Haplotype-based methods for demography

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ELIXIR-IIB – Population Genomics: background and tools
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Introduction

- this lecture/practical will cover haplotype-based methods for demography, in particular:
  1. inferring admixture events between two or more source groups (*GLOBETROTTER*)
  2. inferring past population size changes over time (*PSMC/MSMC*)
- we will use SNP data throughout, with *PSMC/MSMC* requiring sequencing data

Outline

inferring admixture (*GLOBETROTTER*)

inferring pop size changes (*PSMC, MSMC*)

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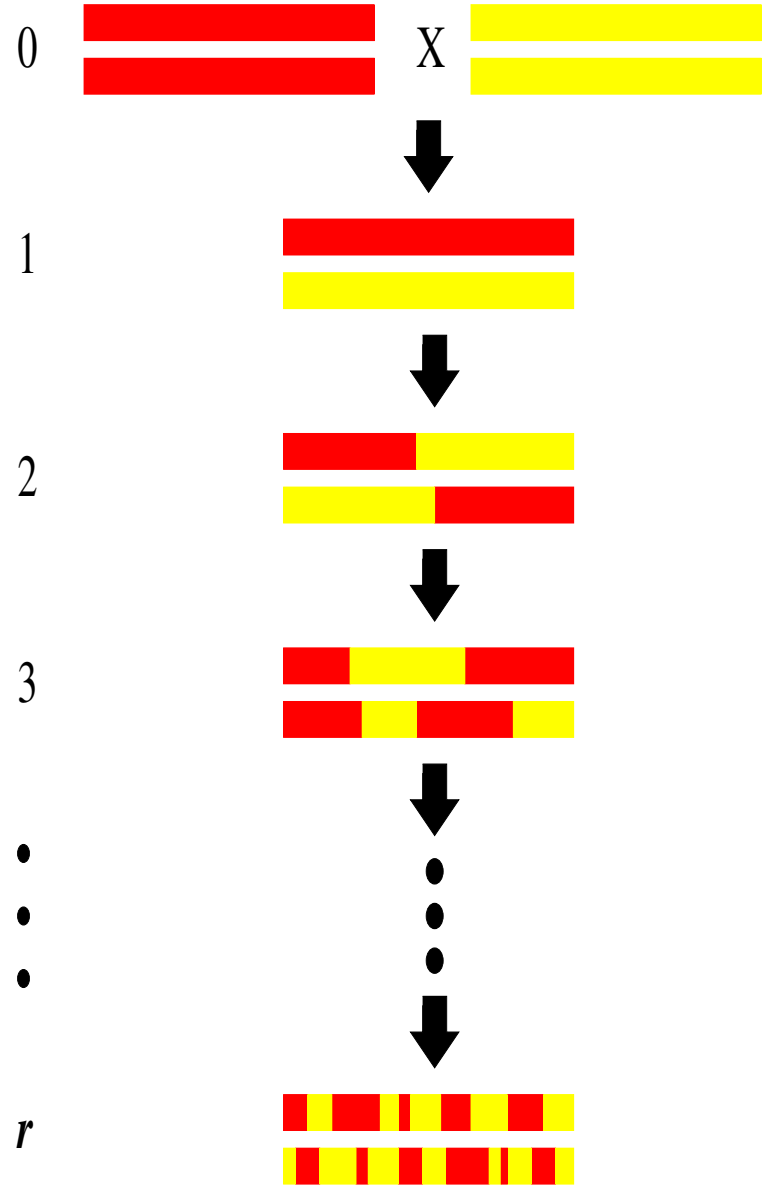
inferring pop size changes (*PSMC, MSMC*)

Inferring admixture using autosomal DNA

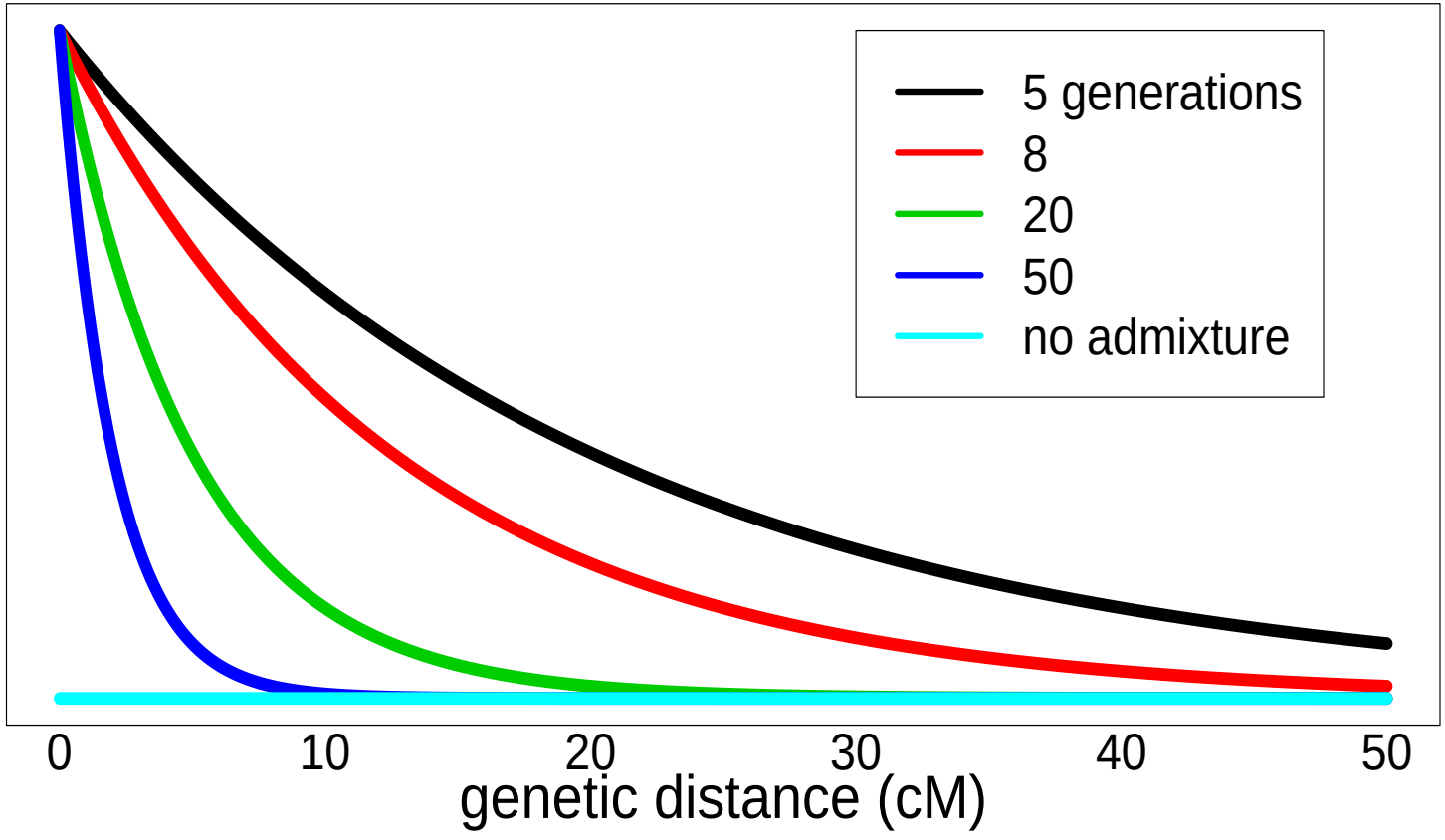
- two populations (**red**,**yellow**) admix *r* generations ago, followed by random mating
- genetic pieces from each population get smaller each subsequent generation due to recombination
- assuming recombination occurs as Poisson process, size of contiguous **red** and **yellow** segments in present-day DNA follow exponential model with rate *r*

(Falush et al 2003, *Genetics* **164**:1567)

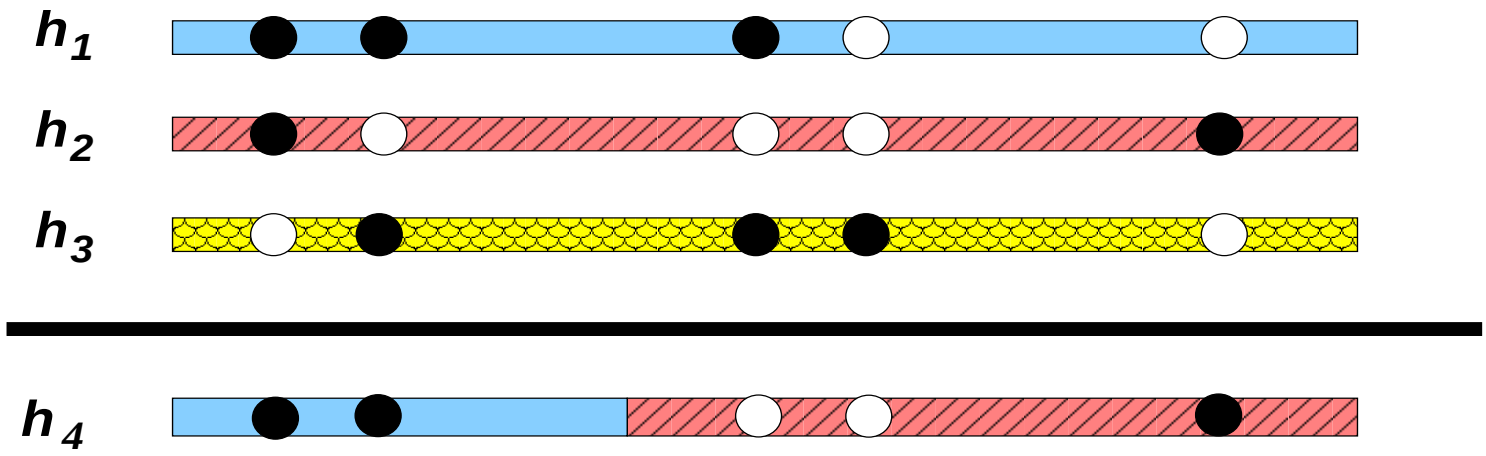


Dating admixture events using autosomal DNA

distribution of **red** and **yellow** segment sizes, based on when the two groups mixed:



Inferring admixture – chromosome painting



- "paint" admixed individual h_4 using donors h_1, h_2, h_3
- e.g. here h_4 appears to be a mixture of **blue**, **red** pops
- size of **blue**/**red** segments tell us when mixture occurred

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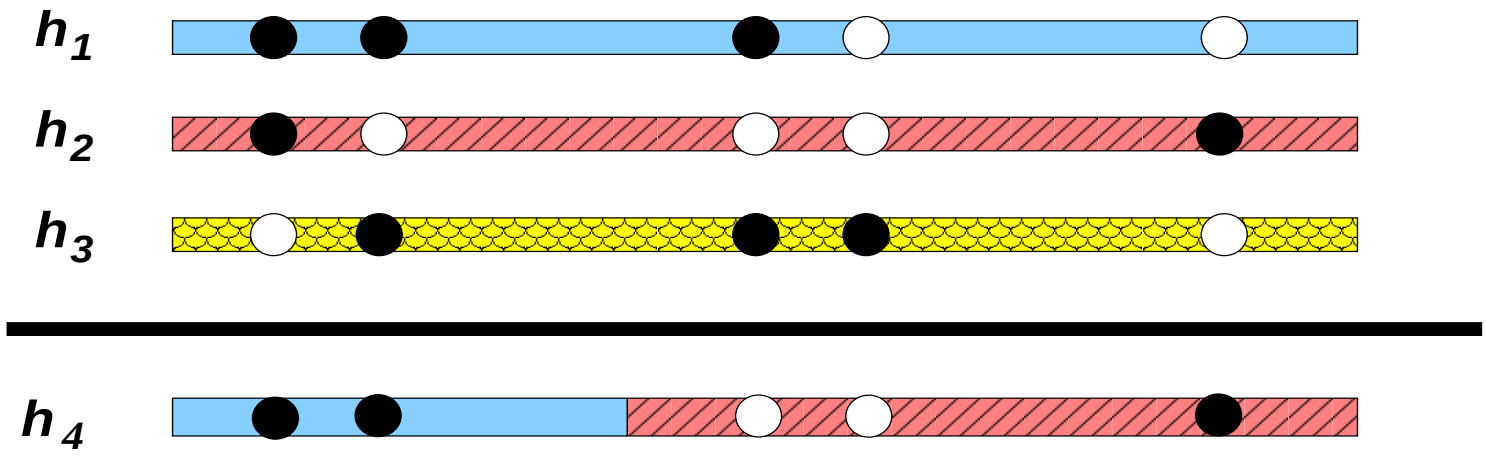

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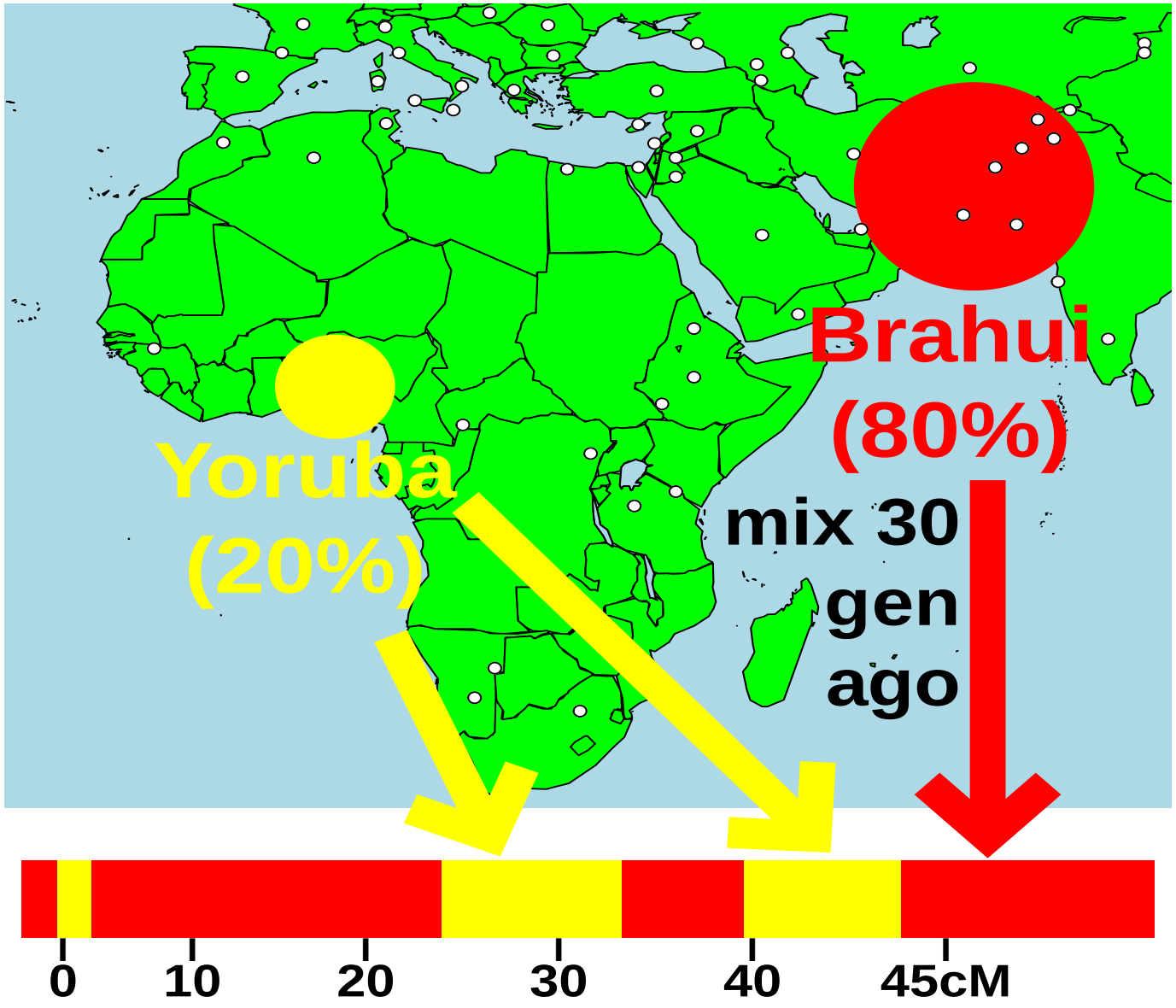
- size of **blue**/**red** segments tell us when mixture occurred

Issue: Accurate painting is challenging. Instead:

1. identify SNPs/haplotypes that *likely* derive from admixing groups
2. plot decay of LD versus cM distance between such SNPs/haplotypes

   Disadvantage: can be computationally demanding

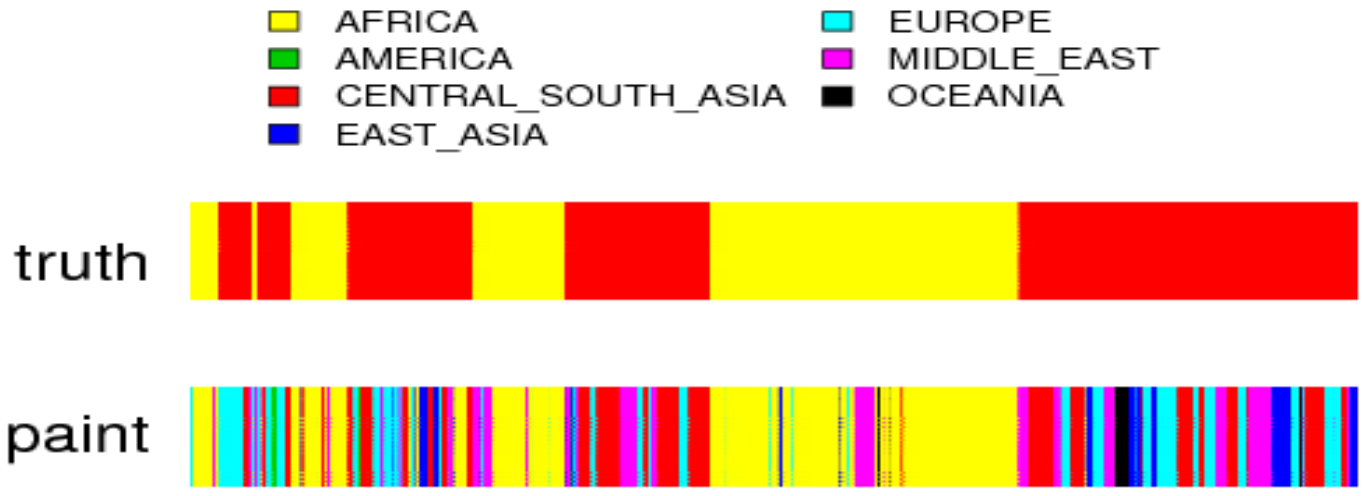
Simulation: 80% Brahui + 20% Yoruba, 30gen



(Hellenthal et al 2014, *Science* **343**:747)

Infer mixing groups (Sim: 80% Brahui + 20% Yoruba, 30gen)

(1) paint admixed inds using 93 world groups (*CHROMOPAINTER*)



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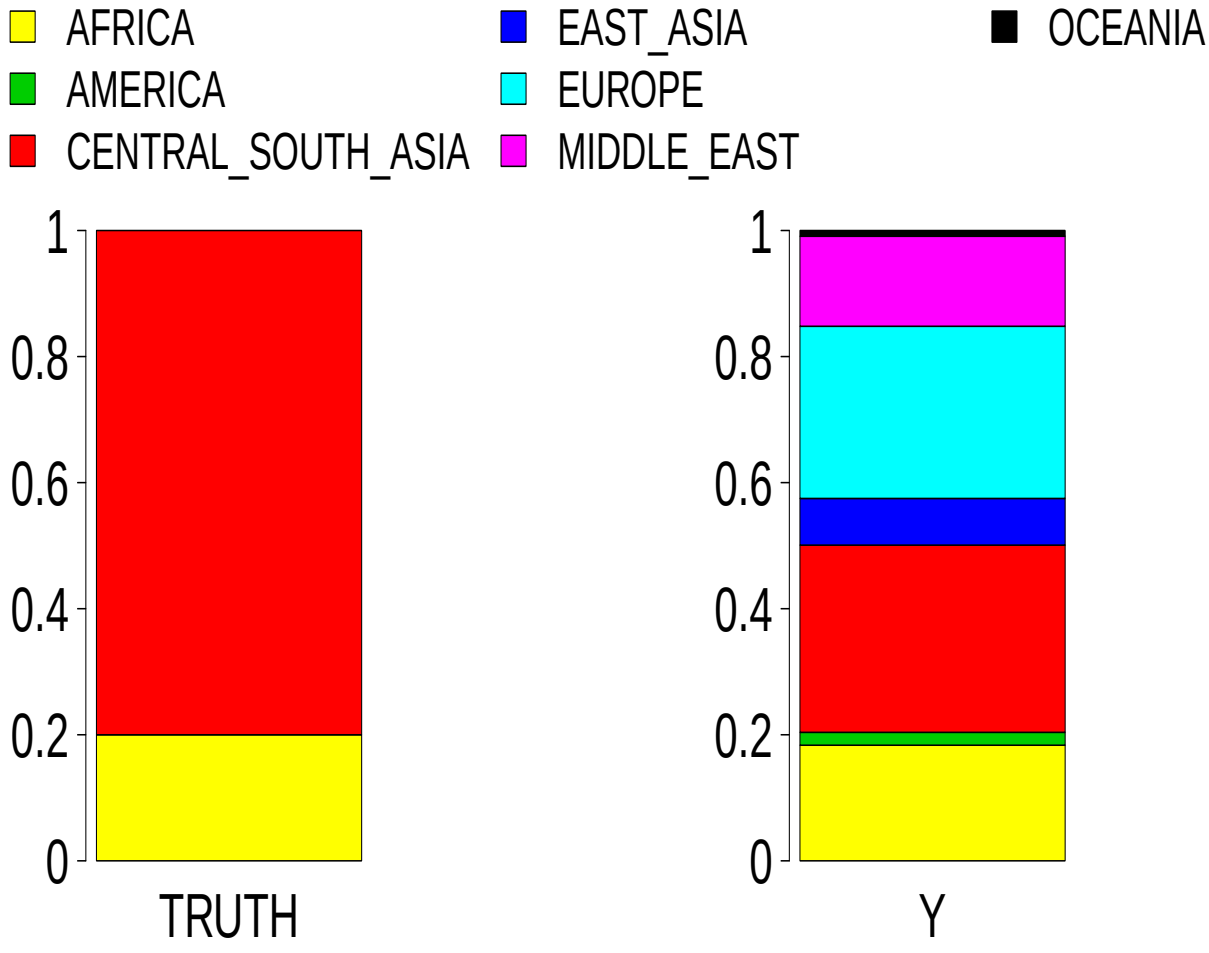

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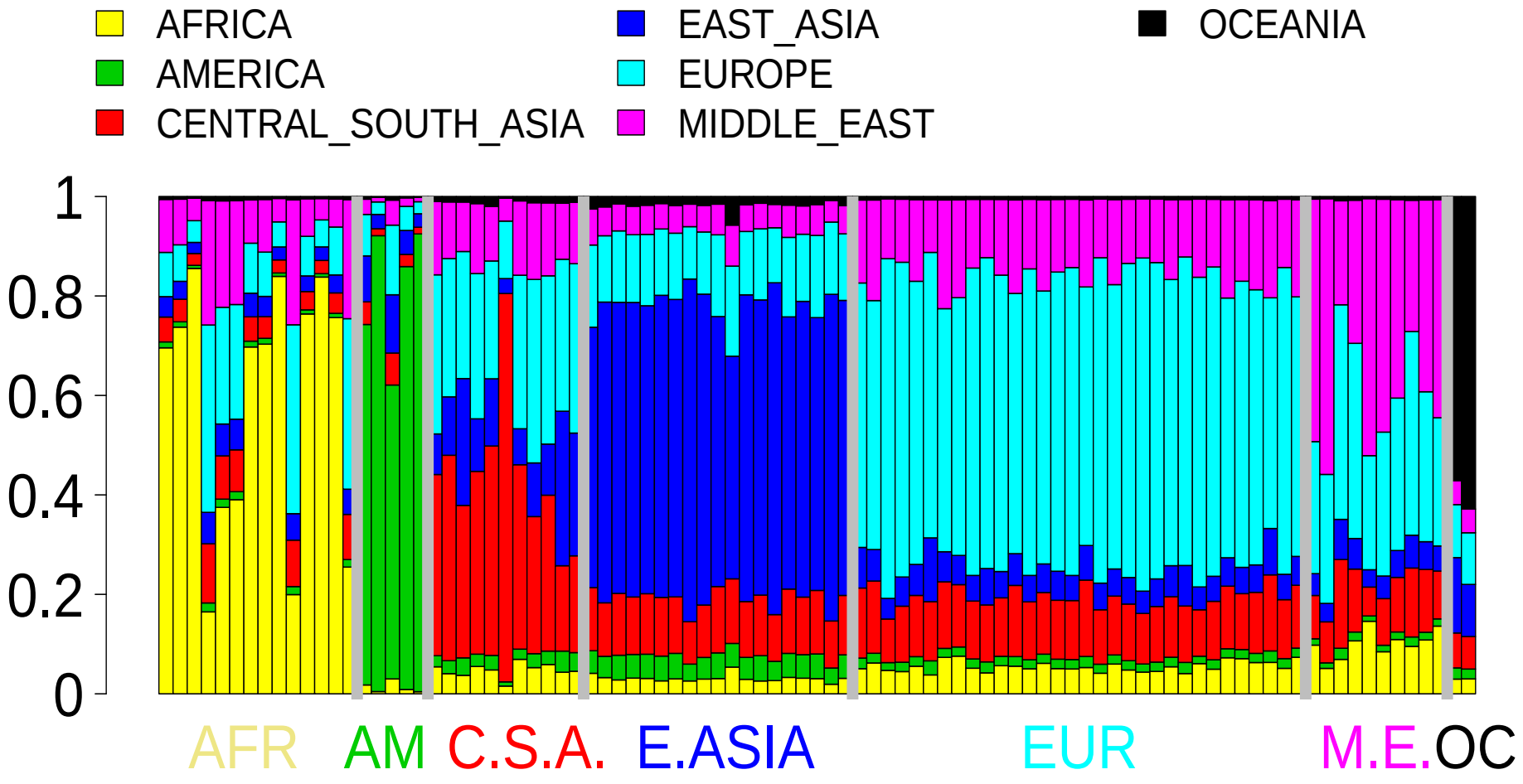

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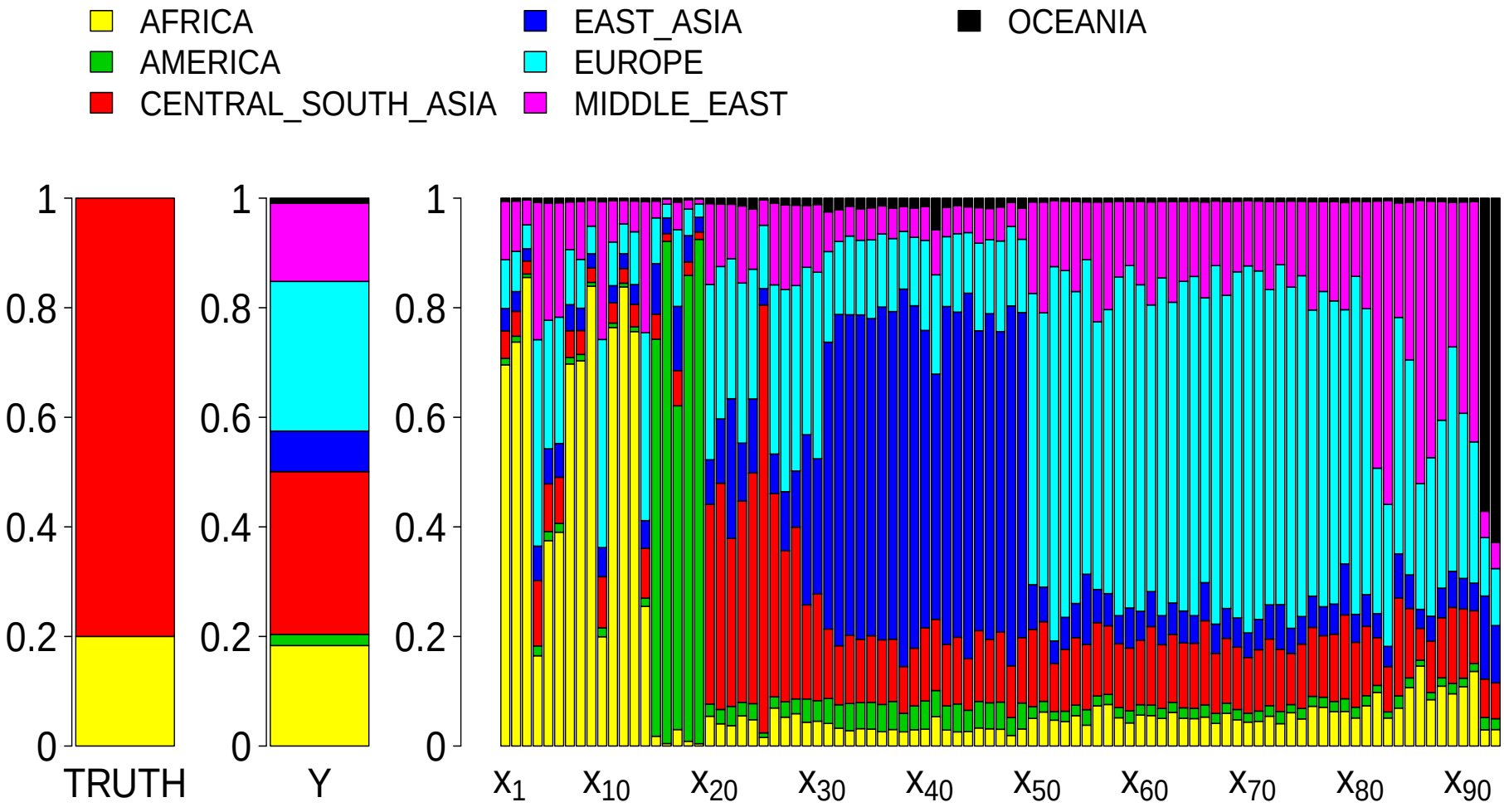

(2) form admixed ind's painting as mixture of that for all 93 groups:

$$Y = \beta_1 X_1 + \beta_2 X_2 + ... + \beta_{93} X_{93} \qquad \text{(with } \sum_i \beta_i = 1.0\text{)}$$

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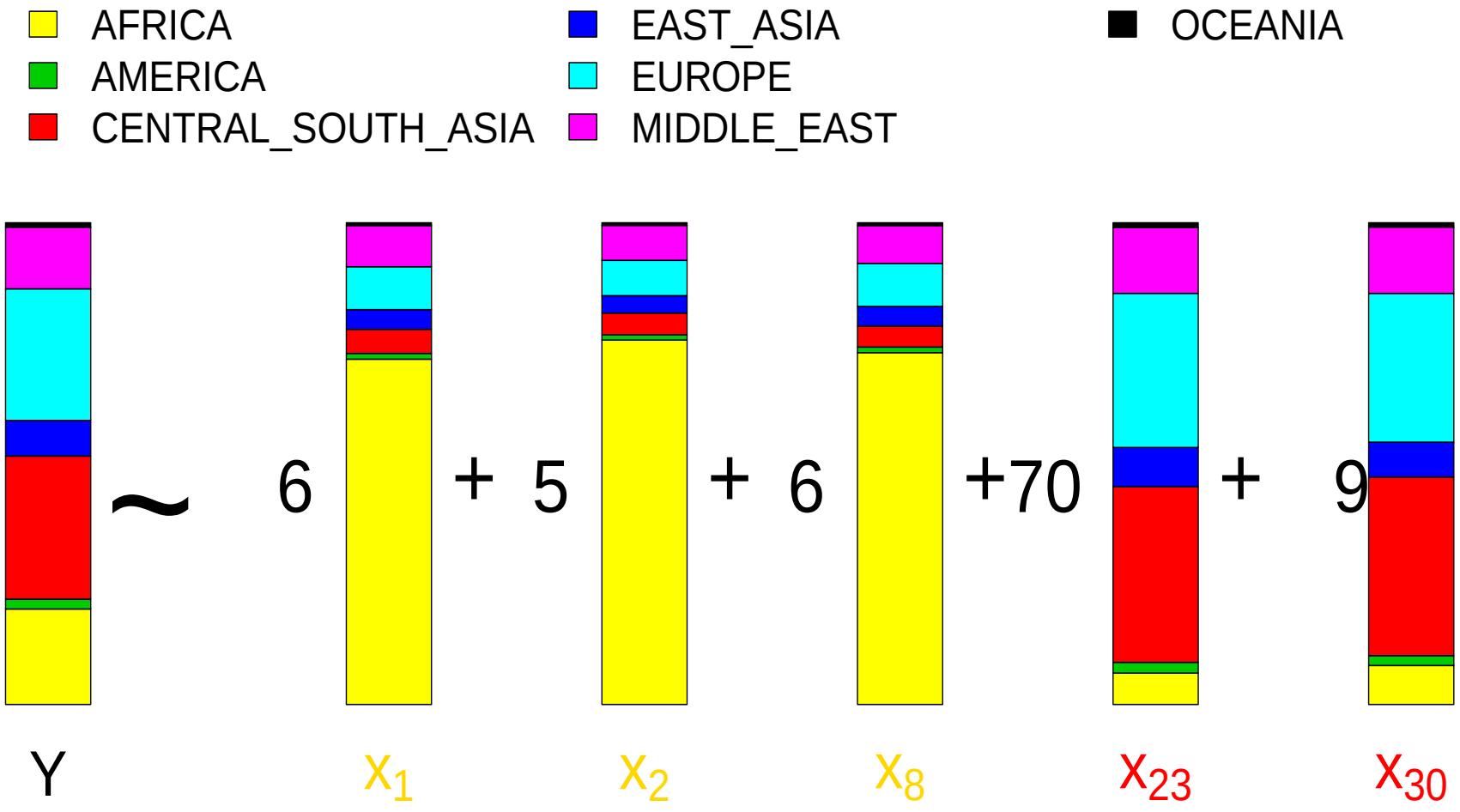

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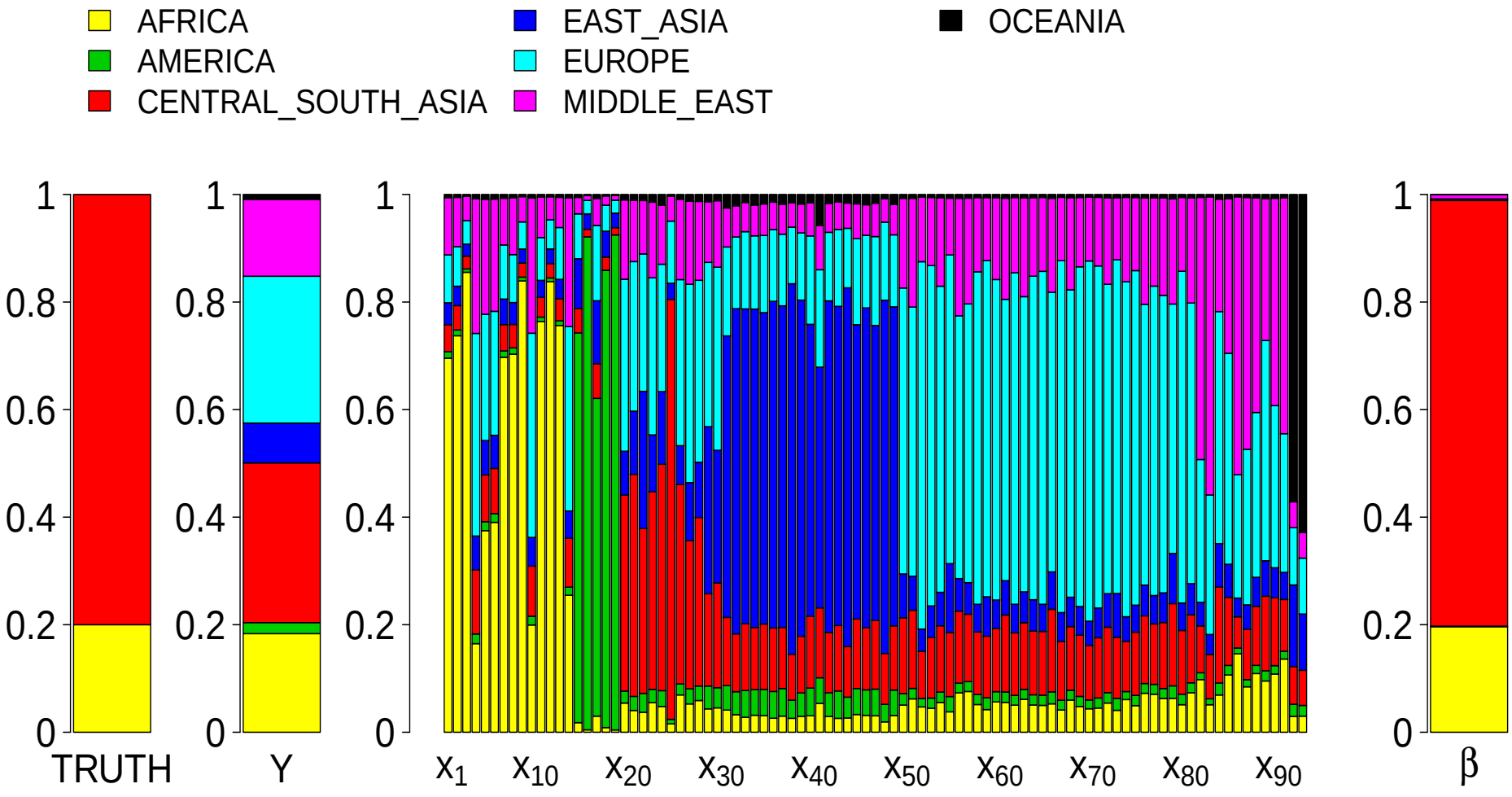

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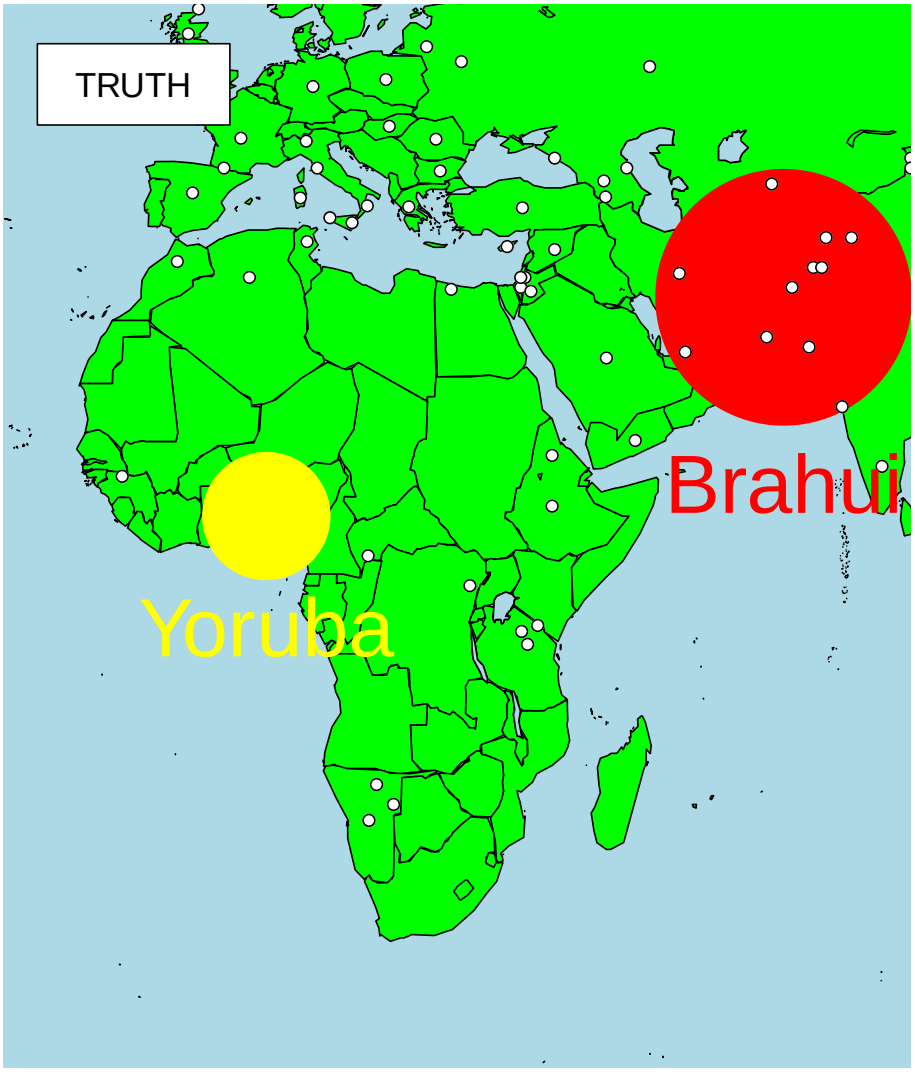

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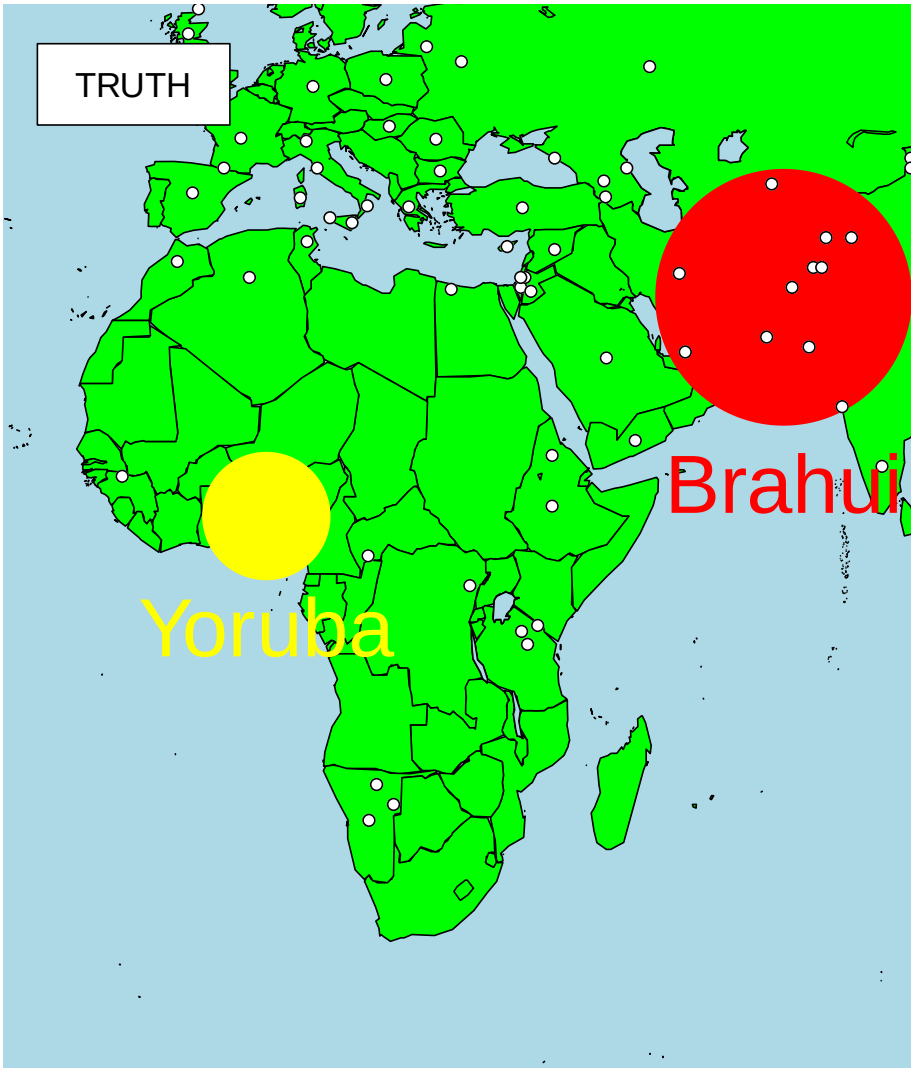
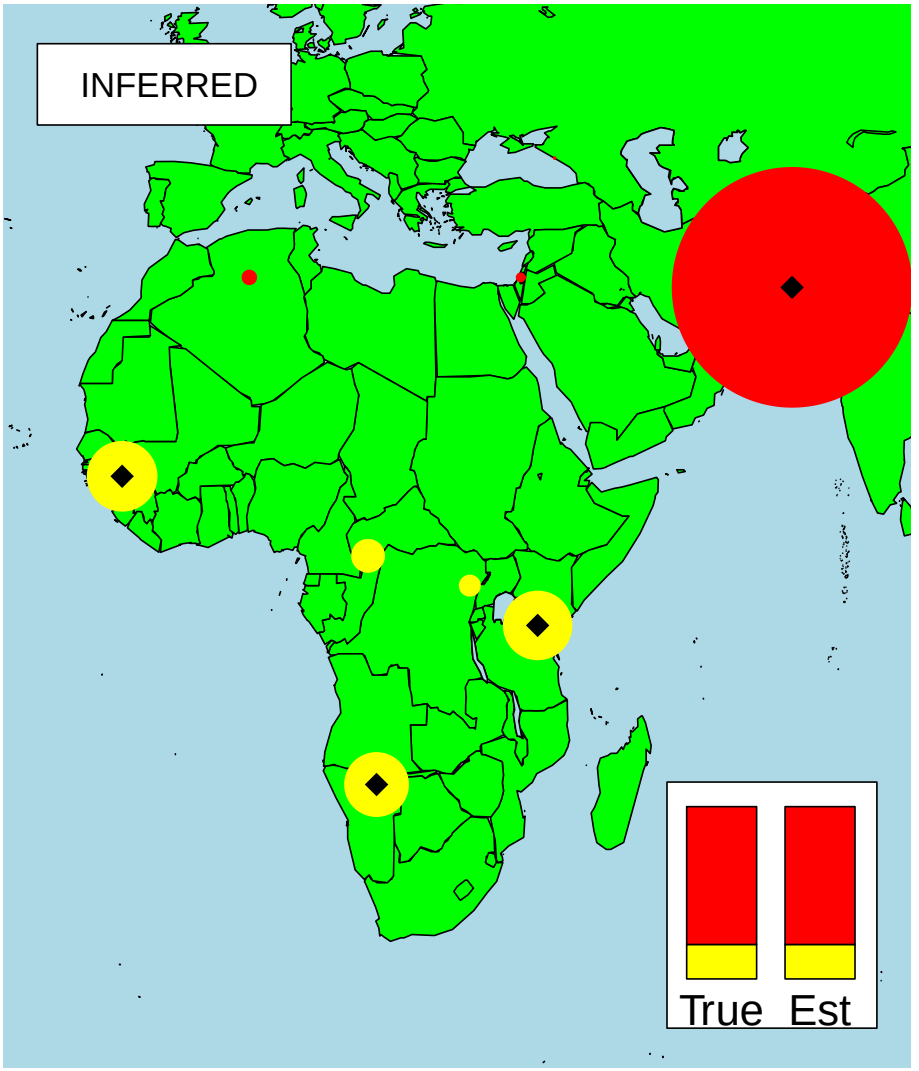
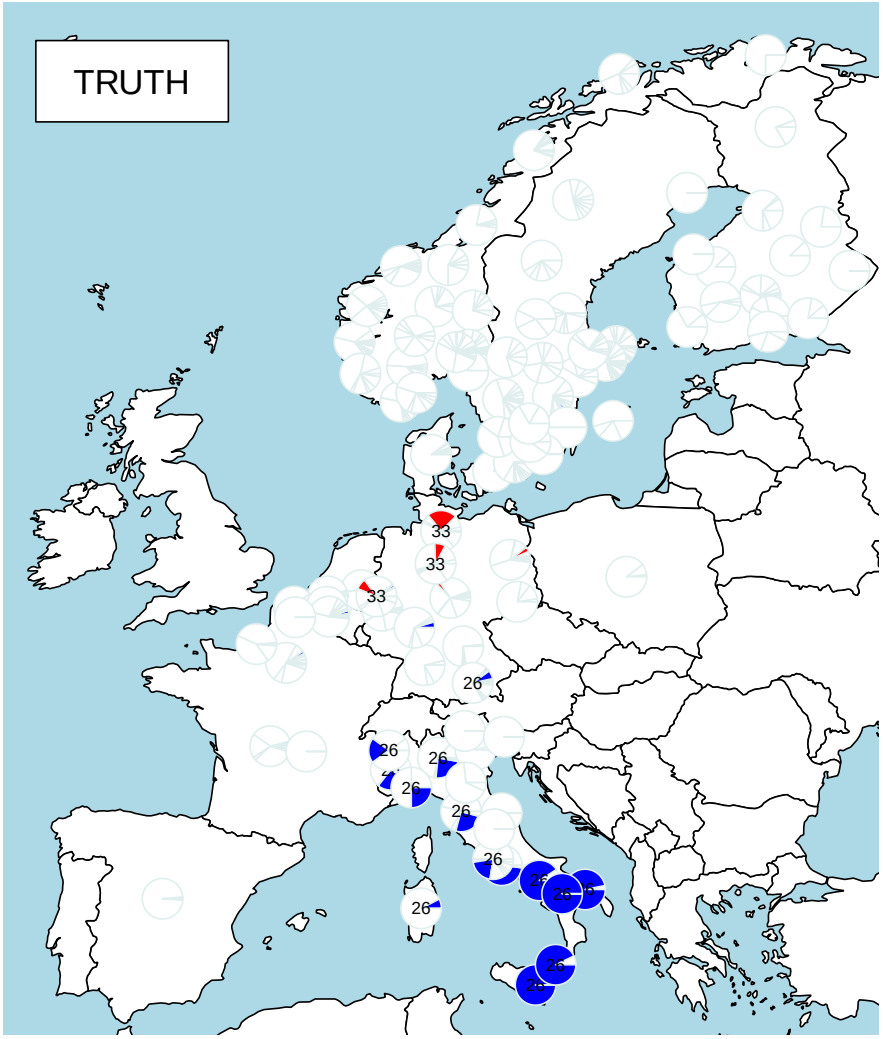




Simulated Europe Admixture: 75% Italy + 25% N.Germany, 40gen



(Leslie et al 2015, *Nature* **519**:309)

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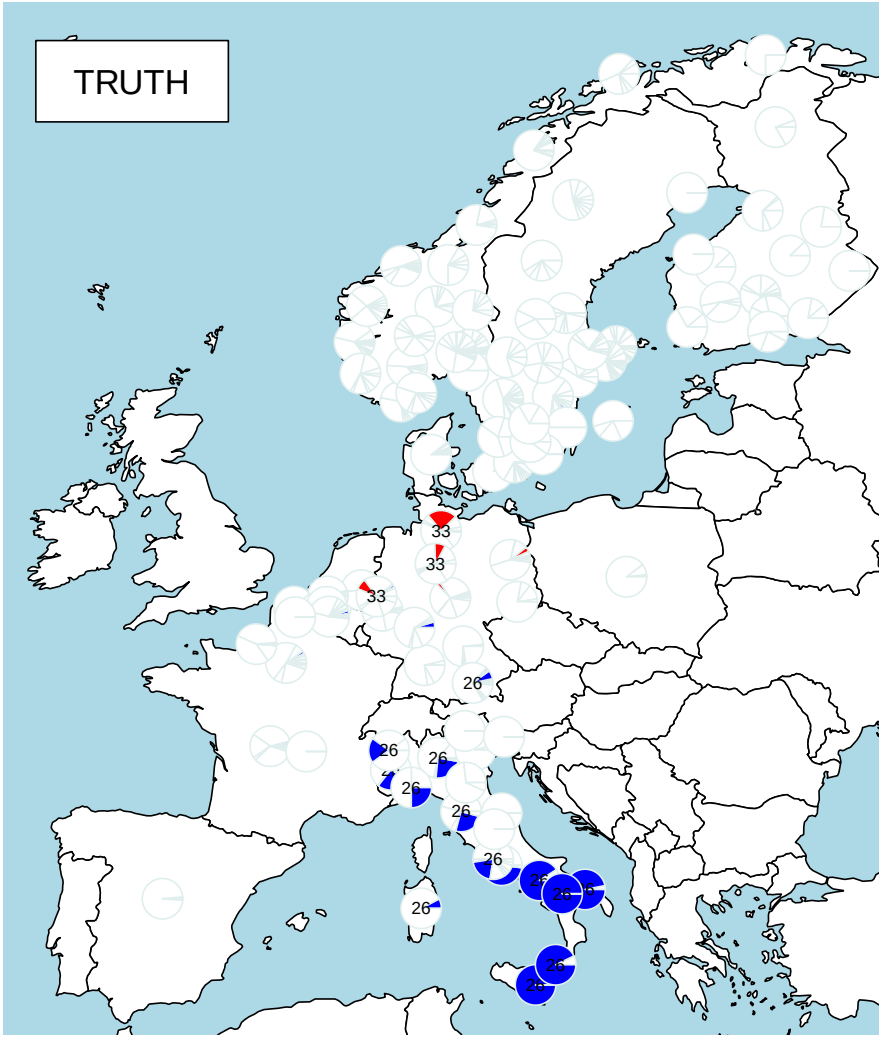

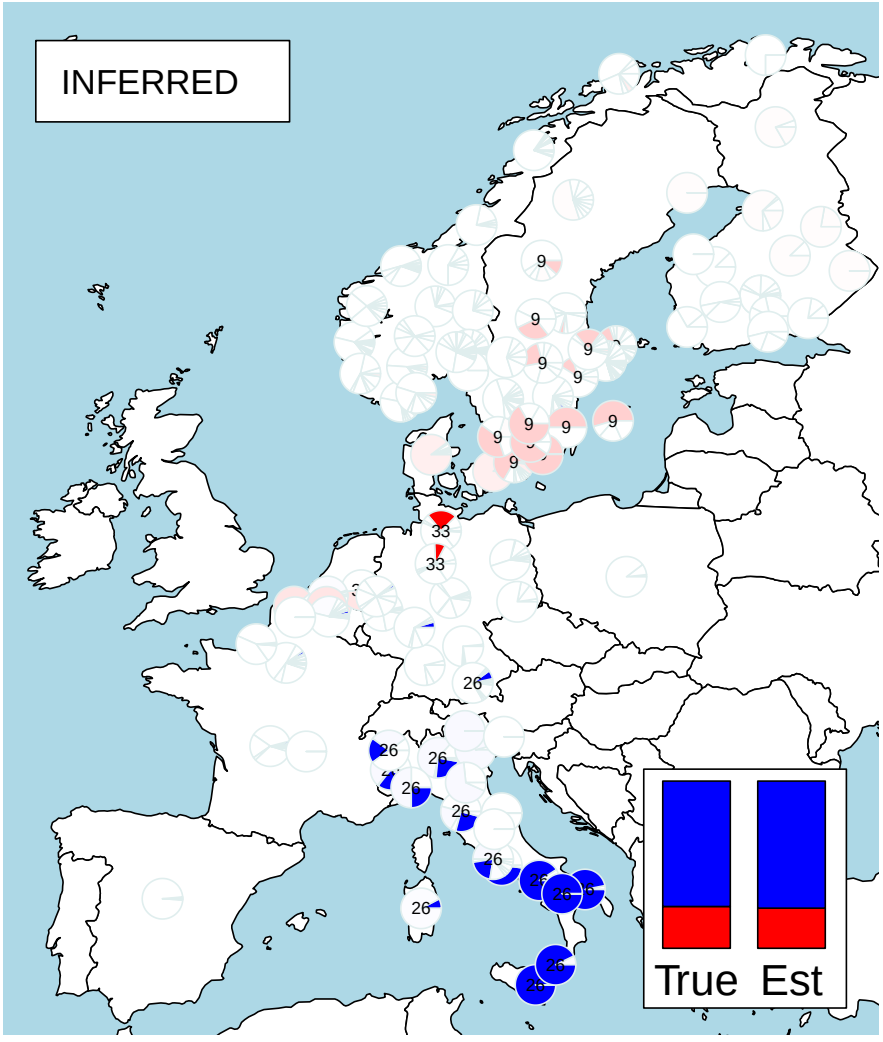

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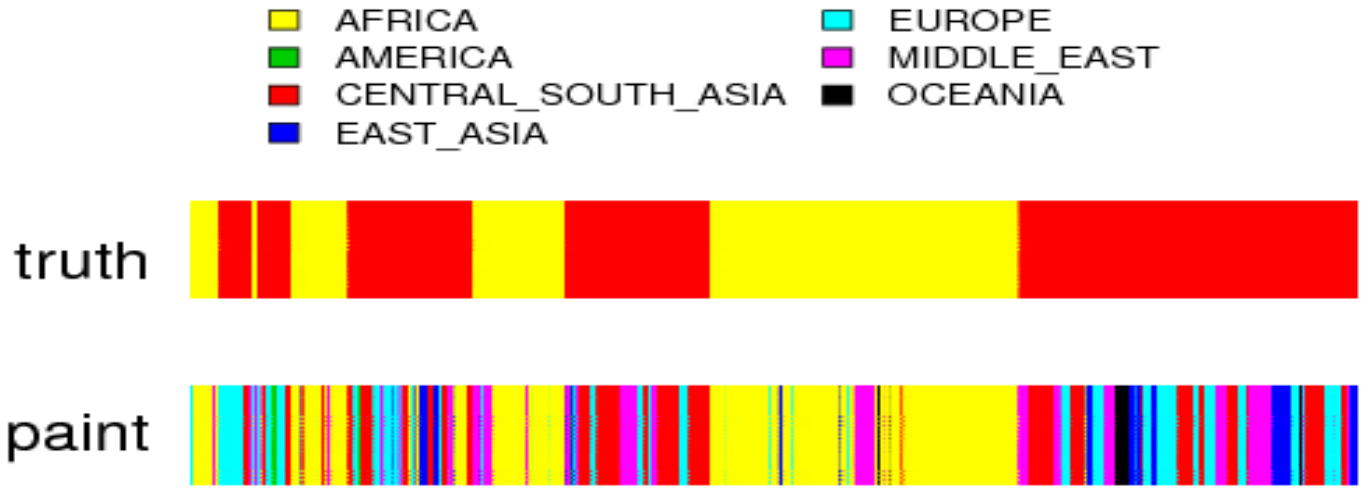
Dating Admixture (Sim: 80% Brahui + 20% Yoruba, 30gen)



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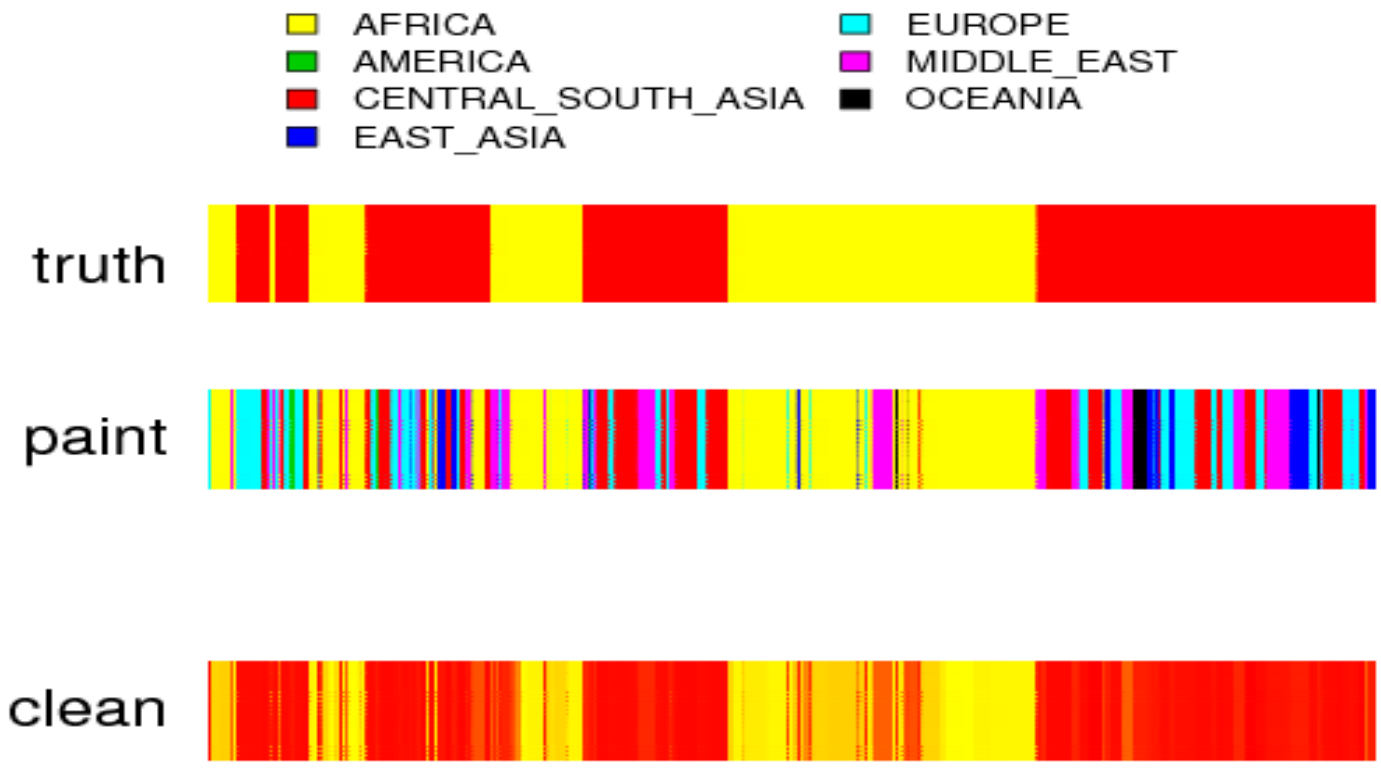

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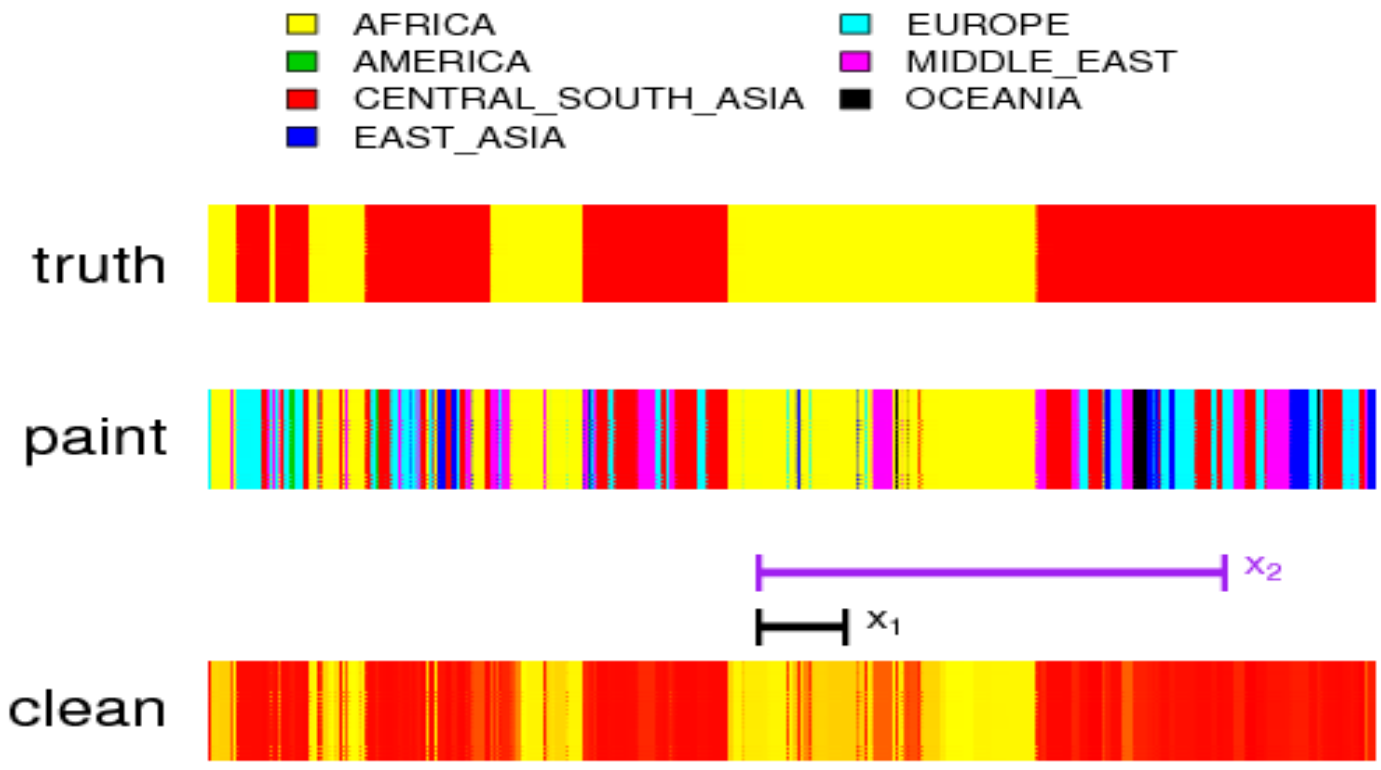

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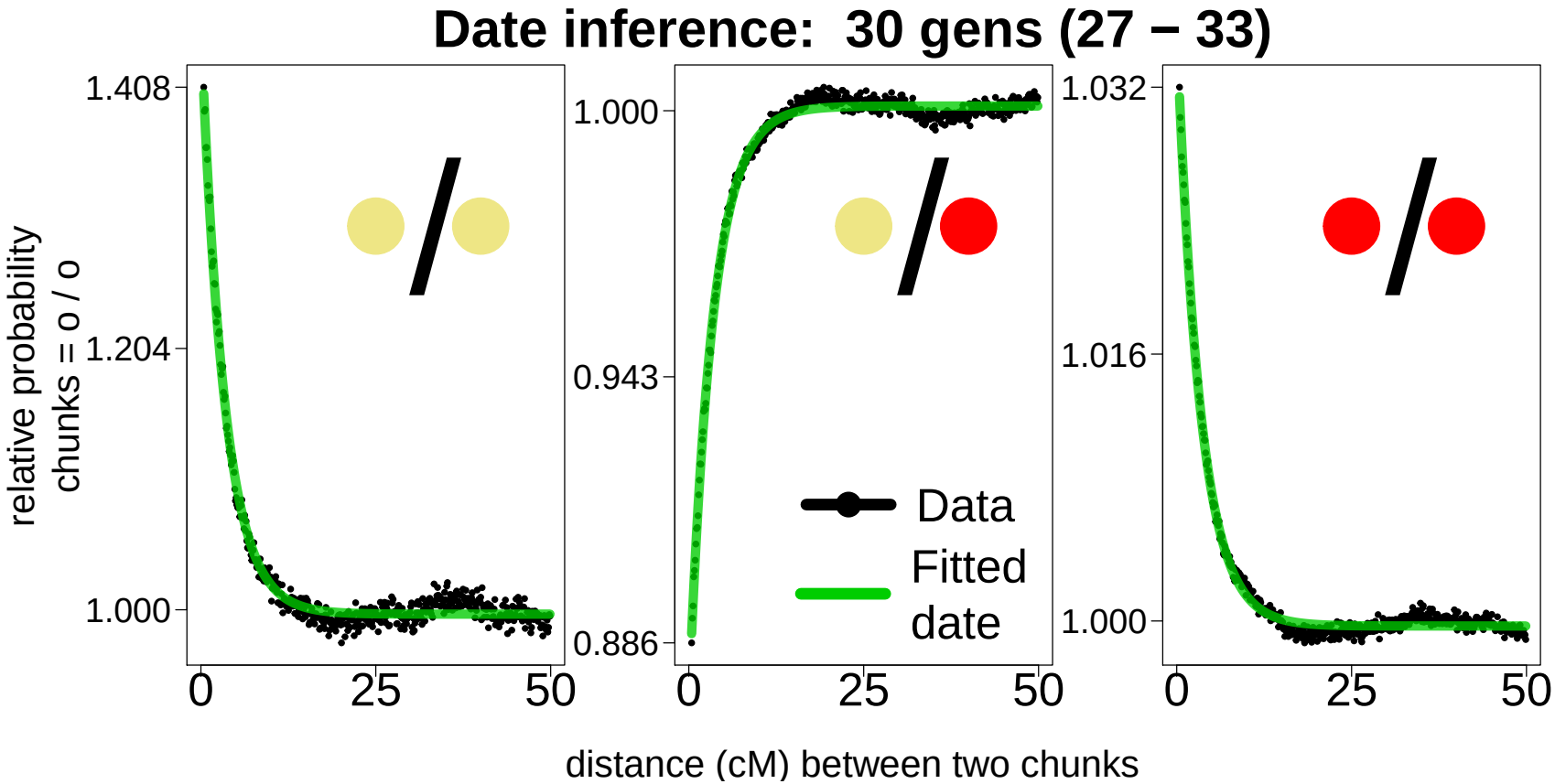

Coancestry curves:

- **left**: (scaled) probability that two DNA segments ("chunks") separated by cM distance *X* are both from **yellow** source
- **middle**: probability one chunk is from **yellow** source, one chunk from **red** source
- **right**: probability both chunks are from **red** source

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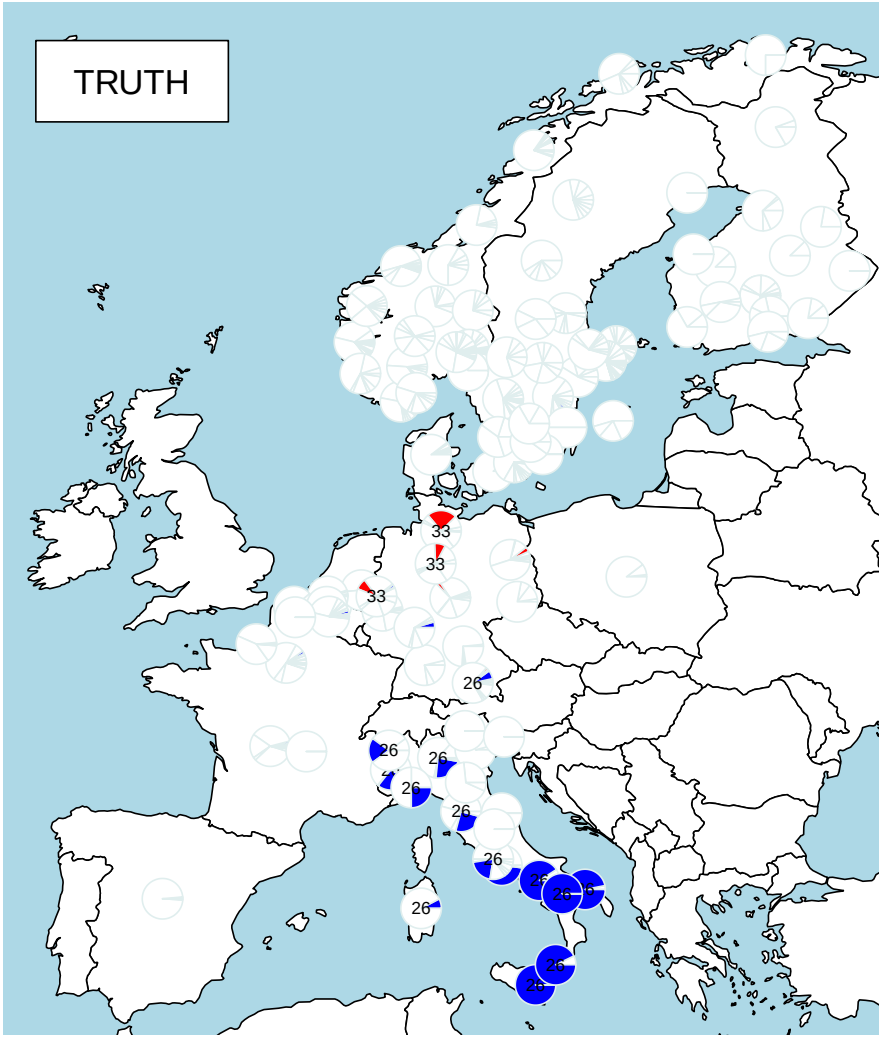

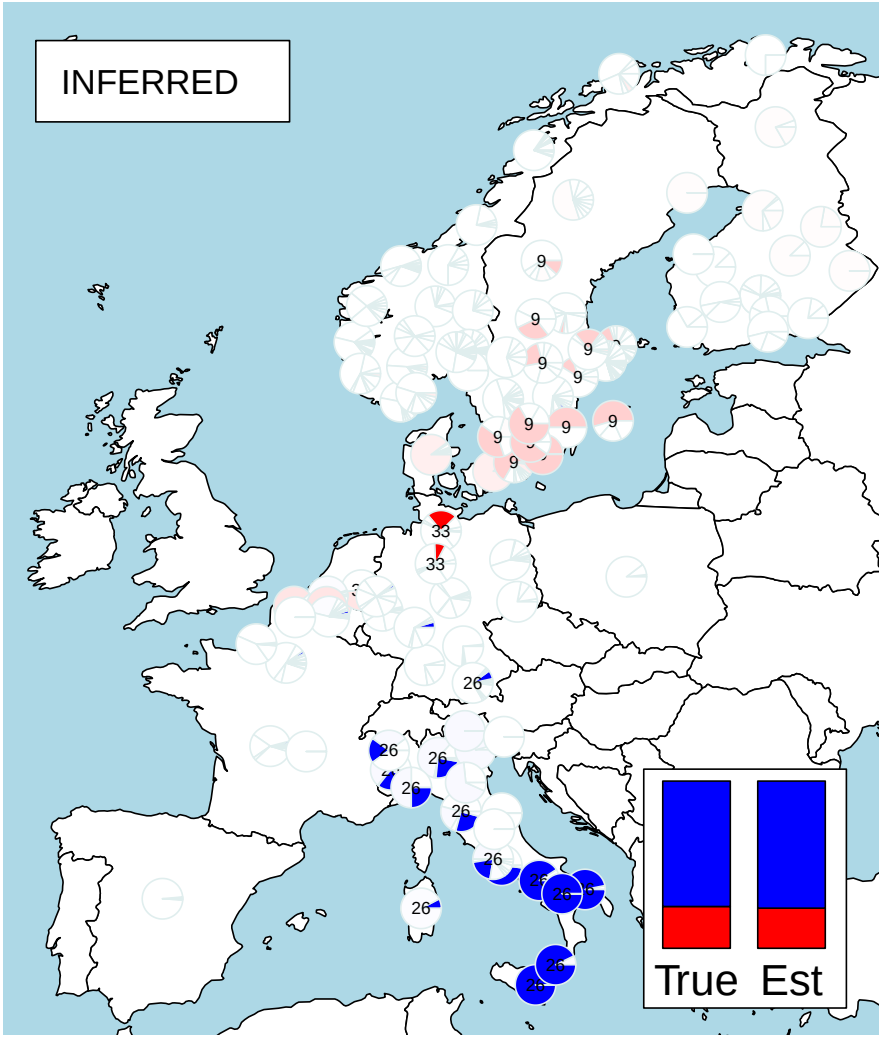

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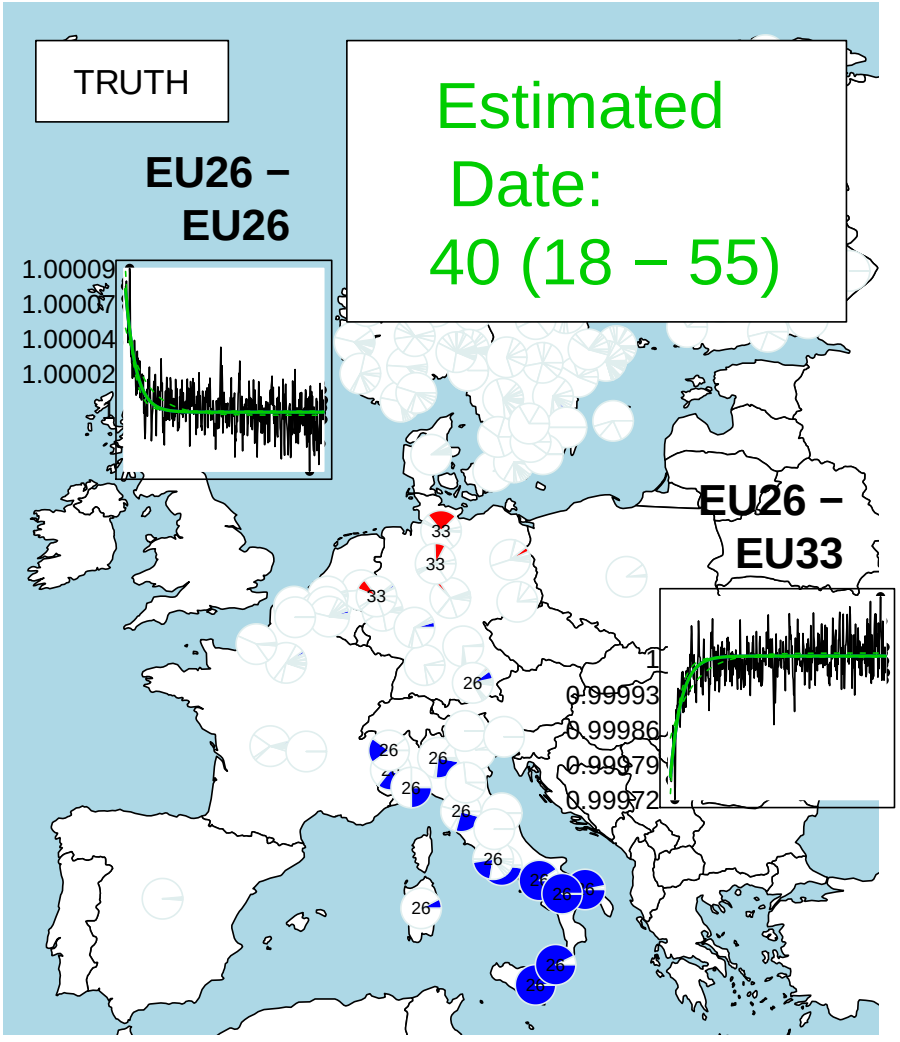

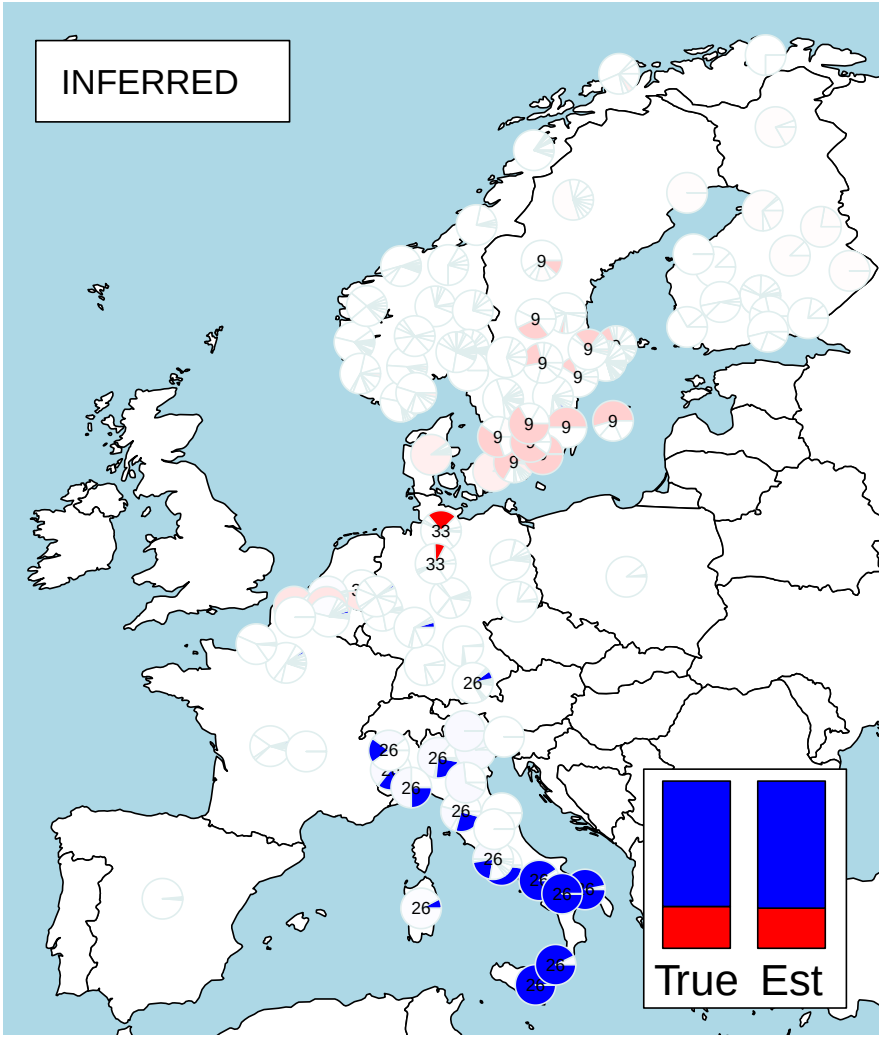

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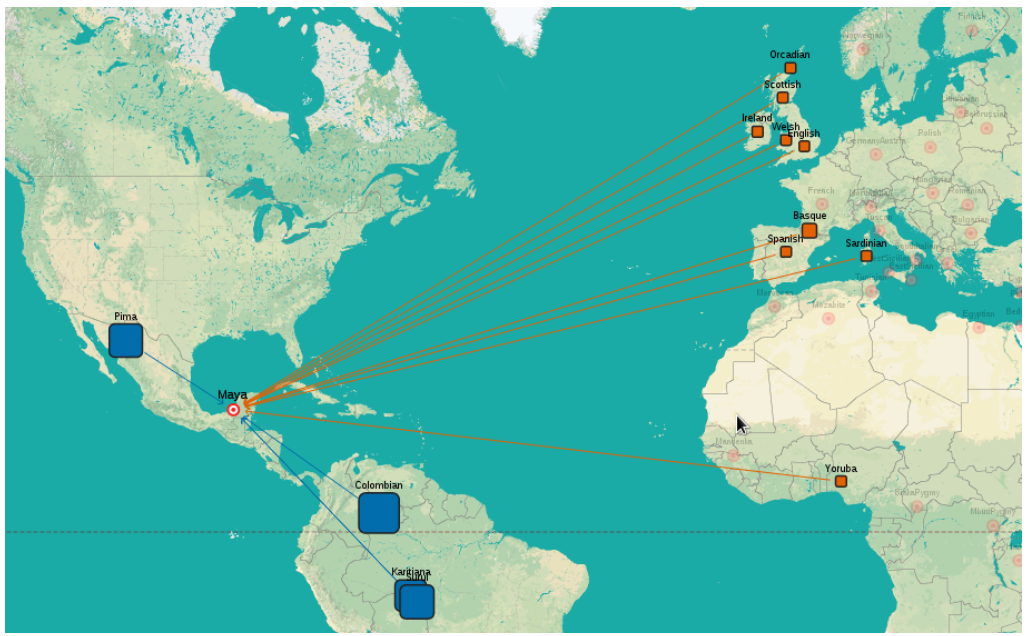
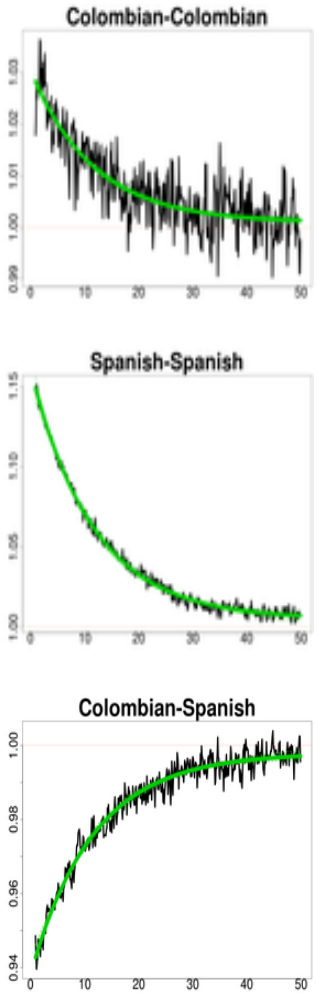
Inferring admixture – *GLOBETROTTER* (example)

- **Maya from Mexico** show evidence for admixture between **Spain-like** and **Native American-like** groups
- dated to 1642-1726AD
- corresponds to colonial-era migration of Europeans to Americas



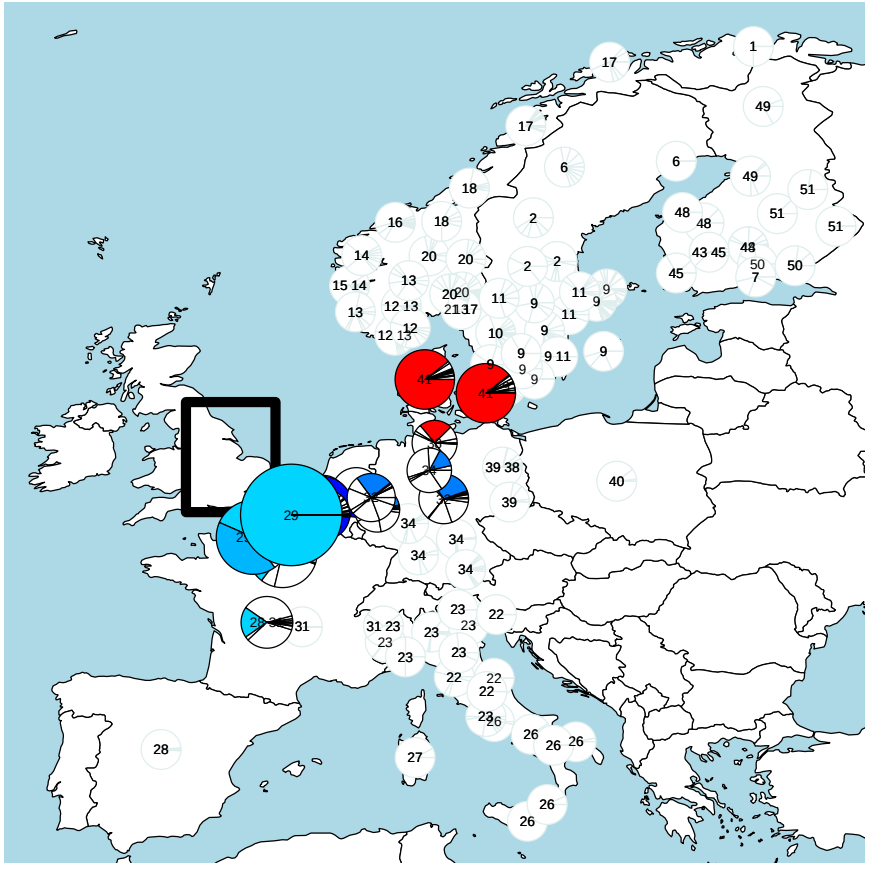


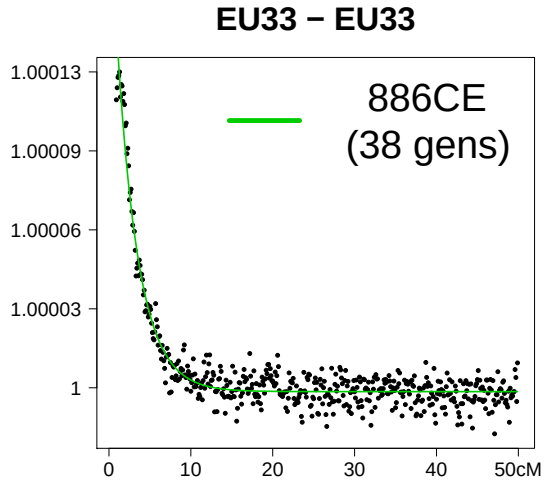
(Hellenthal et al 2014, *Science* **343**:747)

Identifying/Dating admixture in United Kingdom

"SE.England" cluster (Y) as mixture of 51 Europe clusters (X_1,...,X_{51}):

$$Y = \beta_1 X_1 + \beta_2 X_2 + ... + \beta_{51} X_{51}$$





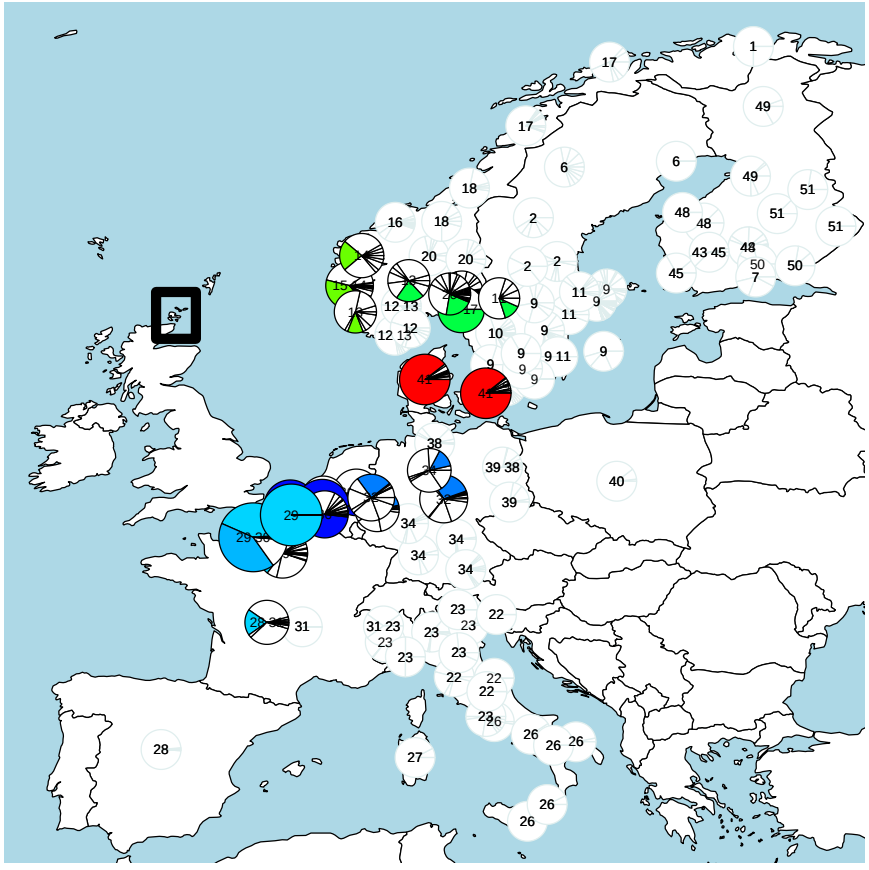
DNA matched to **N.Germany** and **Denmark** $\longrightarrow$ **Anglo-Saxons?**

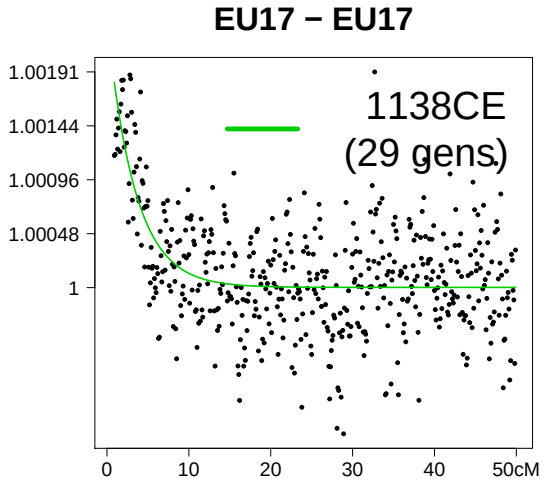
(Leslie et al 2015, *Nature* **519**:309)

Identifying/Dating admixture in United Kingdom

"Orkney" cluster (Y) as mixture of 51 Europe clusters (X_1,...,X_{51}):

$$Y = \beta_1 X_1 + \beta_2 X_2 + ... + \beta_{51} X_{51}$$



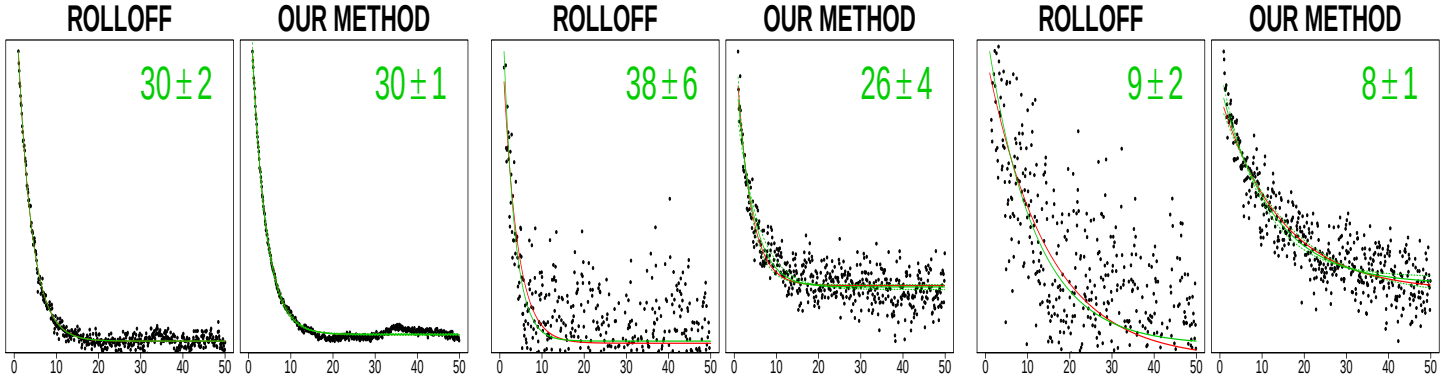


DNA matched to **Norway** ⟶ **Norse Vikings?**

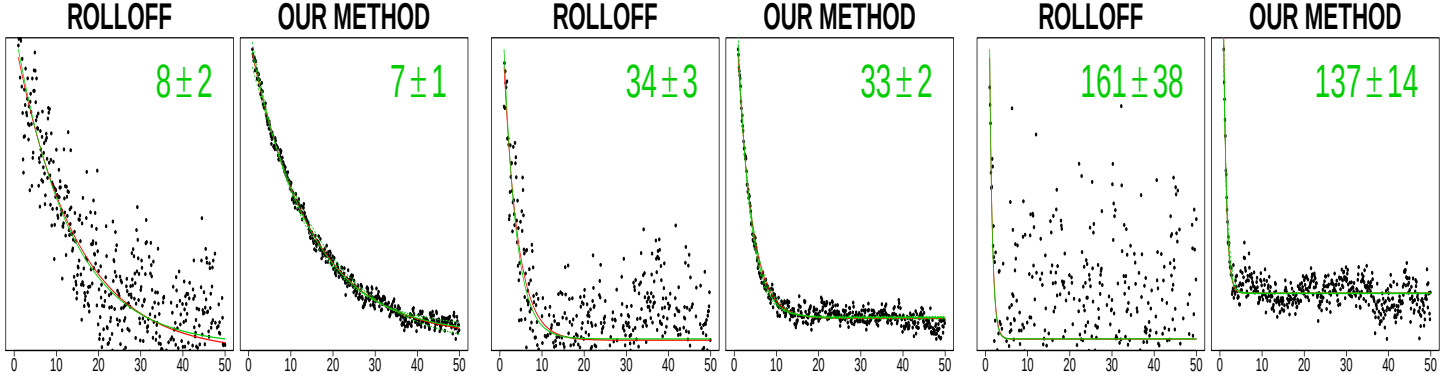
(Leslie et al 2015, *Nature* **519**:309)

Comparison to *ROLLOFF* (e.g. Patterson et al 2012, *Genetics* **192**:1065)

- compared to *ROLLOFF*, fixing two "known" admixing sources
- increased power/precision when using haplotype information



Brahui-Yoruba (20%) French-Brahui (50%) French-Brahui (20%)



Colombia-Han (20%) Colombia-Han (20%) Colombia-Han (50%)

Outline

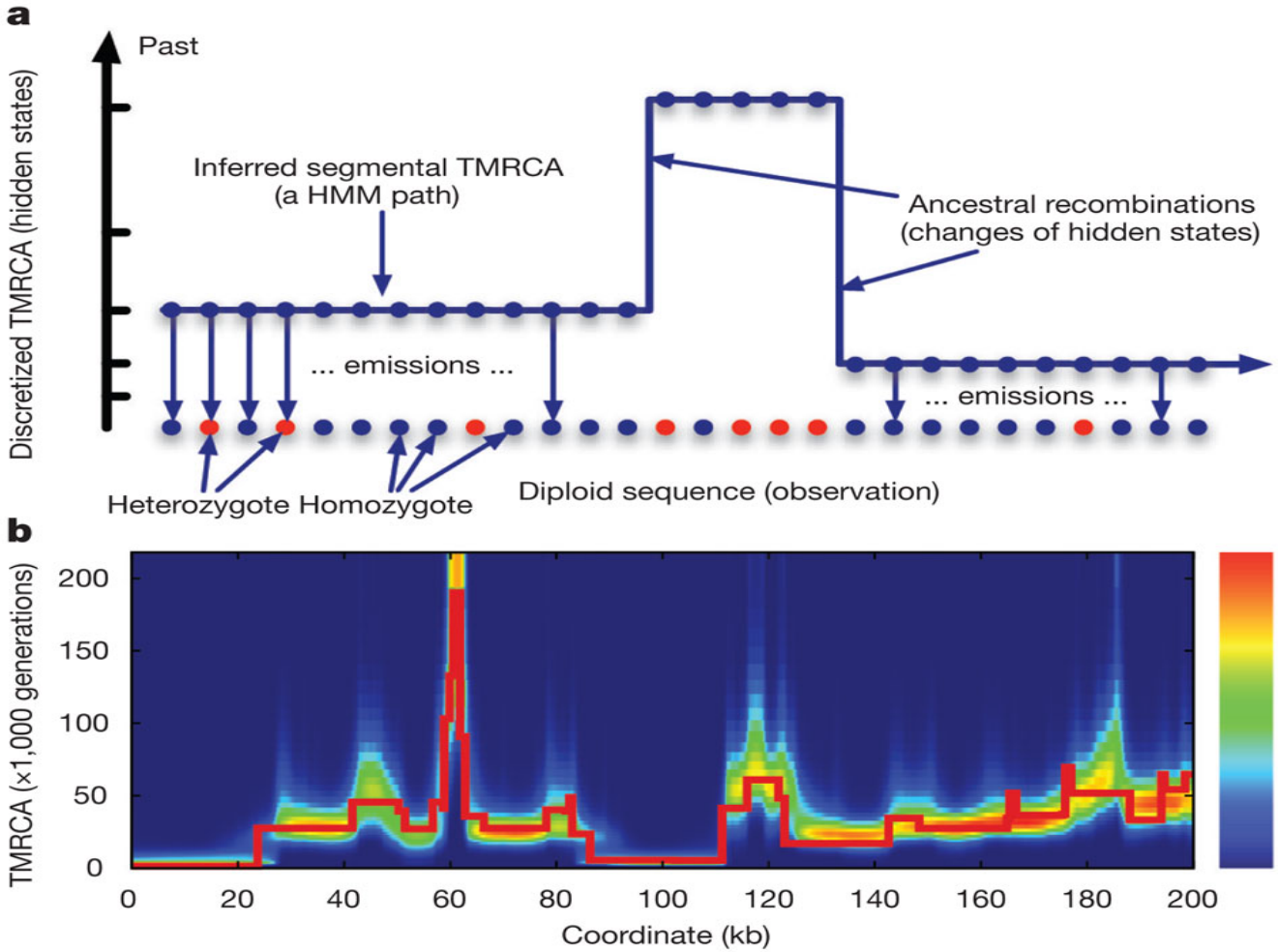
inferring admixture (*GLOBETROTTER*)

inferring pop size changes (*PSMC, MSMC*)

Inferring population size changes over time

- aim is to infer how population sizes changed over time (e.g. due to expansions/bottlenecks)
- powerful technique to do so: Pairwise Sequential Markovian Coalescent (PSMC) (Li & Durbin 2011, *Nature* **475**:493)
  - requires sequencing data $\rightarrow$ use mutations as a "clock" to infer time
  - to convert to years, must assume mutation rate per generation $\rightarrow$ some debate over appropriate rate to use (e.g. Scally & Durbin 2012, *Nature Rev Genet* **13**:745)

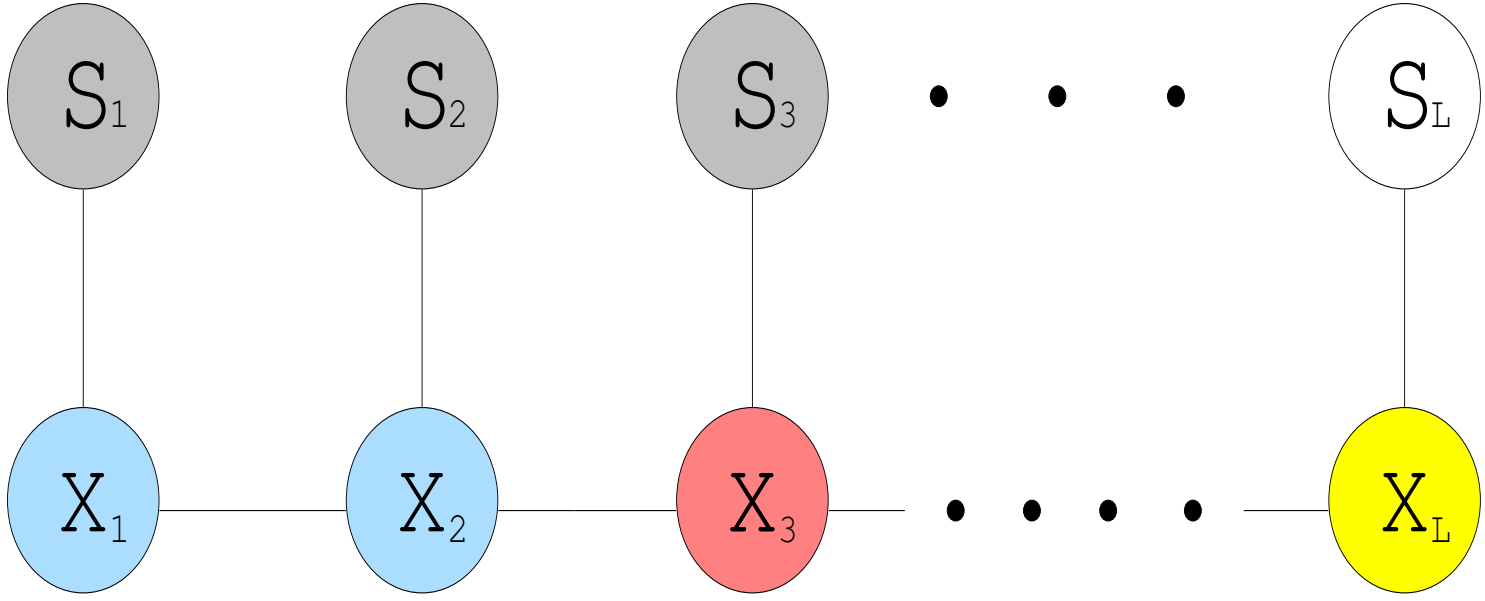
PSMC (Li & Durbin 2011, *Nature* **475**:493)



- consider a single diploid individual: infer TMRCA (The Most Recent Common Ancestor) of individuals' two haplotypes
- **switches in TMRCA** depends on recombination rate
- **How to determine TMRCA?** lots of heterozygotes in region → higher TMRCA

PSMC – HMM (Li & Durbin 2011, *Nature* **475**:493)

- S_l = (observed state) whether 100bp bin *l* is heterozygous or not
- X_l = (hidden state) time to most recent common ancestor (TMRCA) at 100bp bin *l*



- each TMRCA is depicted with a unique color here
- assume “switches” in TMRCA depend on recombination rate ρ
- “switches” also depend on TMRCA

PSMC – HMM (Li & Durbin 2011, *Nature* **475**:493)

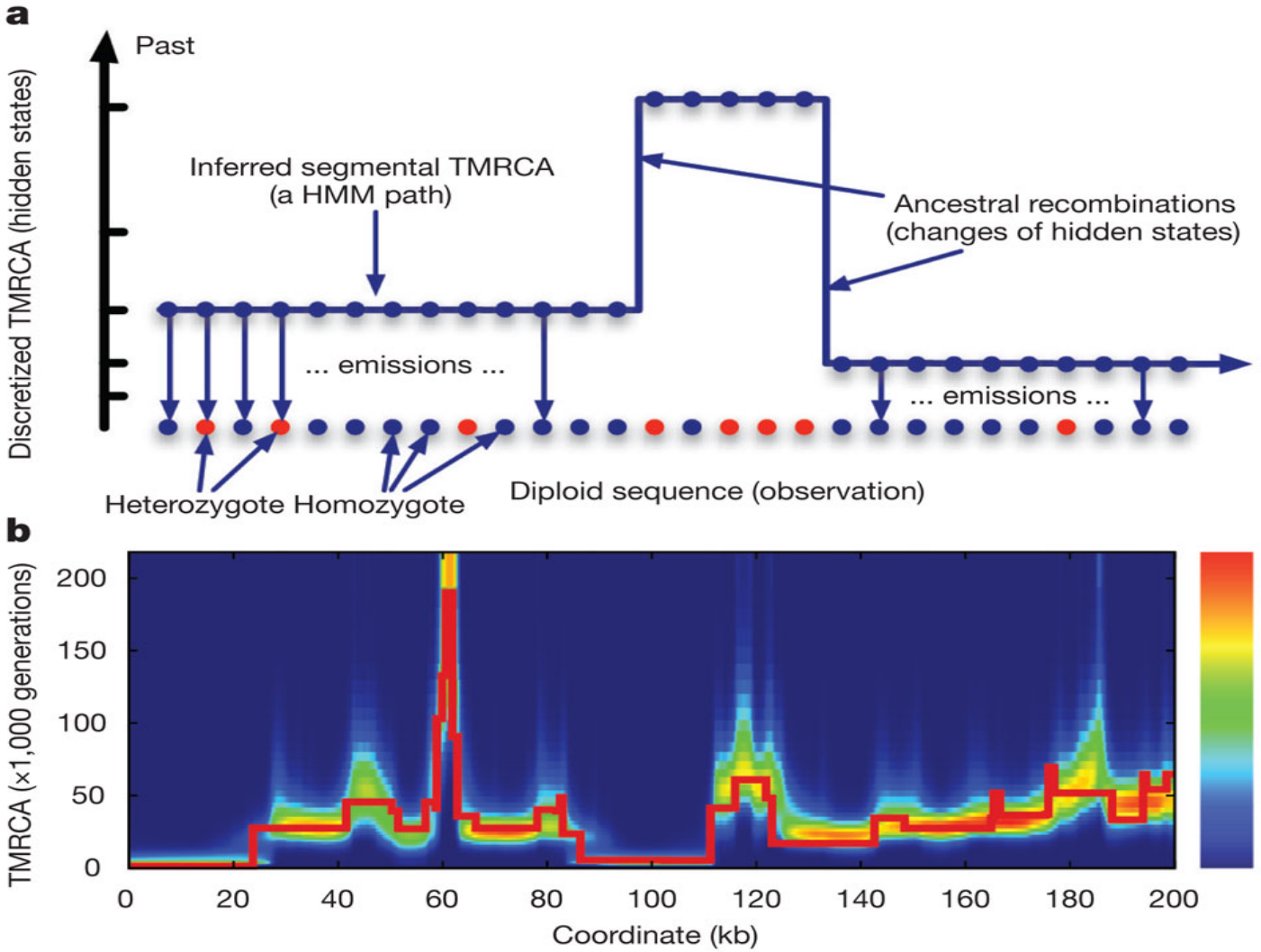
Observed State (for given 100bp bin):

- "missing": $\geq$90bp uncalled (SAMtools) or filtered
- "heterozygous": $>$10bp called and $\geq$1 heterozygote
- "homozygous": else
- $\Pr(\textit{missing} \mid t) = 1$
- $\Pr(\textit{heterozygous} \mid t) = \exp^{-\theta t}$ (??)
- $\Pr(\textit{homozygous} \mid t) = 1 - \exp^{-\theta t}$ (??)
- $\theta = 4N_0\mu$ (with $\mu = 2.5 \times 10^{-8}$)

Hidden State: (switches in TMRCA from $s \rightarrow t$ between two 100bp bins; ρ=recombination rate):

- $\Pr(t \mid s) = (1 - \exp^{-\rho t})q(t \mid s) + \exp^{-\rho s}\,\delta(t - s)$
- $q(t \mid s) = \Pr(t \mid s, \textit{recomb}) = \frac{1}{\lambda(t)} \int_0^{\min(s,t)} \left[\frac{1}{s} \exp^{-\int_u^t \frac{1}{\lambda(v)} dv}\right] du$
- $\lambda(t) = \frac{N_e(t)}{N_0}$
- $\delta(t - s) =$ Dirac-delta function

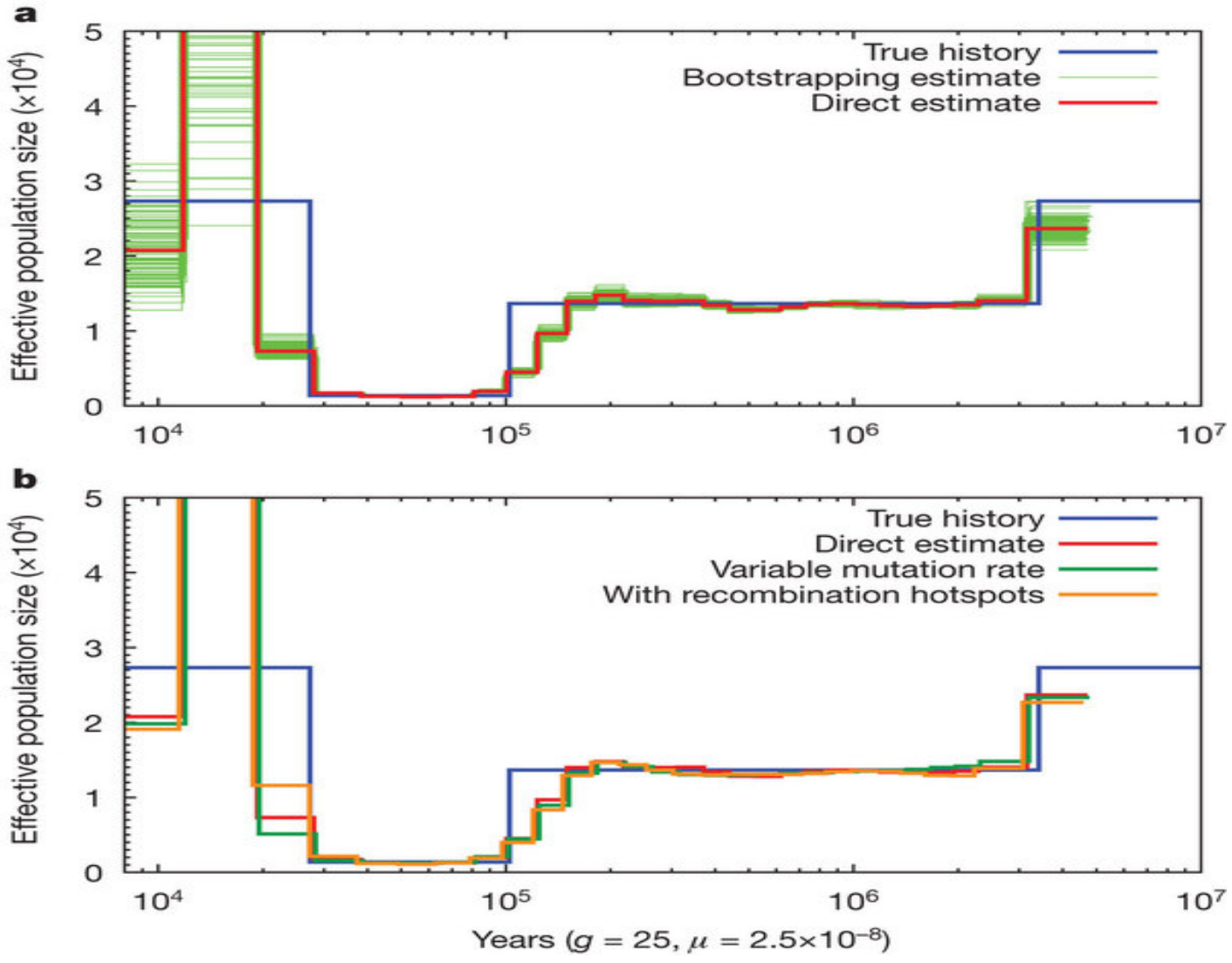
PSMC (Li & Durbin 2011, *Nature* **475**:493)



Aim: infer (effective) population size at different times in the past

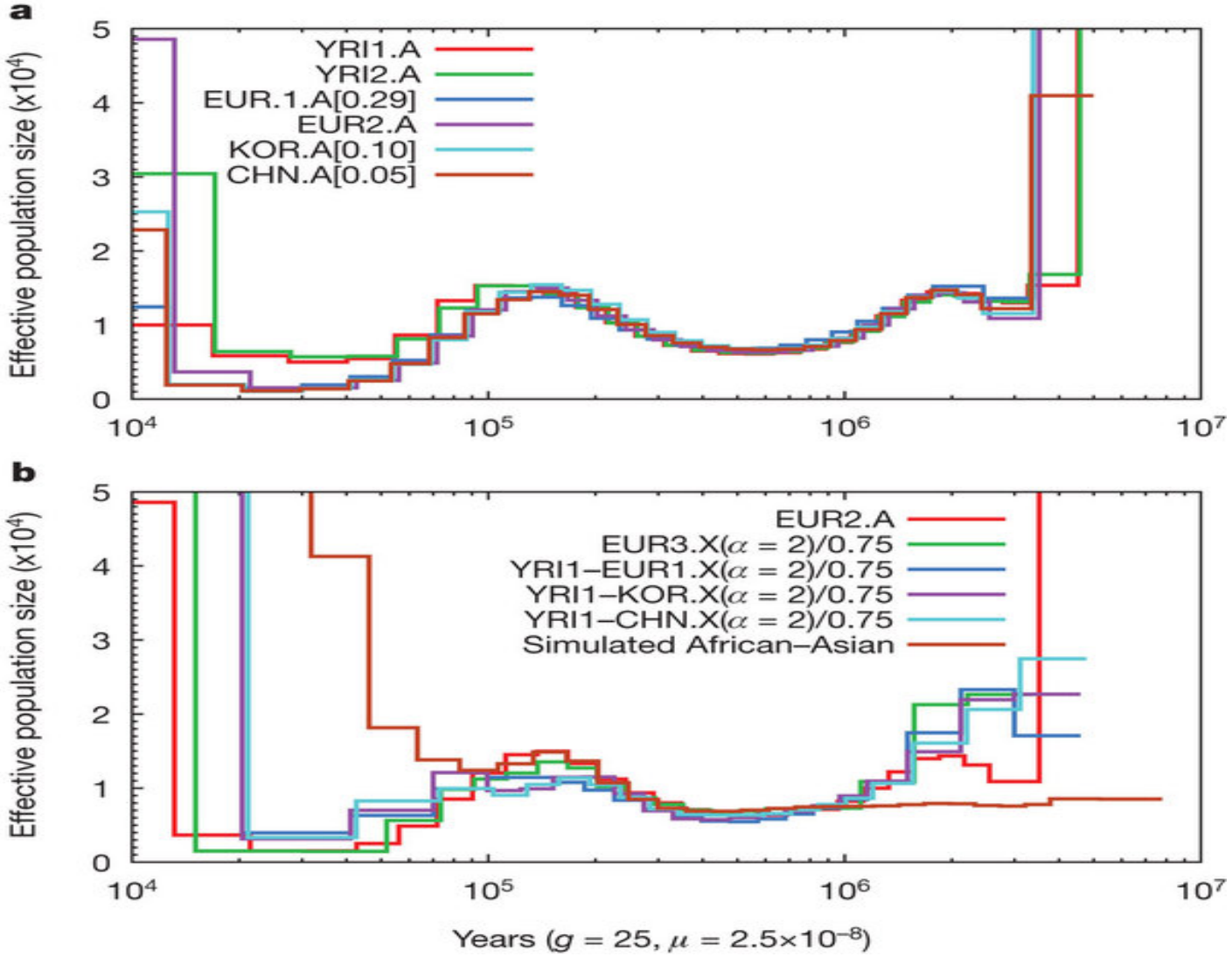
How? if lots of genome segments have the same TMRCA $t \longrightarrow$ decrease in population size at t

PSMC – simulations (Li & Durbin 2011, *Nature* **475**:493)



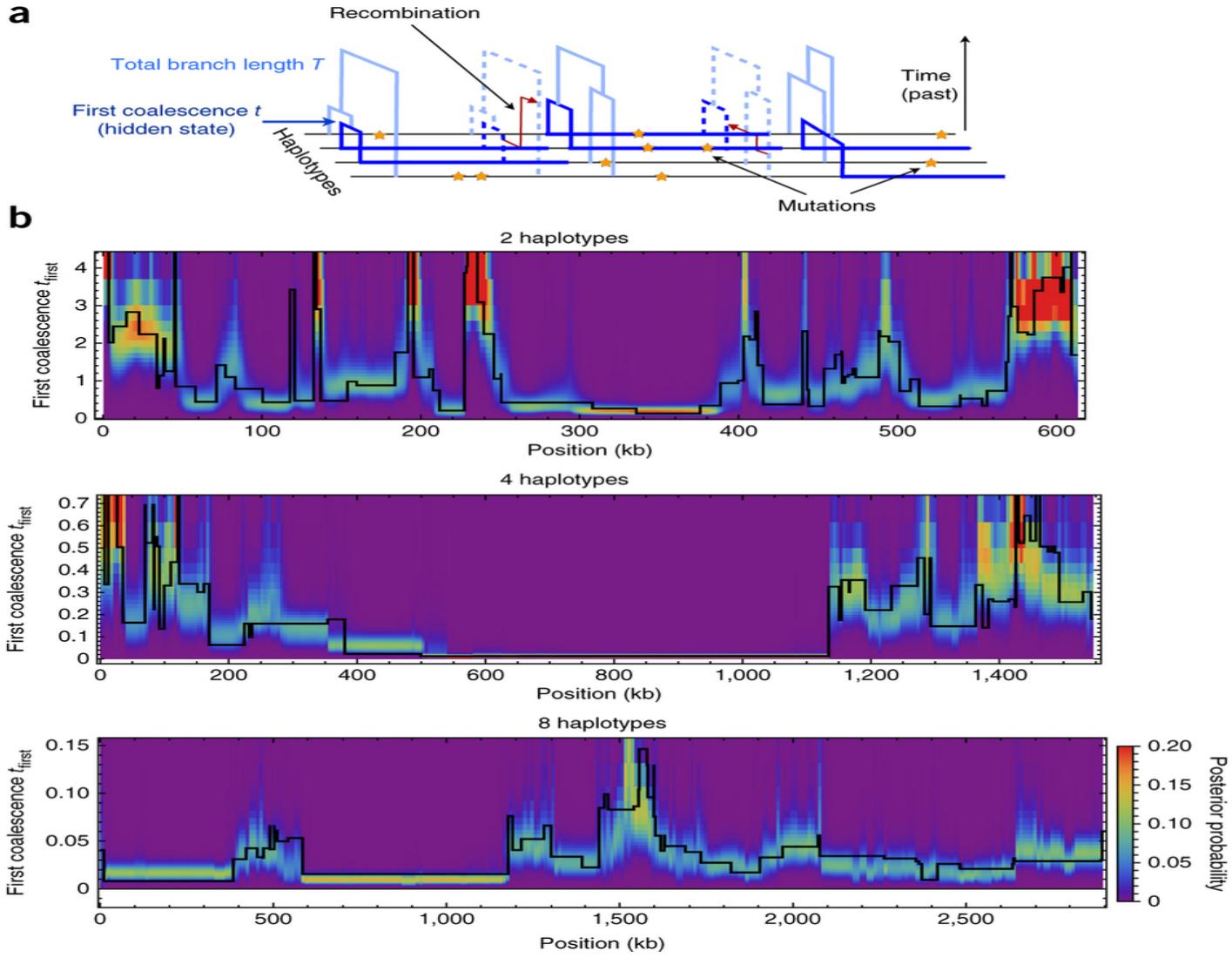
- nicely tracks population size over time (ms simulation), except at recent dates
- **green lines** – bootstrap re-sampling of 5Mb genetic regions

PSMC – results (Li & Durbin 2011, *Nature* **475**:493)



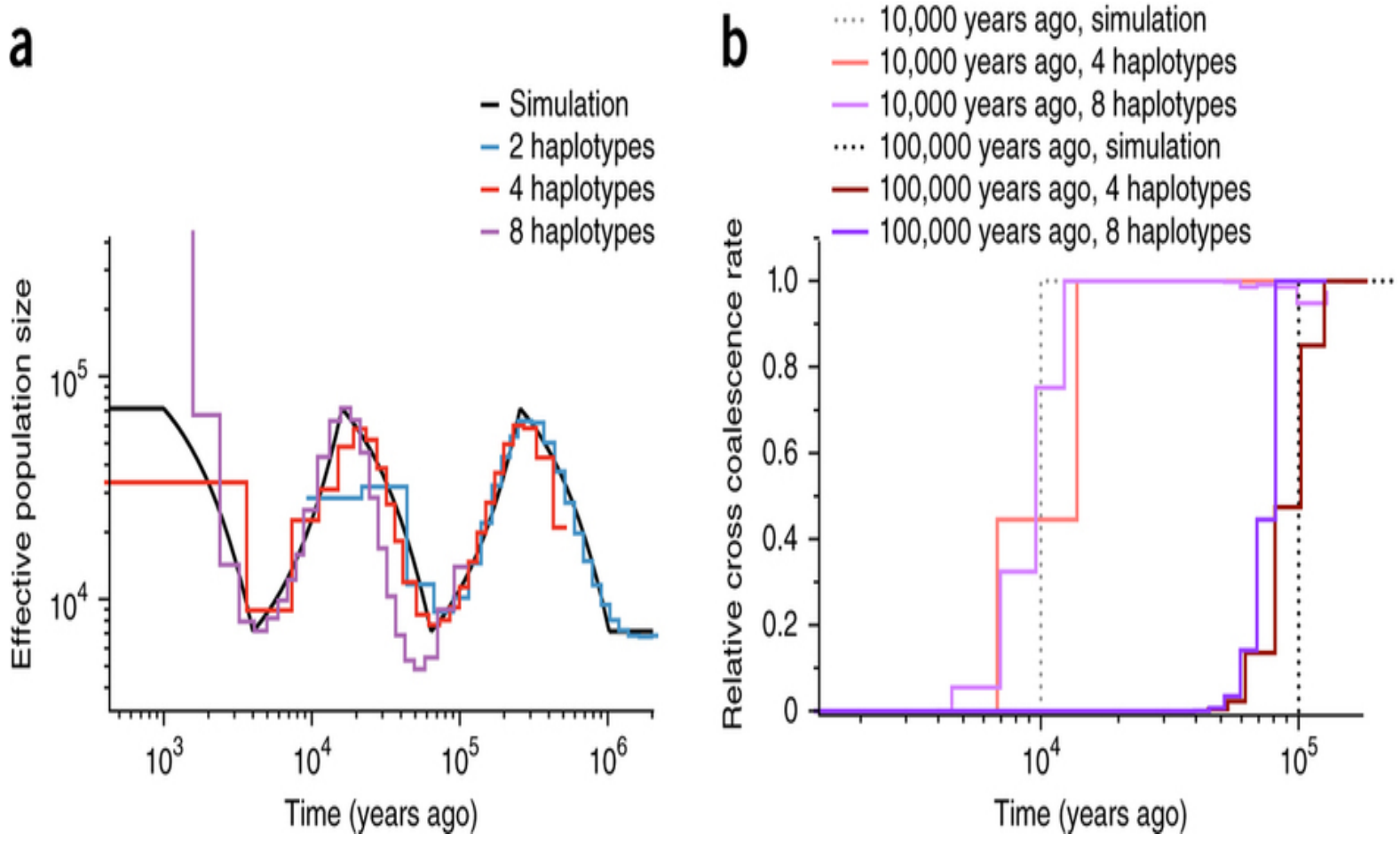
- **(top:)** dip in population size from around 100-150kya to about 40-20kya
- **(bottom:)** N_e between groups (e.g. Africa-Europe) very low relative to **simulation** where populations split 60kya

MSMC (Schiffels & Durbin 2014, *Nature Genetics* **46**:919)



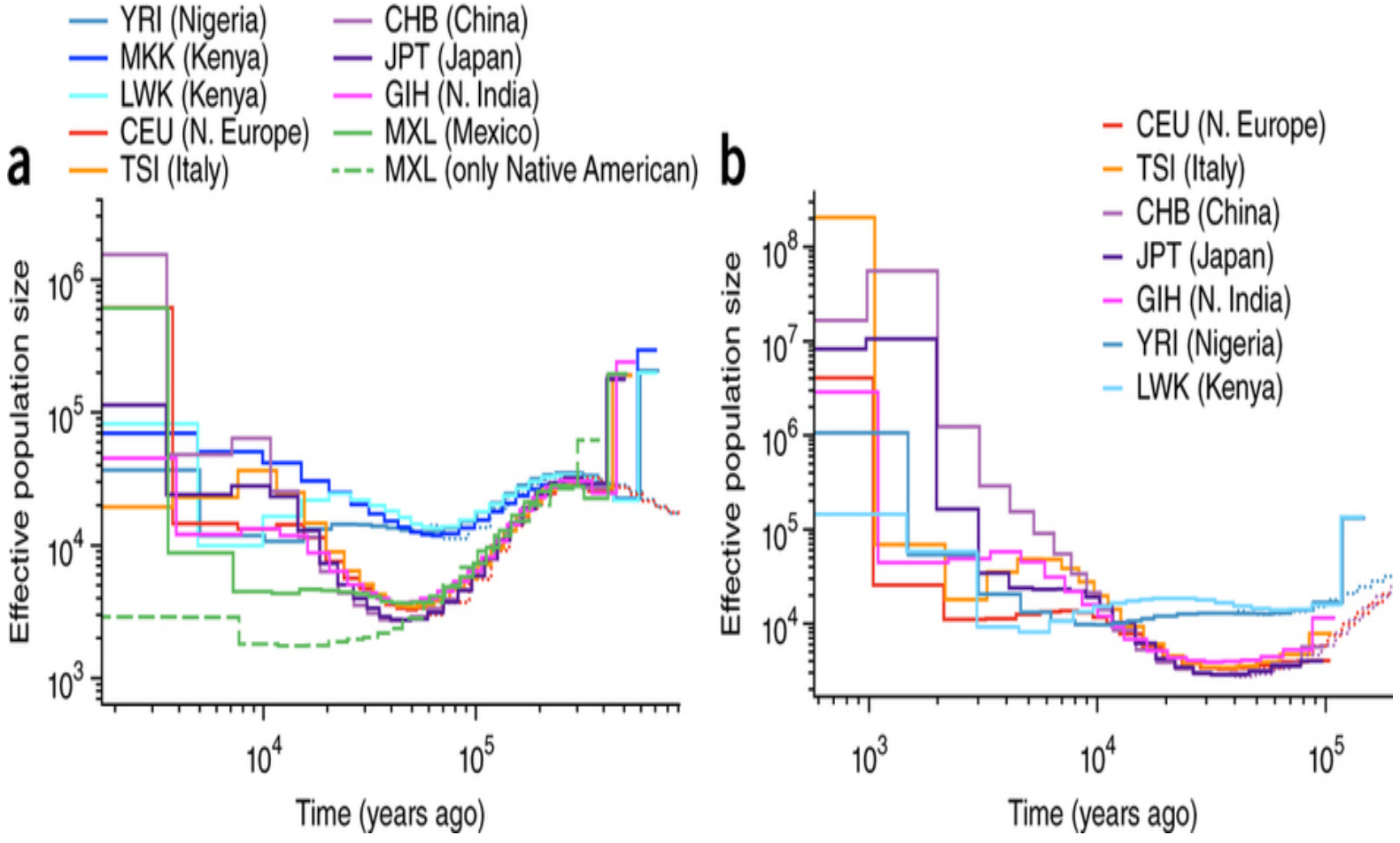
- consider 2-4 individuals, and find *first coalesence* in each genetic region
- first coalesence becomes more recent (and spans longer regions) as number of (phased) haplotypes increases (i.e. $E[t] = \frac{2}{n(n-1)}$)

MSMC – Simulations (Schiffels & Durbin 2014, *Nature Genetics* **46**:919)



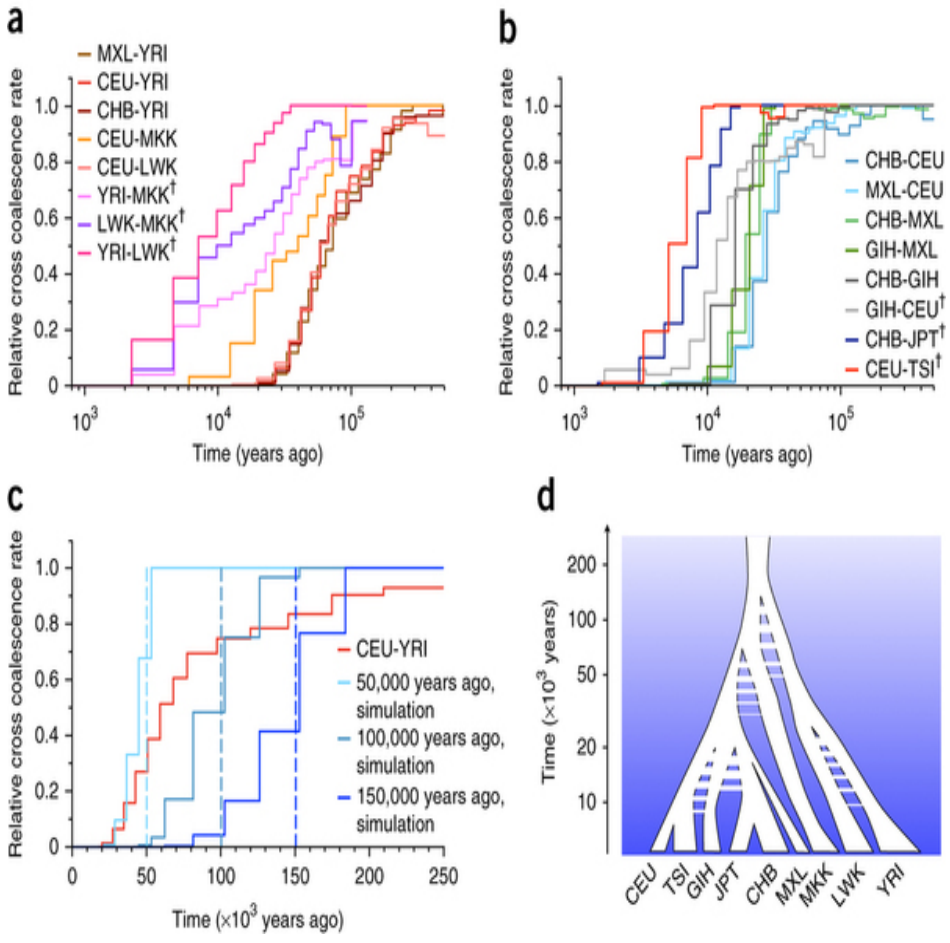
- **(left:)** using 4,8 haplotypes is more accurate for recent population sizes
- **(right:)** 8 haplotypes gives better estimates for more recent split; 4 haplotypes better for older split

MSMC – Results (Schiffels & Durbin 2014, *Nature Genetics* **46**:919)



- **(left:)** estimates using 4 haplotypes per population
- **(right:)** estimates using 8 haplotypes per population

MSMC – Results (Schiffels & Durbin 2014, *Nature Genetics* **46**:919)



- **(top left:)** cross-coalescence rates between YRI and non-Africans drop 40-200Kya
- **(bottom left:)** gradual decline not consistent with “clean” split

Summary

- using haplotypes can increase power, e.g. for:
  1. inferring admixture (*GLOBETROTTER*)
  2. inferring population size changes over time and population splits (*PSMC, MSMC*)
- can be computationally demanding; *GLOBETROTTER* & *MSMC* require pre-phased haplotypes
- *PSMC:* population structure can give similar signals as pop size changes (Mazet et al 2016, *Heredity* **116**:362)
- other programs (instead of *PSMC/MSMC*):
  - *diCal* (Sheehan et al 2013, *Genetics* **194**:647)
  - *SMC++* (Terhorst et al 2017, *Nature Genetics* **49**:303)
  - *ASMC* (Palamara et al 2018, *BioRxiv* https://www.biorxiv.org/content/early/2018/03/07/276931