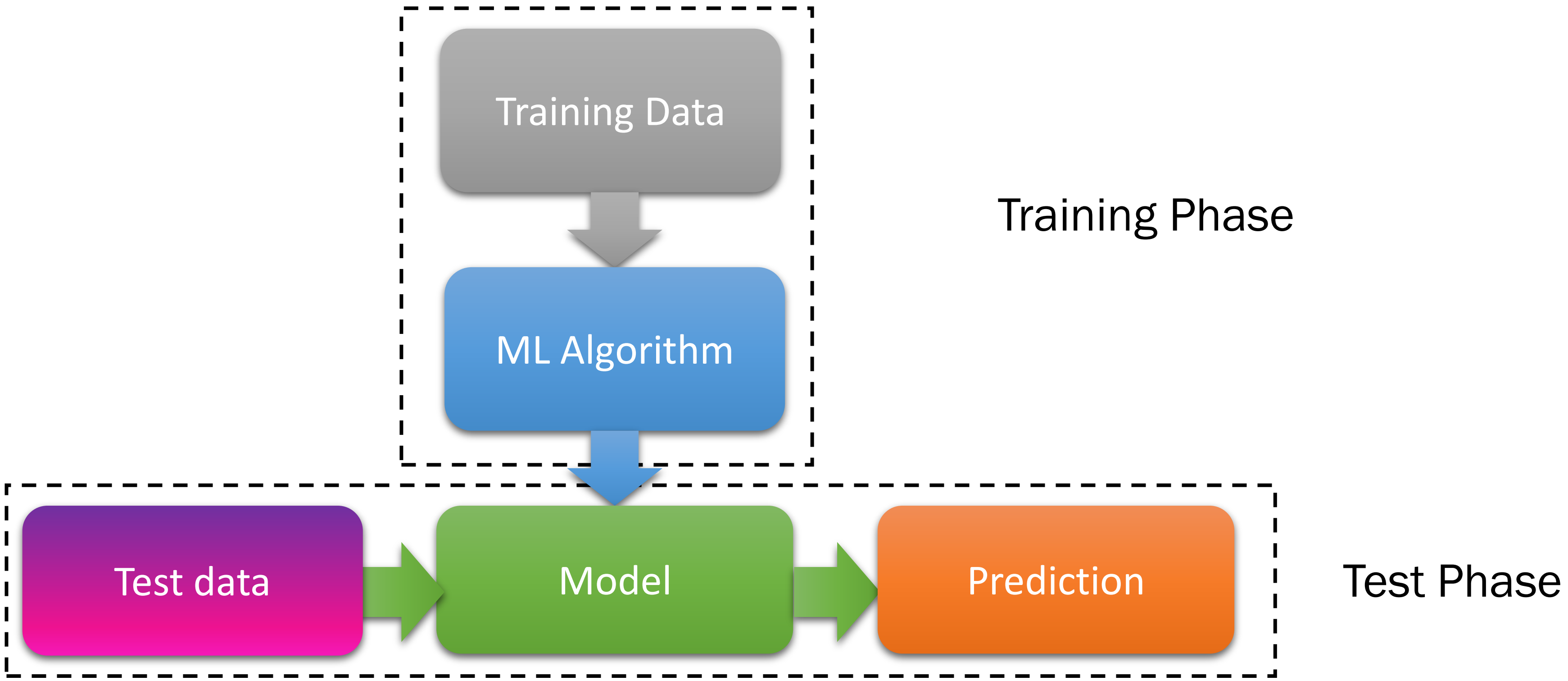


Machine Learning

Machine learning (ML) is the discipline which aims at giving machines the ability to learn to perform tasks, without being explicitly programmed to conduct these tasks (Arthur Samuel 1959)

Supervised Machine learning

- The ML algorithm is trained in a known dataset in order to yield a model which can make predictions on an unknown dataset



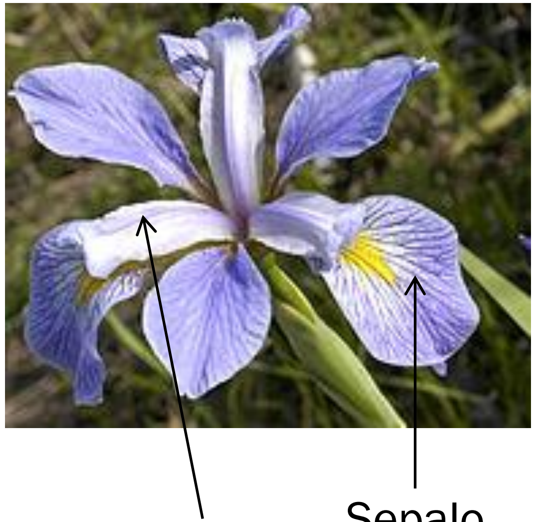
Classification

- Dataset of iris flowers (by Roland Fisher, 1936)

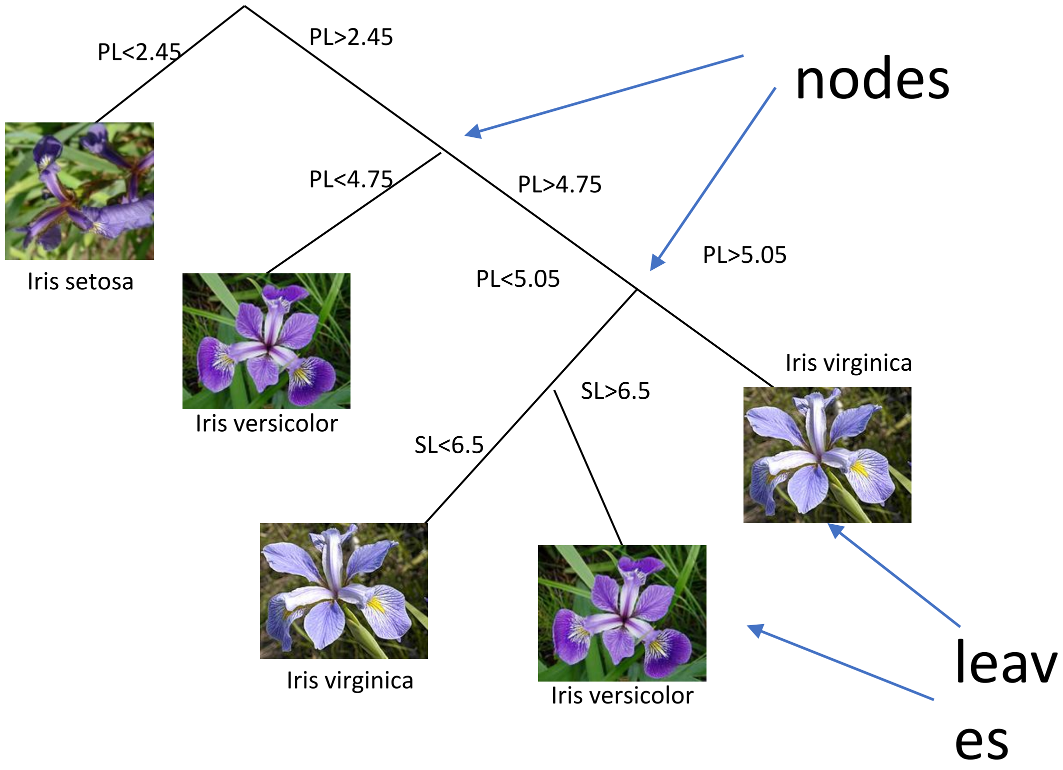
Iris setosa

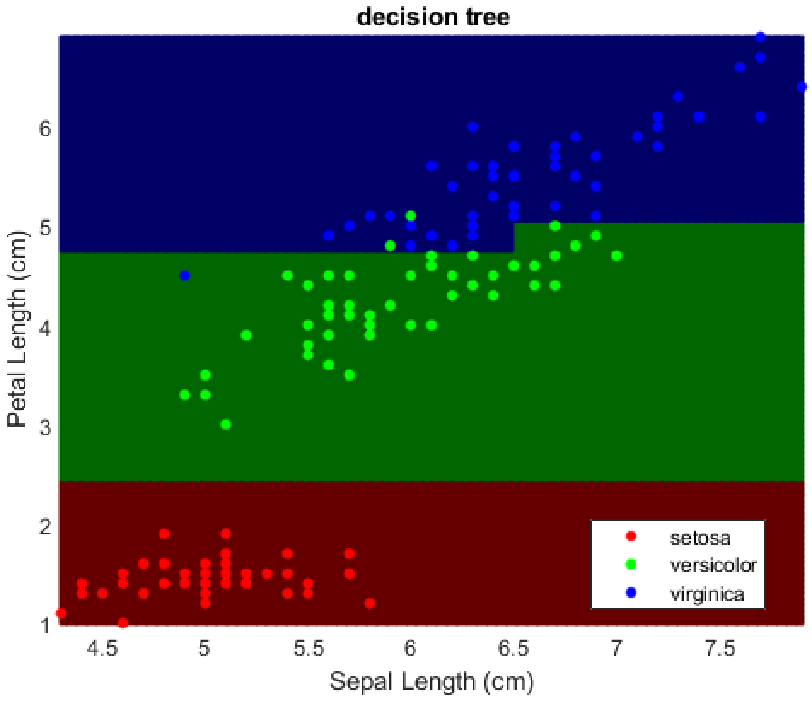
Iris versicolor

Iris virginica



Decision Trees





https://victorzhou.com/blog/gini-impurity/

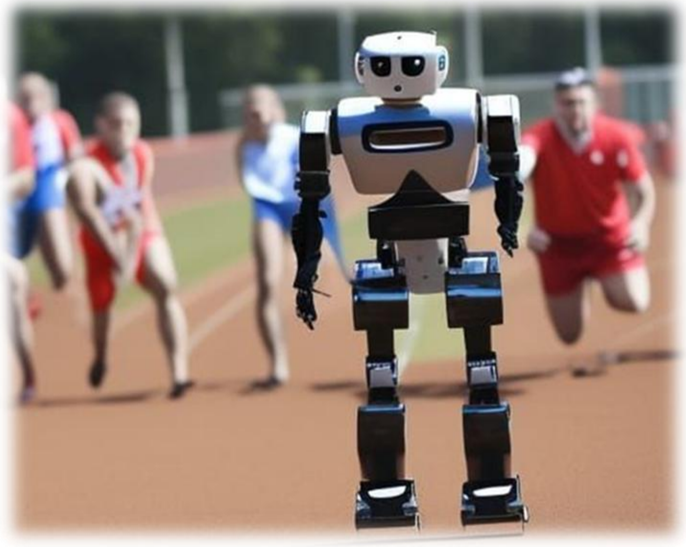
Metrics for performance

		Predicted	
		N	P
Actual	N	TN	FP
	P	FN	TP

$$sensitivity = \frac{TP}{TP + FN}$$

$$specificity = \frac{TN}{FP + TN}$$

$$\text{accuracy}= \frac{TP+TN}{TP+FP+TN+FN}$$

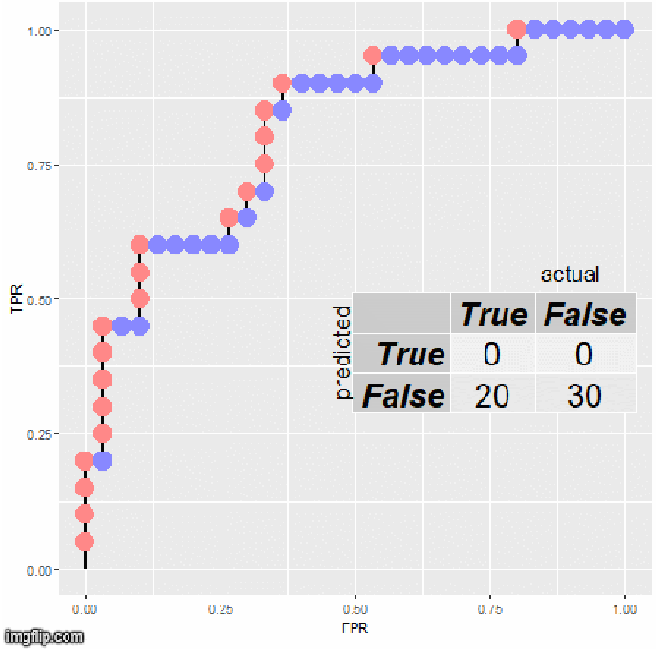


- A highly sensitive test is preferable for screening, as it gives less false negatives
- A highly specific test gives less *false positives,* so it is useful to confirm a pathology

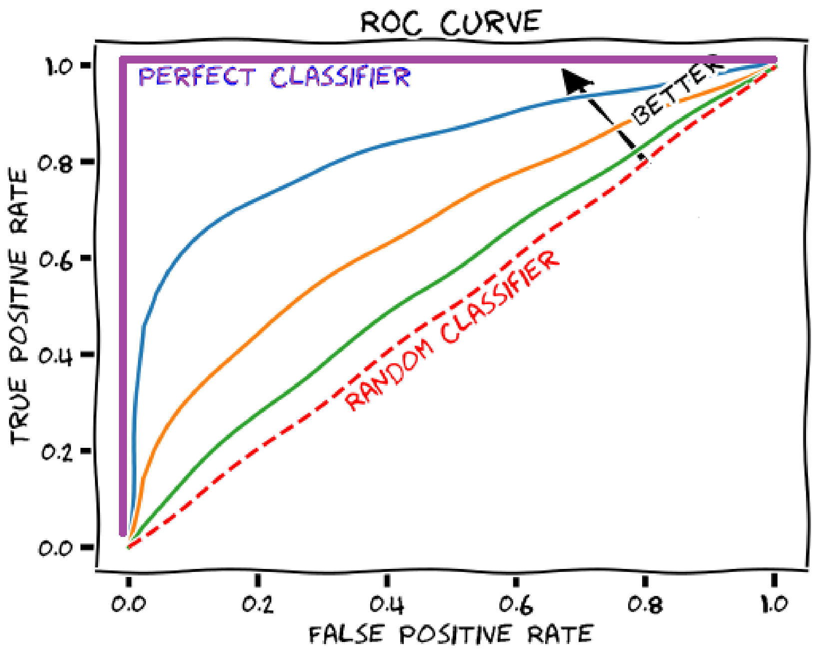
Curva Receiver Operating Characteristic (ROC)

- Consider a classifiers that, instead of a binary output, provides the probability of being positive
- ROC curve shows true positives vs false positives for different thresholds of the continuous index

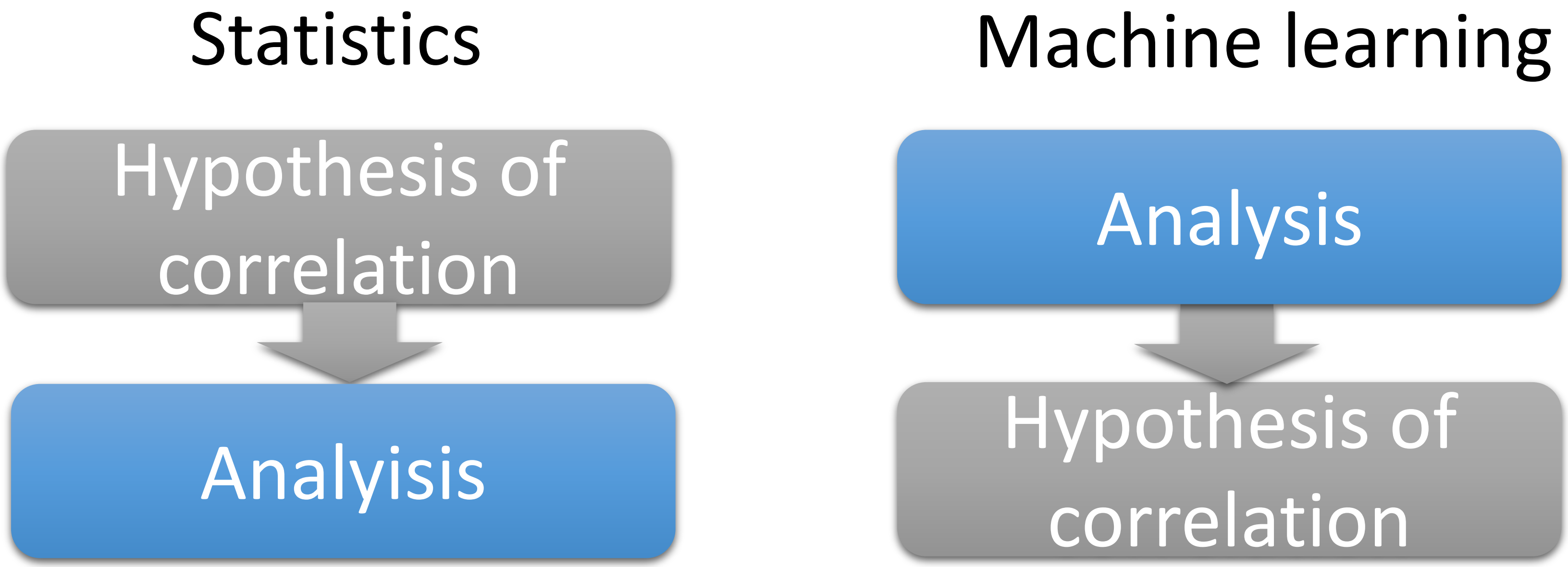
Sensitivity (true positives)



1−specificity=false positives



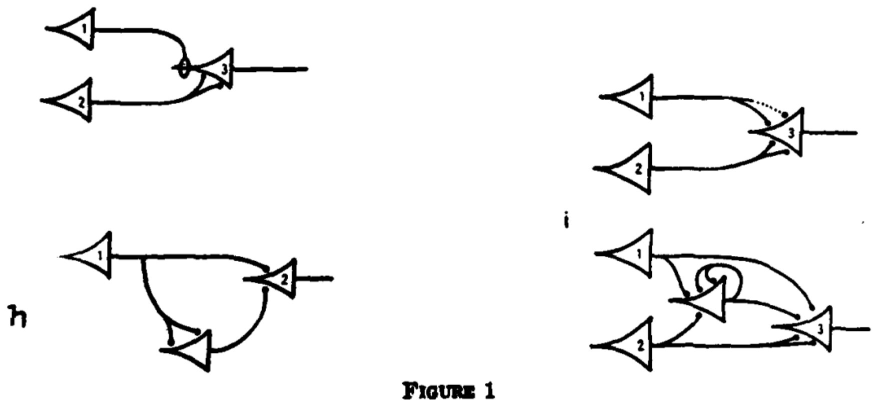
Statistics vs machine learning



Machine learning algorithms analyze a dataset and then extract correlations, a reversal of traditional data analysis, where the hypothesis is chosen first and then the data queried to test the hypothesis.

- For the same reason, ML needs large datasets to learn, rather than just a statistically relevant sample.

Neural networks

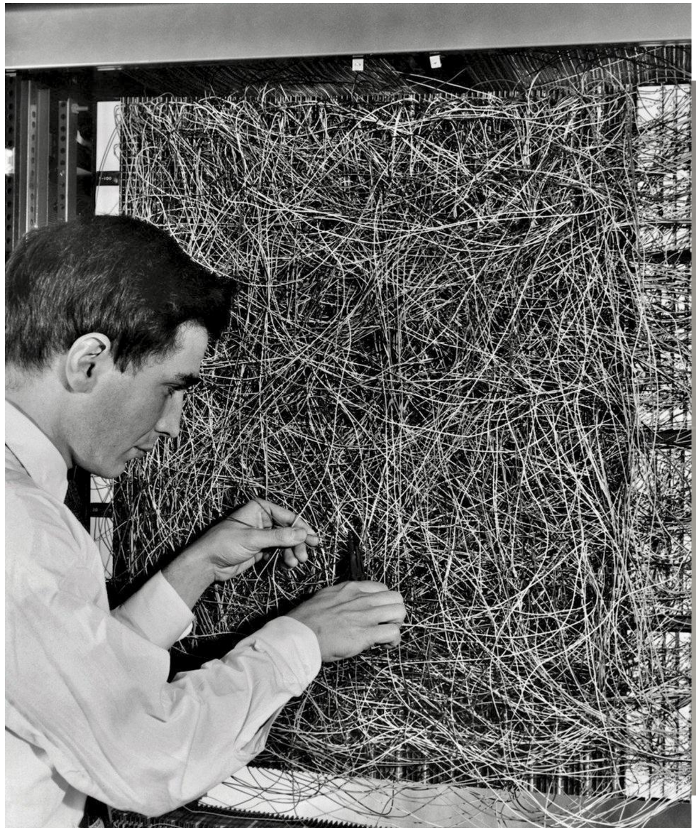


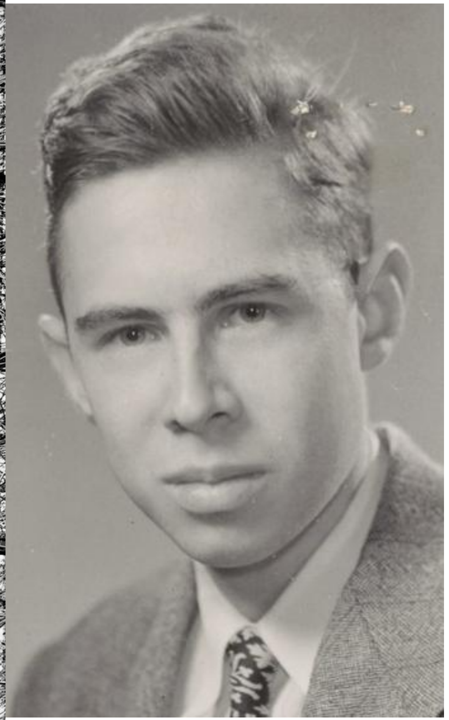
Mccullough e Pitts (1943) describe the brain using an abstract model of neural network

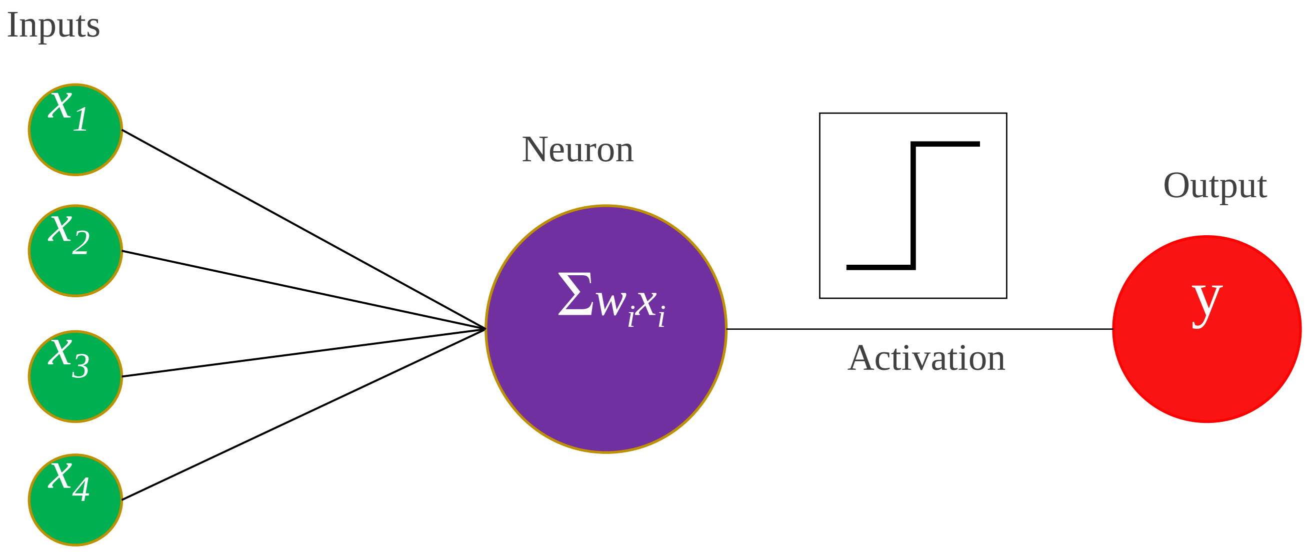
Harold Hebb (1949): “Cells that fire together wire together”

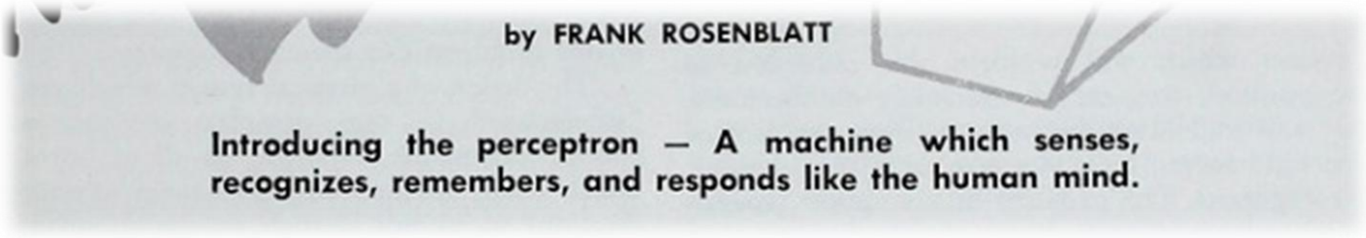
Neural networks

- Perceptron by Frank Rosenblatt (1959)





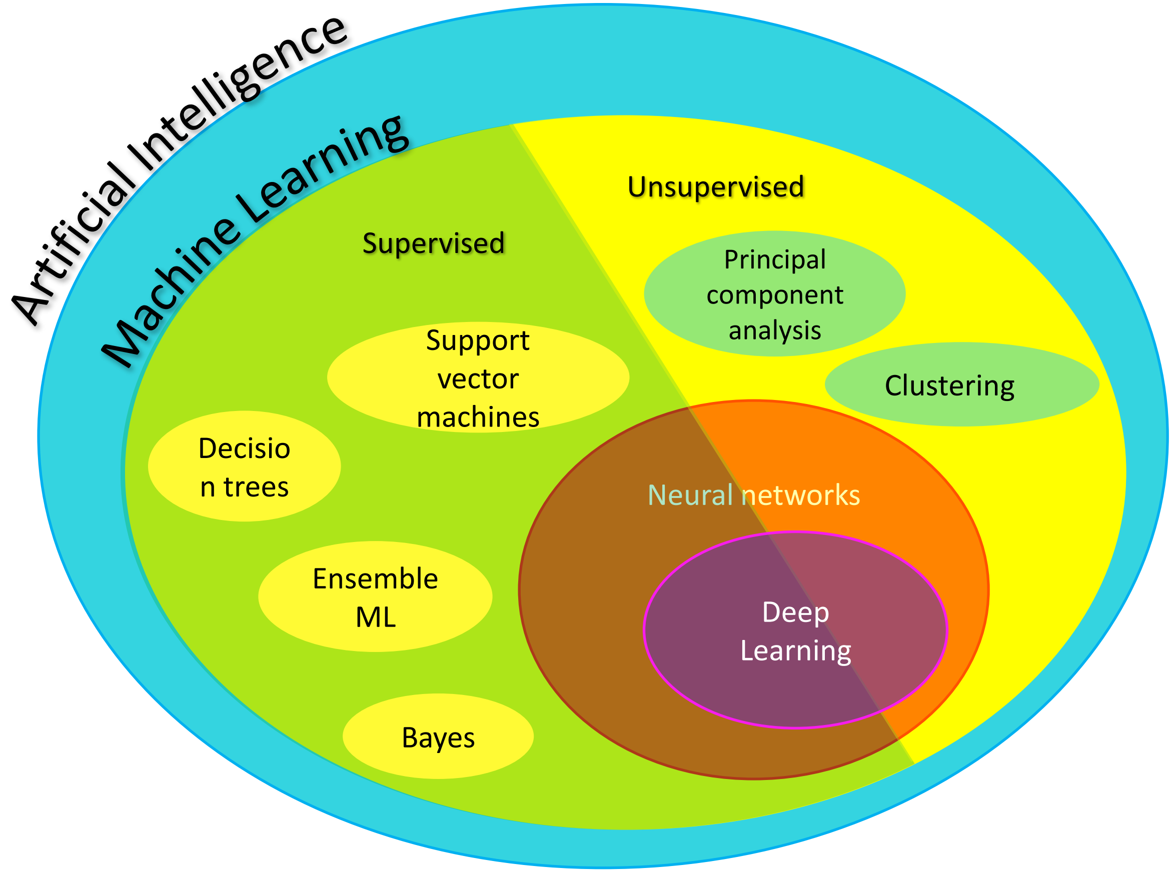




by FRANK ROSENBLATT

Introducing the perceptron — A machine which senses, recognizes, remembers, and responds like the human mind.

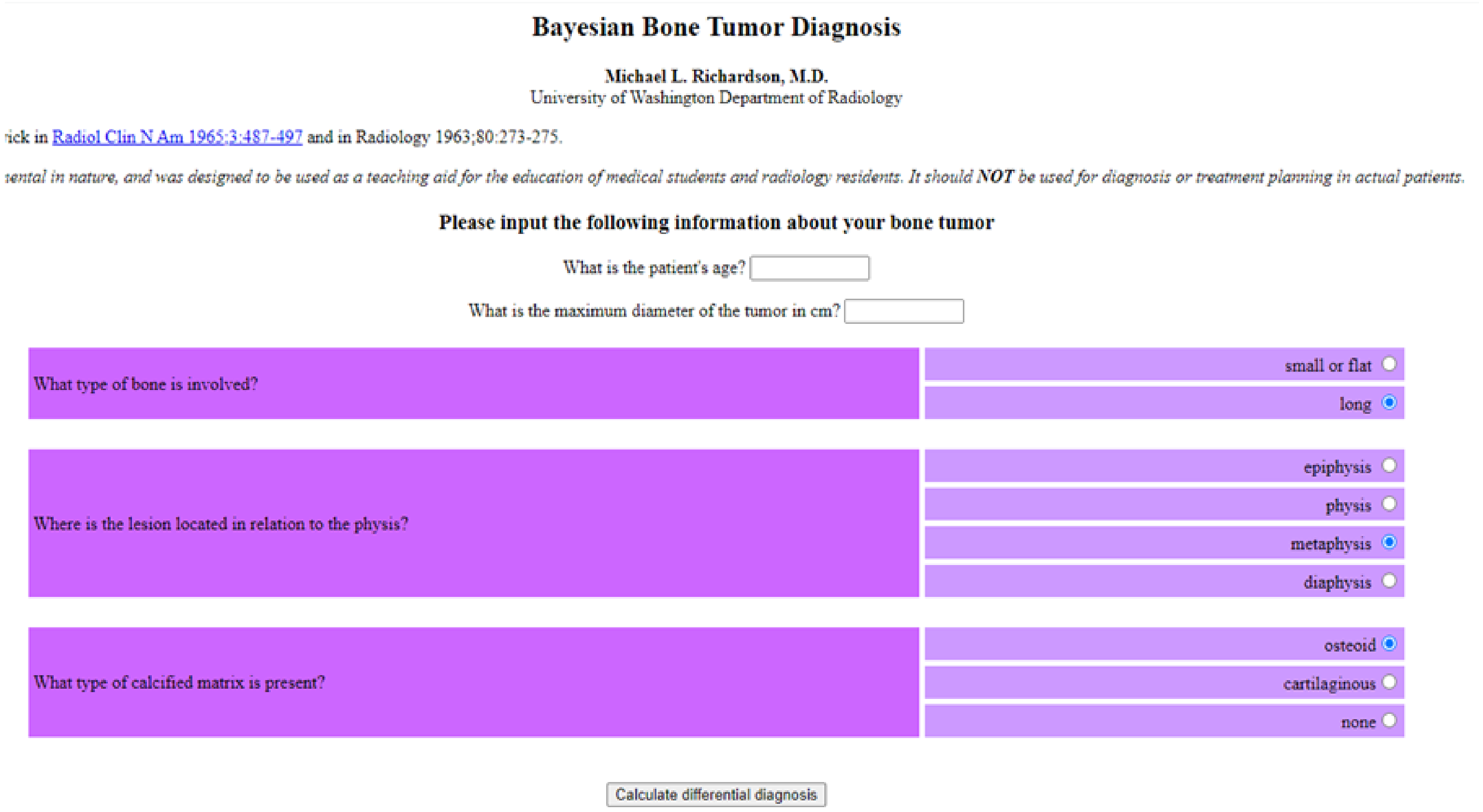
Cathegories of machine learning



Physica Medica Volume 83, March 2021, Pages 221-241

AI applied to imaging

- Lodwick, 1963



Bayesian Bone Tumor Diagnosis

Michael L. Richardson, M.D.
University of Washington Department of Radiology

ick in Radiol Clin N Am 1965;3:487-497 and in Radiology 1963;80:273-275.

*ental in nature, and was designed to be used as a teaching aid for the education of medical students and radiology residents. It should **NOT** be used for diagnosis or treatment planning in actual patients.*

Please input the following information about your bone tumor

What is the patient's age?

What is the maximum diameter of the tumor in cm?

What type of bone is involved?	small or flat long
Where is the lesion located in relation to the physis?	epiphysis physis metaphysis diaphysis
What type of calcified matrix is present?	osteoid cartilaginous none

Calculate differential diagnosis

Radiomic variables or “features”

Shape

$$compactness\ 2 = 36\pi \frac{A^2}{V^3}$$

Histogram

$$kurtosis = \frac{\frac{1}{N}\sum_i \left(X(i) - \bar{X}\right)^4}{\left(\frac{1}{N}\sum_i \left(X(i) - \bar{X}\right)^2\right)^2}$$

$$entropy = \sum_i \left(P(i)\log_2 P(i)\right)$$

Texture

$$cluster\ shade = \sum_{i.j} \left(i + j - 2\mu\right)^3 * P(i,j)$$

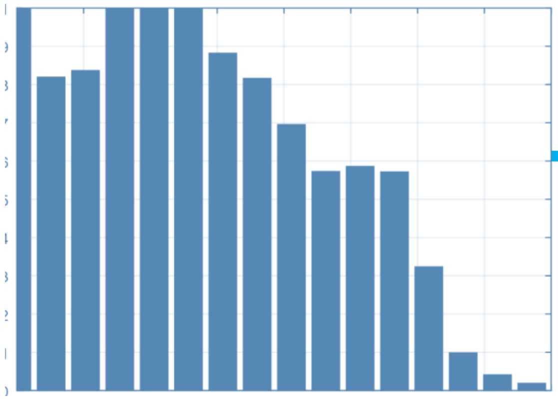
$$coarseness = \frac{1}{\varepsilon + \sum_i P(i)s(i)}$$

Avanzo et al. Phys Med 38 (2017) 122-139

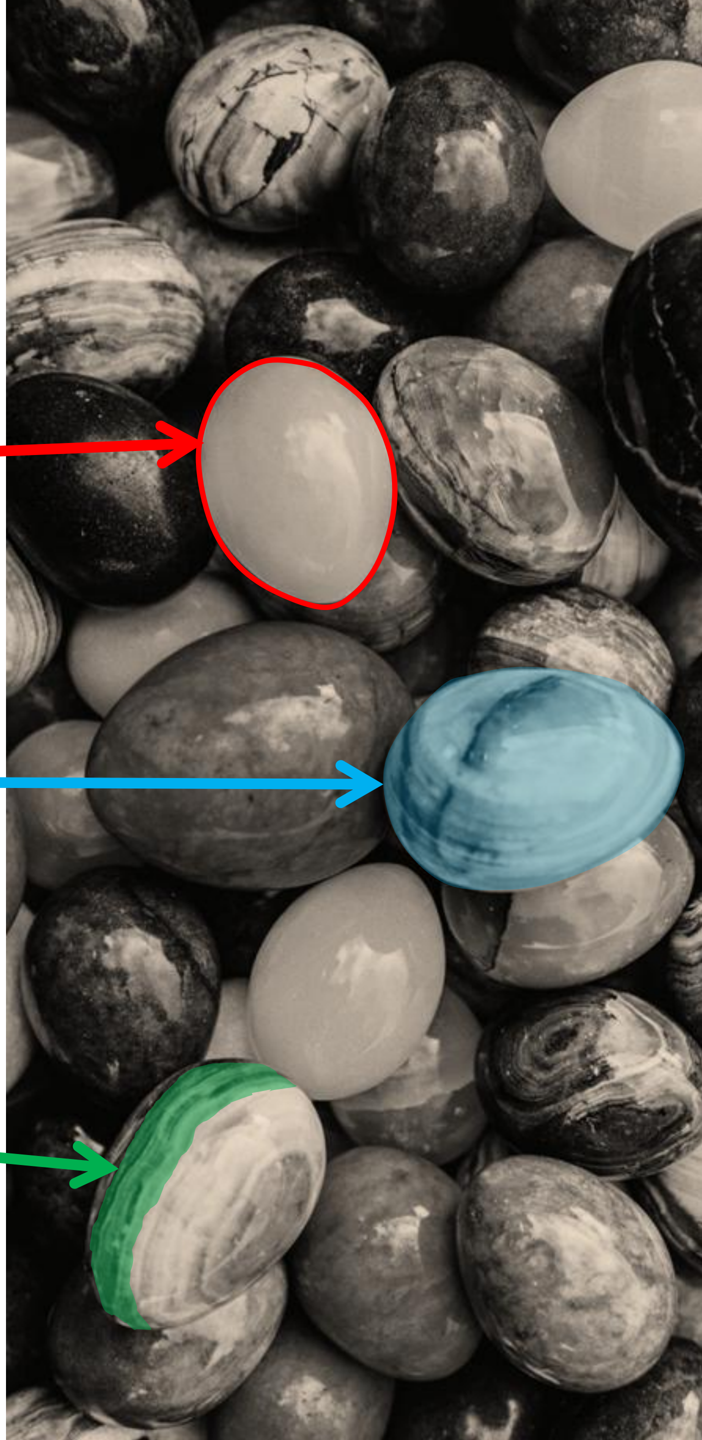
Radiomic variables or “features”

Shape

Histogram



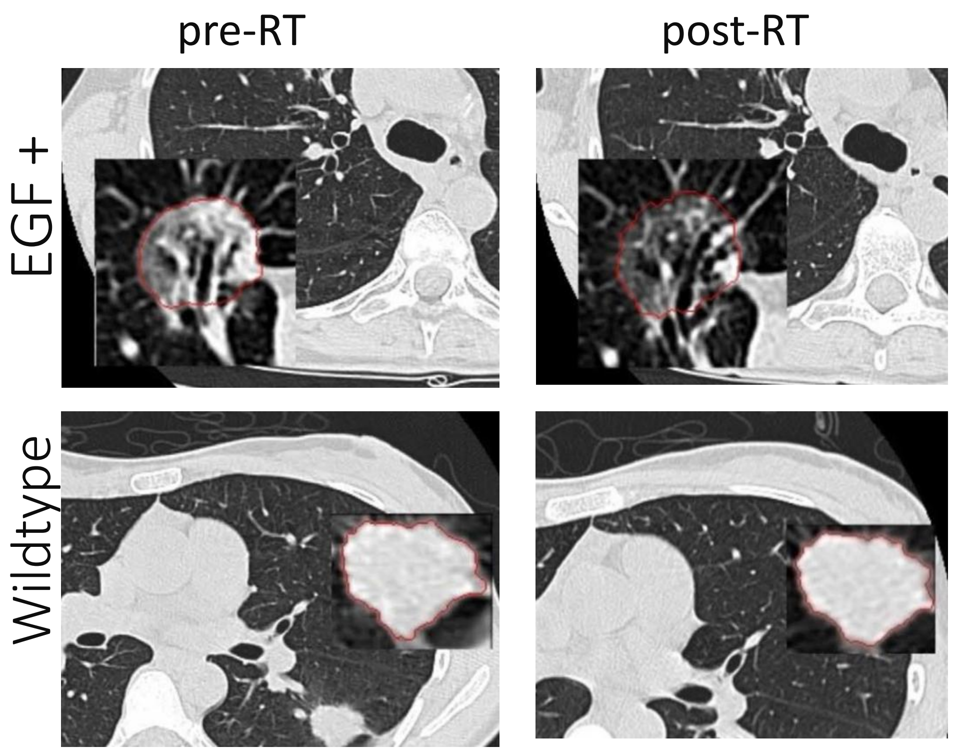
Texture



Avanzo et al. Phys Med 38 (2017) 122-139

Example

- Analizzare e capire le variabili selezionate e perchè

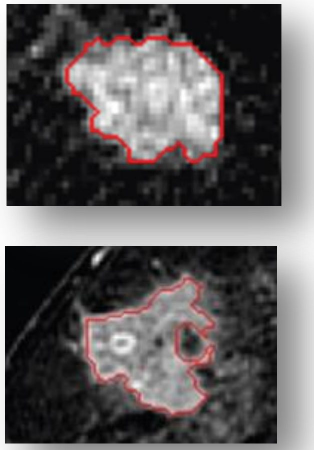


EGFR status	CT acquisition	Volume	Radius_Std	Shape_SI6	Gabor_Energy-dir135-w3	Gabor_Energy-dir45-w9	Laws_Energy-10	Laws_Energy-13
EGFR positive	Baseline (Fig 1-a)	7766.5	1.522	0.145	5337.9	419770.4	475.2	1369.6
	Followup (1-b)	7195.8	1.657	0.151	4043.5	327365.1	512.0	1352.9
	Change	**-570.6**	**0.135**	**0.006**	**-1294.4**	**-92405.3**	**36.8**	**-16.6**
Wild type	Baseline (Fig 1-c)	3502.4	1.422	0.173	11601.7	419578.9	367.7	353.9
	Followup (1-d)	4522.8	1.251	0.165	10605.5	361191.5	326.3	349.3
	Change	**1020.4**	**-0.171**	**-0.009**	**-996.2**	**-58387.4**	**-41.5**	**-4.5**

Aerts et al. Sci Rep 6 (2016) 33860

Radiomic profile

Sfericità Densità Disomogeneità



Biomarkers

Radiomic profile

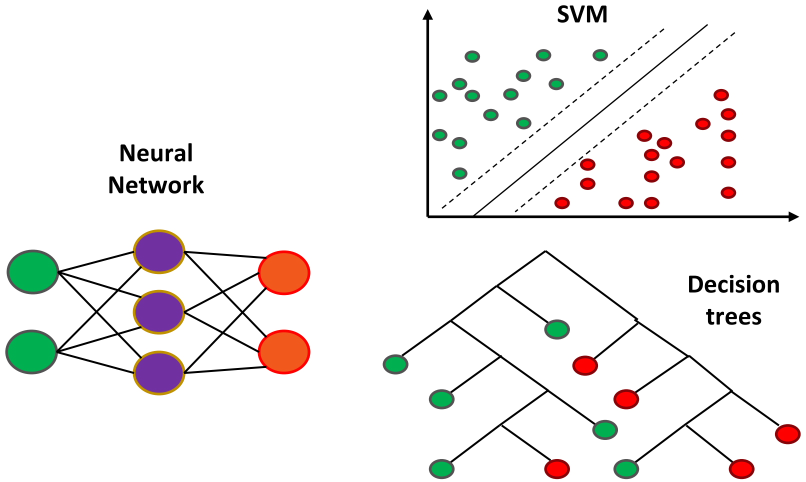
Prognosis

ML in radiomics

- High number of often redundant variables:

29 shape + (174-shape=145) * (filters LoG, wavelet…) * (imaging modalities: PET, CT, MRI)

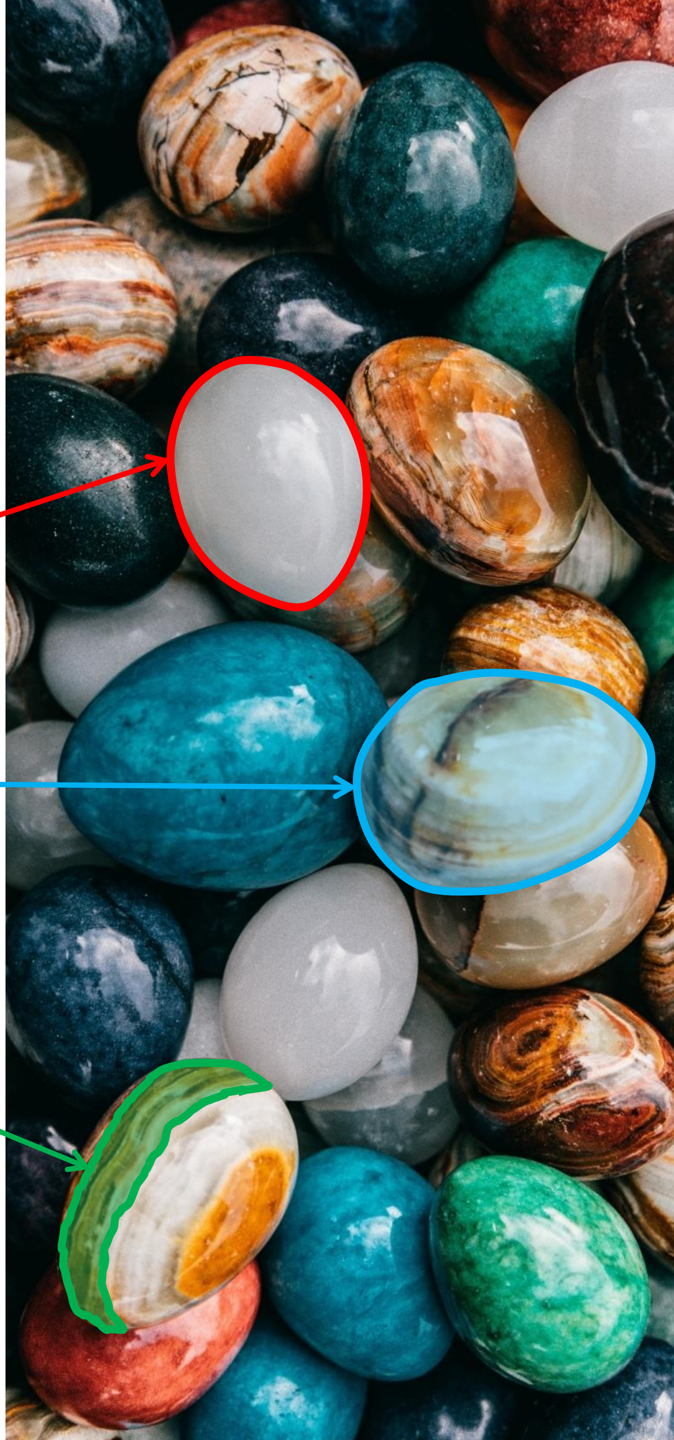
- Complex, non-linear dependencies on outcome

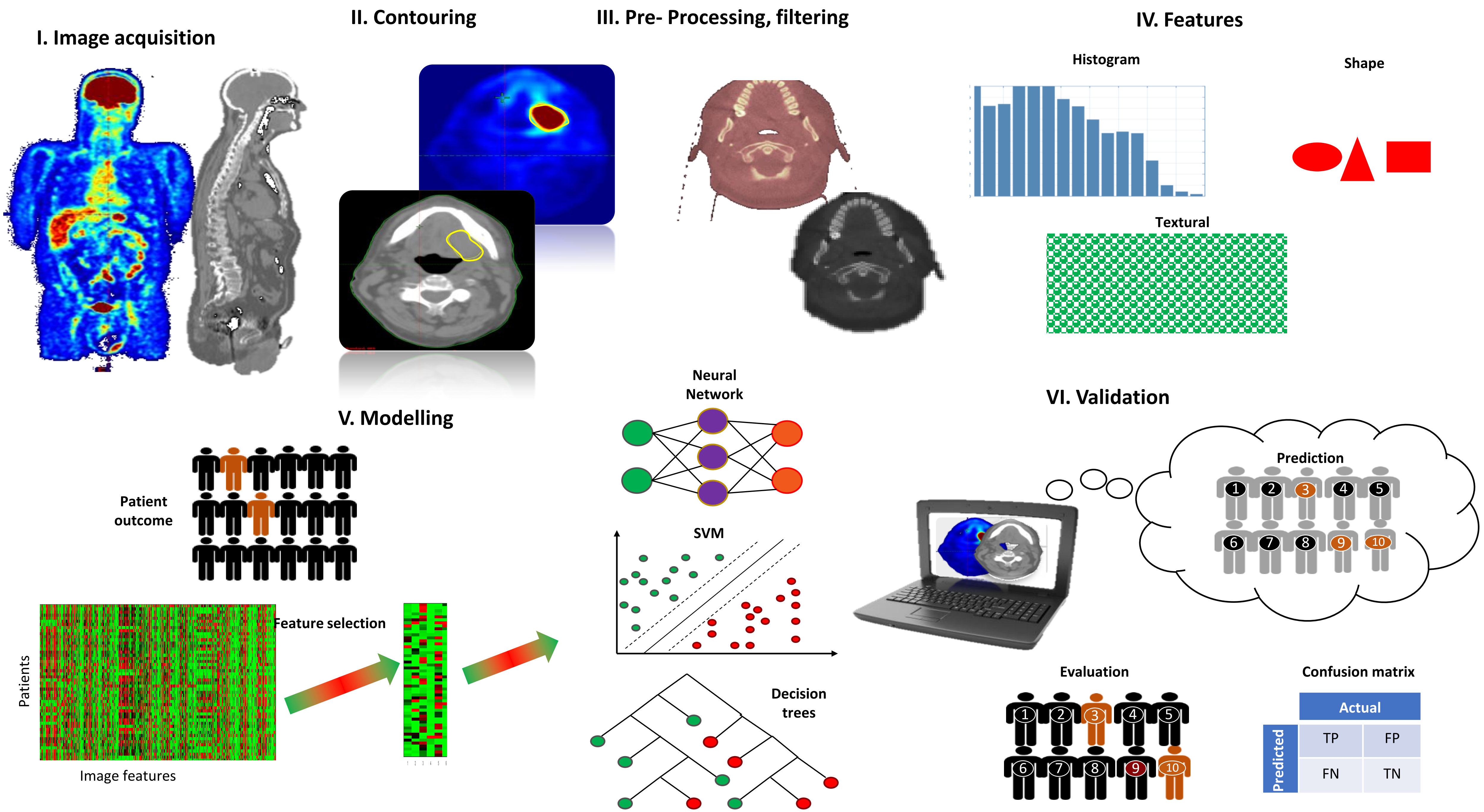


Shape

Histogram (1st Order)

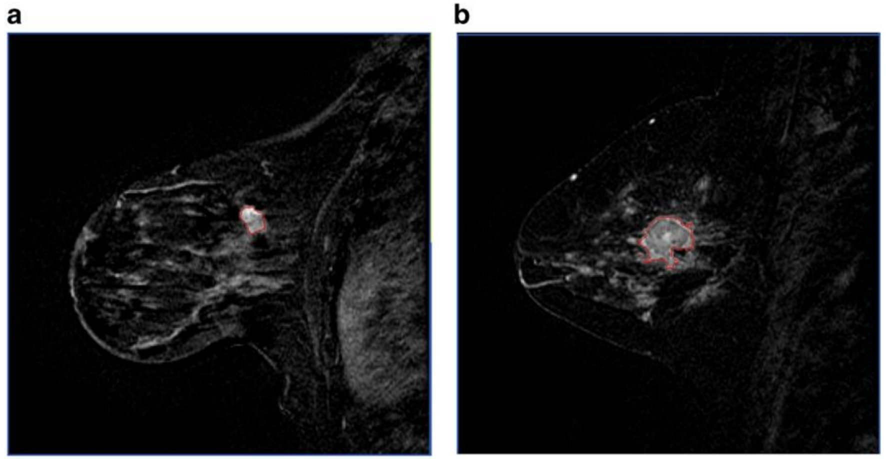
Textural (2nd order)




I. Image acquisition
II. Contouring
III. Pre- Processing, filtering
IV. Features
Histogram
Shape
Textural
V. Modelling
Patient outcome
Patients
Image features
Feature selection
Neural Network
SVM
Decision trees
VI. Validation
Prediction
1 2 3 4 5
6 7 8 9 10
Evaluation
1 2 3 4 5
6 7 8 9 10
Confusion matrix
Actual
Predicted
TP FP
FN TN

Characterization of lesion

- Molecular subtype of breast cancer
- stepwise feature selection and linear discriminant analysis



c

	ER Positive Case (a)	ER Negative Case (b)
Cancer Subtype	Luminal A	HER2-enriched
MRI CEIP Size (Effective Diameter) Range [7.8 54.0]	12.9 mm	23.8 mm
MRI CEIP Shape (Irregularity) Range [0.40 0.84]	0.452	0.602

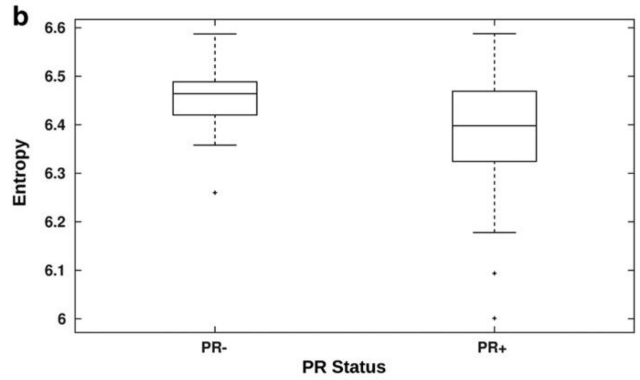


Table 1. Results from the Mann–Whitney *U*-test indicating association between MRI phenotypes and molecular classifications for phenotypes shown in Figures 2–4

Classification task	*Number of tumors*	*MRI phenotype*	*Mean value (s.d.) positive versus negative*	P-*value*	*Significance level* ($\alpha^T = 0.05$)
ER+ versus ER–	91 (77 vs. 14)	Effective diameter	17.6 mm (5.6) vs. 24.8 mm (10.4)	0.001[a]	0.0167
		Irregularity	0.61 (0.11) vs. 0.65 (0.11)	0.23	0.05
		Entropy	6.40 (0.11) vs. 6.45 (0.09)	0.08	0.025
PR+ versus PR–	91 (72 vs.19)	Effective diameter	18.0 mm (5.6) vs. 21.6 mm (10.5)	0.14	0.025
		Irregularity	0.61 (0.11) vs. 0.63 (0.10)	0.43	0.05
		Entropy	6.39 (0.11) vs. 6.45 (0.07)	0.03	0.0167
HER2+ versus HER2–	91 (19 vs. 72)	Effective diameter	18.4 mm (5.7) vs. 18.8 mm (7.3)	1.0	0.05
		Irregularity	0.59 (0.12) vs. 0.62 (0.11)	0.36	0.0167
		Entropy	6.41 (0.10) vs. 6.40 (0.11)	0.93	0.025
TN versus others	91 (11 vs. 80)	Effective diameter	17.8 mm (5.6) vs. 25.6 (11.5)	0.006[a]	0.0167
		Irregularity	0.60 (0.11) vs. 0.68 (0.09)	0.03	0.025
		Entropy	6.40 (0.10) vs. 6.45 (0.10)	0.13	0.05

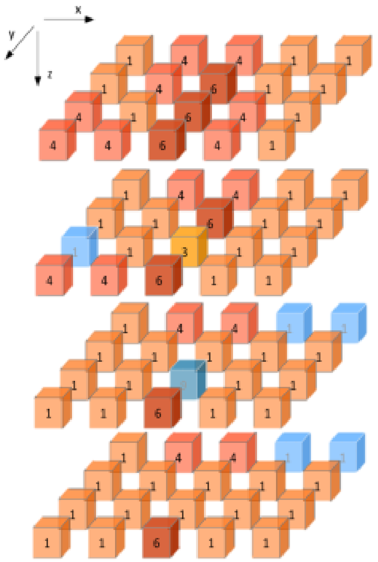
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; PR, progesterone receptor; TN, triple negative.
[a]Indicates statistical significance was achieved after correction for multiple comparisons.

https://www.nature.com/articles/npjbcancer201612

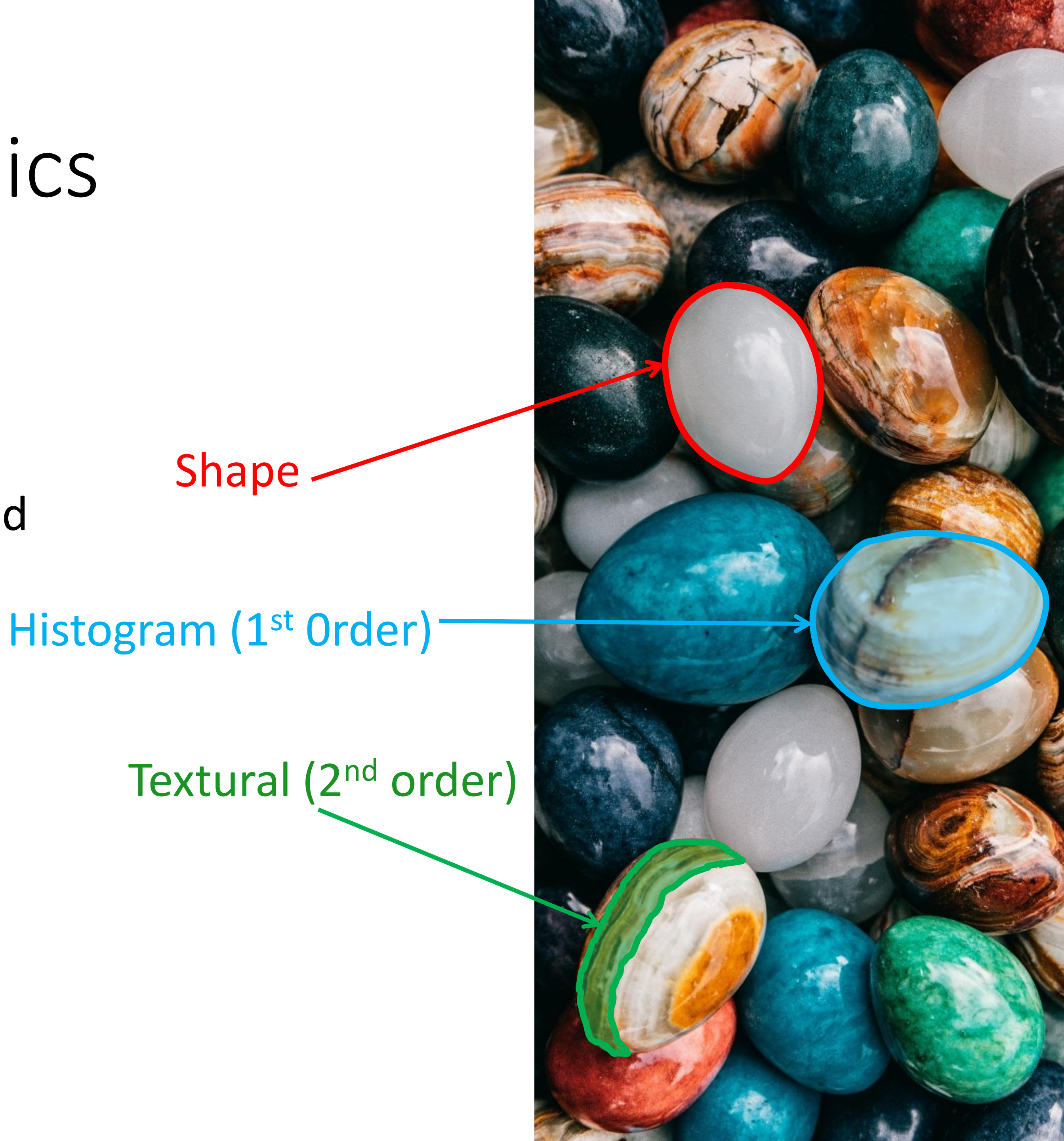
Advantages of radiomics

- Standardization
- Interpretability
- Less computational resources needed

IBSI
image biomarker standardisation initiative

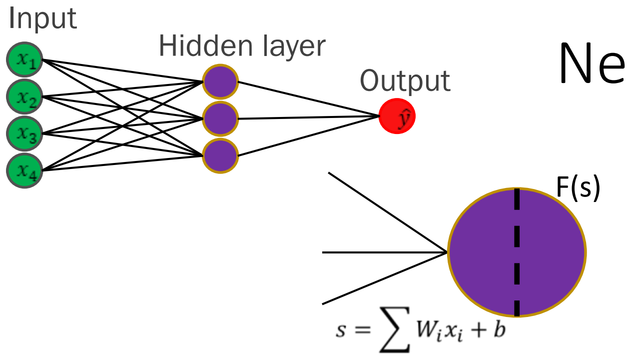


IBSI digital phantom

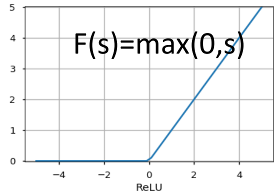


Neural networks and deep learning

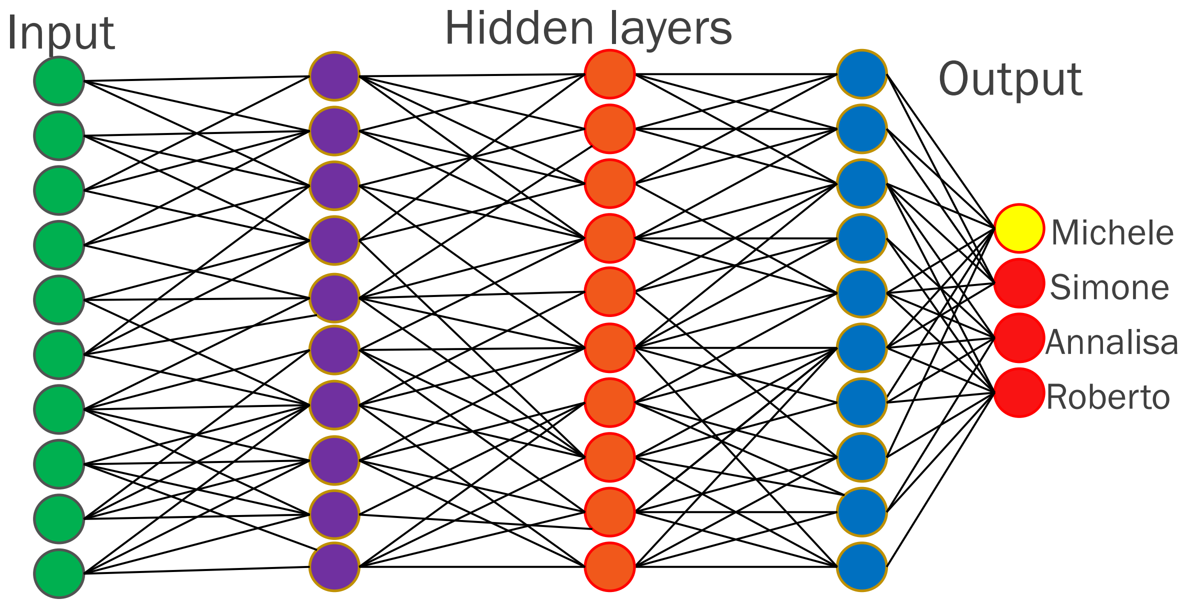
- Deep learning was introduced to model outputs with more complex, non-linear dependencies from input



Neural networks



ReLU=rectified linear unit



https://www.pnas.org/content/116/4/1074

Convolutional networks

- Layers to extract image features through convolution with learable filters ("kernels")

12	4	9	1	4
2	1	4	4	1
5	1	2	1	11
8	23	4	7	7
17	5	11	8	1

Image

1	0	-1
2	0	-2
1	0	-1

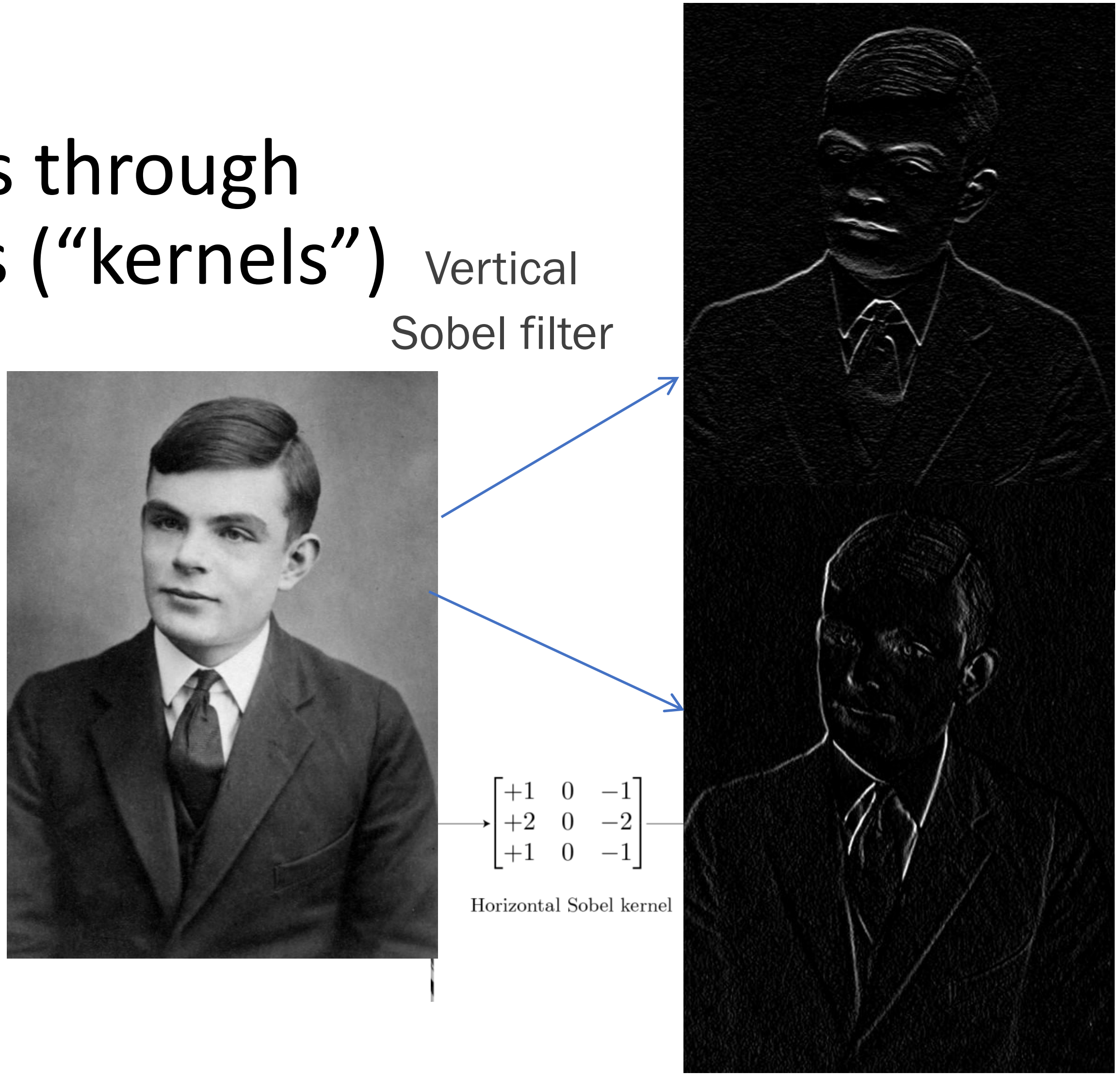
Filter/kernel

1			

Feature

3_0	3_1	2_2	1	0
0_2	0_2	1_0	3	1
3_0	1_1	2_2	2	3
2	0	0	2	2
2	0	0	0	1

12.0	12.0	17.0
10.0	17.0	19.0
9.0	6.0	14.0



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5479722/

Other layers

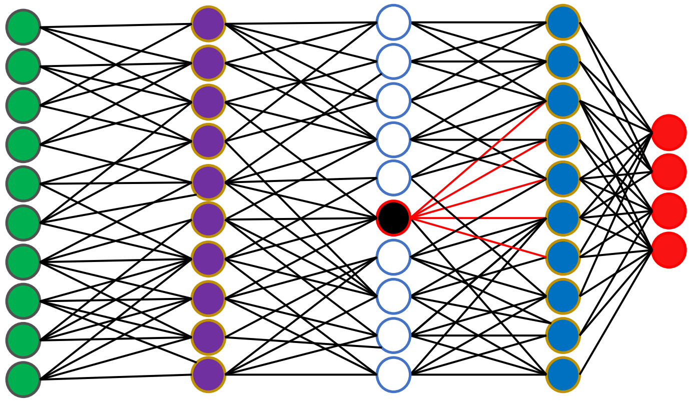
- Pooling layers reduce size of feature map e.g. by calculating maximum or average in a group of voxels
- Dropout layers zero random inputs to prevent overfitting
- Softmax layers calculate probability of classes

21	60	37	-10	4
28	53	63	20	15
14	22	23	8	19
-8	20	49	1	23
11	55	17	22	1

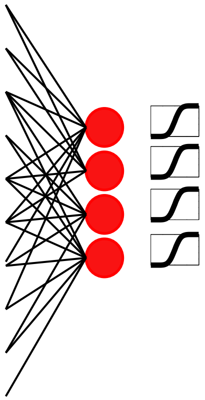
feature

60			

Max pooled

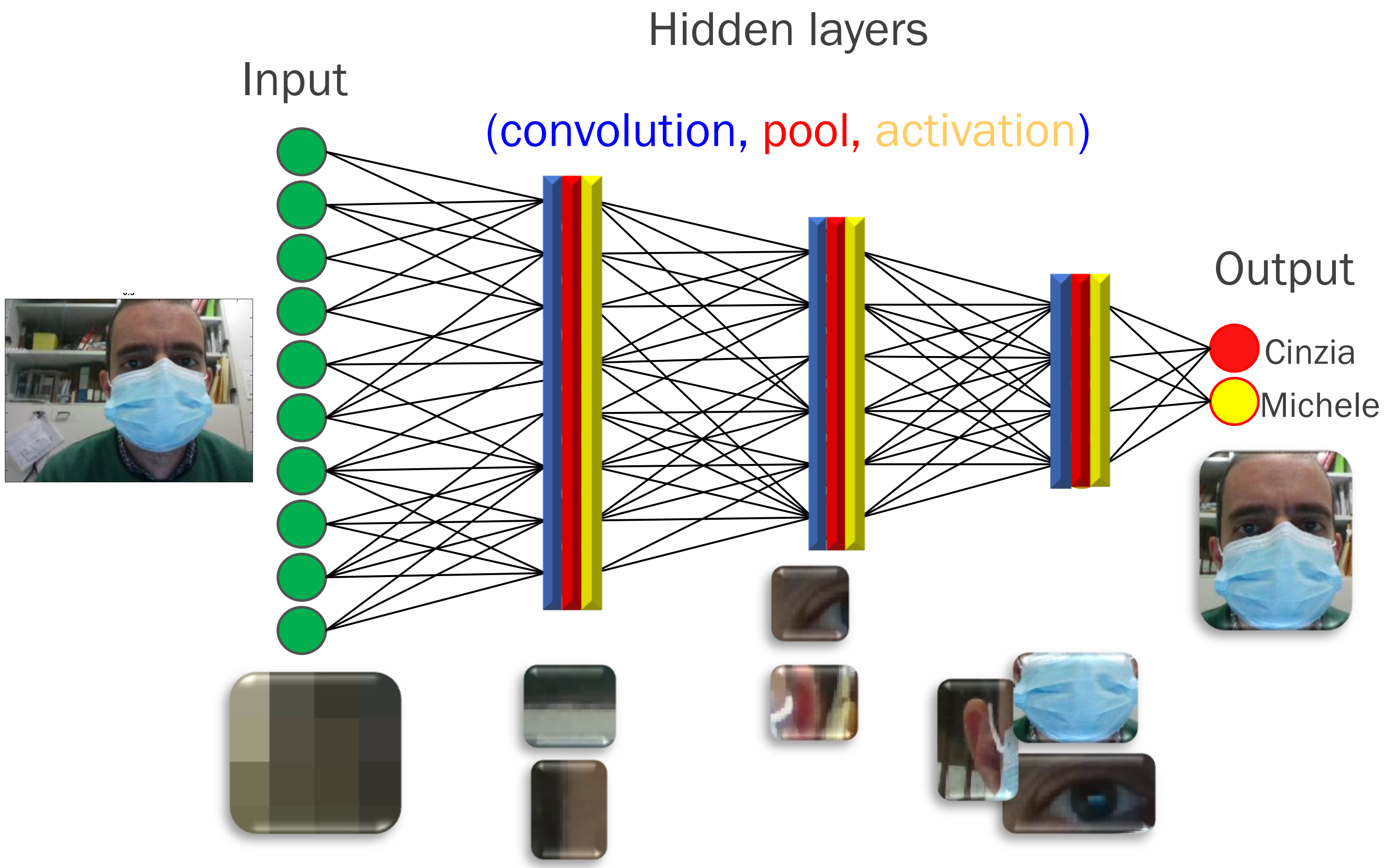


Dropout



Softmax

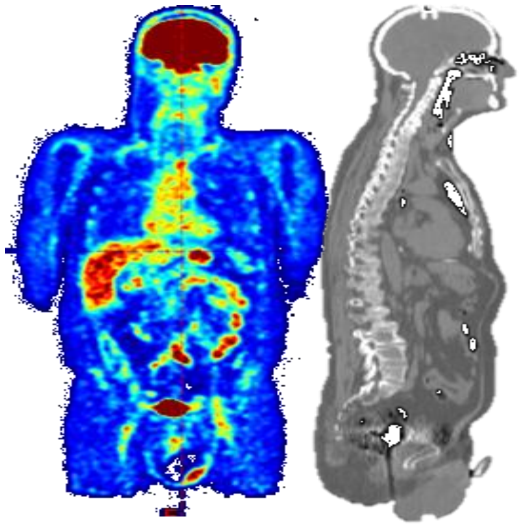
Convolutional neural networks (CNN)

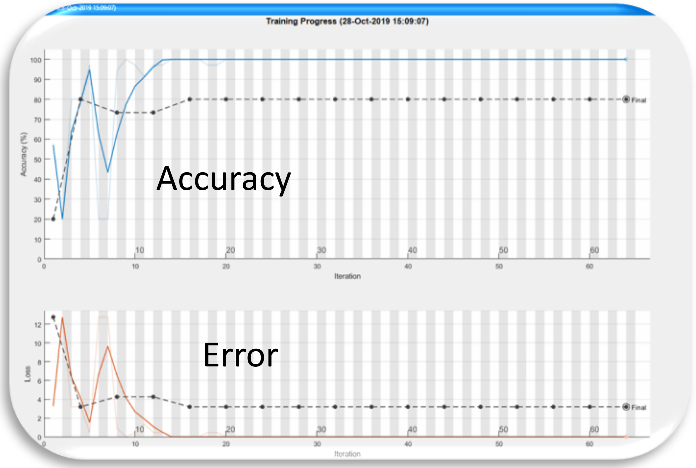


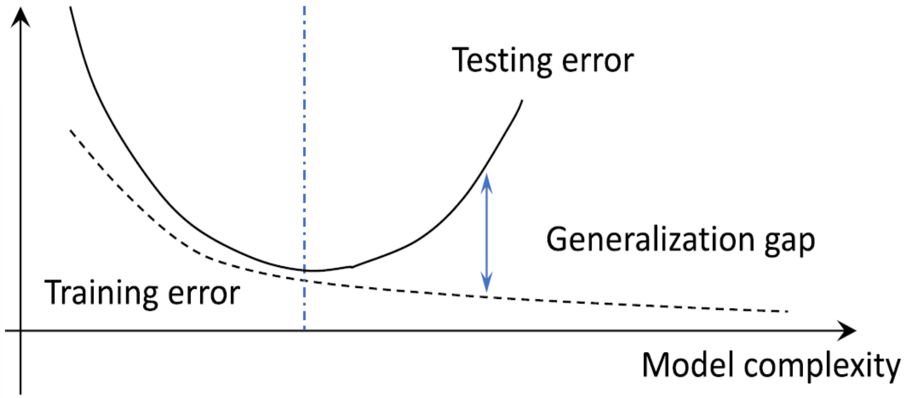
Classification of objects

I. Image acquisition

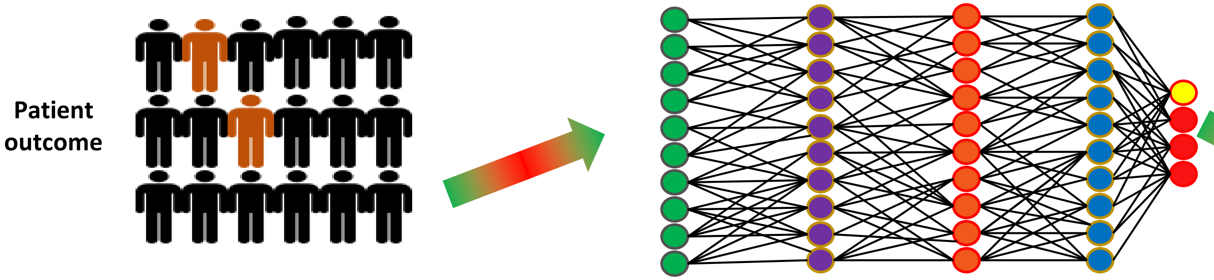
Chenyang Shen *et al* 2020 *Phys. Med. Biol.* **65** 05TR01



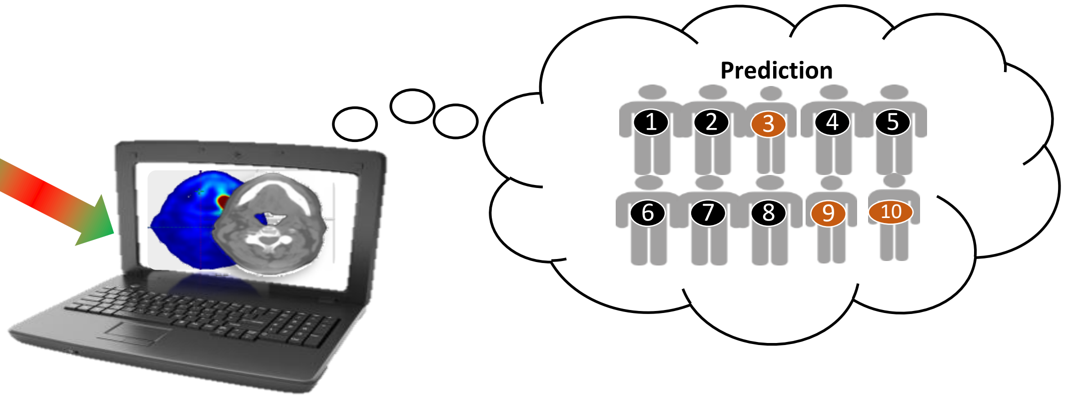




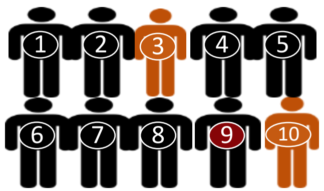
V. Modelling



VI. Validation



Evaluation

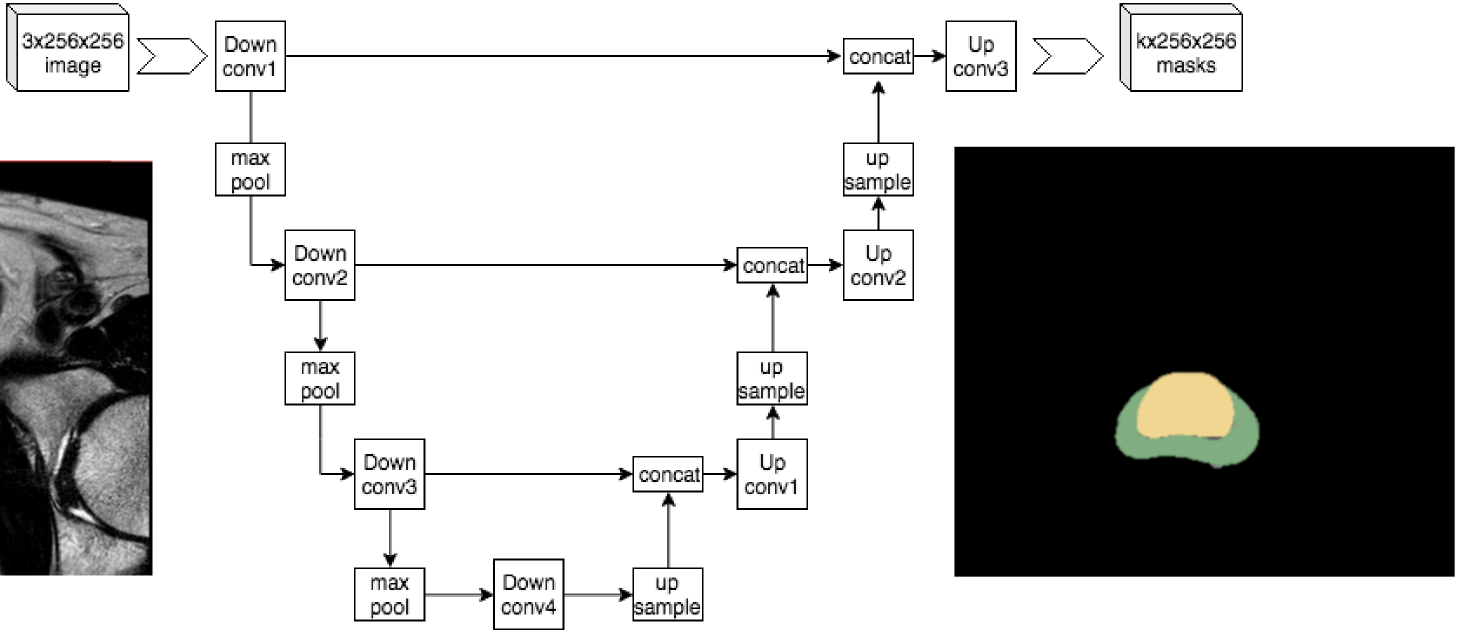


Confusion matrix

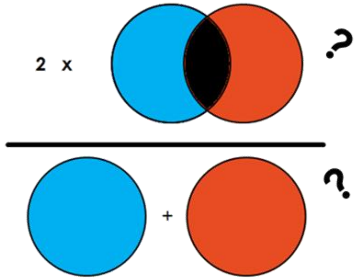
	Actual	
Predicted	TP	FP
	FN	TN

Deep Learning

Segmentation by CNN

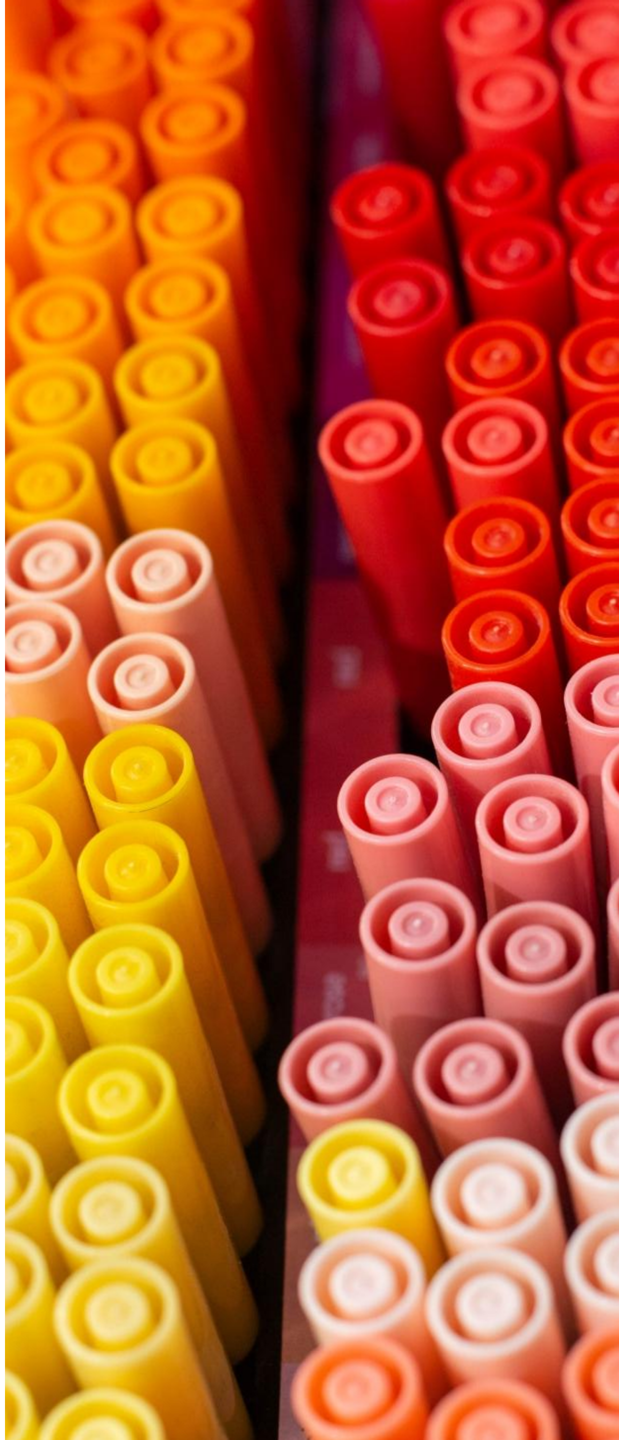


Rete neurale “U-net”



Dice Score

Contouring



Example: tumor detection and segmentation

- Patient data from public databases, IVO and prostate X
- Comparison against PIRADS 4+

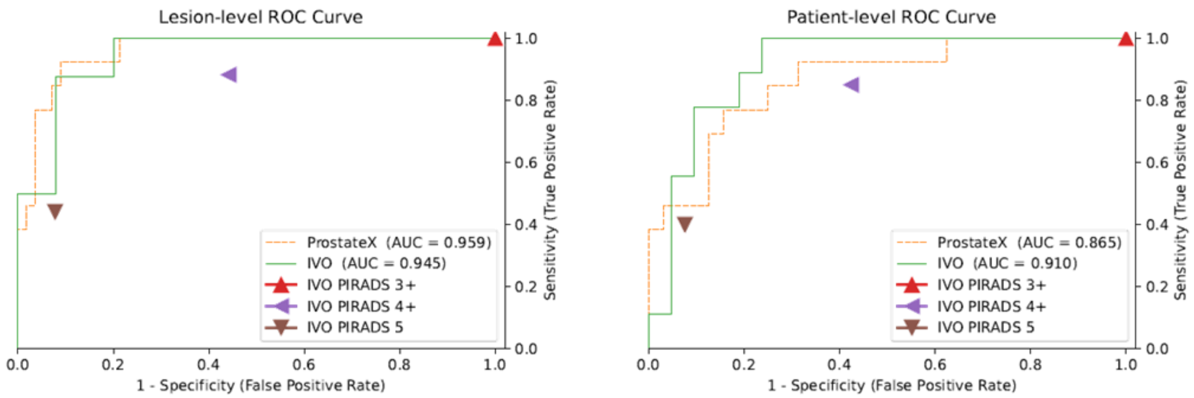


Figure 6: ROC curve of the model for significance criterion GGG$\geq$2, evaluated at the lesion level (left) and the patient level (right). For comparison, triangular marks represent the radiologist-assigned pre-biopsy PI-RADS.

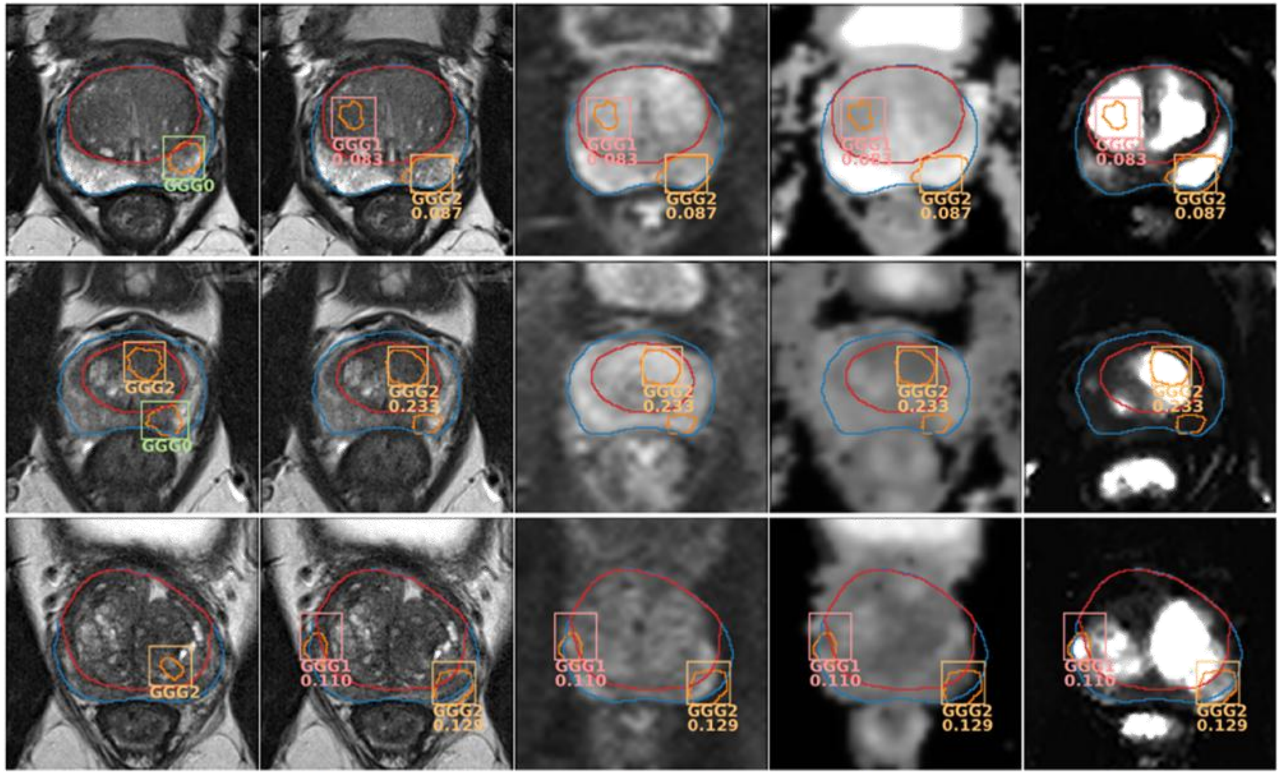
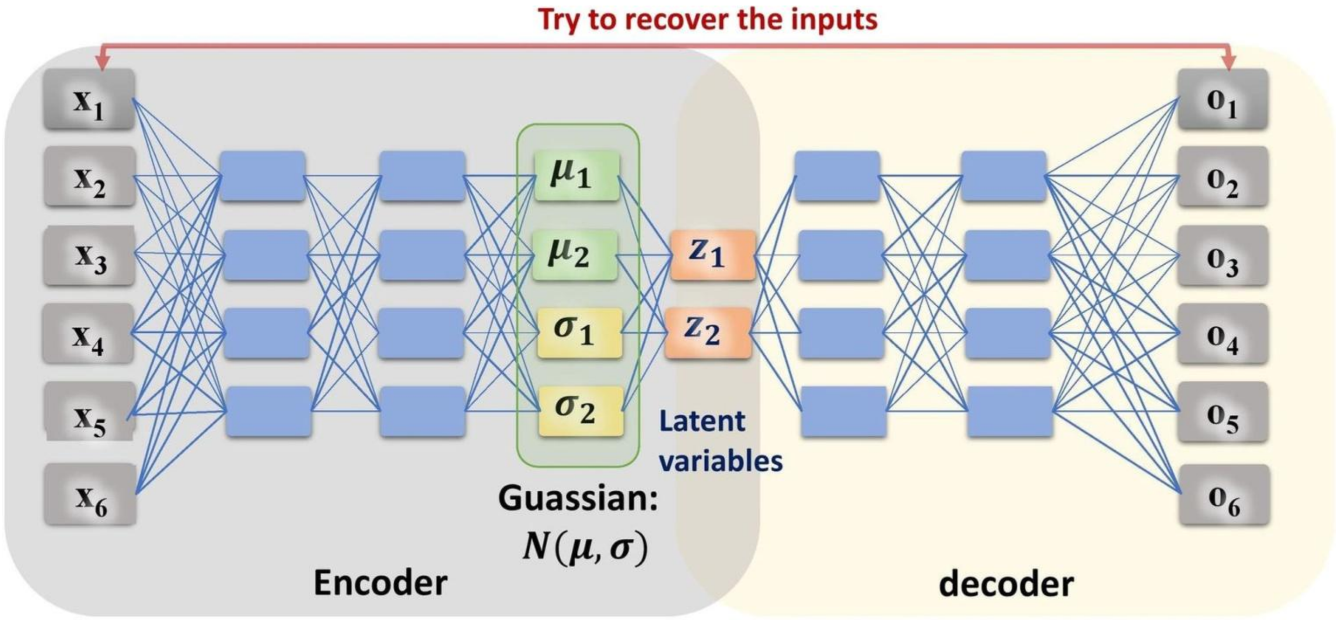


Figure 8: Output of the model evaluated on three ProstateX test patients. First image from the left shows the GT on the T2; the rest show the output predictions of the model on different sequences (from left to right: T2, b800, ADC, K^{trans}.

Pellicer-Valero et al, arXiv:2103.12650

CNN "Variational autoencoders"

- **Encoder**: neural network producing a representation of data
- **Decoder**: neural network trying to reconstruct the original image from the representation of data



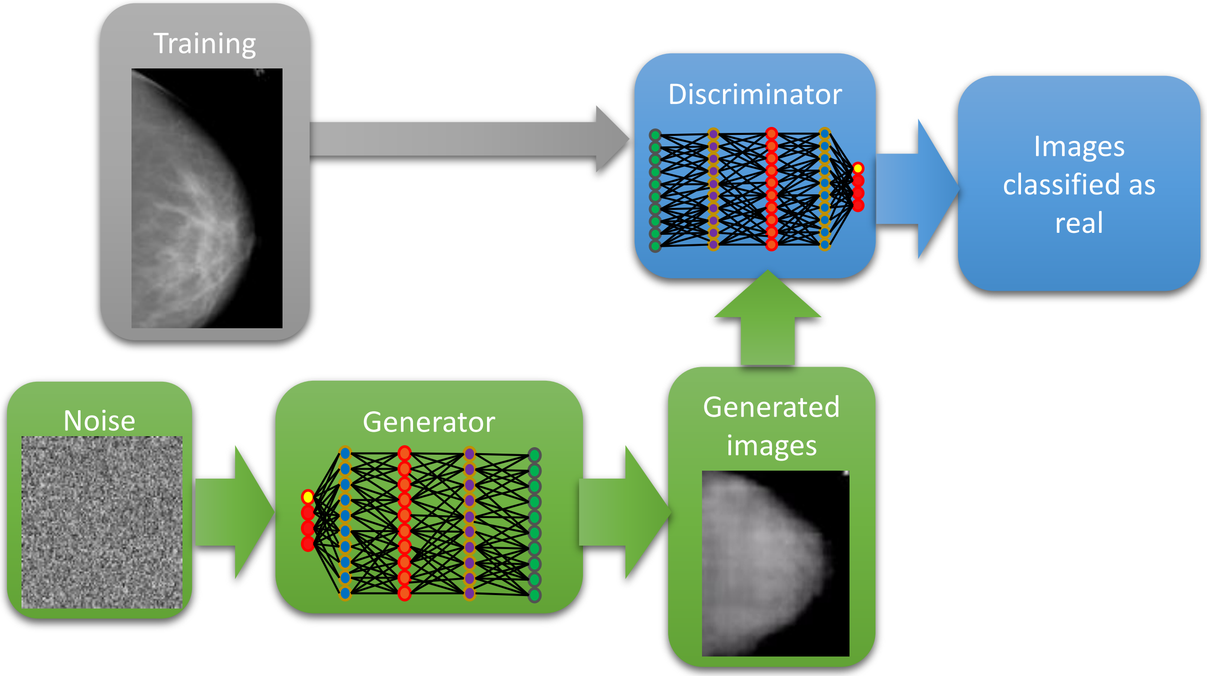
Cuiet al.: ML/DL for medical physicists , Medical Physics, 2020

Artifact correction

Superresolution

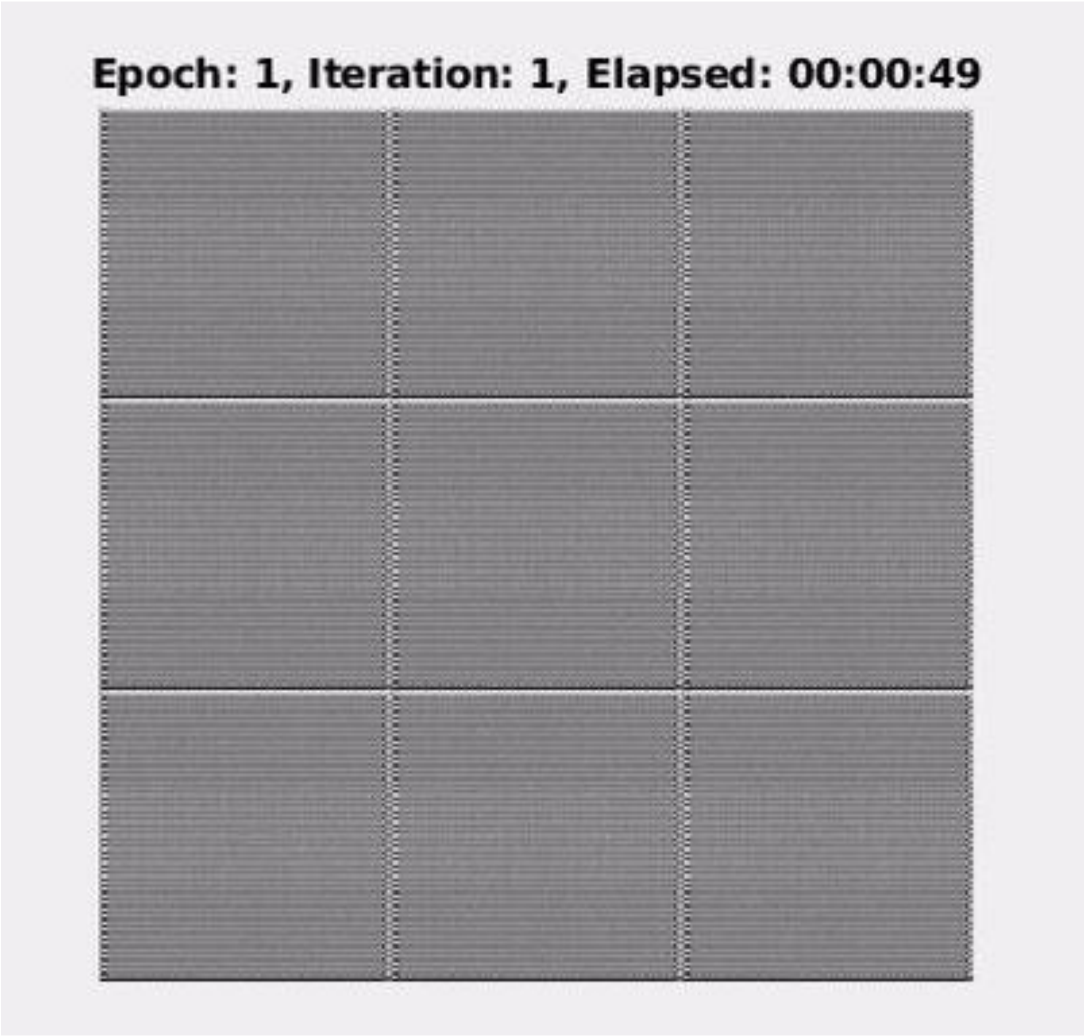
Reconstruction

Generative Adversarial Network



Cross-modality

Image registration



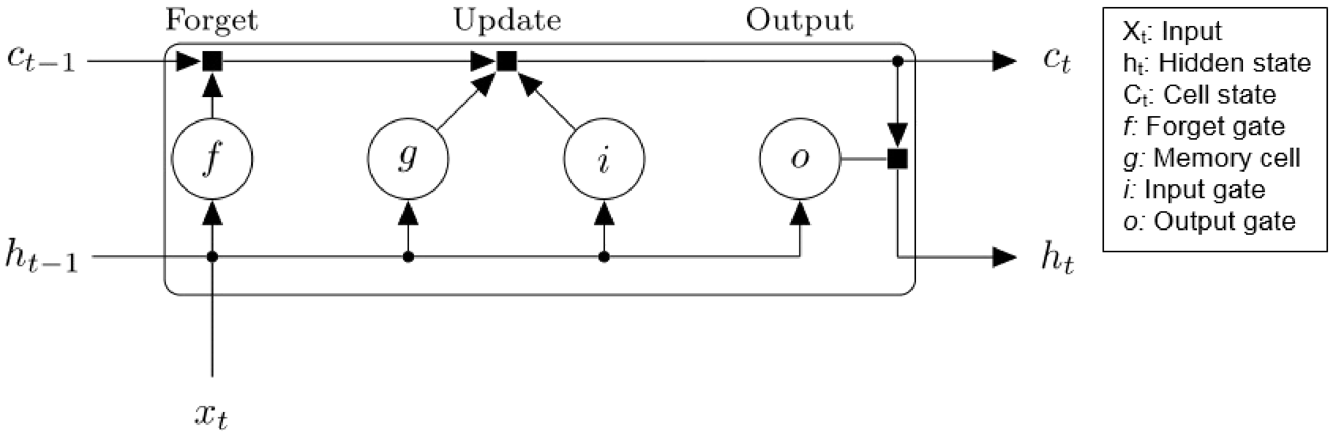




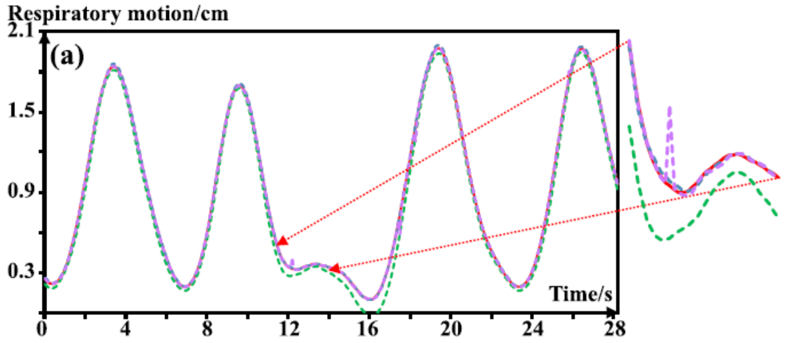


Signal analysis

LSTM networks



Prediction of respiratory signal



glucose

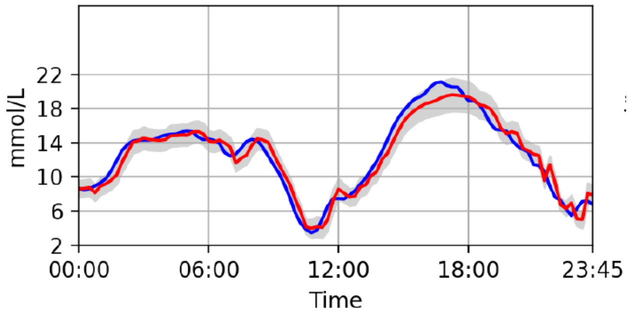


Figure 6.1: A plot of the 30 minute predictions of LSTM-2 (in red) versus the target values (in blue) for one of SP92's test days. The grey area around the prediction line shows the standard deviation of the output distribution.

Wang et al. DOI: 10.1109/ACCESS.2018.2869780

http://publications.lib.chalmers.se/records/fulltext/251317/251317.pdf

Availability of Open Source ML/DL tools

Machine Learning

Nome	Interfaccia
R CARET, GLMNET, E1071 packages	Python, C++
scikit learn	Python, R
Weka	
Open for Innovation KNIME	KNIME

Deep Learning

Nome	Open Source?	Interface
PyTorch	Y	Python, C++
K Keras	Y	Python, R
TensorFlow	Y	Python (Keras), C/C++, Java, JavaScript, R,[Jul ia, Swift

Distributions of python:

ANACONDA

WinPython

Web interface:

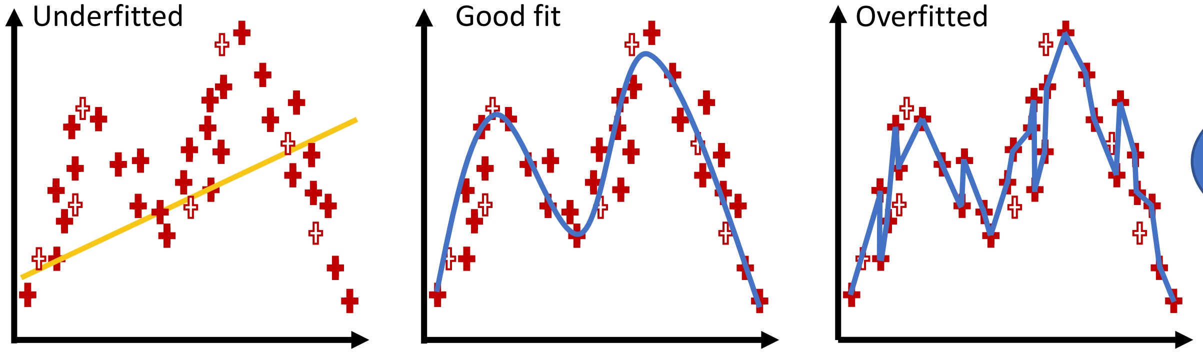
colab

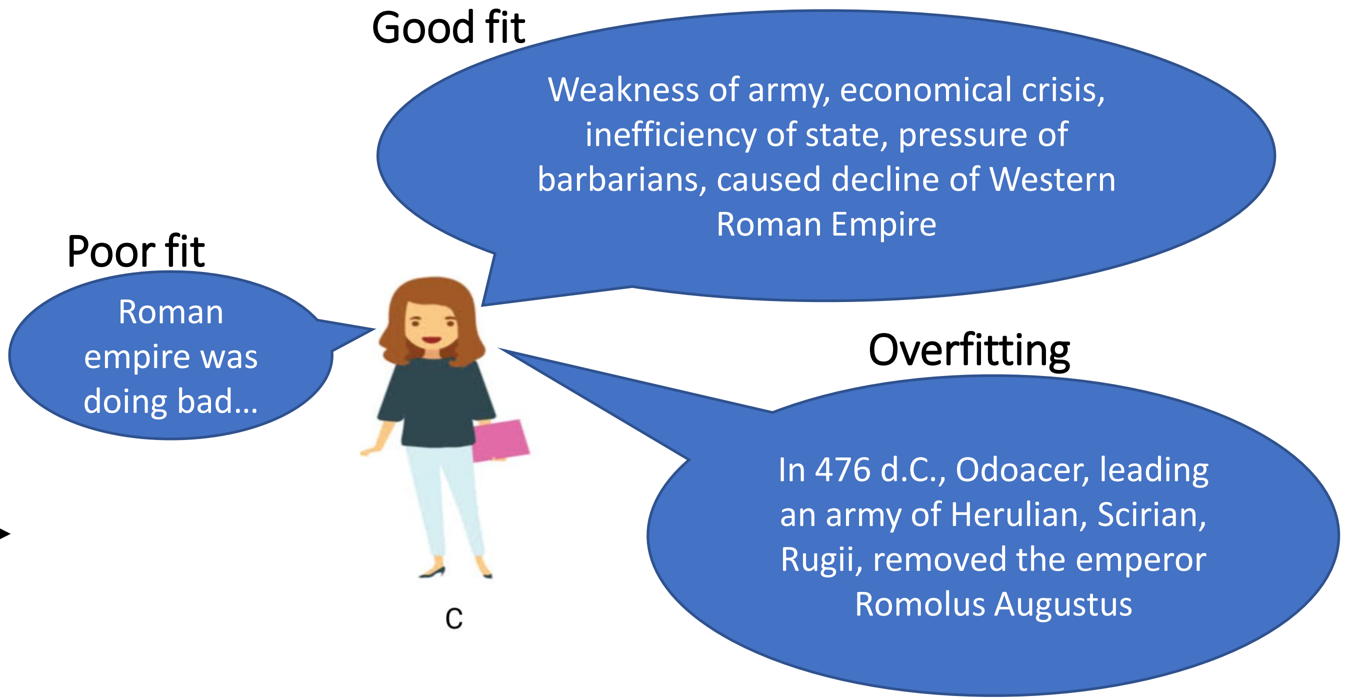
Data repositories:

CANCER IMAGING ARCHIVE

Overfitting

- ML algorithms are highly opportunistic: they learn what boosts their performance during training, without worrying for generalizability

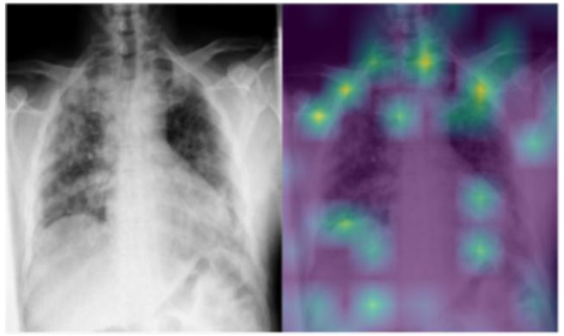




Covid diagnosis challenge

- A popular open-source dataset, COVIDx, was used to develop many deep learning tools to diagnose COVID from chest radiographies
- It was found that these models performed poorly on other datasets

COVID-19



Prediction probability: 0.938

Figure 5: Grad-CAM saliency map generated by DarkCovidNet COVIDx test data predictions. This is a correct prediction of COVID-19, with a prediction probability of 0.938

Table 1– DarkCovidNet test data performance metrics.

Test set	Precision	Recall	F1 score	Accuracy
COVIDx	0.87±0.00	0.80±0.00	0.82±0.00	0.88±0.00
External	0.44±0.00	0.43±0.00	0.41±0.00	0.43±0.00
LTHT	0.47±0.01	0.46±0.00	0.44±0.01	0.45±0.00

Table 2 - CoroNet test data performance metrics.

Test set	Precision	Recall	F1 score	Accuracy
COVIDx	0.81±0.05	0.90±0.01	0.84±0.05	0.88±0.03
External	0.18±0.07	0.34±0.02	0.19±0.03	0.35±0.01
LTHT	0.24±0.01	0.30±0.00	0.15±0.01	0.22±0.00

Table 3 – COVIDNet test data performance metrics.

Test set	Precision	Recall	F1 score	Accuracy
COVIDx	0.86±0.03	0.69±0.05	0.72±0.05	0.86±0.02
External	0.34±0.05	0.36±0.01	0.29±0.02	0.38±0.01
LTHT	0.43±0.01	0.39±0.00	0.37±0.01	0.44±0.03

Harkness et al, https://arxiv.org/ftp/arxiv/papers/2109/2109.08020.pdf

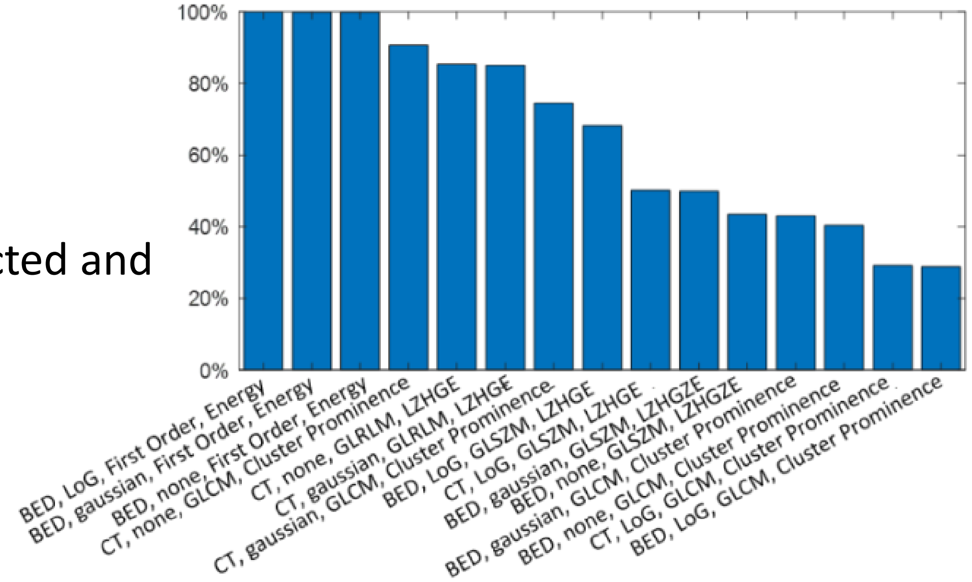
Covid diagnosis challenge

- the pneumonia class within the COVIDx contains other pathologies, including, pleural effusion, infiltration, consolidation, emphysema and masses.
- The non-COVID data included paediatric chest Xray images which were the only significant source of paediatric images within COVIDx
- the images had different resolutions: 1024x1024 and 299x299. Models resize images (smaller images up-sampled and larger images must be down-sampled). This risks generation of artefacts.
- A dataset had presence of disk-shaped markers in COVID-19 chest X-rays

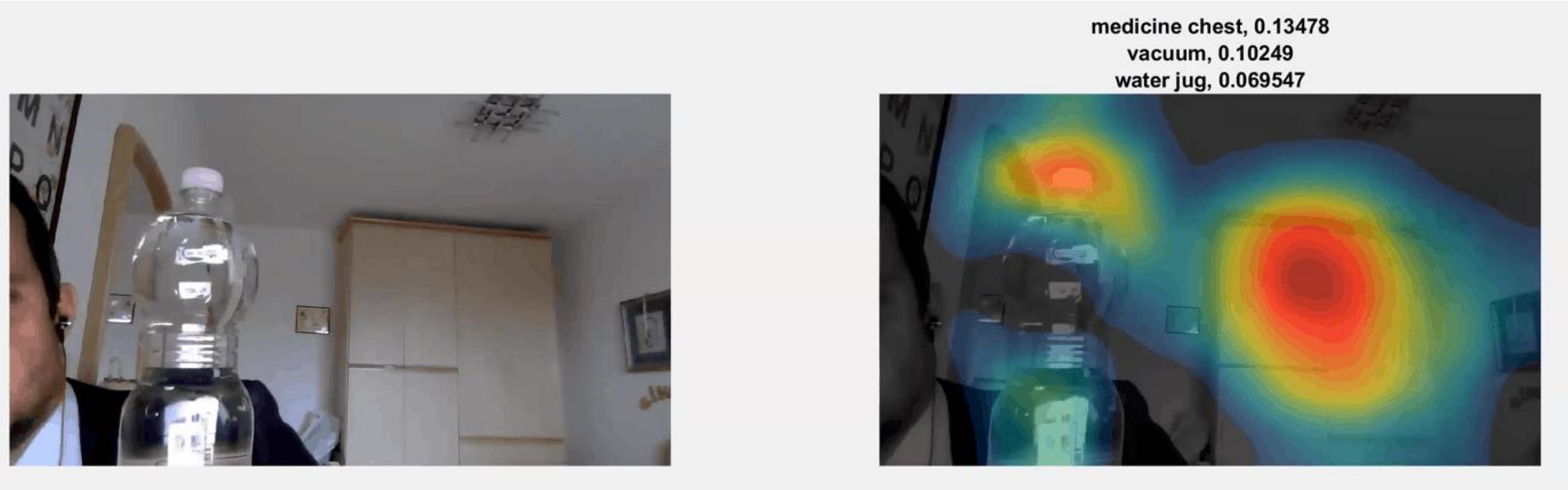
Black box

- AI methods are perceived as a “black box” which limits their use
- The clinician does not use a decision system when it’s not clear how it reaches its decision

Machine learning:
Look at the features selected and used by ML

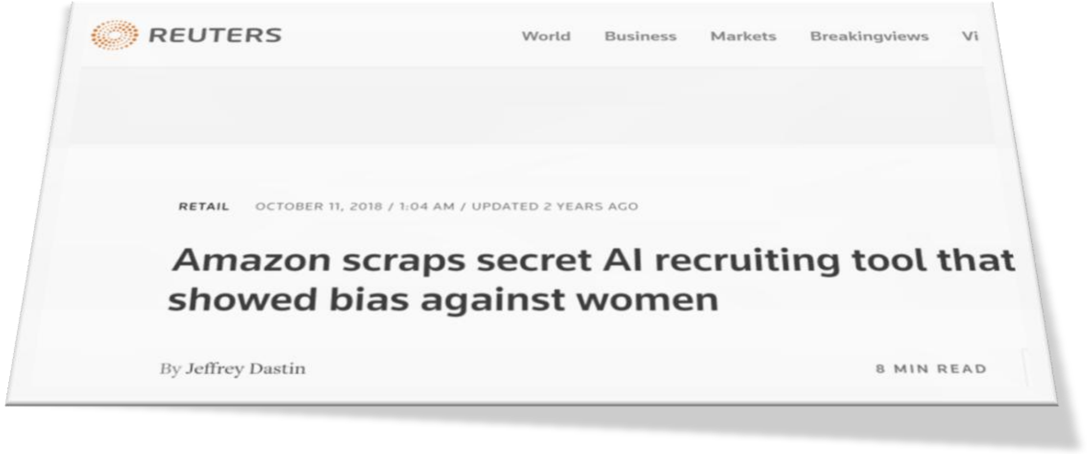


Activation maps for deep learning



Bias in dataset

- Bias in a dataset may include: confounding factors (e.g. comorbidities) but also dataset imbalance in factors such as gender, ethnic, social, environmental, or economic factors.
- A biased training dataset produces biased model (“garbage in, garbage out”)



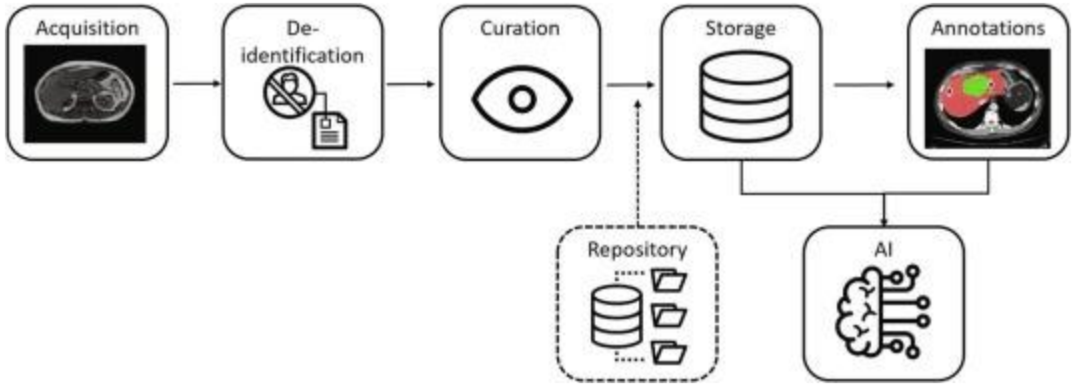
Data curation

- The MP can ensure that the images are acquired according to the protocol required for correct AI use free from relevant imaging artifacts, and correctly preprocessed and harmonized to reduce variability.
- MPs can significantly aid in the management of aggregate data from multiple modalities (PET, CT, radiography, MRI, ultrasound, daily CBCT, hybrid imaging, such as PET/CT and PET/MRI, 3D/4D and image time series, dose from RT etc.)
- MP should be involved in the development of metrics to assess the quality and completeness of data, methods to curate data, and QA programs of data archives

Physica Medica 83 (2021) 25–37

Data preparation for artificial intelligence in medical imaging: A comprehensive guide to open-access platforms and tools

Oliver Diaz [a,*], Kaisar Kushibar [a], Richard Osuala [a], Akis Linardos [a], Lidia Garrucho [a], Laura Igual [a], Petia Radeva [a], Fred Prior [b], Polyxeni Gkontra [a], Karim Lekadir [a]



Data preparation pipeline prior developing and/or evaluation of AI solution.

Why physicists in AI?

- MP knows the basic physical mechanisms at the root of signal change and image contrast

Ehsan Samei, Thomas M. Grist, Physica Medica 64(1):319-322

- MPs are also trained in mathematics and can understand the principles of ML and DL better than other healthcare professionals

M. Avanzo

- “a change of focus from equipment to operation; from quality to consistency of quality, from testing performance to estimating outcome – and doing this with objective, standardisable and quantitative methods”

Editorial

The European Federation of Organisations for Medical Physics (EFOMP) White Paper: Big data and deep learning in medical imaging and in relation to medical physics profession

ABSTRACT

Mika Kortesniemi , Virginia Tsapaki, Annalisa Trianni, Paolo Russo, Ad Maas, , Hans-Erik Källman , Marco Brambilla, John Damilakis

Regulations

- The MP involved in research will be required to apply the statements and recommendations released by governmental agencies regarding privacy, security, secure access to health information, de-identification of sensitive data, and obtaining informed consent
- General data protection regulation (GDPR) in Europe, HIPAA in the US
- Understand medical devices regulations regarding AI (CE marking, FDA etc.)

Quality assurance of AI

International Journal of Medical Informatics 102 (2017) 71–79

Decaying relevance of clinical data towards future decisions in data-driven inpatient clinical order sets

Jonathan H. Chen[a,*], Muthuraman Alagappan[d], Mary K. Goldstein[b,c], Steven M. Asch[a,f], Russ B. Altman[a,e]

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[b] Geriatrics Research Education and Clinical Center, Veteran Affairs Palo Alto Health Care System, Palo Alto, CA, USA
[c] Primary Care and Outcomes Research (PCOR), Stanford University, Stanford, CA, USA
[d] Internal Medicine Residency Program, Beth Israel Deaconess Medical Center, Boston, MA USA
[e] Departments of Bioengineering and Genetics, Stanford University, Stanford, CA, USA
[f] Center for Innovation to Implementation (Ci2i), Veteran Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Training with more longitudinal data (2009–2012) was no better than using only the most recent (2012)data, unless applying a decaying weighting scheme with a "half-life" of data relevance about 4 months.

Table 1. Summary of stages in the adoption of a AI-based Clinical Decision Support System.

Stages	Objective
Selection	Pick most appropriate CDSS in terms of match with target use case and clinical workflow, five "rights," performance, and user acceptability
Acceptance testing	Test that CDSS satisfies security, privacy, and safety requirements applicable to medical devices, covering typical error scenarios, exceptions, and unforeseen conditions
Commissioning	Prepare the CDSS for optimized use in the clinic (including potential customization) and test its safety and performance within the local context
Implementation	Roll out the CDSS and transition from the old workflow to the new after training the end users and managing their expectations
Quality assurance	Ensure that the quality of the CDSS remains fit for purpose by monitoring internal and external updates as well as context drift

Artificial intelligence-based clinical decision support in modern medical physics: Selection, acceptance, commissioning, and quality assurance

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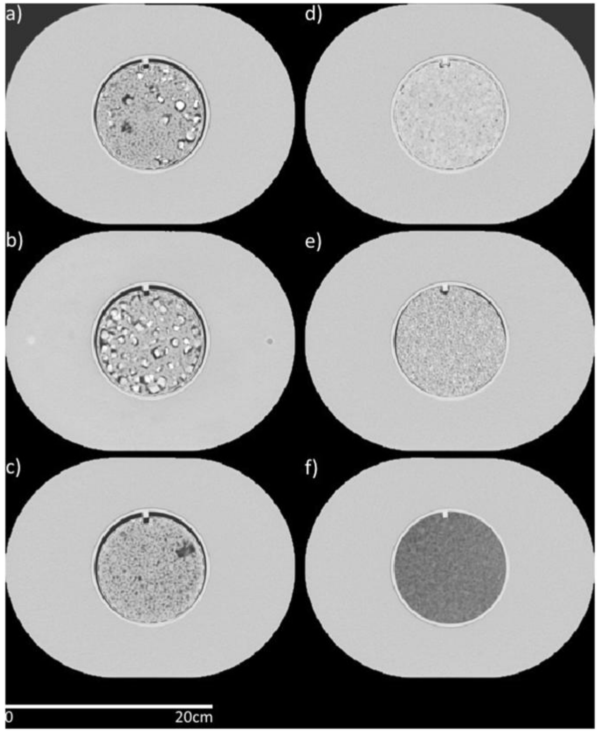
Med. Phys. 47 (5), May 2020 0094-2405/2020/47(5)/e228/8

Quality assurance of AI

Phantoms



Ground truth images

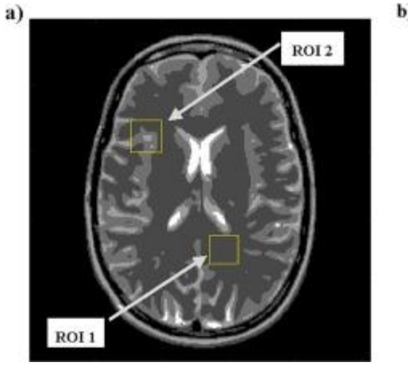
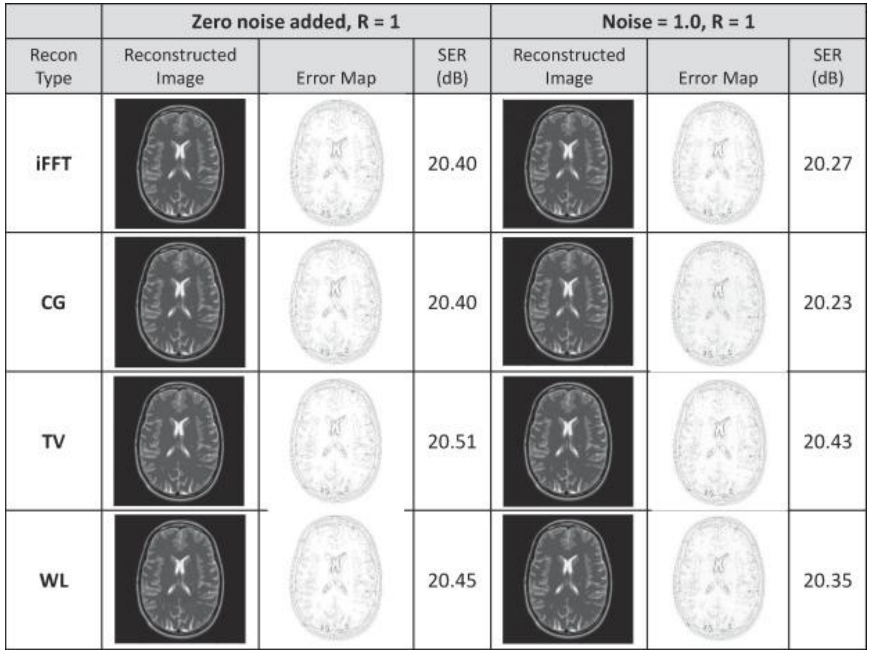


Fig. 1. (a) Digital ground truth phantom used as input to the MRI simulator.



	Zero noise added, R = 1			Noise = 1.0, R = 1		
Recon Type	Reconstructed Image	Error Map	SER (dB)	Reconstructed Image	Error Map	SER (dB)
iFFT			20.40			20.27
CG			20.40			20.23
TV			20.51			20.43
WL			20.45			20.35

Physica Medica Volume 50, June 2018, Pages 26-36

https://www.nature.com/articles/s41598-018-31509-z

Quality assurance in AI

- ”a <u>set of past cases</u>, which includes <u>difficult and rare cases</u> along with a <u>representative sample of the local case population</u> could be retrospectively tested if a database with past cases exists.”
- At the same time, a “<u>repeated local validation” cohort</u> should be assembled from time to time or preferably continuously to critically reexamine the tests done during the commissioning stage.
- The repetition may help to ensure that the CDSS remains clinically valid”

<u>Med Phys.</u> 2020 May; 47(5): e228–e235

Safety/Risk Management

- The responsibility to prevent errors due to use of AI falls to humans.
- Automation errors:
  - omission when humans do not notice the failure of an AI tool and
  - commission when an action is performed following wrong AI's decision when there is evidence
- One of the key activities of the MP is patient safety management that is the evaluation of medical devices and procedures to guarantee the safety of patients.
- MPs are trained to prevent and analyze

accidents by using risk assessment
  - failure modes and effects analysis (FMEA),
  - incident reporting programs

Physica Medica 48 (2018) 162–168

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journal homepage: www.elsevier.com/locate/ejmp

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EFOMP Policy Statement

EFOMP policy statement 16: The role and competences of medical physicists and medical physics experts under 2013/59/EURATOM

Carmel J. Caruana[1], Virginia Tsapaki, John Damilakis, Marco Brambilla, Guadalupe Martín Martín, Asen Dimov, Hilde Bosmans, Gillian Egan, Klaus Bacher, Brendan McClean

EFOMP, United Kingdom

Multidisciplinary team

- «A fundamental role of the medical physicist is team member — working together with physicians, technologists, nurses, therapists, engineers, and even patients in the effective, efficient, and safe delivery of health care»
- “In a similar vein, another key role of the medical physicist is education and training, not only of junior level and medical physicists in training but also of other health care professionals including residents and fellows.”

Artificial intelligence will soon change the landscape of medical physics research and practice

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[https://doi.org/10.1002/mp.12831]

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THANK
YOU