Representing long-range genetic similarity on a background of spatially heterogeneous IBD

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PUERTO VALLARTA

Acknowledgements

<u>Labs</u>:

- Berg
- Novembre
- Steinrücken

<u>Community</u>:

Program in Computational Biology

Biological Sciences Division

Outline

- Introduction + Motivation

- Spatially heterogeneous models of isolation-by-distance (IBD)

- Our model for long-range gene flow events (`FEEMSmix`)

- Results:
    1. Simulations
    2. North American grey wolves
    3. Afro-Eurasian panel of humans

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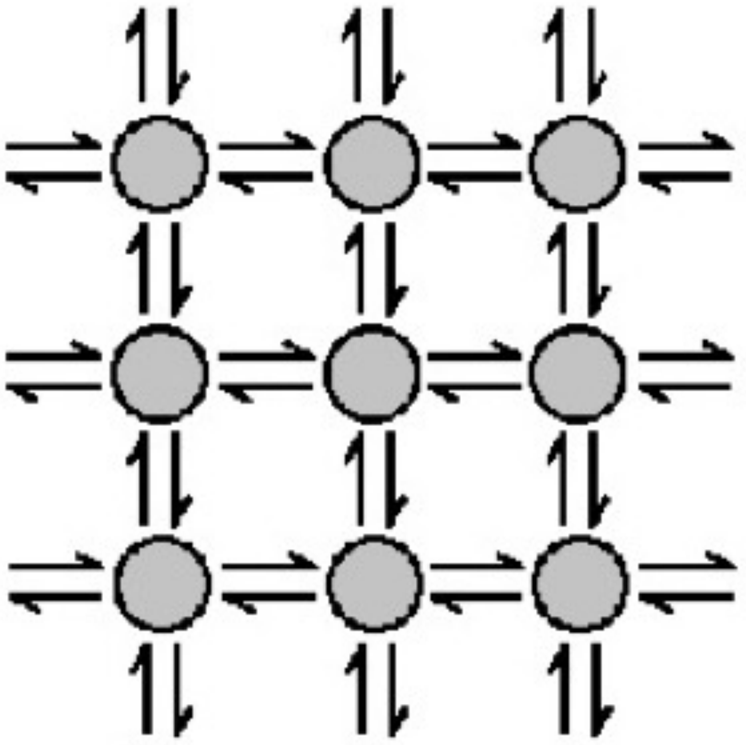
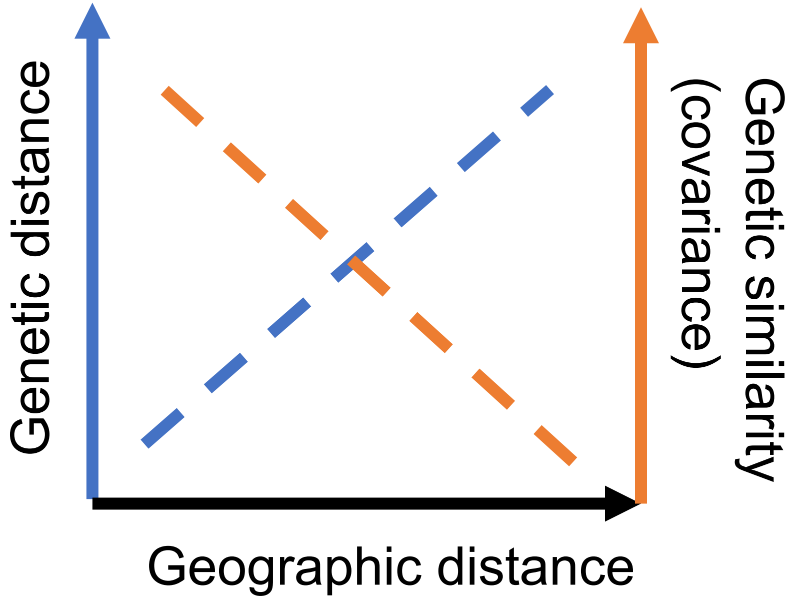
Major mode of gene flow in most species: IBD

"…accumulation of local genetic differences under geographically restricted dispersal."



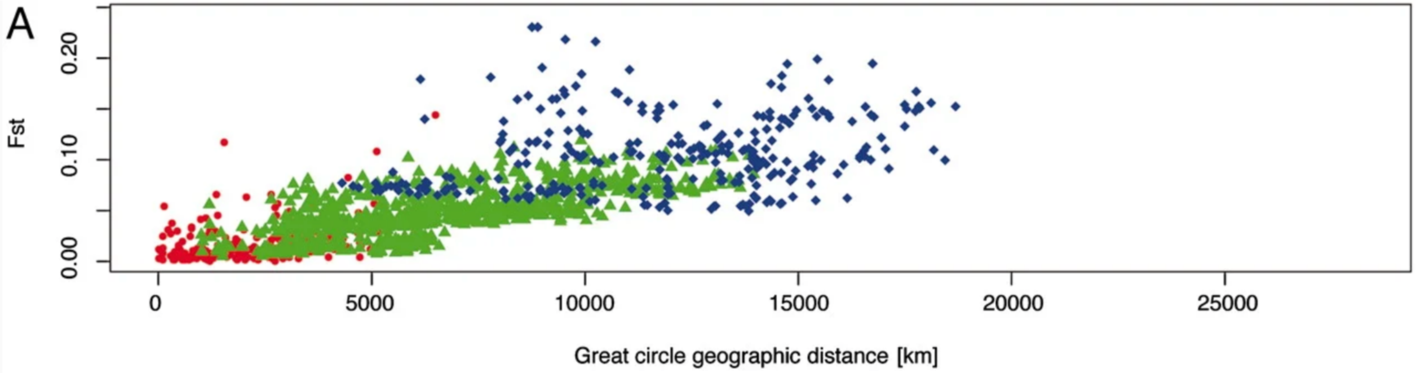
Pattern of IBD



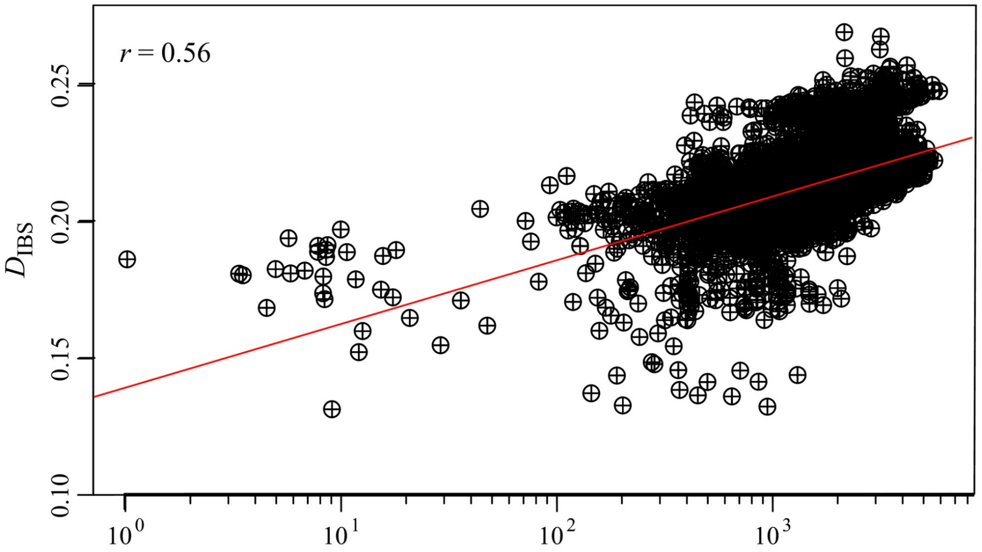
(initially formulated by Wright 1943)

A few examples of IBD in different species

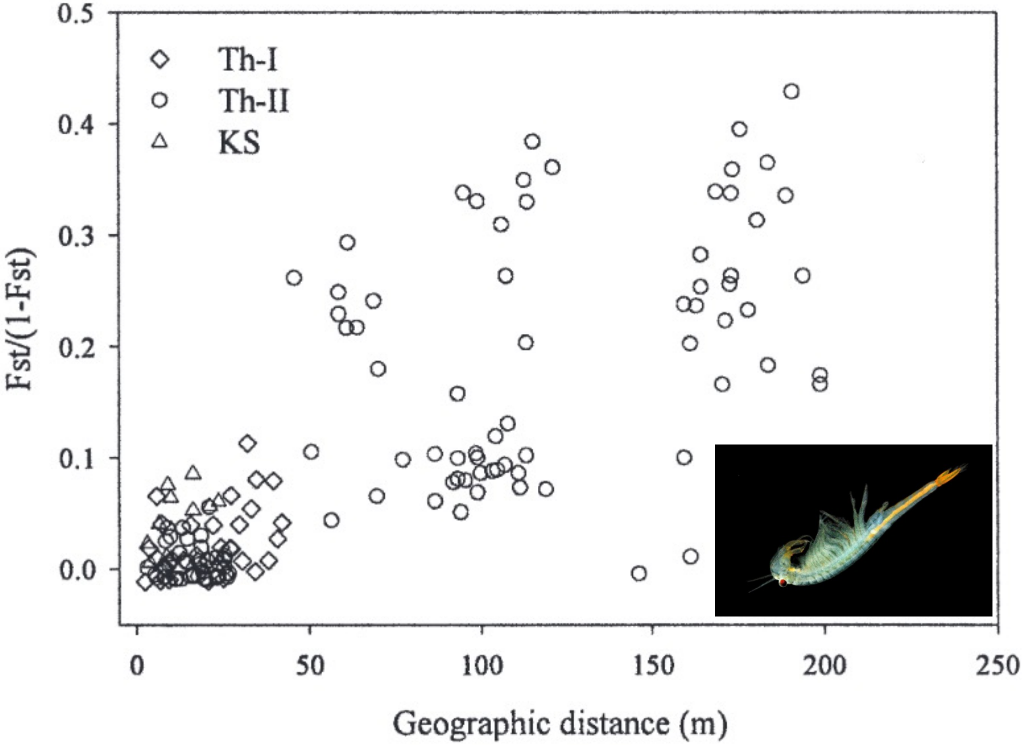
Humans (Ramachandran *et al* 2005)

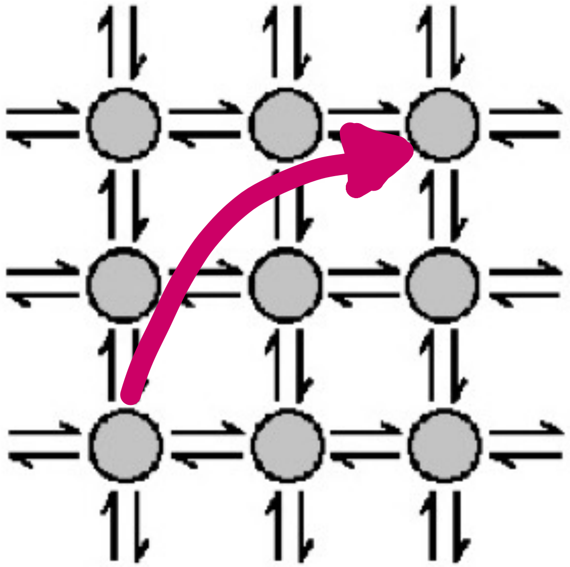


Grey wolves (Schweizer *et al* 2016)



Fairy shrimp (Hulsmans *et al* 2007)





Long-range gene flow events can cause deviations from this pattern of IBD…

Long-range gene flow events can cause deviations from this pattern of IBD…

…but so can a host of other genetic processes like fluctuating population size & assortative mating and other ecological processes like spatially heterogeneous landscapes & habitat fragmentation

Long-range gene flow can be caused by:

- Human-mediated translocations

Wolves in Yellowstone

Long-range gene flow can be caused by:

- Human-mediated translocations

- Extreme weather events

Tornado carrying a cow

Long-range gene flow can be caused by:

- Human-mediated translocations
- Extreme weather events
- Natural migration for greener pastures

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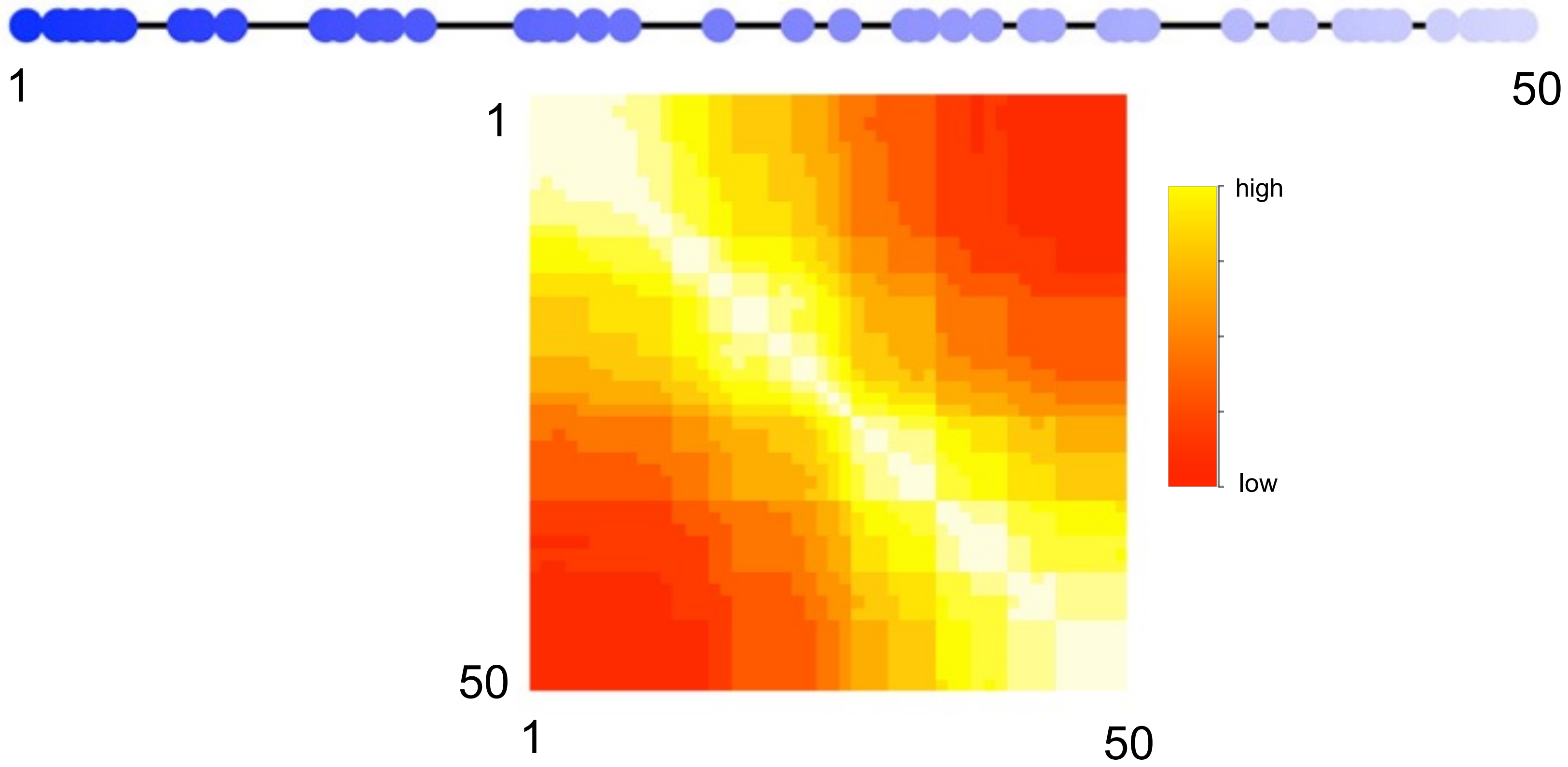
Spatial models of genetic variation

- Typically, revolves around modeling the **observed covariance matrix** of genotypes with an **expected covariance matrix**

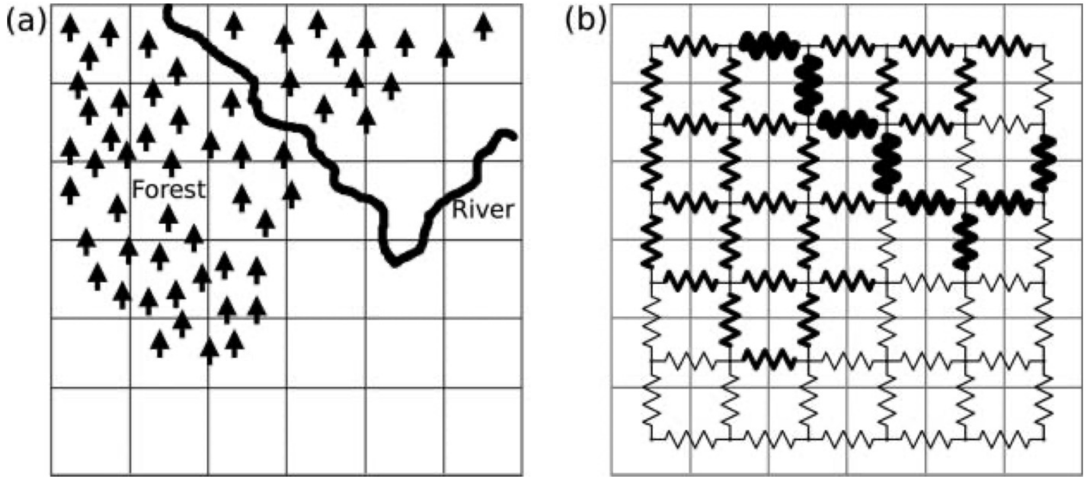


Constructing the expected covariance matrix

1. Parametric variogram (`SpaceMix`)

2. Deep neural networks (`disperseNN` & `Locator`)

3. **Pairwise coalescent times (approximated in `EEMS/FEEMS` using circuit theory)**

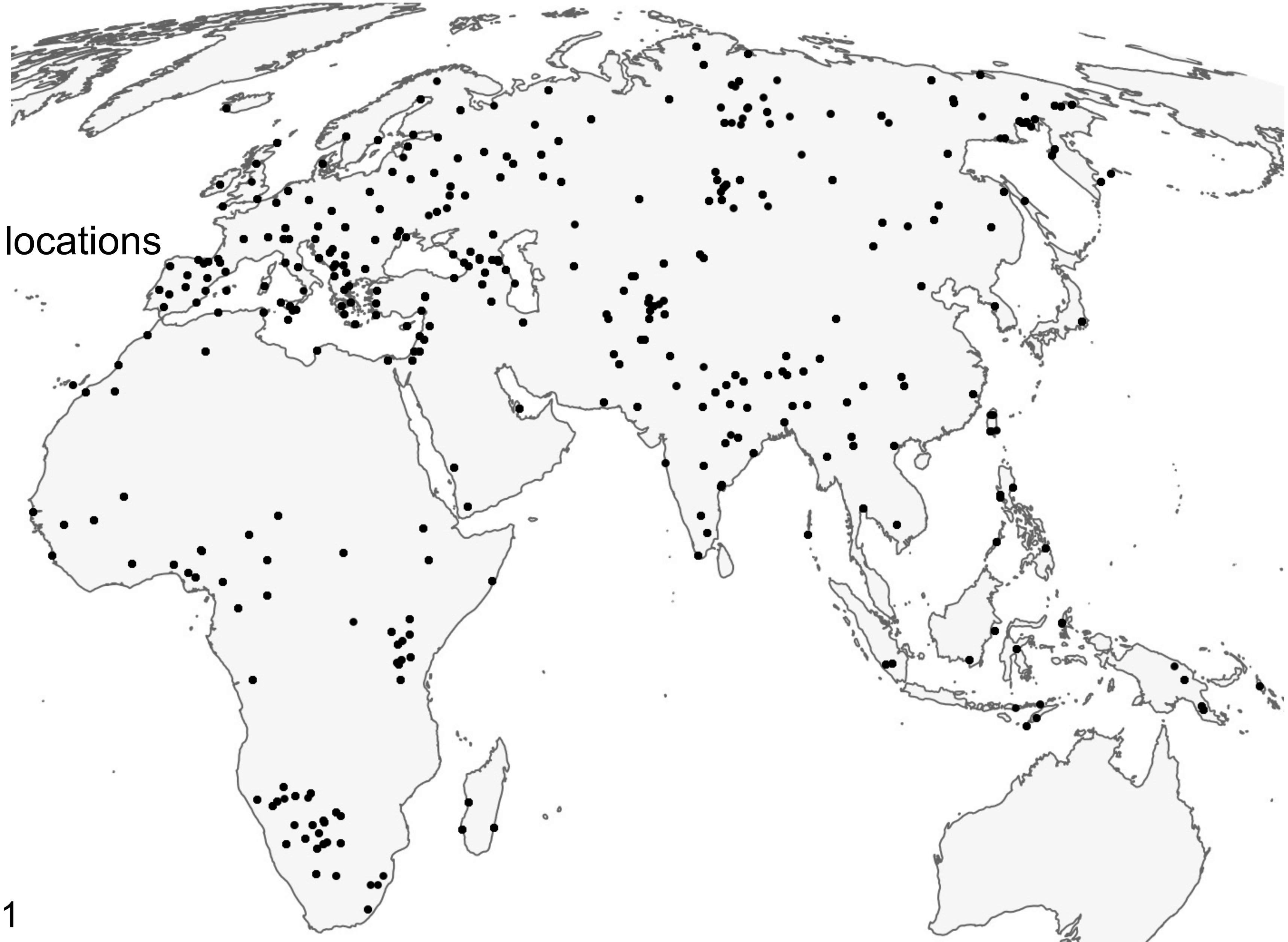


Fast
Estimation of
Effective
Migration
Surfaces

1. Bradburd *et al* 2016
2. Smith *et al* 2020
   Battey *et al* 2020
3. Hanks & Hooten 2013
   Petkova *et al* 2016
   Lundgren & Ralph 2017
   Marcus, Ha *et al* 2021

Brief overview of FEEMS

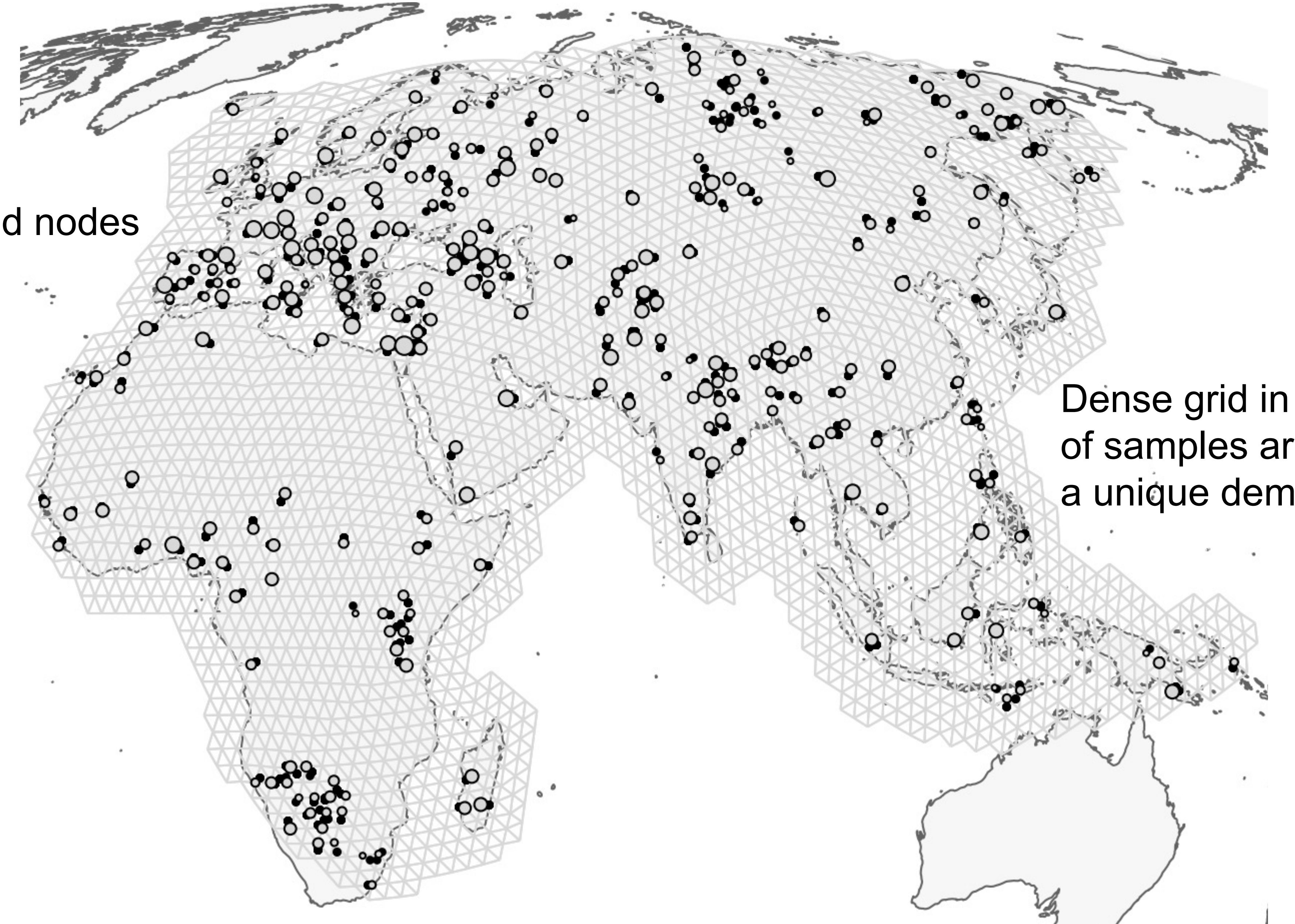
Sample locations



Marcus, Ha *et al* 2021

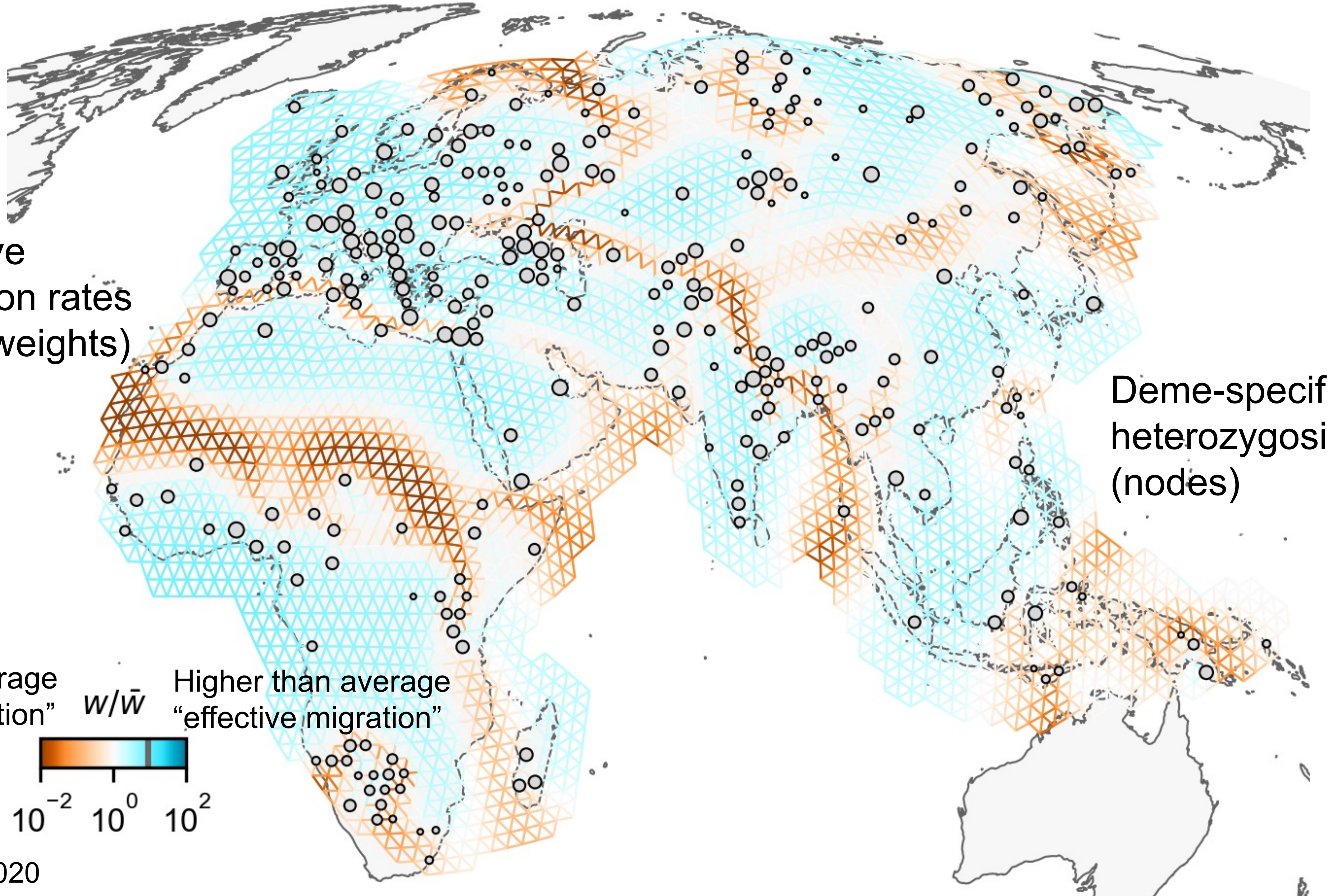
Graph construction & spatial assignment

Observed nodes (demes)



Dense grid in which ~80% of samples are assigned to a unique deme

Penalized likelihood estimation



Effective migration rates (edge weights)

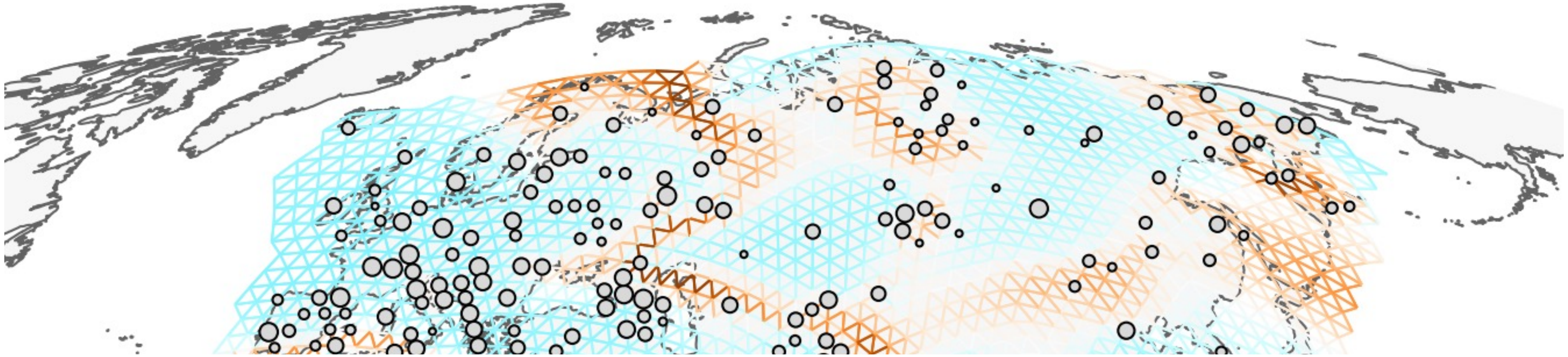
Deme-specific heterozygosity (nodes)

Lower than average “effective migration”

Higher than average “effective migration”

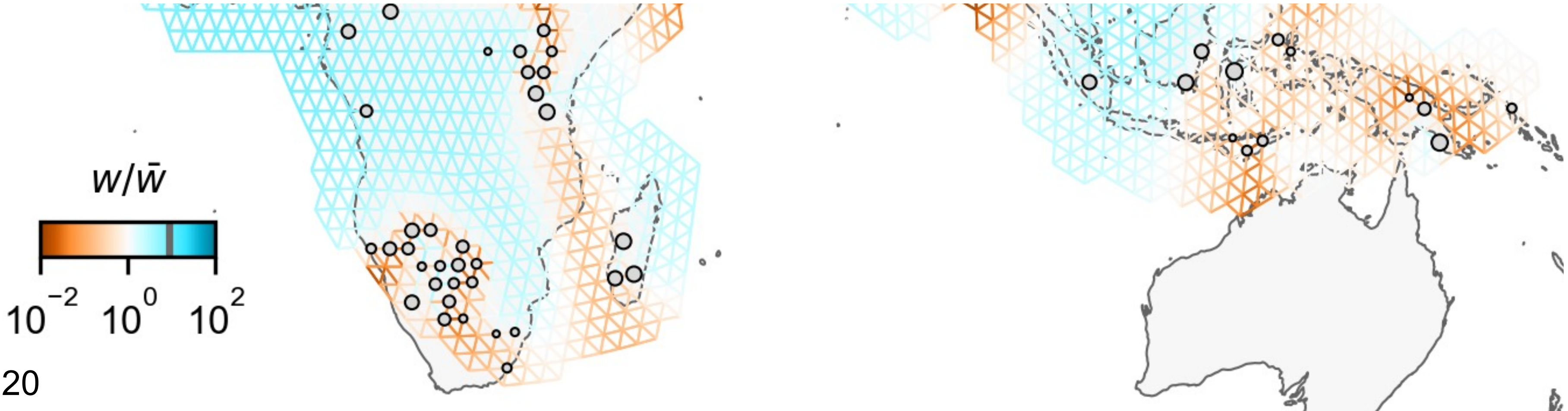
Data from Peter *et al* 2020

Penalized likelihood estimation



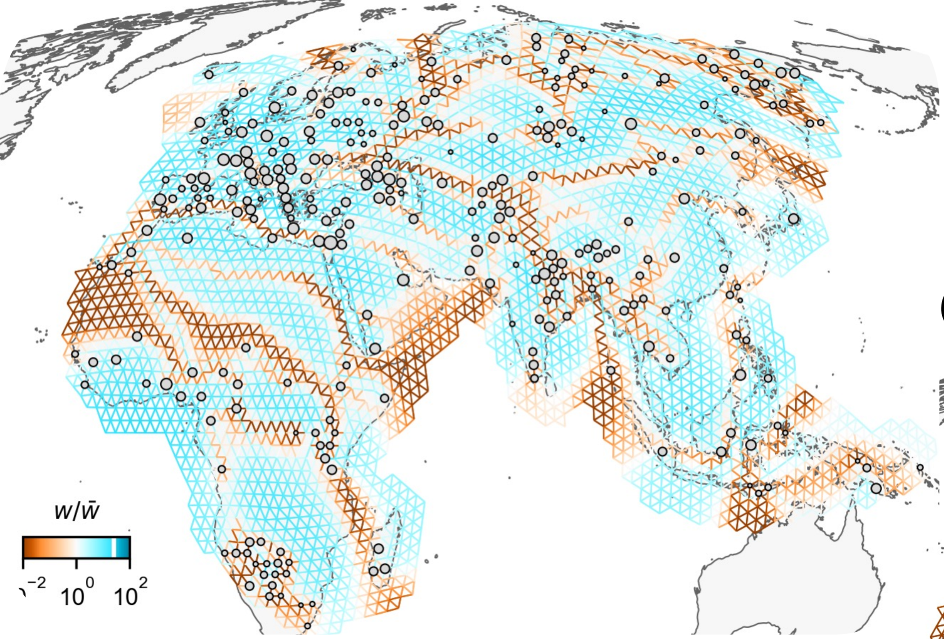
Assumptions:

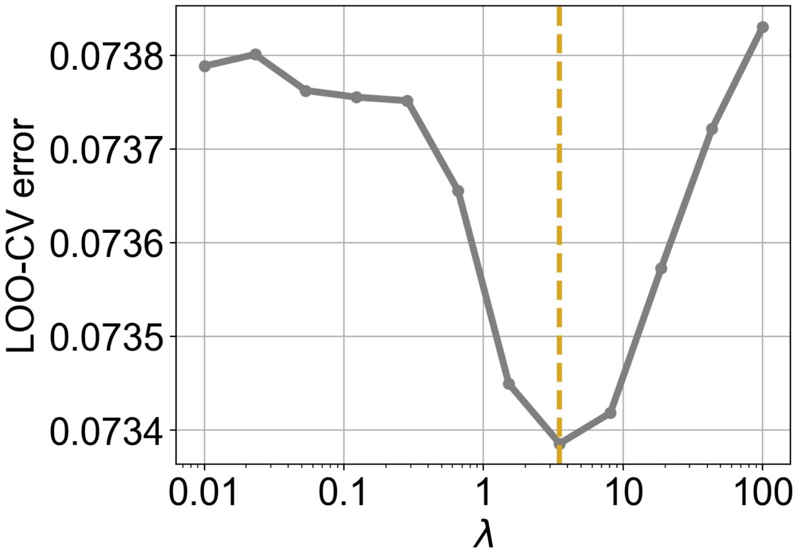
- •Allele frequency in a deme is normally distributed (unlinked SNPs)
- •Individuals are exchangeable within a deme
- •**Symmetric, time-stationary migration rates**



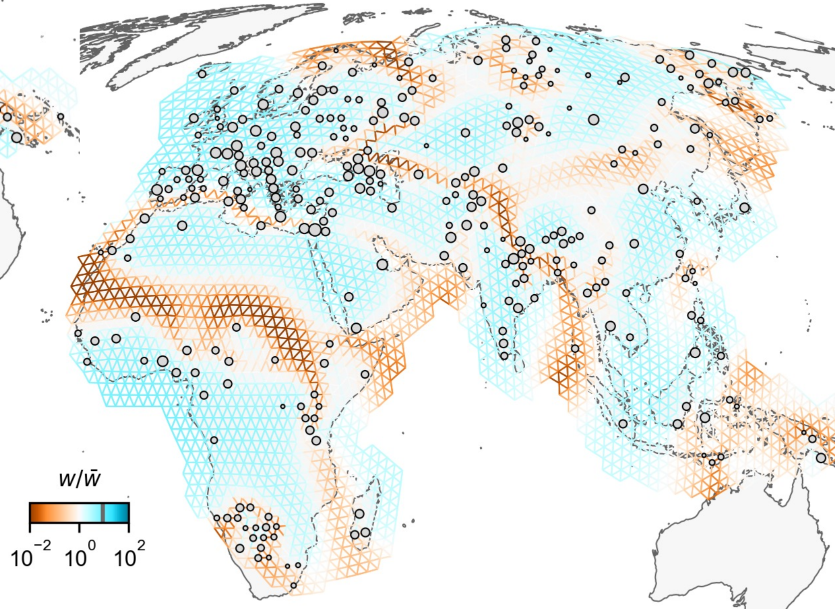
Data from Peter *et al* 2020

Lower λ ➔ discontinuous maps

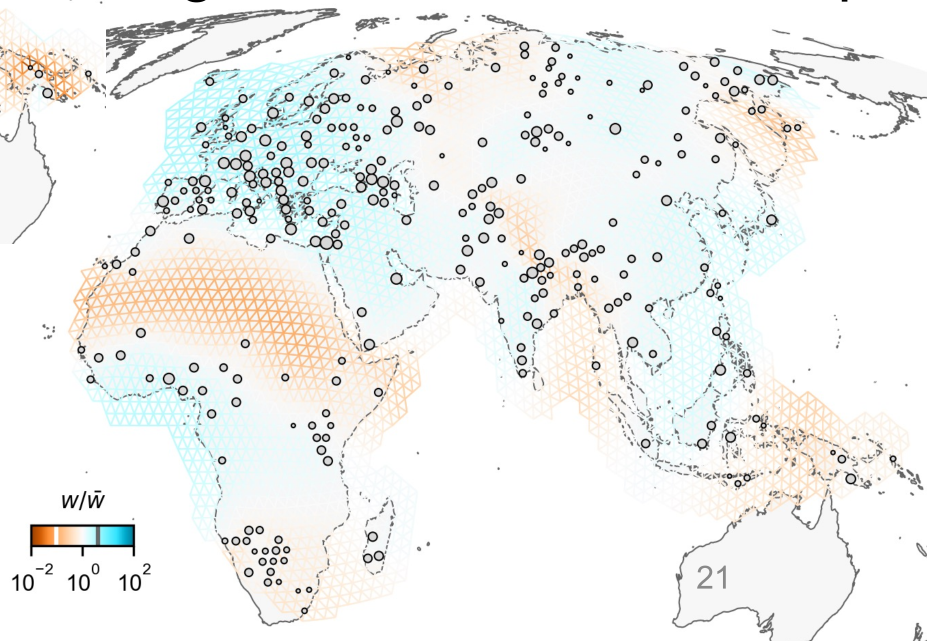




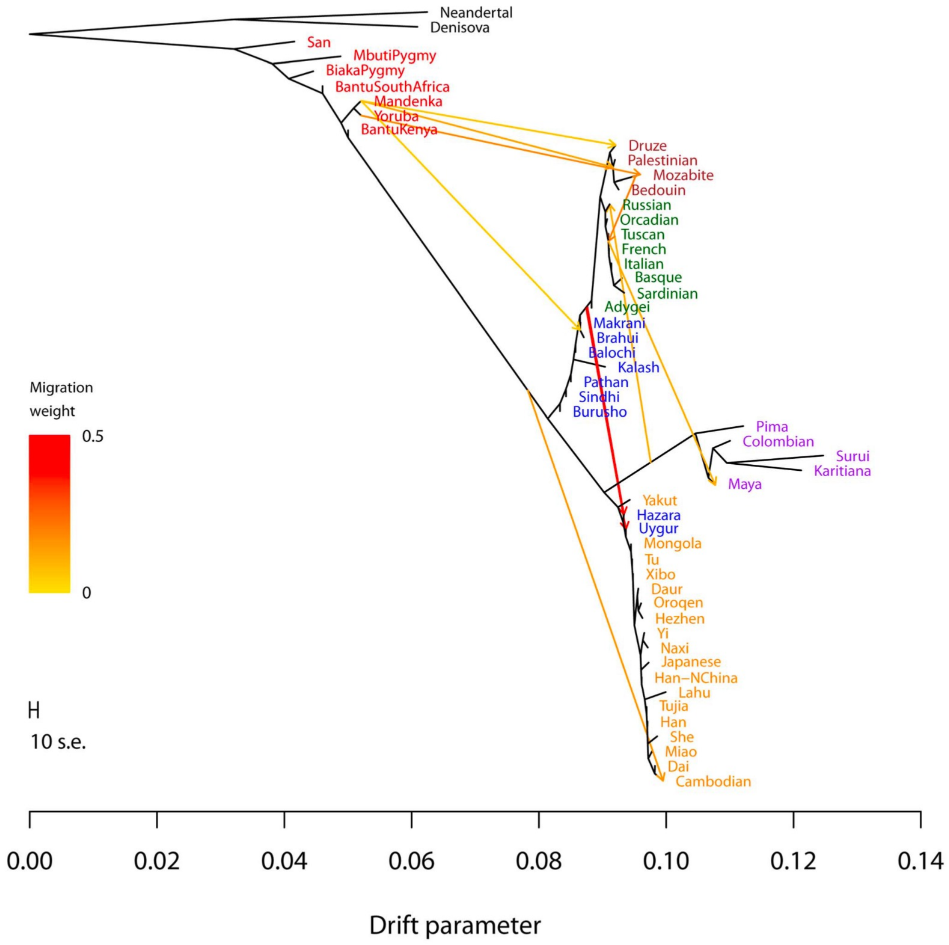
Optimal λ (chosen by CV)



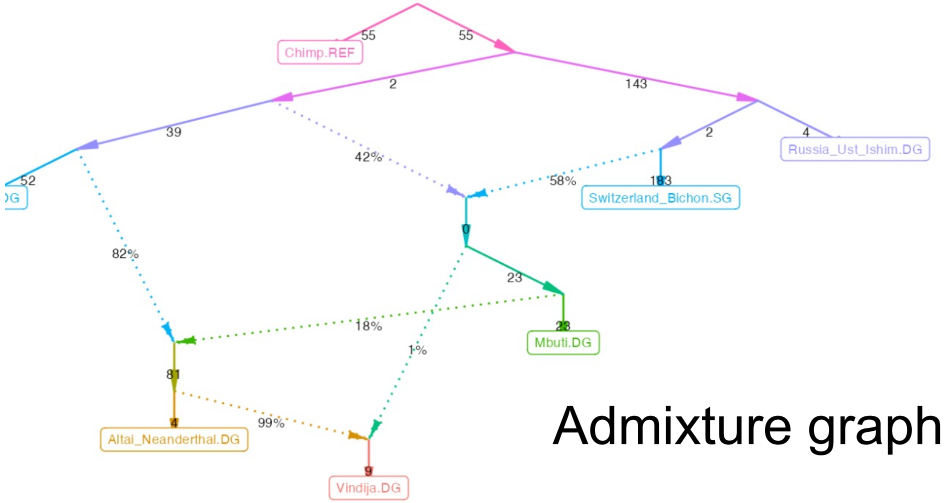
Higher λ ➔ smoother maps



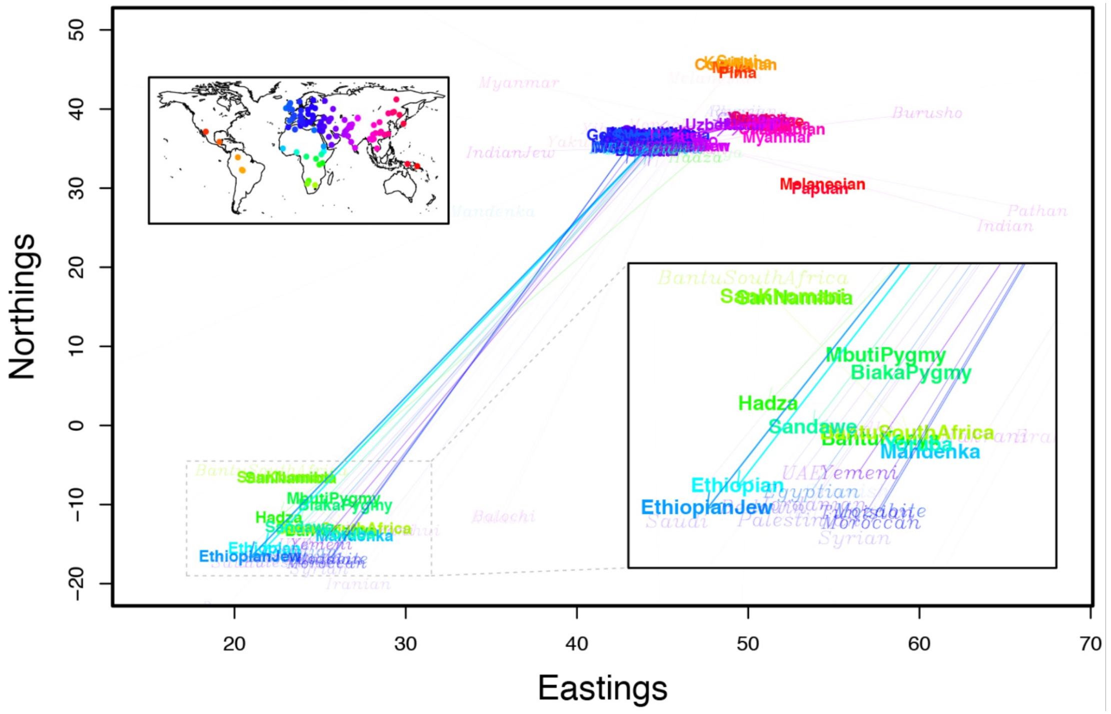
Previous work in estimating “long-range” gene flow events



`TreeMix` (Pickrell & Pritchard 2012)



Admixture graphs (Lipson *et al* 2013)



`SpaceMix` (Bradburd *et al* 2016)

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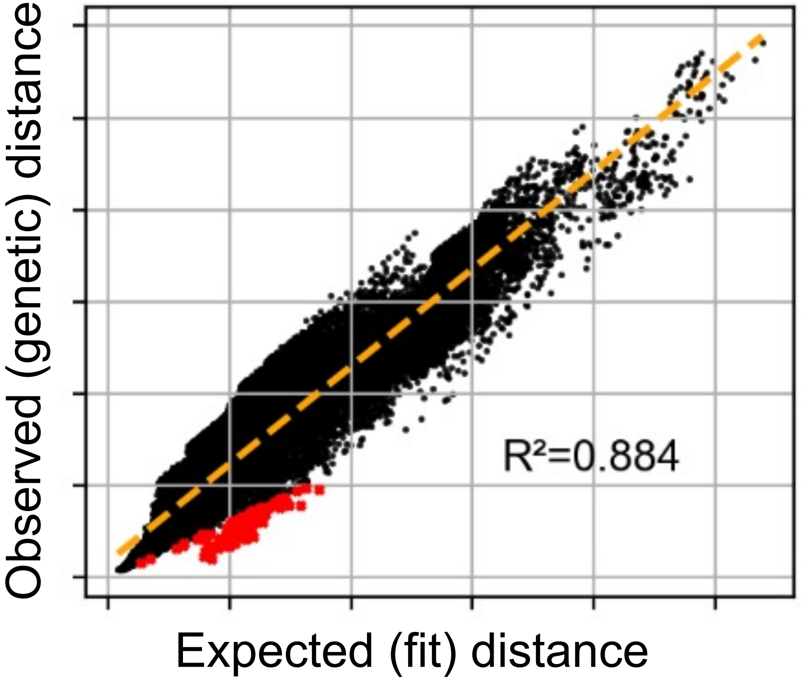
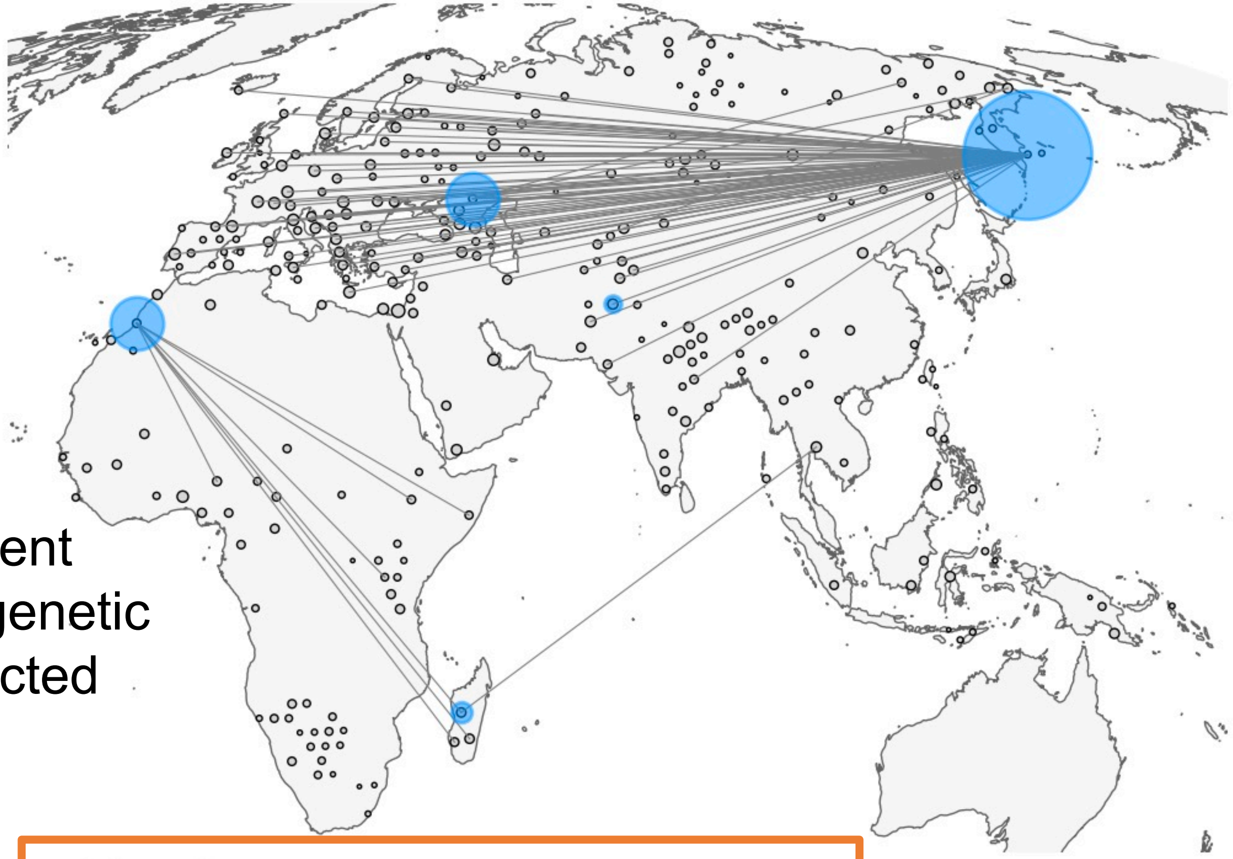
- Empirical results:
  1. North American grey wolves
  2. Afro-Eurasian panel of humans

FEEMSmix workflow



(red outliers represent pairs with smaller genetic distance than expected under the model)



$$T'_{ss} = T_{ss}$$
$$T'_{sd} = cT_{sd} + (1 - c)T_{ss}$$
$$T'_{dd} = (1 - c)^2 T_{dd} + 2c(1 - c)T_{sd} + c^2 T_{ss}$$

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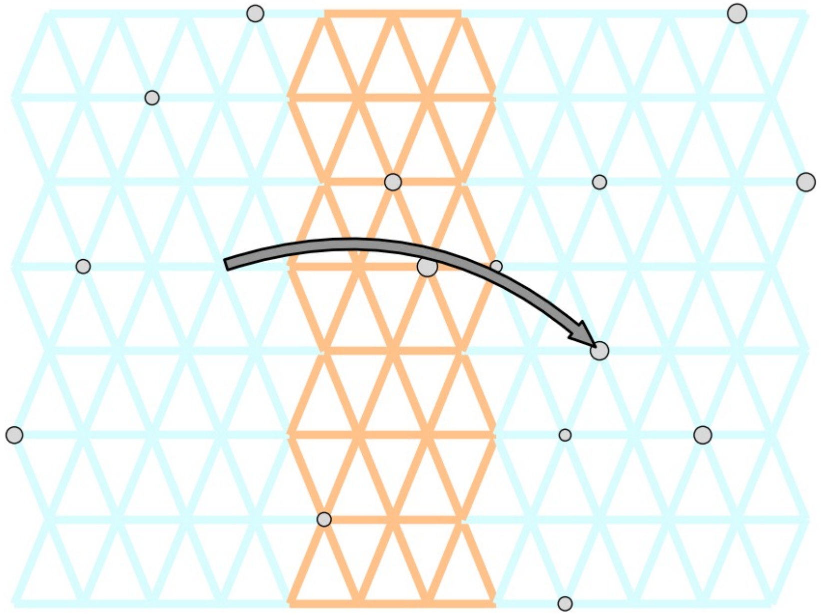
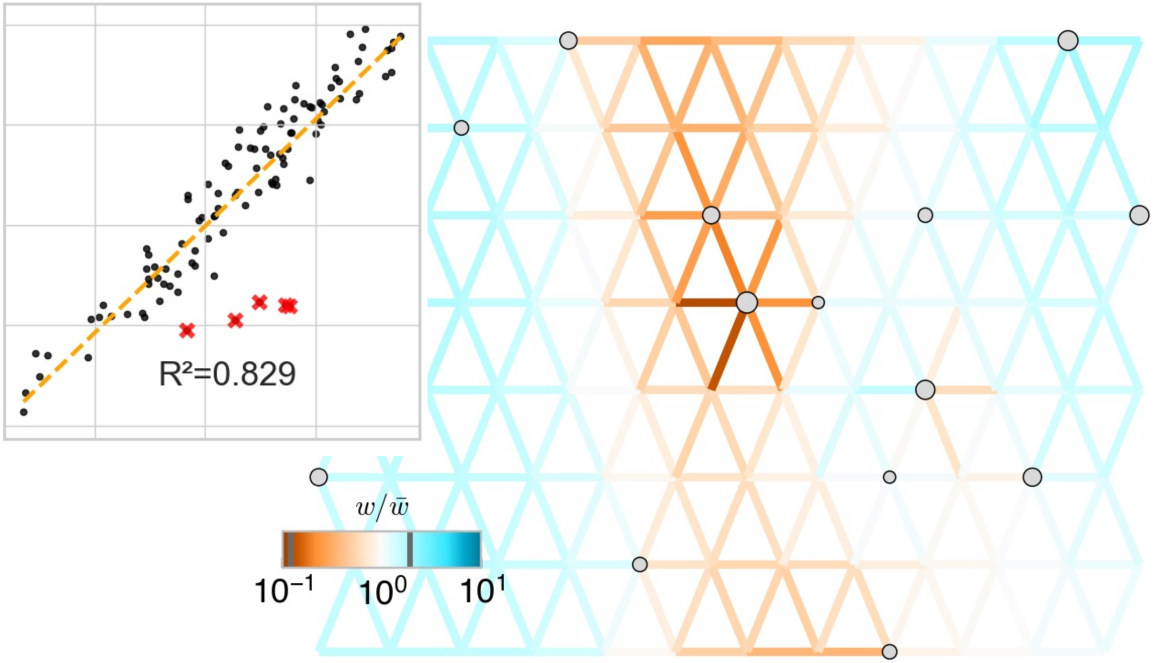
Brief simulation results

- 8x12 grid (only 15% sampled)
- 1-10 samples/deme
- 1,000 SNPs
- Corridor *m* is 10x barrier *m*
- Varying population size *N* across grid

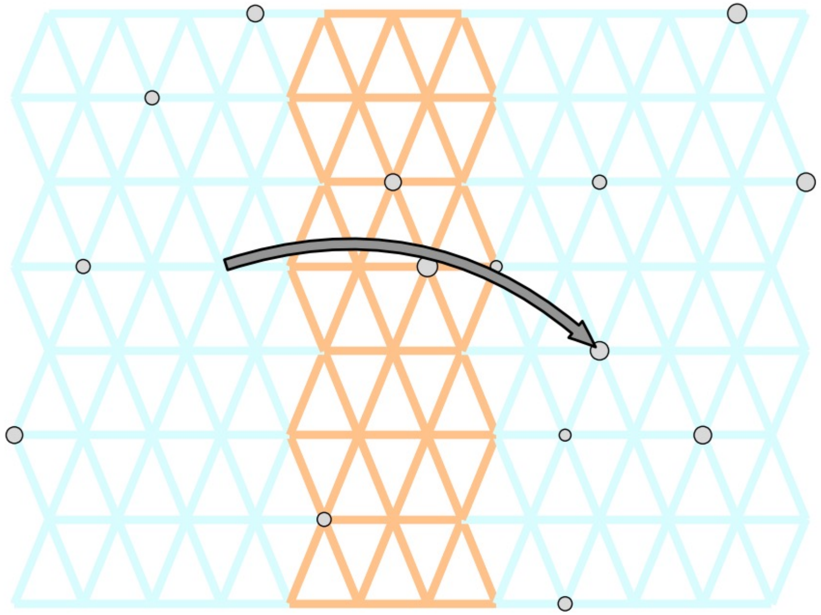
F_{ST} across barrier ≈ 0.1



Simulated truth
(instantaneous pulse of *c* = 0.5)

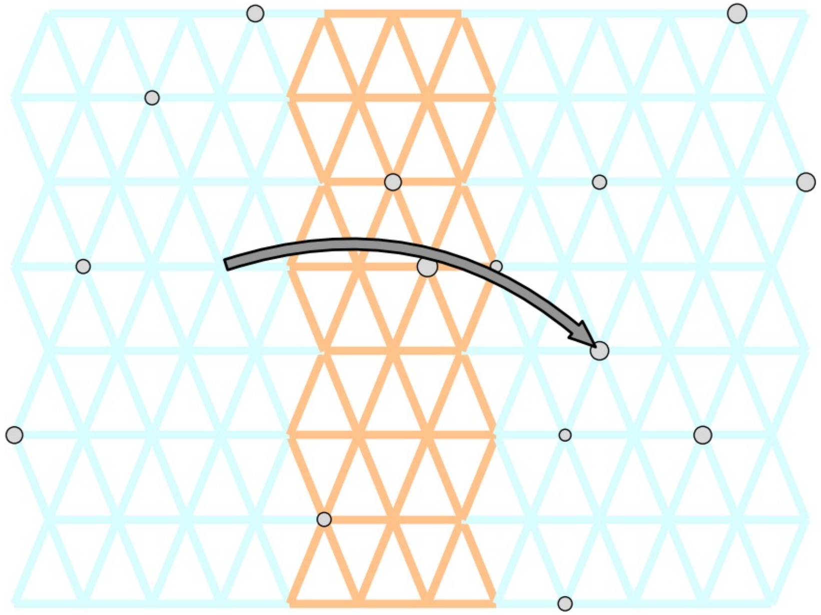


Initial FEEMS fit

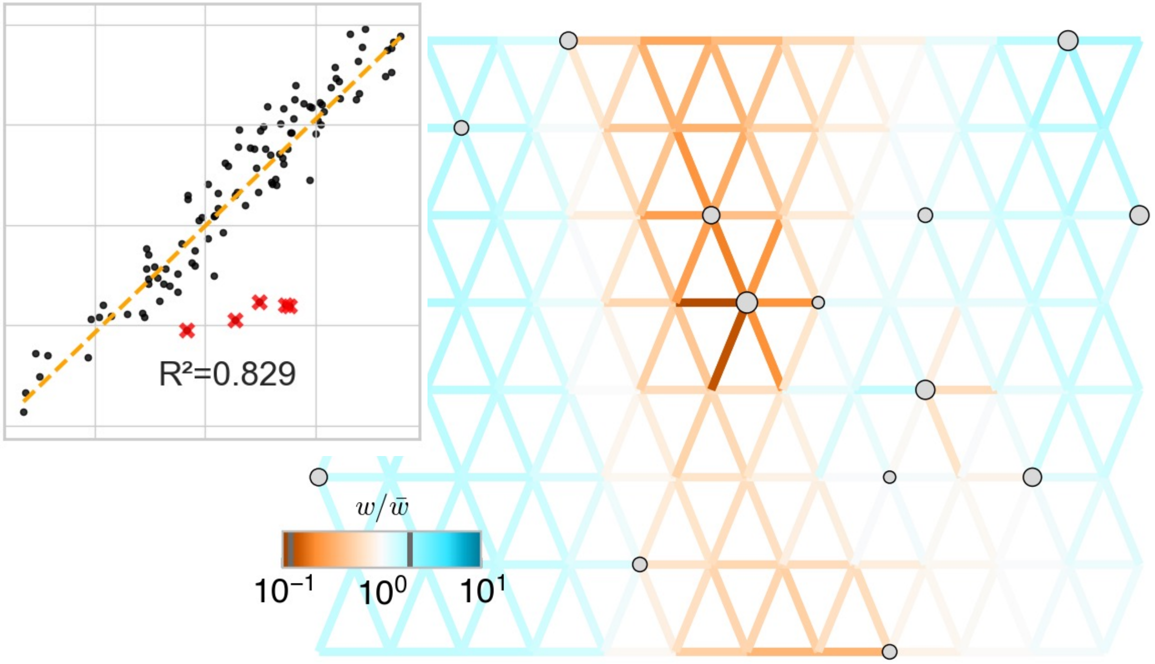


Simulated truth

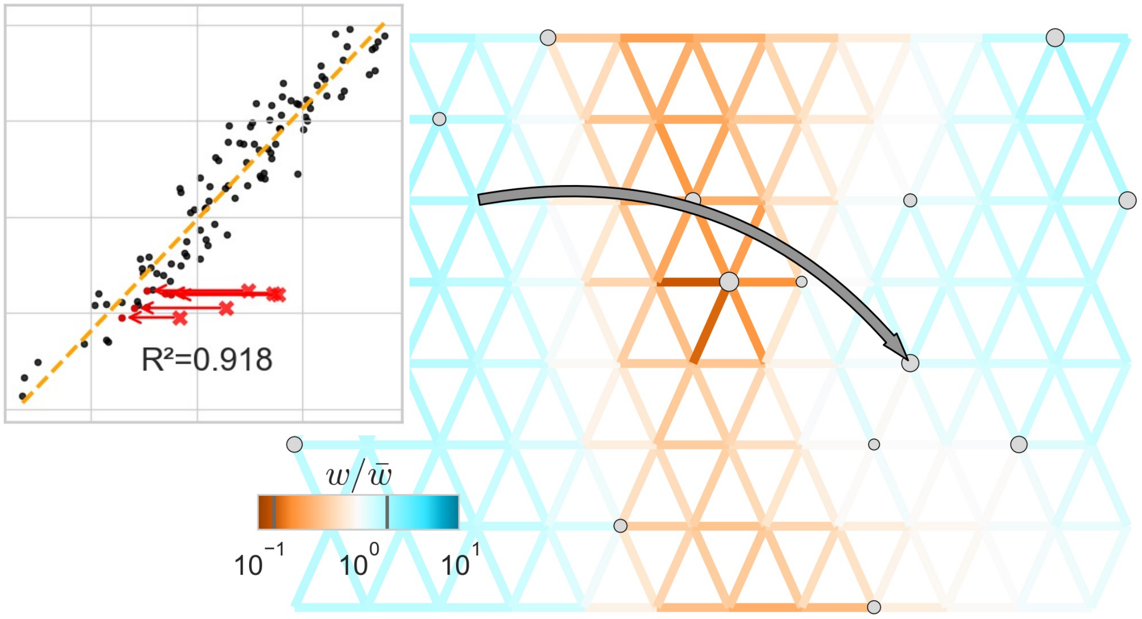
F_{ST} across barrier ≈ 0.1



Simulated truth

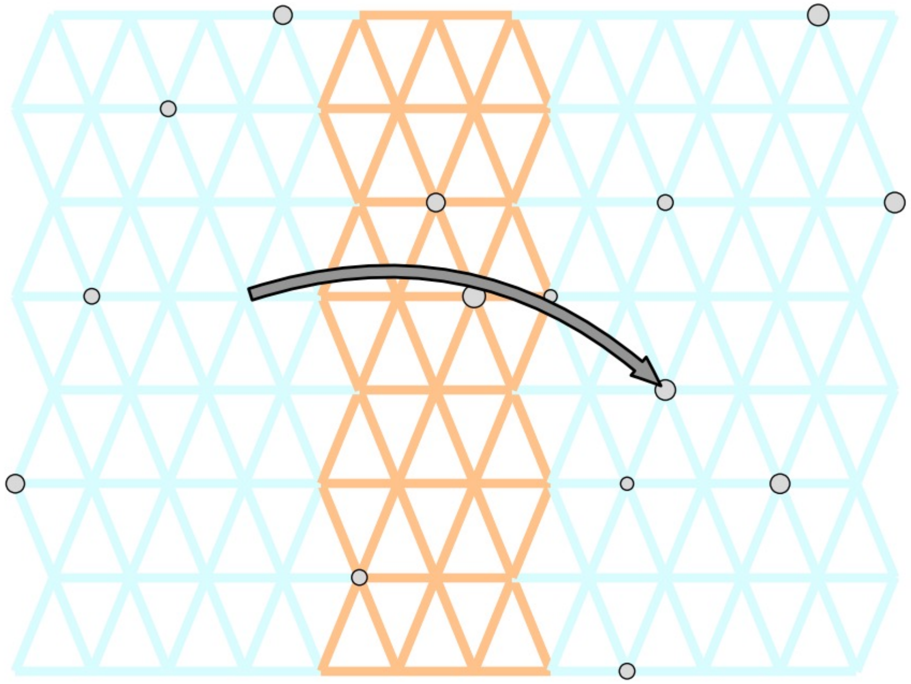


Initial `FEEMS` fit

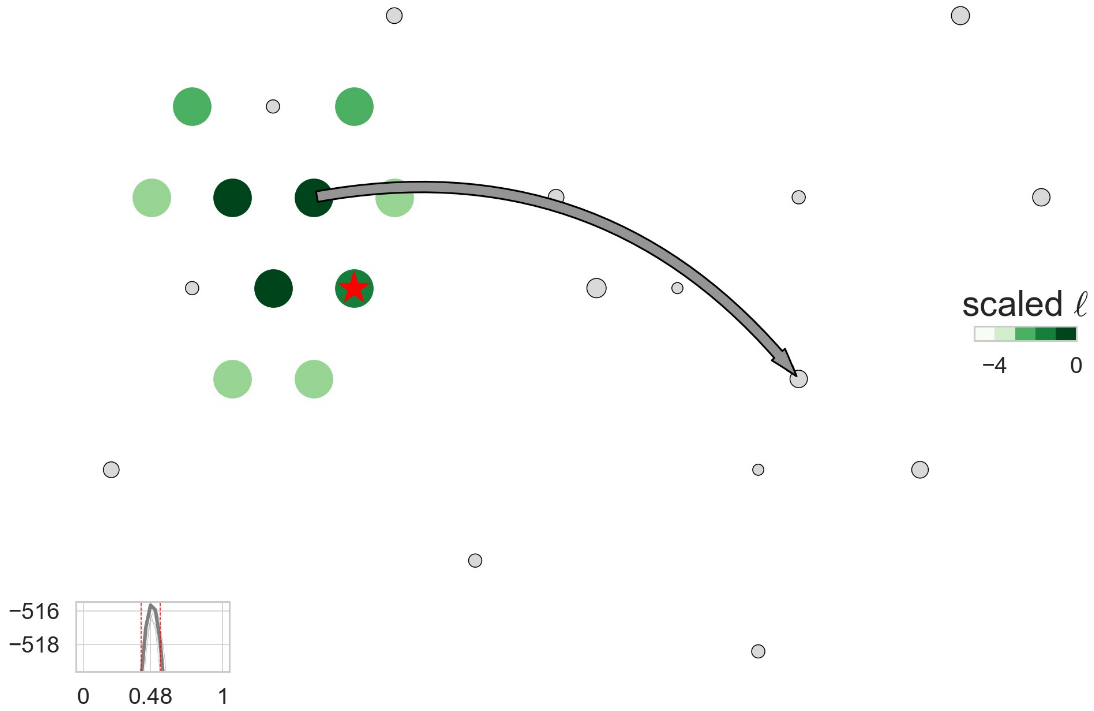


`FEEMSmix` fit

True source is within <u>two</u> log-likelihood units of MLE source



Simulated truth
(c = 0.5)



Estimated `FEEMSmix` contour
(est. c = 0.48)

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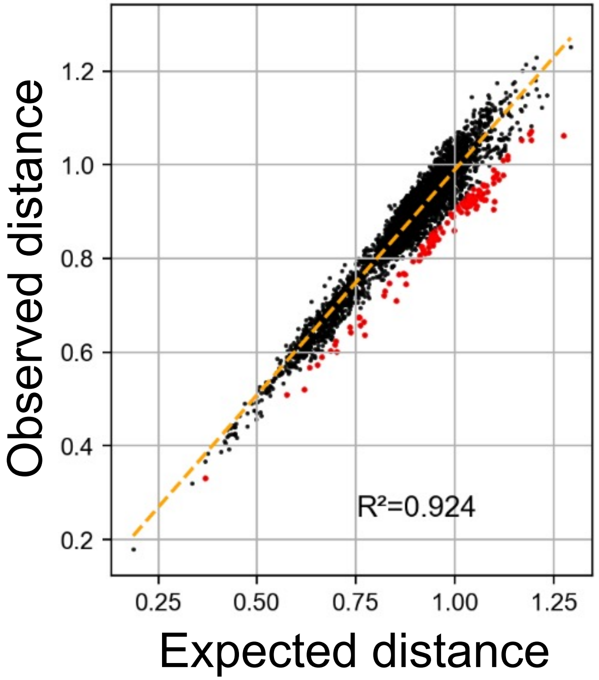
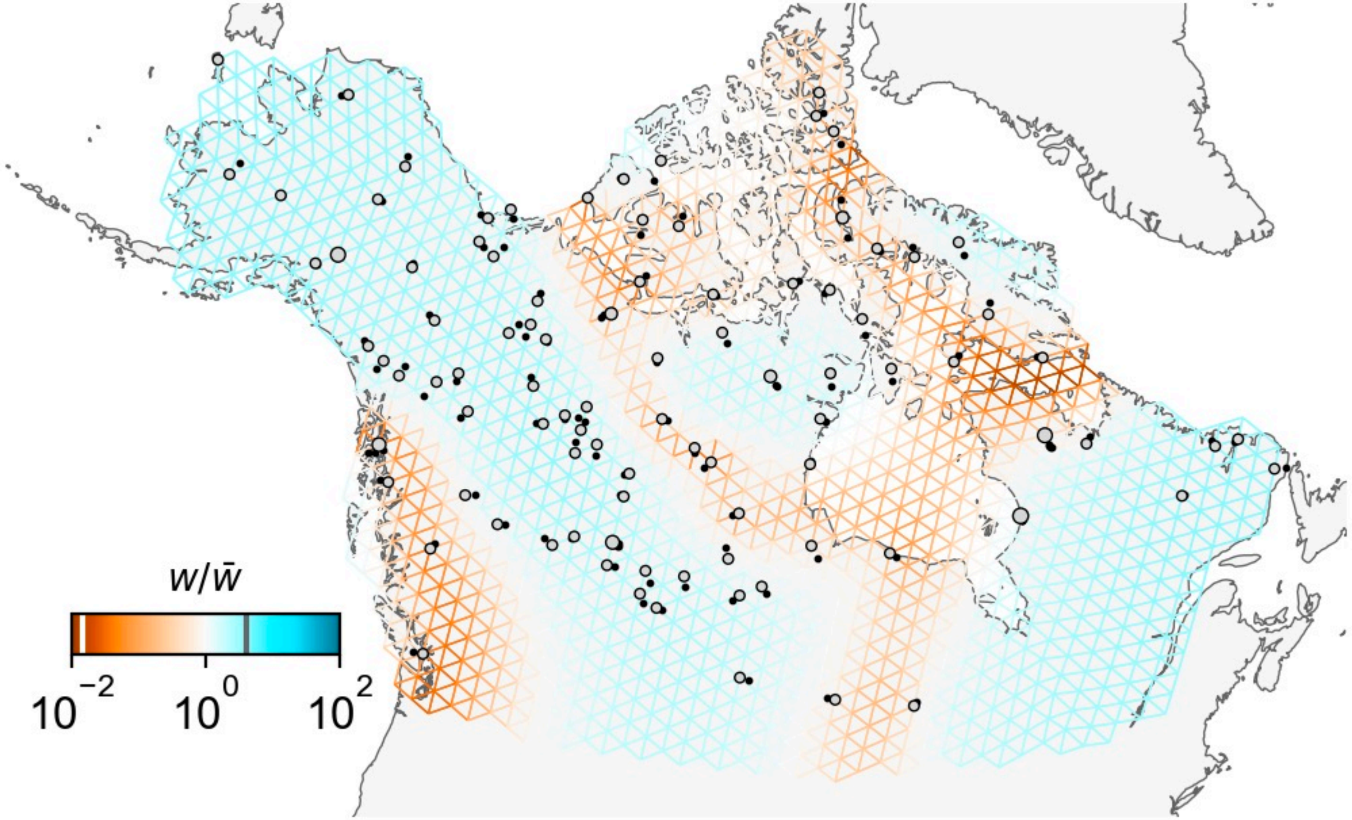
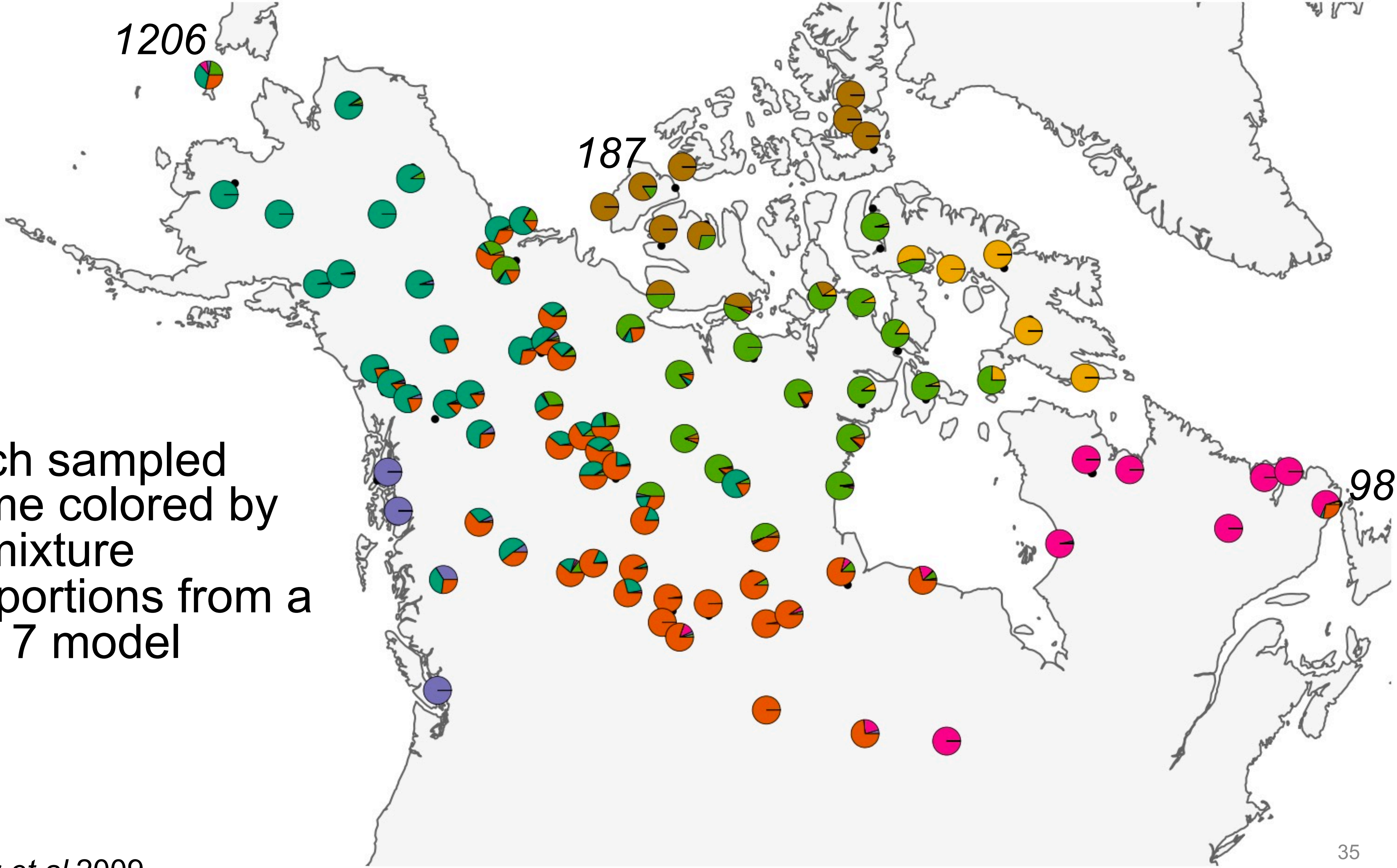
North American grey wolves

- 111 samples
- 17.8k SNPs
- 94 demes (~1 sample/deme)



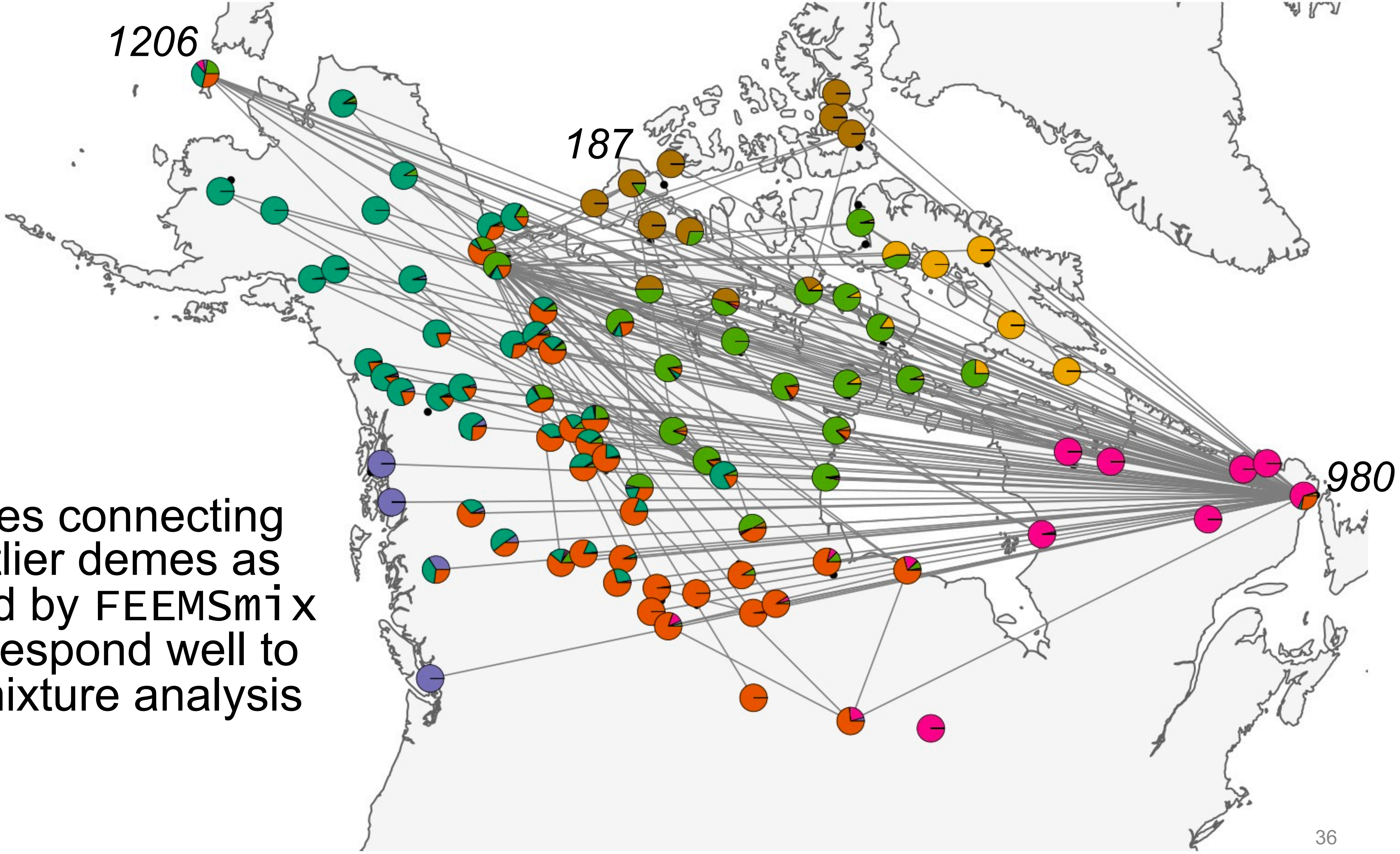


Schweizer *et al* 2016



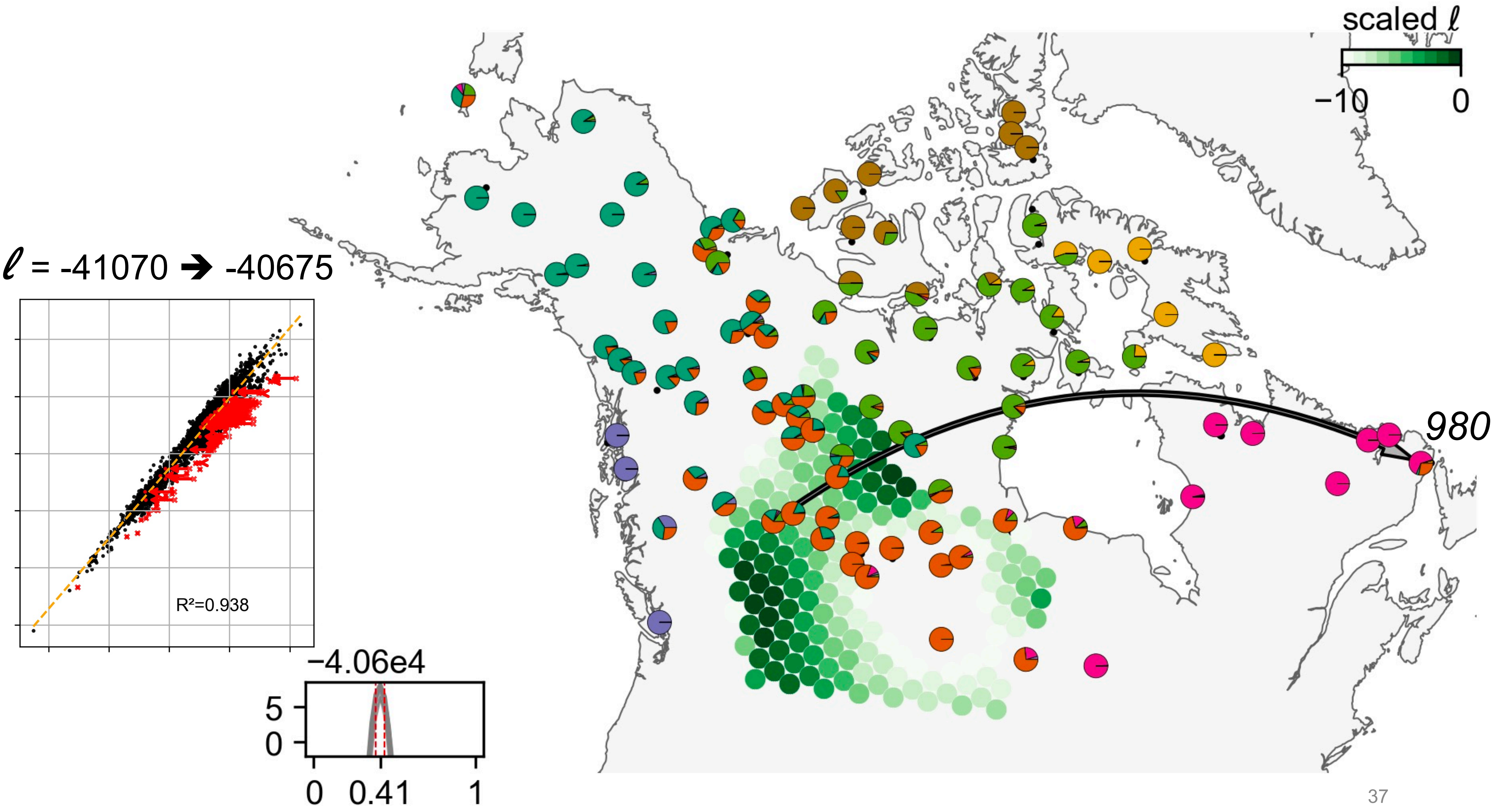
Each sampled deme colored by admixture proportions from a *K* = 7 model

Alexander *et al* 2009

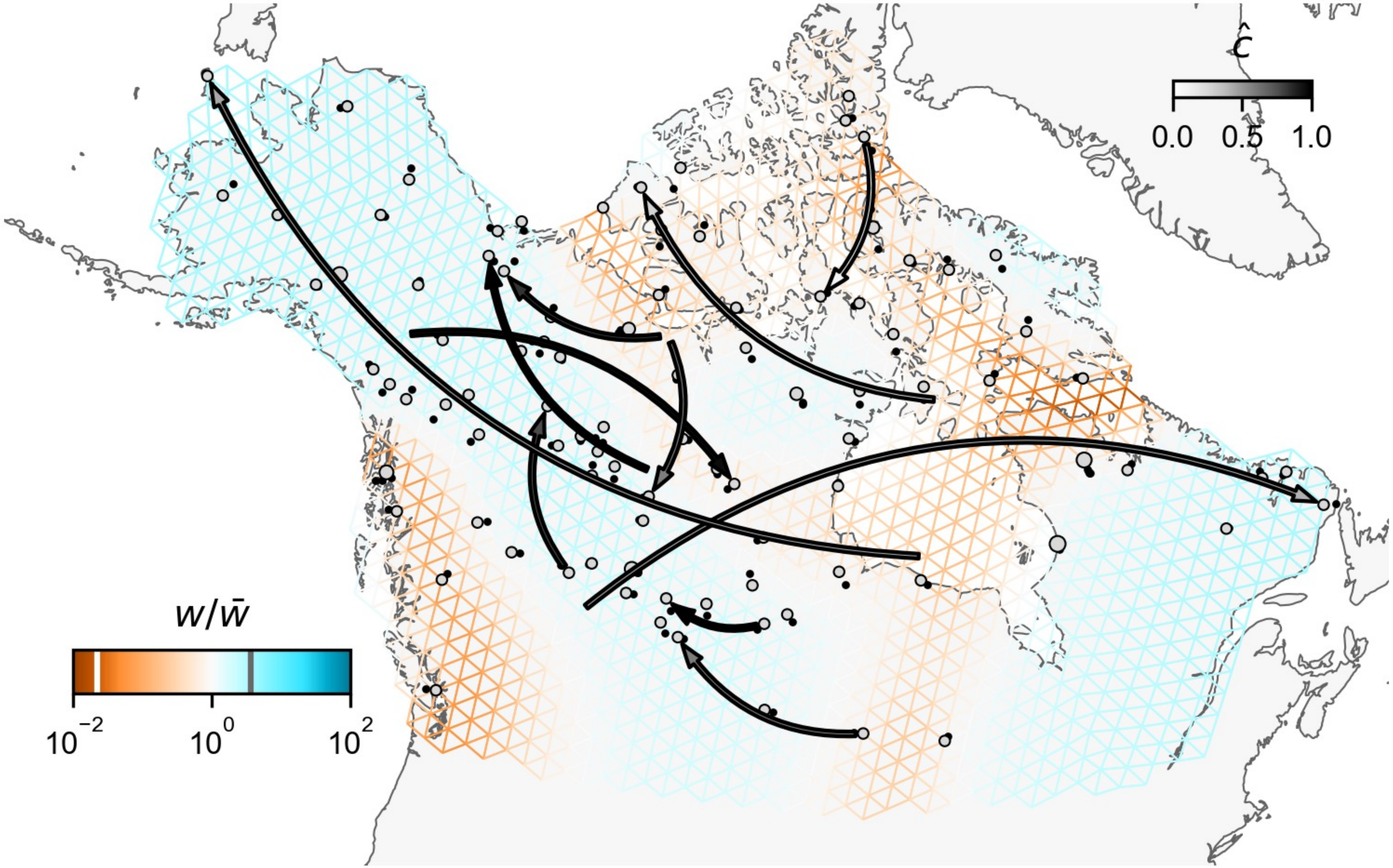


Lines connecting outlier demes as found by `FEEMSmix` correspond well to admixture analysis

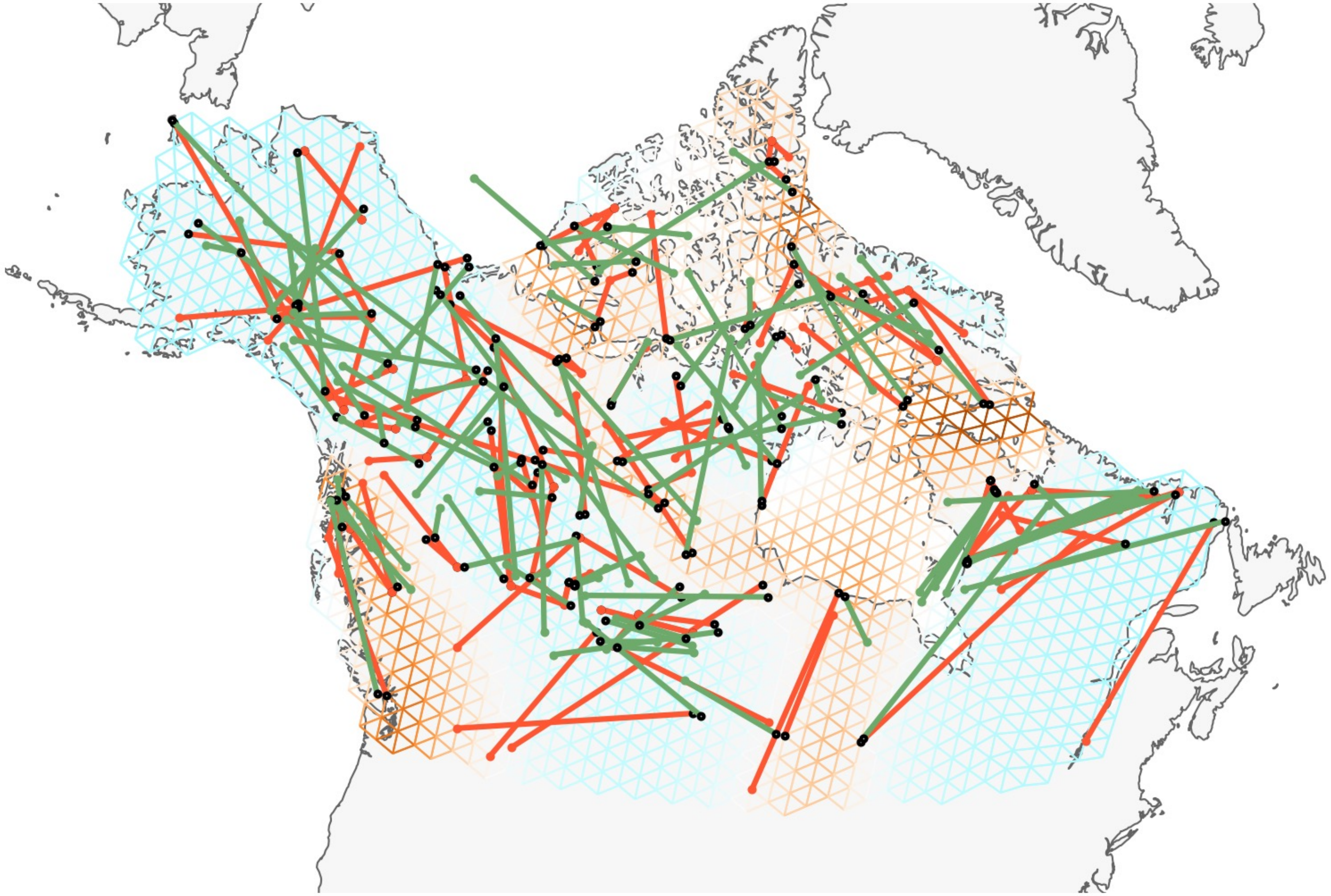
ℓ = -41070 ➔ -40675



The full picture: wolves move around a lot

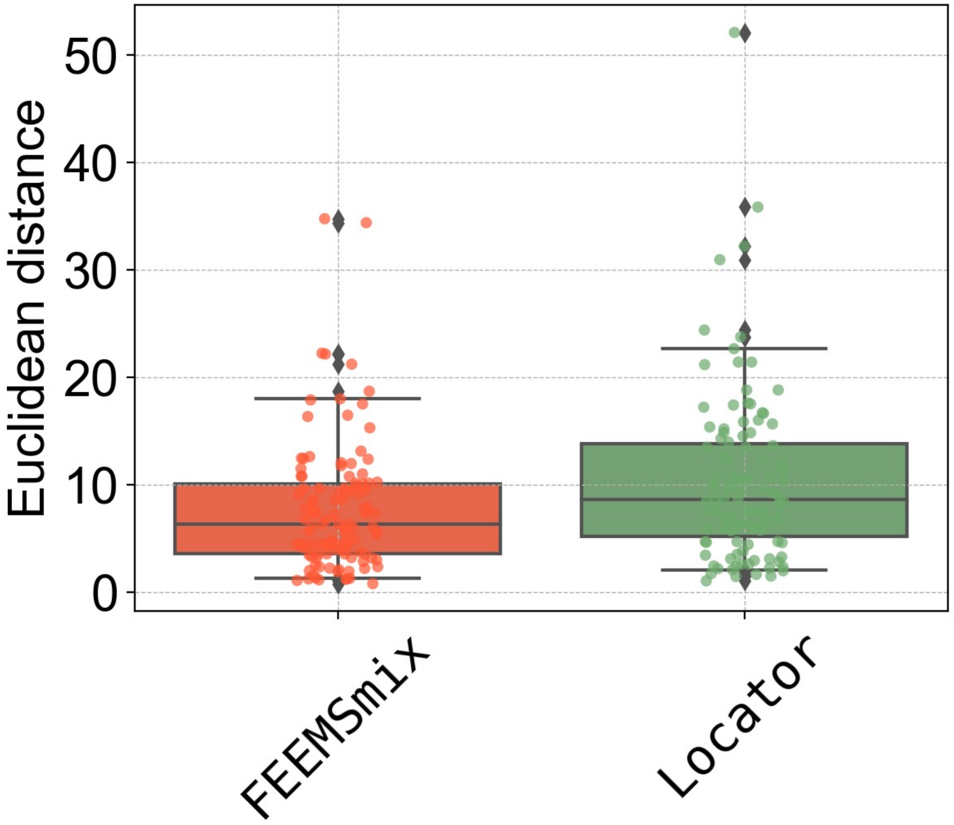


Bonus: spatial prediction!



Median error

~6.4 km ~8.6 km



Battey *et al* 2020

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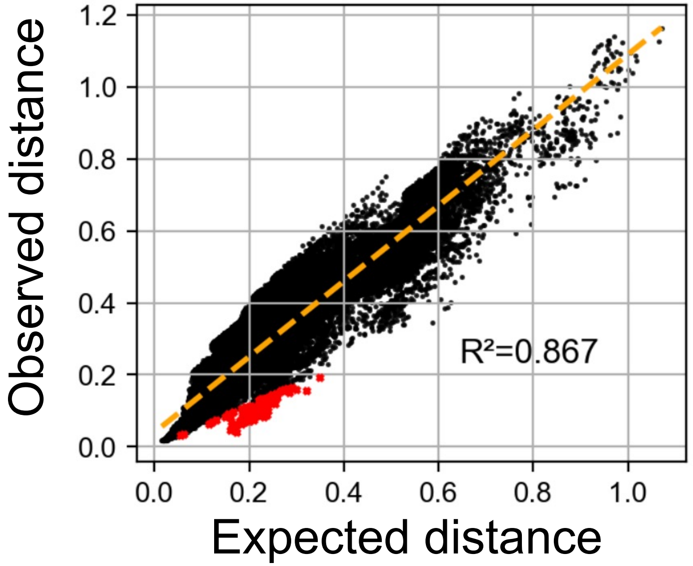
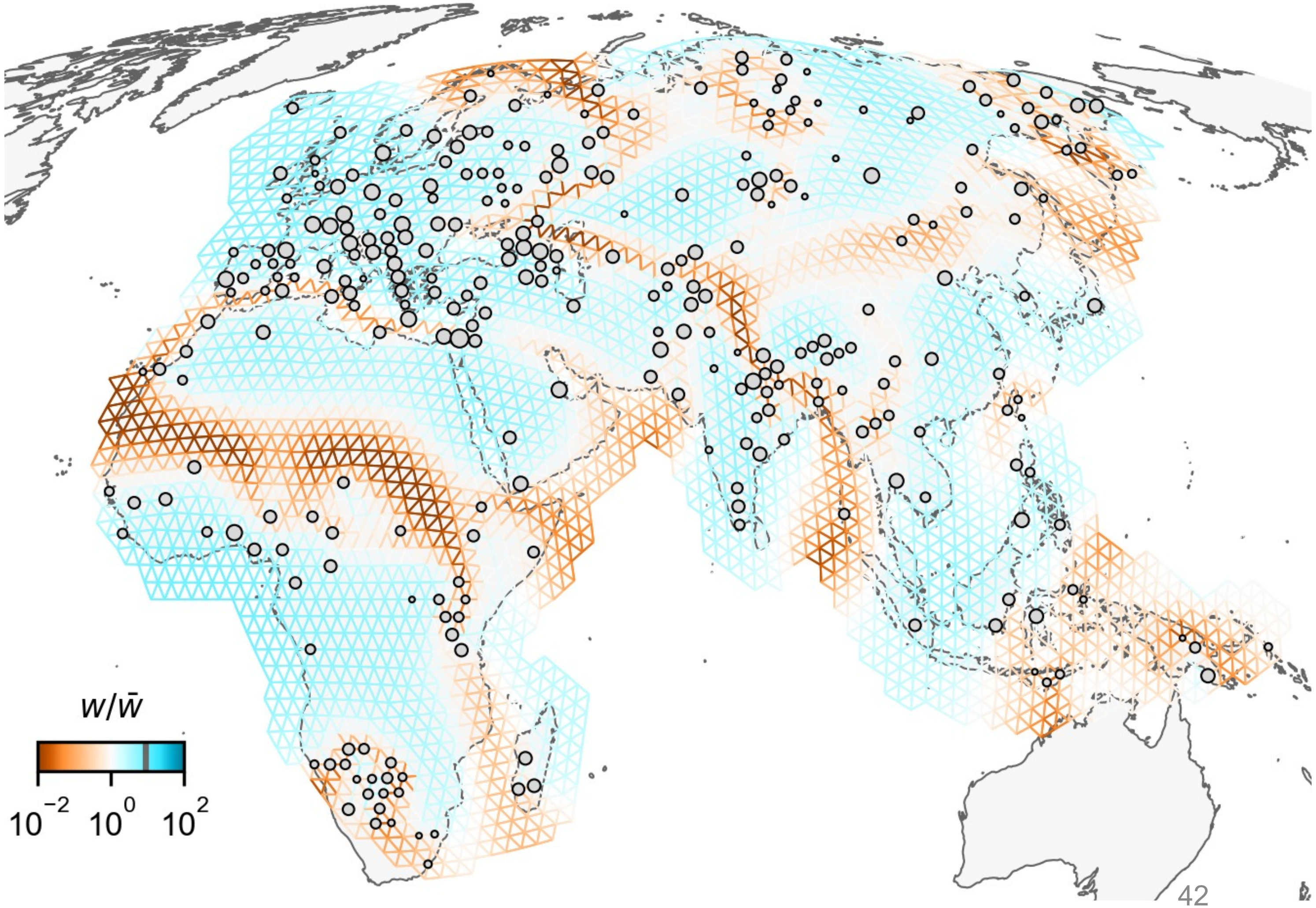
Afro-Eurasian panel of humans

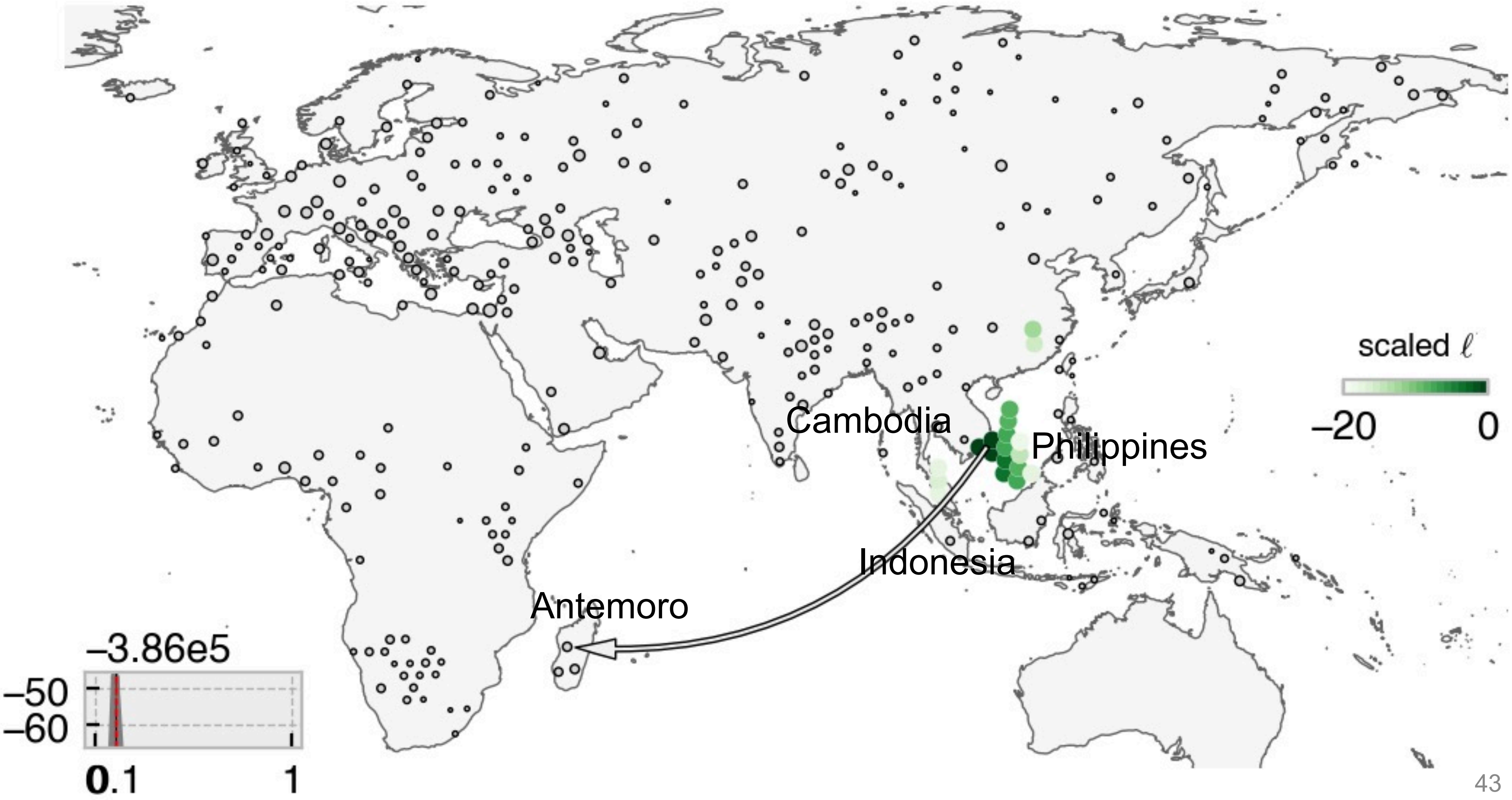
- 4,700 samples
- 20k SNPs
- 297 demes





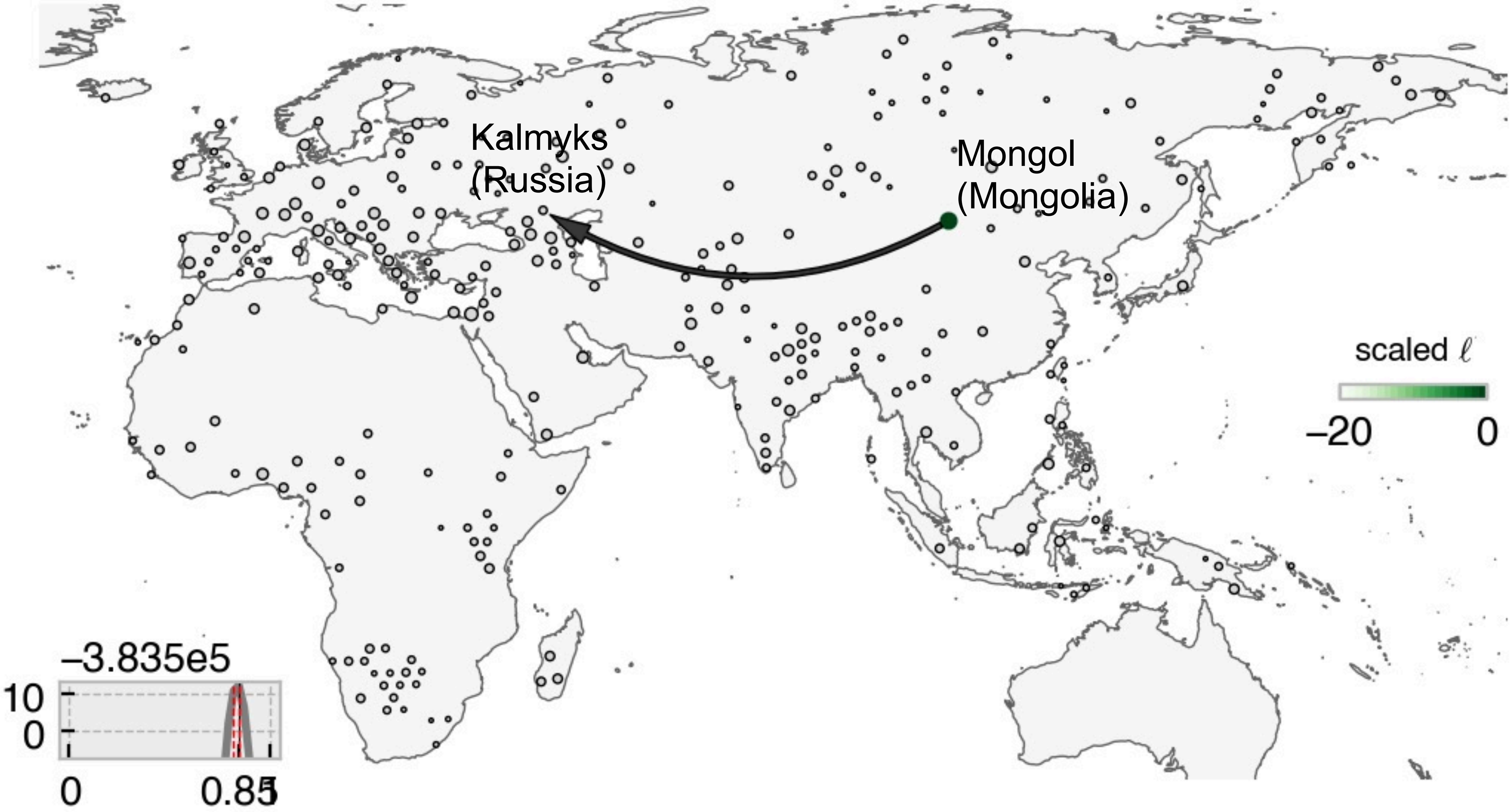
Peter *et al* 2020

Southeast Asian ancestry source detected in Malagasy



Pierron *et al* 2017

Kalmyks: only Mongolic-speaking people living in Europe



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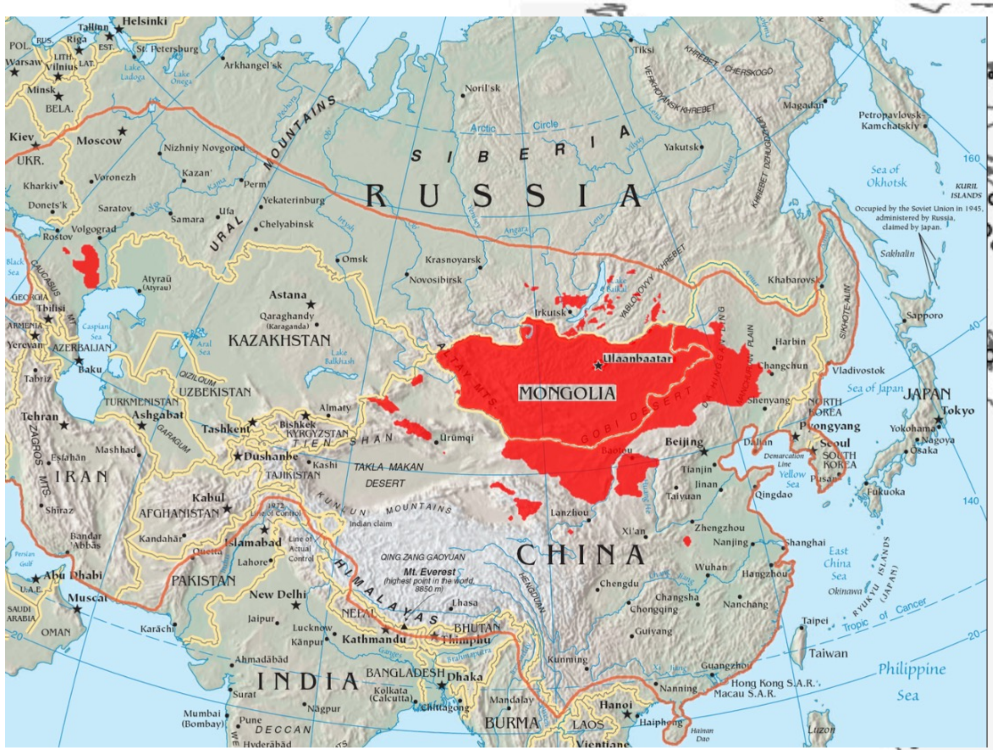
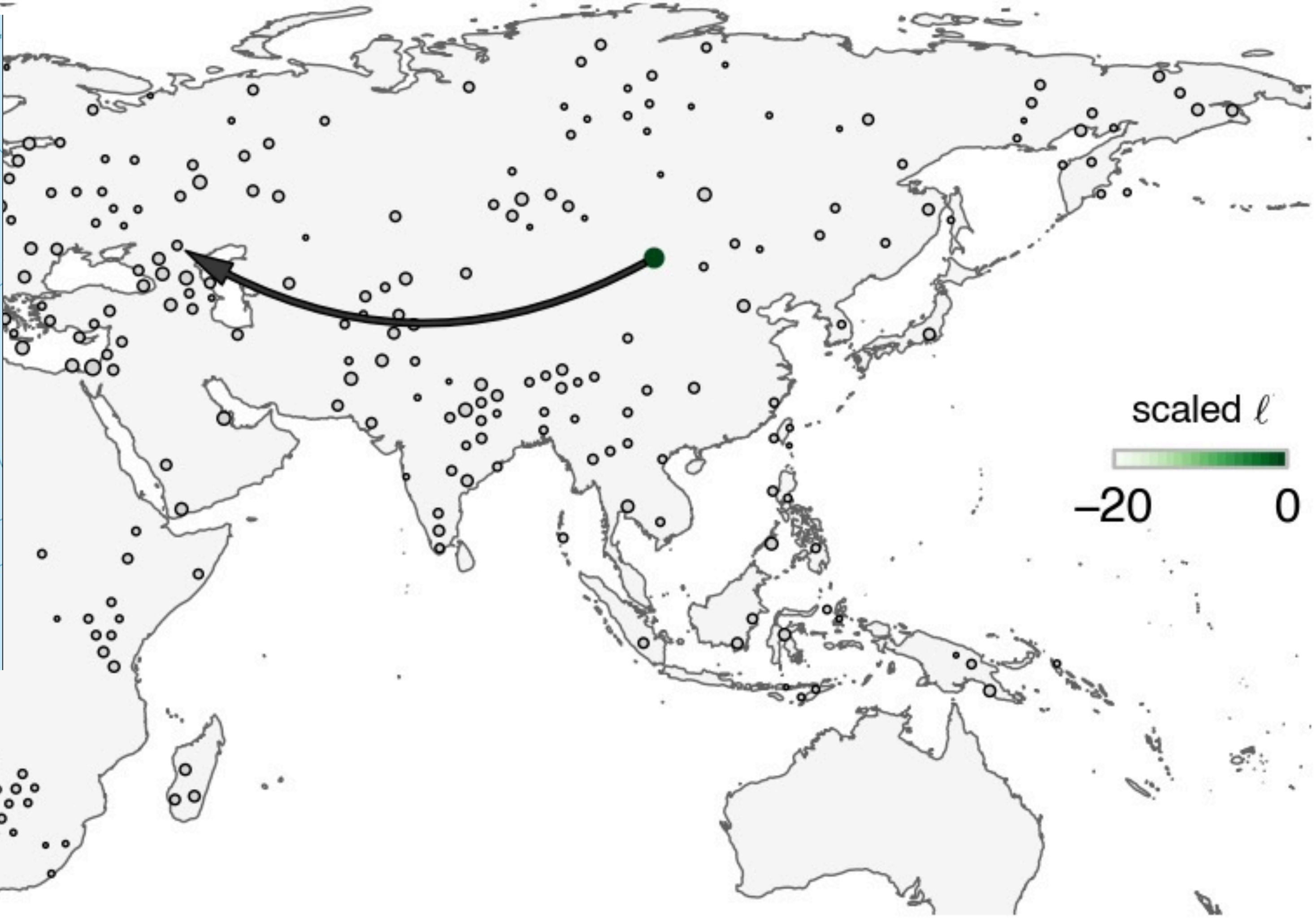
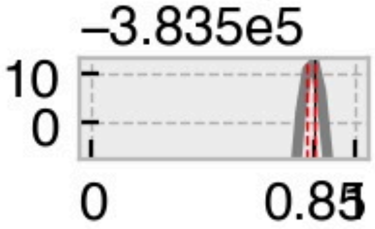
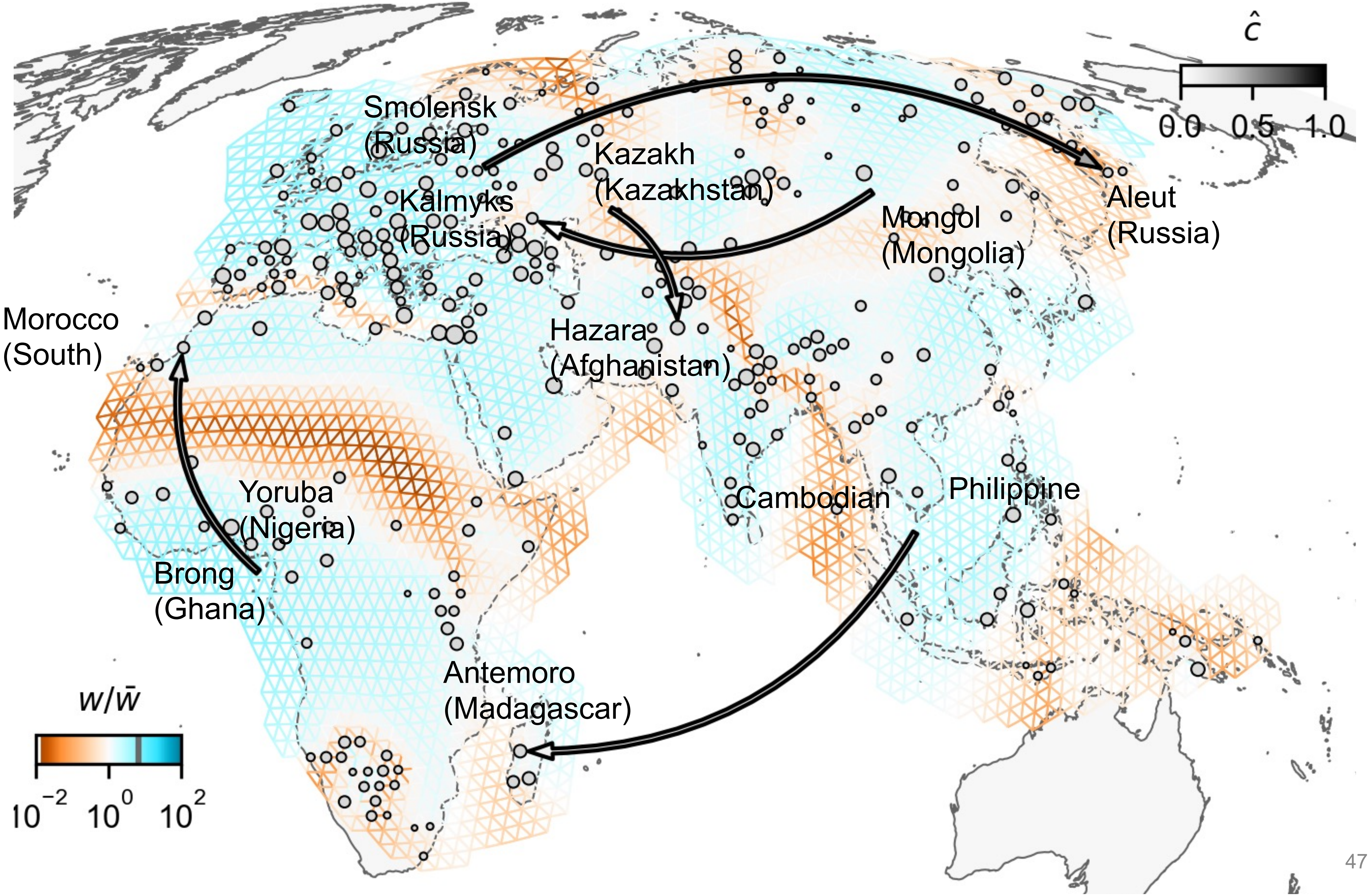






Erdeniev 1985


$\hat{c}$
0.0
0.5
1.0
Smolensk (Russia)
Kazakh (Kazakhstan)
Kalmyks (Russia)
Aleut (Russia)
Mongol (Mongolia)
Morocco (South)
Hazara (Afghanistan)
Yoruba (Nigeria)
Brong (Ghana)
Cambodian
Philippine
Antemoro (Madagascar)
$w/\bar{w}$
10^{-2}
10^{0}
10^{2}

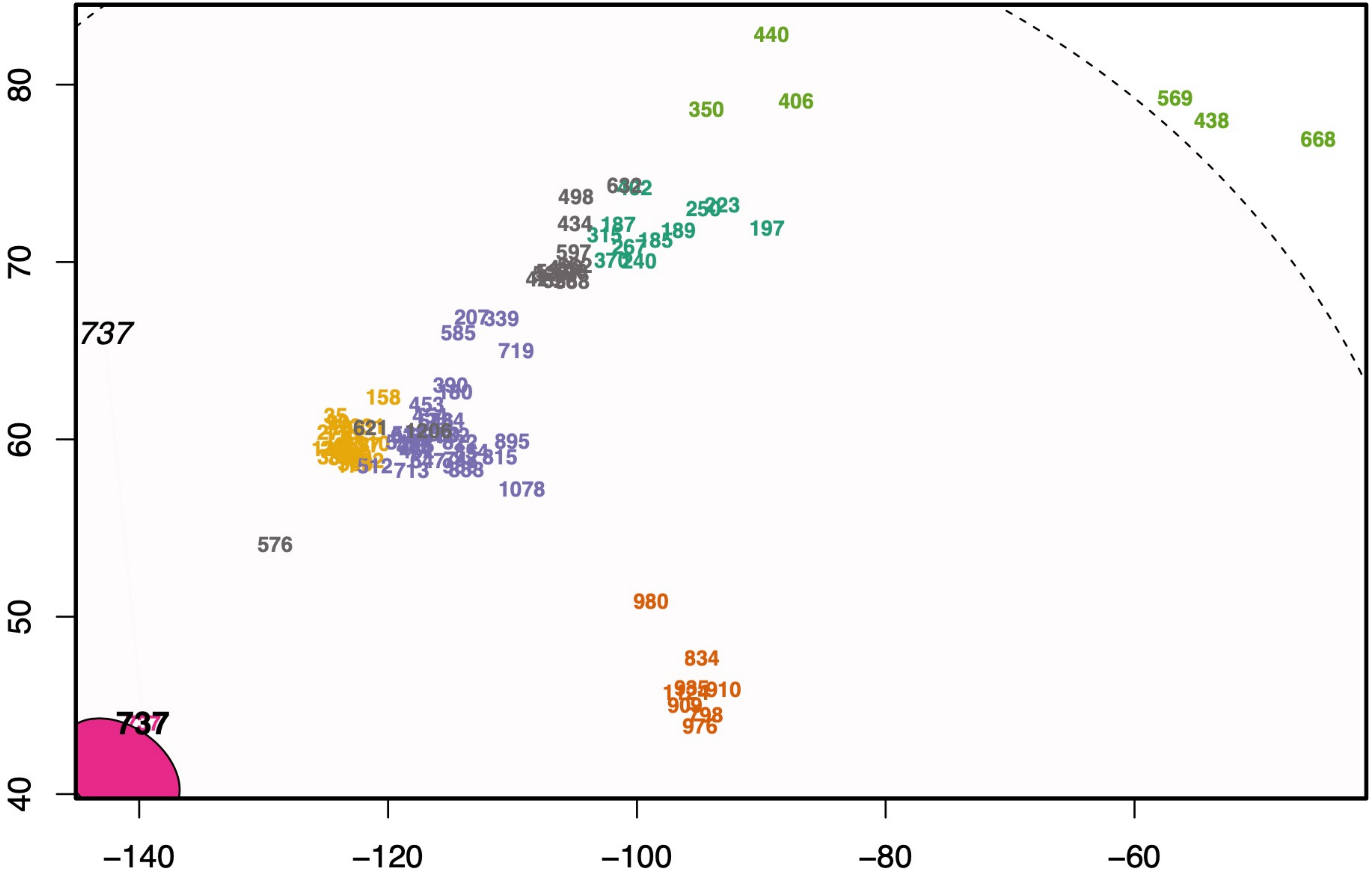
Watch this space for updates coming *very* soon!

Conclusions

- `FEEMSmix`: a method to include long-range gene flow events in `FEEMS`
- Paints a fuller picture of the spatial patterns in genetic structure

⚠️ Caution ⚠️

- Interpret value of *c* as an informed suggestion, not as truth (e.g., if *c* > 0.5, it probably means high recent admixture)
- Reckon with uncertainty in source location (area-area vs point-point migration)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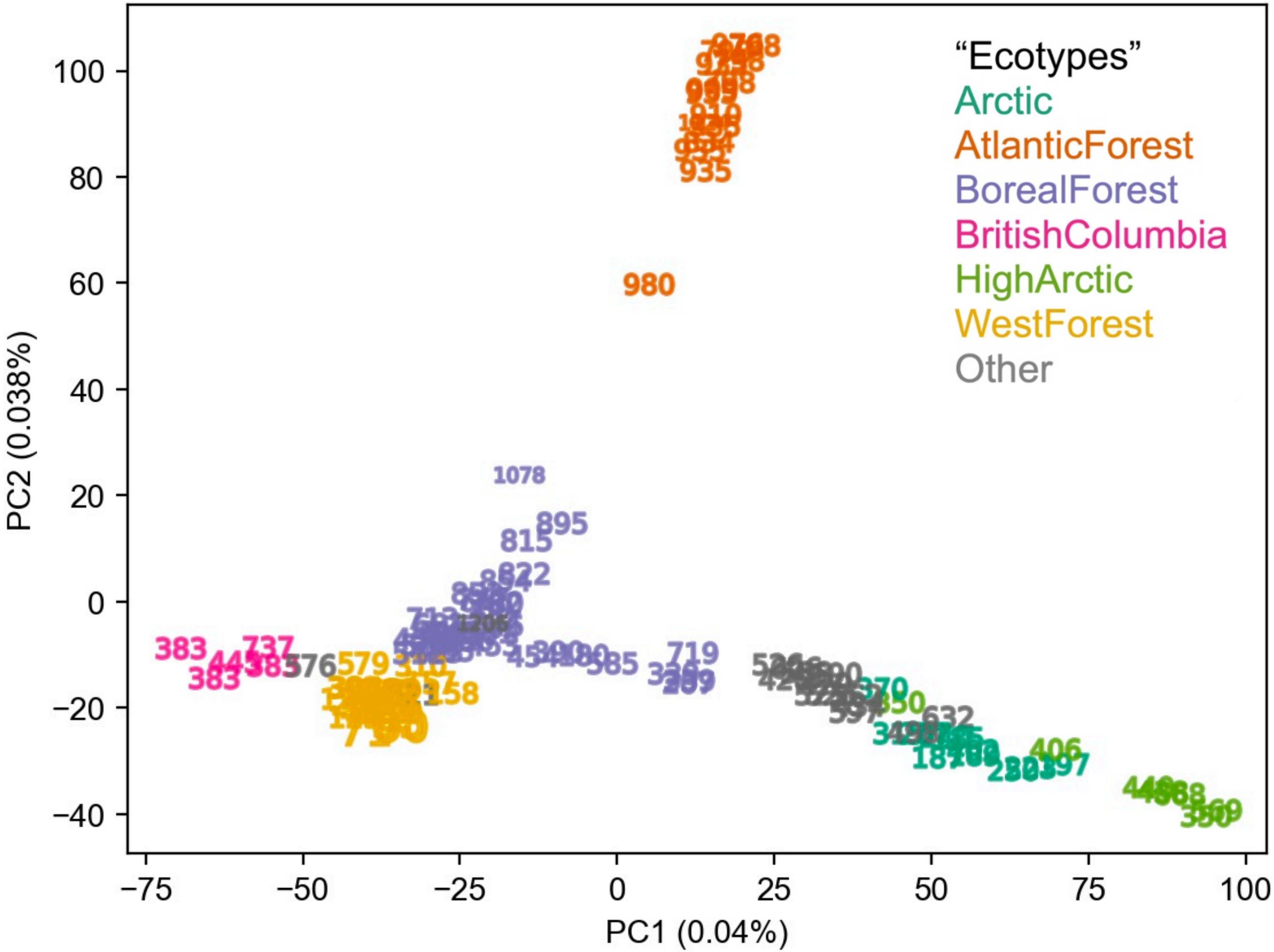
−60


"Ecotypes"
Arctic
AtlanticForest
BorealForest
BritishColumbia
HighArctic
WestForest
Other
PC1 (0.04%)
PC2 (0.038%)
−75
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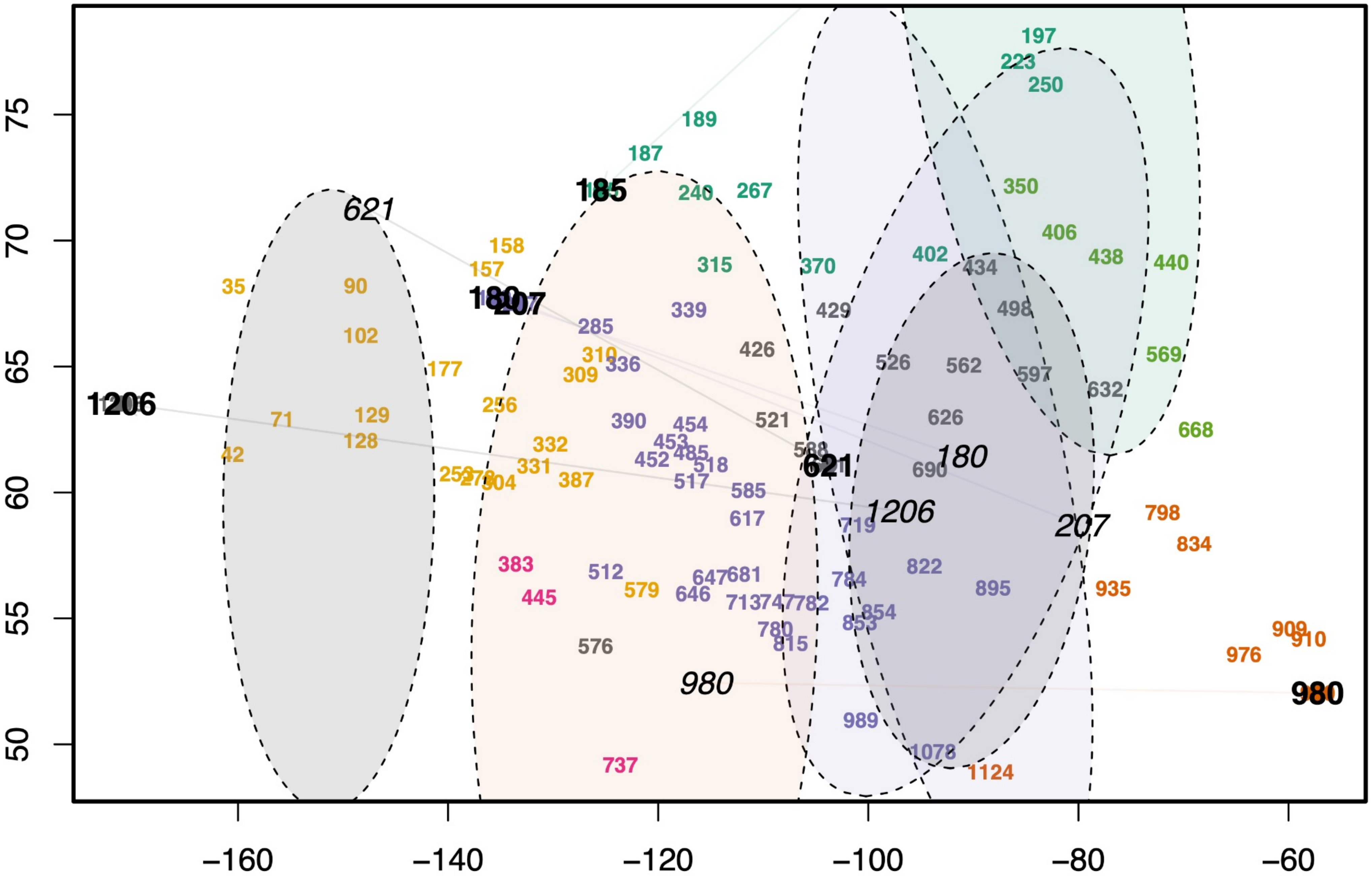

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