Artificial Intelligence in Medicine

Mon Dec 27, 2022: 10:15-11:00 and 11:15-12:00

Deep Learning in Medical Image Processing

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האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

Outline

1. Motivation: Medical Image Processing (MIP)
2. Machine Learning in MIP - *very briefly*
3. Deep Learning classification methods in MIP
4. State of the art and conclusions

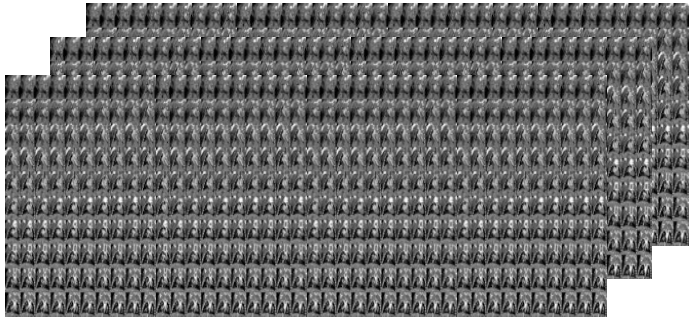
1. Motivation: Medical Image Processing (MIP)

Medical imaging plays a central role in medicine!

- <u>30%</u> of all patients that reach a hospital get an image
- Over <u>**2 billion/year**</u> worldwide!

  → 750M CT; 250M MRI; growth of **+10% per year**.
- **Imaging devices** are now widespread worldwide.

  → They get better (and larger) all the time.
- Manpower shortage: **+2% per year**, junior radiologists



BUT…

- ***Who is going to look at them?***
- ***For what purpose? For how long?***
- ***What information will be extracted?***
- ***What about the population at large?***

Joskowicz, 2022

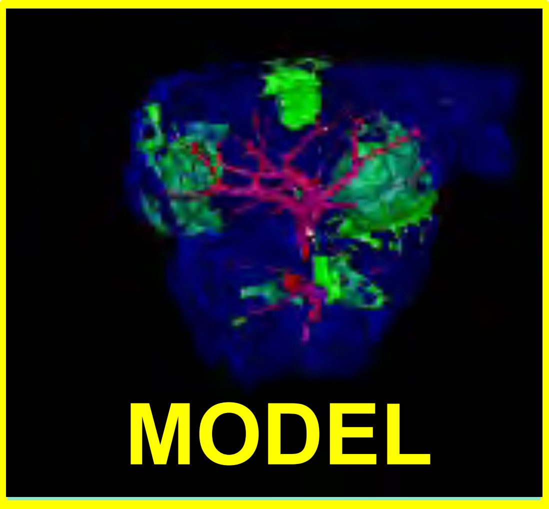
Models in the patient treatment cycle

Diagnosis

CAD mammography
Virtual colonoscopy

Planning

Neurosurgery – biopsy trajectory
Orthopaedics – spine fixation



Delivery

Interventional Radiology
Navigation
Robotics

Evaluation

Tumor follow-up
Implant location

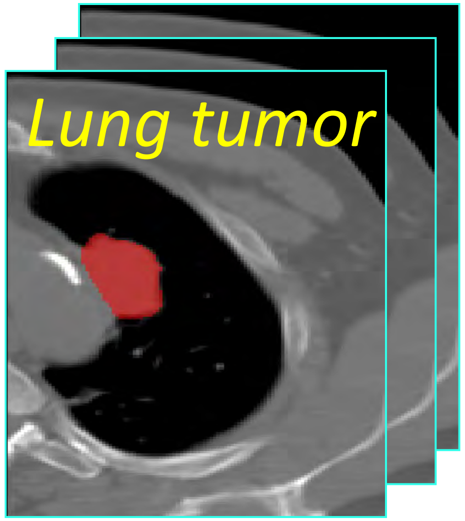
Training
Learning
Data mining

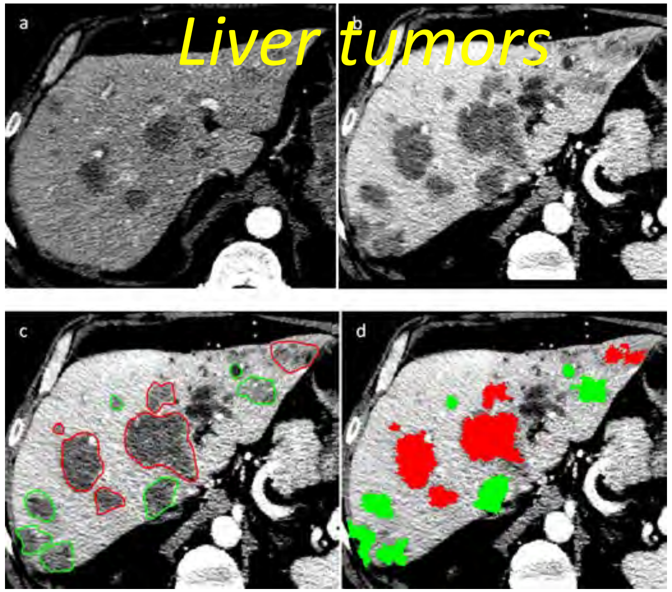
Classification in Medical Image Processing

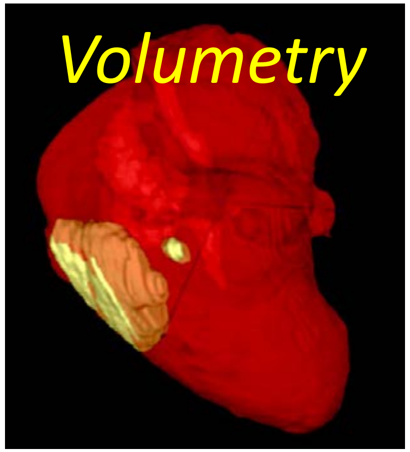
Determine to which class a scan/set of pixels/voxels belongs to

TECHNICAL → CLINICAL

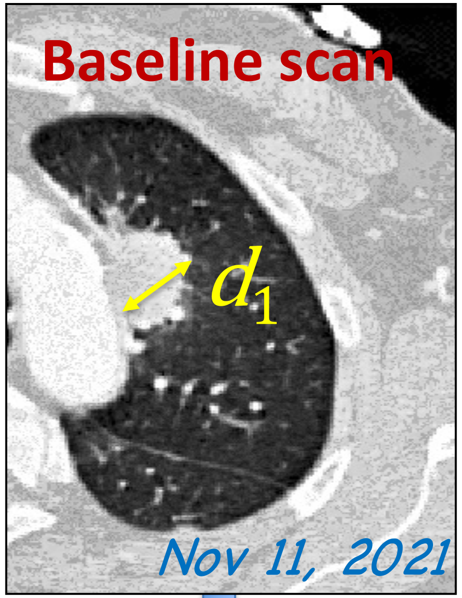
Classification → *Detection*, *Identification*, *Segmentation*, *Grading* → *Volumetry*, *Incidental findings*, *Follow-up*, *Triage, ranking*

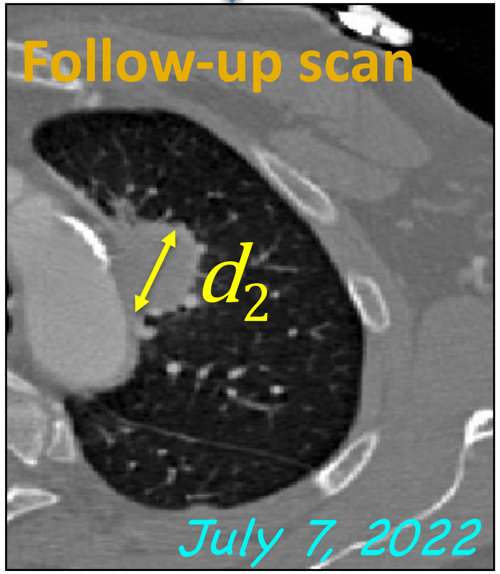






Classification: example





Clinical task: tumor follow-up in chest CT scan

FEATURES

Tumor diameter: d_1, d_2

Diameter change: $\Delta d\,\%$

RELATION

$$\Delta d = \left(\frac{d_2 - d_1}{d_1}\right) \text{x}\, 100\%$$

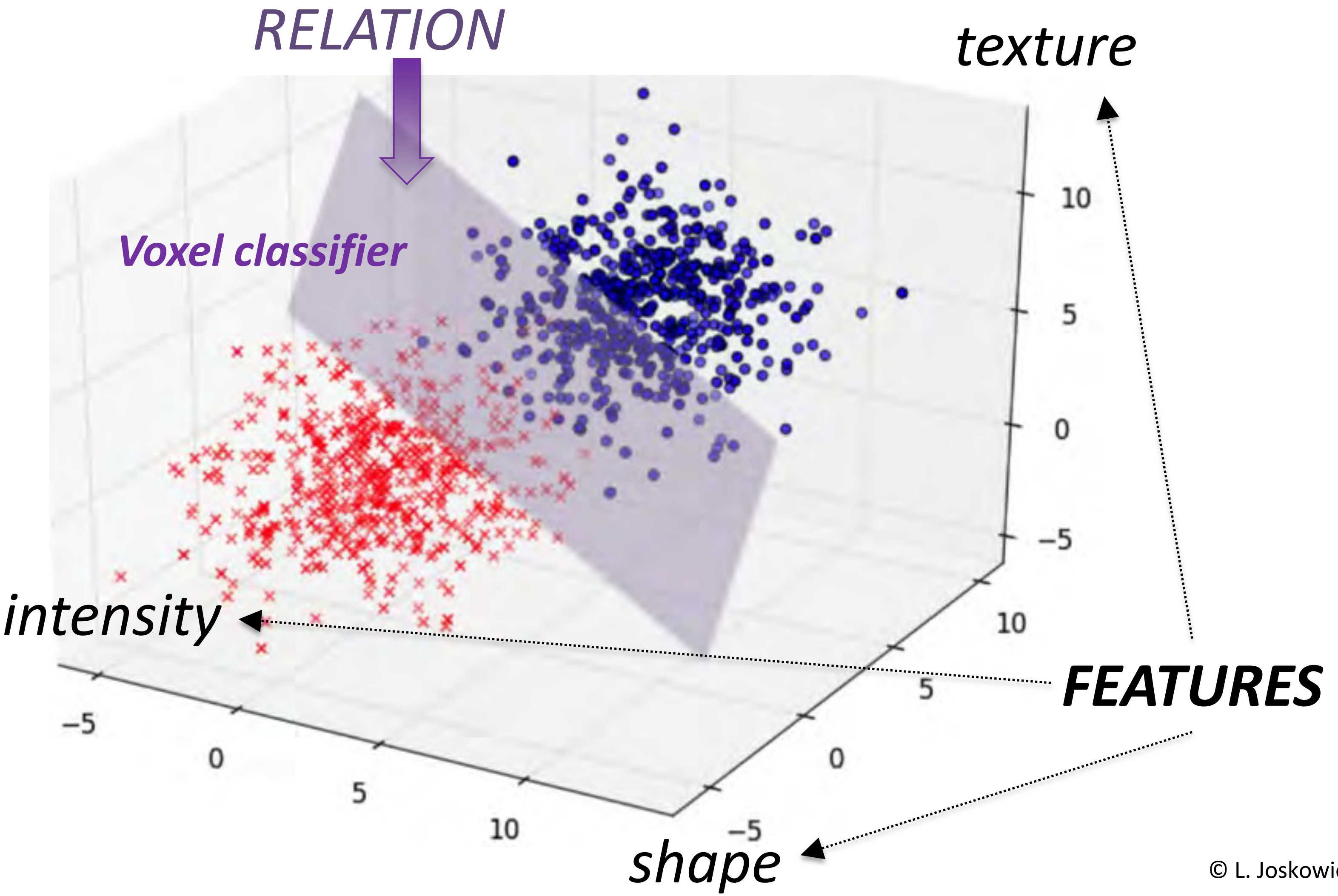
CLASSES

Progression	$\Delta d \geq +20\%$
Regression	$\Delta d \leq -30\%$
Stable	$-30\% \leq \Delta d \leq +20\%$

Classification: features space

Clinical task: tumor volume by segmentation

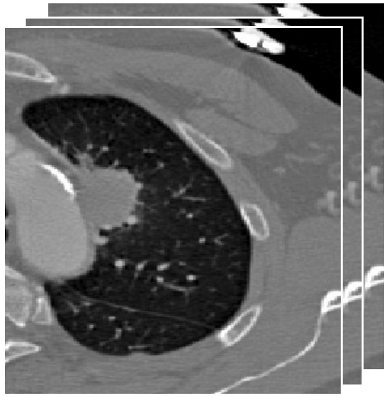
Voxel classification



Models in computational radiology

Model = features + relations between features

Task: tumor segmentation by voxel classification



Program

```
void saveToFile(void *data, size_t nBytes, std::string fileName) {
  FILE * fp = fopen(fileName.c_str(), "wb");
  if (!fp) {
    LOG_ERR("Can't access " << fileName);
  }

  size_t n = fwrite(data, 1, nBytes, fp);
  if (n != nBytes) {
    LOG_ERR("Error saving vector to " << fileName);
  }
  fclose(fp);
}
```

Manual modeling

Features
intensity, texture shape, location

MANUAL

Relations
Boundary differences, …

MANUAL

Machine learning

Features
intensity, texture shape, location

MANUAL

Relations
Derived by regression, SVM,…

AUTOM

Deep learning

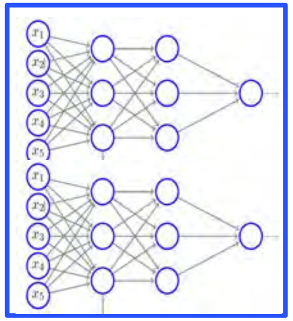
Features
Derived from data Implicit

AUTOM

Relations
Derived from data Implicit

AUTOM

Network



Models in Medical Image Processing

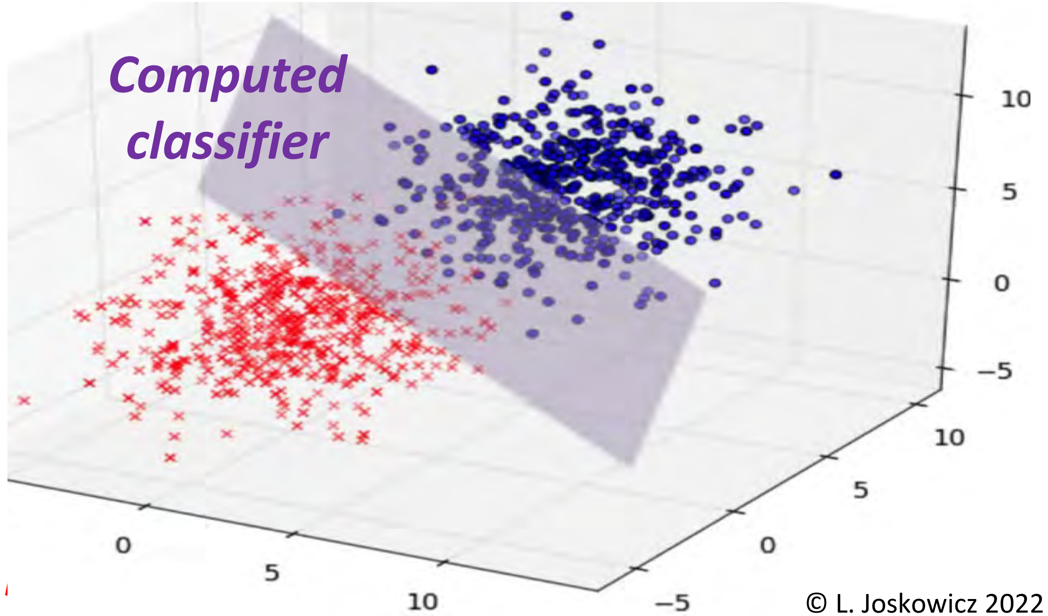
Manual modeling	*Machine learning*	*Deep learning*
Mostly knowledge Limited data	Some knowledge Some data	Mostly data Limited expert knowledge

The NO FREE LUNCH axiom

- *Each approach requires effort and data*
- *The type of effort and size of data is different*
- *The effort by engineers and clinicians is different*

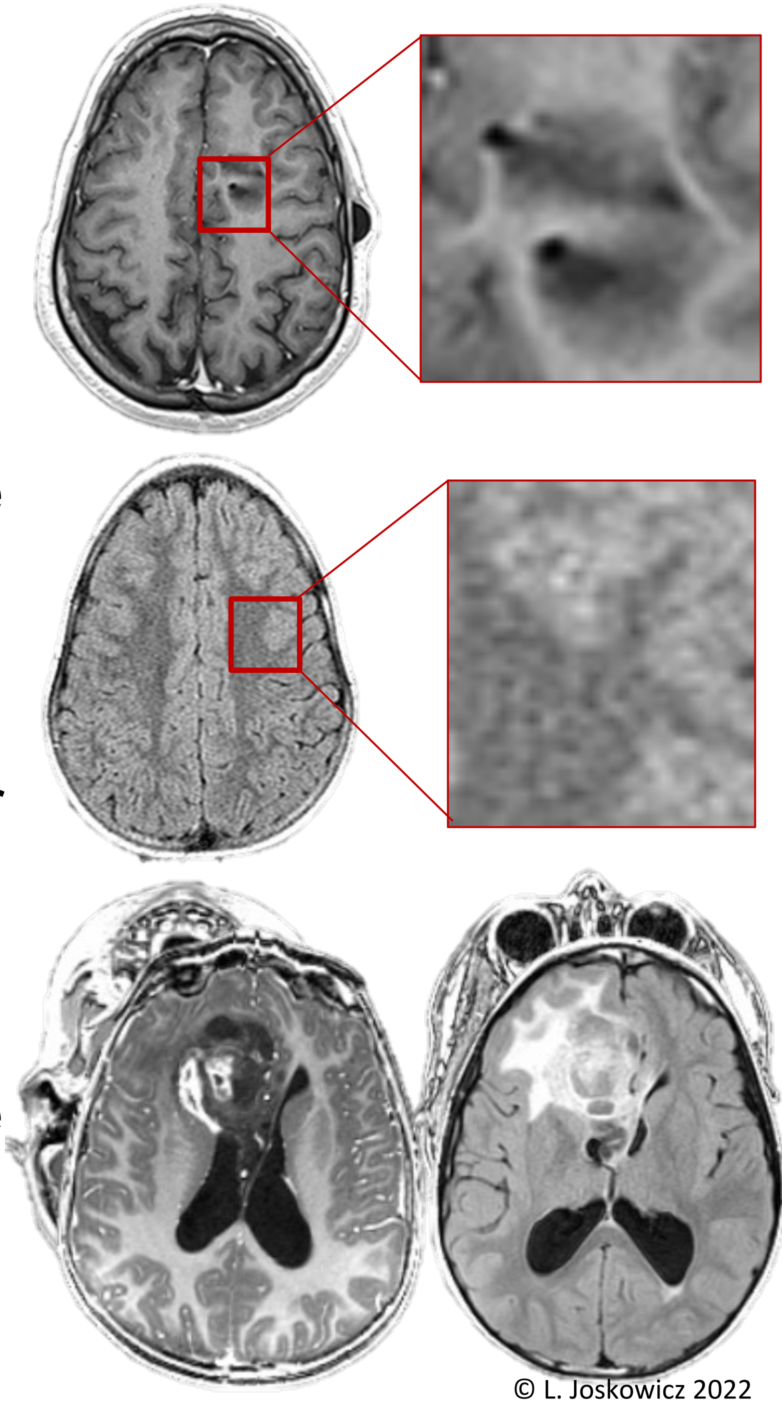
2. Machine learning methods in MIP

1. Define the regions of interest (ROI) on the image
2. Define the features to be computed for each ROI (10-50)
3. Define a way to compute feature values in each ROI to obtain a *k*-dimensional vector
4. Choose a classifier to classify the resulting *k*–dimensional vectors. Common classifiers are:
   – Regression
   – Single Value Decomposition
   – k Nearest Neighbors
   – Decision trees
   – …



Typical requirements

- Sample size: ~50 cases per label
- Data set homogeneity: sequence type, resolution, etc.
- Exclusion criteria: scans of patients with multiple pathologies from different origins
- Good data quality
- Clear criteria for segmentation of the target area for classification
- Manual labeling of cases relative to a gold standard
- Prior knowledge regarding important characteristics of the target area for classification - not mandatory but useful!
- Adequate computational power



Machine learning: classification features

Common features

Sum average:

$$sum\ average = \sum_{i=2}^{2N_g}\left[i\mathbf{P}_{x+y}(i)\right]$$

Sum entropy:

$$sum\ entropy = -\sum_{i=2}^{2N_g}\mathbf{P}_{x+y}(i)\log_2\left[\mathbf{P}_{x+y}(i)\right]$$

Sum variance:

$$sum\ variance = \sum_{i=2}^{2N_g}(i-SE)^2\mathbf{P}_{x+y}(i)$$

Variance:

$$variance = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}(i-\mu)^2\mathbf{P}(i,j)$$

Long Run Emphasis (LRE)

$$LRE = \frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} j^2 p(i,j|\theta)}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} p(i,j|\theta)}$$

Gray Level Non-Uniformity (GLN)

$$GLN = \frac{\sum_{i=1}^{N_g}\left[\sum_{j=1}^{N_r} p(i,j|\theta)\right]^2}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} p(i,j|\theta)}$$

Run Length Non-Uniformity (RLN)

$$RLN = \frac{\sum_{j=1}^{N_r}\left[\sum_{i=1}^{N_g} p(i,j|\theta)\right]^2}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} p(i,j|\theta)}$$

Energy:

$$energy = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\left[\mathbf{P}(i,j)\right]^2$$

Entropy (*H*):

$$entropy = -\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\mathbf{P}(i,j)\log_2\left[\mathbf{P}(i,j)\right]$$

Homogeneity 1:

$$homogeneity\ 1 = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{\mathbf{P}(i,j)}{1+|i-j|}$$

Homogeneity 2:

$$homogeneity\ 2 = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{\mathbf{P}(i,j)}{1+|i-j|^2}$$

Informational measure of correlation 1 (IMC1):

$$IMC1 = \frac{HXY - HXY1}{\max\{HX, HY\}}$$

Autocorrelation:

$$autocorrelation = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g} ij\mathbf{P}(i,j)$$

Cluster Prominence:

$$cluster\ prominence = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\left[i+j-\mu_x(i)-\mu_y(j)\right]^4\mathbf{P}(i,j)$$

Cluster Shade:

$$cluster\ shade = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\left[i+j-\mu_x(i)-\mu_y(j)\right]^3\mathbf{P}(i,j)$$

Cluster Tendency:

$$cluster\ tendency = \sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\left[i+j-\mu_x(i)-\mu_y(j)\right]^2\mathbf{P}(i,j)$$

Contrast:

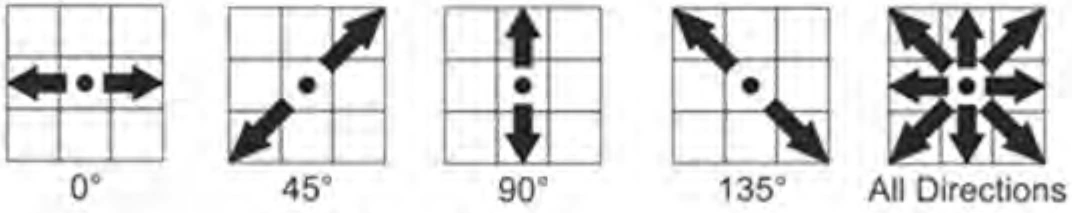
$$contrast = \sum\sum|i-j|^2\mathbf{P}(i,j)$$

	1	2	3	4	5	6	7	8
1	66	16	17	8	4	0	0	0
2	16	0	9	7	3	2	0	0
3	17	9	2	9	5	2	1	0
4	8	7	9	12	4	4	2	0
5	4	3	5	4	4	6	2	1
6	0	2	2	4	6	2	5	2
7	0	0	1	2	2	5	2	3
8	0	0	0	0	1	2	3	0

Σ=312

	1	2	3	4	5	6	7	8
1	0.21	0.05	0.05	0.03	0.01	0.00	0.00	0.00
2	0.05	0.00	0.03	0.02	0.01	0.01	0.00	0.00
3	0.05	0.03	0.01	0.03	0.02	0.01	0.00	0.00
4	0.03	0.02	0.03	0.04	0.01	0.01	0.01	0.00
5	0.01	0.01	0.02	0.01	0.01	0.02	0.01	0.00
6	0.00	0.01	0.01	0.01	0.02	0.01	0.02	0.01
7	0.00	0.00	0.00	0.01	0.01	0.02	0.01	0.01
8	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.00

Energy:	0.067
Contrast:	2.493
Homogeneity:	0.785
Entropy:	1.444
Cluster Tend.	39.231

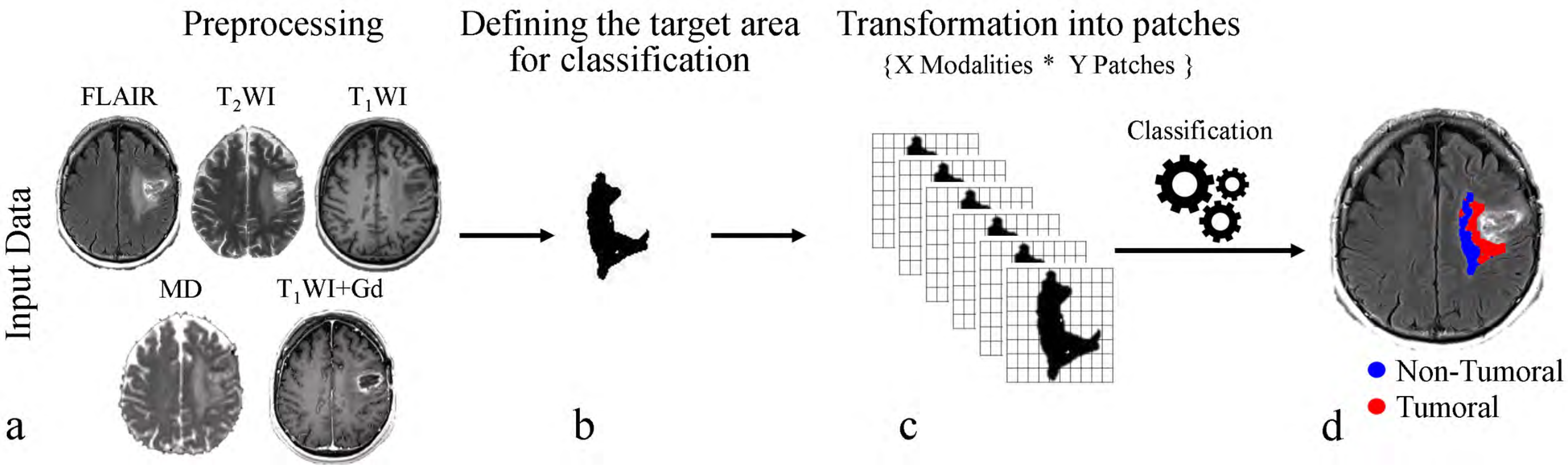


Courtesy of Dr. Artzi Moran, Sagol Center for Brain Research, Tel Aviv U.

Example: classification of tumor components

Differentiation between vasogenic edema and infiltrative tumor in patients with high grade gliomas using texture patch based analysis

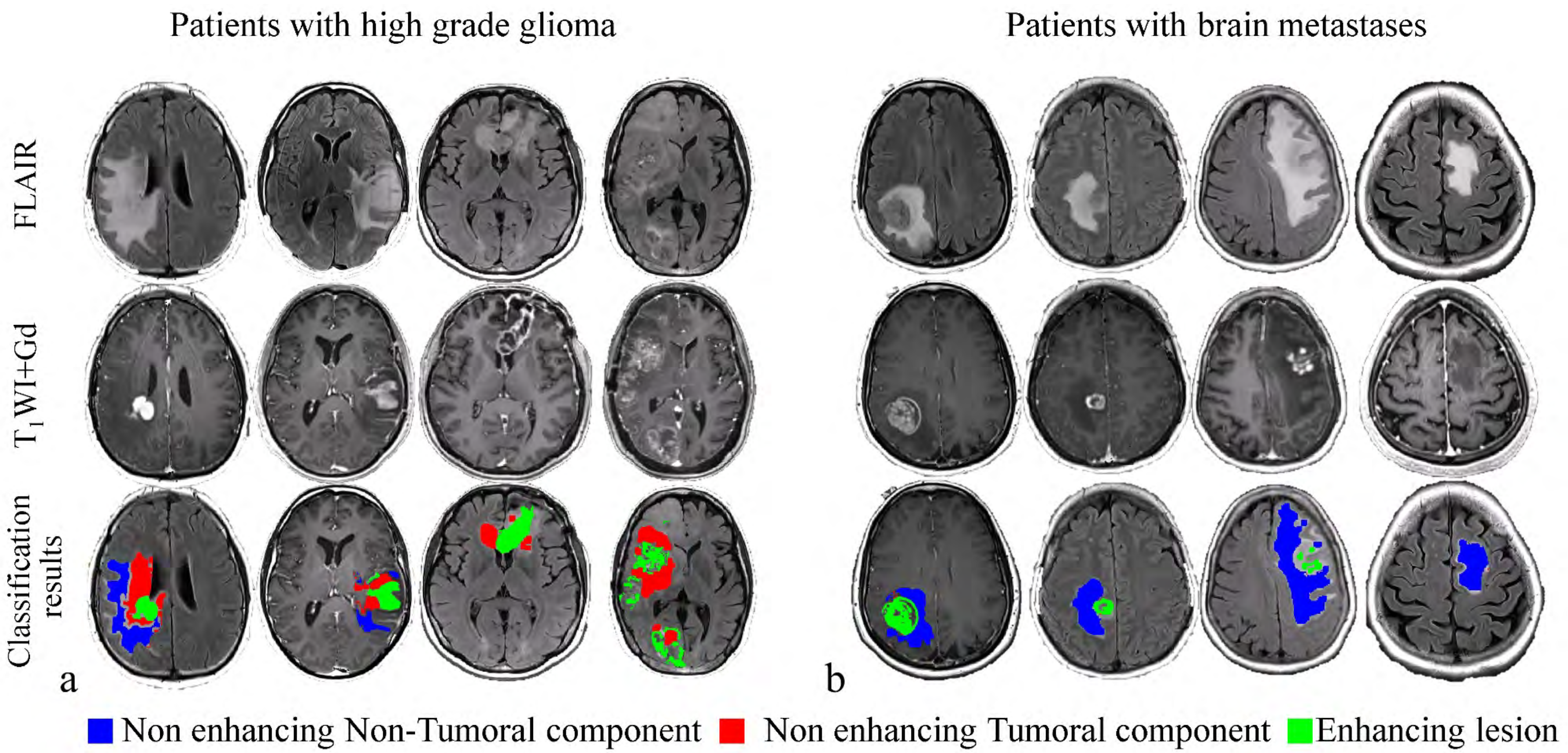
DATA ANALYSIS



Artzi et al. Journal of Magnetic Resonance Imaging. 2017

Example: classification of tumor components

*Differentiation between **vasogenic edema** and **infiltrative tumor** in patients with high grade gliomas using a texture patch based analysis*



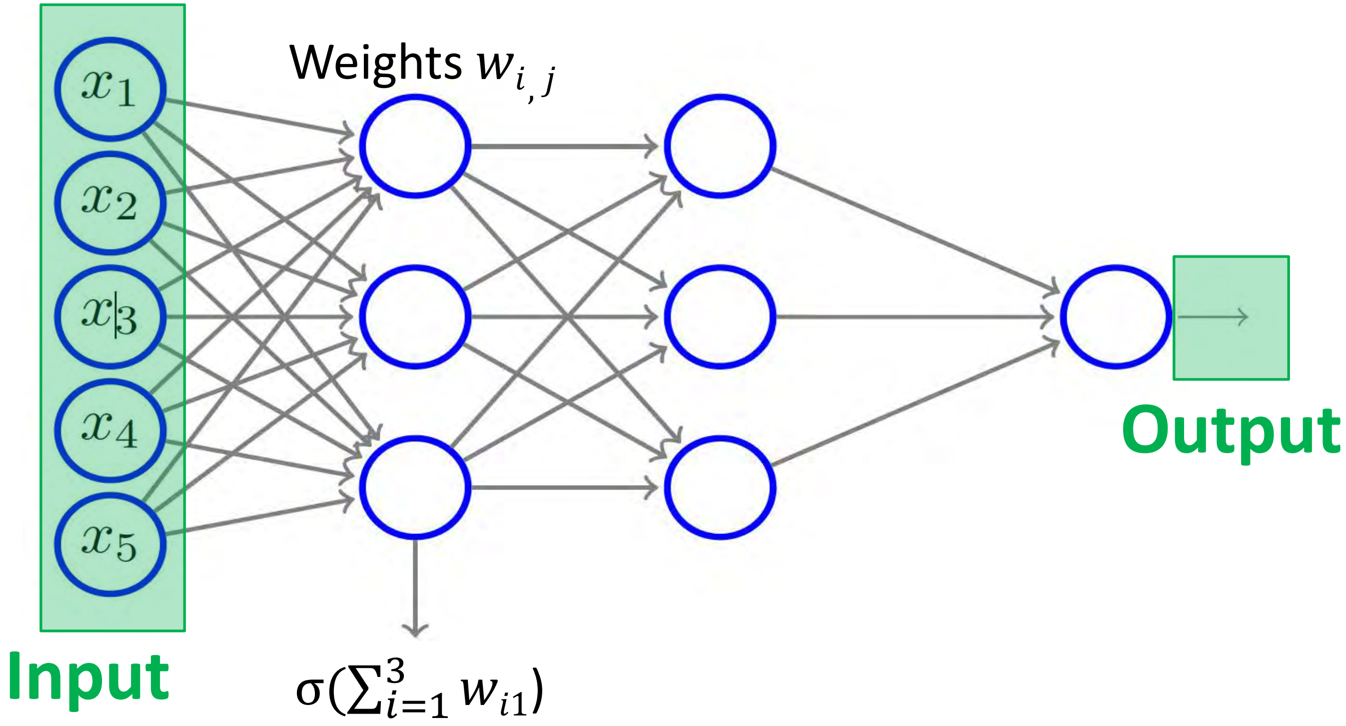
Artzi et al. *Journal of Magnetic Resonance Imaging*. 2017

3. Deep learning methods in MIP

- Useful for tasks for which it is **hard to find an algorithm** but for which we can **collect examples** of the input-output of the desired results
- Classification is based on a **Neural Network**
- **Training data** is required as in machine learning
- **Layers**: input and output layers, hidden layers
- Many layers → deep neural network → deep learning

Neural networks

Deep learning = set the weights of an **artificial neural network** to implement an **unknown classification function**



Neurons
Individual processing units

Network
input-output connections

Training consists of adjusting the weights of the various units/layers based on the input-output pairs

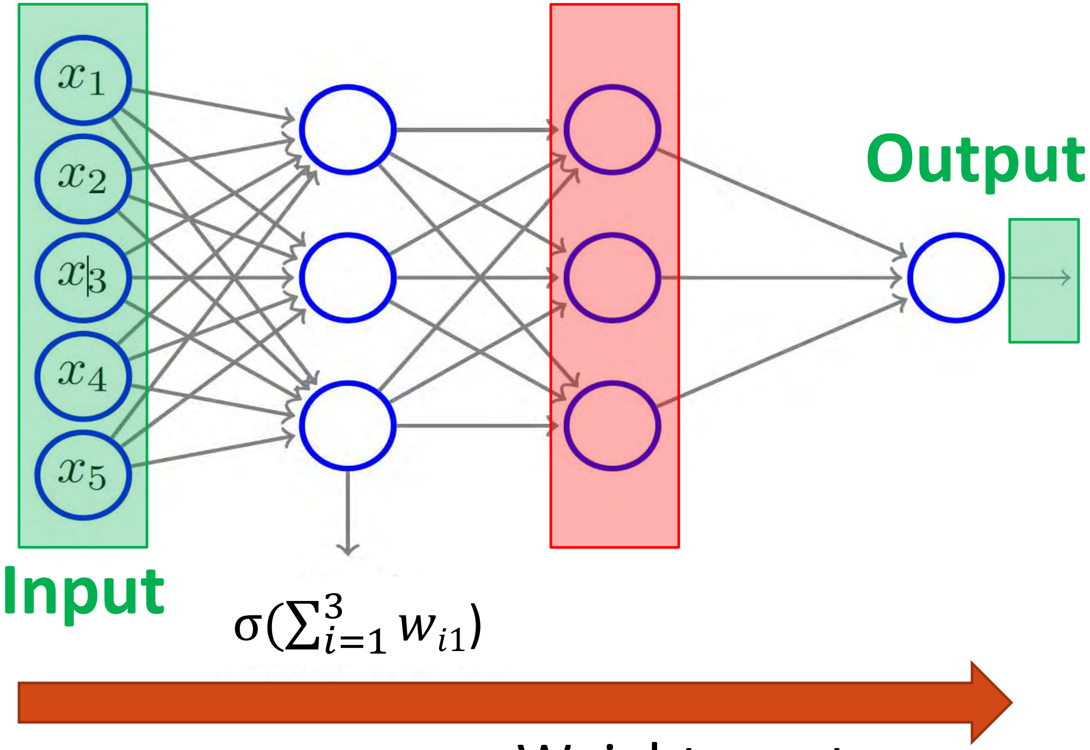
Neural network model (1)

Neuron model

- $\mathbf{x}$: input features vector
- a: output neuron activation

$$\boxed{a = \sigma(\mathbf{w}^T\mathbf{x} + b)}$$

- $\mathbf{w}$ and b: learned parameters vectors
- σ: neuron non-linear function



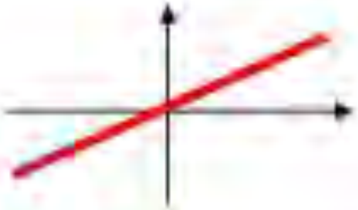
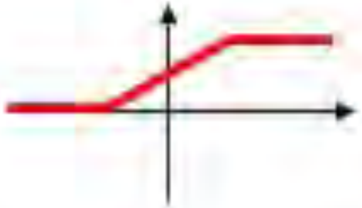
Neural network model

- L layers of stacked neurons
- Signal is **propagated** by layers

Weights vector
$\mathbf{w}_i = (w_{i1,} w_{i2,} \ldots, w_{in})$
$\mathbf{w}_i^T$ transpose

$$a_L = \sigma(\mathbf{w}_L^T\, \boldsymbol{\sigma}(\mathbf{w}_{L-1}^T \ldots (\mathbf{w}_1^T\, \mathbf{x} + b_1) \ldots) + b_L)$$

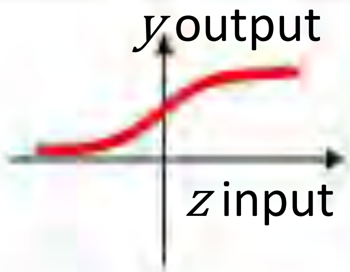
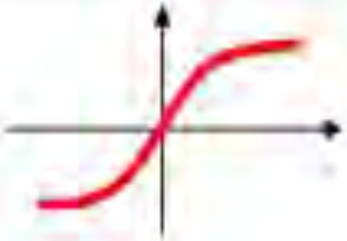
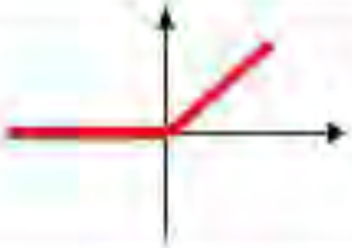
Neural networks: activation units

Activation function	Equation	Example	1D Graph
Unit step (Heaviside)	$\phi(z) = \begin{cases} 0, & z < 0, \\ 0.5, & z = 0, \\ 1, & z > 0, \end{cases}$	Perceptron variant	
Sign (Signum)	$\phi(z) = \begin{cases} -1, & z < 0, \\ 0, & z = 0, \\ 1, & z > 0, \end{cases}$	Perceptron variant	
Linear	$\phi(z) = z$	Adaline, linear regression	
Piece-wise linear	$\phi(z) = \begin{cases} 1, & z \geq \frac{1}{2}, \\ z + \frac{1}{2}, & -\frac{1}{2} < z < \frac{1}{2}, \\ 0, & z \leq -\frac{1}{2}, \end{cases}$	Support vector machine	

Neuron Function

$y = \phi(z)$

Neural networks: activation units

Activation function	Equation	Example	1D Graph
Logistic (sigmoid)	$\phi(z) = \frac{1}{1+e^{-z}}$	Logistic regression, Multi-layer NN	
Hyperbolic tangent	$\phi(z) = \frac{e^{z}-e^{-z}}{e^{z}+e^{-z}}$	Multi-layer Neural Networks	
Rectifier, ReLU (Rectified Linear Unit)	$\phi(z) = max(0, z)$	Multi-layer Neural Networks	

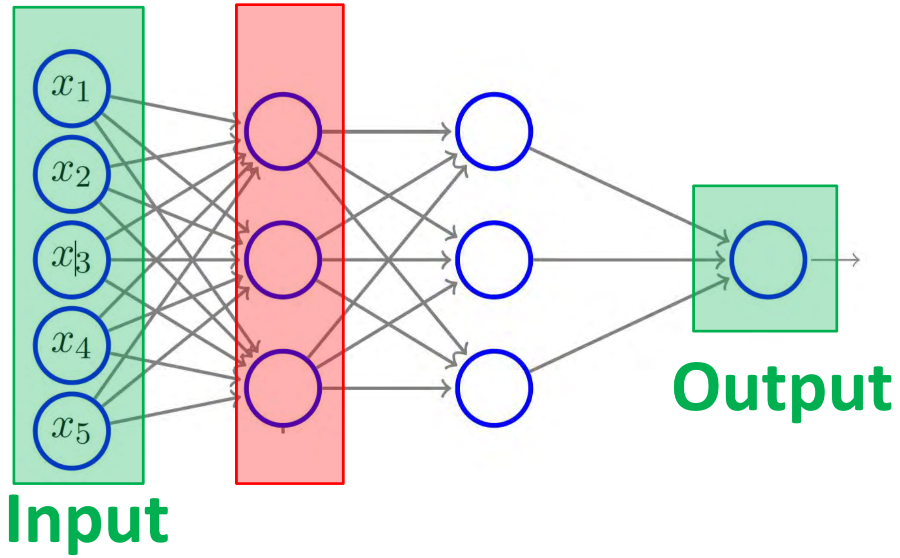
Neuron Function

$y = \phi(z)$

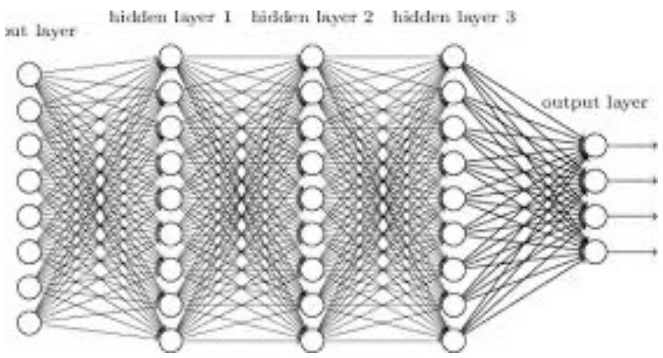
Neural networks: architectures

Terminology

- Input layer: x
- Output layer: a_L
- Intermediate layers: hidden
- Many layers L → deep network



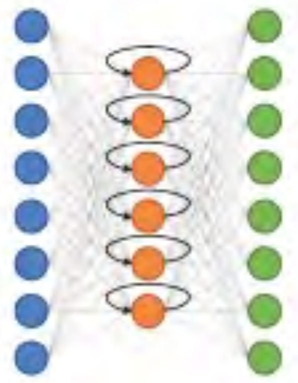
Network architectures



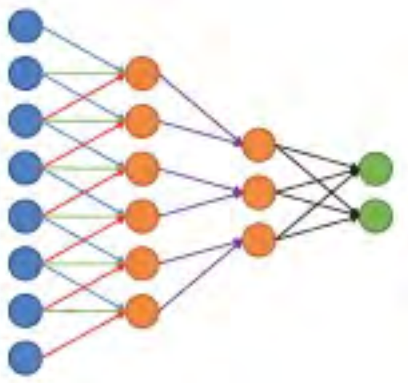
FCN: Fully Connected Network

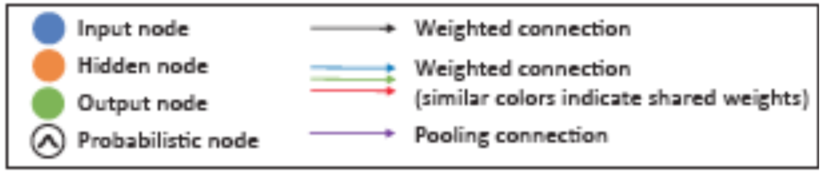
Auto-encoder

Bolzman Machine



RNN: Recurrent





Neural networks principles

The neural network computes the function:

$$a_L = \sigma(\boldsymbol{w}_L^T\,\boldsymbol{\sigma}(\boldsymbol{w}_{L-1}^T \ldots(\boldsymbol{w}_1^T\,\mathbf{x} + b_1)\ldots) + b_L)$$

Three phases

1. **Training**: compute the weights of each neuron by optimization using input-output pairs
2. **Validation**: fine-tune the network hyper-parameters to improve its performance
3. **Testing**: perform classification on unseen examples

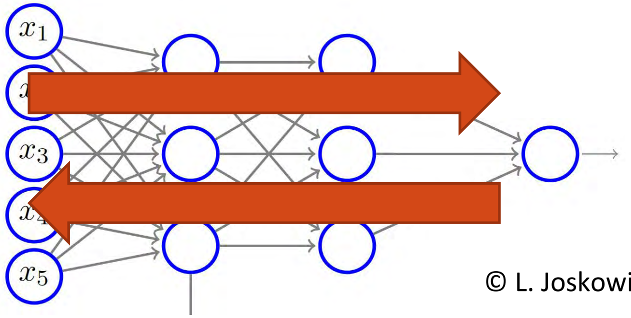
Neural networks principles

1. Training

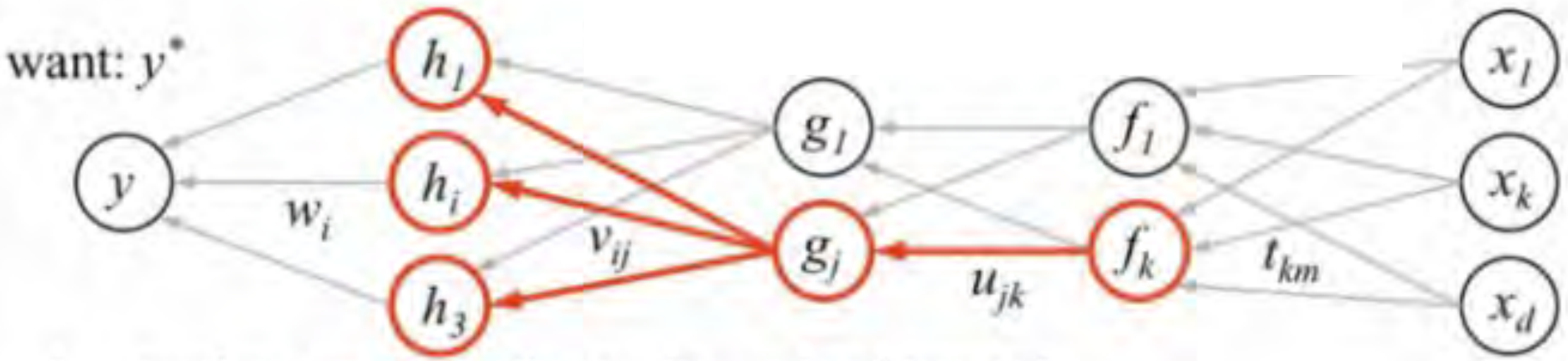
$$a_L = \sigma(\boldsymbol{w}_L^T\, \boldsymbol{\sigma}(\boldsymbol{w}_{L-1}^T \ldots (\boldsymbol{w}_1^T\, \mathbf{x} + b_1) \ldots) + b_L)$$

Compute the weights of each neuron by optimization using input-output pairs.

- The computation is performed by **multi-parameter optimization.**
- The function that is optimized is called a **loss function.** It is the **difference** between the **observed** and the **computed** values.
- The loss function is optimized by iterative methods, e.g., gradient descent by **forward** and **backwards** propagation of training examples through the network.
- The training stops upon convergence.



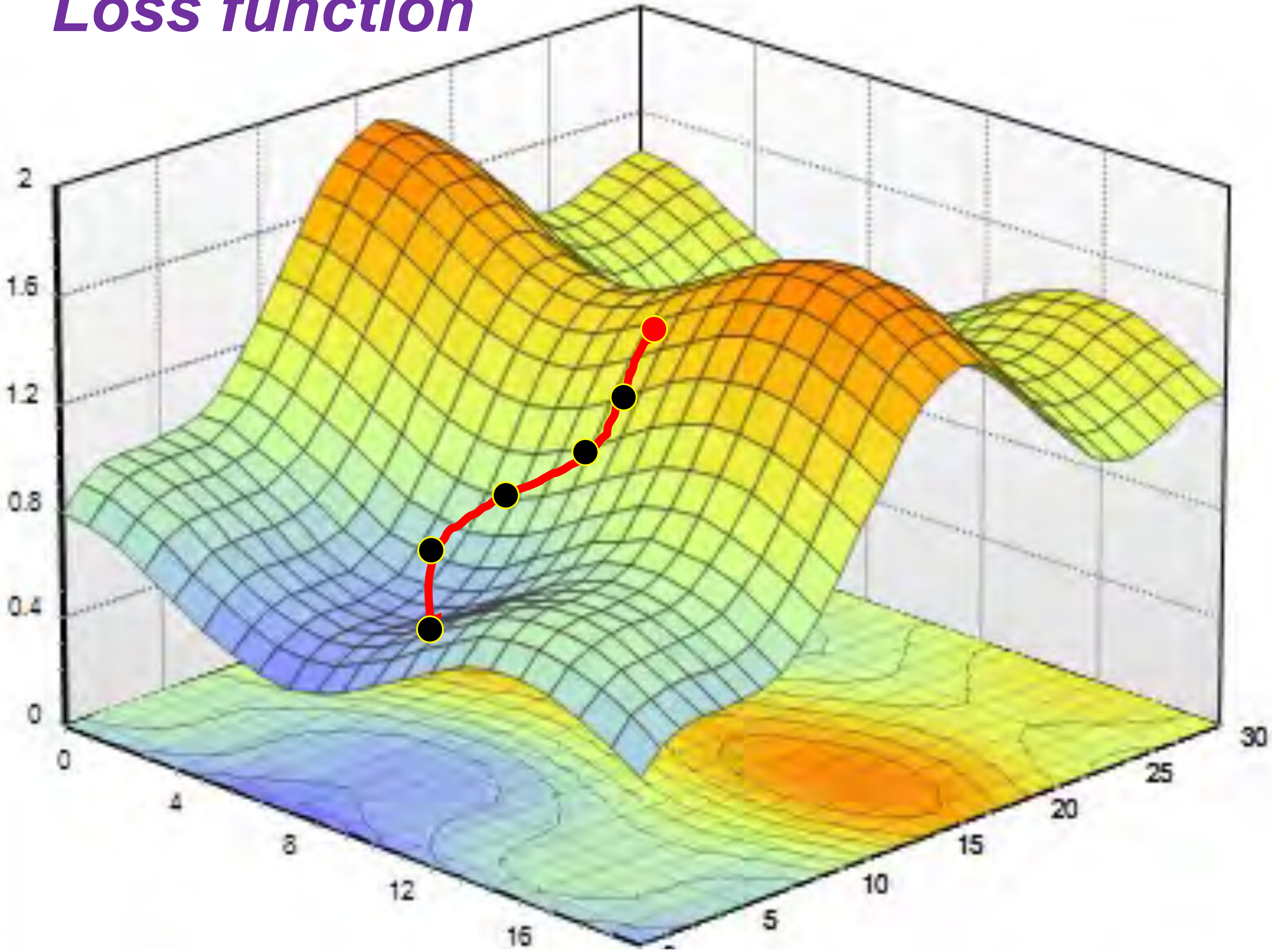
Forward and backward propagation



1. receive new observation $\boldsymbol{x} = [x_1 \ldots x_d]$ and target y^*
2. **feed forward:** for each unit g_j in each layer 1…L
   compute g_j based on units f_k from previous layer: $g_j = \sigma\left(u_{j0} + \sum_k u_{jk} f_k\right)$
3. get prediction y and error $(y\text{-}y^*)$
4. **back-propagate error:** for each unit g_j in each layer L…1

Optimization

Loss function

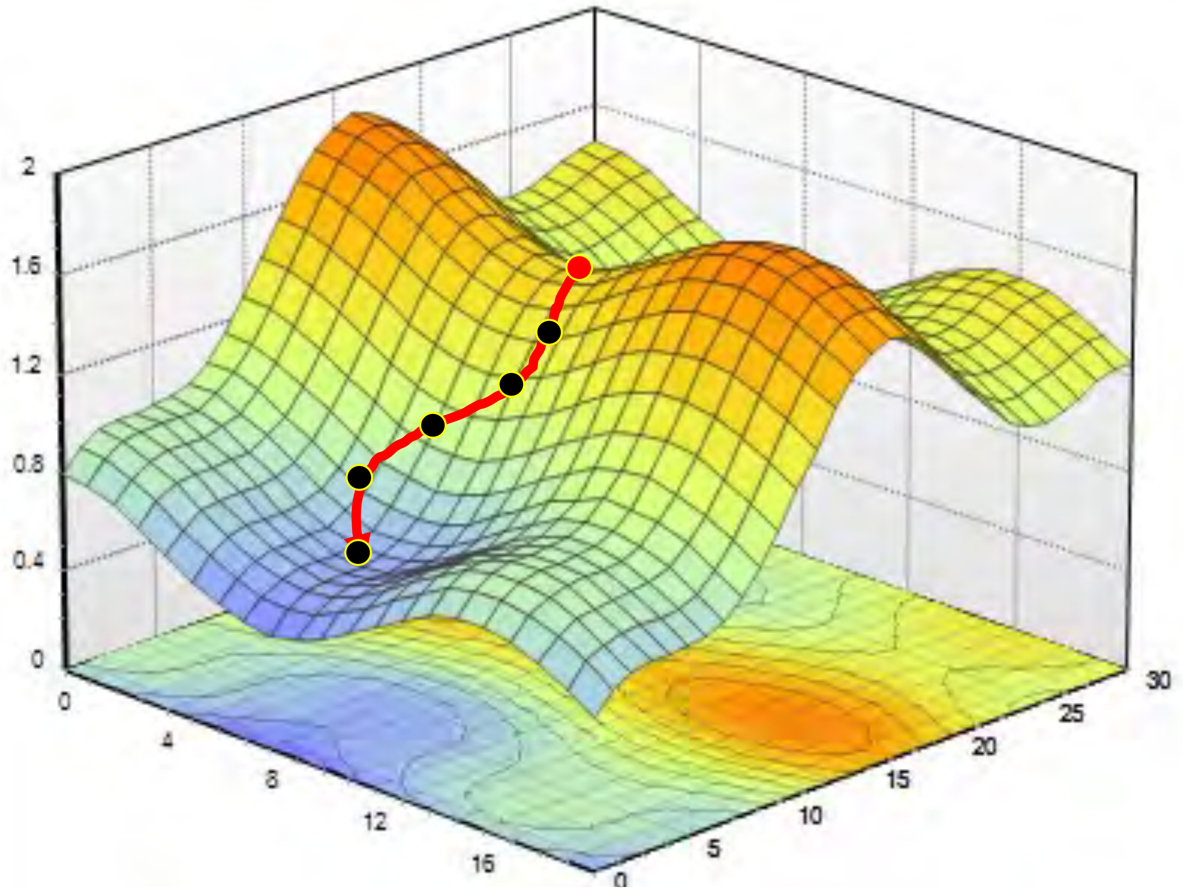


Sketch of the high-dimensional weights parameter space

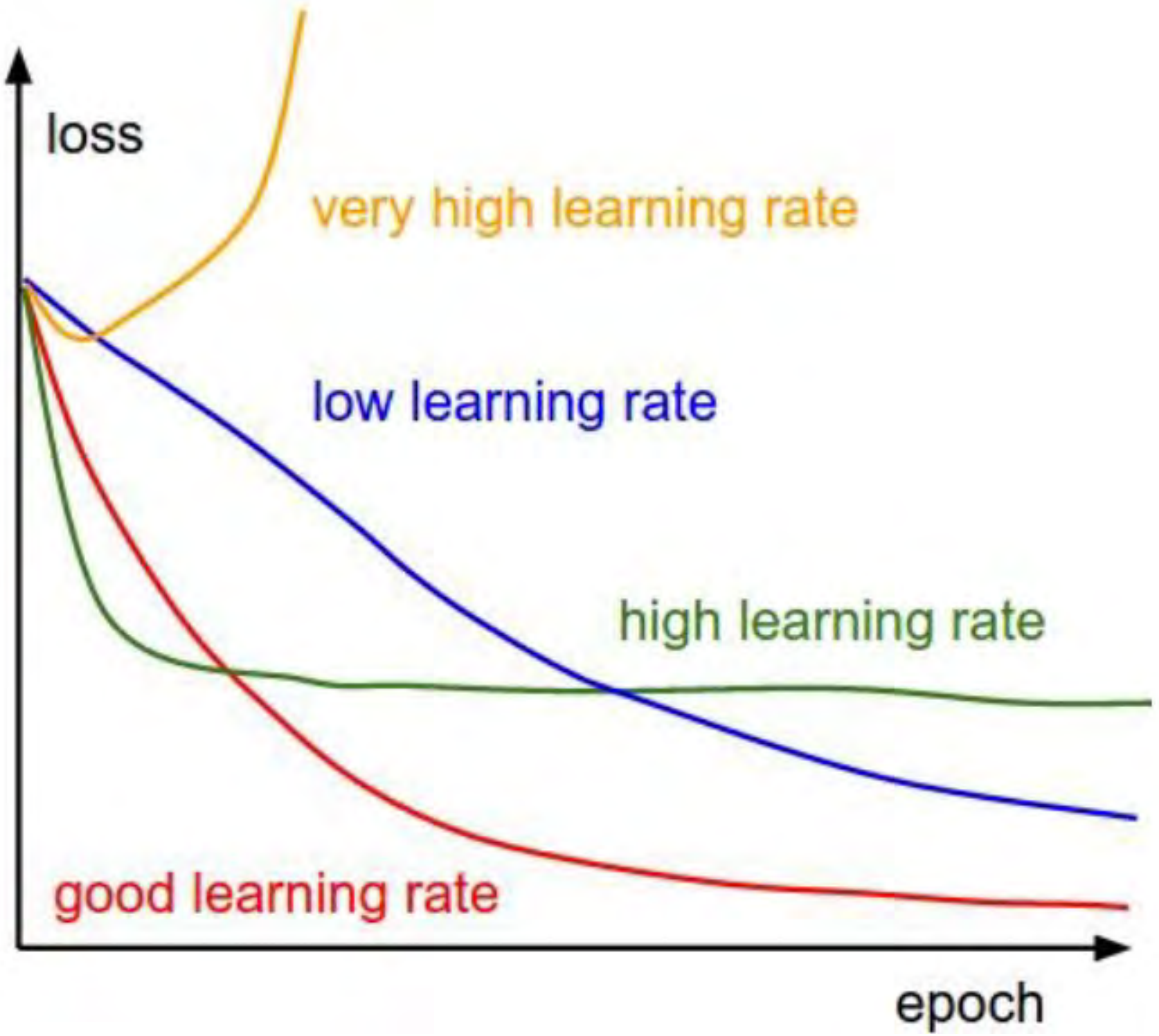
Method	Update equation
SGD	$g_t = \nabla_{\theta_t} J(\theta_t)$ $\Delta\theta_t = -\eta \cdot g_t$ $\theta_t = \theta_t + \Delta\theta_t$
Momentum	$\Delta\theta_t = -\gamma\, v_{t-1} - \eta g_t$
NAG	$\Delta\theta_t = -\gamma\, v_{t-1} - \eta \nabla_\theta J(\theta - \gamma v_{t-1})$
Adagrad	$\Delta\theta_t = -\frac{\eta}{\sqrt{G_t + \epsilon}} \odot g_t$
Adadelta	$\Delta\theta_t = -\frac{RMS[\Delta\theta]_{t-1}}{RMS[g]_t} g_t$
RMSprop	$\Delta\theta_t = -\frac{\eta}{\sqrt{E[g^2]_t + \epsilon}} g_t$
Adam	$\Delta\theta_t = -\frac{\eta}{\sqrt{\hat{v}_t} + \epsilon} \hat{m}_t$

Optimizers

Loss function



Sketch of the high-dimensional weights parameter space

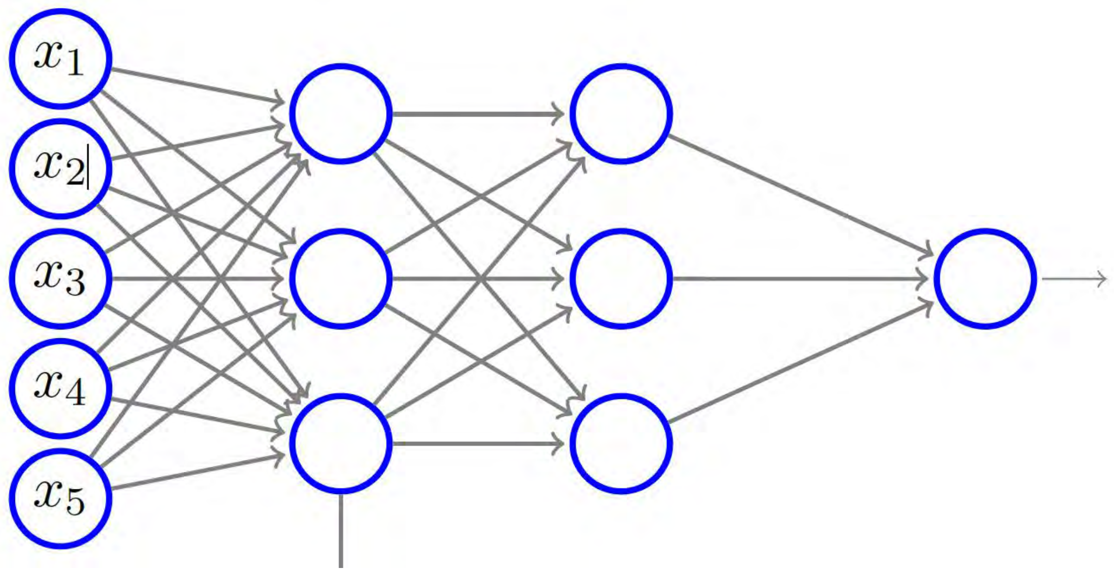


Neural networks principles

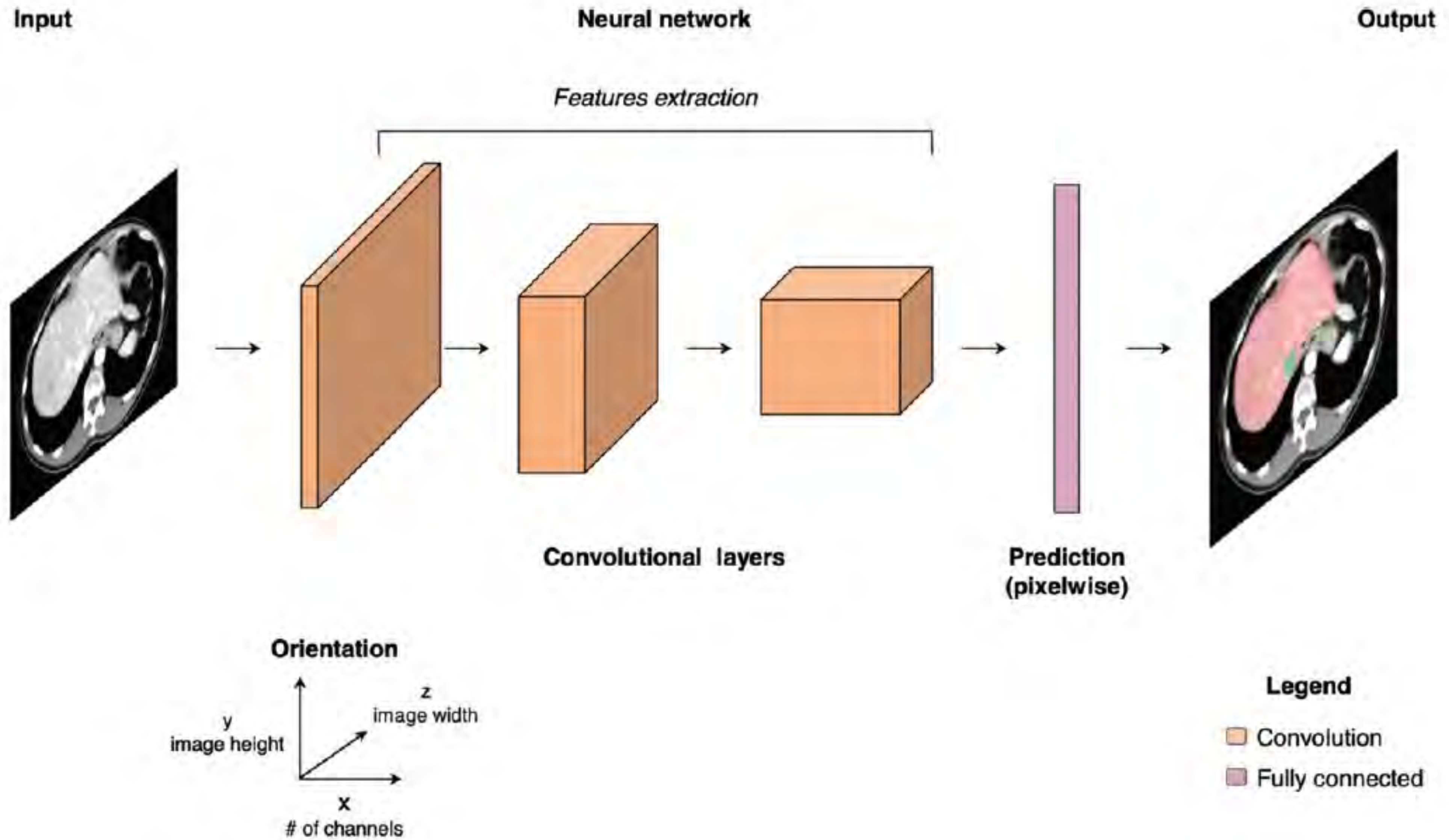
2. Validation

Fine-tune the network hyper-parameters to improve its performance

- Hyper-parameters include:
  - number of hidden layers and units
  - learning rate
  - activation functions
  - …

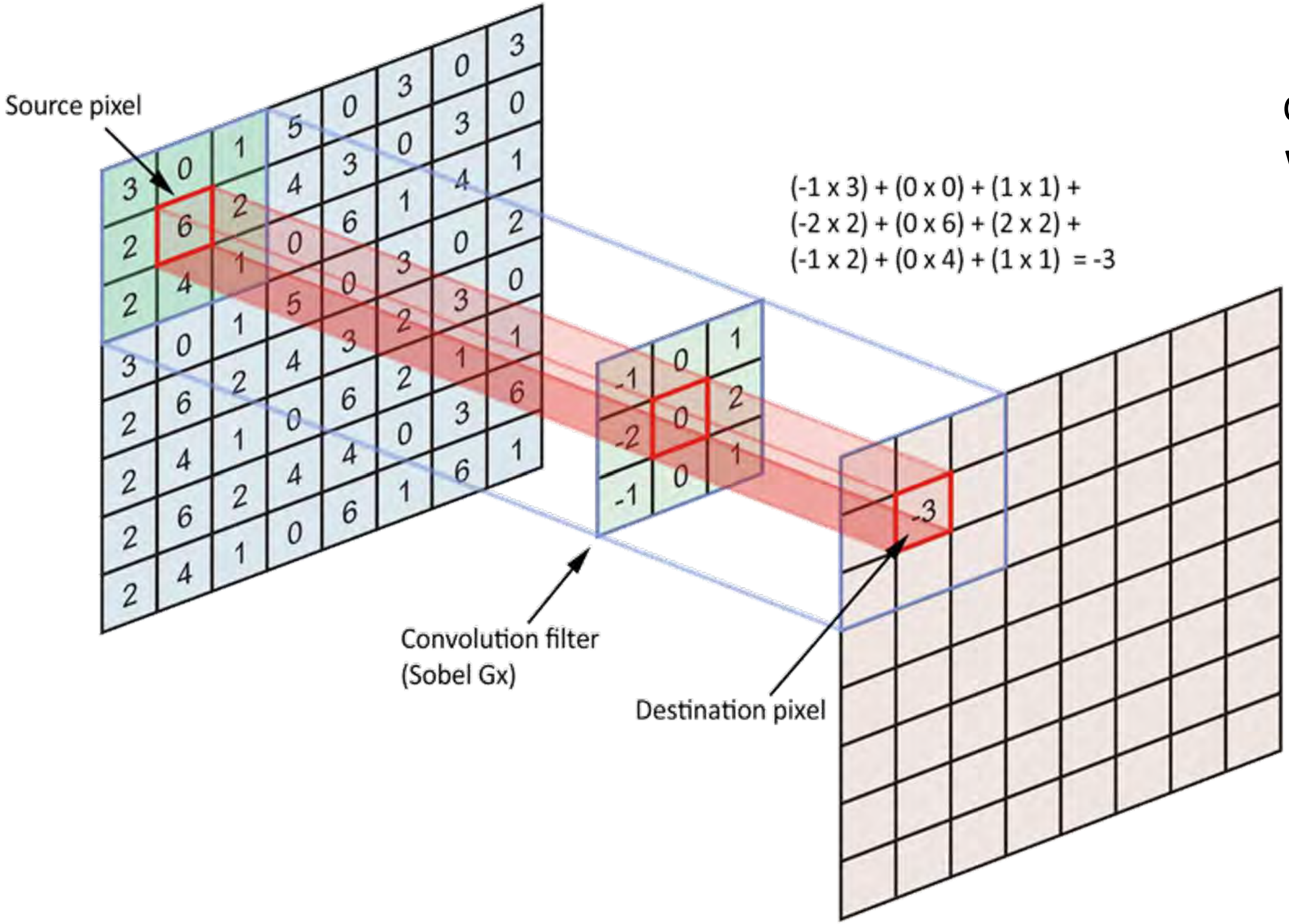


Convolutional Neural Network for MIP



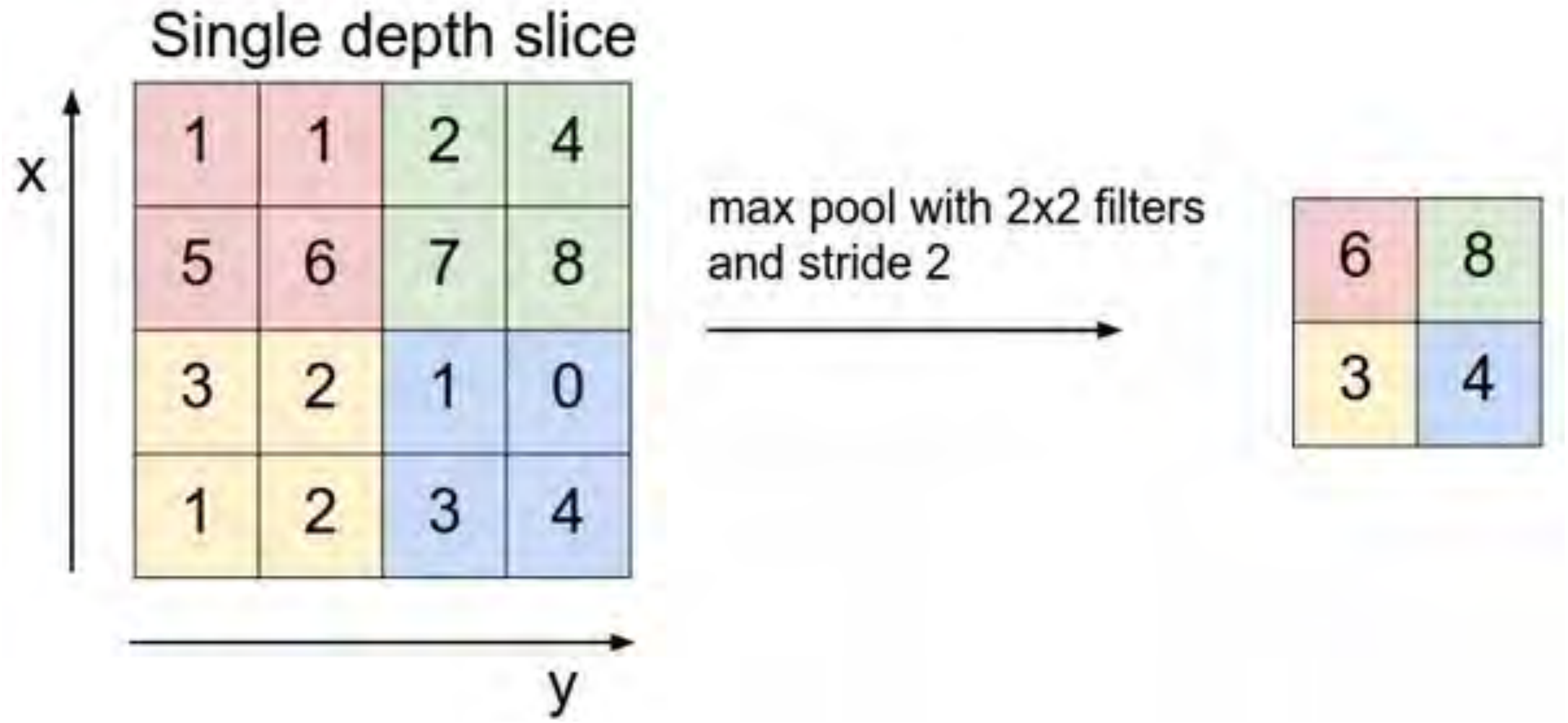
Deep Learning: An Update for Radiologists. Cheng P. et al, Radiographics, Sept-Oct 2021.

Convolution layer



Convolution is a kind of **weighted averaging** on a patch of the image

Max pooling layer



Characteristics

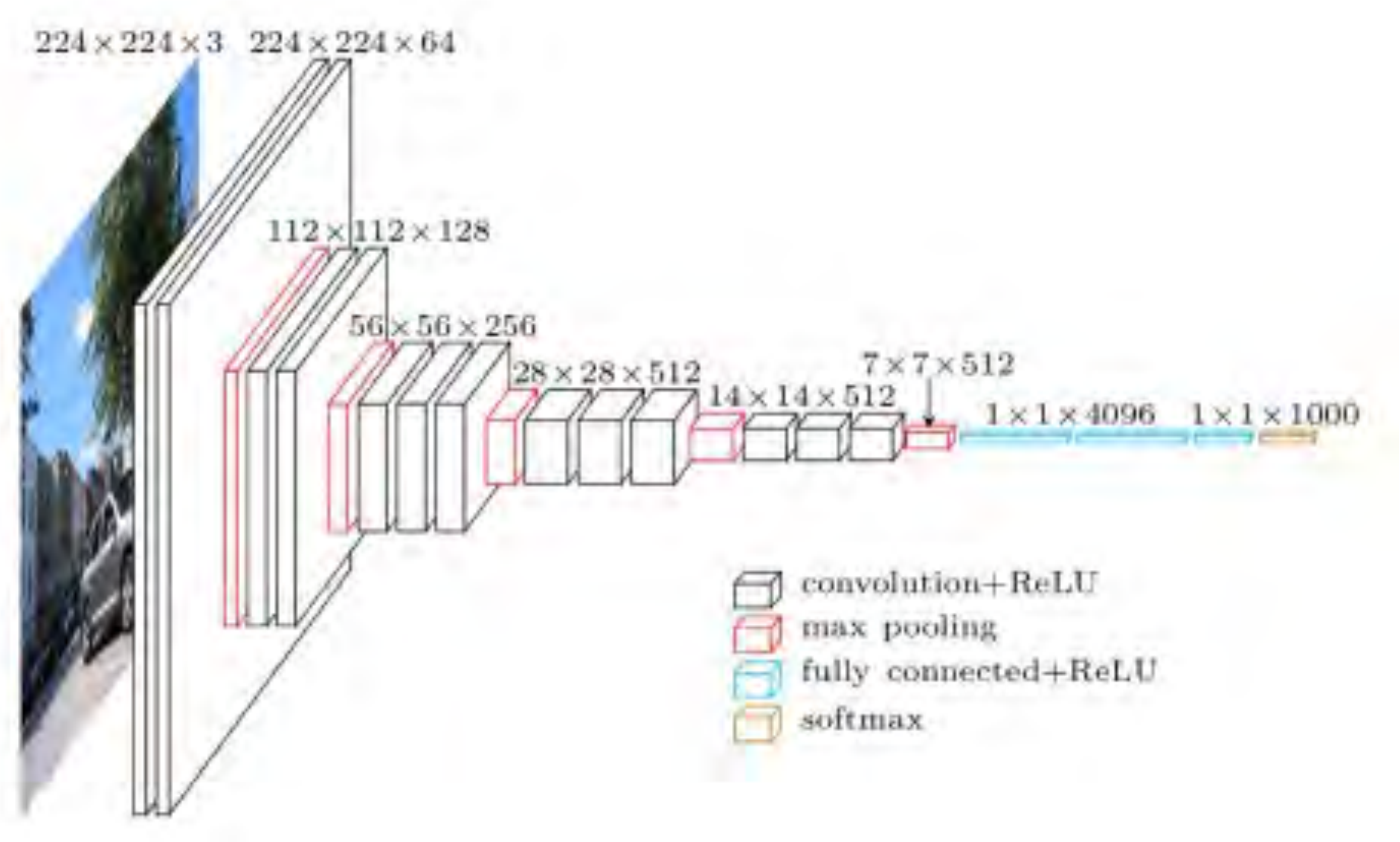
- Decreases image size by factor of 4
- Decreases location dependence
- Reduces memory requirements

Convolutional Neural Network

Components

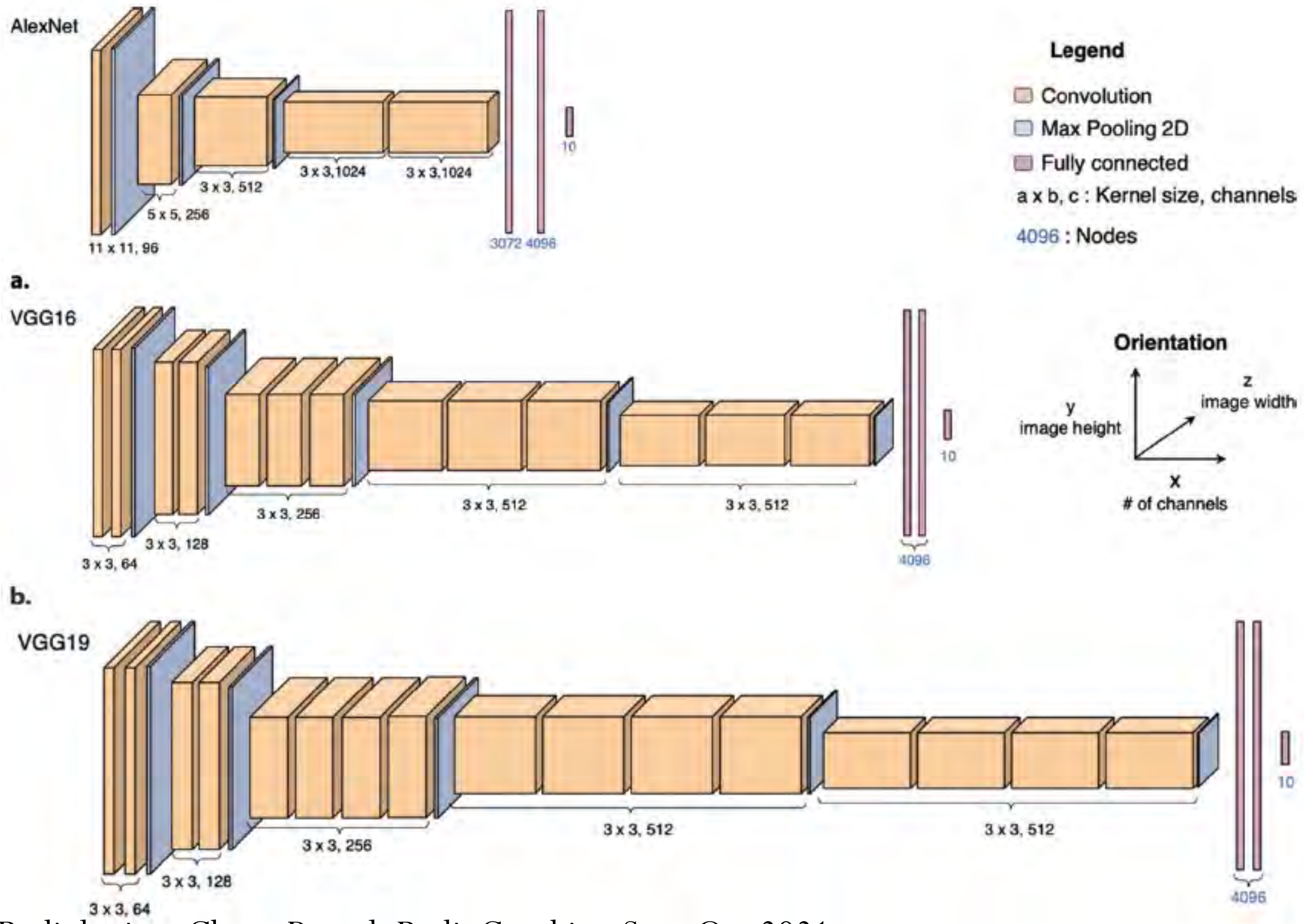
- Activation functions
  - ReLU, ELU, SReLU, PreLU
- Convolutional layers
  - Dimensionality vs complexity
  - Dilated convolution
- Aggregation layers
  - Global Pooling
  - Max/Mean Pooling
  - Convolutions

Image patch size x # of features



Convolutional Neural Networks: depth

Evolution in time:
2016-2022



Deep Learning: An Update for Radiologists. Cheng P. et al, RadioGraphics, Sept-Oct 2021.

The deep learning pipeline

Computer Methods and Programs in Biomedicine 158 (2018) 113–122

Contents lists available at ScienceDirect

Computer Methods and Programs in Biomedicine

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

ELSEVIER

NiftyNet: a deep-learning platform for medical imaging

Eli Gibson[a,b,1], Wenqi Li[a,1,*], Carole Sudre[b], Lucas Fidon[a], Dzhoshkun I. Shakir[a], Guotai Wang[a], Zach Eaton-Rosen[b], Robert Gray[c,d], Tom Doel[a], Yipeng Hu[b], Tom Whyntie[b], Parashkev Nachev[c,d], Marc Modat[b], Dean C. Barratt[a,b], Sébastien Ourselin[a], M. Jorge Cardoso[b,2], Tom Vercauteren[a,2]

[a] Wellcome / EPSRC Centre for Interventional and Surgical Sciences (WEISS), University College London, UK
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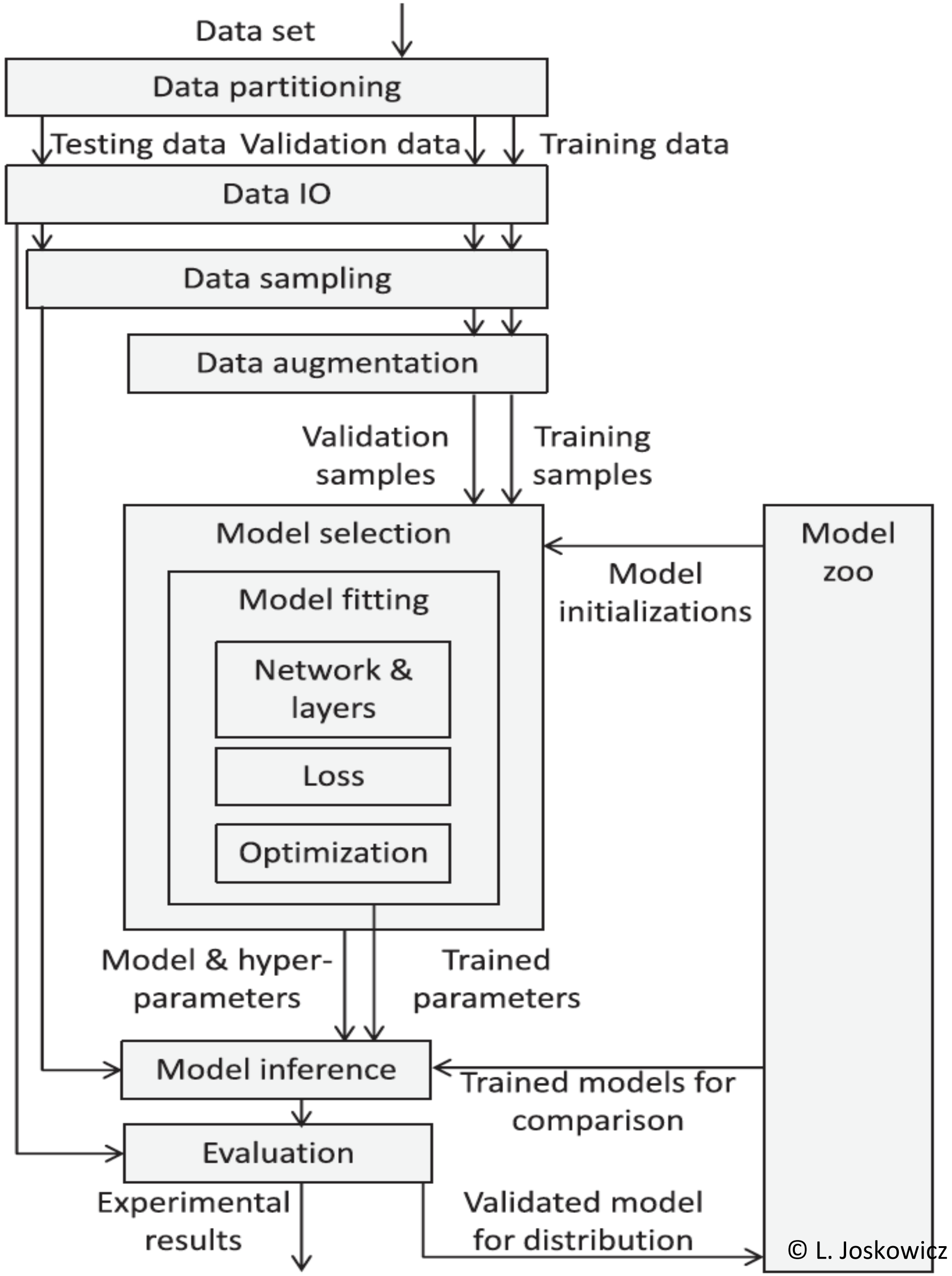
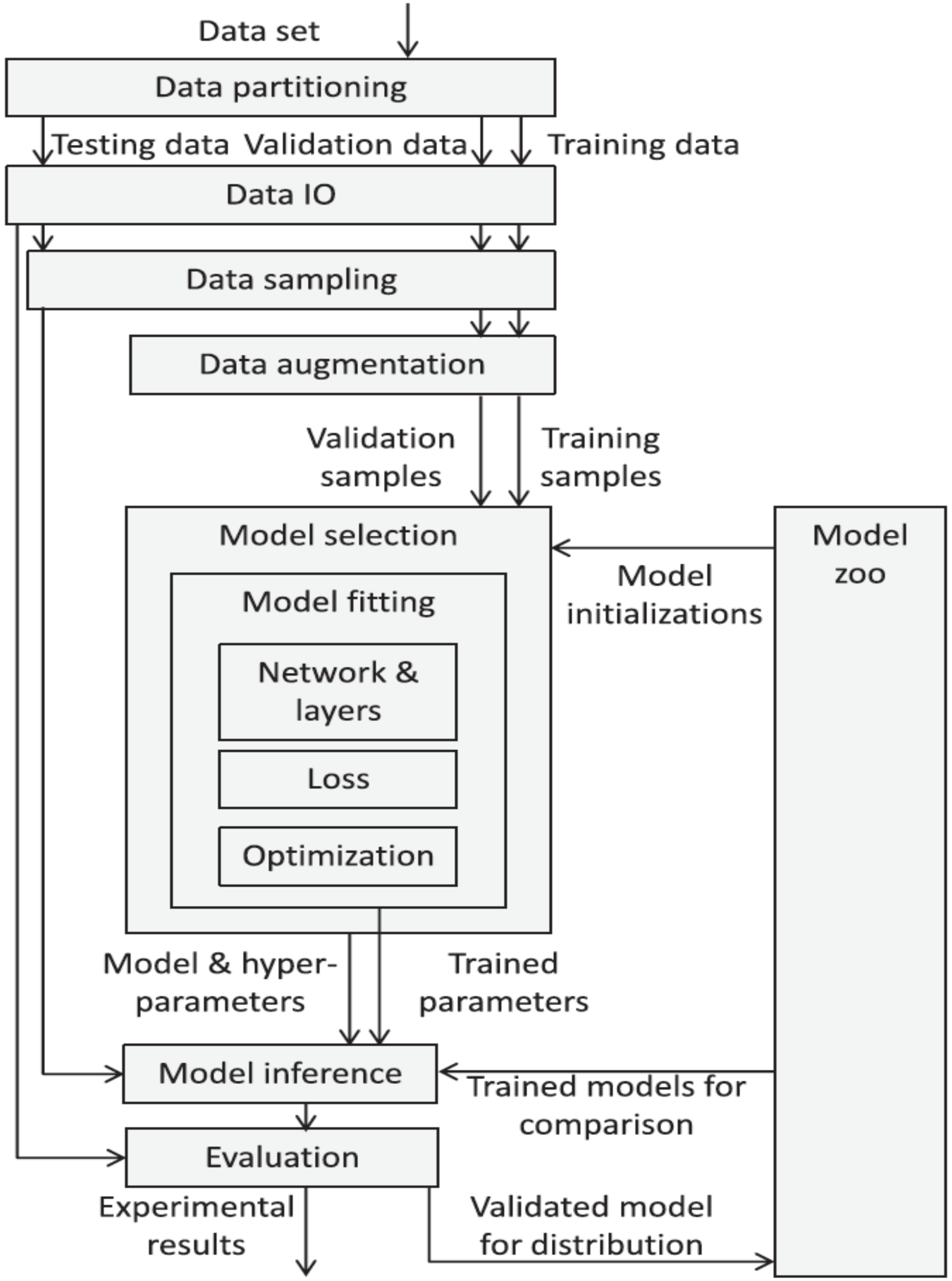
[d] National Hospital for Neurology and Neurosurgery, London, UK



Key issues

- **Data partitioning**: training, testing and validation sets
- **Randomized sampling**: during training
- Image data loading and sampling
- Data augmentation
- **Network architecture**
- Evaluation metrics for performance during training/ inference

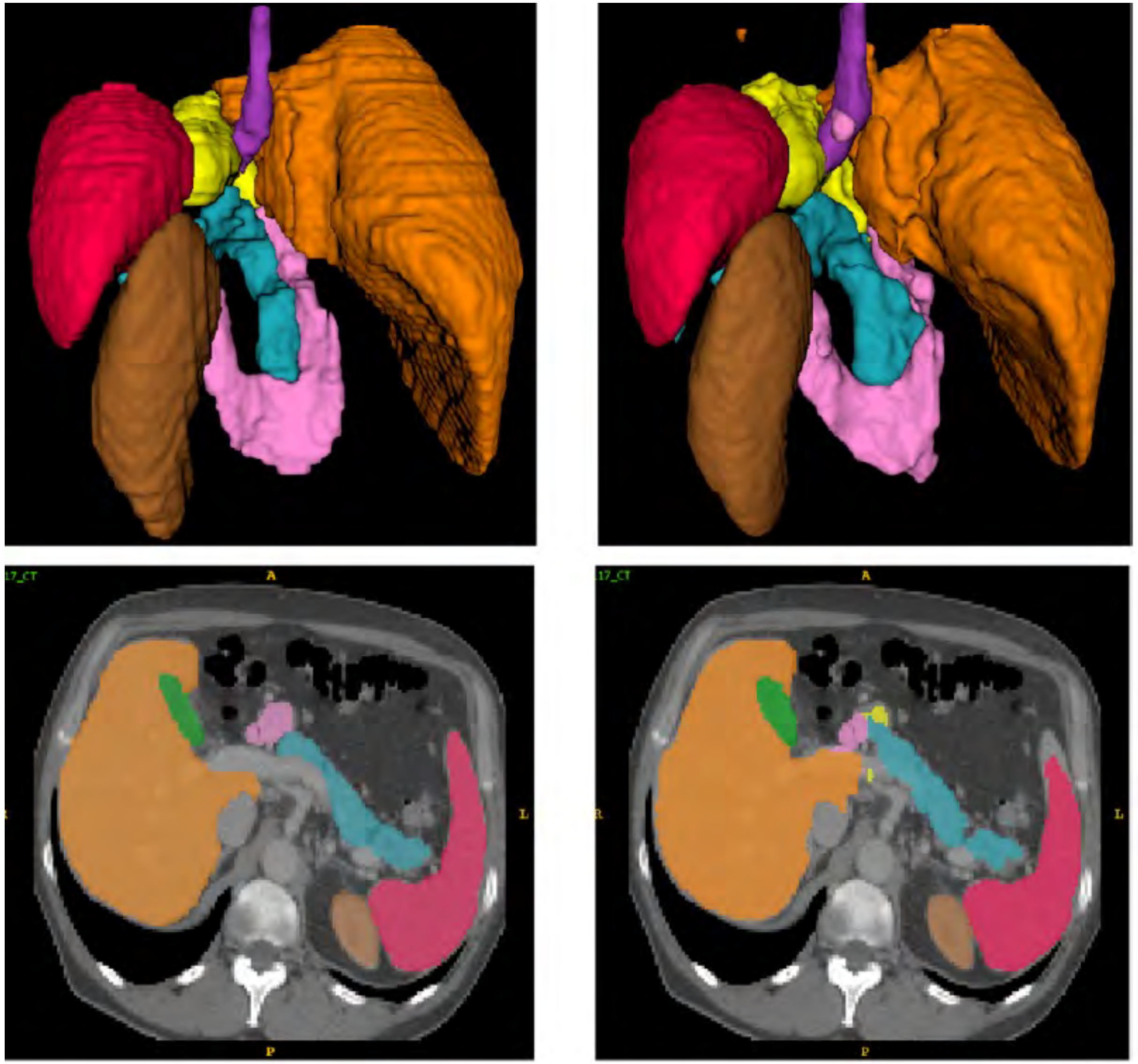


Abdominal organ segmentation in CT

- Network trained on 90 abdominal CTs with manual segmentations from two public data sets

- V-Net segmentation: evaluated with 9-fold cross-validation

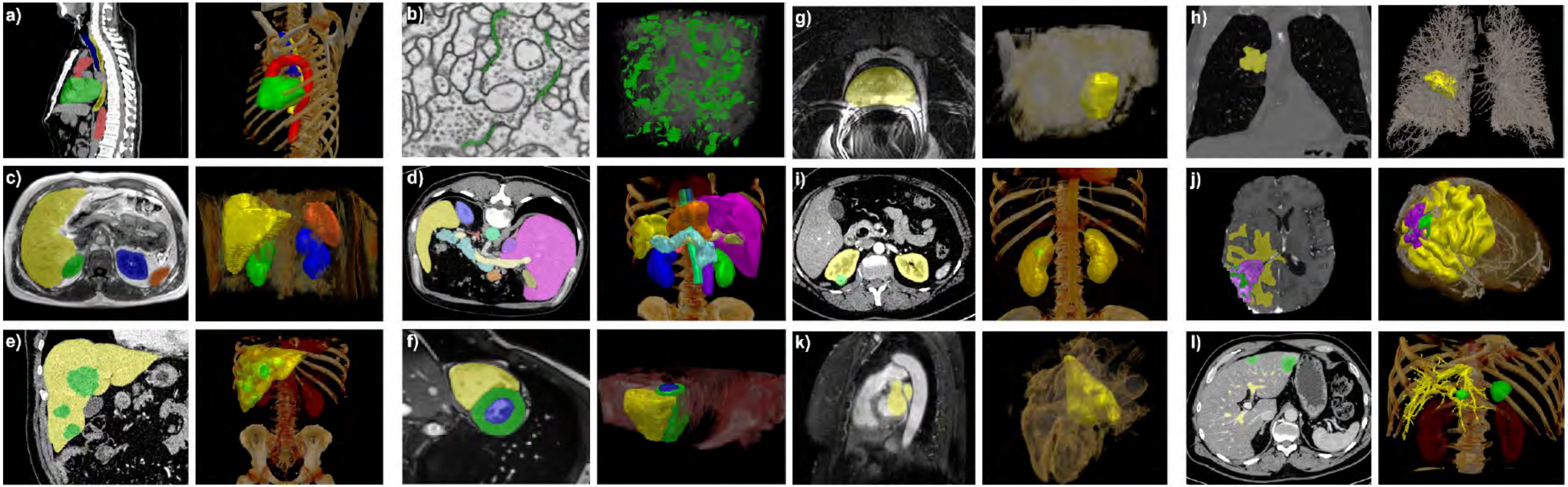
	Dice score	Relative volume difference	Mean absolute distance (voxels)
Spleen	0.94	0.03	1.07
L. Kidney	0.93	0.04	1.06
Gallbladder	0.79	0.17	1.55
Esophagus	0.68	0.57	2.05
Liver	0.95	0.02	1.42
Stomach	0.87	0.09	2.06
Pancreas	0.75	0.19	1.93
Duodenum	0.62	0.24	3.05



Reference standard   NiftyNet segmentation

State of the art: nnU-Net

- Tested for the segmentation of a wide variety of images and structures
- Excellent results in 49 tasks in 19 public international competitions

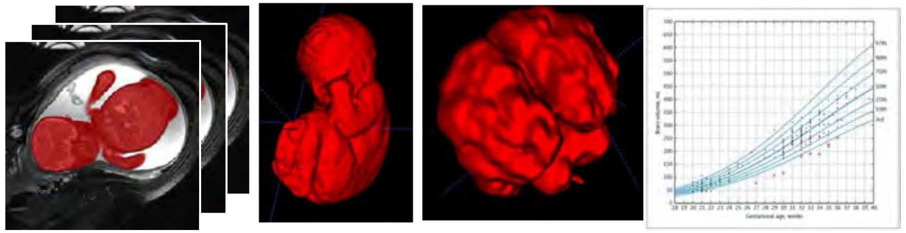


Isensee et al. Automated Design of Deep Learning Methods for Biomedical Image Segmentation, arXiv. Apr 2020

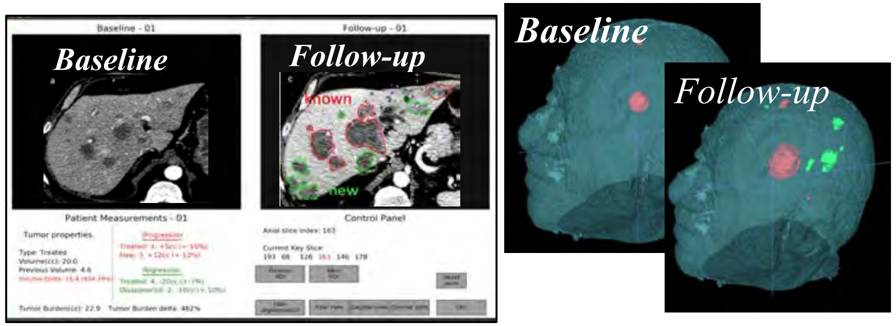
CASMIP Lab Projects

CASMIP
Computer Aided Surgery and Medical Image Processing Laboratory

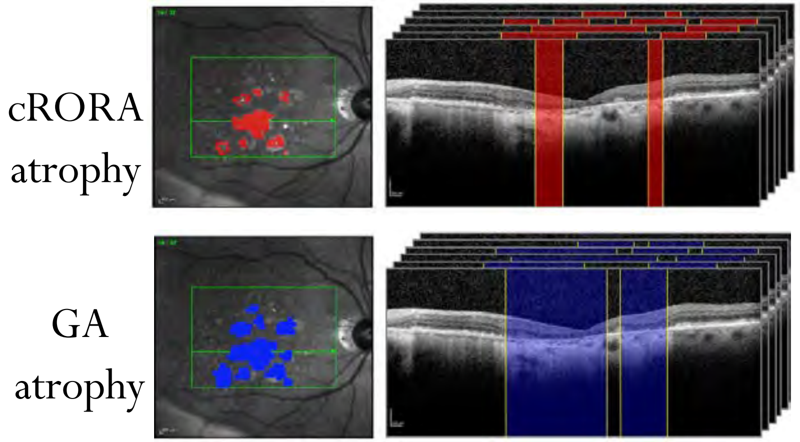
1. Fetal development in MRI (with TASME)
   Segmentation and linear measurements of fetal body, brain, and placenta



2. Tumors follow-up in liver and lungs CT and brain MRI (with Profs. J. Sosna, Y. Shoshan)
   Detection, segmentation and lesion changes analysis



3. Macular atrophy in OCT scans (with Prof. J. Levy)
   Detection and segmentation of dry AMD atrophy in OCT



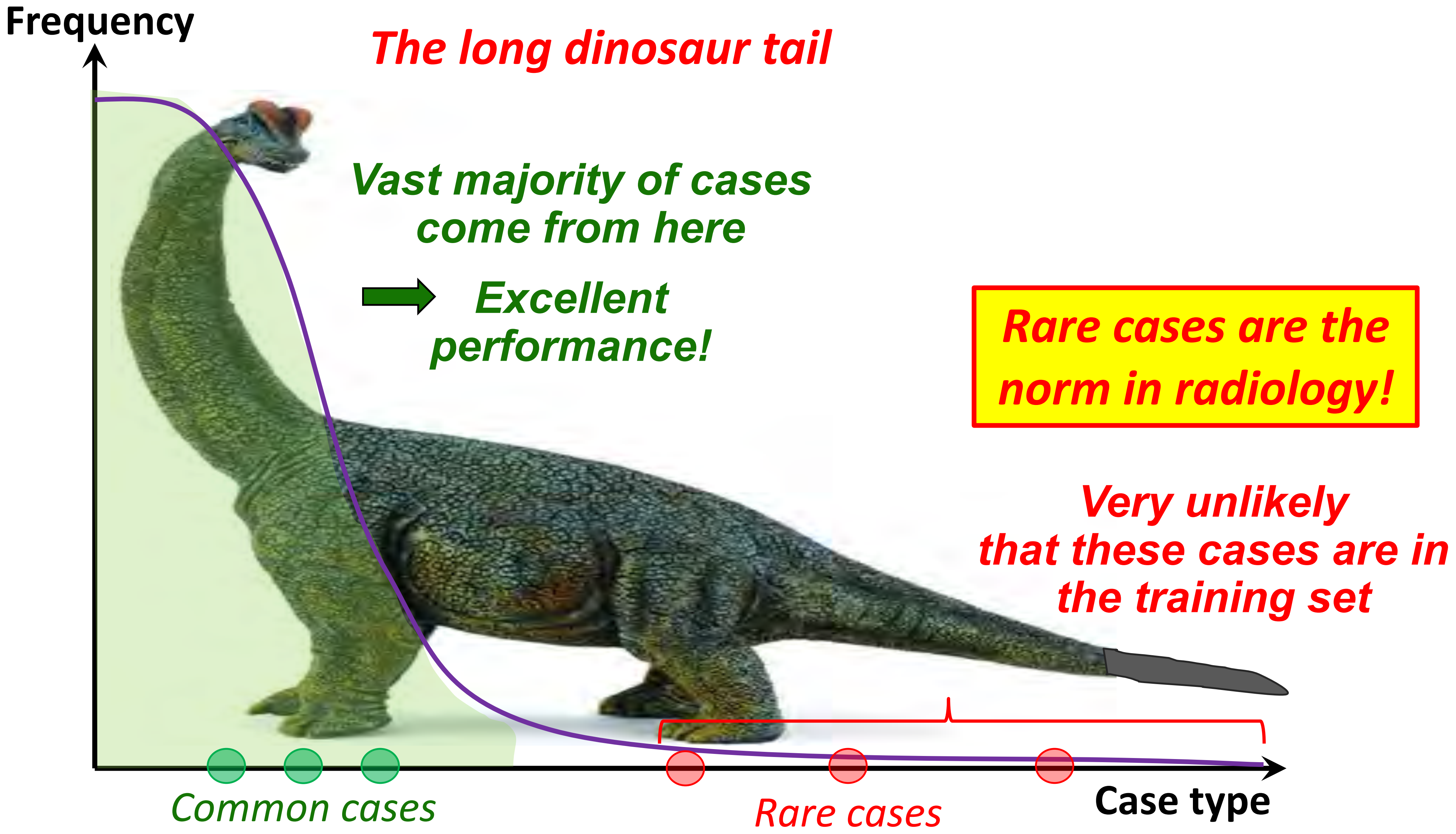
Deep learning: cautionary tales

Deep learning heavily relies on the training data

Size and distribution of the dataset

- GIGO effect: garbage in, garbage out
- Not enough data
- Data is not representative
- Beware of rare cases!
- Beware of imaging variations and noise
- More data is not always better

Cases distribution

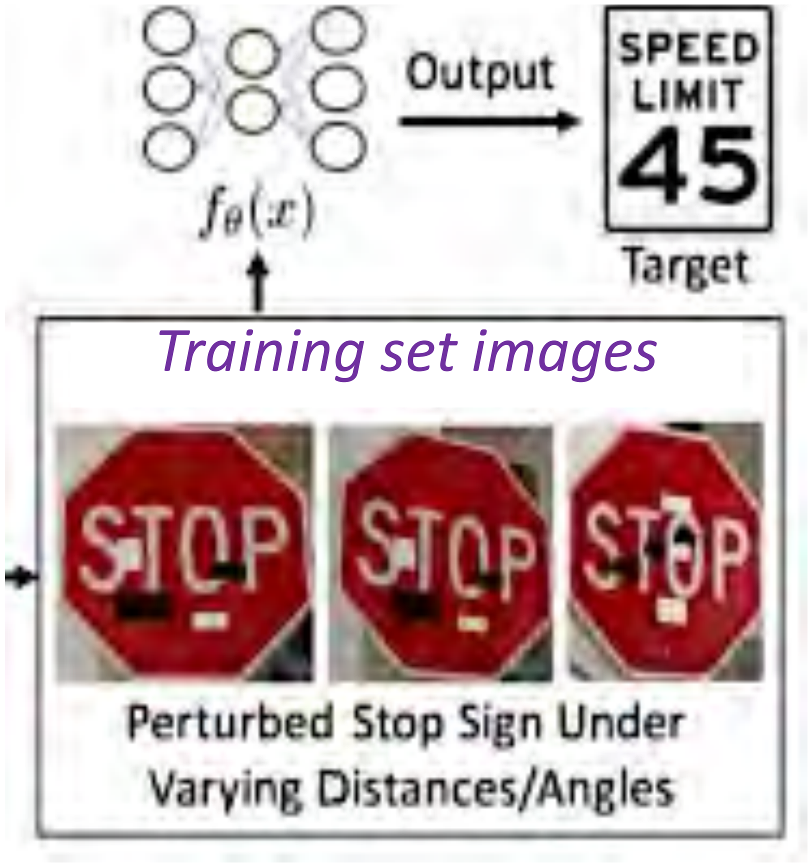


Deep learning: misclassification

Lack of robustness in the presence of small changes

New image

CNN classifier *Misclassification*



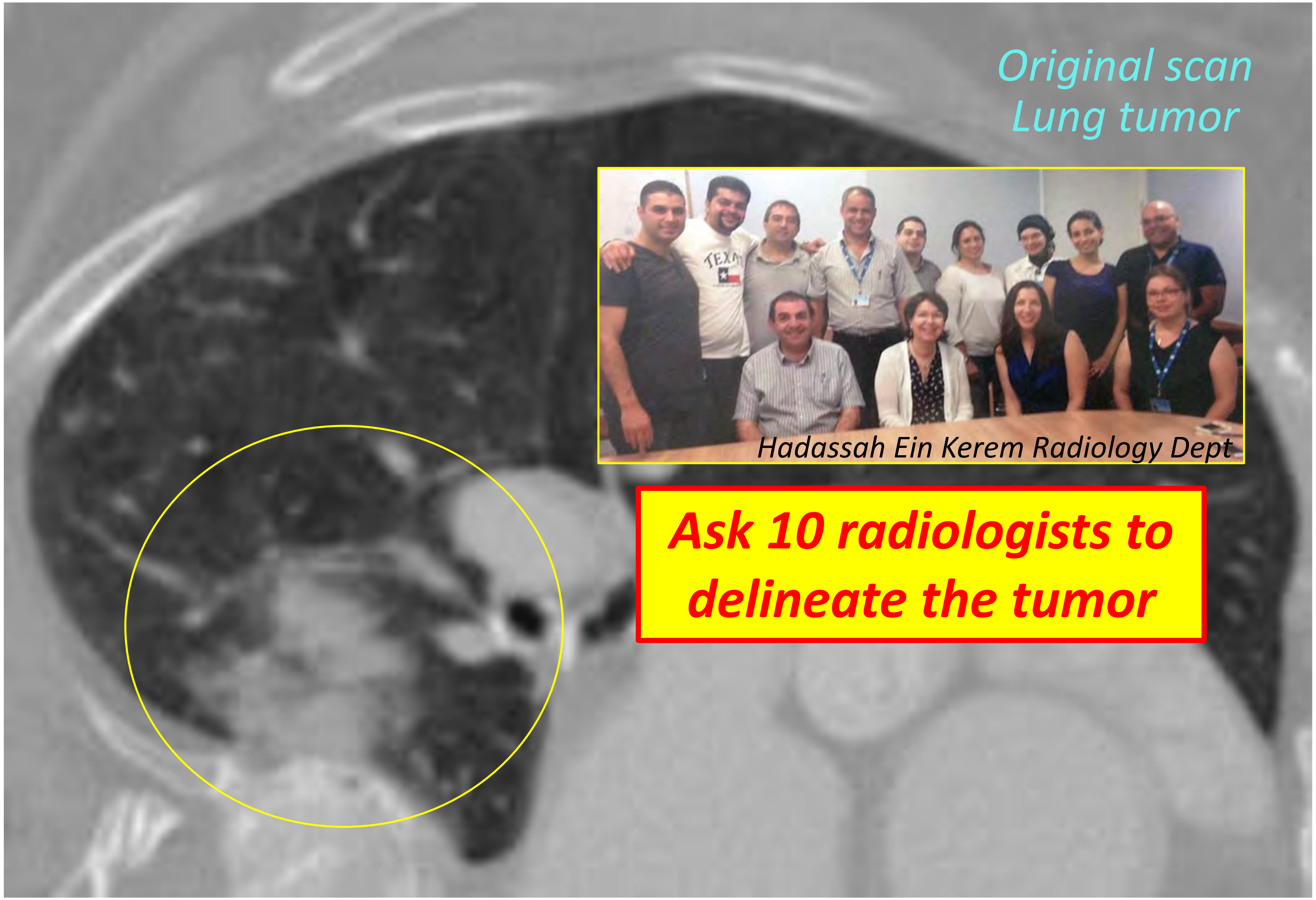
Eykholt et al. "Robust Physical-World Attacks on Deep Learning Visual Classification" CVPR 2018.

Deep learning: misclassification

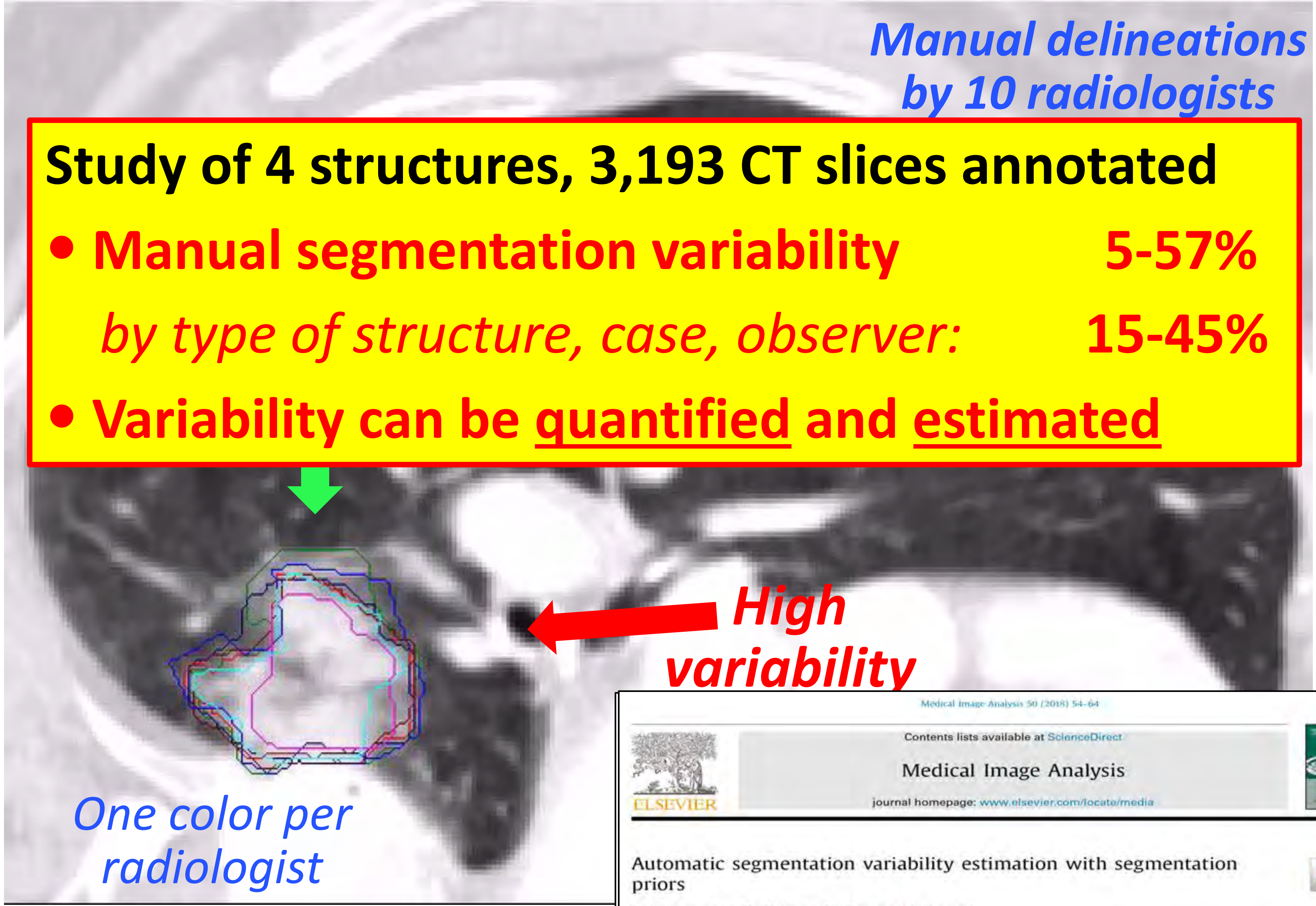
Distance/Angle	Subtle Poster	Subtle Poster Right Turn	Camouflage Graffiti	Camouflage Art (LISA-CNN)	Camouflage Art (GTSRB-CNN)
5′ 0°					
5′ 15°					
10′ 0°					
10′ 30°					
40′ 0°					
Misclassification rate	*100%*	*73.33%*	*66.67%*	*100%*	*80%*

Eykholt et al. "Robust Physical-World Attacks on Deep Learning Visual Classification" CVPR 2018.

Observer variability – what to aim for?



Observer variability – what to aim for?



Study of 4 structures, 3,193 CT slices annotated

- **Manual segmentation variability 5-57%**

  by type of structure, case, observer: **15-45%**

- **Variability can be <u>quantified</u> and <u>estimated</u>**

Medical Image Analysis 50 (2018) 54–64

Contents lists available at ScienceDirect

Medical Image Analysis

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

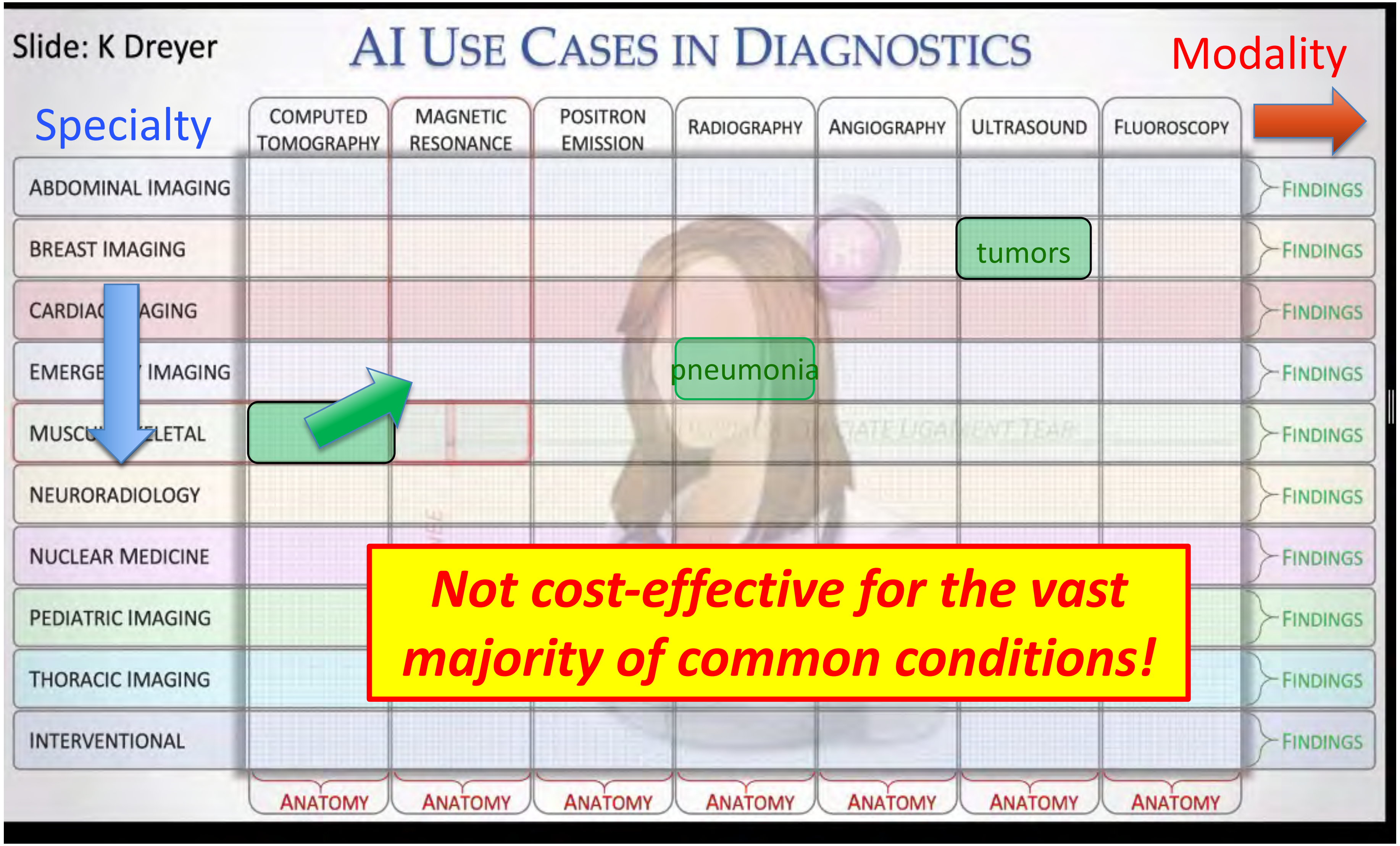
ELSEVIER

Automatic segmentation variability estimation with segmentation priors

L. Joskowicz[a,*], D. Cohen[a], N. Caplan[b], J. Sosna[b]

[a] The Rachel and Selim Benin School of Computer Science and Engineering, The Hebrew University of Jerusalem, Israel
[b] Department of Radiology, Hadassah Hebrew University Medical Center, Jerusalem, Israel

Narrow AI – long time and high costs!



Not cost-effective for the vast majority of common conditions!

AI and Radiology: bottlenecks

Developing AI-based radiology solutions requires

- ***Large collection*** of representative ***datasets of scans***: ~1-5K for segmentation, 10-50K for classification

- ***Manual expert annotation***: ~1,000+ radiologist hours for initial deployment, ~1,000+ for robustness and coverage

- ***Custom development*** of ***solutions*** for 100's of specific organs, structures, pathologies, and imaging protocols
  → ***Narrow AI***: one Rad App for each!

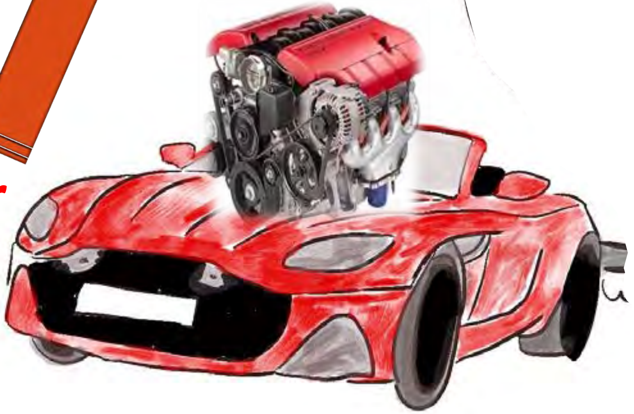
- ***Lengthy*** and ***costly development process*** with several iterations until regulatory approval is obtained!

Deep learning and race cars

where's the catch?

Key Problem!

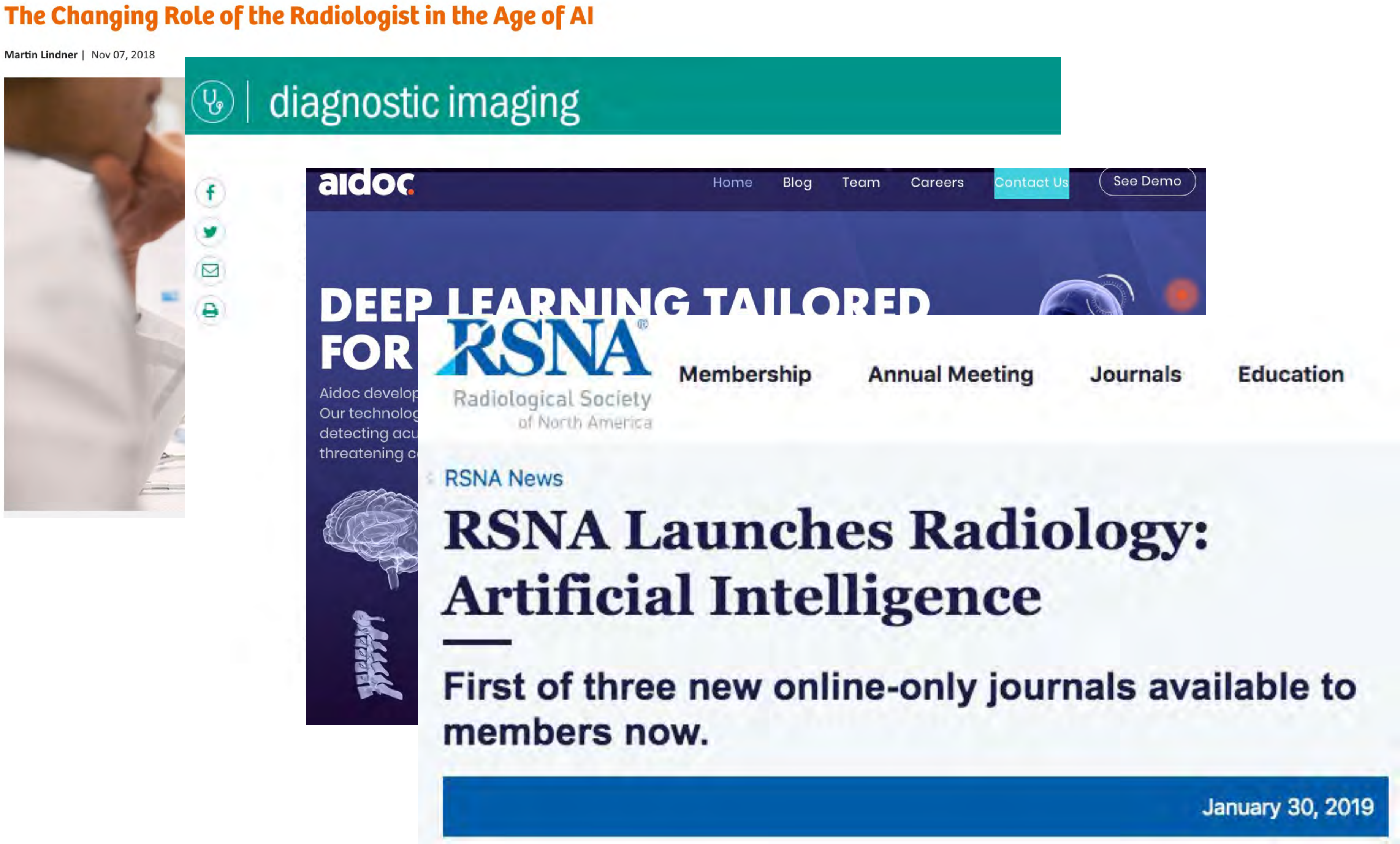
Deep network



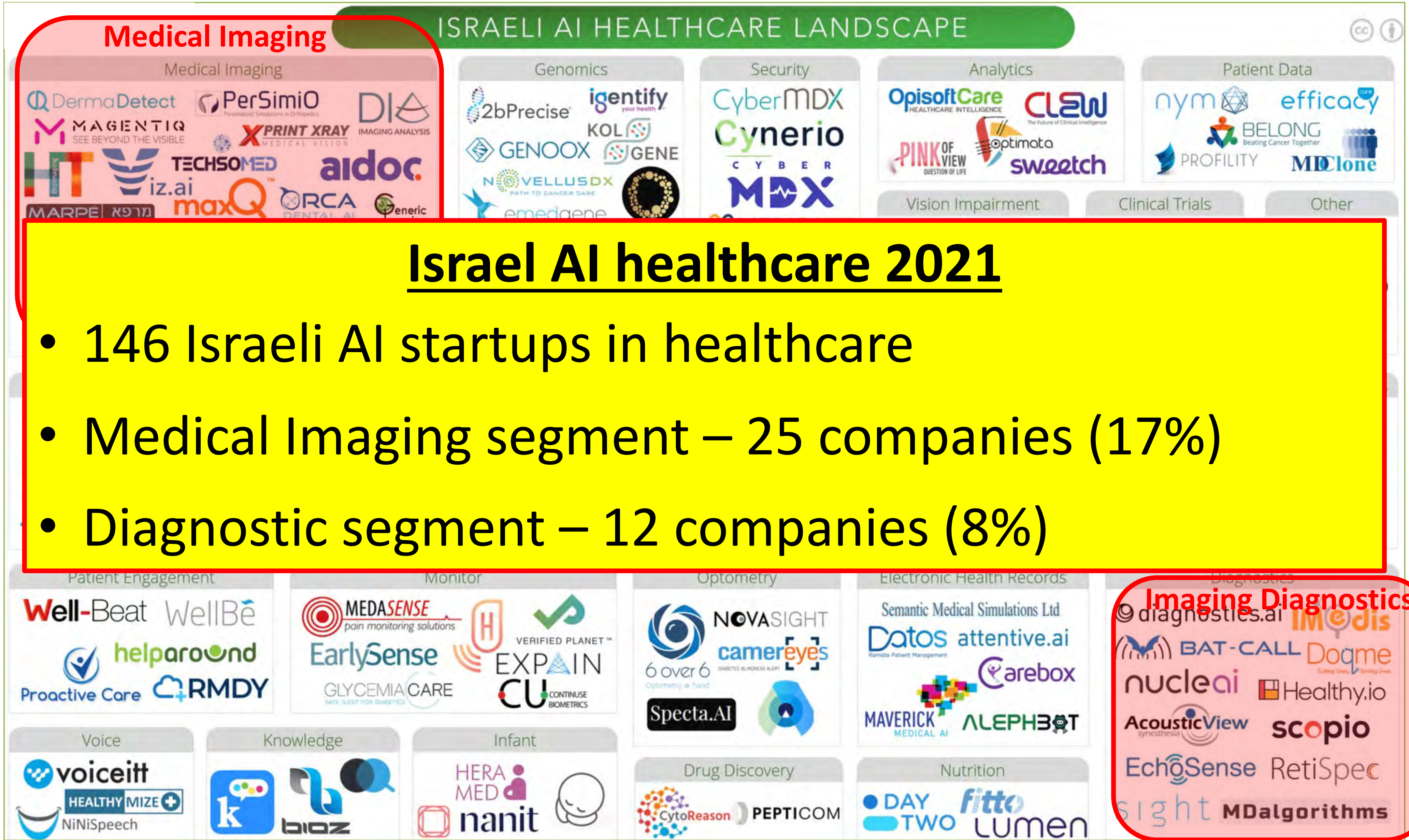
Race car

Present and future:
AI in Radiology is hot!!

AI and Radiology is hot!!



The Radiology Market in Israel



Israel AI healthcare 2021

- 146 Israeli AI startups in healthcare
- Medical Imaging segment – 25 companies (17%)
- Diagnostic segment – 12 companies (8%)

The future

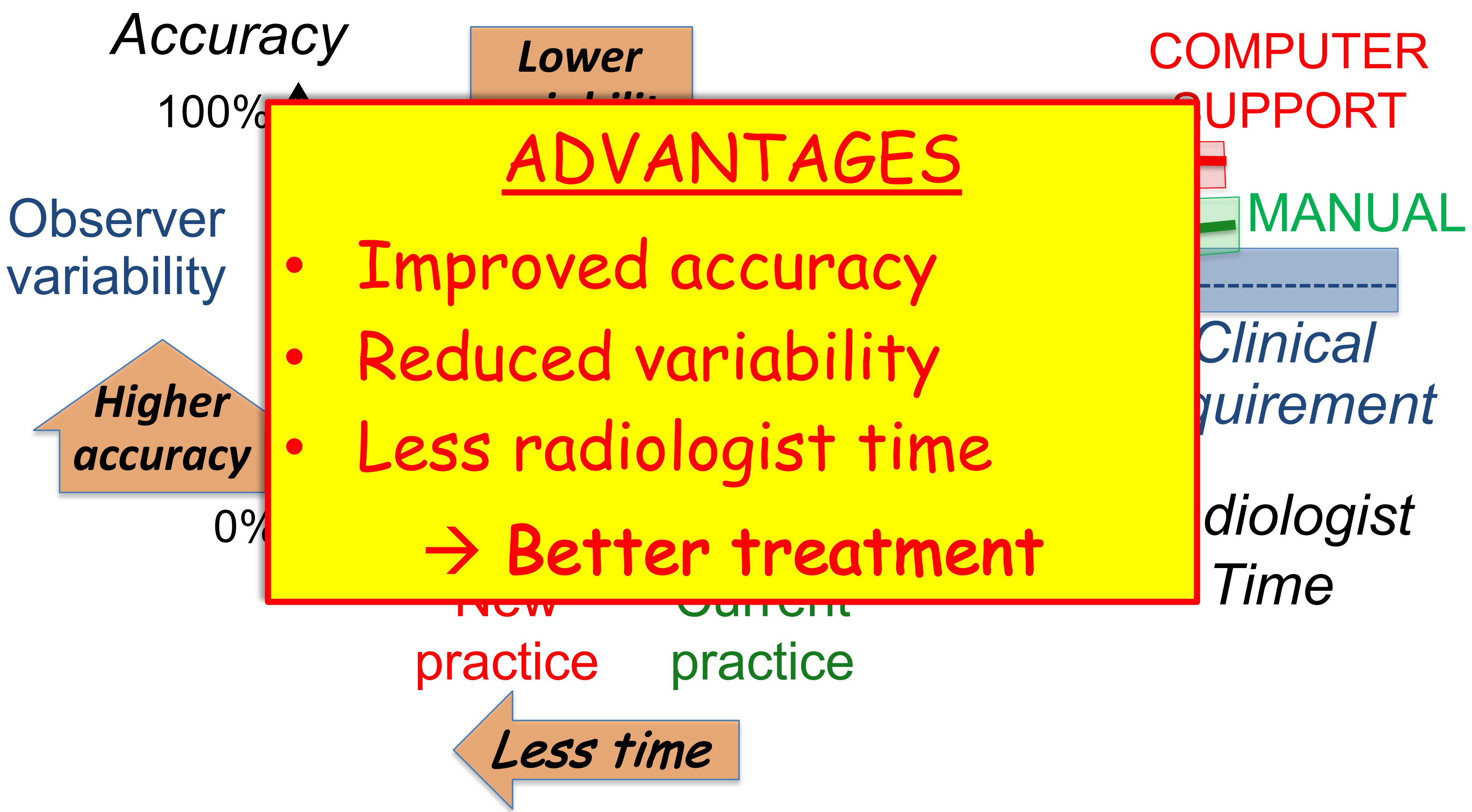
- **Narrow intelligence** by deep learning is very effective for specific tasks!
- Expensive and time-consuming: ***clinicians are not annotators***!
- "Low hanging fruits" will be picked in the next 1 to 3 years

AI will NOT replace radiologists any time soon

It will replace radiologists that do not use AI!

- Accelerate and increase coverage by involving the clinicians reducing effort and cost
- **Clinician in the loop bootstrapping** approach with unique methods for uncertainty estimation, error correction, and correction prioritization
- **Longer term viability** presents very significant challenges

Computational radiology: paradigm shift



ADVANTAGES

- Improved accuracy
- Reduced variability
- Less radiologist time

→ **Better treatment**

The future: combined imaging and patient data

Workflow of Radiomics in Neuro-Oncology

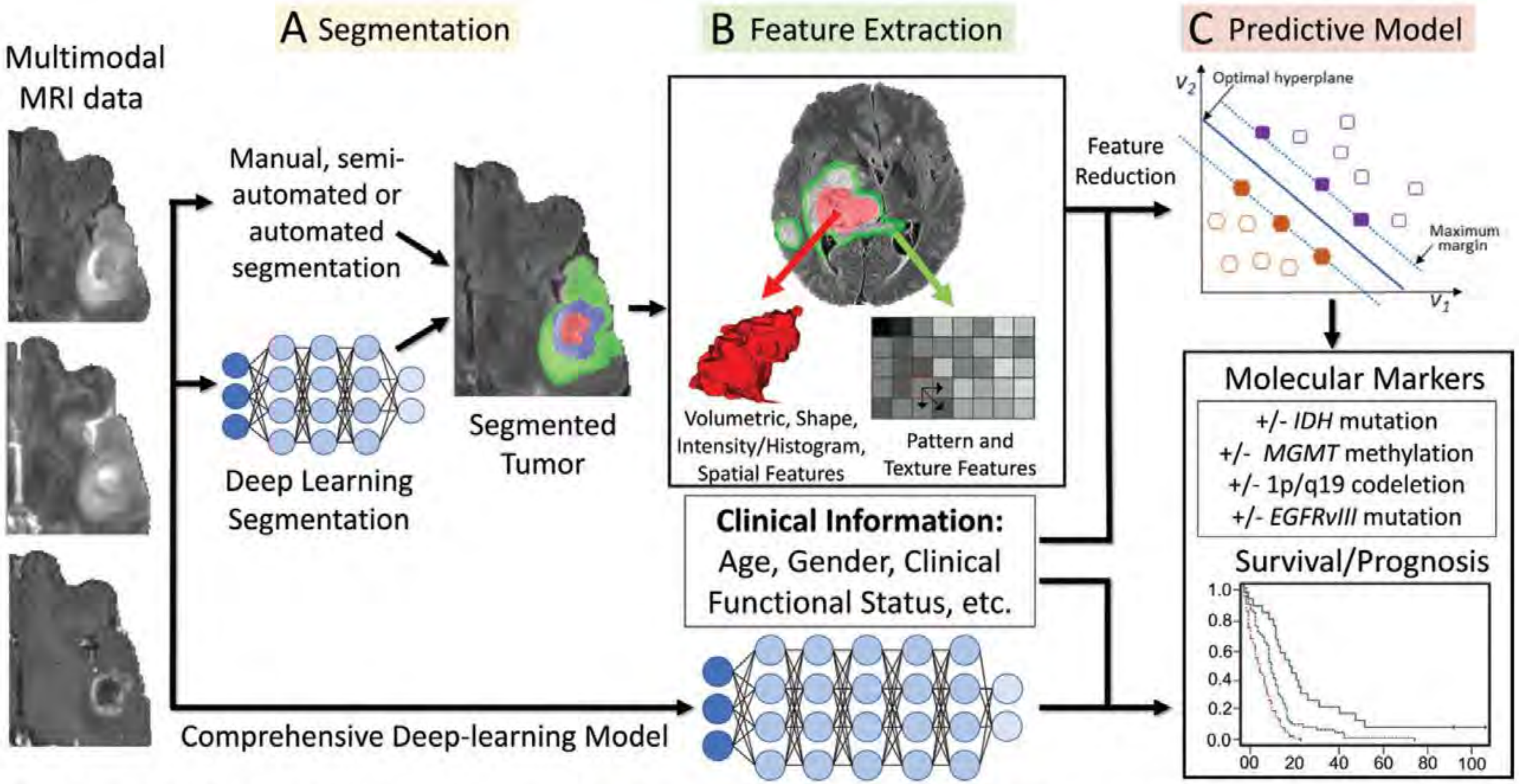


Figure 2: Workflow of radiomics in neuro-oncology. *A*, After preprocessing steps, multimodal MR images are segmented by using automated or manual methods. *B*, This is followed by feature extraction with use of a variety of different techniques. *C*, Machine learning methods are then trained on the features to generate models of underlying molecular markers and predict survival. Deep learning models can be used for performing each of the described steps individually or in a more comprehensive fashion (bottom pathway of figure). *EGFRvIII* = epidermal growth factor receptor variable III, *IDH* = isocitrate dehydrogenase, *MGMT* = O^6-methylguanine-DNA-methyltransferase.

Rudie et al. Emerging Applications of Artificial Intelligence in Neuro-Oncology. Radiology 2019.

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Dr. Amit Davidson

Refael Vivanti
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Yigal Shenkman
Clara Herscu
Many others …

novocure

HIGH RAD

Funding: Two grants from the Israel Innovation Authority 2018-20 and 2020-22

Thanks for your attention!

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