Haplotype-based methods for demography

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EMBO – Population Genomics: background, tools and programming
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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, RELATE*)
- we will use SNP data throughout, with *PSMC/MSMC/RELATE* requiring sequencing data

Outline

inferring admixture (*GLOBETROTTER*)

inferring pop size changes (*PSMC, MSMC, RELATE*)

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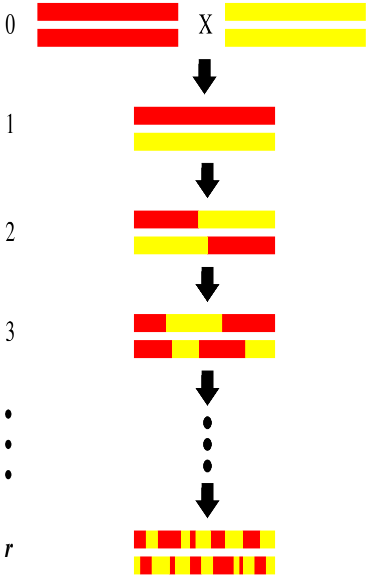
inferring admixture (*GLOBETROTTER*)

inferring pop size changes (*PSMC, MSMC, RELATE*)

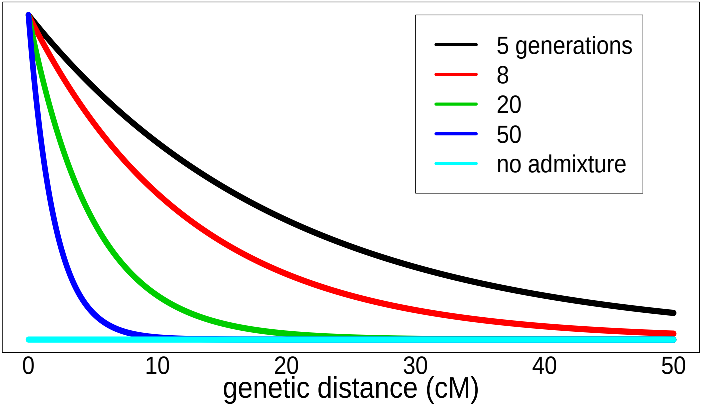
Inferring admixture using autosomal DNA

- 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)

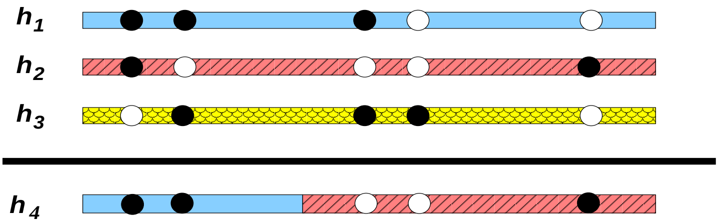


Dating admixture events using autosomal DNA

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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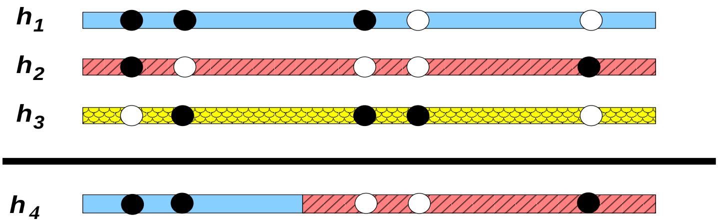

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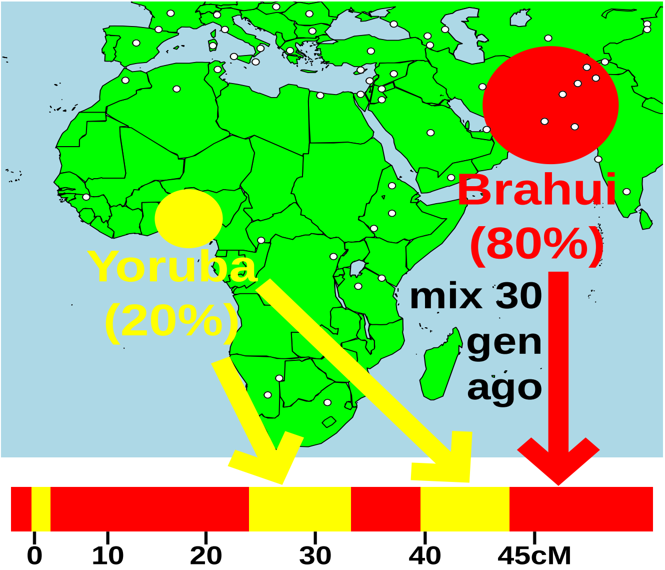
Issue: Accurate painting is challenging. Instead:

1. calculate probabilities two segments derive from an admixing source
2. plot (average) decay of probabilities versus cM distance between the two segments

   Disadvantage: can be computationally demanding

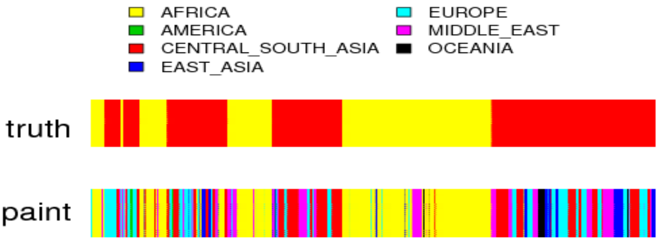
Simulation: 80% Brahui + 20% Yoruba, 30gen



(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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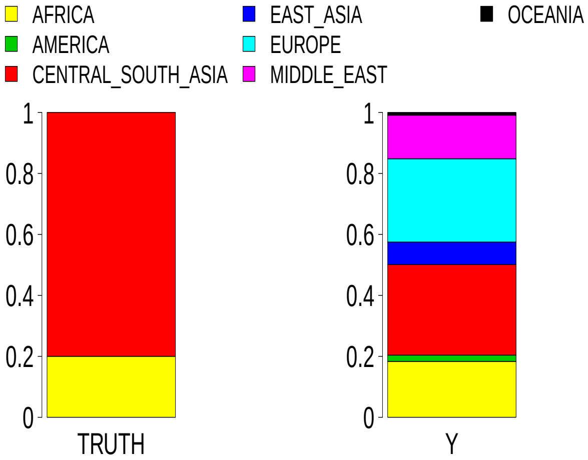

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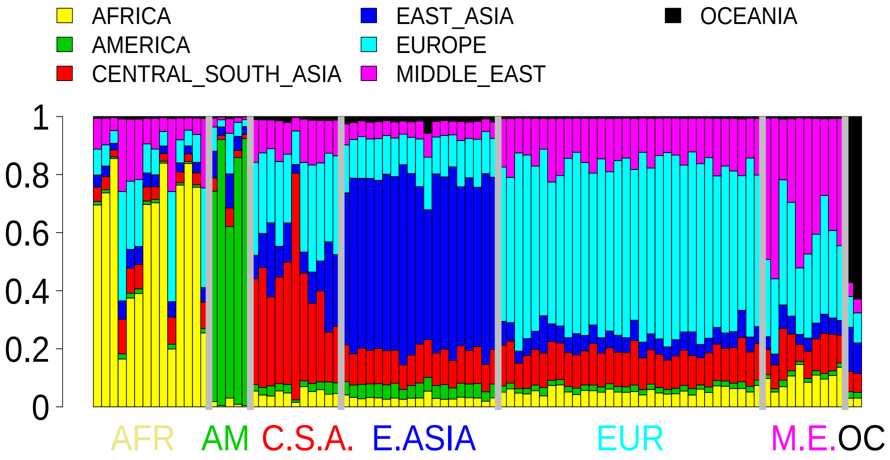

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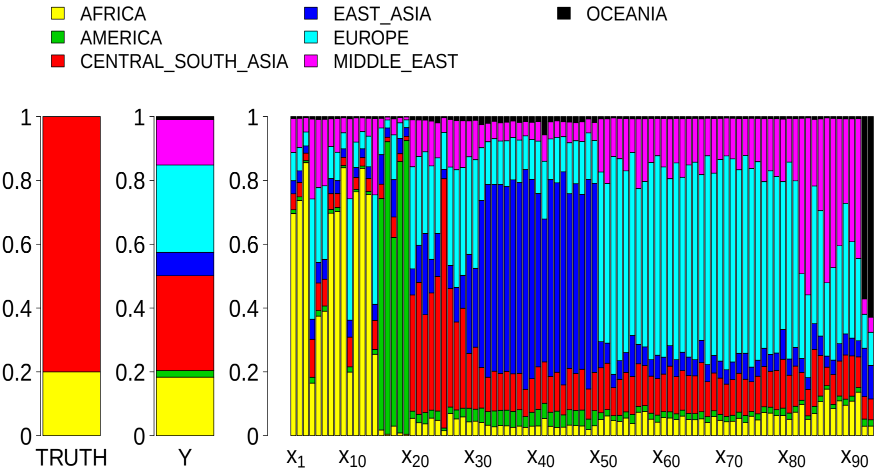

(2) form admixed ind's painting as mixture of that for all 93 groups:

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

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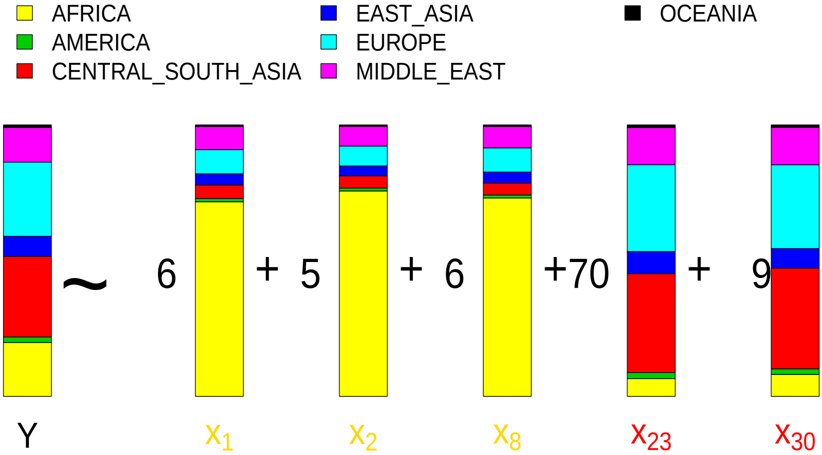

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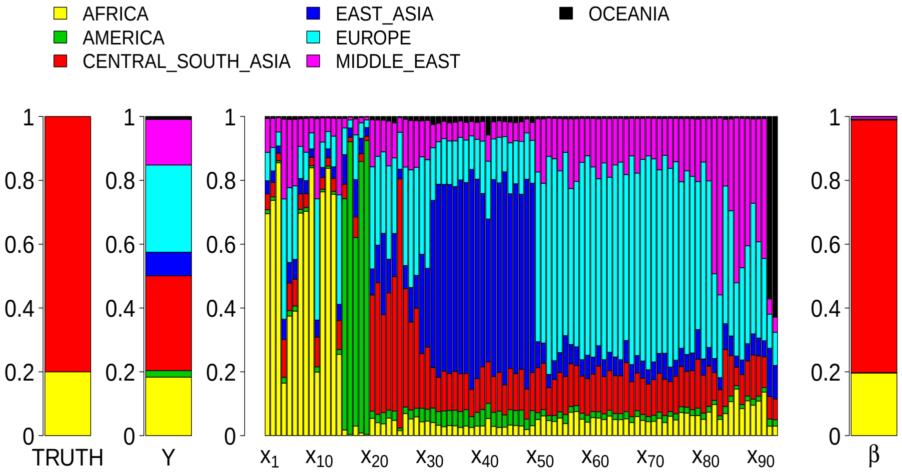

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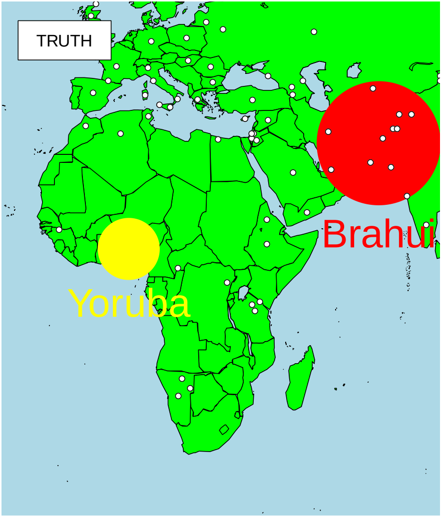

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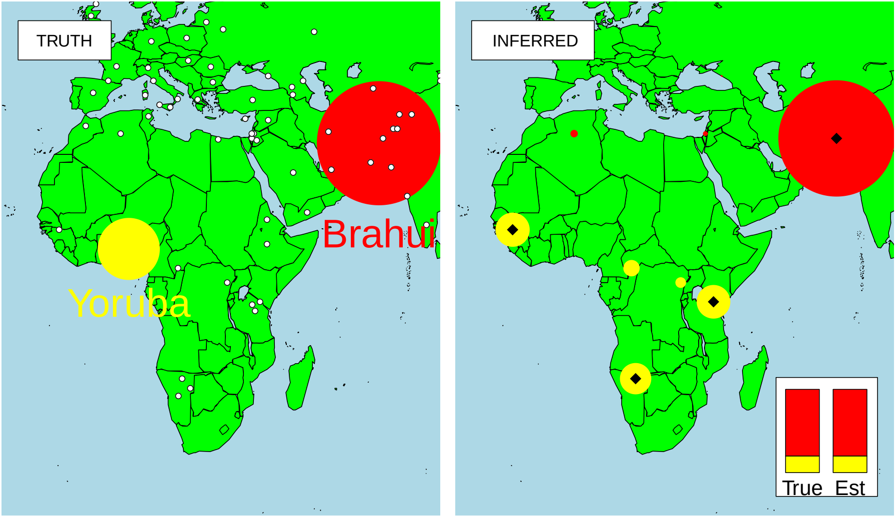
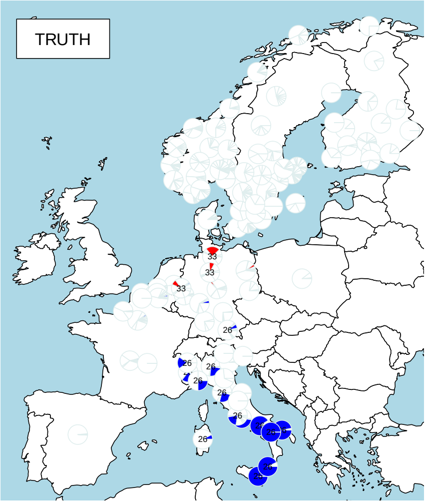


Simulated Europe Admixture: 75% **Italy** + 25% **N.Germany**, 40gen



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

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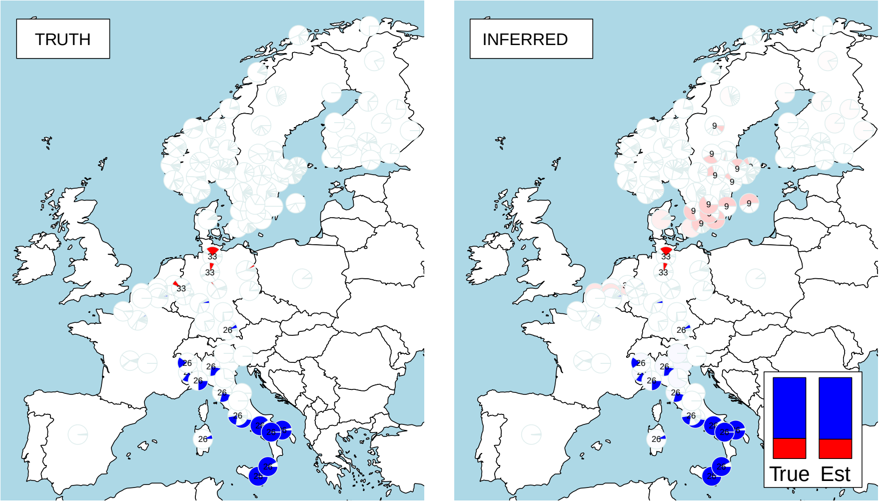

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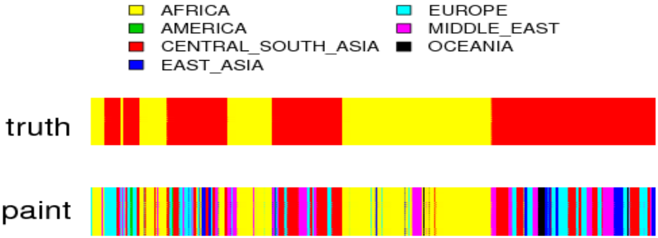
Dating Admixture (Sim: 80% Brahui + 20% Yoruba, 30gen)



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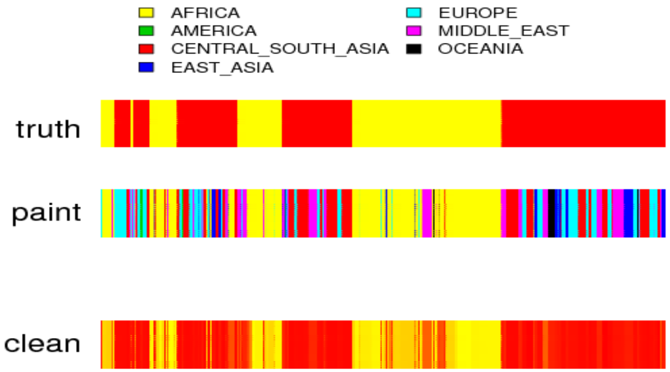

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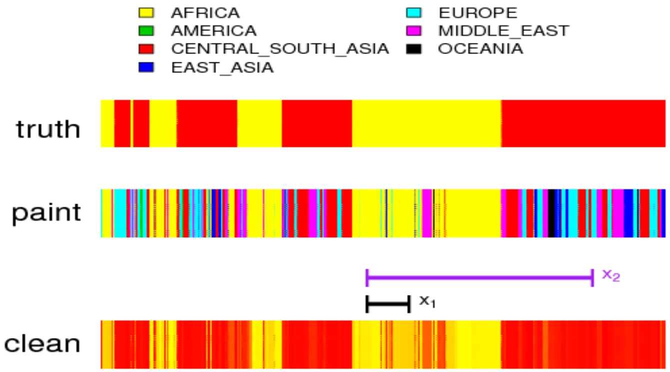

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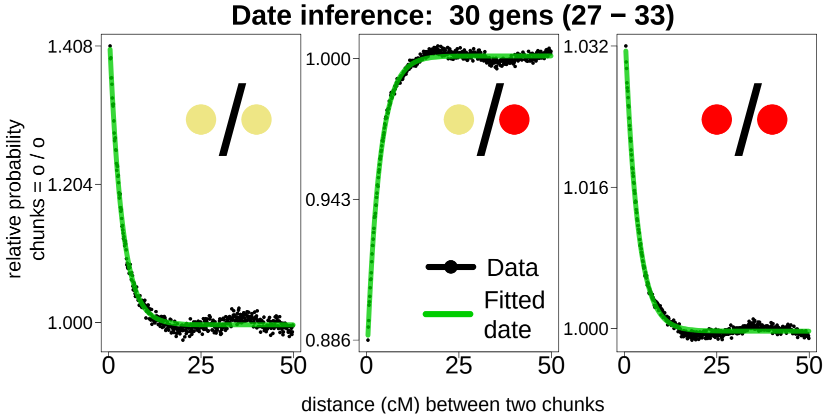
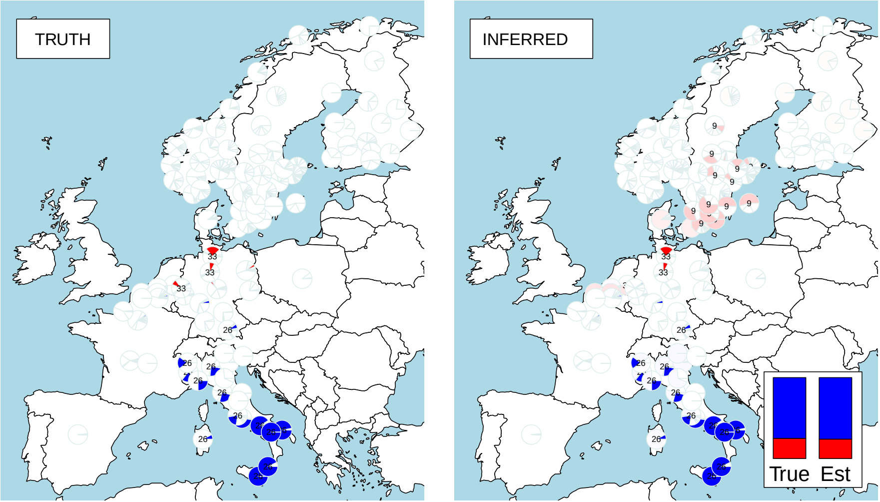


Coancestry curves:

- **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

Dating Admixture (Sim: 75% **Italy** + 25% **N.Germany**, 40gen)



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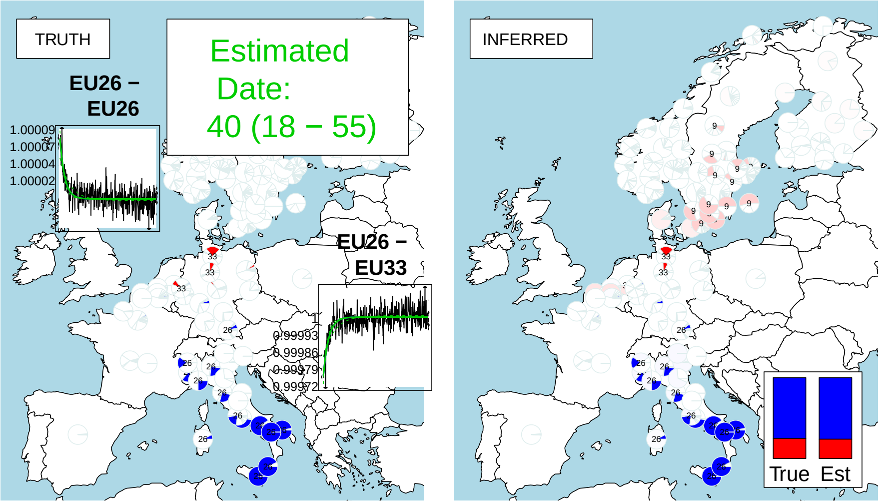

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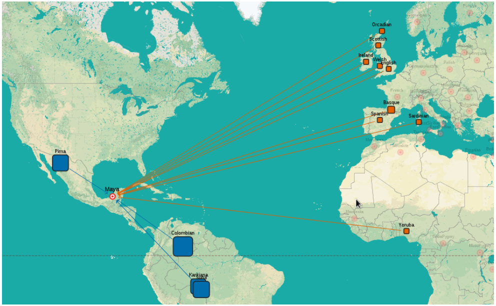
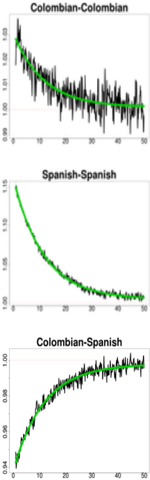
Inferring admixture – *GLOBETROTTER* (example)

- **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



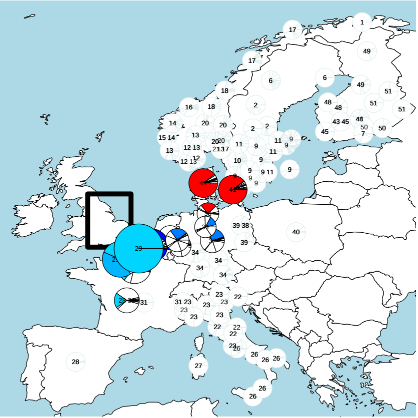


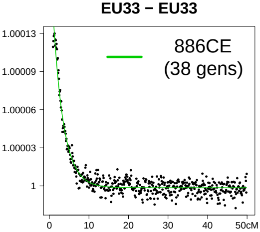
(Hellenthal et al 2014, *Science* **343**:747)

Identifying/Dating admixture in United Kingdom

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

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





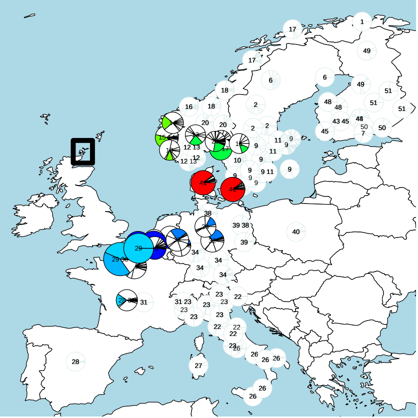
DNA matched to **N.Germany** and **Denmark** $\longrightarrow$ **Anglo-Saxons?**

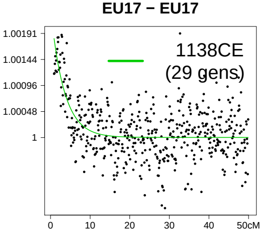
(Leslie et al 2015, *Nature* **519**:309)

Identifying/Dating admixture in United Kingdom

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

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



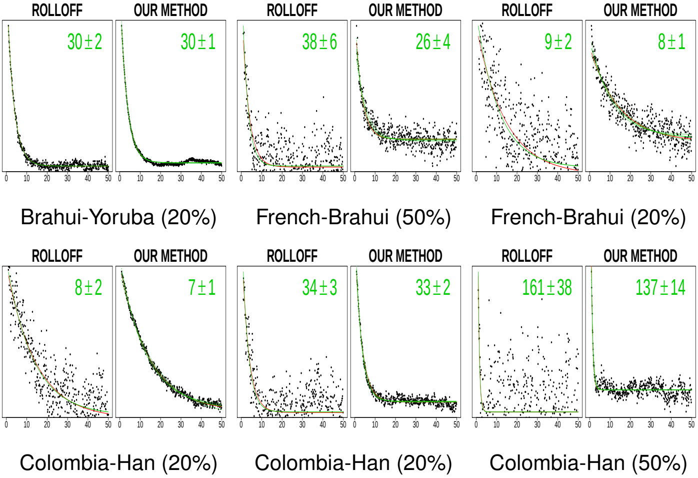


DNA matched to **Norway** ⟶ **Norse Vikings?**

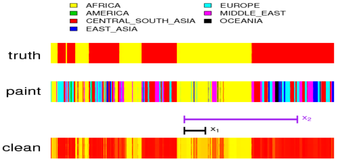
(Leslie et al 2015, *Nature* **519**:309)

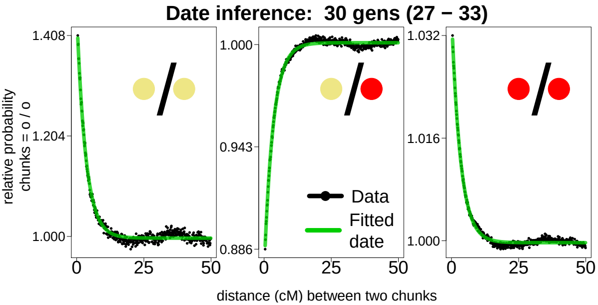
Comparison to *ROLLOFF* (e.g. Patterson et al 2012, *Genetics* **192**:1065)

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

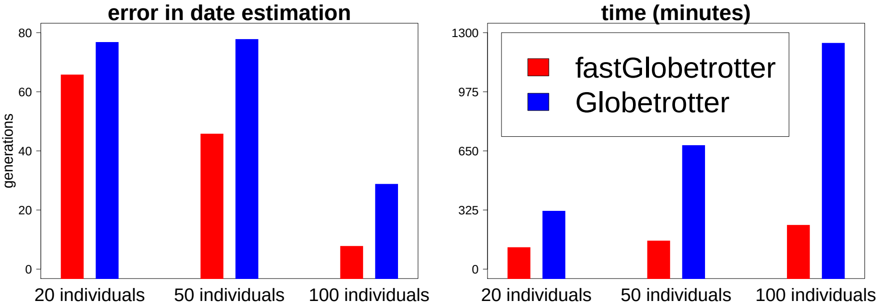


efficient dating – *fastGLOBETROTTER*





fastGLOBETROTTER vs *GLOBETROTTER*



simulated admixture 150gen ago

French + **Brahui** ($F_{ST} \approx 0.02$)

If **only** inferring mixture proportions: SOURCEFIND

(1) *GLOBETROTTER:* $E[Y] = \beta_1 X_1 + \beta_2 X_2 + ... + \beta_K X_K$

(2) *SOURCEFIND:* $Y \sim \text{Multinom}\left(\vec{p} \equiv \sum_{i=1}^{K} \left[\beta_i X_i\right]\right)$

(number of $\beta_i > 0$) $\sim$ Poisson(λ)

Chacon-Duque et al 2018, *Nat Comm* **9**:5388

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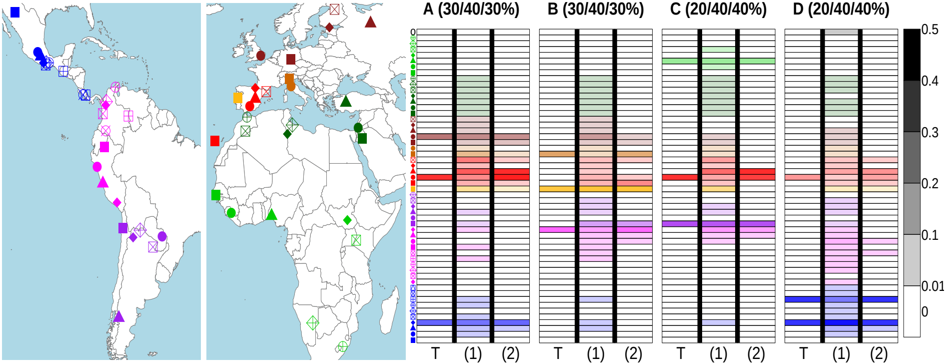

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Outline

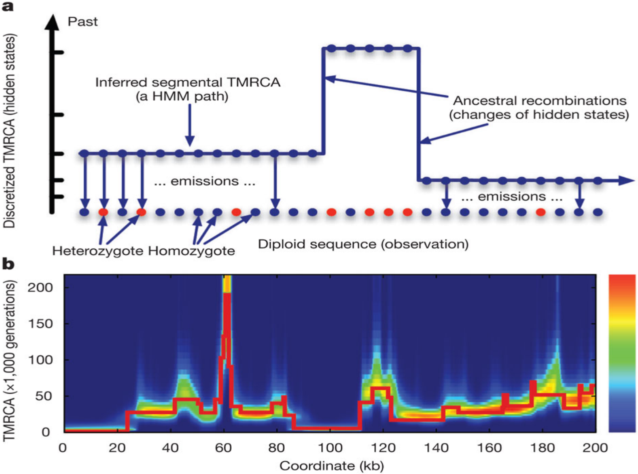
inferring admixture (*GLOBETROTTER*)

inferring pop size changes (*PSMC, MSMC, RELATE*)

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 → use mutations as a “clock” to infer time
    - to convert to years, must assume mutation rate per generation → some debate over appropriate rate to use (e.g. Scally & Durbin 2012, *Nature Rev Genet* **13**:745)

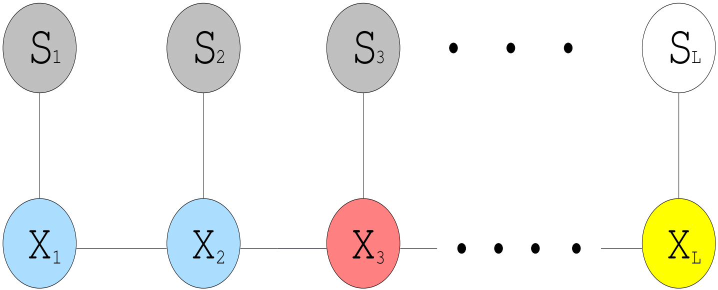
PSMC (Li & Durbin 2011, *Nature* **475**:493)



- consider a single diploid individual: infer TMRCA (The Most Recent Common Ancestor) of individuals' two haplotypes
- **switches in TMRCA** depends on recombination rate and observed density of mutations
- **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)

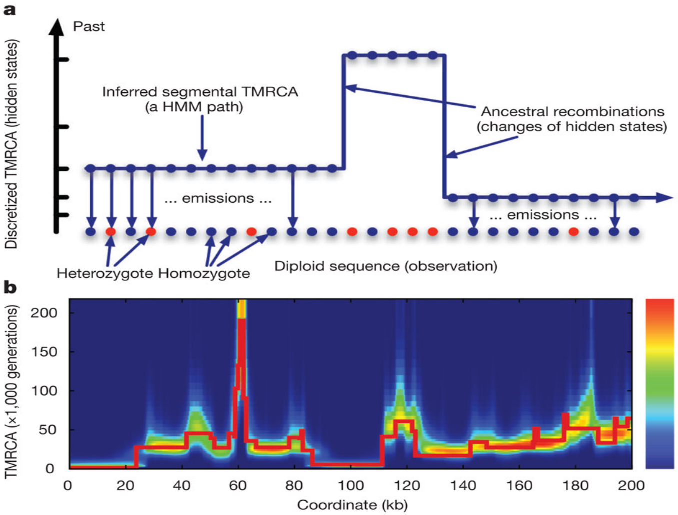
Observed State (for given 100bp bin):

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

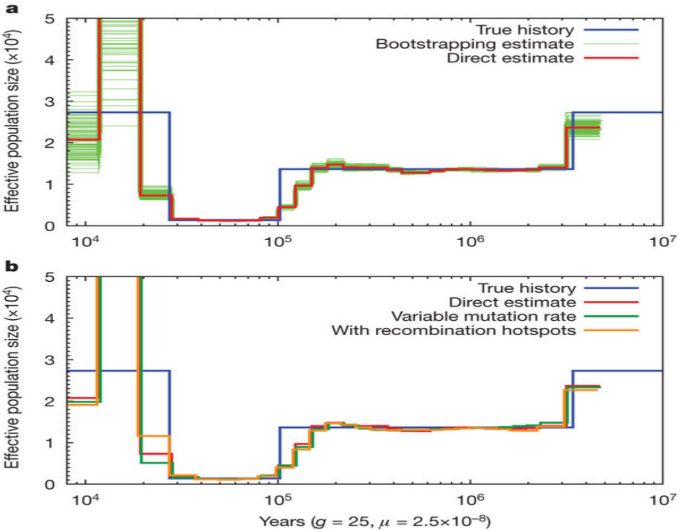
PSMC (Li & Durbin 2011, *Nature* **475**:493)



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

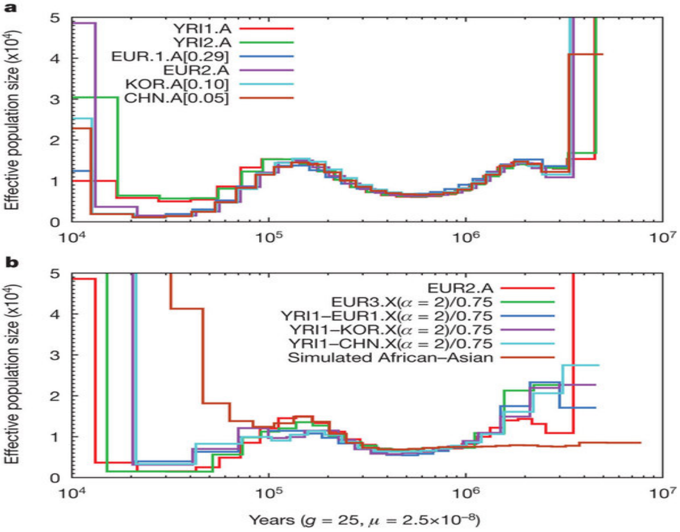
How? if lots of genome segments have the same TMRCA $t \longrightarrow$ decrease in population size at t

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



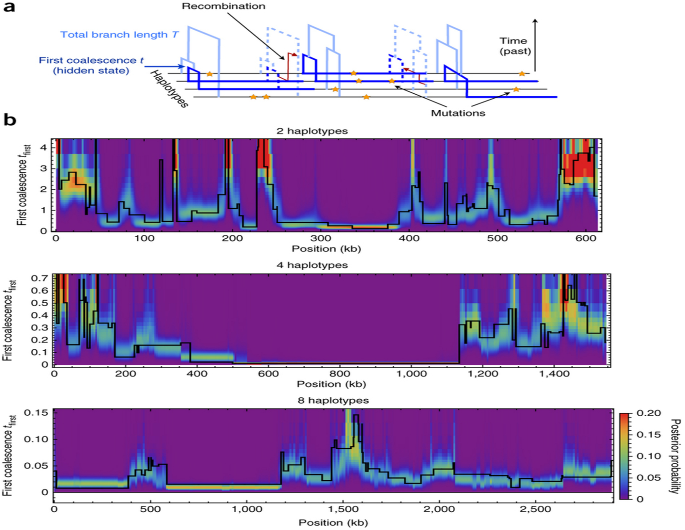
- nicely tracks population size over time (ms simulation), except at recent dates
- **green lines** – bootstrap re-sampling of 5Mb genetic regions

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



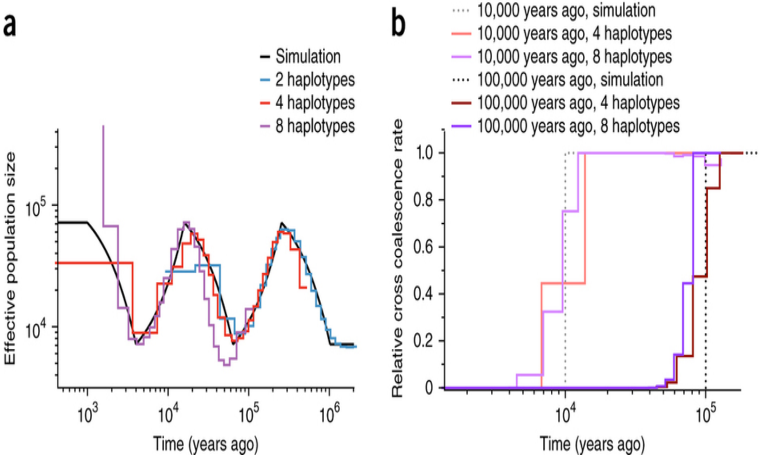
- **(top:)** dip in population size from around 100-150kya to about 40-20kya
- **(bottom:)** N_e between groups (e.g. Africa-Europe) very low relative to **simulation** where populations split 60kya

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



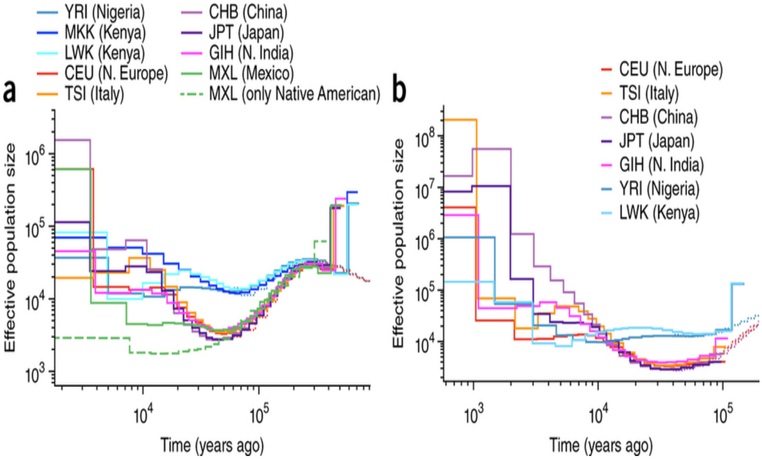
- consider 2-4 individuals, and find *first coalesence* in each genetic region
- first coalesence becomes more recent (and spans longer regions) as number of (phased) haplotypes increases (i.e. $E[t] = \frac{2}{n(n-1)}$)

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



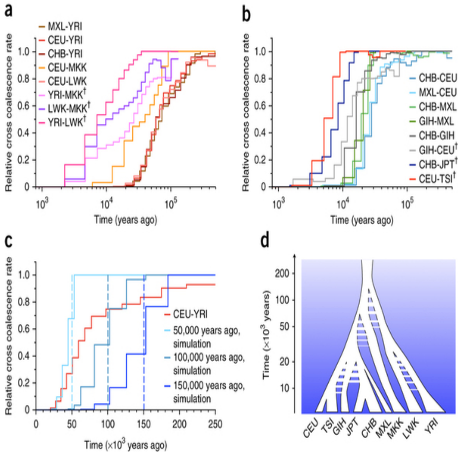
- **(left:)** using 4,8 haplotypes is more accurate for recent population sizes
- **(right:)** 8 haplotypes gives better estimates for more recent split; 4 haplotypes better for older split

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

RELATE (Spiedel et al 2019, https://www.biorxiv.org/content/10.1101/550558v1)

1. use Li & Stephens (e.g. *CHROMOPAINTER*) to build distance matrix comparing individuals per SNP (painting each individual at derived SNPs only)

2. build hierarchical trees based on (1), starting with SNP at 5' end

3. add mutations on tree under infinite-sites model (if enough mutations do not fit, make new tree)

4. Iteratively:
   - estimate branch lengths using MCMC (intuitively by counting mutations, with coalescent prior assuming random mating and fixed population sizes)
   - estimate pairwise coalescent times (and hence population sizes) over time epochs

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, RELATE*)

- can be computationally demanding; *GLOBETROTTER*, *MSMC* & *RELATE* require pre-phased haplotypes

- *PSMC, etc:* population structure can give similar signals as pop size changes (Mazet et al 2016, *Heredity* **116**:362)

- other programs (instead of *PSMC/MSMC, RELATE*):
  - *diCal* (Sheehan et al 2013, *Genetics* **194**:647)
  - *SMC++* (Terhorst et al 2017, *Nature Genetics* **49**:303)
  - *ASMC* (Palamara et al 2018, *Nature Genetics* **50**:1311)