Modelling complex traits with ancestral recombination graphs

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Overview

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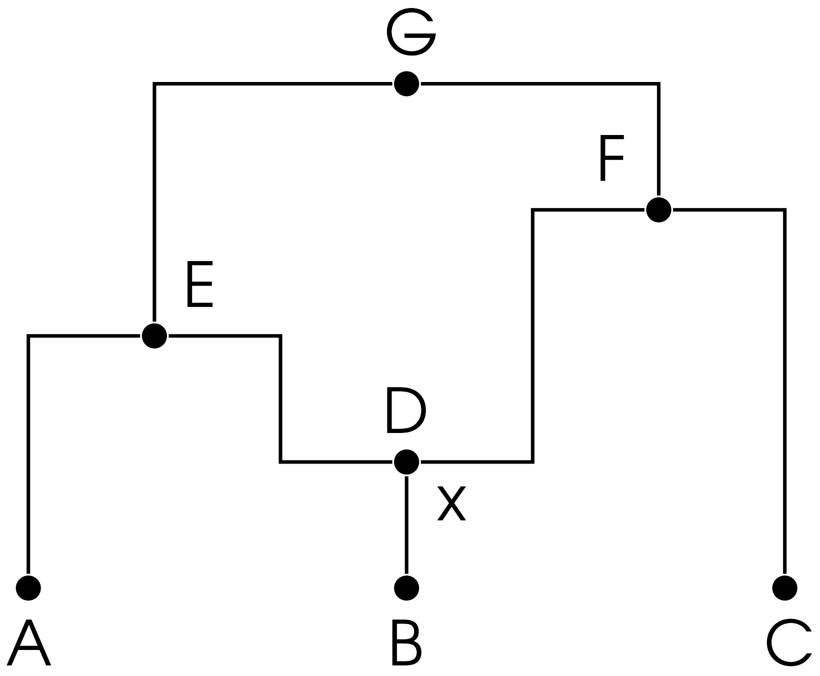
The ancestral recombination graph (ARG) describes the evolutionary relationship between genetic materials in the presence of recombination and drift



From (Wong et al. 2024)

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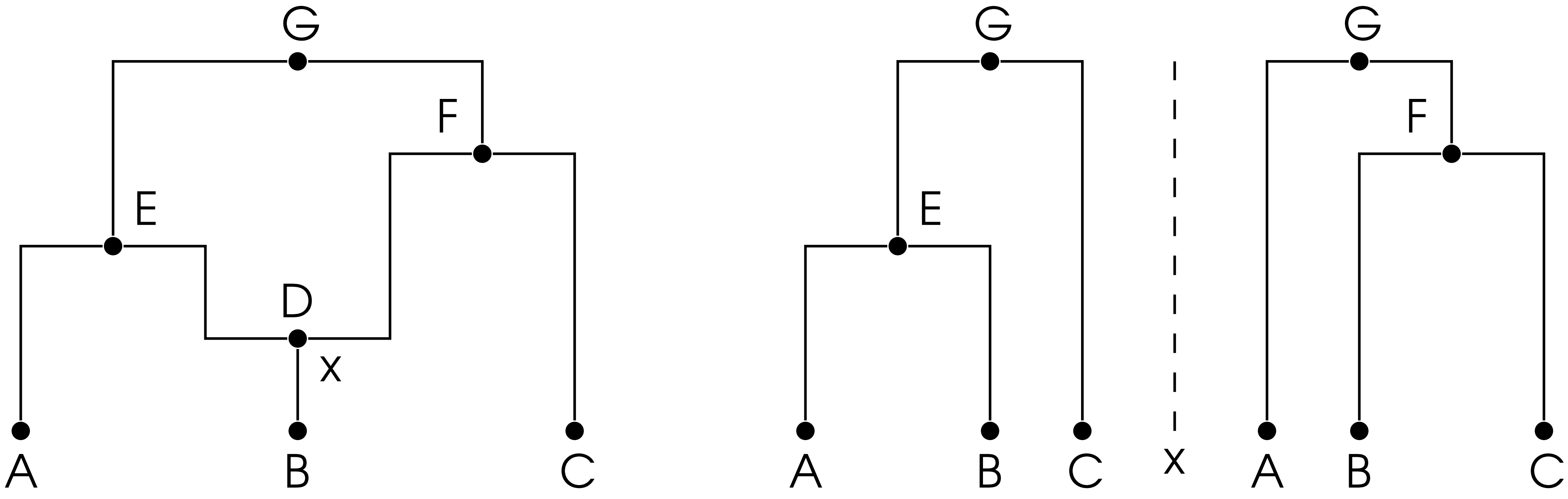

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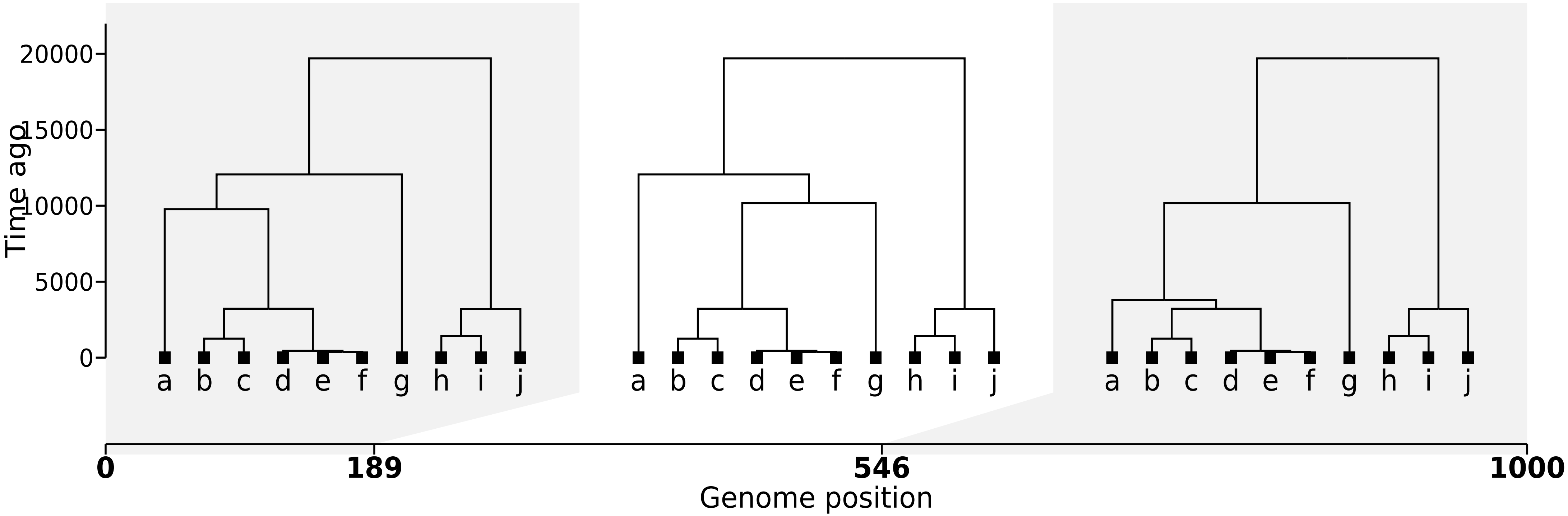
Overview

The full probabilistic process is complicated

In this work, we condition on the realized ARG, resulting a sequence of local trees



From tskit docs

Overview

What is the conditional distribution of a trait given the trees?

Since the genealogy is fixed, the only randomness that remains is mutation

$$\text{Trait} \mid \text{Local trees} \quad \sim \quad ?$$

Linear mixed model

Linear mixed model

Linear mixed models are popular in quantitative genetics

$$\mathbf{y} = \underbrace{\mathbf{Z}\mathbf{u}}_{\text{random effects}} + \underbrace{\mathbf{X}\mathbf{b}}_{\text{fixed effects}} + \boldsymbol{\varepsilon}$$

where $\mathbf{Z}$ includes genotyped variants and $\mathbf{X}$ is the covariate matrix

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We answer these questions from a genealogical perspective

Setup and derivation

Setup and derivation

The trait $\mathbf{y}$ is a linear function of the genotype $\mathbf{G}$

$$\mathbf{y} = \mathbf{G}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$$

$\mathbf{y} \in \mathbb{R}^N, \mathbf{G} \in \mathbb{R}^{N \times P}, \boldsymbol{\beta} \in \mathbb{R}^P$, and $\boldsymbol{\varepsilon} \in \mathbb{R}^N$

$\mathbf{G}$ contains *all* positions the genome including genotyped ones

N: number of samples, P: length of the genome

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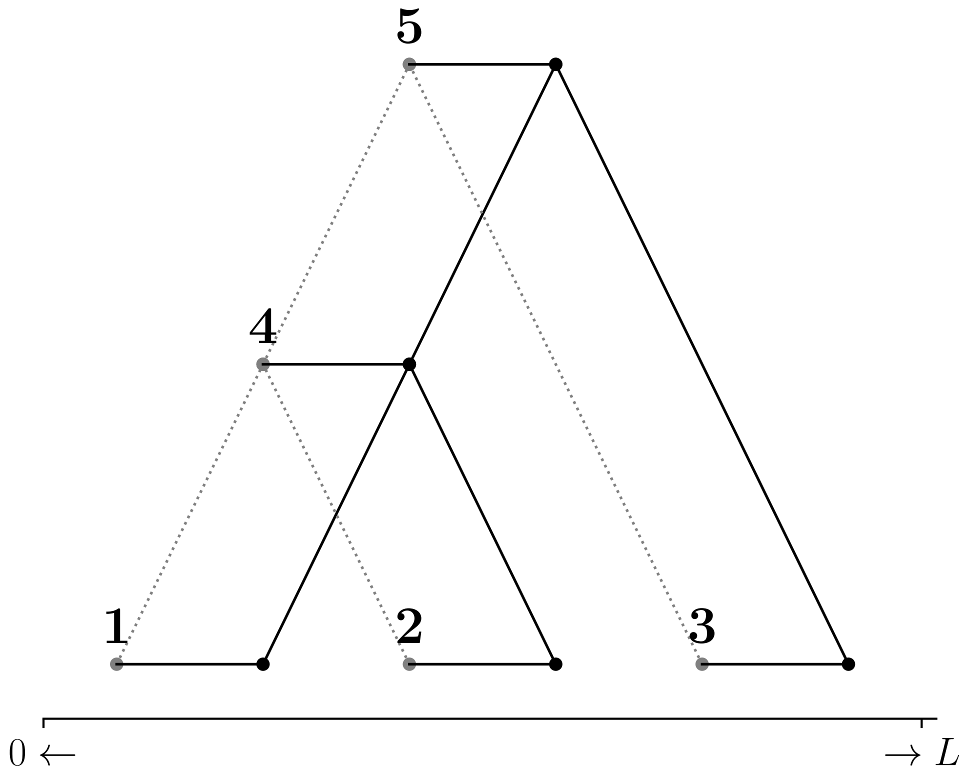
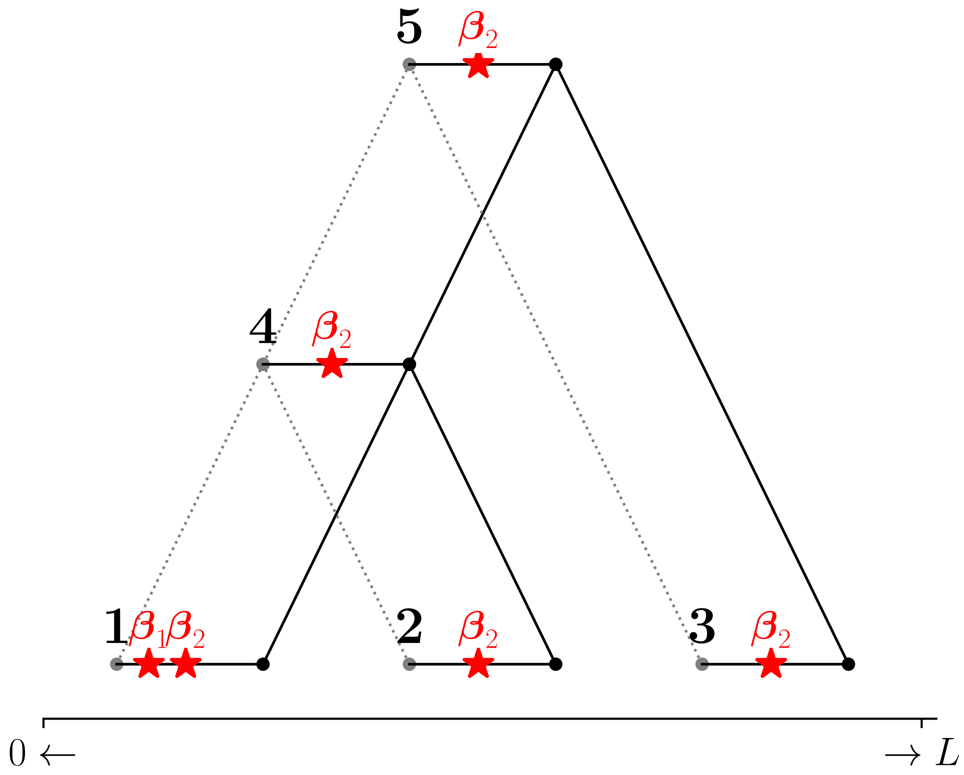


Consider a local tree that spans over a region

We get trait values by adding up effect sizes (β)

How do we get traits?

$$\mathbf{y}_1 = \boldsymbol{\beta}_1 + \boldsymbol{\beta}_2,\ \mathbf{y}_2 = \boldsymbol{\beta}_2,\ \mathbf{y}_3 = \boldsymbol{\beta}_2$$



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- $\mathbf{y}_n = \mathbf{G}_{n1}\boldsymbol{\beta}_1 + \mathbf{G}_{n2}\boldsymbol{\beta}_2$

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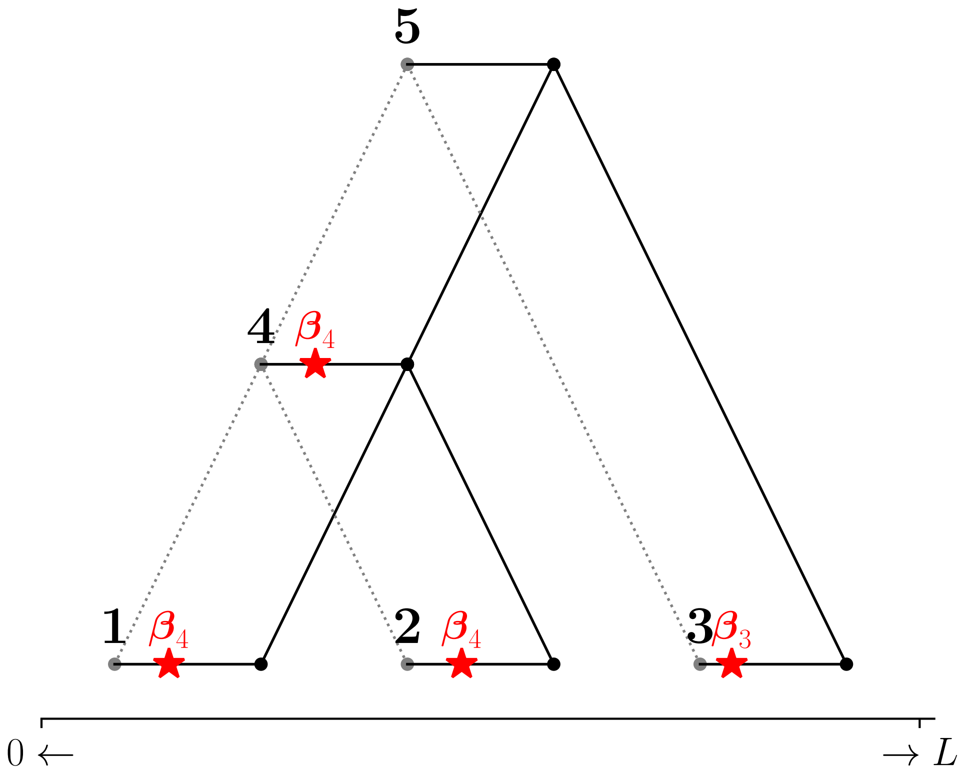
$$\mathbf{y}_1 = \boldsymbol{\beta}_4,\ \mathbf{y}_2 = \boldsymbol{\beta}_4,\ \mathbf{y}_3 = \boldsymbol{\beta}_3$$



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- $\mathbf{y}_n = \mathbf{G}_{n3}\boldsymbol{\beta}_3 + \mathbf{G}_{n4}\boldsymbol{\beta}_4$

Branch-centric view of trait transmission

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Inherit a branch first, then a mutation

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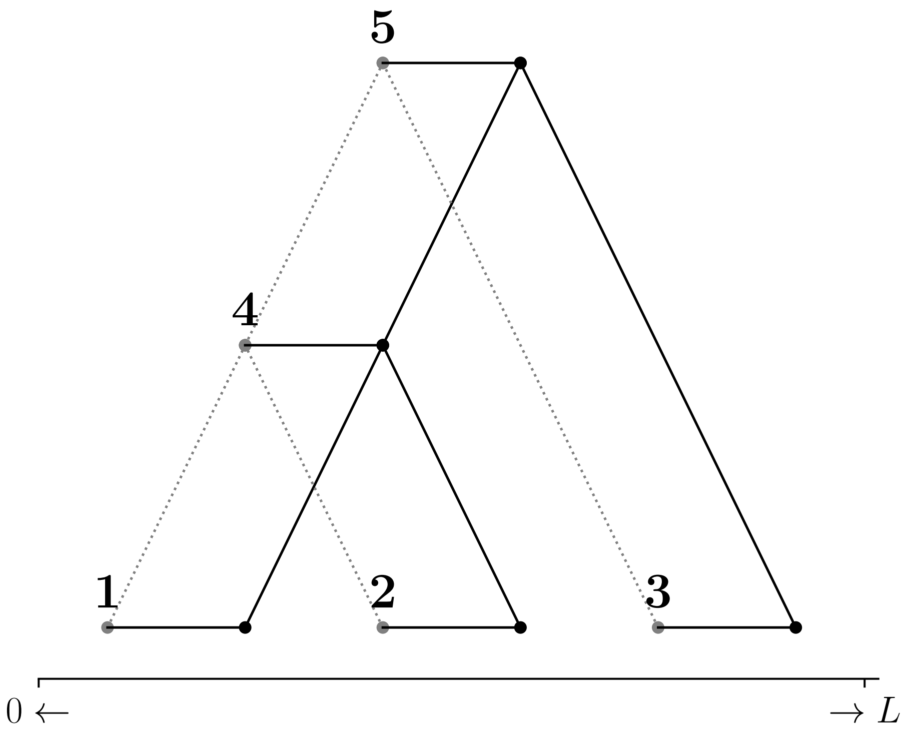

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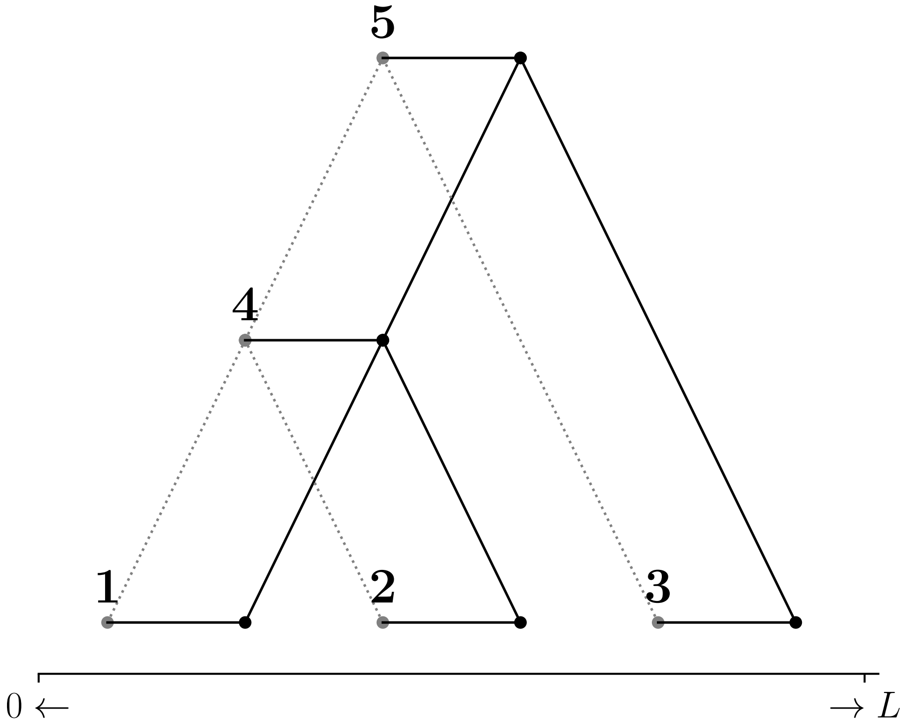

Inherit a branch first, then a mutation

- Sample 1 inherits edges $1 - 4$ and $4 - 5$

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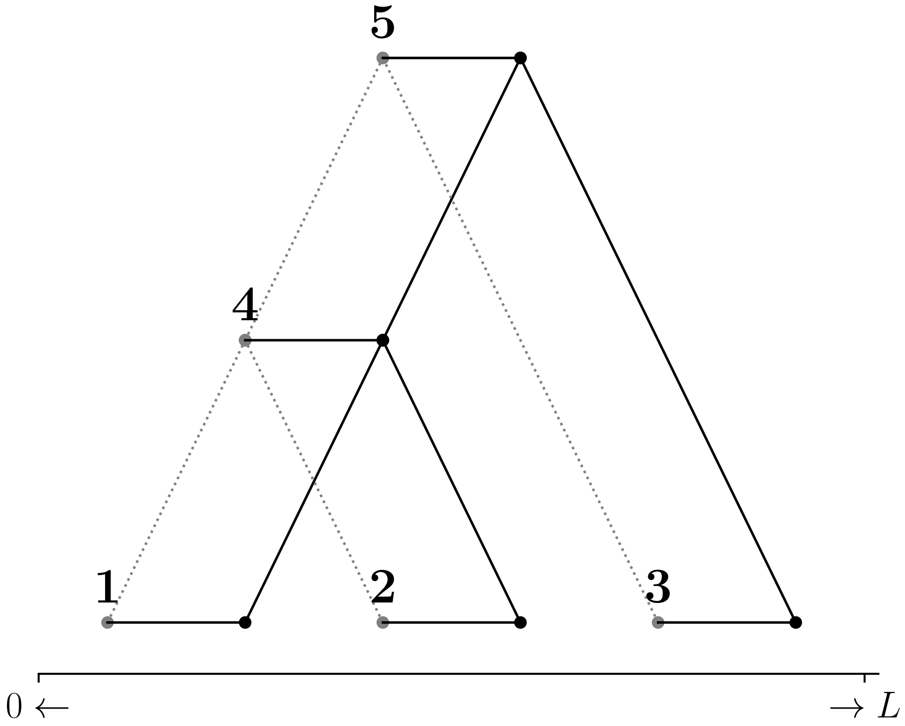

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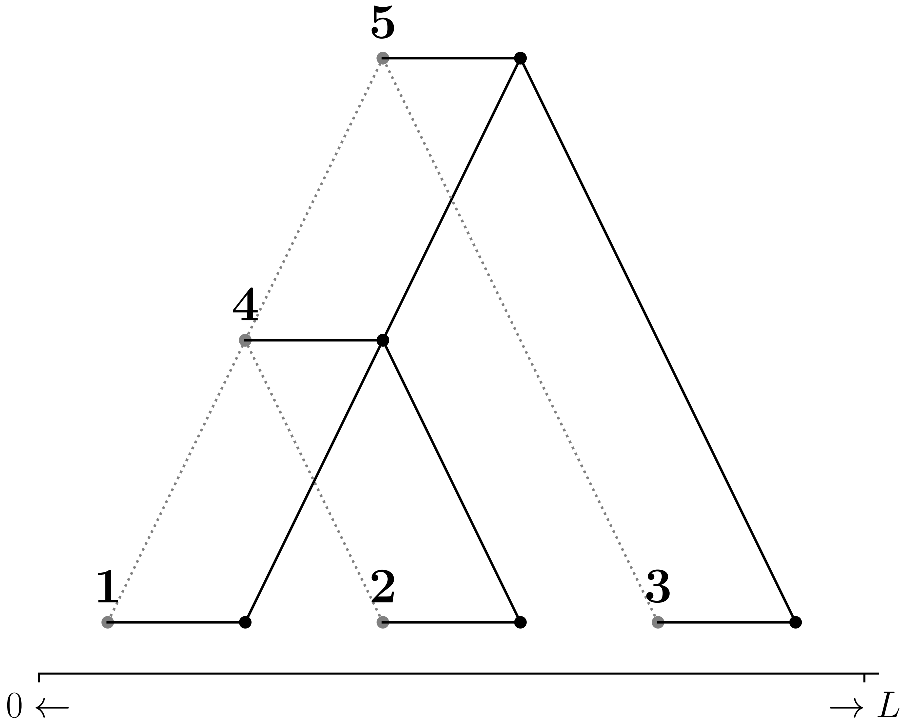

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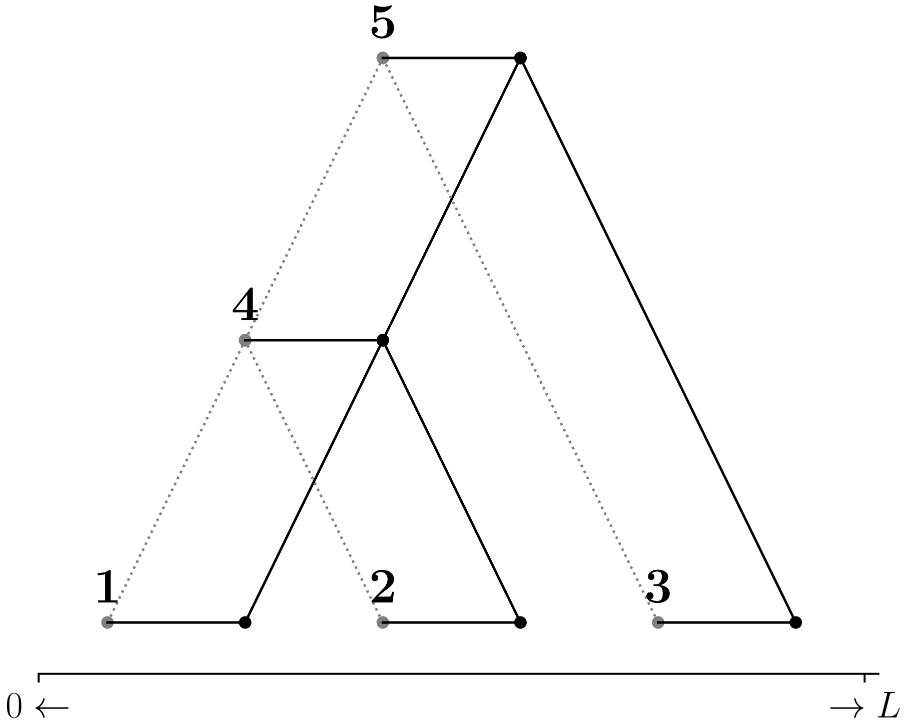

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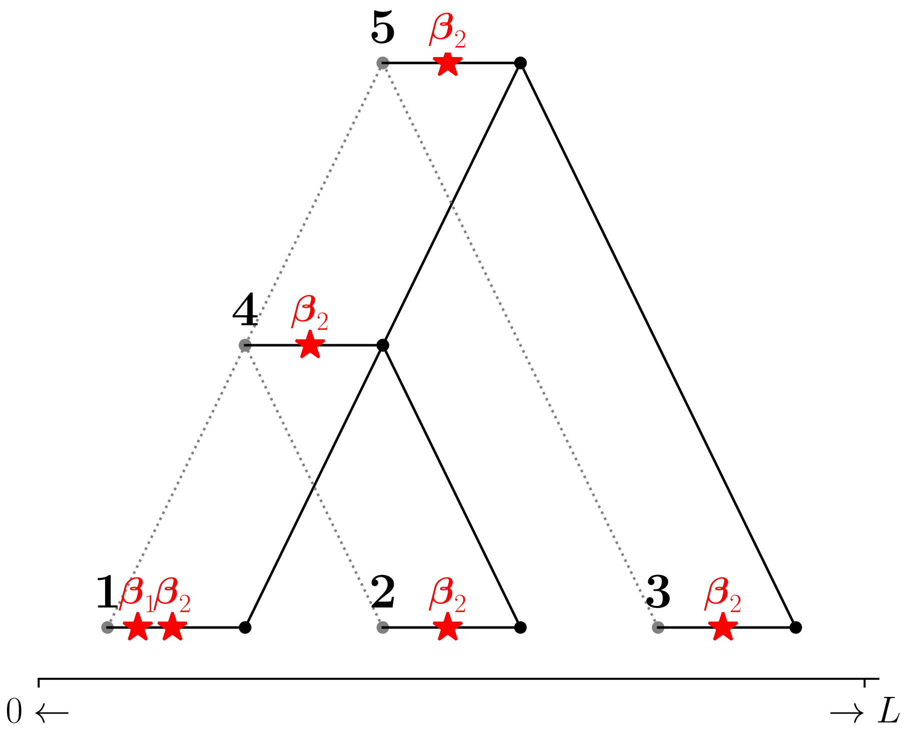

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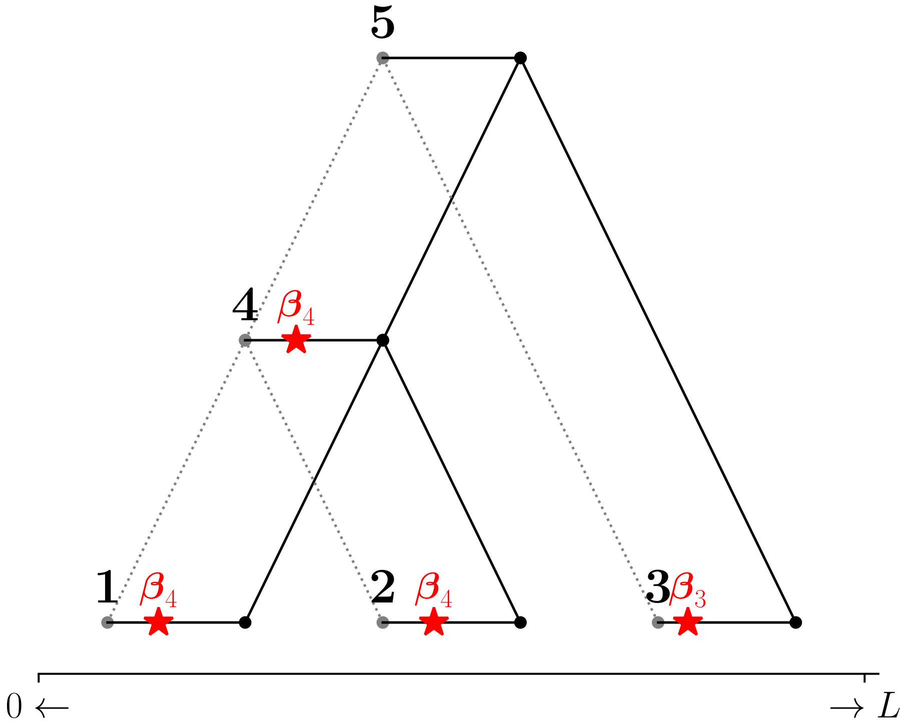

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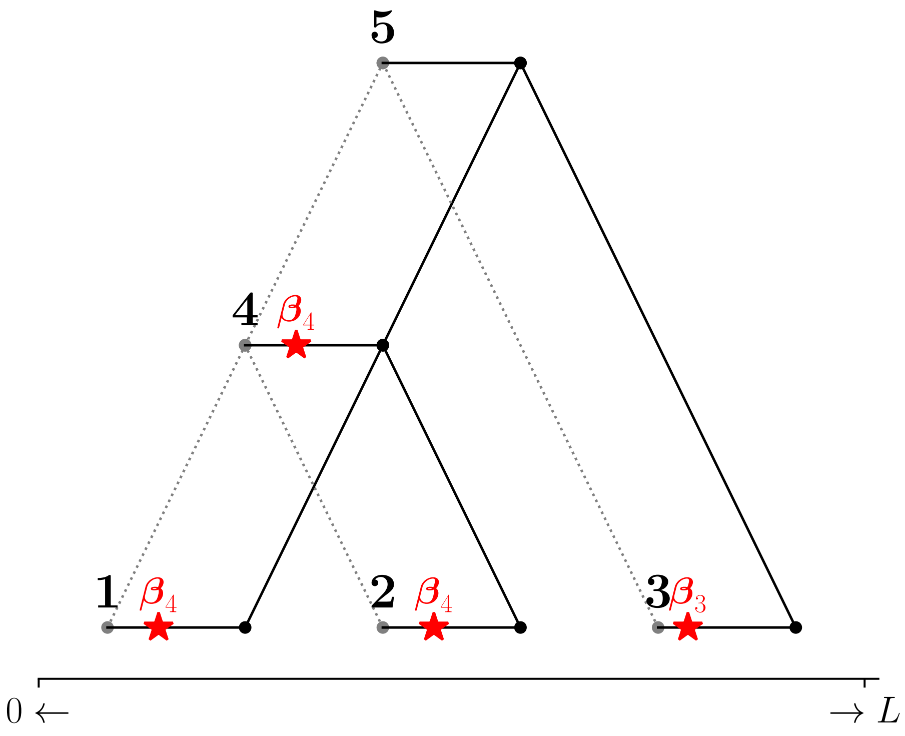

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Branch effect is a random variable!

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$$\mathbf{y} = \sum_p \mathbf{G}_p \boldsymbol{\beta}_p + \boldsymbol{\varepsilon} \quad \Rightarrow \quad \mathbf{y} = \sum_e \mathbf{Z}_e \boldsymbol{\upsilon}_e + \boldsymbol{\varepsilon}$$

where $\mathbf{Z}_{ne} =$ the number of haplotypes of n that inherit e

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- We start from more lower-level evolutionary statements to recover mixed model assumptions
- Independent random effects, random effect weights, normality, . . .

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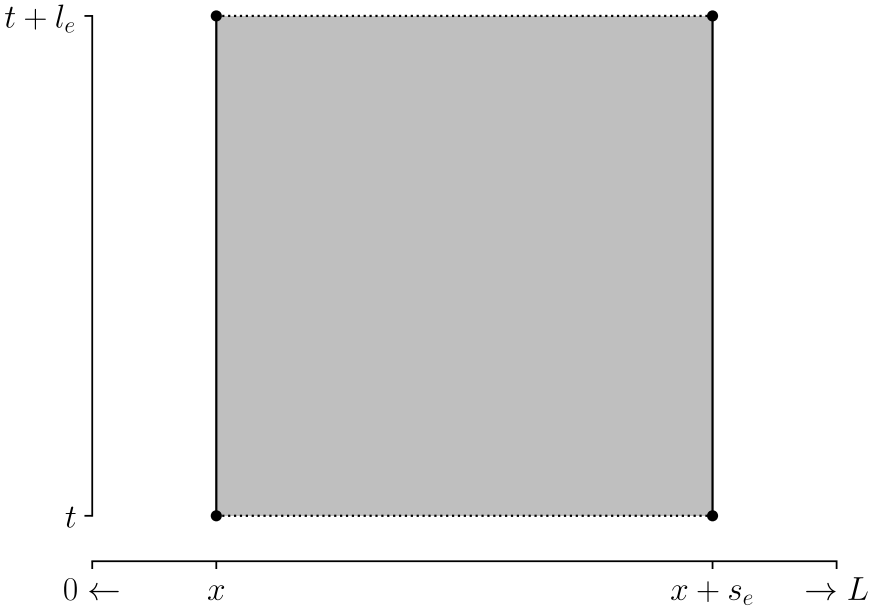
l_e : length in time $\quad$ s_e : span in base pairs



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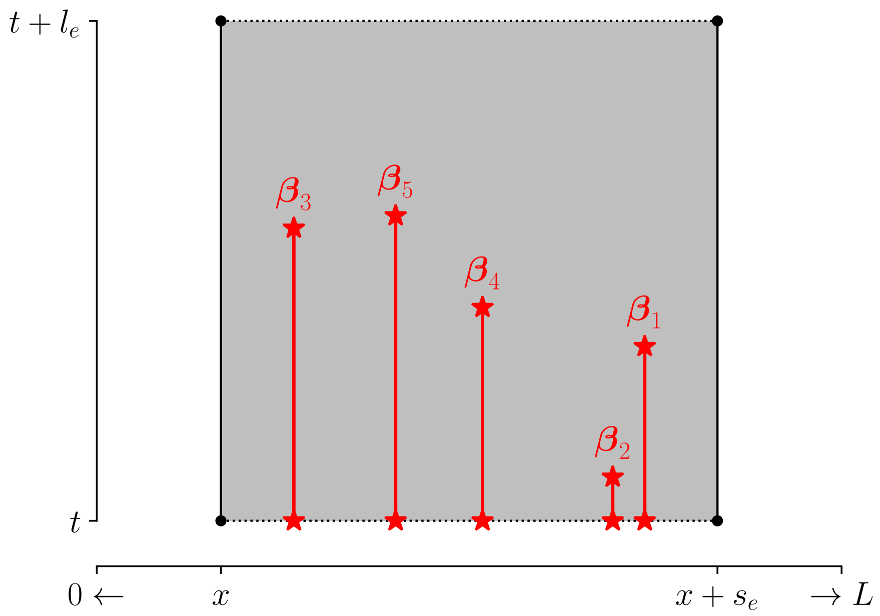

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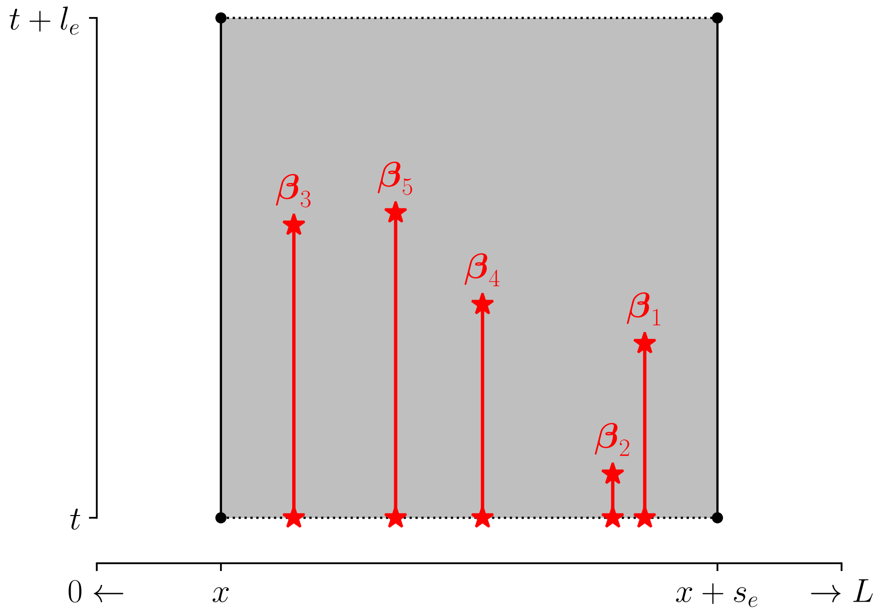

$$\mathrm{Var}(\mathbf{u}_e) \quad \propto \quad \text{Number of mutations} \quad \propto \quad \text{Area} = l_e s_e$$

Complex traits through the lens of ARG-LMM

What does ARG-LMM tell us about complex trait analysis?

Genetic value covariance

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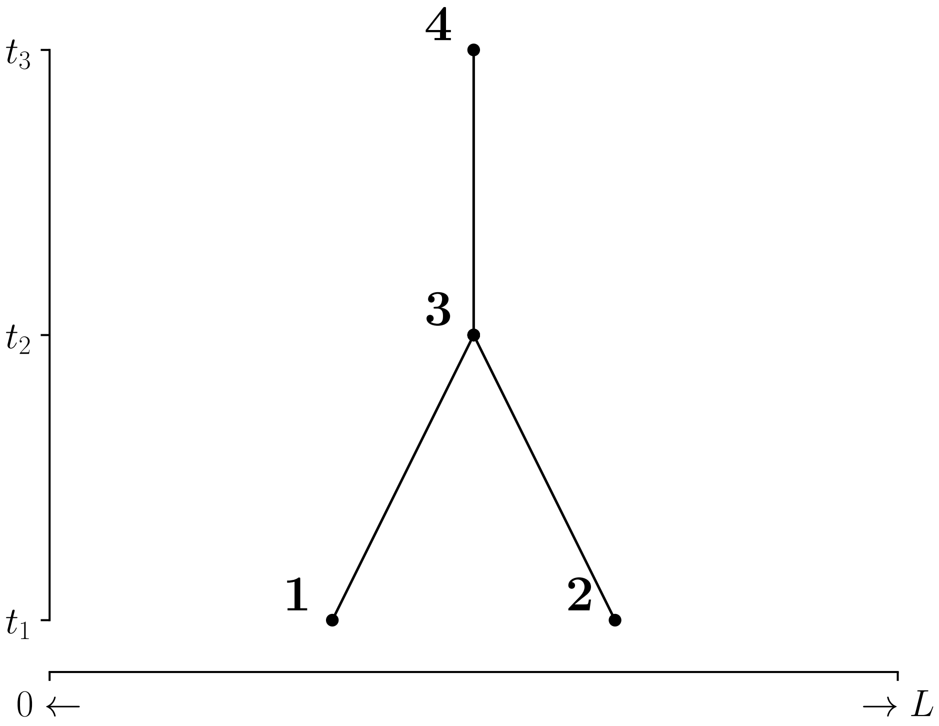
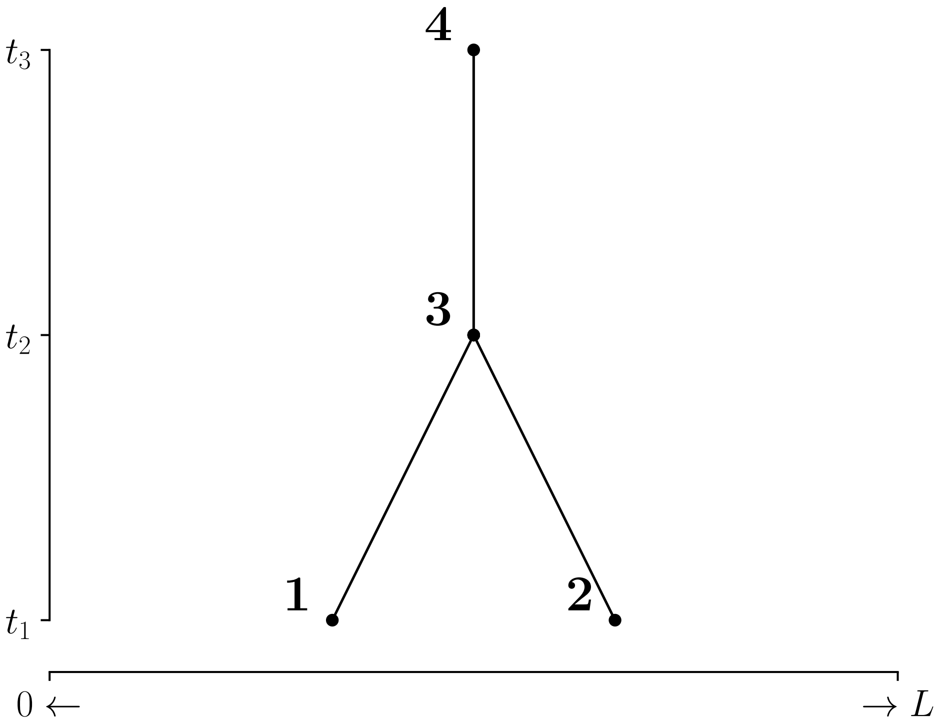
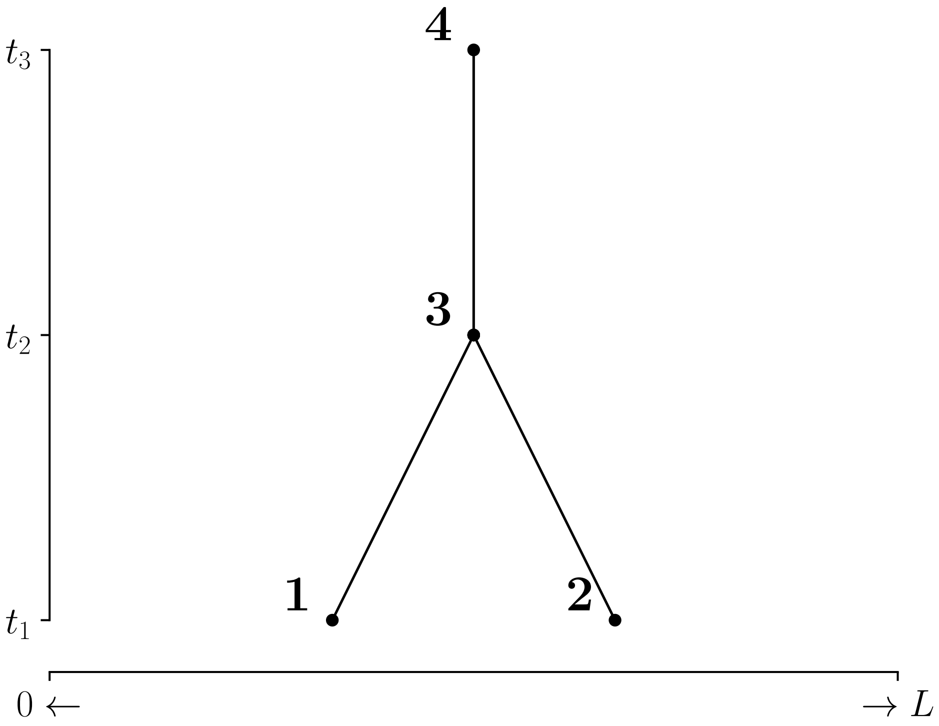


Genetic value covariance



$$\mathbf{y}_1 = \mathbf{u}_{13} + \mathbf{u}_{34} \quad \text{and} \quad \mathbf{y}_2 = \mathbf{u}_{23} + \mathbf{u}_{34}$$

Genetic value covariance



$$\mathrm{Cov}(\mathbf{y}_1, \mathbf{y}_2) = \mathrm{Cov}(\mathbf{u}_{13} + \mathbf{u}_{34}, \mathbf{u}_{23} + \mathbf{u}_{34}) = \mathrm{Cov}(\mathbf{u}_{34}, \mathbf{u}_{34}) = \mathrm{Var}(\mathbf{u}_{34}) \propto t_3 - t_2$$

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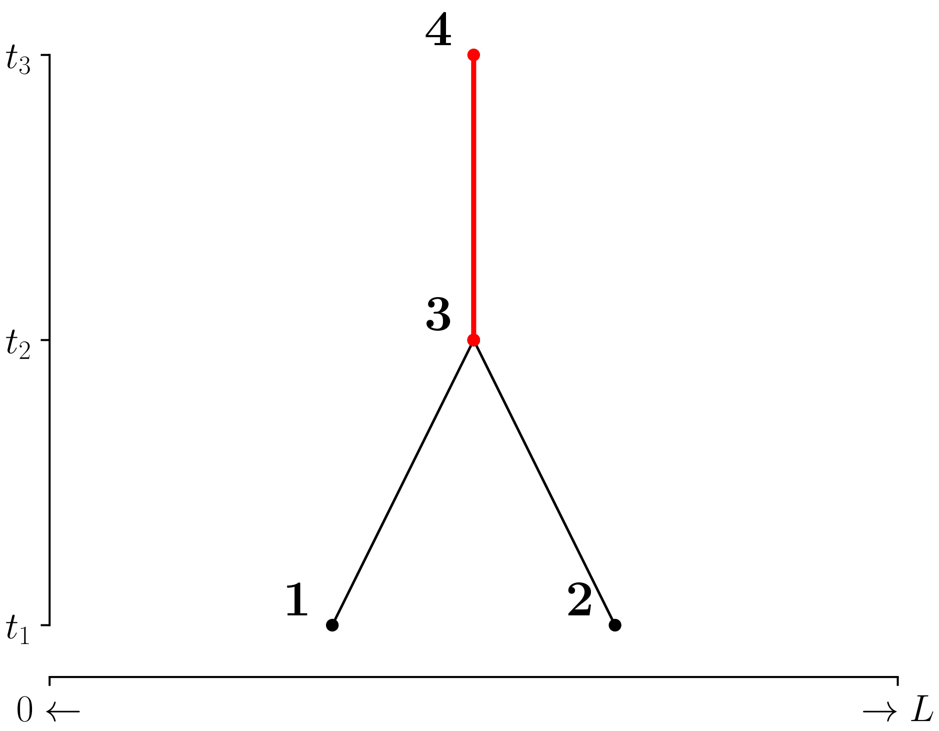

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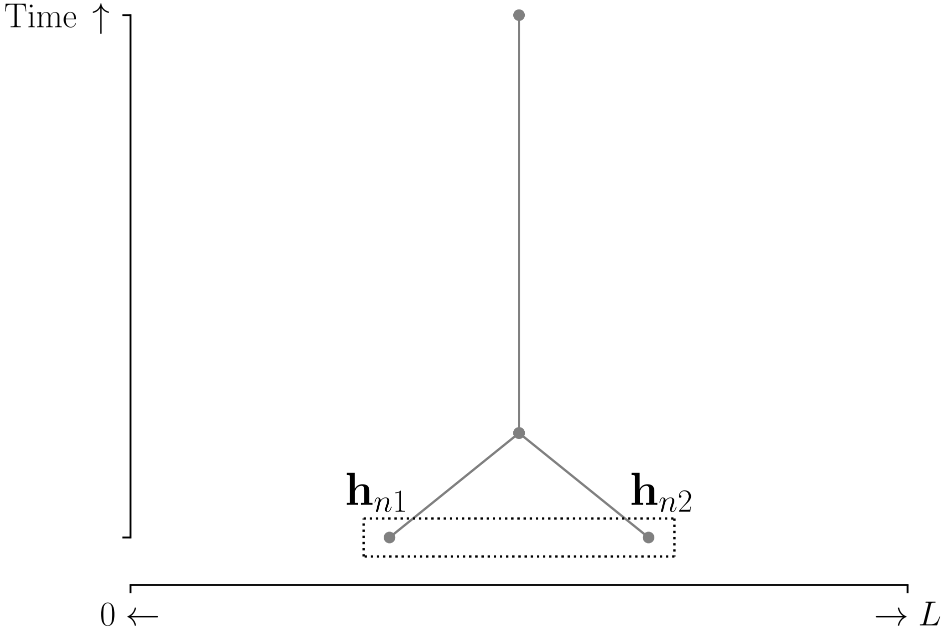
$$\text{Heritability: } h_g^2 = \frac{\mathrm{Var}(\mathbf{g}_n)}{\mathrm{Var}(\mathbf{y}_n)} = \frac{\mathrm{Var}(\mathbf{g}_n)}{\mathrm{Var}(\mathbf{g}_n) + \mathrm{Var}(\boldsymbol{\varepsilon}_n)}$$

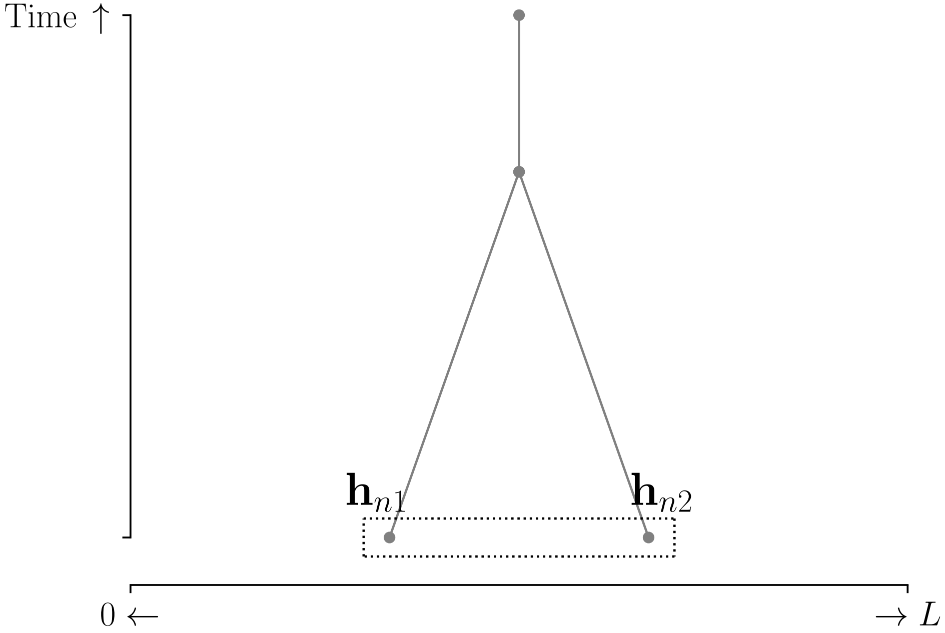
This applies to all individuals $n \in \{1, \ldots, N\}$

Heritability is *ill*-defined in ARG-LMM

However, all individuals have a different amount of genetic variance (except haploids)

$$\mathrm{Var}(\mathbf{g}_n) = \mathrm{Var}(\mathbf{h}_{n1} + \mathbf{h}_{n2}) = \mathrm{Var}(\mathbf{h}_{n1}) + \mathrm{Var}(\mathbf{h}_{n2}) + 2\mathrm{Cov}(\mathbf{h}_{n1}, \mathbf{h}_{n2})$$





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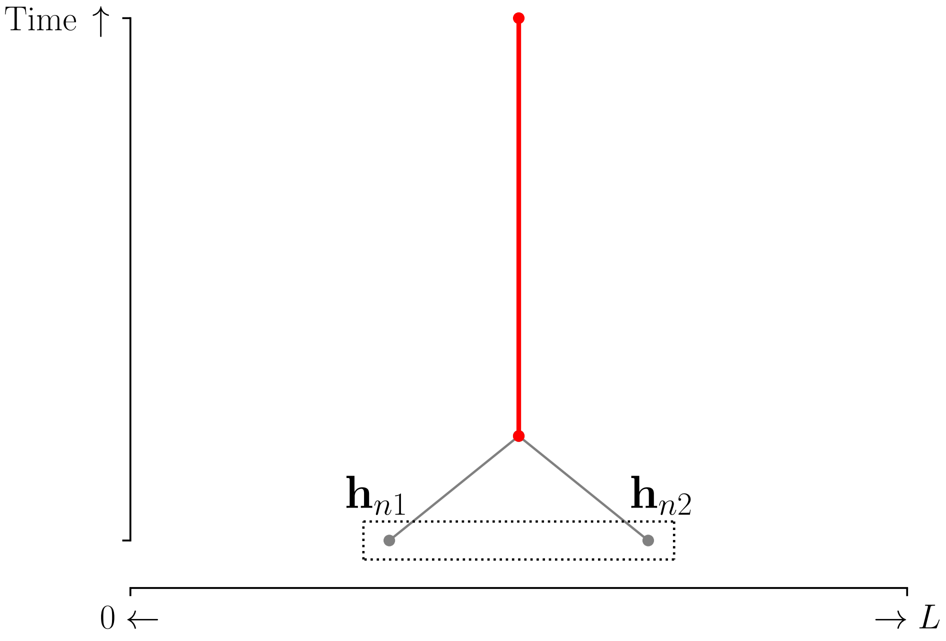
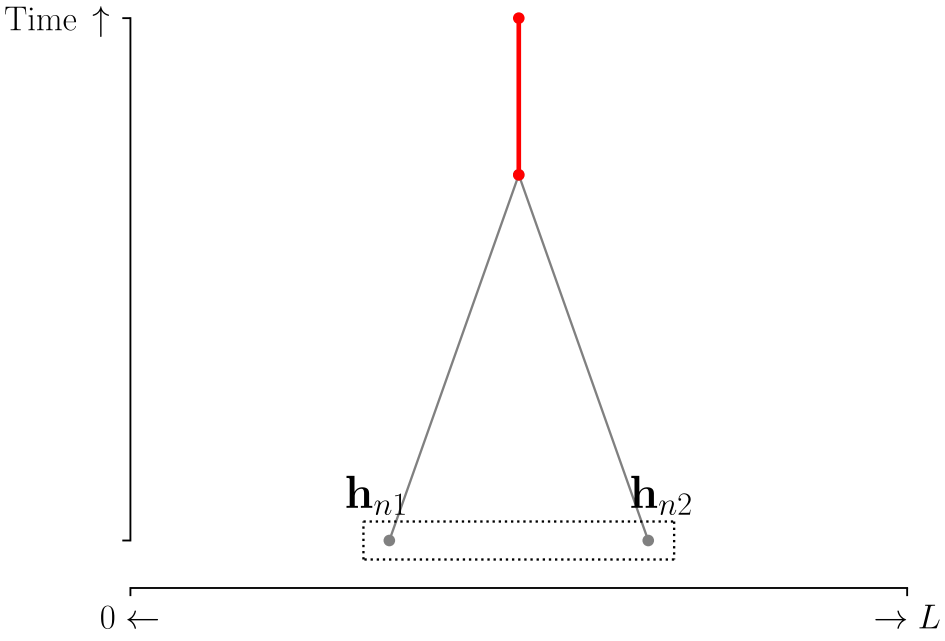
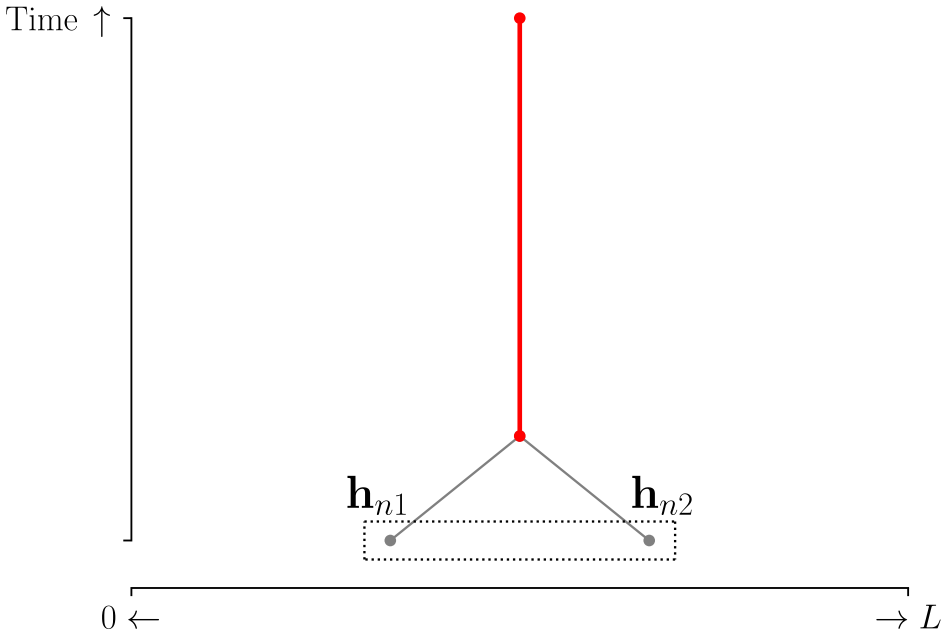
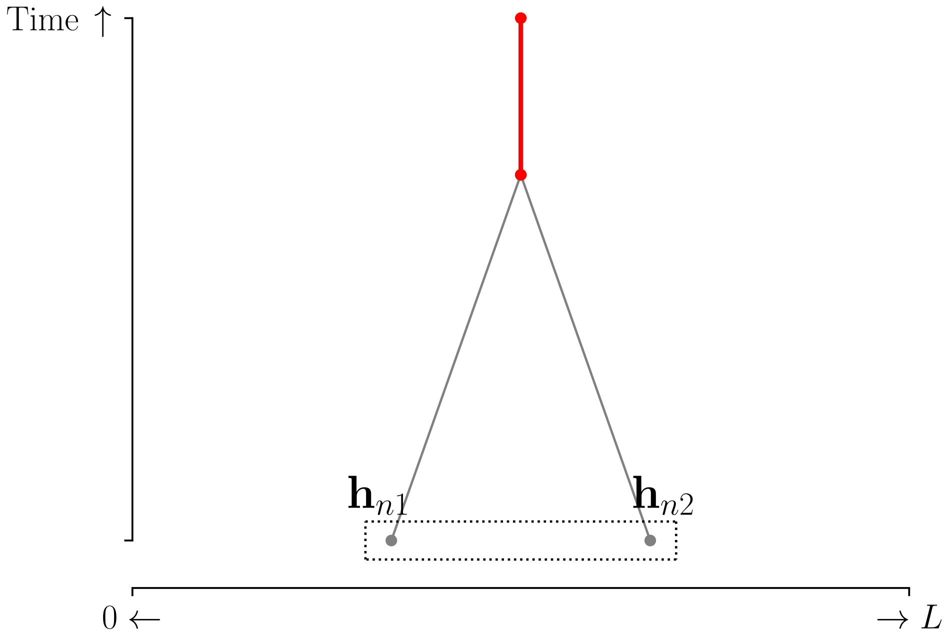




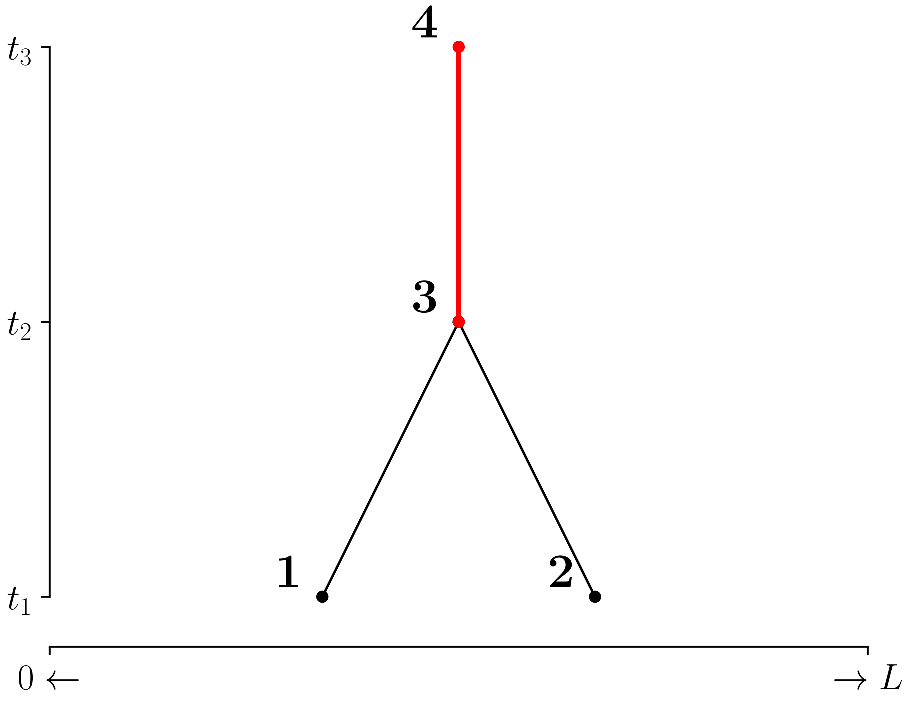
Heritability is *ill*-defined in ARG-LMM

We can’t define a single quantitity $h_g^2 = \frac{\mathrm{Var}(\mathbf{g}_n)}{\mathrm{Var}(\mathbf{g}_n)+\mathrm{Var}(\boldsymbol{\varepsilon}_n)}$ for everyone





Polygenic prediction is constrained by demography



Demographic model from (Browning et al. 2018)

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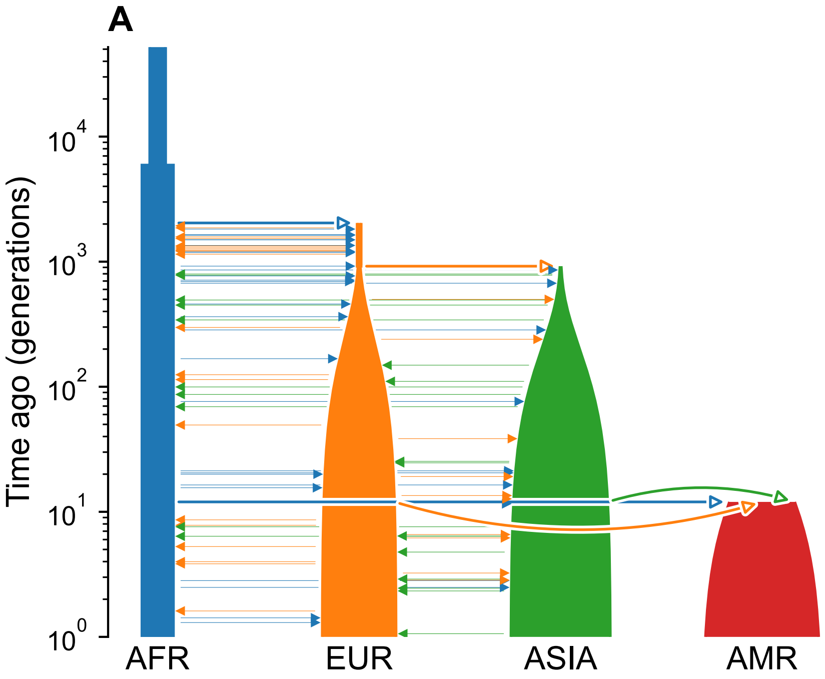

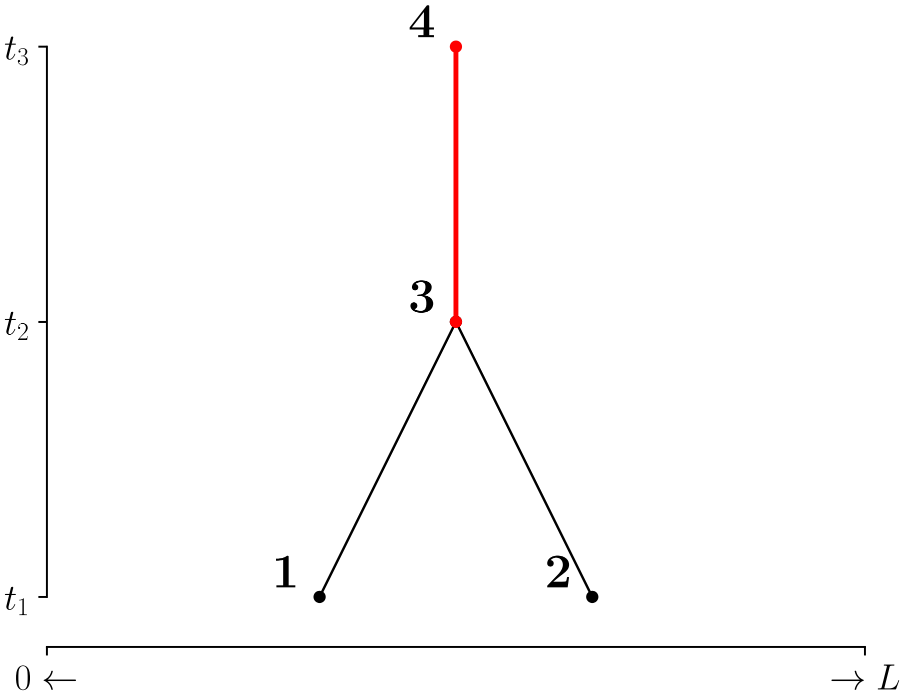

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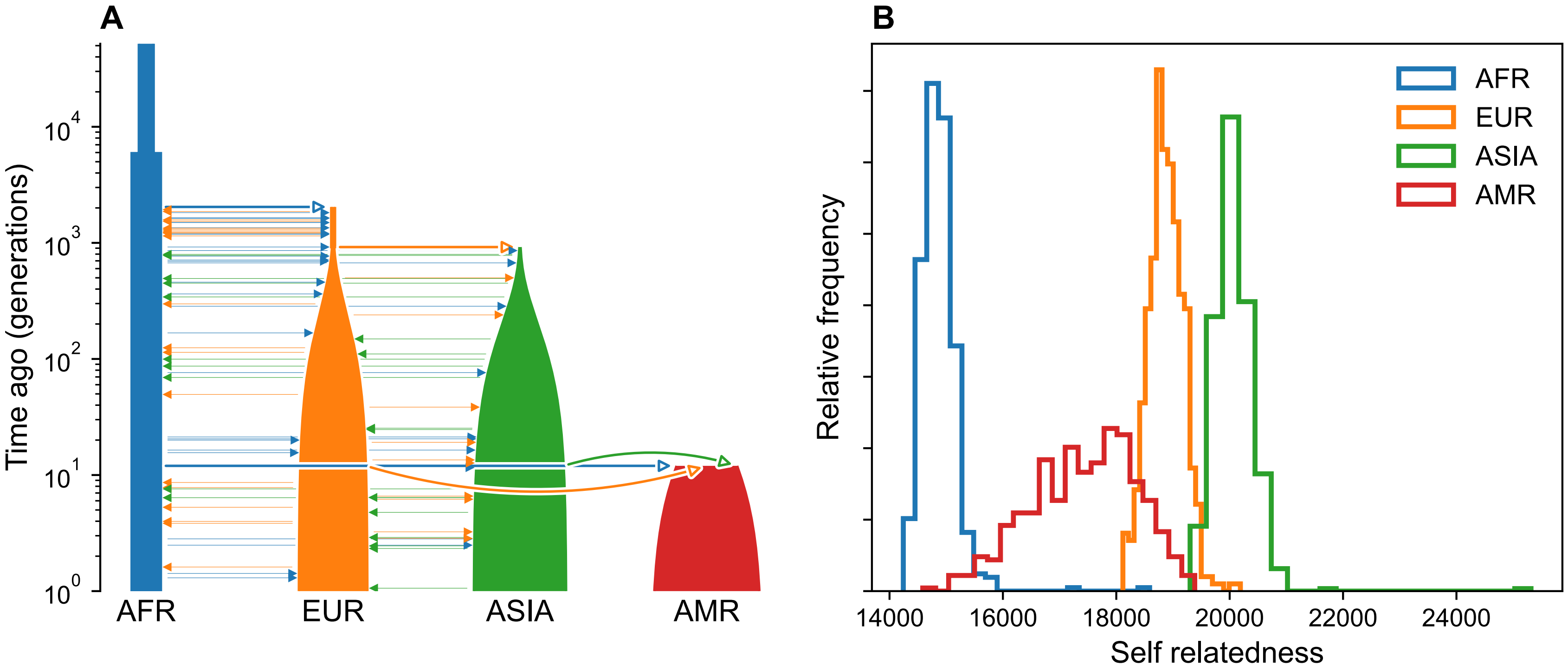

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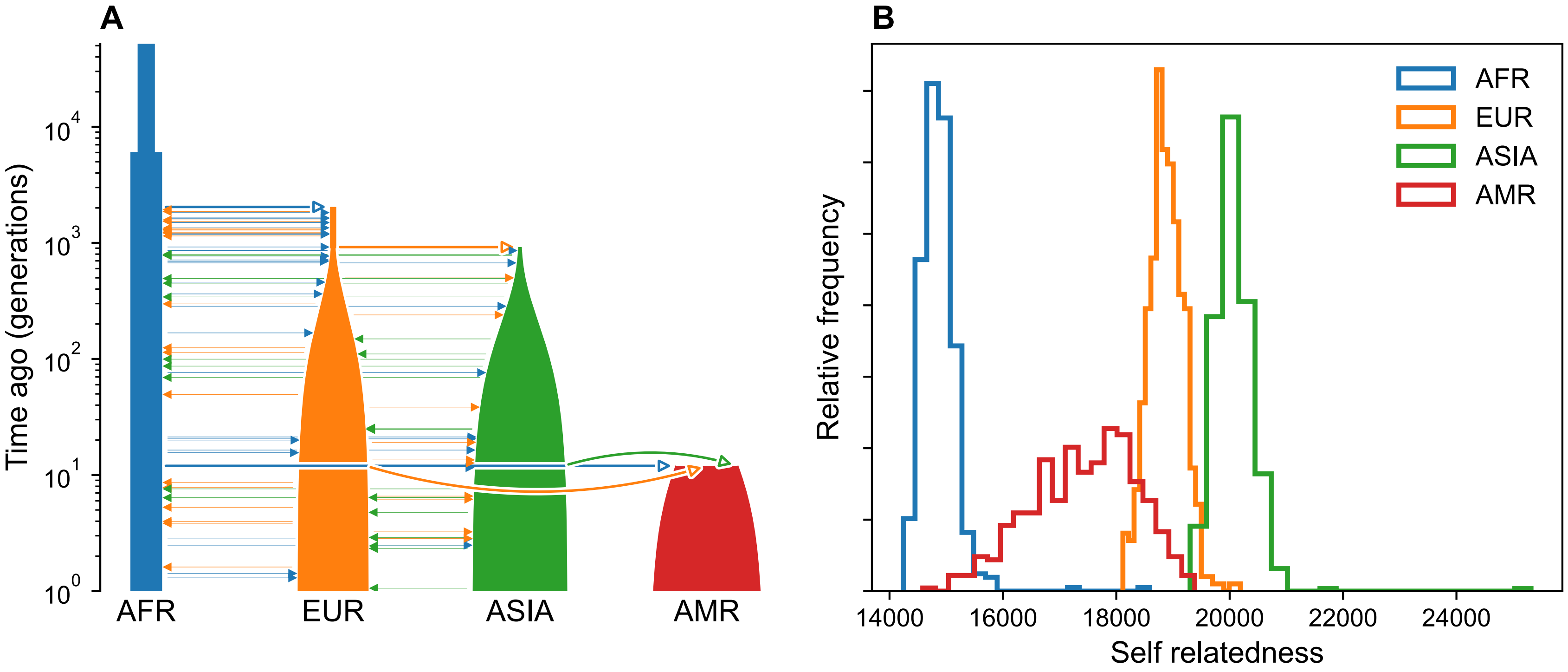

Some people are less genetically variable than others

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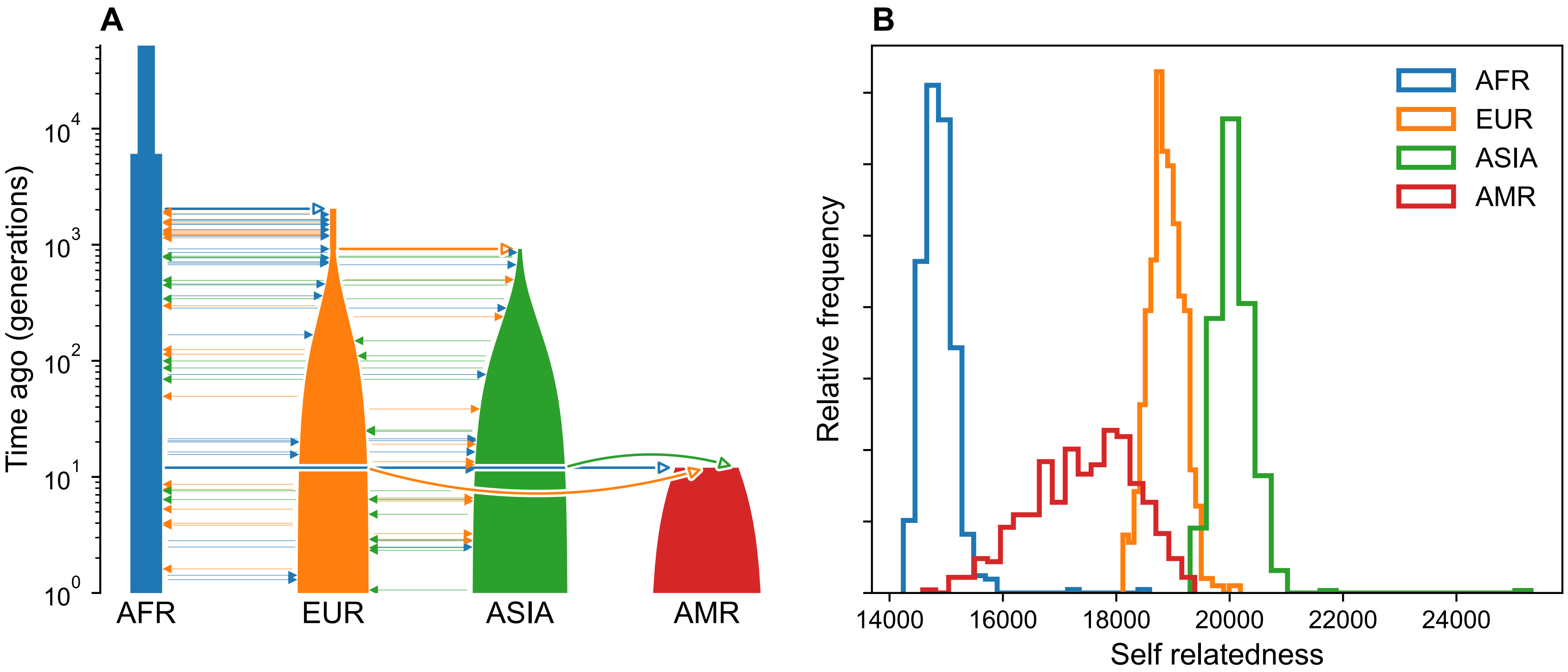

Some people are harder to predict genetically than others

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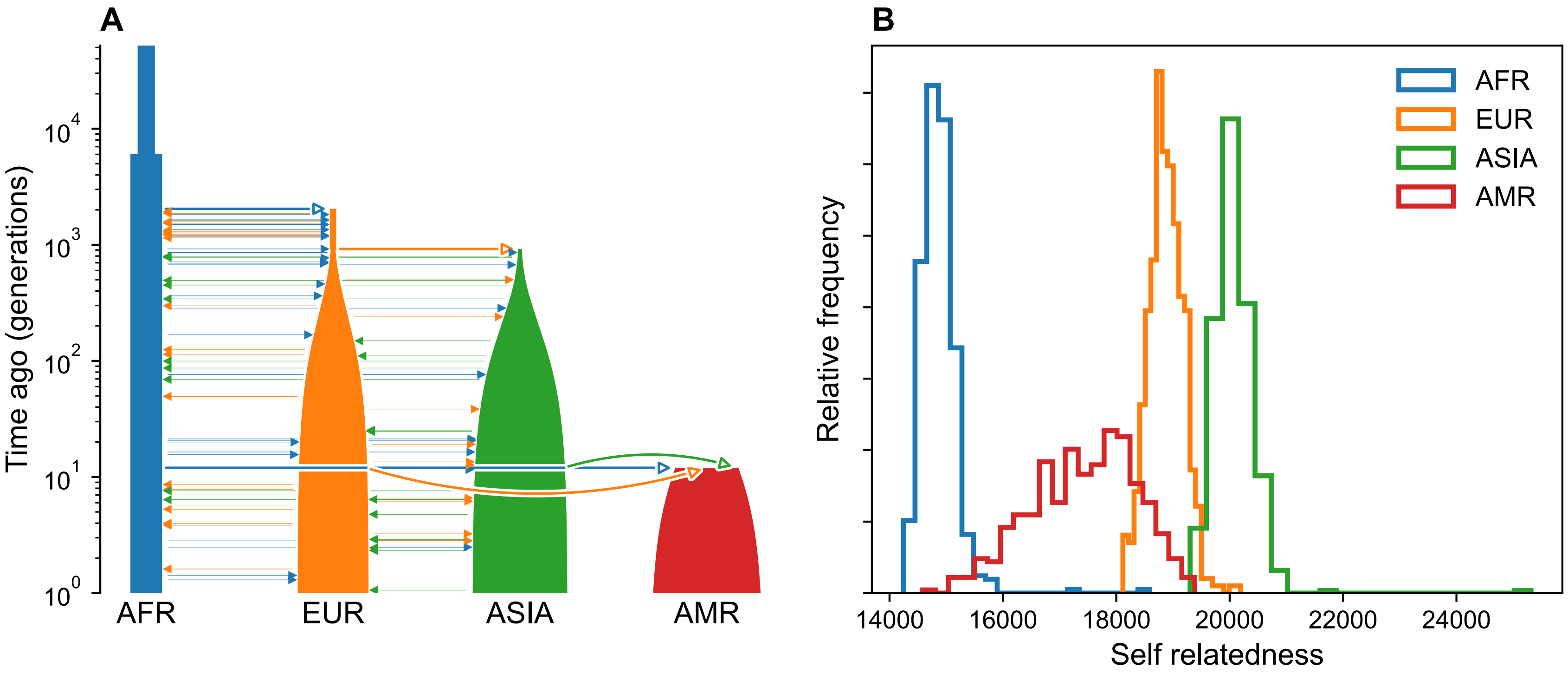

Some populations are inherently harder to predict!

Demographic model from (Browning et al. 2018)

tslmm, fitting ARG-LMM to tree sequences

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tslmm utilizes an efficient *genetic relatedness matrix - vector product* to fit the restricted maximum likelihood (REML) objective

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It can estimate variance components and compute polygenic scores by best linear unbiased prediction (BLUP)

The matrix-vector product algorithm

Modified figures by Nathaniel Pope (Oregon)

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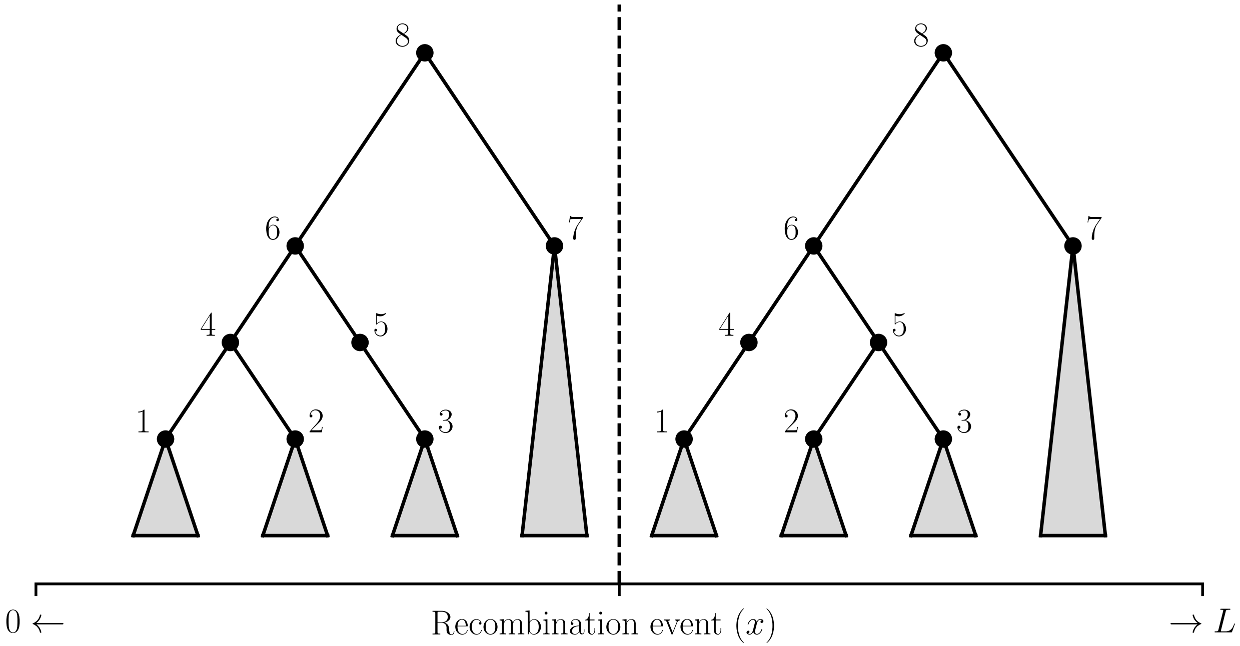
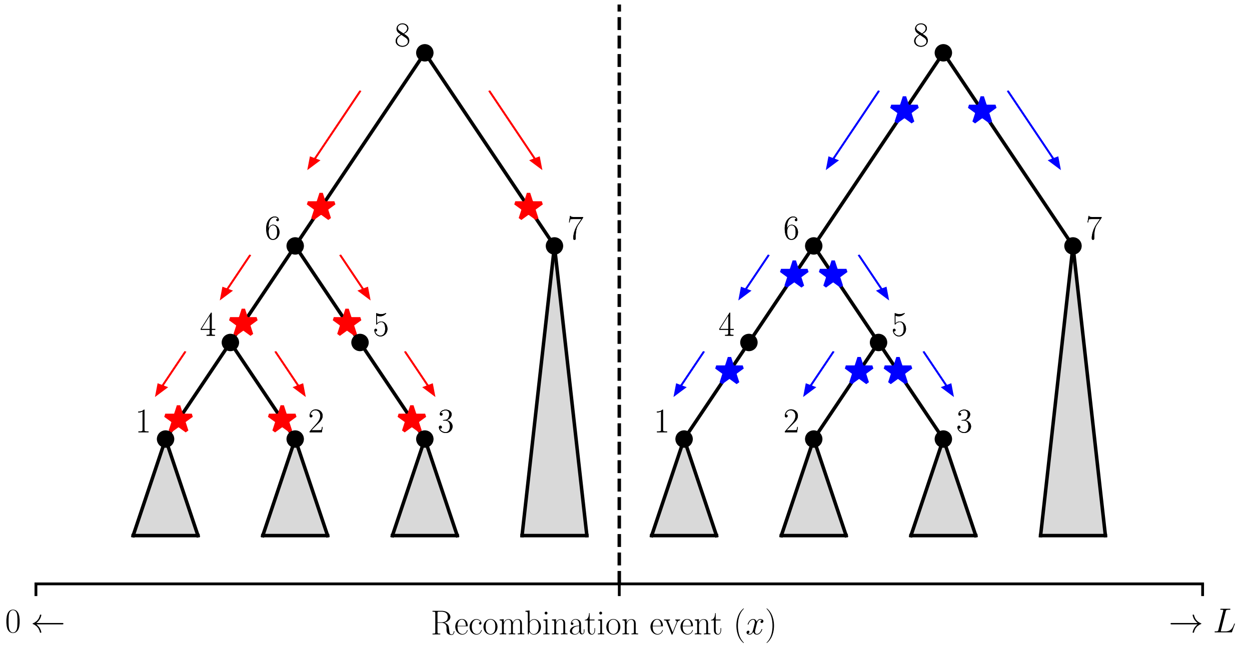


The algorithm needs to pass mutations to the correct samples

Modified figures by Nathaniel Pope (Oregon)

The matrix-vector product algorithm



A naive approach is to push the mutations down to the leaves every time

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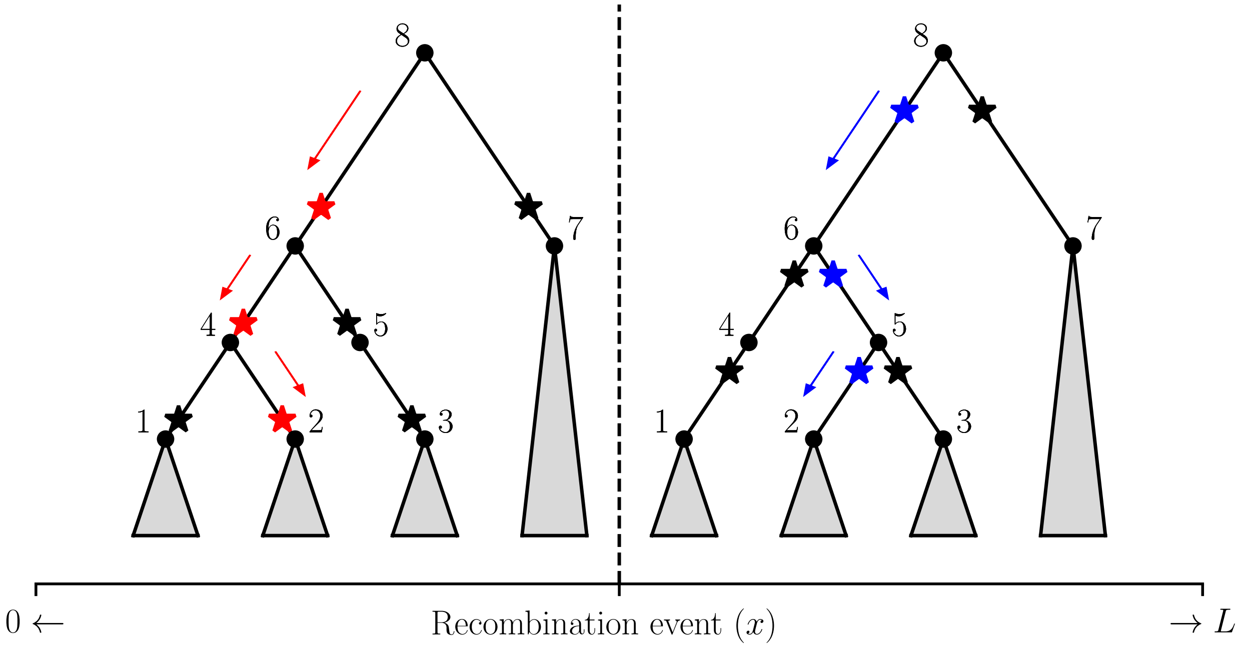

Wait until the subtree's topology changes due to edge insertion/deletion

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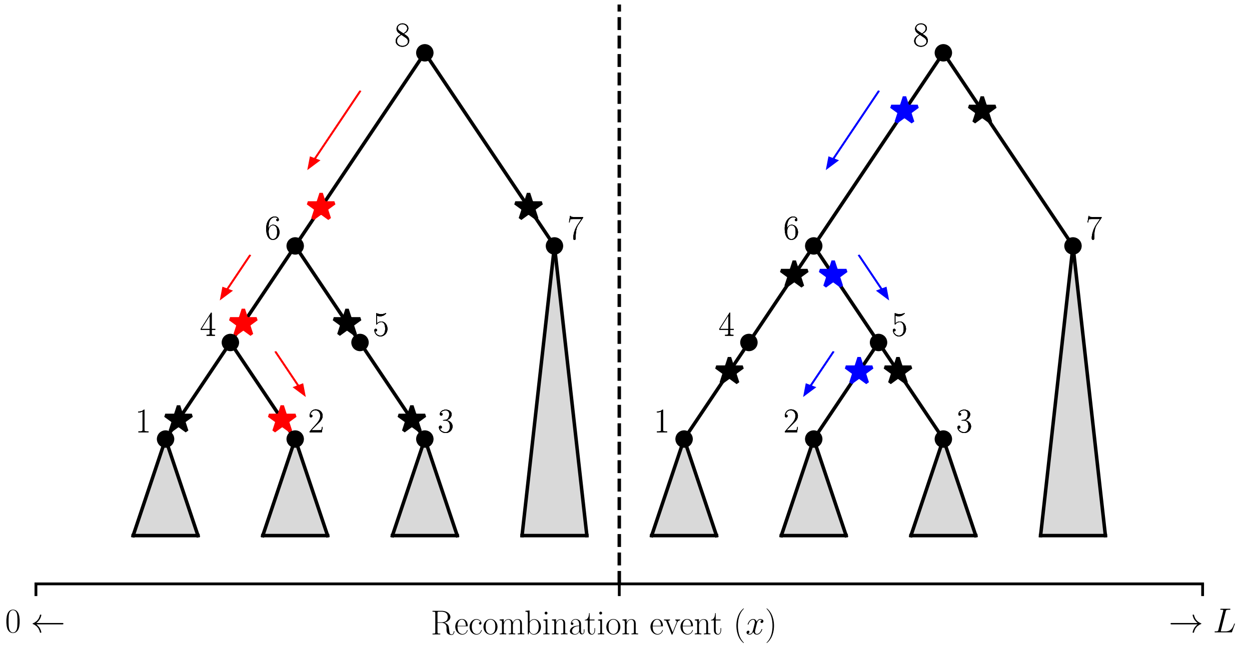

The wrong recipient will receive the mutations if we procrastinate further

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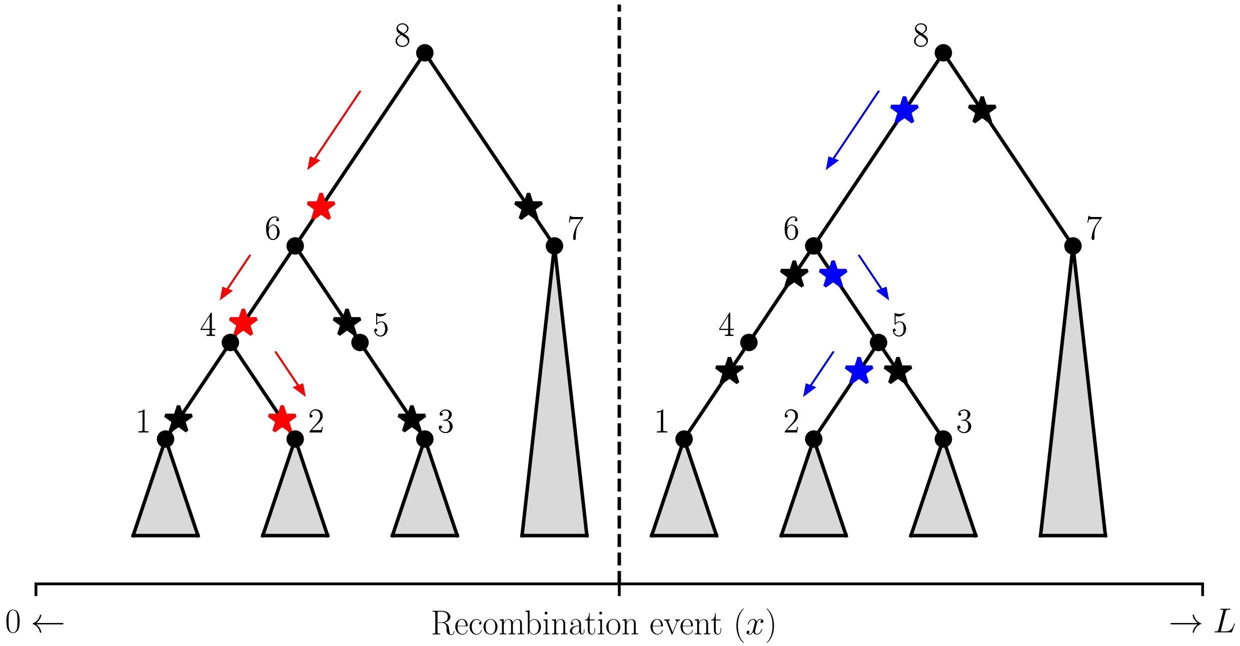

Fitting REML $\mathcal{O}(n_s^3) \;\Rightarrow\; \mathcal{O}(n_s + n_t \log n_s)$

n_s: number of samples, n_t: number of trees

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Runtime for variance component estimation

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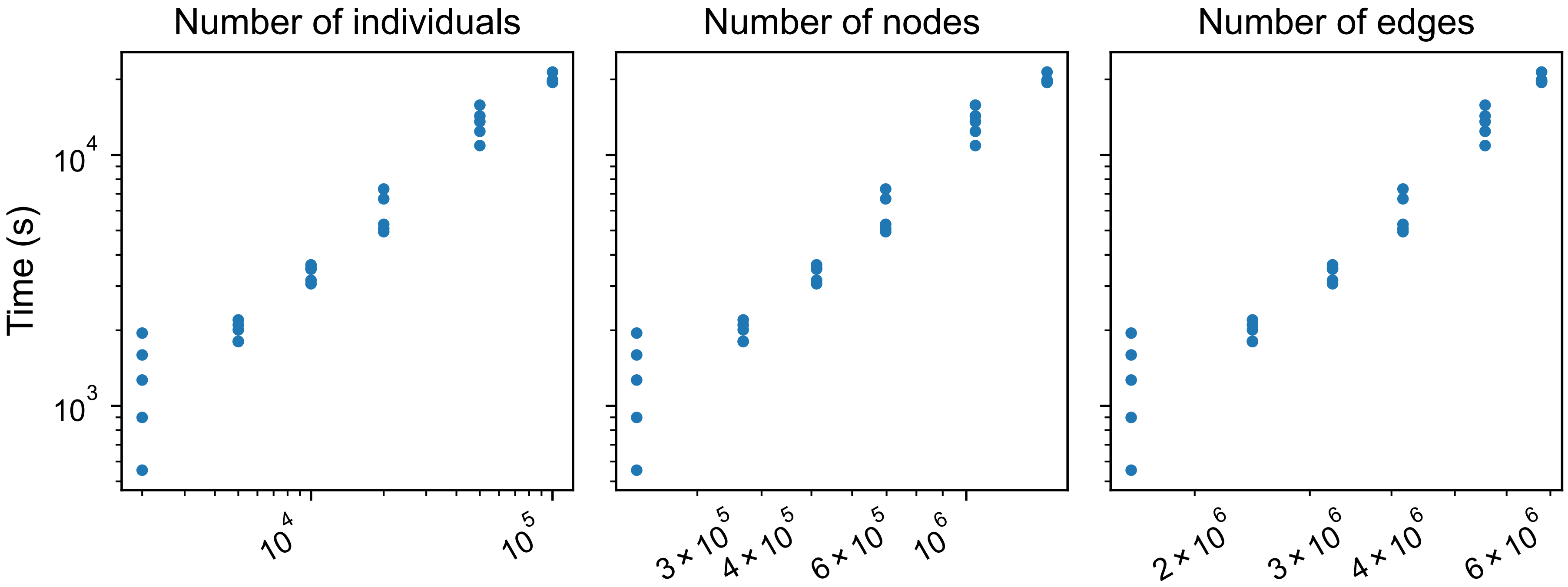

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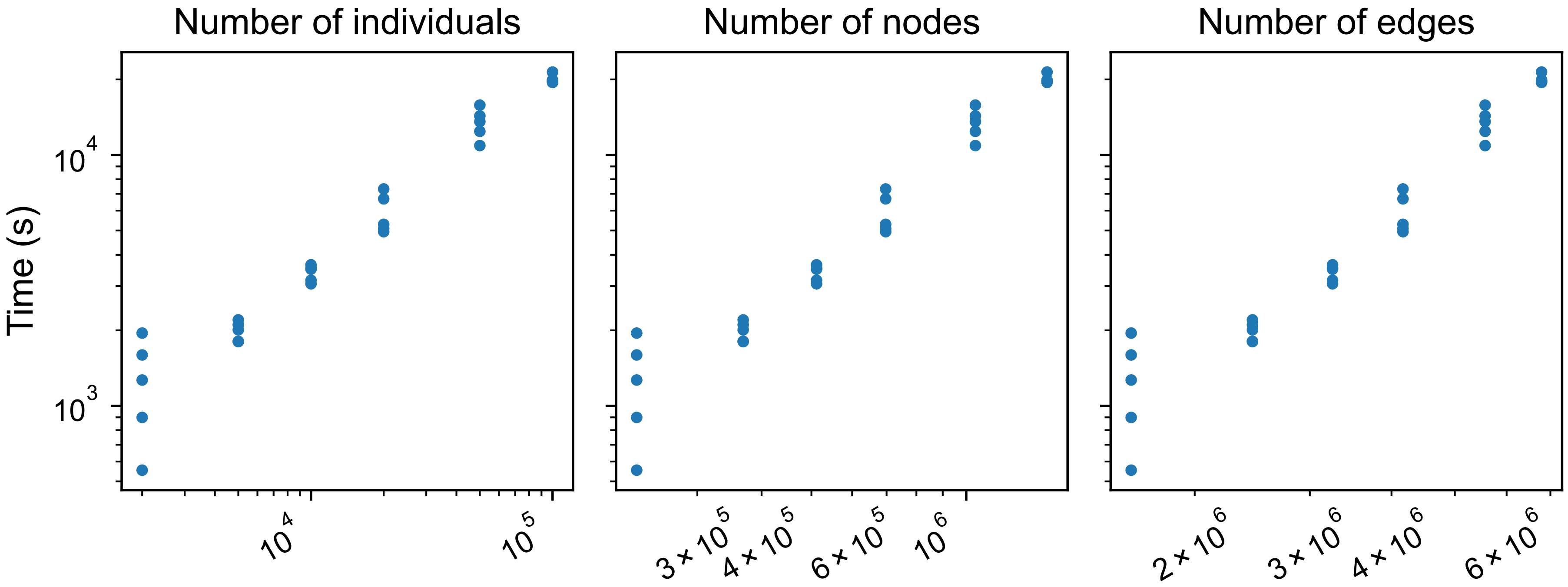

The runtime scales linearly with respect to the number of individuals (genome length = 10^8)

Best linear unbiased prediction (BLUP)

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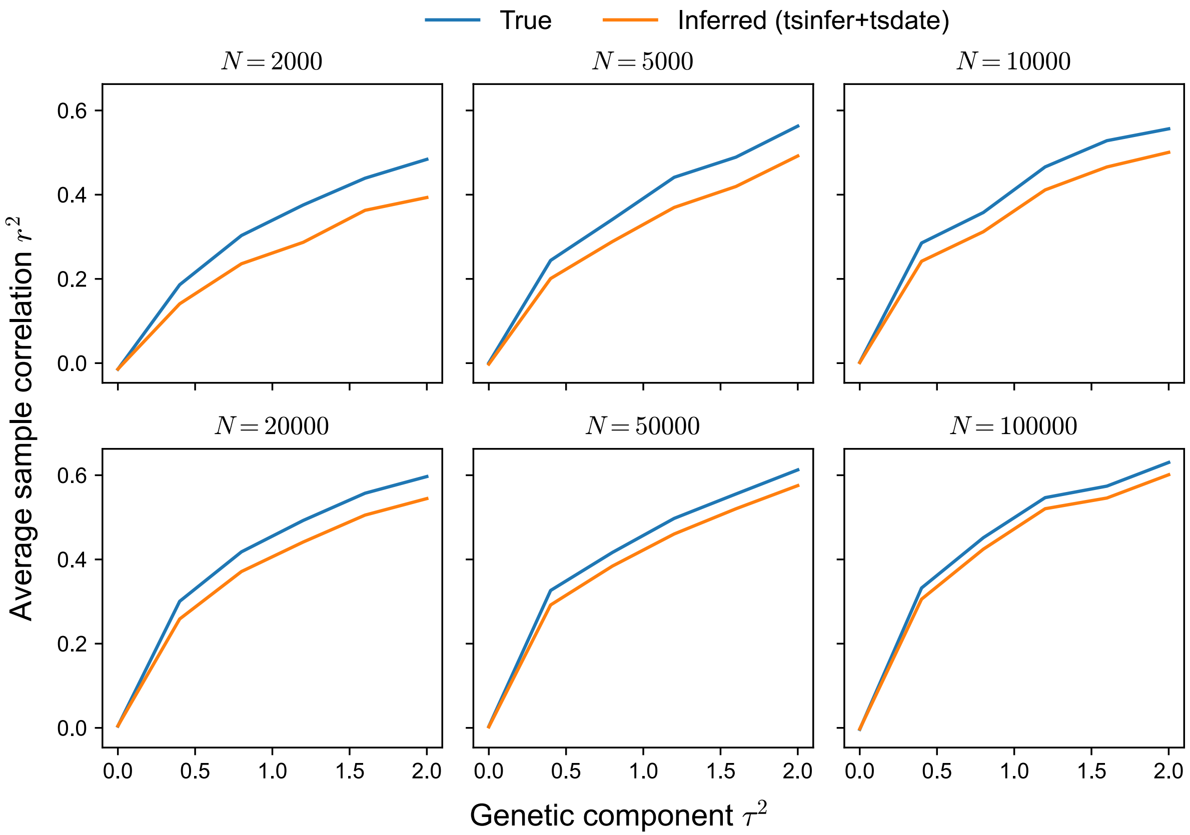

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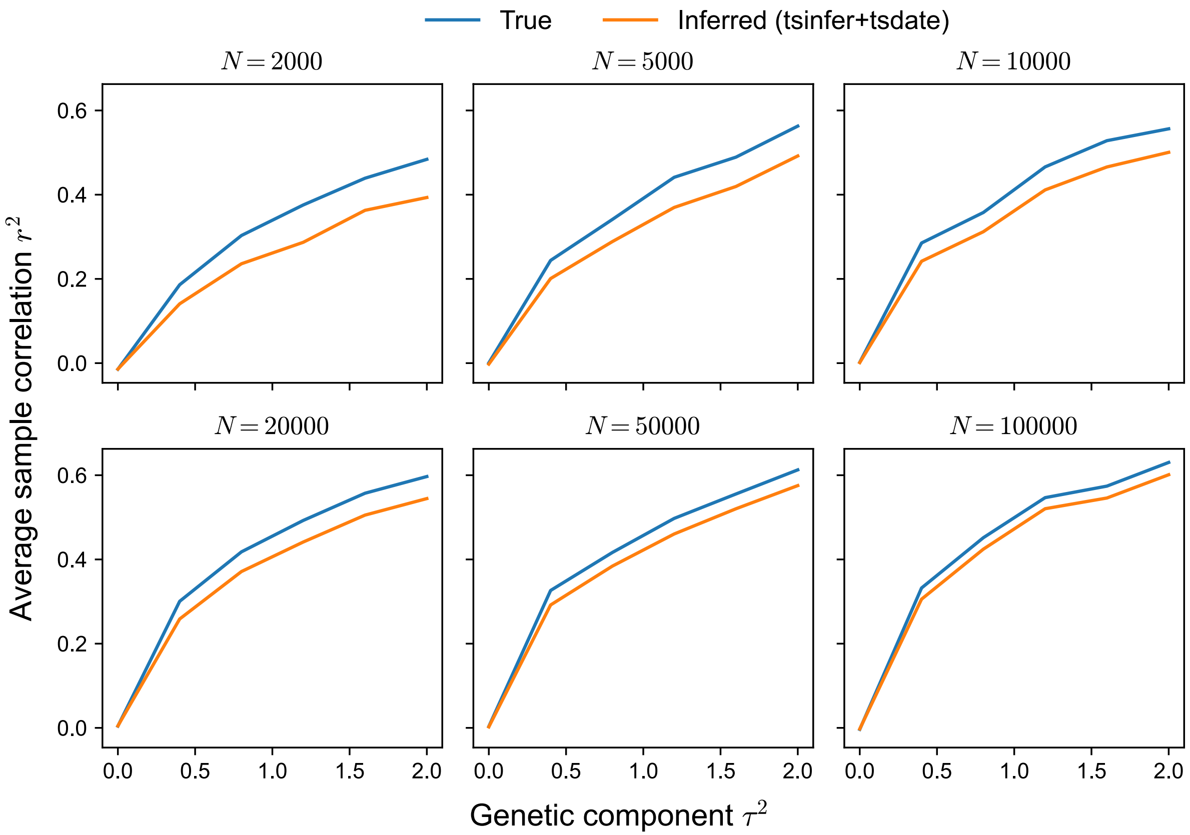
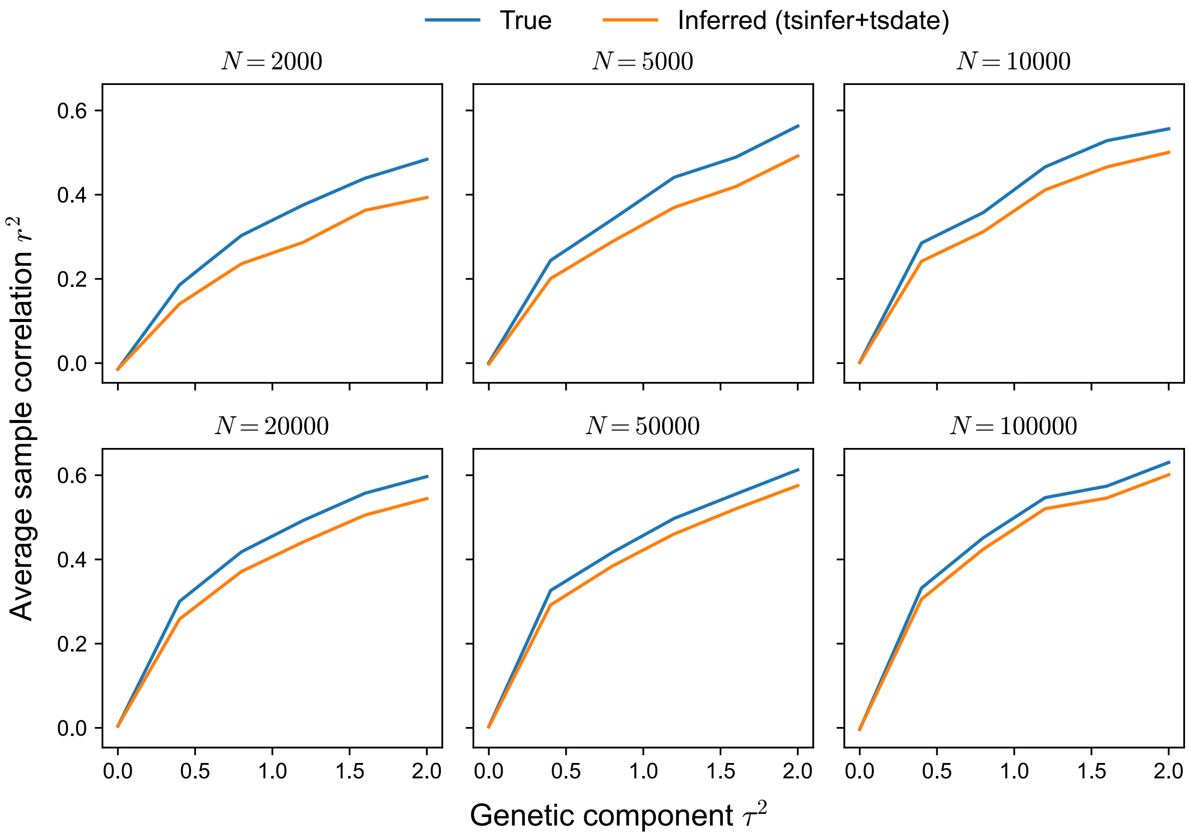


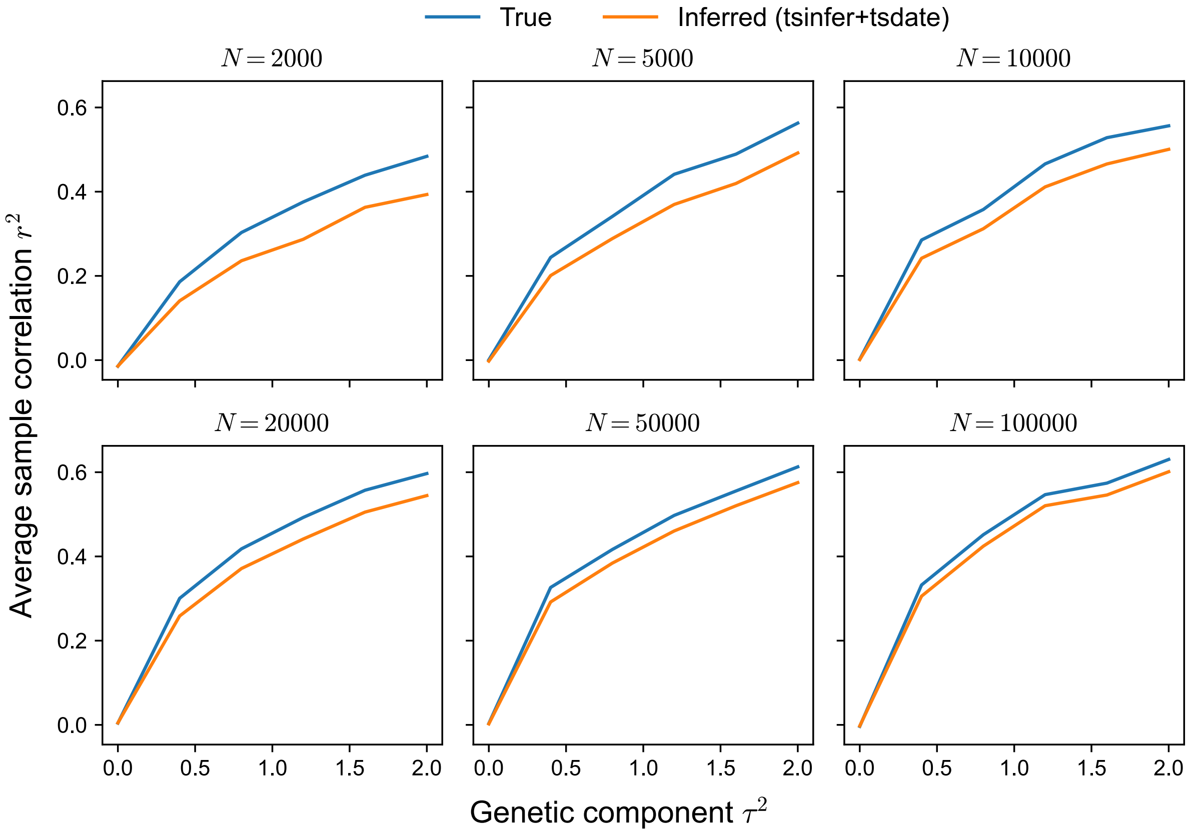
We measured the accuracy of polygenic scores computed from **tslmm**

Best linear unbiased prediction (BLUP)



Training and testing on two non-overlapping groups embedded in the same tree sequence

Best linear unbiased prediction (BLUP)



True trees are better, but inferred trees are not too behind!

Summary & Future directions

ARG-LMM lays an explicit connection between population and quantitative genetics

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Time conditioned analysis (random vs fixed effects) (Fan, Mancuso, and Chiang 2022)

Thank you for listening

Link to (Lehmann et al. 2025), **tslmm** preprint coming soon

Collaborators: Nathaniel Pope (Oregon), Jerome Kelleher (Oxford), Gregor Gorjanc (Edinburgh), and Peter Ralph (Oregon)

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Technical Notes

Edge splitting

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- Nodes and edges are reused across multiple trees in a tree sequence

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- Edges, in particular, may not have a unique set of samples along their span
- Salehi Nowbandegani and colleagues *bricked* the edges to divide them (Salehi Nowbandegani et al. 2023)
- Henceforth, we assume that edges are splitted to have a unique subtopology

$$\mathbf{Z}_{ne} = \text{The number of haplotypes of individual } n \text{ that inherit } e$$

The overall matrix $\mathbf{Z}$ is an individual-edge design matrix.

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$$\mathbf{G}_{np} = \sum_{e:p \in e} \mathbf{Z}_{ne} \mathbf{1}_{ep} \quad \Leftrightarrow \quad \mathbf{G}_{p} = \sum_{e:p \in e} \mathbf{Z}_{e} \mathbf{1}_{ep}$$

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- Assumes that there are no parent-child mutation pairs, but allows *some* recurrent mutations

Exchange the summations

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Recall $\mathbf{G}_p = \sum_{e:p\in e} \mathbf{Z}_e \mathbf{1}_{ep}$ and $\mathbf{y} = \sum_{p=1}^{P} \mathbf{G}_p \boldsymbol{\beta}_p + \boldsymbol{\varepsilon}$

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Substitute $\mathbf{G}_p$

$$\color{red}{\sum_{p=1}^{P} \sum_{e:p\in e}} \mathbf{Z}_e \boldsymbol{\beta}_p \mathbf{1}_{ep} + \boldsymbol{\varepsilon}$$

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Exchange the inner and the outer summation

$$\sum_{e=1}^{E} \sum_{p:p\in e} \mathbf{Z}_e \boldsymbol{\beta}_p \mathbf{1}_{ep} + \boldsymbol{\varepsilon}$$

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$$\begin{aligned} &\sum_{e=1}^{E} \mathbf{Z}_e \left(\sum_{p:p\in e} \boldsymbol{\beta}_p \mathbf{1}_{ep} \right) + \boldsymbol{\varepsilon} \\ &= \sum_{e=1}^{E} \mathbf{Z}_e \boldsymbol{\upsilon}_e + \boldsymbol{\varepsilon} \\ &= \mathbf{Z}\boldsymbol{\upsilon} + \boldsymbol{\varepsilon} \end{aligned}$$

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$\boldsymbol{\upsilon}$ is a random variable made up of mutation-driven random variables $\mathbf{1}_{ep}$!

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$$\mathrm{Cov}(\mathbf{u}_e, \mathbf{u}_{e'}) = \sum_{p \in e, e'} \boldsymbol{\beta}_p^2 \mathrm{Cov}(\mathbf{1}_{ep}, \mathbf{1}_{e'p})$$

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- The covariance between the indicators are higher-order terms of mutation rates, so we ignore it (Wakeley 2008)

$$\begin{aligned}\mathrm{Cov}(\mathbf{1}_{ep}, \mathbf{1}_{e'p}) &= \mathrm{E}[\mathbf{1}_{ep}\mathbf{1}_{e'p}] - \mathrm{E}[\mathbf{1}_{e'p}]\mathrm{E}[\mathbf{1}_{ep}] \\ &= 0 - l_e u_{ep} l_{e'} u_{e'p} \approx 0\end{aligned}$$

where l_e is the (time-)length of edge e.

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- The convergence is unlikely to be fast enough given the small value of $\mathbf{E}[\mathbf{1}_{ep}]$ (Berry-Esseen).
- Fortunately, the variance is computable and is

$$\text{Var}(\mathbf{u}_e) = l_e \boldsymbol{s}_e \cdot \frac{1}{\boldsymbol{s}_e} \sum_{p:p \in e} \boldsymbol{\beta}_p^2 u_{ep}$$

More on $\mathrm{Var}(\mathbf{u}_e)$

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$$\tau_e^2 = \frac{1}{\boldsymbol{s}_e} \sum_{p:p \in e} \boldsymbol{\beta}_p^2 u_{ep}$$

- As a measure of functional significance, variance components are confounded by the area

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$$[\mathbf{Zf}]_n = \sum_{e=1}^{E} \mathbf{Z}_{ne} \mathbf{E}\left[\sum_{p:p \in e} \boldsymbol{\beta}_p \mathbf{1}_{ep}\right]$$

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$$\sum_{p=1}^{P} \boldsymbol{\beta}_p u_p \left(\sum_{e:p \in e} \mathbf{Z}_{ne} l_e \right) = \sum_{p=1}^{P} \boldsymbol{\beta} u_p \cdot 2t_{\text{root},p} = \text{const. resp. to } n$$

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Conjecture: selection $\Rightarrow$ fixed effects?

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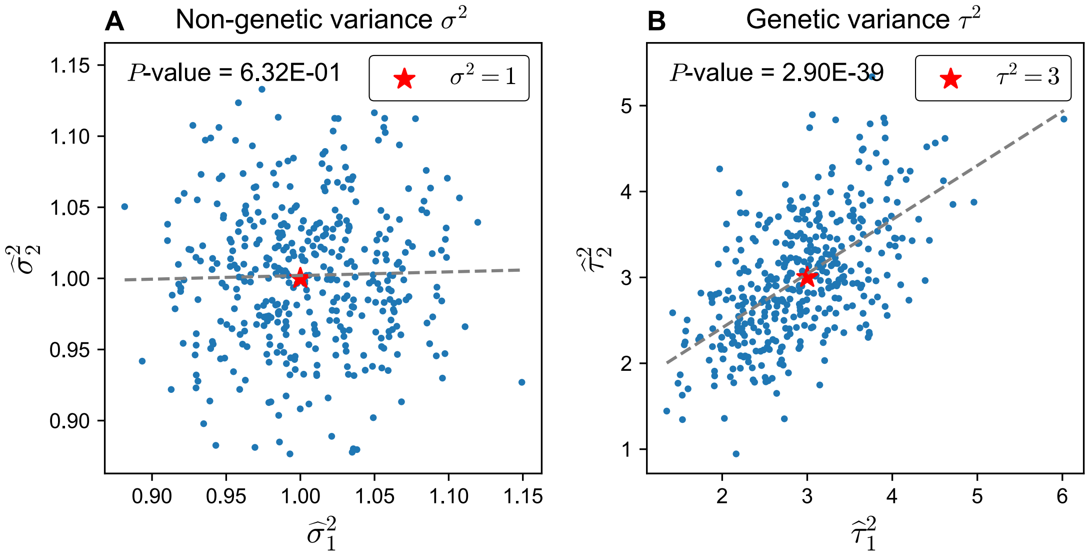

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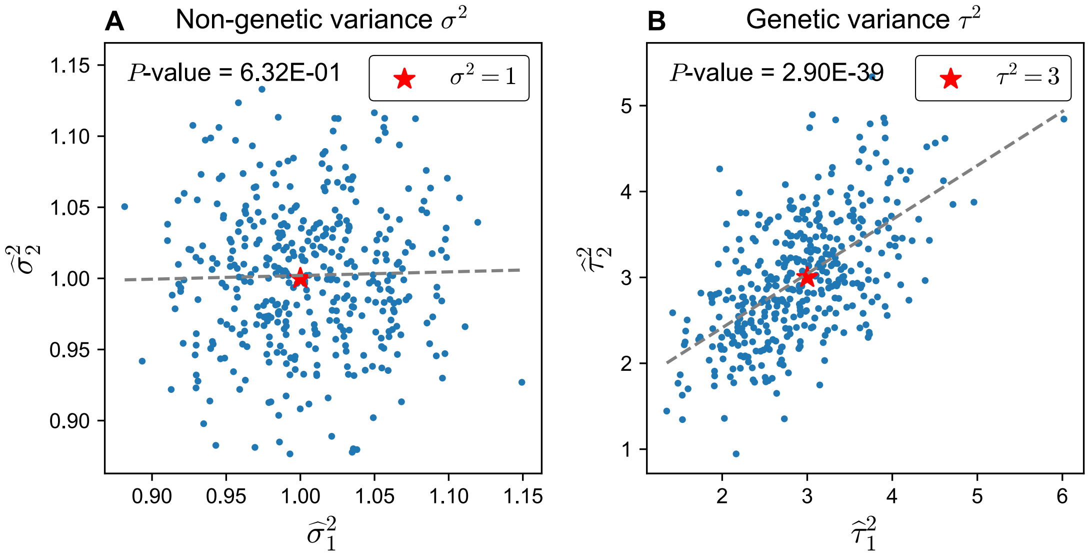

This is also the very reason why BLUP works

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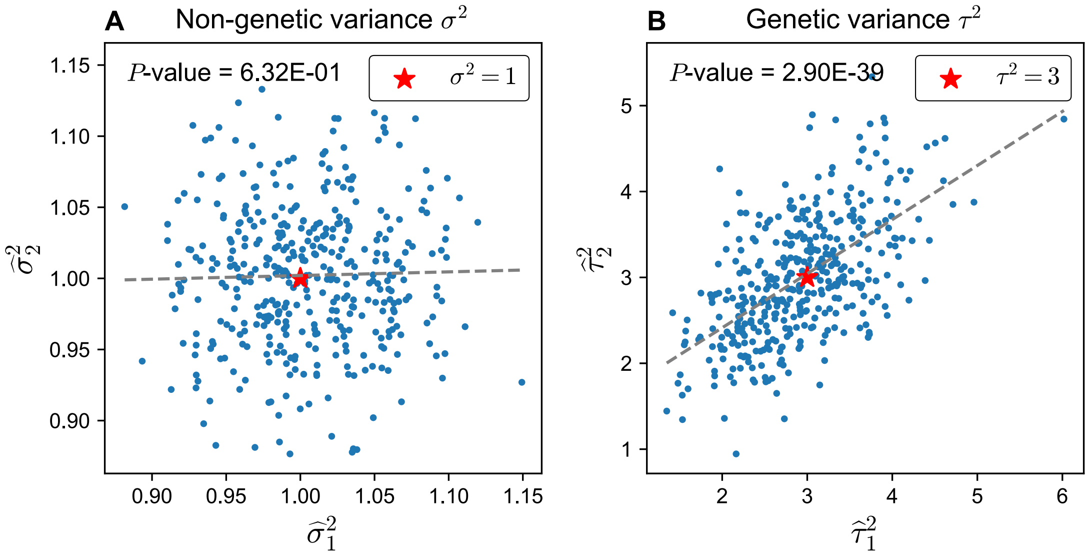

We are all correlated!

Missing heritability?

Figure from Whalebone Magazine

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ARG-LMM variance component only reflects mutational variability

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Figure from Whalebone Magazine

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Figure from Whalebone Magazine

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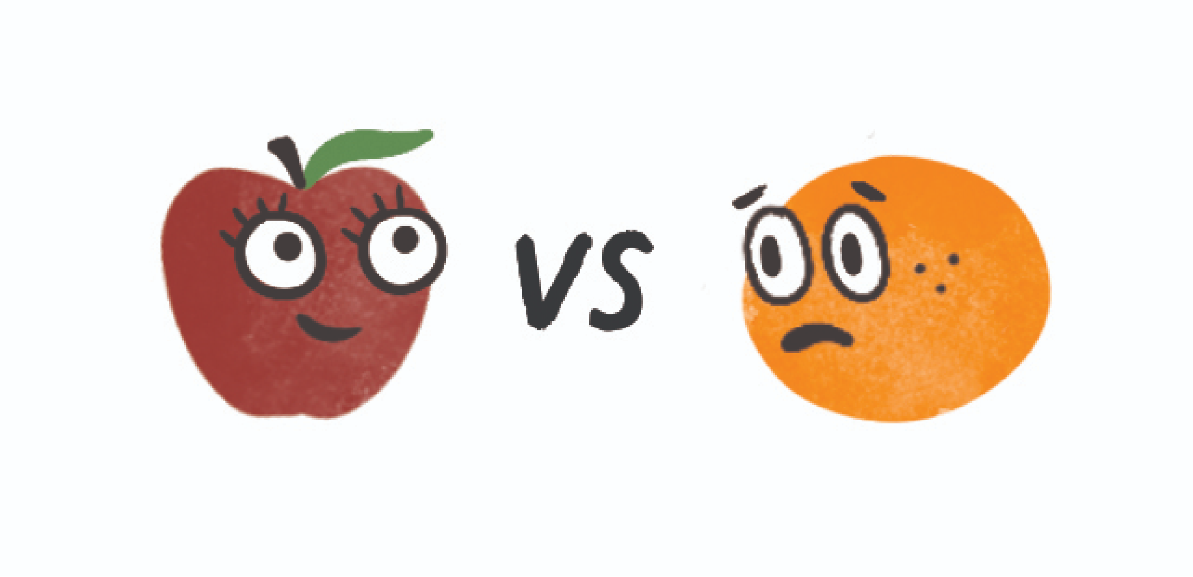

Figure from Whalebone Magazine

Estimation quality of variance components

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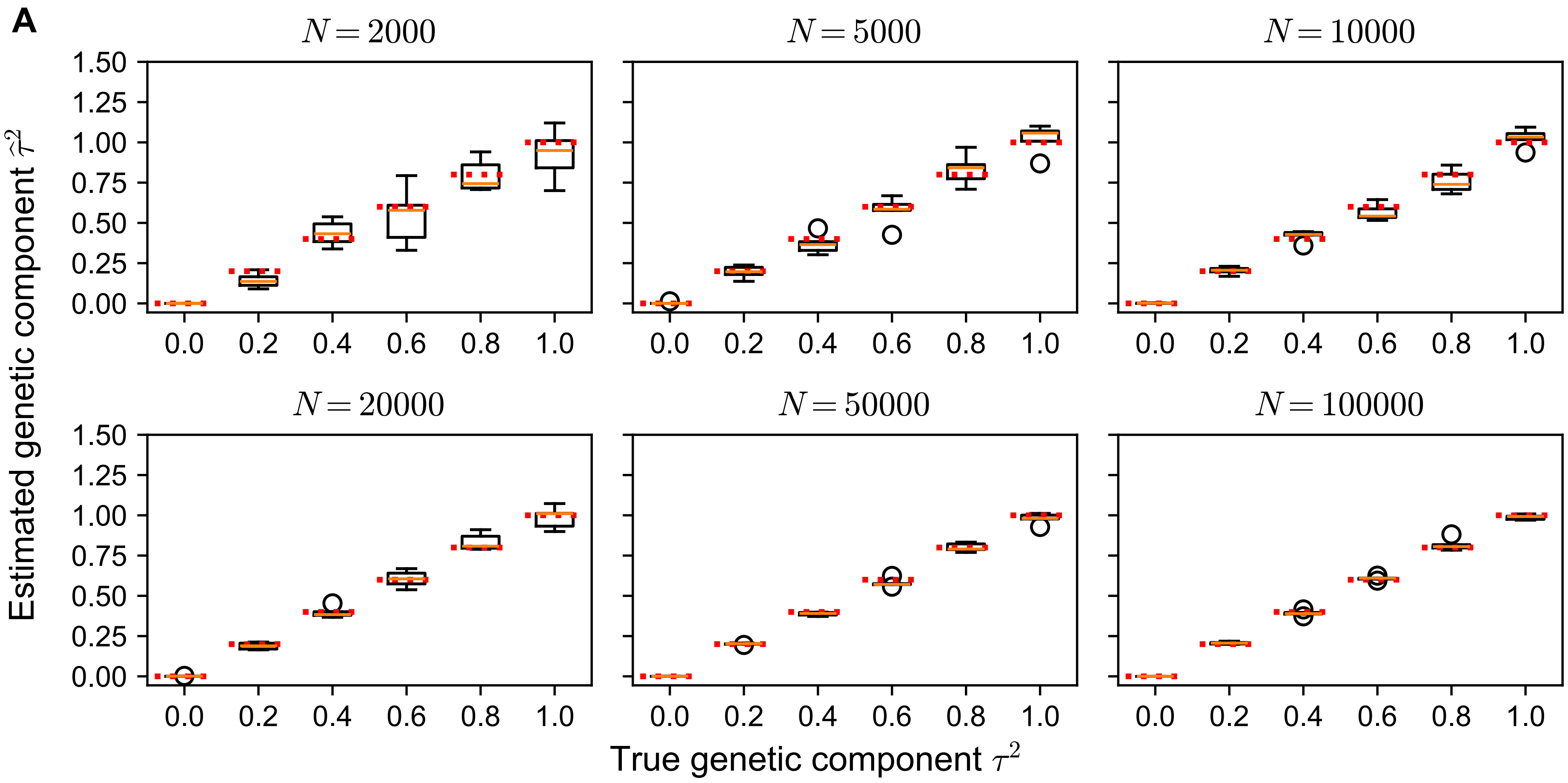
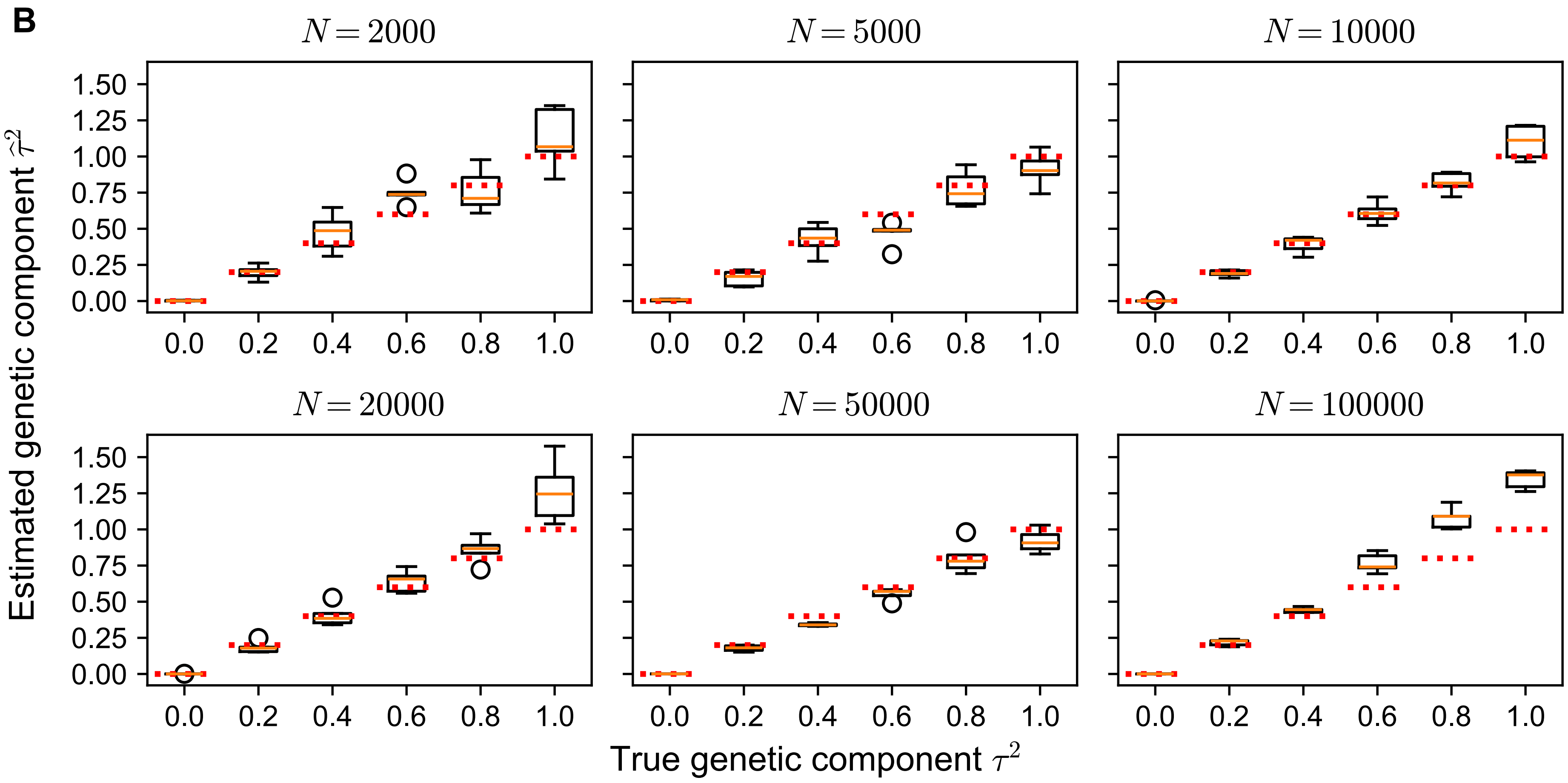
Simulated trees



Estimation quality of variance components

Inferred (tsinfer+tsdate) trees



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- Demography-conditioned variance

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There are many genetic variances

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$$\mathrm{Var}(\mathbf{y} \mid \mathrm{ARG})$$

- Pedigree-conditioned variance

$$\mathrm{Var}(\mathbf{y} \mid \mathrm{Pedigree})$$

- Demography-conditioned variance

$$\mathrm{Var}(\mathbf{y} \mid \mathrm{Demography})$$

- Time conditioning (reference population)