Estimating haplotype and mutation effects in the context of genome sequence via ancestral recombination graphs

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Ancestral Recombination Graph (ARG)

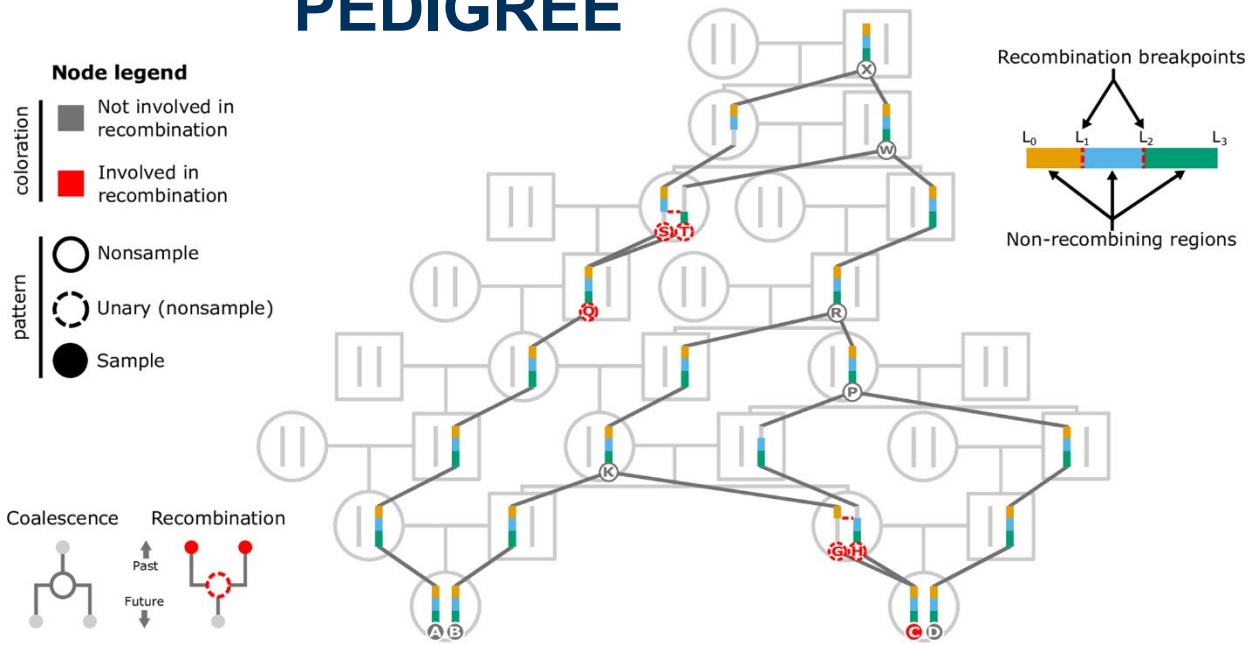
- **Representation of DNA variation by focusing on DNA events**
  - *branch/coalescent events* (where DNA molecule split/merge),
  - *mutation events* (where DNA molecule changes), and
  - *recombination events* (where DNA molecules exchange)

- **Insight into evolutionary history**
  (time and place of DNA events, demography, divergence, introgression, …)

- **Succinct data representation!**
  (can handle large scale WGS datasets)

How do ARGs look like?

PEDIGREE



Lewanski et al. (2024)

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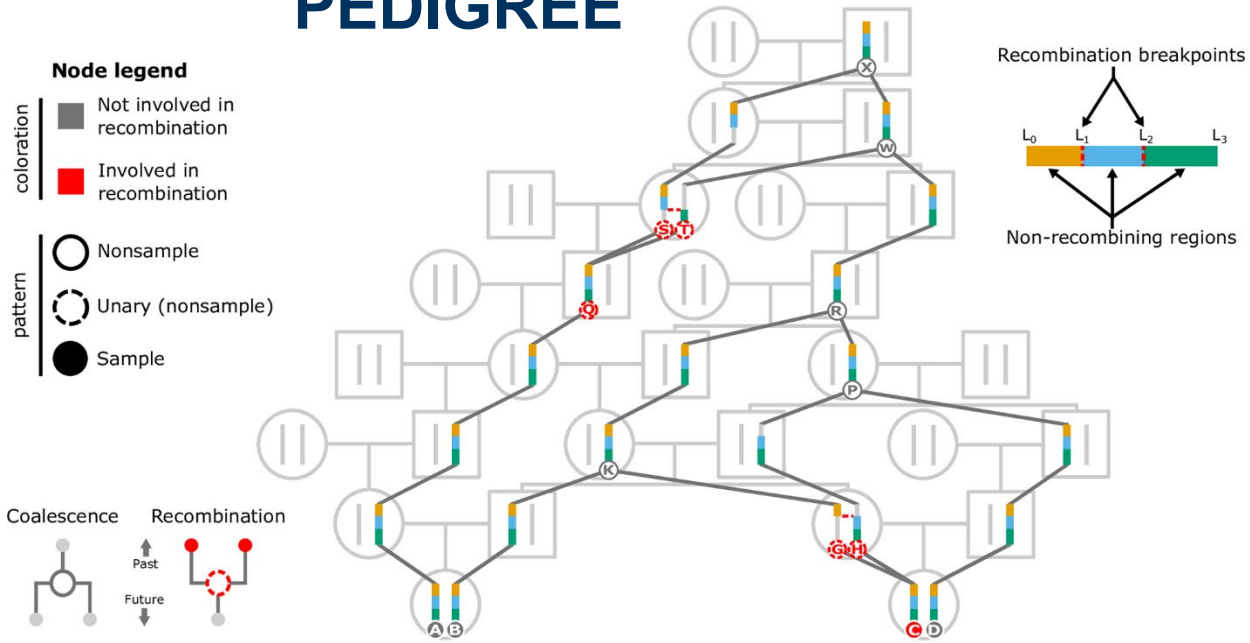
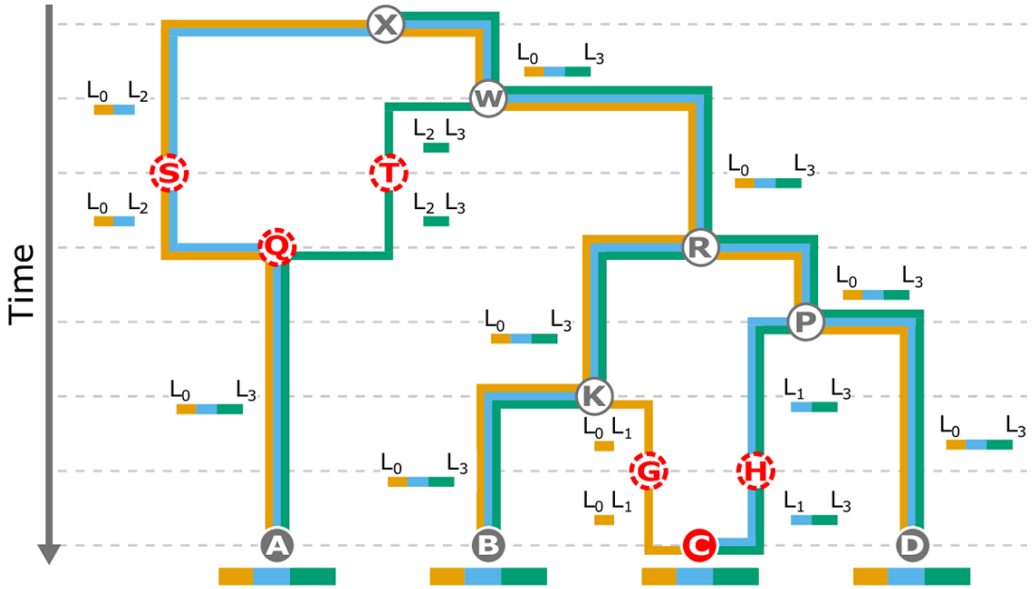


ARG



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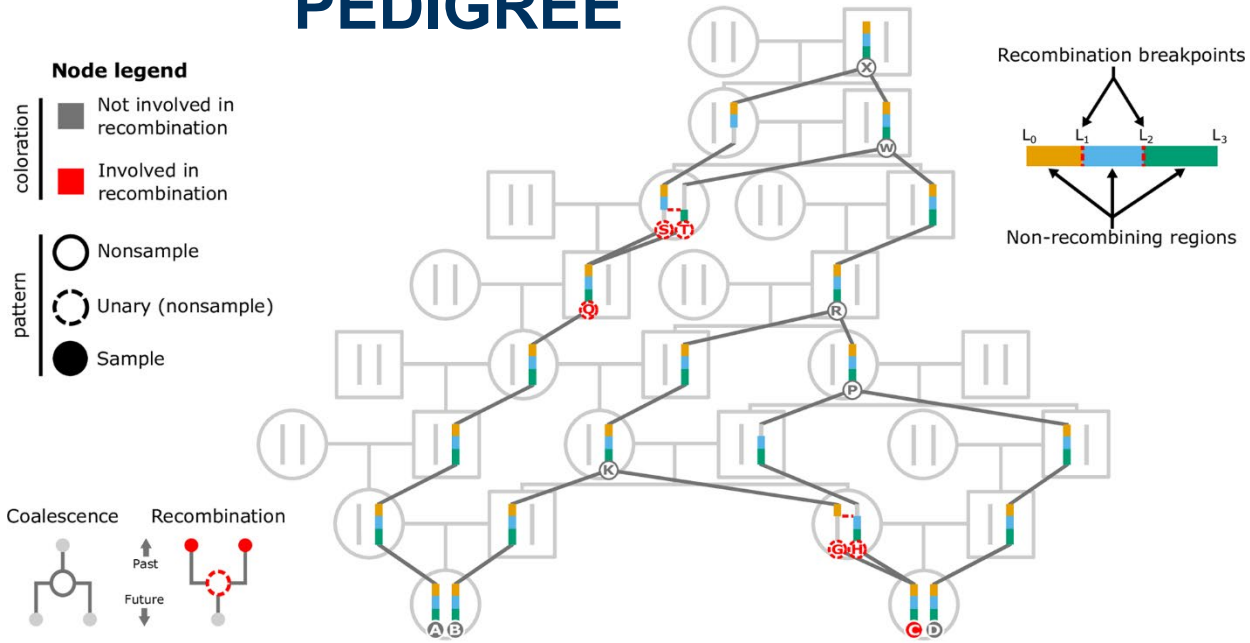

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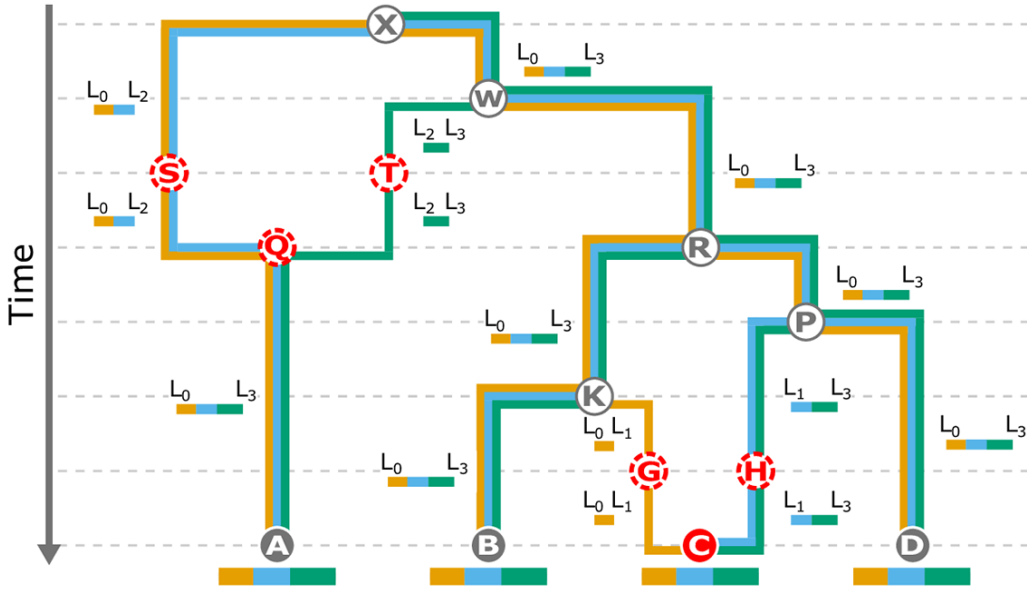
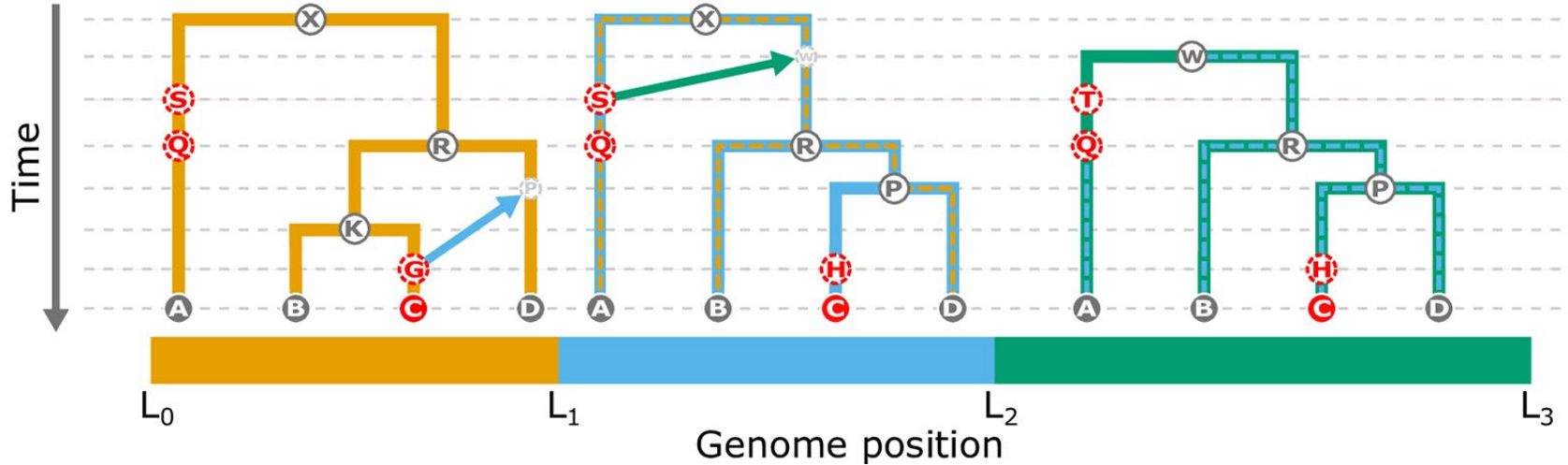


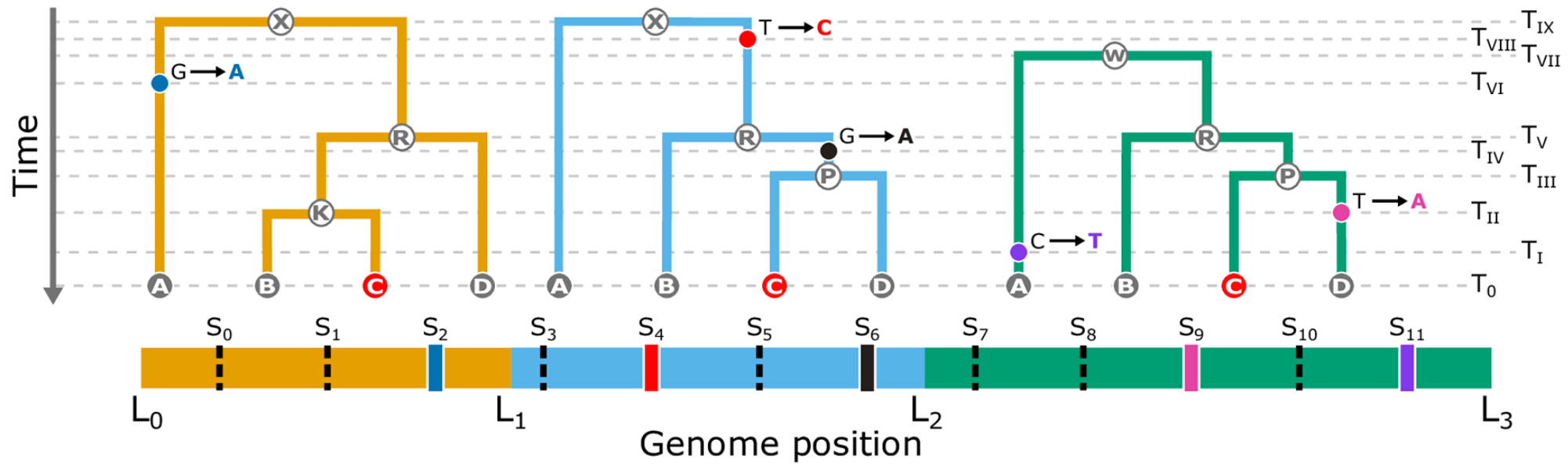
LOCAL TREES



Lewanski et al. (2024)

Genotypes → Haplotypes → ARG

Sample	Site ID 0	1	2	3	4	5	6	7	8	9	10	11
A	G	T	A	G	T	C	G	T	A	T	A	T
B	G	T	G	G	C	C	G	T	A	T	A	C
C	G	T	G	G	C	C	A	T	A	T	A	C
D	G	T	G	G	C	C	A	T	A	T	A	C



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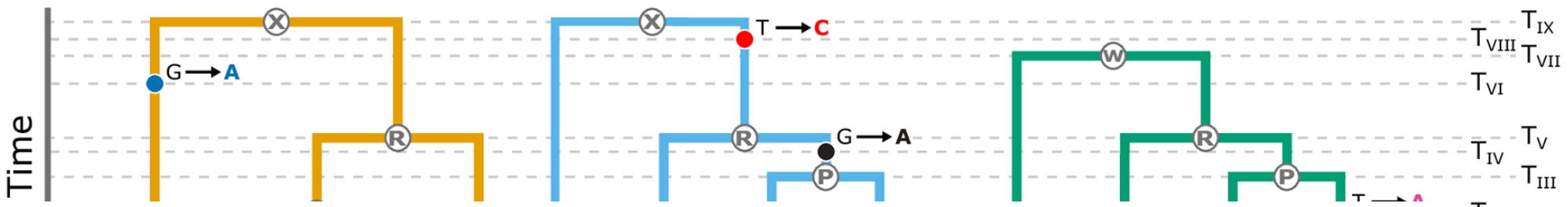
C	G	T	G	G	C	C	A	T	A	T	A	C
D	G	T	G	G	C	C	A	T	A	T	A	C



Nodes

Node ID	Age
A	T_0
B	T_0
C	T_0
D	T_0
K	T_{II}
P	T_{III}
R	T_V
W	T_{VII}
X	T_{IX}

Edges

Genome start	Genome end	Parent	Child
L_0	L_2	X	A
L_0	L_1	K	B
L_0	L_1	K	C
L_0	L_2	X	R
L_0	L_1	R	D
L_0	L_1	R	K
L_1	L_3	R	B
L_1	L_3	R	P
L_1	L_3	P	C
L_1	L_3	P	D
L_2	L_3	W	A
L_2	L_3	W	R

Sites

Site ID	Position	Ancestral
0	S_0	G
1	S_1	T
2	S_2	G
3	S_3	G
4	S_4	T
5	S_5	C
6	S_6	G
7	S_7	T
8	S_8	A
9	S_9	T
10	S_{10}	A
11	S_{11}	C

Mutations

Mutation ID	Site	Node	Derived	Age
0	2	A	A	T_{VI}
1	4	R	C	T_{VIII}
2	6	P	A	T_{IV}
3	9	D	A	T_{II}
4	11	A	T	T_I

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Ancestral Recombination Graph (ARG)

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  - *branch/coalescent events* (where DNA molecule split/merge),
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  - *recombination events* (where DNA molecules exchange)

- **Insight into evolutionary history**
  (time and place of DNA events, demography, divergence, introgression, …)

- **Succinct data representation!**
  (can handle large scale WGS datasets)

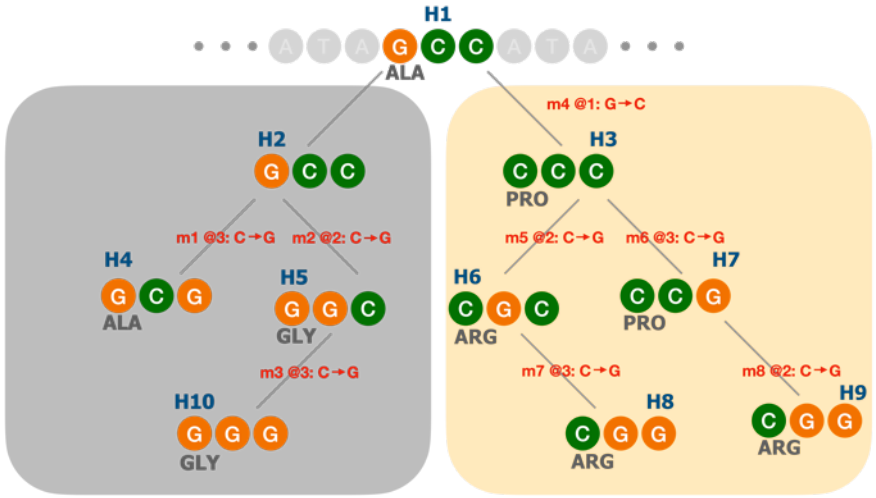
- **AIM: Quantitative genetic modelling based on ARGs!?**

TODAY: QG model for non-recombining DNA

Model options:

a) SNP-BLUP

b) G-BLUP



Based on

1. Allele dosages

Allele dosages

$$\mathbf{X} = \begin{array}{c} \\ \text{Individual} \end{array} \overset{\text{SNP}}{\begin{pmatrix} 0 & 1 & 1 \\ 0 & 1 & 1 \\ 1 & 1 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \\ 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}}$$

TODAY: QG model for non-recombining DNA

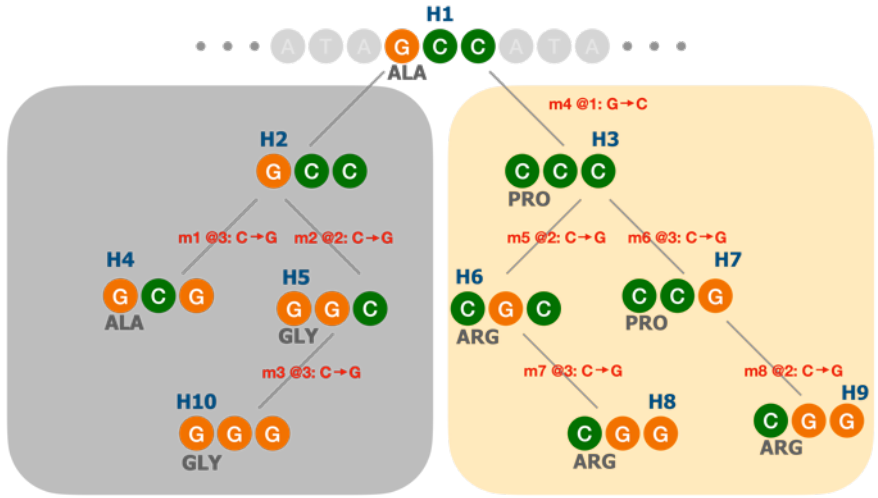
Model options:

a) SNP-BLUP

b) G-BLUP

Based on

1. Allele dosages
2. Mutation dosages



Allele dosages

$$\mathbf{X} = \begin{matrix} \\ \text{Individual} \end{matrix} \begin{matrix} \text{SNP} \\ \begin{pmatrix} 0 & 1 & 1 \\ 0 & 1 & 1 \\ 1 & 1 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \\ 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \end{matrix}$$

$$\mathbf{X} = \begin{matrix} \\ \text{Individual} \end{matrix} \begin{matrix} \text{Mutation} \\ \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \end{matrix}$$

Mutation dosages

TODAY: QG model for non-recombining DNA

Model options:

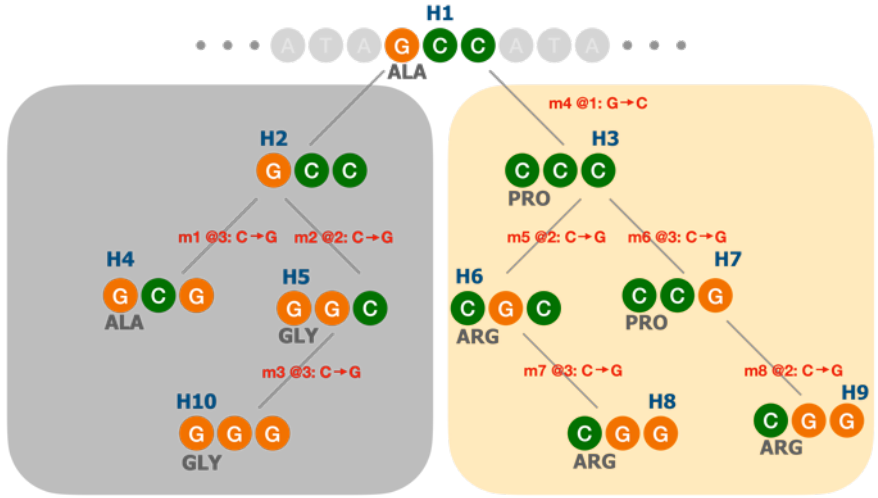
a) SNP-BLUP

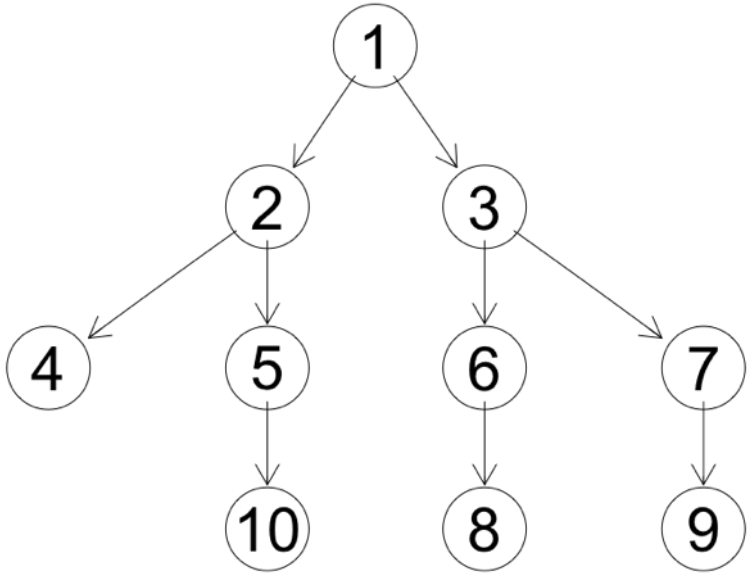
b) G-BLUP

c) Tree-BLUP / ARG-BLUP

Based on

1. Allele dosages
2. Mutation dosages
3. Tree / ARG structure

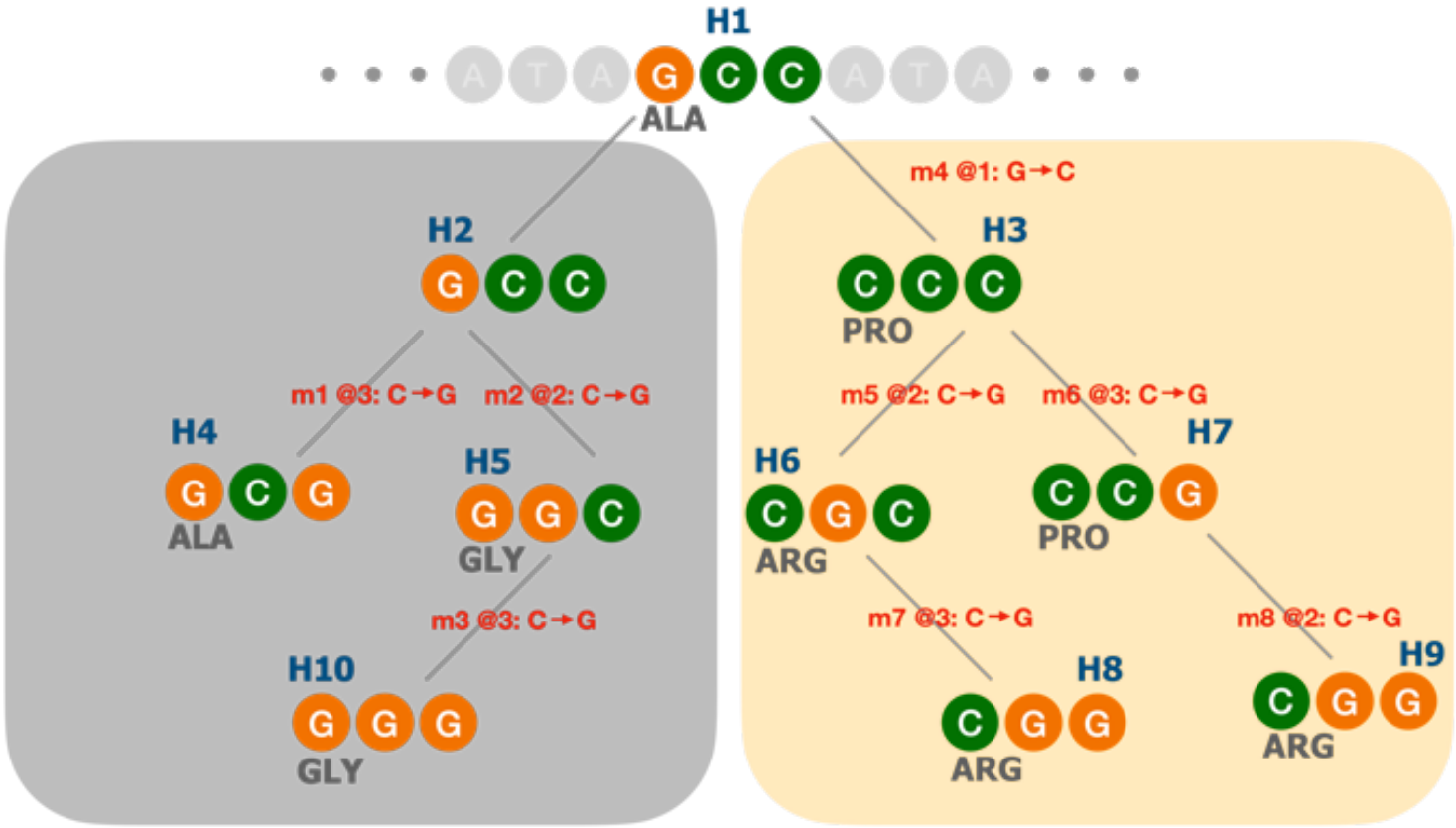




Haplotype tree model

Haplotype's value can be modelled as the value of it's parental haplotype plus an "innovation" term

(mutation, structural variants, unobserved biology, epistasis, …)



$$h_1 \sim N(0, \sigma_h^2)$$
$$h_2 \sim N(0, \sigma_h^2)$$
$$h_2 | h_1 \sim N(h_1, \sigma_m^2)$$

…

$$h_2 = h_1 + e_2$$
$$h_3 = h_1 + m_{1\to3} + e_3$$
$$h_4 = h_2 + (m_{2\to4} + e_4)$$

Tree-BLUP

- Phenotype model

$$\boldsymbol{y} = \mathbf{1}b + \boldsymbol{Zh} + \boldsymbol{e}$$

- Haplotype tree model

$$\boldsymbol{h} \sim N(\mathbf{0}, \boldsymbol{H}(\sigma_m^2 + \sigma_\epsilon^2))$$

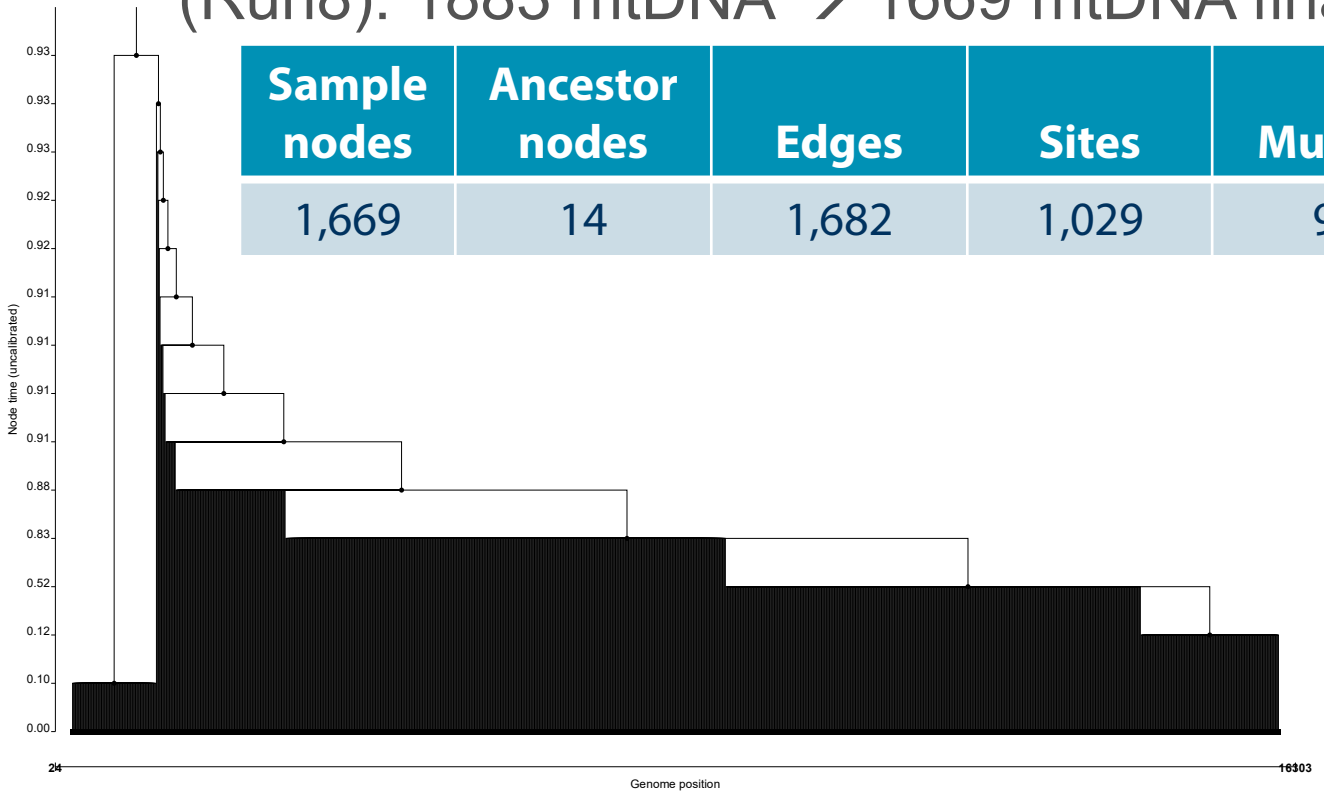
- Covariance coef. matrix between haplotypes **H** has a simple inverse (precision matrix) due to DNA tree structure

- Can fit with most linear mixed model software (ASReml, blupf90, INLA, Mix99, MixBLUP, …)

Proof of concept – real data + simulations

- **Real data**
  - Cattle mtDNA
  - Inferred mtDNA ancestral alleles
  - Inferred mtDNA tree for 1000 Bull Genomes (Run8): 1883 mtDNA → 1669 mtDNA final

Sample nodes	Ancestor nodes	Edges	Sites	Mutations
1,669	14	1,682	1,029	9,598



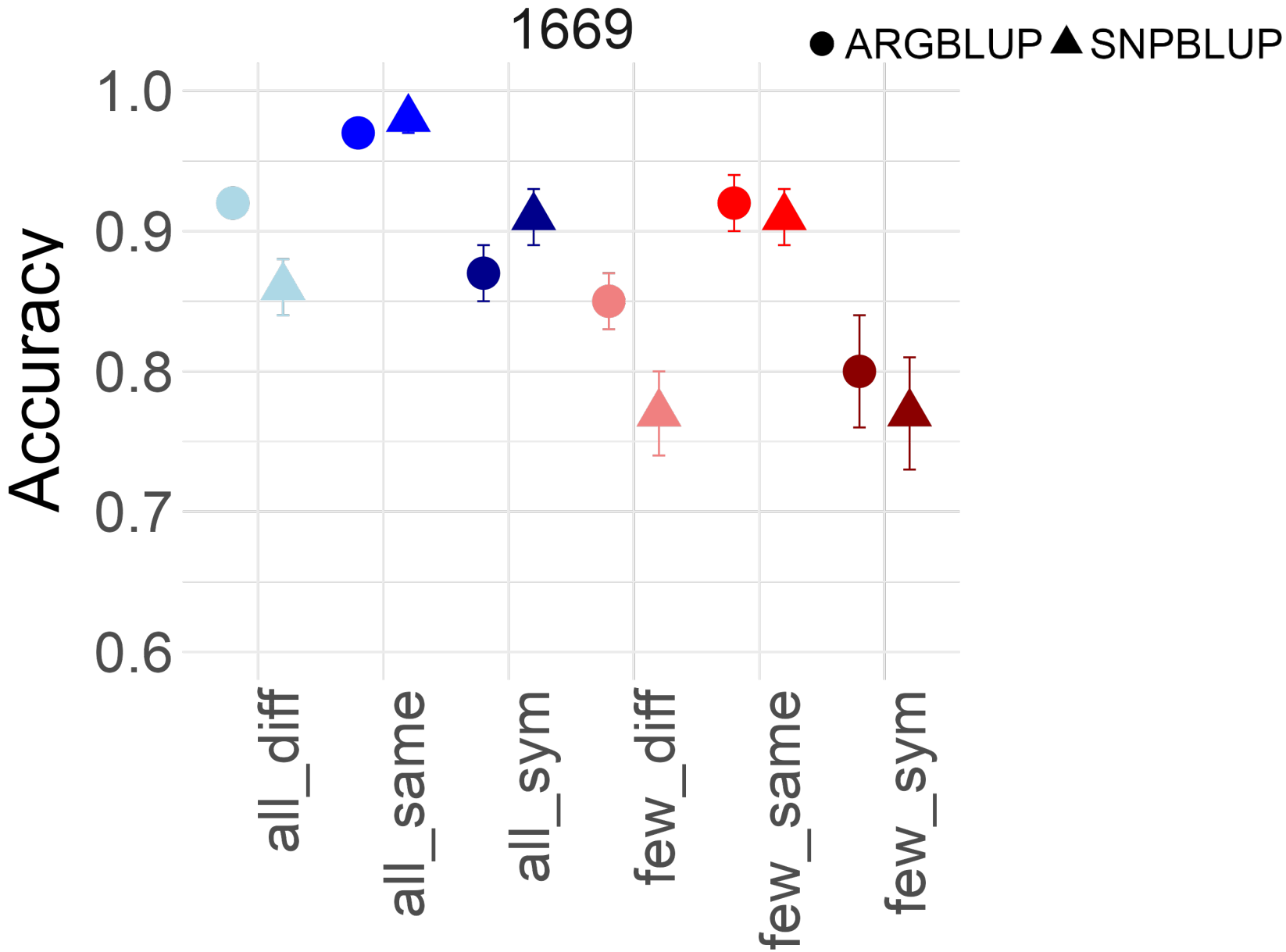
Simulations

ALL all mutations are causative
FEW 10% of mutations are causative

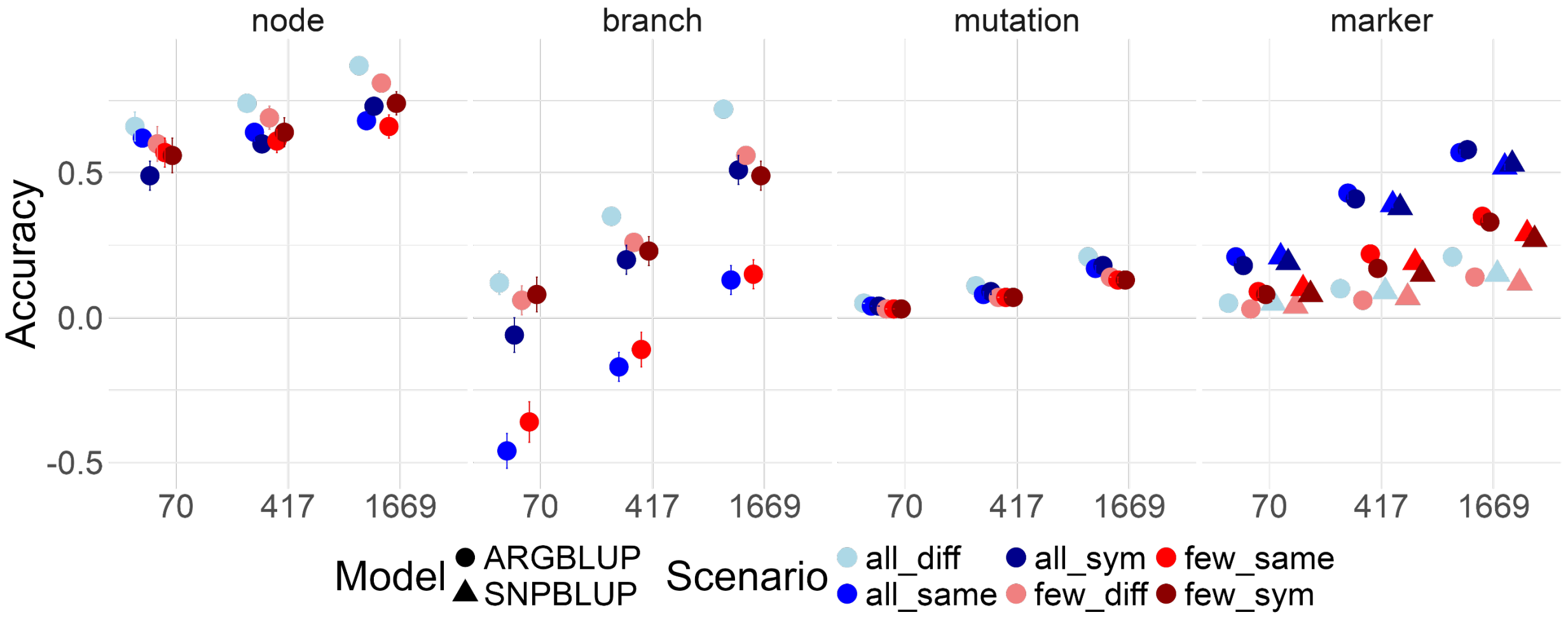
DIFF all mutation effects are different
SAME mutation type defines effect
SYM symmetric mutation effects

1669 phenotypes
417 phenotypes
70 phenotypes

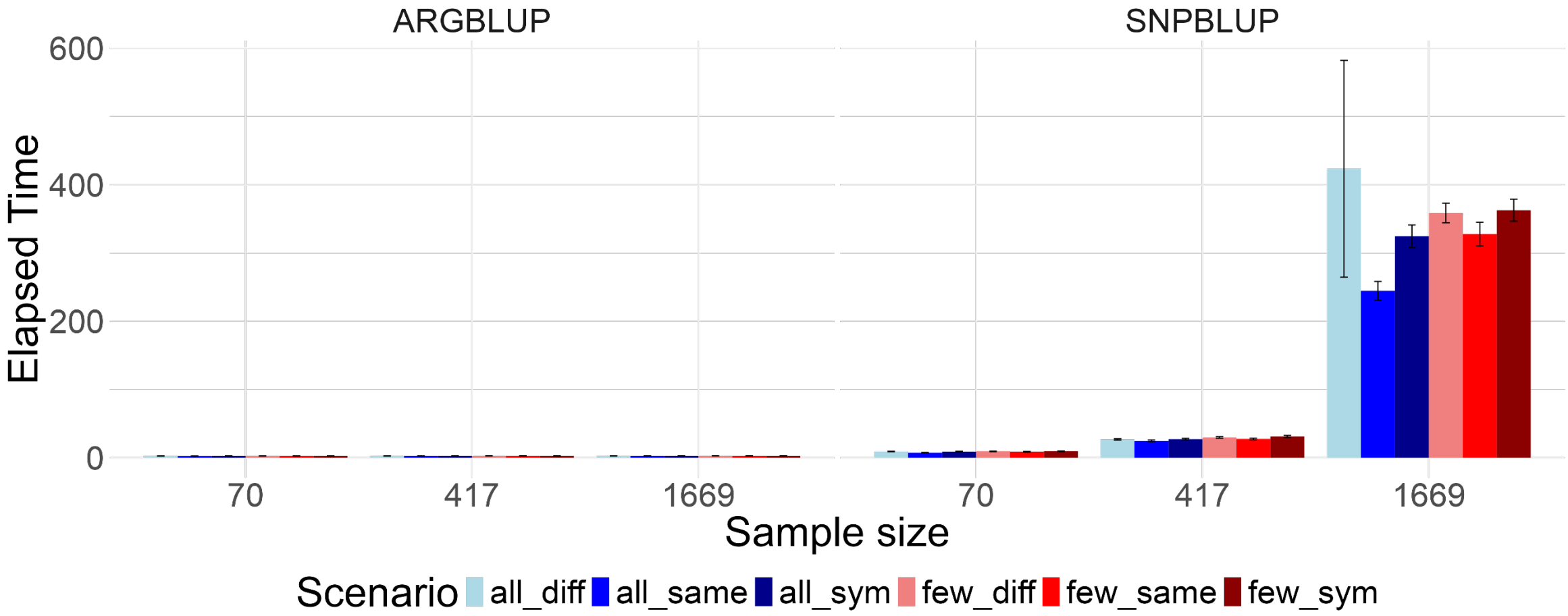
Accuracy of estimated haplotype effects (samples/tips)



Accuracy of various estimated effects



Execution time with INLA (seconds)



Conclusion

- Ancestral Recombination Graphs (ARGs) are the ultimate object in population genetics/genomics → now feasible & popular
- We are interested in quantitative genetic modelling with ARGs
- Here we presented a Tree-BLUP to work with a single non-recombining DNA region (mtDNA real data & simulation)
- QG modelling with the full ARG involves recombination events (haplotypes of different lengths) → we have a good working model for that in the pipeline

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