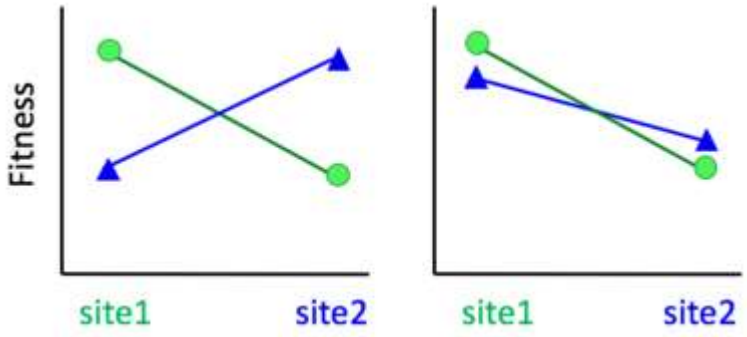
Genome-scans
Landscape genomics

Claire Mérot & Anna Tigano
Physalia Courses
September 2020

Basic principle: Local adaptation

Geographic heterogeneity in environment

Local populations have been selected by local ecological conditions

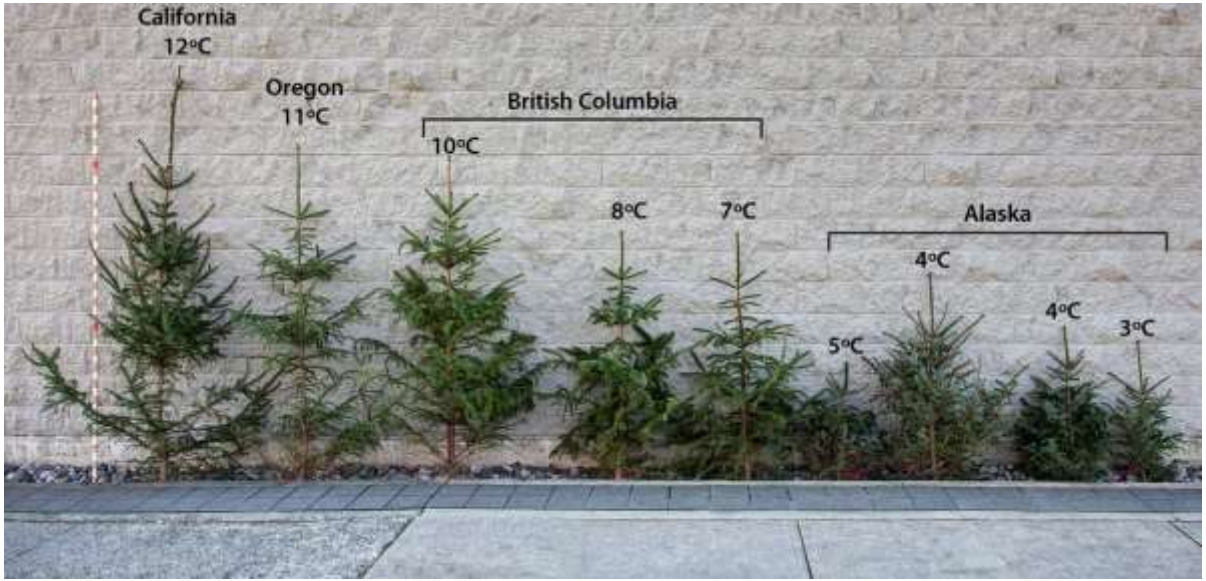


Basic principle: Local adaptation

Common garden experiment

⇒ local adaptation has heritable genetic basis

⇒ phenotypes related to local adaptation



Provenance variation in 8-year-old *Picea sitchensis* from across the species range grown in a common garden in Vancouver, BC, Canada

Aitken et al, 2015 Evol.App https://www.onlinelibrary.wiley.com/doi/10.1111/eva.12293

⇒ *This may be visible as « signature of selection »*

⇒ *We expect differences of allelic frequency between sites*

Basic principle: Local adaptation

Can we use genomic data to understand the genetic basis of local adaptation?

Can we find the loci contributing to divergence between populations?

Can we find the loci possibly associated with relevant traits or relevant ecological variables?

Genome-scan for local adaptation

Approach 1 : detect outliers of divergence

-> Search for unexpected patterns in allele frequencies accross the genome

Approach 2: detect associations with environment/phenotype

-> Search for correlations between allelic frequencies and variables

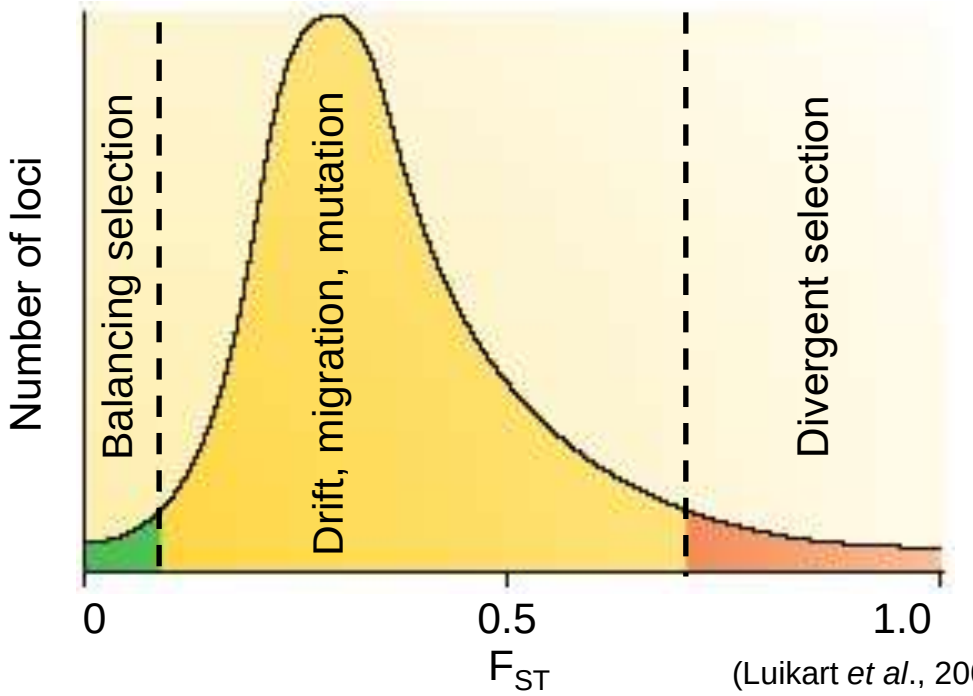
Outliers of divergence – signature of selection

Fst statistics

- A measure of differentiation between populations relatively to intra-population diversity

Fst=1 : complete fixation of the alleles in each population

Fst=0 : same allelic frequencies



(Luikart *et al*., 2003)

Outliers of divergence – signature of selection

Fst statistics

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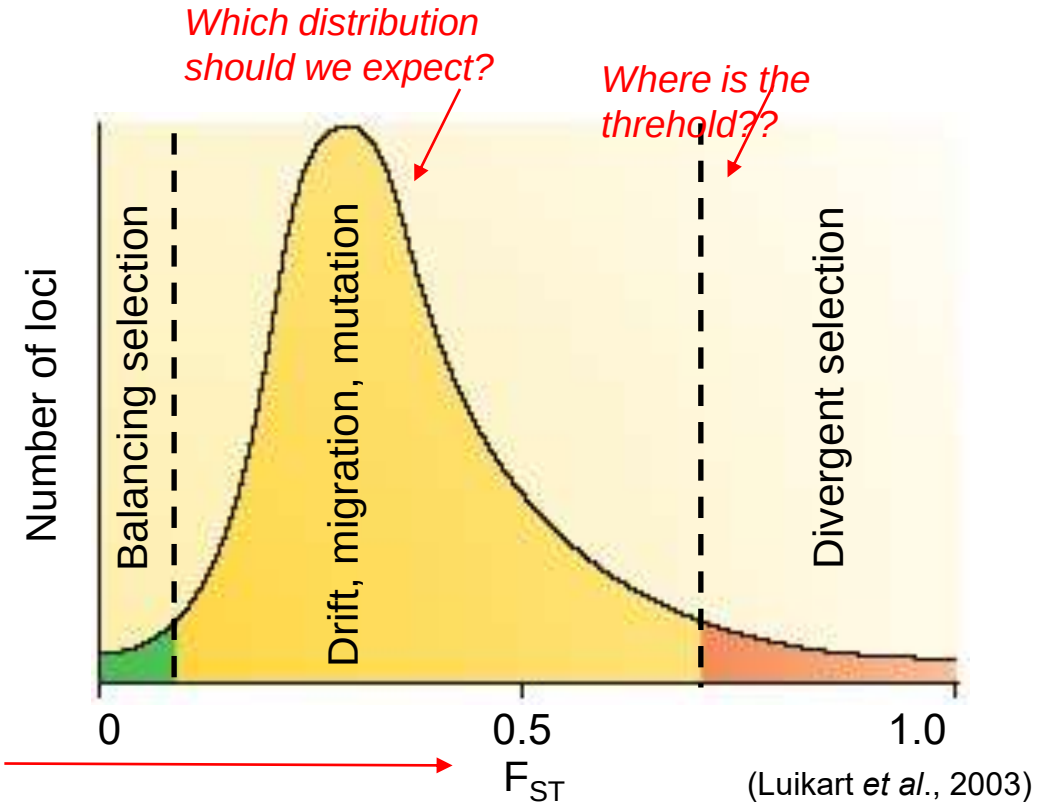
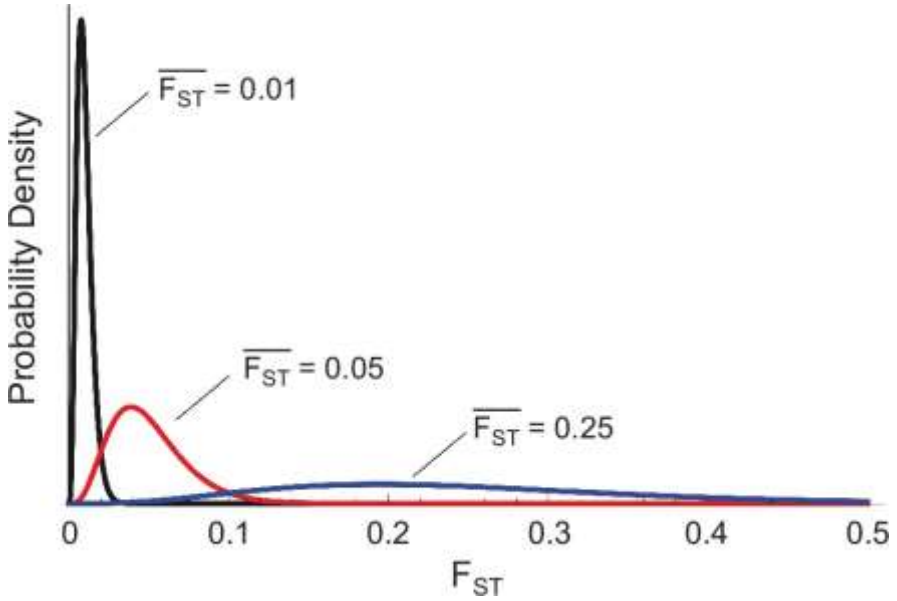


(Luikart *et al.*, 2003)

Outliers of divergence – signature of selection

Problem 1: Population structure

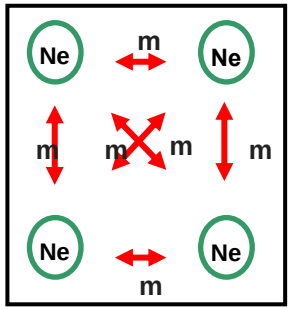
When the average level of differentiation is high,, the variance in F_{ST} values among loci increases with average F_{ST}, which makes detection of outlier loci difficult for highly differentiated populations



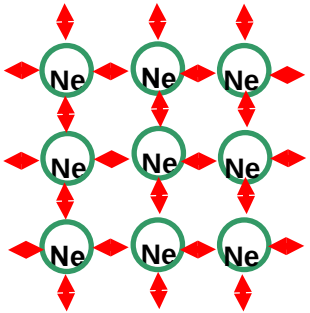
Outliers of divergence – signature of selection

Problem 2: Demography

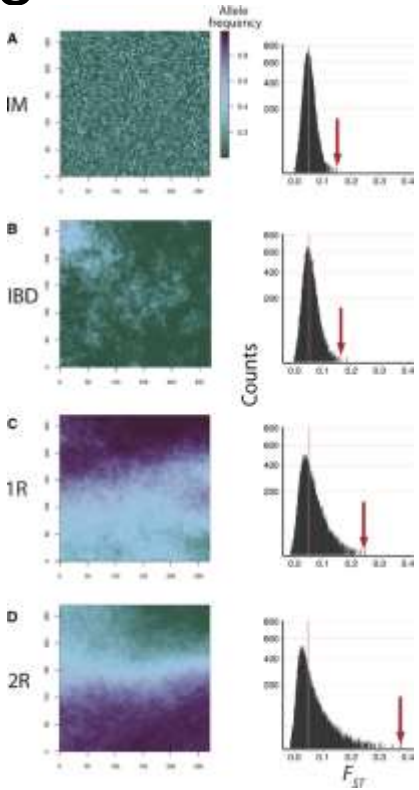
The distribution of FST will depend on the real demography of the populations



island model



Stepping-stone



island model

isolation by distance

expansion from one refugium

expansion from two refugia with secondary contact

Landscapes of frequency and FST for an outlier neutral locus at the end of the simulation (75 random samples)

Lotterhos & Whitlock 2014 Mol Ecol

Outliers of divergence – signature of selection

1st solution: assume a model of dispersion and demography
(Fdist, Bayescan)

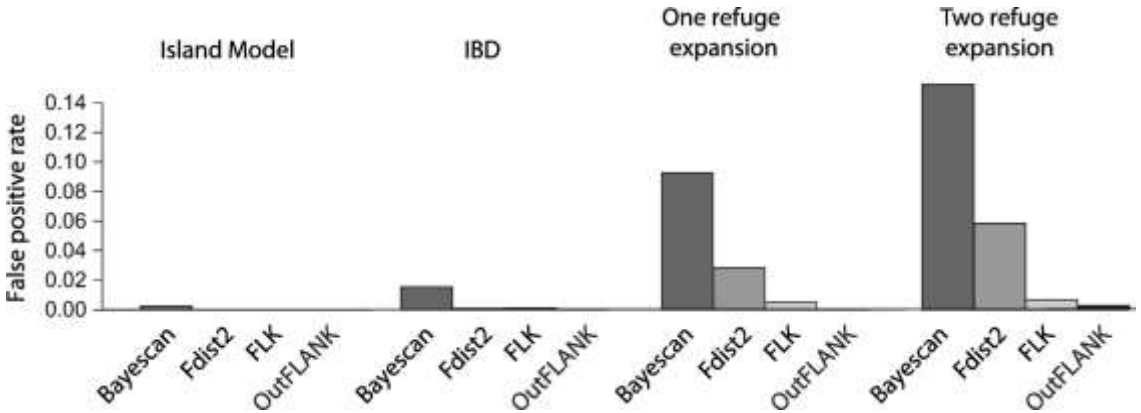
2nd solution: try to estimate a neutral model from data

-> covariance matrix between pop (Baypass/Bayenv2, FLK)

-> X^2 distribution of pruned SNPs (OutFLANK)

Outliers of divergence – signature of selection

Many « false positive »…



Or capturing effects unlinked to selection (sampling bias, unaccounted structure, hybrididdation)…

Lotterhos & Whitlock 2014 Mol Ecol

Outliers of divergence – signature of selection

Problem 3: Sample size

The power to detect meaningful differences based on genome-scan will depend on the number of populations, and the number of samples within a population

Table 2: Power for the one-refuge case analyzed with OutFLANK as a function of sample sizes, based on loci with $s_L = 0.01$, using >1,700 tests per case with a q value threshold of 5%

No. individuals per population	5 populations	10 populations	20 populations	40 populations
5	0	.09	.52	.84
10	.10	.56	.82	.94
20	.37	.75	.90	.95
40	.55	.81	.94	.97

Note: Parameters otherwise similar to those in figure 2.

Few samples per pop
-> stochasticity in allelic frequency

Few populations
-> low statistical power

Lotterhos & Whitlock 2014 Mol Ecol

Outliers of divergence – signature of selection

Problem 4: Background selection

Fst is a relative measure of variation among populations. Low heterozygosity can inflate Fst values even for small differences in allelic frequencies…

For e.g. background selection (negative selection in regions of low-recombination)

-> Should we use other measures: dxy ? (but lower power for early stages of divergence)

AFD : Allelic frequency differences?

(Berner 2019, Genes 10.3390/genes10040308)

-> but the effect of background selection on Fst may not be that bad for populations connected by high gene flow.

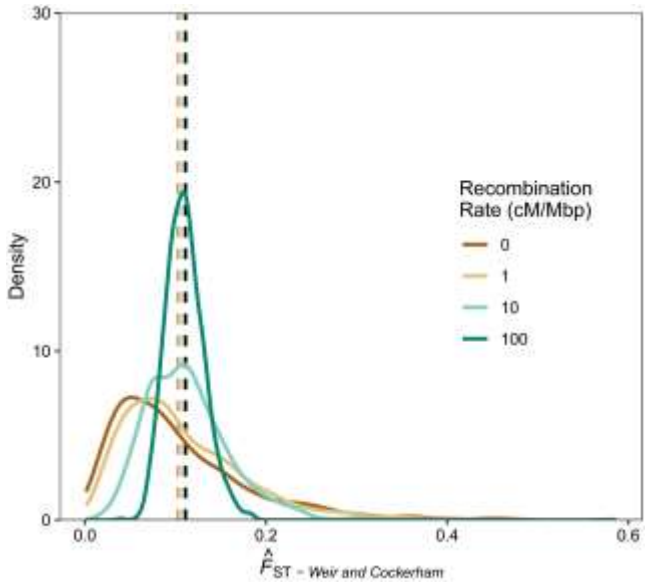
See Matthey-Doret & Whitlock 2019 MolEcol https://onlinelibrary.wiley.com/doi/abs/10.1111/mec.15197

Outliers of divergence – signature of selection

Problem 5: Recombination

Even without selection, Fst variance is expected to be higher in low-recombination regions…
-> Should we use a different threshold depending on recombination??

See Booker, Yeaman & Whitlock 2020 MolEcol
https://onlinelibrary.wiley.com/doi/abs/10.1111/mec.15501



A field in development with upcoming whole-genome data…

Outliers of divergence – signature of selection

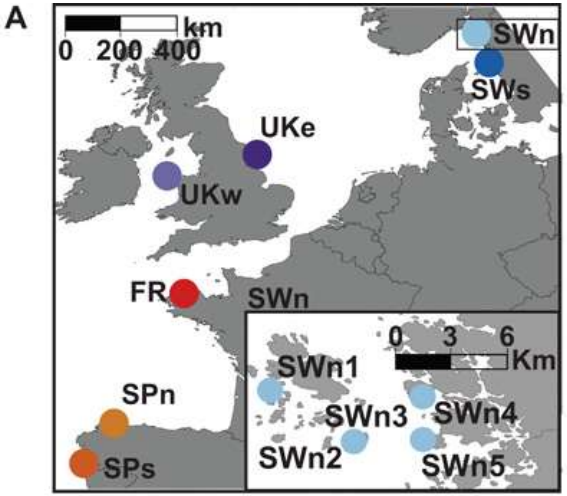
But the main problem is: how can we interpret the results?

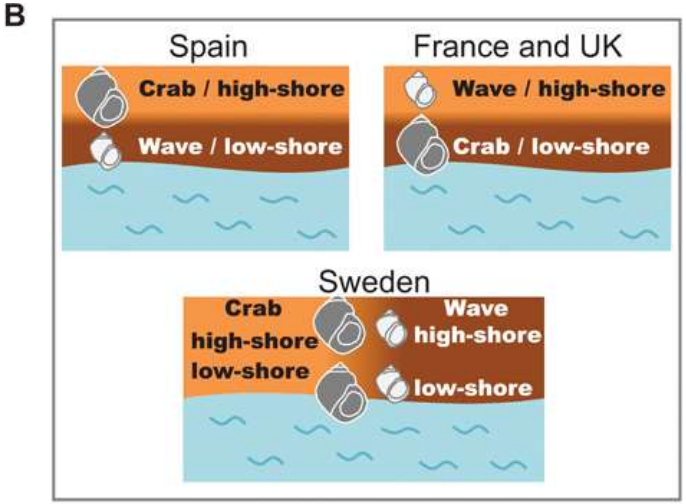
Outliers tests can be useful to remove “putatively-adaptive” loci from analysis of neutral structure/demography…
->But do we want to avoid taking into account adaptation or specific loci showing traces of differentiation?!

What does outliers of differentiation means?
-> depend on the study design/ecological information…

Outliers of divergence – signature of selection

Pairs of populations: contrast Fst



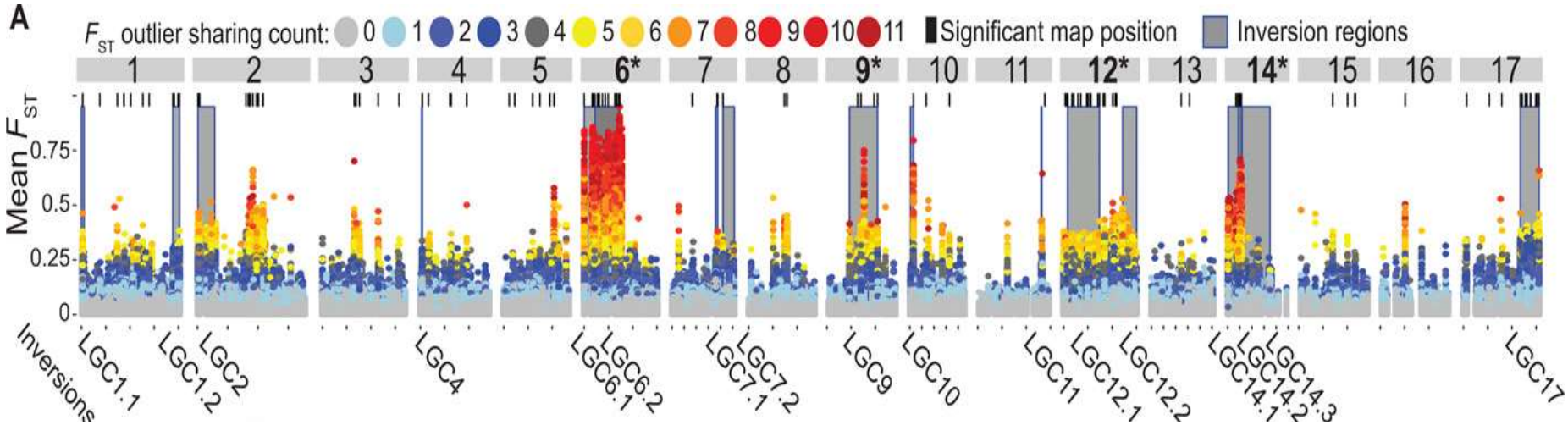


Outliers in pairs of *Littorina* ecotypes Crab vs Wave at different localities accross Europe…

Morales et al, 2019 Science advances
https://doi.org/**10.1126/sciadv.aav9963**

Outliers of divergence – signature of selection

Pairs of populations: contrast Fst

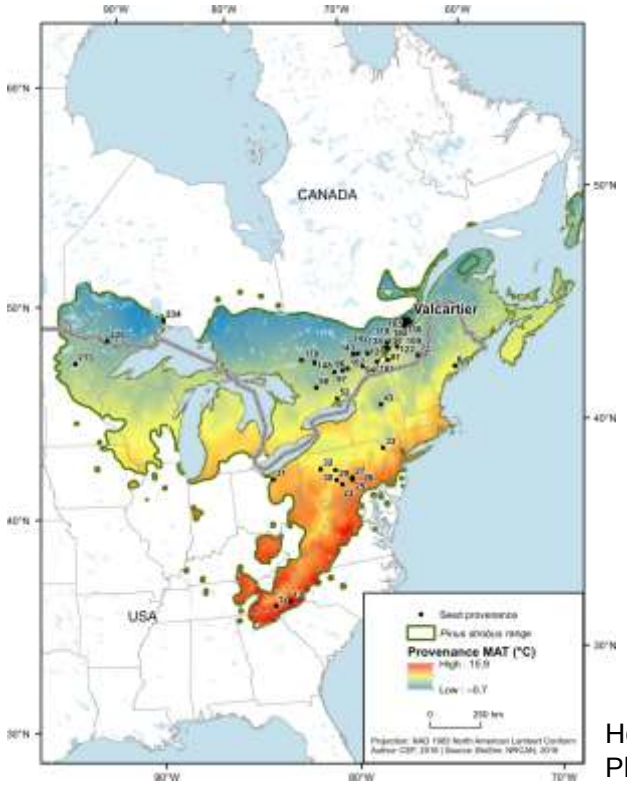


Fst Crab vs Wave at different localities accross Europe: outlier sharing

Morales et al, 2019 Science advances https://doi.org/**10.1126/sciadv.aav9963**

Outliers of divergence – signature of selection

Along a cline, accross a geogaphic gradient



Housset, 2018, New Phytologist

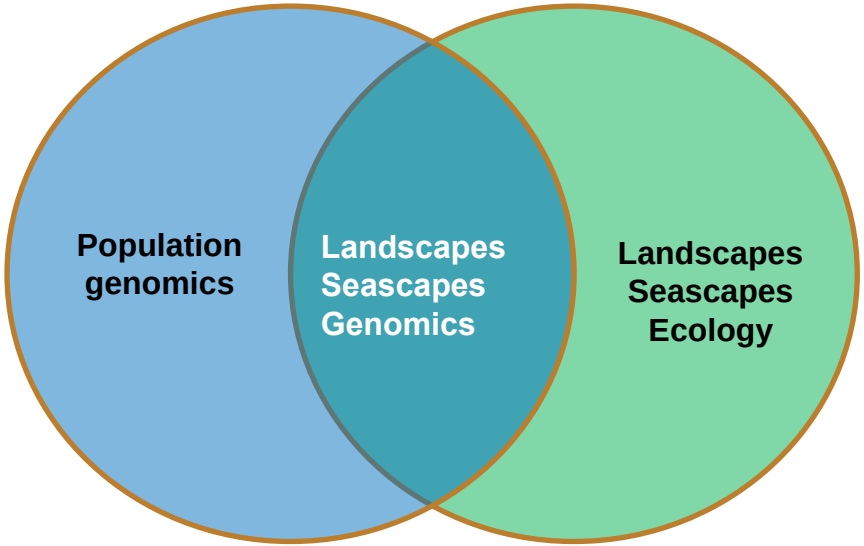
Ecological information
+
Genetic information

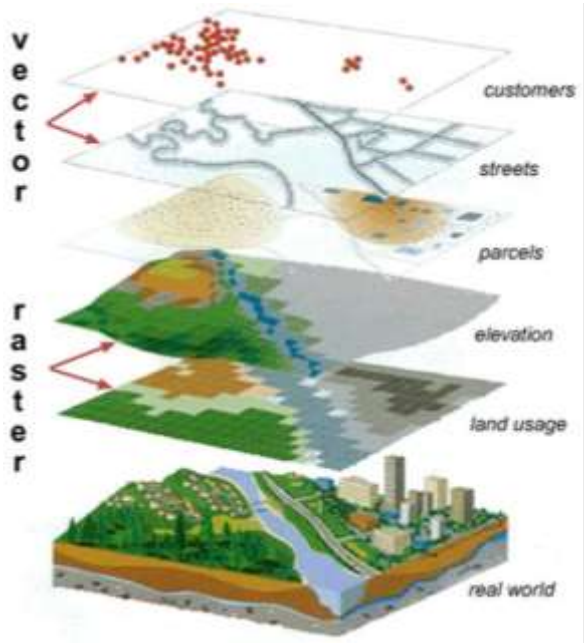
⇒ hypothesis: populations experiencing the same selective pressures (same environment) will be less differentiated then populations experiencing different ecological conditions at adaptive loci

Landscapes genomics and environmental associations

Lanscapes or seascapes genomics contribute to understand both neutral and adaptive genetic variation

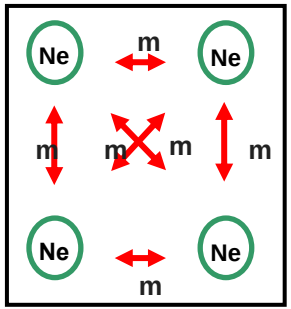
Genetic diversity
- Many samples
- Many populations

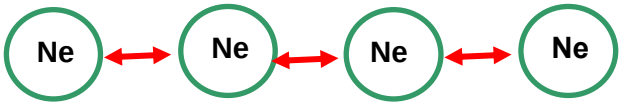




Landscapes genomics and environmental associations

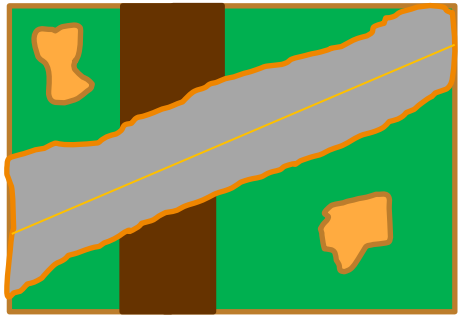
- a better understanding of gene flow & connectivity



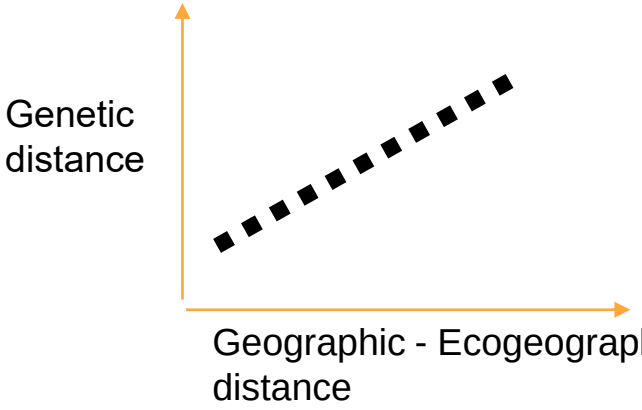


Isolation-by-distance?

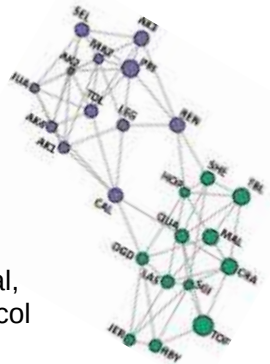
Isolation-by-distance
along least-cost-path?

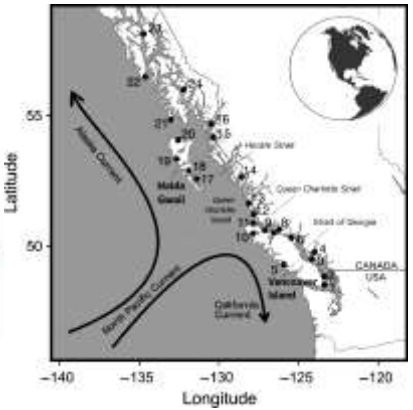


Isolation-by-resistance?



Complex
connectivity





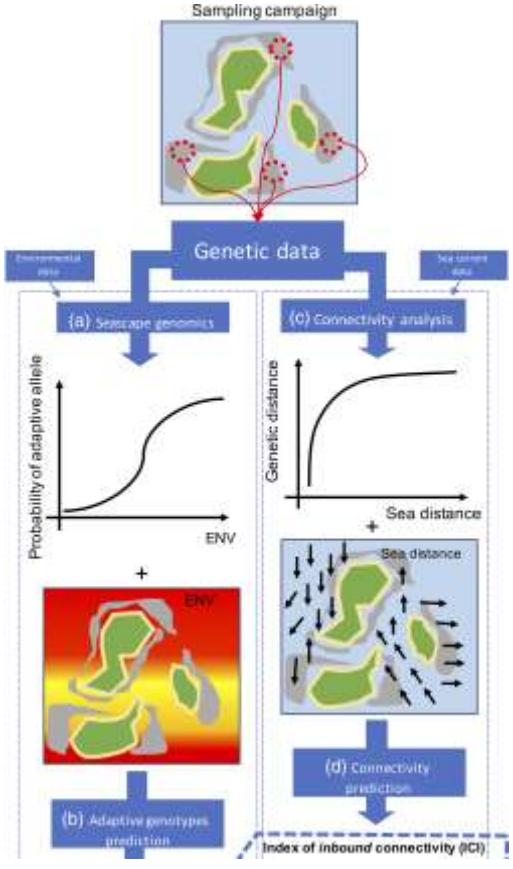
Xuereb et al,
2018 MolEcol

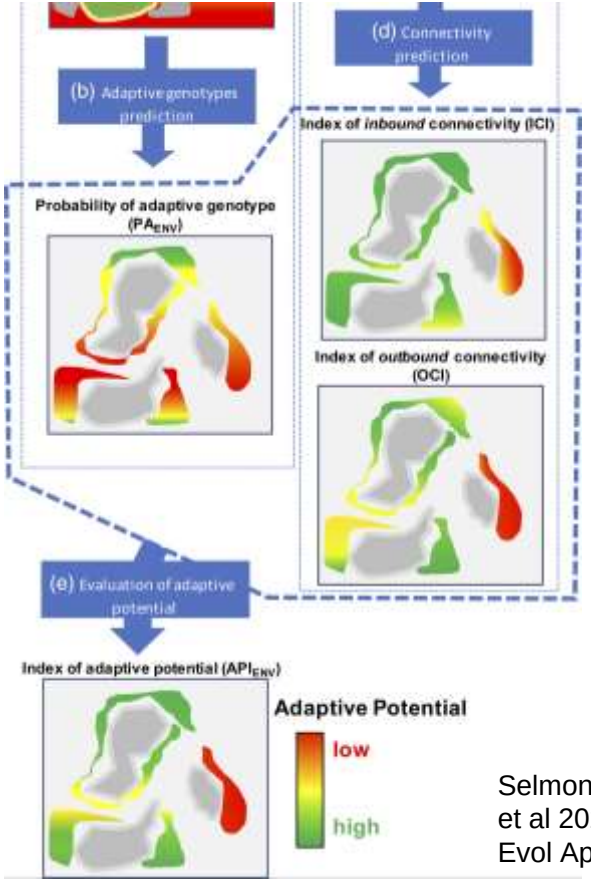
Landscapes genomics and environmental associations

- Analyzing adaptation to known ecological variables

⇒ A better sense of why populations are differentiated?

⇒ Predictions for models of adaptation, response to climate change, etc



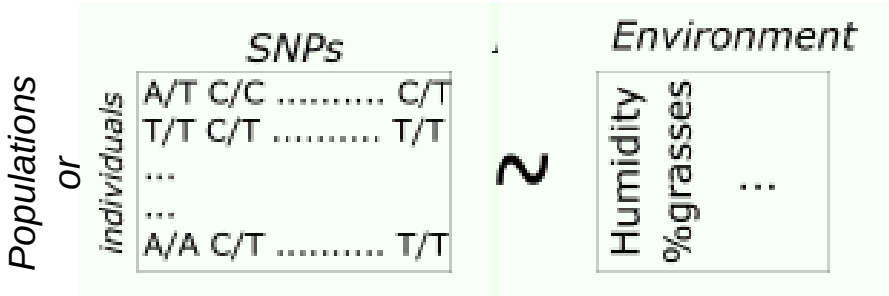


Selmoni et al 2020 Evol App.

Landscapes genomics and environmental associations

Environmental associations methods

G ~ E (+ correction?)



- Univariate methods : locus by locus

(correlation freq/env, LFMM, Bayenv/Baypass, etc)

Genome scan methods against more complex models: when and how much should we trust them? (Villemereuil et al, 2014 MolEcol)

- Multivariate methods

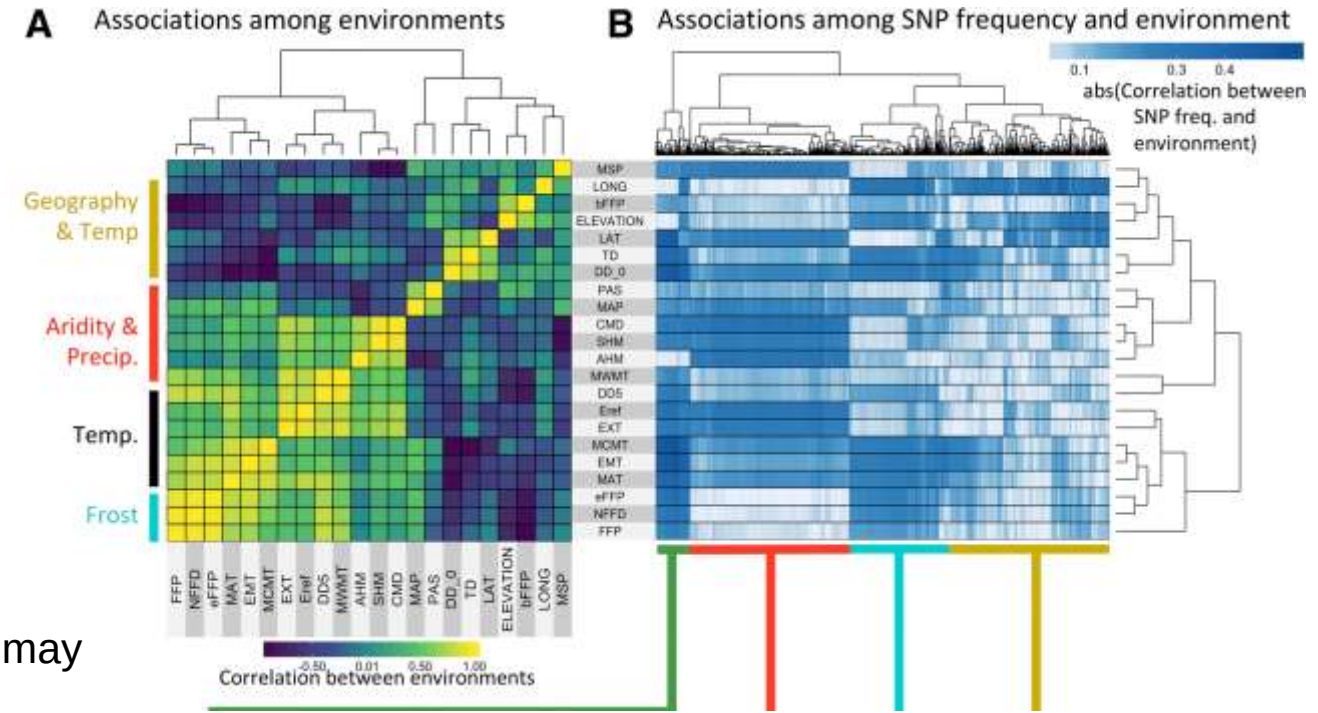
(redundancy analysis RDA)

Comparing methods for detecting multilocus adaptation with multivariate genotype–environment associations (Forester et al 2018, MolEcol)

Landscapes genomics and environmental associations

Univariate associations:

Which locus is associated with which environmental variable?
-> Spearman's correlation



Caution:

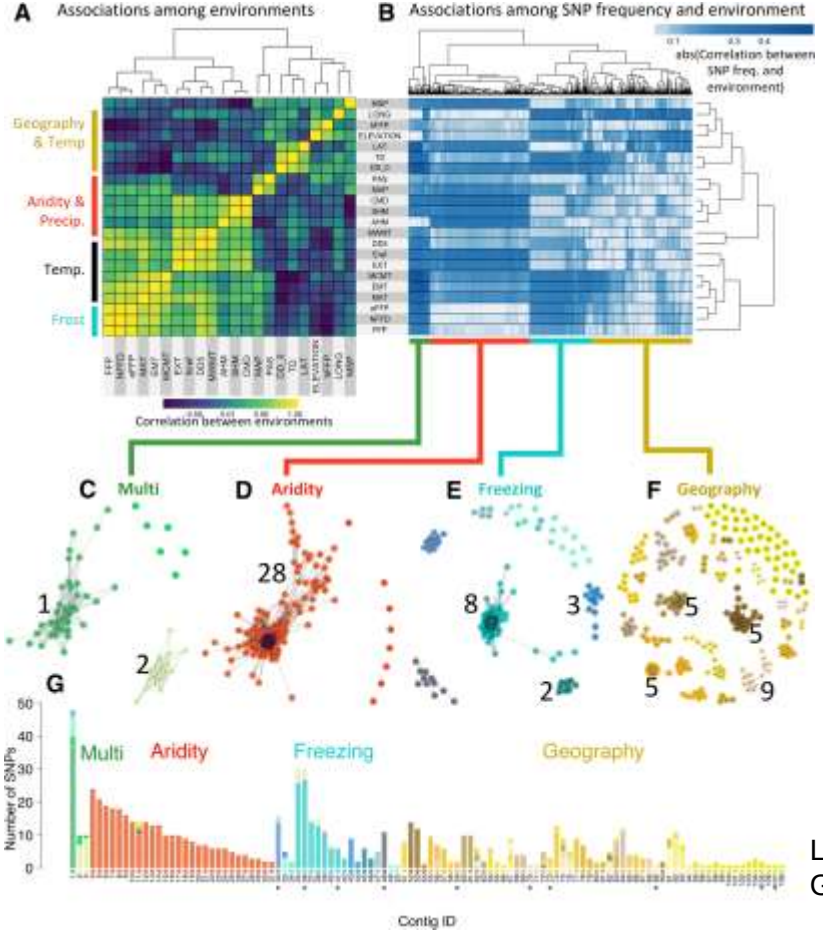
- environmental variables may be correlated!
- SNPs may be in physical LD

Lotterhos et al, 2018
Genome Biology

Landscapes genomics and environmental associations

Univariate associations:

Modular group of adaptive loci to different axis of environmental variation

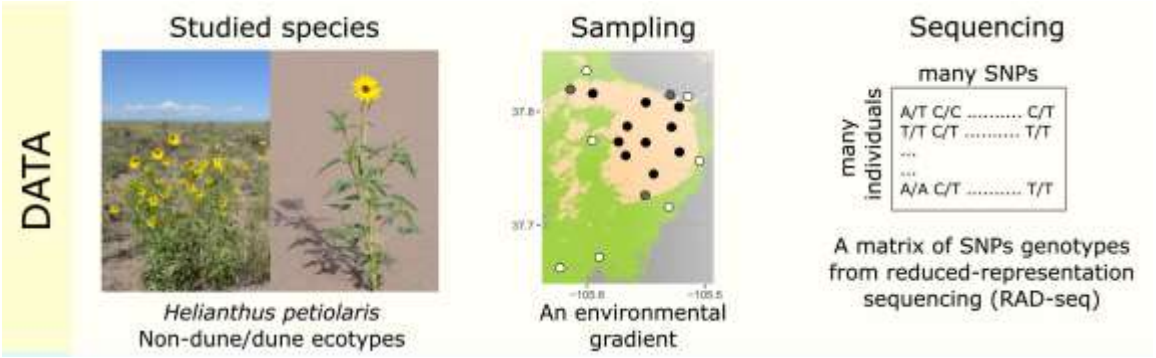


Lotterhos et al, 2018
Genome Biology

Landscapes genomics and environmental associations

Univariate associations:

Bayenv2 – Baypass



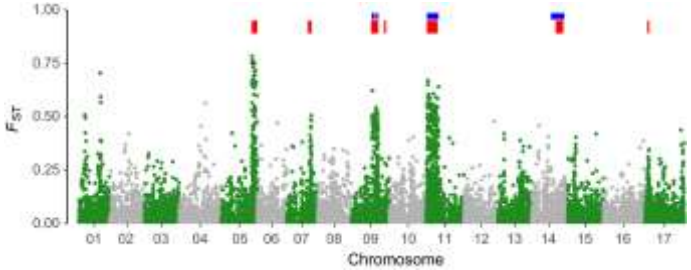
Huang et al, 2020 MolEcol

Landscapes genomics and environmental associations

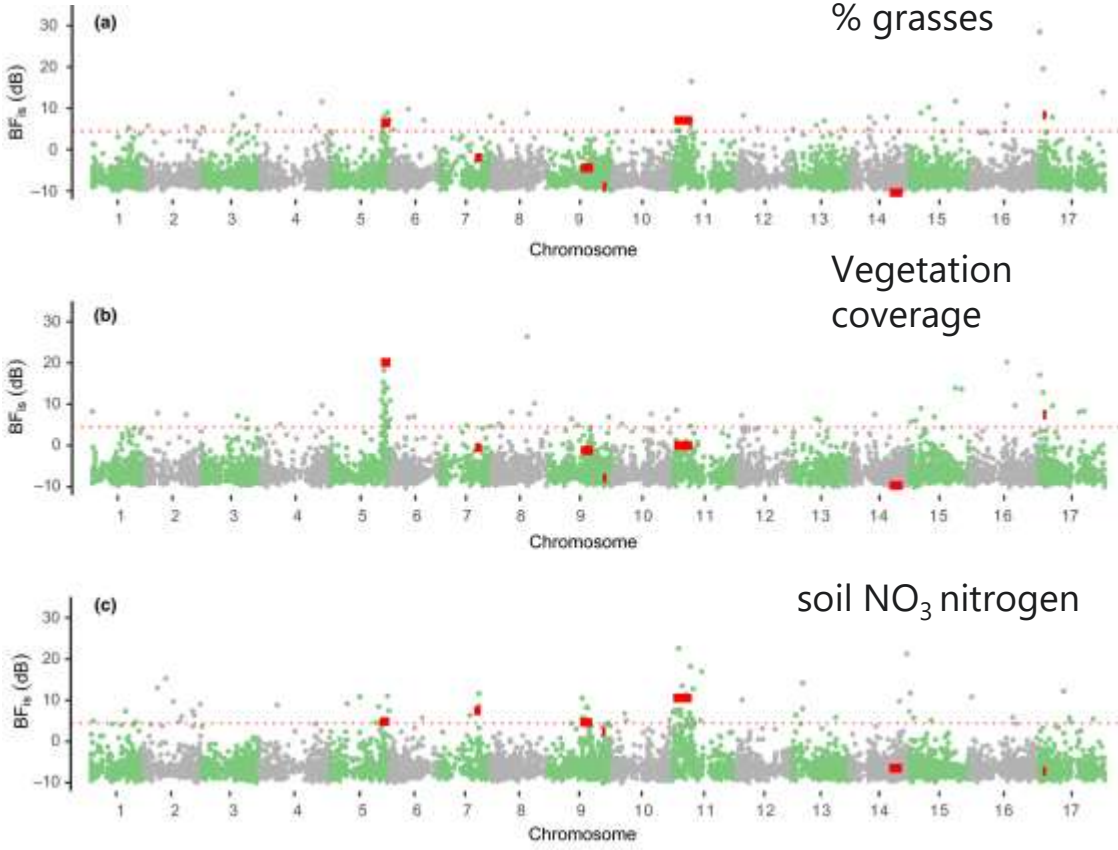
Univariate associations:

Bayenv2 – Baypass

FST outliers



Env. Assoc.



Huang et al, 2020 MolEcol

Landscapes genomics and environmental associations

- Univariate associations: LFMM (latent factor mixed model)

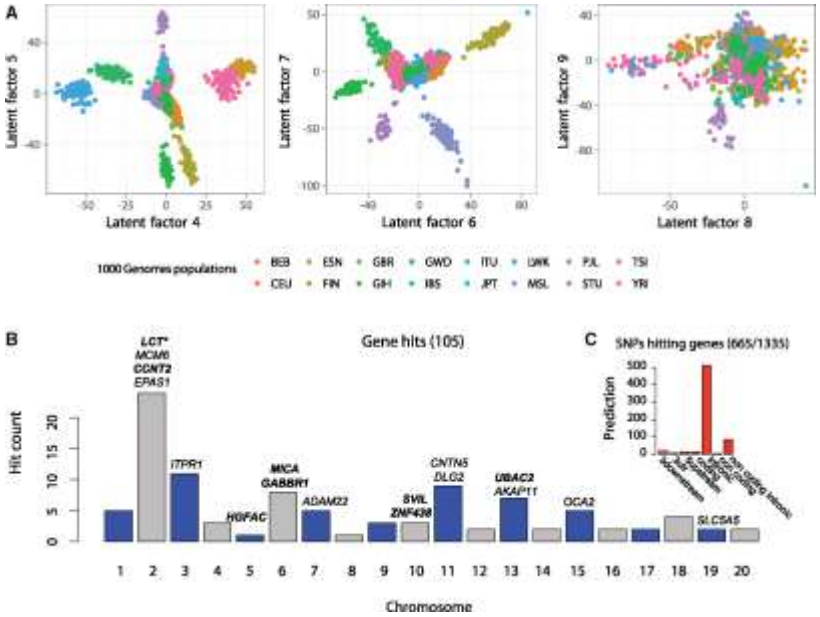
- Detects correlations between environmental and genetic variation while simultaneously inferring background levels of population structure

- Residual population structure is introduced via unobserved K (latent) factors

- Latent factors represent demographic history, IBD, hidden substructure

- Lfmm2: New & faster version which can works on SNP or methylation matrix

Caye et al, 2019, Molecular Biology and Evolution https://doi.org/10.1093/molbev/msz008



Human GEA study. Association study based on genomic data from the 1000 Genomes Project database and climatic ...

Landscapes genomics and environmental associations

Univariate associations:

Recommendation:

- intersect of several methods

⇒ More likely to be strong candidates for adaptation

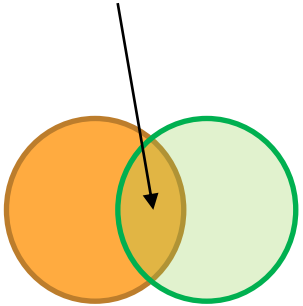
⇒ Reduce false positive but may also miss variants with less signal…

- Controlling false discovery rate

- Correct for population structure

⇒ An open debate?

⇒ Likely depends on the system: high gene flow? IBD? Geography correlated with environmental variation?

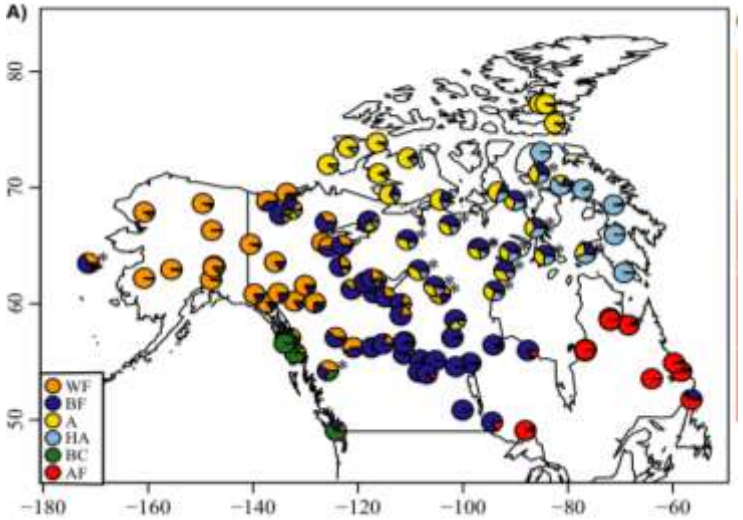


Controlling false discoveries in genome scans for selection
François et al, 2015, Molecular Ecology
https://doi.org/10.1111/mec.13513

Landscapes genomics and environmental associations

RDA

Multivariate associations:

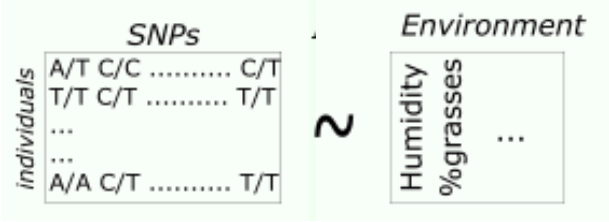


94 wolves
42 597 SNPs

species

sites

In community ecology (package vegan!)

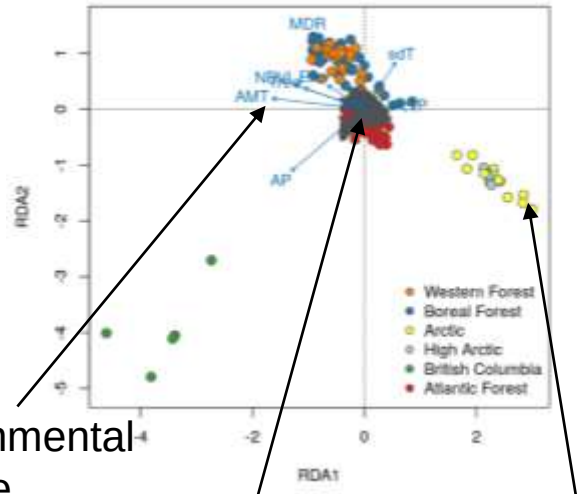


Forester et al 2018 Mol Ecol

Landscapes genomics and environmental associations

```
points(X.rda, display="sites")
```

Triplot RDA (individual centered)



Environmental variable

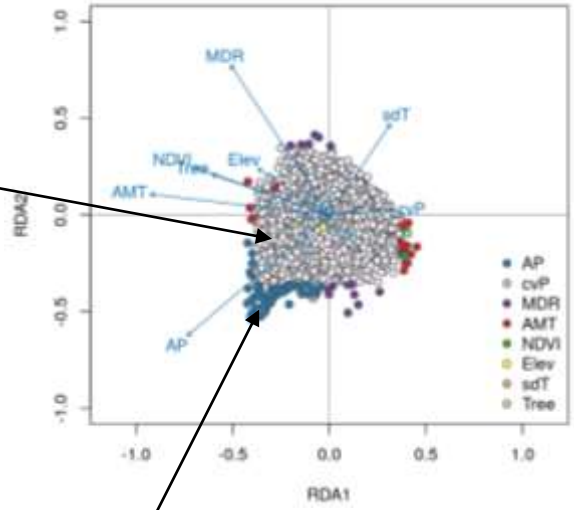
Genetic markers

Individual

RDA

```
points(X.rda, display="species")
```

Triplot RDA (SNPs centered)



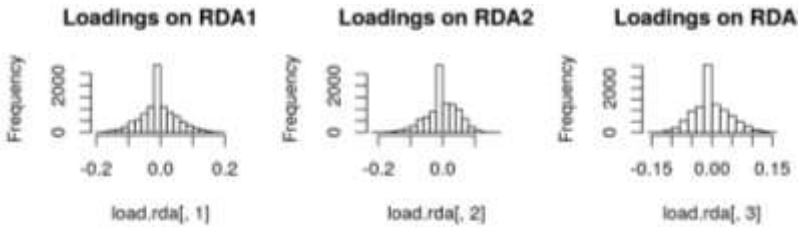
Neutral marker

Outlier marker putatively associated to *AP* variation

Forester et al 2018
Mol Ecol

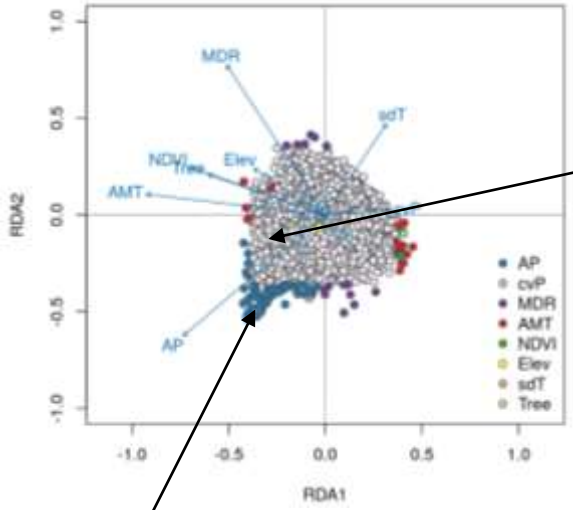
Use the contribution of genetic markers along the different axis to detect putatively-selected loci

Landscapes genomics and environmental associations



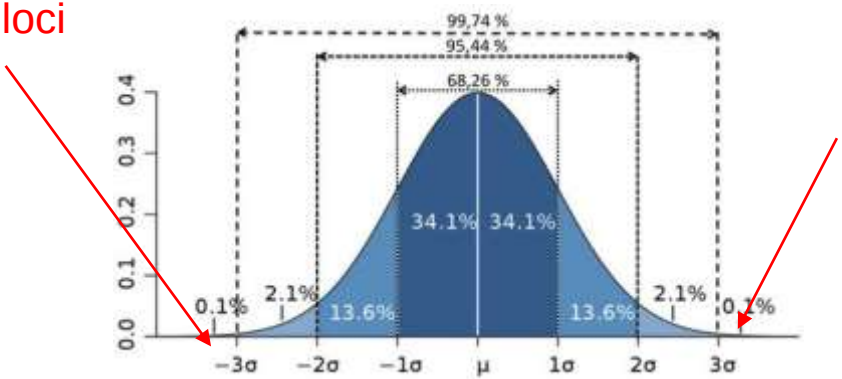

```
points(X.rda, display="species")
```

Triplot RDA (SNPs centered)



Neutral marker

Outlier loci

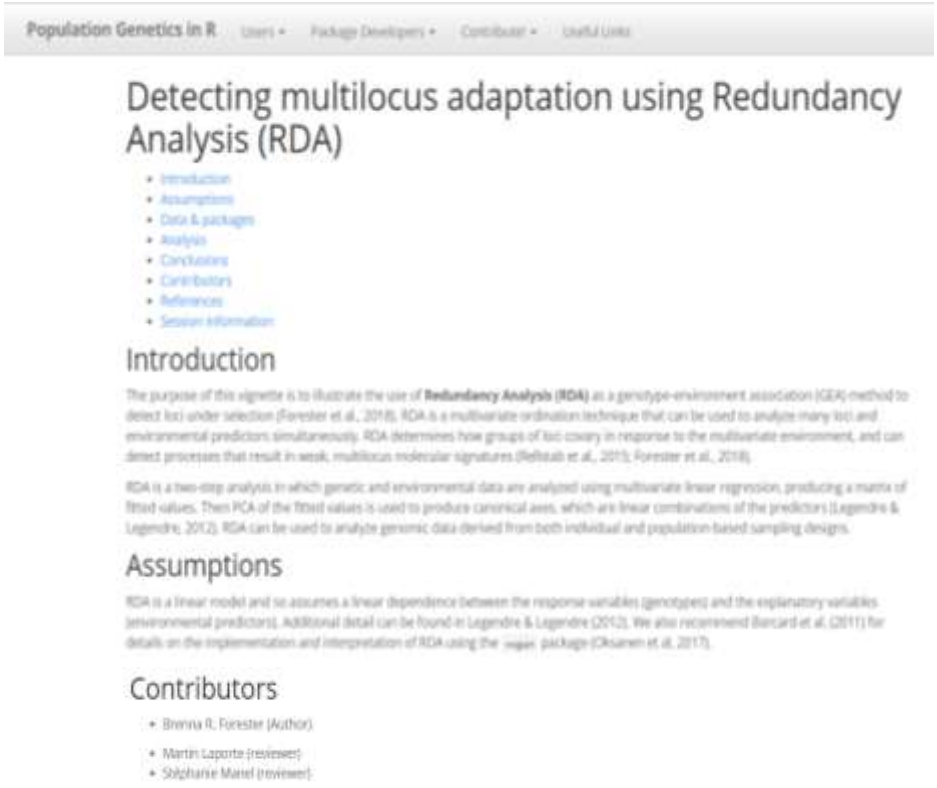


Outlier marker putatively associated to *AP* variation

Forester et al 2018
Mol Ecol

Use the contribution of genetic markers along the different axis to detect putatively-selected loci

A super good vignette to understand and do Rda analysis:
https://popgen.nescent.org/2018-03-27_RDA_GEA.html


Population Genetics in R

Detecting multilocus adaptation using Redundancy Analysis (RDA)

Introduction

Assumptions

Contributors

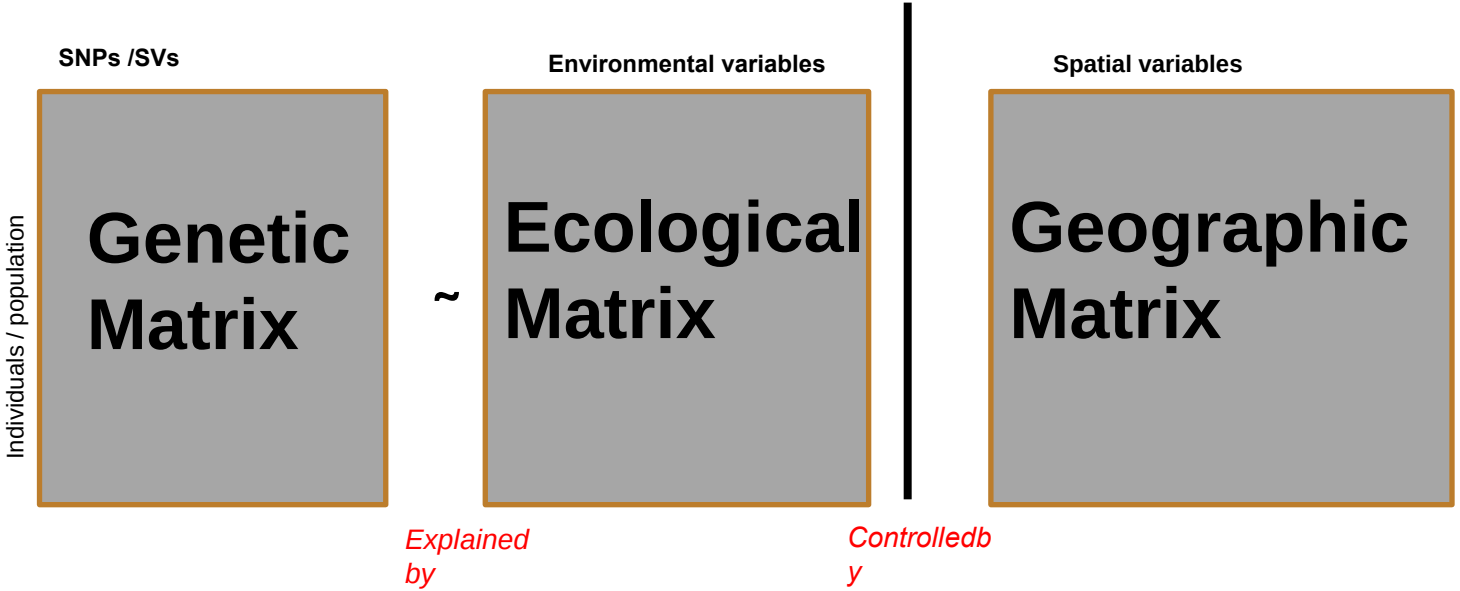
Multi-locus
-> Polygenic adaptation possible to detect?

Multi-variable analysis
-> realistic environmental caracterisation

Very fast + Global information:
- Which variables explain genetic variance?
- Correction possible by population/geographic structure

Landscapes genomics and environmental associations

RDA



https://doi.org/10.1016/B978-0-444-53868-0.50014-9

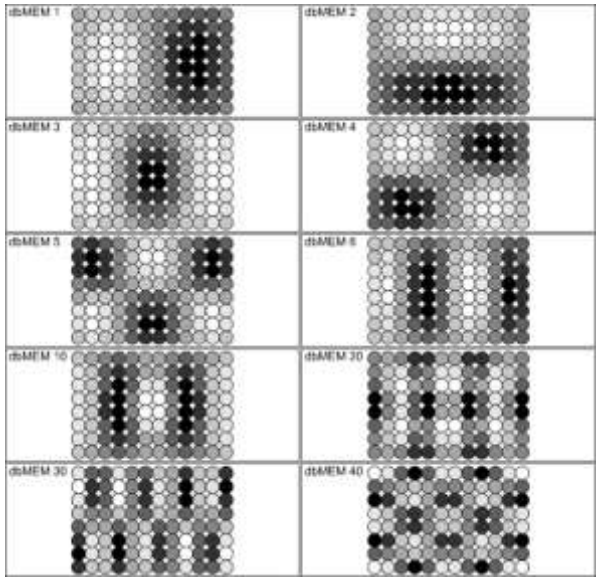
RDA

Spatial-eigen vectors are a way to reduce a distance matrix between samples/populations
-> not necessarily neutral
-> describe different possible spatial combination

G ~ E | S

Latitude + Longitude
or
Spatial eigenvectors

= db-MEM



More information:
Legendre & Legendre
https://doi.org/10.1016/B978-0-444-53868-0.50014-9

Landscapes genomics and environmental associations

A must-read:

Finding the Genomic Basis of Local Adaptation: Pitfalls, Practical Solutions, and Future Directions
Hoban et al 2016 Am Nat
https://www.journals.uchicago.edu/doi/full/10.1086/688018