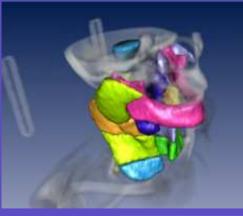


## Design and Use of Anatomical Atlases for Radiotherapy

#### **Olivier COMMOWICK**

February 14, 2007

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE 



Jury:

- Patrick Clarysse (reviewer) CNRS
- Grégoire Malandain (advisor) INRIA
- Nicholas Ayache INRIA
- Pierre-Yves Bondiau Centre Antoine Lacassagne
- Guido Gerig University of North Carolina
- Vincent Grégoire Université Catholique de Louvain
- Hanna Kafrouni (invited) DOSIsoft S.A





#### Road Map

- Introduction
- Incorporating Priors in Non Linear Registration
- Atlas-Based Brain Segmentation
- Head and Neck Atlas-Based Segmentation
- Conclusion and Perspectives





#### **Medical Context**

- Different cancer treatments
  - Chemotherapy
    - Drugs killing cells in division
  - Surgery
    - Remove physically the tumor
  - Radiotherapy
    - High irradiation killing cells in division
- Treatment of tumors on two regions
  - Brain
  - Head and Neck

DOSI-Soft





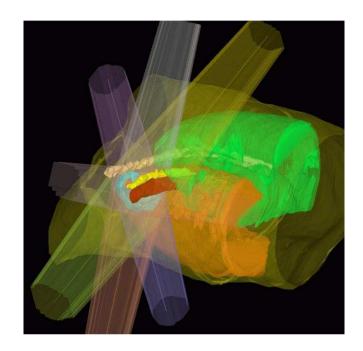
### Radiotherapy

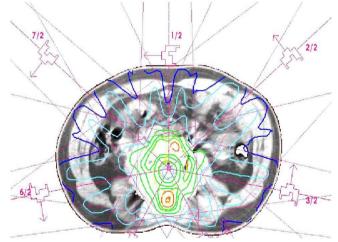
- Radiotherapy principle:
  - Use of high energy irradiation beams
  - Optimize dose on the tumor
  - Control irradiation of critical structures (OAR)

#### ➔ Need for high precision planning

DOSI-%soft

- Irradiation doses computed on each organ
- Compare doses with expected levels
- Requires delineation of structures









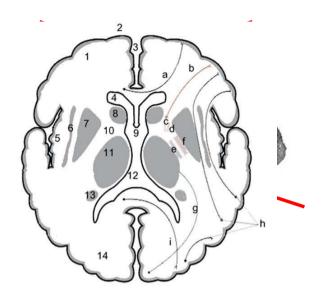
#### **Brain Anatomy**

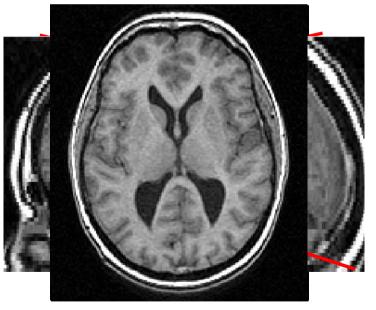
- Many organs at risk
  - Eyes, optic nerves, chiasma
  - Brainstem, cerebellum
  - Grey nuclei
- Different categories [Pontvert, 2004]
  - Very high risk (eyes)

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- High risk (optic nerves, brainstem)
- Medium risk (grey nuclei)

[Pontvert, 2004]: Radiothérapie des tumeurs cérébrales. 2004.





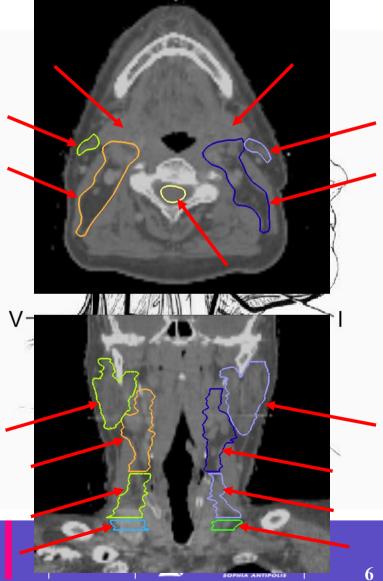


#### Head and Neck Anatomy

- Structures of interest
  - Lymph nodes areas
    - Separated using visible landmarks
    - Tumor dissemination regions
  - Parotids
  - Spinal cord
  - Sub-mandibular glands

[Grégoire et al., 2003] CT-based delineation of lymph node levels and related CTVs in the node-negative neck : DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines. Radiotherapy Oncology, 2003.

DOSI-%-soft



### Radiotherapy planning

- Requires an accurate delineation
  - Head and Neck radiotherapy
    - Only CT image acquired, necessary for dosimetry
  - Brain radiotherapy
    - MRI exam often added
    - Better differentiation of soft tissues
- Segmentation done manually
  - Time consuming (2 to 4 hours)
  - Not reproducible
- Objective: provide fast and automatic segmentation tools





### Automatic Segmentation for Radiotherapy

- Goal: automatic segmentation of organs at risk
- Available segmentation methods
  - Intensity based (adaptive thresholding, EM)
    - No prior on shape or position
  - Deformable models, level-sets, active contours
    - Possible priors on structures
  - Atlas based segmentation

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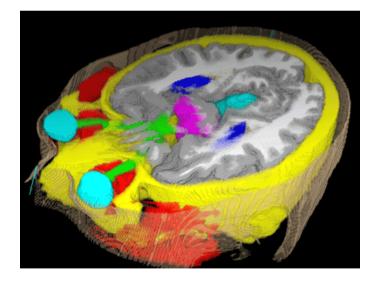
- Atlas: image and its segmentation
- A priori on respective positions and shapes

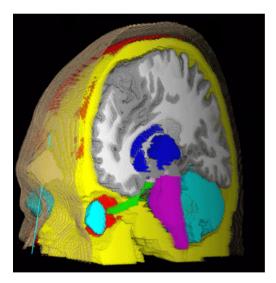
Increasing prior knowledge



#### **Atlas Construction**

- First approach:
  - One image delineated by an expert
    - Brain atlas (from Dr. Pierre-Yves Bondiau [Bondiau, PhD, 2004])
    - must be representative (possible bias)





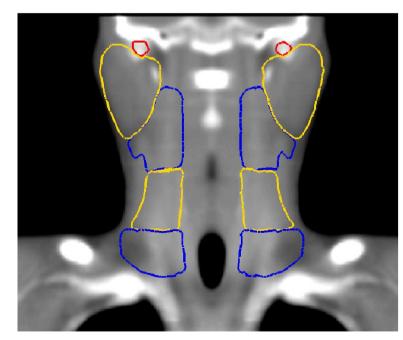
[Bondiau, PhD, 2004]: Mise en oeuvre et évaluation d'outils de fusion d'image en radiothérapie. November 2004.

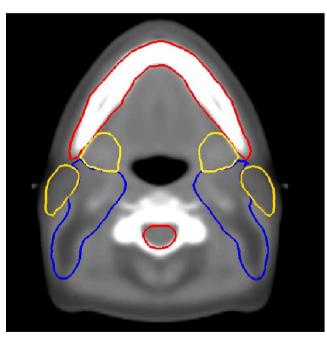




#### **Atlas Construction**

- Second approach:
  - Average image from a dataset of images
  - Head and neck atlas
    - Images from Pr. Vincent Grégoire (UCL)

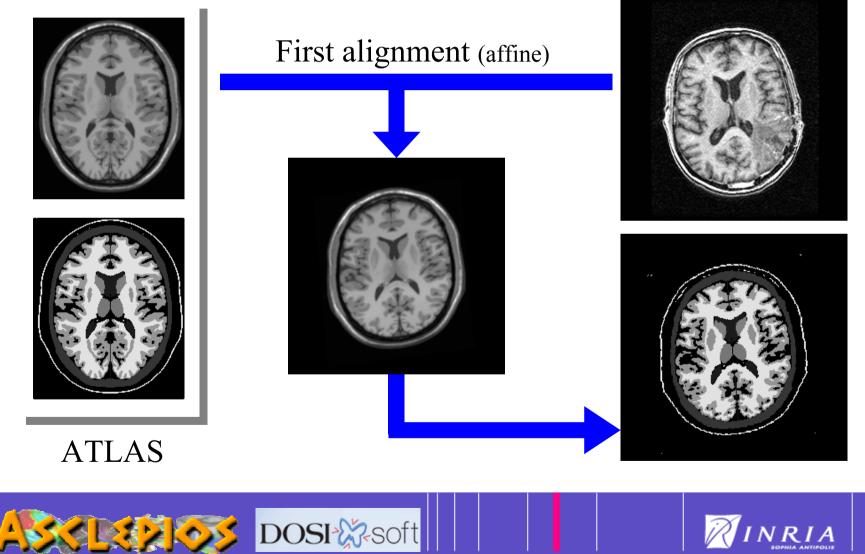






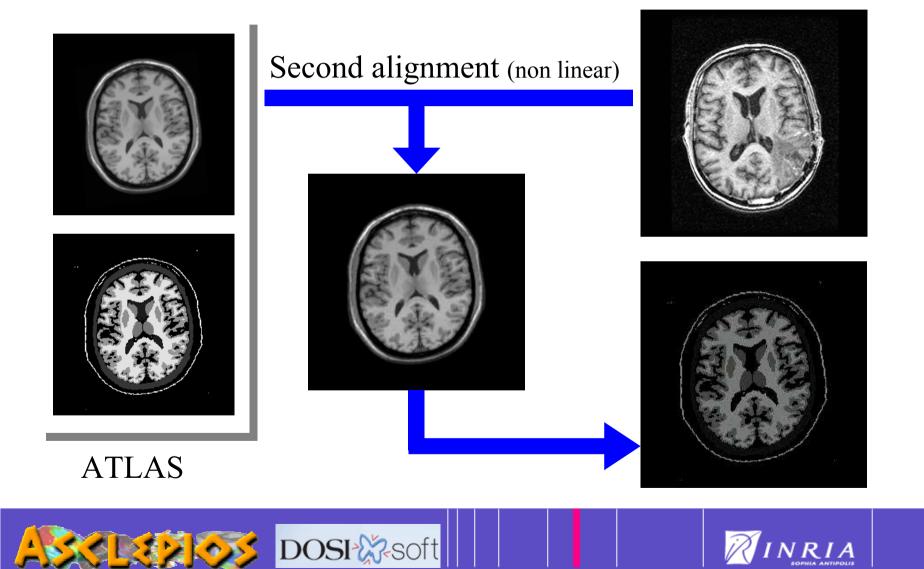


#### **Atlas-based Segmentation Principle**





#### **Atlas-based Segmentation Principle**



#### Non linear transformations

- Tradeoff in non linear registration
  - Able to handle atlas/subject variability
  - Robust and smooth

DOSI & sof

- Transformations:
  - Parametric
    - Interpolated between control points
    - Arbitrary number of degrees of freedom
    - RBF [Rohde et al., 2003], FFD [Rueckert et al., 1999]
  - Dense
    - One displacement vector per voxel
    - Maximal number of degrees of freedom
    - Pasha [Cachier et al, 2003], ...

Increasing degrees of freedom

[Rohde et al., 2003] The adaptive bases algorithm for intensity based nonrigid image registration.. IEEE TMI, 2003.

[Rueckert et al., 1999] Non Rigid Registration Using Free-Form Deformations: Application to Breast MR Images. TMI, 1999.

[Cachier et al., 2003] Iconic Feature Based Nonrigid Registration : The PASHA Algorithm. CVIU, 2003.



## Challenges in Atlas-Based Segmentation

- Goal: Automatic segmentation of critical structures for radiotherapy
- Requirements:
  - Minimal interaction from user
  - Robust to different acquisition protocols
  - Realistic contours in a minimal time
- Key point of the approach: non linear registration
  - Smooth transformation
  - Able to handle atlas/subject variability
  - Robust registration method
  - Method as fast as possible





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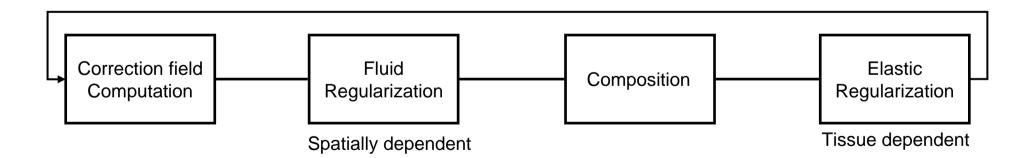




#### **Existing Dense Non Linear Registration**

- Method of [Stefanescu et al., 2004]: Runa
  - Spatially inhomogeneous regularization
  - Fluid regularization on highly variable regions
  - More elastic regularization elsewhere

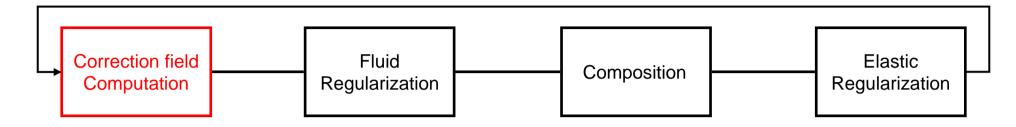
#### • Iterative process



[Stefanescu et al., 2004]: Grid Powered Nonlinear Image Registration with Locally Adaptive Regularization, MedIA, 2004.



#### **Runa: Correction Field Computation**



• Computation of correction  $\delta T$ 

• Gradient descent on a similarity measure:

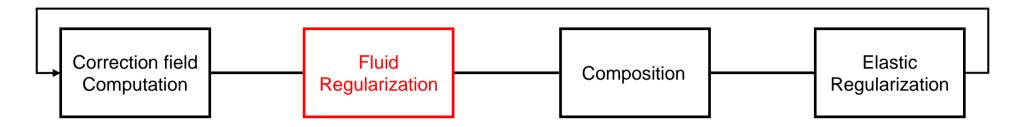
$$\delta T = \nabla SSD(R, F \circ T^{l-1}) = (R - F \circ T^{l-1}) \cdot \nabla (F \circ T^{l-1})$$

- SSD: Sum of Squared Differences
- R : reference image
- F : floating image
- $T^{l-1}$ : transformation obtained at iteration l-1





### Runa: Fluid Regularization



• Regularization of correction field

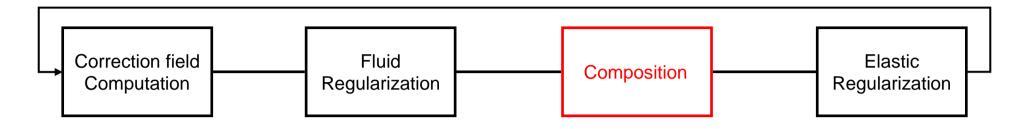
$$\frac{\partial \delta T}{\partial t}(x) = (1 - k(x))\Delta \delta T(x)$$

- Weighted by a factor  $k(x) = f_1(||\nabla R||)$ 
  - Spatially dependent
  - Less confidence (more regularization) in homogeneous regions





#### Runa: Composition of Correction



• Regularized correction field:  $\delta \widetilde{T}$ 

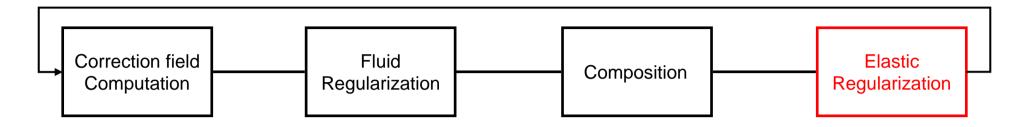
• Composition with transformation at iteration l-1

 $T^{l} \leftarrow T^{l-1} \circ \delta \widetilde{T}$ 





#### **Runa: Elastic Regularization**



• Regularization of the transformation

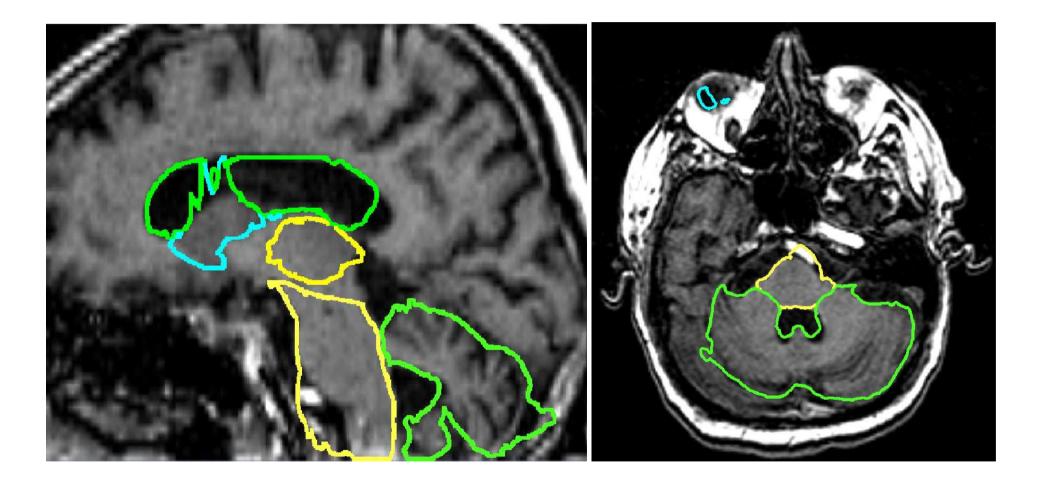
$$\frac{\partial T^l}{\partial t} = \nabla . (D(x) \nabla T^l)$$

- Weighted by  $D(x) = f_2(i(x))$ 
  - Scalar, tissue dependent i(x), heuristic model
  - White and grey matter: high regularization
  - CSF: low regularization





#### Segmentation Result (Runa)







#### Summary

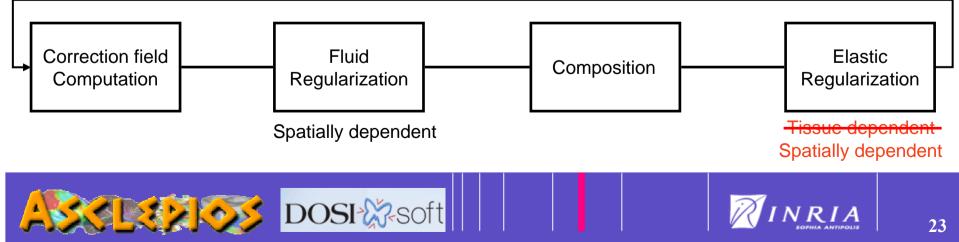
#### Advantages

- Precise deformations
- Inhomogeneous regularization

#### • Drawbacks

- Noisy contours (not realistic)
- Registration parameters
  - Need to be set for each patient
  - Need to be set for each acquisition protocol

#### Solution



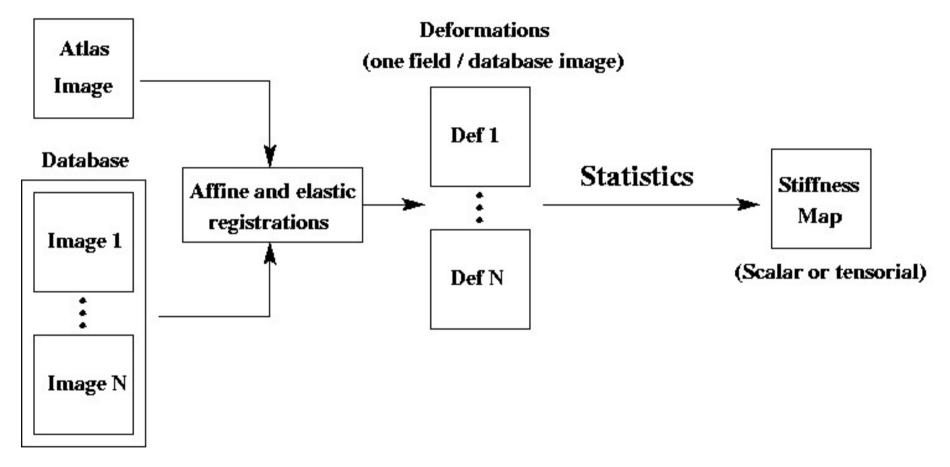
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#### **Statistics Computation Pipeline**

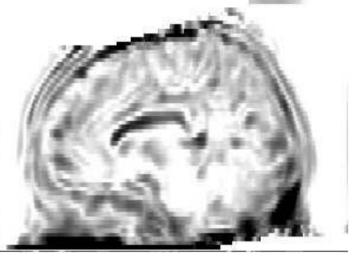


[Rueckert et al., 2003]: Automatic Construction of 3D Statistical Deformation Models of the Brain using Non Rigid Registration. IEEE TMI, 2003.



#### **Scalar Mean Deformability**

- Isotropic measure of deformability
- Determinant of the Jacobian matrix  $\left|J_{i}(x)\right|$ 
  - $|J_i(x)| > 1$  : local dilation
  - $|J_i(x)| < 1$  : local contraction



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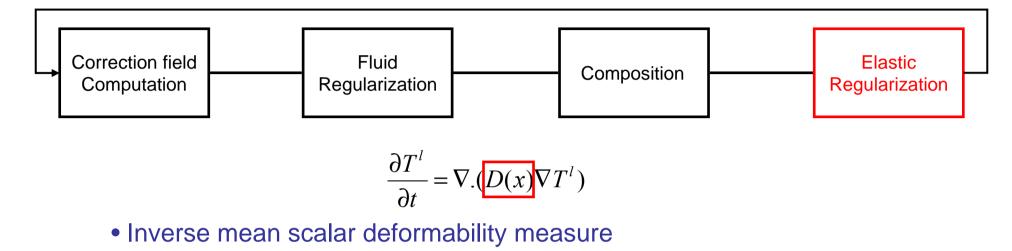
• Mean deformability:

DOSI-Soft

$$\overline{Def}(x) = \frac{1}{N} \sum_{i} \operatorname{abs}(\log(|J_i(x)|))$$



### **Incorporating Statistics in Regularization**



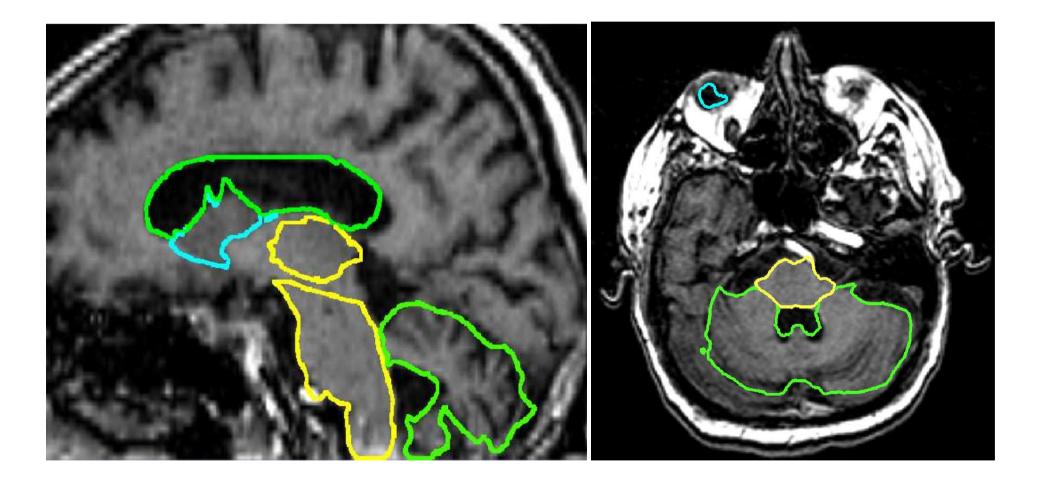
$$D(x) = \left(1 + \lambda \overline{Def}(x)\right)^{-1}$$

- Values of D(x)
  - Between 0 and 1
  - Close to 1: High regularization
  - Close to 0: Low regularization





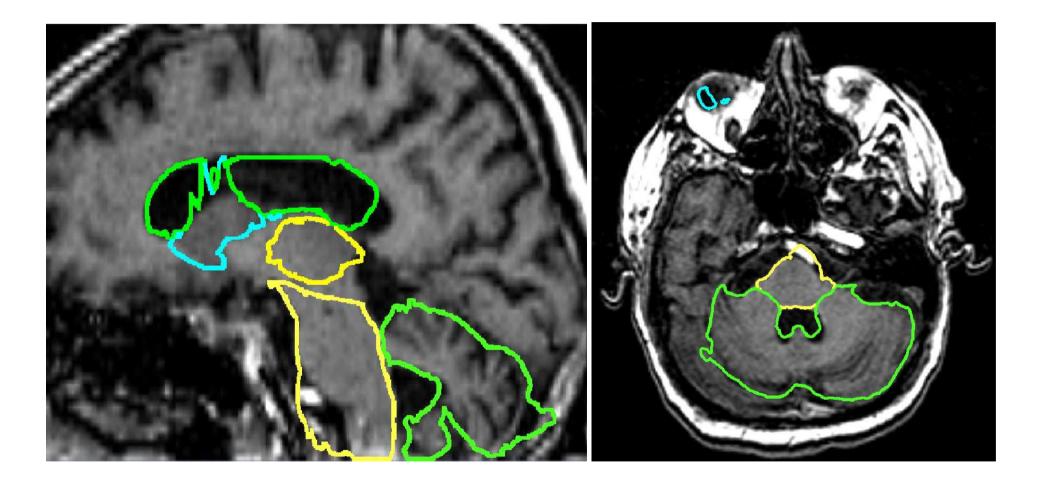
# Segmentation Result (Runa, Scalar Statistics)







#### Segmentation Result (Runa)







#### **Tensor-based Mean Deformability**

• Based on tensor derived from the Jacobian matrix

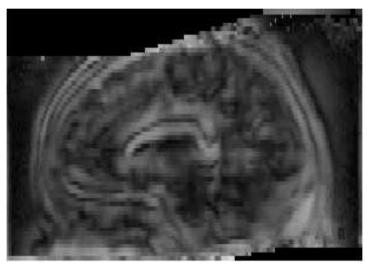
 $W_i(x) = J_i^T(x) J_i(x)$ 

• Mean deformability

DOSI-Second

$$\overline{\Sigma}(x) = \frac{1}{N} \sum_{i} \operatorname{abs}(\log(W_i(x)))$$

• Quantification of anisotropy in deformability

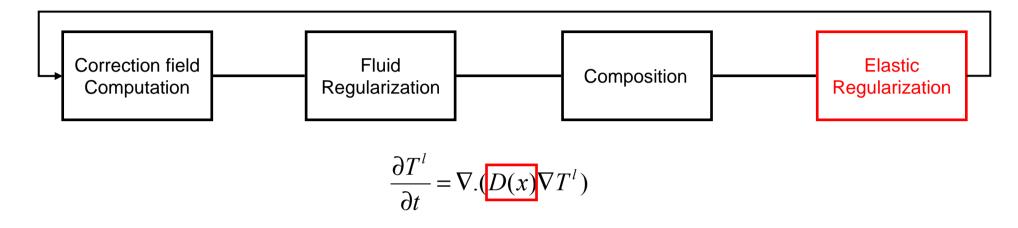


Mean Tensor-based Map

[Lepore et al., 2006]: Multivariate Statistics of the Jacobian Matrices in Tensor Based Morphometry and their Application to HIV / AIDS. MICCAI, 2006.



#### **Incorporating Statistics in Regularization**



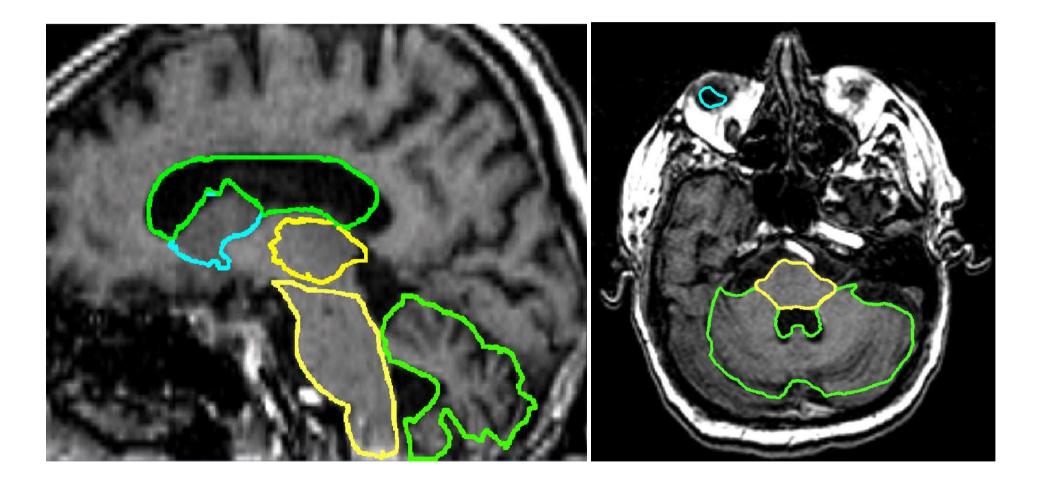
- Inverse mean tensor-based deformability measure
  - Formula analogous to the scalar case

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$$D(x) = (Id + \lambda \overline{\Sigma}(x))^{-1}$$



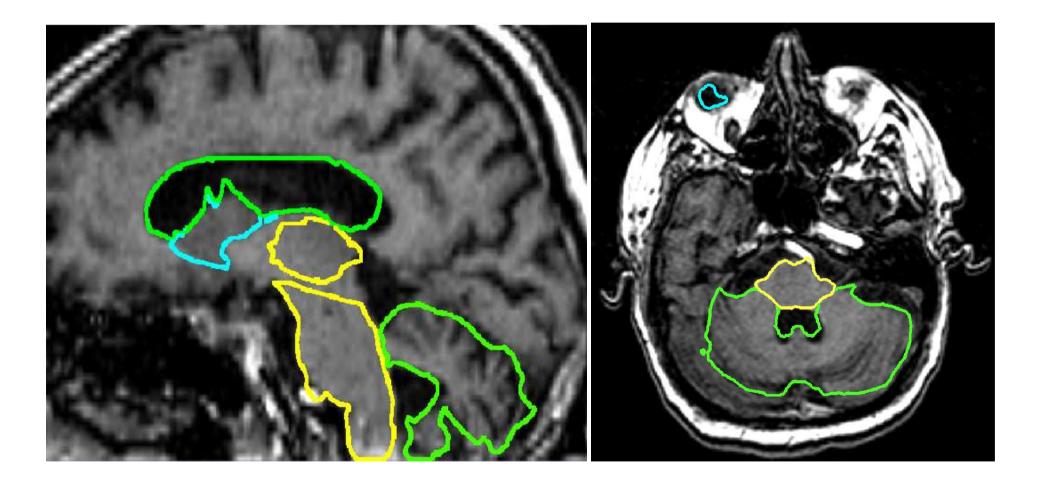
# Segmentation Result (Runa, Tensor Based Statistics)







# Segmentation Result (Runa, Scalar Statistics)







#### Summary

- Introduction of deformability statistics [Commowick et al., 2005]
  - Reduced dependency to registration parameters
  - Smoother and more precise contours
- Problems:
  - Time consuming: around 40 minutes
  - Still regularity problems (eyes)
  - Parameters to set for each acquisition protocol

#### → Objective: Introduce more robustness and regularity

[Commowick et al., 2005]: Incorporating Statistical Measures of Anatomical Variability in Atlas-to-Subject Registration for Conformal Brain Radiotherapy. MICCAI, October 2005.





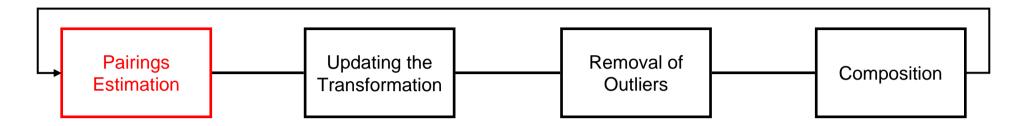
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# Non Linear Registration with Outlier Rejection



• Block-Matching method [Ourselin et al., 2000]

- Move blocks in a neighborhood
- Pairing: chosen according to a similarity value
- Pairings Estimation (Block-Matching [Ourselin et al., 2000])
  - Sparse pairings field *C*

DOSI-Second

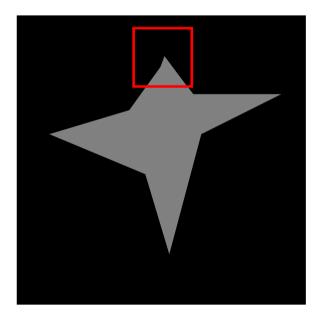
Associated to confidence field k: similarity value of each pairing

[Ourselin et al., 2000]: A General Framework to Improve Robustness of Rigid Registration of Medical Images. MICCAI, 2000.



# "Block Matching" Technique

1. Consider regularly sampled sub-images (or "blocks")



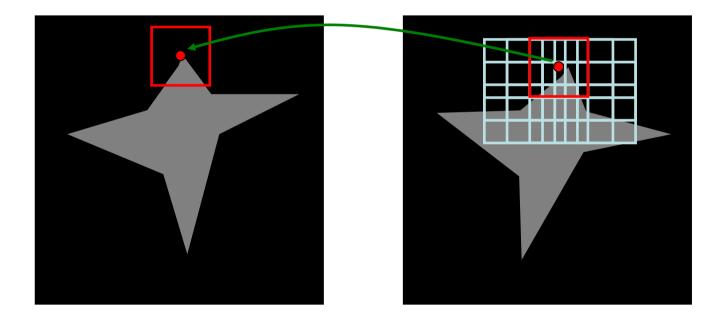






#### "Block Matching" Technique

2. Search the "most similar" block: gives point to point correspondence

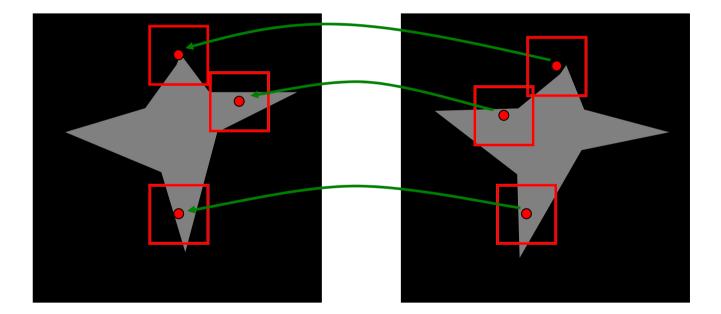






## "Block Matching" Technique

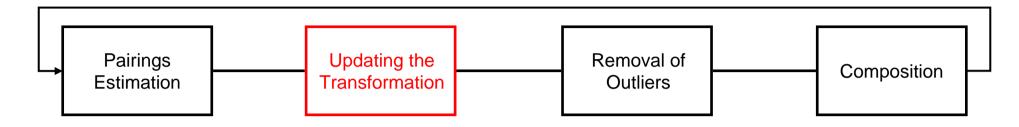
3. Obtain pairings sparse field from  $(x_v, y_v), C(x_v) = y_v - x_v$ 







## Baloo: Updating the Transformation



- Transformation correction  $\delta T$  estimation
- Interpolated from pairings weighted by confidence field

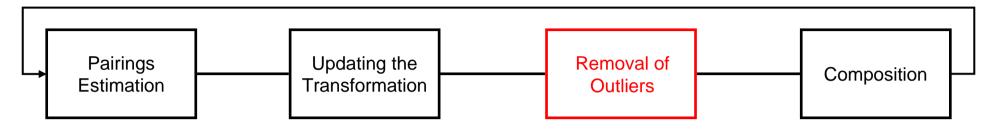
$$\delta T = \frac{G_{\sigma} * kC}{G_{\sigma} * k}$$

•  $G_{\sigma}$ : Gaussian kernel of variance  $\sigma$ 





#### **Baloo: Removal of Outliers**



• Comparison between pairings and interpolated corrections

• Outlier criterion  $||C(x_v) - \delta T(x_v)|| > s$ 

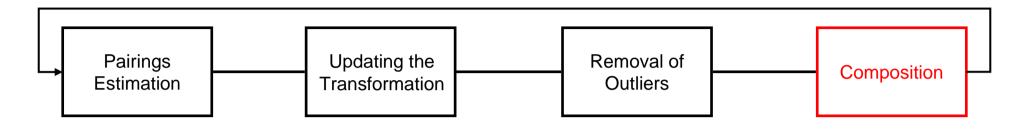
DOSI-Soft

• *s* depends on mean *e* and variance of errors  $\sigma_e$ 

$$e = \frac{1}{N} \sum_{v} \|C(x_{v}) - \delta T^{l}(x_{v})\| \qquad \sigma_{e}^{2} = \frac{1}{N} \sum_{v} \left(e - \|C(x_{v}) - \delta T^{l}(x_{v})\|\right)^{2}$$



# **Baloo: Composition of Corrections**



•  $\delta \widetilde{T}$  : correction interpolated from pairings minus outliers

• Composition of current transformation  $T^{l-1}$ 

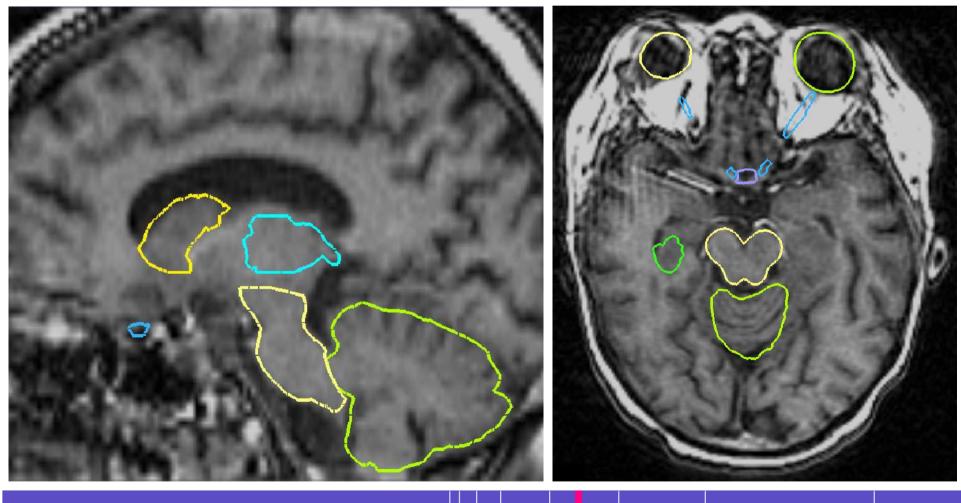
**DOSI** Soft

$$T^{l-1}: T^l \leftarrow T^{l-1} \circ \delta \widetilde{T}$$



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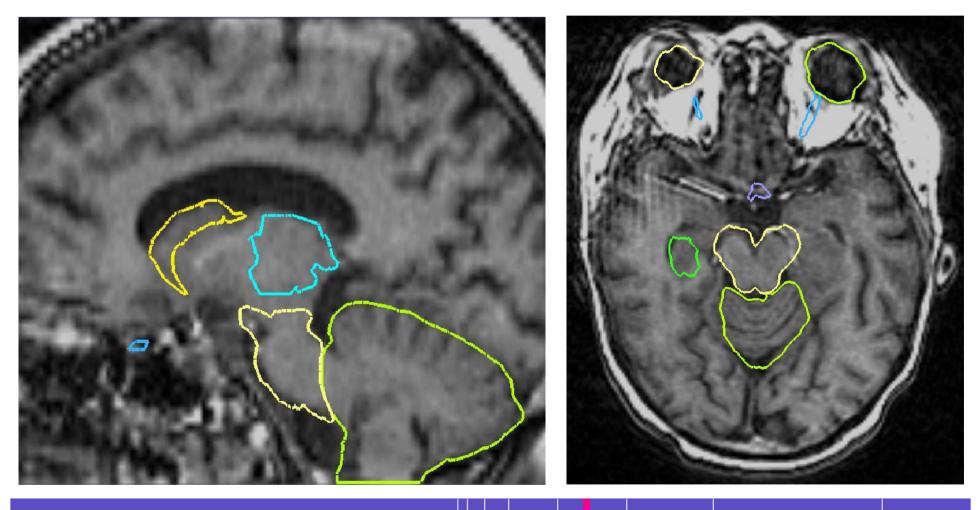
#### Segmentation Result (Baloo)







#### Segmentation Result (Runa)







#### Summary

- Dense Registration with Outlier Rejection (Baloo)
  - Faster than classical dense registration (20 minutes)
  - Smooth transformation
  - Precise contours
- Problems left:
  - Still depends on images quality (eyes)
  - Larger slice thickness
- Objectives
  - More robustness by constraining the transformation
  - Registration only on regions of interest





# Road Map

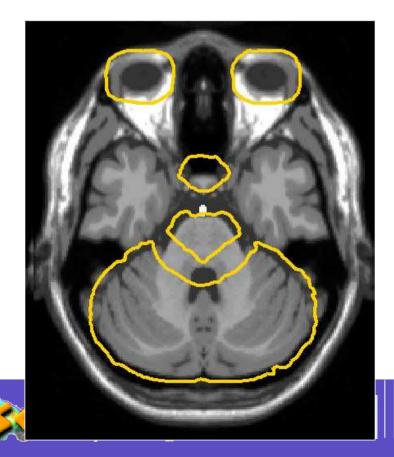
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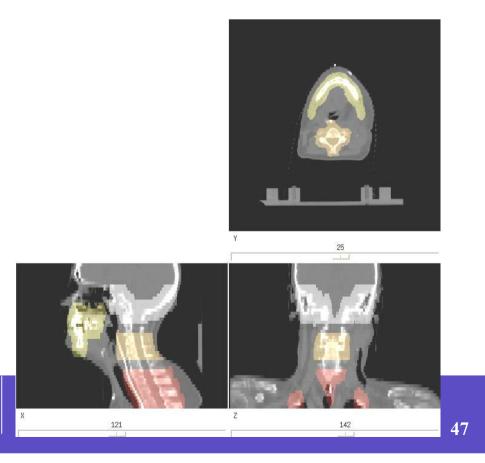




#### Locally Affine Framework

- Principle:
  - Register only anatomic areas of interest
  - Interpolate a global transformation from all local transformations





# Locally Affine Transformation

- Local transformation
  - Affine transformation  $A_i$  associated to each region  $R_i$
  - Weight function  $w_i(x)$ 
    - Relative influence of each region at point x

$$w_i(x) = \frac{1}{1 + \lambda d(x, R_i)}$$

- Global transformation:
  - Solution 1: Weighted interpolation of affine components

$$T(x) = \sum_{i=1}^{N} w_i(x) A_i(x)$$

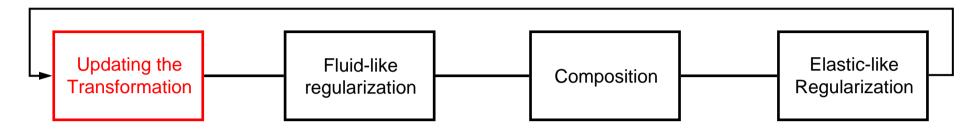
• Solution 2: Using an ordinary differential equation [Arsigny, PhD, 2006]

[Little et al., 1997]: Deformations Incorporating Rigid Structures. CVIU, 1997.

[Arsigny, PhD, 2006]: Processing Data in Lie Groups: An Algebraic Approach. Application to Non-Linear Registration and Diffusion Tensor MRI. November 2006.



# LAF: Updating the Transformation



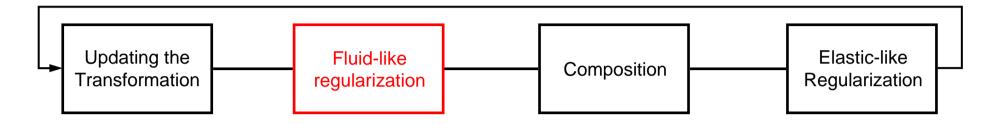
• Local affine correction  $\delta A_i$  estimation

- Block-Matching algorithm
- Outlier rejection in the estimation process
- Least Trimmed Squares Weighted Estimation
  - Weighted by similarity measure values
  - Weighted by  $w_i(x_v)$





# LAF: Fluid-like Regularization



• Fluid-like regularization of local transformation corrections

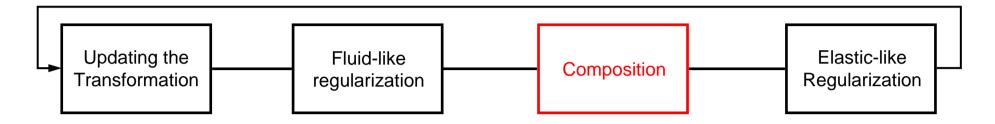
• Gradient descent on 
$$\operatorname{Reg}(\delta A_i, w_i) = \sum_{i=1}^{N} \sum_{j \neq i} p_{i,j} \left\| \log(\delta A_i) - \log(\delta A_j) \right\|^2$$

- Log-Euclidean polyaffine framework
  - $log(A_i)$  belongs to a vector space
  - Generalization of usual regularization energies





# LAF: Composition of Corrections



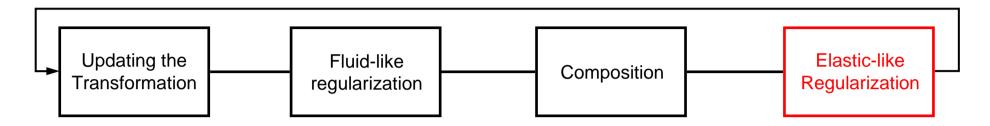
• Regularized corrections:  $\delta \widetilde{A}_i$ 

• Composition of corrections with the current transformation

$$A_i^l = A_i^{l-1} \circ \delta \widetilde{A}_i$$



# LAF: Elastic-like Regularization



Gradient descent on

$$\operatorname{Reg}(A_{i}^{l}, w_{i}) = \sum_{i=1}^{N} \sum_{j \neq i} p_{i,j} \left\| \log(A_{i}^{l}) - \log(A_{j}^{l}) \right\|^{2}$$

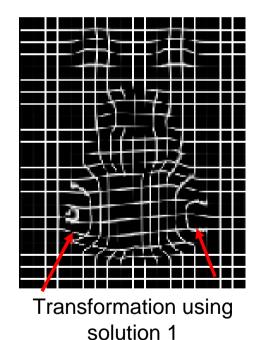
- Similar to fluid-like regularization
  - Regularization on transformations  $A_i^l$

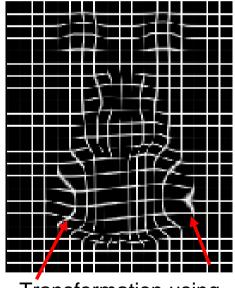




# Locally Affine Registration

- Final global transformation computation
  - Solution 1 (weighted interpolation): Fast but not always invertible
  - Solution 2 (polyaffine): Slower but always invertible



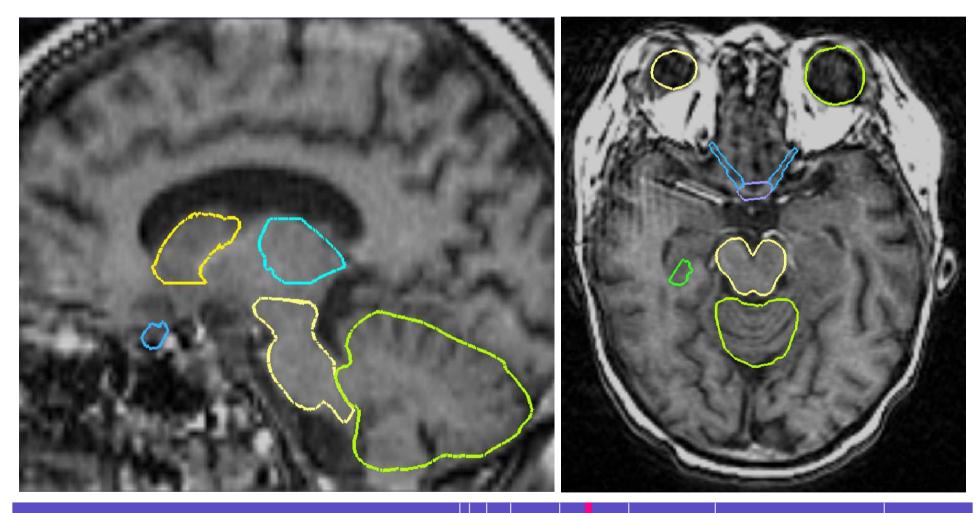


Transformation using solution 2





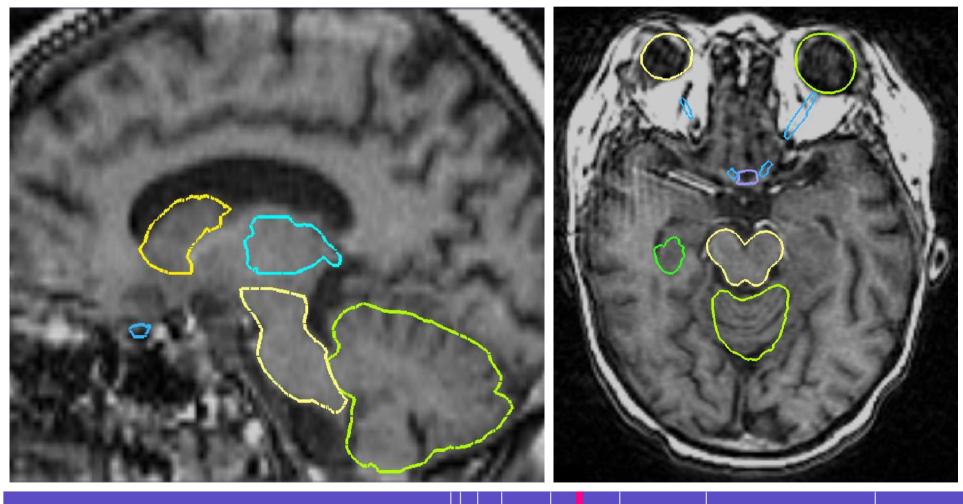
#### Segmentation Result (Locally Affine)







#### Segmentation Result (Baloo)







### Conclusion

• Locally Affine Registration [Commowick et al., 2006a], [Commowick et al., 2006b]

- Smooth transformation
- Robust registration
  - One parameter set for all tested acquisition protocols
- Fast computation time (10 minutes)
- Registration method able to recover large displacements
  - Ideal for articulated structures (head and neck)

[Commowick et al., 2006a]: An Efficient Locally Affine Framework for the Registration of Anatomical Structures. ISBI, 2006.

[Commowick et al., 2006b]: An Efficient Locally Affine Framework for the Smooth Registration of Anatomical Structures. Medical Image Analysis, 2006. *Submitted.* 





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# **Evaluation Methodology**

- Three evaluation methods
  - Visual inspection
  - Semi-quantitative validation
    - Visual inspection by a clinician
    - Graduation between 0 and 5
  - Quantitative validation
    - Experts manual segmentations
    - Two steps:

**DOSI** Sof

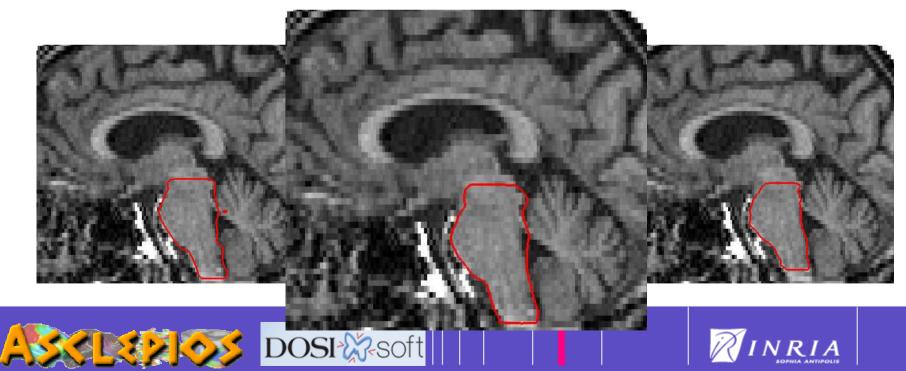
- Ground truth computation using STAPLE [Warfield et al., 2004]
- A posteriori computation of sensitivity/specificity

[Warfield et al., 2004]: Simultaneous Truth and Performance Level Estimation (STAPLE): an Algorithm for the Validation of Image Segmentation, IEEE TMI, 2004.

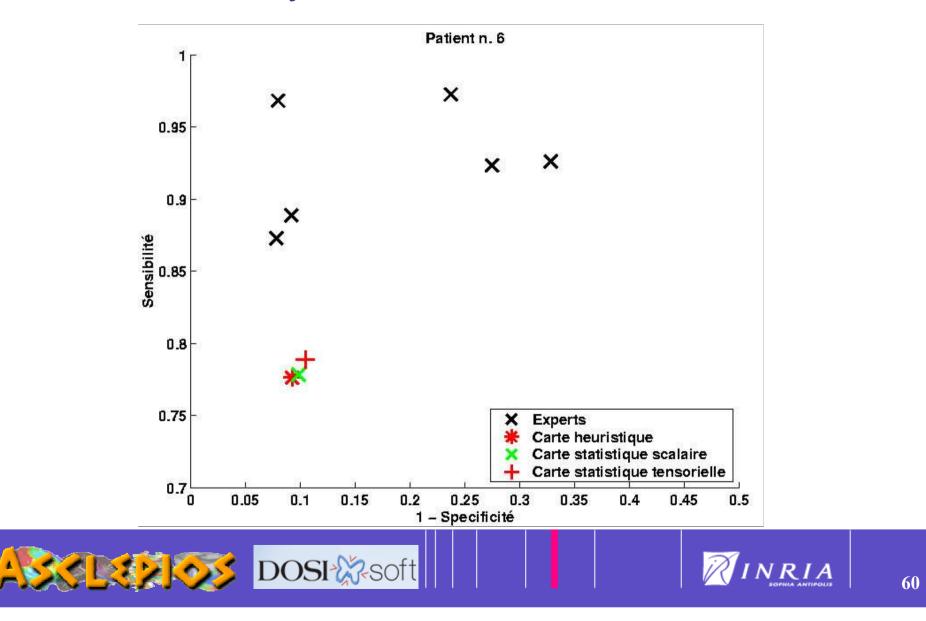


#### **Brain Evaluation**

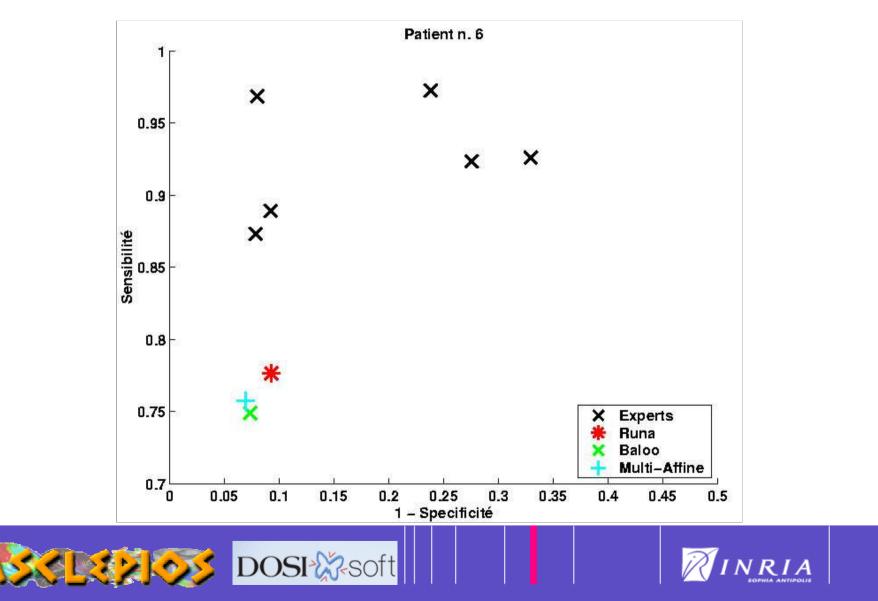
- Database of MRI from CAL Nice (Dr. P.-Y. Bondiau)
  - 2mm slice thickness
- Use of manual expert segmentations
  - Brainstem: 7 experts, 6 patients



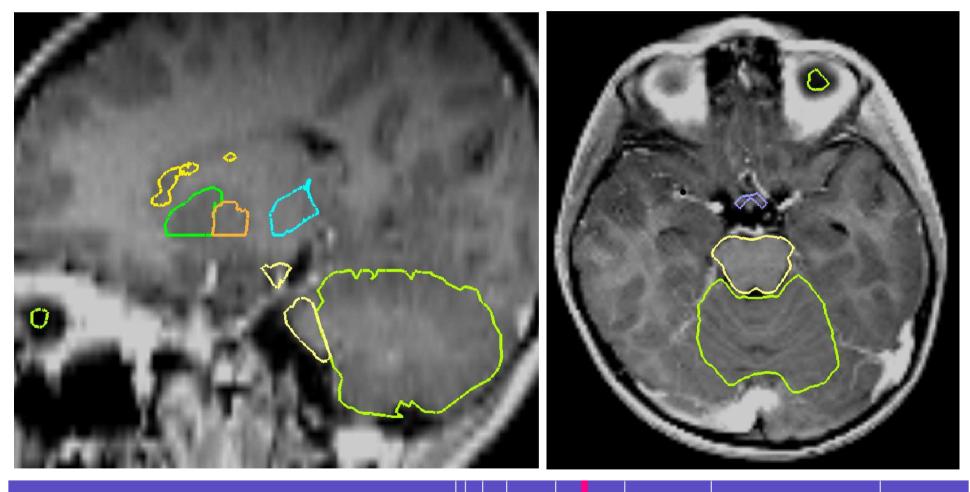
# Quantitative Evaluation (I): Introduction of Deformability Statistics



# Quantitative Evaluation (II): Runa, Baloo, LAF



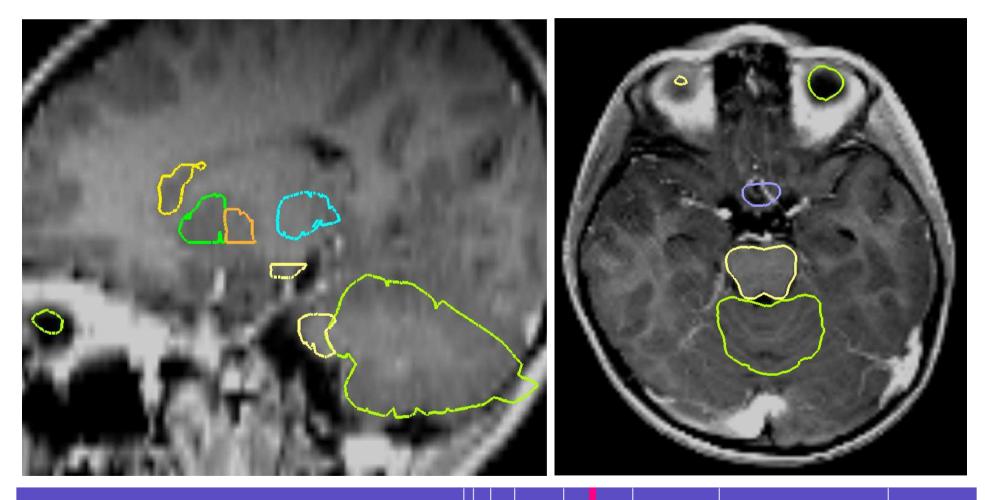
#### **Evaluation in Clinical Conditions (Runa)**







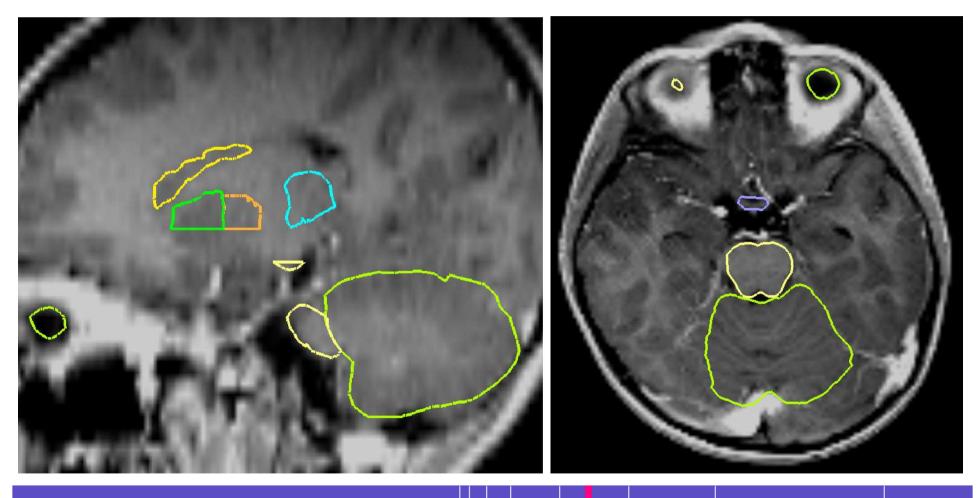
#### **Evaluation in Clinical Conditions (Baloo)**







#### **Evaluation in Clinical Conditions (LAF)**





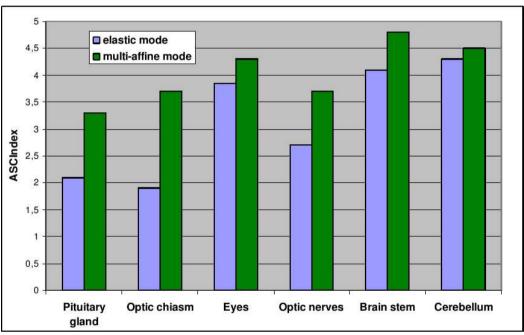


# Semi-Quantitative Evaluation in Clinical Conditions

- Evaluation in clinical conditions [Isambert et al., 2005]
  - Done at Institut Gustave Roussy

50 22 055

In the frame of MAESTRO European project



[Isambert et al., 2005]: Requirements for the use of an atlas-based automatic segmentation for delineation of Organs at Risk (OAR) in conformal radiotherapy (CRT): quality assurance (QA) and preliminary results for 22 adult patients with primary brain tumors. ESTRO, 2005.





# Road Map

- Introduction
- Incorporating Priors in Non Linear Registration
- Atlas-Based Brain Segmentation
- Head and Neck Atlas-Based Segmentation
  - Atlas Construction Method
  - Atlas Evaluation
  - Results

Conclusion and Perspectives





#### Head and Neck Atlas Construction

#### Atlas construction

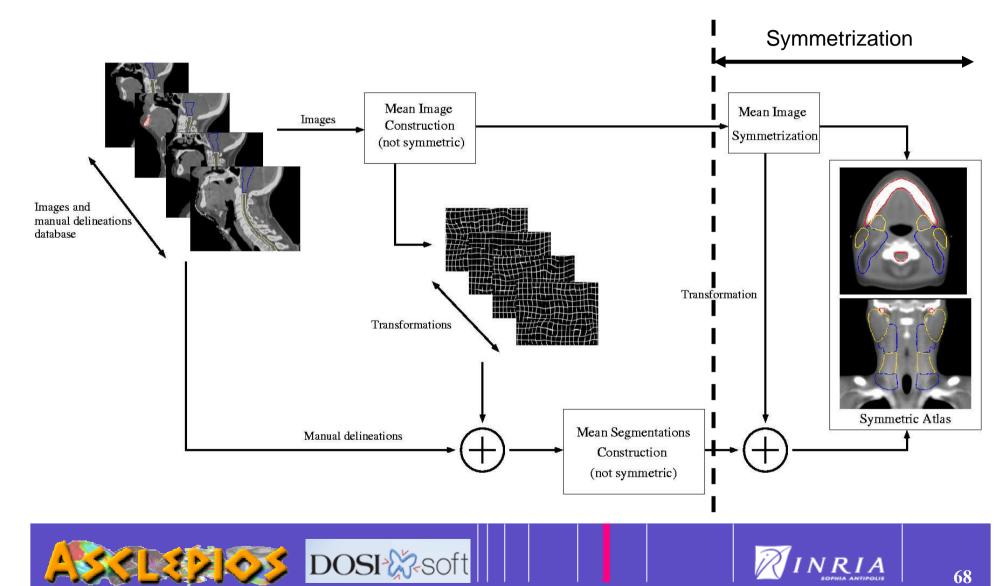
- From a dataset of delineated images
- Needs to be representative of all patients
  - Symmetric atlas construction method
- Other possible method: [Grabner et al., 2006]
- Three steps construction method
  - Mean image construction
  - Mean segmentations
  - Atlas symmetrization

[Grabner et al., 2006]: Symmetric Atlasing and Model Based Segmentation: an Application to the Hippocampus in Older Adults. MICCAI, 2006.





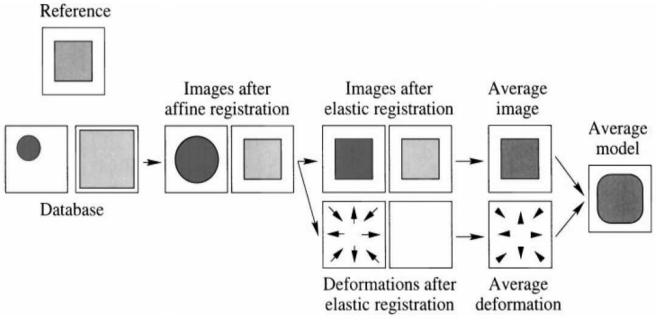
#### **Atlas Construction Method**



**68** 

# Mean Image Construction

- Unbiased atlas construction [Guimond et al., 2000]:
  - Iterate the following process



• Take the average model as new reference image

[Guimond et al., 2000]: Average Brain Models: A Convergence Study, CVIU, 2000.



#### **Mean Segmentations**

- One transformation for each patient
  - All segmentations in the mean image referential
- Mean segmentation using STAPLE [Warfield et al., 2004]:
  - Estimation of mean segmentations
  - Computation of performance parameters

- Probability maps for each class (including background)
  - A posteriori classification into structures

**DOSI** Sof

[Warfield et al., 2004]: Simultaneous Truth and Performance Level Estimation (STAPLE): an Algorithm for the Validation of Image Segmentation, IEEE TMI, 2004



## **Atlas Symmetrization**

- Method of [Prima et al., 2002]
  - Obtain transformation R bringing I on its mid-sagittal plane
  - Principle: registration between I and the mirrored image  $I \circ S$
  - *R* satisfies the relation  $I \circ R = I \circ R \circ S$
- Mean symmetric image obtained from  $\widetilde{M}$

$$\widetilde{M}_{S} = \frac{\widetilde{M} \circ R + \widetilde{M} \circ R \circ S}{2}$$

- Mean symmetric segmentations obtained in two steps
  - Symmetrization of the probability maps from STAPLE
  - A posteriori classification into structures

[Prima et al., 2002]: Computation of the Mid-Sagittal Plane in 3D Brain Images. IEEE TMI, 2002.



# Road Map

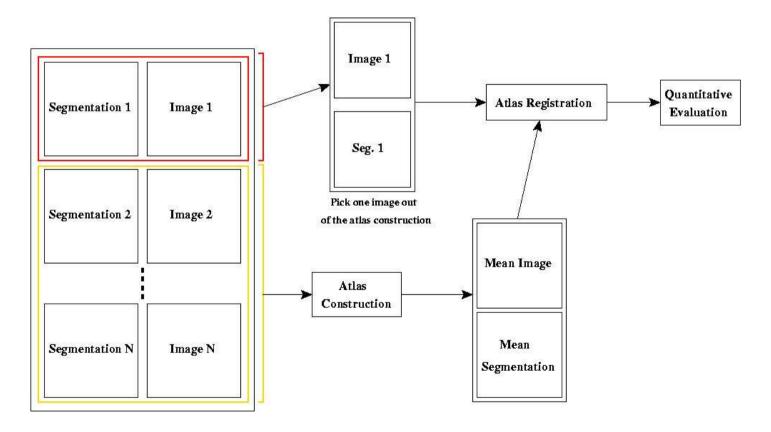
- Introduction
- Incorporating Priors in Non Linear Registration
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## **Atlas Evaluation Strategy**

• Leave-One-Out method







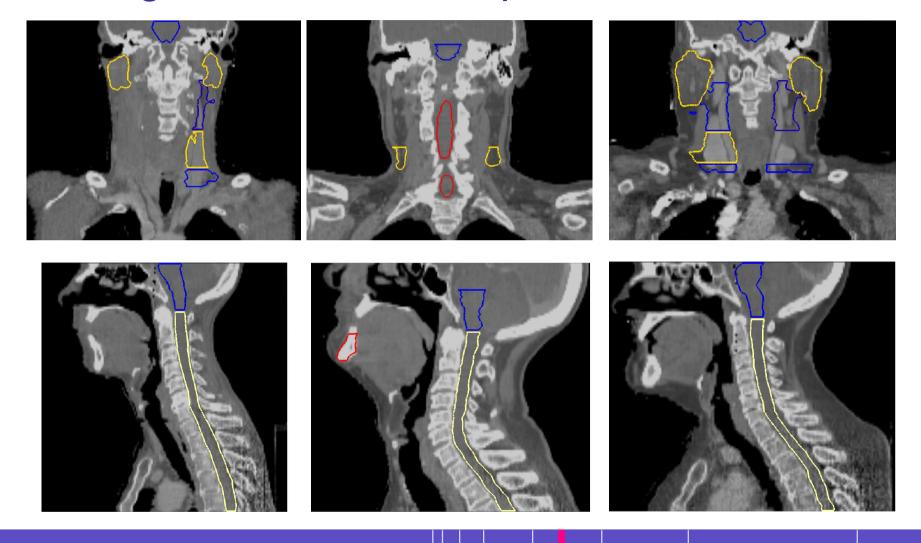
## **Evaluation protocol**

- Image database:
  - 45 patient CT-scan images (Pr. V. Grégoire, MAESTRO)
  - Different tumors shapes at different localizations
  - Small tumors not deforming the surrounding anatomy (N0 grade)
  - Various patient position and anatomy
- Three registration methods compared:
  - M<sub>1</sub>: Block-Matching based dense registration method
  - M<sub>2</sub>: Locally-affine registration method
  - M<sub>3</sub>: M<sub>2</sub> followed by M<sub>1</sub>





#### Image Database Examples







# Road Map

- Introduction
- Towards a Better Control of Registration Transformations
- Atlas-Based Brain Segmentation

#### • Head and Neck Atlas-Based Segmentation

- Atlas Construction Method
- Atlas Evaluation Strategy
- Results

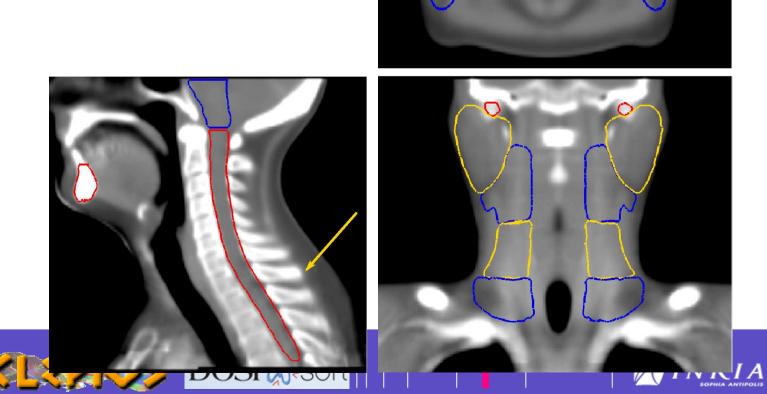
Conclusion and Perspectives





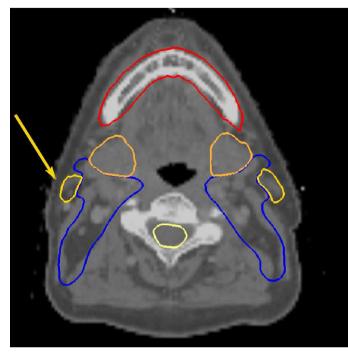


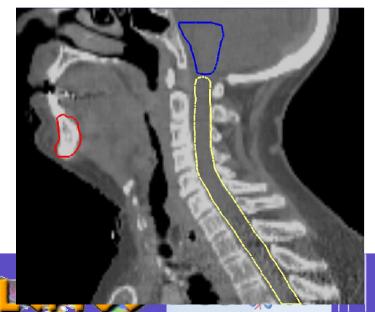
#### $M_3 N M t_A H = 0$

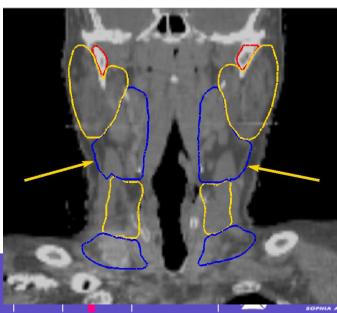


### **Qualitative Results**

#### MgaAtlas Segmentation



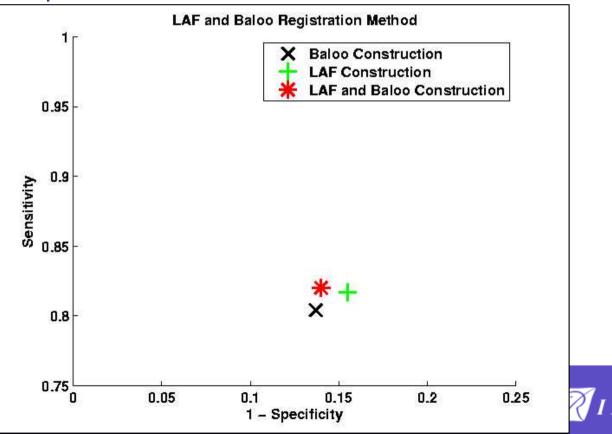




Α

### **Quantitative Atlas Evaluation**

- Use of Leave-One-Out method:
  - Mean over 12 patients completely delineated (13 structures)
- M<sub>3</sub> Atlas performs better for atlas construction





## Conclusion

- Symmetric atlas construction method
  - From existing techniques
- Atlas Evaluation method [Commowick et al., 2006c]
  - Registration method to build the atlas
  - Registration method to register the atlas
- Application to Head and Neck
  - Hierarchical registration (M<sub>3</sub>): well adapted in this context
  - Promising results
  - Many perspectives on atlas construction

[Commowick et al., 2006c]: Evaluation of Atlas Construction Strategies in the Context of Radiotherapy Planning. SA2PM Workshop, held in conjunction with MICCAI. 2006.





## Road Map

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## Contributions

- Registration
  - Introduction of deformability statistics in registration
  - Dense registration with outlier rejection
  - Locally affine framework
    - Good results without changing parameters
- Head and neck atlas
  - Atlas construction method from a dataset of CT images
  - Evaluation via leave one out method
- Other contributions (not presented here)
  - Taking pathology into account in registration process
  - Ad-Hoc method for optic nerves segmentation

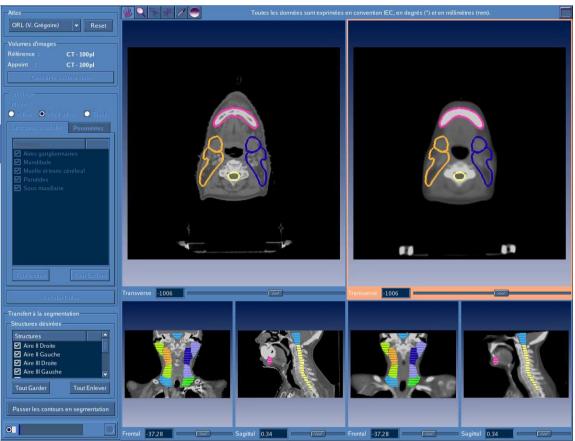




## **Software Integration**

- Integration in DOSIsoft radiotherapy planning system
  - Atlas-based segmentation module
  - Both brain and head and neck atlases
- Validation in clinical conditions at IGR
  - MAESTRO European project

ASSESSION DOSI & soft





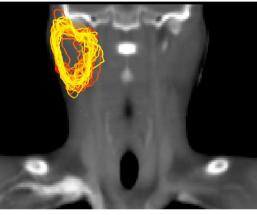
## **Discussion on Head and Neck Atlas**

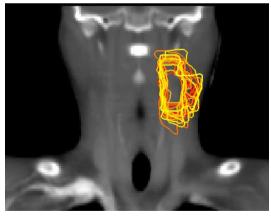
- Problem: Over-segmentation of the lymph nodes areas
- First reason: inside the atlas
  - Contours dispersion
    - Large inter-patient variation
  - STAPLE for generating mean segmentations
    - Influence of the background class
- Possible solutions

DOSI & sof

- Cluster dataset in several groups
- Use of new methods [Warfield et al., 2006]
  - No background class

[Warfield et al., 2006]: Validation of Image Segmentation by Estimating Rater Bias and Variance. MICCAI 2006.







## **Discussion on Head and Neck Atlas**

- Second reason: when registering the atlas
  - Large atlas/patient differences
    - Corpulence
    - Neck flexion

➔ Results in local discrepancies

- Possible solutions
  - Build several atlases from one database
    - Clustering of the dataset
  - Choose the closest image among the dataset images
    - Definition of distance





### Perspectives

- Registration methods
  - Computation of statistics of deformability
    - Several registration methods to build unbiased statistics
  - Locally affine framework
    - Refining local affine regions
- Study of robustness of registration methods
  - With respect to registration parameters
  - Other type of validation
- Measure of quality of registration
  - Based only on images
  - Is a region well registered or not ?



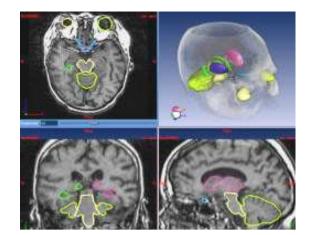


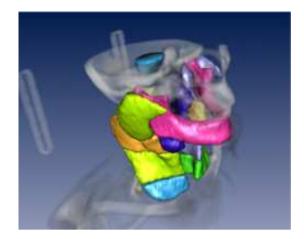
#### Perspectives

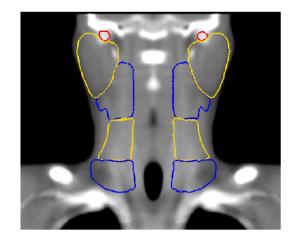
- Further validation
  - on more structures and more patients
  - Other quantitative measures
  - Fully quantitative validation in clinical conditions
- Taking into account pathology
  - Model the deformation caused by the tumor

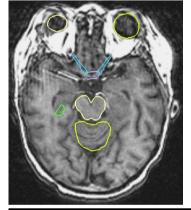












Questions

