Inferring human population history from multiple genome sequences

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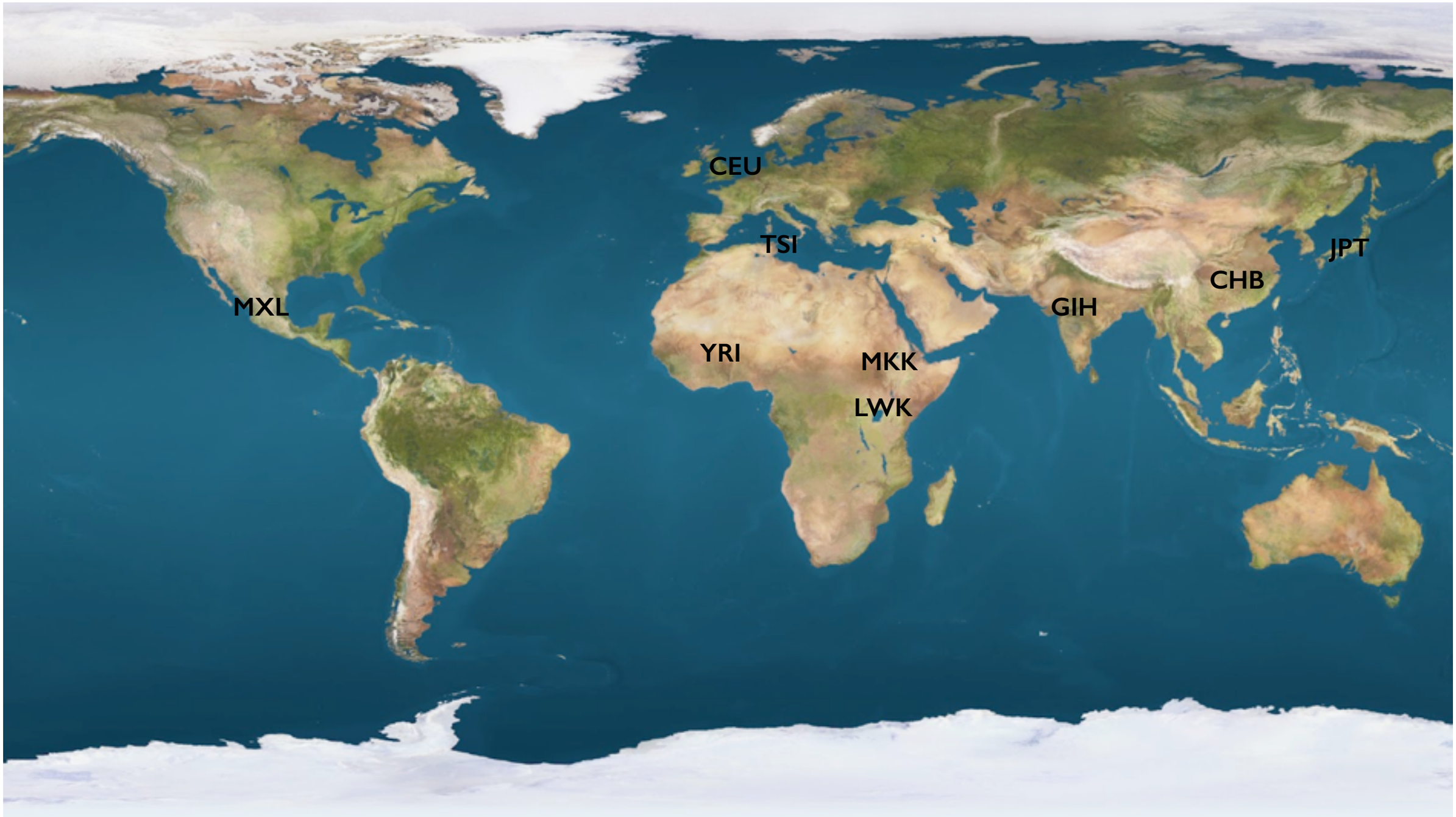
EMBO Fellow

wellcome trust sanger institute

From genome sequences to human history



[Sequence data from Complete Genomics]

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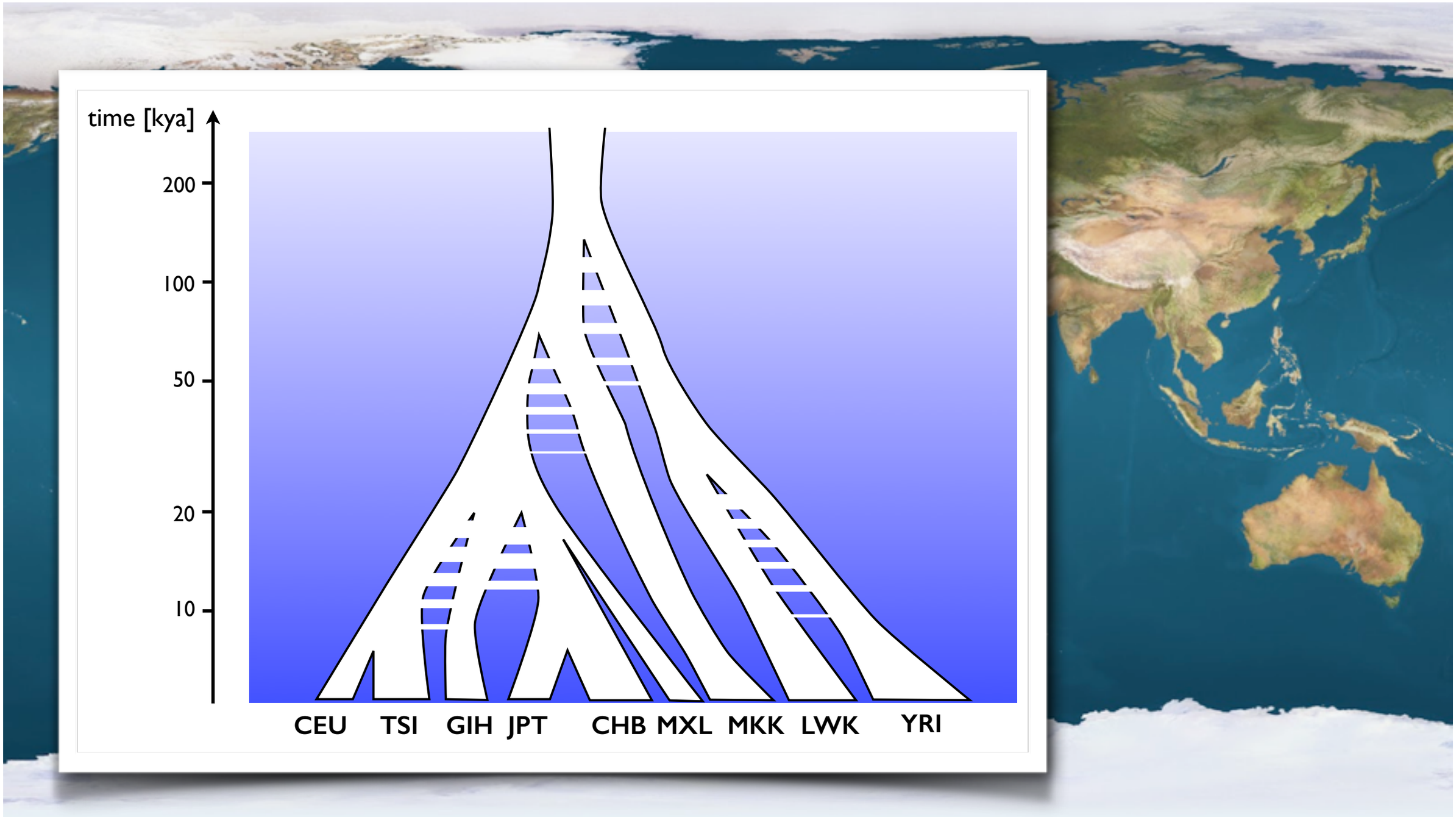
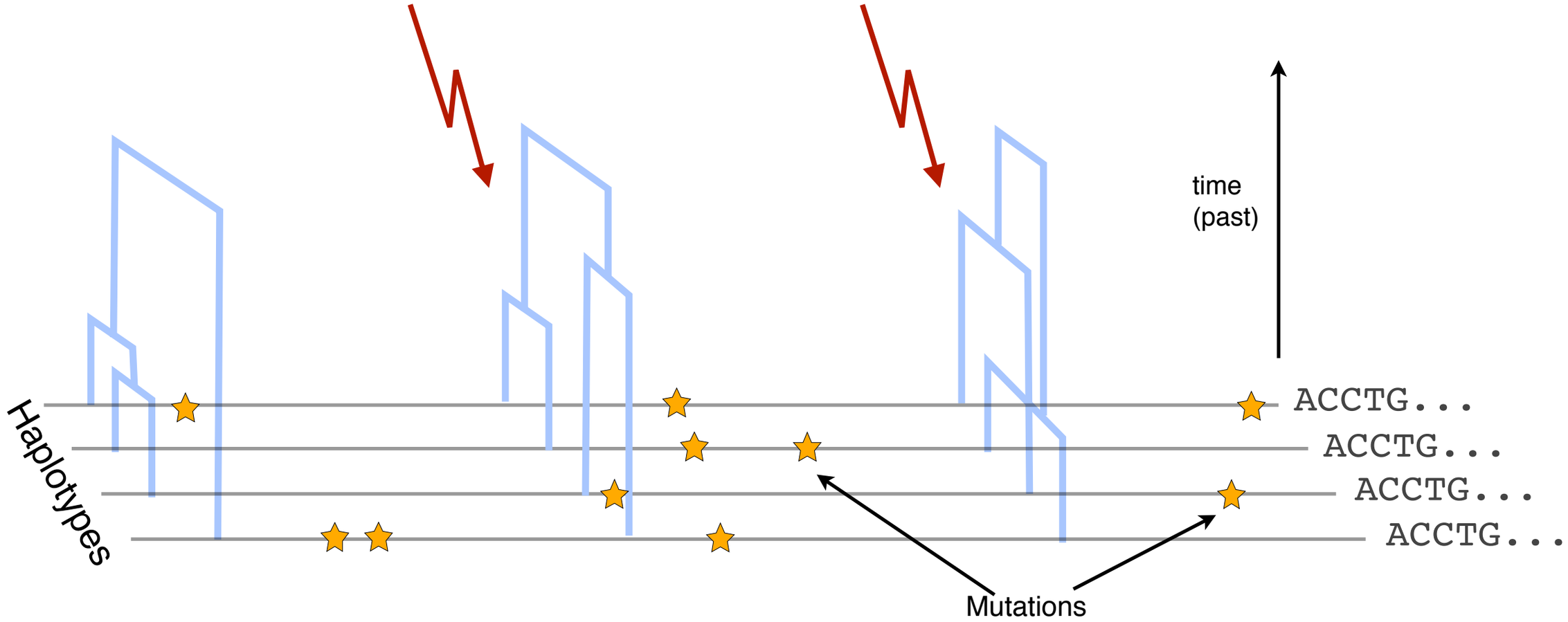


[Sequence data from Complete Genomics]

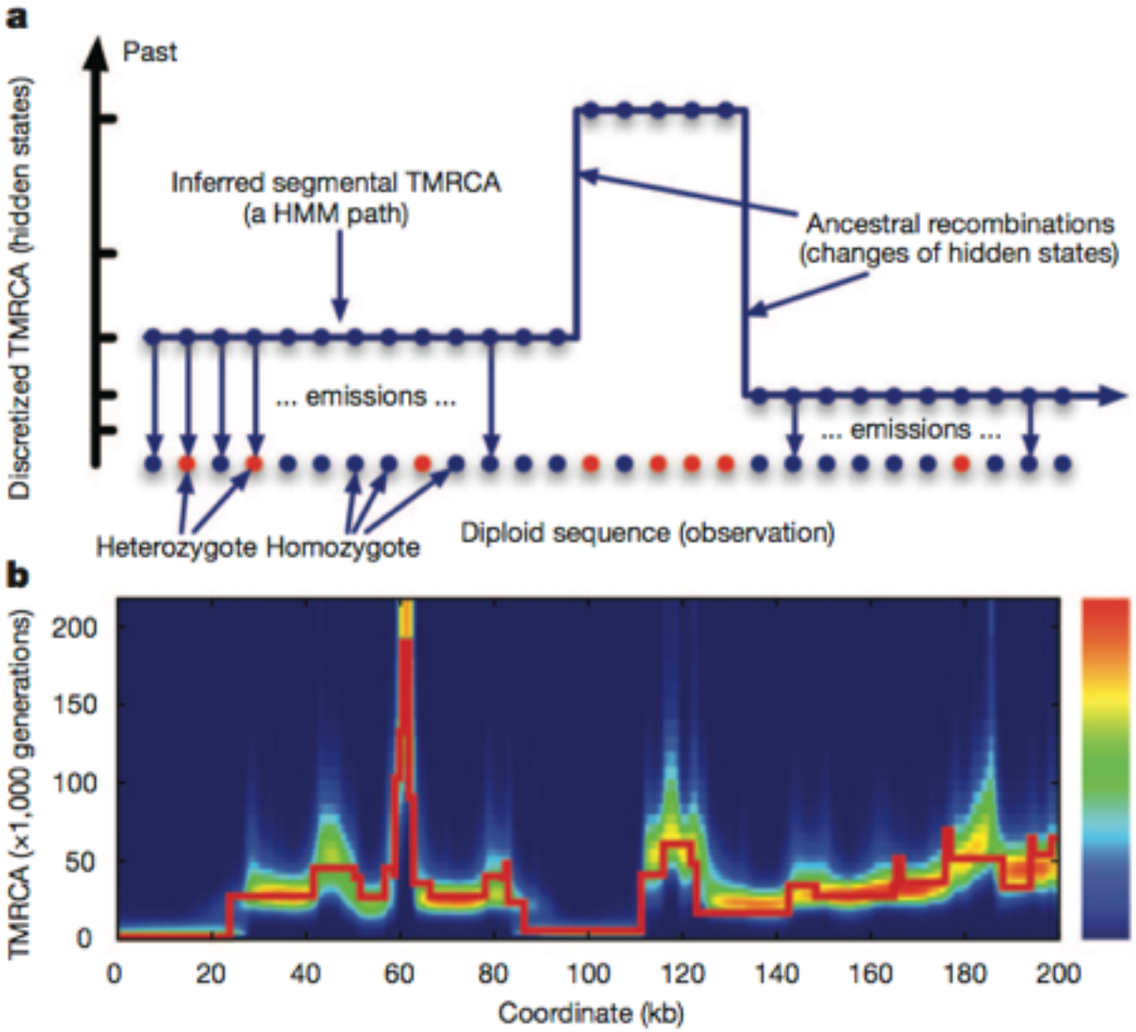
How are sequences related?

Ancestral recombinations change trees along the sequences



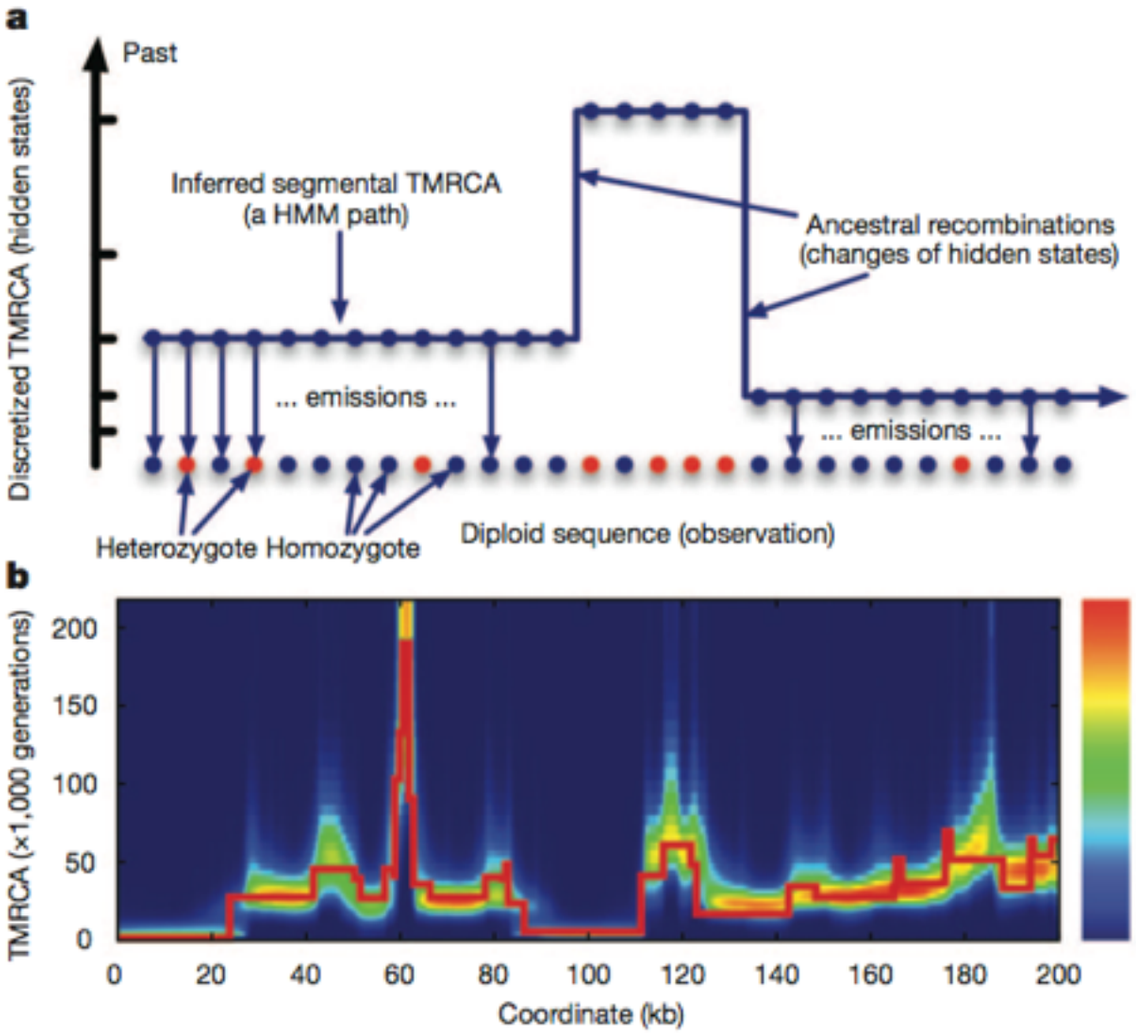
Problem: Estimate trees only from observed mutations

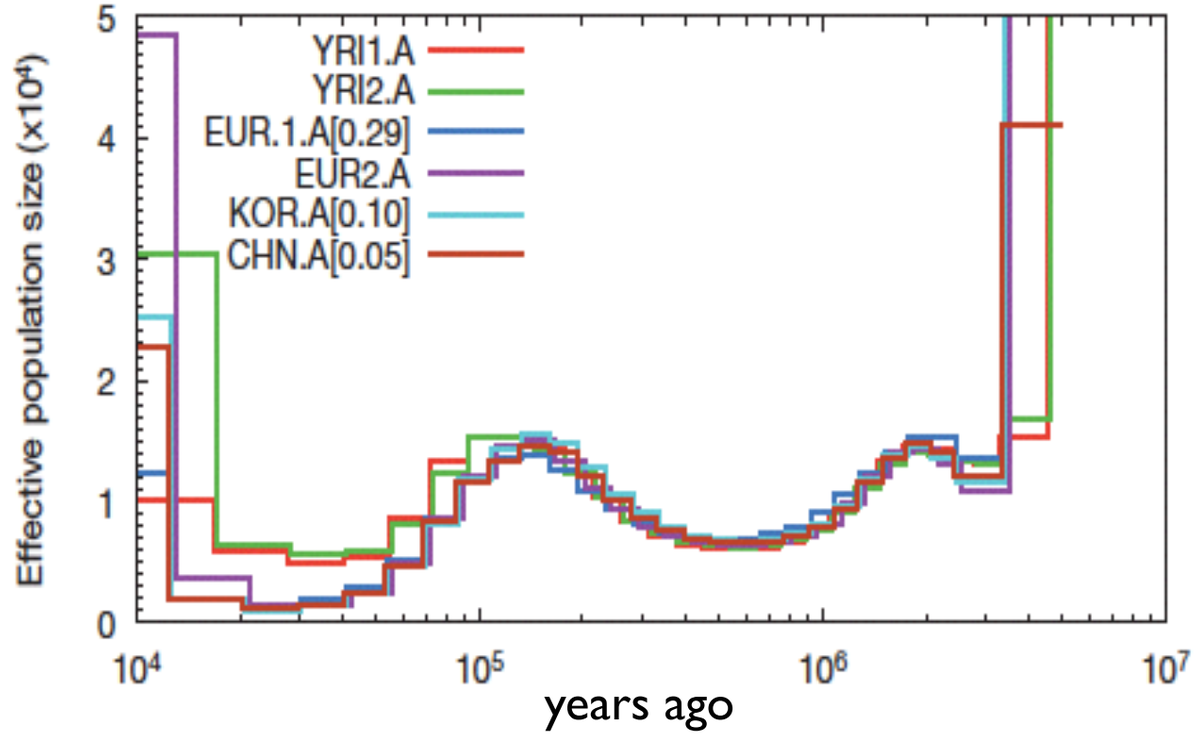
Previous work: PSMC



[Li and Durbin, 2011]

Previous work: PSMC





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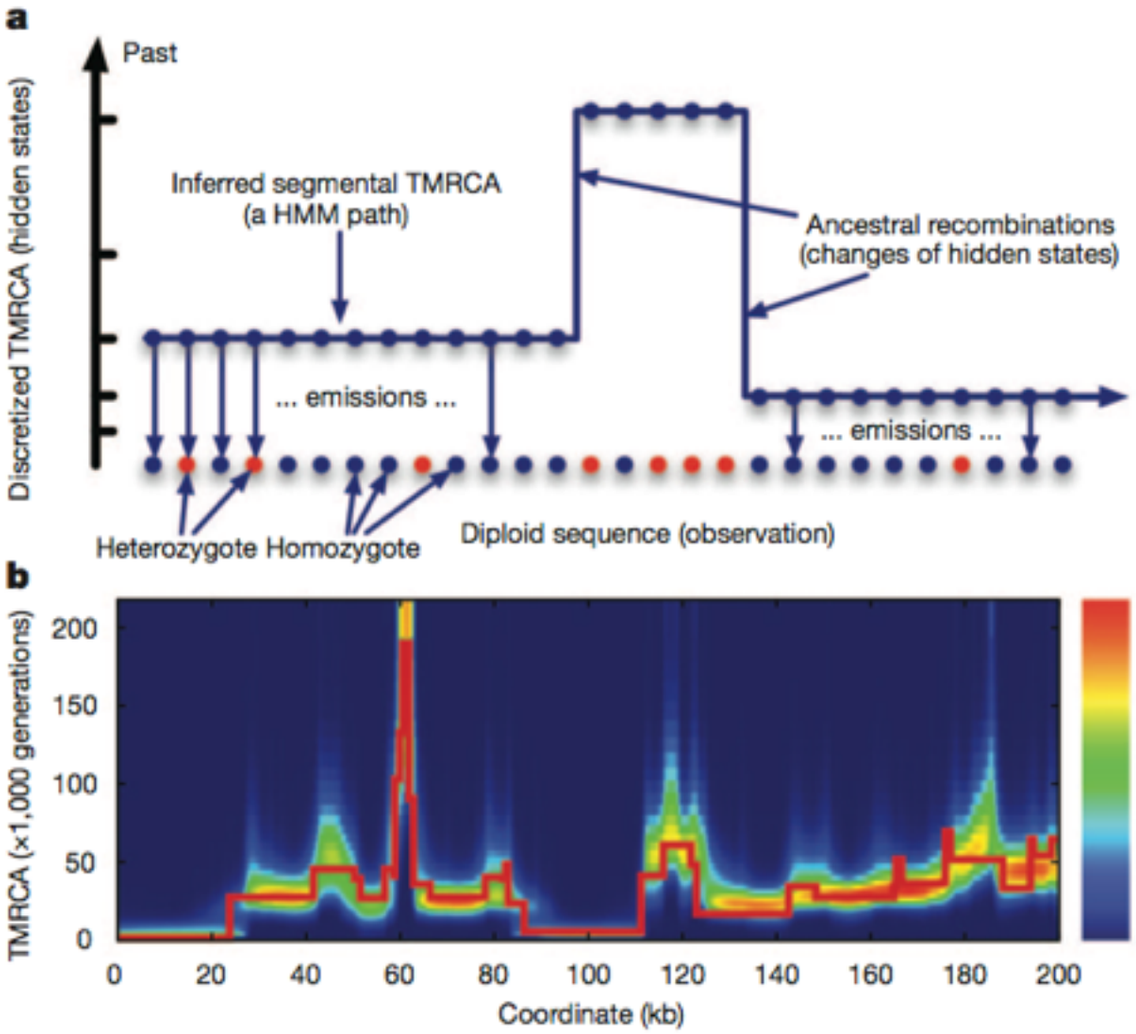
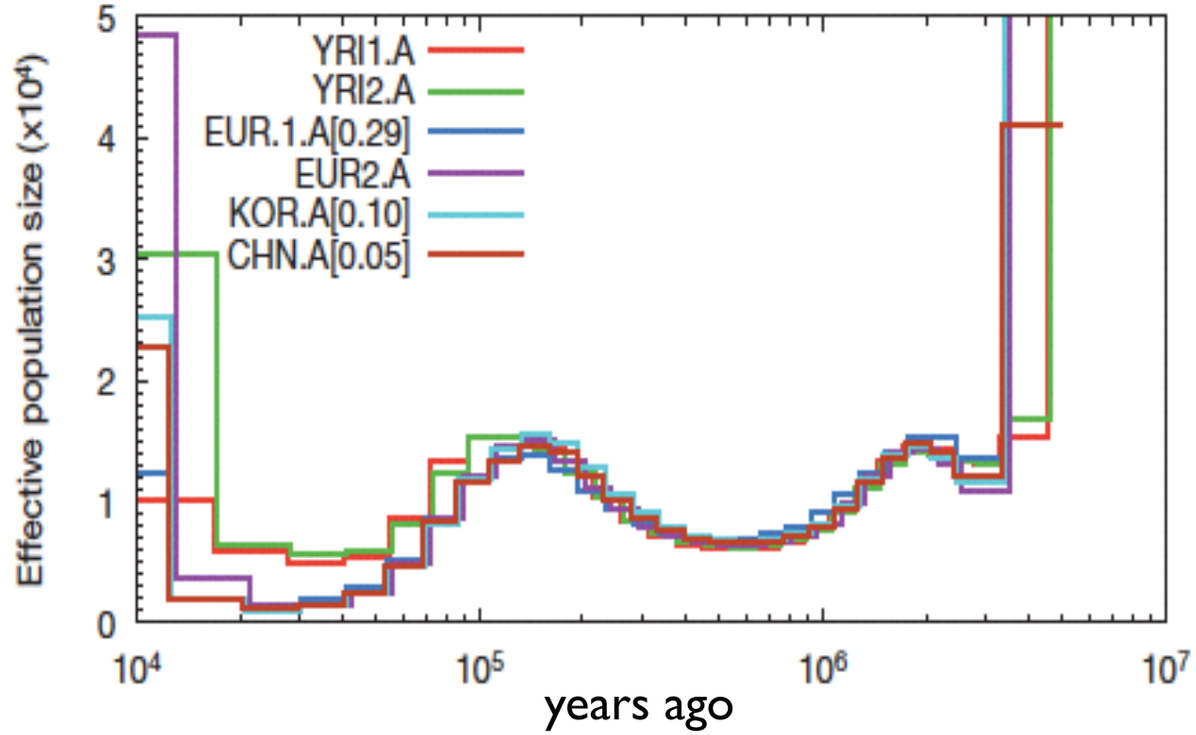
Previous work: PSMC

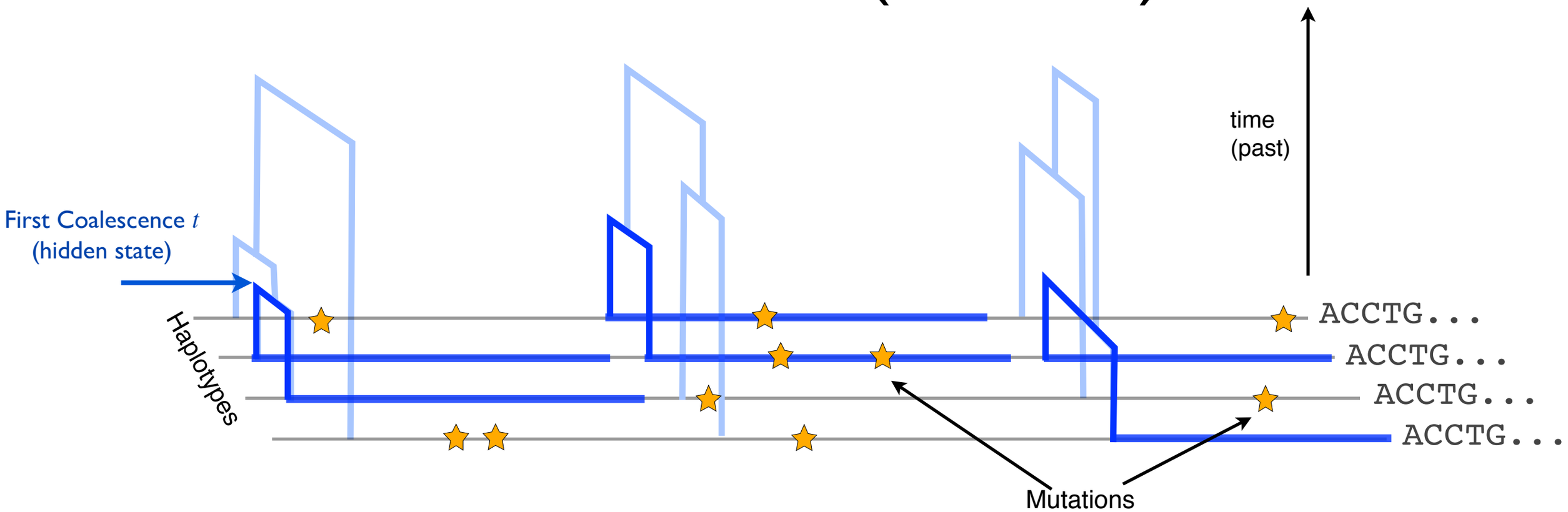




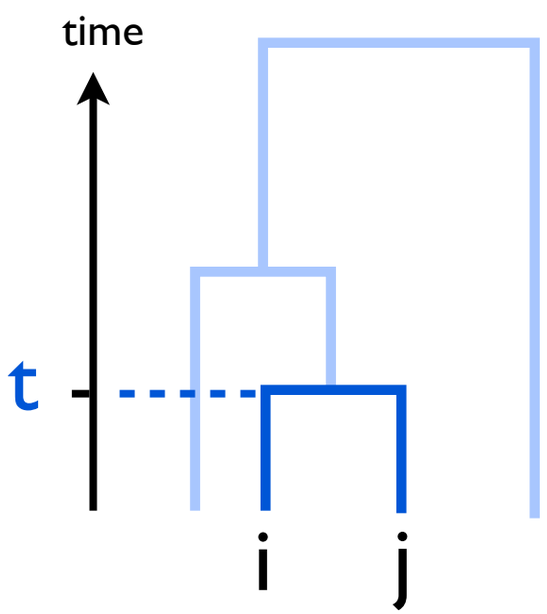
But: Inference from only two sequences limited to times beyond 20kya. Also: population splits difficult to model

[Li and Durbin, 2011]

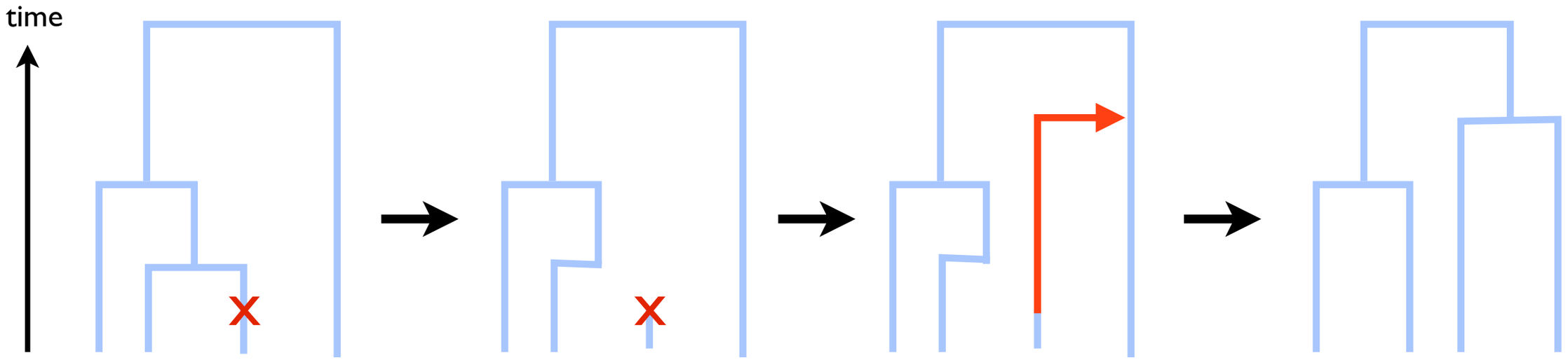
Multiple sequentially Markovian Coalescent (MSMC)



MSMC hidden state:
triple (t, i, j)



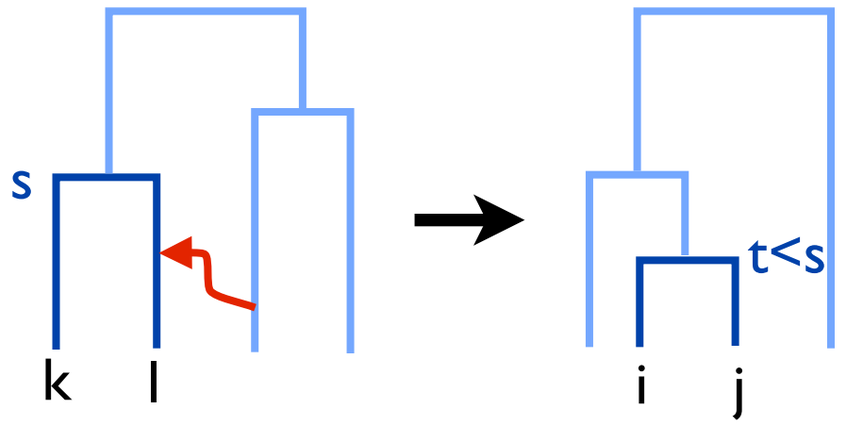
Effect of recombination on Genealogies



[*Sequentially Markovian Coalescent*, McVean and Cardin, 2005]

MSMC: state transitions

(s,k,l) → (t,i,j)
where t<s



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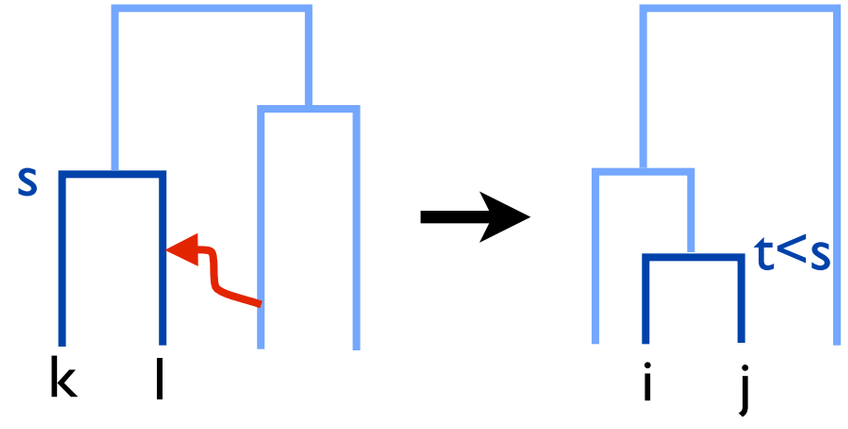
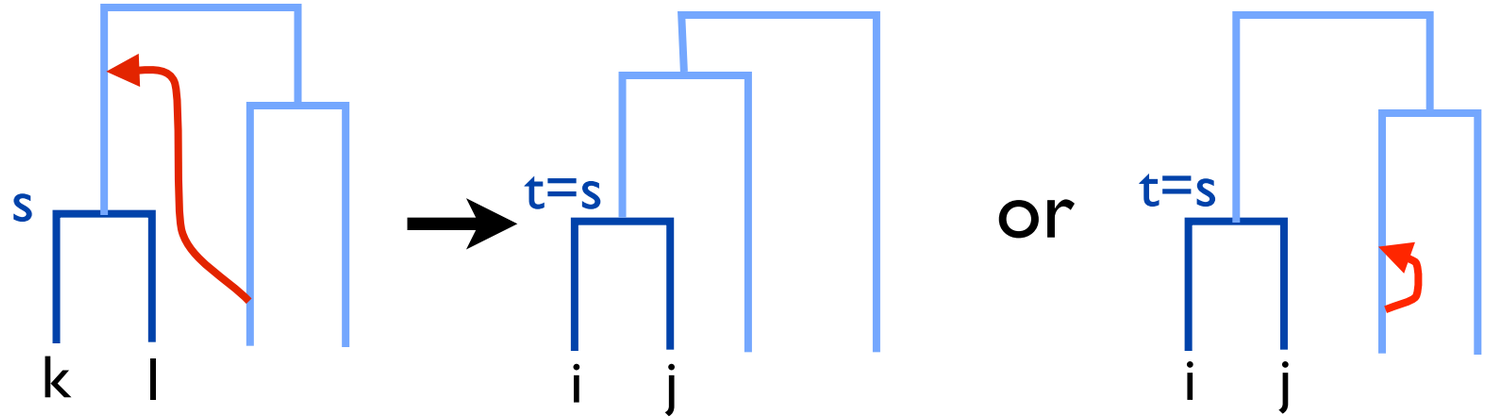


(s,k,l) → (t,i,j)
where t=s



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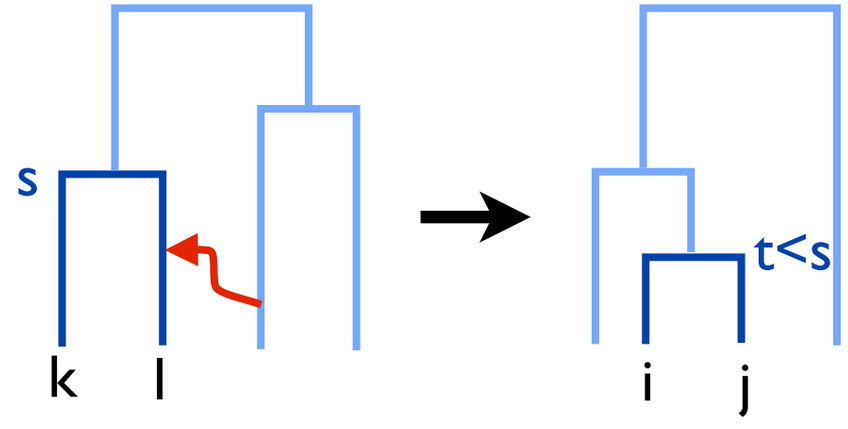

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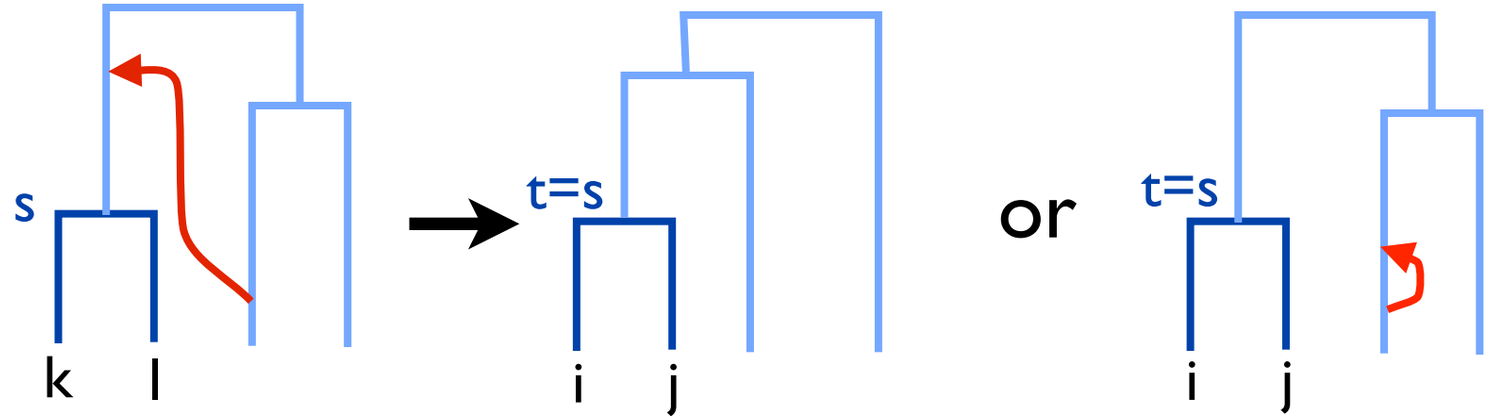

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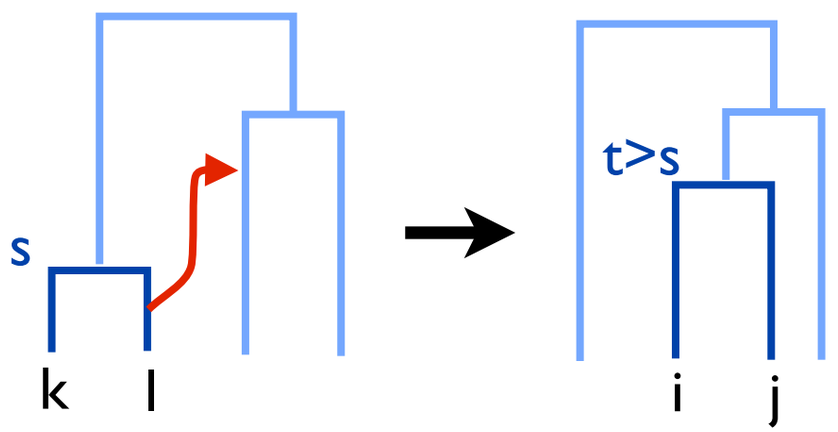
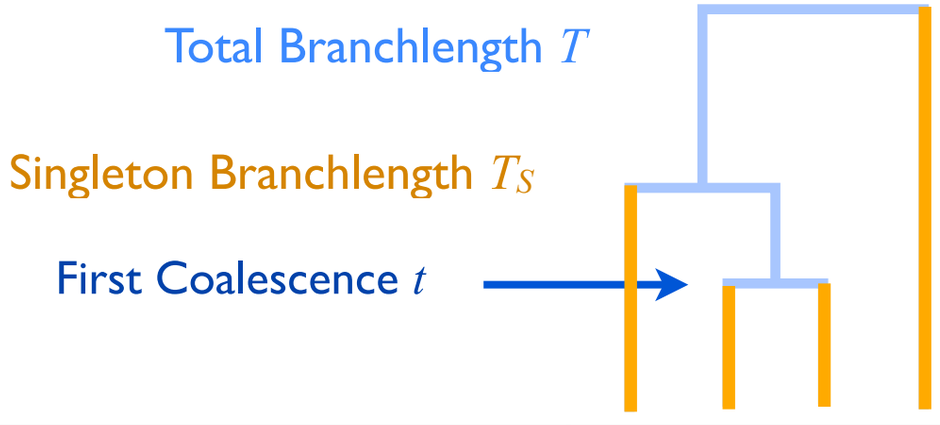


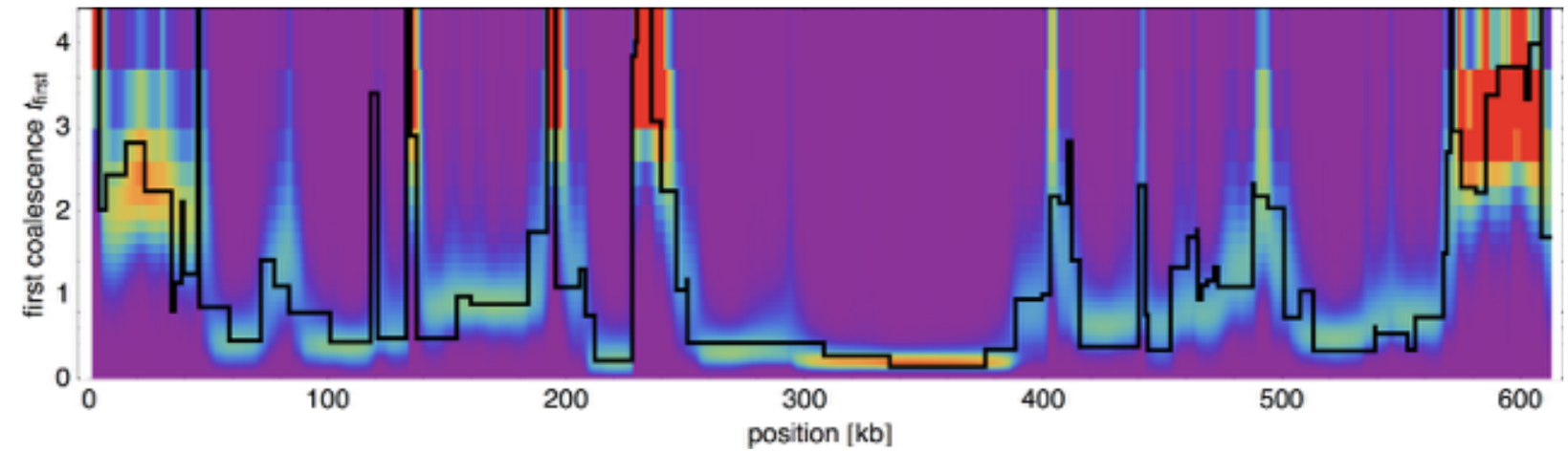
MSMC: mutation probability



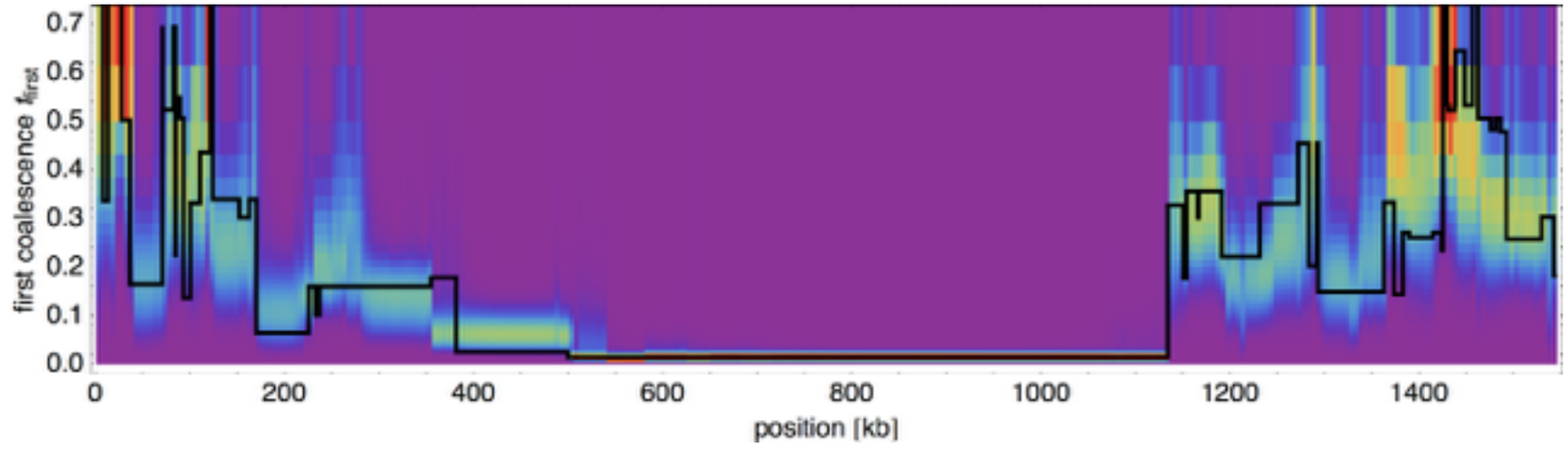
No mutation	$1 - \mu T$	A	A	A	A
Singleton within pair	$\mu\, t$	A	C	A	A
Singleton outside pair	μ	A	A	A	T
Double mutation	0	A	T	A	T
Higher Frequency	μ	A	T	T	A
Missing Data	1	A	A	-	-

Local Inference of first coalescence time

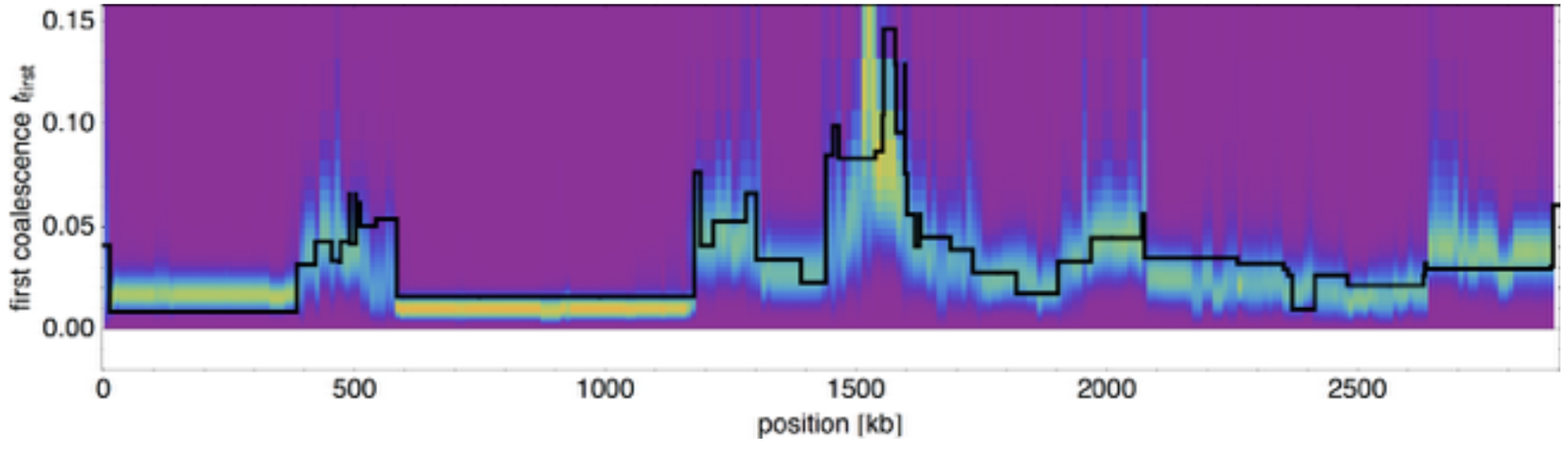
2 haplotypes,
similar to PSMC
[Li and Durbin, 2011]



4 haplotypes

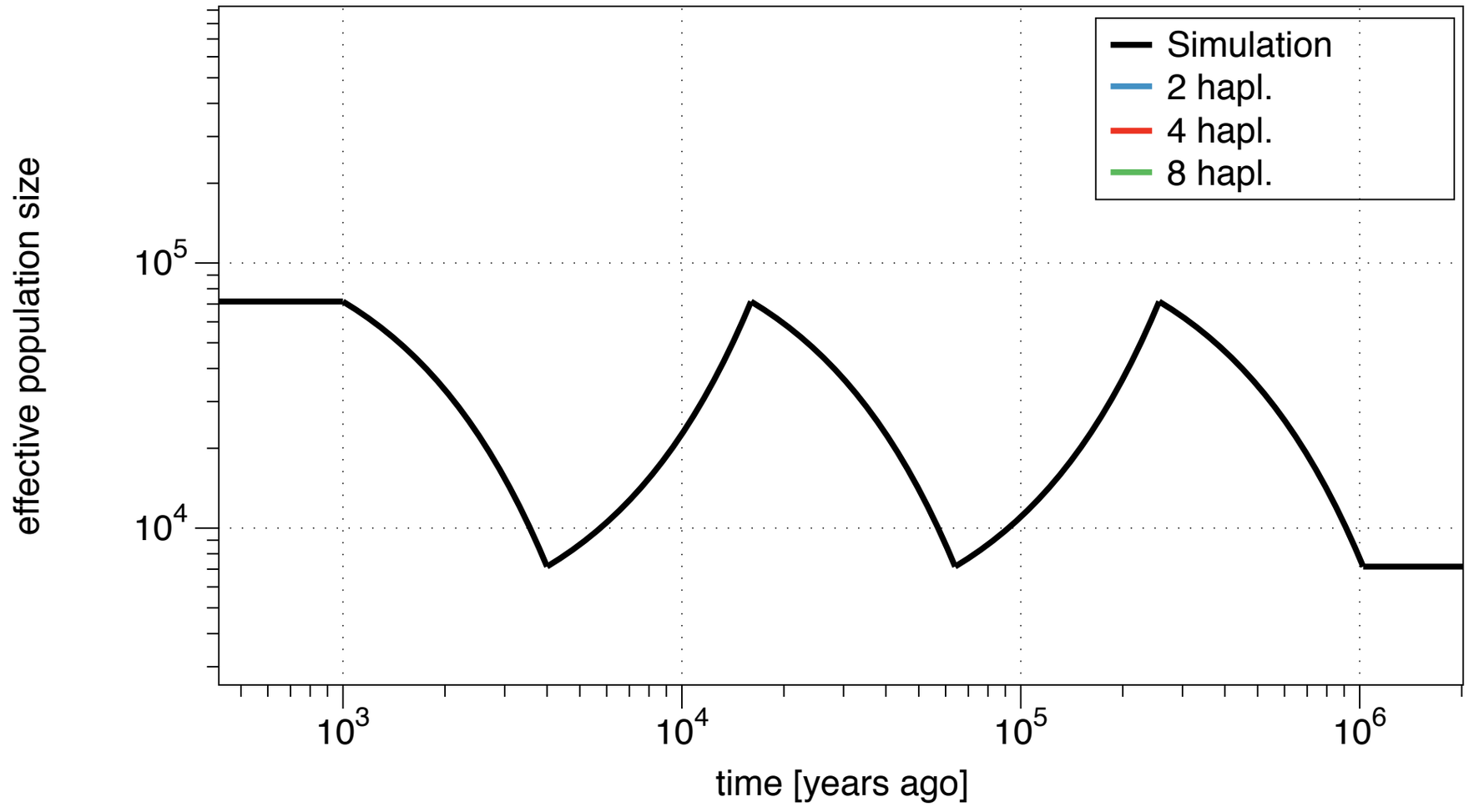


8 haplotypes



Test with simulations

Example: Exponentially growing and shrinking population size



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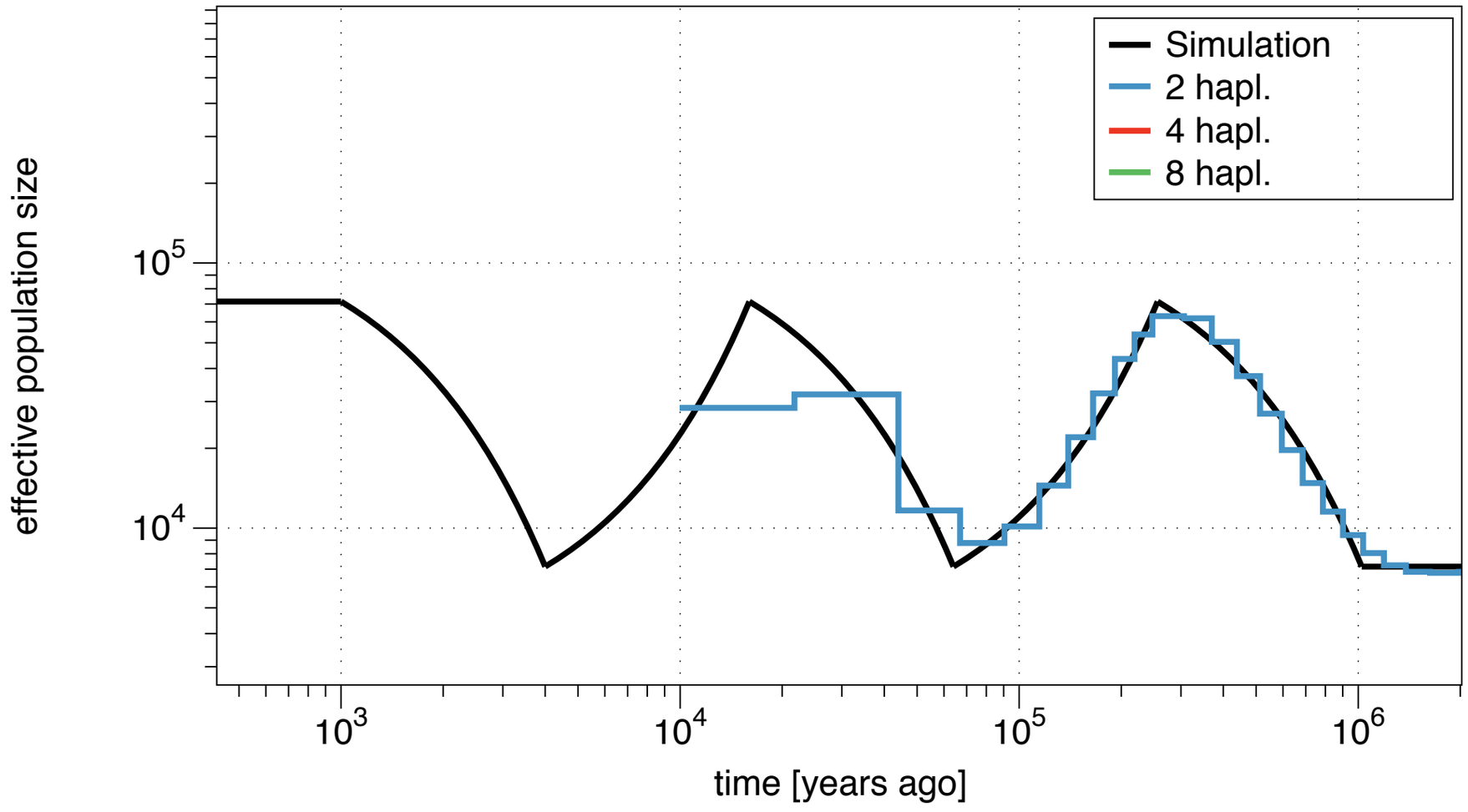

2 haplotypes: 40kya-3Mya

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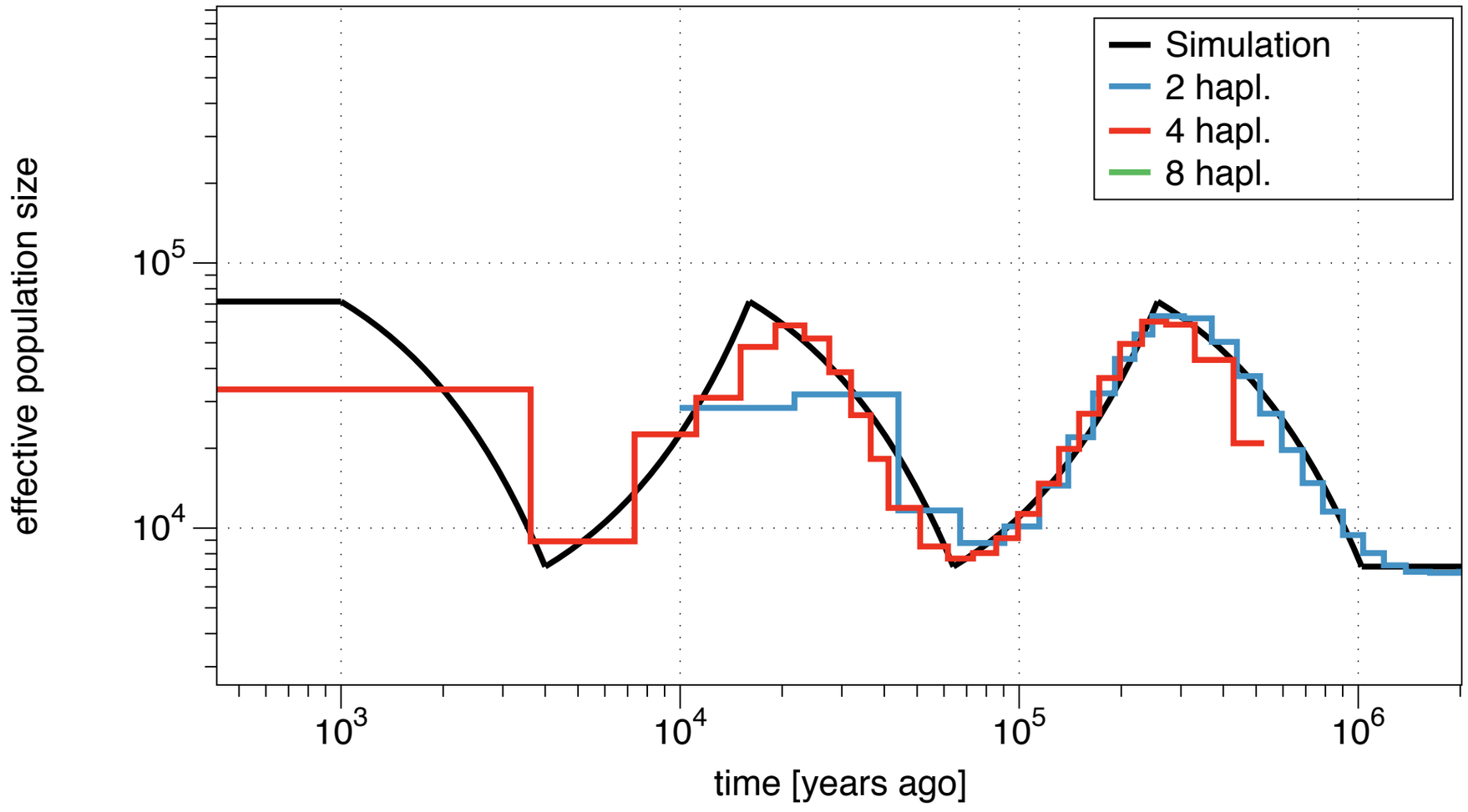

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4 haplotypes: 8kya-300kya

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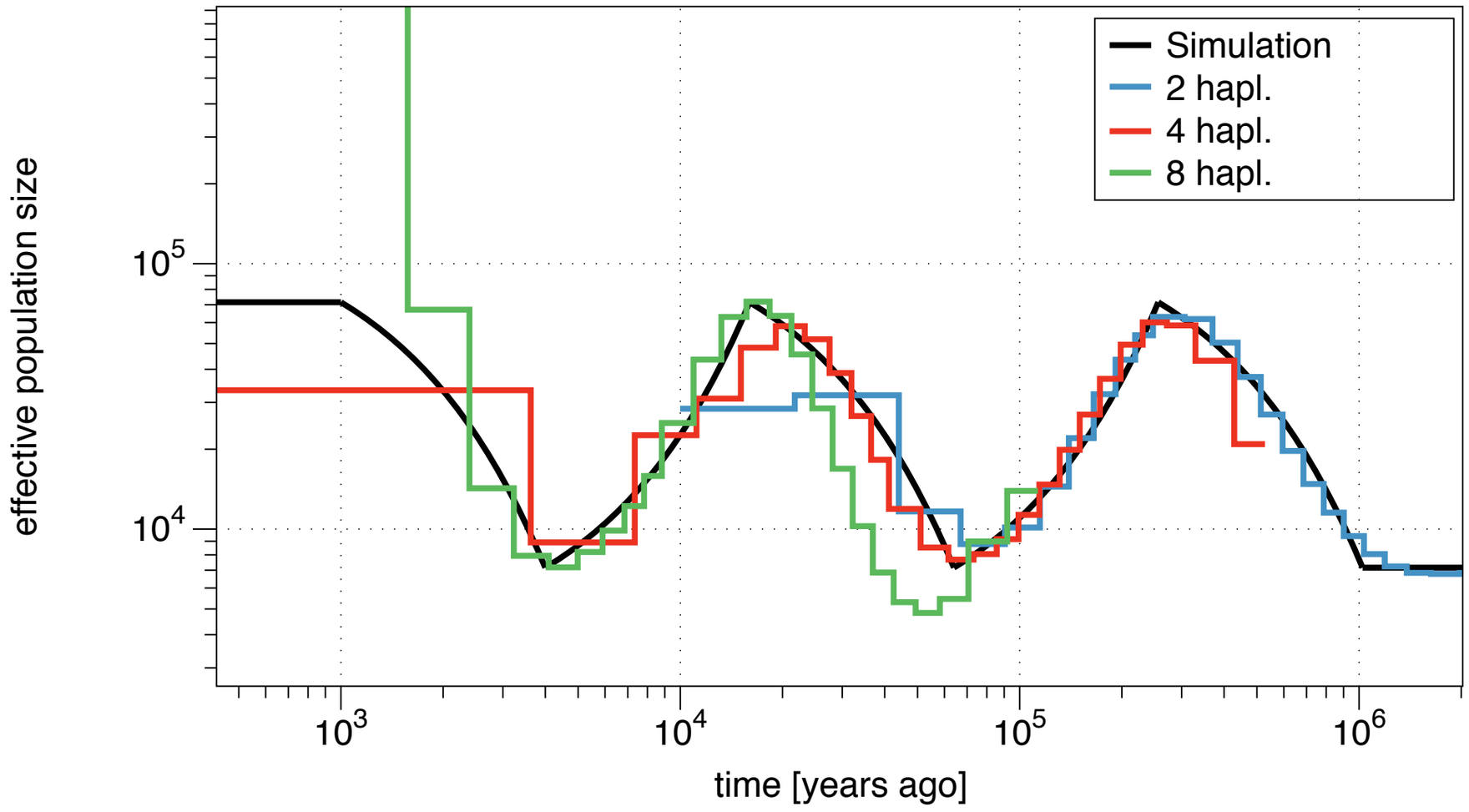
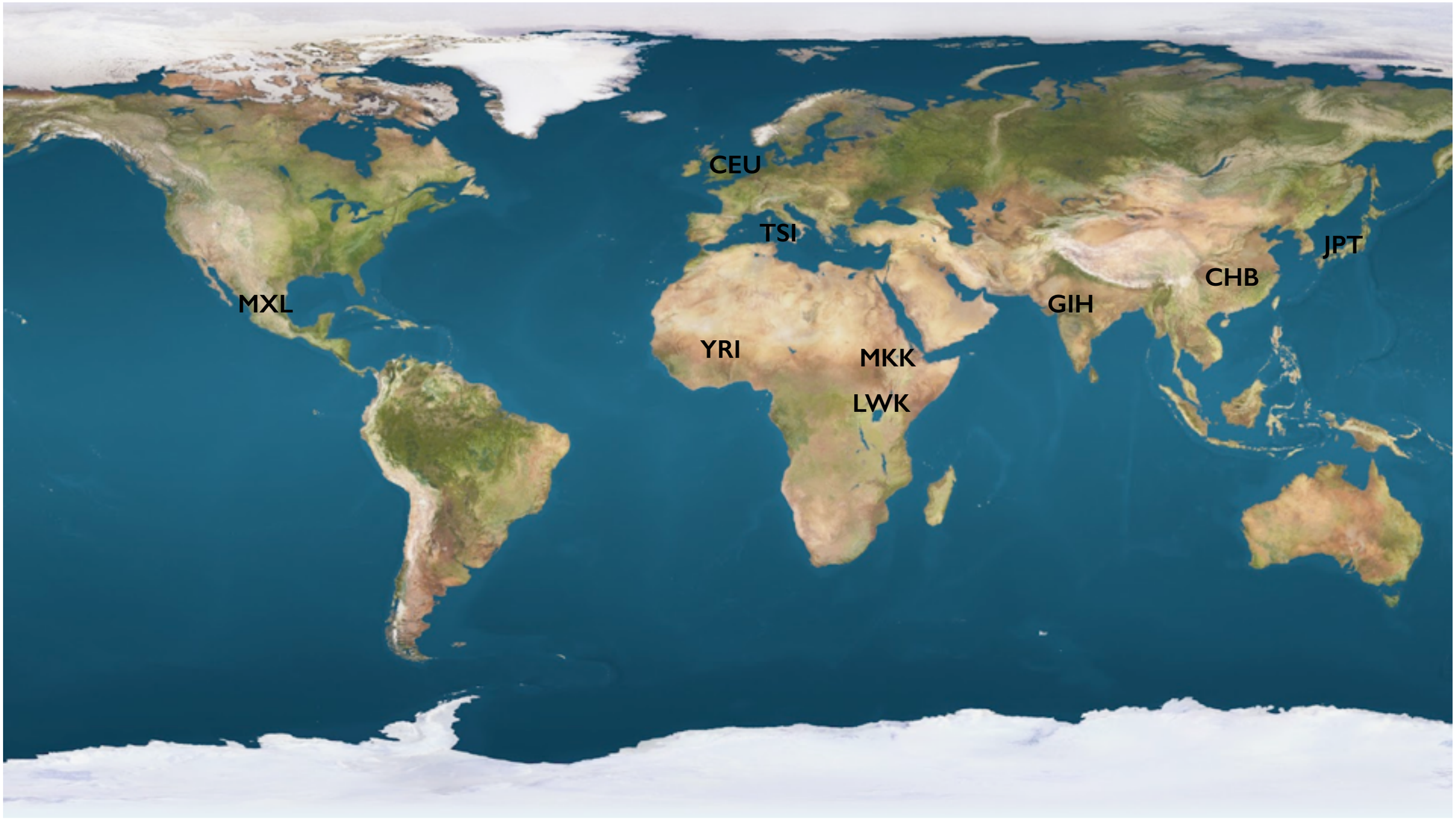


2 haplotypes: 40kya-3Mya

4 haplotypes: 8kya-300kya

8 haplotypes: 2kya-80kya

From genome sequences to human history

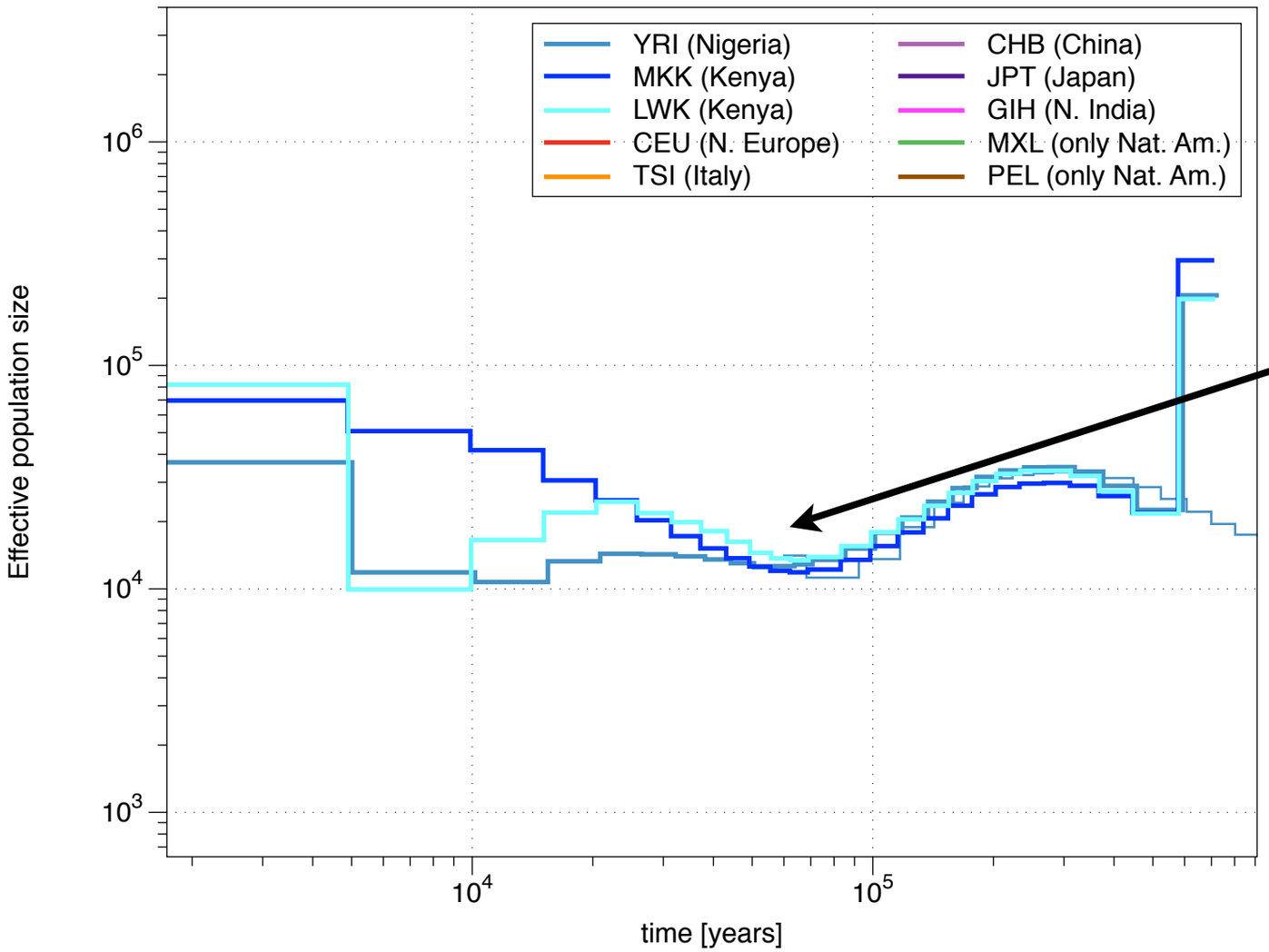


[Sequence data from Complete Genomics]

Inferring historical Population Sizes

real time scaling using
mutation rate per generation
$\mu = 1.25 \times 10^{-8}$ and a generation
time of 30 years

Inferring historical Population Sizes



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Mild bottleneck in African ancestors

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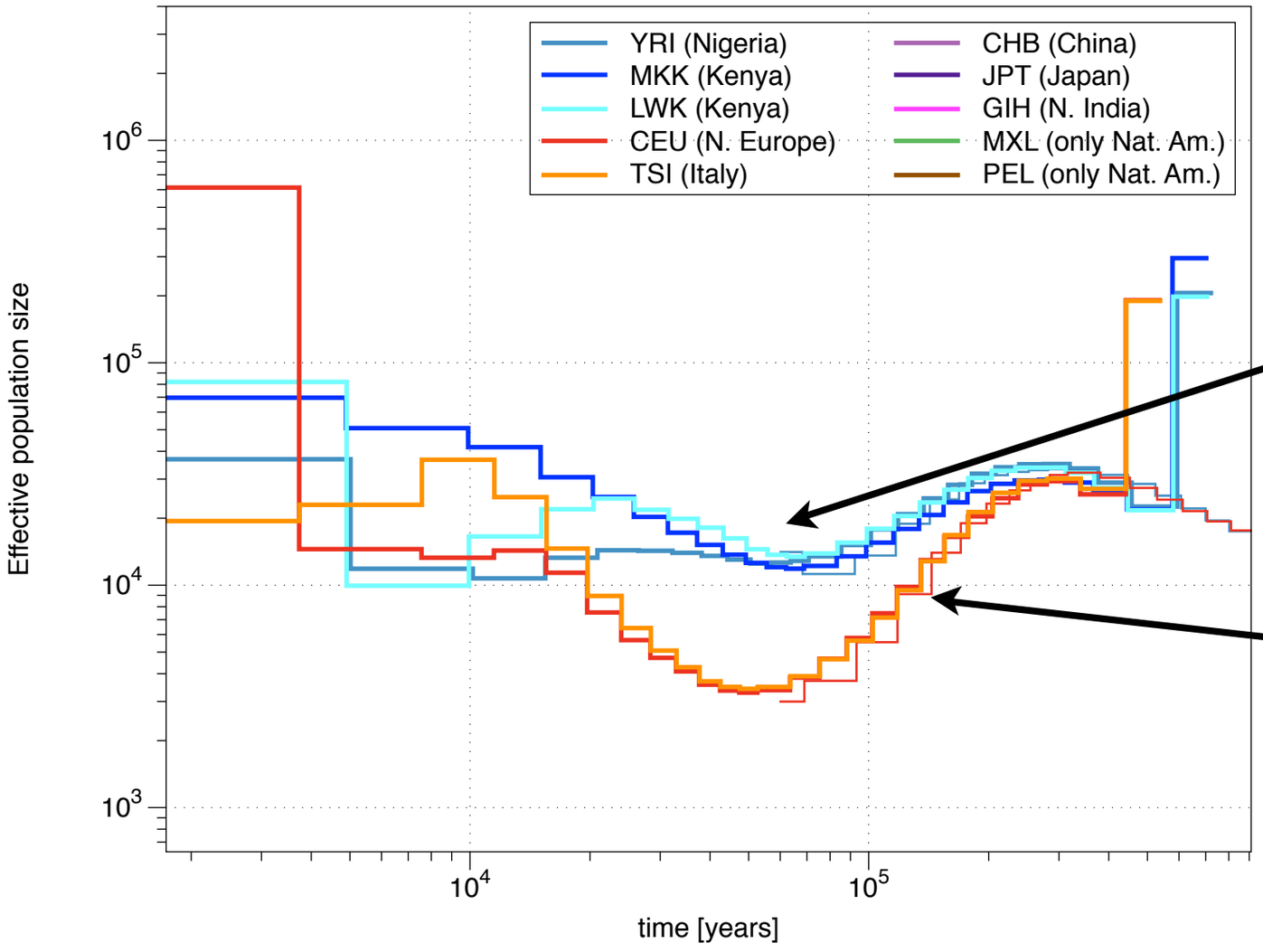

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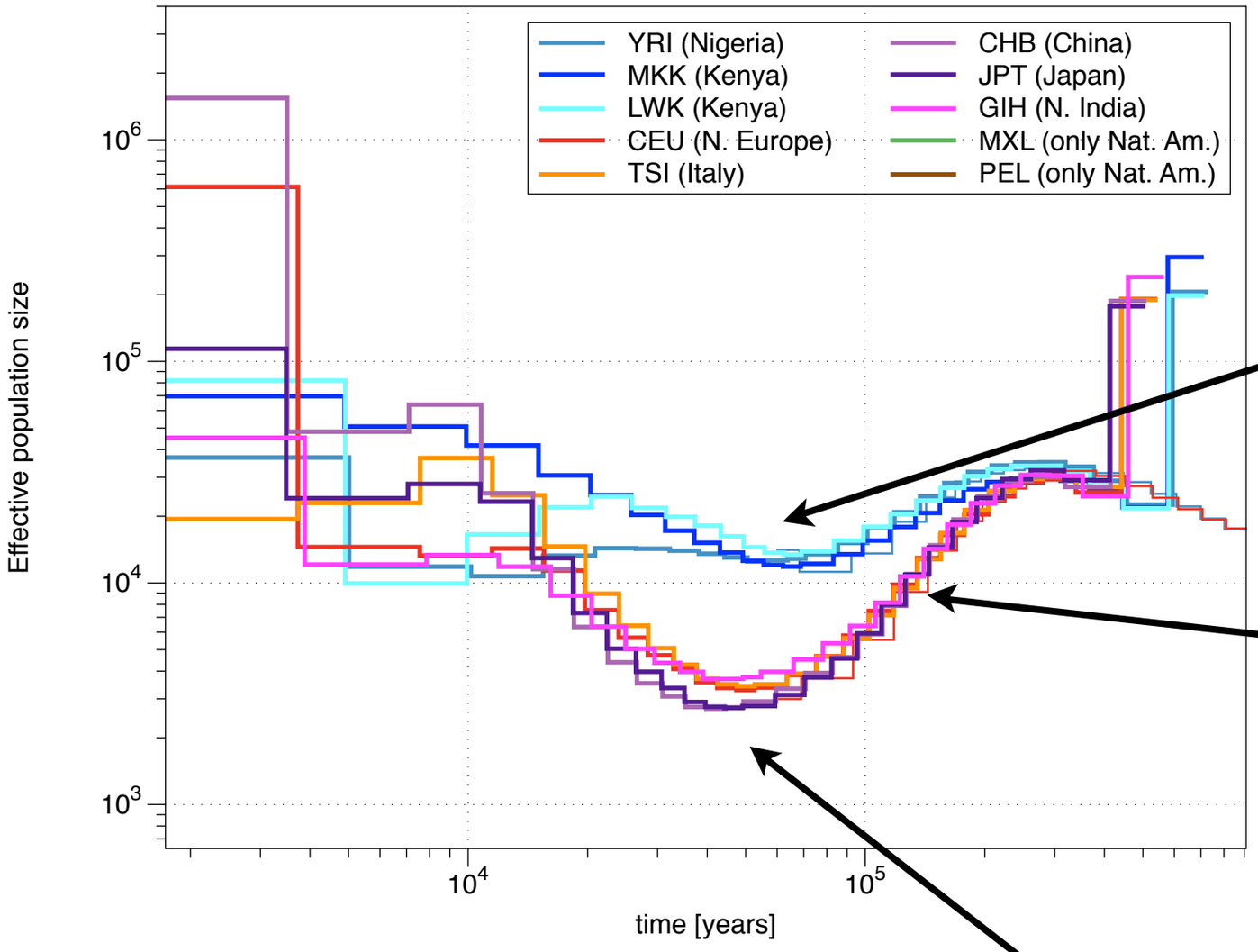
Mild bottleneck in African ancestors

identical history of non-African populations before 50kya

Inferring historical Population Sizes



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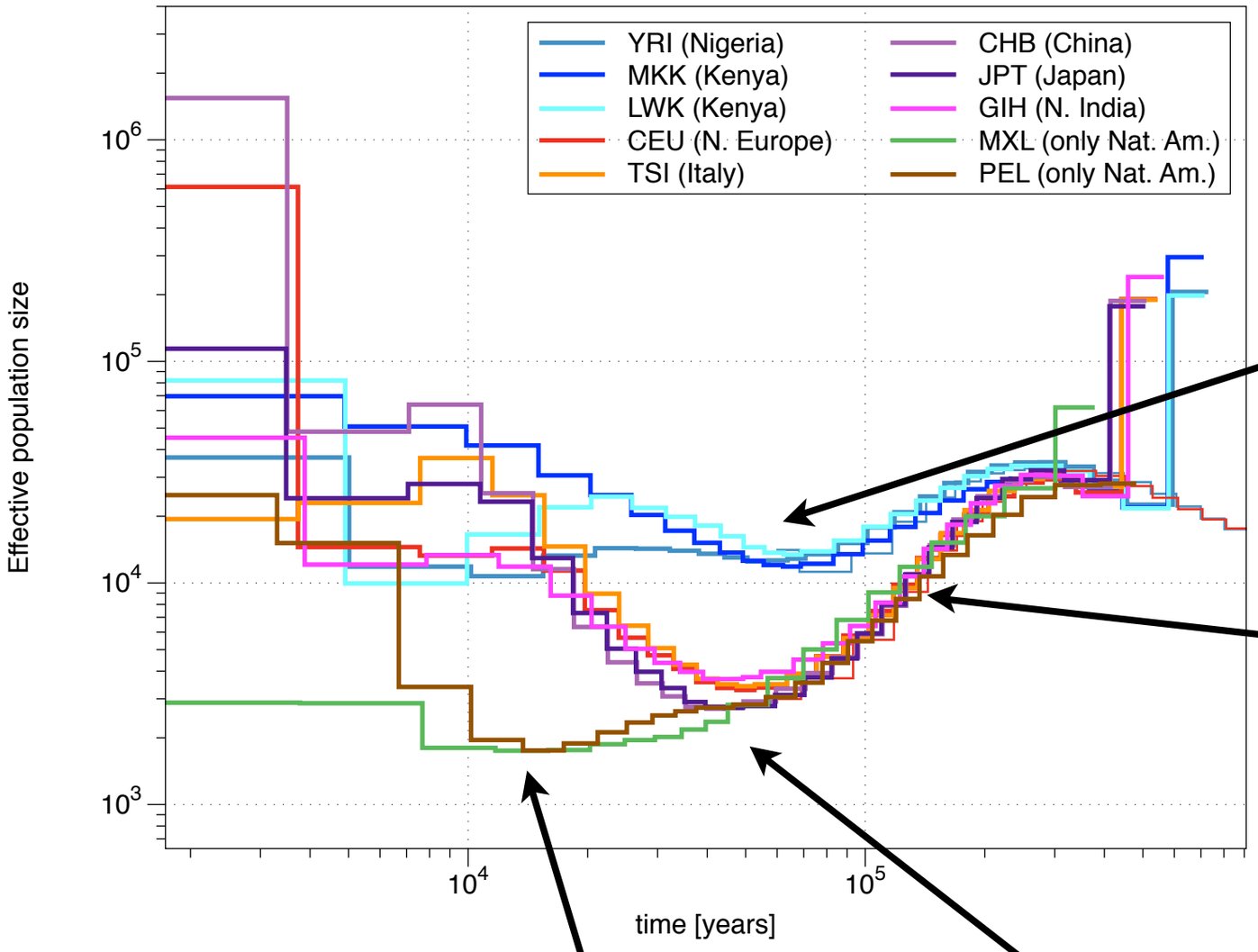
strong bottleneck in non-African populations 50-60kya, coincides with out-of-Africa dispersal

Inferring historical Population Sizes



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deep bottleneck in Native American populations around 15kya: Beginning of the Peopling of America via Alaskan Landbridge

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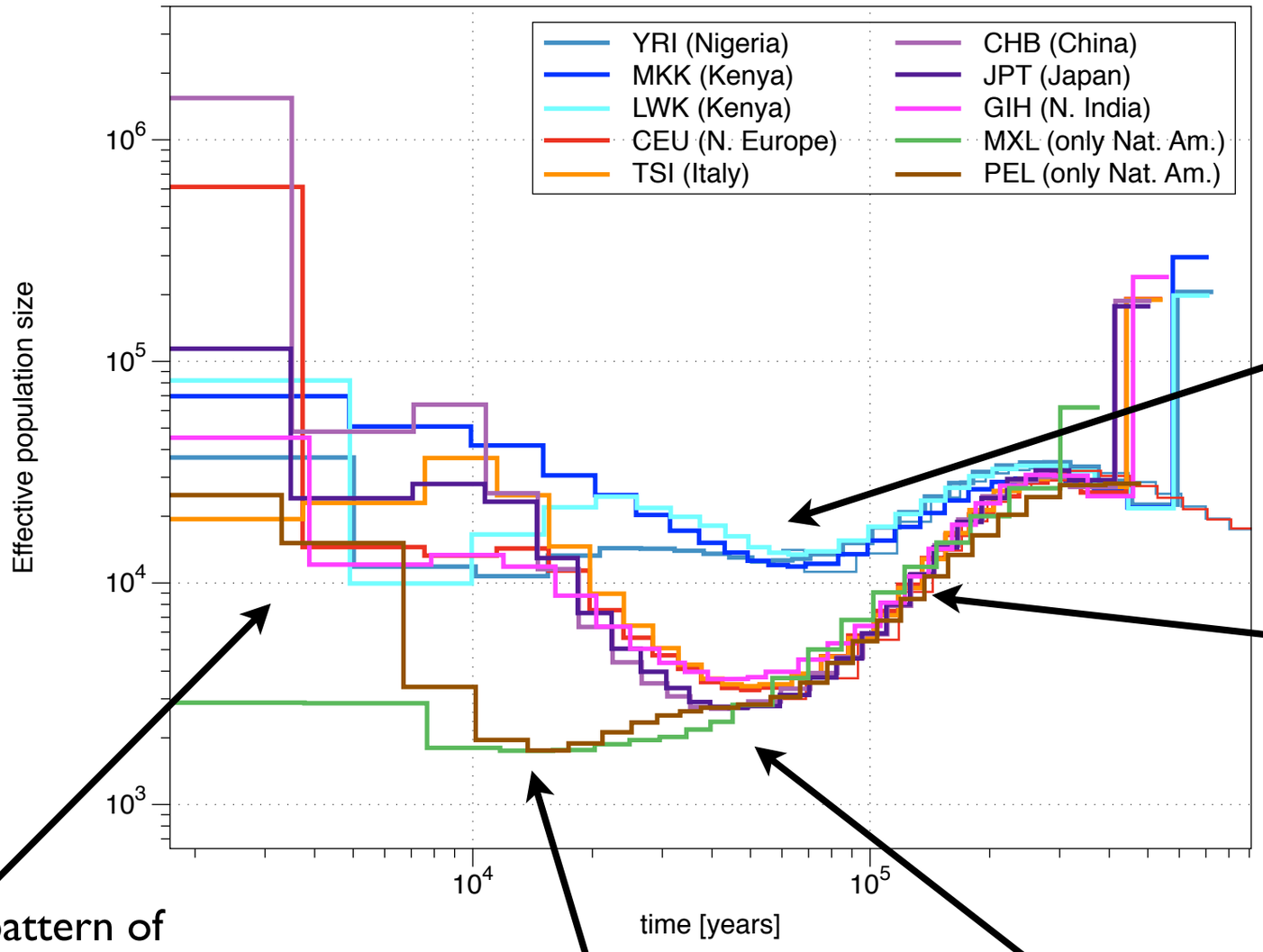

real time scaling using mutation rate per generation $\mu = 1.25 \times 10^{-8}$ and a generation time of 30 years

Mild bottleneck in African ancestors

identical history of non-African populations before 50kya

Complex pattern of neolithic expansions in the last 10,000 years within Europe, Asia and Africa

deep bottleneck in Native American populations around 15kya: Beginning of the Peopling of America via Alaskan Landbridge

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Population size inference from 8 haplotypes

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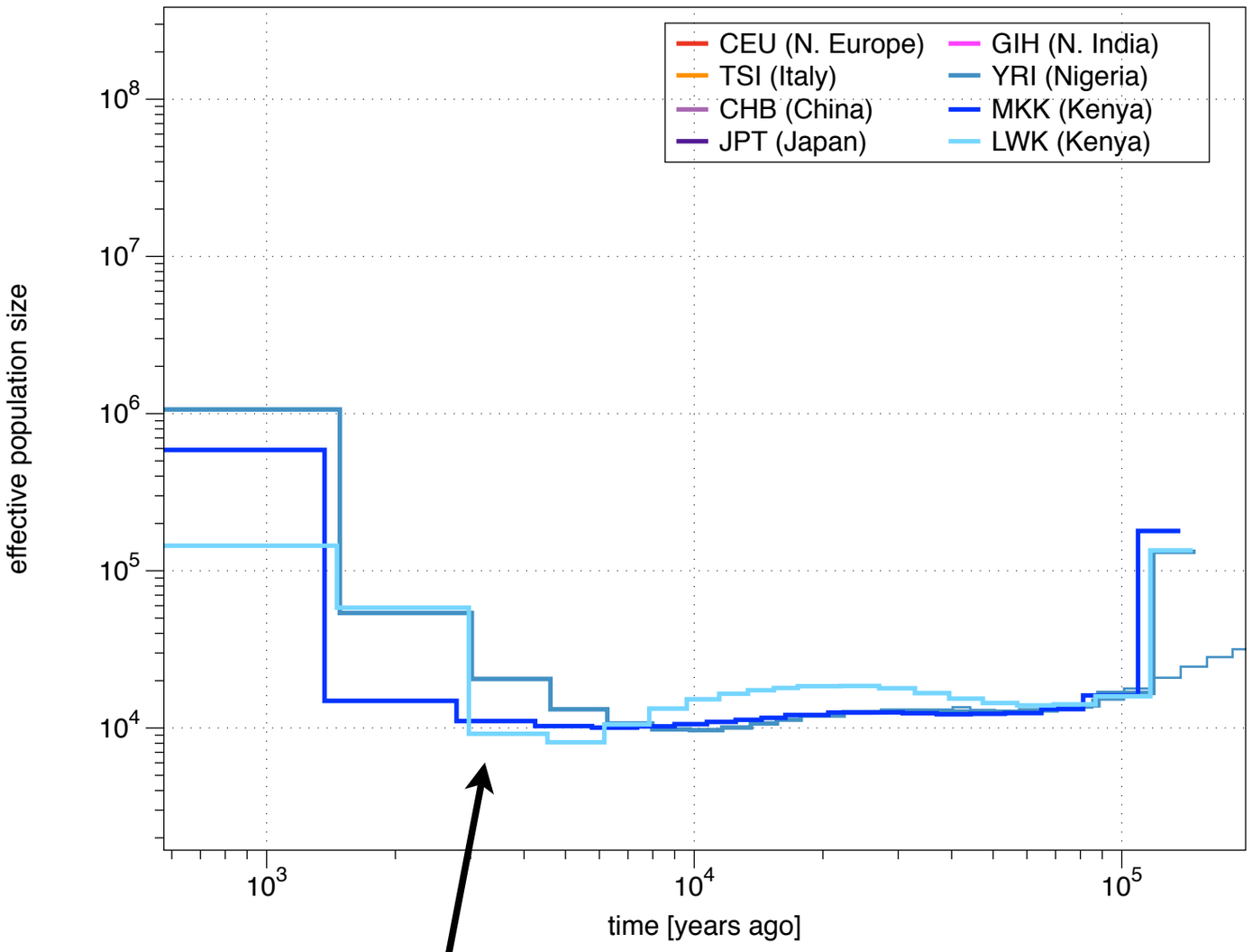
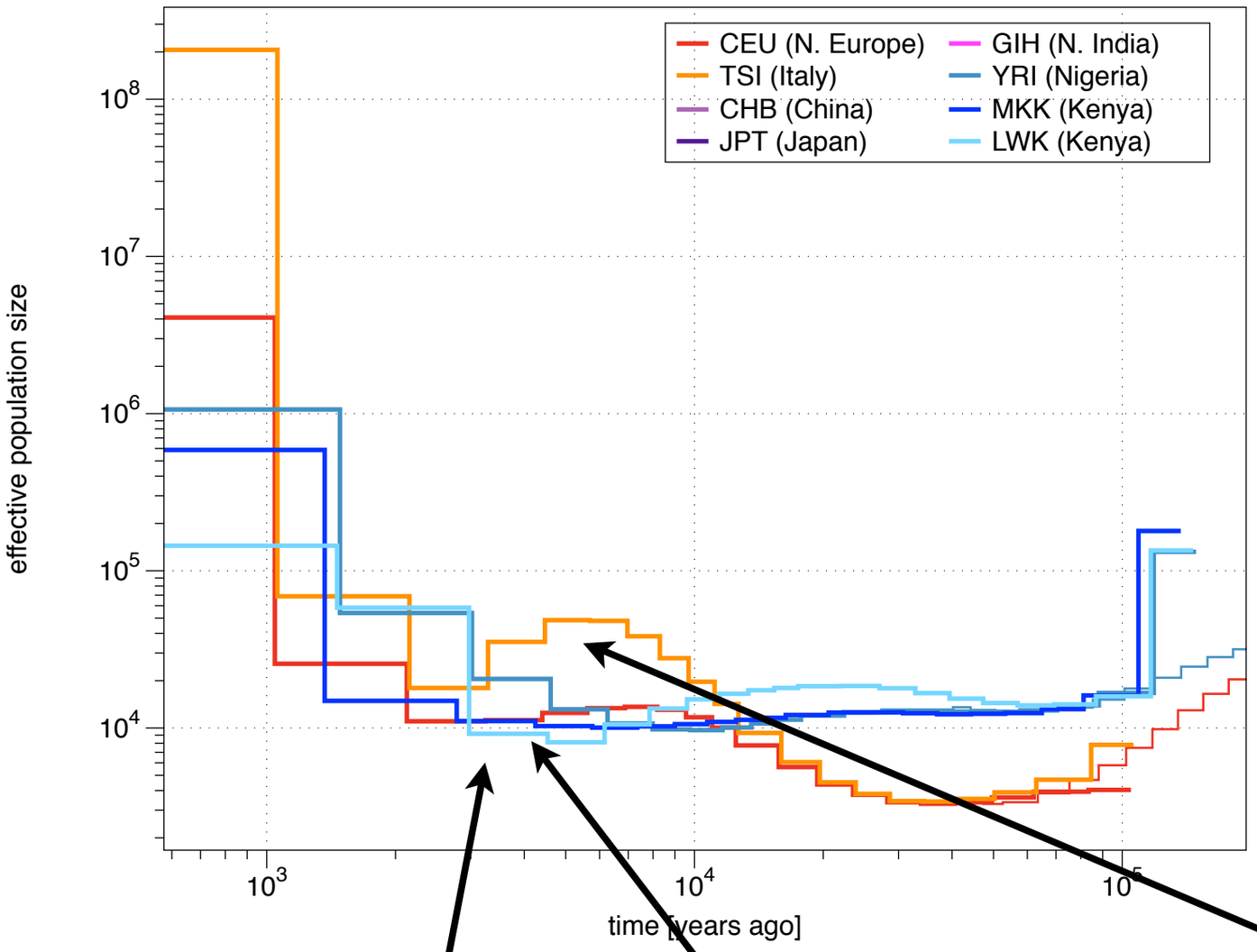


Bantu Expansion within Africa?

Population size inference from 8 haplotypes



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CEU: Constant population size until 2kya, then expansion

Structure and admixture in Southern Europe [see Botigué et al., 2013]

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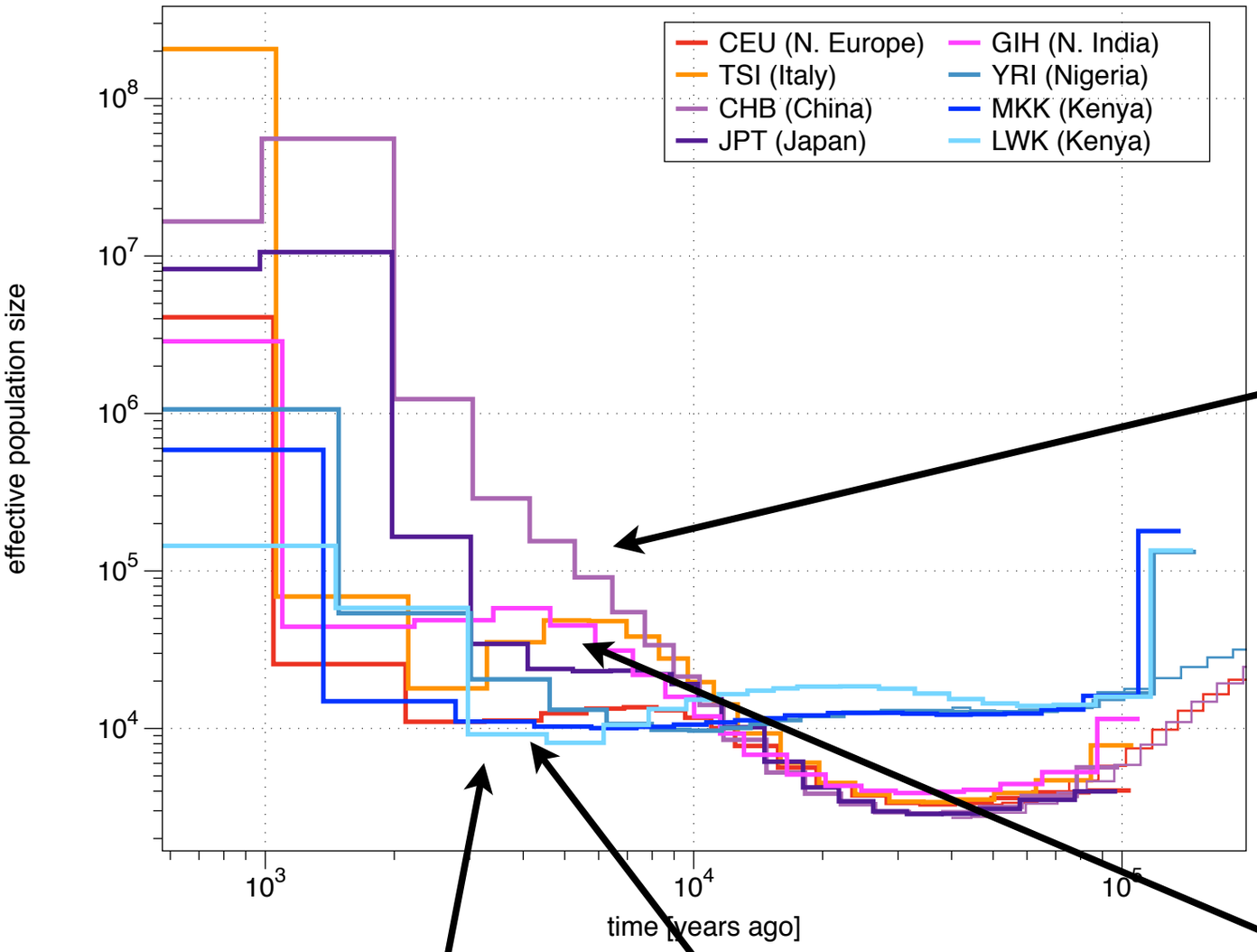


Continuous expansion in Chinese ancestors

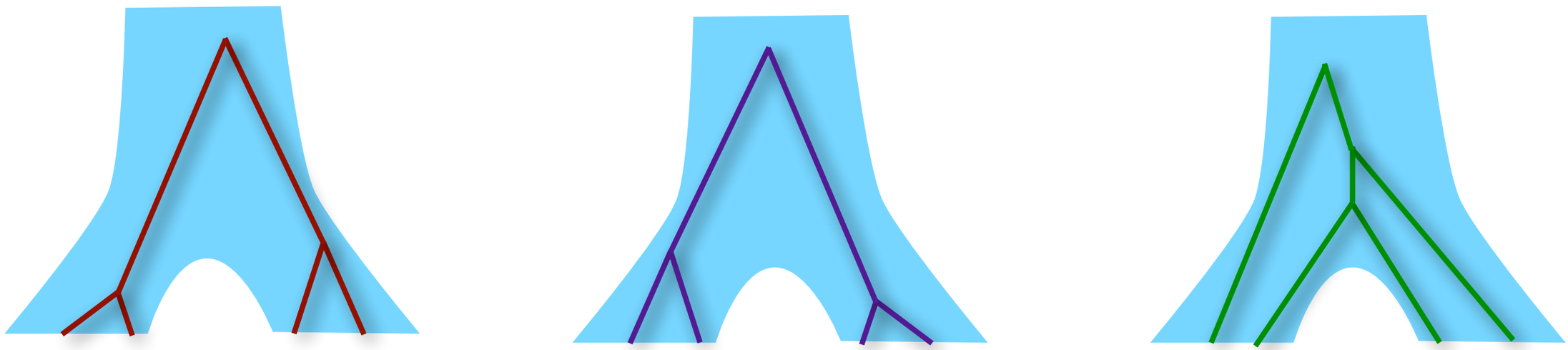
Structure and admixture in Southern Europe [see Botigué et al., 2013]

CEU: Constant population size until 2kya, then expansion

Bantu Expansion within Africa?

Divergence between populations

- Idea: Infer separate coalescence rates within and between populations:



First Coalescence within Population 1

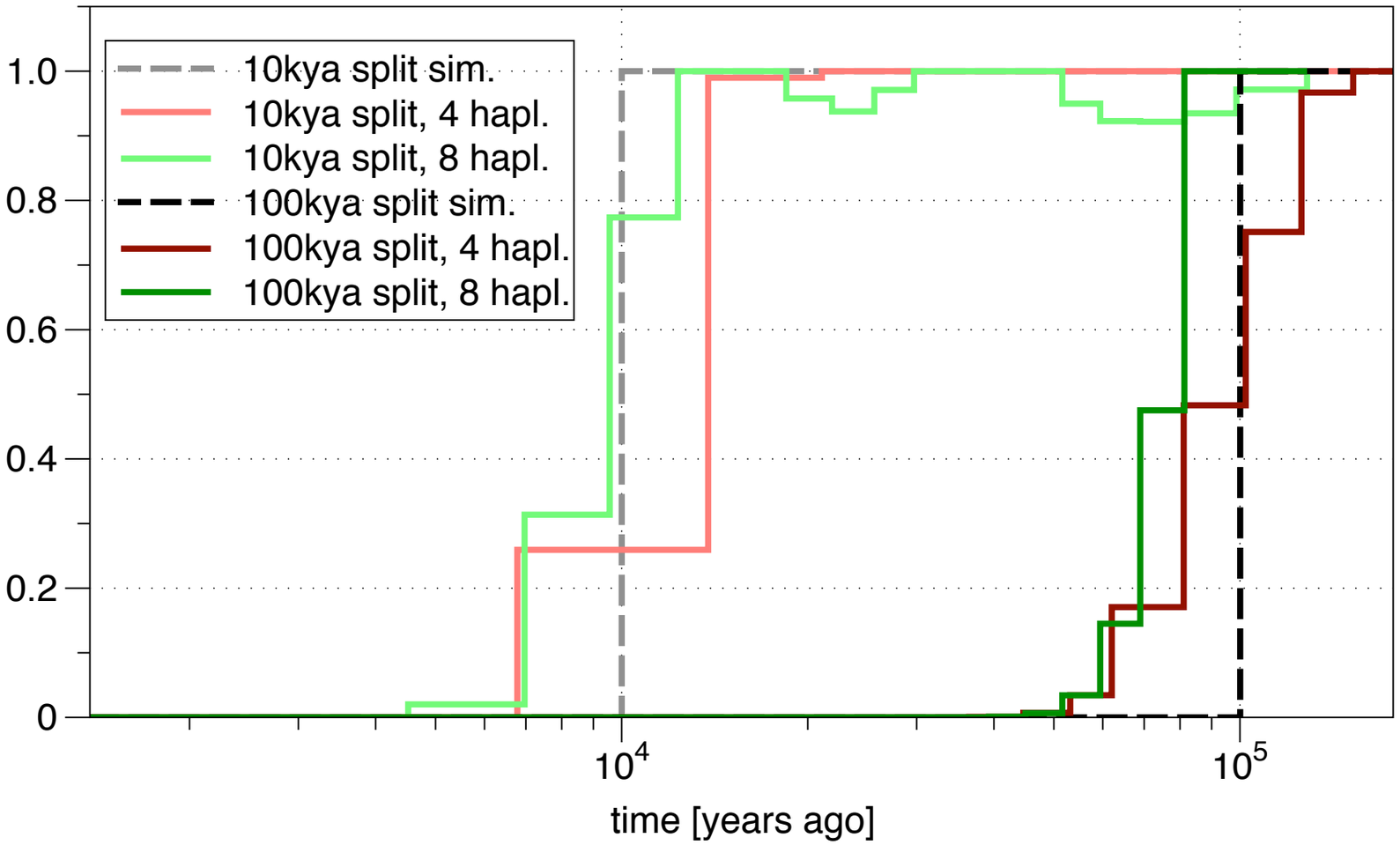
First Coalescence within Population 2

First Coalescence across both populations

- MSMC can infer separate coalescence rates within populations,
- Given rates within populations, $\lambda_{11}(t)$ and $\lambda_{22}(t)$, and across populations, $\lambda_{12}(t)$, compute relative gene flow as ratio

$$m(t) = \frac{\lambda_{12}(t)}{[\lambda_{11}(t) + \lambda_{22}(t)] / 2}$$

Testing gene flow inference with simulated split



☜ $m(t)=1$: perfectly mixed

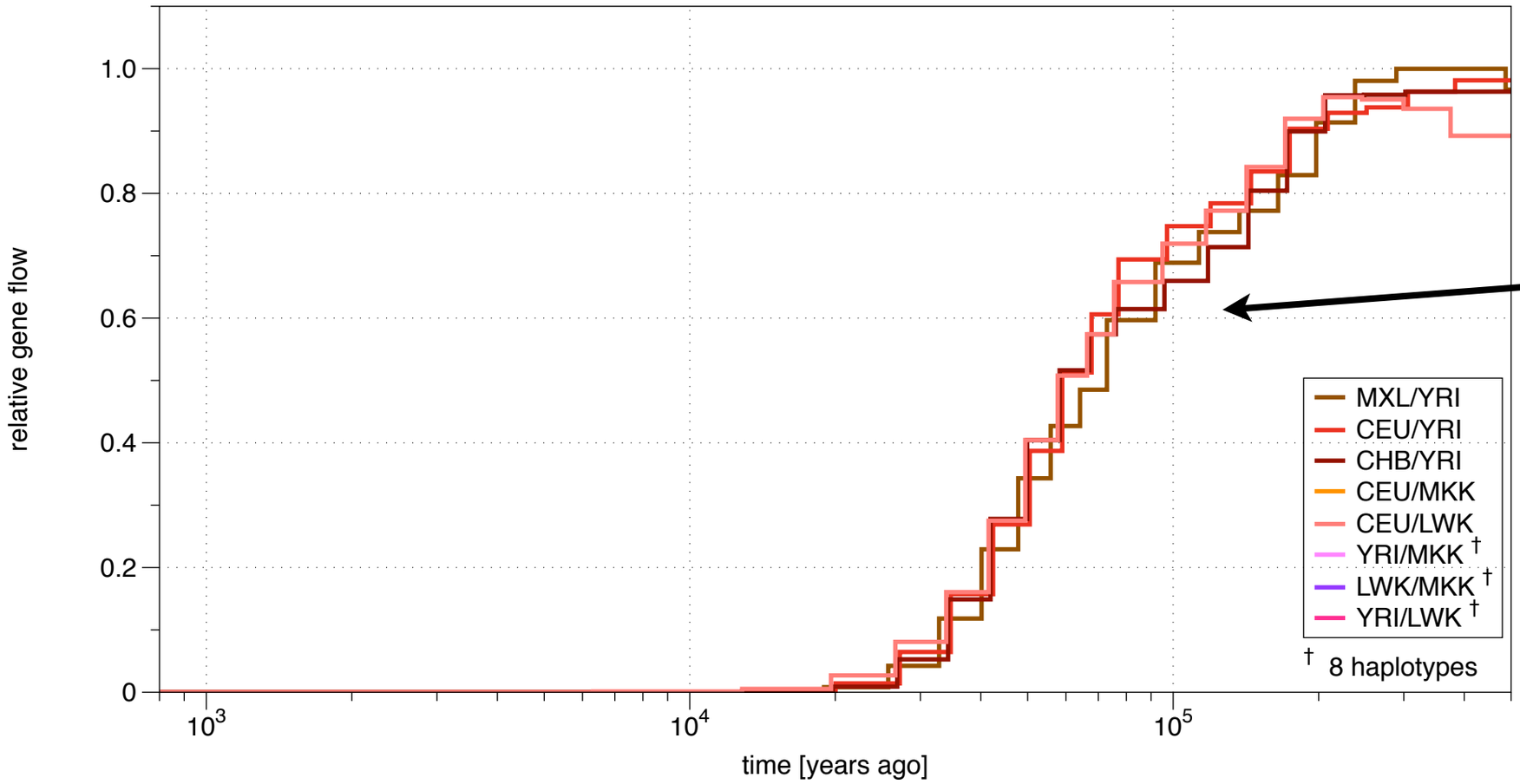
☜ $m(t)=0$: perfectly split

4 haplotypes: good for splits 50-200kya.

8 haplotypes: good for splits 5-50kya.

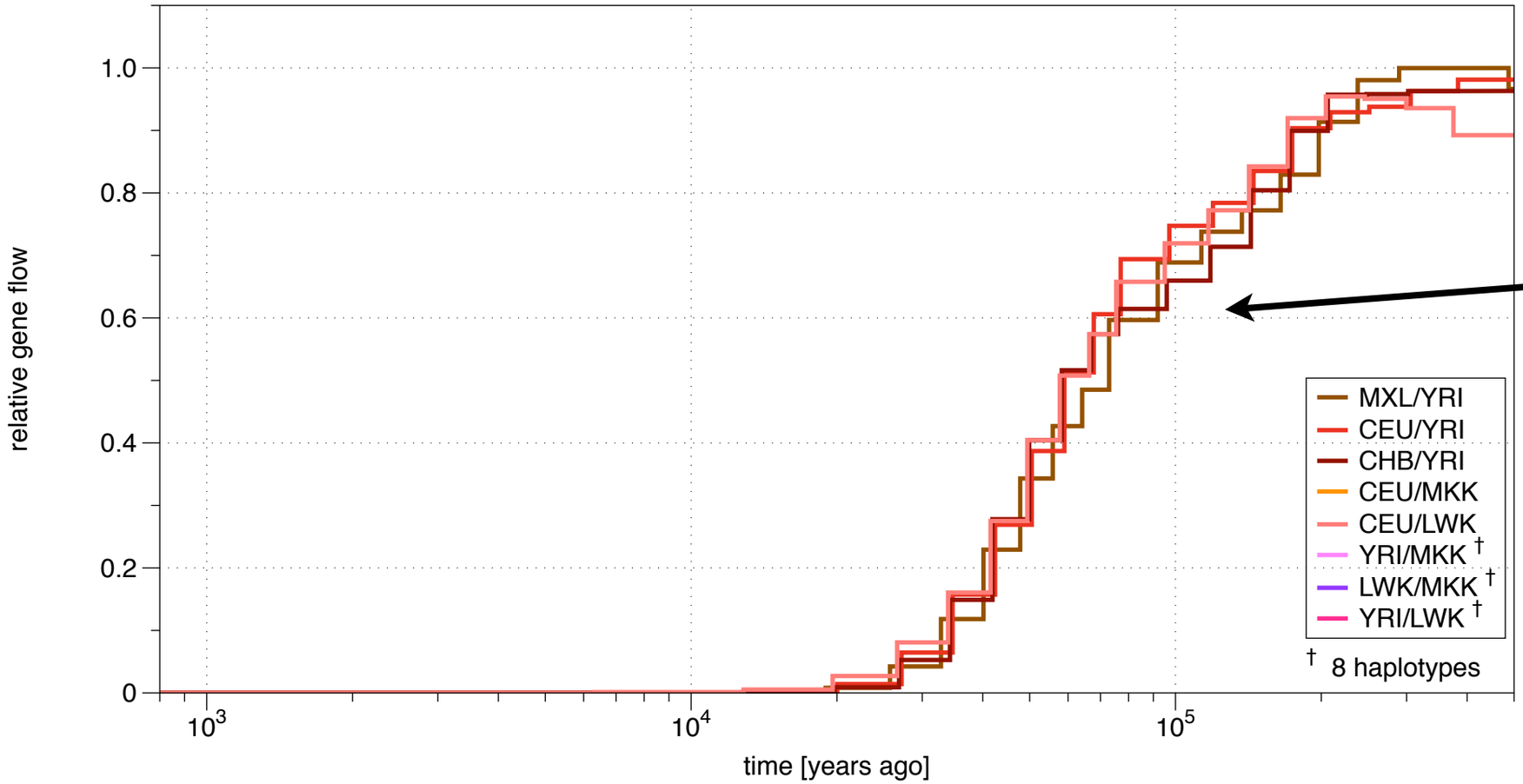
African Population separations

African Population separations



African(YRI)/Non-African separation: 150kya-40kya

African Population separations



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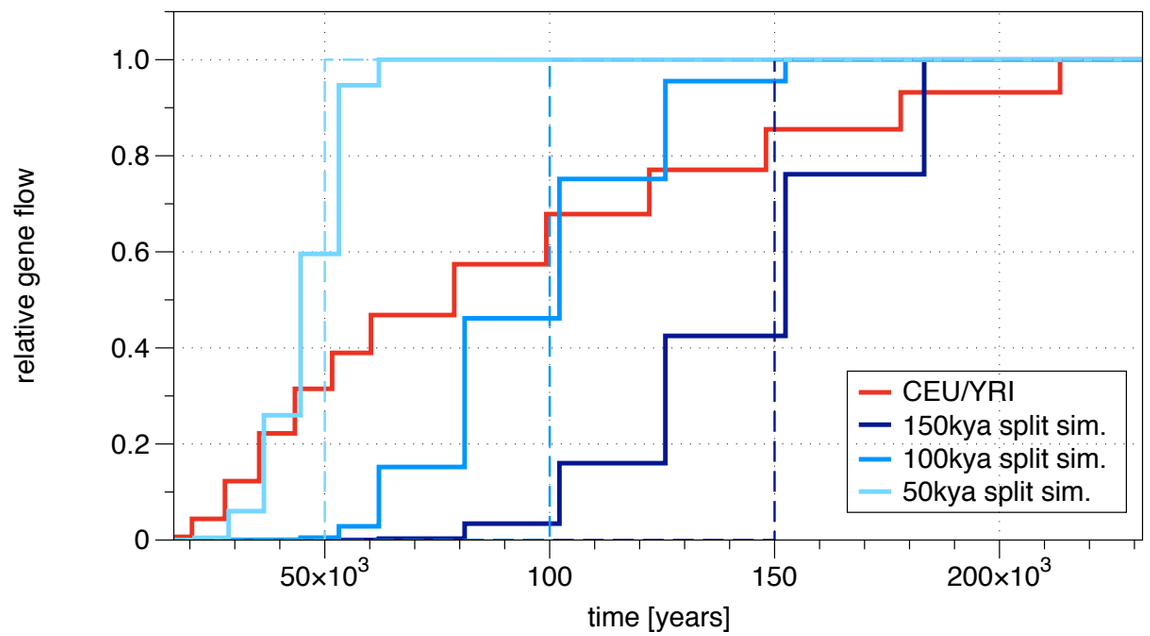

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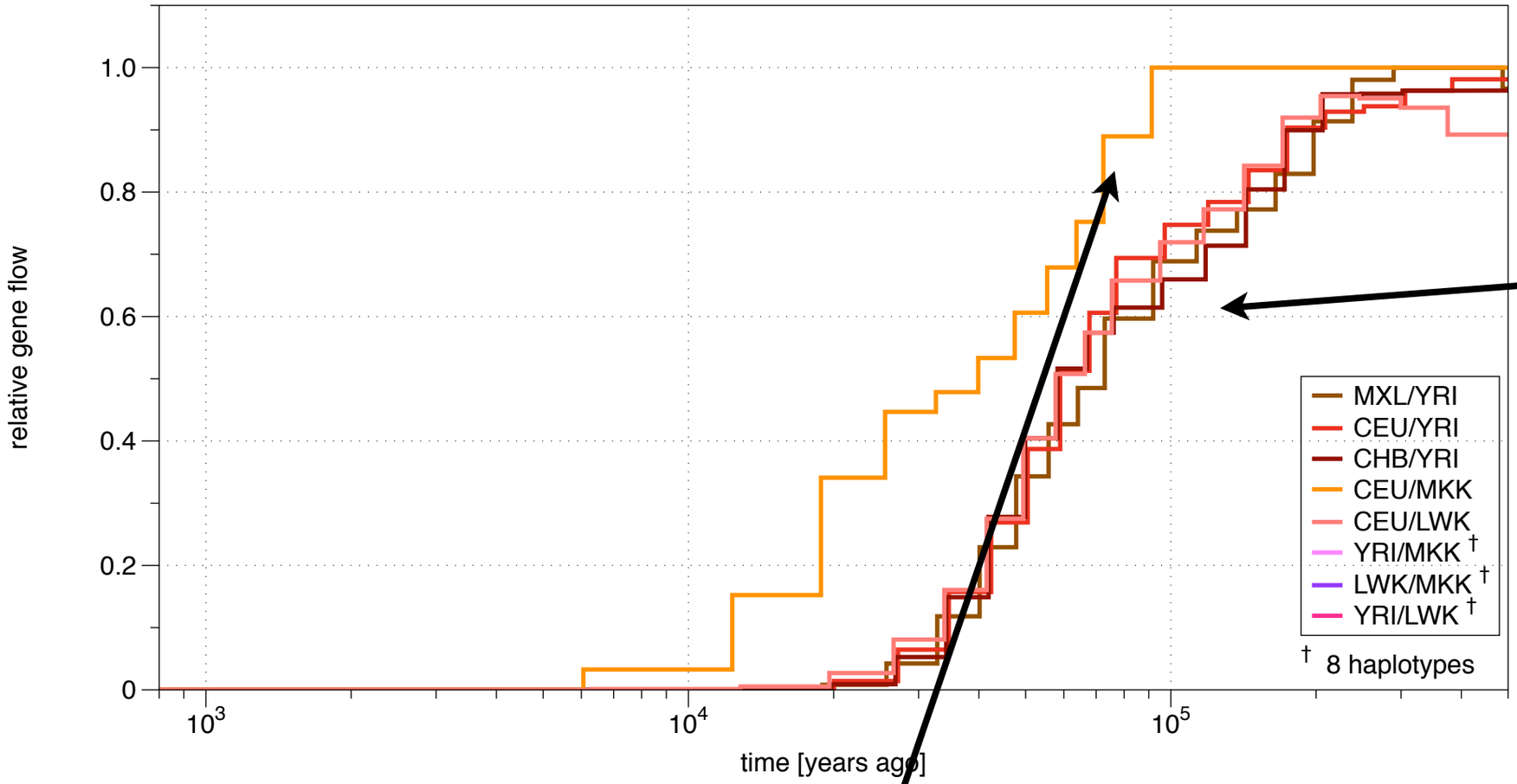
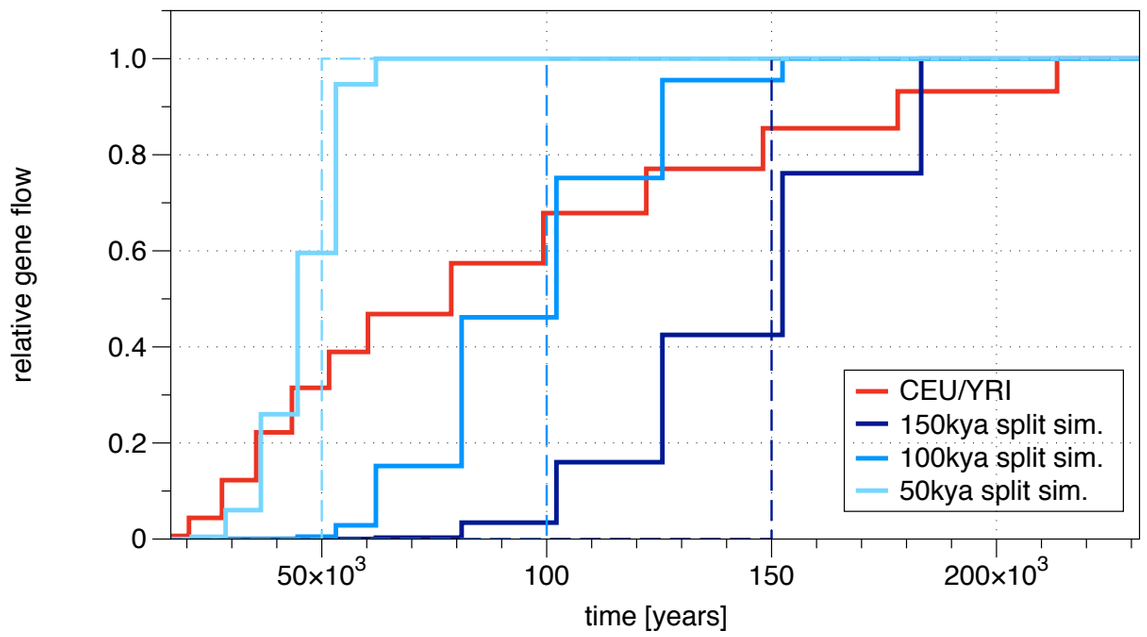


African(YRI)/Non-African separation: 150kya-40kya

Masaai remained mixing with European ancestors until ~80kya



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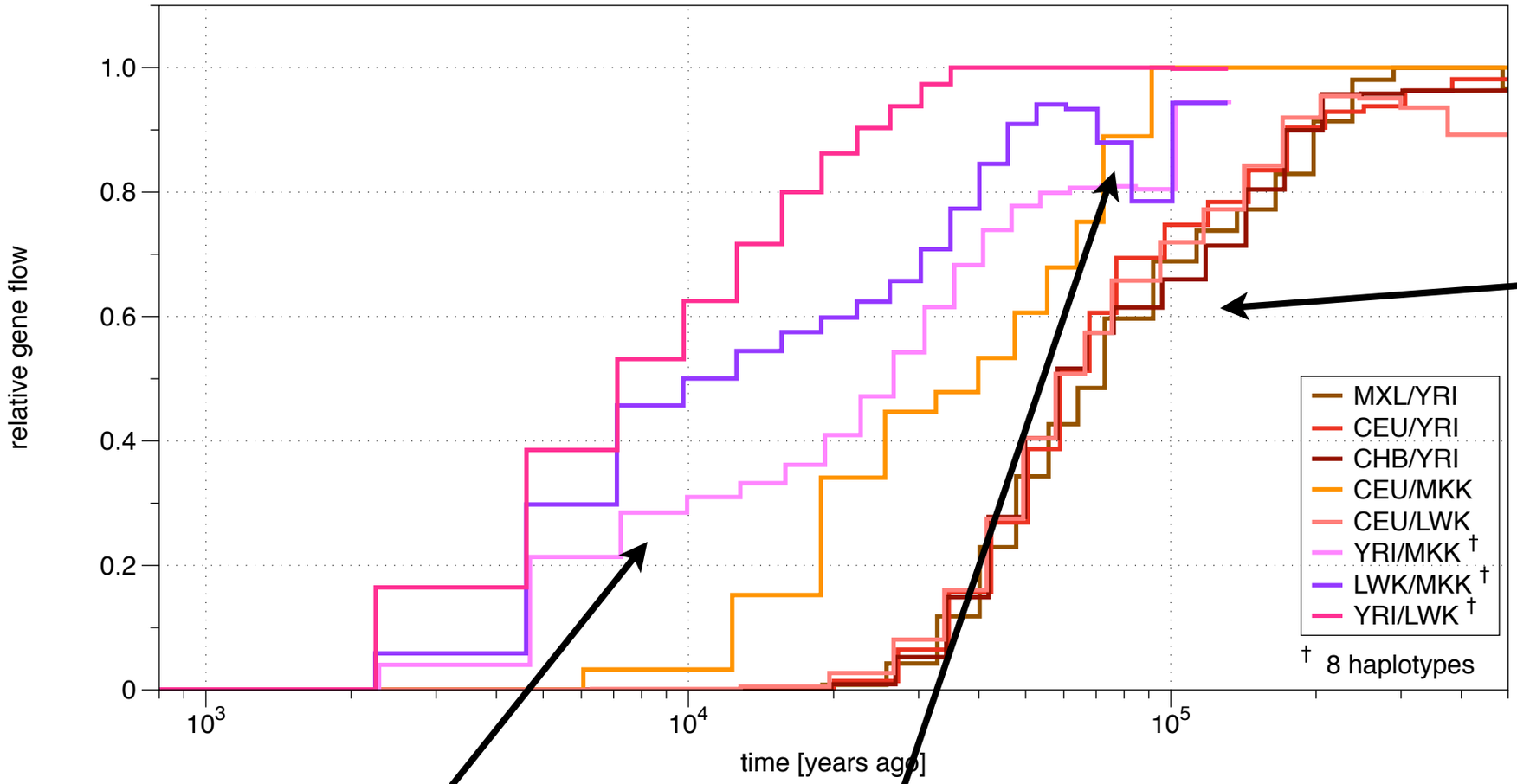
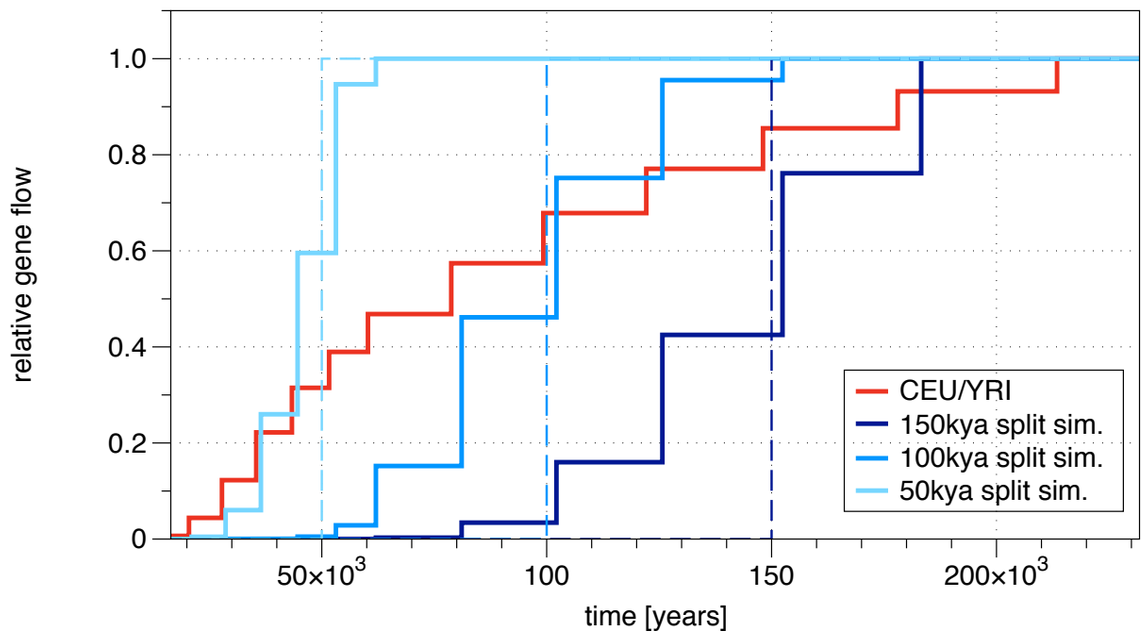


African(YRI)/Non-African separation: 150kya-40kya

Complex splits within Africa: 5kya-30kya

Masaai remained mixing with European ancestors until ~80kya



Non-African Population Separations

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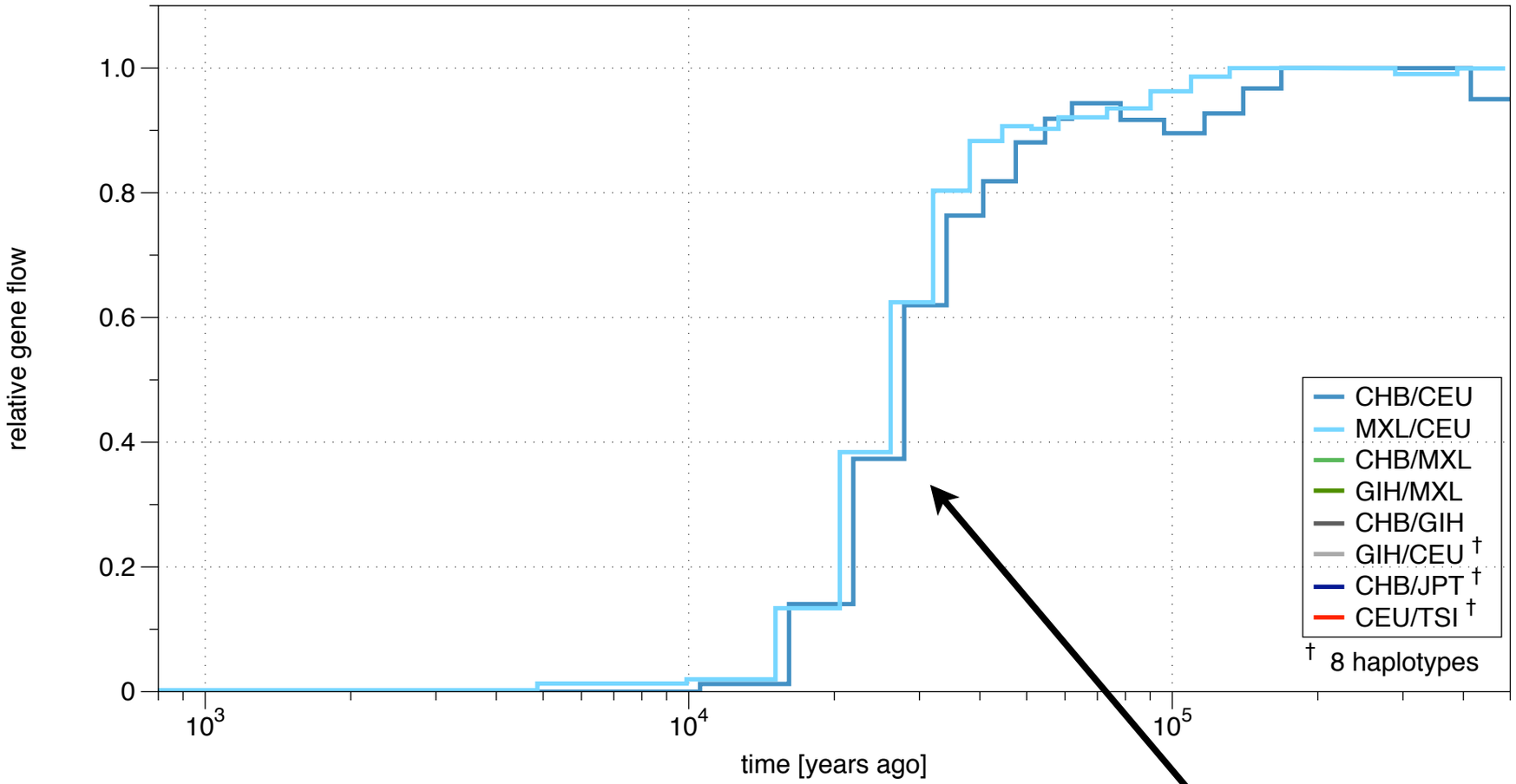
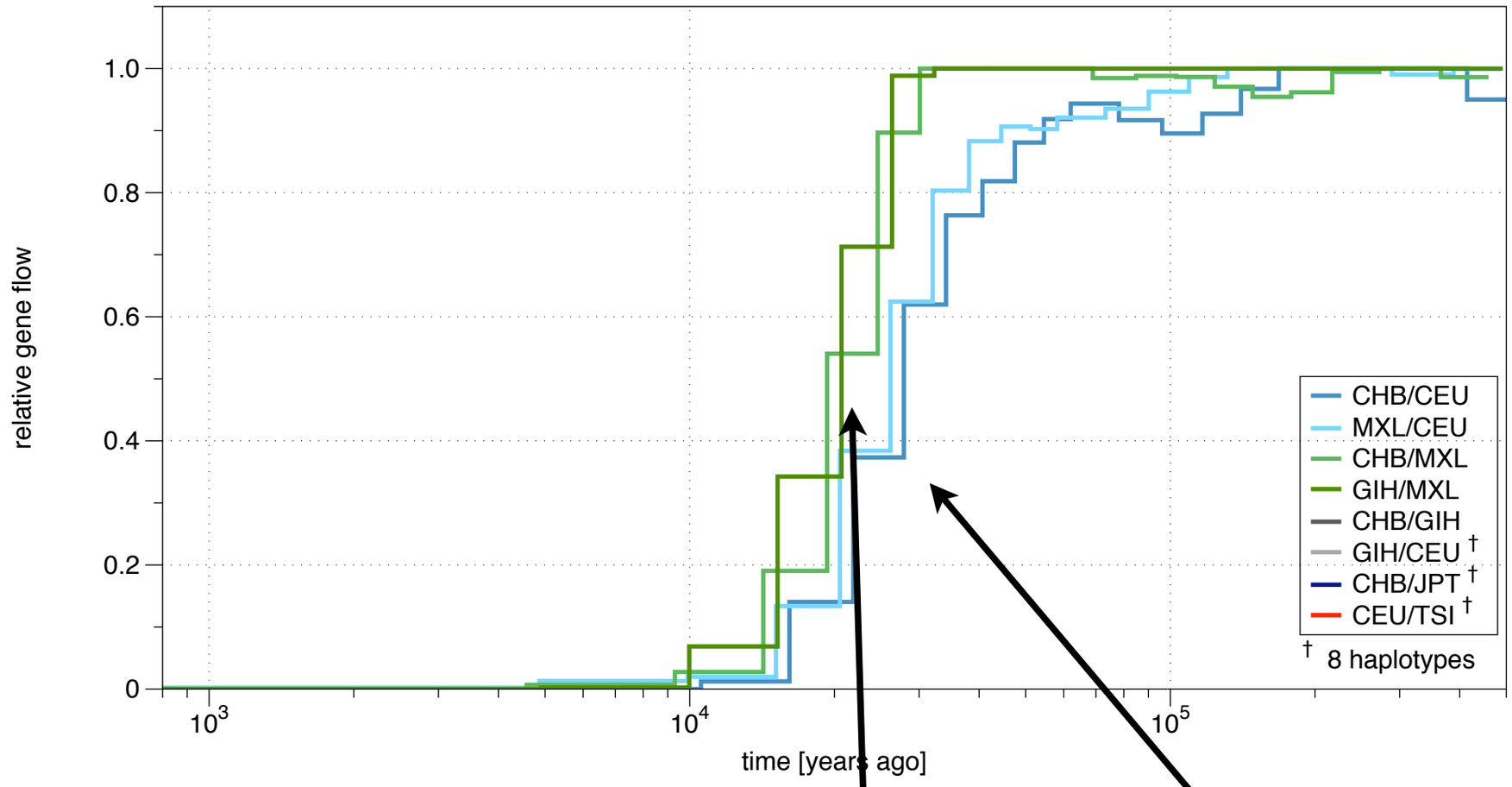


European/East-Asian split: 30kya, small older component?

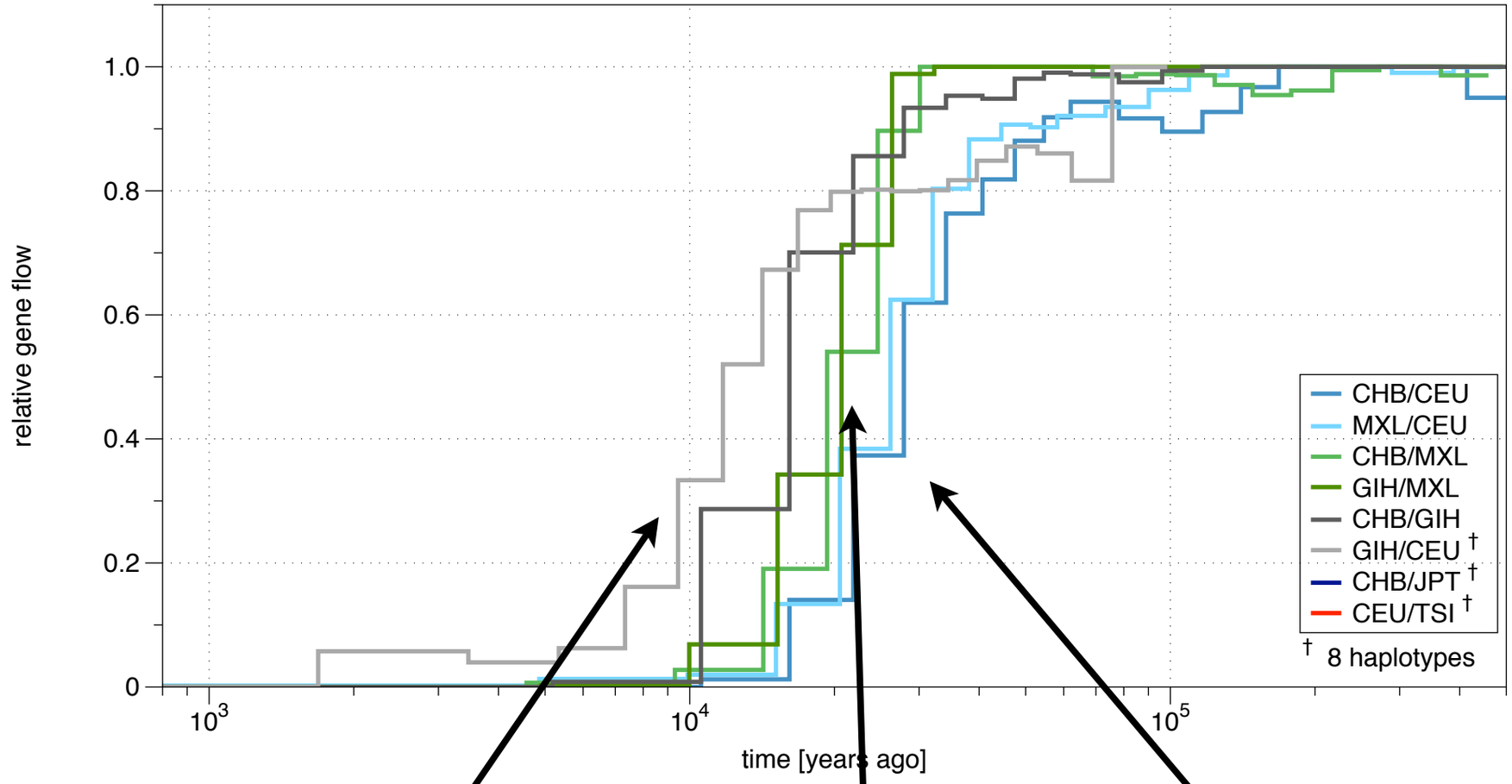
Non-African Population Separations



Asian/American
split: 20kya

European/East-Asian
split: 30kya, small older component?

Non-African Population Separations

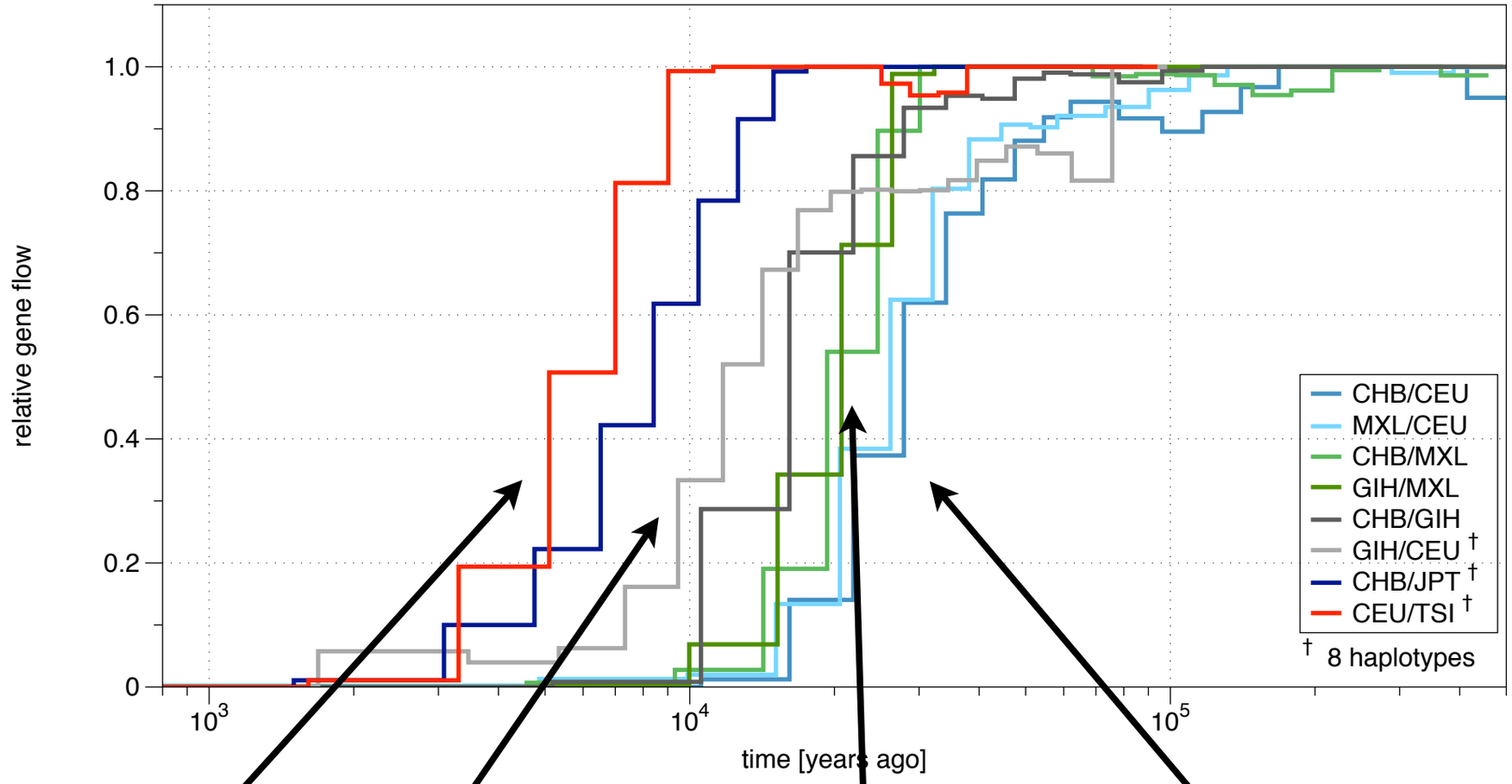


Complex Indian separations between 8kya and 20kya

Asian/American split: 20kya

European/East-Asian split: 30kya, small older component?

Non-African Population Separations



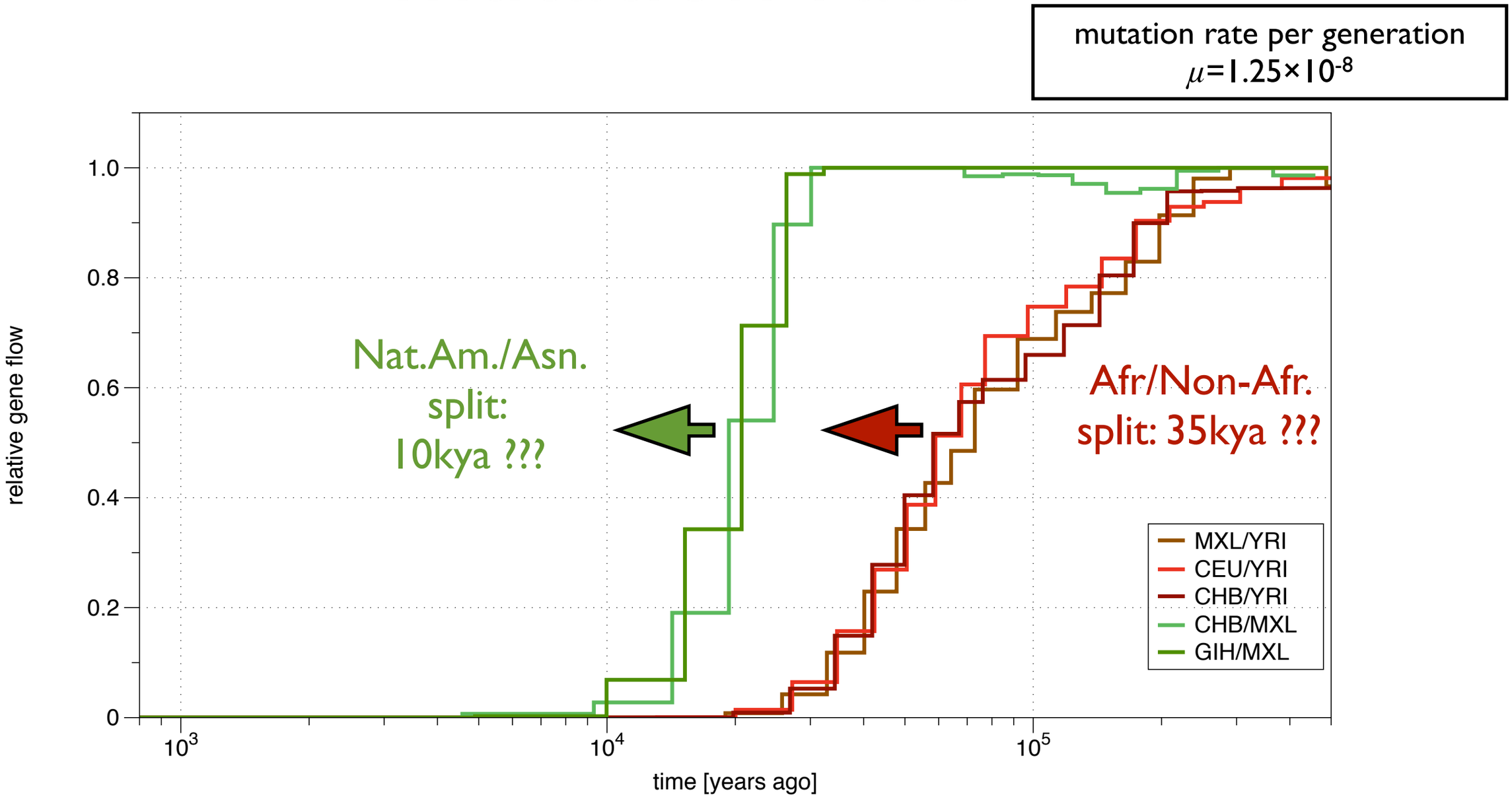
Splits within Europe and within East-Asia

Complex Indian separations between 8kya and 20kya

Asian/American split: 20kya

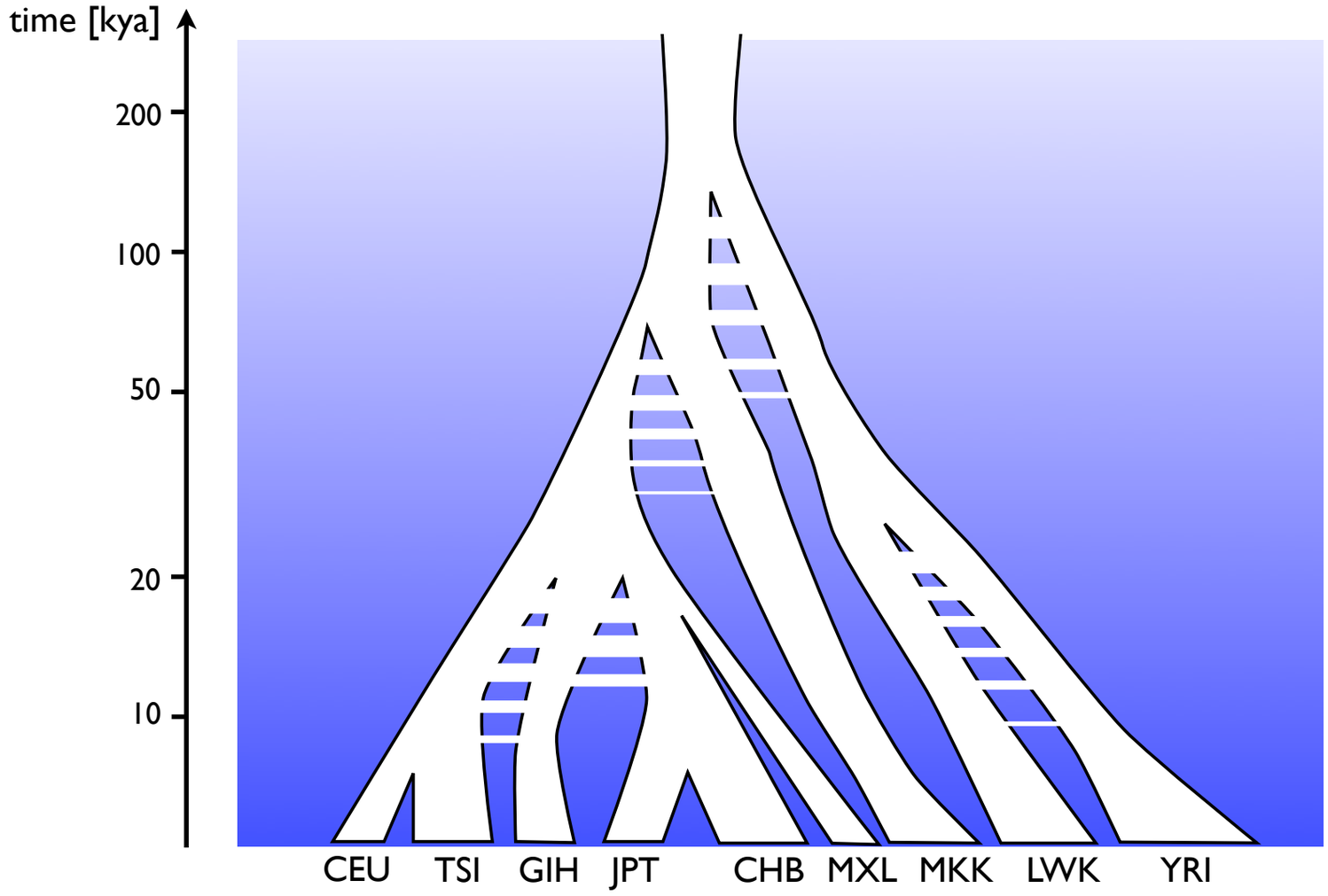
European/East-Asian split: 30kya, small older component?

Implications of higher human mutation rate



A higher mutation rate of 2.5×10^{-8} would push these splits towards too recent times

MSMC Summary on separation history



[Schiffels and Durbin, *Nature Genetics*, in press]

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- Article in press: Schiffels and Durbin, Nature Genetics
  Preprint available on biorxiv.

- Software available on https://github.com/stschiff/msmc

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EMBO Fellow

Transition probability

$$q(i,\, j,\, t \mid k,\, l,\, s) = \delta(t-s)\,\delta_{i,k}\,\delta_{j,l}\,q_1(t) + q_2(t \mid s)$$

Probability to remain in state (i,j,t)

Probability to change time (and pair) of first coalescence

$$q_1(t) = e^{-M r t} + \left(1 - e^{-M r t}\right)\frac{1}{t}\,\frac{1}{M}\int_0^t \left(1 + (M-3)\exp\left(-M\int_u^t \lambda(v)\,dv\right)\right)du$$

$$q_2(t \mid s) = \left(1 - e^{-M r s}\right)\frac{1}{s}\,\frac{1}{M}\,2\,\lambda(t)\begin{cases} \int_0^t \exp\left(-M\int_u^t \lambda(v)\,dv\right)du & \text{if } t < s \\ \exp\left(-\binom{M}{2}\int_s^t \lambda(v)\,dv\right)\int_0^s \exp\left(-M\int_u^s \lambda(v)\,dv\right)du & \text{if } t > s. \end{cases}$$

depends on:

- coalescence rates λ(t)
- recombination rate r
- Number of sequences M