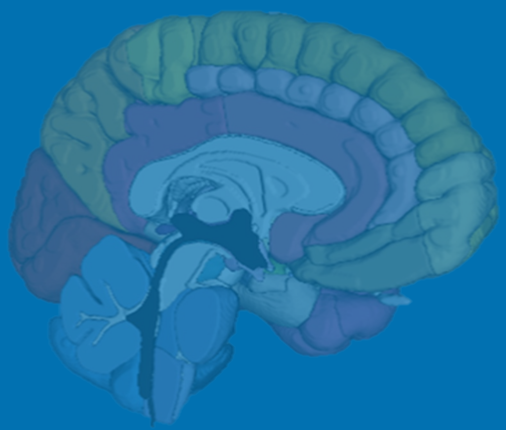
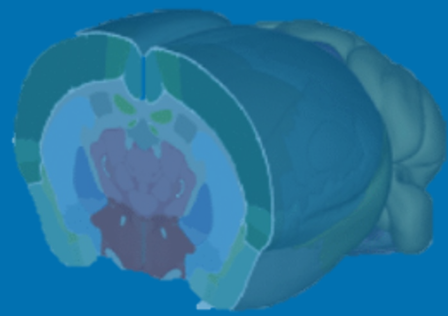
CIBM
Center for Biomedical Imaging



BRAIN MR IMAGE SEGMENTATION



Meritxell Bach Cuadra[1,2]

[1]CIBM Center for Biomedical Imaging

[2]Radiology Department, Lausanne University Hospital and University of Lausanne

Invited lecture, CIBM translational MR neuroimaging & spectroscopy (PHYS-760), EPFL

*Images from Allen Brain Atlases

UNIL | Université de Lausanne

mial Medical Image Analysis Laboratory

CHUV

OBJECTIVES

- Understand the importance of medical image segmentation, including brain MRI.
- Understand the basics of Bayesian framework brain tissue segmentation:
  - Intensity and partial-volume
  - Priors
- Be aware of **challenges** in brain tissue segmentation:
  - Generalization and domain adaption
  - Challenging populations: pathology, fetuses, children, etc

OUTLINE

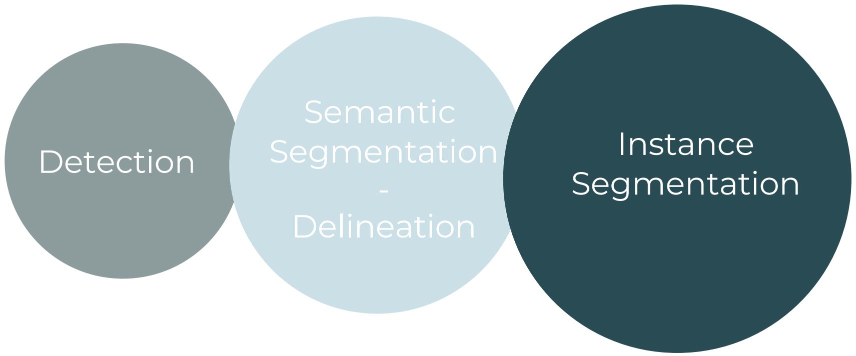
- Definition and motivation
- Chronological overview of segmentation methods
- Selected MRI brain segmentation approaches
  - Atlas-based registration
  - Machine-learning in a nutshell
  - Statistical classification in a Bayesian framework
  - Deep learning methods

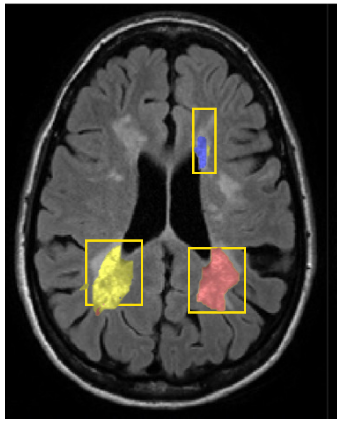
DEFINITION AND MOTIVATION

DEFINITION - IN COMPUTER VISION

Image segmentation* is the process of partitioning a digital image into multiple segments (sets of pixels/voxels).

The goal of segmentation is to simplify and/or change the representation of an image into something that is more meaningful and easier to analyze.





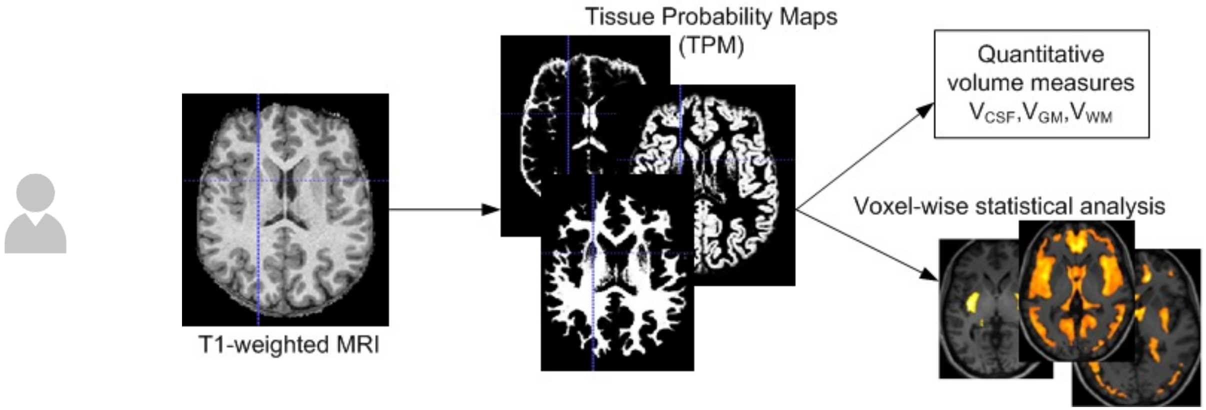
*From L. Shapiro et al, "Computer Vision", pp 279–325, New Jersey, Prentice-Hall.

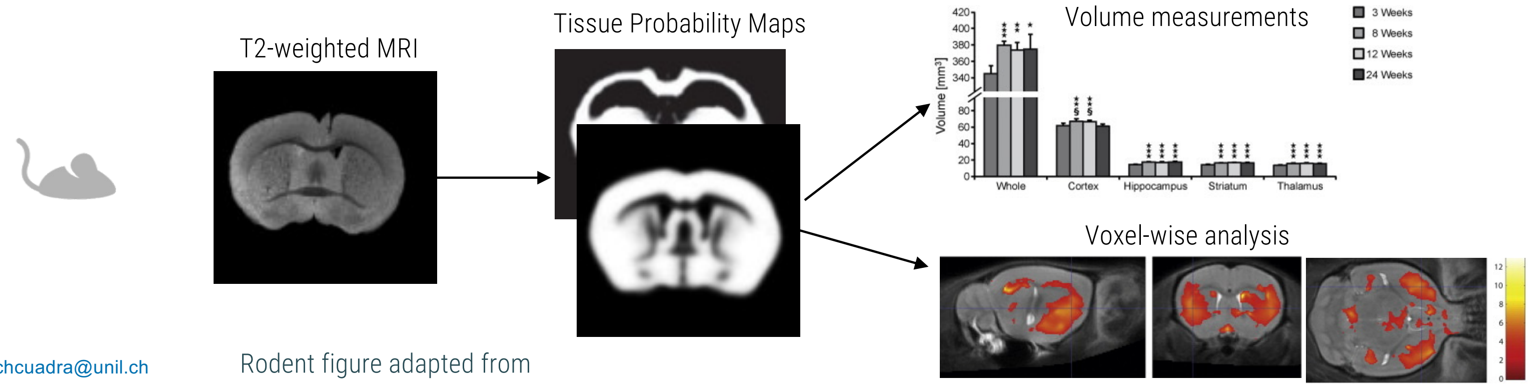
MOTIVATION

- Clinical routine of brain MR imaging (1.5T and 3T)
- Research acquisitions of brain MR (7T)
- Pre-clinical rodent brain MR (4T to 14T)
- Analysis and quantification in an automated and reproducible manner
- Data dimensions
  - Human: 256x256x180 voxels, 1 mm^3 isotropic
  - Rodent: $150 \times 150 \times 100\ \mu m^3$
  - Pre-clinical research, Radiology, neurology, neurosurgery, psychiatry, neuroscience

TISSUE SEGMENTATION

- Tissue volume as ‘biomarker’ for diagnosis in many brain disorders
- Local tissue volume for voxel-based morphometry studies





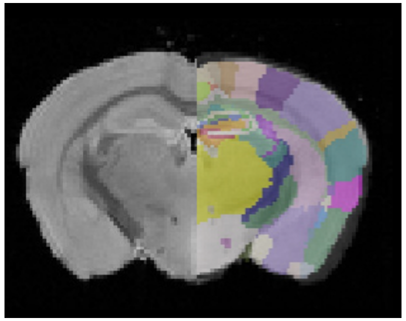
Rodent figure adapted from

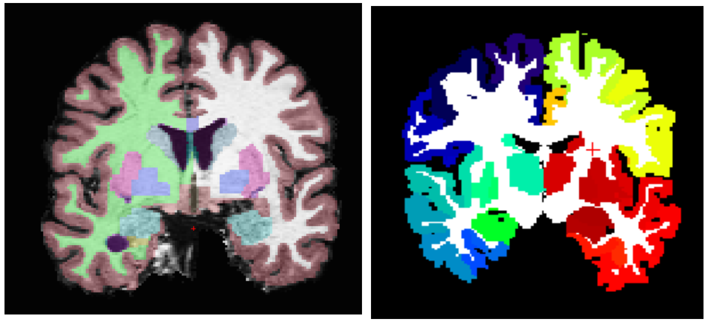
REGIONS OF INTEREST

- White matter and gray matter segmentation for fiber tracking
- Surface extraction (eg brain development studies, thickness, etc)

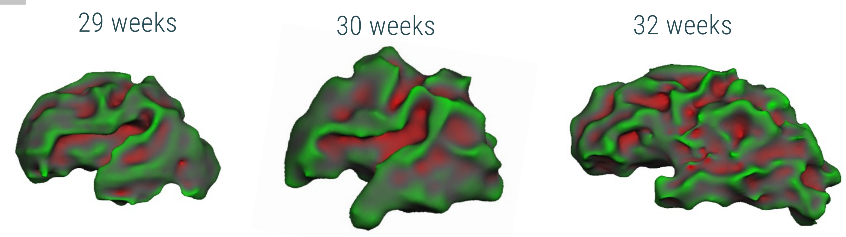
Region of interest parcellation

Freesurfer https://surfer.nmr.mgh.harvard.edu/

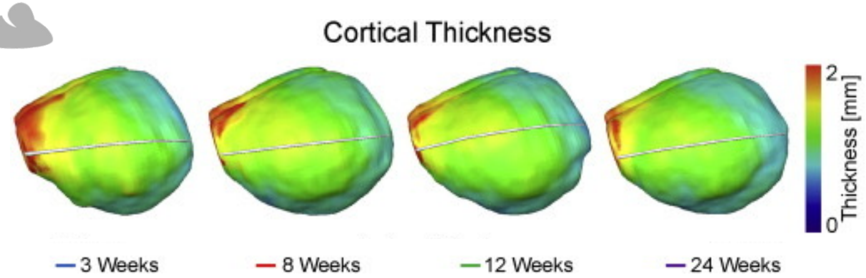




Brain development



Tourbier et al, OHBM, 2016



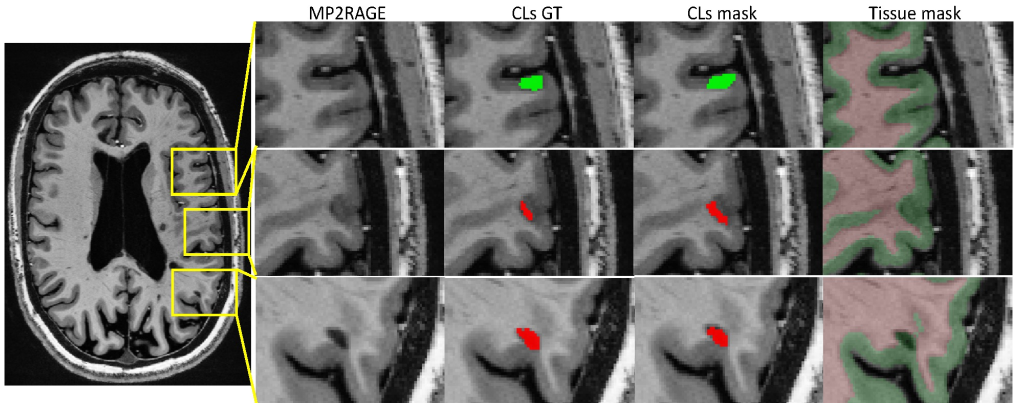
L. Hammelrath et al, NeuroImage 2016

MOTIVATION

Radiology, neurology, neurosurgery, psychiatry, neuroscience

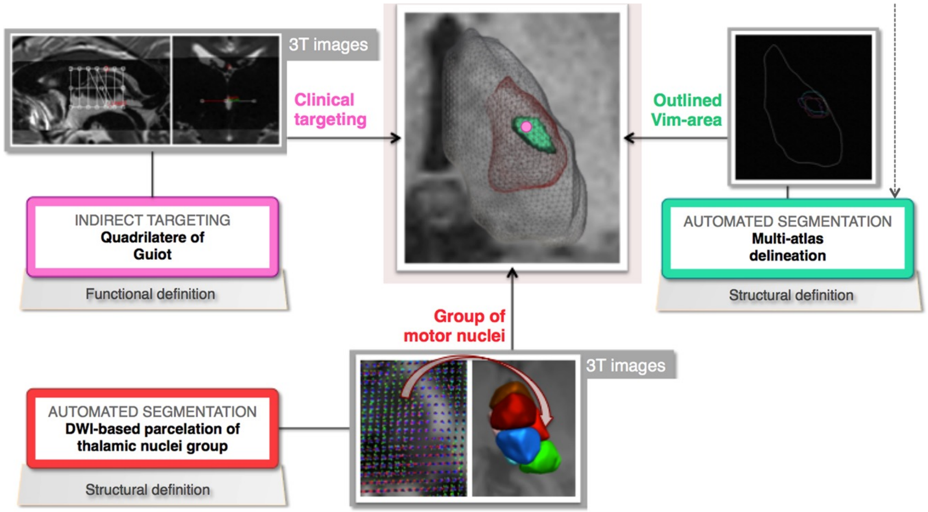
- Support diagnosis and follow up: anomaly / lesion detection, eg. tumor, stroke, multiple sclerosis
- Support precise navigation / treatment planning

Multiple Sclerosis Lesions[1]



[1] La Rosa et al, NMR 2022.

VIM targeting for Gamma Knife Radiosurgery[2]



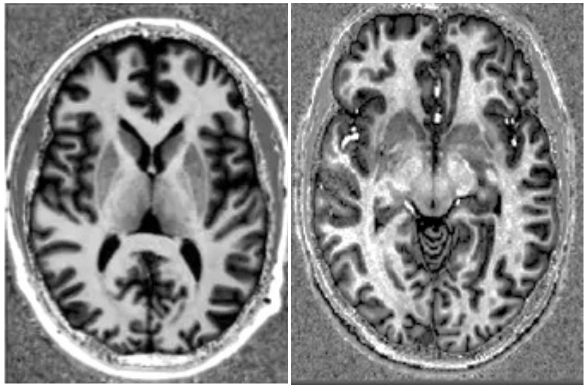
[2] E. Najdenovska et al, Scientific Reports, 2019.

INPUT DATA

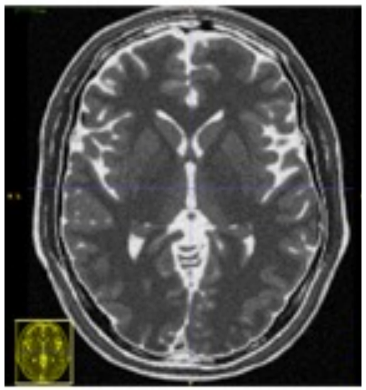
Multiple contrasts…

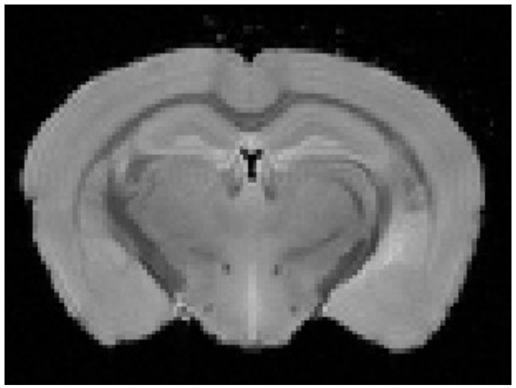
T1w

3T MP2RAGE 7T

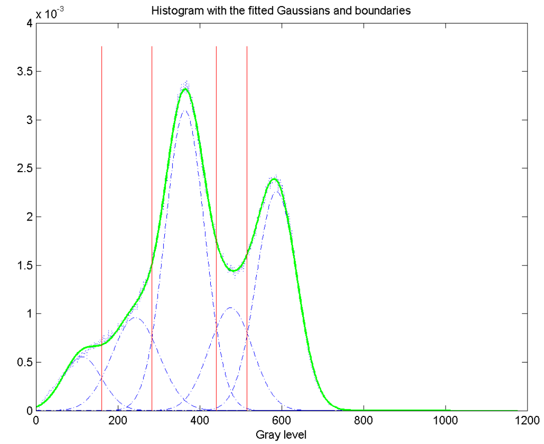


T2w

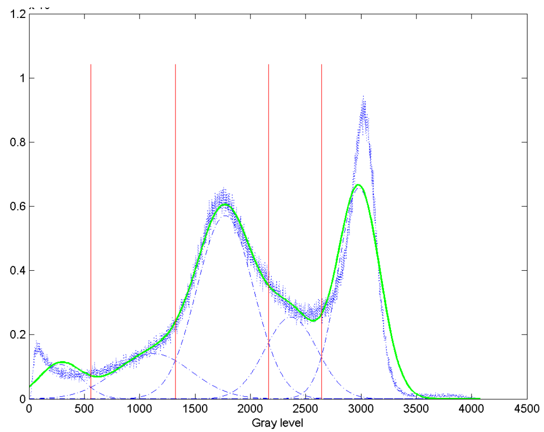




MPRAGE



MP2RAGE



OVERVIEW OF SEGMENTATION METHODS

A BIG ZOO OF SEGMENTATION STRATEGIES

- There is a world outside deep learning
- There is a world outside machine learning
- Categorization of methods is fuzzy
- The same applies in other image processing tasks (eg registration, resolutions, enhancement etc)

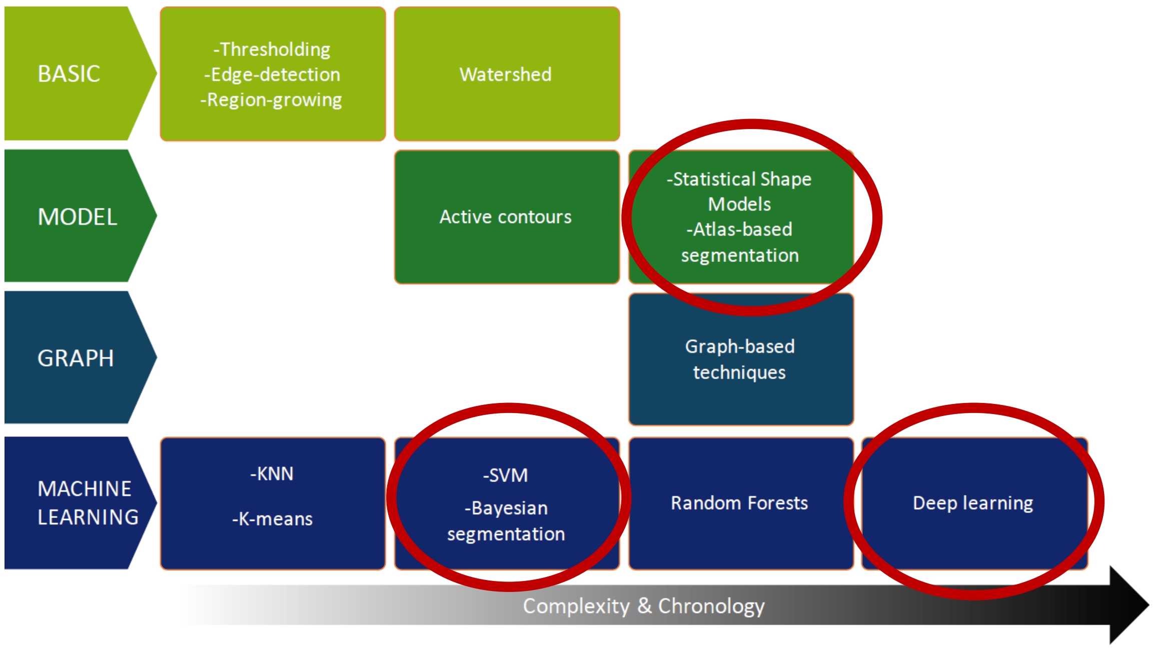


Figure from Bach Cuadra, Favre, Omoumi, Seminars in musculoskeletal radiology, 2020

MODEL

ATLAS-BASED SEGMENTATION

Center for Biomedical Imaging

Atlas

Spatial prior knowledge

Patients

1

2

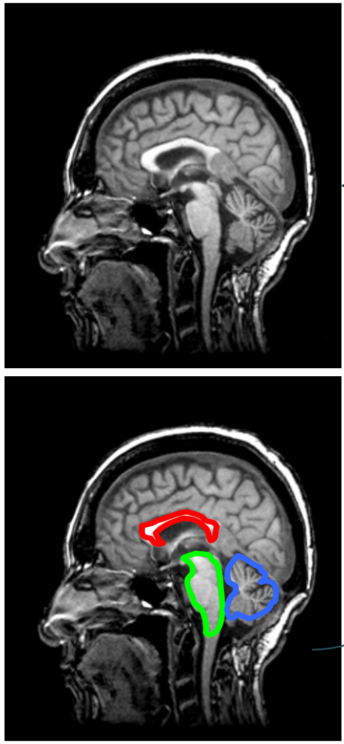
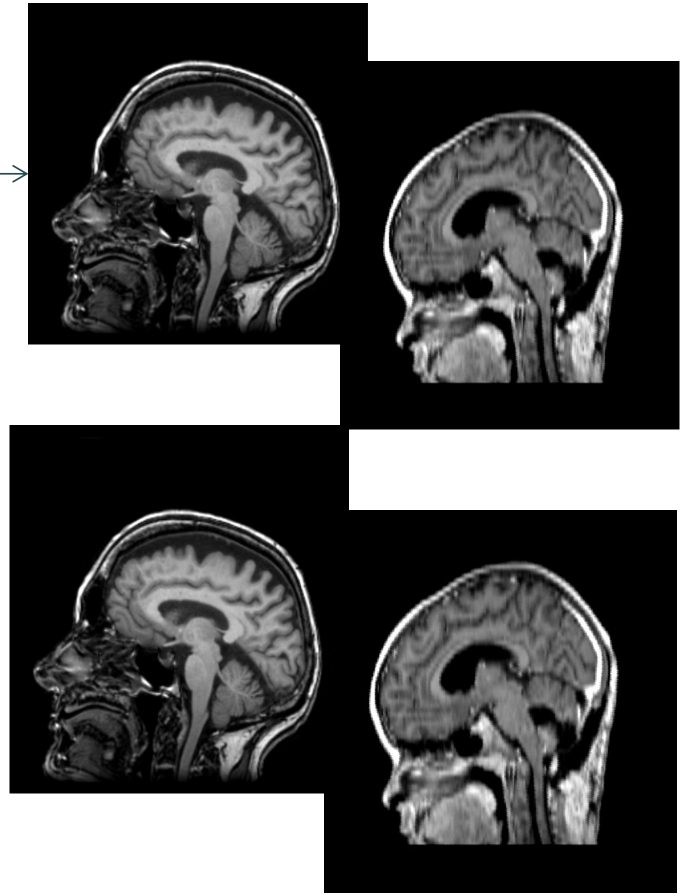


Image registration

$T_{affine} \circ T_{non\text{-}rigid}$

Affine → NR

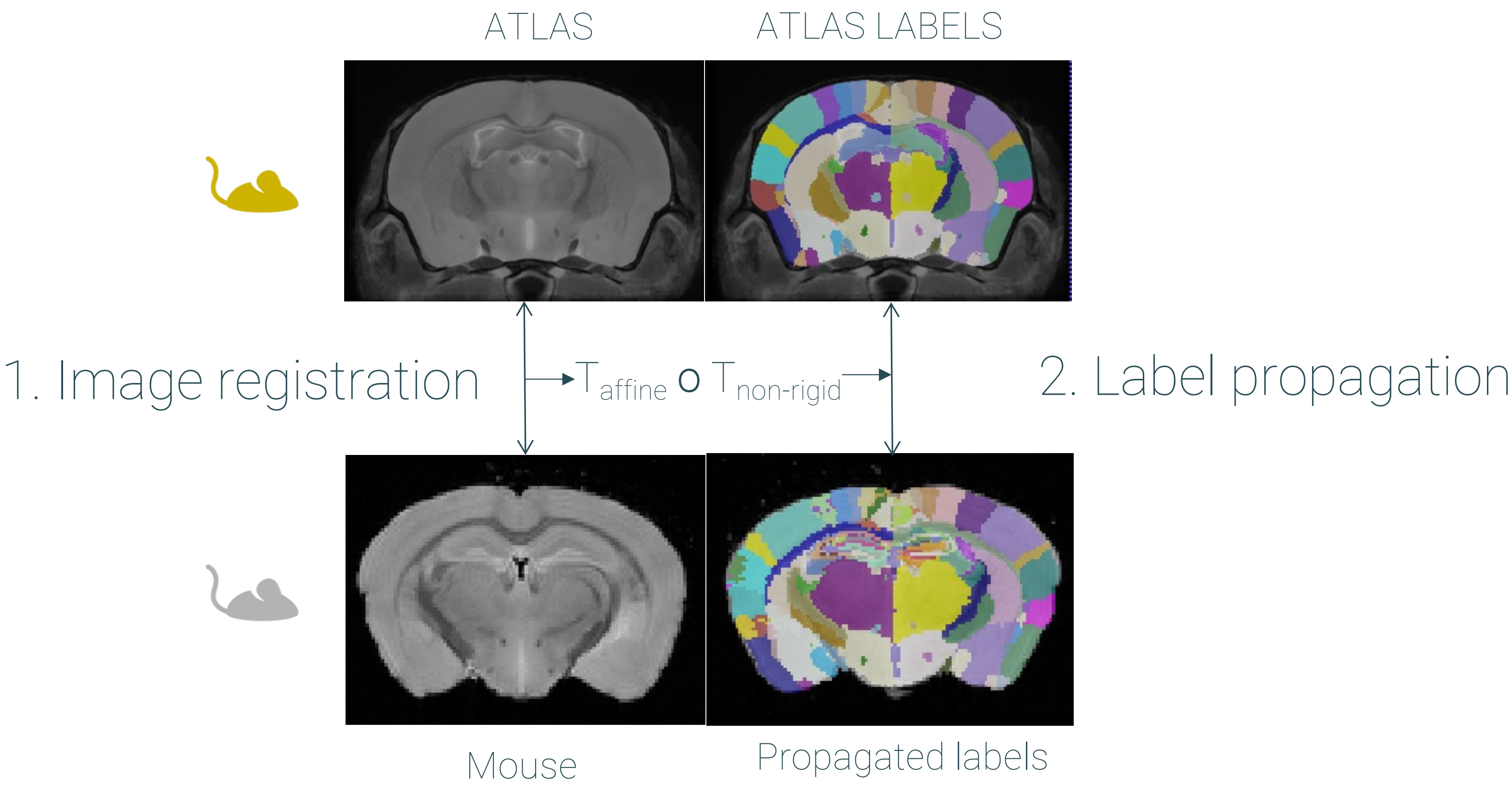


Cabezas et al., Computer Methods and Programs in Biomedicine, 2011, Bach Cuadra et al, Handbook of Biomedical Imaging, 2015.

MODEL

ATLAS-BASED SEGMENTATION

Preferred method in rodent brain ROI segmentation



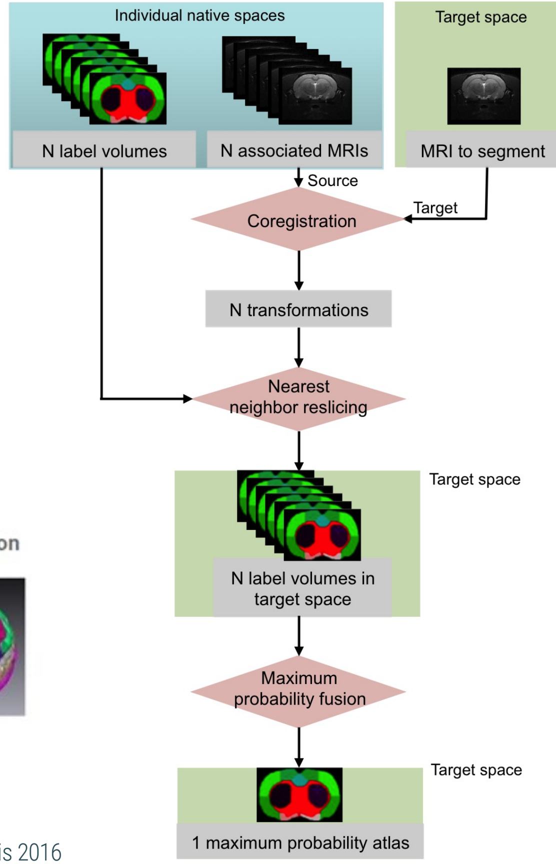
*Prof. Bagni's, Dr. V Mercaldo (UNIL) research project, with I. Jelescu and G. Girard (CIBM)

MODEL

MULTI-ATLAS-BASED SEGMENTATION

- Dependence on chosen atlas
- Template construction
  - Average template
  - Group-wise registration
- Multiple atlas strategies*:
  - Atlas selection[1]
  - Fusion strategies[2,3,4]

Figure from Lancelot et al, PlosOne, 2014



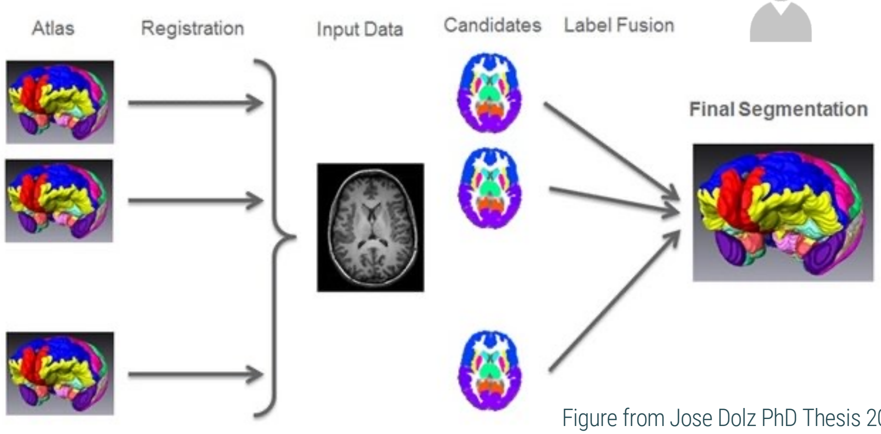
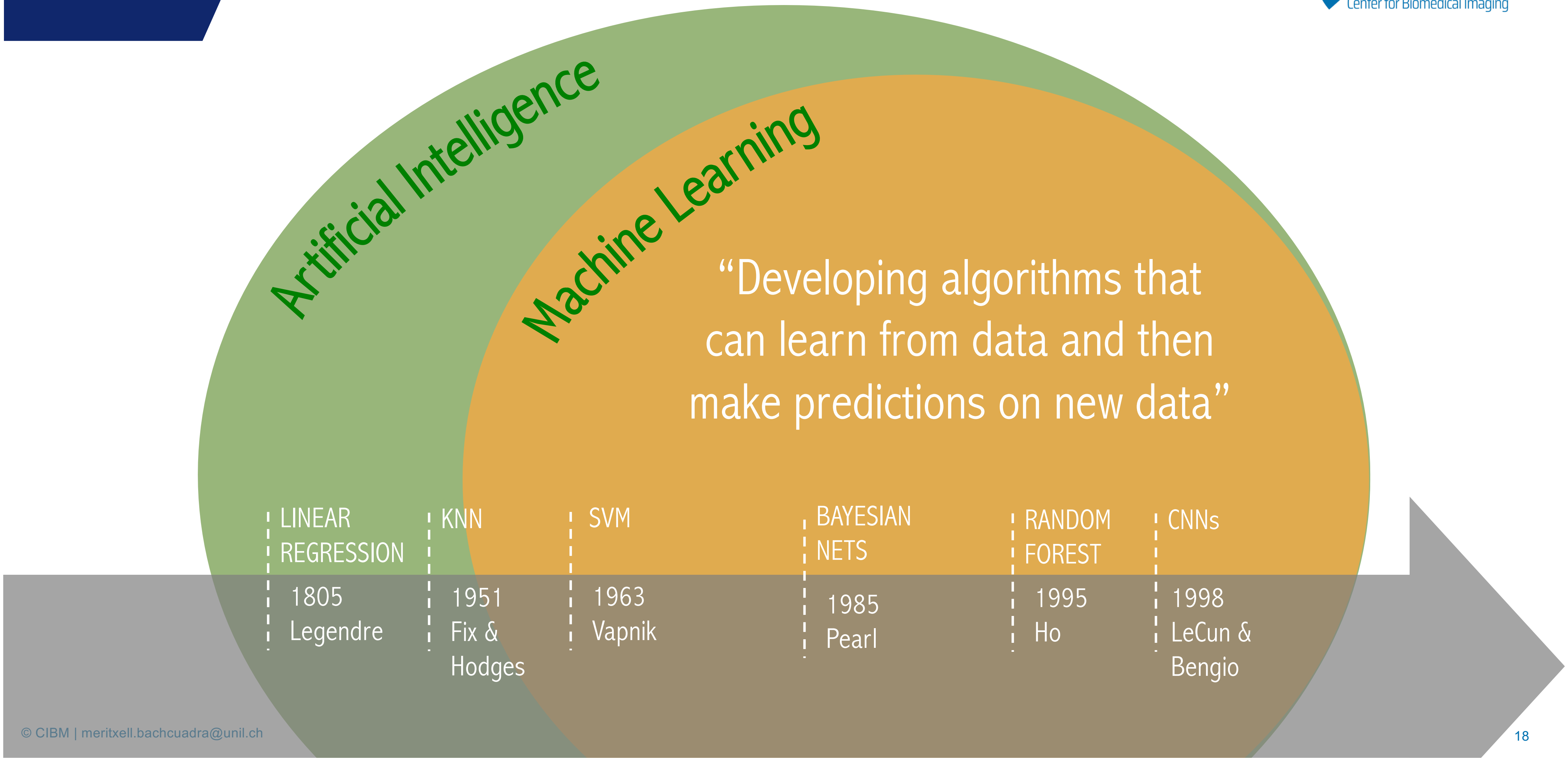


Figure from Jose Dolz PhD Thesis 2016

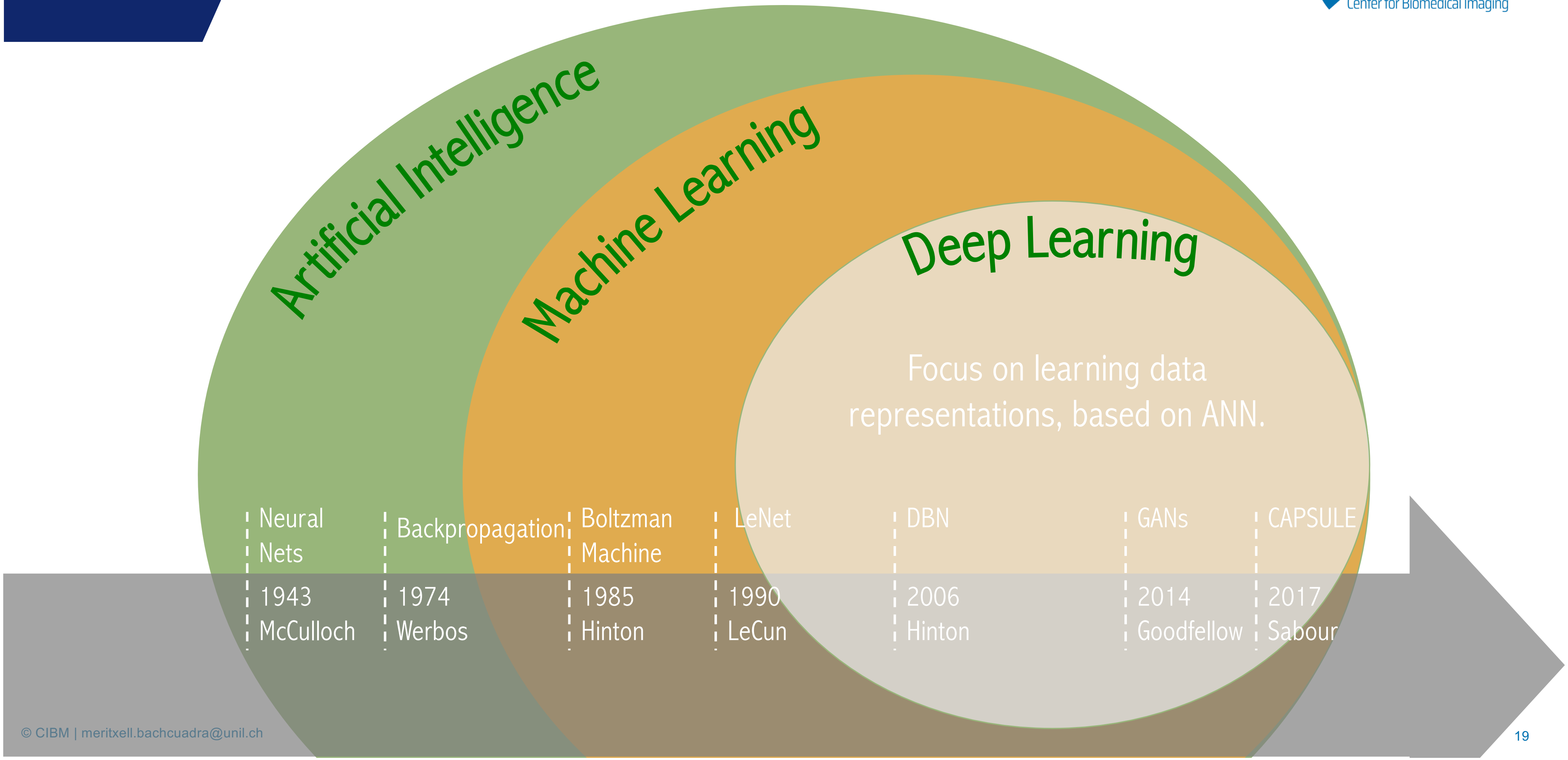
[1] Aljabar et al MICCAI 2007, [2]X. Artaechevarria et al, TMI 2009, [3]Iglesias et al MedIA, 2013, [4] Lancelot et al, PlosOne 2014, *Rohlfing et al Handbook of Biomedical Image Analysis pp 435-486, 2005.

MACHINE LEARNING IN A NUTSHELL

CONTEXT


Artificial Intelligence
Machine Learning
“Developing algorithms that can learn from data and then make predictions on new data”
LINEAR REGRESSION
1805
Legendre
KNN
1951
Fix & Hodges
SVM
1963
Vapnik
BAYESIAN NETS
1985
Pearl
RANDOM FOREST
1995
Ho
CNNs
1998
LeCun & Bengio

CONTEXT

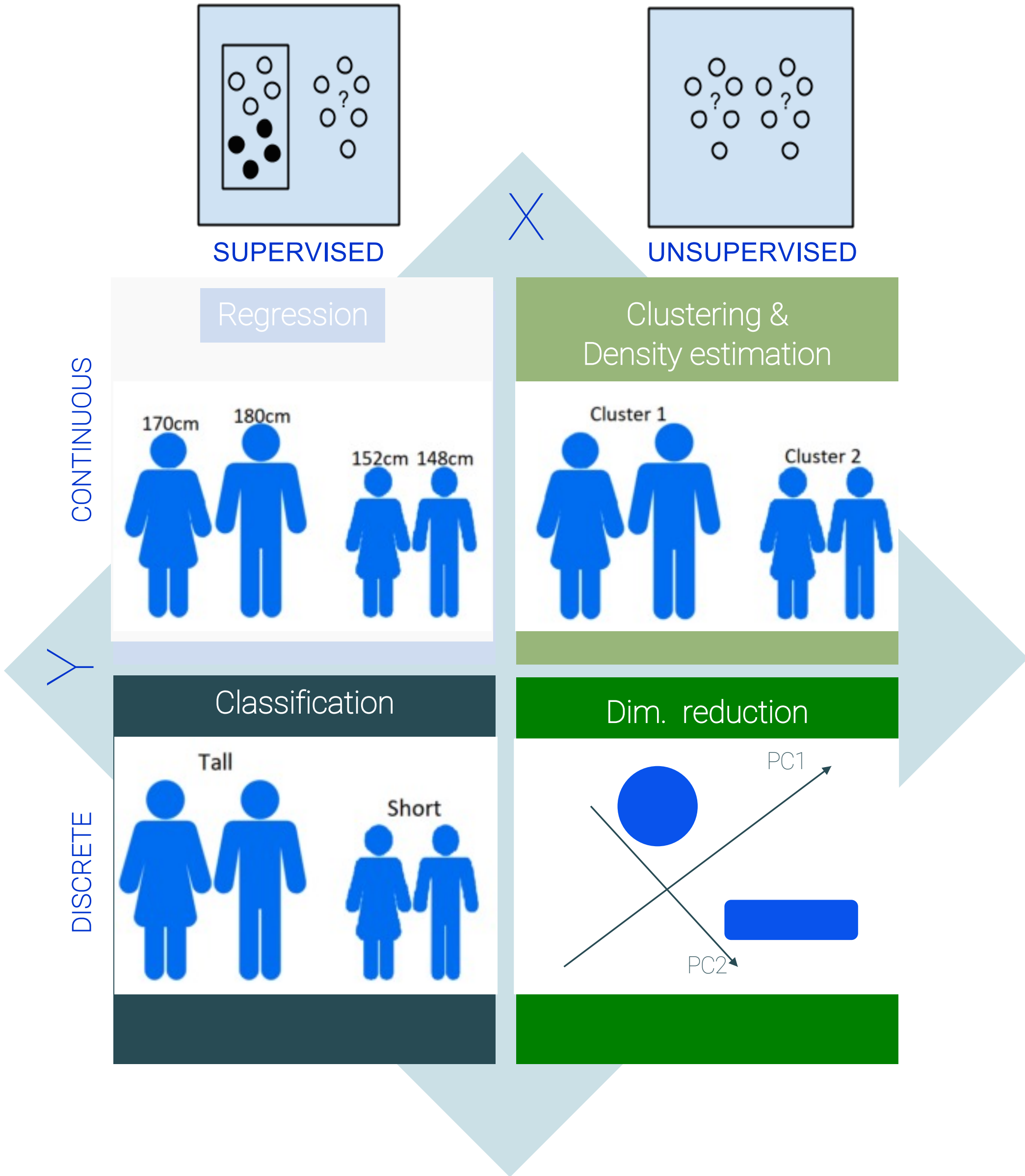

Artificial Intelligence
Machine Learning
Deep Learning
Focus on learning data representations, based on ANN.
Neural Nets
1943
McCulloch
Backpropagation
1974
Werbos
Boltzman Machine
1985
Hinton
LeNet
1990
LeCun
DBN
2006
Hinton
GANs
2014
Goodfellow
CAPSULE
2017
Sabour

Output

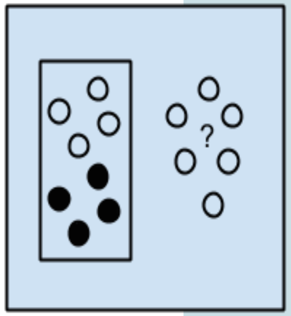
Input data (features)

$$Y = f(X)$$

Model



TYPES OF LEARNING

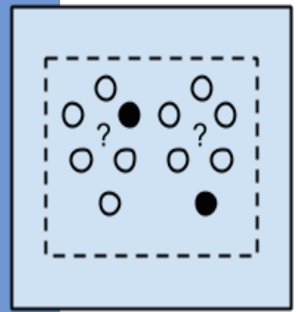


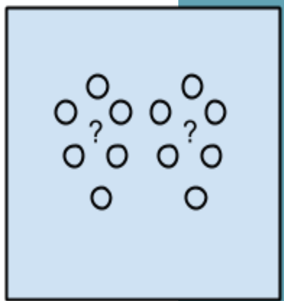
Supervised learning

Training samples, predictive model, task driven, P(y/x)

Semi-supervised learning

Some training samples available



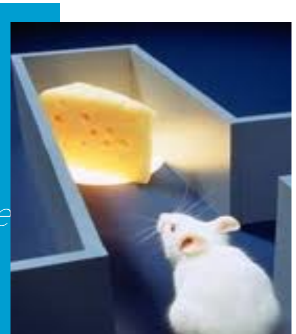


Unsupervised learning

Data driven, density estimation P(x)

Reinforcement learning

Feedback loop between learning syste and experience (reward)



OVERVIEW OF ML ALGORITHMS

Figure from J. Brownlee, Machine Learning Mastery blog

MACHINE LEARNING APPLICATIONS

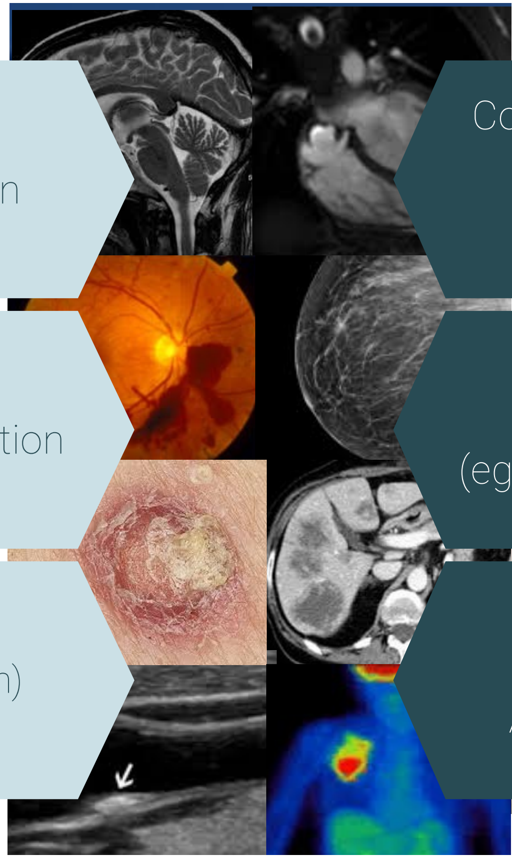
In medical imaging

Organs or lesions

Detection, segmentation and tracking

Computer-aided diagnosis
Therapy planning

Prognosis



Imaging biomarkers

New patterns in population studies

Combining imaging and non-imaging features

(eg Radiogenomics, clinical reports)

Image resotiration (eg denoising, super-resolution)
Image reconstruction

Image retrieval

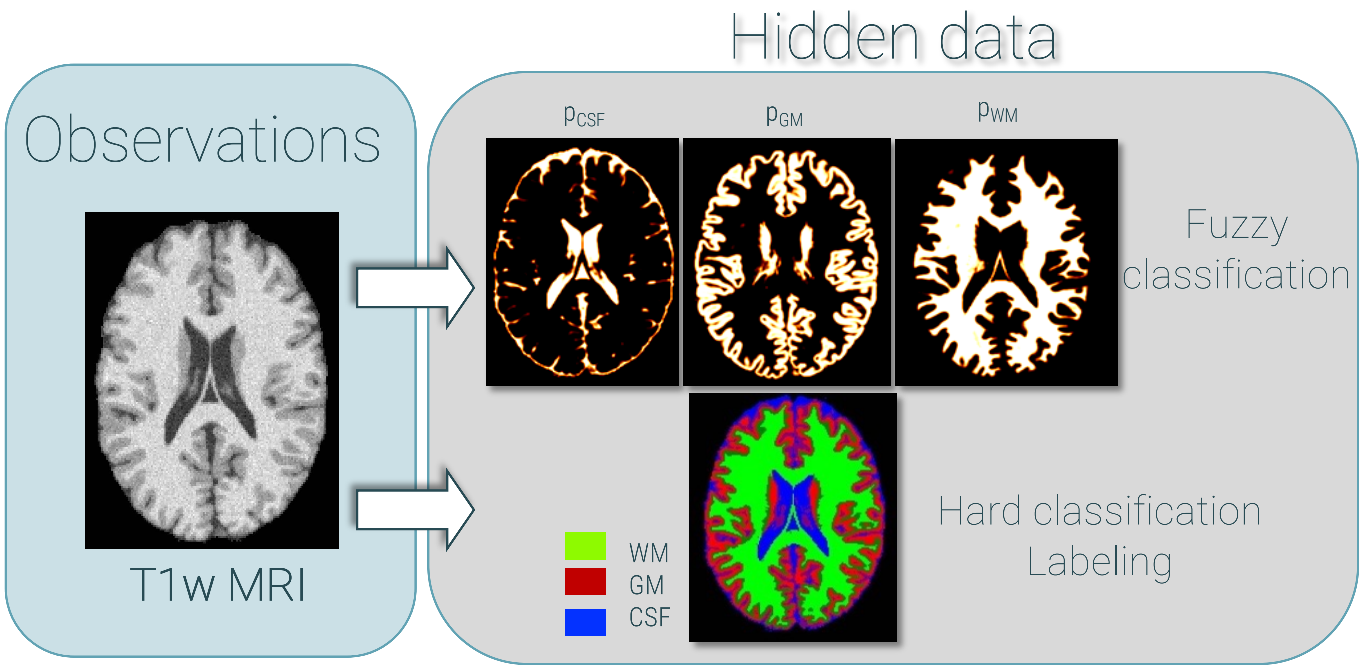
As daily support for RAD

BAYESIAN FRAMEWORK

BAYESIAN FRAMEWORK

Segmentation as unsupervised voxel-wise classification

- Data-driven, density estimation, generative model



$$P(y|x) \qquad P(x)$$

- A maximization problem:

$$\hat{x} = argmax_{x \in X} P(x)P(y|x)$$

MIXTURE OF INTENSITY DISTRIBUTIONS $P(y|x)$

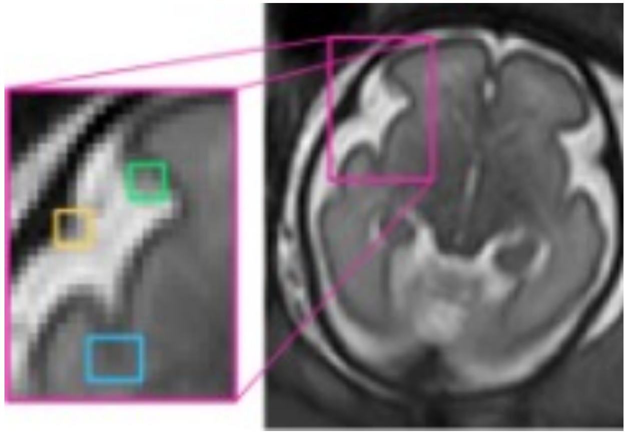
- MR image formation process:

- Pure voxel can be approximated by Gaussian distribution

$$f(x;\mu,\sigma^2) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

- Partial-volume (PV) model[1,2,3,4]:

$$\mu_x(\alpha) = \alpha\mu_{l_1} + (1-\alpha)\mu_{l_2}$$



Partial volume effect (PVE)

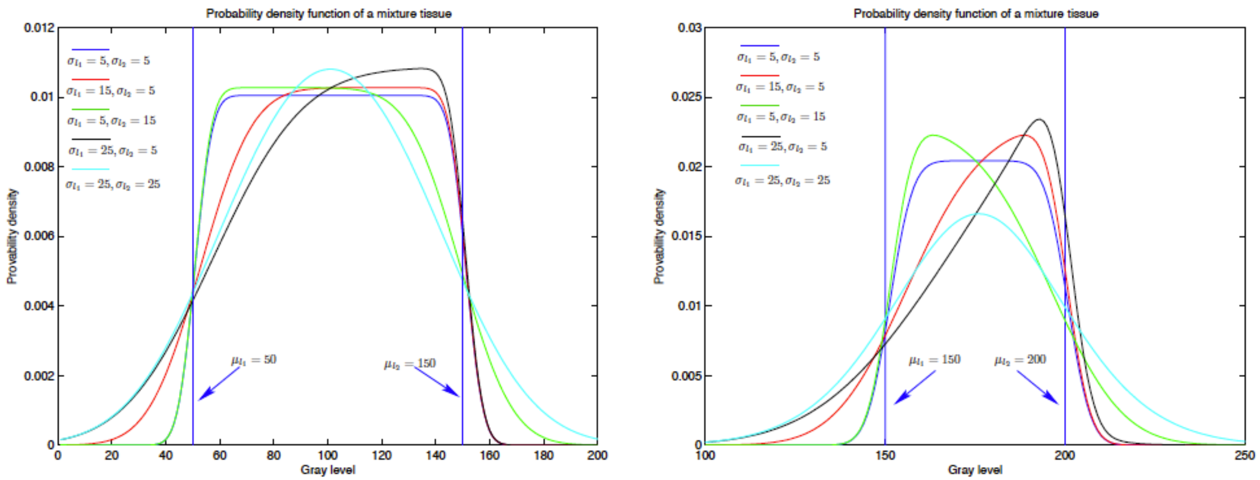


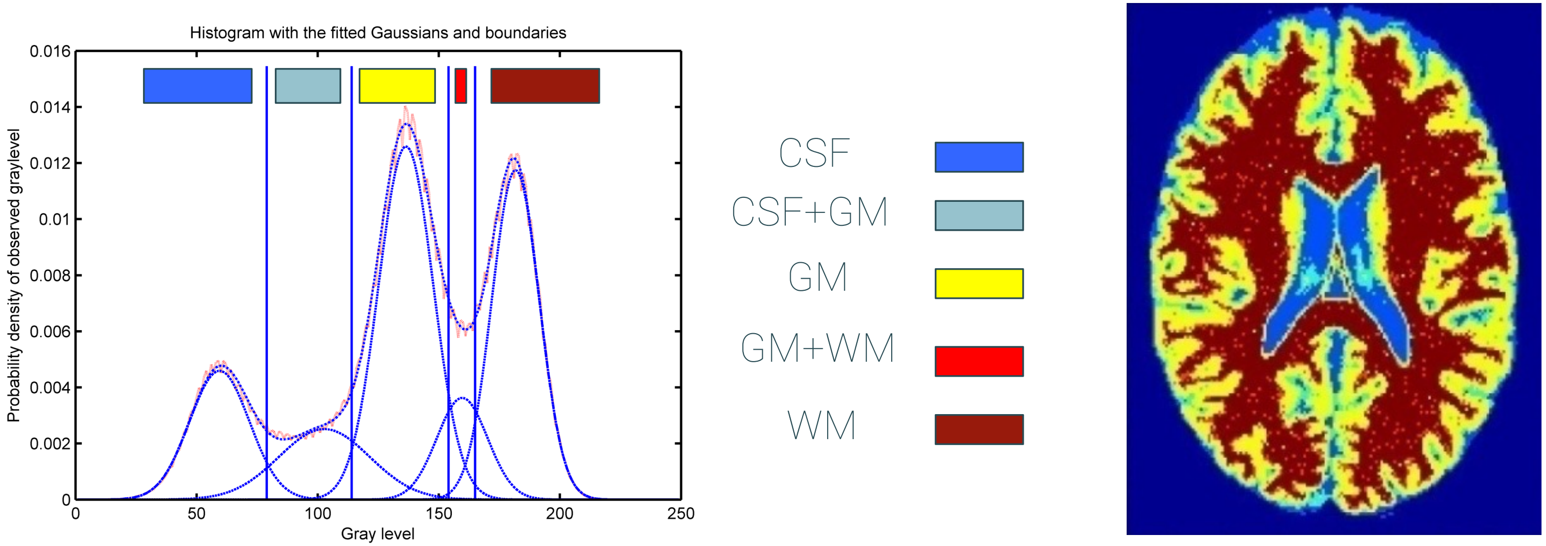
Figure from Bach Cuadra et al, IEEE TMI 2005.

[1]Santago et al, IEEE TMI, 1993, [2] Shattuck et al Neuroimage 2001, [3] Noe et al, IPMI 2001, [4] Choi et al, IEEE TMI 1991.

GAUSSIAN MIXTURE MODEL

$$P(x)$$

$$P(y_i \mid \theta) = \sum_{\forall x_i \in L} w_{x_i} P(y_i \mid x_i) = \sum_{\forall x_i \in L} w_{x_i} f_x(y_i \mid \theta_{x_i})$$



HIDDEN MARKOV RANDOM FIELD (MRF) $P(x)$

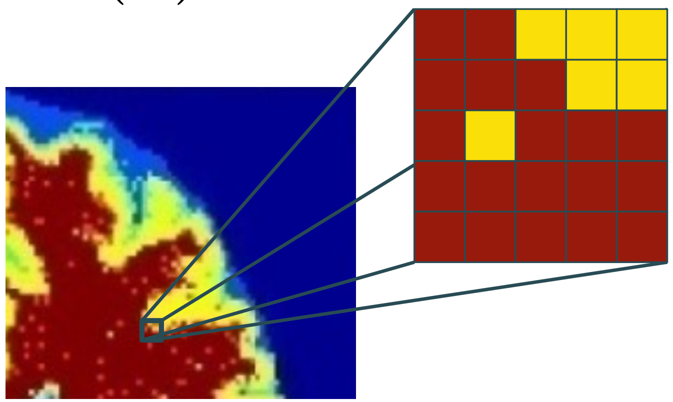
- Relationship between spatial features: **local spatial priors**

$$P(x_i \mid x_{S-\{i\}}) = P(x_i \mid x_{\mathcal{N}_i})$$

- A MRF can be characterized by a Gibbs distribution[1]

  (*Hammersley-Clifford theorem*)

$$P(x) = Z^{-1} e^{-U(x,\beta)}$$



[1]Duda & Hart Pattern Classification and Scene Analysis, Wiley, 1973;
Bach Cuadra, IEEE TMI, 2005; Bach Cuadra et al 2009, Roche et al 2011 MedIA, 2011, O. Esteban et al, CMPB, 2014

GAUSSIAN HIDDEN MARKOV RANDOM FIELD

$$P(y_i|x_{\mathcal{N}_i},\theta) = \sum_{\forall x_i \in \mathcal{L}} \underset{2}{P(x_i|x_{\mathcal{N}_i})}\,\underset{1}{P(y_i|\theta_x)}$$

$$\hat{x} = argmax_{x \in X} P(x)P(y|x)$$

1 Parameter estimation: good if the classification is known

2 Segmentation: good intensity distribution model is needed

FGMM

Initialization of parameters (manually, k-means, atlas priors)

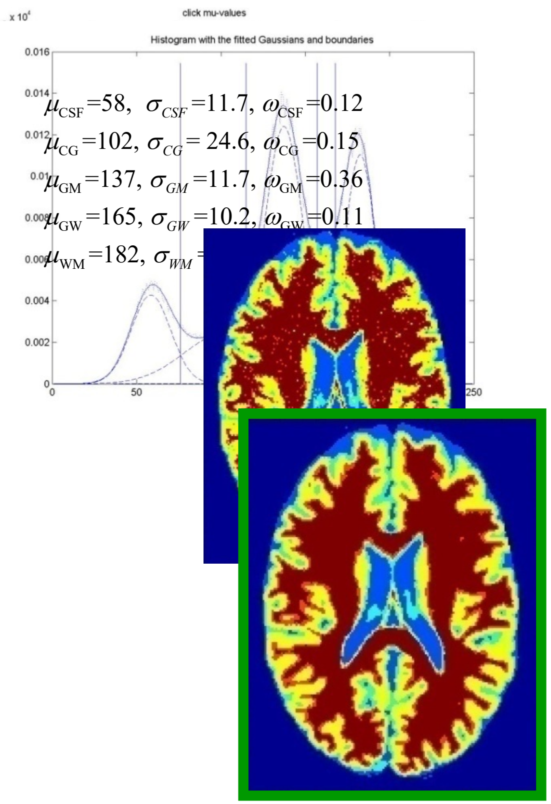
EM

Estimated parameters
Bayesian criterion = Initial label map

GHMRF

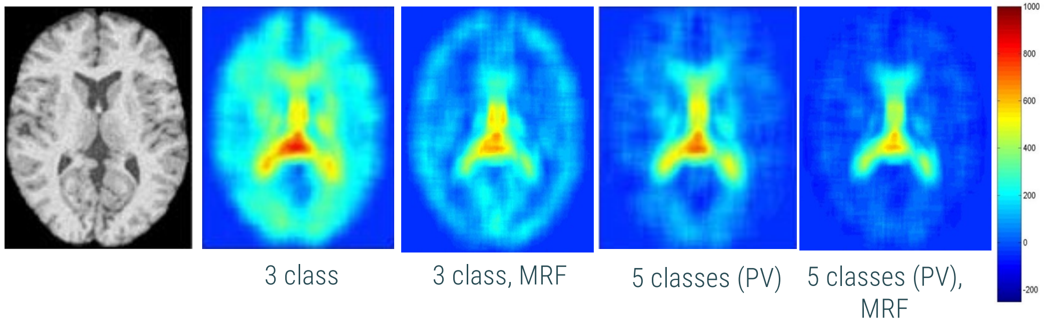
EM-HMRF

Classification by Maximum a Posteriori



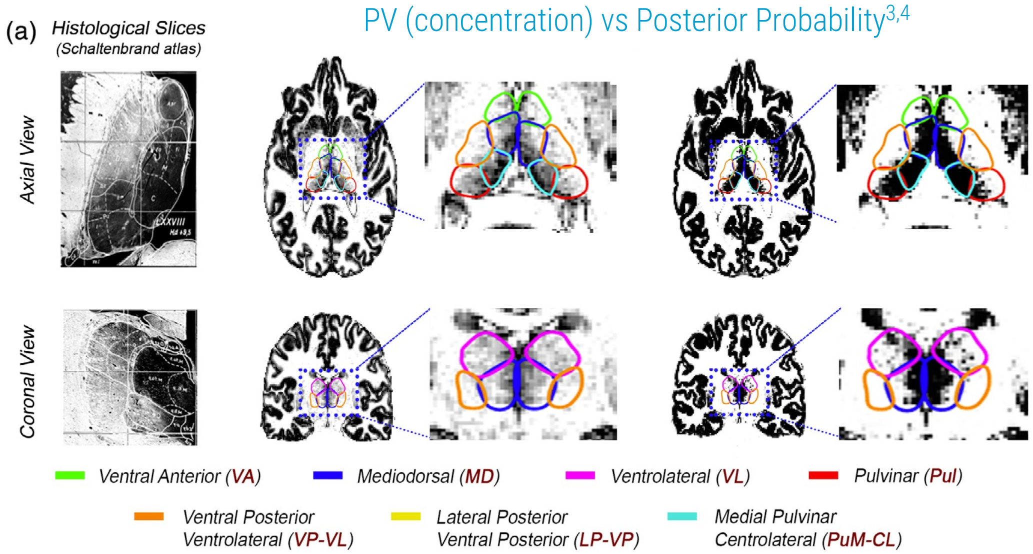
IMPORTANCE OF PARTIAL VOLUME

Global/local tissue volume estimation



- PV modeling, total tissue volume error[1,2] :
  - 7% to 1 % CSF
  - 11% to 5 % GM
  - 10% to 6% WM

Thalamus GM estimation



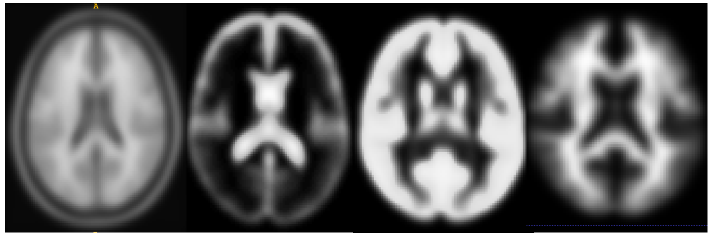
[1]M. Bach Cuadra et al, IEEE TMI 2005, 2 Gonzalez-Ballester et al MedIA 2002, [3] Roche et al MICCAI 2014, [4] Ashburner Neuroimage 2012.

ATLAS PRIORS

Global/local tissue volume estimation

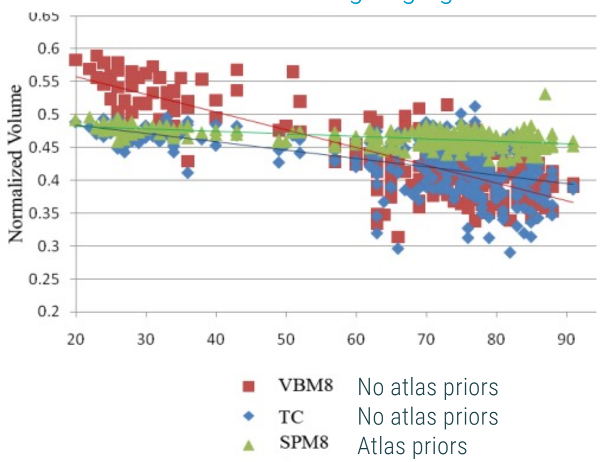
$$\hat{x} = \arg\max_{x \in \mathcal{X}} (P(x) P_{atlas}(x) P(y \mid x))$$

- From probabilistic atlases
  - As initialization only
  - For taking a decision
- Advantage of including additional priors
- Good atlases are needed -> atlas selection and registration
- Maybe not worthy for pathological populations



MNI305 template https://mcin.ca/research/neuroimaging-methods/atlases/

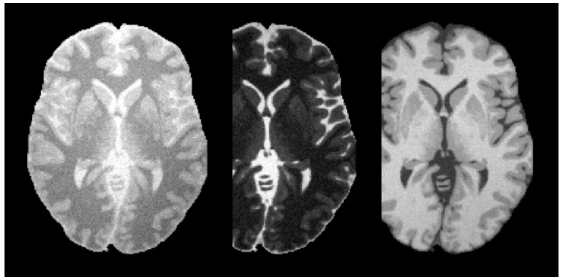
GM volume through aging[1,2]

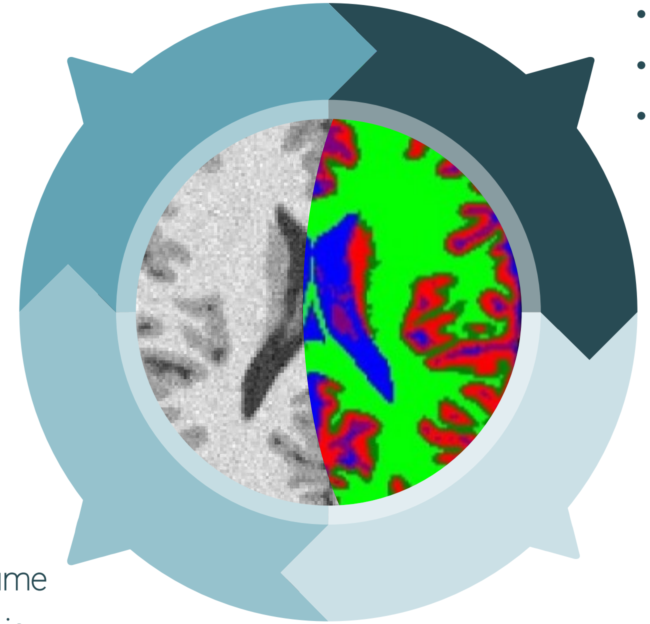


[1]Ribes et al, ISMRM 2011, [2]Roche et al, MedIA 2011

RECAP BAYESIAN TISSUE SEGMENTATION

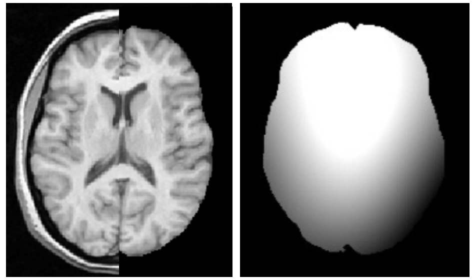
Input data





Pre-processing

- Skull stripping
- Noise
- Bias correction



Prior knowledge

- Local spatial
- Tissue probability atlases
- Partial volume model

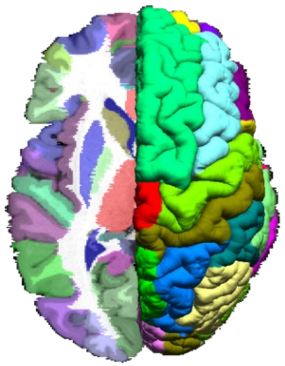


Image from brainsuite.org

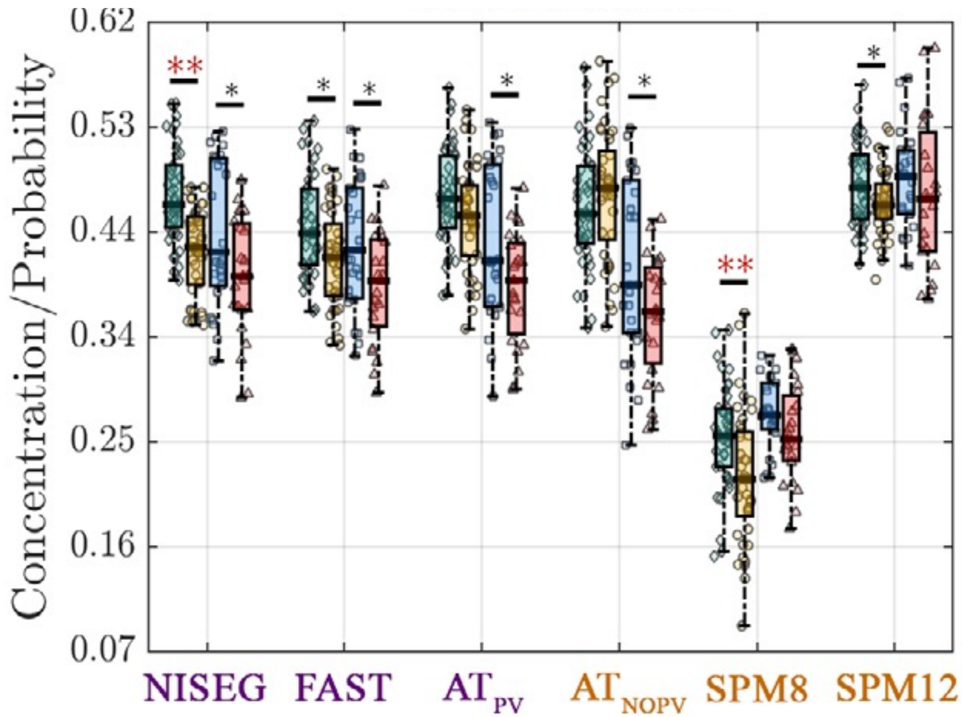
Final application

- Global tissue volume
- Voxel-wise analysis
- White mater mask
- Surface extraction
- etc

1 METHOD BIAS

- Same framework, different priors
- Different methods
- Different pre-processing

GM volume (right hemisphere)[1,2]



No atlas priors

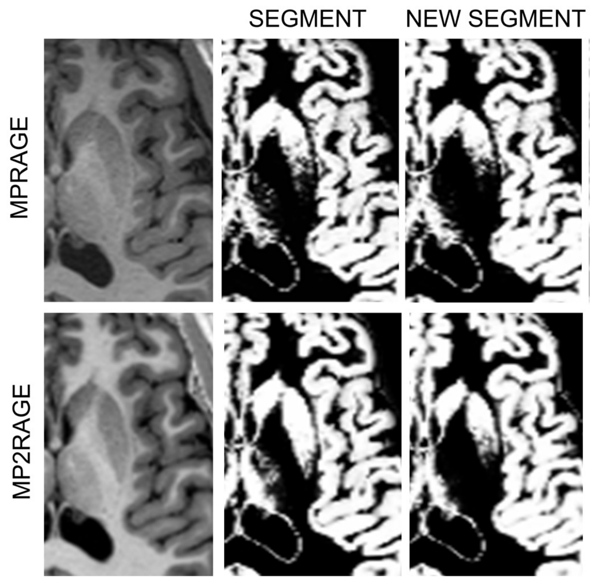
Atlas priors

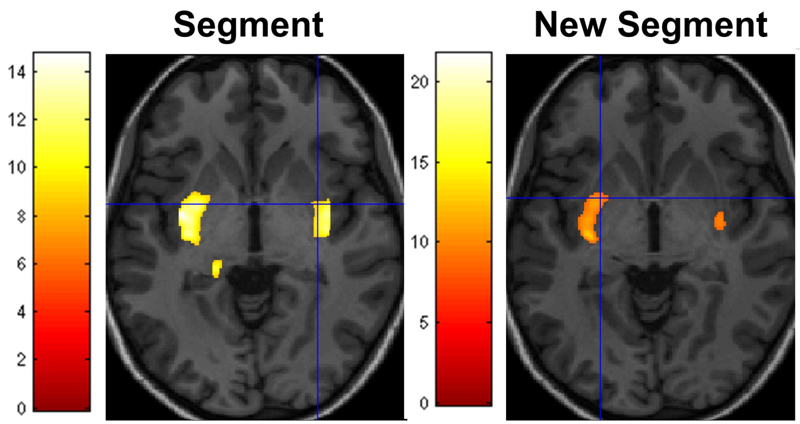
[1]Aleman-Gomez et al Human Brain Mapping, 2020 , [2]Roche et al MICCAI 2014.

2 GENERALIZATION

Unseen data[1]

- Different acquisition parameters
- Different scanners
- Multi-centric, multi-scanner data
- Novel MR sequences: MP2RAGE[2]





Signed paired t-test: $GM_{MPRAGE} < GM_{MP2RAGE}$,
6 mm smoothing; Cluster k= 20 voxels; p<0.05(FWE); Covariate: age

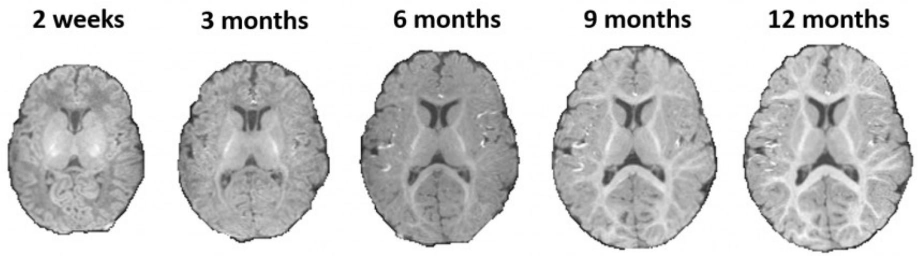
[1] Bach Cuadra et al ISMRM 2013, [2] Marques et al 2010.

3 DIFFERENT POPULATIONS

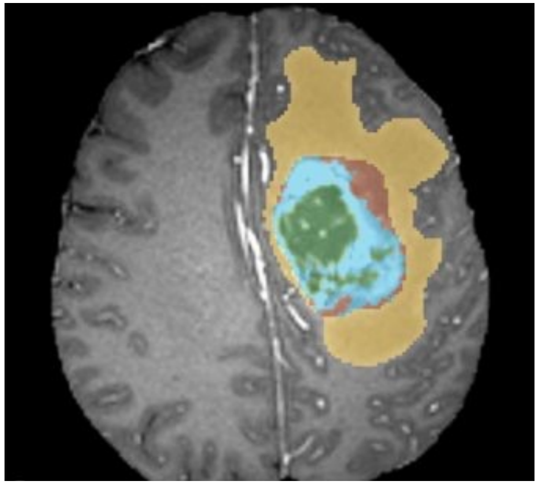
Different from healthy adult brain MRI

- Fetus, pre-term and term newborns
- Aging /Elderly
- Pathology:
  - tumor,
  - stroke,
  - multiple sclerosis,
  - ...

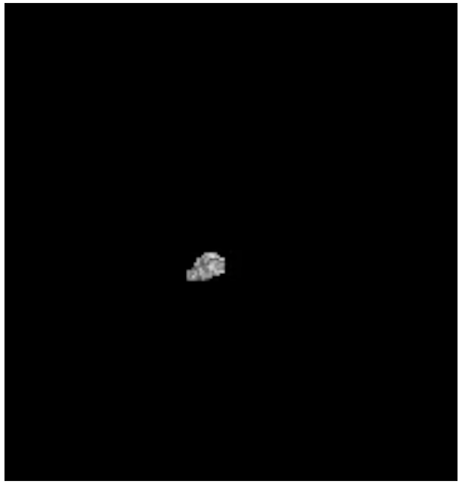
Newborn images from iSeg-2017 MICCAI



Tumor segmentation, adapted from Menze et al, IEEE TMI 2015



Multiple Sclerosis, courtesy of F. La Rosa



TOOLS

Zhang 01 ▪ FAST (FSL, Freesurfer)

Ashburner 05 ▪ SPM 5, 8, 12

Leemput 99 ▪ EMS-ITK

Tohka 04 ▪ VM8 (SPM toolbox)

Avants 11 ▪ ATROPOS / Ants

Cardoso 12 ▪ NiftySeg

Esteban 14 ▪ MBIS

	FAST	SPM8	EMS	ATROPOS	NiftySeg	MBIS
Multivariate	Partial	No	Full	Full	Full	Full
Optimization	ICM	ICM	MC	ICM	Unknown	GC
Bias Correct.	Polynomial	DCT	Polynomial	External	Yes	B-splines
Atlas usage	Available	Intensive	Available	Available	Intensive	Available
License	Freeware	GPL	BSD-like	BSD	BSD	GPL
Platform	Unix	Matlab	SPM8	Any	Any	Any

Esteban PhD Thesis, UPM, 2014

Singh and Singh, Annals of Neurosciences, 2021, https://en.wikipedia.org/wiki/List_of_neuroimaging_software

Feo & Giove, , J. Neuroscience Methods, 2019.,

INTO THE DEEP LEARNING

THE DEEP LEARNING PROMISE

Center for Biomedical Imaging

1 BIG DATA

Explosion of data available in healthcare (including imaging)

2 GPU

High computational resources at affordable cost

3 DL MODELS

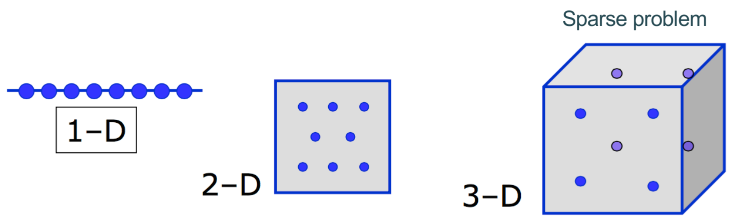
More complex DL models available

Credit: ISTOCKPHOTO

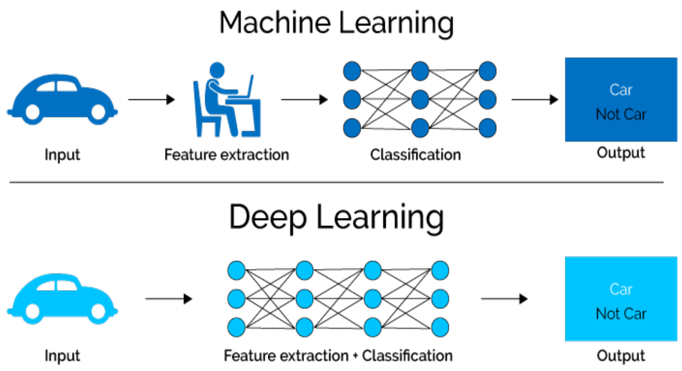
Inspired from A. Romero, Facebook AI Research, MIDL 2018.

MOTIVATION

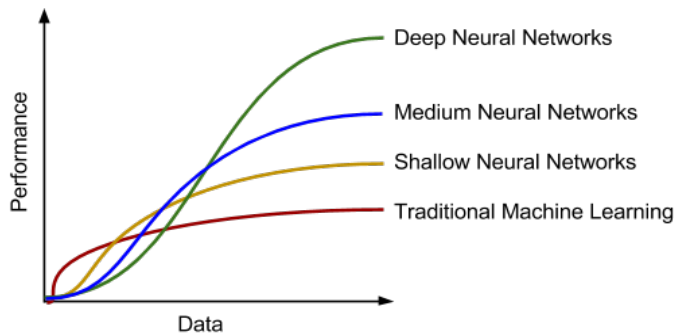
- Curse of dimensionality



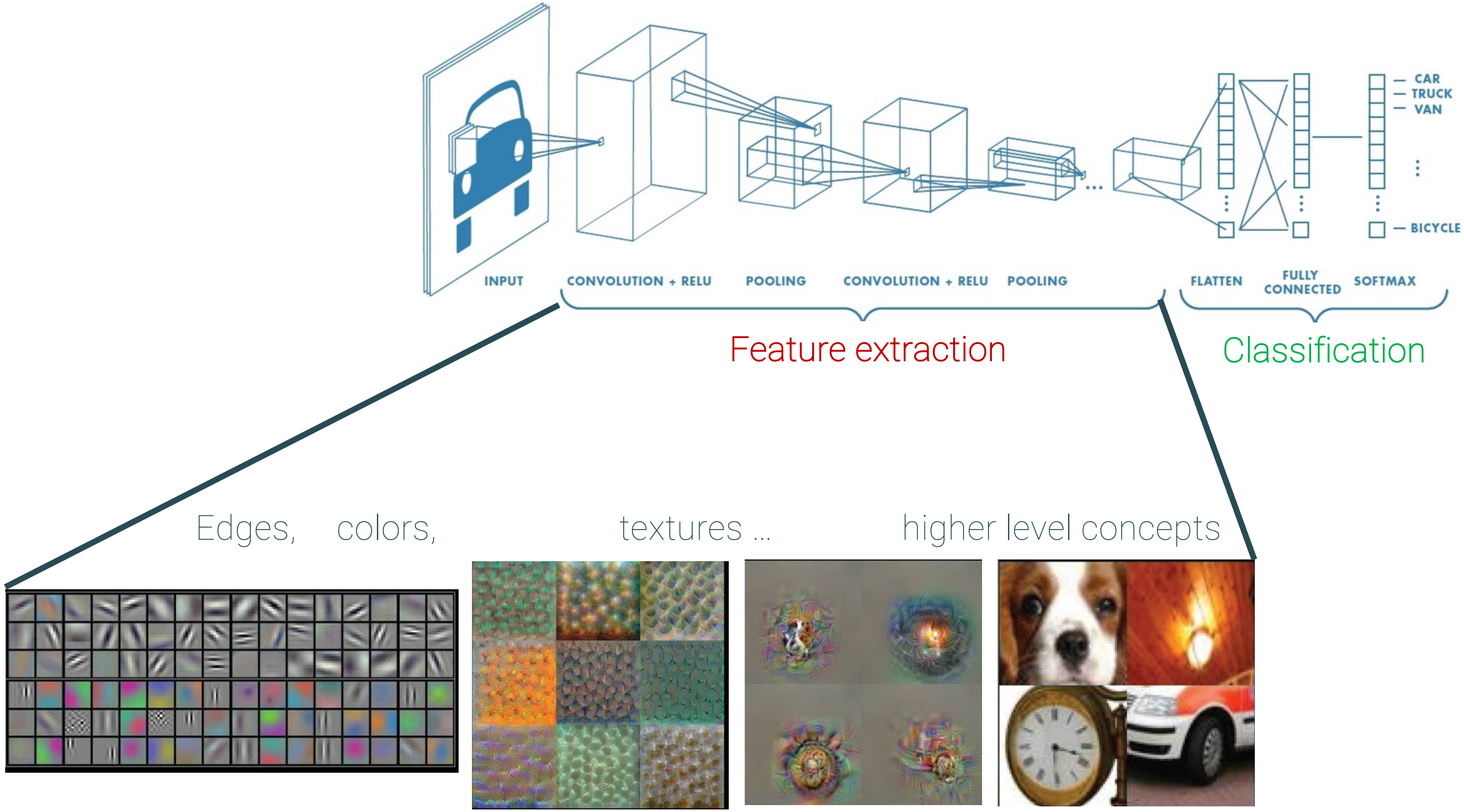
- Feature engineering



- Effective scaling with data

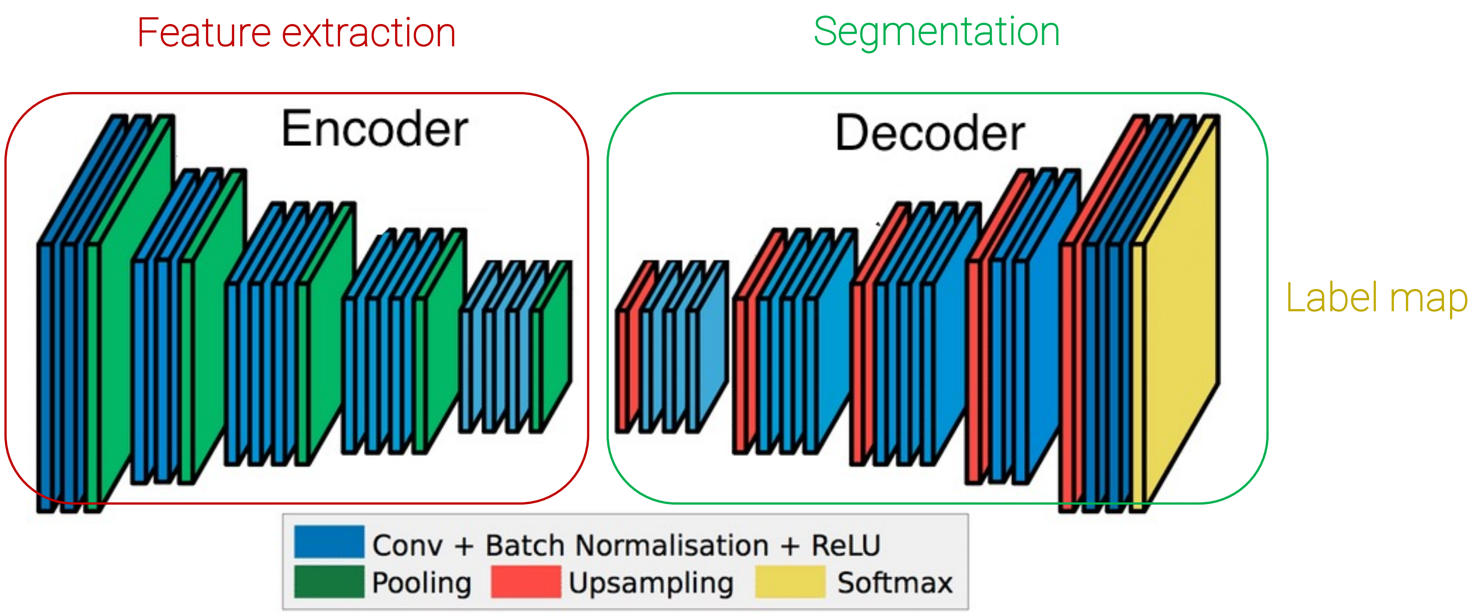


CONVOLUTIONAL NN



Images from https://medium.com/@himadrisankarchatterjee/

ENCODER-DECODER

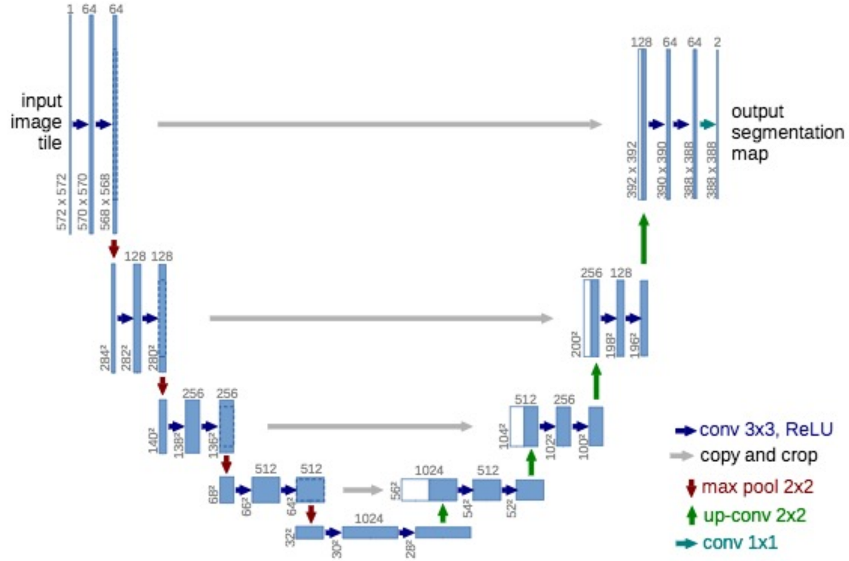


- No pre-processing (or much less)
- No feature extraction BUT decision on 2D/3D and/or patches
- Many decisions still: similarity measure, architecture, etc

U-NET ARCHITECTURE*

Ski connections

- Encoder-decoder, inaccurate segmentation boundaries
- Direct connection between encoder-outputs (features) and decoder



*Ronneberger et. *al*, 2015

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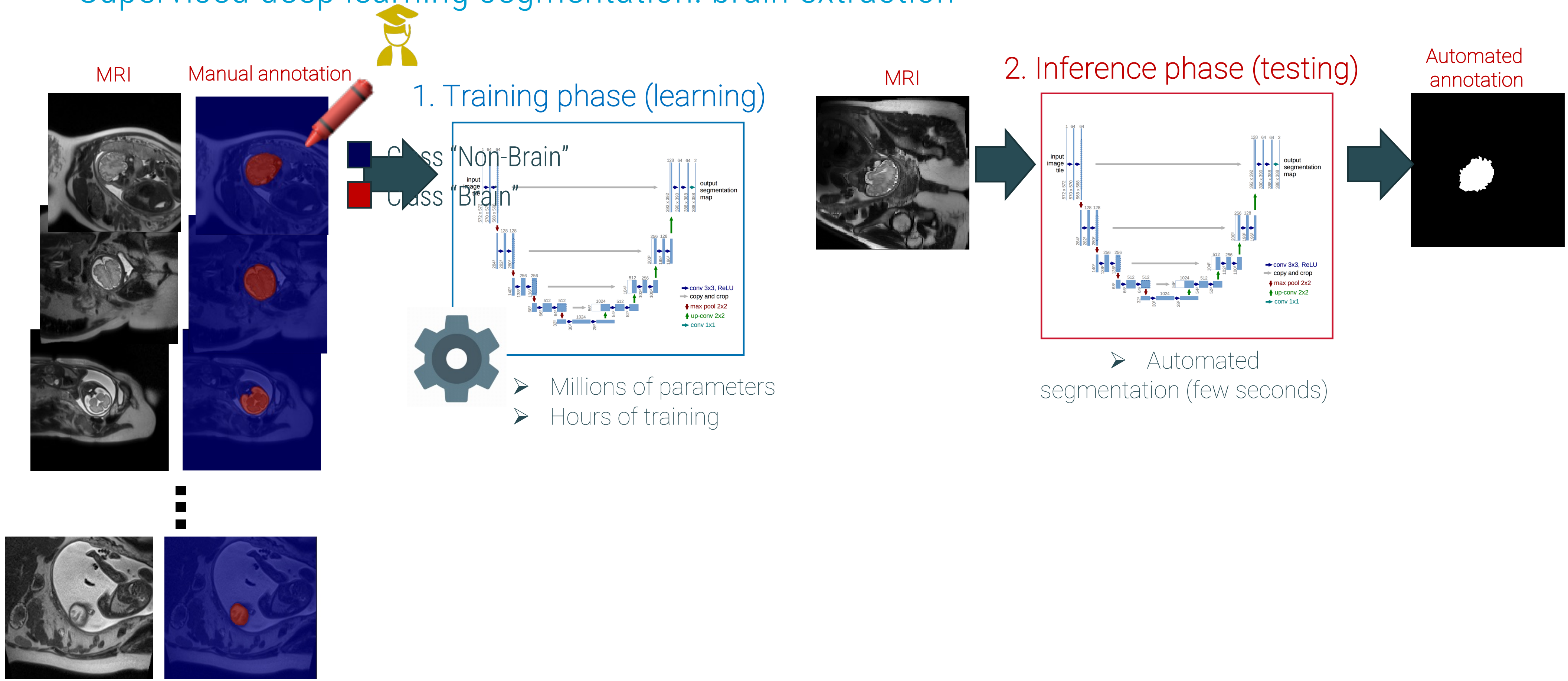
IN PRACTICE

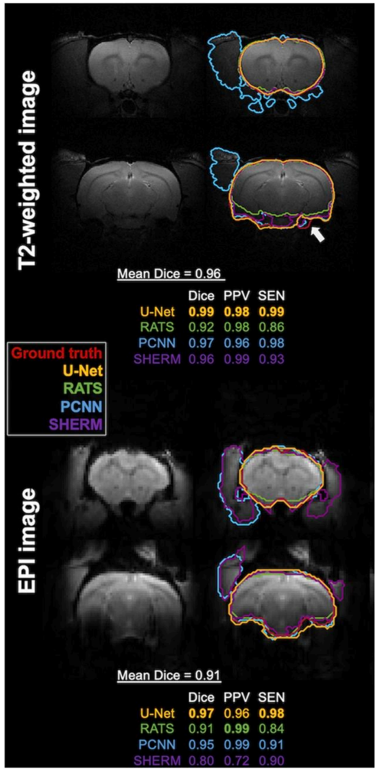
Supervised deep learning segmentation: brain extraction[1]



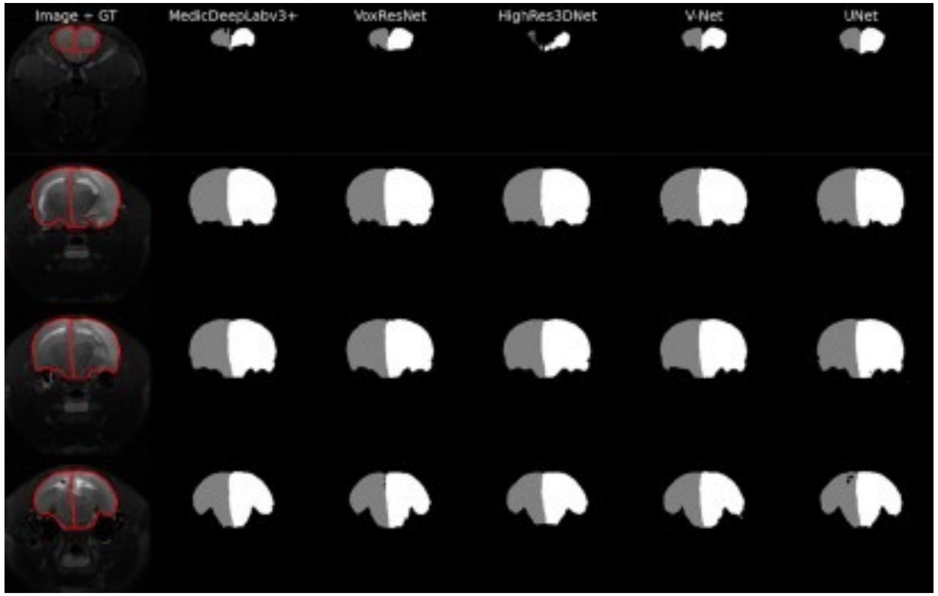
[1]Kebiri et al., ECMRN 2020

DEEP LEARNING SEGMENTATION

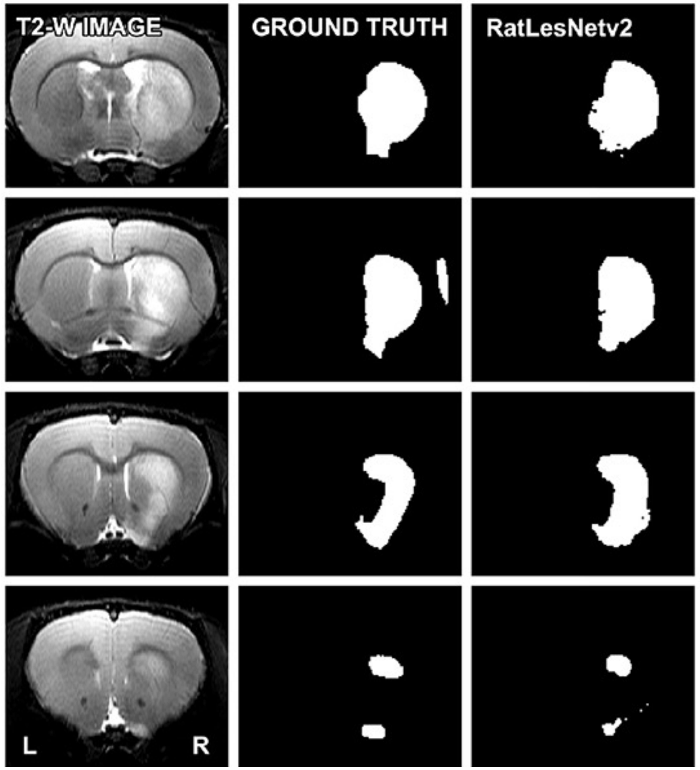
Skull stripping, hemisphere, lesion mask



LM Hsu et al, Front. Neuroscience, 2020



Valverde et al, Neuroinformatics 2023



JM Valverde et al, Front Neuroscience 2020

Feo & Giove, , J. Neuroscience Methods, 2019, Review.

DEEP LEARNING SEGMENTATION

Skull stripping, tissue, lesions

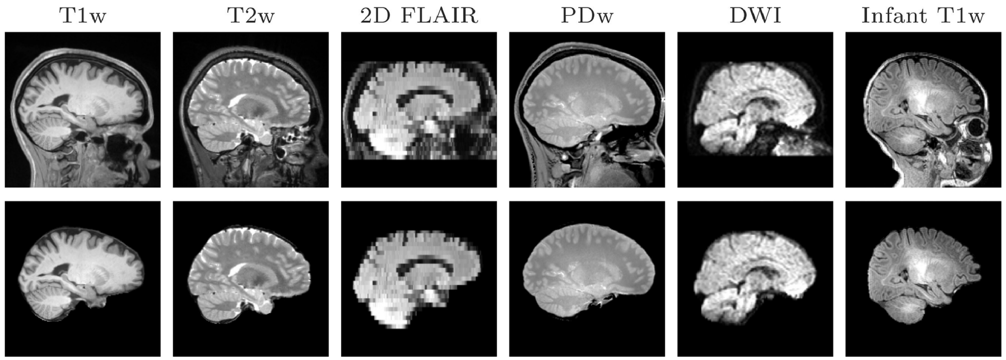
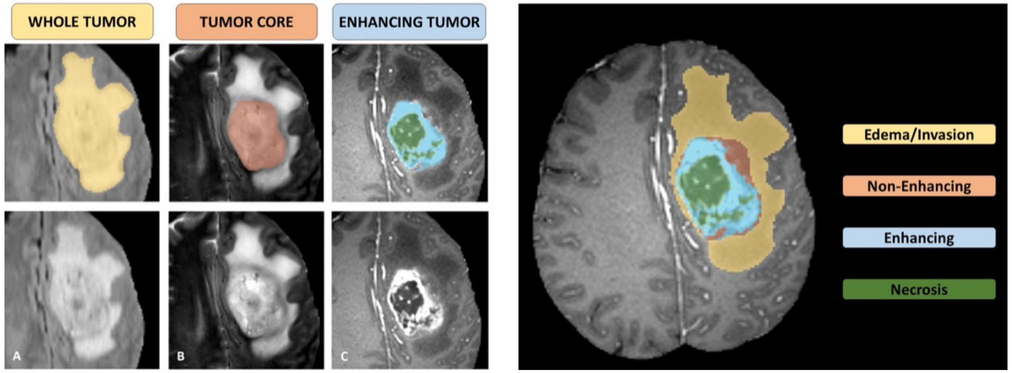


Figure from Hoopes et al Neuroimage 2022



Menze et al, BRATS Challenge

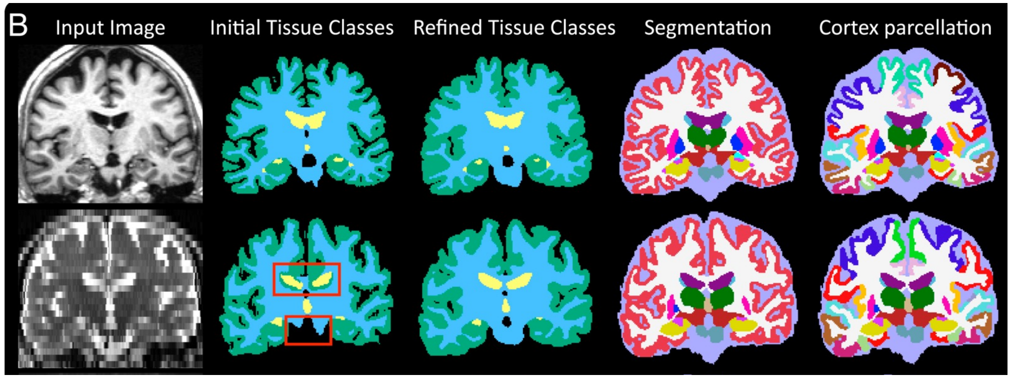


Figure from Billot et al PNAS 2023

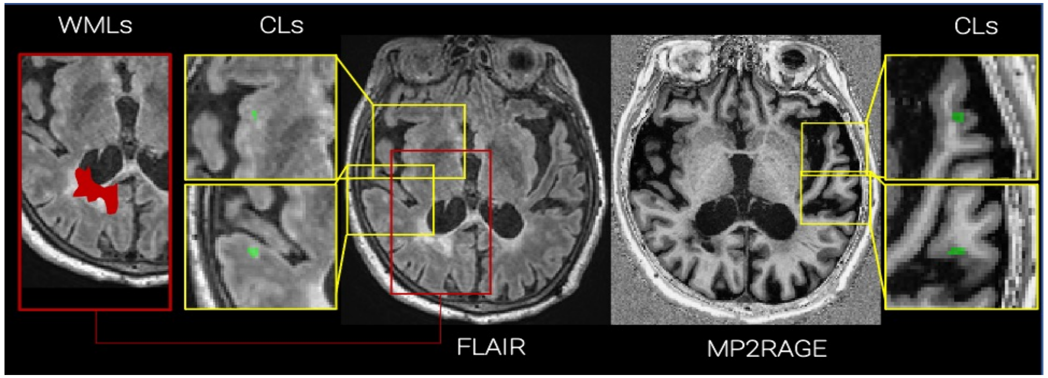


Figure from La Rosa et al Neuroimage Clinical 2020

CHALLENGES OF DEEP LEARNING

1 Feature space

- Medical images are large 3D / 4D
- Multi-modal imaging
- Low number of samples (~hundreds)

2 Training

- Label data is expensive
- Label quality
- Unbalanced samples

3 Generalizability

- Different scanners, sequence parameters
- Different populations

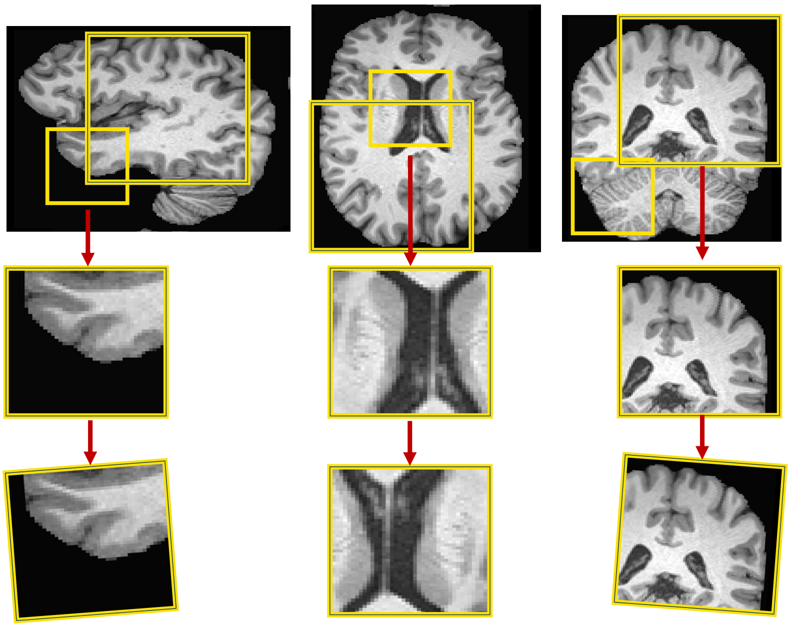
4 Interpretation

- Explainability of the features used
- Interpretability of the decisions
- Uncertainty

CHALLENGES OF DEEP LEARNING

1 Feature space

- 2D/3D Image patches
- 2D slices and 2.5D training



2 Training

- Report class-specific and/or balanced metrics
- Synthetic generated samples and data augmentation
- Resampling samples
- Cost-sensitive learning: class-weighted loss function or focal loss
- Weak/noisy labels
- Transfer of knowledge

CHALLENGES OF DEEP LEARNING

3 Generalizability

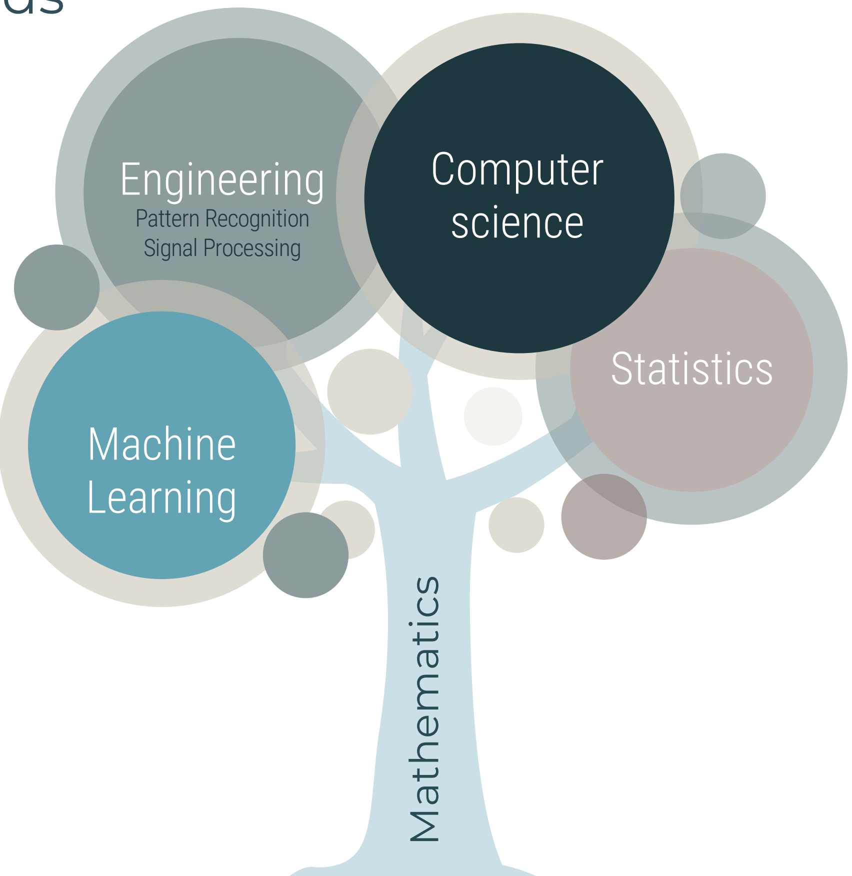
- Domain adaptation methods
- Image to image synthesis
- Multi-scanner/site training (eg. federated learning)
- Cost-sensitive learning

4 Interpretation

- Saliency maps (eg. backpropagation, occlusion etc)
- Link to expert (clinically meaningful) knowledge (eg. concept vectors)
- Uncertainty estimation (eg. Monte Carlo Sampling)

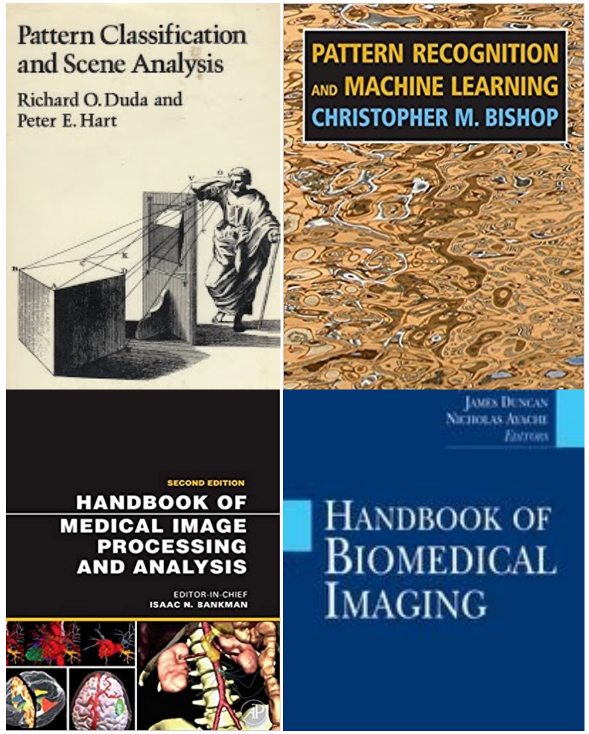
TAKE HOME CONCEPTS

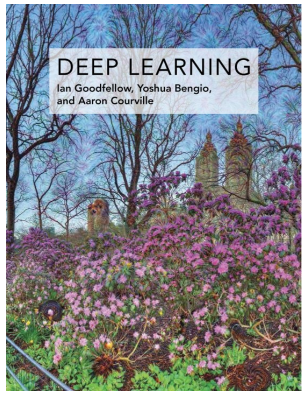
- Segmentation is the pilar of many other further analysis
- Broad landscape of segmentation methods
  - Brain MRI Bayesian framework
  - Atlas-based segmentation
  - Deep-learning methods
- Challenges
  - Bias towards methods and sequences
  - "Challenging" populations
  - Input data and feature space
  - Training
  - Interpretation



FURTHER INFO

- Books
  - Pattern Classification and Scene Analysis
  - Pattern recognition and Machine Learning
  - Handbook of Medical Imaging: Processing and Analysis
  - Handbook on Biomedical Imaging
- Review articles
- Neuroimage analysis tools / software





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THANK YOU FOR YOUR ATTENTION

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Medical Image Analysis Laboratory