PERSYVAL-Lab

UNIVERSITÉ GRENOBLE ALPES

Spatially regularized NMF for population genetic applications

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Outline

- Method to estimate individual ancestry coefficients from population genetic and spatial data
- Graph regularized non-negative matrix factorization
- Alternating least squares algorithm
- Results

Genotypic data

- Single nucleotide polymorphism (SNP)
  - single nucleotide variation occurring commonly within a population

Ind 1 ....AAGC C TA........

Ind n ....AAGC T TA........

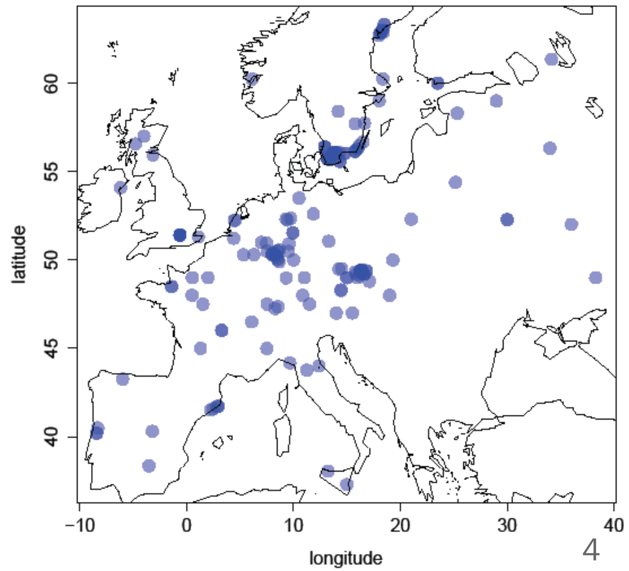
- Data matrix: L loci for n individuals ($n \sim 10^2 - 10^3$, $L \sim 10^6 - 10^7$)

Our data

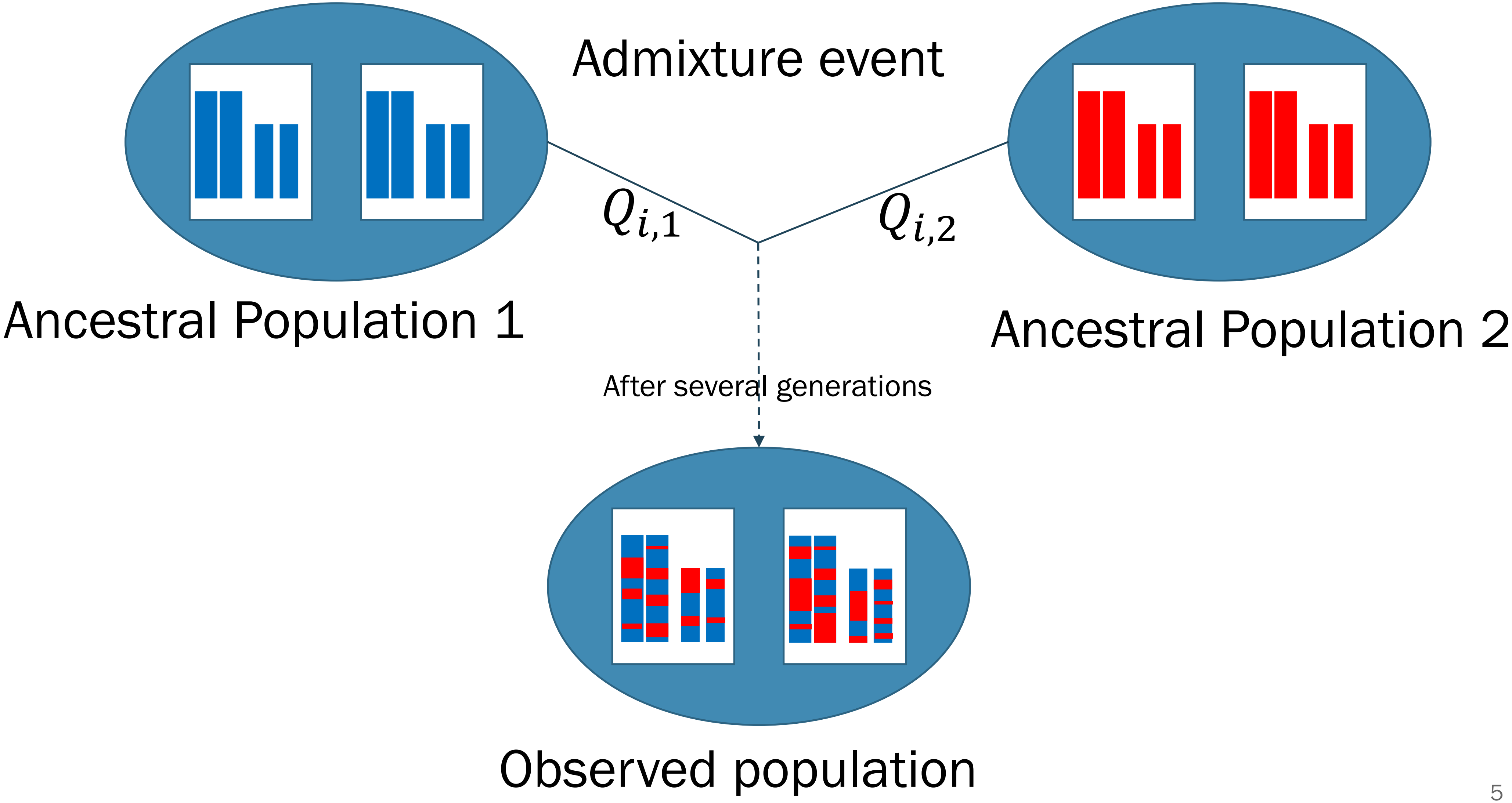
- Genotypic matrix for diploid individuals: number of mutations observed for each individual and locus (0, 1 or 2)

$$X = \underbrace{\begin{pmatrix} 1 & \cdots & 0 \\ \vdots & X_{i,l} & \vdots \\ 2 & \cdots & 1 \end{pmatrix}}_{L \text{ loci}} \Bigg\updownarrow \; n \text{ ind}$$

- Geographic data for each individual



Goal: Estimating individual ancestry coefficients



Definition of ancestry coefficients

- We assume there are K ancestral populations (K unknown)

- The observed allele frequencies are a convex combination of ancestral frequencies

$$P(X_{i,l} = j) = \sum_{k=1}^{K} Q_{i,k} F_{k,l}(j)\,, \qquad \forall i, l, j$$

$Q_{i,k}$ = the fraction of individual i's genome that originates from ancestral population k

State of the art

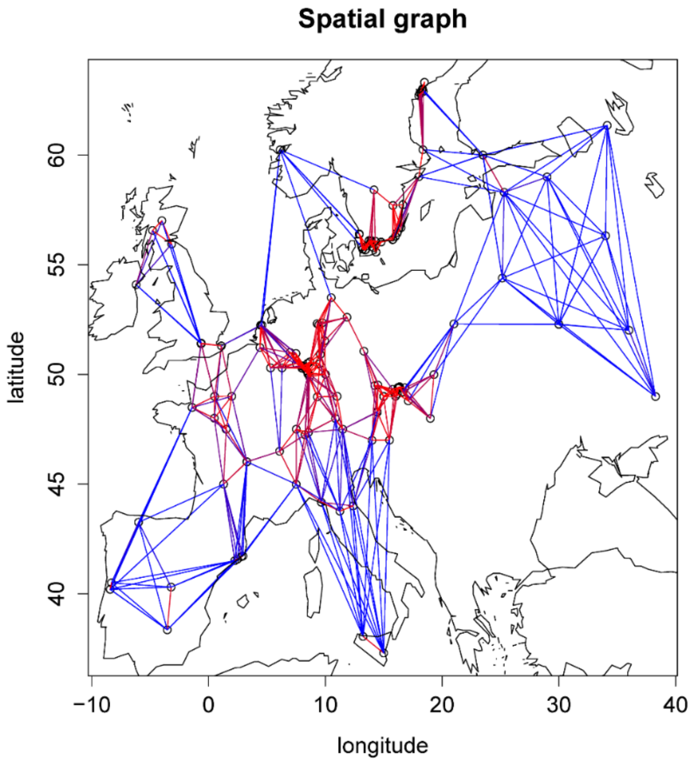
- Estimation of ancestry coefficients without spatial information:
  - Bayesian method: Structure (Pritchard et al. 2000)
  - sparse NMF: sNMF (Frichot et al. 2014)
- With spatial information:
  - Bayesian method: Tess (Durand et al. 2009)

Least square minimization

- Graph regularized NMF (Cai et al. 2011)

$$\min_{Q\geq 0, F\geq 0} \|X - QF\|^2 + \alpha \, \frac{1}{2} \sum_{m,r}^{N} \|Q_{m,:} - Q_{r,:}\|^2 W_{m,r}$$

$W \in \mathbb{R}^{N\times N}$: weight coefficients



- Additional constraints

$$\sum_{k=1}^{K} Q_{i,k} = 1, \; \sum_{j=0}^{2} F_{l,k}(j) = 1, \quad \forall i, l, k$$

Our approach

- Rewriting the error functional as follows

$$\boxed{||X - QF^T||^2 + \alpha||\Gamma Q||^2}$$

$\Gamma \in \mathbb{R}^{N\times N}$: Cholesky decomposition of the graph Laplacian matrix

- Rewriting the error functional to use Alternating least squares

$$\boxed{\left\|\begin{pmatrix} Vec(X^T) \\ 0 \end{pmatrix} - \begin{pmatrix} Id\otimes F \\ \sqrt{\beta}(\Gamma\otimes Id) \end{pmatrix} Vec(Q^T)\right\|^2}$$

Numerical algorithm

- Alternating non-negativity-constrained least squares using the active set method (Kim and Park 2011)
- Computing F by solving

$$\min_{\mathrm{F}\geq 0}\left\|\mathrm{X}-\mathrm{QF}^{\mathrm{T}}\right\|^2$$

$$\sum_{j=0}^{2} F_{l,k}(j) = 1$$

- Computing Q by solving

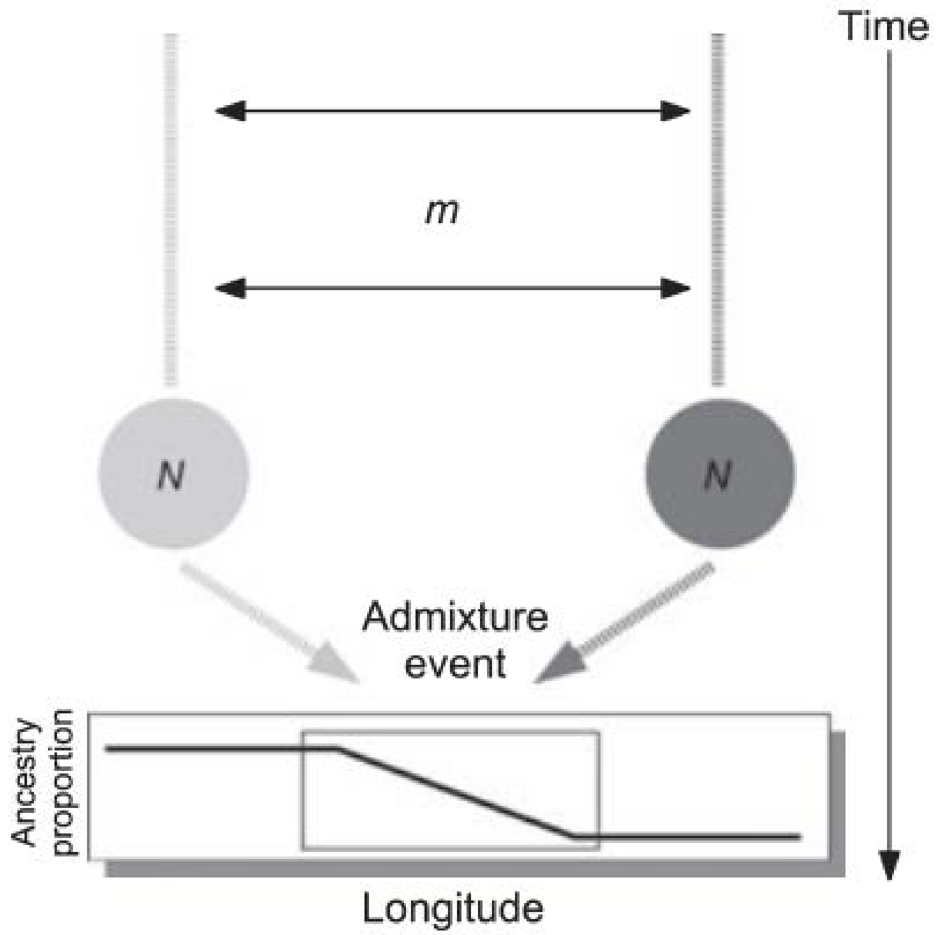
$$\min_{\mathrm{Q}\geq 0}\left\|\begin{pmatrix} Vec(X^T) \\ 0 \end{pmatrix} - \begin{pmatrix} Id\otimes F \\ \sqrt{\beta}(\Gamma\otimes Id) \end{pmatrix} Vec(Q^T)\right\|^2$$

$$\sum_{k=1}^{K} Q_{i,k} = 1$$

Simulation study

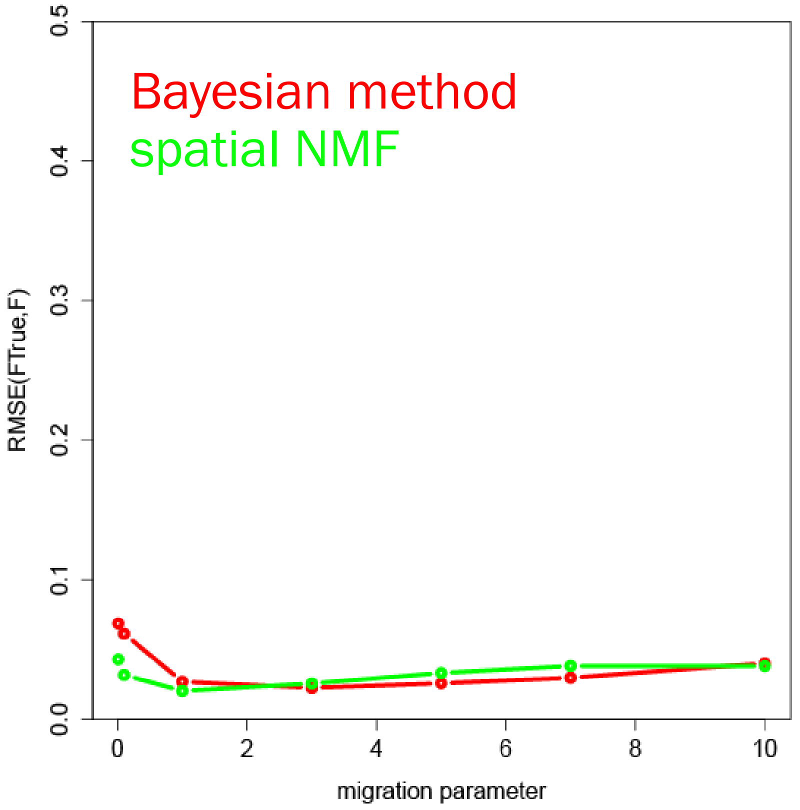
- Simulation of 2 populations with an admixture event

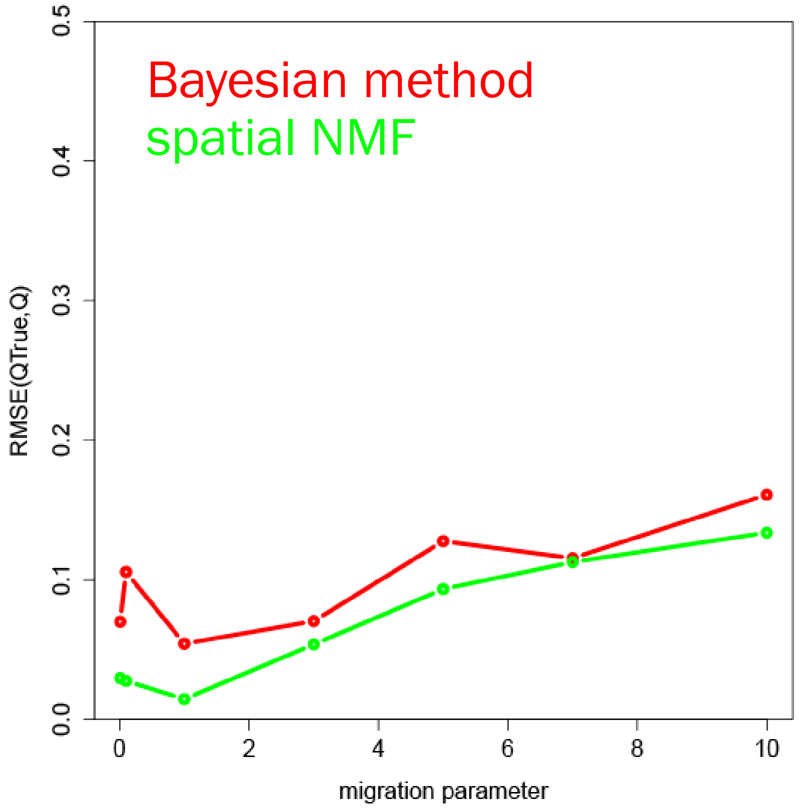
$$n = 200$$
$$L = 10^5$$



Statistical error comparison with Tess

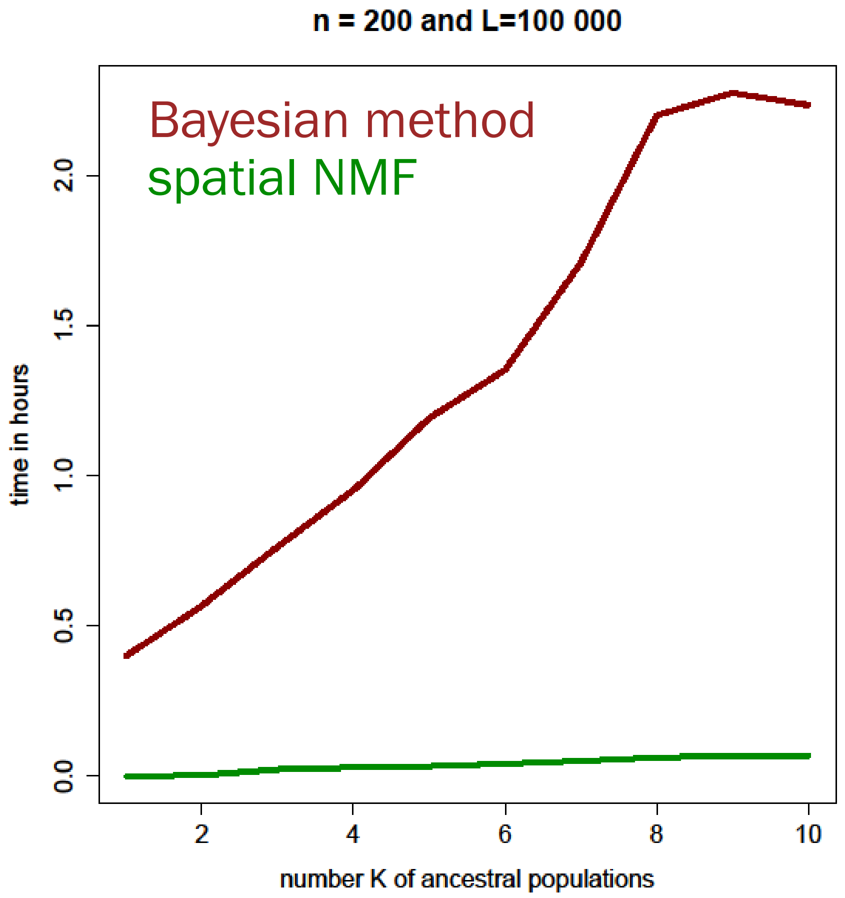
$$RMSE(Q^{TRUE}, Q) = \sqrt{\frac{1}{nK}\sum_{i,k}(Q_{i,k}^{TRUE} - Q_{i,k})^2}$$





Benefit of the least square approach

- Run time analysis: spatial NMF about 10-100 fold faster



Statistic to detect local adaptation

- After computing Q and F
  - q_k is the mean value of $Q_{i,k}$ over all individuals
  - $F_{k,j}$ is the allele frequence of the locus j in the ancestral population k

$$\sigma_{T,j}^2 = \left(\sum_k q_k F_{k,j}\right)\left(1 - \sum_k q_k F_{k,j}\right)$$

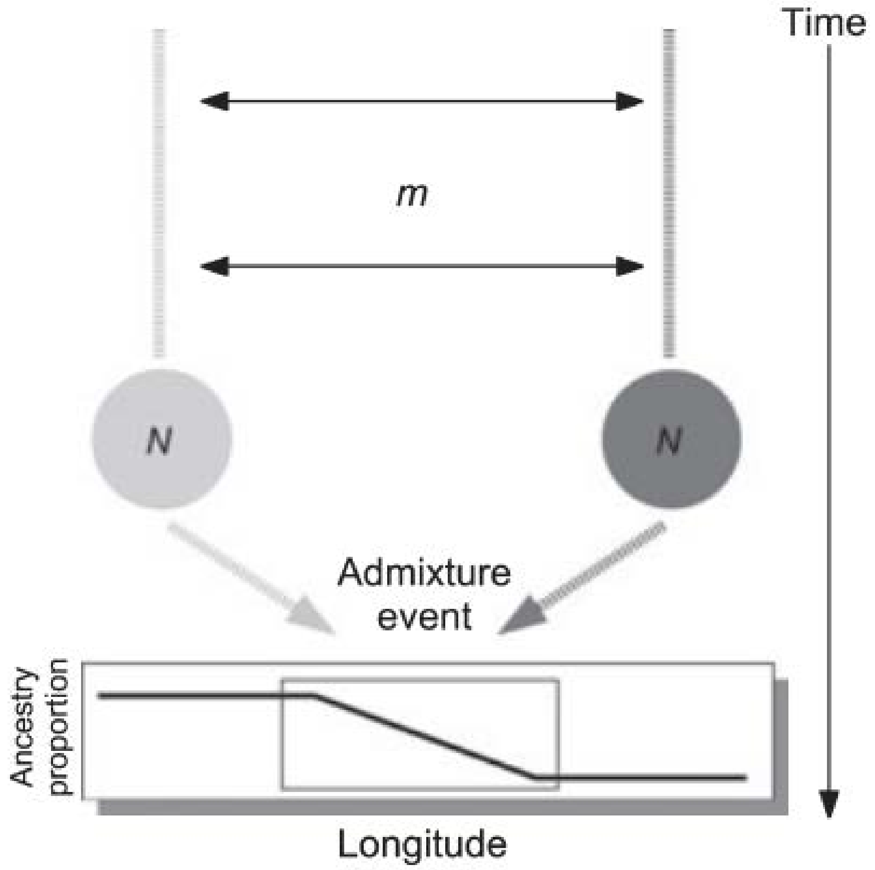
$$\sigma_{S,j}^2 = \sum_k q_k F_{k,j}(1 - F_{k,j})$$

$$\boxed{Fst_j = \frac{\sigma_{T,j}^2 - \sigma_{S,j}^2}{\sigma_{T,j}^2}, \quad \forall\, j\ locus}$$

Simulation of local adaptation

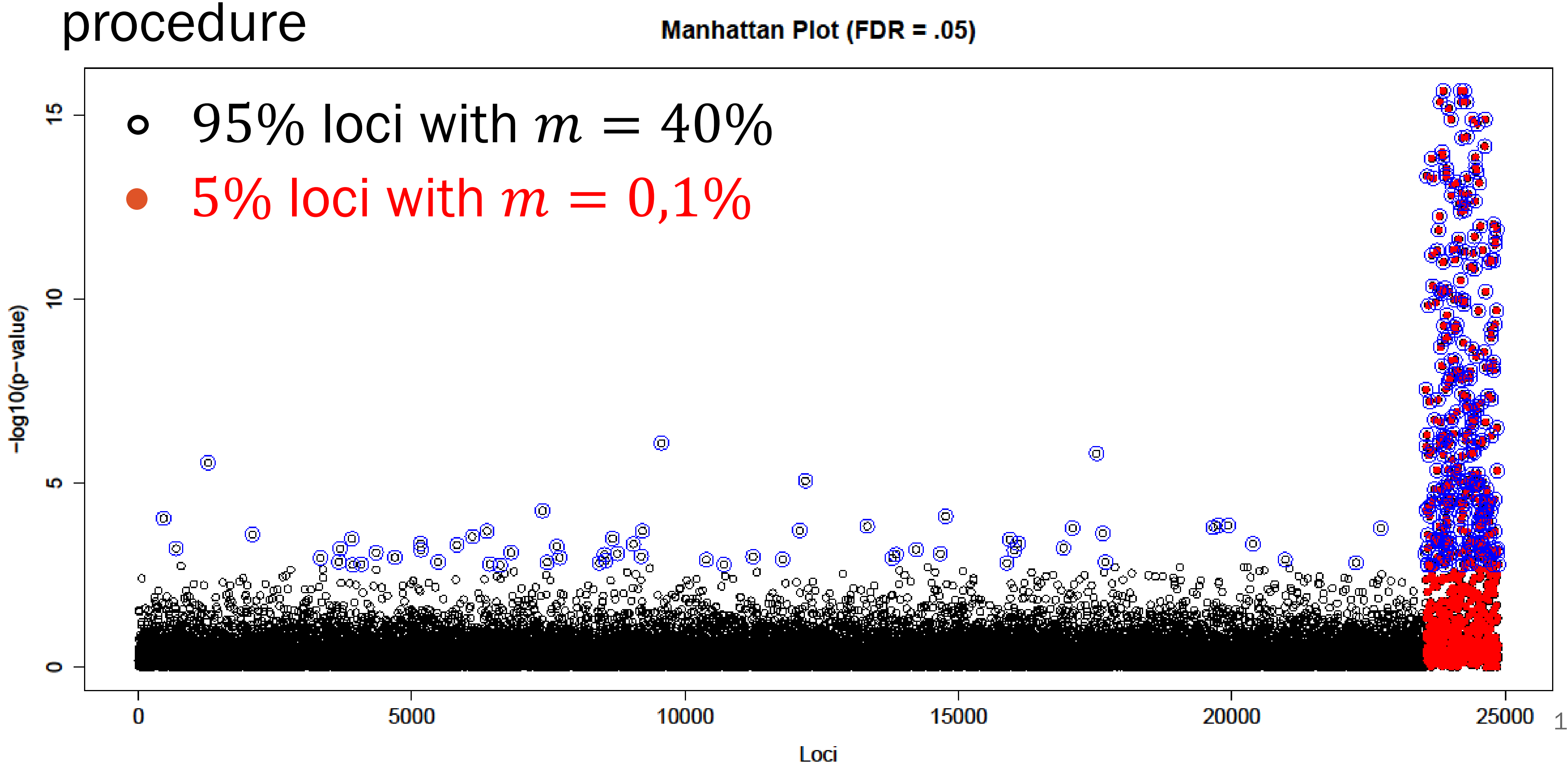
- Simulation of neutral loci :
  - Migration rate: $m = 40\%$
  - Proportion: 95%

- Simulation of outlier loci :
  - Migration rate: $m = 0{,}1\%$
  - Proportion: 5%



Detection of local adaptation on simulation

- Control of false discovery rate with Benjamini Hochberg procedure

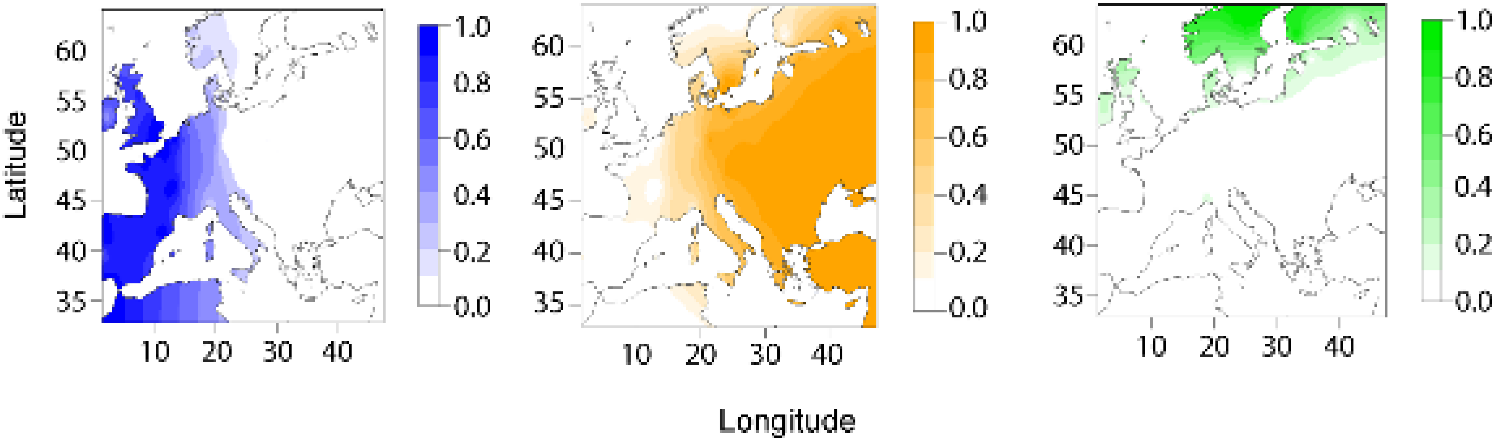


○ 95% loci with $m = 40\%$

● 5% loci with $m = 0{,}1\%$

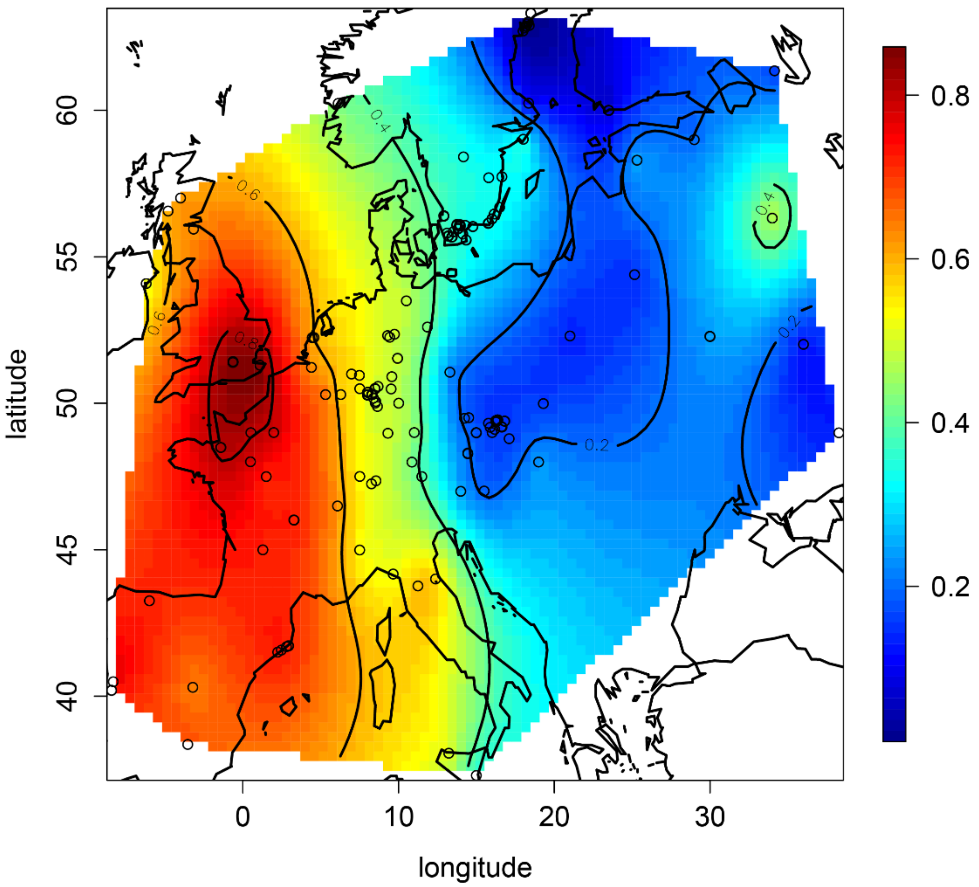
Analysis of *Arabidopsis thaliana* data

- Popular model organism in plant biology
- 170 European individuals genotyped at 230 000 loci (Atwell et al. 2010)
- Three spatially consistent ancestral populations in Europe (Francois et al. 2008):

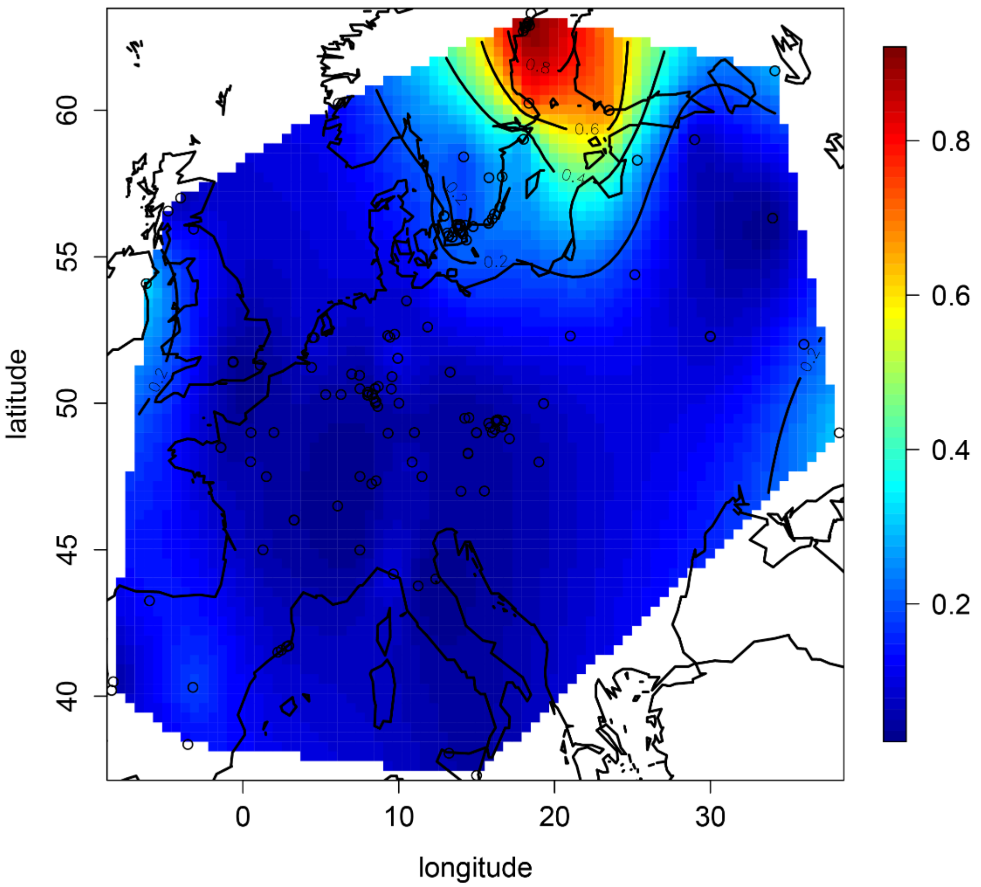


Ancestry map results (K = 3)

Western ancestral population coefficient



Scandinavian ancestral population coefficient



Discussion

- Graph regularized NMF combines spatial and genetic data

- We rewrote the problem of graph NMF to use ALS algorithm

- We observed that Tess and our method provide close estimations

- The algorithm is much faster than Bayesian methods

Acknowledgments

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Schedule

- Tess update :
  - Article
  - Documentation
  - Release command-line software
- Method article: What do we want to expose?
  - Estimating population structure with graph : models and algorithms (spatial NMF , Achetypal anilysis with spatial)
  - Graph regularized NMF algorithm (ALS, MU)
- Develop R package with spatial NMF and visualization tools
- And then?
  - Lfmm : fdr on association study
  - Hypothesis testing on linear mixed model