A guided tour
to multivariate models in imaging-genetics

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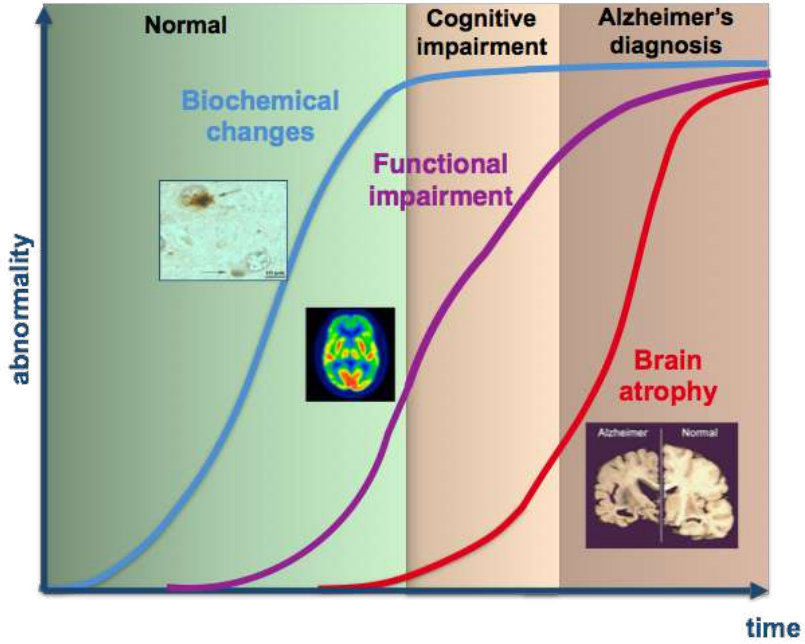
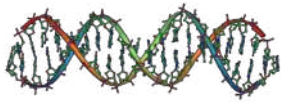
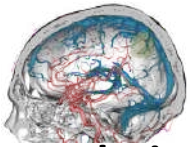
Late Onset Alzheimer's Disease

Jack et al, Lancet Neurol 2010;
Frisoni et al, Nature Rev Neurol 2010





Genetics



Vascularity

?

Sociodemographic

Microbiome

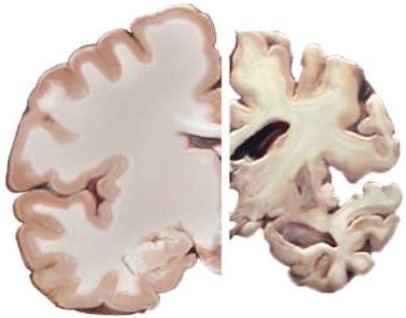
...

New opportunities (and challenges)

Data science & statistical learning

+

Alzheimer's research & Brain imaging

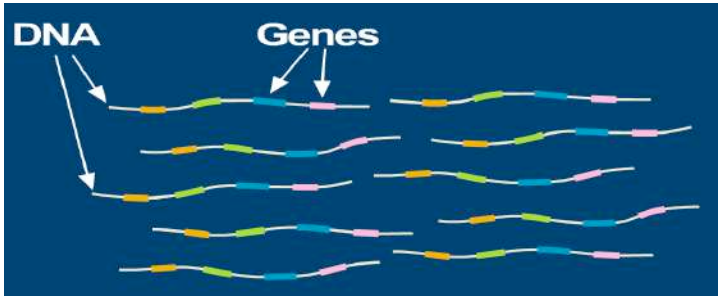


Towards novel disease models and improved diagnostic

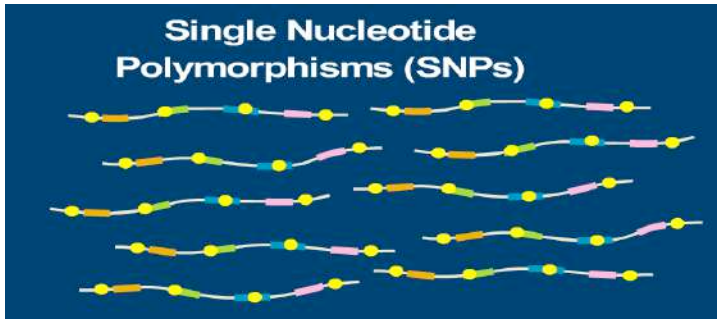
Imaging Genetics

Genotype - phenotype

DNA is the blueprint of individuals

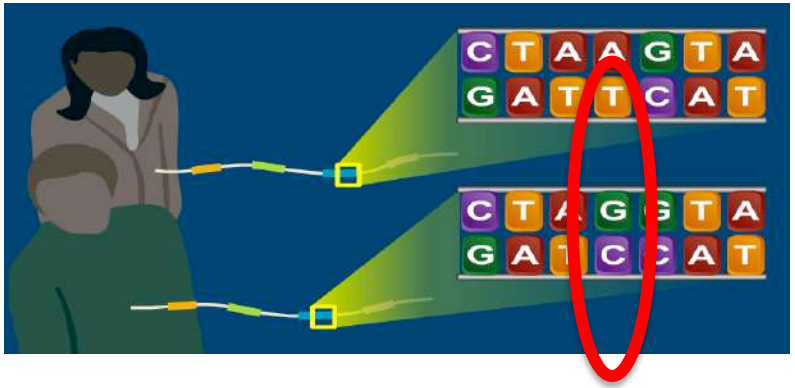


SNPs and individual variability

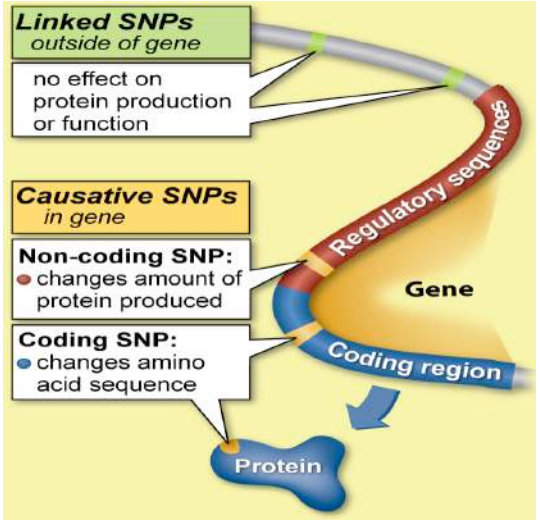


Many inter-subject differences are due to single variations in DNA

A single difference at a specific nucleotide position



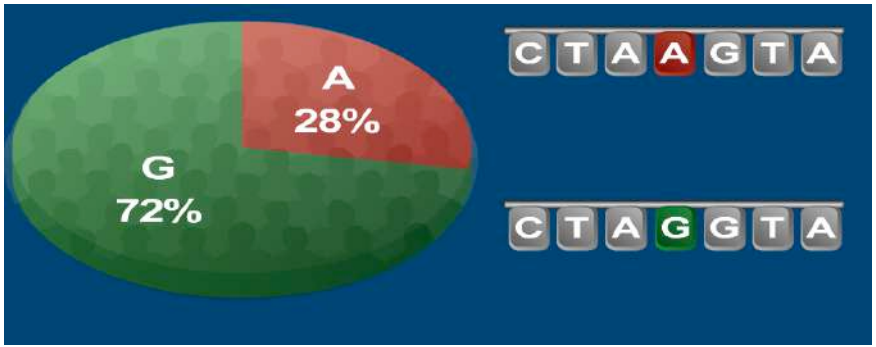
SNPs and individual variability



> ~10^7 estimated SNPs in human genome

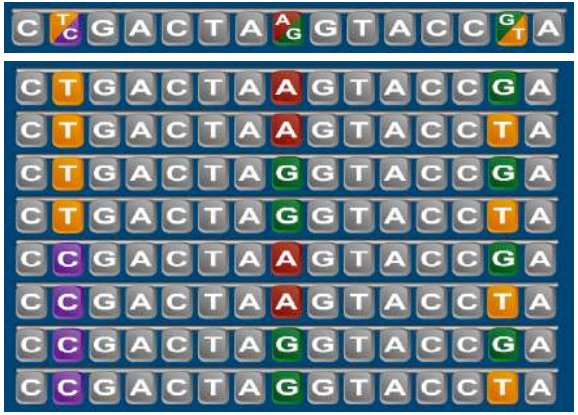
A statistical characterization of SNPs

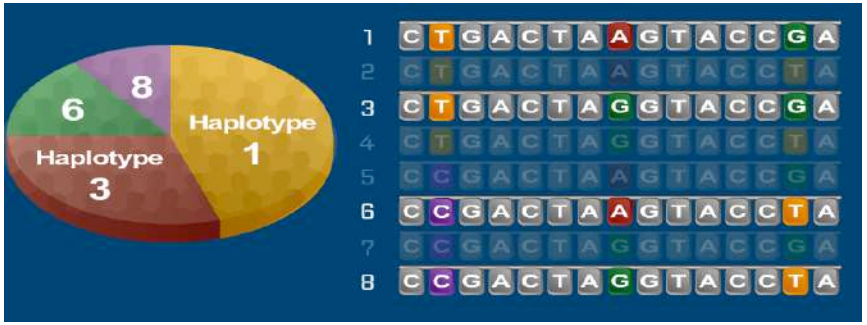
>1% population without same nucleotide

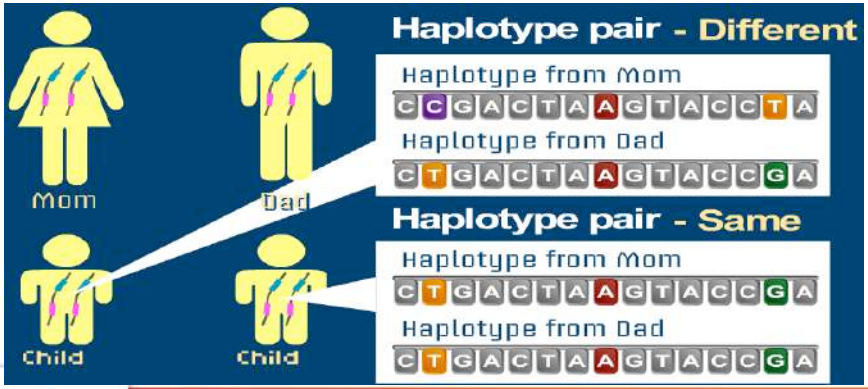


Haplotype

Individual's combination of SNPs

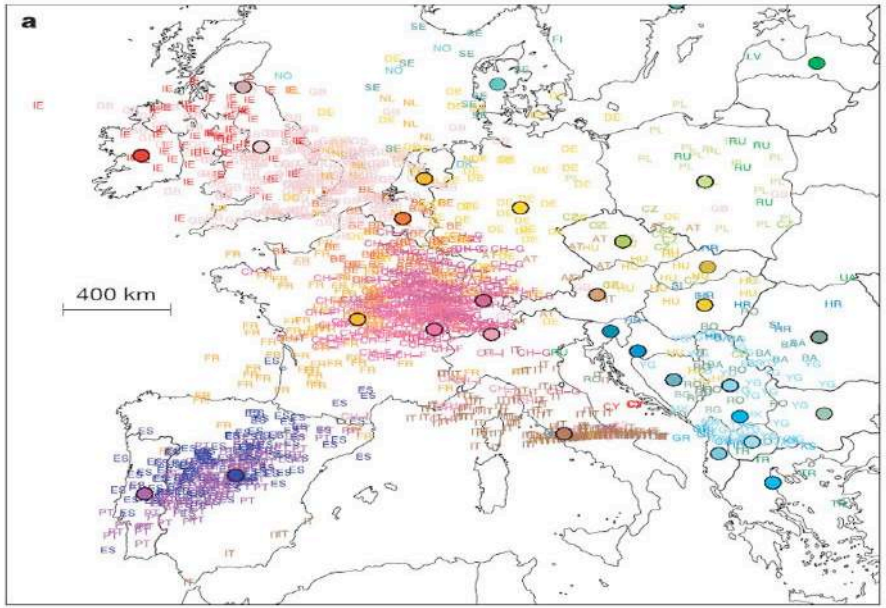






Individual SNP profiles

What is in there?



Novembre et al, Genes mirror geography within Europe, Nature 456, 2008

~500k SNPs

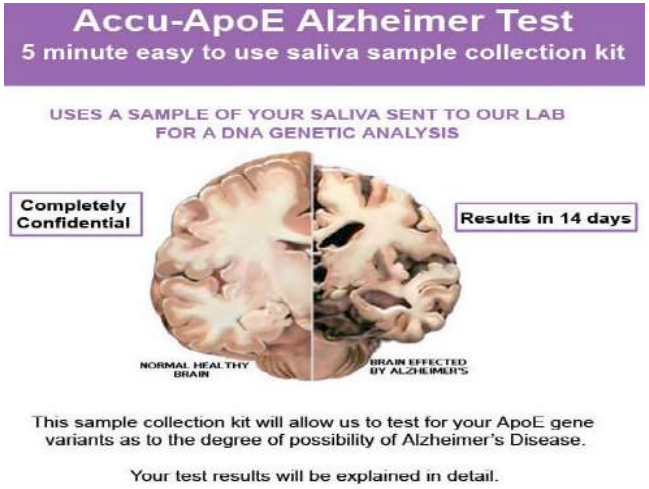
1st and 2nd PCA components

- Avg prediction error: 310 km
- 90% within 700 km

What about disease susceptibility?

Pharmacological intervention

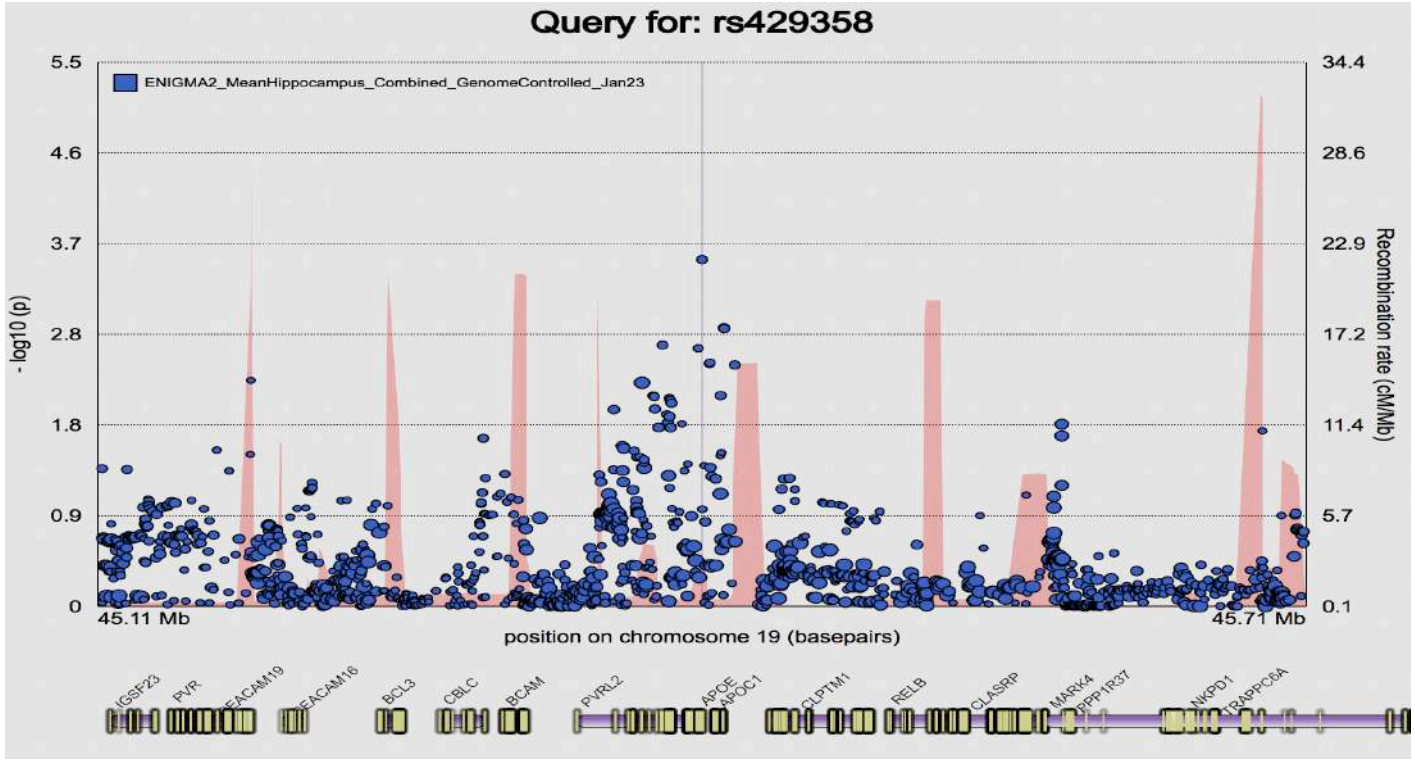
SNP profile	Drug Response
A	Poor
B	Good
C	None
D	Good



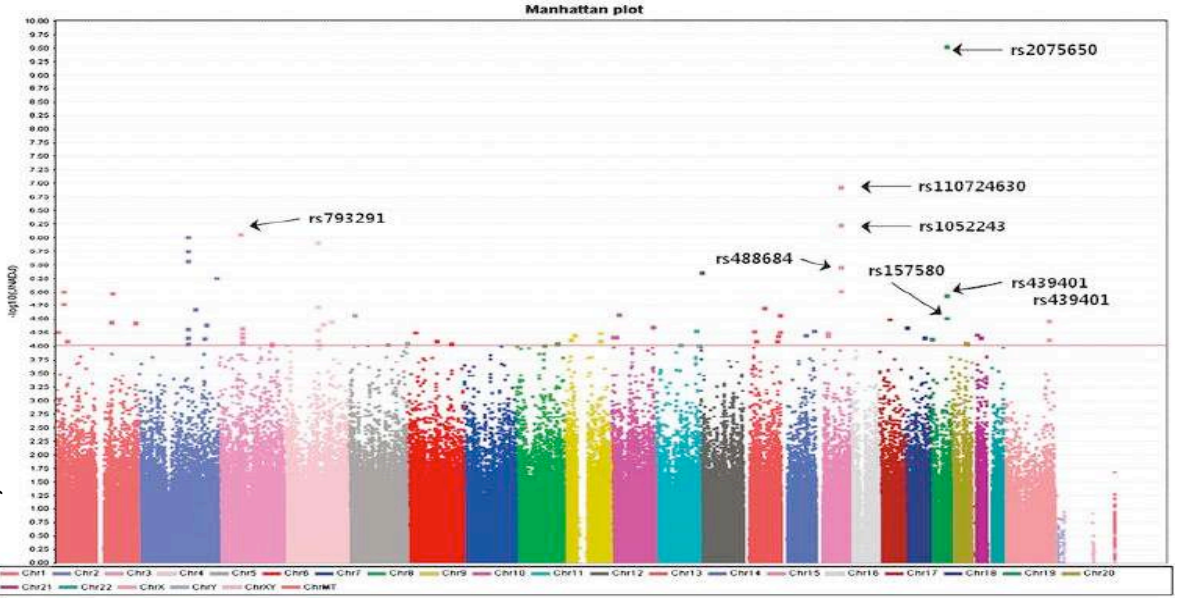
Disease understanding

Minor Allele	ε2	ε3	ε4
General Frequency	8.4%	77.9%	13.7%
AD Frequency	3.9%	59.4%	36.7%

Genetic basis of (sporadic) Alzheimer



Is it all about APOE?



Seok Woo et al, Journal of Alzheimer's Disease, 2015

Majority of current studies based on MASS UNIVARIATE ANALYSIS (GWAS)

Very large samples required (~10-100K)

Low explained variability

GWAS in Alzheimer's disease

Genetic heritability in twins up to 80%

Gatz et al, Arch Gen Psychiatry 2006

A handful of established genes
APOE, CLU, PICALM, CR1, …
overall leading to **small risk factor**

Table 1 | Genetic loci identified by the largest GWAS in AD

Locus	SNP	OR
APOE	rs2075650	2.53 (2.41–2.66)*
CLU	rs11136000	0.87 (0.84–0.89)*
PICALM	rs3851179	0.87 (0.84–0.90)*
	rs541458	0.87 (0.83–0.90)*
CR1	rs3818361	1.18 (1.13–1.23)*
	rs6656401	3.5×10^{-9}†
BIN1	rs744373	1.15 (1.11–1.20)*

Guerreiro et al,
Biochemincal Society Trans. 2011

AD missing heritability remains extensive

Imaging-genetics:
multimodal analysis of heterogeneous data

- **Multivariate Modeling in Imaging Genetics**
- **Online learning for multicentric studies**
- **Genetic analysis through disease progression modeling**

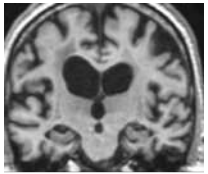
Imaging-genetics:
multimodal analysis of heterogeneous data

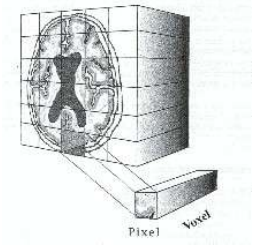
- **Multivariate Modeling in Imaging Genetics**
- Online learning for multicentric studies
- Genetic analysis through disease progression modeling

Imaging-genetics

Identifying genetic modulators of the brain phenotype

Brain imaging

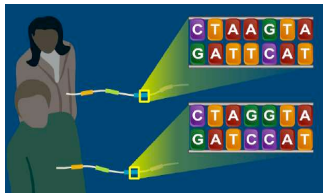


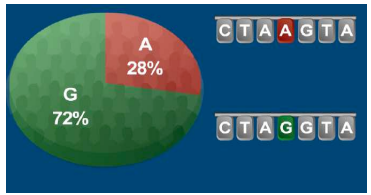


100’000 to 1’000’000 voxels

Genetics

Genetic variants (Single Nucleotide Polymorphism - SNP -)





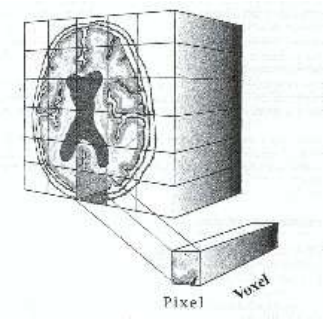
> 1’000’000 known SNPs


CTAAGTACTAAGTACTAAGTA
GATTCATGATTCATGATTCAT

...


CTAAGTACTAAGTA
GATTCATGATTCAT

...

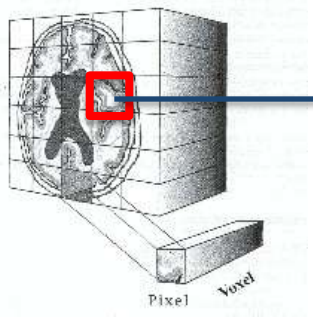

Pixel
Voxel

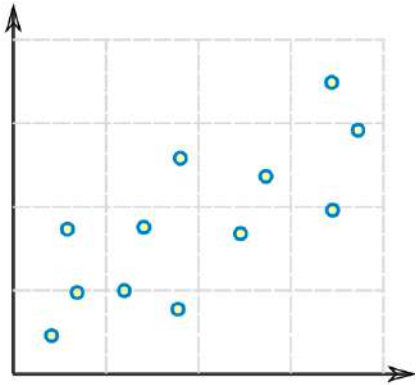

CTAAGTACTAAGTACTAAGTA
GATTCATGATTCATGATTCAT

...


CTAAGTACTAAGTA
GATTCATGATTCAT

...


Pixel
Voxel

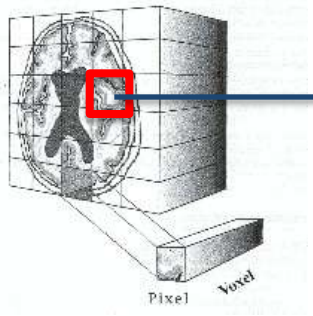


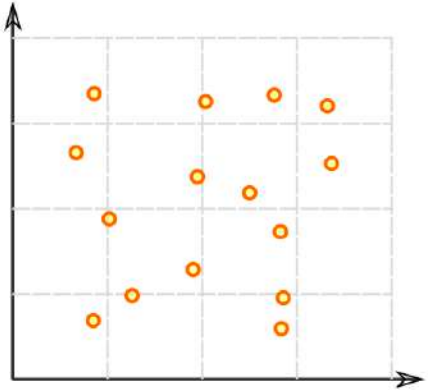

CTAAGTACTAAGTACTAAGTA
GATTCATGATTCATGATTCAT

...


CTAAGTACTAAGTA
GATTCATGATTCAT

...


Pixel
Voxel

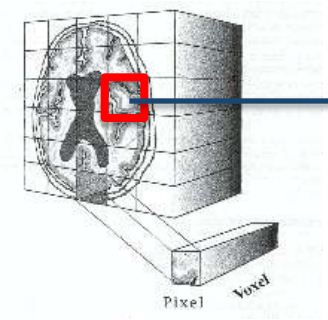


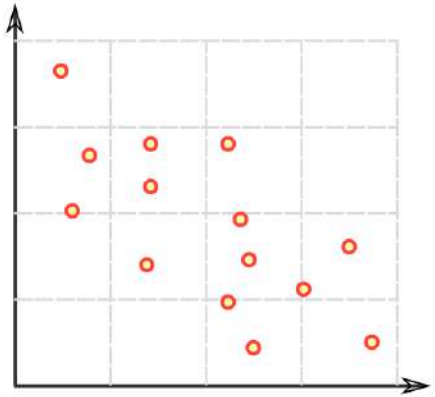

CTAAGTACTAAGTACTAAGTA
GATTCATGATTCATGATTCAT

...


CTAAGTACTAAGTA
GATTCATGATTCAT

...


Pixel
Voxel

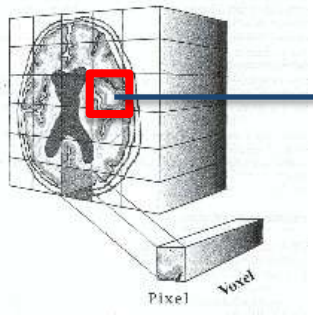


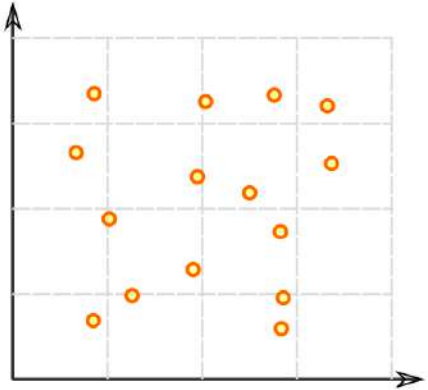

CTAAGTACTAAGTACTAAGTA
GATTCATGATTCATGATTCAT

...

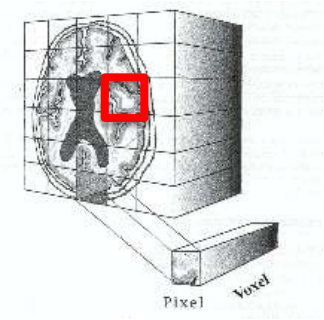

CTAAGTACTAAGTA
GATTCATGATTCAT

...

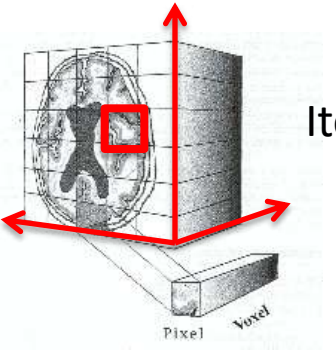

Pixel
Voxel



Iterate for > 1’000’000 variants

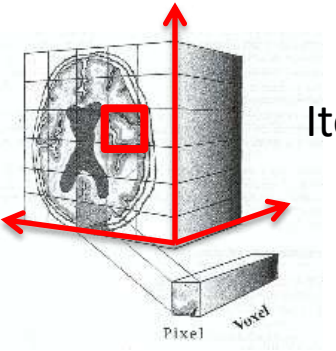


Iterate for > 1’000’000 variants



Iterate for > 1’000’000
image locations

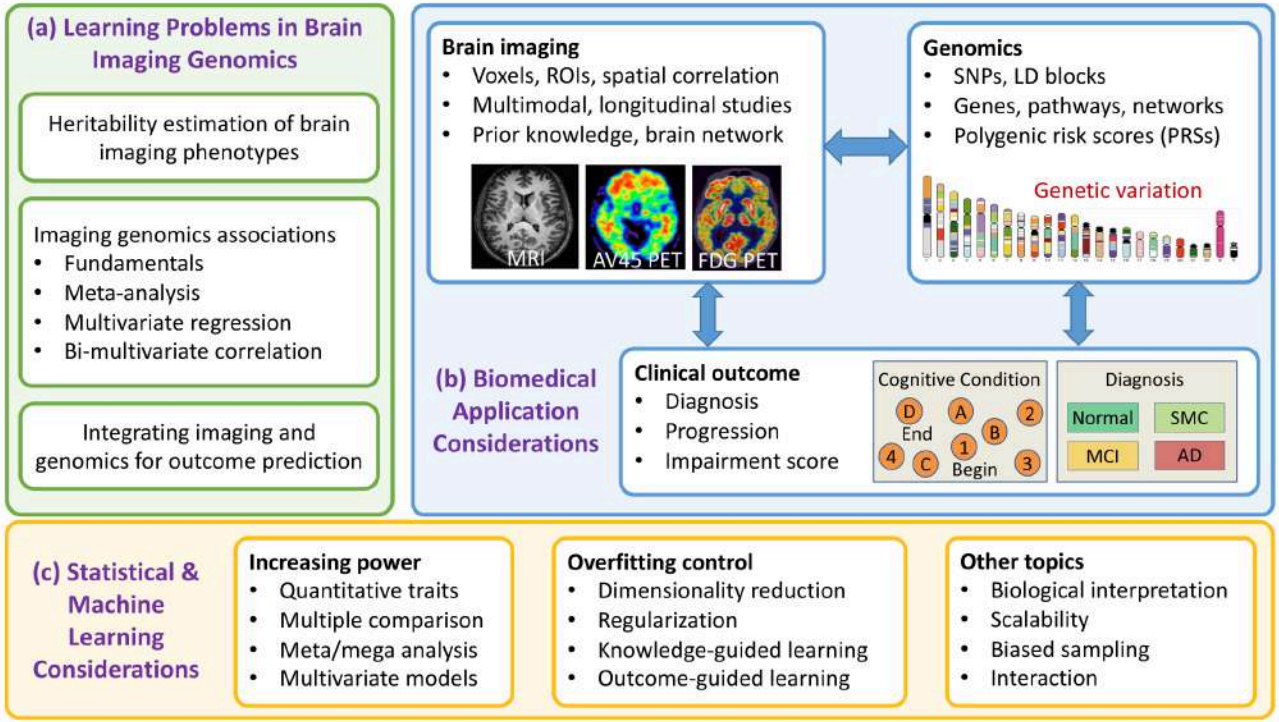
Iterate for > 1’000’000 variants



Iterate for > 1’000’000 image locations

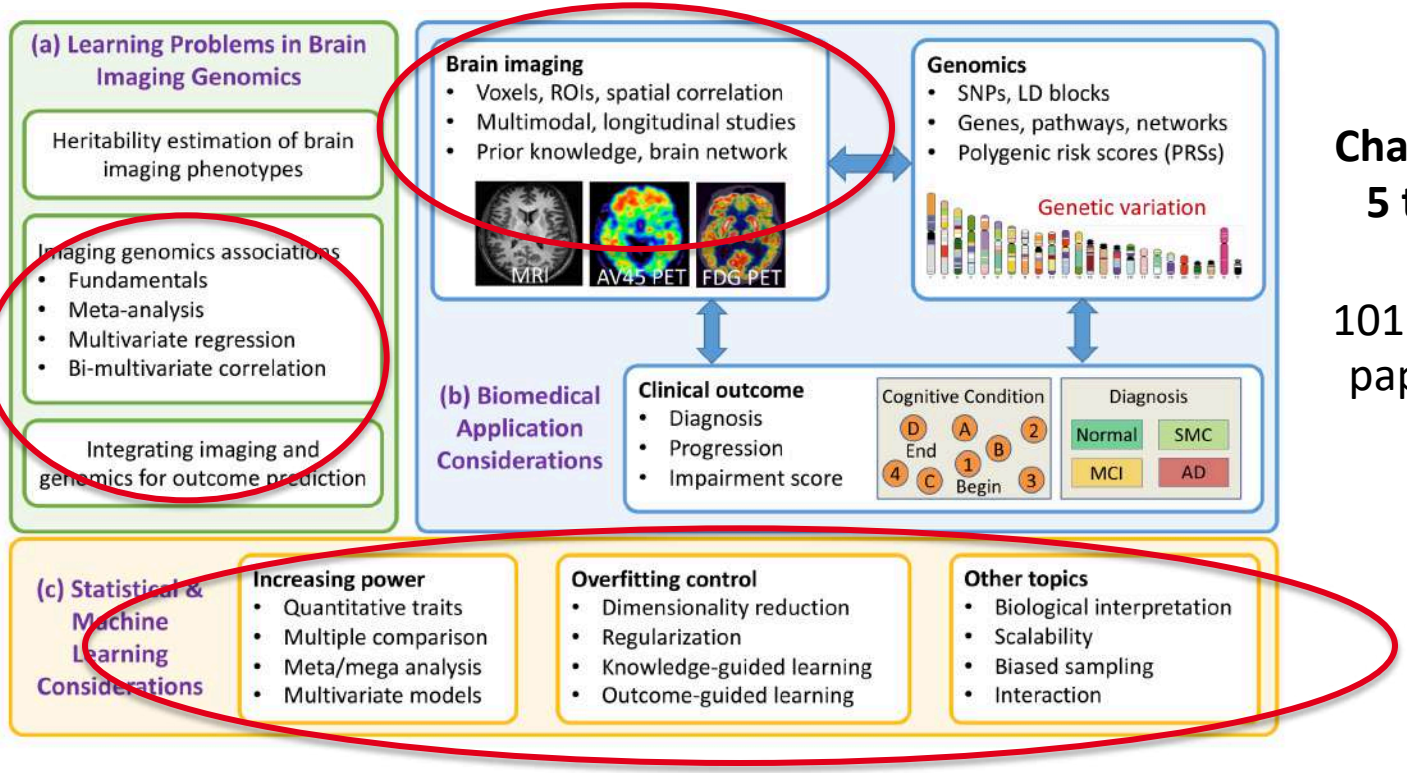
- Hard interpretability
- False positive discoveries
- No interaction across brain and genetic areas

A recent review paper (Shen and Thompson 2019)



Li Shen and Paul Thompson, Brain Imaging Genomics: Integrated Analysis and Machine Learning, Proceedings of the IEEE, 2019.

A recent review paper (Shen and Thompson 2019)

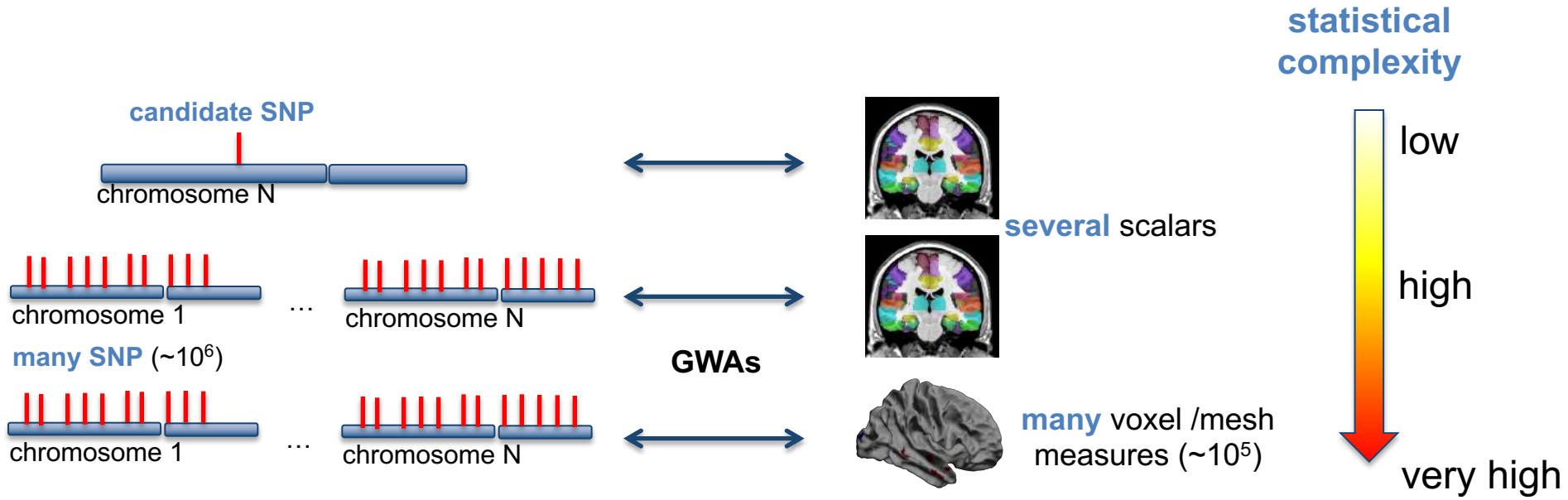


Chapters 5 to 7

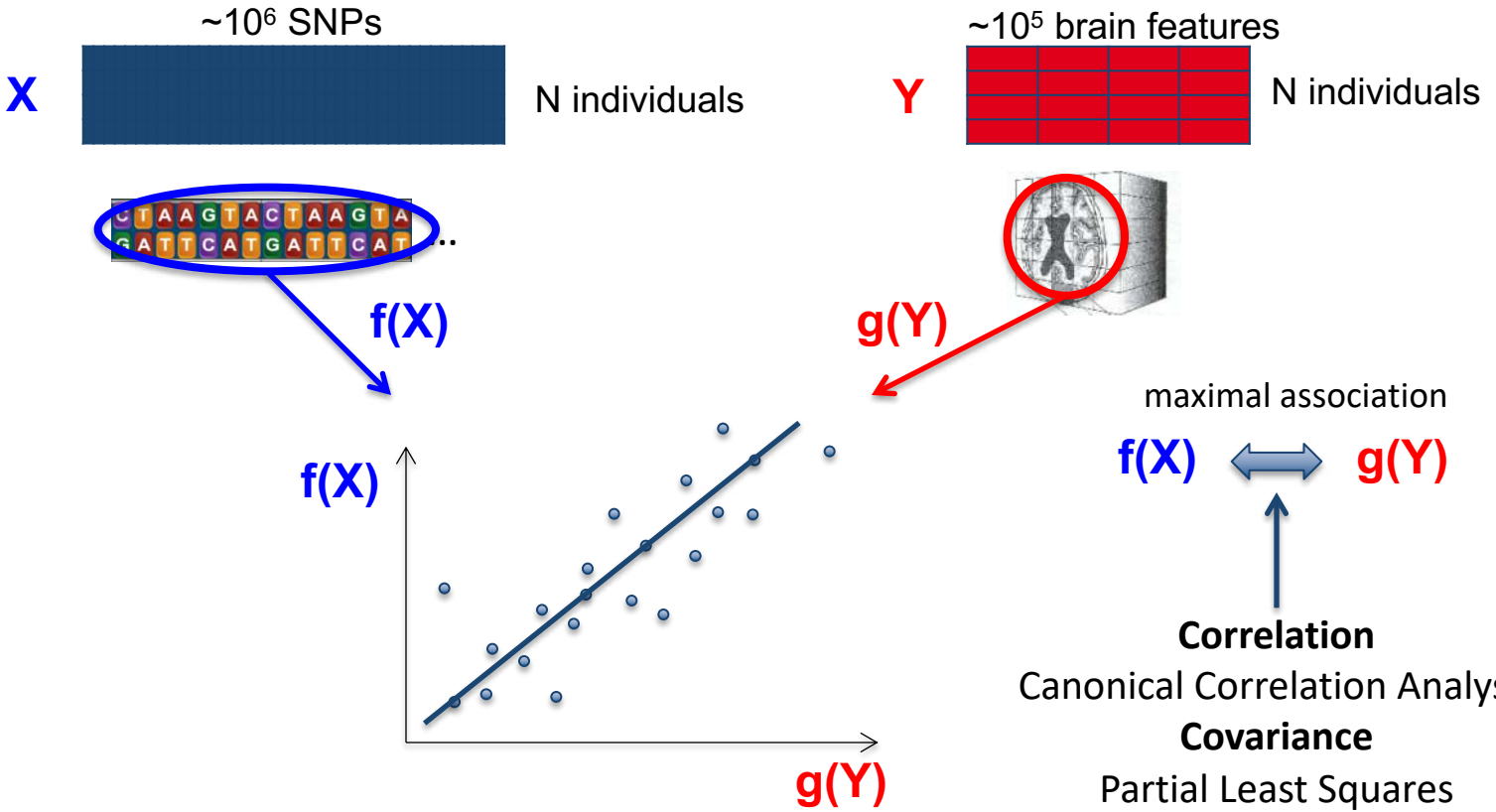
101 cited papers!

Li Shen and Paul Thompson, Brain Imaging Genomics: Integrated Analysis and Machine Learning, Proceedings of the IEEE, 2019.

Association between SNP and brain features



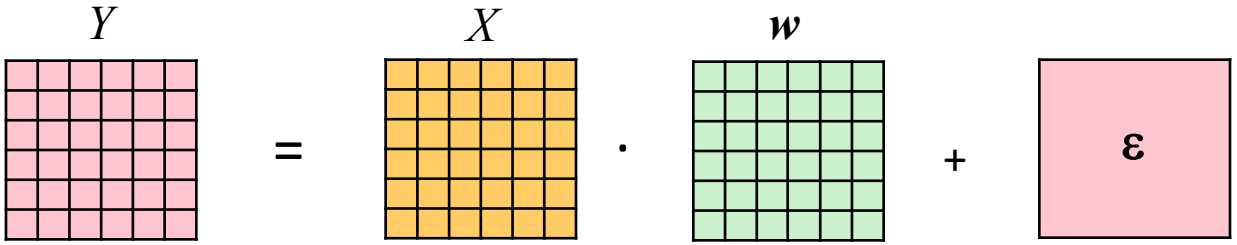
Multivariate modeling and dimensionality reduction



Latent variable models

The building-block: linear model

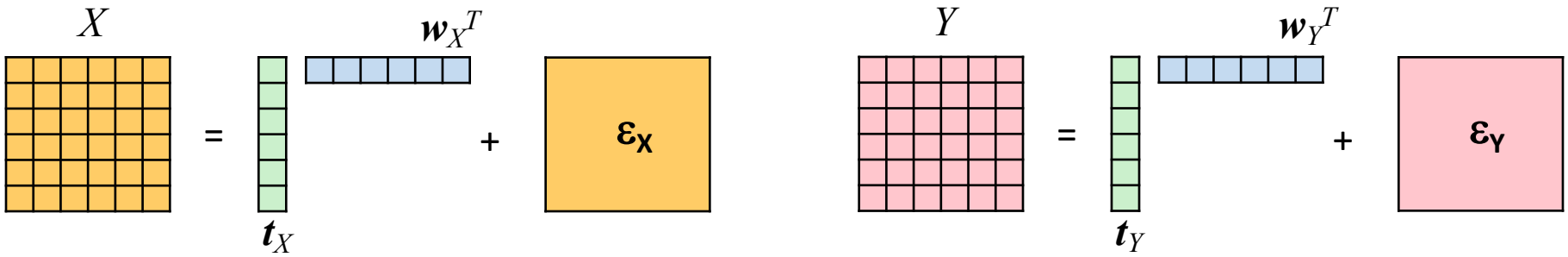
$$Y = Xw + \epsilon$$



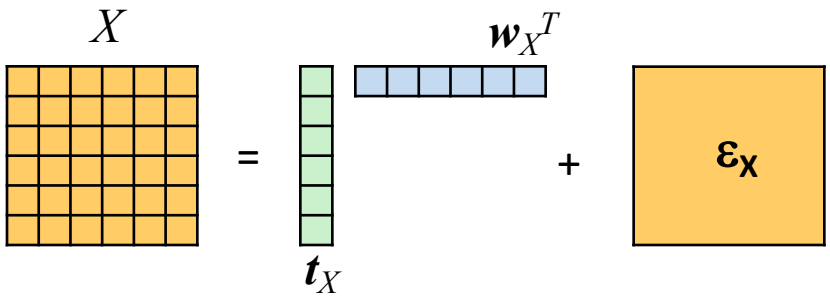
$$||Y - X\mathbf{w}||^2 = (Y - X\mathbf{w})^T(Y - X\mathbf{w})$$
$$= Y^TY - 2Y^TX\mathbf{w} + \mathbf{w}^TX^TX\mathbf{w}$$

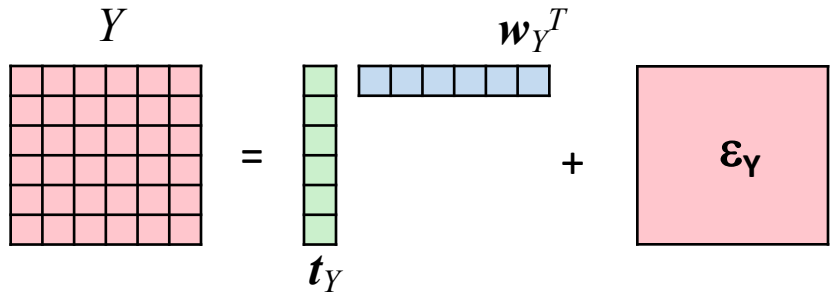
$$\frac{d||Y - X\mathbf{w}||^2}{d\mathbf{w}} = -2Y^TX + \mathbf{w}^TX^TX$$
$$\mathbf{w} = (X^TX)^{-1}X^TY$$

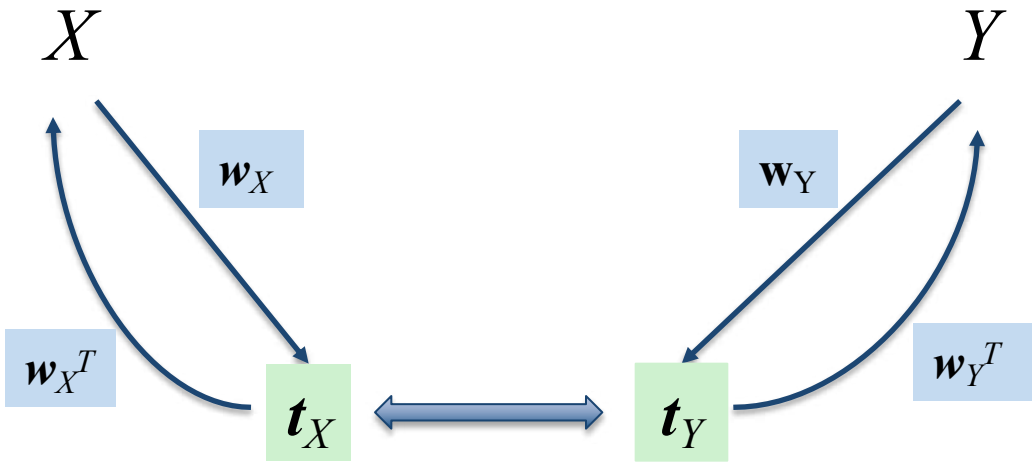
Formalization of latent variable models



Formalization of latent variable models





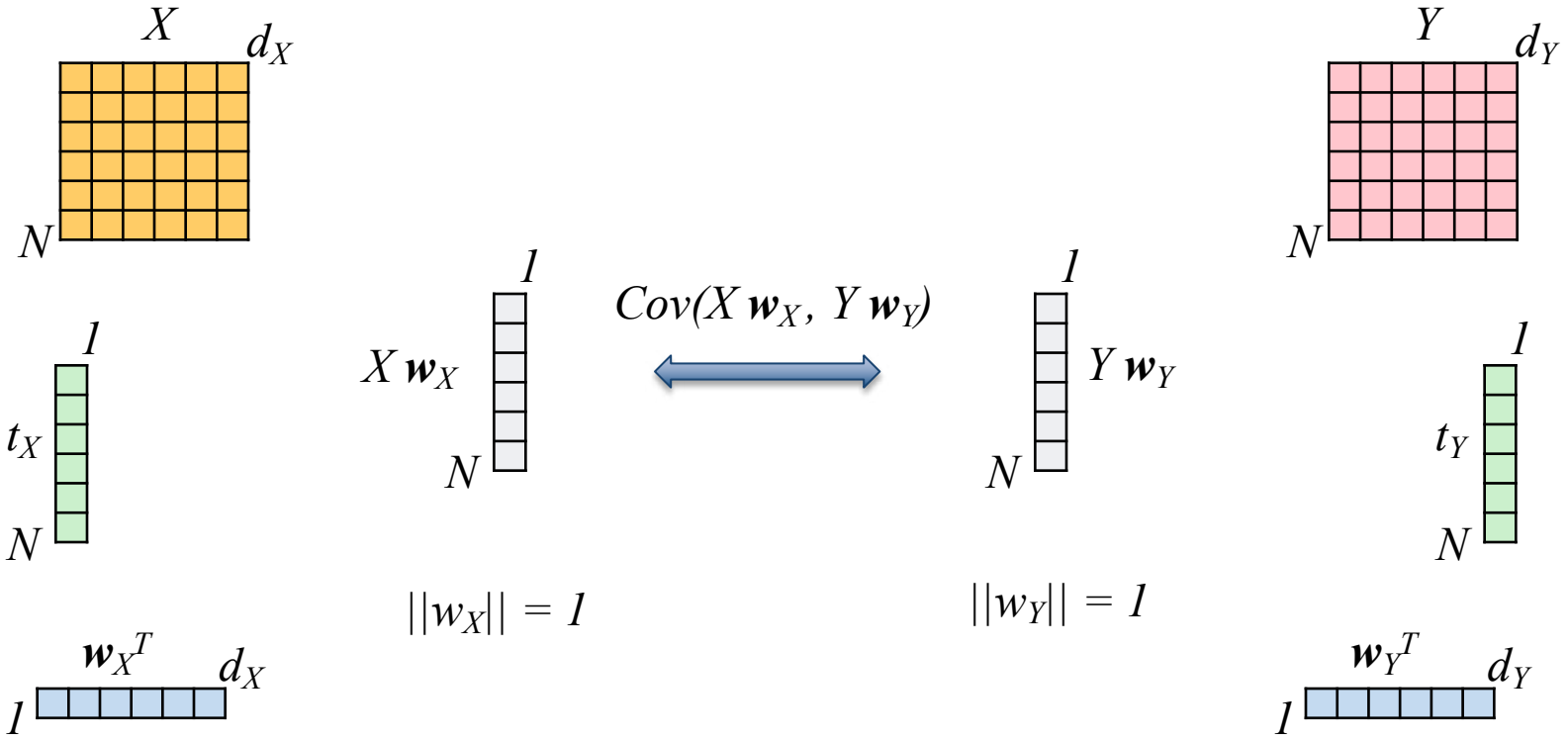


Goal:

Identifying
- Projections (loadings) **w**
- Latent representation (scores) **t**

Formalization of latent variable models

Formalization of latent variable models



Principal Components Analysis (case X=Y)

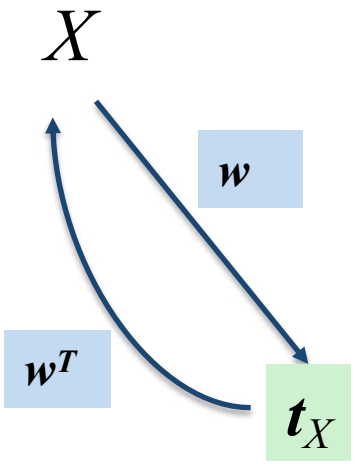
A **variance** maximisation problem:

$$\begin{aligned}\mathbf{w} &= \text{argmax}_{||\mathbf{w}||=1}(X\mathbf{w})^T(X\mathbf{w}) \\ &= \text{argmax}_{||\mathbf{w}||=1}\mathbf{w}^T X^T X\mathbf{w} \\ &= \text{argmax}_{||\mathbf{w}||=1}\mathbf{w}^T S_{XX}\mathbf{w}\end{aligned}$$

$$\nabla_w \mathcal{L}(\mathbf{w}, \lambda) = \nabla_w(\mathbf{w}^T S_{XX}\mathbf{w} - \lambda\mathbf{w}^T\mathbf{w}) = 0$$

$$\mathbf{S_{XX}w} = \lambda\mathbf{w}.$$

Non-linear iterative partial least squares - NIPALS
Wold 1975



1. Random initialization $\mathbf{w}$
2. Solve :

$$\text{argmin}_{\mathbf{t}} ||X - \mathbf{t}\mathbf{w}^T||^2$$

$$\mathbf{t} = X\mathbf{w}(\mathbf{w}^T\mathbf{w})^{-1}$$

3. Normalize :

$$\mathbf{t} = \frac{\mathbf{t}}{||\mathbf{t}||}$$

4. Update :

$$\text{argmin}_{\mathbf{w}} ||X - \mathbf{t}\mathbf{w}^T||^2$$

$$\mathbf{w} = X^T\mathbf{t}(\mathbf{t}^T\mathbf{t})^{-1}$$

5. Iterate 2-4 until convergence

Why it works:

$$4 \rightarrow const\, \mathbf{w} = X^T$$

$$2 \rightarrow const\, \mathbf{w} = X^T X \mathbf{w}$$

Then

$$const\, \mathbf{w} = S_{XX}\mathbf{w}$$

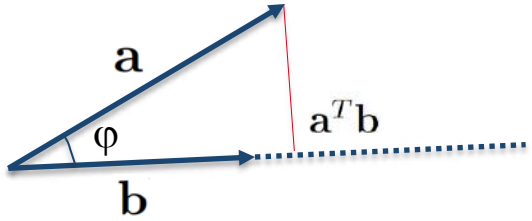
eigen-solution of the covariance matrix $X^T X$

Canonical Correlation Analysis

A **correlation** maximisation problem:

$$\mathbf{w}_x, \mathbf{w}_y = \underset{\mathbf{w}_x, \mathbf{w}_y}{\operatorname{argmax}} \rho(\mathbf{X}\mathbf{w}_x, \mathbf{Y}\mathbf{w}_y)$$

$$\rho(\mathbf{a}, \mathbf{b}) = \mathbf{a}^T\mathbf{b} / (\sqrt{\mathbf{a}^T\mathbf{a}}\sqrt{\mathbf{b}^T\mathbf{b}})$$



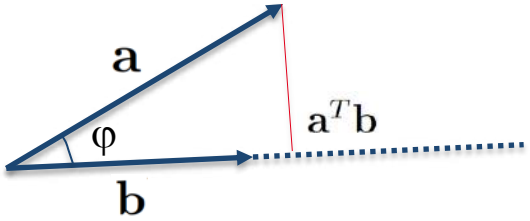
$$\rho(\mathbf{X}\mathbf{w}_x, \mathbf{Y}\mathbf{w}_y) = \frac{\mathbf{w}_x^T\mathbf{S}_{\mathbf{XY}}\mathbf{w}_y}{\sqrt{\mathbf{w}_x^T\mathbf{S}_{\mathbf{XX}}\mathbf{w}_x}\sqrt{\mathbf{w}_y^T\mathbf{S}_{\mathbf{YY}}\mathbf{w}_y}}$$

Canonical Correlation Analysis

A **correlation** maximisation problem:

$$\mathbf{w}_x, \mathbf{w}_y = \underset{\mathbf{w}_x, \mathbf{w}_y}{\operatorname{argmax}} \rho(\mathbf{X}\mathbf{w}_x, \mathbf{Y}\mathbf{w}_y)$$

$$\rho(\mathbf{a}, \mathbf{b}) = \mathbf{a}^T\mathbf{b} / (\sqrt{\mathbf{a}^T\mathbf{a}}\sqrt{\mathbf{b}^T\mathbf{b}})$$



Cross-covariance

$$\rho(\mathbf{X}\mathbf{w}_x, \mathbf{Y}\mathbf{w}_y) = \frac{\mathbf{w}_x^T \mathbf{S}_{\mathbf{XY}} \mathbf{w}_y}{\sqrt{\mathbf{w}_x^T \mathbf{S}_{\mathbf{XX}} \mathbf{w}_x}\sqrt{\mathbf{w}_y^T \mathbf{S}_{\mathbf{YY}} \mathbf{w}_y}}$$

Within-modality covariance

Canonical Correlation Analysis

$$\mathcal{L}(\mathbf{w}_x, \mathbf{w}_y, \lambda_x, \lambda_y) = \mathbf{w}_x^T \mathbf{S_{XY}} \mathbf{w}_x - \lambda_x(\mathbf{w}_x^T \mathbf{S_{XX}} \mathbf{w}_x - 1) - \lambda_y(\mathbf{w}_y^T \mathbf{S_{YY}} \mathbf{w}_y - 1)$$

Canonical Correlation Analysis

$$\mathcal{L}(\mathbf{w}_x, \mathbf{w}_y, \lambda_x, \lambda_y) = \mathbf{w}_x^T \mathbf{S_{XY}} \mathbf{w}_x - \lambda_x(\mathbf{w}_x^T \mathbf{S_{XX}} \mathbf{w}_x - 1) - \lambda_y(\mathbf{w}_y^T \mathbf{S_{YY}} \mathbf{w}_y - 1)$$

$$\begin{cases} \mathbf{S_{XY}}\,\mathbf{w}_x &= \lambda_\mathbf{X} \mathbf{S_{XX}}\,\mathbf{w}_x\,, \\ \mathbf{S_{YX}}\,\mathbf{w}_y &= \lambda_\mathbf{Y} \mathbf{S_{YY}}\,\mathbf{w}_y \end{cases}$$

$$\lambda_\mathbf{X}\,\mathbf{w}_x^T \mathbf{S_{XX}}\,\mathbf{w}_x = \mathbf{w}_x^T \mathbf{S_{XY}}\,\mathbf{w}_y = \mathbf{w}_y^T \mathbf{S_{YX}}\,\mathbf{w}_x = \lambda_\mathbf{Y}\,\mathbf{w}_y^T \mathbf{S_{YY}}\,\mathbf{w}_y$$

Canonical Correlation Analysis

$$\mathcal{L}(\mathbf{w}_x, \mathbf{w}_y, \lambda_x, \lambda_y) = \mathbf{w}_x^T \mathbf{S_{XY}} \mathbf{w}_x - \lambda_x(\mathbf{w}_x^T \mathbf{S_{XX}} \mathbf{w}_x - 1) - \lambda_y(\mathbf{w}_y^T \mathbf{S_{YY}} \mathbf{w}_y - 1)$$

$$\begin{cases} \mathbf{S_{XY}}\,\mathbf{w}_x &= \lambda_\mathbf{X}\mathbf{S_{XX}}\,\mathbf{w}_x\,, \\ \mathbf{S_{YX}}\,\mathbf{w}_y &= \lambda_\mathbf{Y}\mathbf{S_{YY}}\,\mathbf{w}_y \end{cases}$$

$$\lambda_\mathbf{X}\,\mathbf{w}_x^T\mathbf{S_{XX}}\,\mathbf{w}_x = \mathbf{w}_x^T\mathbf{S_{XY}}\,\mathbf{w}_y = \mathbf{w}_y^T\mathbf{S_{YX}}\,\mathbf{w}_x = \lambda_\mathbf{Y}\,\mathbf{w}_y^T\mathbf{S_{YY}}\,\mathbf{w}_y$$

$$\begin{bmatrix} \mathbf{0} & \mathbf{S_{XY}} \\ \mathbf{S_{YX}} & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{w}_x \\ \mathbf{w}_y \end{bmatrix} = \lambda \begin{bmatrix} \mathbf{S_{XX}} & \mathbf{0} \\ \mathbf{0} & \mathbf{S_{YY}} \end{bmatrix} \begin{bmatrix} \mathbf{w}_x \\ \mathbf{w}_y \end{bmatrix}$$

CCA is solved as a generalized eigenvalue problem

Canonical Correlation Analysis (alternative formula)

$$\begin{bmatrix} \mathbf{0} & \mathbf{S}_{\mathbf{XX}}^{-1/2}\mathbf{S}_{\mathbf{XY}}\mathbf{S}_{\mathbf{YY}}^{-1/2} \\ \mathbf{S}_{\mathbf{YY}}^{-1/2}\mathbf{S}_{\mathbf{YX}}\mathbf{S}_{\mathbf{XX}}^{-1/2} & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{v}_x \\ \mathbf{v}_y \end{bmatrix} = \lambda \begin{bmatrix} \mathbf{v}_x \\ \mathbf{v}_y \end{bmatrix} \qquad \begin{aligned} \mathbf{v}_x &= \mathbf{S}_{\mathbf{XX}}^{1/2T}\mathbf{w}_x \\ \mathbf{v}_y &= \mathbf{S}_{\mathbf{YY}}^{1/2T}\mathbf{w}_y \end{aligned}$$

$$\rho(\mathbf{X}\mathbf{v}_x, \mathbf{Y}\mathbf{v}_y) = \frac{\overbrace{\mathbf{u}^T}\overbrace{\mathbf{v}_x^T\mathbf{S}_{\mathbf{XX}}^{-1/2}\mathbf{S}_{\mathbf{XY}}\mathbf{S}_{\mathbf{YY}}^{-1/2}}\mathbf{v}_y}{\sqrt{\mathbf{v}_x^T\mathbf{v}_x}\sqrt{\mathbf{v}_y^T\mathbf{v}_y}}$$

The quantity is maximized when $\mathbf{v}_y$ parallel to $\mathbf{u}$

Canonical Correlation Analysis (alternative formula)

$$\rho'(\mathbf{X}\mathbf{v}_x, \mathbf{X}\mathbf{v}_x) = \frac{\mathbf{u}^T\mathbf{u}}{\sqrt{\mathbf{v}_x^T\mathbf{v}_x}} = \frac{\mathbf{v}_x^T\mathbf{S}_{\mathbf{XX}}^{-1/2}\mathbf{S}_{\mathbf{XY}}\mathbf{S}_{\mathbf{YY}}^{-1}\mathbf{S}_{\mathbf{YX}}\mathbf{S}_{\mathbf{XX}}^{-1/2}\mathbf{v}_x}{\sqrt{\mathbf{v}_x^T\mathbf{v}_x}}$$

Eigen-solution for the matrix

$$\mathbf{S}_{\mathbf{XX}}^{-1/2}\mathbf{S}_{\mathbf{XY}}\mathbf{S}_{\mathbf{YY}}^{-1}\mathbf{S}_{\mathbf{YX}}\mathbf{S}_{\mathbf{XX}}^{-1/2}$$

Partial Least Squares

A **co-variance** maximisation problem:

$$\mathbf{w}_x, \mathbf{w}_y = \underset{\mathbf{w}_x, \mathbf{w}_y}{\operatorname{argmax}} \, cov(\mathbf{X}\mathbf{w}_x, \mathbf{Y}\mathbf{w}_y)$$

$$cov(\mathbf{X}\mathbf{w}_x, \mathbf{Y}\mathbf{w}_y) = \frac{\mathbf{w}_x^T \mathbf{S}_{\mathbf{XY}} \mathbf{w}_y}{\sqrt{\mathbf{w}_x^T \mathbf{w}_x} \sqrt{\mathbf{w}_y^T \mathbf{w}_y}}$$

Partial Least Squares

$$\begin{bmatrix} \mathbf{0} & \mathbf{S_{XY}} \\ \mathbf{S_{YX}} & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{w}_x \\ \mathbf{w}_y \end{bmatrix} = \lambda \begin{bmatrix} \mathbf{w}_x \\ \mathbf{w}_y \end{bmatrix}$$

The PLS problem is solved via singular value decomposition (SVD) of the covariance matrix $\mathbf{S_{XY}}$

PLS and regularized CCA

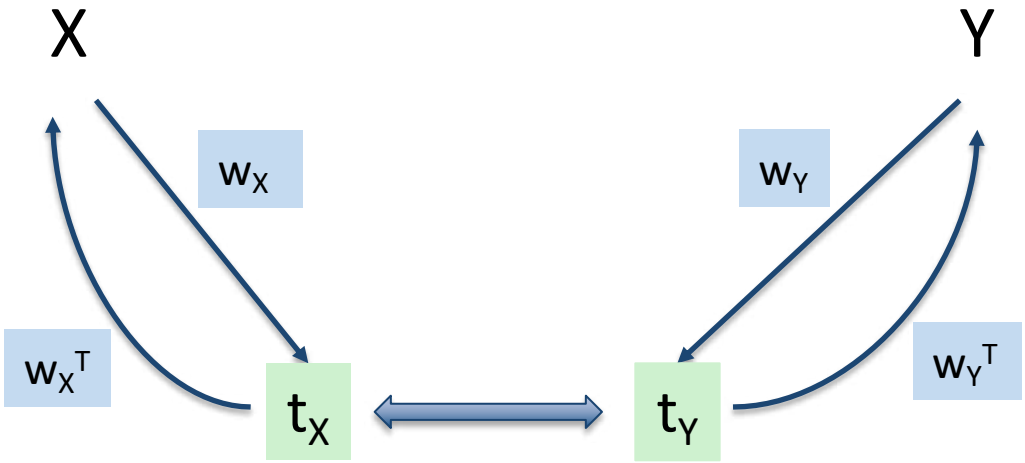
$$\begin{bmatrix} \mathbf{0} & \mathbf{S_{XY}} \\ \mathbf{S_{YX}} & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{w}_x \\ \mathbf{w}_y \end{bmatrix} = \lambda \begin{bmatrix} \mathbf{S_{XX}} + \delta\mathbf{I} & \mathbf{0} \\ \mathbf{0} & \mathbf{S_{YY}} + \delta\mathbf{I} \end{bmatrix} \begin{bmatrix} \mathbf{w}_x \\ \mathbf{w}_y \end{bmatrix}$$

$\delta \rightarrow \infty$

PLS

Non-linear iterative partial least squares - NIPALS

scikit-learn/sklearn/cross_decomposition



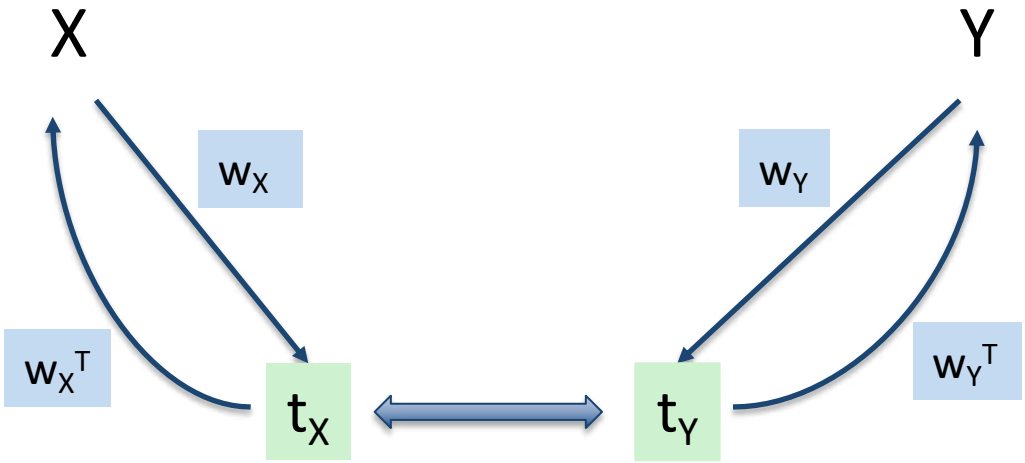
1. Random initialization $\mathbf{t}_x$
2. Update $\mathbf{w}_y$:
   $\text{argmin}_{\mathbf{w}_y} ||Y - \mathbf{t}_x \mathbf{w}_y^T||^2$
   $\mathbf{w}_y = Y^t \mathbf{t}_x (\mathbf{t}_x^T \mathbf{t}_x)^{-1}$
3. Normalize :
   $\mathbf{w}_y = \frac{\mathbf{w}_y}{||\mathbf{w}_y||}$
4. $\mathbf{t}_y = Y \mathbf{w}_y$
5. Update $\mathbf{w}_x$:
   $\text{argmin}_{\mathbf{w}_x} ||X - \mathbf{t}_y \mathbf{w}_x^T||^2$
   $\mathbf{w}_x = X^T \mathbf{t}_y (\mathbf{t}_y^T \mathbf{t}_y)^{-1}$
6. Normalize :
   $\mathbf{w}_x = \frac{\mathbf{w}_x}{||\mathbf{w}_x||}$
7. $\mathbf{t}_x = X \mathbf{w}_x$
8. Iterate 2-7 until convergence

$$const\, \mathbf{w}_x = X^T Y Y^T X \mathbf{w}_x$$

left eigen-solution of $X^T Y$

Non-linear iterative partial least squares - NIPALS

scikit-learn/sklearn/cross_decomposition



$$const\, \mathbf{w}_x = (X^T X)^{-1} X^T Y (Y^T Y)^{-1} Y^T X \mathbf{w}_x$$

$$const\, \mathbf{w}_x (X^T X)^{\frac{1}{2}} = (X^T X)^{-\frac{1}{2}} X^T Y (Y^T Y)^{-1} Y^T X \mathbf{w}_x$$

$$const\, \mathbf{w}_x (X^T X)^{\frac{1}{2}} = (X^T X)^{-\frac{1}{2}} X^T Y (Y^T Y)^{-1} Y^T X (X^T X)^{-\frac{1}{2}} (X^T X)^{\frac{1}{2}} \mathbf{w}_x$$

$$const\, \mathbf{v}_x = S_{XX}^{-\frac{1}{2}} X_{XY} S_{YY}^{-1} S_{YX} S_{XX}^{-\frac{1}{2}} \mathbf{v}_x$$

1. Random initialization $\mathbf{t}_x$
2. Update $\mathbf{w}_y$:

$$\text{argmin}_{\mathbf{w}_y} ||Y\mathbf{w}_y - \mathbf{t}_x||^2$$

$$\mathbf{w}_y = (Y^T Y)^{-1} Y^T \mathbf{t}_x$$

3. Normalize :

$$\mathbf{w}_y = \frac{\mathbf{w}_y}{||\mathbf{w}_y||}$$

4. $\mathbf{t}_y = Y\mathbf{w}_y$
5. Update $\mathbf{w}_x$:

$$\text{argmin}_{\mathbf{w}_x} ||X\mathbf{w}_x - \mathbf{t}_y||^2$$

$$\mathbf{w}_x = (X^T X)^{-1} X^T \mathbf{t}_y$$

6. Normalize :

$$\mathbf{w}_x = \frac{\mathbf{w}_x}{||\mathbf{w}_x||}$$

7. $\mathbf{t}_x = X\mathbf{w}_x$
8. Iterate 2-7 until convergence

Geladi and Kowalski, Analytica Chimica Acta, 1985

Non-linear iterative partial least squares - NIPALS Deflation

$$\mathbf{X}^{(i+1)} = \mathbf{X}^{(i)} - \boldsymbol{t}^{(i)} \frac{\boldsymbol{t}^{(i)T} \mathbf{X}^{(i)}}{\boldsymbol{t}^{(i)T} \boldsymbol{t}^{(i)}},$$

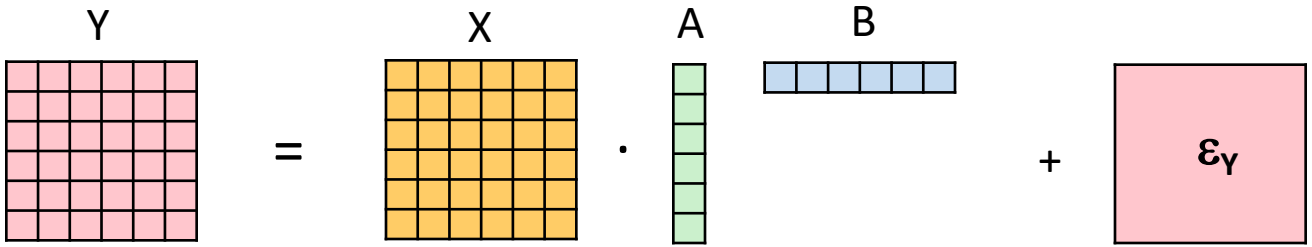
$$\mathbf{Y}^{(i+1)} = \mathbf{Y}^{(i)} - \boldsymbol{u}^{(i)} \frac{\boldsymbol{u}^{(i)T} \mathbf{Y}^{(i)}}{\boldsymbol{u}^{(i)T} \boldsymbol{u}^{(i)}}.$$

Iterate until

- residual component negligible epsilon
- Difference between consecutive residual components negligible

Reduced Rank Regression

$$\mathbf{Y} = \mathbf{XC} + \epsilon. \qquad \mathbf{C} = \mathbf{AB}$$



$$f(\mathbf{A}, \mathbf{B}) = tr\{(\mathbf{Y} - \mathbf{XAB})\Gamma(\mathbf{Y} - \mathbf{XAB})^T\}$$

Reduced Rank Regression

Solution associated to the eigen-decomposition of the matrix

$$\mathbf{R} = \Gamma^{1/2}\mathbf{S}_{\mathbf{YX}}\mathbf{S}_{\mathbf{XX}}^{-1}\mathbf{S}_{\mathbf{XY}}\Gamma^{1/2}$$

Matrix encoding prior knowledge on Y

Reduced Rank Regression

Solution associated to the eigen-decomposition of the matrix

$$\mathbf{R} = \Gamma^{1/2}\mathbf{S}_{\mathbf{YX}}\mathbf{S}_{\mathbf{XX}}^{-1}\mathbf{S}_{\mathbf{XY}}\Gamma^{1/2}$$

Matrix encoding prior knowledge on Y

RRR solutions:

$$\mathbf{A} = \Gamma^{-1/2}\mathbf{U}, \qquad \mathbf{B} = \mathbf{U}^T\Gamma^{1/2}\mathbf{S}_{\mathbf{YX}}\mathbf{S}_{\mathbf{XX}}^{-1}$$

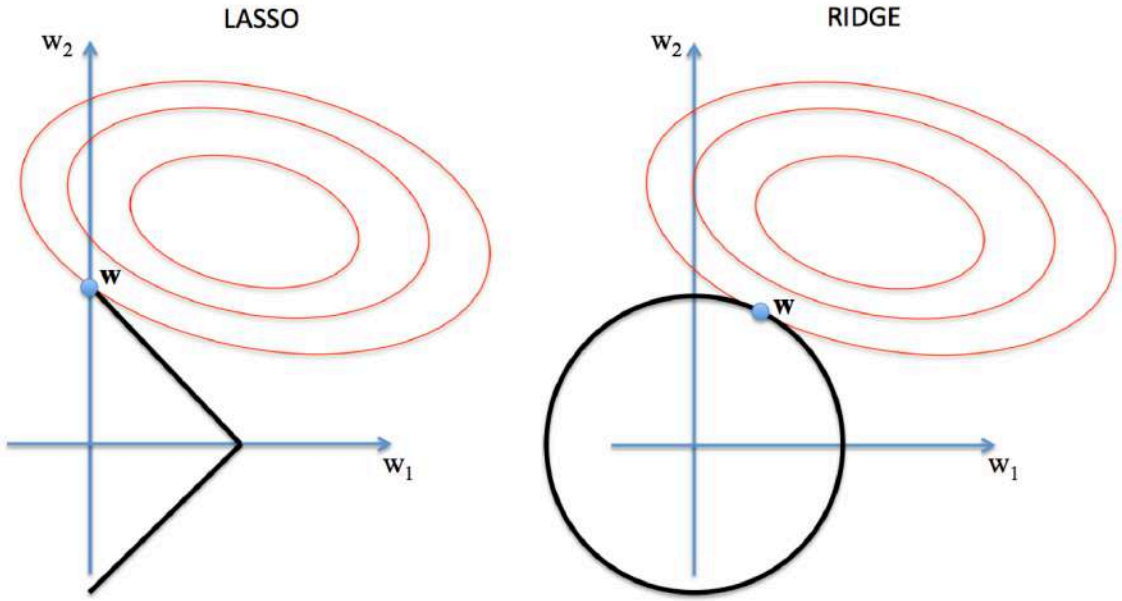
Special case:

$$\Gamma = \mathbf{S}_{\mathbf{YY}} \quad \Rightarrow \quad \text{CCA}$$

Sparsity in latent variable models

$$\underset{\mathbf{w}}{\operatorname{argmin}}\, f(\mathbf{w}) + \lambda ||\mathbf{w}||_1$$

$$\underset{\mathbf{w}}{\operatorname{argmin}}\, f(\mathbf{w}) + \lambda ||\mathbf{w}||_2^2$$



Worked example: Ridge linear regression

$$\mathcal{L}(\mathbf{w}) = ||Y - X\mathbf{w}||^2 + \lambda||\mathbf{w}||^2$$

$$\frac{d\mathcal{L}}{d\mathbf{w}} = -2Y^T X + \mathbf{w}^T X^T X + \lambda \mathbf{w}^T$$

$$\mathbf{w} = (X^T X + \lambda Id)^{-1} X^T Y$$

Shrinkage parameter towards zero solutions

Algorithm Regularization of projections parameters $\mathbf{w}_x$ and $\mathbf{w}_y$ in NIPALS.

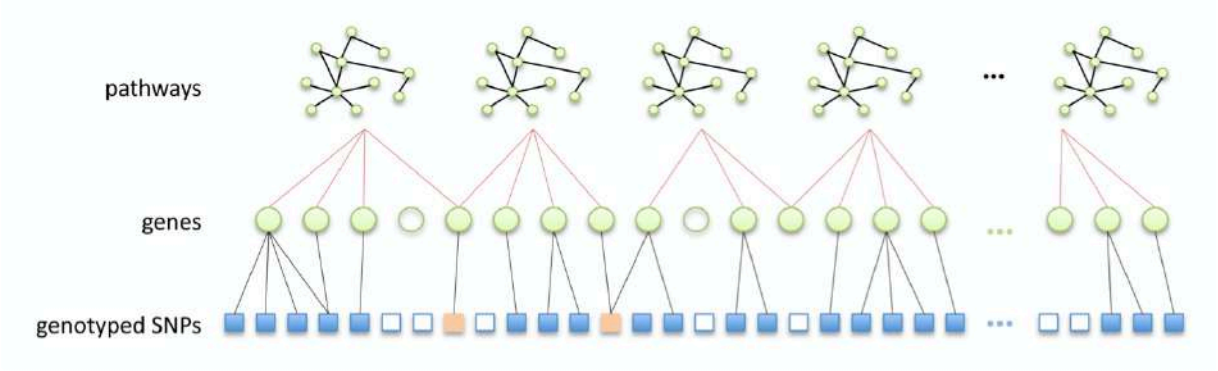
Given current estimates of $\mathbf{w}_x$ and $\mathbf{w}_y$.

While not converged do:

1. compute $\mathbf{t} = \mathbf{X}\mathbf{w}_x$,
2. compute $\mathbf{u} = \mathbf{Y}\mathbf{w}_y$,
3. compute $\overline{\mathbf{w}_x}$ by solving the Elastic-Net regression:
$$\overline{\mathbf{w}_x} = \arg\min_{\mathbf{v}} (\mathbf{t} - \mathbf{X}\mathbf{v})^2 + \lambda_{x2}\|\mathbf{v}\|_2^2 + \lambda_{x1}\|\mathbf{v}\|_1,$$
4. compute $\overline{\mathbf{w}_y}$ by solving the Elastic-Net regression:
$$\overline{\mathbf{w}_y} = \arg\min_{\mathbf{v}} (\mathbf{u} - \mathbf{Y}\mathbf{v})^2 + \lambda_{y2}\|\mathbf{v}\|_2^2 + \lambda_{y1}\|\mathbf{v}\|_1,$$
3. Normalize $\overline{\mathbf{w}_x}$ and $\overline{\mathbf{w}_x}$,
4. Set $\mathbf{w}_x = \overline{\mathbf{w}_x}$, $\mathbf{w}_y = \overline{\mathbf{w}_y}$.

S. Waaijenborg, A. H. Zwinderman, Penalized canonical correlation analysis to quantify the association between gene expression and dna markers, in: BMC proceedings, Vol. 1, BioMed Central, 2007

Group-wise penalization



$$\mathbf{a}_1 = \{snp_1^1, snp_2^1, \ldots, snp_k^1\}$$

$$\mathbf{a}_2 = \{snp_1^2, snp_2^2, \ldots, snp_l^2\}$$

$$f(\mathbf{a}) = ||\mathbf{y} - \mathbf{X}\mathbf{a}||_2^2 + \lambda \sum_{l=1}^{L} w_l ||\mathbf{a}_l||_2$$

Vonou et al, NeuroImage 2010; Silver et al, NeuroImage, 2012; Zhu et al, 2017; …

Group-wise penalization

Reduced-rank regression proposed by Silver et al, 2012:

Imaging features

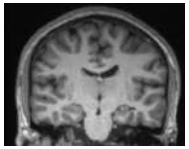
genetic data

$$f(\mathbf{a}, \mathbf{b}) = tr\{(\mathbf{Y} - \mathbf{Xab})(\mathbf{Y} - \mathbf{Xab})^T\} + \lambda \sum_{l=1}^{L} w_l ||\mathbf{a}_l||_2$$

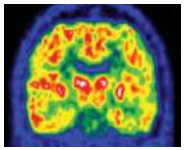
Mapping from genetics to latent space

Rank	KEGG pathway name	π^{path}	Size (# SNPs)	Lasso selected genes in pathway[1]	Known AD genes[2] in pathway
1.	Chemokine signaling pathway	0.261	2769	*PRKCB PIK3R3 PIK3CG ADCY8 ADCY2 ITK GNAI1 XCL1 GNG2* GRK5	*CCR2 IL8*
2.	Jak stat signaling pathway	0.234	1311	*PIK3R3 PIK3CG IL2RA*	
3.	Tight junction	0.227	3332	*PRKCB PRKCA YES1 ACTN1 GNAI1 CTNNA2*	
4.	Insulin signaling pathway	0.218	1517	*PIK3R3 PIK3CG HK2 G6PC ACACA*	
5.	Leukocyte transendothelial migration	0.213	2289	*PRKCB PIK3R3 PRKCA PIK3CG ACTN1 ITK GNAI1 CTNNA2*	
6.	Leishmania infection	0.204	620	*CR1 PRKCB*	*CR1*
7.	Calcium signaling pathway	0.202	5111	*PRKCB PRKCA ADCY8 ADCY2 MYLK ATP2B2 RYR2 SLC8A1*	

Generative representation of multimodal data



X_1

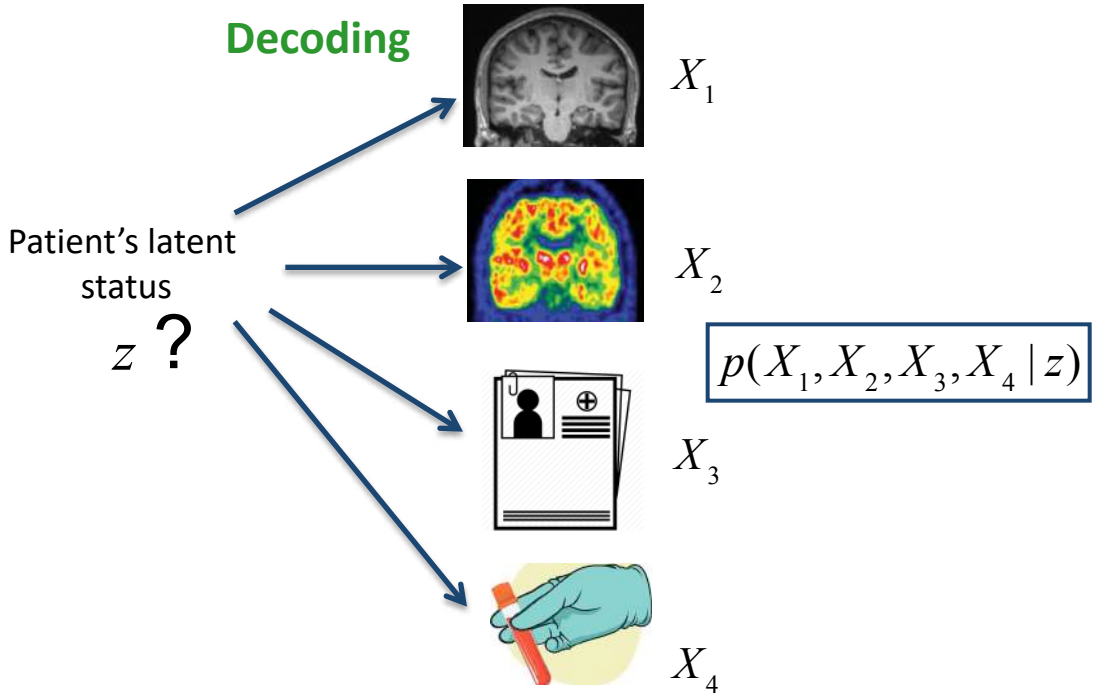


X_2

X_3

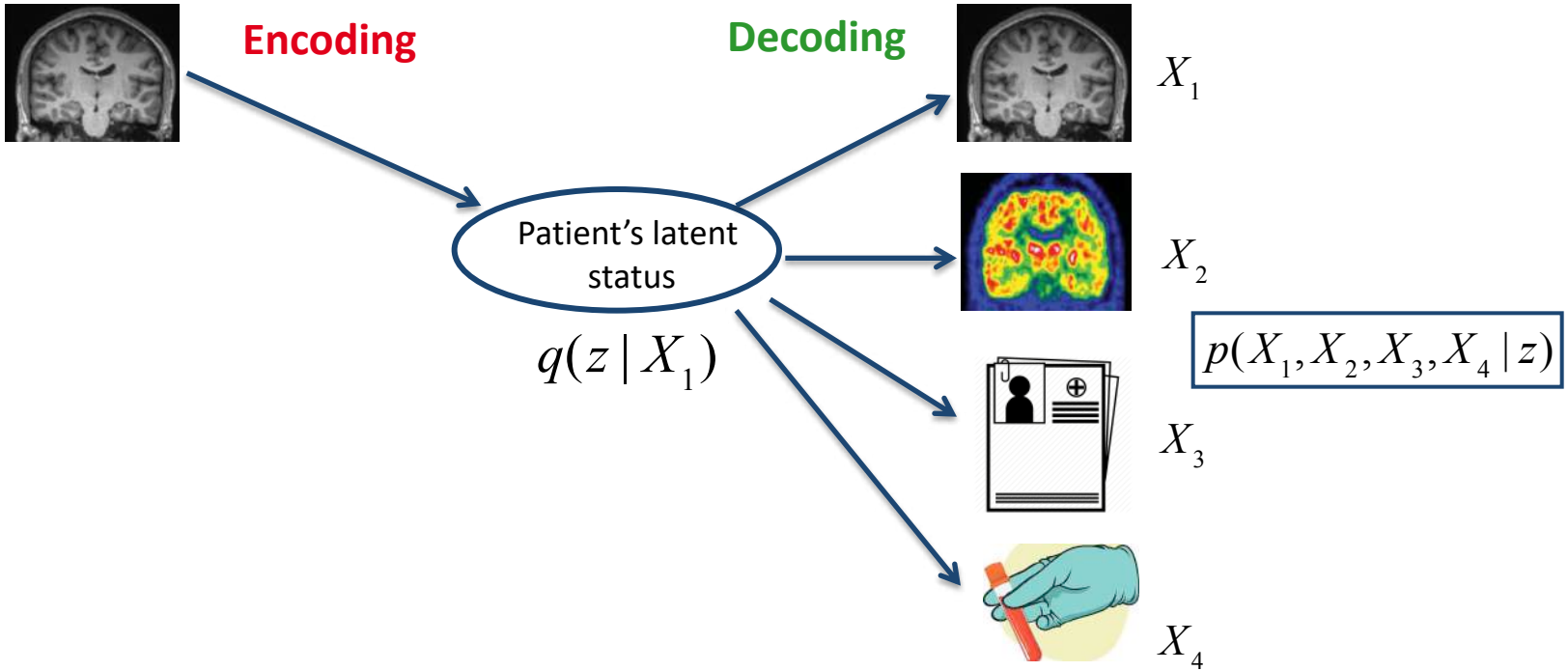
X_4

Generative representation of multimodal data



Decoding: data reconstruction from the latent representation

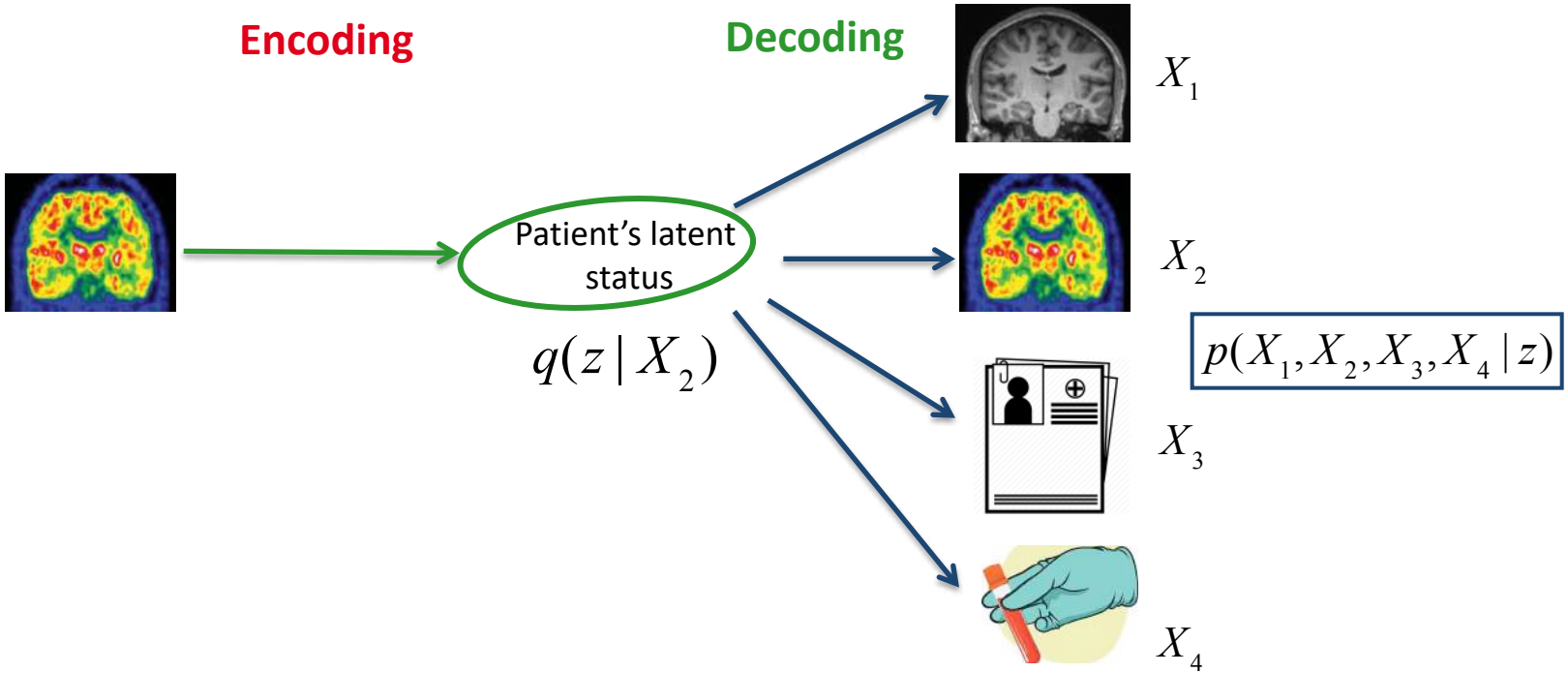
Generative representation of multimodal data



Decoding: data reconstruction from the latent representation

Encoding: latent representation from the data

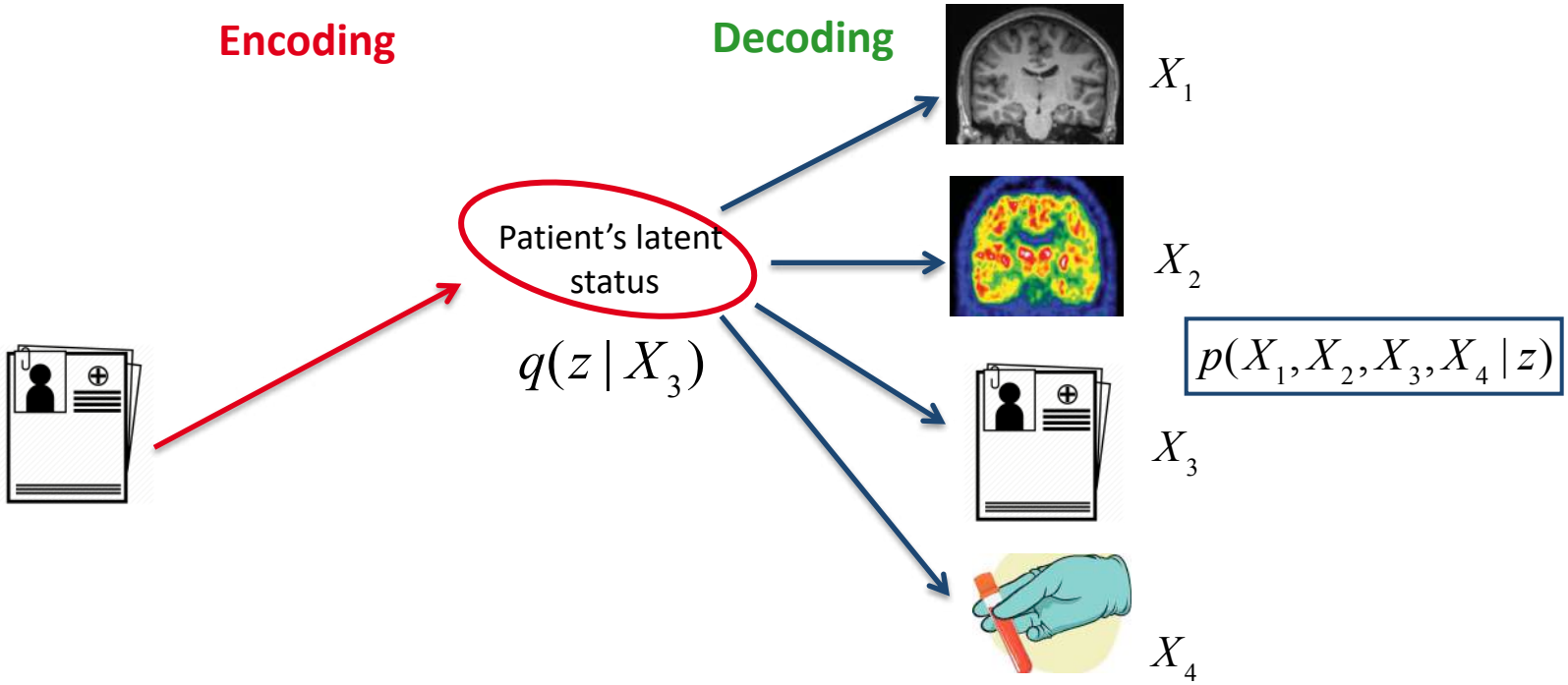
Generative representation of multimodal data



Decoding: data reconstruction from the latent representation

Encoding: latent representation from the data

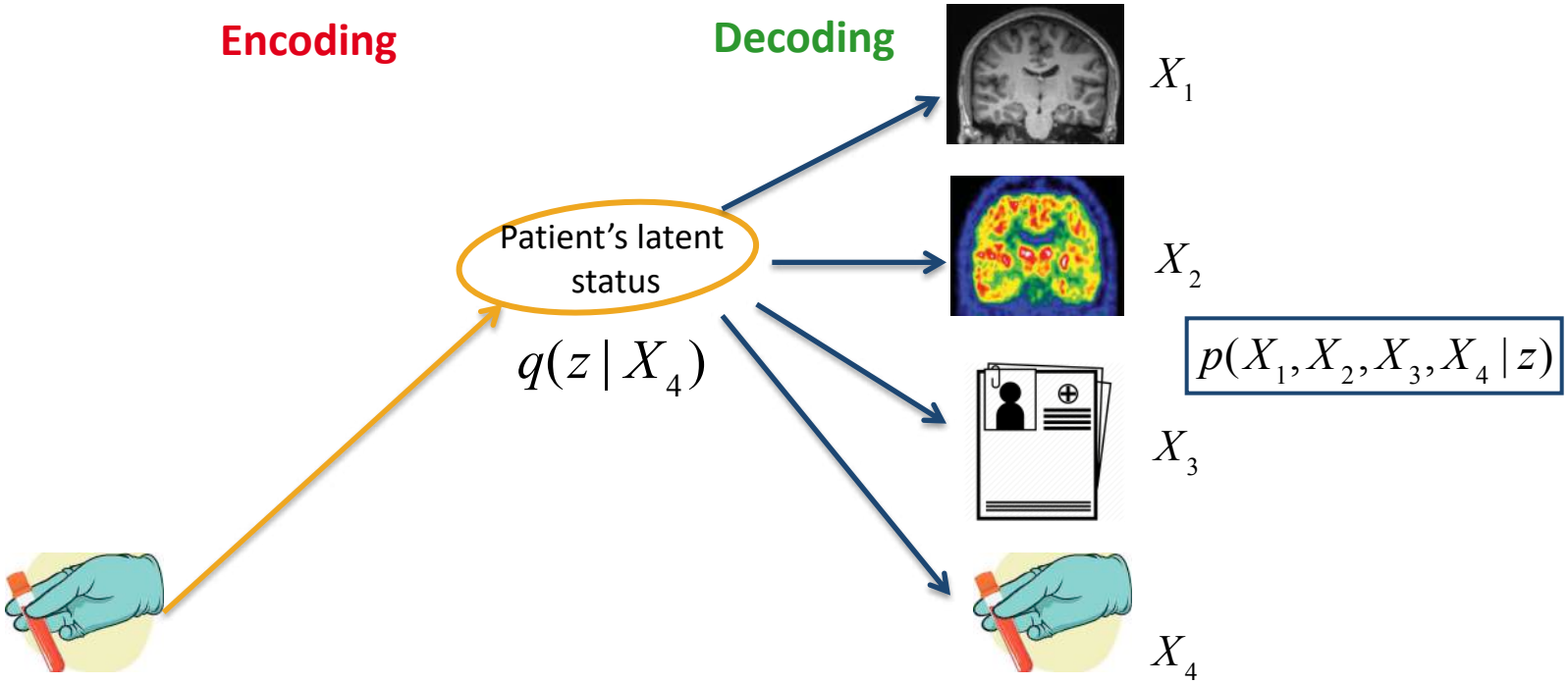
Generative representation of multimodal data



Decoding: data reconstruction from the latent representation

Encoding: latent representation from the data

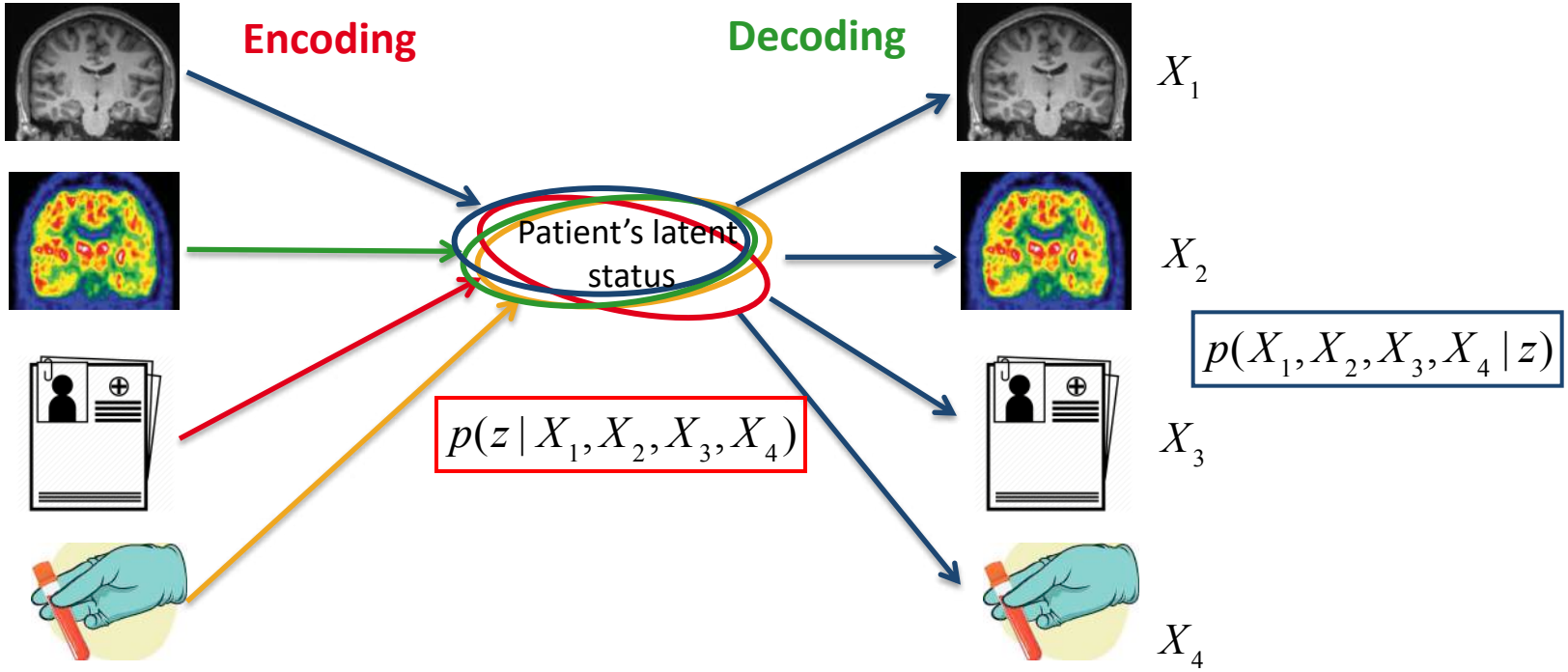
Generative representation of multimodal data



Decoding: data reconstruction from the latent representation

Encoding: latent representation from the data

Generative representation of multimodal data



Decoding: data reconstruction from the latent representation

Encoding: latent representation from the data

Latent variable models via Variational Autoencoders

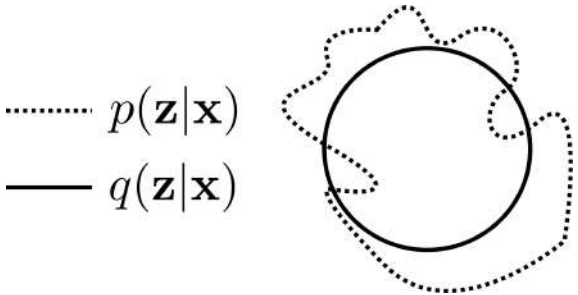
Kingma &Welling, 2014; Rezende et al. 2014

$\mathbf{z} \longrightarrow \mathbf{x}$

Posterior $p(\mathbf{z}|\mathbf{x})$ $p(\mathbf{x}|\mathbf{z})$ Likelihood

$$p(\mathbf{z}|\mathbf{x}) = \int_{\mathbf{z}} p(\mathbf{x}|\mathbf{z})p(\mathbf{z})d\mathbf{z}$$

Difficult to compute



Idea: find a "close enough" and simple approximation $q(\mathbf{z}|\mathbf{x})$

Latent variable models via Variational Autoencoders

Kingma &Welling, 2014; Rezende et al. 2014

$$D_{KL}[q(\mathbf{z}|\mathbf{x})||p(\mathbf{z}|\mathbf{x})] = \mathbf{E}_{\mathbf{z}\sim q}\log[q(\mathbf{z}|x)] - \mathbf{E}_{\mathbf{z}\sim q}\log[p(\mathbf{z}|x)]$$

C. M. Bishop, Pattern Recognition and Machine Learning, Ch.10, Ed. 2006

Latent variable models via Variational Autoencoders

Kingma &Welling, 2014; Rezende et al. 2014

$$D_{KL}[q(\mathbf{z}|\mathbf{x})||p(\mathbf{z}|\mathbf{x})] = \mathbf{E}_{\mathbf{z}\sim q}\log[q(\mathbf{z}|x)] - \mathbf{E}_{\mathbf{z}\sim q}\log[p(\mathbf{z}|x)]$$

Evidence lower bound (ELBO)

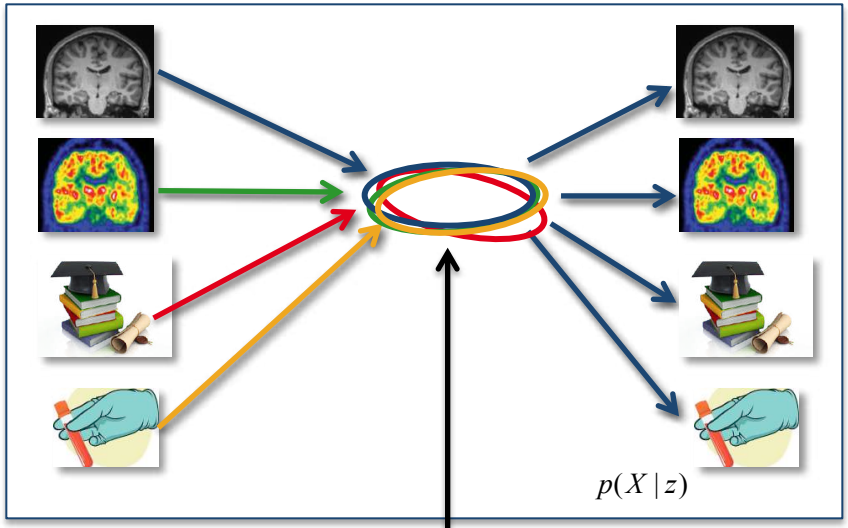
$$\mathcal{L} = \mathbf{E}_{\mathbf{z}\sim q}\log[p(\mathbf{x}|\mathbf{z})] - D_{KL}[q(\mathbf{z}|\mathbf{x})||p(\mathbf{z})]$$

reconstruction

regularization

C. M. Bishop, Pattern Recognition and Machine Learning, Ch.10, Ed. 2006

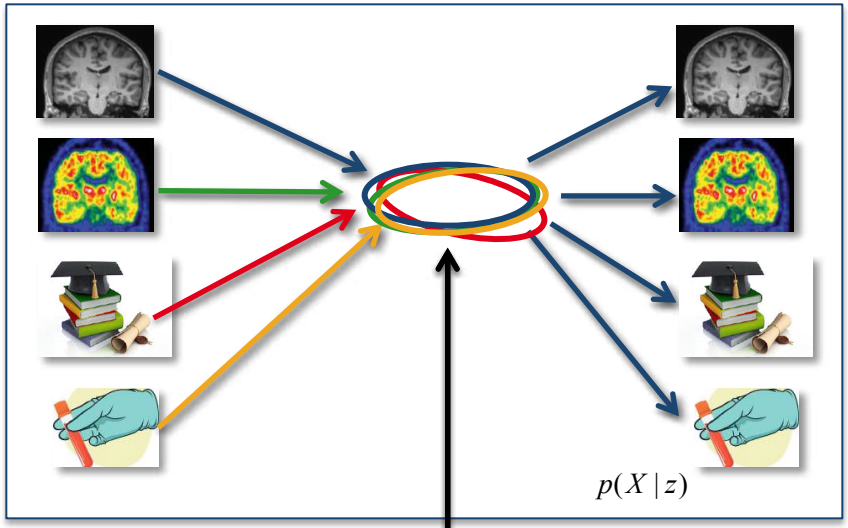
Generative representation of multimodal data



minimize

$$dist\left(q(z \mid X_c), p(z \mid X_1, X_2, ..., X_c)\right)$$

Generative representation of multimodal data



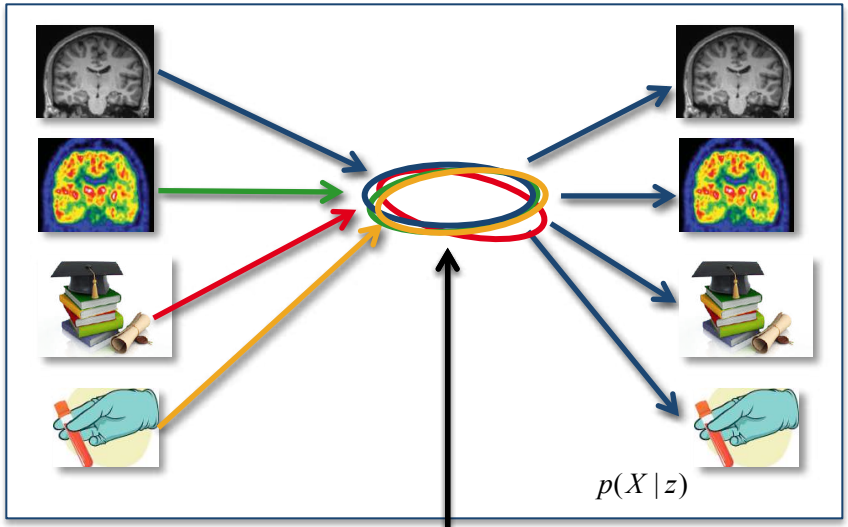
minimize

$$dist\left(q(z \mid X_c), p(z \mid X_1, X_2, ..., X_c)\right)$$

Evidence Lower bound (ELBO)

$$\frac{1}{C}\sum_{c=1}^{C} E_{q(z|X_c)}[\sum_i \ln p(X_i \mid z)] - DKL\left(q(z \mid X_c) \,\|\, p(z)\right)$$

Generative representation of multimodal data



minimize

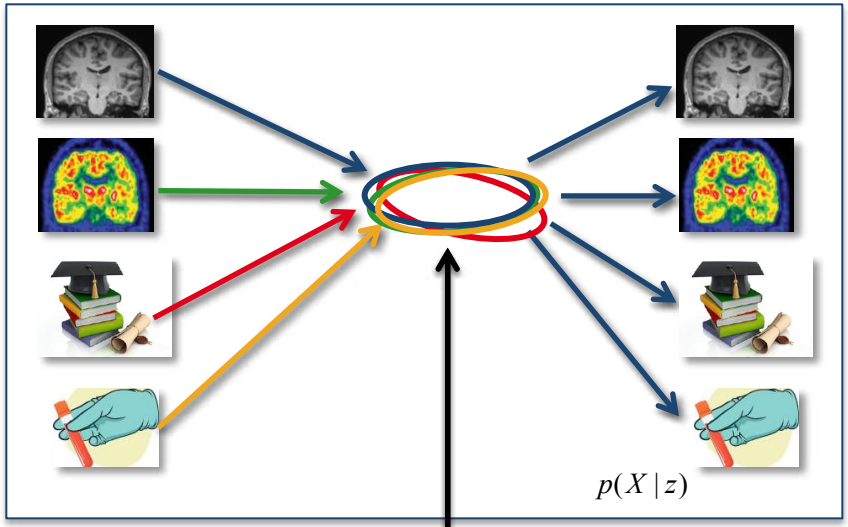
$$dist\left(q(z \mid X_c), p(z \mid X_1, X_2, ..., X_c)\right)$$

Evidence Lower bound (ELBO)

$$\frac{1}{C}\sum_{c=1}^{C} E_{q(z|X_c)}[\sum_i \ln p(X_i \mid z)] - DKL\left(q(z \mid X_c) \,\|\, p(z)\right)$$

Encoding for given channel

Generative representation of multimodal data



minimize

$$dist\left(q(z \mid X_c), p(z \mid X_1, X_2, ..., X_c)\right)$$

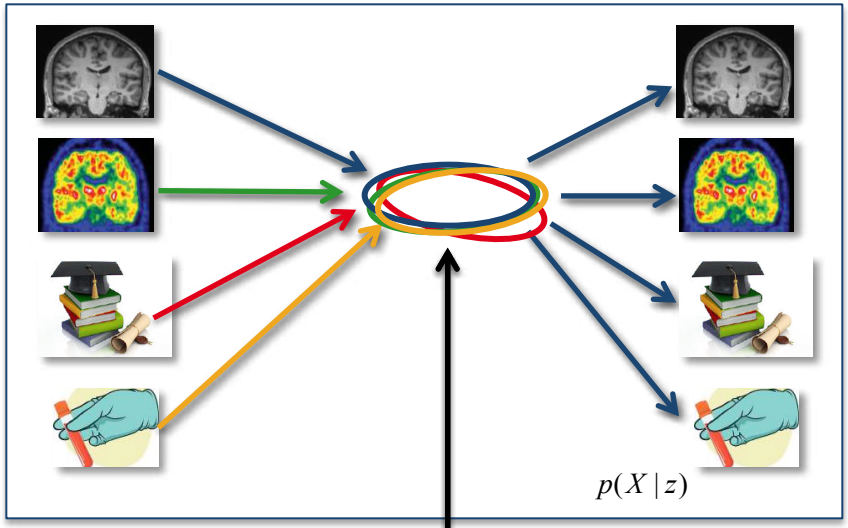
Evidence Lower bound (ELBO)

$$\frac{1}{C}\sum_{c=1}^{C} E_{q(z|X_c)}\left[\sum_i \ln p(X_i \mid z)\right] - DKL\left(q(z \mid X_c) \,\|\, p(z)\right)$$

Encoding for given channel

Reconstruction of all channels

Generative representation of multimodal data



minimize

$$dist\left(q(z \mid X_c), p(z \mid X_1, X_2, ..., X_c)\right)$$

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$$\frac{1}{C}\sum_{c=1}^{C} E_{q(z|X_c)}\left[\sum_i \ln p(X_i \mid z)\right] - DKL\left(q(z \mid X_c) \,\|\, p(z)\right)$$

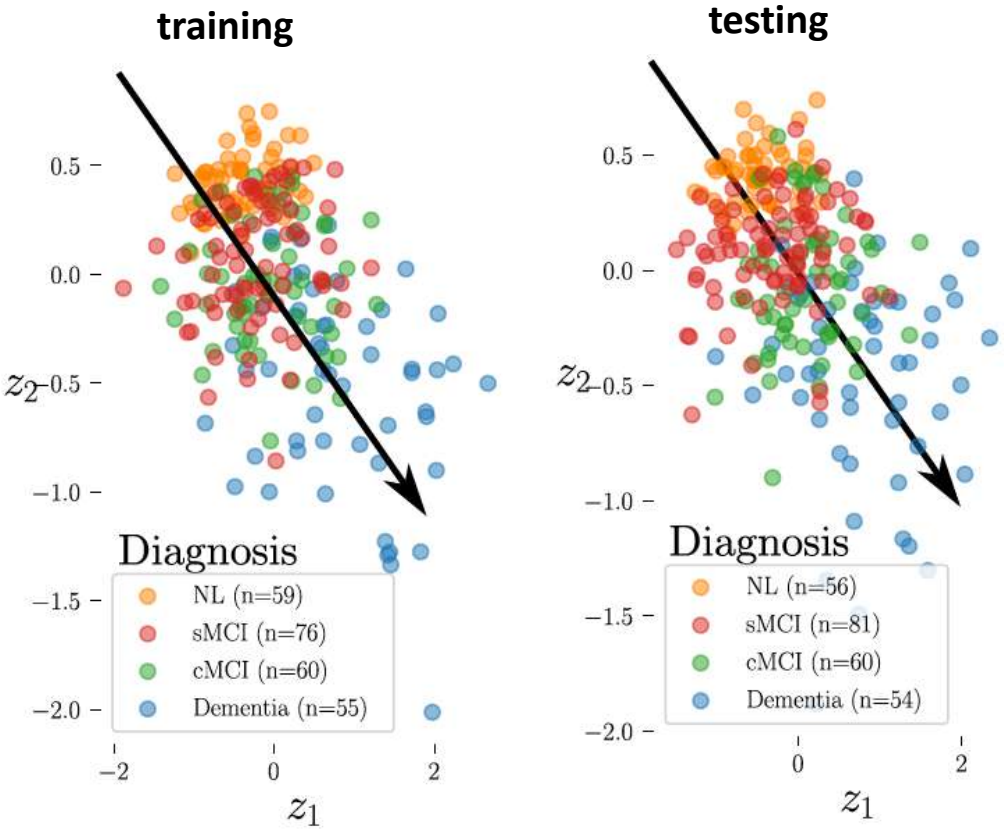
Encoding for given channel

Reconstruction of all channels

Regularization: sparsity inducing prior

[Kingma et al, NIPS, 2015; Molchanov et al, ICML 2017]

Prediction from latent space

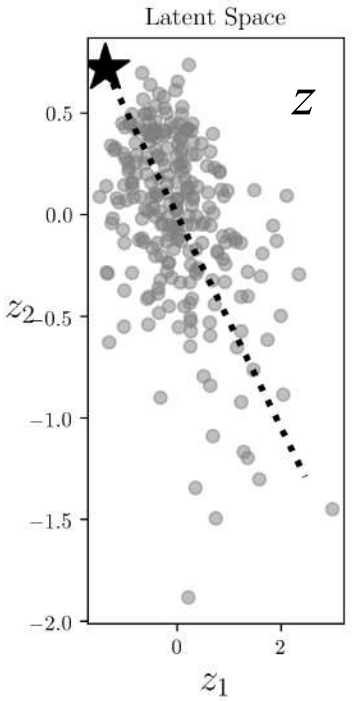


Joint modeling of

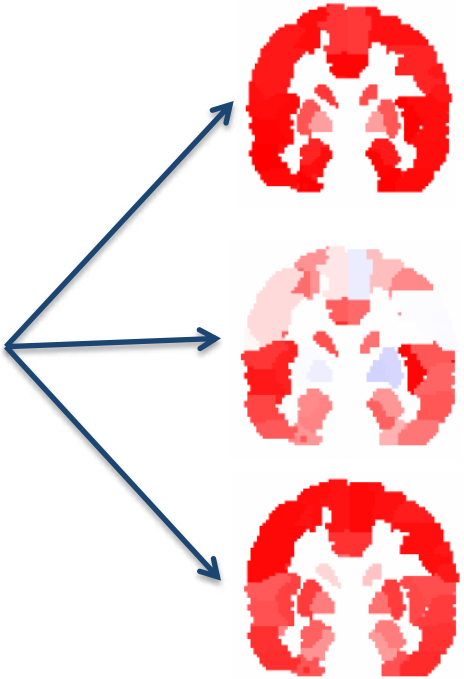
- Brain imaging:
  - Structural (T1 MRI)
  - Molecular (FDG-PET + Amy-PET)
- Socio-demographic factors
- Clinical scores

	Accuracy (SD)
Cognitively Healthy	**0.89 (0.03)**
Stable Mild Cognitive Impairment (sMCI)	**0.75 (0.02)**
MCI converting to Dementia (cMCI)	**0.70 (0.05)**
Dementia	**0.94 (0.05)**

Generation from latent space



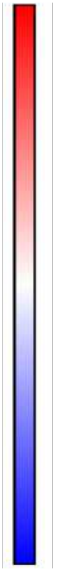
Patient's latent status
from cognitive scores only



Atrophy abnormality (MRI)

Metabolism abnormality (FDG)

Amyloid abnormality (AV45)

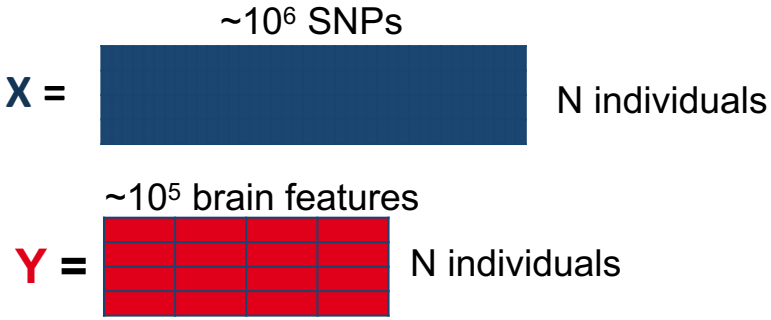


- Improved interpretability
- Multi-channel: working with missing data/data imputation
- Simulations for clinical trials

An example of PLS in imaging-genetics

Multivariate Association studies

Maximizing the joint relationship between genetic variants and brain features



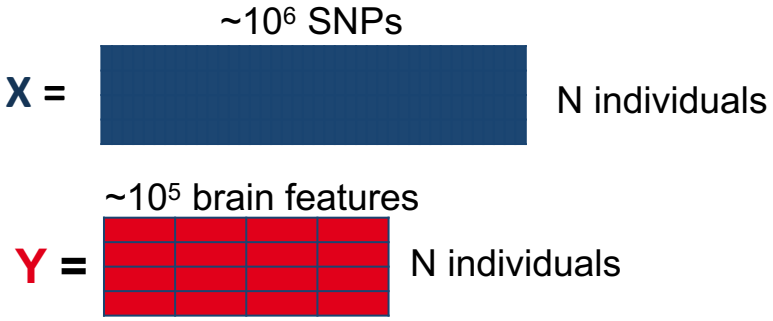
Partial least squares (PLS)

$\max_{p,q} \mathrm{Cov}(X \cdot p, Y \cdot q)$

Liu et al, Front in Neuroinformatics, 2014; Silver et al, NeuroImage 2012; Szymczak et al, Genetic Epidemiology 2009; …

Multivariate Association studies

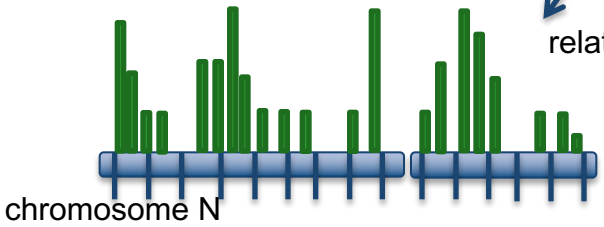
Maximizing the joint relationship between genetic variants and brain features

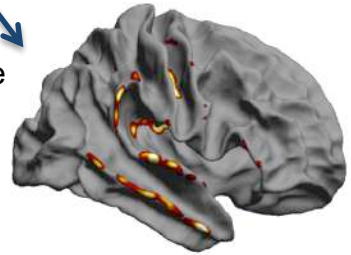


Partial least squares (PLS)

$$\max_{p,q} \mathrm{Cov}(X \cdot p, Y \cdot q)$$

PLS weights
=
relative importance





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Multivariate Association studies

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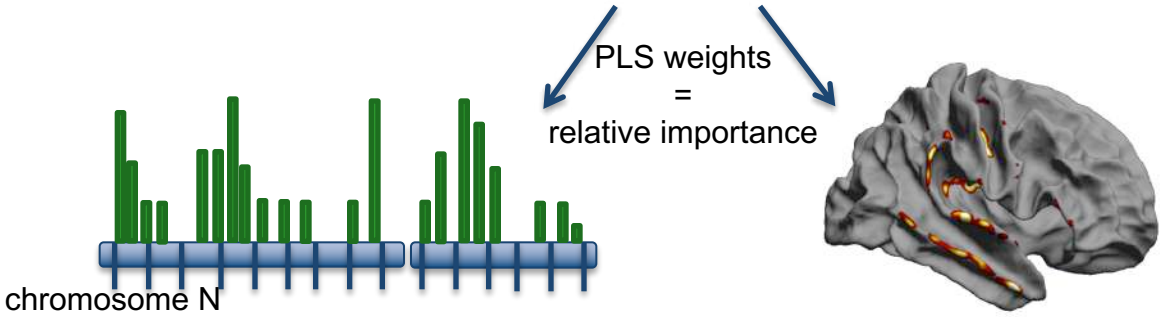


Pros. Overcomes issues of mass univariate analysis
- Avoiding independent **multiple testing**
- Exploring **SNP-SNP interaction** (epistatic effects)

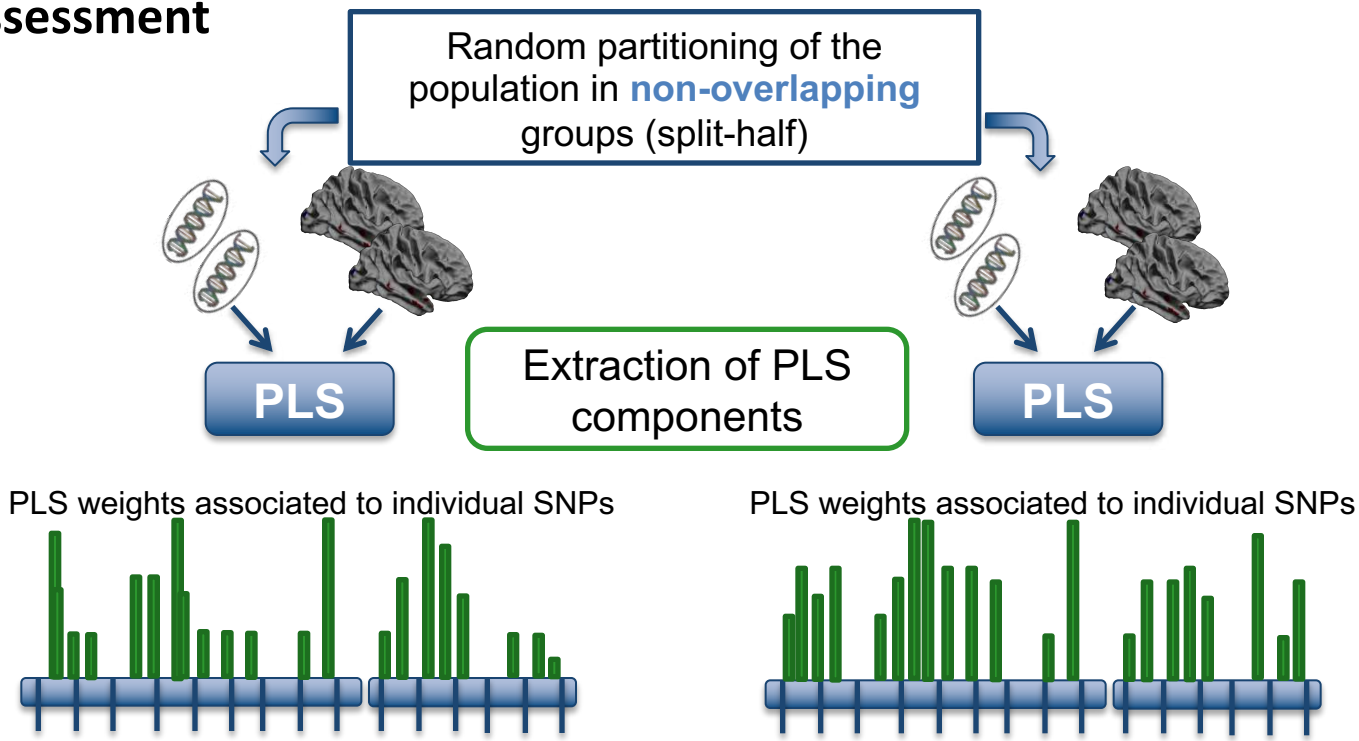
Cons.
- **Overfitting** and reproducibility
- Computational **complexity**

Liu et al, Front in Neuroinformatics, 2014; Silver et al, NeuroImage 2012; Szymczak et al, Genetic Epidemiology 2009; …

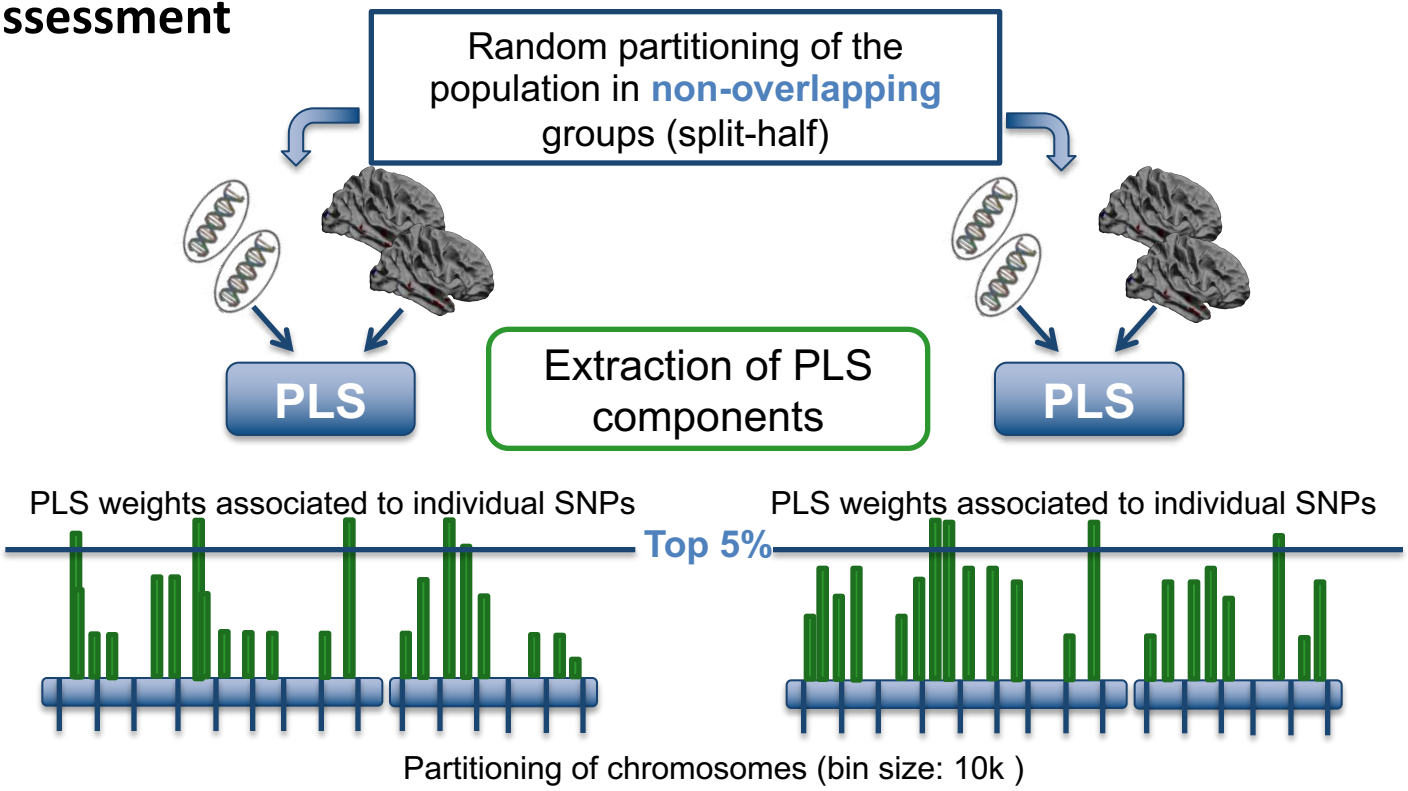
Stability assessment

Random partitioning of the population in **non-overlapping** groups (split-half)

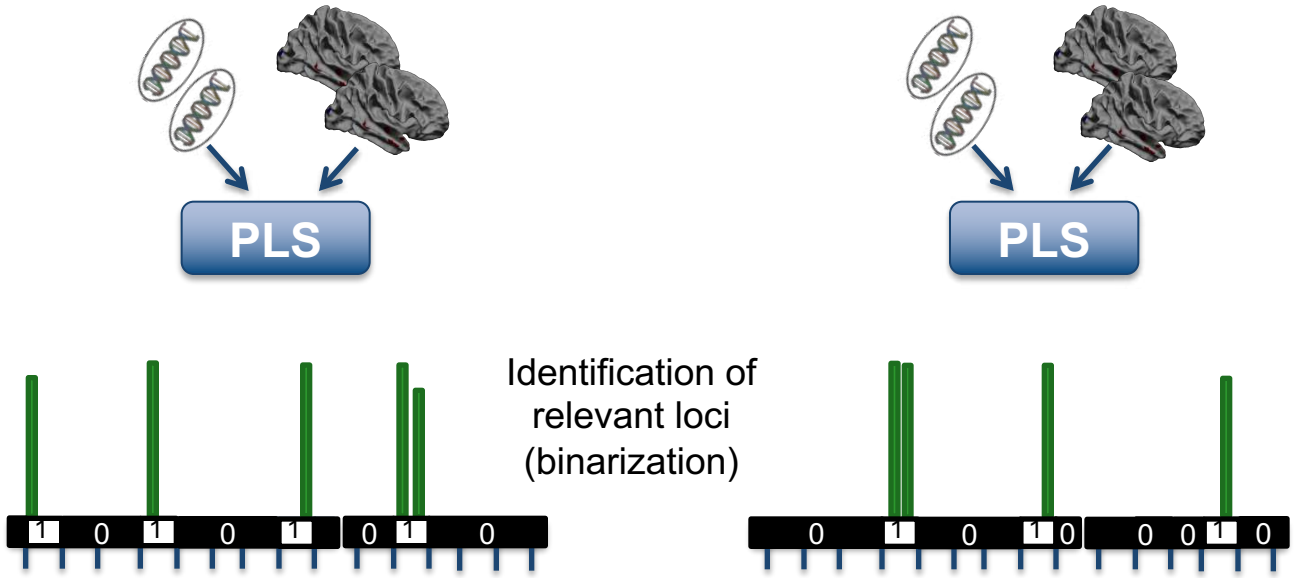
Stability assessment



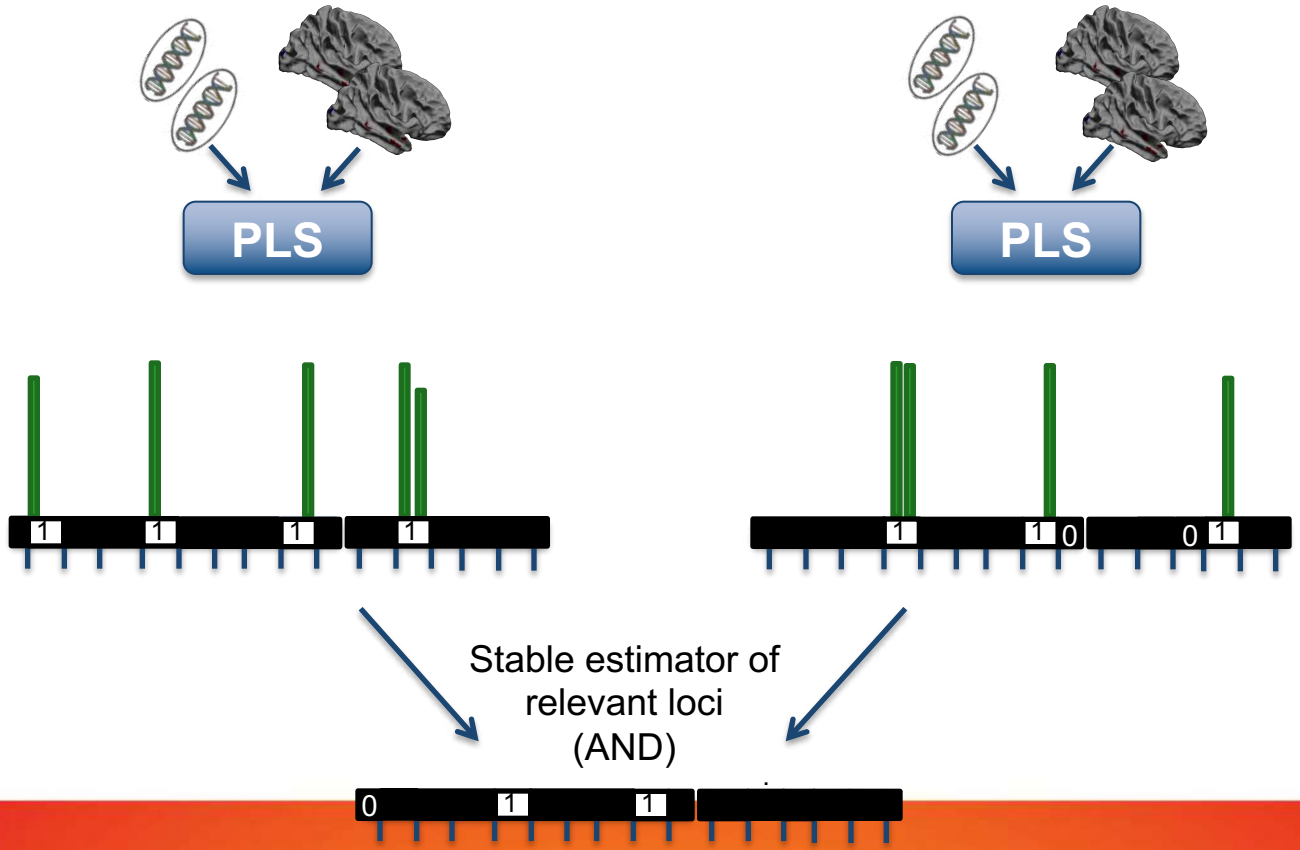
Stability assessment



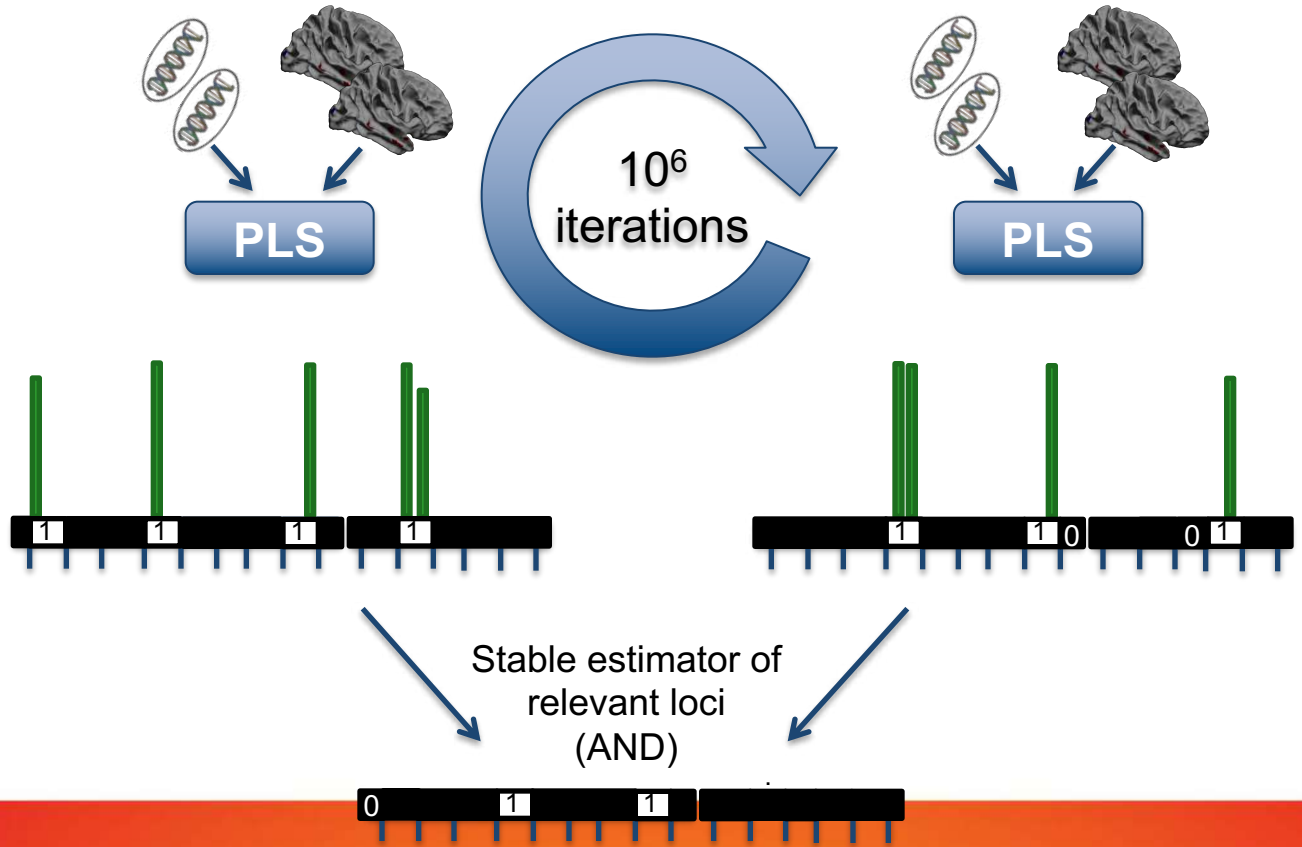
Stability assessment



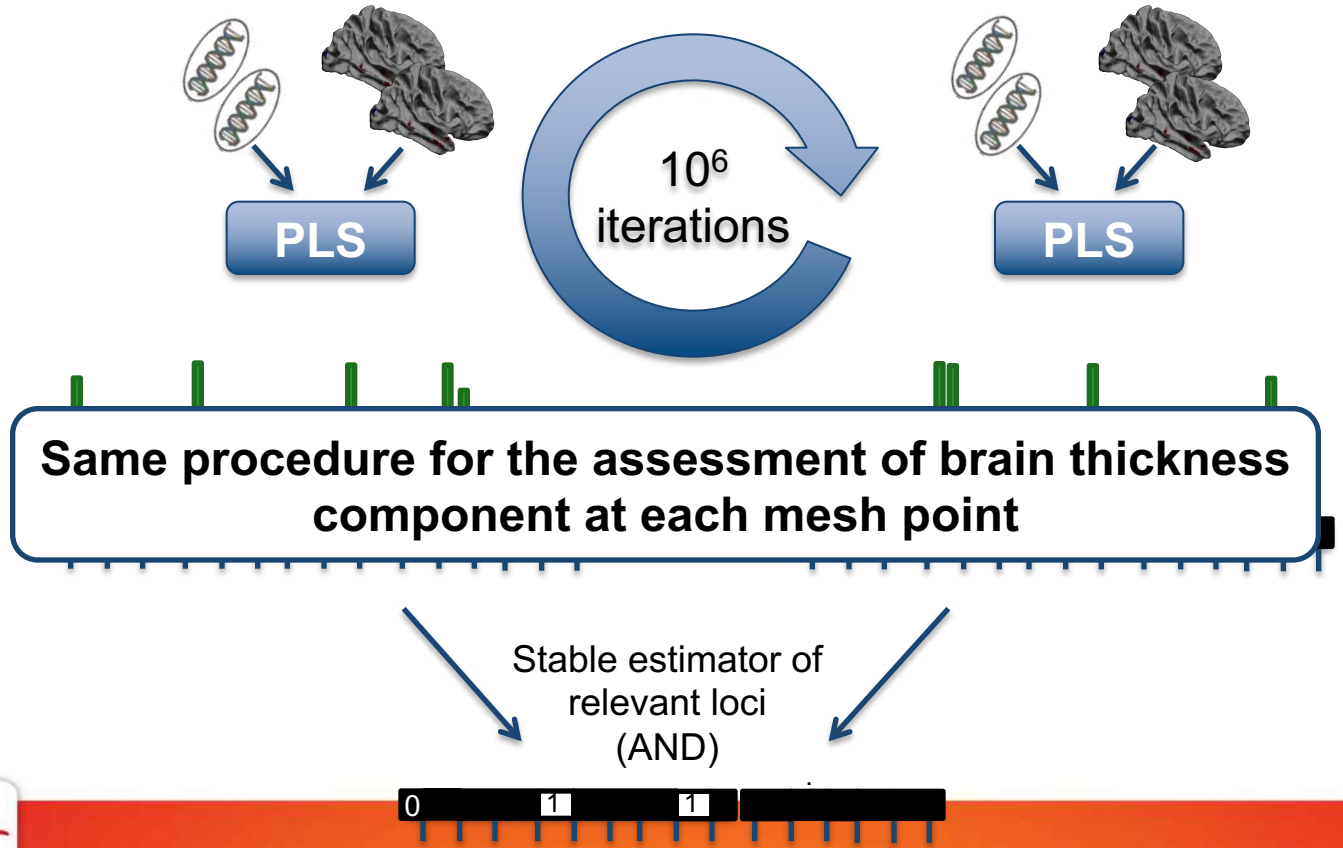
Stability assessment



Stability assessment



Stability assessment



Study cohort

USC University of Southern California

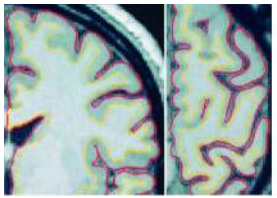

B. Gutman

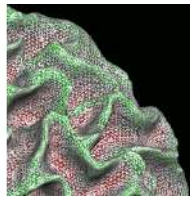

Paul M. Thompson

	Healthy	AD
N	401	238
Age (years)	74.45	74.72
Sex (% females)	49	45
MMSE	29.1	23.2
Apoe4 (% 0/1/2)	72/26/2	31/48/21

ADNI

adni.loni.usc.edu





Phenotype features

- Freesurfer **brain cortical thickness** maps (327,684 mesh points)
- **Radial distance** of hippocampi and amygdalae (27,120 mesh points) [Gutman et al, NeuroImage 2013]

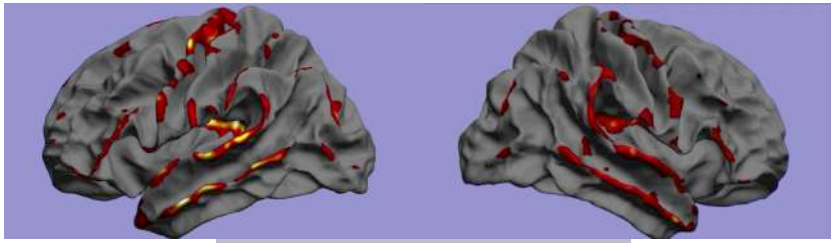
Genotype features

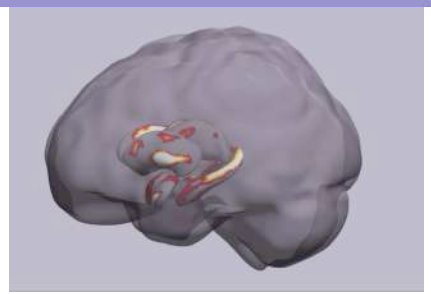
- Individuals' minor allele counts for **1,167,126 SNPs** in chromosomes 1 to 22

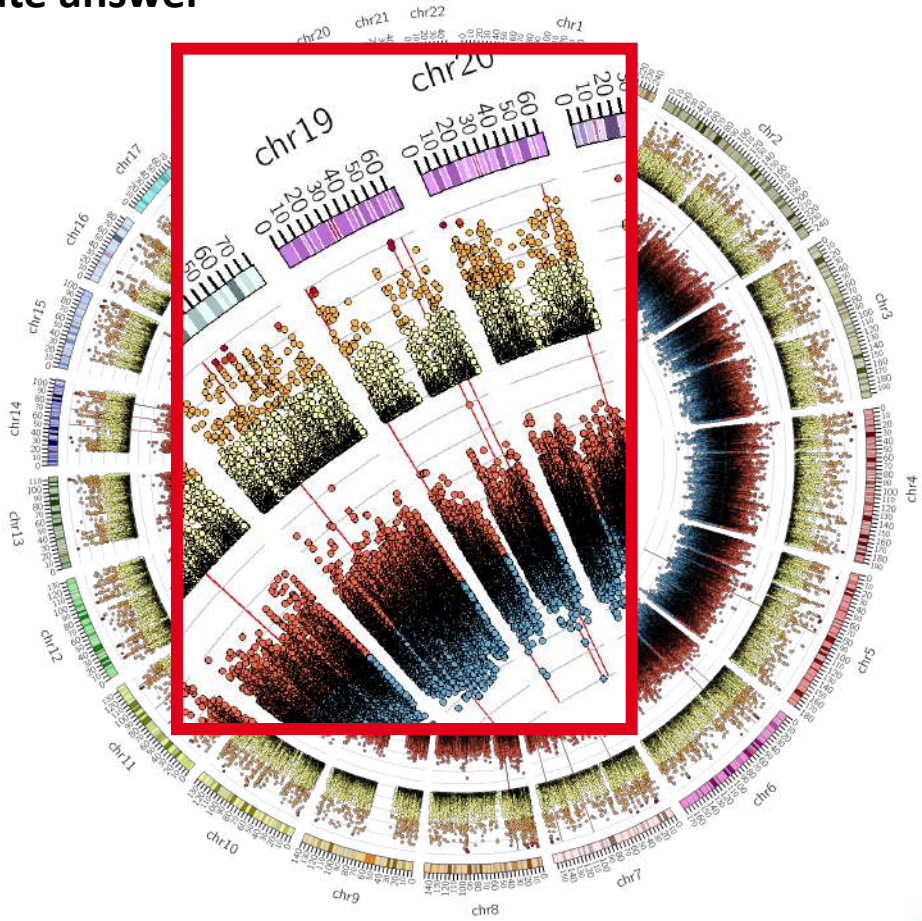
Standard quality control: MAF < 0.01, Genotype Call Rate <95% , Hardy-Weinberg Equilibrium < $1x10^{-6}$.
Imputation to HapMap III reference panel, quality controlled (MAF > 0.01 and R-squared > 0.3)

A. Altmann

A multivariate answer

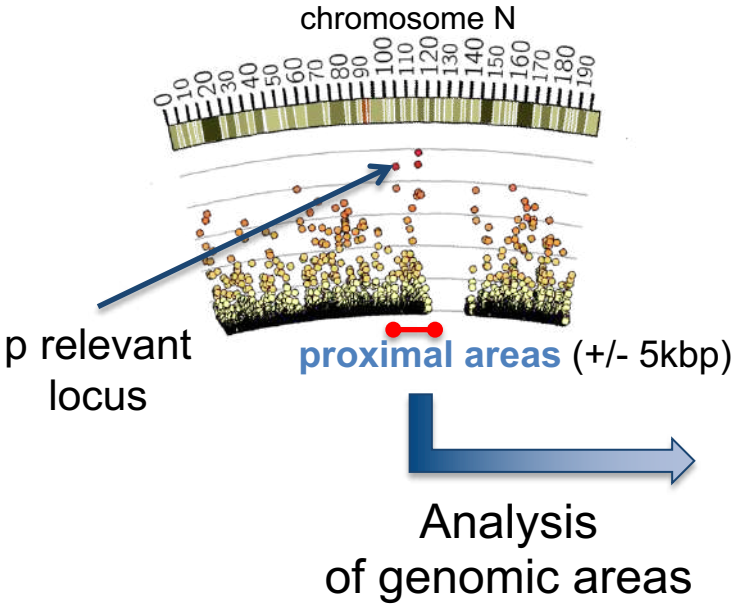






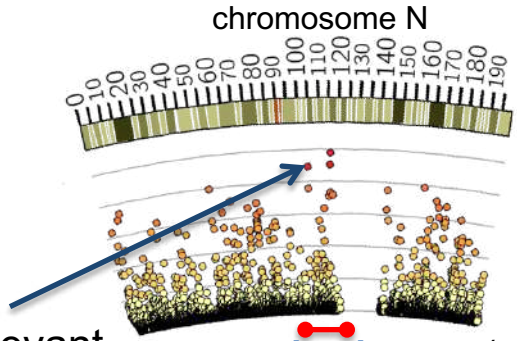
Investigating biological mechanisms through Meta-analysis

PLS statistical result



Investigating biological mechanisms through Meta-analysis

PLS statistical result



p relevant locus

proximal areas (+/- 5kbp)

Analysis of genomic areas

Querying gene annotation databases

McLaren et al. The Ensembl Variant Effect Predictor. Genome Biology, 2016

Investigating biological mechanisms through Meta-analysis

S. Wray

VeIP → 148 SNP-gene combinations

6 tested tissues

hippocampus, whole blood, Adipose subcutaneous, artery tibia, nerve tibial, treated fibroblast

14 Significantly expressed genes

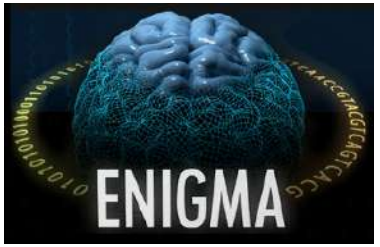
TM2D1 (amyloid-beta binding protein)**,**
IL10RA (increase in hippo in mouse model)**,**
TRIB3
(neuronal cell death, modulates PSEN1 stability, interacts with APP)

	Significance (p-value)	
	training	testing
TM2D1	0.005	0.053
IL10RA	0.107	0.620
TRIB3	0.003	0.003
ZBTB7A	0.036	0.913
LYSMD4	0.000	0.206
CRYL1	0.621	0.118
FAM135B	0.000	0.559
IP6K3	0.000	0.465
ITGA1	0.099	0.731
KIN	0.001	0.206
LAMC1	0.002	0.062
LINC00941	0.000	0.690
RBPMS2	0.000	0.215
RP11-181K3.4	0.002	0.053

Imaging-genetics:
multimodal analysis of heterogeneous data

- Multivariate Modeling in Imaging Genetics
- **Online learning for multicentric studies**
- Genetic analysis through disease progression modeling

Large multicentric clinical studies



Data for ~100’000 individuals

Big Data in medicine

Single hospital: 100s – 1’000s patients

Data from many hospitals needed

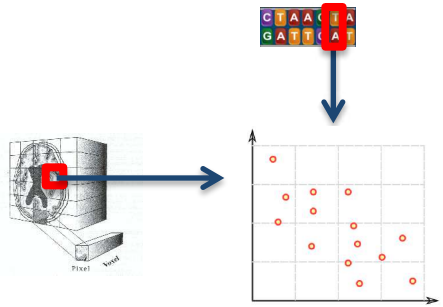
Access to multiple centers data
falls into General Data Protection Regulation (GDPR):
Privacy, confidentiality, security, ...

Data cannot be gathered in a single centre!
Standard learning algorithms cannot be used in multicentric data

Big Data in medicine

Circumventing the problem of data access

Federated-analysis (or meta-analysis)



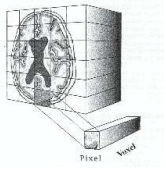
Is the association significant?

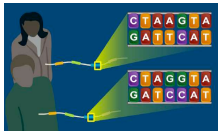
Hospital	1	2	3	4	…
Answer	yes	yes	no	yes	…

→ Meta-answer: yes

- No data sharing
- Ok for standard statistical testing (p-values, effect size)
- No complex modeling possible

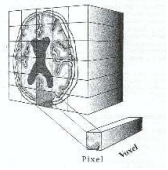
Advanced Data Science through federated learning

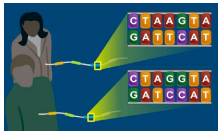




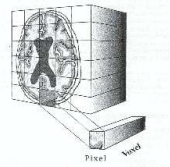
C_2

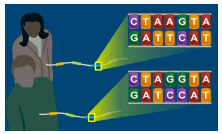
C_3



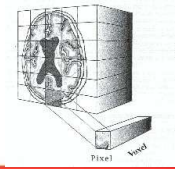


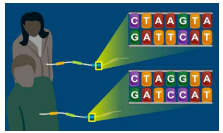
C_1



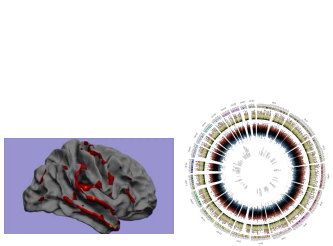


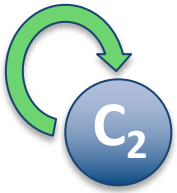
C_N

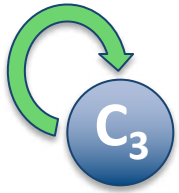


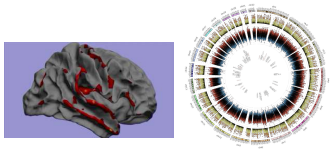
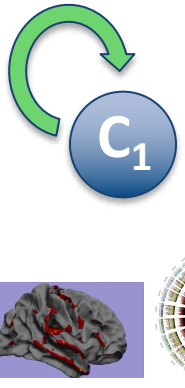
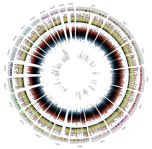


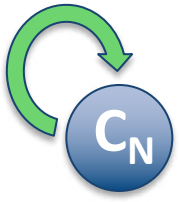
Advanced Data Science through federated learning

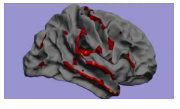
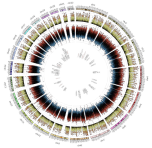






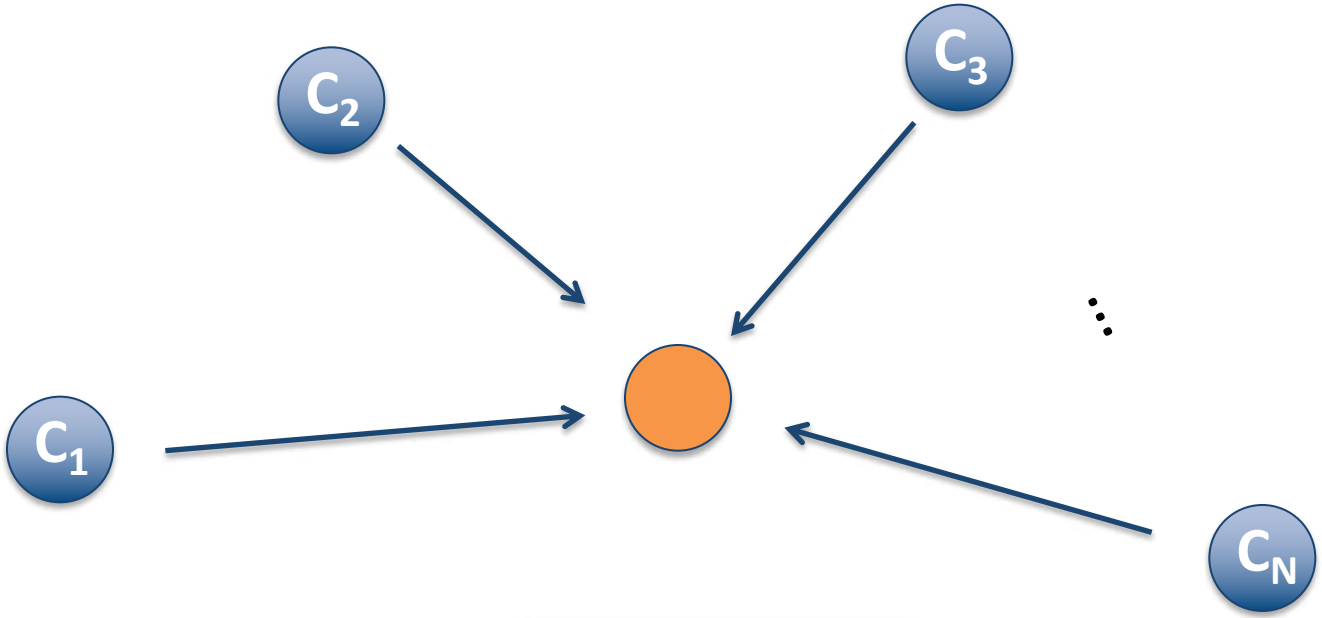






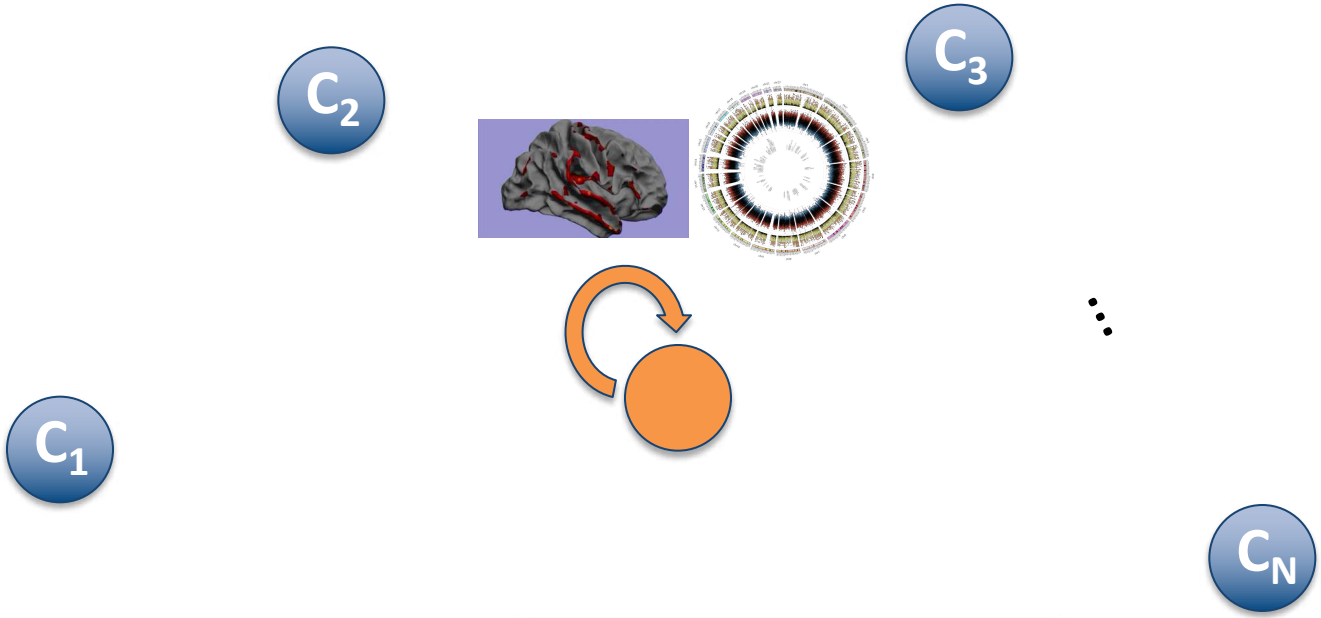



Parameters are computed locally

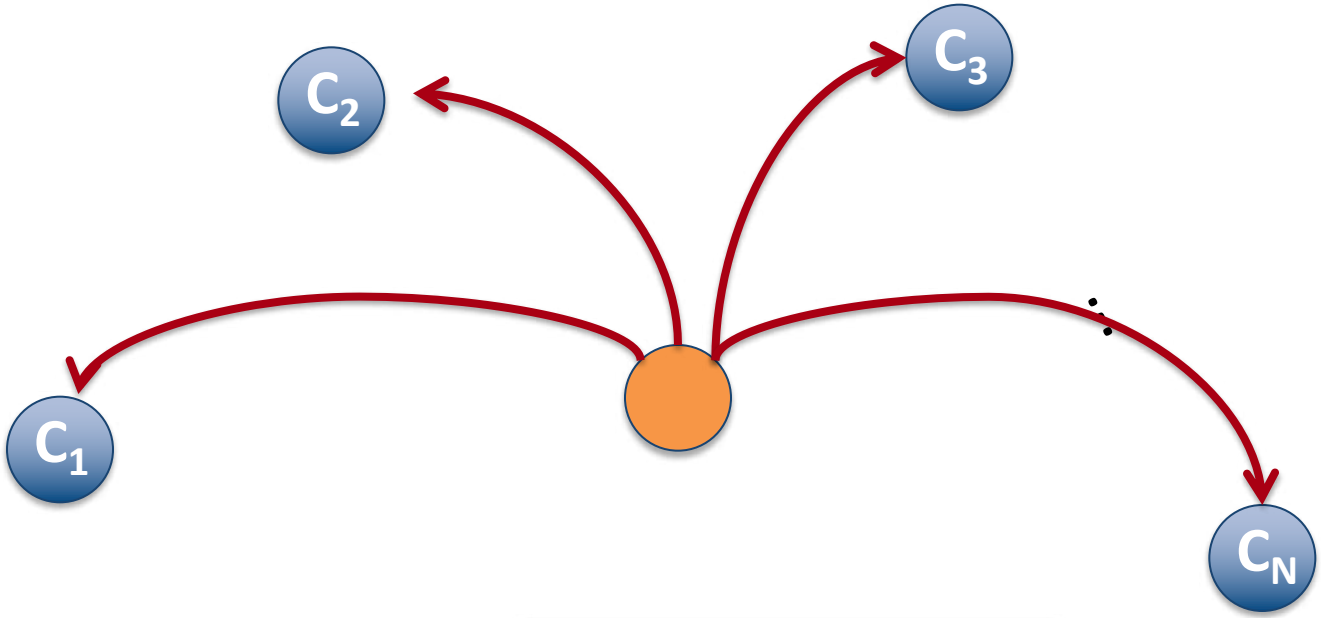
Advanced Data Science through federated learning



Advanced Data Science through federated learning

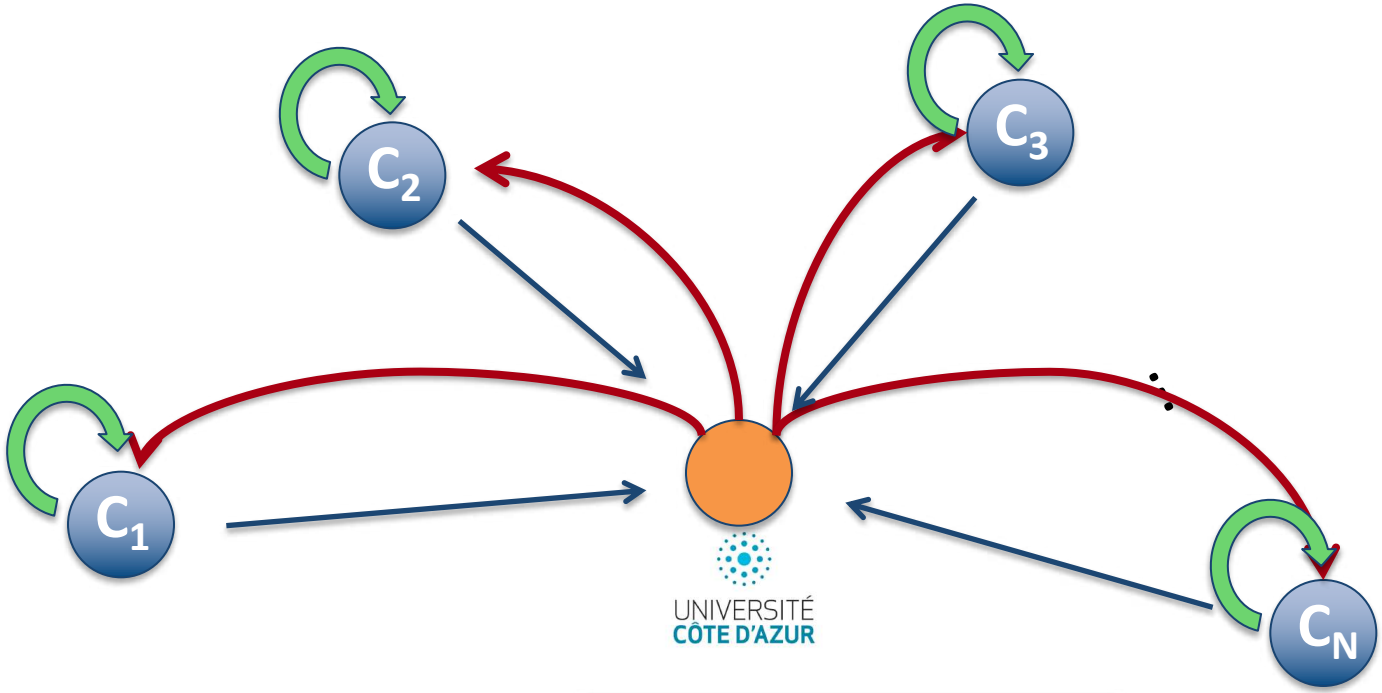


Advanced Data Science through federated learning



The federated model is shared

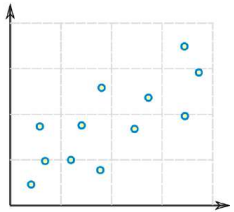
Advanced Data Science through federated learning



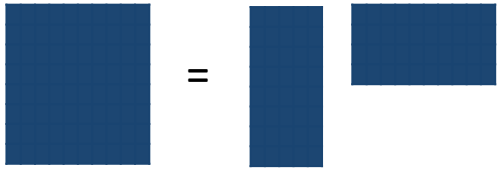
The procedure is iterated

Federated analysis toolkit

A methodology for distributed



Linear modeling



Matrix factorization

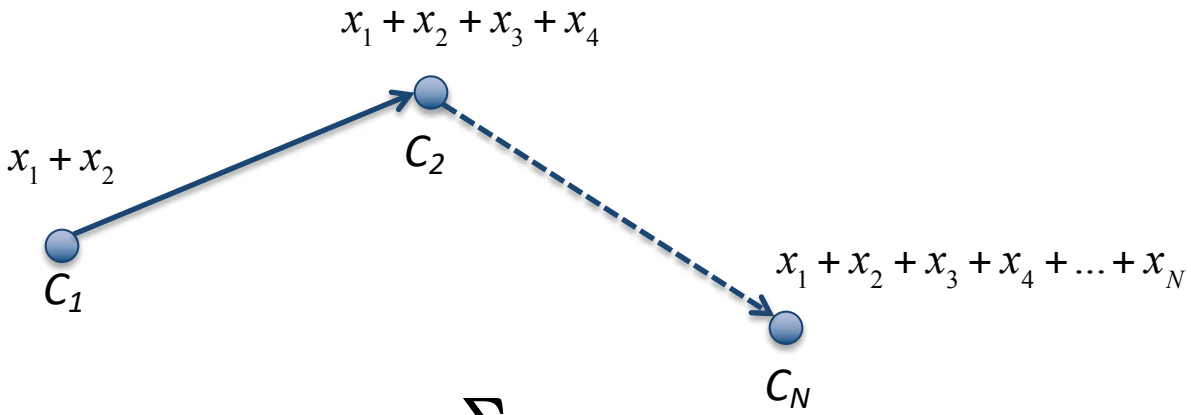
Allows a federated framework for several key statistical operations:
Data standardization, accounting for covariates, dimensionality reduction, ...

Standard statistical pipeline in multivariate analysis

- Data standardization
- Confounding effect correction
- Multivariate analysis

Federated moment estimation: Mean

$$\frac{x-\mu}{\sigma}$$



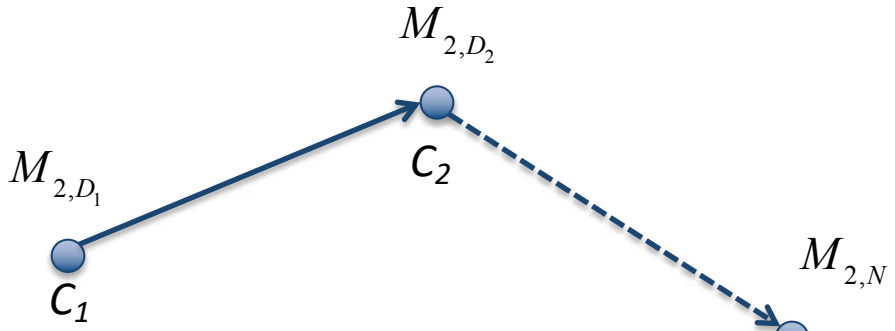
$$\mu = \frac{\sum x_i}{N}$$

Federated moment estimation: SD

$$\frac{x-\mu}{\sigma}$$

$$M_{2,n} = M_{2,n-1} + (x_n - \bar{x}_{n-1})(x_n - \bar{x}_n)$$

$$\sigma^2 = \frac{\sum (x_i - \mu)^2}{N-1}$$

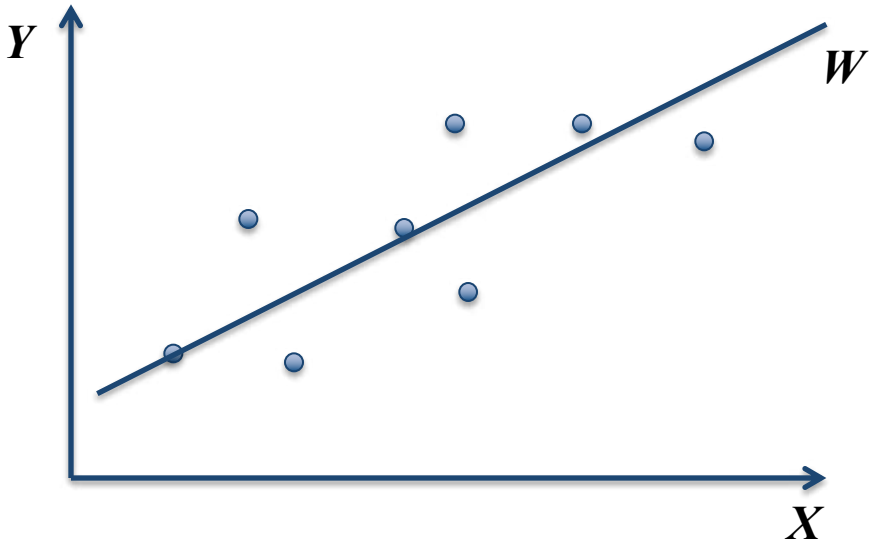


$$\sigma^2 = \frac{M_{2,N}}{N}$$

Federated linear modeling

$$L(Y \mid X, W) = \left\| Y - XW^T \right\|^2$$

$$W = (X^T X)^{-1} X^T Y$$



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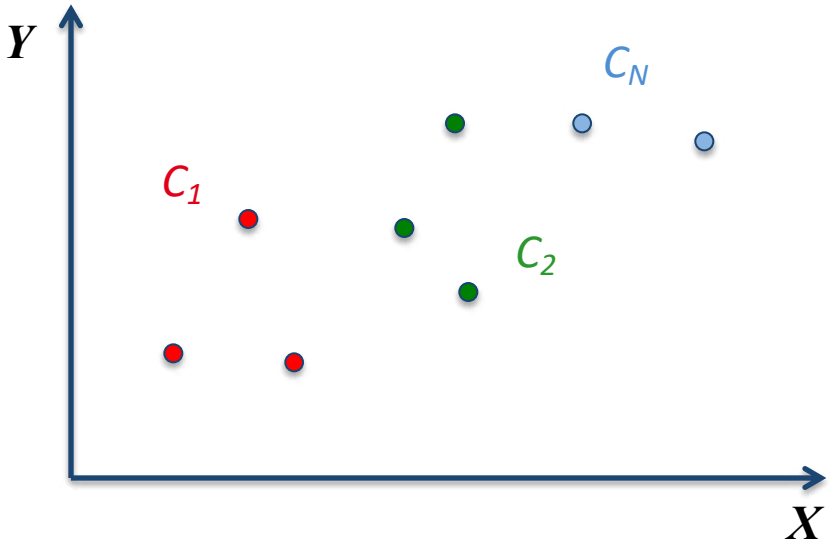

Federated linear modeling

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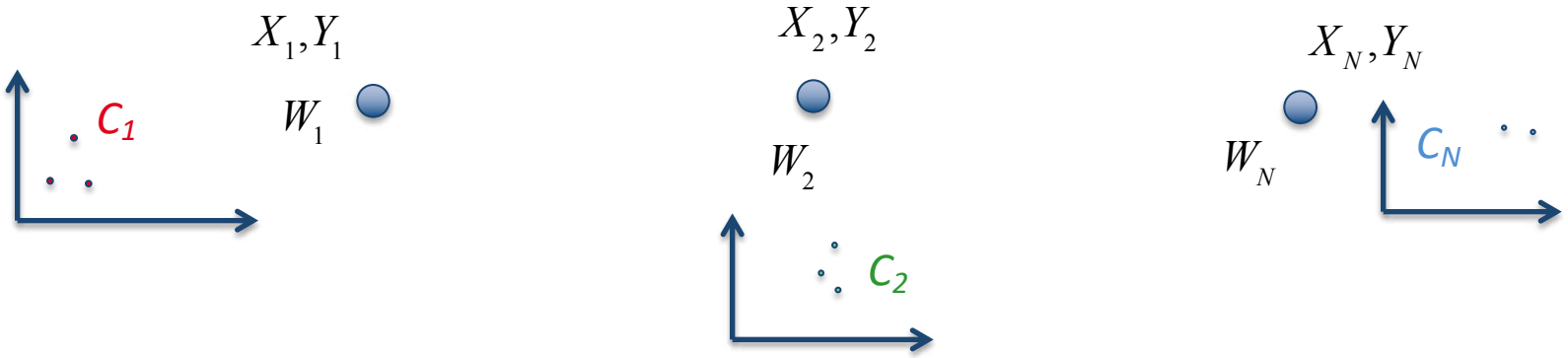
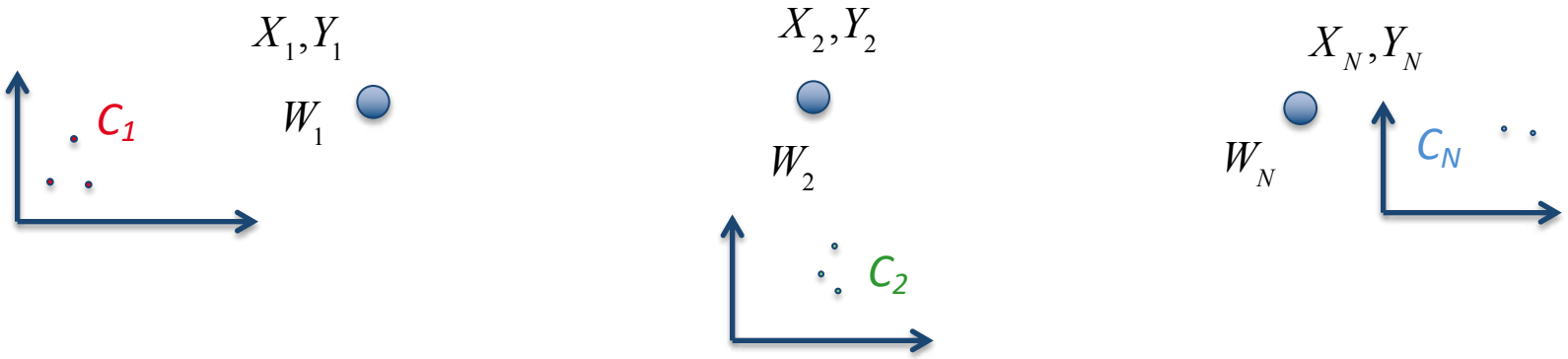


Federated linear modeling

$$L(Y \mid X, W) = \left\| Y - XW^T \right\|^2$$

$$L(Y_c \mid X_c, W_c) = \left\| Y_c - X_c W_c^T \right\|^2$$

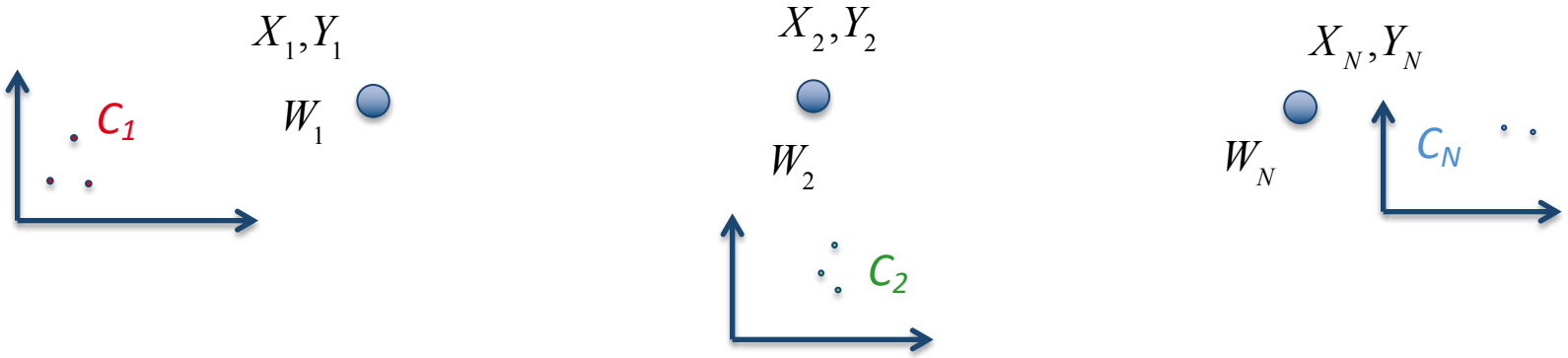


Federated linear modeling

$$L(Y \mid X, W) = \left\| Y - XW^T \right\|^2$$

$$L(Y_c \mid X_c, W_c) = \left\| Y_c - X_c W_c^T \right\|^2$$

$$W_c = W$$



Alternating direction method of multipliers

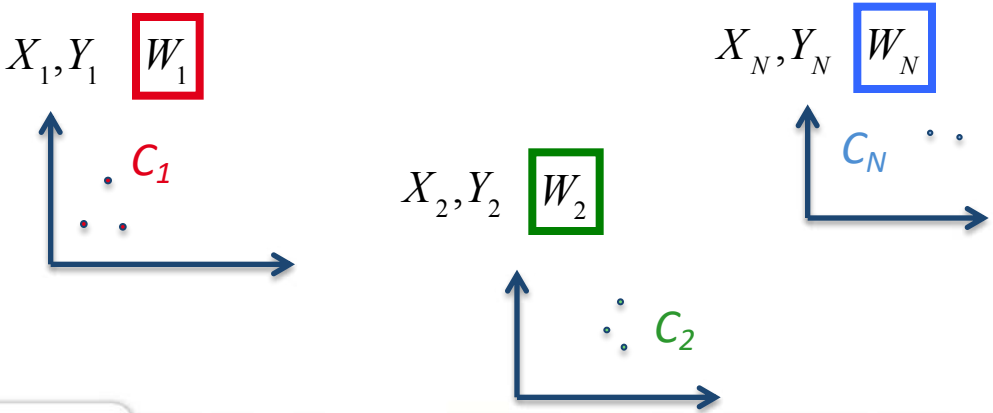
$$L_\rho(W_c, \tilde{W}, \alpha) = \sum_c L(Y_c \mid X_c, W_c) + \left\langle \alpha_c, W_c - \tilde{W} \right\rangle + \frac{\rho}{2} \left\| W_c - \tilde{W} \right\|_2^2$$

Alternating direction method of multipliers

$$L_\rho(W_c, \tilde{W}, \alpha) = \sum_c L(Y_c \mid X_c, W_c) + \left\langle \alpha_c, W_c - \tilde{W} \right\rangle + \frac{\rho}{2} \left\| W_c - \tilde{W} \right\|_2^2$$

Iteratively:

$$W_c^{(k+1)} = \text{argmin}_{W_c} L_\rho(W_c, \tilde{W}^{(k)}, \alpha_c^{(k)}) = (X_c^T X_c + \frac{\rho}{2} Id)^{-1} (X_c^T Y_c - \frac{1}{2}\alpha_c^{(k)} + \frac{\rho}{2}\tilde{W}^{(k)})$$

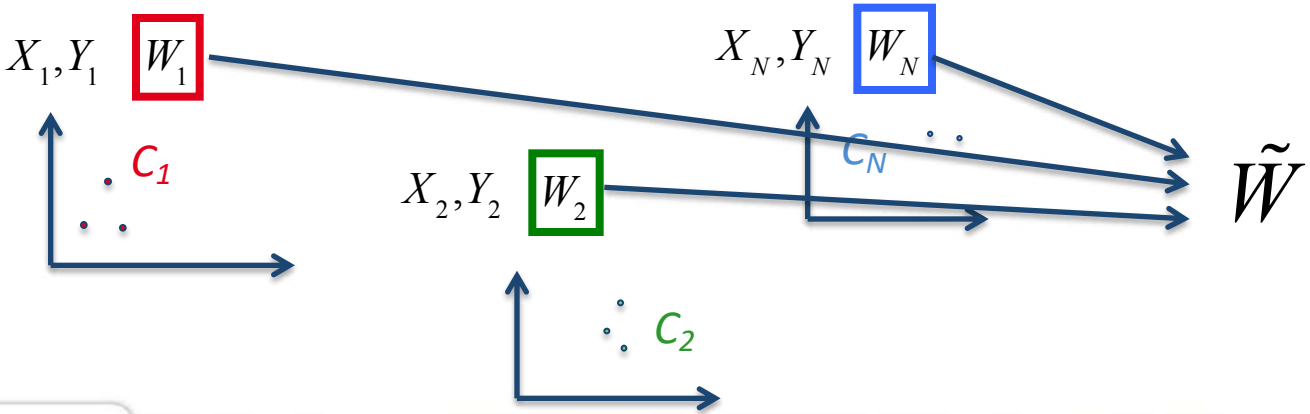


Alternating direction method of multipliers

$$L_\rho(W_c,\tilde{W},\alpha)=\sum_c L(Y_c\mid X_c,W_c)+\left\langle \alpha_c,W_c-\tilde{W}\right\rangle+\frac{\rho}{2}\left\|W_c-\tilde{W}\right\|_2^2$$

Iteratively:

$$\tilde{W}^{(k+1)}=\text{argmin}_{\tilde{W}}\ L_\rho(W_c^{(k+1)},\tilde{W}\ ,\alpha_c^{(k)})=\frac{1}{C}\sum\frac{\alpha_c^{(k)}}{\rho}+W_c^{(k+1)}$$



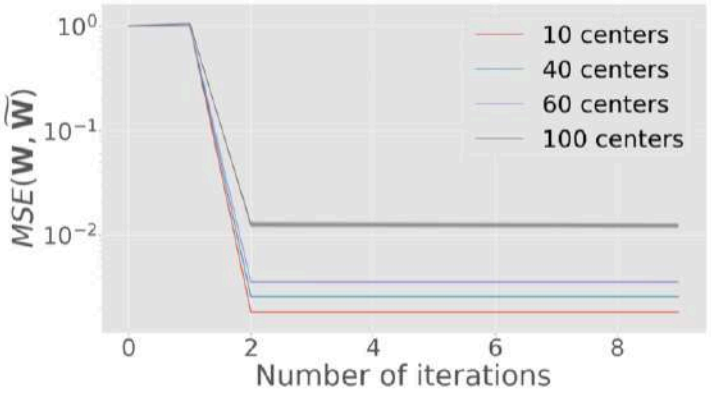
Alternating direction method of multipliers

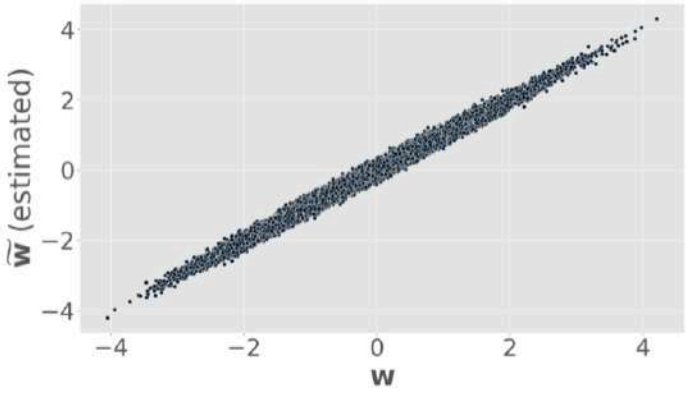
$$L_\rho(W_c, \tilde{W}, \alpha) = \sum_c L(Y_c \mid X_c, W_c) + \left\langle \alpha_c, W_c - \tilde{W} \right\rangle + \frac{\rho}{2} \left\| W_c - \tilde{W} \right\|_2^2$$

Iteratively:

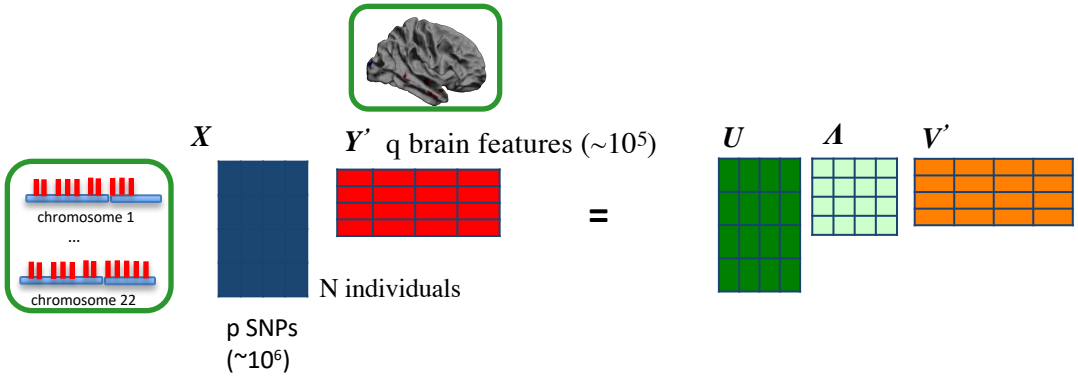
$$\alpha_c^{(k+1)} = \alpha_c^{(k)} + \rho(W_c^{(k+1)} - \tilde{W}^{(k+1)})$$

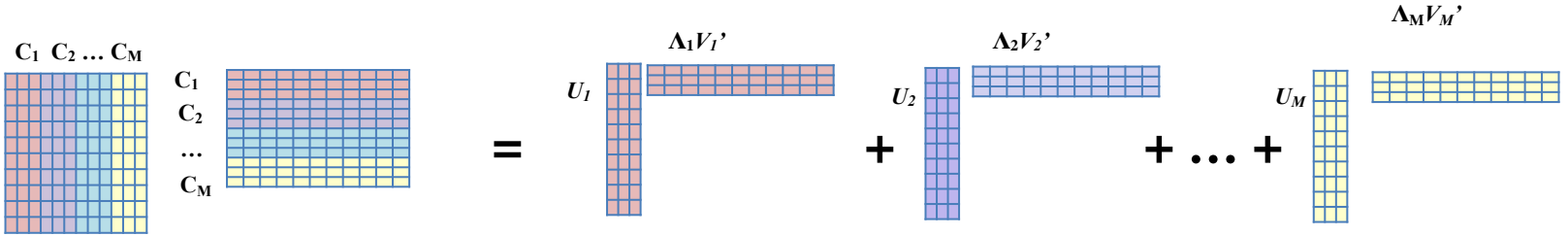
Results on synthetic tests



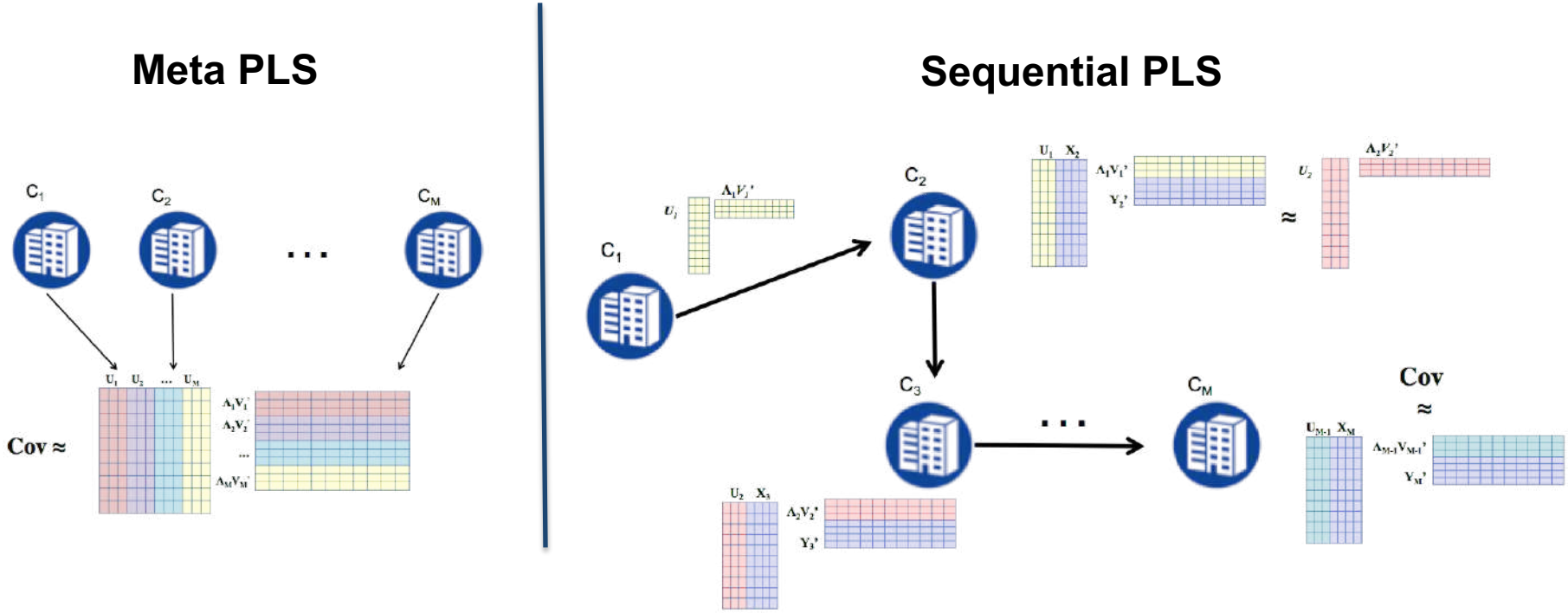


Covariance estimation and eigen-decomposition



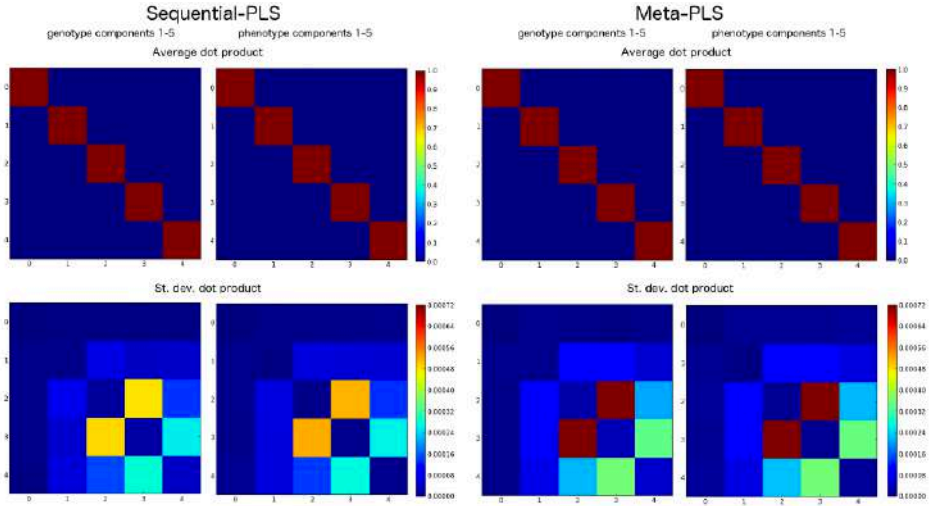


Covariance estimation and eigen-decomposition

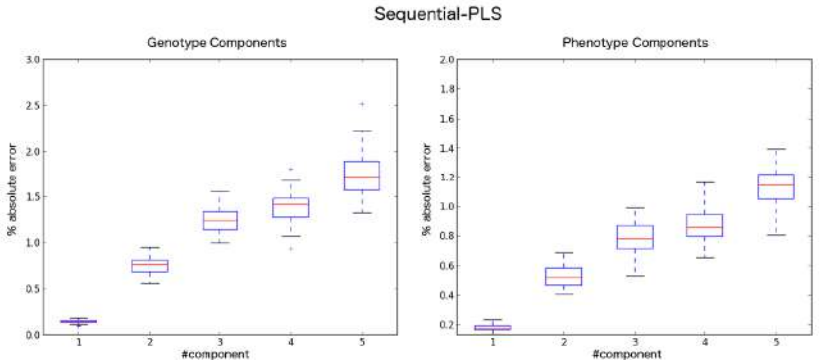


Testing

Mean and sd of dot product



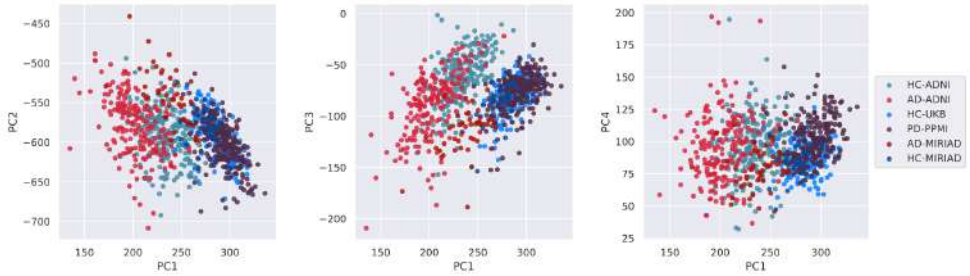
Absolute feature-wise error



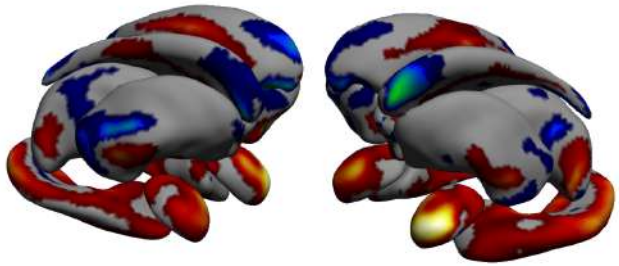
Federated analysis of subcortical brain regions in dementia

ADNI	PPMI	UK Biobank	Miriad
Alzheimer's	Parkinson's	Healthy	Alzheimer's
802	232	208	68

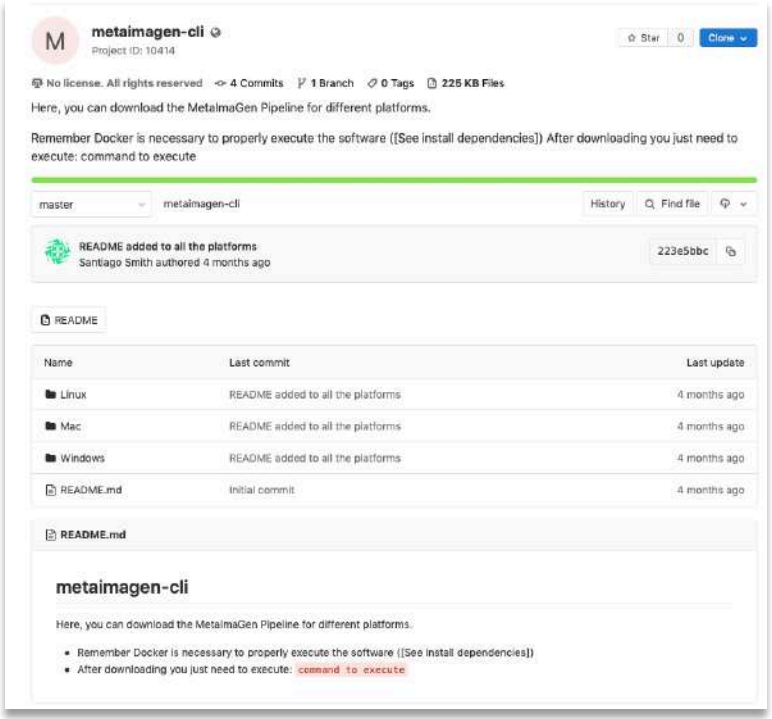
Projection on latent components



Brain subcortical components



Meta-ImaGen
future steps



- Software freely released
- Dedicated server purchase (expected May 2019)
- Application to large scale imaging-genetics analysis

PARKINSON'S PROGRESSION MARKERS INITIATIVE
biobank
ENIGMA
Stanford MEDICINE
ADNI
SANTA LUCIA NEUROSCIENZE E RIABILITAZIONE

UCA IPMC, FR
Poston Lab – Stanford, USA
IRCCS Santa Lucia, IT
UCL, UK

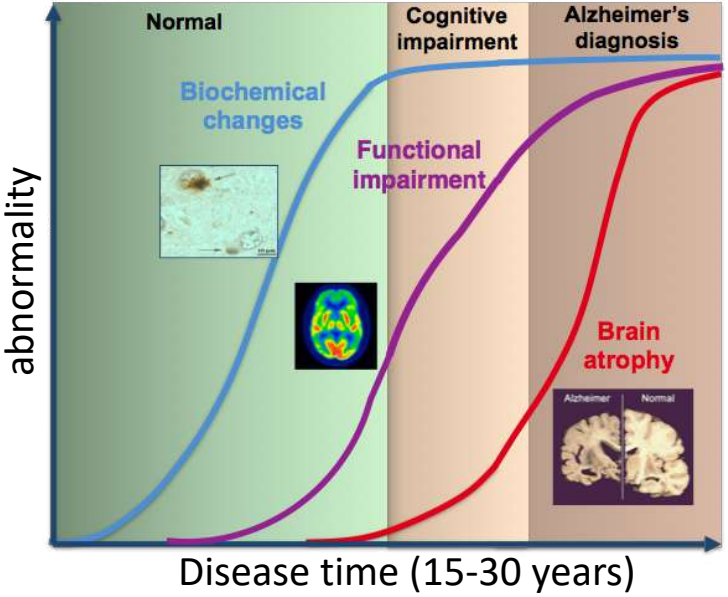
- Industry application:
  starting collaboration with Accenture Labs

Imaging-genetics:
multimodal analysis of heterogeneous data

- Multivariate Modeling in Imaging Genetics
- Online learning for multicentric studies
- **Genetic analysis through disease progression modeling**

Modeling the natural history of neurodegeneration

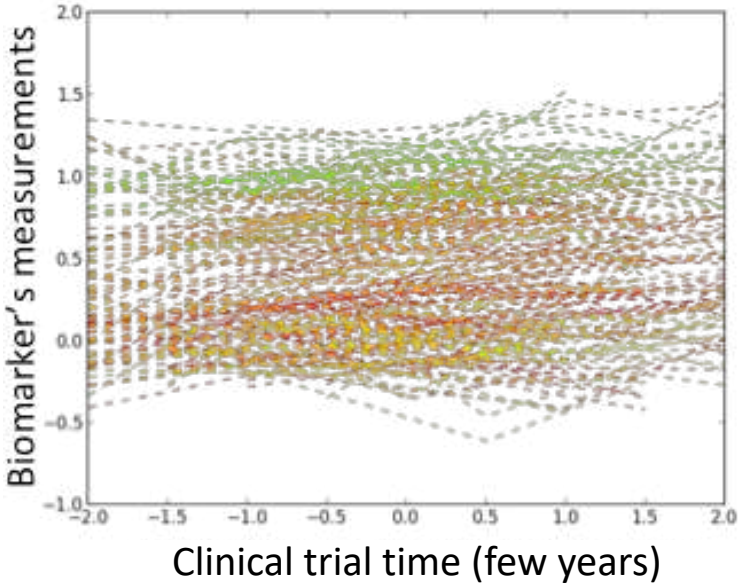
Hypothetical model



?

Assessing
- Patient severity
- Drugs effect

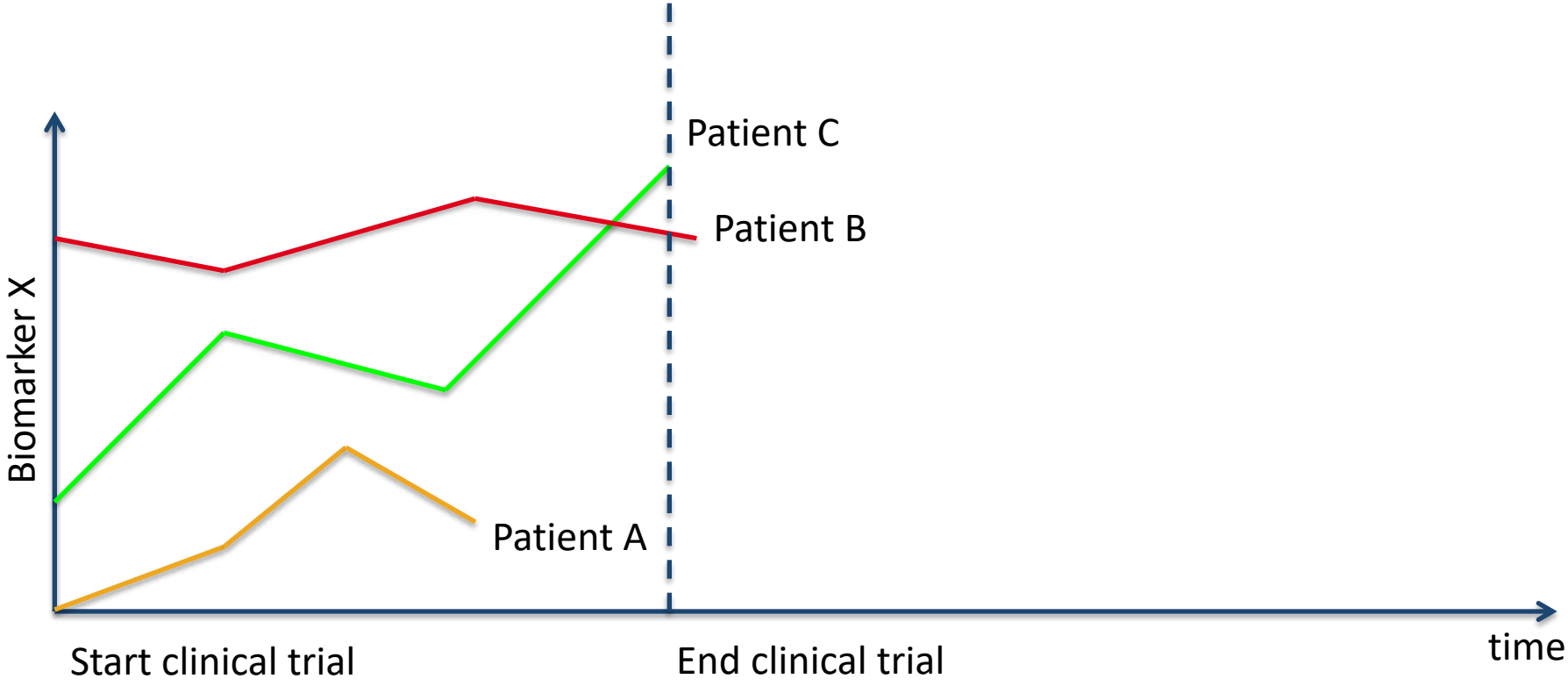
The reality



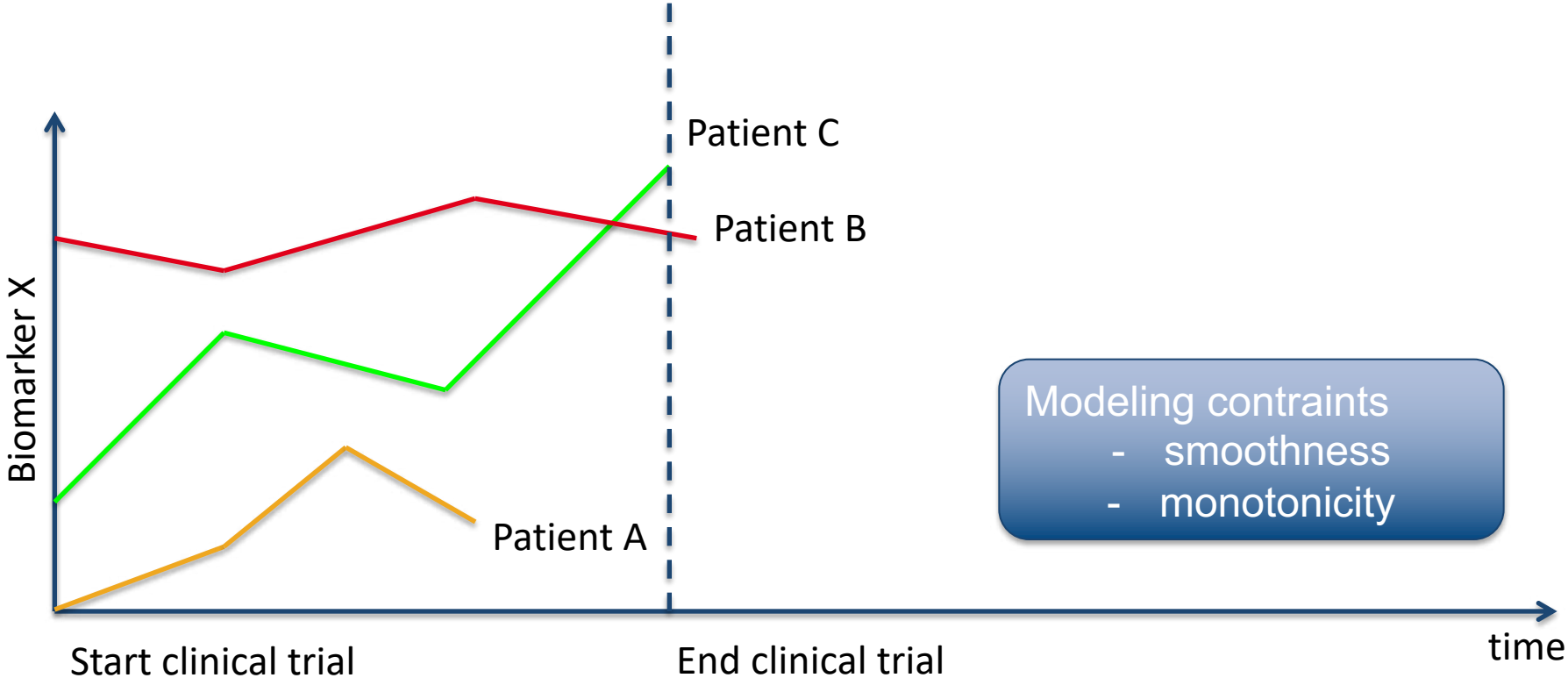
Large time span

Short time span

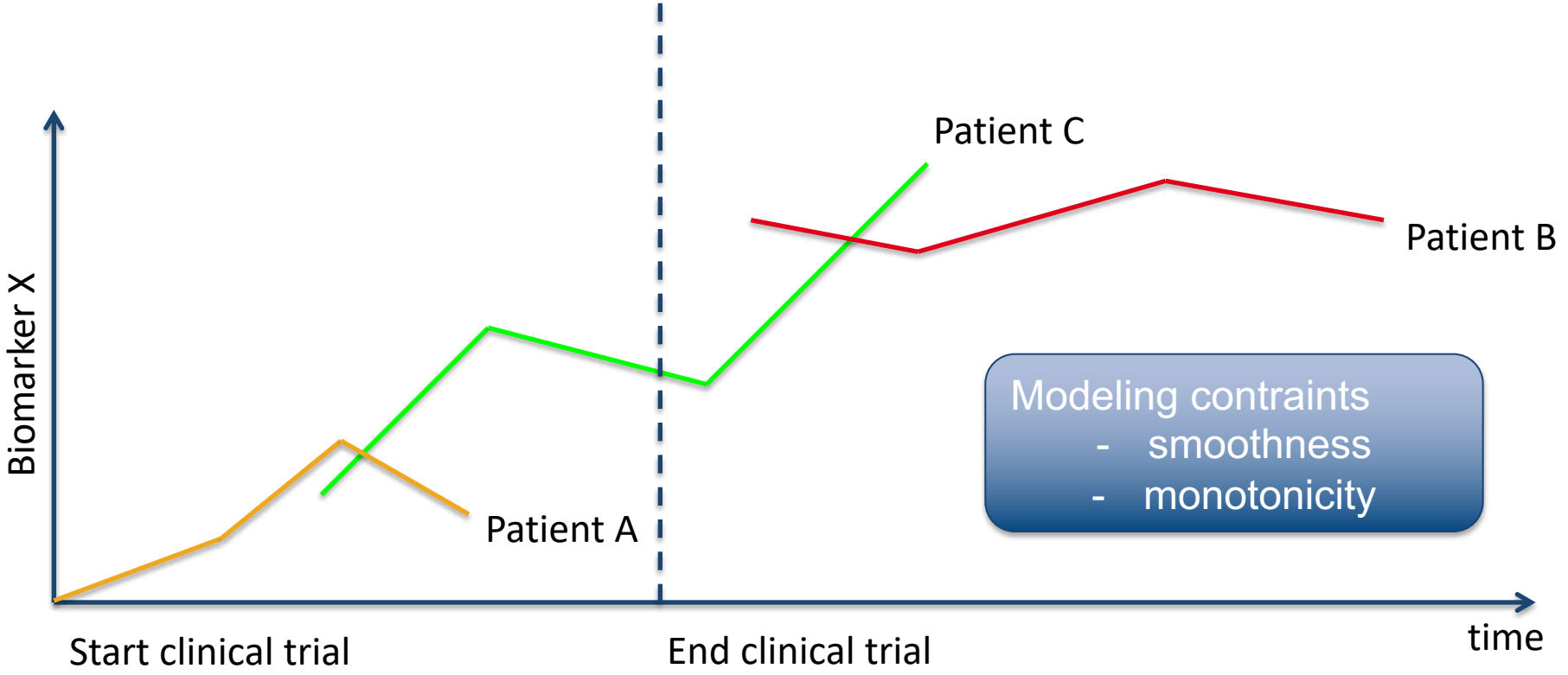
Statistical disease progression model



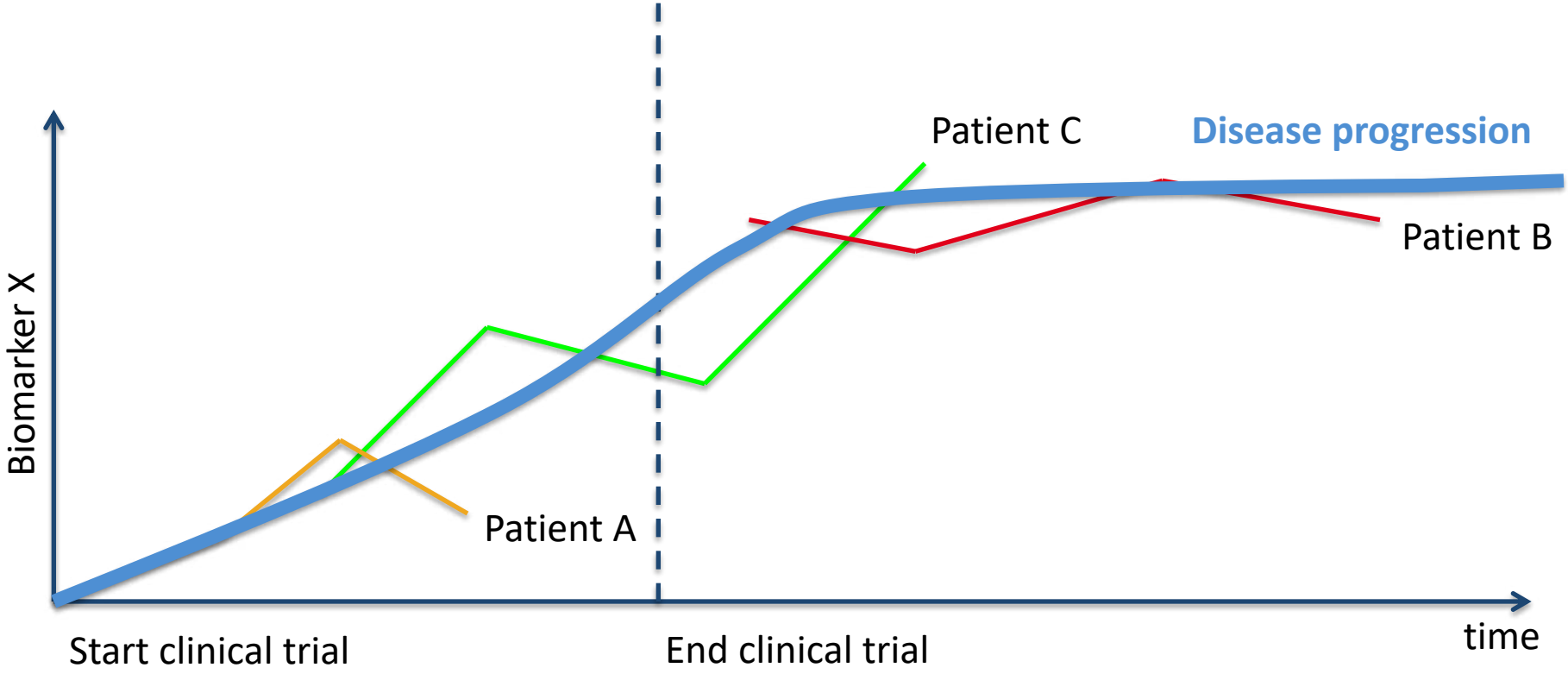
Statistical disease progression model



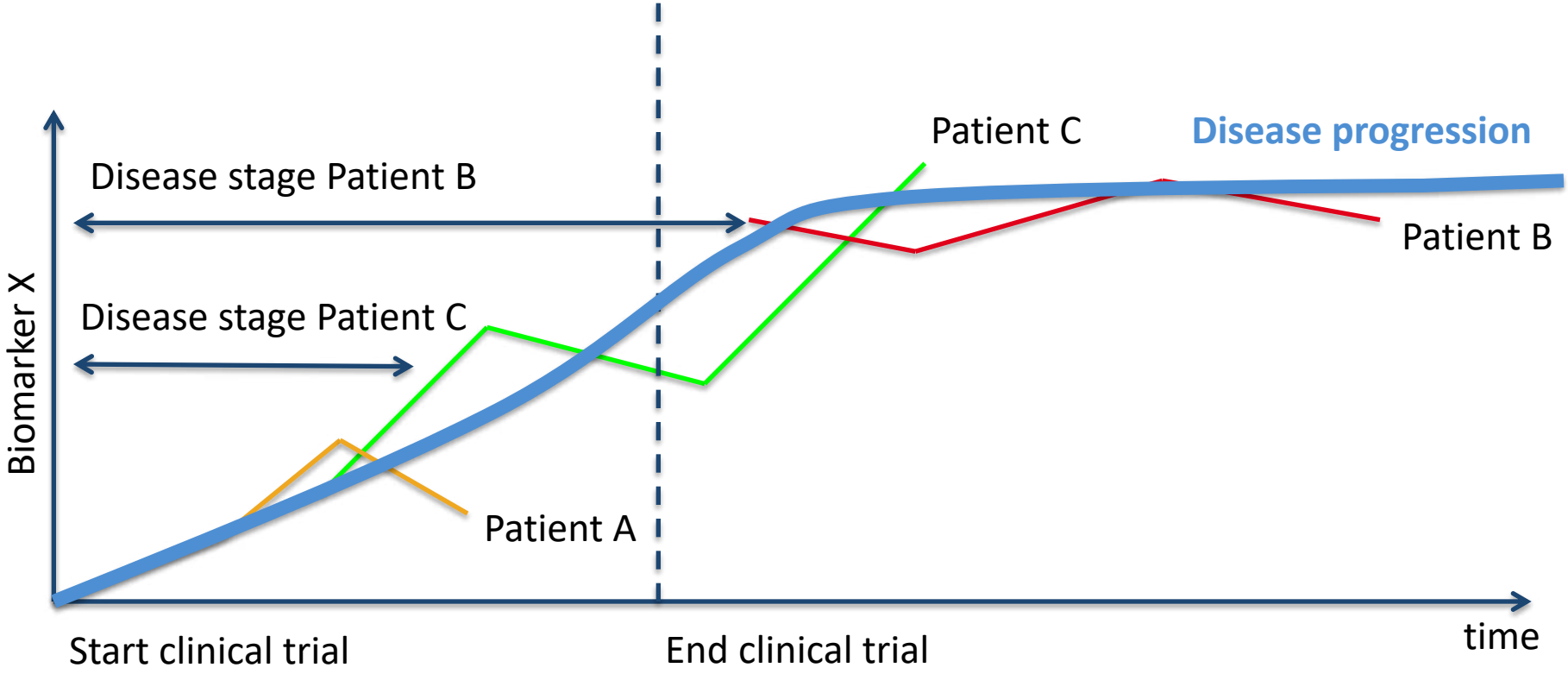
Statistical disease progression model



Statistical disease progression model

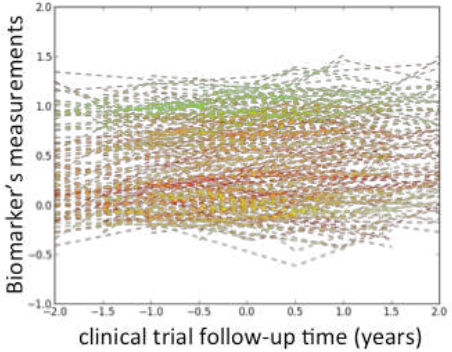


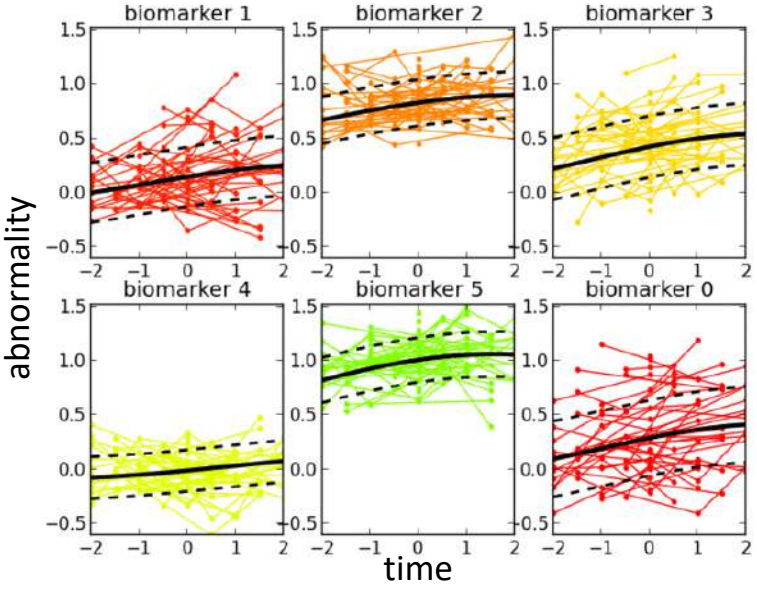
Statistical disease progression model



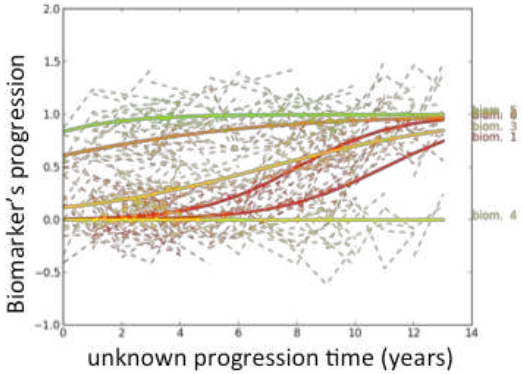
Statistical disease progression model via monotonic Gaussian Processes (GP)

Short term data



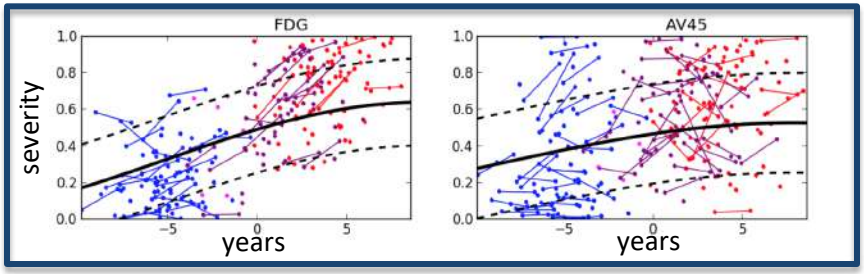


Estimated long term progressions



- Multivariate non-parametric random effects modeling
- Monotonic GP [Riihimäki & Vehtari, PMLR, 2010; Lorenzi & Filippone, ICML, 2018]
- Time reparameterization [Jedynak et al, NeuroImage 2012; Durrleman et al, IJCV, 2013; Schiratti et al, NIPS 2015]

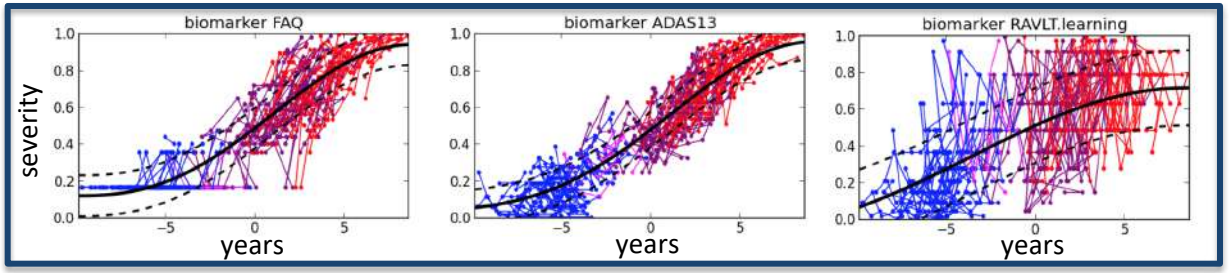
Highlighting **dynamics and relationship** between biomarkers



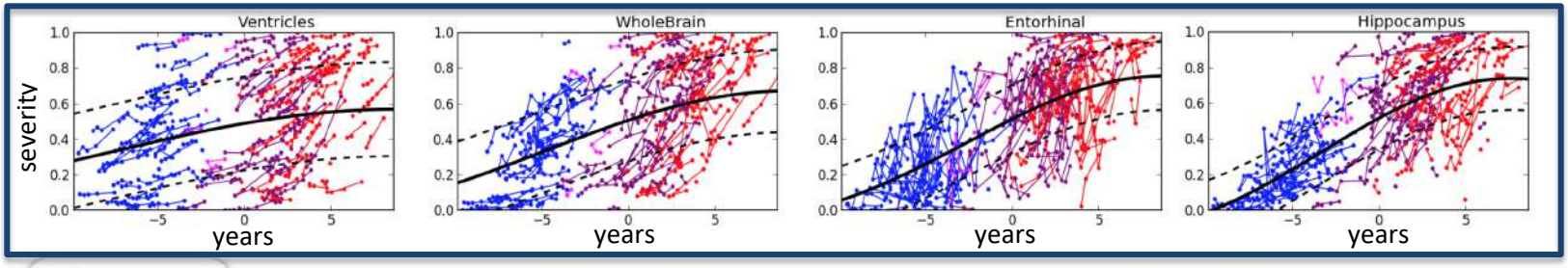
Metabolism + Amyloid

200 training subjects
- 67 healthy
- 75 AD
- 53 MCI converted
- 5 healthy converted

5 years observational time

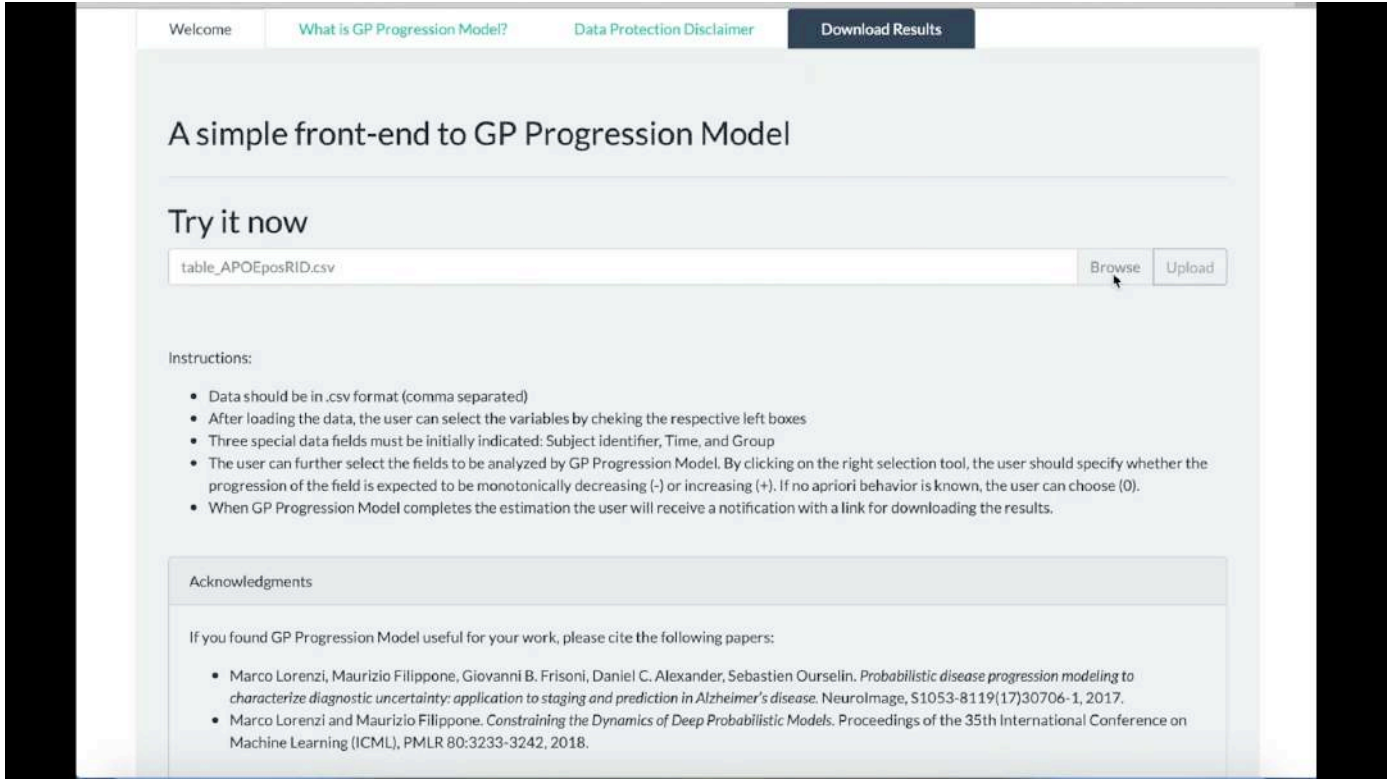


Cognition

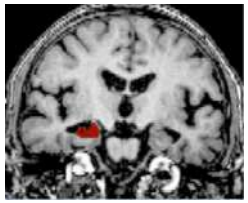


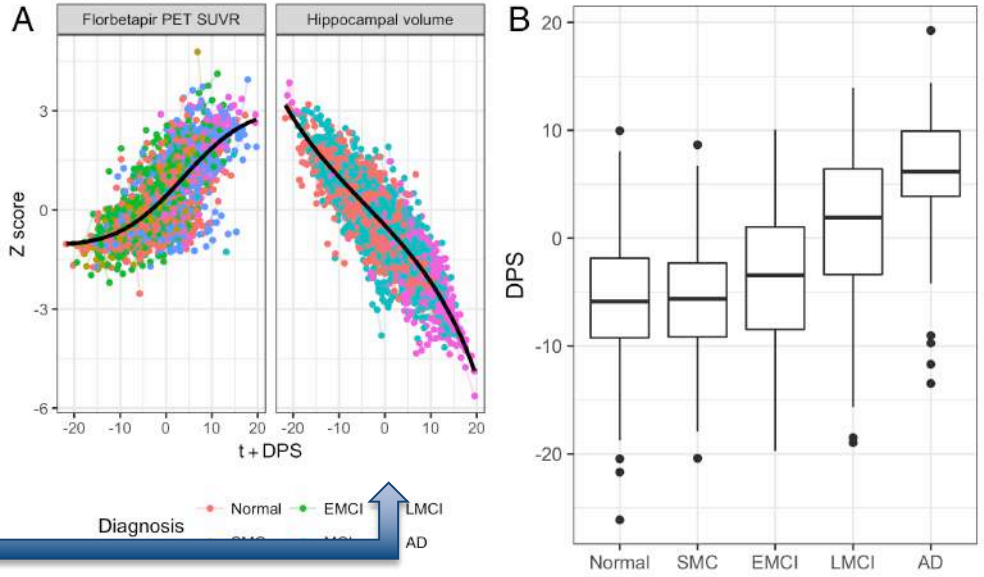
Brain Volumes

gpprogressionmodel.inria.fr



Disease staging from cortical amyloid and hippocampal volume

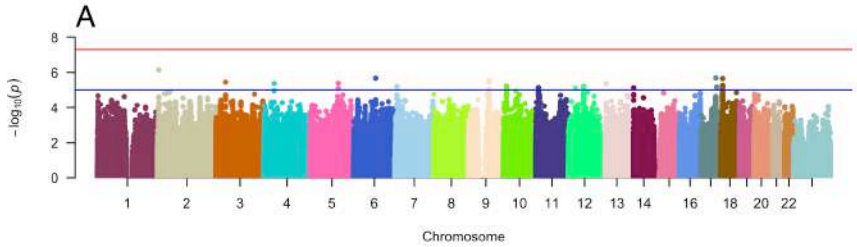




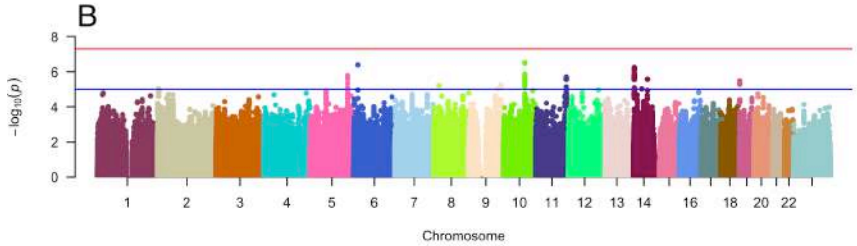
M.A. Scelsi A. Altmann

Disease staging as composite biomarker

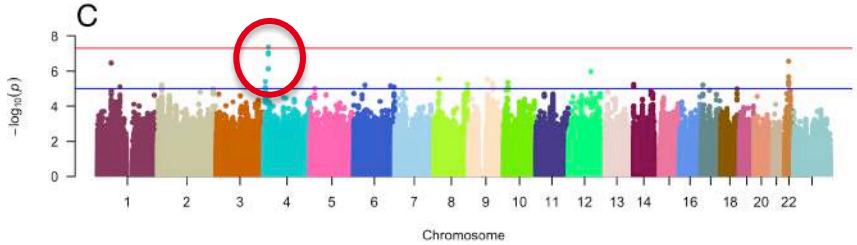
GWAS results



Hippocampal volume

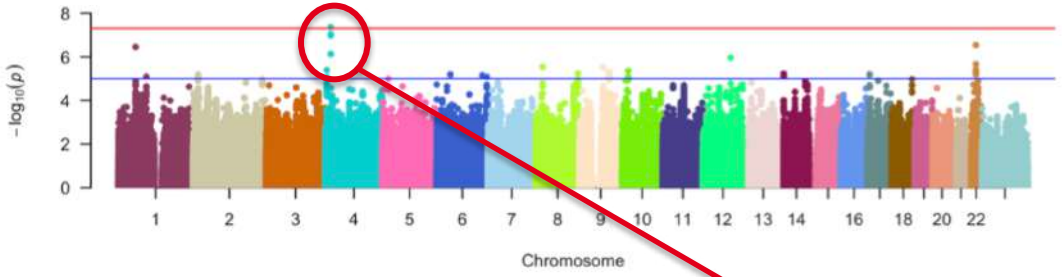


Amyloid burden



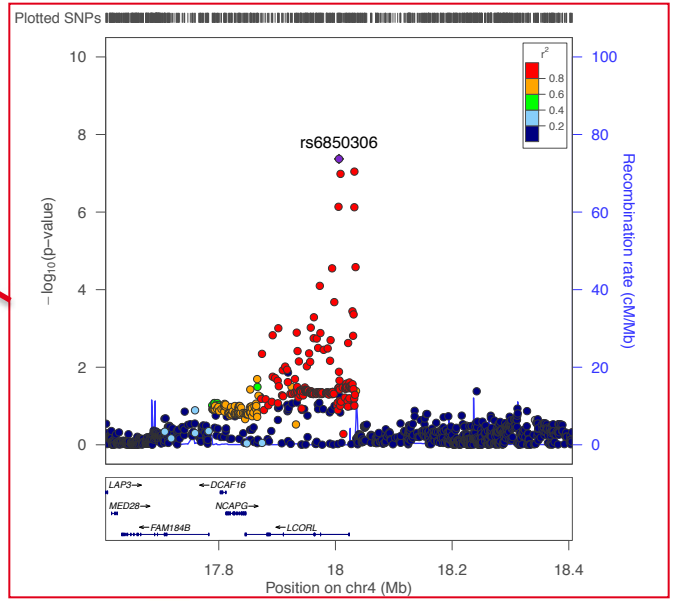
Disease staging

GWAS results



LCORL gene on chromosome 4p15.31

- Mediates activity-dependent synapse-to-nucleus communication
- Known relationship with amyloid precursor protein (APP)



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C. Abi Nader


L. Antelmi

Meta-ImaGen


S.S. Silva

UCA MDLab


M. Milanesio

UCA-Ville de Nice Young Researcher award


S. Garbarino

Brain-Heart


J. Banus


M. Sermesant

EURECOM
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HUG Hôpitaux Universitaires Genève


G.B Frisoni


F. Ribaldi

Thank you