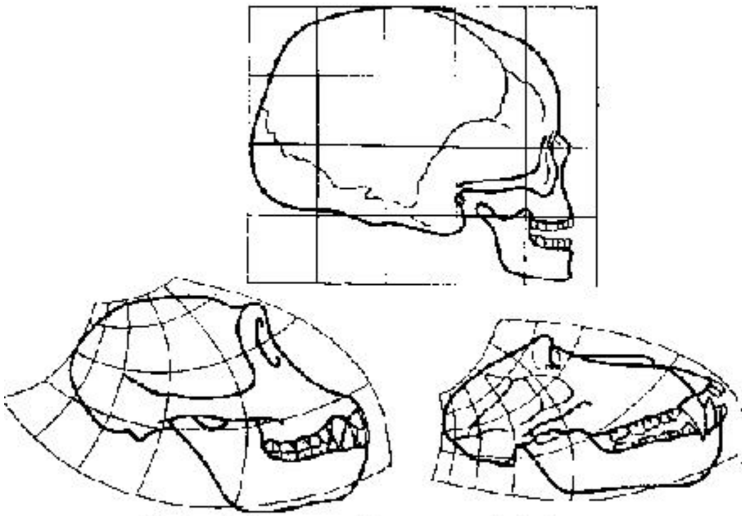
*Xavier Pennec*
*&*
*Marco Lorenzi*

*Asclepios team, INRIA Sophia-Antipolis – Mediterranée, France*

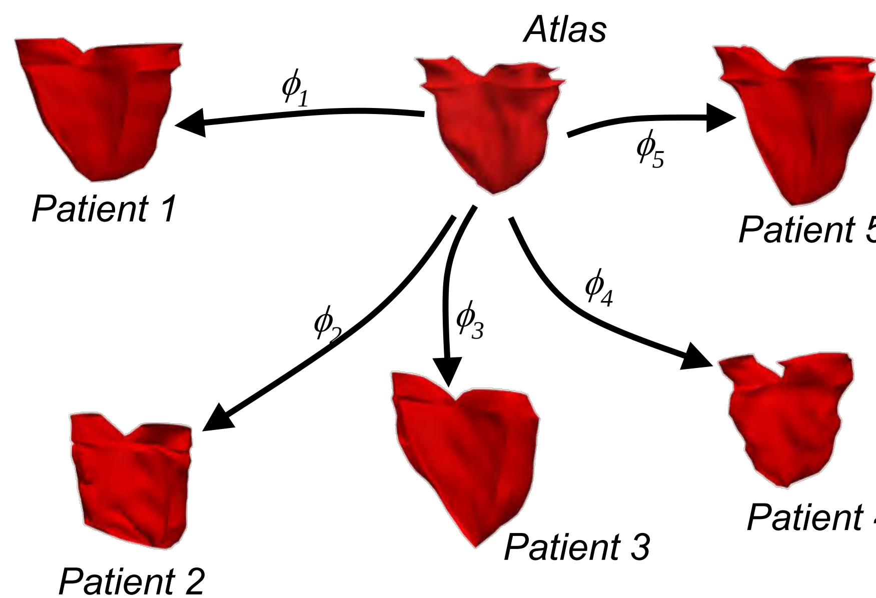
# The SVF framework for longitudinal statistics on deformations

STIA – MICCAI at MIT, Sep. 2014

# Morphometry through Deformations



Skulls of a human, a chimpanzee and a baboon and transformations between them




**Measure of deformation [D'Arcy Thompson 1917, Grenander & Miller]**

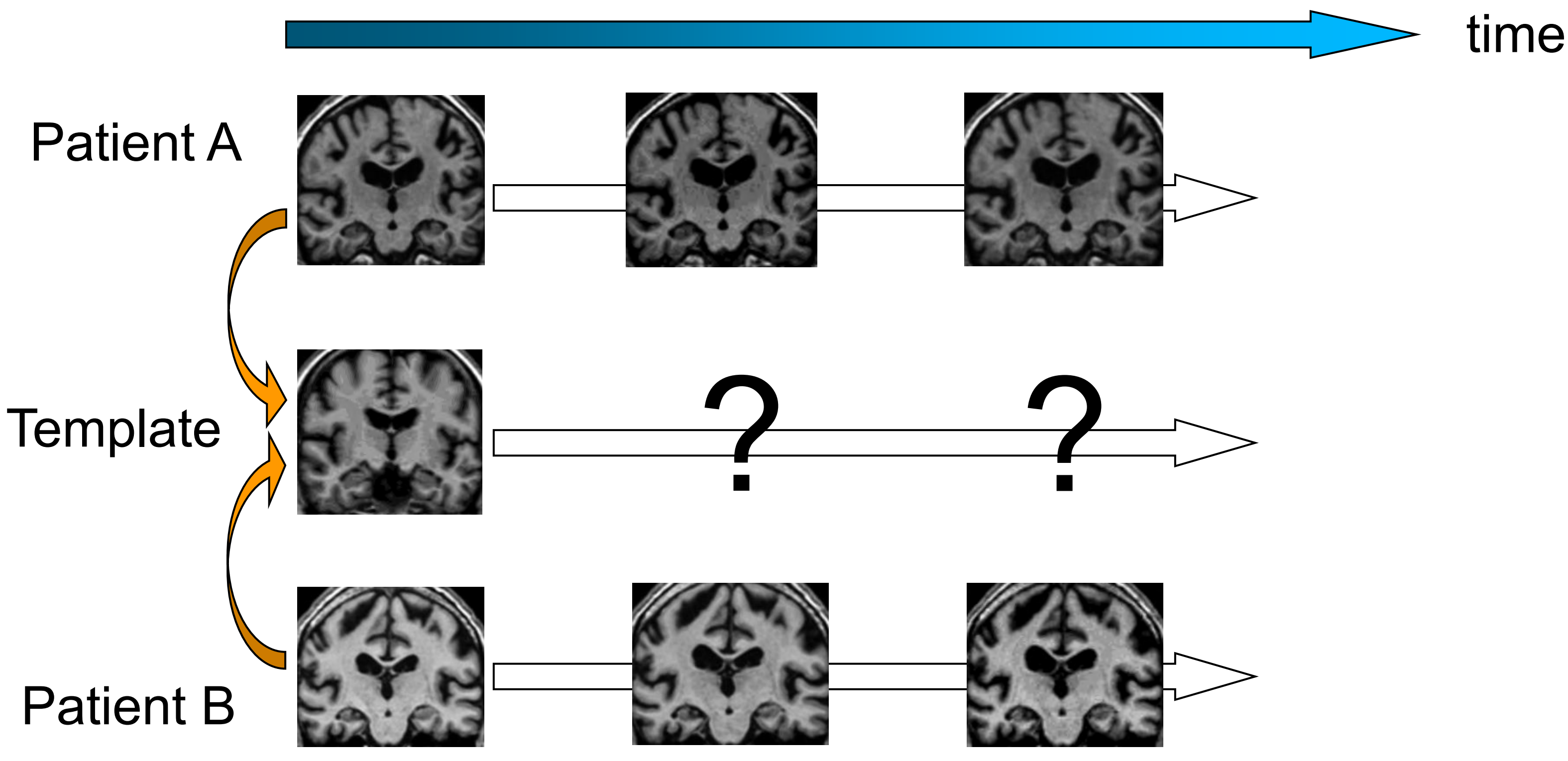
- Observation = "random" deformation of a reference template
- Reference template = Mean (atlas)
- Shape variability encoded by the deformations

**Statistics on groups of transformations (Lie groups, diffeomorphism)?**

**Consistency with group operations (non commutative)?**

# *Longitudinal deformation analysis*

## Dynamic obervations




**How to transport longitudinal deformation across subjects?**

**What are the convenient mathematical settings?**

# Outline

**Foundations of statistics on manifolds**

- The Riemannian framework
- Lie groups as affine connection spaces
- The SVF framework for diffeomorphisms

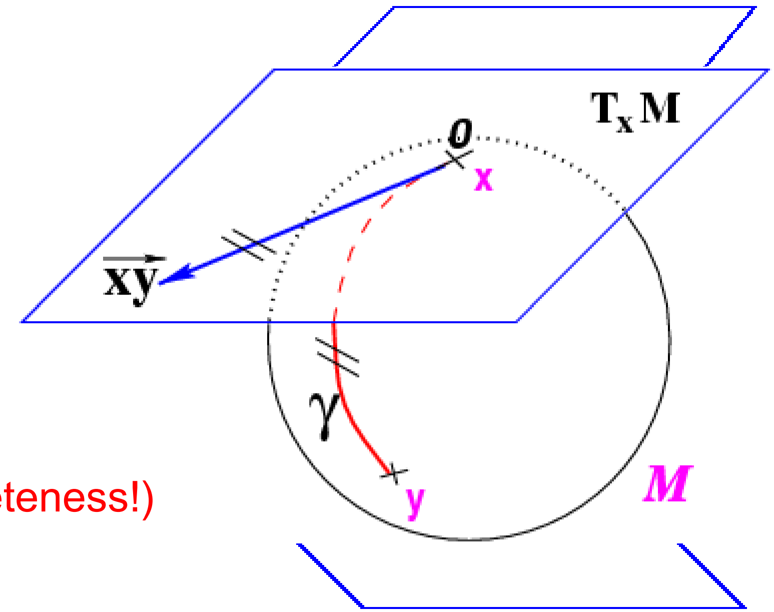
**Longitudinal analysis of deformations with SFVs**

- Parallel transport of deformations germs
- Longitudinal modeling of brain atrophy in AD
- Morphological analysis with Helmoltz decomposition

# *Bases of Algorithms in Riemannian Manifolds*

## Riemannian metric :

- Dot product on tangent space
- Speed, length of a curve
- Geodesics are length minimizing curves
- Riemannian Distance




## Exponential map (Normal coord. syst.) :

- Geodesic shooting: $Exp_x(v) = \gamma_{(x,v)}(1)$
- Log: find vector to shoot right (geodesic completeness!)

## Unfolding ($Log_x$), folding ($Exp_x$)

- Vector -> Bipoint (no more equivalent class)

| Operator | Euclidean space | Riemannian manifold |
|---|---|---|
| Subtraction | $\overrightarrow{xy} = y - x$ | $\overrightarrow{xy} = Log_x(y)$ |
| Addition | $y = x + \overrightarrow{xy}$ | $y = Exp_x(\overrightarrow{xy})$ |
| Distance | $\text{dist}(x,y) = \lVert y - x \rVert$ | $\text{dist}(x,y) = \lVert \overrightarrow{xy} \rVert_x$ |
| Gradient descent | $x_{t+\varepsilon} = x_t - \varepsilon \nabla C(x_t)$ | $x_{t+\varepsilon} = Exp_{x_t}(-\varepsilon \nabla C(x_t))$ |

# Statistical tools: Moments

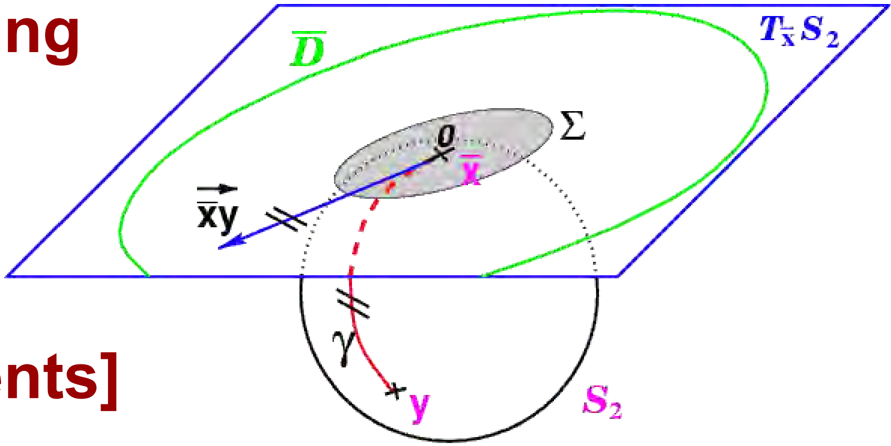
## Frechet / Karcher mean minimize the variance

$$\mathrm{E}[\mathbf{x}] = \underset{y \in \mathcal{M}}{\operatorname{argmin}} \left( \mathrm{E}\left[\operatorname{dist}(y, \mathbf{x})^2\right] \right) \quad \Rightarrow \quad \mathrm{E}\left[\overrightarrow{\bar{\mathrm{x}}\mathbf{x}}\right] = \int_{\mathcal{M}} \overrightarrow{\bar{\mathrm{x}}\mathbf{x}} . p_{\mathbf{x}}(z) . d\mathcal{M}(z) = 0 \quad [P(C) = 0]$$

**Existence and uniqueness : Karcher / Kendall / Le / Afsari**

## Gauss-Newton Geodesic marching

$$\bar{\mathrm{x}}_{t+1} = \exp_{\bar{\mathrm{x}}_t}(v) \quad \text{with} \quad v = \mathrm{E}\left[\overrightarrow{\mathrm{y}\mathbf{x}}\right]$$




## Covariance (PCA) [higher moments]

$$\Sigma_{\mathbf{xx}} = \mathrm{E}\left[\left(\overrightarrow{\bar{\mathrm{x}}\mathbf{x}}\right)\left(\overrightarrow{\bar{\mathrm{x}}\mathbf{x}}\right)^{\mathrm{T}}\right] = \int_{\mathcal{M}} \left(\overrightarrow{\bar{\mathrm{x}}z}\right)\left(\overrightarrow{\bar{\mathrm{x}}z}\right)^{\mathrm{T}} . p_{\mathbf{x}}(z) . d\mathcal{M}(z)$$

[Oller & Corcuera 95, Battacharya & Patrangenaru 2002, Pennec, JMIV06, NSIP'99 ]

# *Limits of the Riemannian Framework*

## Lie group: Smooth manifold with group structure

- Composition g o h and inversion $g^{-1}$ are smooth
- Left and Right translation $L_g(f) = g \circ f$   $R_g(f) = f \circ g$
- Natural Riemannian metric choices
  - Chose a metric at Id: $<x,y>_{Id}$
  - Propagate at each point g using left (or right) translation
    $<x,y>_g = < DL_{g^{(-1)}} .x , DL_{g^{(-1)}} .y >_{Id}$

## No bi-invariant metric in general

- **Incompatibility of the Fréchet mean with the group structure**
  - Left of right metric: different Fréchet means
  - The inverse of the mean is not the mean of the inverse
- Examples with simple 2D rigid transformations

- **Can we design a mean compatible with the group operations?**
- **Is there a more convenient structure for statistics on Lie groups?**

# Outline

**Foundations of statistics on manifolds**

- The Riemannian framework
- Lie groups as affine connection spaces
- The SVF framework for diffeomorphisms

**Longitudinal analysis of deformations with SFVs**

- Parallel transport of deformations germs
- Longitudinal modeling of brain atrophy in AD
- Morphological analysis with Helmoltz decomposition

# Basics of Lie groups

**Flow of a left invariant vector field $\tilde{X} = DL.x$ starting from e**

- $\gamma_x(t)$ exists for all time
- One parameter subgroup: $\gamma_x(s+t) = \gamma_x(s).\,\gamma_x(t)$

**Lie group exponential**

- Definition: $x \in \mathfrak{g} \rightarrow Exp(x) = \gamma_x(1) \epsilon\, G$
- Local chart (not true in general for inf. dim)
- Baker-Campbell Hausdorff (BCH) formula

$$BCH(x,y) = Log\big(Exp(x).Exp(y)\big) = x + y + \frac{1}{2}[x,y] + \ \ldots$$

**3 curves at each point parameterized by the same tangent vector**

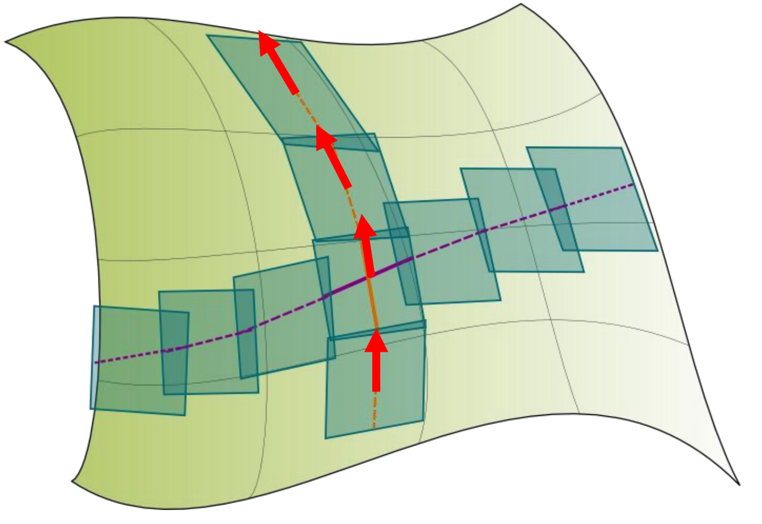
- Left / Right-invariant geodesics, one-parameter subgroups

**Question: Can one-parameter subgroups be geodesics?**

# *Affine connection spaces*

## Affine Connection (infinitesimal parallel transport)

- Acceleration = derivative of the tangent vector along a curve
- Projection of a tangent space on a neighboring tangent space



Adapted from Lê Nguyên Hoang, science4all.org

## Geodesics = straight lines

- Null acceleration: $\nabla_{\dot{\gamma}} \dot{\gamma} = 0$
- 2nd order differential equation: Normal coordinate system
- Local exp and log maps

# *Cartan-Schouten Connection on Lie Groups*

## A unique connection

- Symmetric (no torsion) and bi-invariant
- For which geodesics through Id are one-parameter subgroups (group exponential)
  - Matrices : M(t) = A.exp(t.V)
  - Diffeos : **translations of Stationary Velocity Fields (SVFs)**

## Levi-Civita connection of a bi-invariant metric (if it exists)

- Continues to exists in the absence of such a metric (e.g. for rigid or affine transformations)

## Two flat connections (left and right)

- **Absolute parallelism**: no curvature but torsion (Cartan / Einstein)

# Statistics on an affine connection space

## ~~Fréchet mean~~: exponential barycenters

- $\sum_i Log_x(y_i) = 0$ [Emery, Mokobodzki 91, Corcuera, Kendall 99]
- Existence & **local uniqueness** if local convexity [Arnaudon & Li, 2005]

## For Cartan-Schouten connections [Pennec & Arsigny, 2012]

- Locus of points *x* such that $\sum Log(x^{-1}.y_i) = 0$
- Algorithm: fixed point iteration (**local convergence**)

$$x_{t+1} = x_t \circ Exp\left(\frac{1}{n}\sum Log(x_t^{-1}.y_i)\right)$$

- **Mean stable by left / right composition and inversion**
  - If $m$ is a mean of $\{g_i\}$ and $h$ is any group element, then $h \circ m$ is a mean of $\{h \circ g_i\}$ , $m \circ h$ is a mean of the points $\{g_i \circ h\}$ and $m^{(-1)}$ is a mean of $\left\{g_i^{(-1)}\right\}$

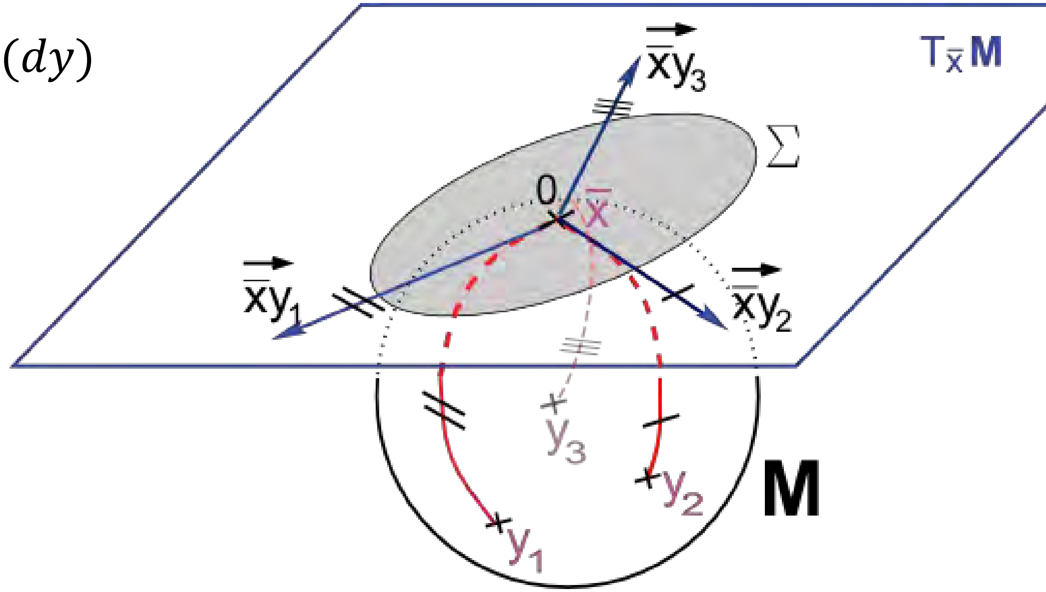
# Generalization of the Statistical Framework

## Covariance matrix & higher order moments

- Defined as tensors in tangent space

$$\Sigma = \int Log_x(y) \otimes Log_x(y)\, \mu(dy)$$

- Matrix expression changes according to the basis




## Other statistical tools

- Mahalanobis distance well defined and bi-invariant
- ~~Tangent Principal Component Analysis (t-PCA)~~
- Principal Geodesic Analysis (PGA), provided a data likelihood
- Independent Component Analysis (ICA)

# Outline

**Foundations of statistics on manifolds**

- The Riemannian framework
- Lie groups as affine connection spaces
- The SVF framework for diffeomorphisms

**Longitudinal analysis of deformations with SFVs**

- Parallel transport of deformations germs
- Longitudinal modeling of brain atrophy in AD
- Morphological analysis with Helmoltz decomposition

# Riemannian Metrics on diffeomorphisms

## Space of deformations

- Transformation y=$\phi$(x)
- Curves in transformation spaces: $\phi$(x,t)
- Tangent vector = speed vector field $v_t(x) = \frac{d\phi(x,t)}{dt}$

## Right invariant metric

$$\|v_t\|_{\phi_t} = \|v_t \circ \phi_t^{-1}\|_{Id}$$

- Lagrangian formalism
- Sobolev Norm $H_k$ or $H_\infty$ (RKHS) in LDDMM → diffeomorphisms
  [Miller, Trouve, Younes, Holm, Dupuis, Beg… 1998 – 2009]
- Geometric Mechanics [Arnold, Smale, Souriau, Marsden, Ratiu, Holmes, Michor…]

## Geodesics determined by optimization of a time-varying vector field

- Distance $d^2(\phi_0, \phi_1) = \arg\min_{v_t}\left(\int_0^1 \|v_t\|_{\phi_t}^2 dt\right)$
- Geodesics characterized by initial velocity / momentum
- Optimization by shooting/adjoint or path-straightening methods

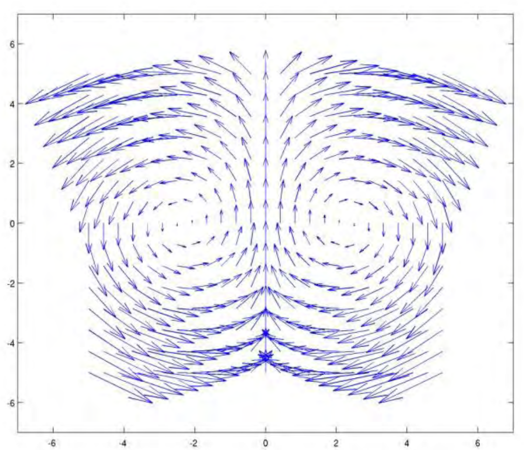
# The SVF framework for Diffeomorphisms

**Framework of [Arsigny et al., MICCAI 06]**

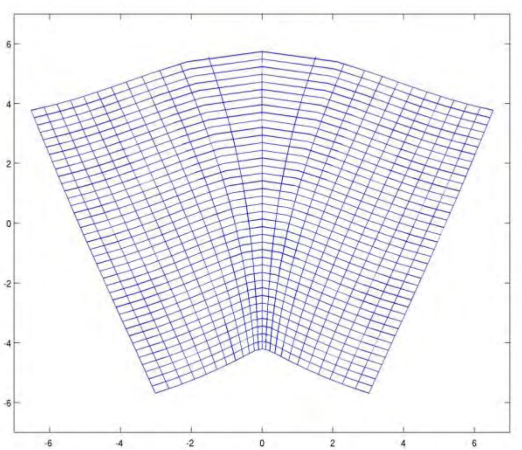
- Use one-parameter subgroups

**Exponential of a smooth vector field is a diffeomorphism**

- $\boldsymbol{u}$ is a smooth **stationary velocity field**
- Exponential: solution at time 1 of ODE $\partial x(t) / \partial t = \boldsymbol{u}( x(t) )$



Stationary velocity field



Diffeomorphism

# The SVF framework for Diffeomorphisms

## Efficient numerical methods

- Take advantage of algebraic properties of exp and log.
  - exp(t.V) is a one-parameter subgroup.

⟶ Direct generalization of numerical matrix algorithms.

## Efficient parametric diffeomorphisms

- Computing the deformation: Scaling and squaring
  recursive use of exp($\boldsymbol{v}$)=exp($\boldsymbol{v}$/2) o exp($\boldsymbol{v}$/2)
  **[Arsigny MICCAI 2006]**

- Updating the deformation parameters:
  BCH formula **[Bossa MICCAI 2007]**

  $$\exp(\boldsymbol{v}) \circ \exp(\varepsilon \boldsymbol{u}) = \exp( \boldsymbol{v} + \varepsilon \boldsymbol{u} + [\boldsymbol{v},\varepsilon \boldsymbol{u}]/2 + [\boldsymbol{v},[\boldsymbol{v},\varepsilon \boldsymbol{u}]]/12 + \dots )$$

  - Lie bracket $[\boldsymbol{v},\boldsymbol{u}](p) = \mathrm{Jac}(\boldsymbol{v})(p).\boldsymbol{u}(p) - \mathrm{Jac}(\boldsymbol{u})(p).\boldsymbol{v}(p)$

# *Symmetric log-demons [Vercauteren MICCAI 08]*

## Idea: [Arsigny MICCAI 2006, Bossa MICCAI 2007, Ashburner Neuroimage 2007]

- Parameterize the deformation by SVFs
- Time varying (LDDMM) replaced by stationary vector fields
- Efficient scaling and squaring methods to integrate autonomous ODEs

## Log-demons with SVFs

$$\mathcal{E}(\mathbf{v}, \mathbf{v}_c) = \underbrace{\frac{1}{\sigma_i^2} \|F - M \circ \exp(\mathbf{v}_c)\|_{L_2}^2}_{\text{Similarity}} + \underbrace{\frac{1}{\sigma_x^2} \|\log(\exp(-\mathbf{v}) \circ \exp(\mathbf{v}_c))\|_{L_2}^2}_{\text{Coupling}} + \underbrace{\mathcal{R}(\mathbf{v})}_{\text{Regularisation}}$$

**Similarity**: *Measures how much the two images differ*

**Coupling**: *Couples the correspondences with the smooth deformation*

**Regularisation**: *Ensures deformation smoothness*

- Efficient optimization with BCH formula
- Inverse consistent with symmetric forces
- Open-source ITK implementation
  - Very fast
  - http://hdl.handle.net/10380/3060

**[ T Vercauteren, et al.. *Symmetric Log-Domain Diffeomorphic Registration: A Demons-based Approach,* MICCAI 2008 ]**

# Cartan Connections vs Riemannian

## What is similar

- Standard differentiable geometric structure [curved space without torsion]
- Normal coordinate system with $\text{Exp}_x$ et $\text{Log}_x$ [finite dimension]

## Limitations of the affine framework

- No metric (but no choice of metric to justify)
- The exponential does always not cover the full group
  - Pathological examples close to identity in finite dimension
  - In practice, similar limitations for the discrete Riemannian framework

## What we gain

- A globally invariant structure invariant by composition & inversion
- Simple geodesics, efficient computations (stationarity, group exponential)
- The simplest linearization of transformations for statistics?

# *Outline*

**Foundations of statistics on manifolds**

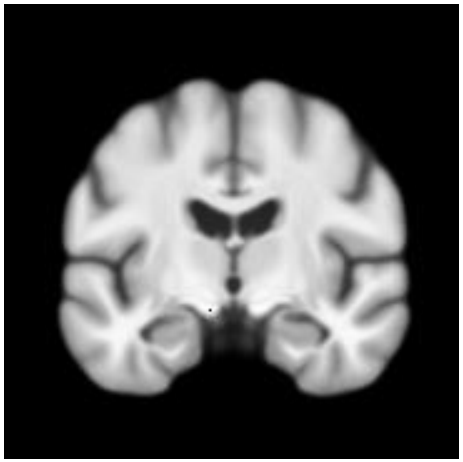
- The Riemannian framework
- Lie groups as affine connection spaces
- The SVF framework for diffeomorphisms

**Longitudinal analysis of deformations with SFVs**

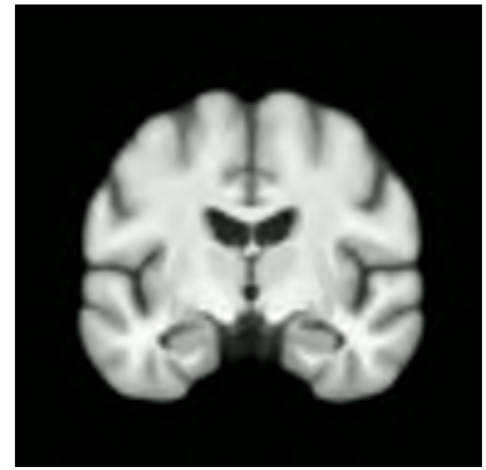
- Parallel transport of deformations germs
- Longitudinal modeling of brain atrophy in AD
- Morphological analysis with Helmoltz decomposition

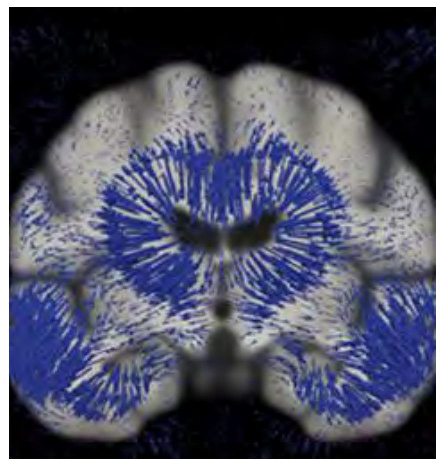
# *Measuring Temporal Evolution with deformations*

## Fast registration with deformation parameterized by SVF



$$\varphi_t(x) = exp(t.v(x))$$



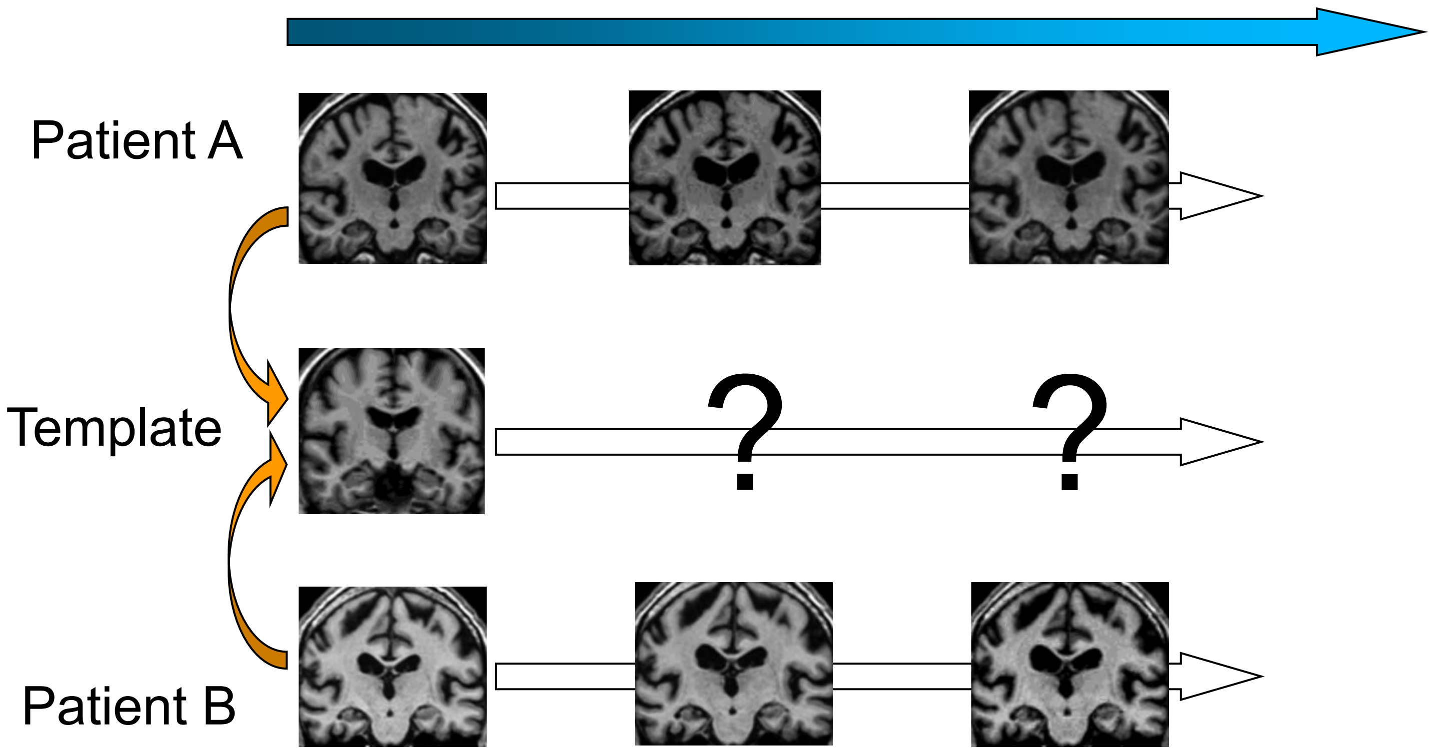


https://team.inria.fr/asclepios/software/lcclogdemons/

[ Lorenzi, Ayache, Frisoni, Pennec, Neuroimage 81, 1 (2013) 470-483 ]

# *Longitudinal deformation analysis in AD*

- From patient specific evolution to population trend (parallel transport of deformation trajectories)
- Inter-subject and longitudinal deformations are of different nature and might require different deformation spaces/metrics




**PhD Marco Lorenzi - Collaboration With G. Frisoni (IRCCS FateBenefratelli, Brescia)**

# Parallel transport of deformations

**Encode longitudinal deformation by its initial tangent (co-) vector**

- Momentum (LDDMM) / SVF

**Parallel transport**

- (small) longitudinal deformation vector
- along the large inter-subject normalization deformation

**Existing methods**

- Vector reorientation with Jacobian of inter-subject deformation
- Conjugate action on deformations (Rao et al. 2006)
- Resampling of scalar maps (Bossa et al, 2010)
- LDDMM setting: parallel transport along geodesics via Jacobi fields [Younes et al. 2008]

**Intra and inter-subject deformations/metrics are of different nature**

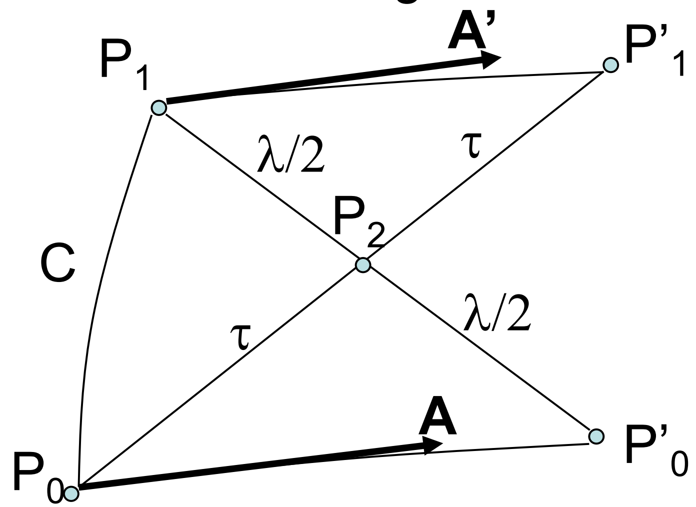
# *Parallel transport along arbitrary curves*

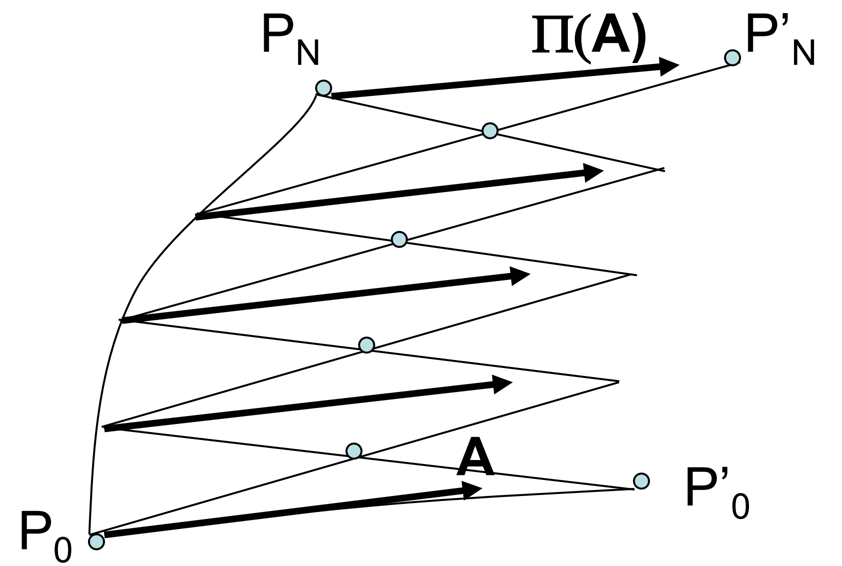
**Infinitesimal parallel transport = connection**

$\nabla_{\gamma'}(X) : TM \rightarrow TM$

**A numerical scheme to integrate for symmetric connections: Schild's Ladder [Elhers et al, 1972]**

- Build geodesic parallelogrammoid
- Iterate along the curve

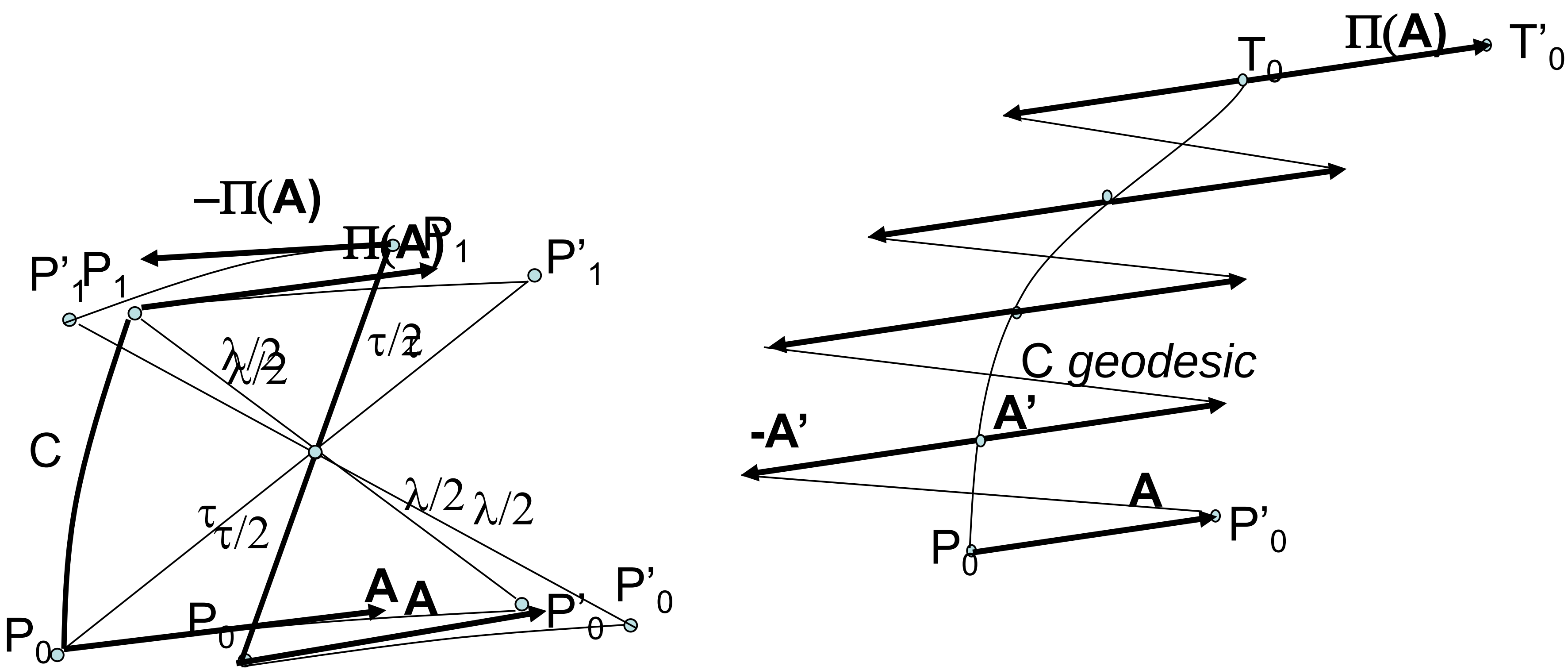



**[Lorenzi, Ayache, Pennec: Schild's Ladder for the parallel transport of deformations in time series of images, IPMI 2011 ]**

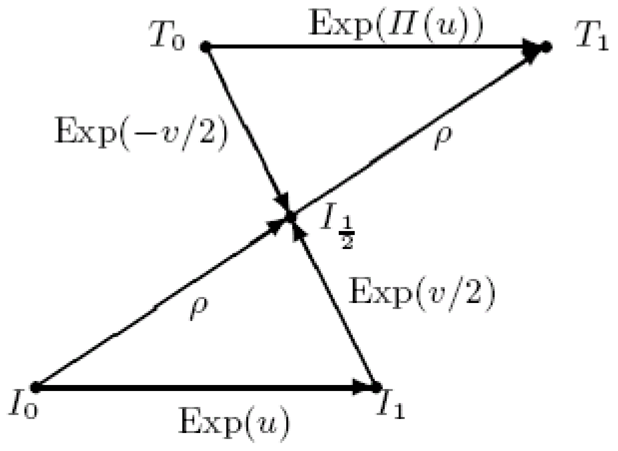
# *Parallel transport along geodesics*

**Along geodesics: Pole Ladder [Lorenzi et al, JMIV 2013]**




**[ Lorenzi, Pennec: Efficient Parallel Transport of Deformations in Time Series of Images: from Schild's to pole Ladder, JMIV 2014 ]**

# Efficient Pole and Schild's Ladder with SVFs



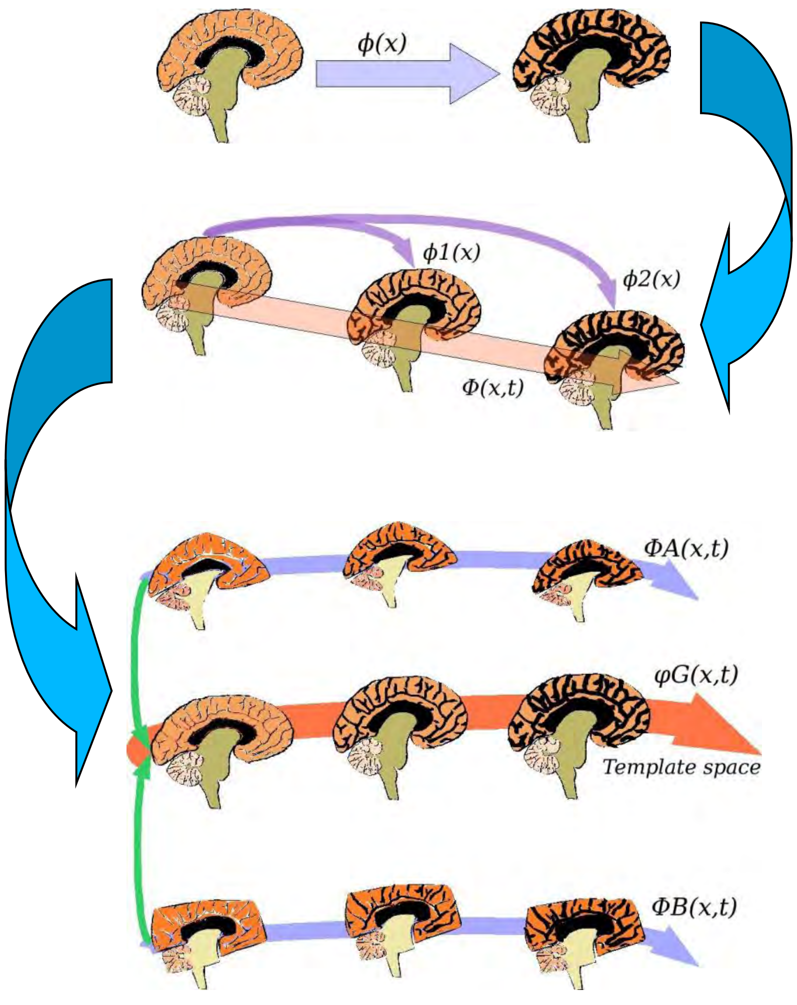

$$\mathrm{Exp}(\Pi(u)) = \mathrm{Exp}(v/2) \circ \mathrm{Exp}(u) \circ \mathrm{Exp}(-v/2)$$

## Numerical scheme

- Direct computation $\Pi_{conj}(u) = \mathrm{D}\left(\mathrm{Exp}(v)\right)|_{\mathrm{Exp}(-v)} \cdot u \circ \mathrm{Exp}(-v)$
- Using the BCH: $\Pi_{BCH}(u) = u + [v, u] + \frac{1}{2}[v[v, u]]$

**[Lorenzi, Ayache, Pennec: Schild's Ladder for the parallel transport of deformations in time series of images, IPMI 2011 ]**
**Runner-up for the IPMI Erbsmann 2011 prize**

# Analysis of longitudinal datasets
# Multilevel framework




**Single-subject, two time points**

*Log-Demons (LCC criteria)*

**Single-subject, multiple time points**

*4D registration of time series within the Log-Demons registration.*

**Multiple subjects, multiple time points**

*Pole or Schild's Ladder*

**[Lorenzi et al, in Proc. of MICCAI 2011]**

# *Outline*

**Foundations of statistics on manifolds**

- The Riemannian framework
- Lie groups as affine connection spaces
- The SVF framework for diffeomorphisms

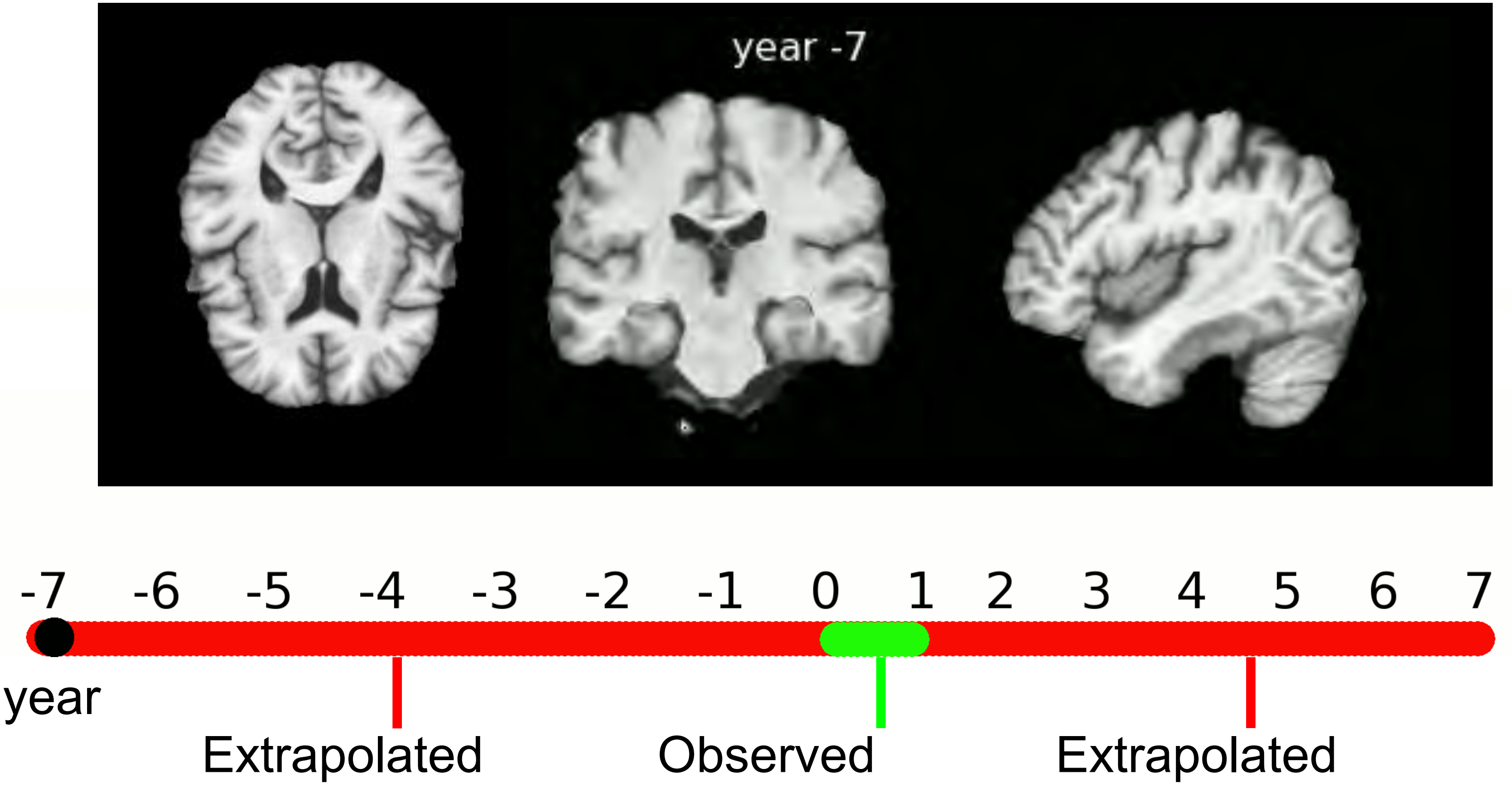
**Longitudinal analysis of deformations with SFVs**

- Parallel transport of deformations germs
- Longitudinal modeling of brain atrophy in AD
- Morphological analysis with Helmoltz decomposition

# Mean Longitudinal Model for AD

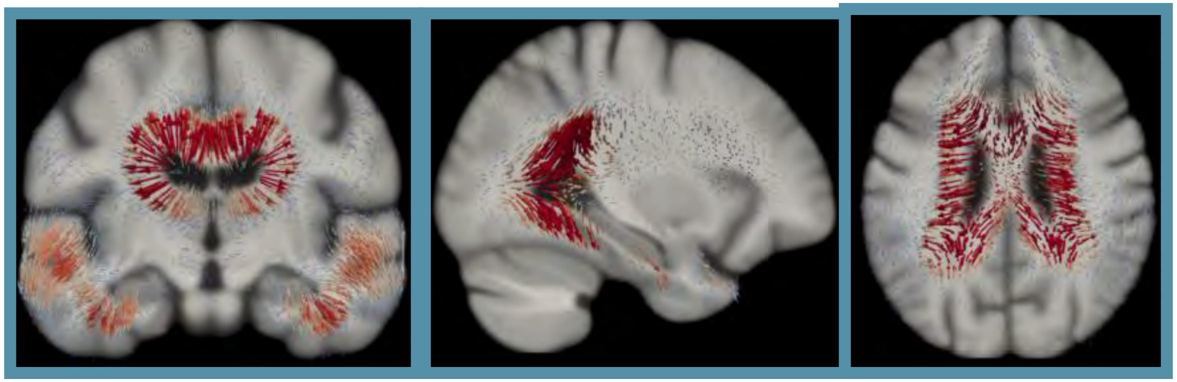
**Estimated from 1 year changes – Extrapolation to 15 years**

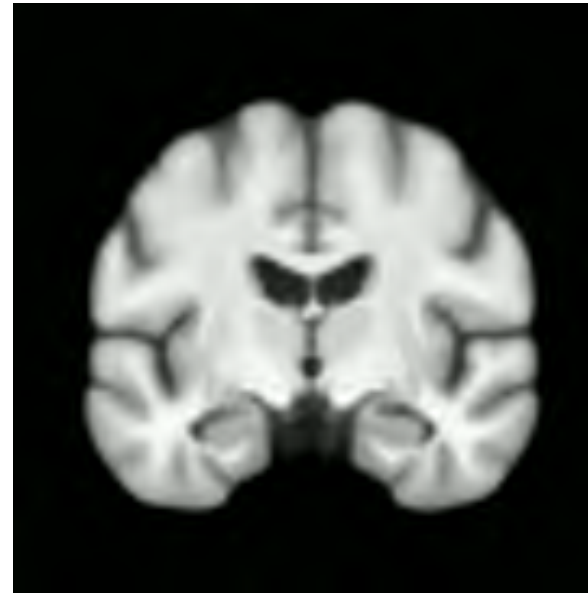
**70 AD subjects (ADNI data)**



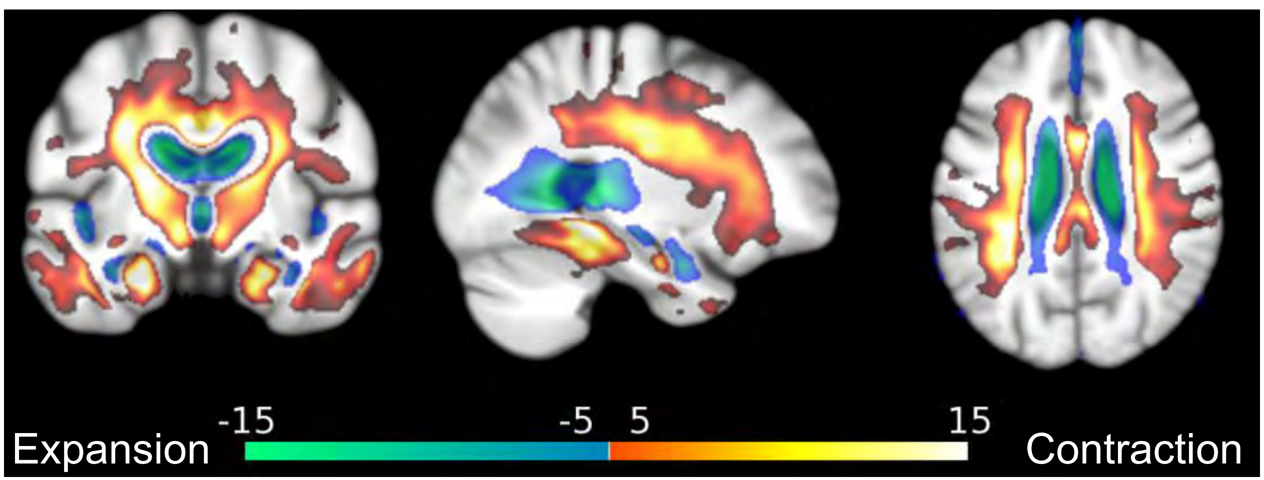
# Longitudinal changes in Alzheimer's disease

**(141 subjects – ADNI data)**

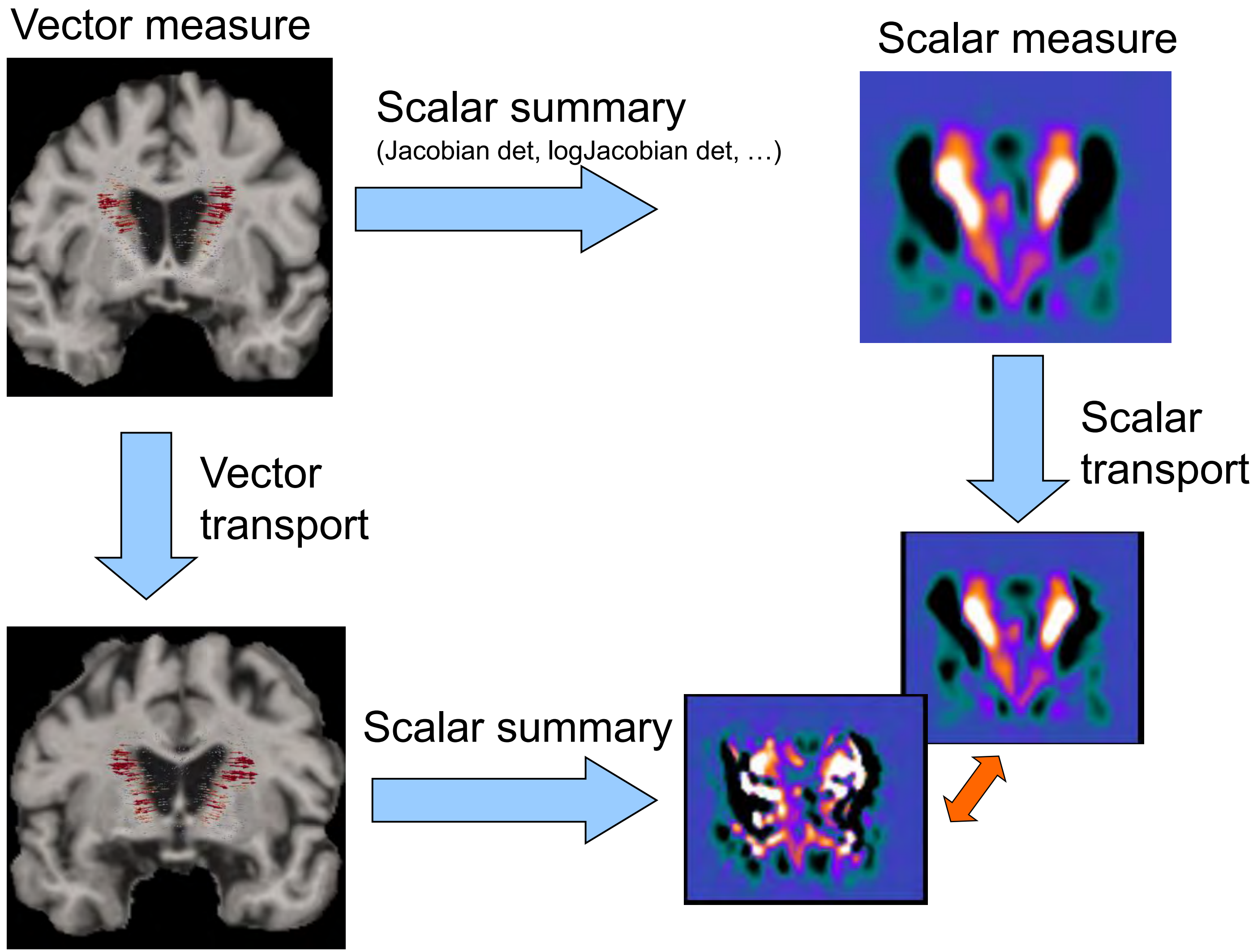




Student's
t statistic



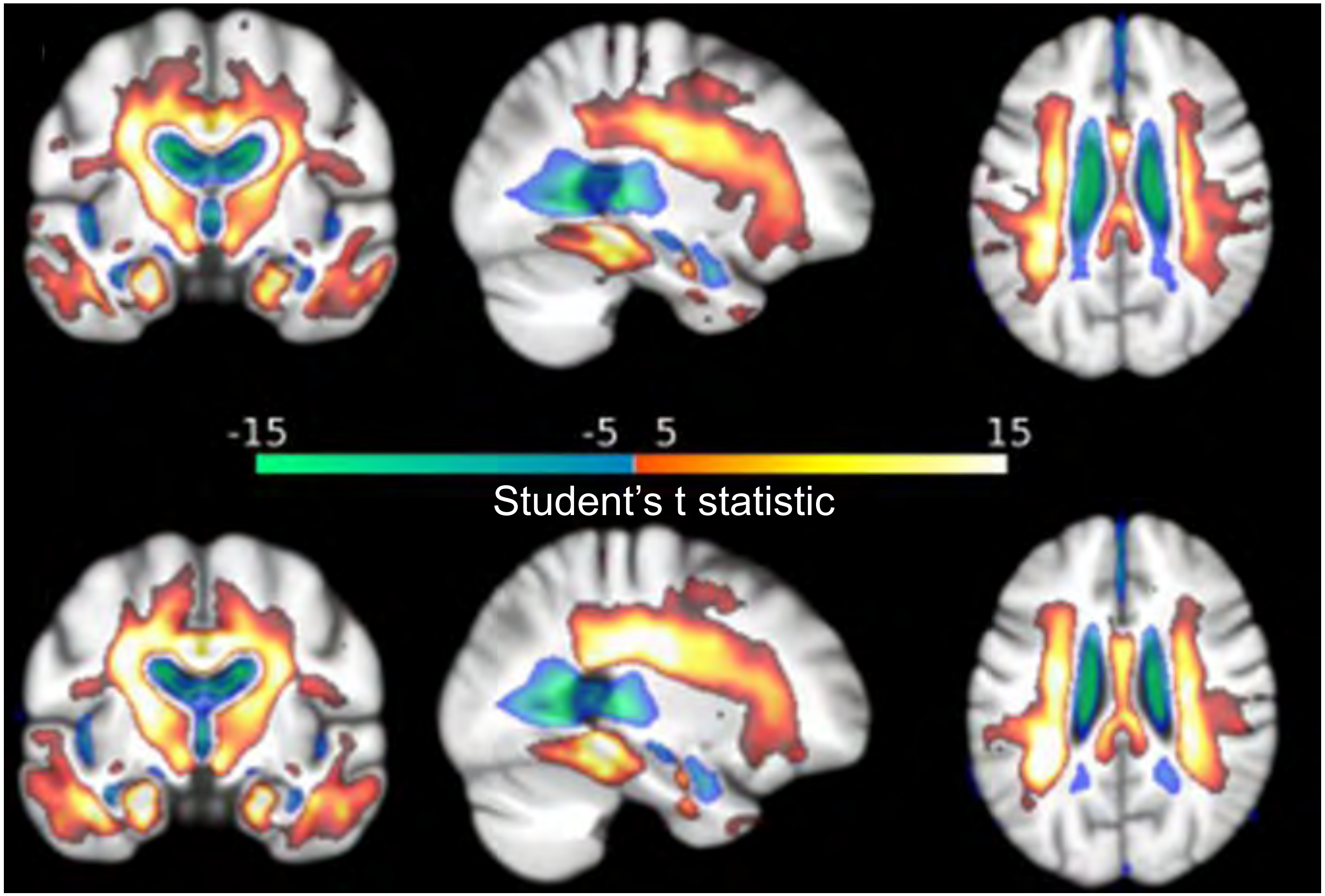
# Consistency and numerical stability



# Longitudinal changes in Alzheimer's disease

**(141 subjects – ADNI data)**

## Comparison with standard TBM




Pole ladder

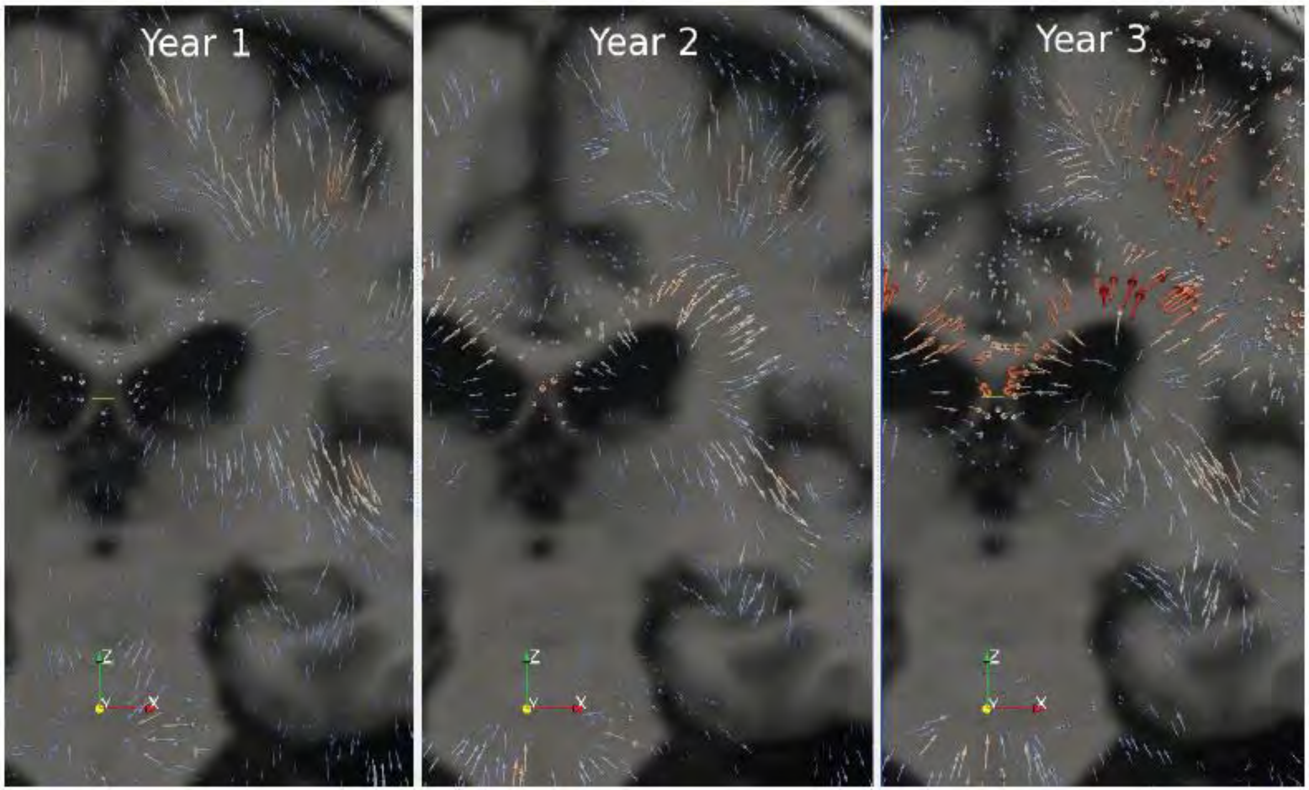
Scalar transport

Consistent results

Equivalent statistical power

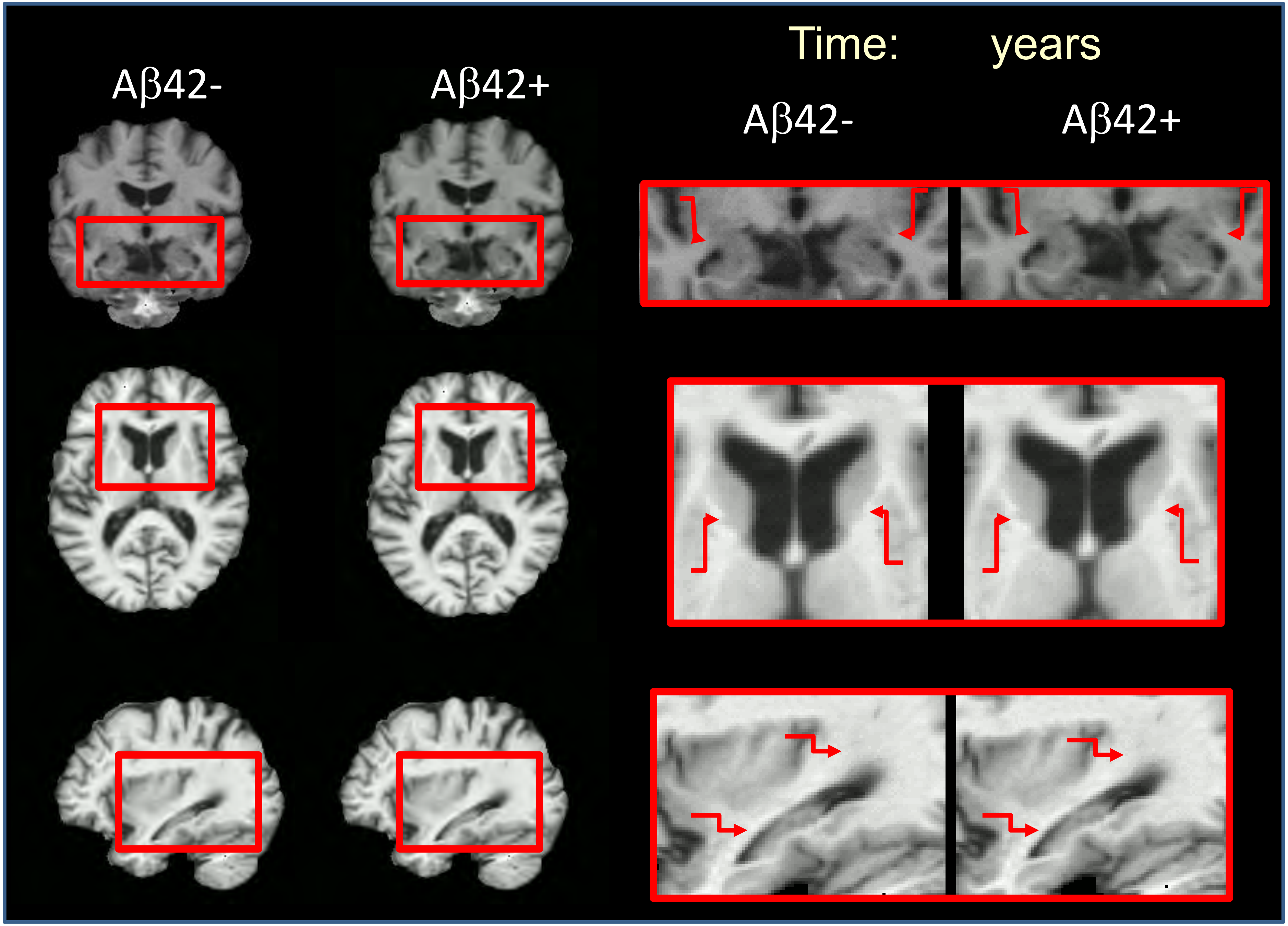
# Study of prodromal Alzheimer's disease

- 98 **healthy subjects**, 5 time points (0 to 36 months).
- 41 subjects Aβ42 positive ("at risk" for Alzheimer's)
- **Q: Different morphological evolution for Aβ+ vs Aβ-?**




Average SVF for normal evolution (Aβ-)

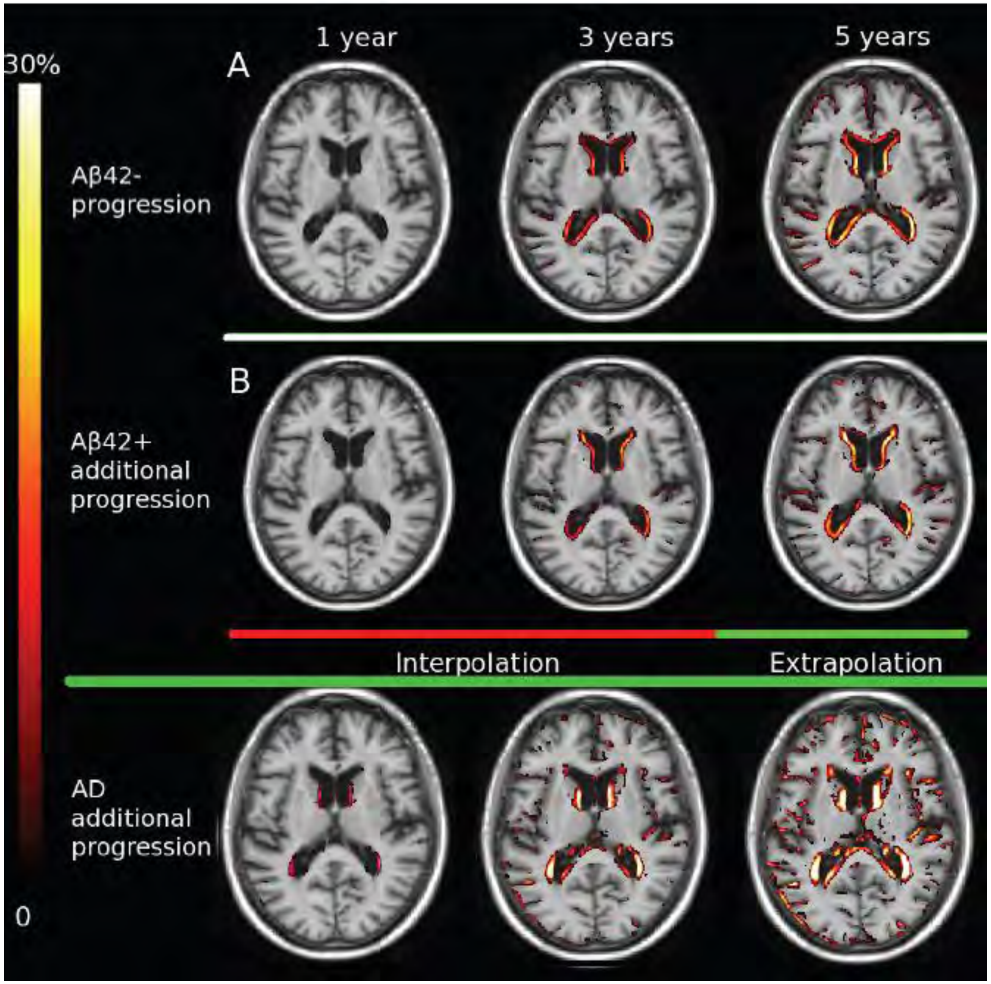
**[Lorenzi, Ayache, Frisoni, Pennec, in Proc. of MICCAI 2011]**



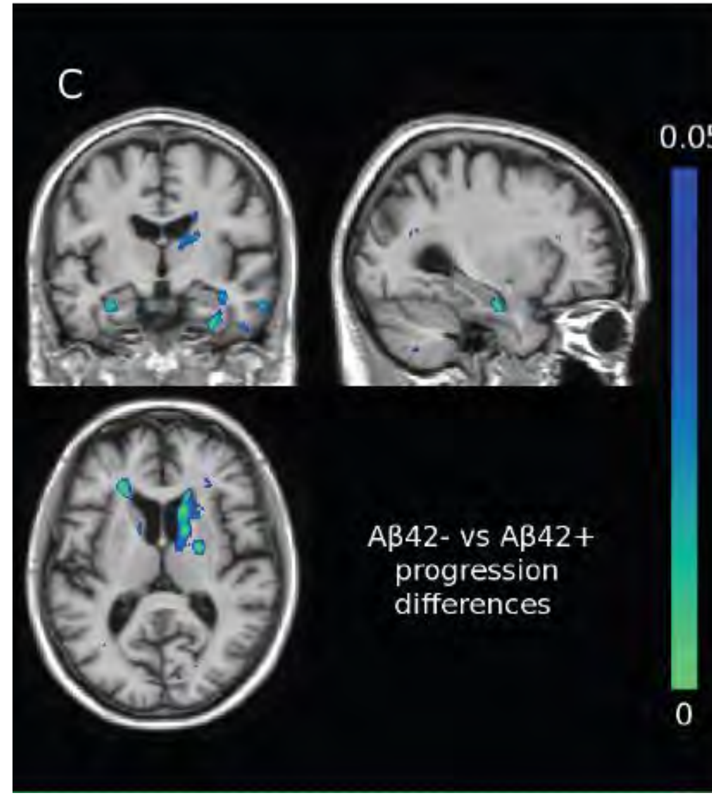
Time: years
Aβ42-
Aβ42+
Aβ42-
Aβ42+

# Study of prodromal Alzheimer's disease

Linear regression of the SVF over time: interpolation + prediction




$$T(t) = Exp(\tilde{v}(t)) * T_0$$




*Multivariate group-wise comparison of the transported SVFs shows statistically significant differences (nothing significant on log(det) )*

**[Lorenzi, Ayache, Frisoni, Pennec, in Proc. of MICCAI 2011]**

# Outline

**Foundations of statistics on manifolds**

- The Riemannian framework
- Lie groups as affine connection spaces
- The SVF framework for diffeomorphisms

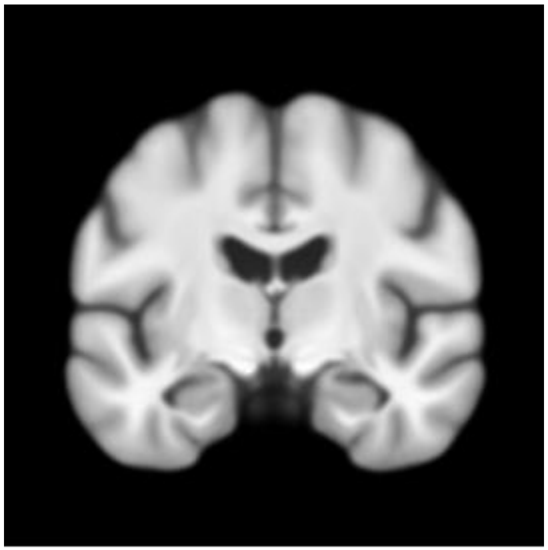
**Longitudinal analysis of deformations with SFVs**

- Parallel transport of deformations germs
- Longitudinal modeling of brain atrophy in AD
- Morphological analysis with Helmoltz decomposition

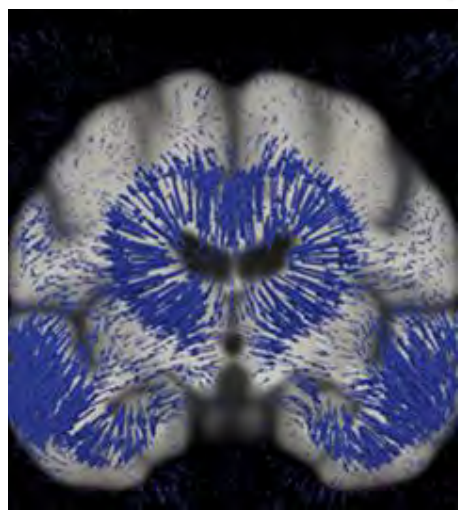
# Non-rigid registration for longitudinal analysis

Alzheimer's atrophy trajectory

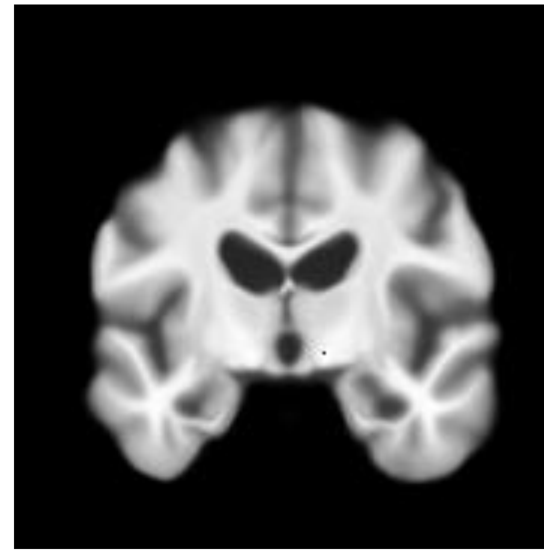
Baseline MRI



$\varphi = \exp(v)$

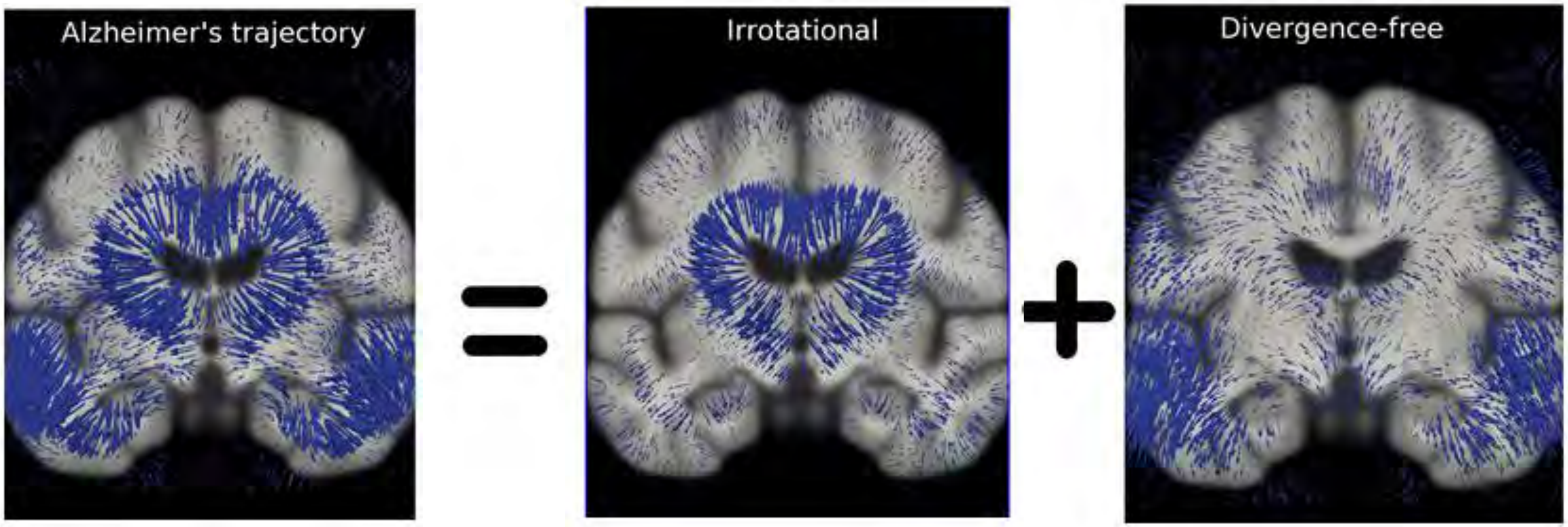


Follow-up MRI



**Atrophy flow encoded by the dense stationary velocity field**

# Morphological analysis of SVF




$v =$ Volur $\nabla p$ anges $+ \nabla \times A$

Helmholtz decomposition

Atrophy!!

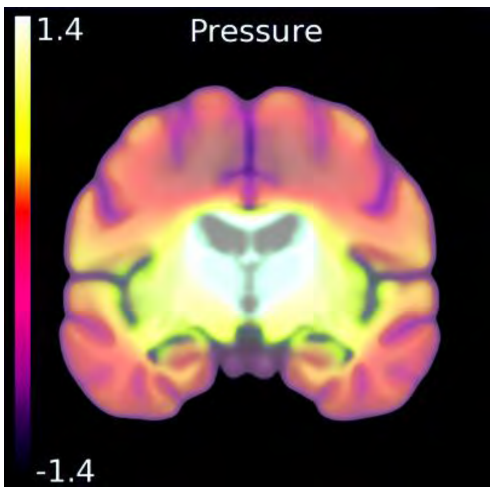
Structural readjustments

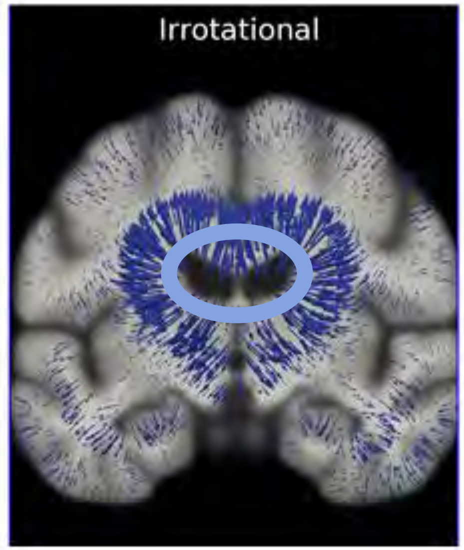
# Morphological analysis of SVF

***Discovery***

**Pressure** $p$

Defines **sources and sinks** of the atrophy process



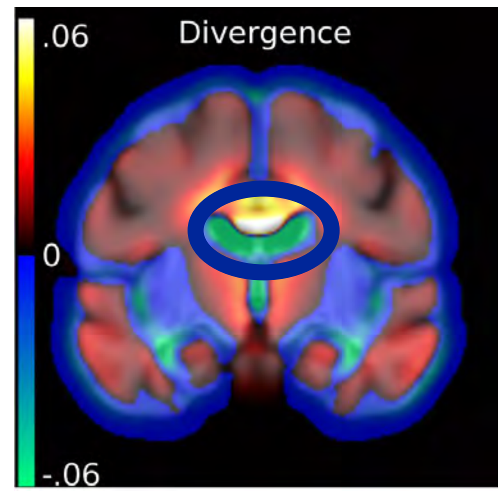




$$\nabla p$$

***Quantification***

**Divergence** $\nabla \cdot \nabla p$

Defines **flux** across expanding/contracting regions



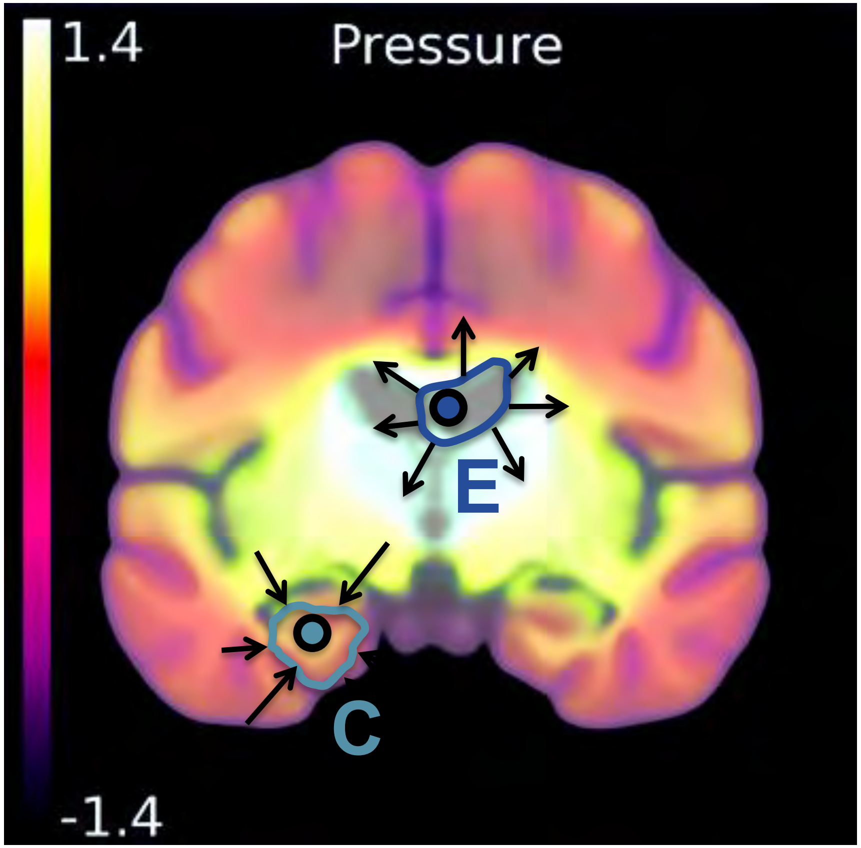

**Divergence Theorem**

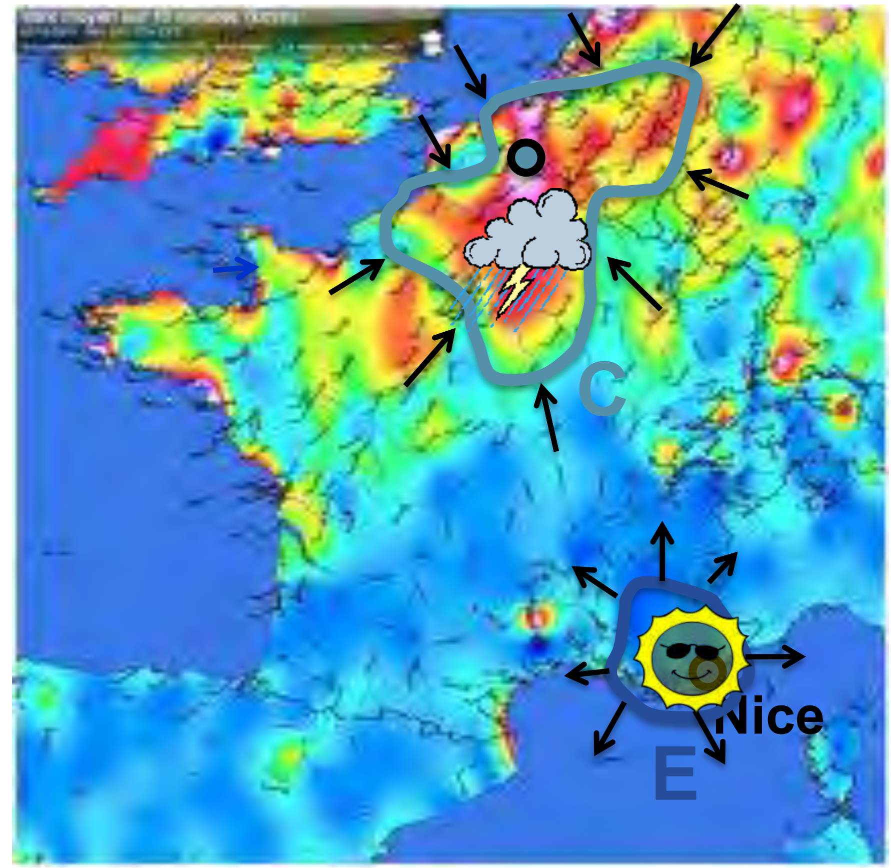
$$\oint_{\partial V} v \cdot \boldsymbol{n} \, dS = \int_V \nabla \cdot v \, dV$$



[Lorenzi et al, MICCAI 2012]

# Probabilistic definition of the atrophy topography




$$P(\text{Critical area}) \approx \text{Proximity to critical point} + \text{Surrounding flux}$$

Step1. Finding local maxima and minima for the pressure field (sources,sinks)

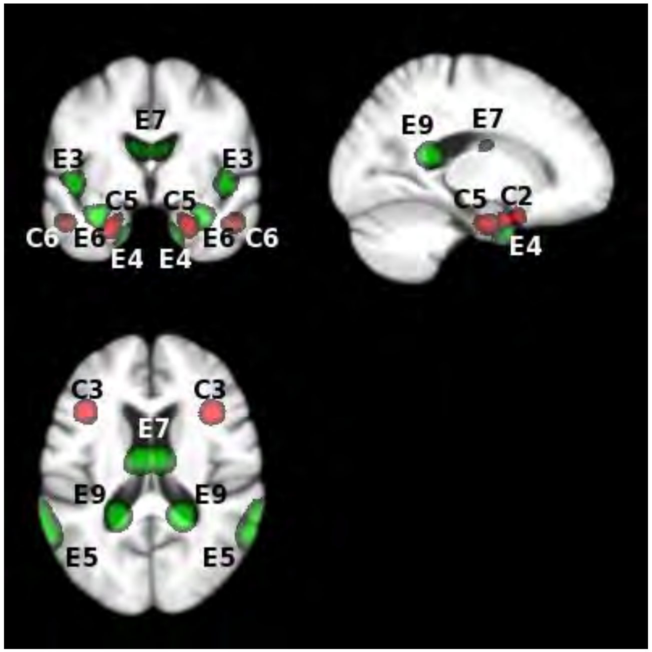
Step2. Finding surrounding areas of maximal outwards/inwards flux (Expansion and Contraction)

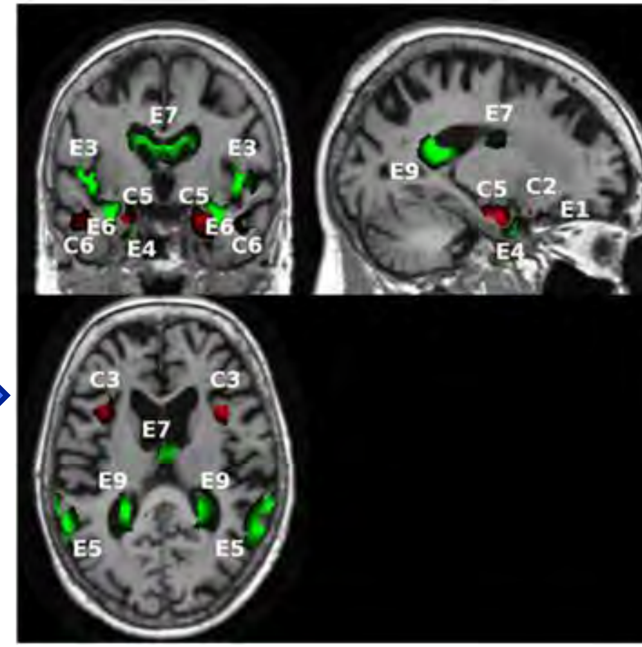


[Lorenzi et al, MICCAI 2012]

# *Group-wise flux analysis in Alzheimer's disease: Quantification*

From group-wise… …to subject specific




**sample size ∝ sd/(mean$_1$-mean$_2$)**

| | Regional flux (all regions) | Hippocampal atrophy [Leung 2010] *(Different ADNI subset)* |
|---|---|---|
| AD vs controls | 164 [106,209] | 121 [77, 206] |
| MCI vs controls | 277 [166,555] | 545 [296, 1331] |

**Effect size on left hippocampus**

| Group | six months | one year | two years |
|---|---|---|---|
| INRIA - Regional Flux | 1.02 | 1.33 | 1.47 |

**NIBAD'12 Challenge:**
**Top-ranked on Hippocampal atrophy measures**

# Conclusion

## Cartan connections: a nice setting for transformation groups

- A connection defines geodesics but no length along them
- Cartan connection: one-parameters subgroups are bi-invariant geodesics
- ~~Fréchet / Karcher means~~ → exponential barycenter = bi-invariant mean
  - Fine existence [Pennec & Arsigny 2012] (Uniqueness?)

## Algorithms for SVFs

- Log-demons: Open-source ITK implementation **http://hdl.handle.net/10380/3060**
- Tensor (DTI) Log-demons: **https://gforge.inria.fr/projects/ttk**
- LCC time-consistent log-demons for AD available soon
- ITK class for SVF diffeos currently under development

## Schilds Ladder for parallel transport

- Effective instrument for the transport of deformation trajectories
- Key component for multivariate analysis and modeling of longitudinal data
- Stability and sensitivity

# *The Stationnary Velocity Fields (SVF) framework for diffeomorphisms*

- SVF framework for diffeomorphisms is algorithmically simple
- Compatible with "inverse-consistency"
- Vector statistics directly generalized to diffeomorphisms
- Efficient parallel transport of deformation trajectories with Schilds/pole ladders

**Registration algorithms using log-demons:**

- Log-demons: Open-source ITK implementation (Vercauteren MICCAI 2008)
  **http://hdl.handle.net/10380/3060**
  **[MICCAI Young Scientist Impact award 2013]**
- Tensor (DTI) Log-demons (Sweet WBIR 2010):
  **https://gforge.inria.fr/projects/ttk**
- LCC log-demons for AD (Lorenzi, Neuroimage. 2013)
  **https://team.inria.fr/asclepios/software/lcclogdemons/**
- 3D myocardium strain / incompressible deformations (Mansi MICCAI'10)
- Hierarchichal multiscale polyaffine log-demons (Seiler, Media 2012)
  **http://www.stanford.edu/~cseiler/software.html**
  **[MICCAI 2011 Young Scientist award]**

# medInria

- Medical image processing and visualization software
- Open-source, BSD license
- Extensible via plugins
- Provides high-level algorithms to end-users
- Ergonomic and reactive user interface


Available registration algorithms :

- Diffeomorphic Demons
- Incompressible Log Demons
- LCC Log Demons

http://med.inria.fr



INRIA teams involved: Asclepios, Athena, Parietal, Visages