Universitat Pompeu Fabra Barcelona

Department of Information and Communication Technologies, UPF

DTIC-MdM Strategic Program: Data-Driven Knowledge Extraction

Imaging biomarkers: Algorithms, open data and infrastructure for neurological disorders

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Inserm

Plan

- [Frontiers in ICT editorial activity]
- Imaging biomarkers: application to Multiple Sclerosis
- E-infrastructure for data management and analytics

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frontiers in ICT

Computer Image Analysis

frontiers in ICT
Computer Image Analysis

Scope

Our aim is to publish research addressing the scientific and engineering challenges of **Image Processing, Image Analysis, Computer Vision, and Image Perception and their related application fields, with a specific attention to emerging interdisciplinary areas.**

The challenge of Computer Image Analysis is to handle overflowing sets of images that convey imperfect, partial or noisy information on the observed scene, while aiming at contributing to recognition, decision or prediction purposes. To achieve these goals, image analysis must ensure quality and performance criteria capable of producing more robust and accurate perception of physical or human processes.

Applications

- Environmental Sciences
    - Satellite Imaging
    - Flow Visualization
- Life sciences
    - Biological Imaging
    - Medical Imaging
    - Imaging Genetics
- Multimedia
    - Photo and Video Editing
    - 3D Vision
    - 3D TV
    - Mobile Multimedia
- Videosurveillance and Biometrics

Basic research

- Analysis of Images and Shapes
- Change and Motion Detection
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- Computational Photography
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- Early and Biologically-Inspired Vision
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- Image and Video Processing
- Image Classification
- Object Detection and Recognition
- PDE and Variational Methods for Image Analysis
- Registration and Matching
- RGB-D Image and Video Analysis
- Scene Understanding
- Segmentation and Grouping
- Shape Representation and Analysis
- Spectral Methods
- Statistical Methods and Learning for Image Analysis
- Stereovision
- Tracking
- Vision for Graphics
- Vision for Robotics
- 2D and 3D Optical Flow

Research Topics are key

- ✓ You decide the subject matter
- ✓ Cross-listing -- can connect different specialties
- ✓ Open Access e-book (10+ articles):

Proceedings, educatoinal resource

- ✓ Independent website

- Content targeting – pre-IF phase
- Build reputation through good papers – post Inaugural Articles
- The best Topics are typically driven by Editorial Board members

MAPPING: MAnagement and Processing of Images for Population ImagING

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Support
By our Swiss-based editorial team

Plan

- Frontiers in ICT editorial activity
- Imaging biomarkers: application to Multiple Sclerosis
- E-infrastructure for data management and analytics

Imaging biomarkers: application to Multiple Sclerosis

What is a Biomarker?

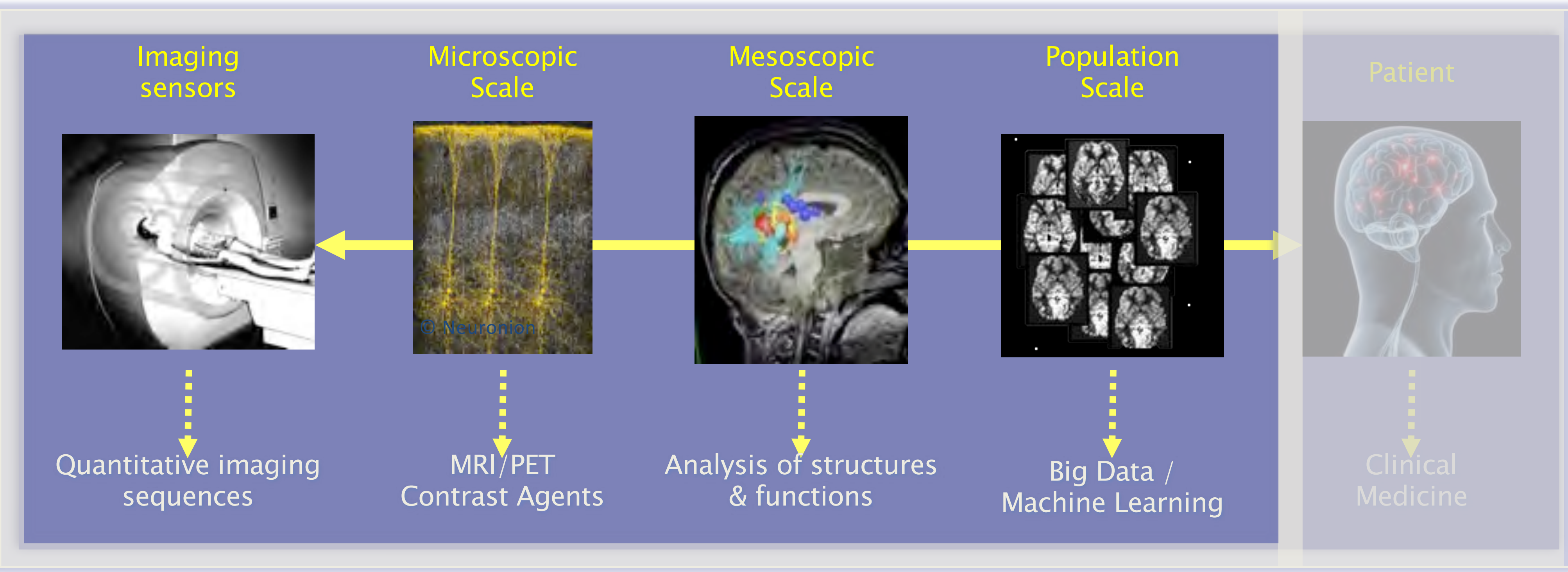
Biomarkers are features that are objectively measured as indicators of normal biological processes, pathological changes, or pharmaceutical responses to a therapeutic intervention*

** Biomarkers definitions working group (2001) - http://www.biomarkersconsortium.org*

Imaging biomarkers: another way to use multimodal images

- Imaging biomarkers are used to:
  - Detect pathologies
  - Predict the level of risk
  - Classified the extent of a disease
  - Evaluate the therapeutic response
- Imaging biomarkers must be:
  - Quantitative
  - Accurate
  - Reproducible
  - Feasible over time

«Brain Imaging Biomarkers»: From Bench to Bed

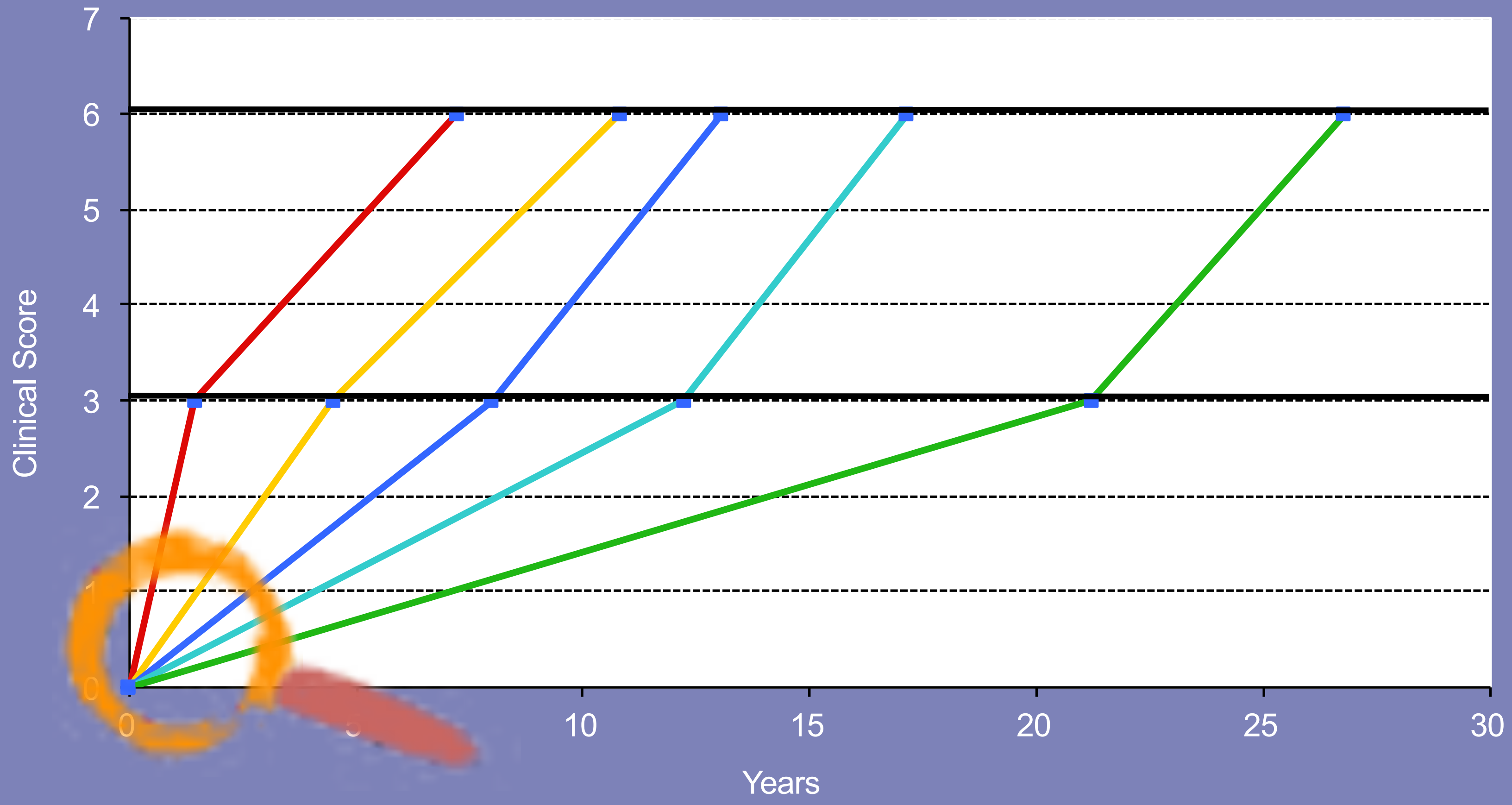


Imaging Biomarkers in Multiple Sclerosis

- **Goal**: To guide the clinician (e.g. a neurologist) within the mass of information to integrate into the medical decision process

- Multiple Sclerosis (MS)
  - Chronic inflammatory-demyelinating CNS disease
  - Lead to acute handicap in young adults (high prevalence in Brittany)
  - Most frequent CNS disease in young adults
- Main Issues and Challenges
  - Early diagnostic and treatment of the pathology
  - Prevention of disease progression and future handicap
  - Better understanding of the pathology (new in-vivo classification of MS lesions)
  - Set-up and evaluate new therapeutic protocols (disease modifying drugs)

Natural Evolution of Multiple Sclerosis (MS)



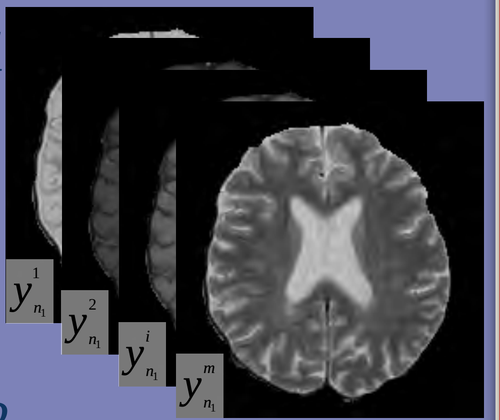
*Study on 2054 MS patients, CHU Rennes**

** Leray E. et al. Brain 2010*

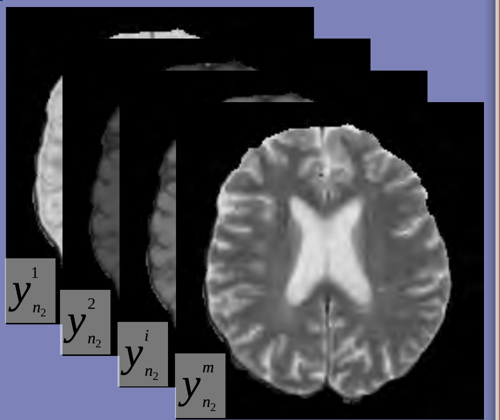
Imaging of Multiple Sclerosis

State of the Art: White matter lesions as markers of evolution

t_1



t_2



t_n

...

Estimation of "normal" appearances

$$\begin{cases} \hat{\theta}_{MLE} = \underset{\theta}{\operatorname{argmax}} \left(\prod_{i=1}^{m} f(y_i|\theta) \right); \; f(y_i|\theta) = \sum_{j=1}^{n} \left[\alpha_j \cdot \mathcal{N}\left(\mu_j, \Sigma_j\right) \right] \\ \hat{\theta}_{TL} = \underset{\theta}{\operatorname{argmax}} \left(\prod_{i=1}^{k} f(y_{sort(i)}|\theta) \right); \; \left(m/2 < k \leq m \right) \end{cases}$$

Identification of "irregular" appearances (e.g. lesions, artifacts)

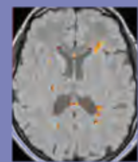
$$d_i = \min_j \left\{ \sqrt{(y_i - \mu_j)^T \Sigma_j^{-1} (y_i - \mu_j)} \right\} > p\left(t \middle| \aleph_n^2\right)$$

Neuroradiological Expertise

(keep WM lesions only)

$$p_{lesion} = \int_{y_{th}}^{\infty} \mathcal{N}\left(\mu_{WM}^{T2}, \sigma_{WM}^{T2}\right) dy$$

t_1

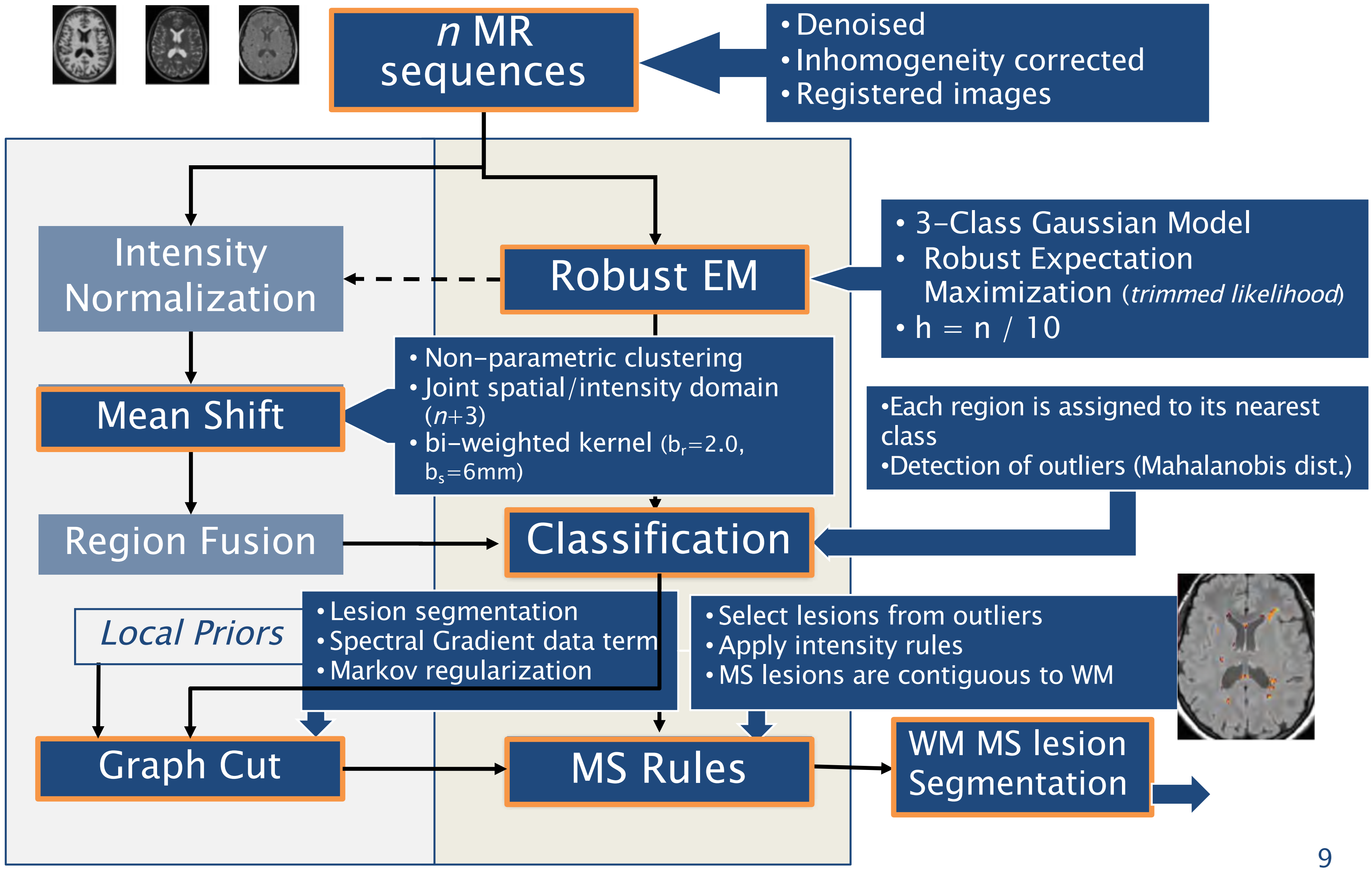


t_2

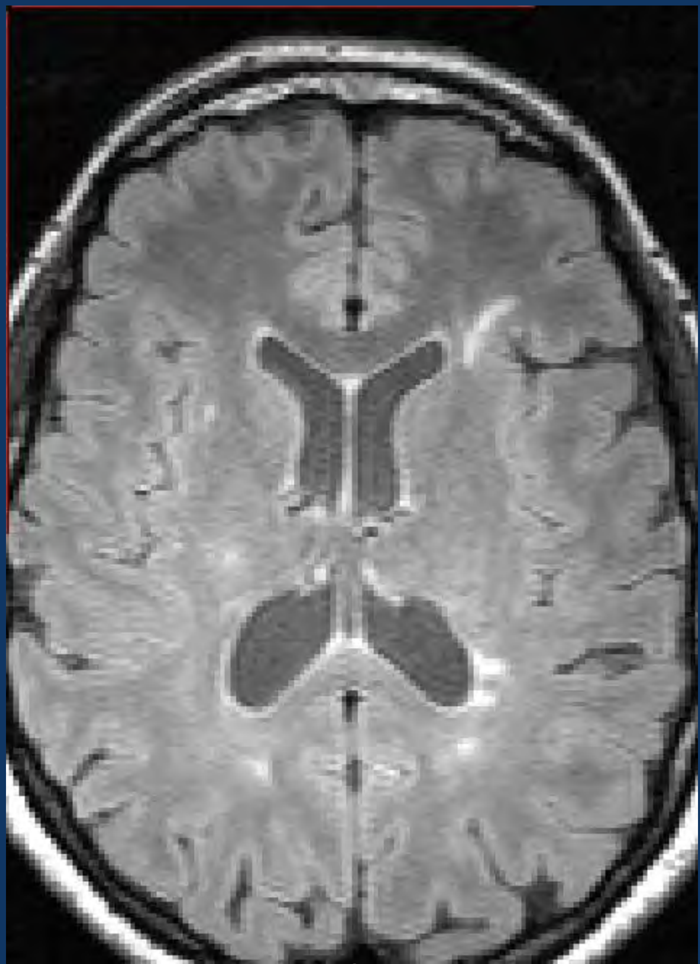
... t_n

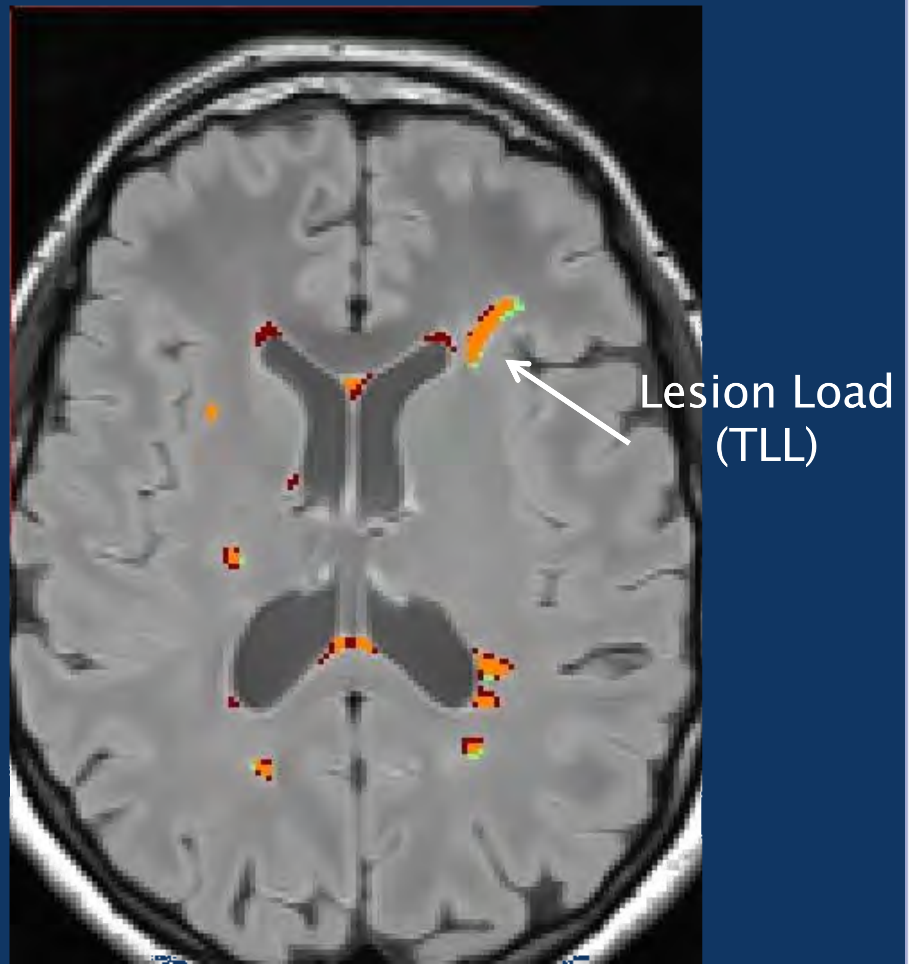
D. Garcia. et al. IEEE-TMI 2011

Segmentation of MS Lesions: a complex workflow



Imaging of Multiple Sclerosis:
Estimation of Total Lesion Load

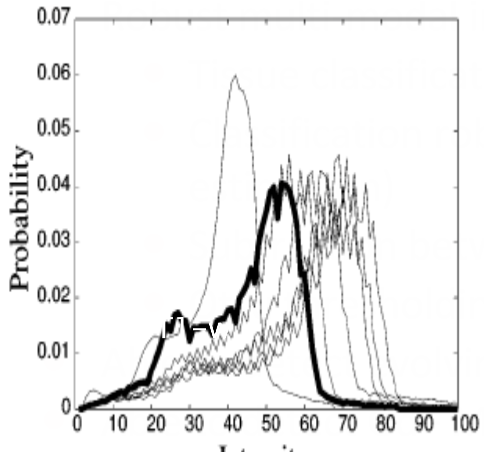

Before

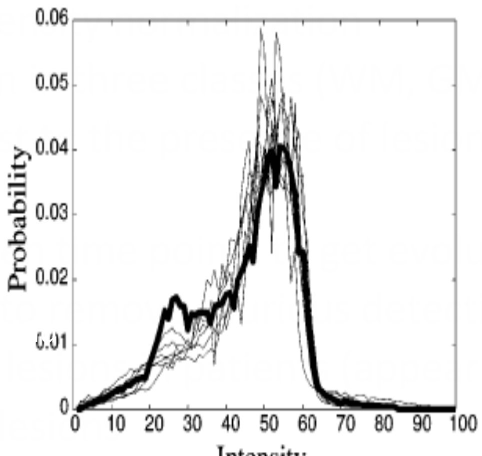


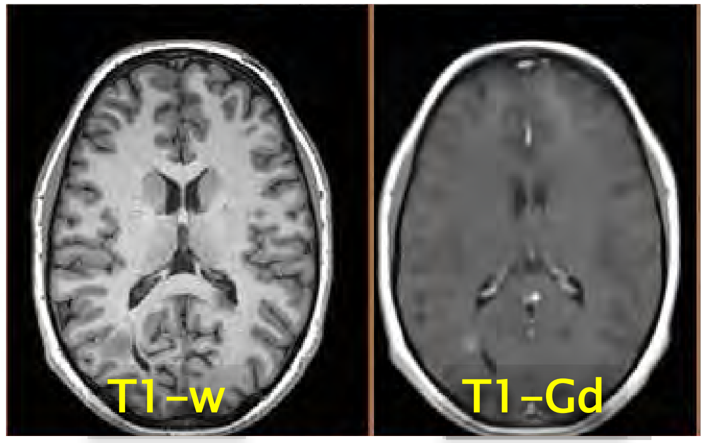
Final

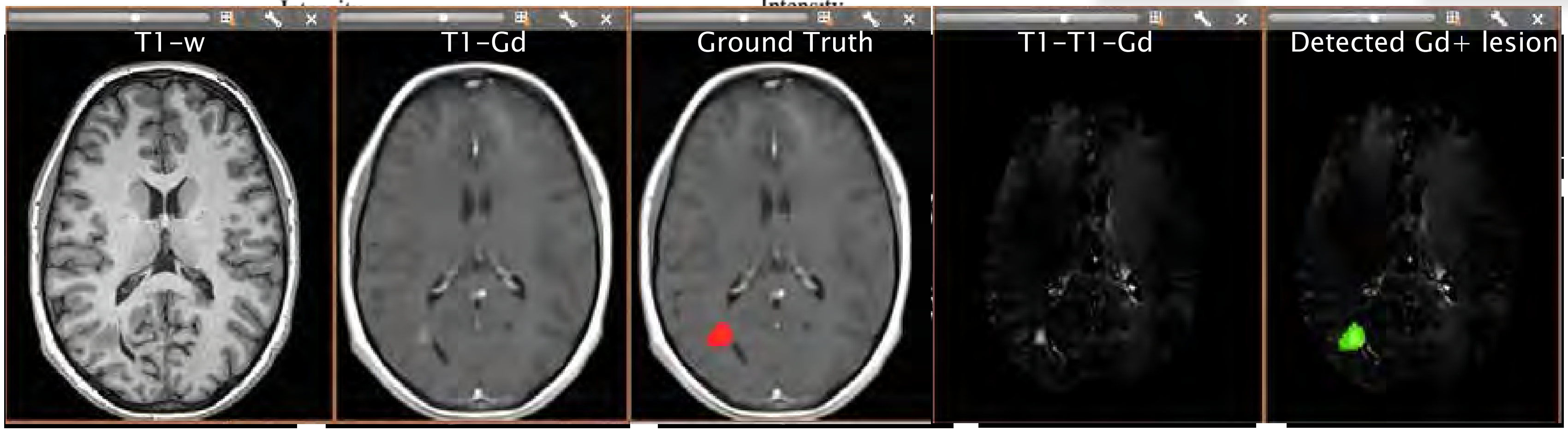
Imaging Biomarker of MS:
Quantification of temporal evolution

- Goal: Robust detection of evolving lesions
- Challenge: Intensity variations between two time points robust to outliers
  - T2, FLAIR, T1 acquisitions not quantitative
- **Intensity Normalization**





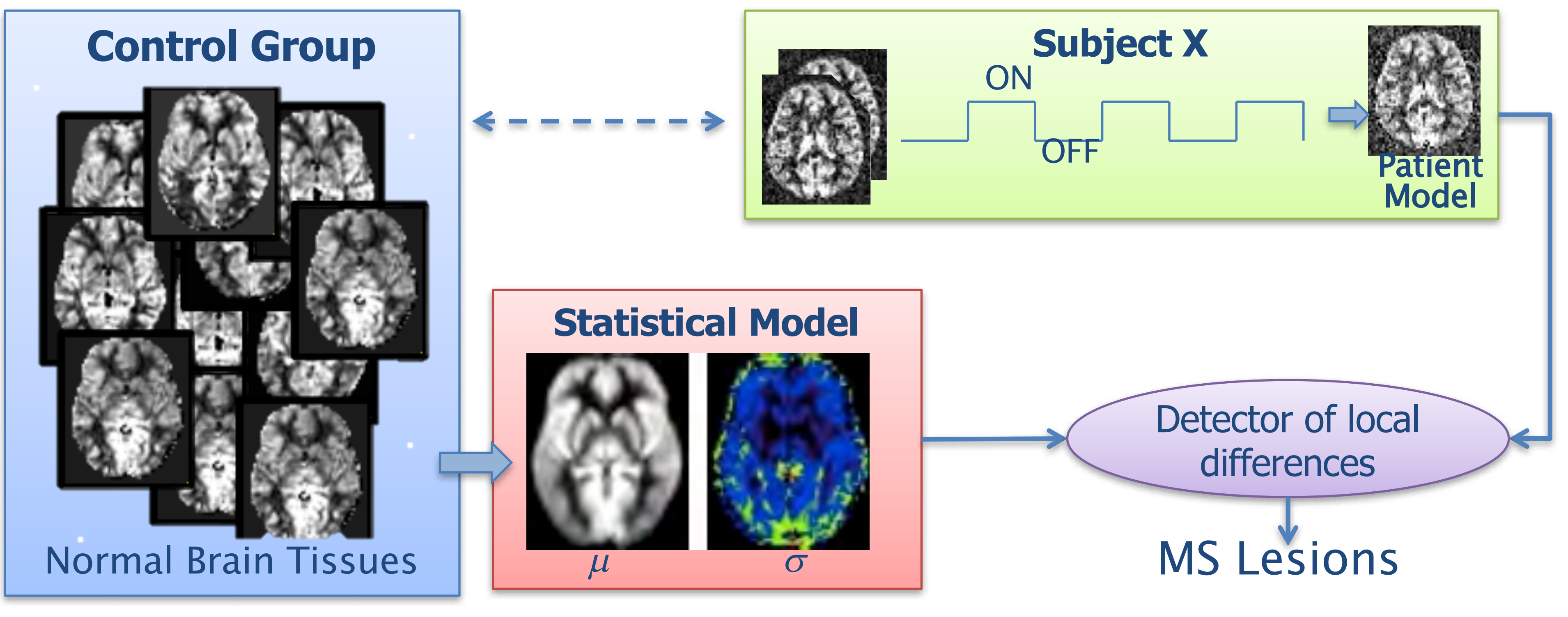




[Karpate et al, 2014]: Longitudinal Intensity Normalization in Multiple Sclerosis Patients Robust Detection of Multiple Sclerosis Lesions from Intensity-Normalized Multi-Channel MRI. Proceedings of MICCAI CLIP 2014

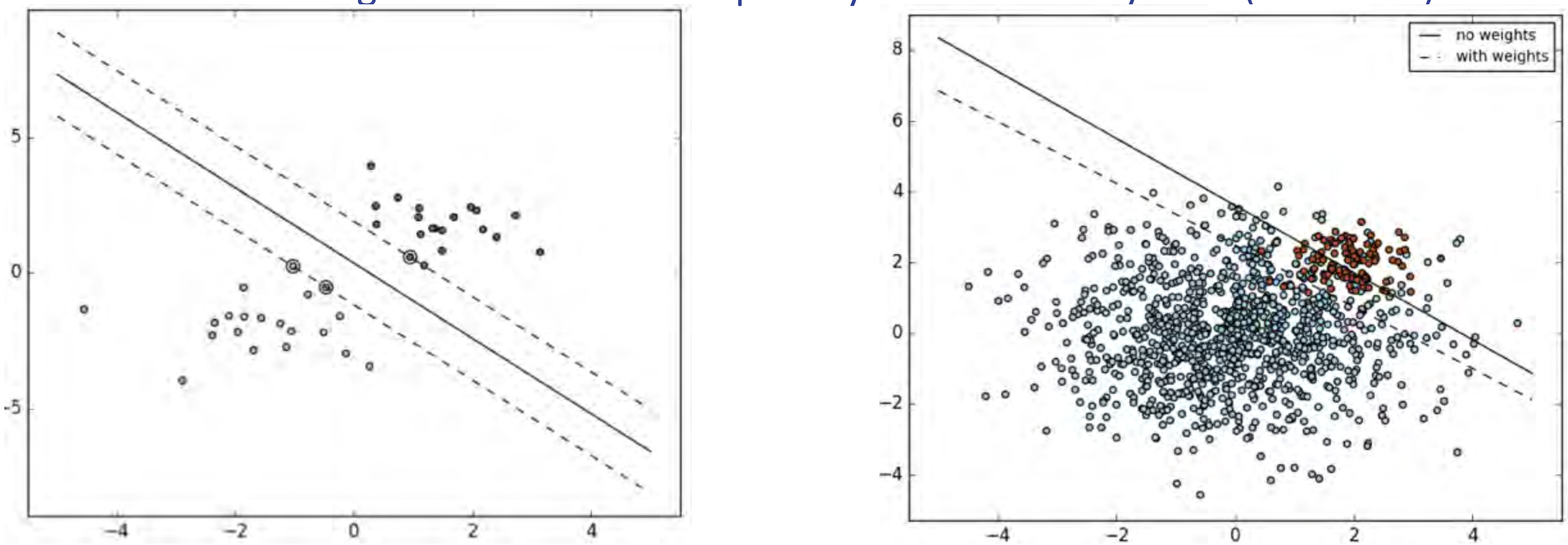
Patient to Population Comparison for MS Lesions Detection

- Goal: Robust detection of lesions as deviation from local tissue intensity distributions
- Challenge: knowing at each voxel the multi-modal intensity distributions
  - Comparing multi-channel intensity of the patient to control intensities distributions
- Contribution:
  - Robust multi-modal intensity normalization
  - Atlas-based detection of intensity abnormalities in a patient (lesions)



Machine learning: Probabilistic One Class SVM for Automatic Detection of MS Lesions

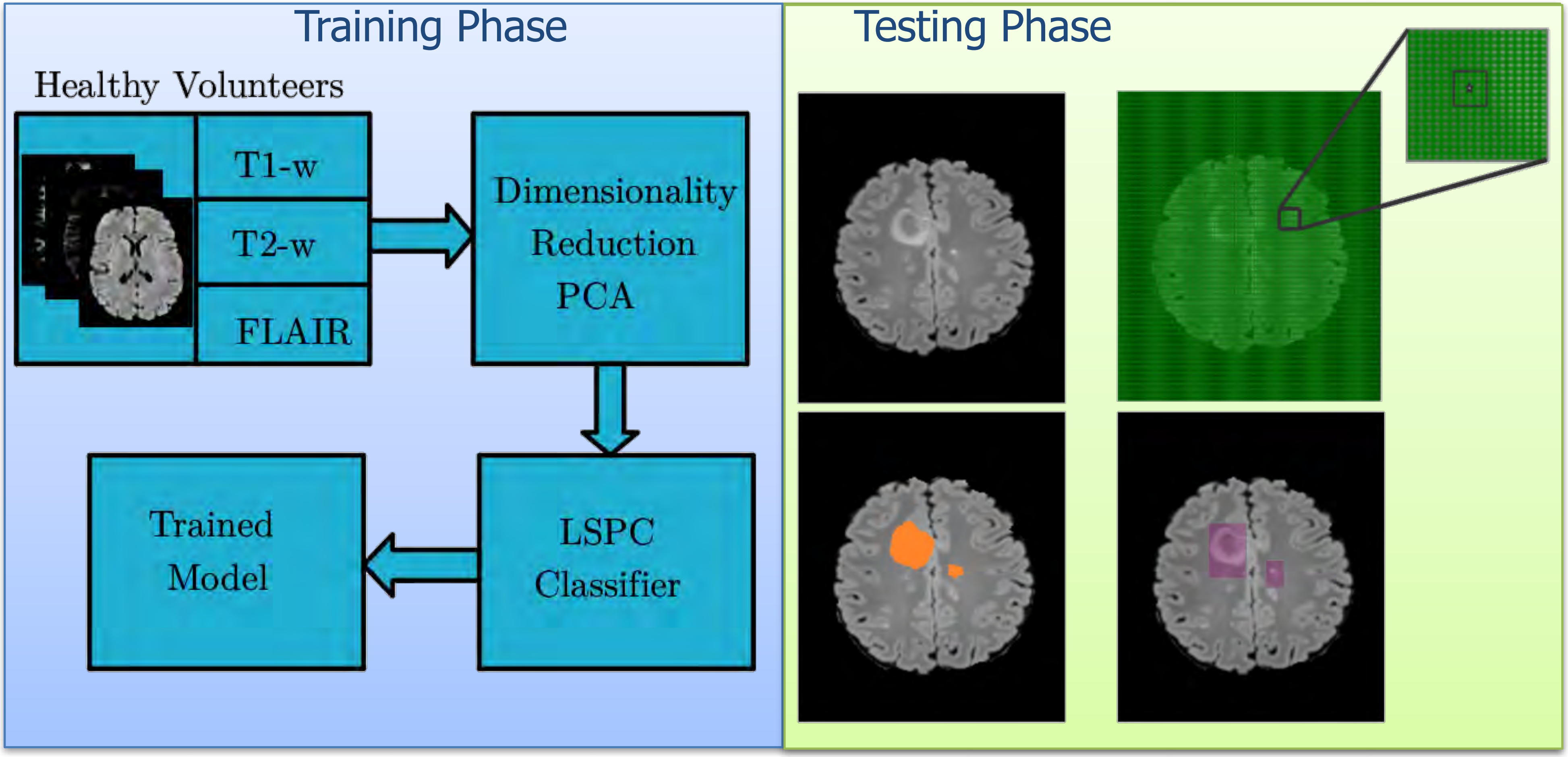
- **Goal:** Propose an automatic framework for MSL Detection based on multichannel MRI patch based information
- State-of-the-art machine learning algorithms:
  - SVM [Vapnik et al.1995], Logistic Regression[Zhang et al.2002], Neural Network…
  - Works well in practice when training examples in classes are balanced
- If not ?
  - Class Imbalance $\Rightarrow$ under-/over-fitting of the Classifier [Chawala 2005]
  - Class imbalance between Normal Brain Tissues and MS lesions
  - Solution : A higher misclassification penalty on the minority class (MS lesion)



Toy example of SVM for balanced and unbalanced classes, Courtesy : www.scikit-learn.org.

Machine learning: Probabilistic One Class SVM for Automatic Detection of MS Lesions

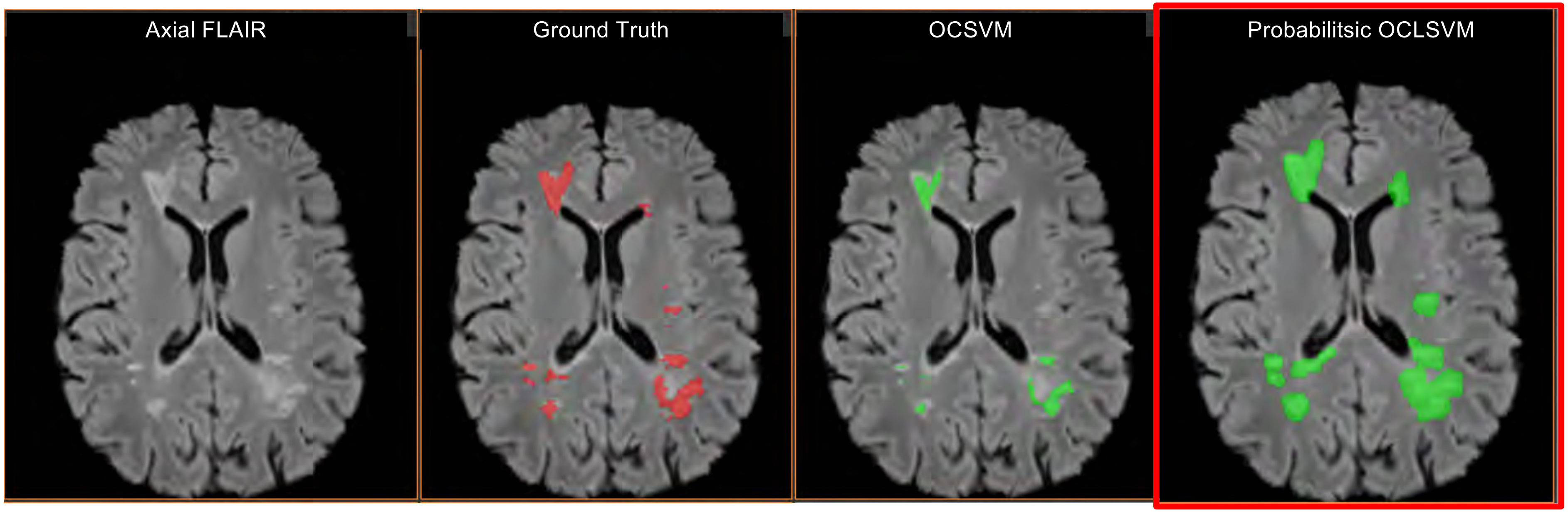
Methodology



[Karpate et al, 2015]: Probabilistic One Class Learning for Automatic Detection of MS Lesions. Proceedings of ISBI 2015

Probabilistic One Class Learning for Automatic Detection of MS Lesions

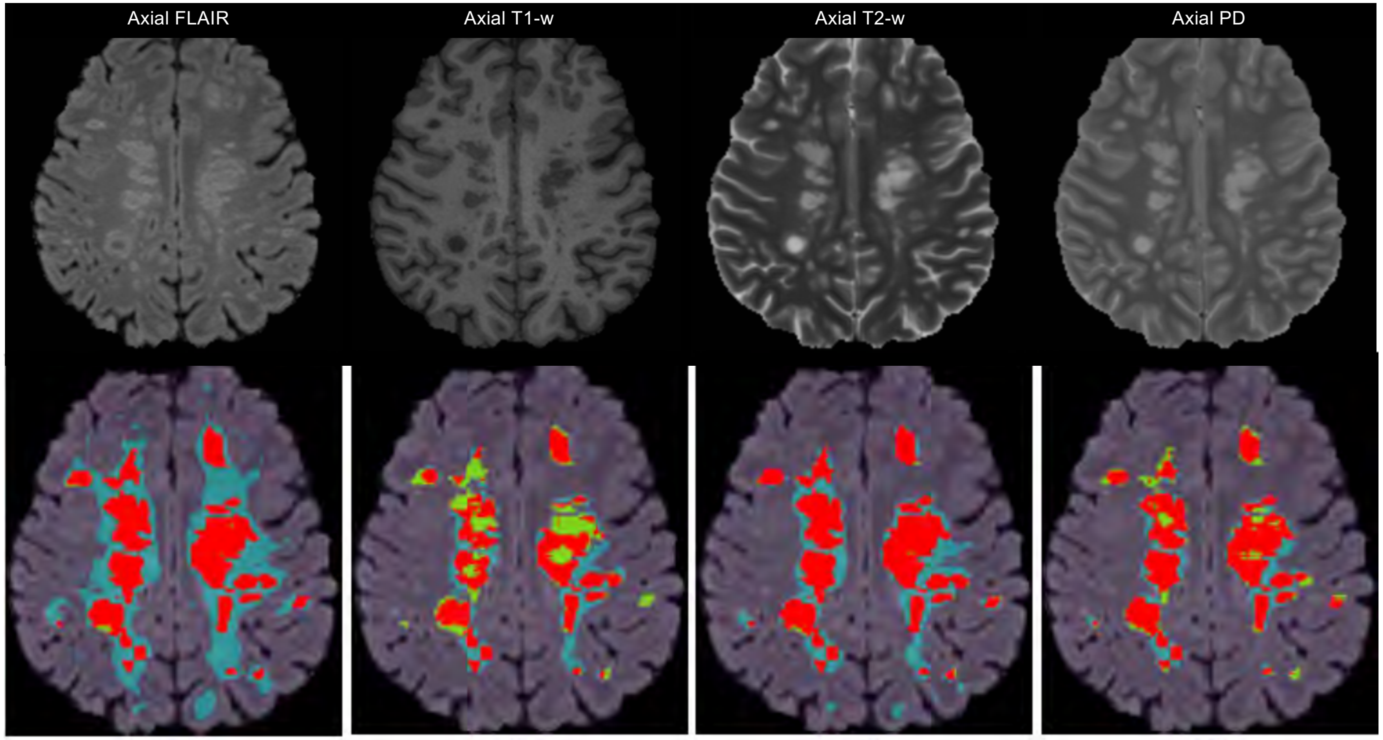
- Goal: Robust detection of lesions as deviation from normal appearing tissues
- Challenge: overcome learning approaches problems with MS lesions:
  - Two-class imbalance problem (much more normal samples than lesions)
- Contribution:
  - Robust spatio-temporal multi-modal intensity normalization for T1-Gd and longitudinal MS lesion detection
  - One class learning for lesion detection from multidimensional MRI
    - Dimensionality reduction of the feature space
    - Lesions modeled as the complementary of the normal class
    - Testing by comparing patient patches characteristics to the *pdf* of the normal class
  - Able to robustly detect lesion locations in patients



[Karpate et al, 2015]: Probabilistic One Class Learning for Automatic Detection of MS Lesions. Proceedings of ISBI 2015

Detection of MS lesions via competitive Dictionary Learning

- Goal: New sparse representation and dictionary learning method for classification
- Challenge: competitive dictionary learning
- Contribution:
  - Adaptation of dictionary size to each class complexity: improved over standard DL or discriminative methods
  - Detection of Multiple Sclerosis Lesions by classification of multimodal MRI images

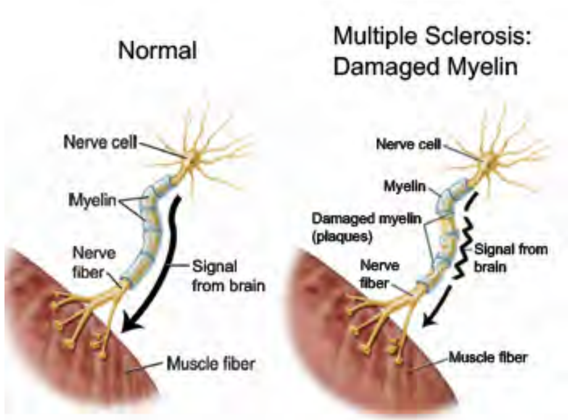


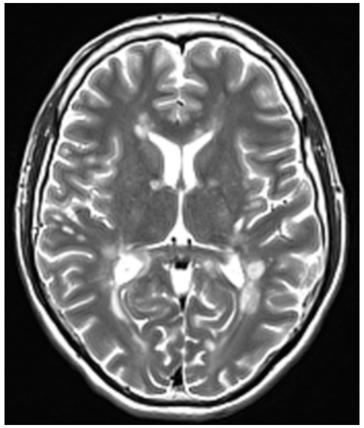
(a) Two dictionaries with 5000 atoms for healthy and lesion classes
(b) Two dictionaries with 5000 atoms for healthy and 1000 for lesion class
(c) Four dictionaries with 2000 atoms for WM, GM, CSF and lesion class
(d) Four dictionaries with 2000 atoms for each tissue, and 1000 for lesion class

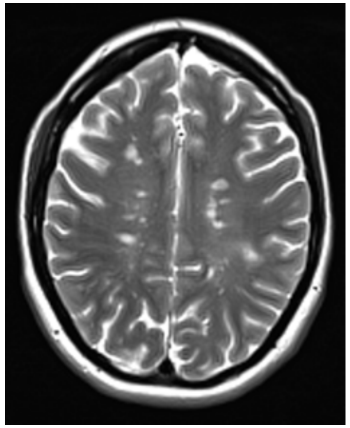
[Deshpande et al, 2015]: Classification of Multiple Sclerosis Lesions using Adaptive Dictionary Learning. Computerized Medical Imaging and Graphics, (*Dec.*), 2015

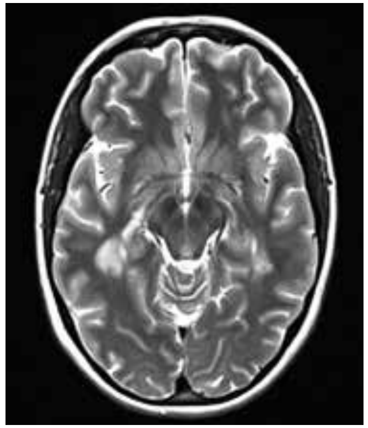
Imaging Biomarkers in Multiple Sclerosis: Current Limits

- Multiple sclerosis: auto-immune demyelinating disease







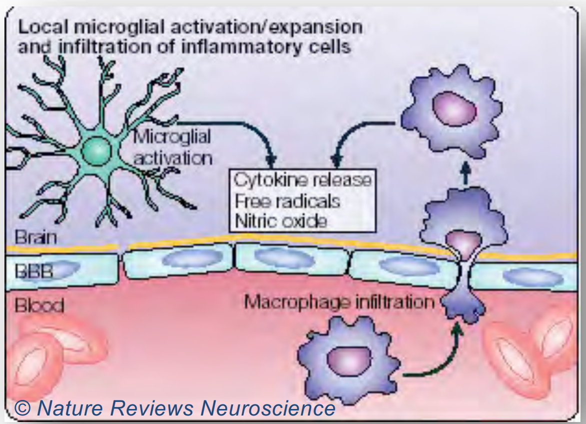


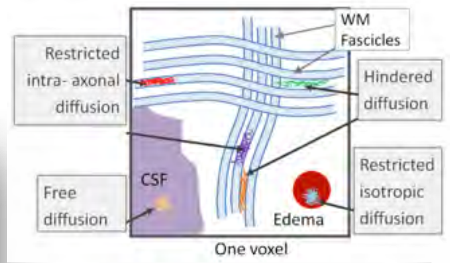
- Clinical radiological paradox [1]
  - Lesion study on conventional MRI (T2, FLAIR) not enough
  - Why? Missing information (lesion severity, position…)

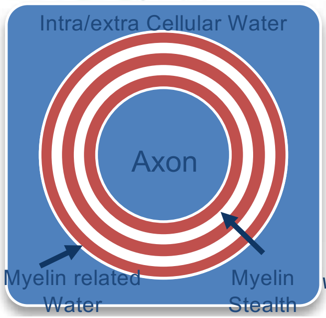
1. Guttmann et al. *The evolution of multiple sclerosis lesions on serial MR.* American journal of neuroradiology 16:1481–1491, 1995.

Imaging Biomarkers in Multiple Sclerosis: A Paradigm Shift

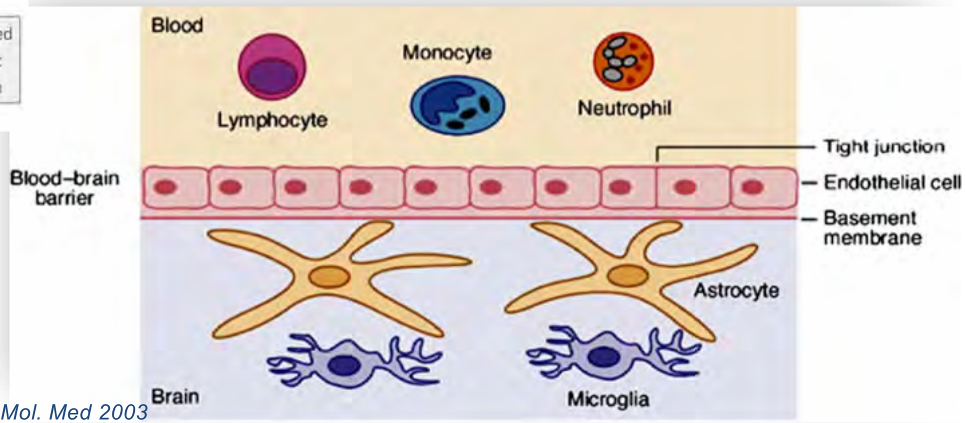
- Current bio-markers are not enough: The clinical-radiological paradox
- Measuring what the human eye cannot see:
  - ☛ Studying the early deposit of macrophages/microglia
  - ☛ Studying the diseases by characterization of axonal degeneration
- Imaging the cells and the microstructure:
  - Nano carriers of iron oxide can tag the macrophages activity (USPIO) in MRI
  - New ligand can tag microglia activity in PET
  - Quantitative MRI can characterize the damaged neuronal microstructure







v. Mol. Med 2003



Imaging neuro-inflammation in MS: spatio-temporal analysis

- Longitudinal Analysis of inflammatory lesions in MRI (USPIO + Gd)
- Discovery of lesion classes to prospectively stratify MS population
- Analysis of the **first 2 time points** (*before any treatment*)

1. Selection of spatio-temporal patterns
2. Use machine learning framework to classify patients

- **Results**
  - Able to predict 2-years evolution of individual patients from the onset

A: High Risk of evolution
B: Medium Risk of evolution
C: Low Risk of evolution

Patient	lesion clusters (and cardinality)	chro hypointense at m24 (cm3)	TLL by m24 (cm3)	Group
6	C2(x1), C3(x1), C1(x38)	13,4	18,9	A
11	C1(x1)	1,8	9,7	B
9	C2(x1)	1,42	6,72	A
10	C2(x2), C1(x8)	1,37	4,82	A
16	C3(x1)	1,46	4,7	A
24	no active lesions at m0 and m3	3,35	4,63	C
4	C2(x1), C1(x2)	1,77	4,29	A
13	C1(x2)	0,12	3,54	B
21	C1(x2)	0,74	3,5	B
18	C1(x4)	0,75	3,4	B
25	C1(x2)	0,96	3,32	B
7	C1(x9)	0,82	2,1	B
12	C1(x6)	0,34	2,1	B
2	C1(x1)	0,46	1,9	B
19	C1(x1)	0,27	1,73	B
5	C1(x2)	0,14	1,7	B
22	C1(x4)	0,1	1,27	B
17	C1(x1)	0,52	1,18	B
1	no active lesions at m0 and m3	0,12	1,18	C
8	C1(x1)	0,31	1,14	B
3	no active lesions at m0 and m3	0,28	0,98	C
15	no active lesions at m0 and m3	0,13	0,68	C
20	no active lesions at m0 and m3	0,18	0,54	C
23	no active lesions at m0 and m3	0,06	0,49	C
14	no active lesions at m0 and m3	0	0,29	C

Conclusion

Early lesion patterns characterization allows population stratification and suggests that belonging to a specific group can have an incidence on the future evolution of the disease.

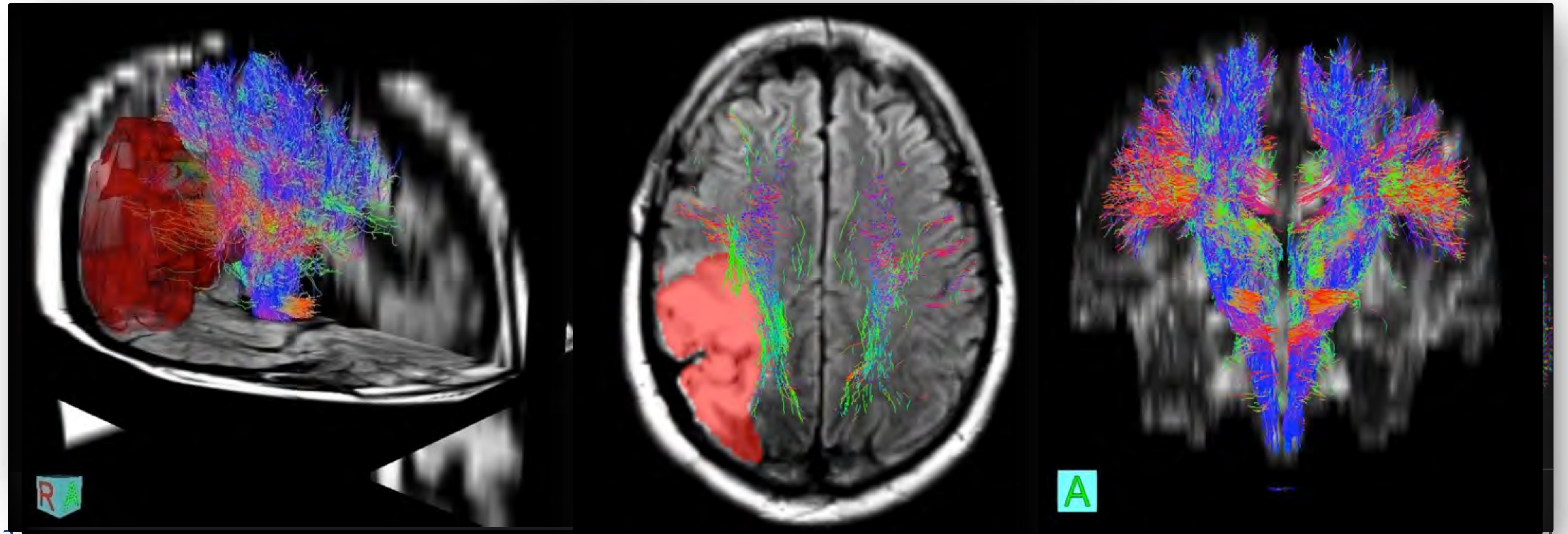
T0 T1

$$f = [\lambda_{x0}, \lambda_{y0}, \lambda_{z0}, \lambda_{x1}, \lambda_{y1}, \lambda_{z1}, \lambda_{x2}, \lambda_{y2}, \lambda_{z2}]$$

A. Crimi. et al. PLOS-One 2014

Imaging Biomarkers in MS: Brain microstructure can help

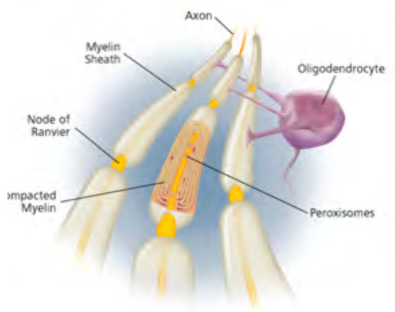
- Brain degeneration is also occurring at a diffuse level
  - Multiple sclerosis ⇒ axonal degeneration
- Challenging problem: overcome limitations of current methods:
  - Capability to be used in clinical routine (standard sequence) and on retrospective studies
  - Capability to exhibit crossing, diverging or kissing bundles and to track these bundles
  - Capability to characterize properties of neural circuits (instead of properties of voxels)



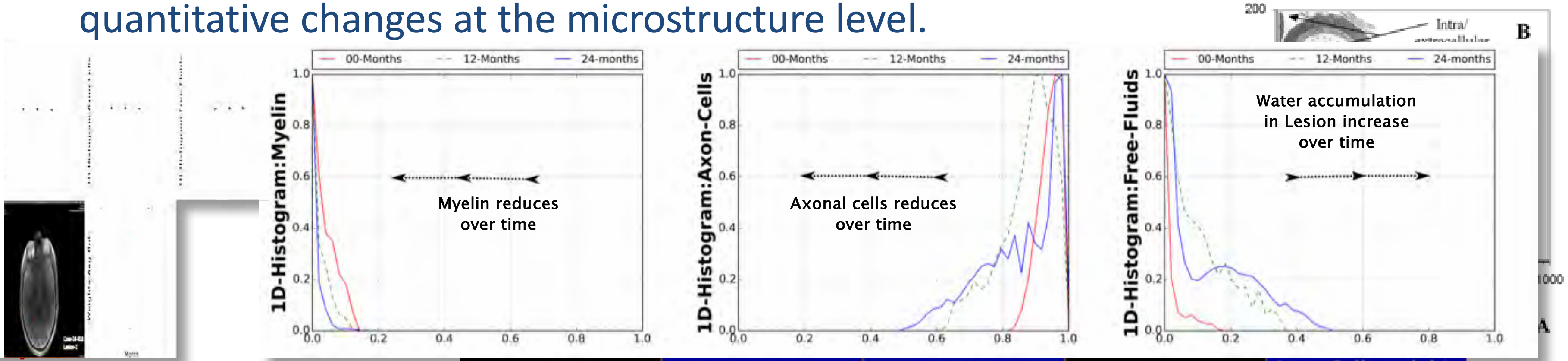
2. Filippi et al. Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology 56, 304-311, 2001.

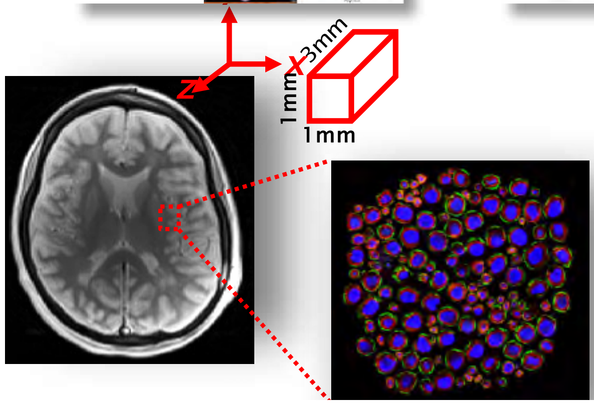
Multi compartment model of MRI relaxometry for myelin quantification

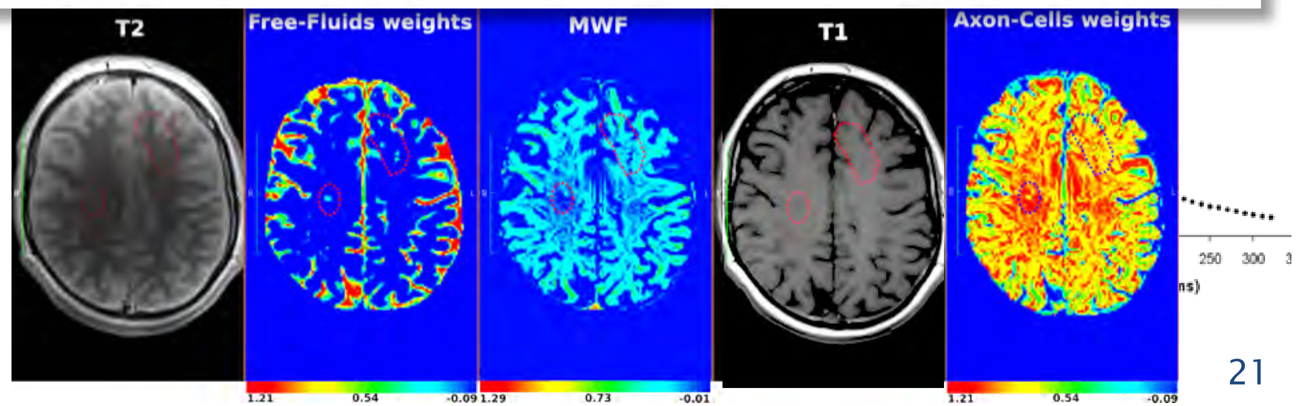
- Brain tissues have different relaxation properties
- Challenging problem
  - Very long sequences, subject to artefacts
  - Pathological events leading to Neuro disease are first reflected as quantitative changes at the microstructure level.



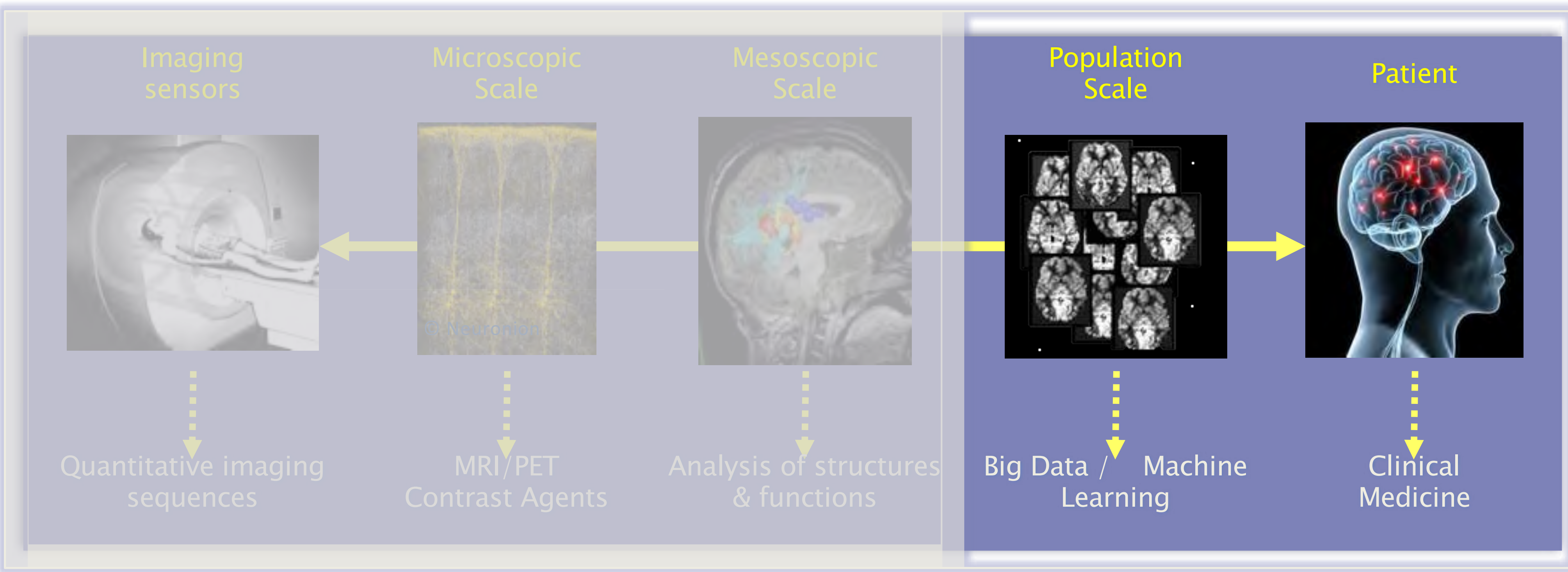
Longitudinal analysis







Imaging Biomarkers in MS: Pooling of data for population studies



Plan

- [Frontiers in ICT editorial activity]
- Imaging biomarkers: application to Multiple Sclerosis
- E-infrastructure for data management and analytics

Medical Imaging: a Big Data application

- Medical image databases
  - 20-40% increase of storage per year
  - A regular hospital produces 100-300 Tb/year of images

Needs for adapt computational solutions for the management of medical images

- Involve Data analytics: Image processing and machine learning
- Involve Data protection: complex legal constraints
- Very different to the e-commerce domain : less instances, more data / people

Big Data and Medical Imaging: Where are we?

- What to do with the data produced?
  - Explosion of production and exchange solutions for imaging data
  - But ... "*Information*" does not mean *“Knowledge”*
- Known Issues:
  - How to exploit this mass of information easily?
  - How to deal with the mass of images?
- For the moment, approaches rather based on:
  - a descriptive analysis than on statistical one,
  - the search of correlations
  - the idea that the *mass* compensates the *quality*

Big Data and Medical Imaging: Where do we go?

- Generalization of digital infrastructures on the Internet
  - Towards "PACS 3.0"
  - Local Storages are overpassed
  - Dissociation acquisition / storage
  - Remote viewing and analytics
- Emergence of dedicated digital infrastructures
  - What operators?
  - What costs and cost models?
  - Emergence of virtual communities of users
  - Emergence of new e-services on top of the image
- Emergence of new usages
  - New ways of working→ **image is shared**
  - Emergence of virtual care networks
  - Evolution of the concept of territorial coverage (the image goes closest to the expert)→ **towards specialized imaging centers**?
  - Image sharing and processing→ **Standardization of imaging protocols**
  - Potential economies of scale

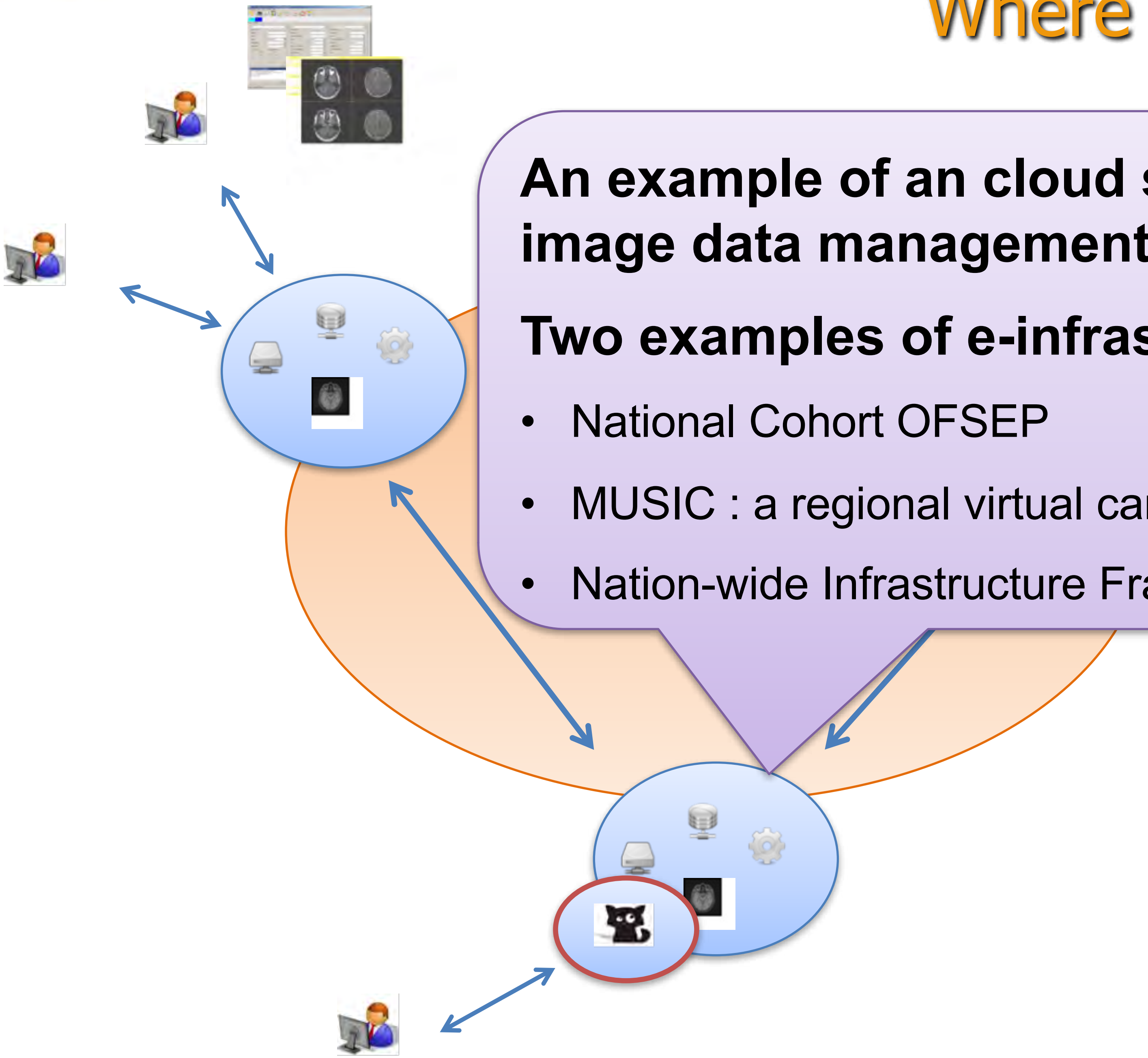
Big Data and Medical Imaging: Towards the Open Data?

- Need to access more and more datasets, for:
  - Building atlases, learning models
  - Data mining, search for similar cases
  - Continuing education / training of health professionals
  - Evaluation / validation of image analytics
  - Certification of digital solutions around the image
  - Encouragements from funding agencies for the Open Data model
  - **Emergence of population imaging**
- Major Issues
  - What type of operators? (Public, Private / National, Global)
  - Which economic model (who bears the cost?)
  - What Standards?
  - Data quality control (*mass does not compensate quality*)
  - Emergence of new players (network operators, data centers, startup, GAFAM, ...)
  - Evolution/adaptation of the regulations
  - Ethical issues

Medical Imaging as a Service

- Medical imaging applications have specific requirements for cloud computing:
  - Data:
    - Are heterogeneous
    - Are multistage
    - Have a strong semantic
    - Need acquisition protocols normalization
    - Are distributed over different sites (medical and/or academic)
    - Are confidential (security issues)
    - Need long term sustainability
  - Data Analytics / Image Processing:
    - Are often correlated (workflows)
    - Need automation for large cohorts (robustness, scalability, ..)
    - Need quality assessment: analytics transform images from qualitative to quantitative information and provide reference values (*imaging biomarkers*)
    - Computation time can be high on population cohorts
    - Computation time can also be sometimes critical (e.g. real time simulation, intervention, emergency, …)

Medical Imaging as a Service: Where do we go?

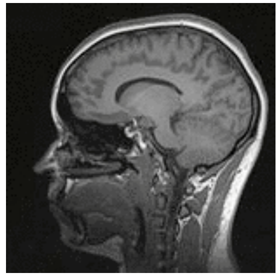


An example of an cloud solution for image data management : SHANOIR

Two examples of e-infrastructures :

- National Cohort OFSEP
- MUSIC : a regional virtual care network
- Nation-wide Infrastructure France-Life-Imaging

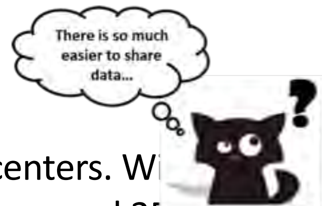
SHANOIR: a Software as a Service Environment to Manage Population Imaging



- Neuro-imaging: large quantity of data – still growing
  - Modalities: MRI, PET, Scanner, …
  - Examples:
    - MRI standard clinical examination: ~ 1400 images (> 100Mo)
    - MRI clinical research examination: ~ 4500 images (> 2Go)
  - Clinical research: multi-centers studies

    → **Need for data storage and archive**
    → **Need for data structuration**
    → **Need for data sharing and accessing**

- Existing solutions
  - CDs: simple solution but
    - Limited lifetime (~ 5 years), Data integrity not guaranteed
    - Physical storage
  - PACS: Picture Archiving and Communication System
    - Local (hospitals), regional or regional network → limited access



- SHANOIR: secure server accessible from <u>any web browser</u>
  - Shanoir is currently operated and used in more than 50 research and clinical centers. W[...]han 200 users connected, it hosts more than 80 multicenter research studies, with around 3500 patients patients and more than 200k data sets

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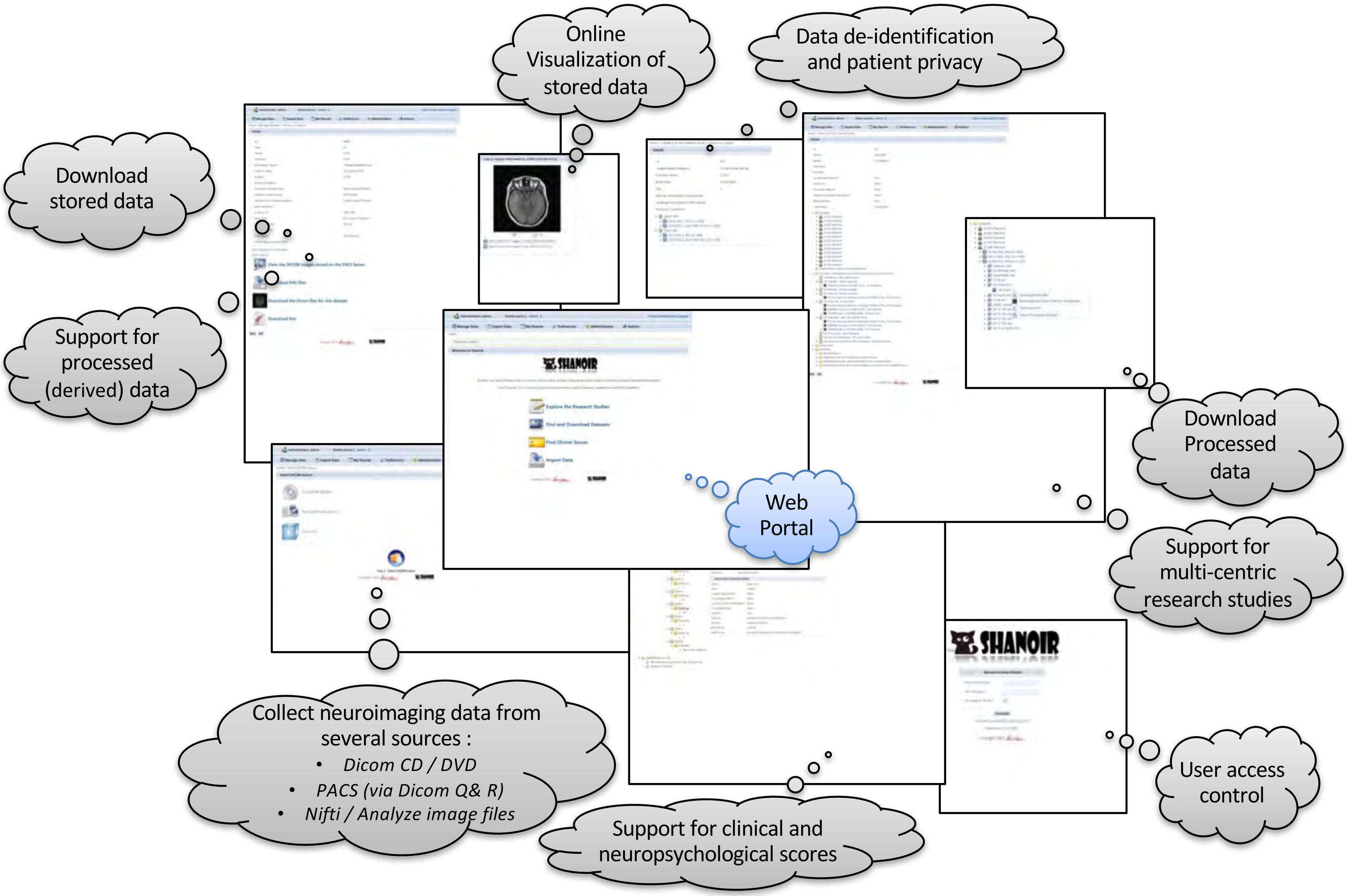
SHAring NeurOImaging Resources
An open source web platform for population imaging



Shanoir: this is more than 50 centers / 200 users connected / 80+ studies / 3500+ subjects connected and more than 200k data sets

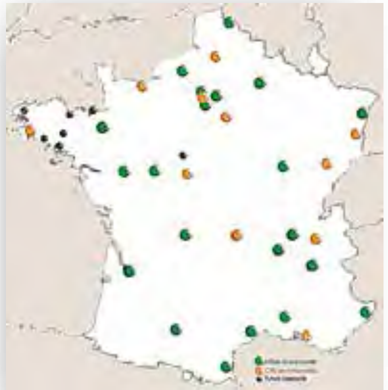
SHANOIR in the OFSEP Cohort

OFSEP

	MRI Manufacturer - Model
8	**Siemens - Aera 1,5T**
7	**Philips - Achieva 3T**
2	General Electric - DISCOVERY MR750w 3T
2	Philips - Ingenia 1,5T
2	Siemens - Avanto 1,5T
2	Siemens - Skyra 3T
1	General Electric - Signa HDxt 3T
1	Philips - Achieva 1,5T
1	Philips - Ingenia 3T
1	Siemens - Espree 1,5T
1	Siemens - Spectra 3T
1	Siemens - Symphony Tim 1,5T
1	Siemens - Trio 3T
1	Siemens - Verio 3T
31	

	PACS Manufacturer	Model
4	GE Healthcare	Centricity PACS
3	Maincare Solutions	McKesson Radiology
2	Agfa	IMPAX
2	Telemis	Telemis
1	Carestream	Carestream Vue PACS
1	Global Imaging	GXD5 Pacs
13		

OFSEP is a nationwide, **clinical**, cohort, representing about half of the MS patients population living in France, for a **longitudinal follow-up** (clinical, biological and neuroimaging data). **Shanoir** has been chosen to be the OFSEP neuroimaging data management platform

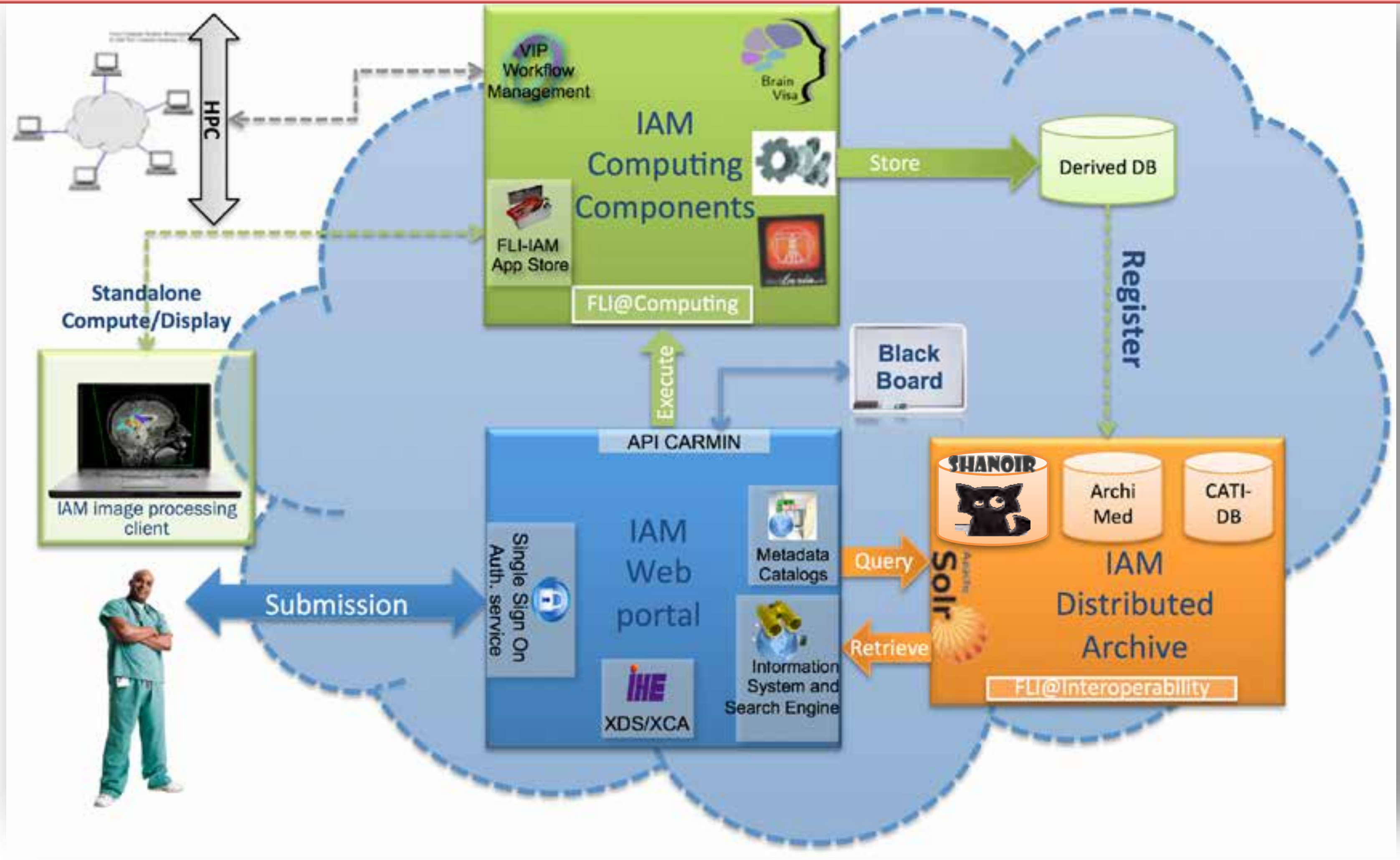


Brain MR imaging protocol (At least one every 3 years)	**Spinal cord MR imaging protocol** (At least one MRI every 6 years)
Recommended	
▪ Sagittal enhanced 3D T1 ▪ Axial DWI with ADC map ▪ Axial 2D TSE T2/DP <u>or</u> 3D T2 ⇨ Gadolinium injection (0.1 mmol/kg) ▪ 3D FLAIR (<u>or</u> 2D FLAIR if not available) ▪ Contrast-enhanced 3D T1	▪ Sagittal T2 In case of lesion occurrence ▪ Axial T2 GRE ▪ Axial T1 TSE with gadolinium injection
Recommended for first and differential diagnosis	
▪ Axial 2D T2 GRE	▪ Sagittal T1 with gadolinium injection
Advanced sequences	
▪ DTI ≥ 15 directions (replace the DWI)	▪ Sagittal STIR

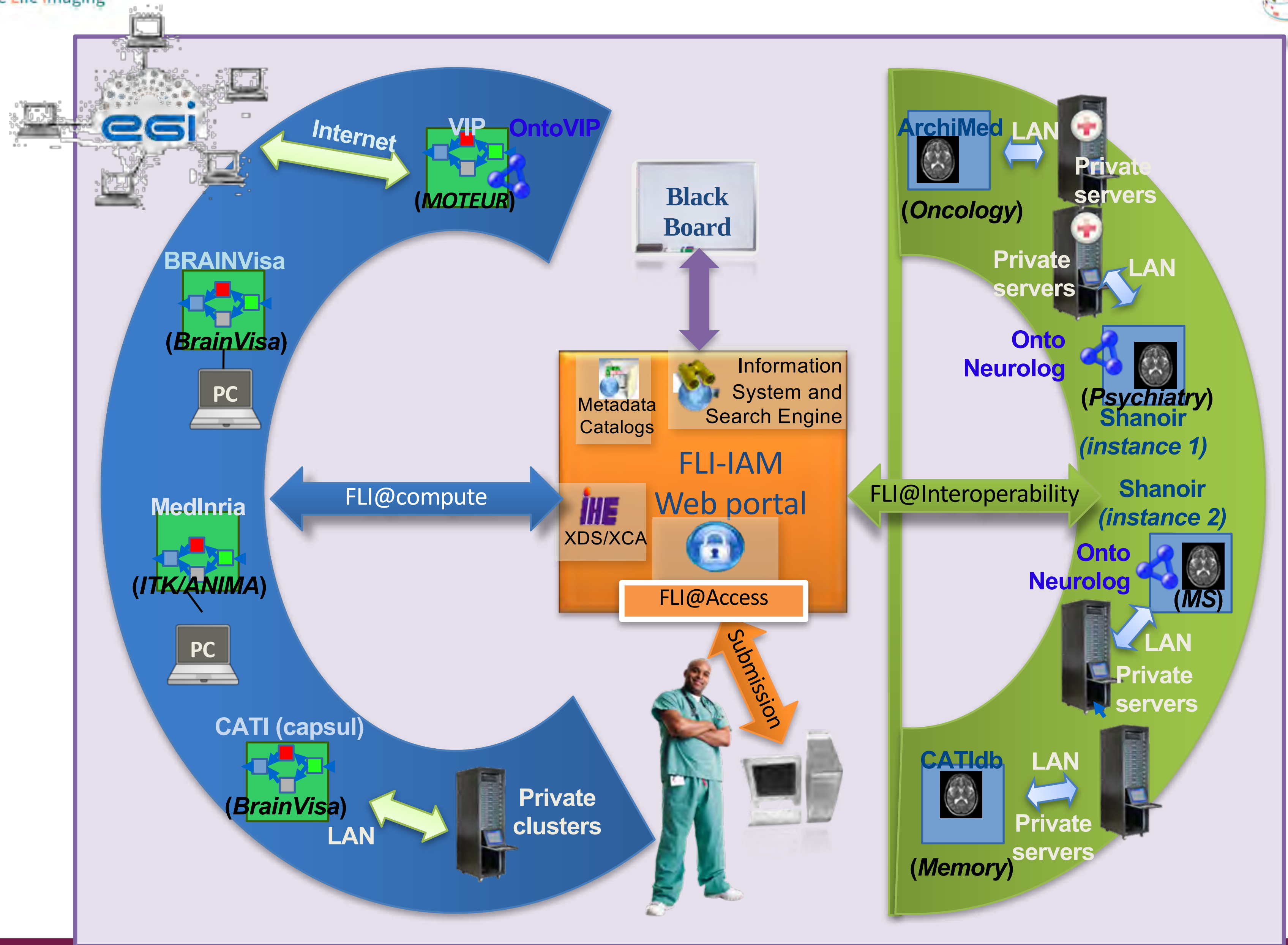
SHANOIR in the FLI e-Infrastructure

FLI + OFSEP = 2016 MICCAI Challenge of MS

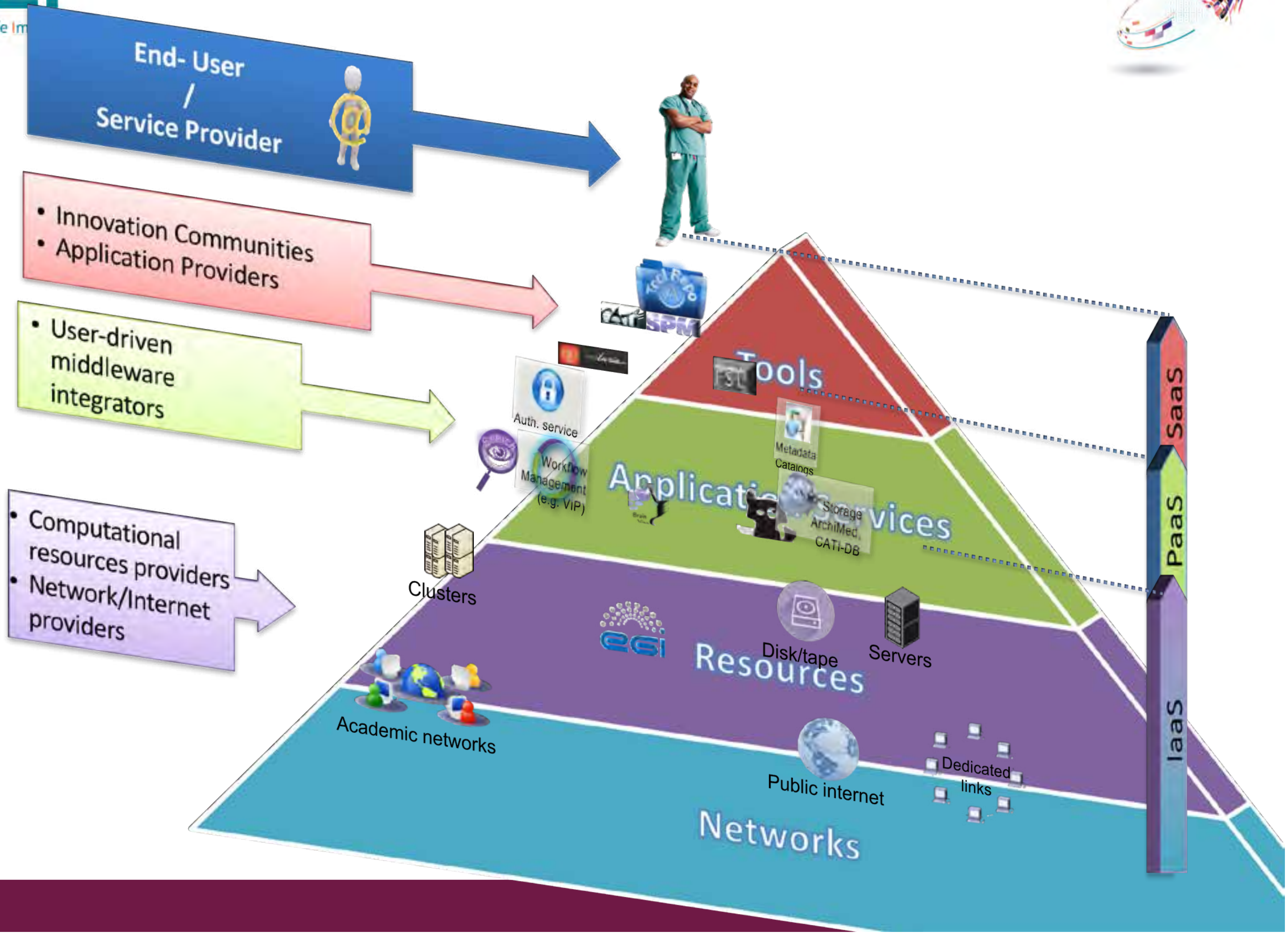
https://portal.fli-iam.irisa.fr/msseg-challenge/



FLI - IAM Computing/Data Architecture



FLI-IAM Stack Architecture



Archiving and Sharing of images: How to change the usages?

- The gathering of data remains an issue
  - Reconciliation of image sources, reconciliation of images with clinical context, image fusion, quality control, harmonization of protocols
- Image analysis remains an emerging field
  - Robustness of tools, computation time, reproducibility of results, responsibility for use
- Who wants to share their data?
  - Conservatism of the community
  - Regulatory constraints
- Who can share their data?
  - Going beyond the "club" of insiders
  - Offer customized solutions
  - Certification of provided solutions
  - Accept the fair cost for these new uses.
- How to ethically manage data sharing and open data?
  - Anticipate before the problems arise: collectively (legally) and individually (e.g. consent)
- Security is and will always remain a challenge
  - Should not be underestimated
  - Do not use excuses for not taking care
  - Properly dimension the response to the risk so as not to kill the use
  - Multidisciplinarity: IT security is not just a medical issue
- Invent new jobs and develop them
  - Nothing can be done without a strong integration between Engineers, researchers, lawyers and doctors

THANK YOU FOR YOUR ATTENTION

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- Lea ITMI [SIEMENS]
- Angelique JARNOUX [Inria]
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