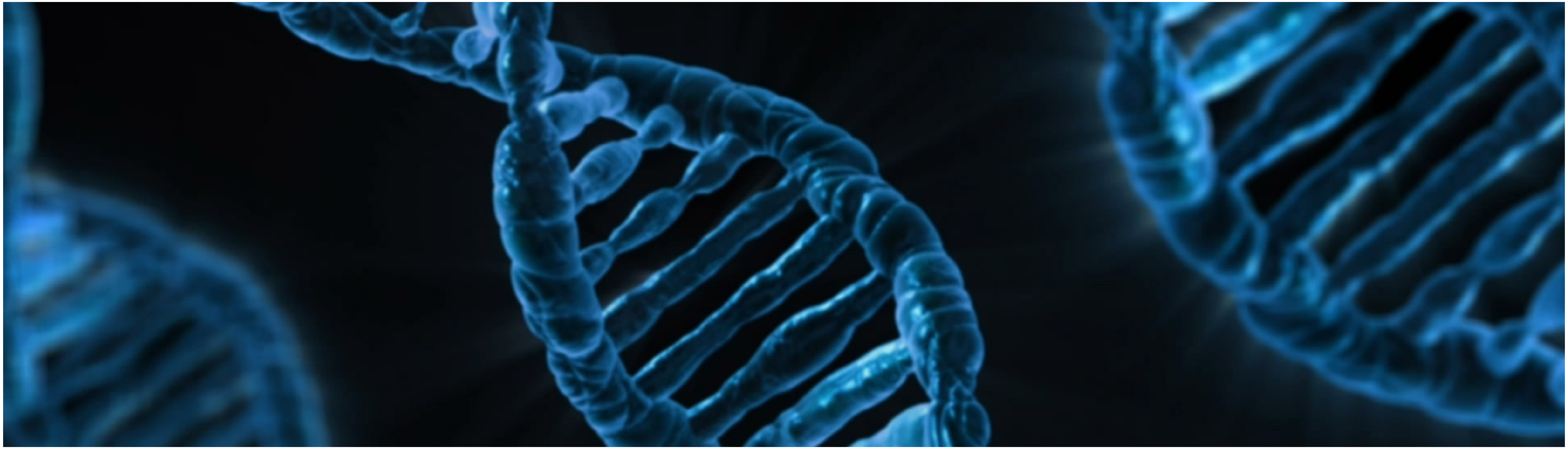
Memoization on Shared Subtrees Accelerates Computations on Genealogical Forests

2024-09-03

Lukas Hübner and Alexandros Stamatakis



Population Genetics

Evolutionary Bioinformatics

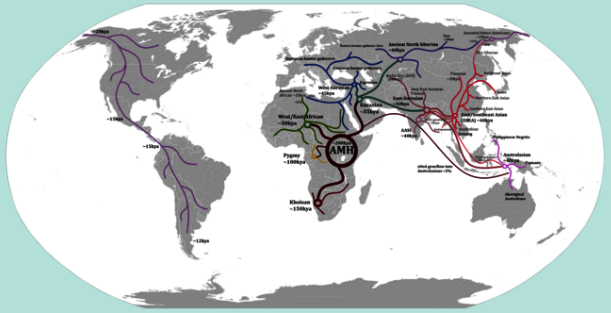
- Living beings organize in a tree modelled based on their genetic code
- Phylogenetics: Evolutionary history among different species
- Genealogy: Evolutionary history among individuals of the same species

applications

understanding evolution

host-parasite interaction

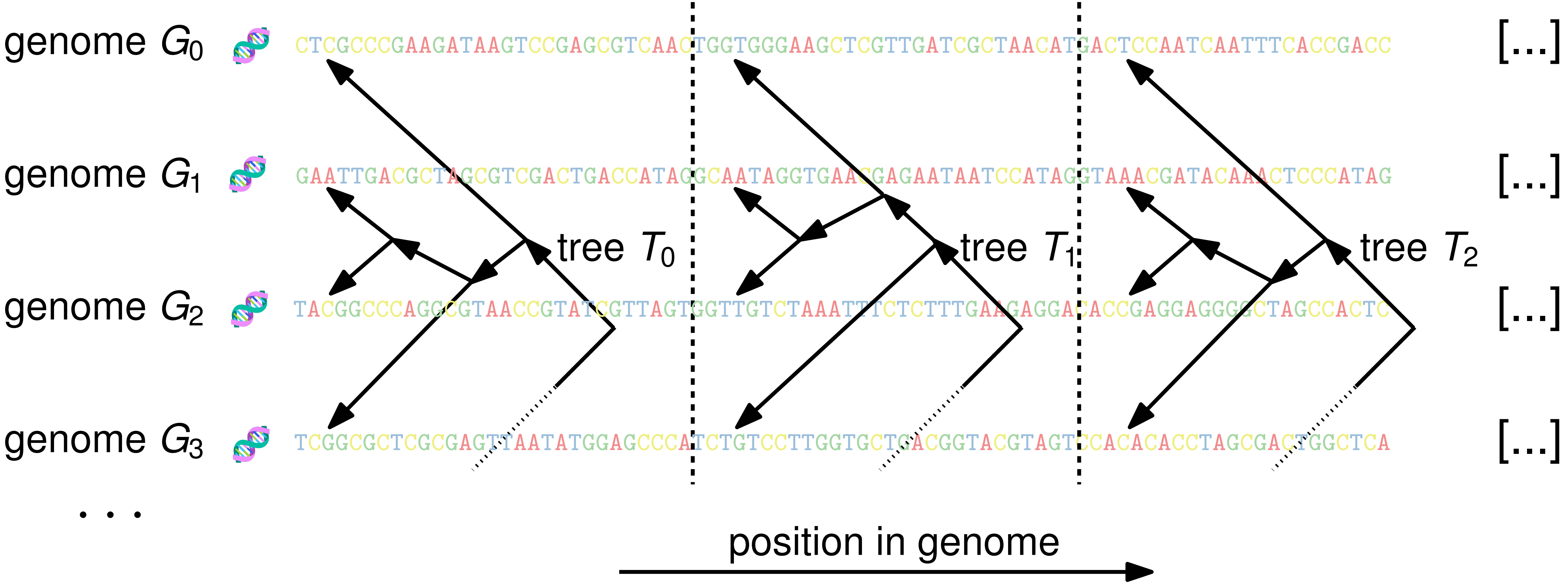
wildlife conservation



human migration patters

Recombination

- Recombination breaks and recombines genomic code
- Degree of shared evolutionary history between two sites correlates with their distance
- Multiple trees provides a more comprehensive picture


genome G_0
CTCGCCCGAAGATAAGTCCGAGCGTCAACTGGTGGGAAGCTCGTTGATCGCTAACATGACTCCAATCAATTTCACCGACC
[...]
genome G_1
GAATTGACGCTAGCGTCGACTGACCATAGGCAATAGGTGAACGAGAATAATCCATAGGTAAACGATACAAACTCCCATAG
[...]
tree T_0
tree T_1
tree T_2
genome G_2
TACGGCCCAGGCGTAACCGTATCGTTAGTGGTTGTCTAAATTTCTCTTTGAAGAGGACACCGAGGAGGGGCTAGCCACTC
[...]
genome G_3
TCGGCGCTCGCGAGTTAATATGGAGCCCATCTGTCCTTGGTGCTGACGGTACGTAGTCCACACACCTAGCGACTGGCTCA
[...]
. . .
position in genome

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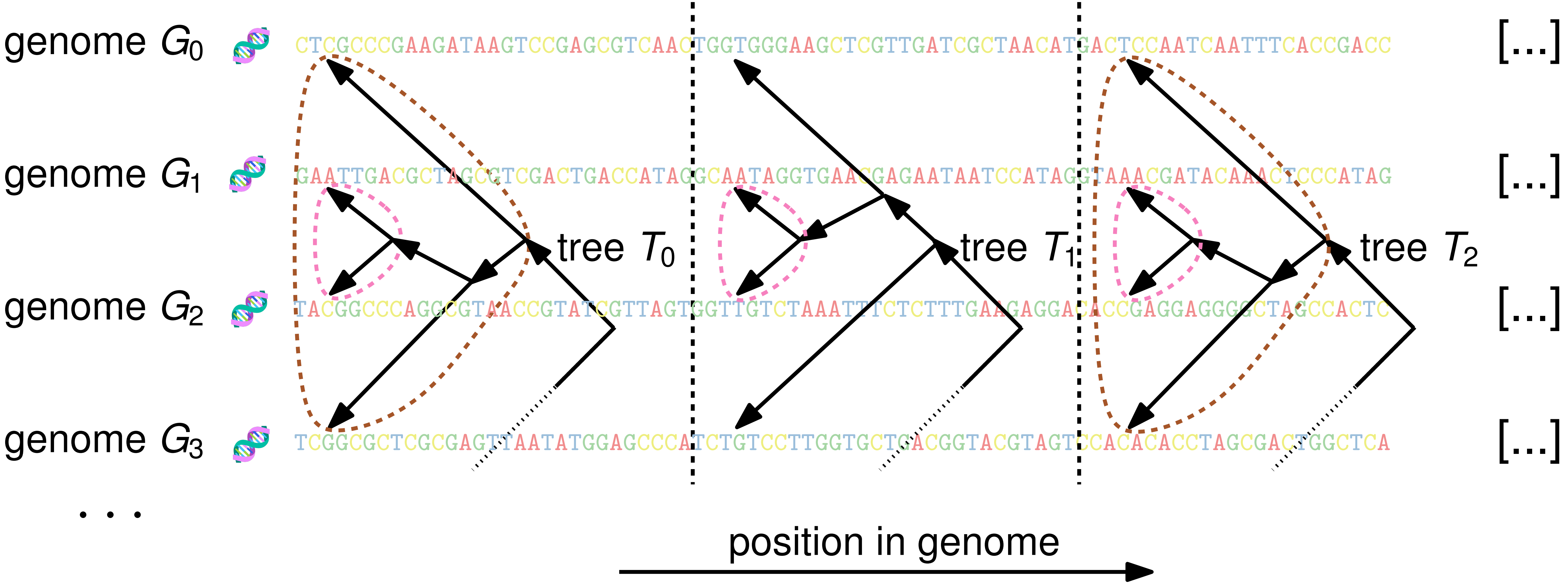
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[...]
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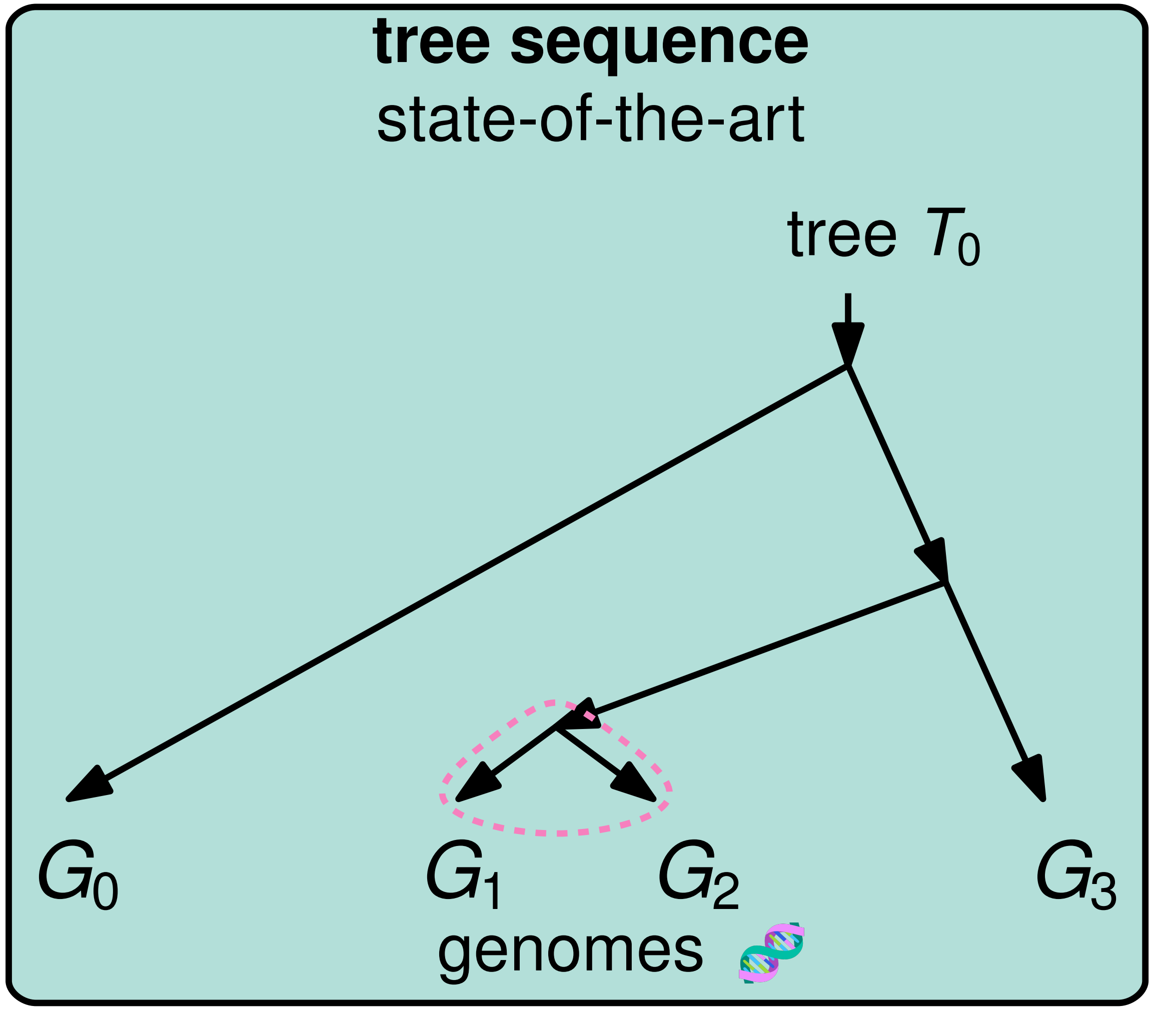
[...]
genome G_2
TACGGCCCAGGCGTAACCGTATCGTTAGTGGTTGTCTAAATTTCTCTTTGAAGAGGATACCGAGGAGGGGCTAGCCACTC
[...]
genome G_3
TCGGCGCTCGCGAGTTAATATGGAGCCCATCTGTCCTTGGTGCTGACGGTACGTAGTCCACACACCTAGCGACTGGCTCA
[...]
. . .
tree T_0
tree T_1
tree T_2
position in genome

Tree Sequences & Genealogical Forests



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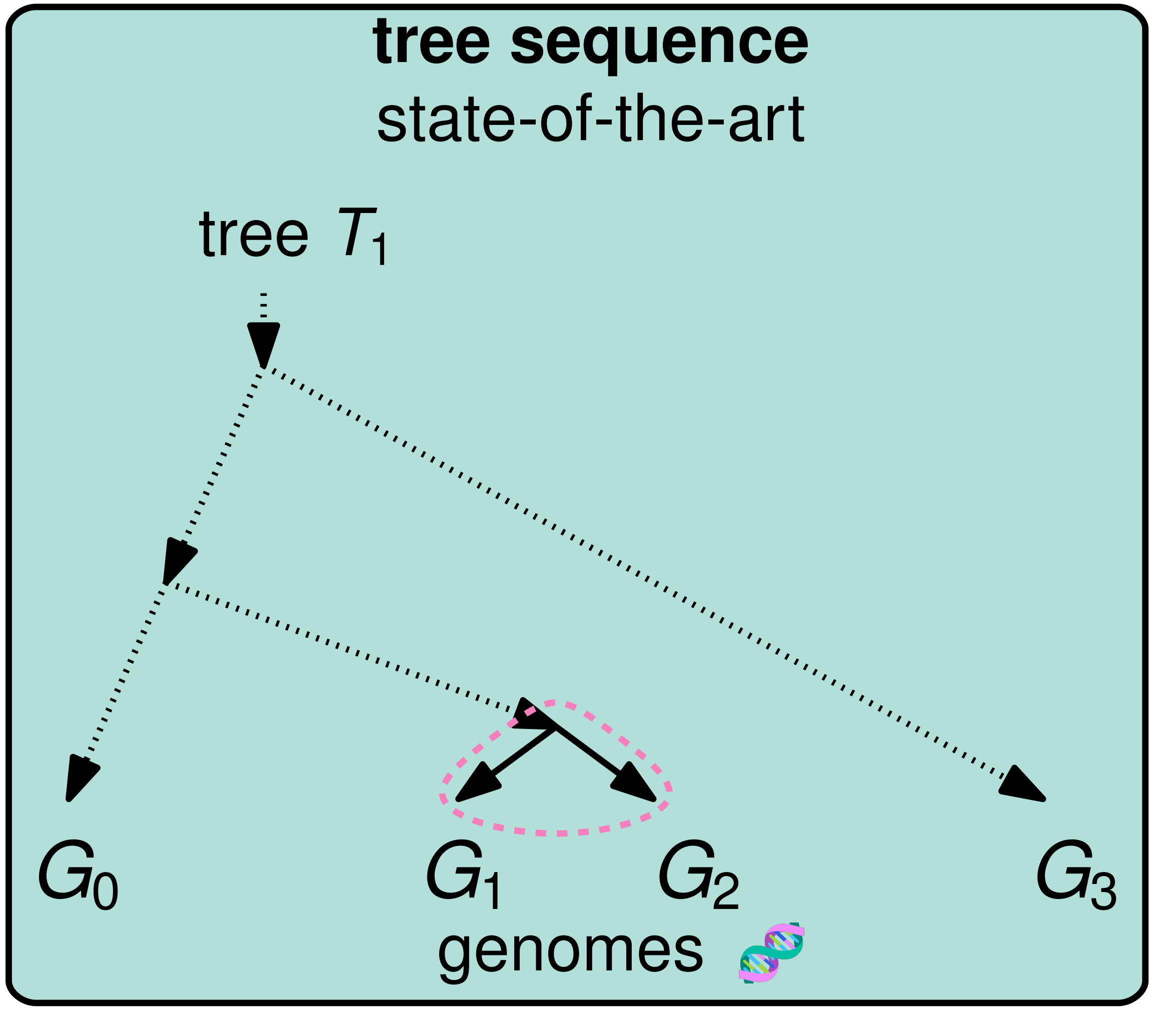

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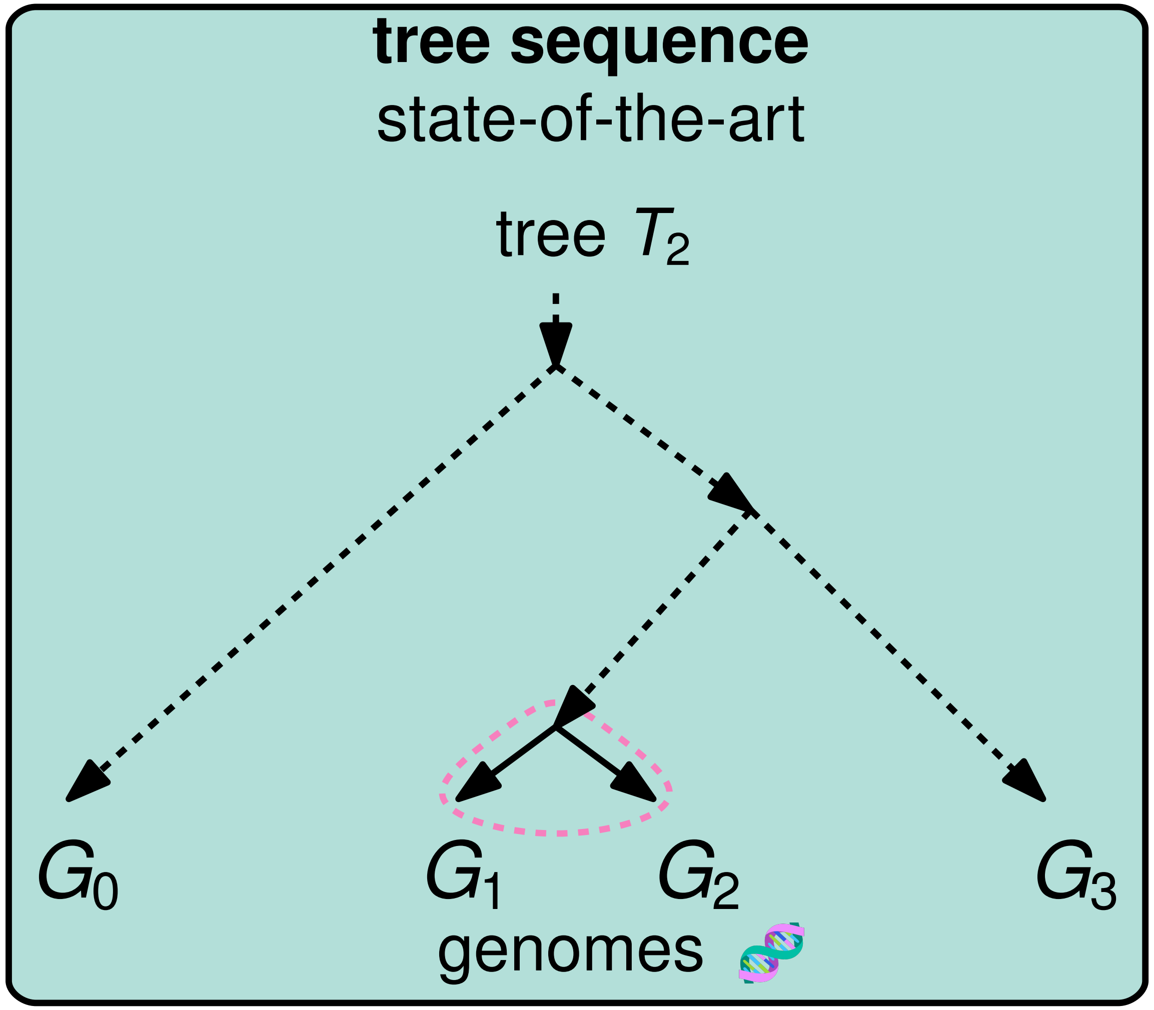

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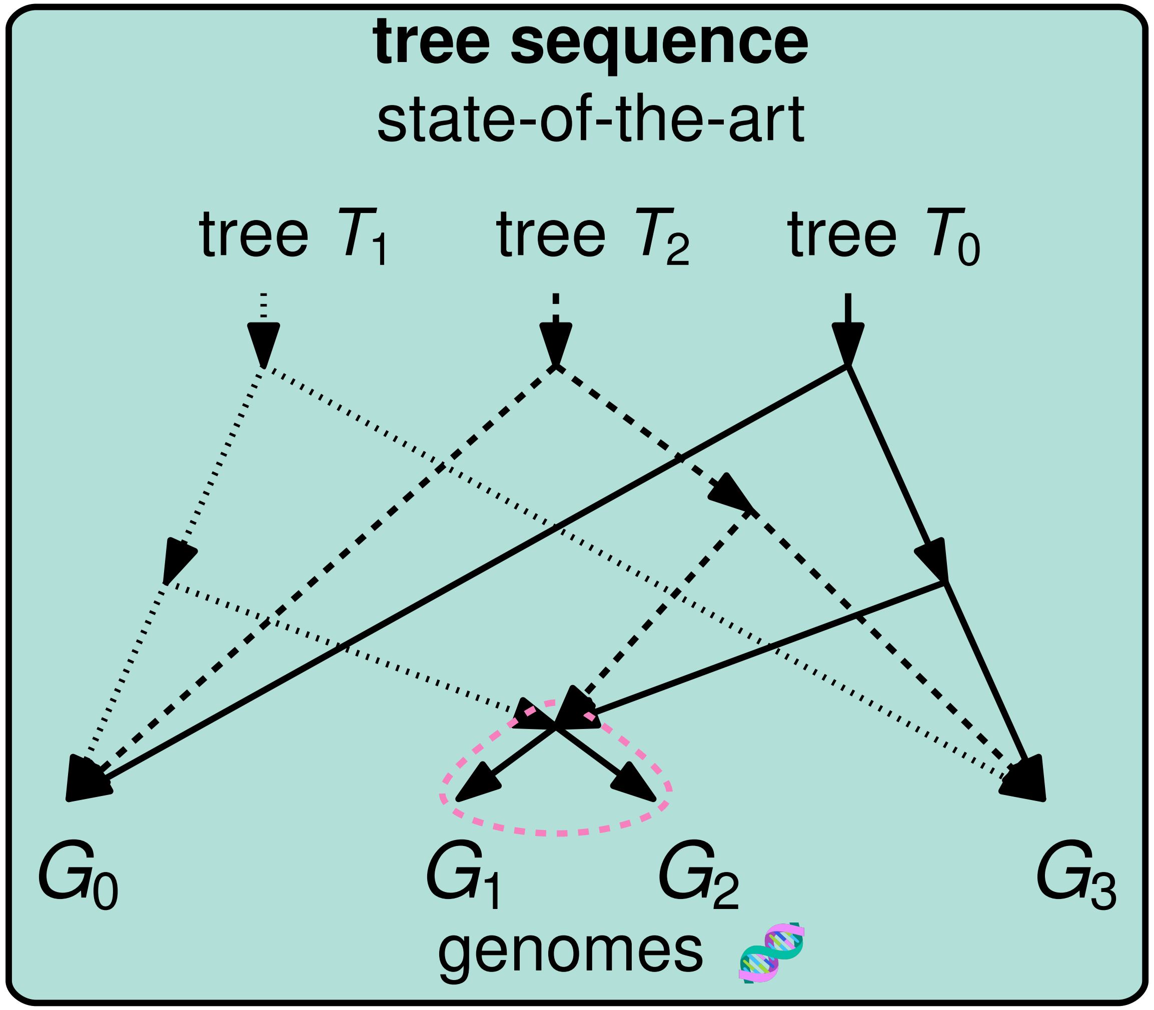
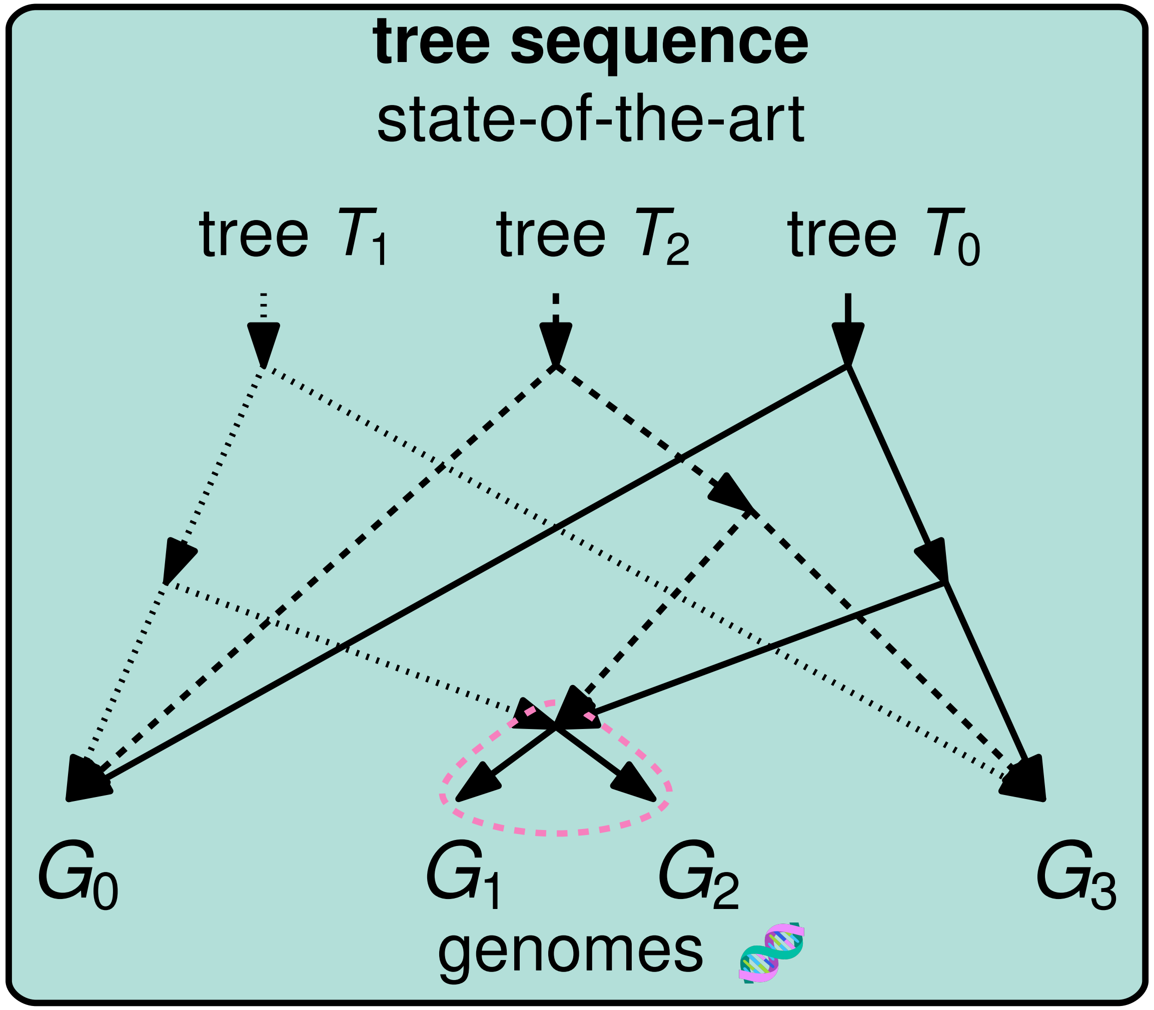


Tree Sequences & Genealogical Forests



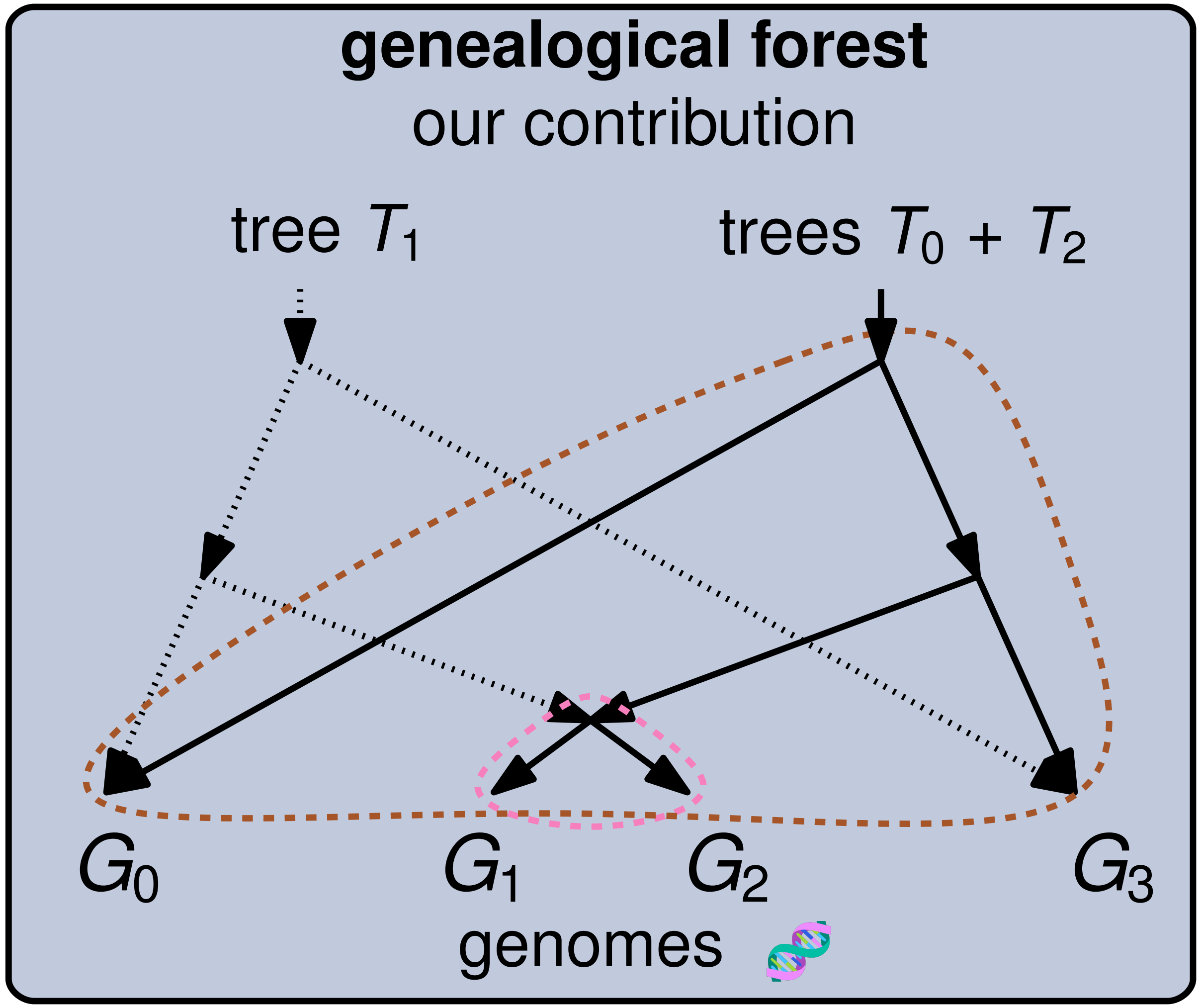
tree sequence

state-of-the-art

tree T_1 tree T_2 tree T_0

G_0 G_1 G_2 G_3

genomes 🧬



genealogical forest

our contribution

tree T_1 trees T_0 + T_2

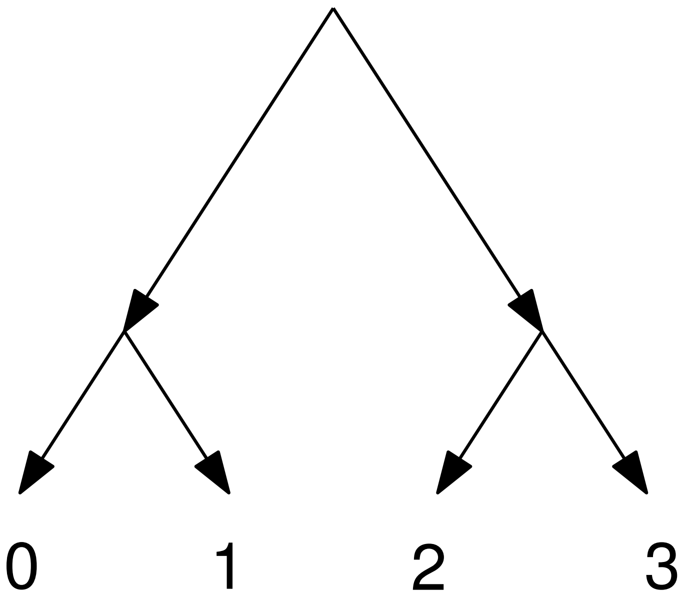
G_0 G_1 G_2 G_3

genomes 🧬

- Advantage: Straigt-forward memoization of intermediate results
- We don’t loose the order of trees

Constructing Genealogical Forests

- For each subtree in each tree in the input tree sequence
- Assign unique IDs to subtrees and represent them as nodes in a DAG



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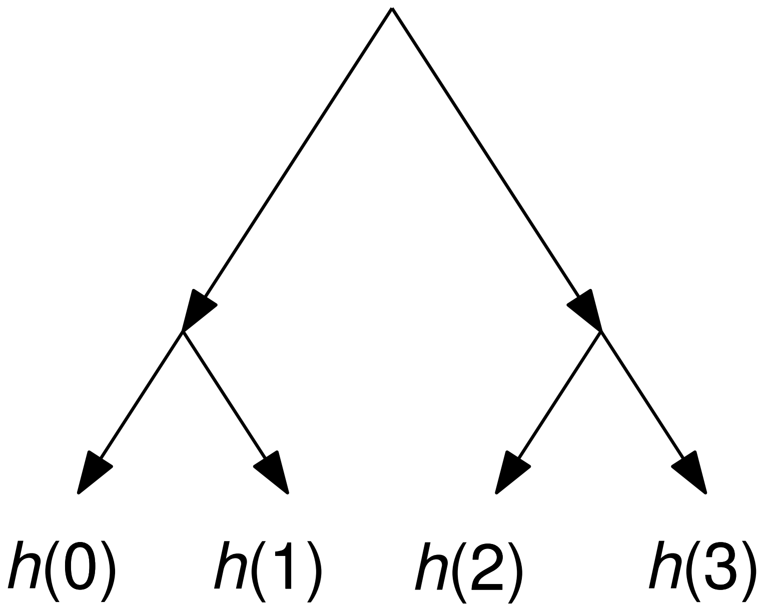

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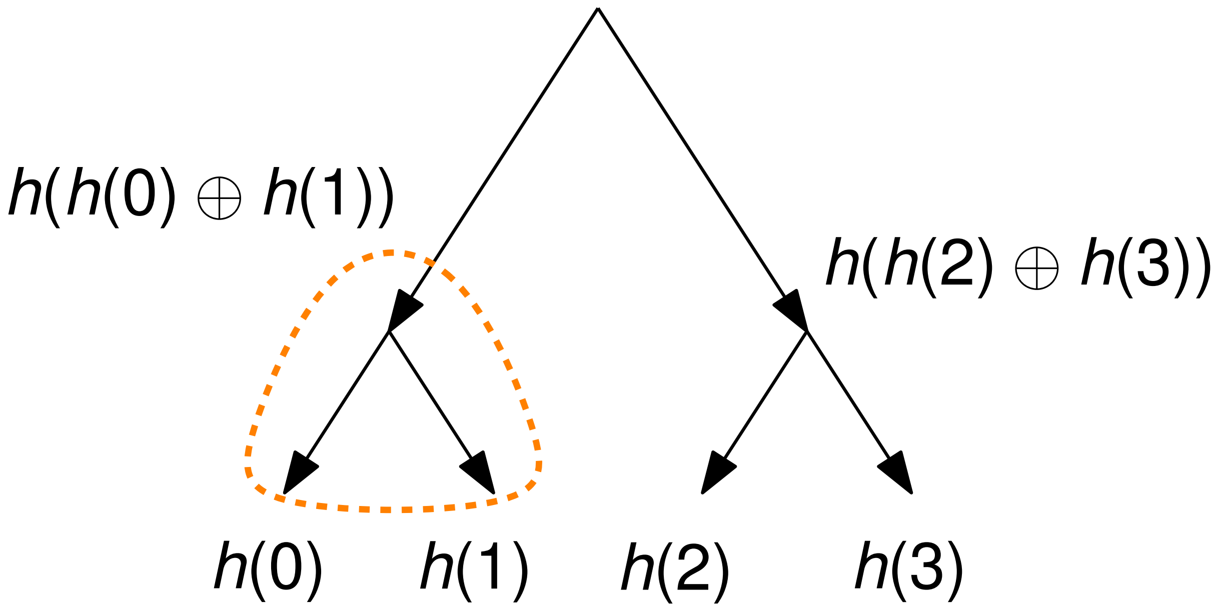

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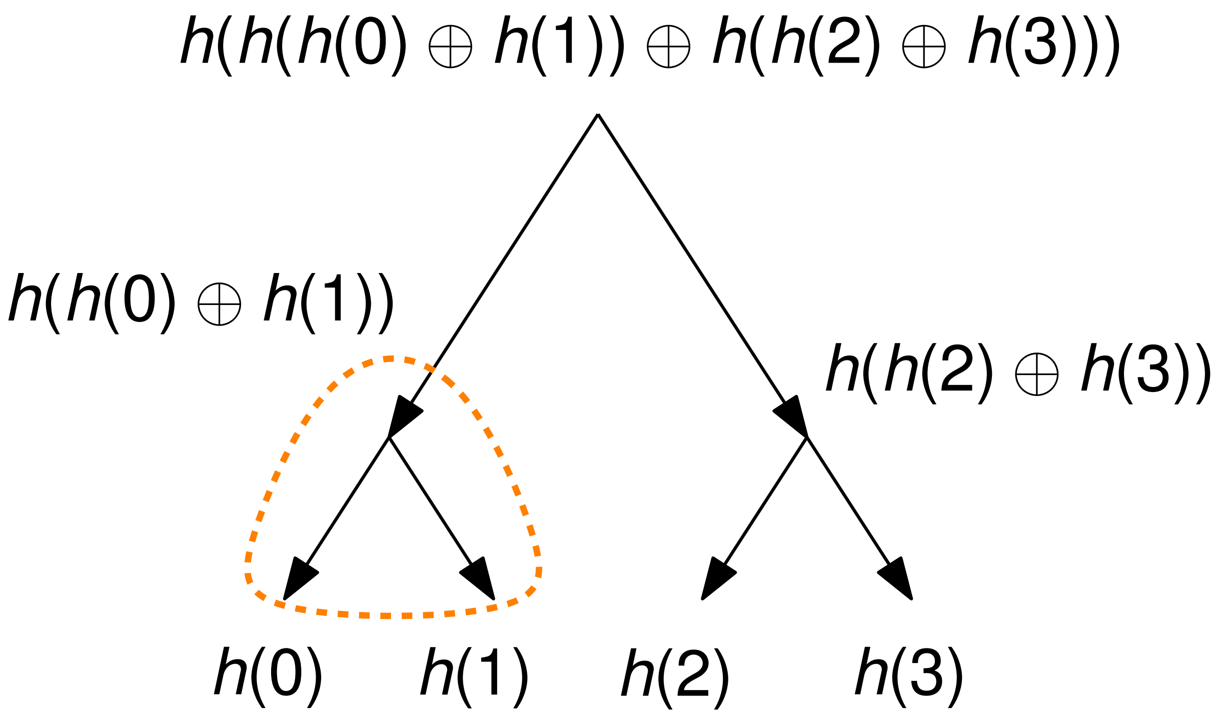

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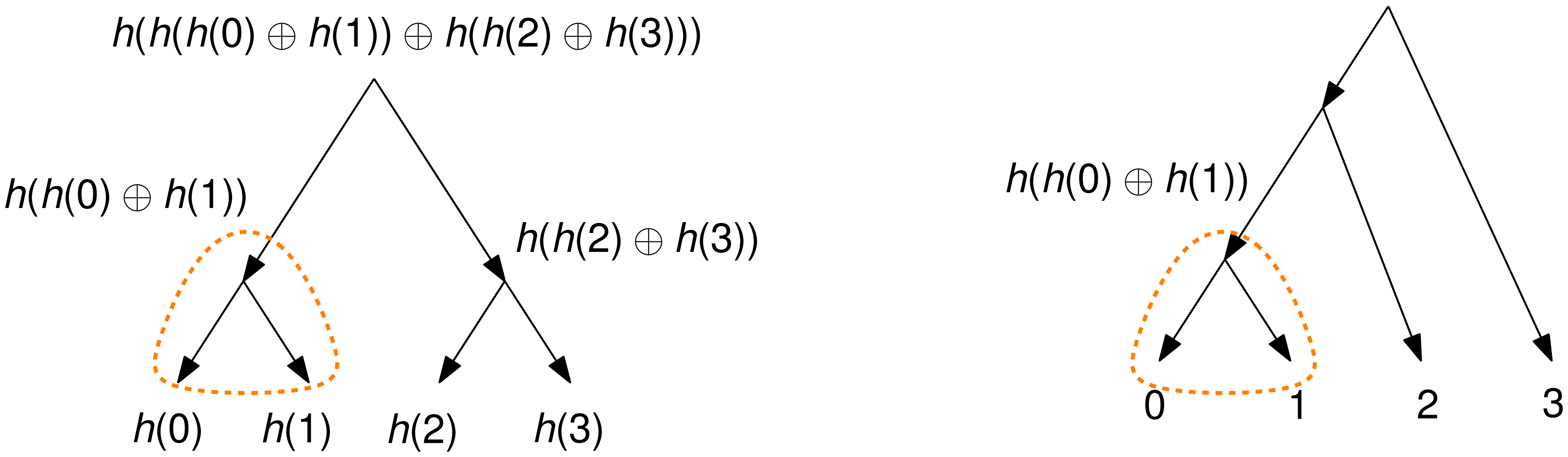

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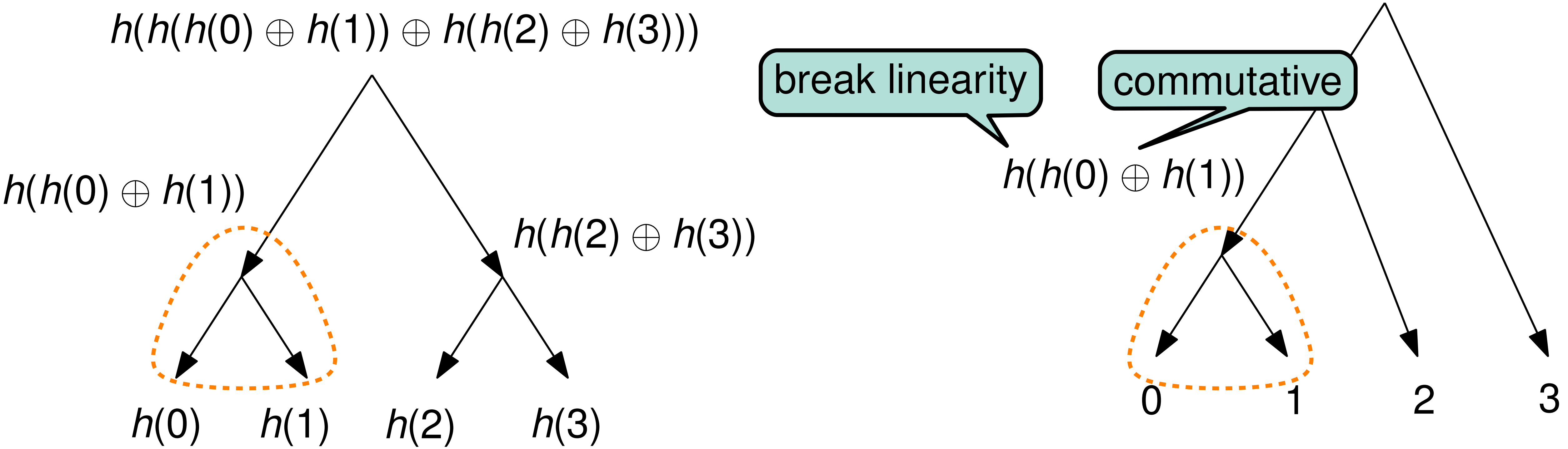

Statistics in Population Genetics

- We consider the genetic states of each genome at each site
- Many common statistics based on these Allele Frequencies
  - Diversity and Divergence
  - Patterson's f_2, f_3, and f_4
  - Fixation Index F_{ST}
  - Tajima's D

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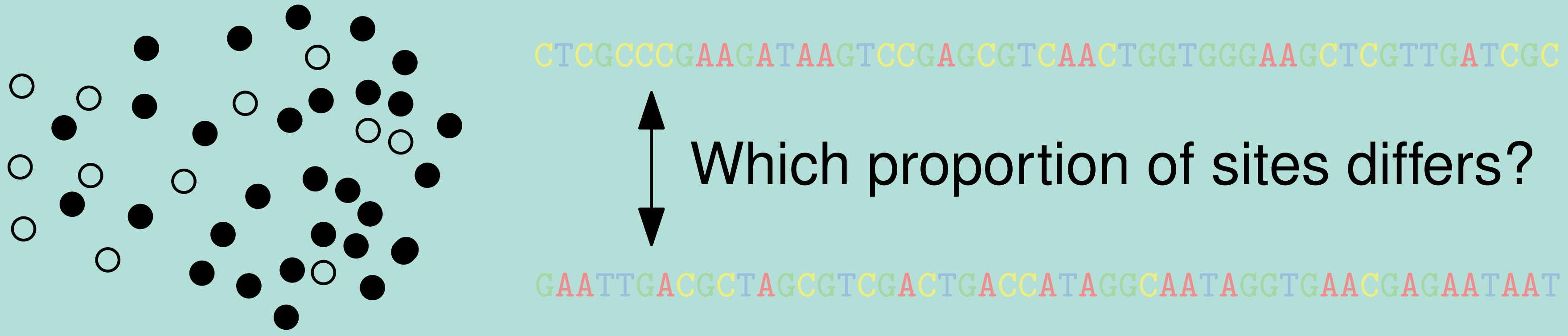
Diversity

average sequence difference


CTCGCCCGAAGATAAGTCCGAGCGTCAACTGGTGGGAAGCTCGTTGATCGC
GAATTGACGCTAGCGTCGACTGACCATAGGCAATAGGTGAACGAGAATAAT

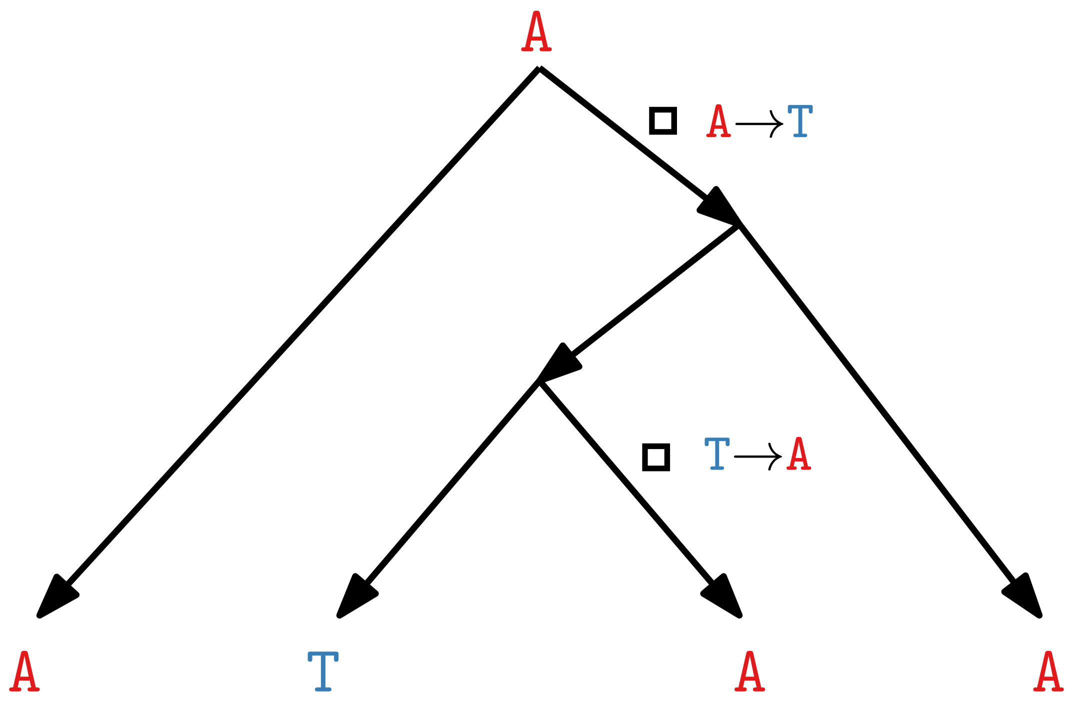
Which proportion of sites differs?

selection of genomes

Storing the Sequence

- These statistics are based on the sequences
- However, storing all sequences base-by-base is not feasible
- Instead, for each site, store the ancestral state and the mutations

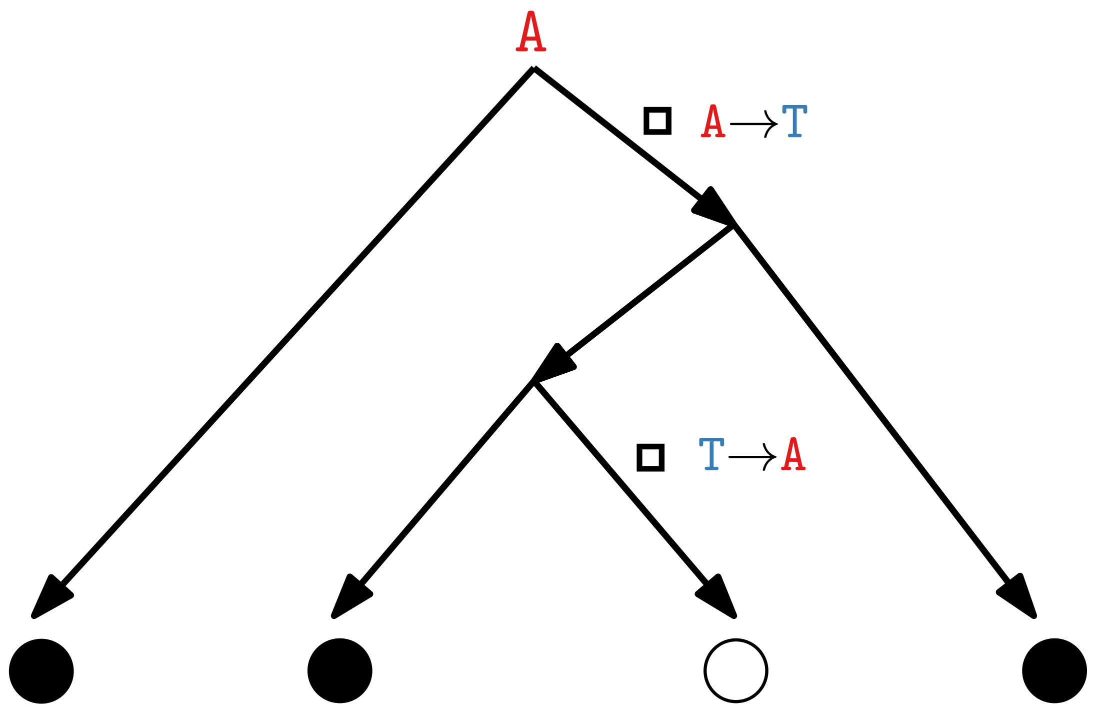
```
TTCGCGCGAAGATAAGTCCGACCGTTAACTGGTGGGAAGCTTGT
CTCGCCCGAAGATAAGTCCGATCGTCAACTGGTAGGGAGCTCGT
CTCGCCCGAAGATAAGTCCGAGCGTACACTGGTGGGAAGCACGT
CTCGCGCGATGTTAAGTCCCACCGTCAACTGGTGGGAAGCTCGT
                    ...
```



Computing Population Genetics Statistics

Diversity: Average sequence difference between two samples

Input: Selection of genomes ●○○●○○● & Tree sequence with mutations □ T→A



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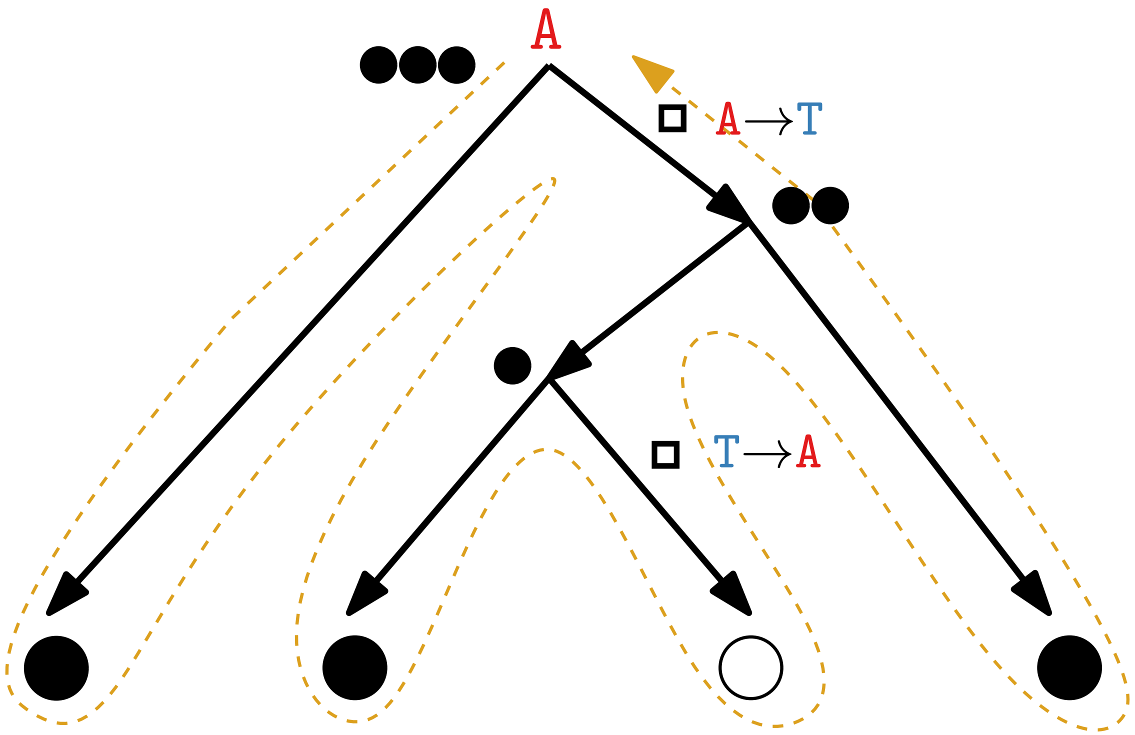

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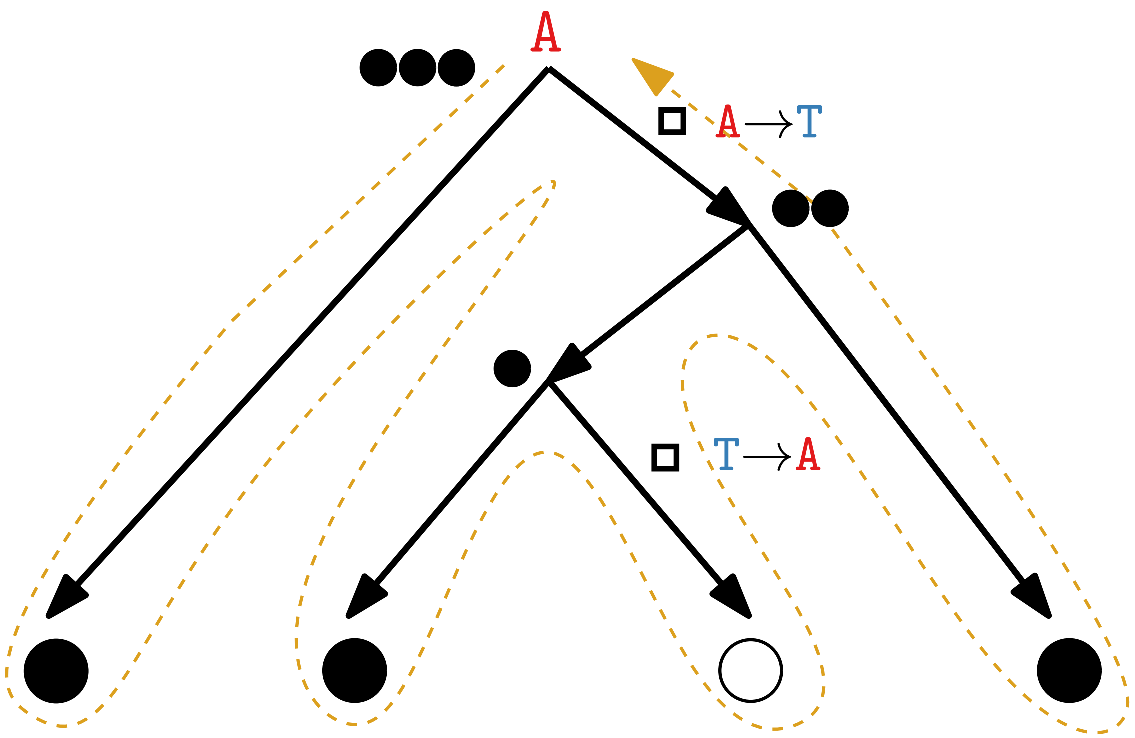
(2) Compute allele frequencies

A: 3 C: 0 T: 0 G: 0

- Ancestral State: A
- Mutation A → T at
- Mutation T → A at



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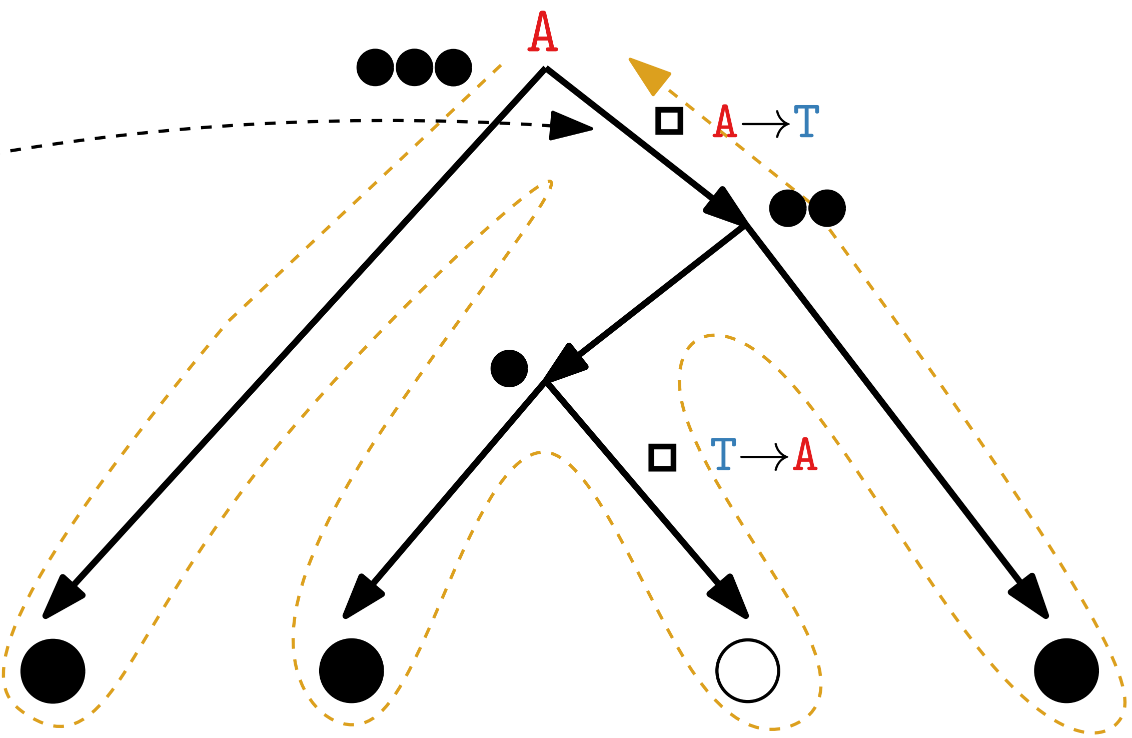
A: 1 C: 0 T: 2 G: 0

- Ancestral State: A
- Mutation A → T at ●
- Mutation T → A at



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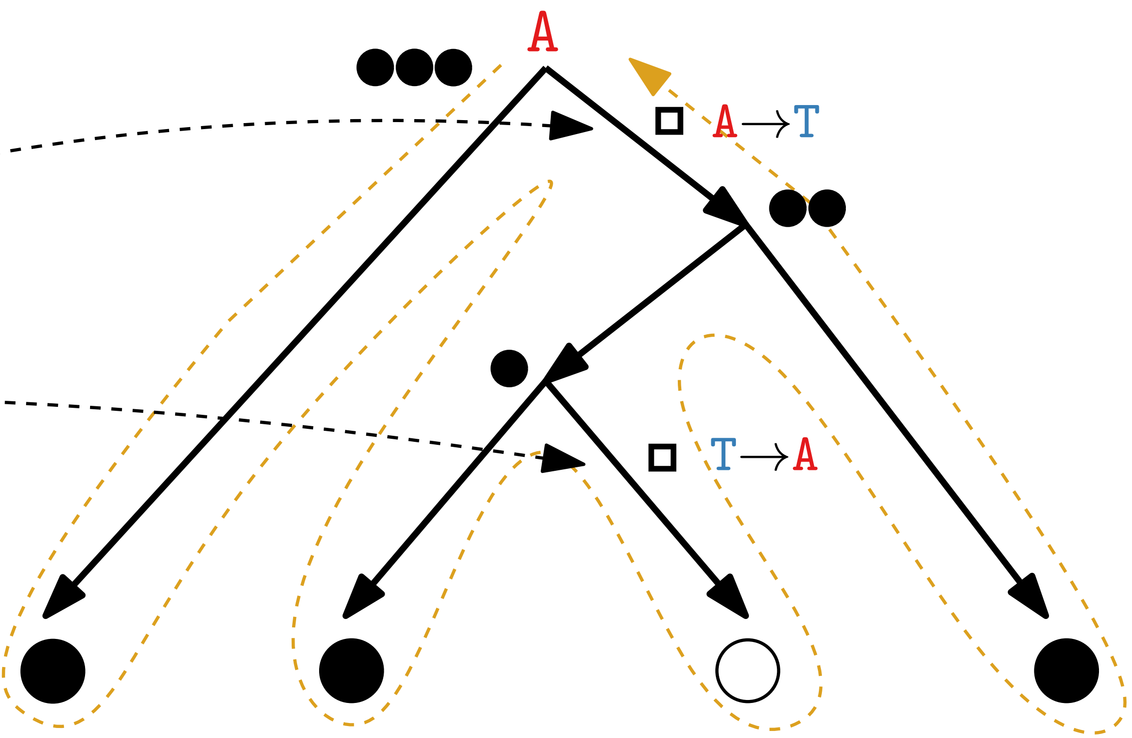

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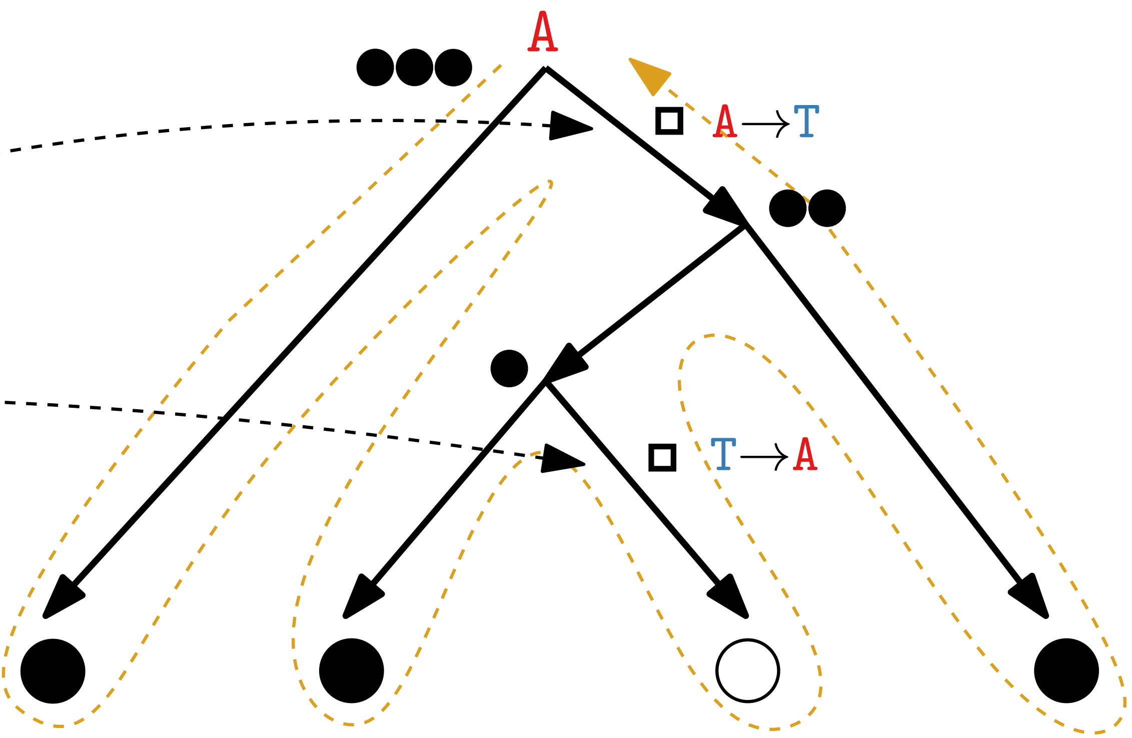
(3) Compute average difference

- Diversity = $\frac{\text{freq}_A \cdot (1 - \text{freq}_A) + \ldots}{n \cdot (n-1)}$



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- post-order traversal

90 % of runtime

(2) Compute allele frequencies

A: 1 C: 0 T: 2 G: 0

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(3) Compute average difference

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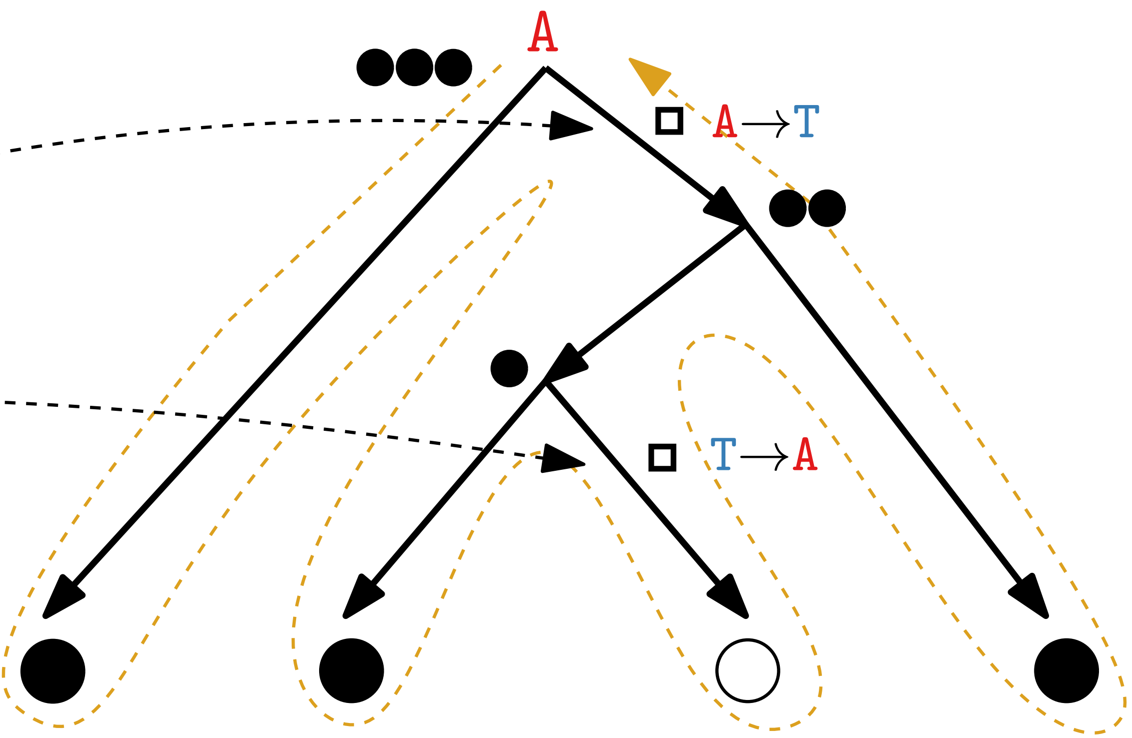
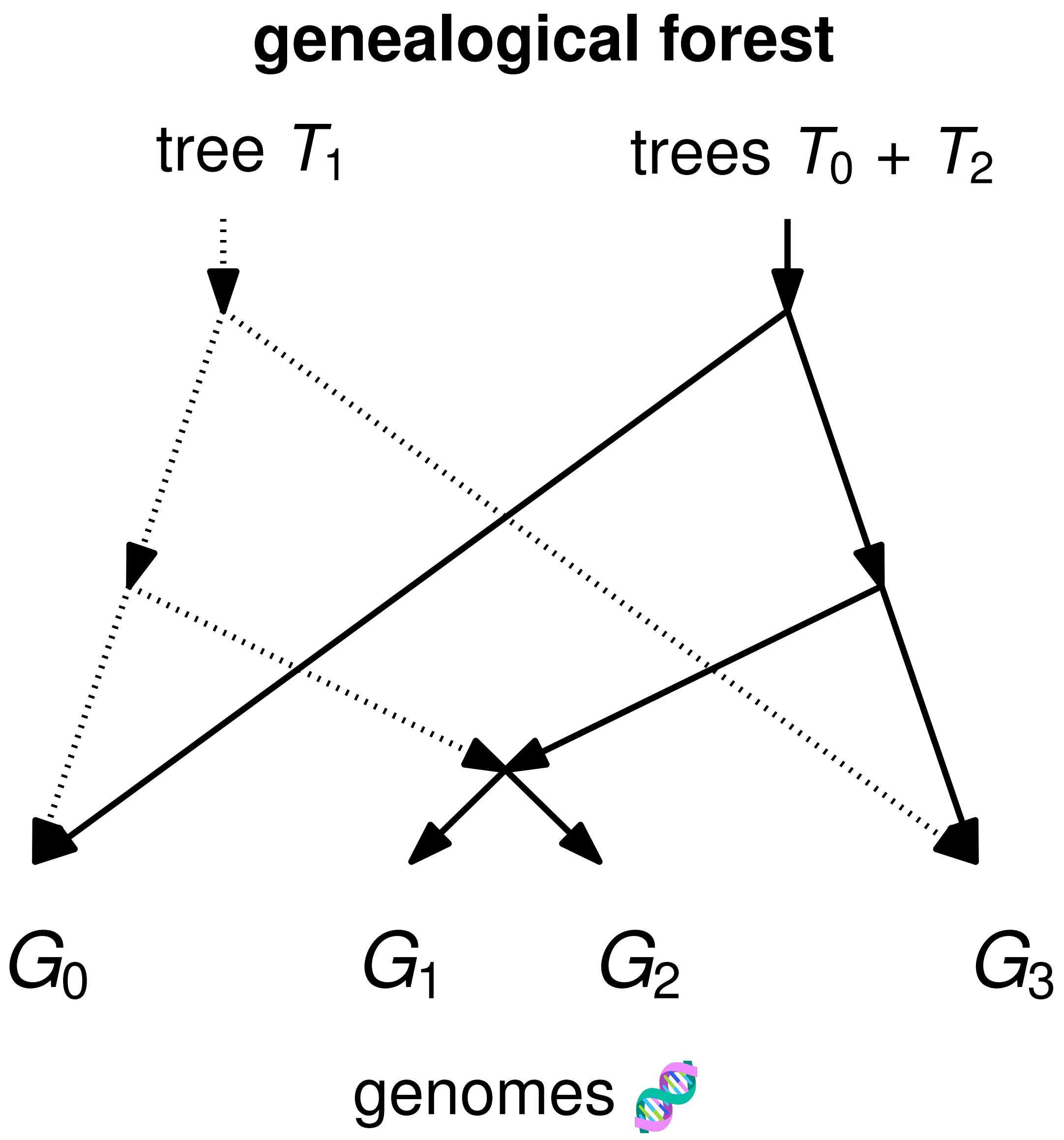


Post-Order Traversal

- Children of a node processed before the node
- Associate a node's result with its DAG node ID
  $\Rightarrow$ Straight-forward memoization



Post-Order Traversal

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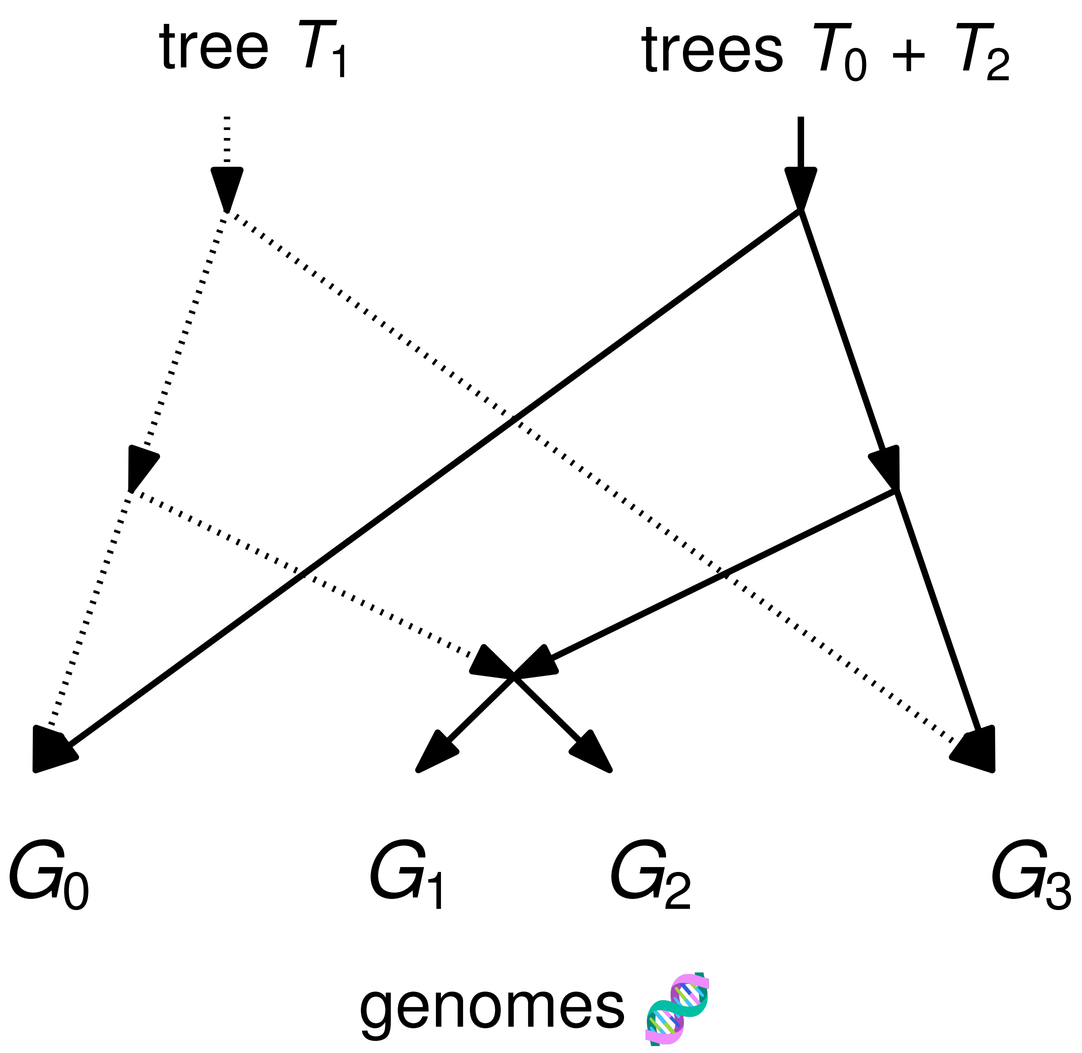
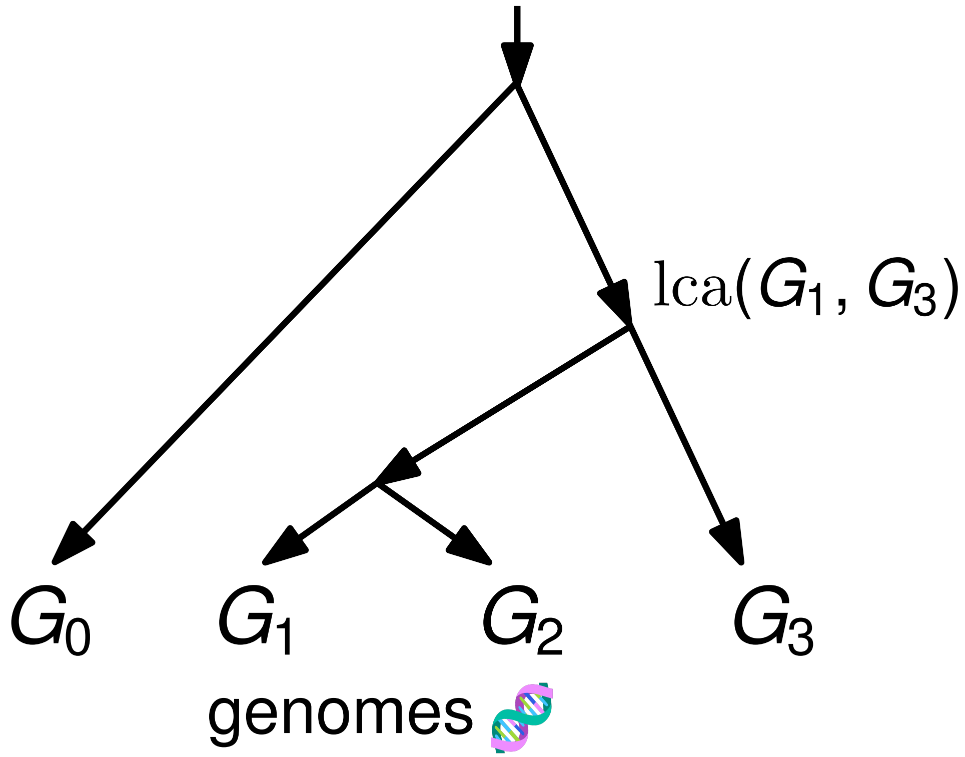
Intermediate results reused
5.1 times on average

genealogical forest



Lowest Common Ancestors



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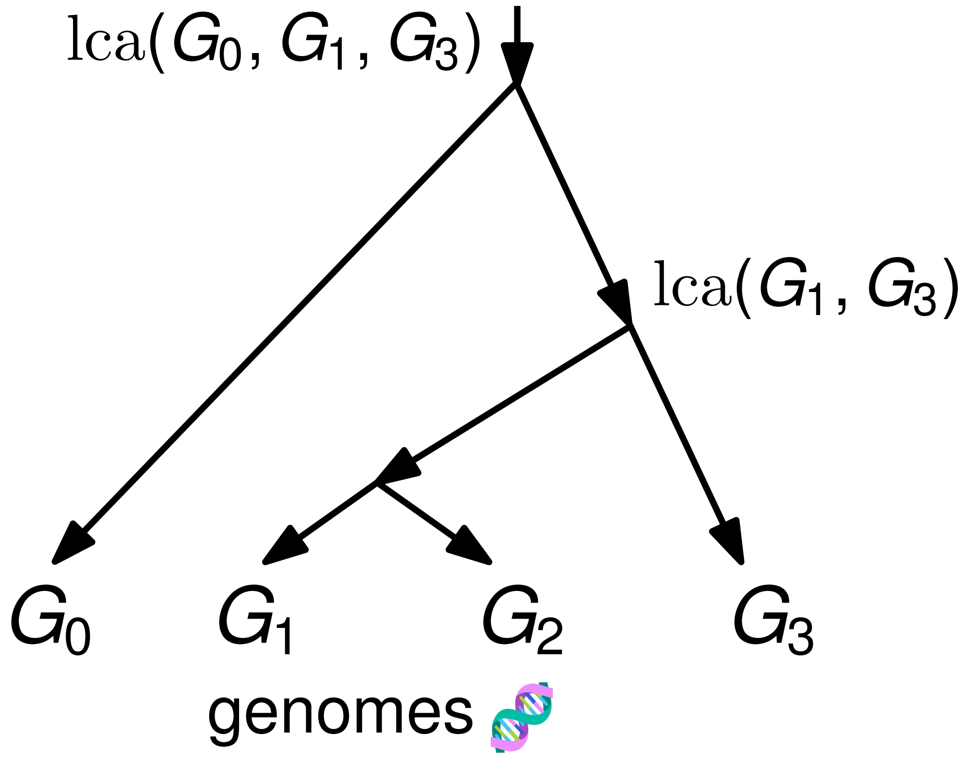

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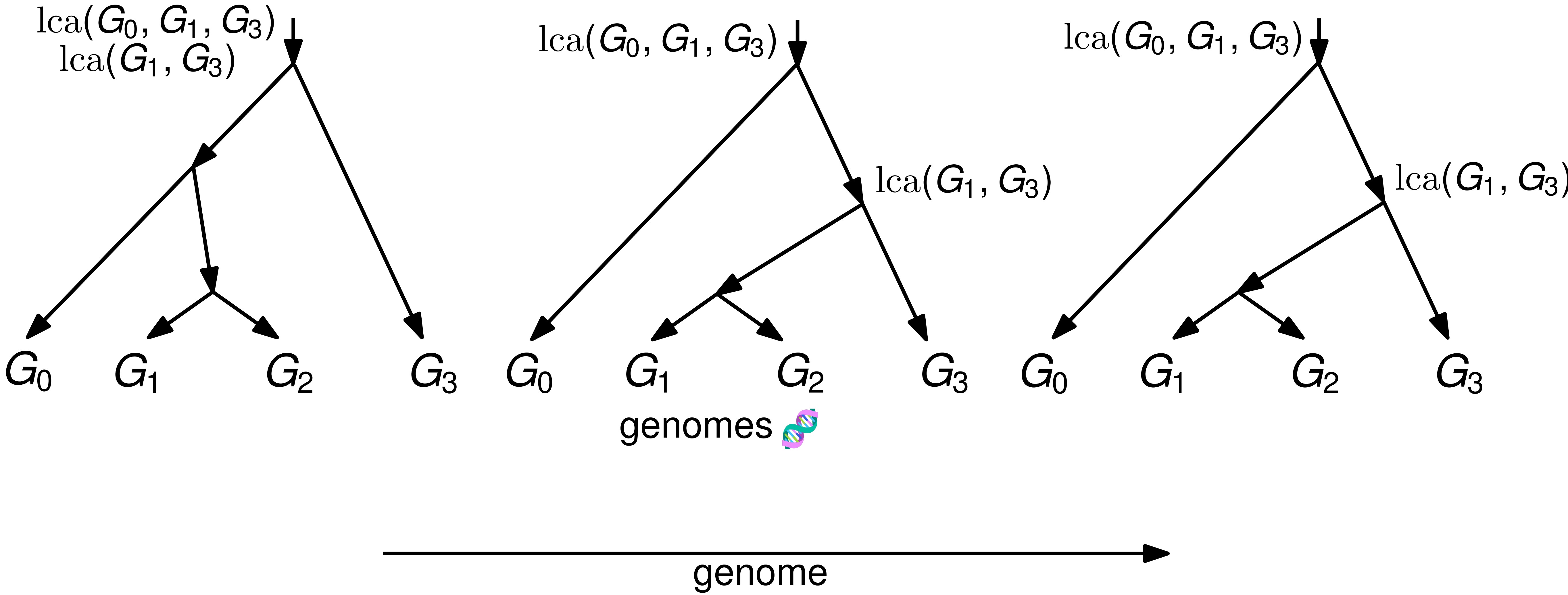


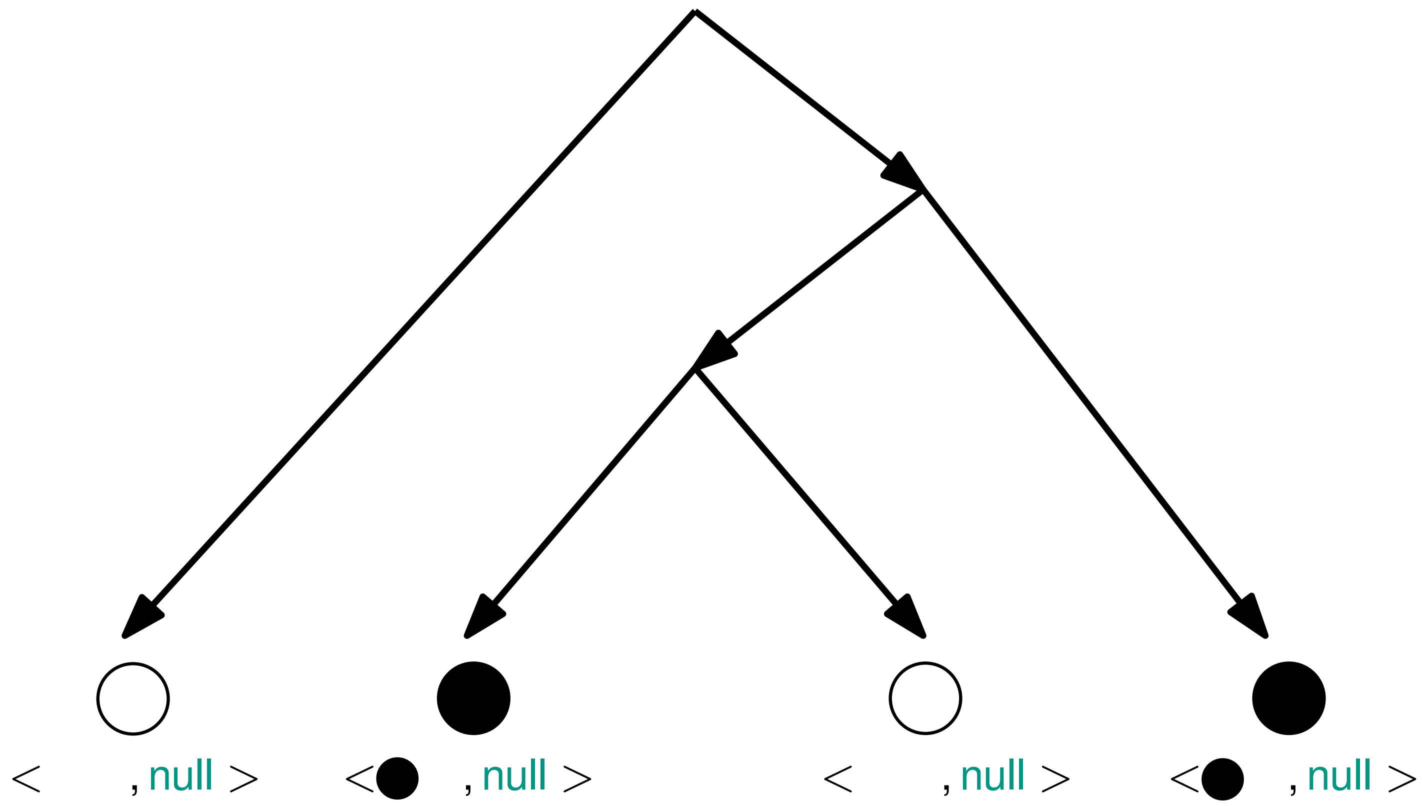
Computing the Lowest Common Ancestor

Lowest Common Ancestor Node farthest from the root where paths to root converge

Input: Selection of samples & Tree sequence

(1) Compute number of samples in subtree

- post-order traversal
- $<$ sample count, LCA $>$



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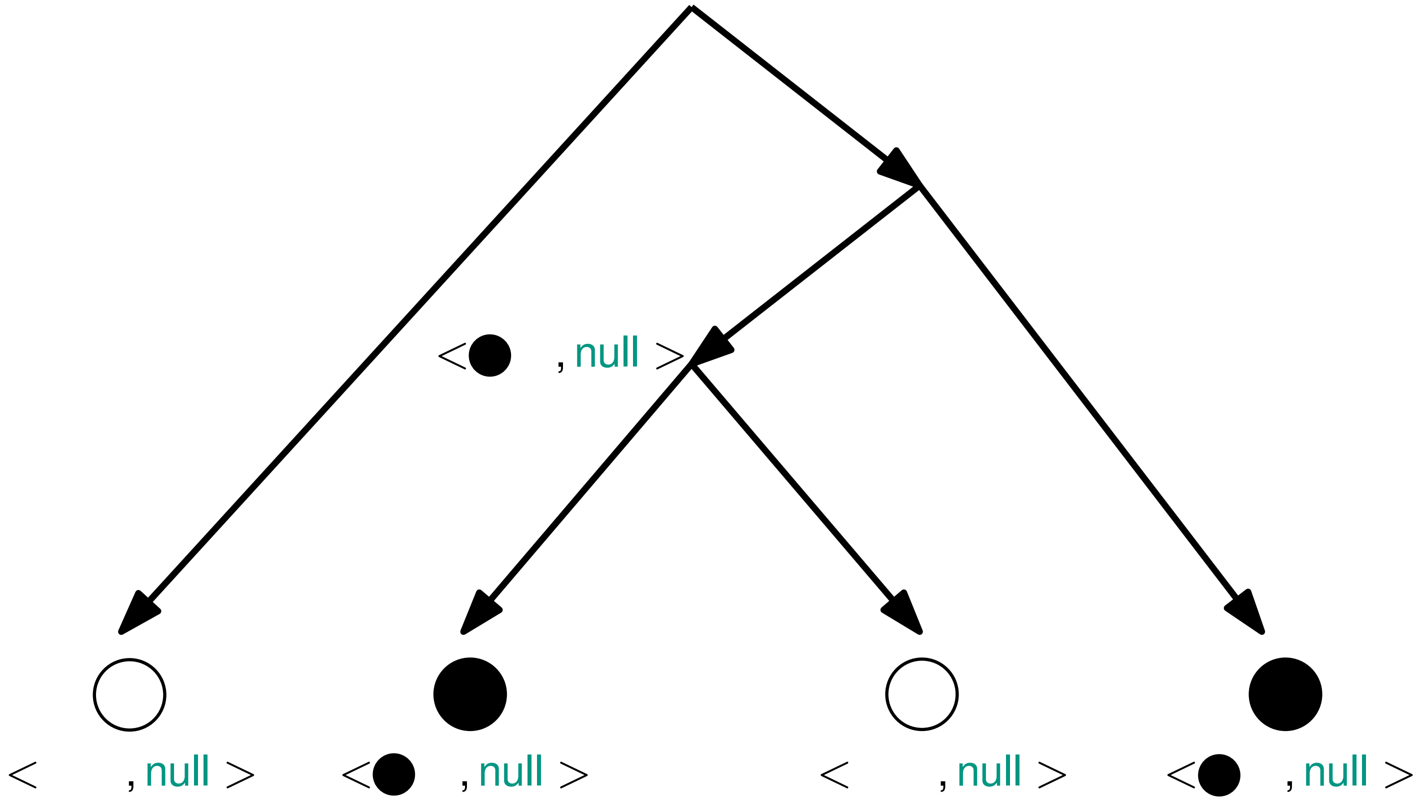

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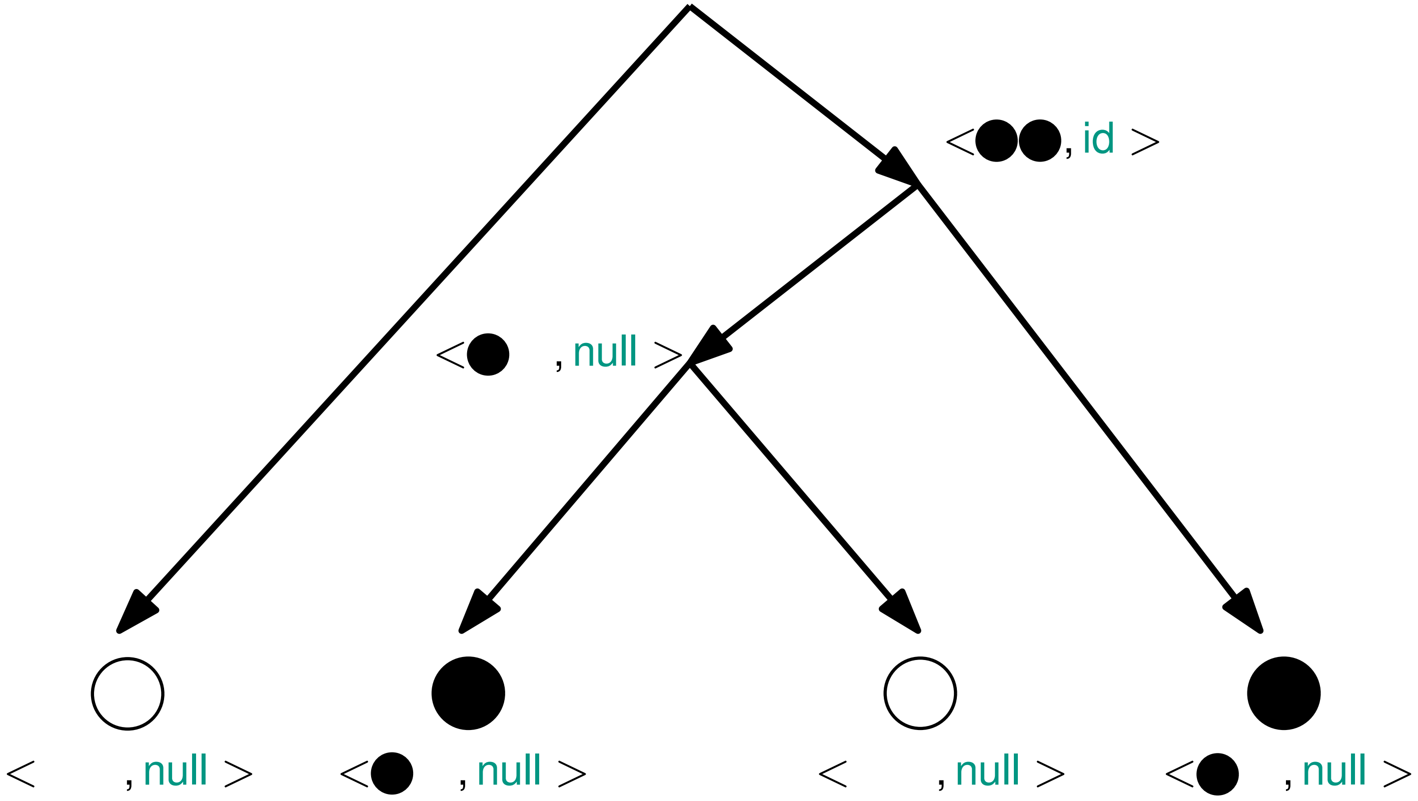

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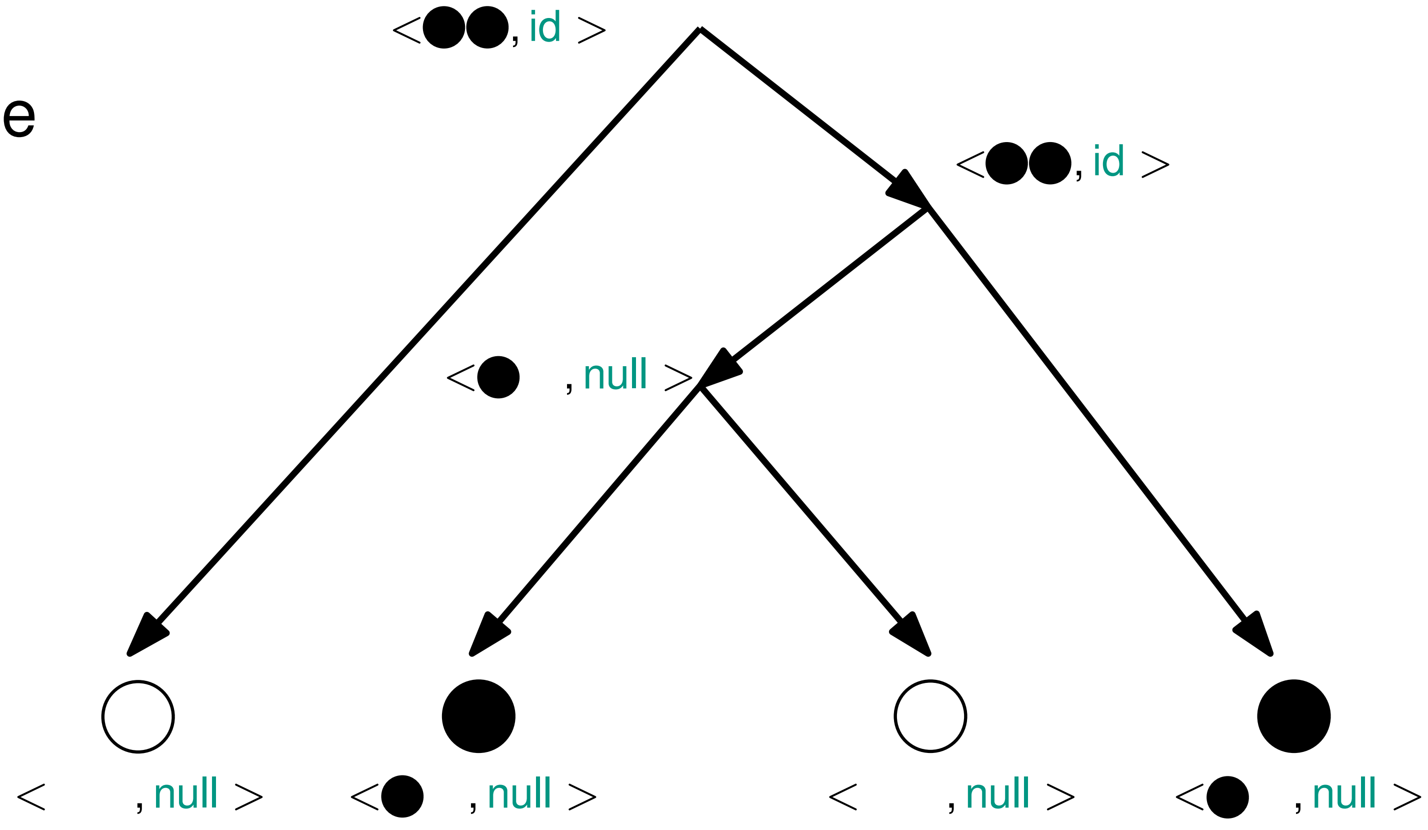
(2) Return LCA per tree in tree sequence



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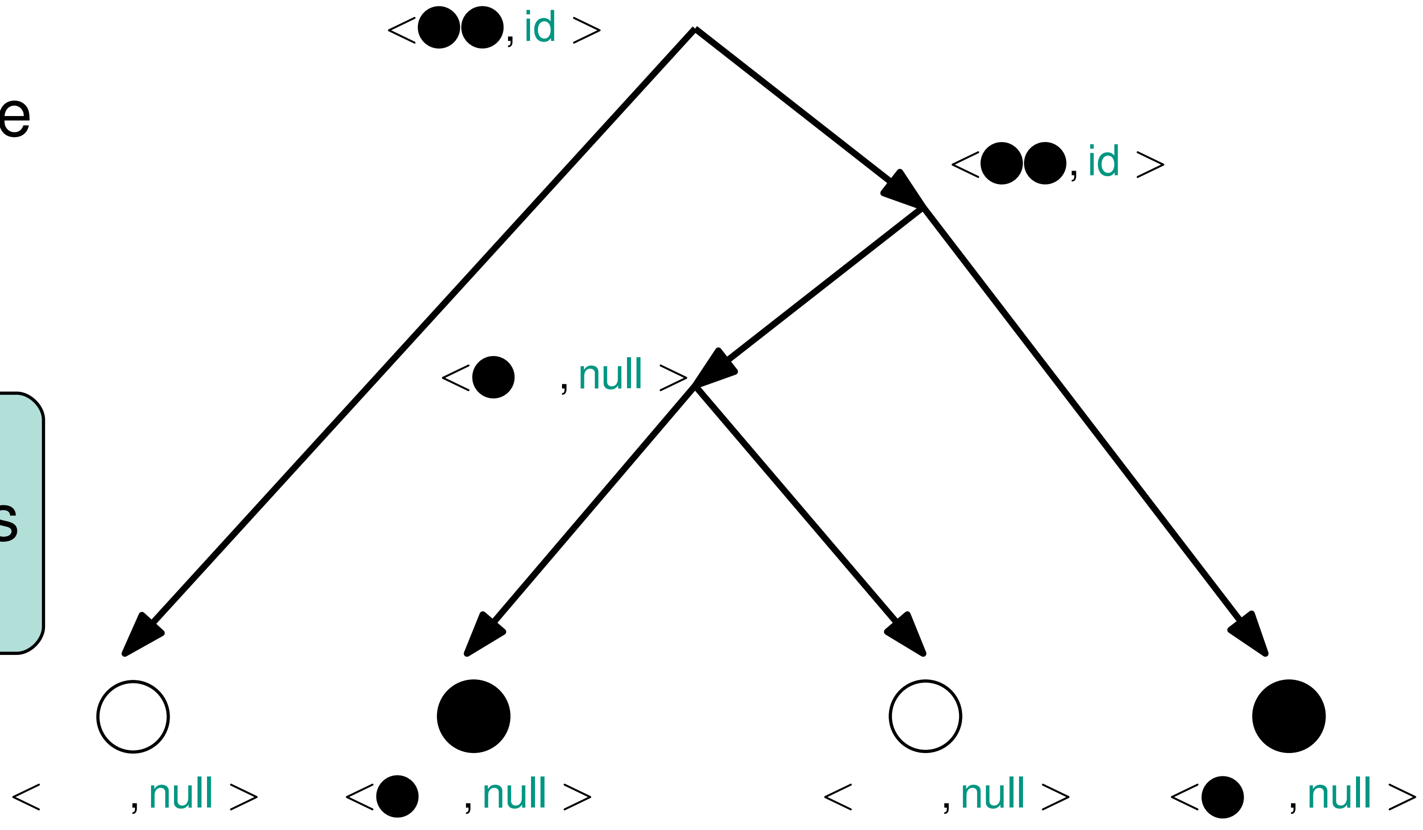
Runtime

`gfkit:` independent of selected samples

`tskit:` chains pair-wise queries



Evaluation

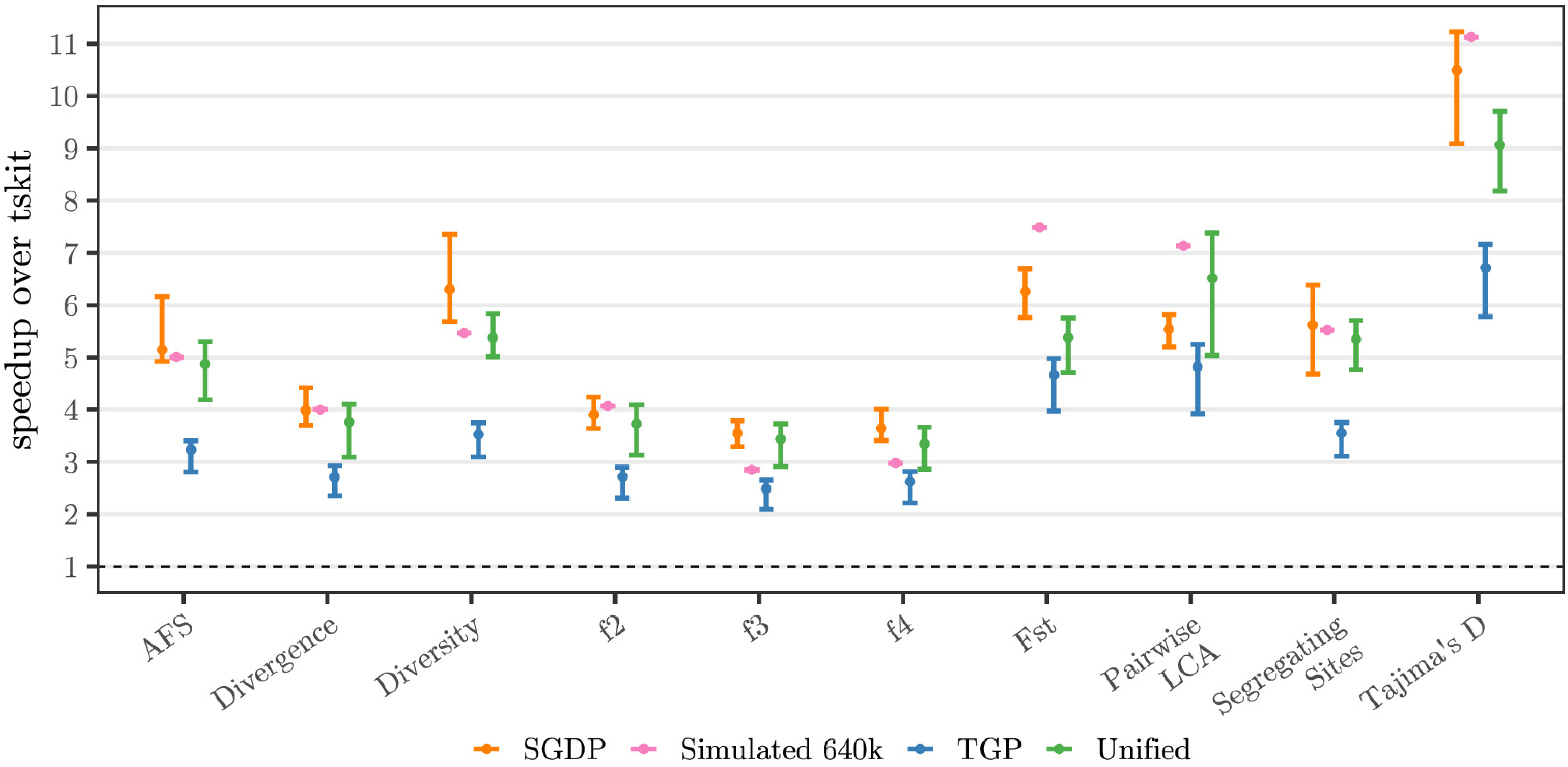
Software and Hardware

- C++20, CMake 3.25.1, gcc 12.1, ld 2.38
- AMD EPYC 7551P CPU
- 8 banks of 32 GiB DDR4 RAM
- All experiments are single-threaded

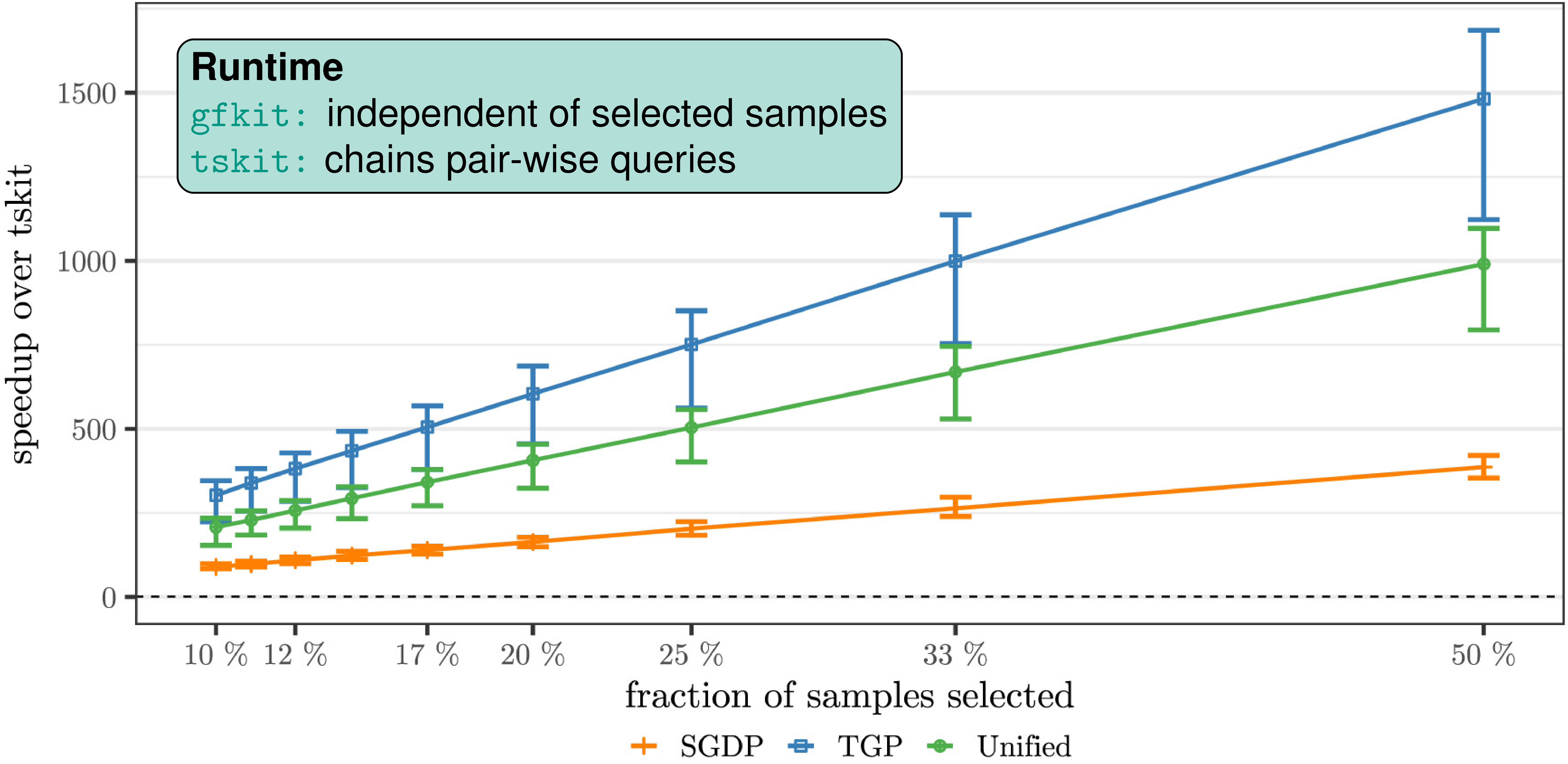
Datasets

- Human (GRCh38)
- Empirical
  - Thousand Genomes Project (Auton et al., 2015)
  - Simons Genome Diversity Project (Mallik et al., 2016)
  - Unified (TGP+SGDP+Ancestral; Wohns et al., 2022)
- Simulated: Chromosome 20, $640\,000$ samples

Evaluation: Computing Statistics



Evaluation: Computing the LCA



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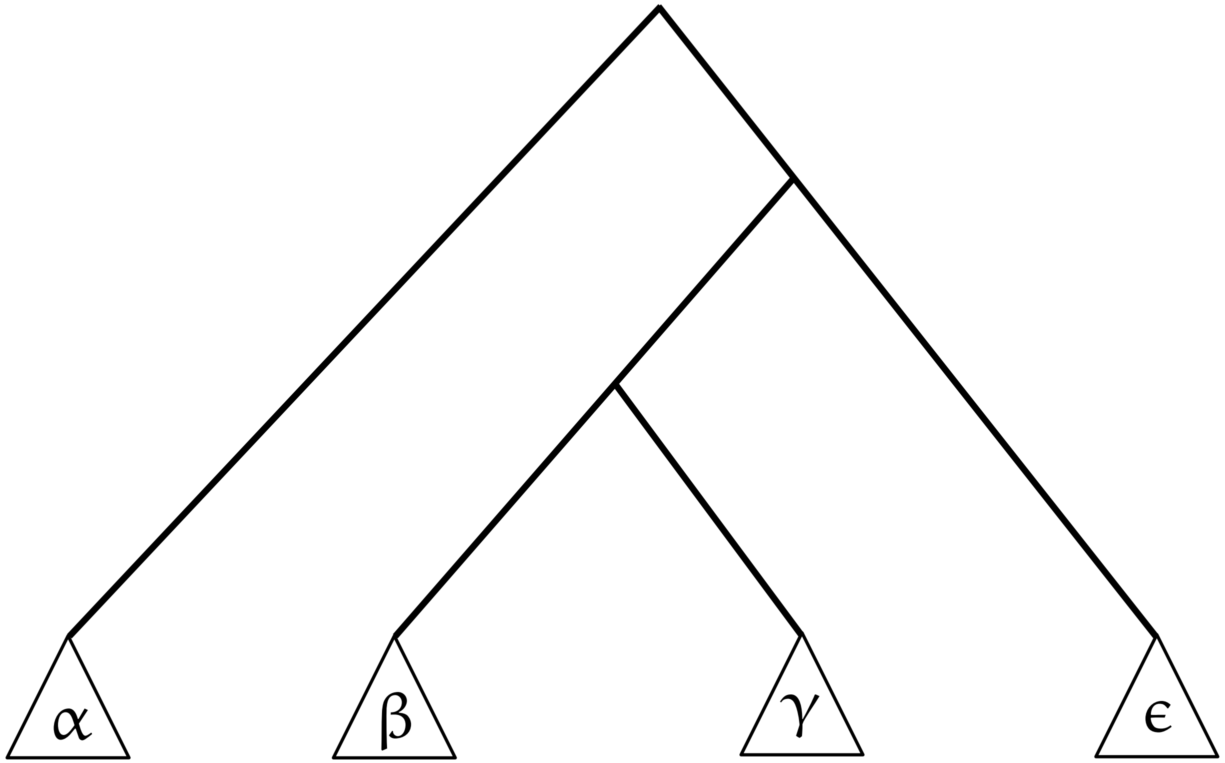

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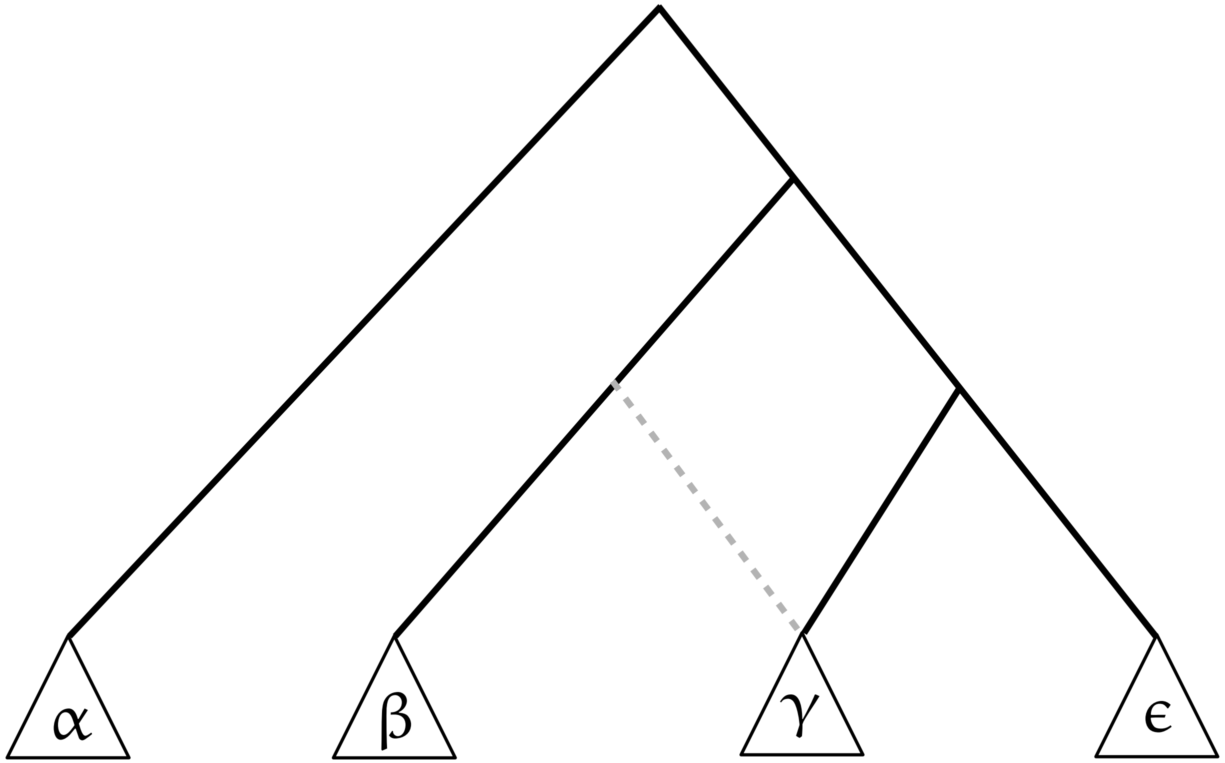

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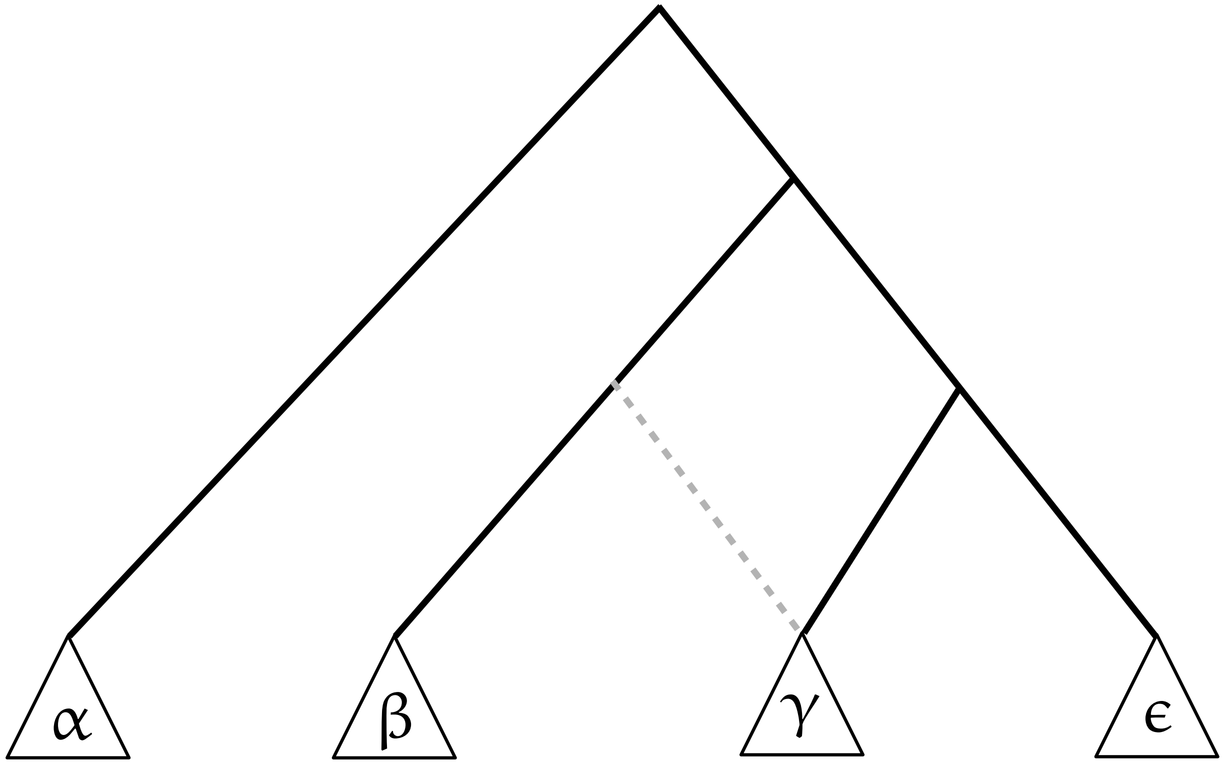


Factoring out all unique subtrees

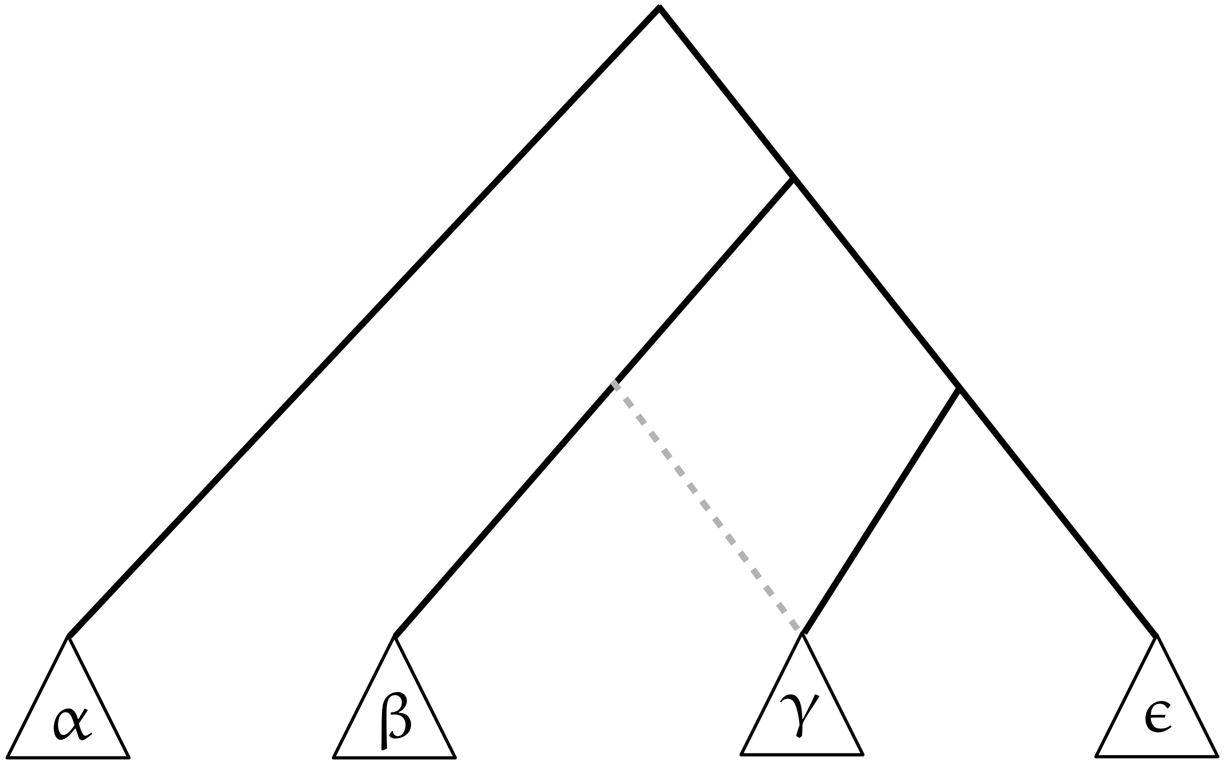
- A single edit (edge out/edge in)
- Possibly many new subtrees

↕ vs.

Reusing subtrees across all trees

- Unique subtrees encoded once, even if far apart along the genome
- Each subtree reused 5.1 times

Memory Consumption



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`gfkit` needs 2.7 to 7.90 more space to store the trees

Limitations & Future Work

Current Limitations

- Higher memory usage on current empirical data
- Not all of `tskit`'s features supported yet, e.g.
  - branch and node-based statistics
  - partial trees
  - augmentation to full ARGs

Future Work

- Parallelization
- Top-tree based compression possible?
- Balanced-Parenthesis based encoding + string compression
- “Almost all” LCA-queries & All-Pairs LCA
- Automatic subpopulation detection

Conclusion

- Evolutionary history of recombining organisms better modelled with multiple trees
- State-of-the-art: Store edit operations between trees along the genome
- Novel approach: Encode trees as DAG, storing unique subtrees only once
- Advantage: Straight-forward memoization of intermediate results
- Speedup: 2.1 to 11.2 (median 4.0; AFS-based statistics), 100 to 1000 (LCA)
- Main drawback: Higher memory usage