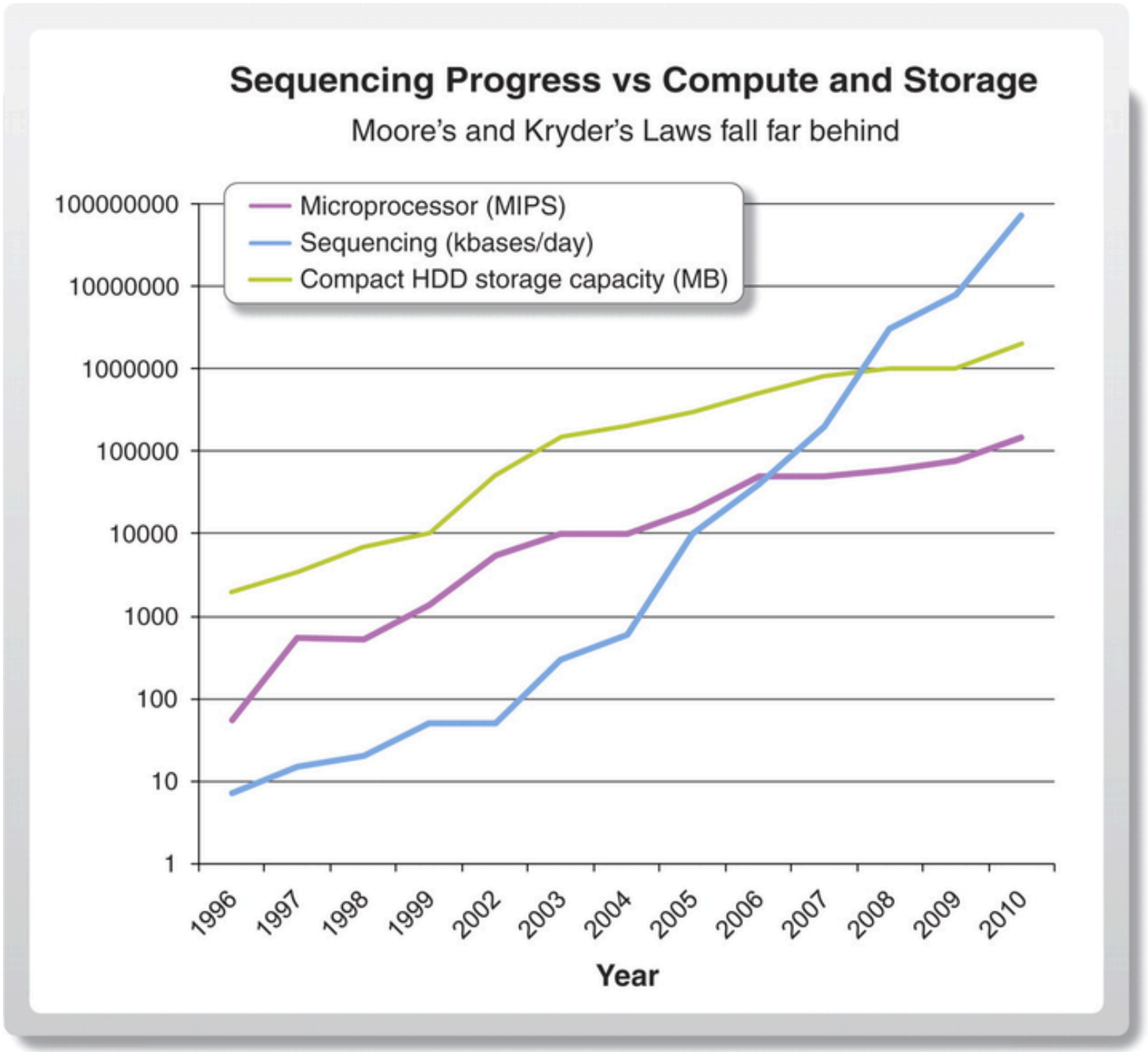
Genealogical analysis

Trees, tree sequences, and tskit

Genomic data is big

and tedious to analyse



Kahn, S: 2011 (!)
doi: 10.1126/science.119789

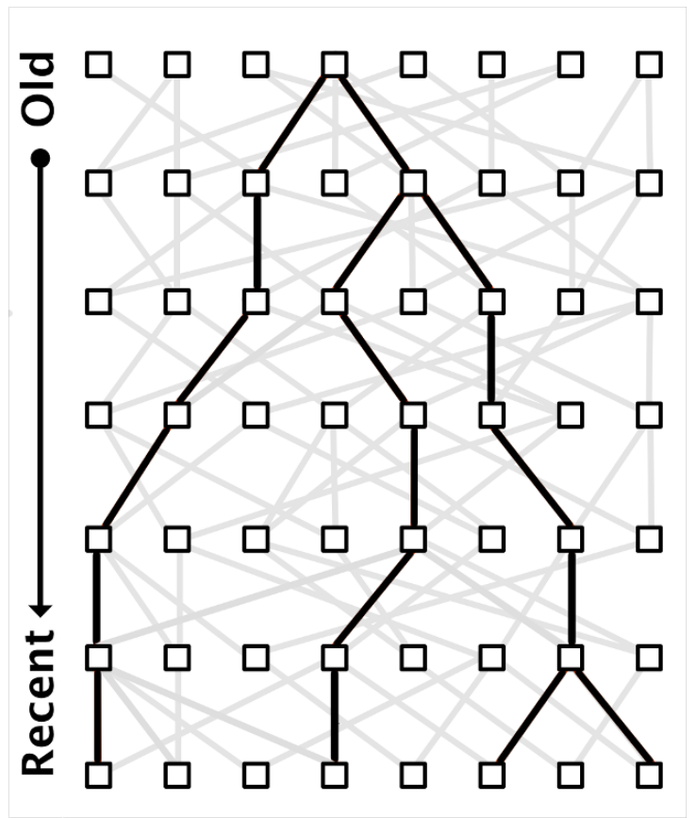
How can the right data structure help?

(1) Succinct

- stores each bit of information once …
- … but still allows efficient query operations

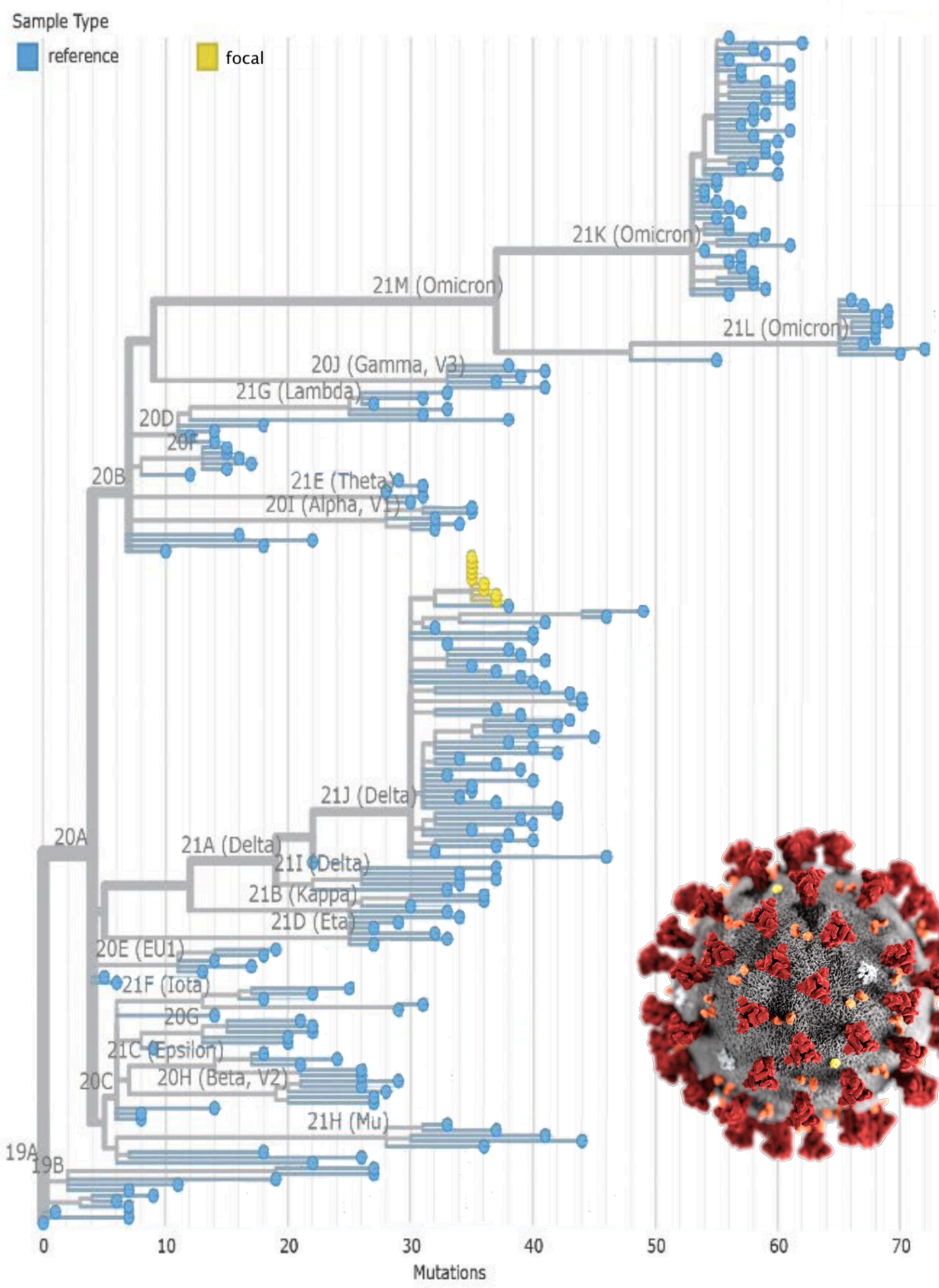
(2) Descriptive

- reflects underlying generative process

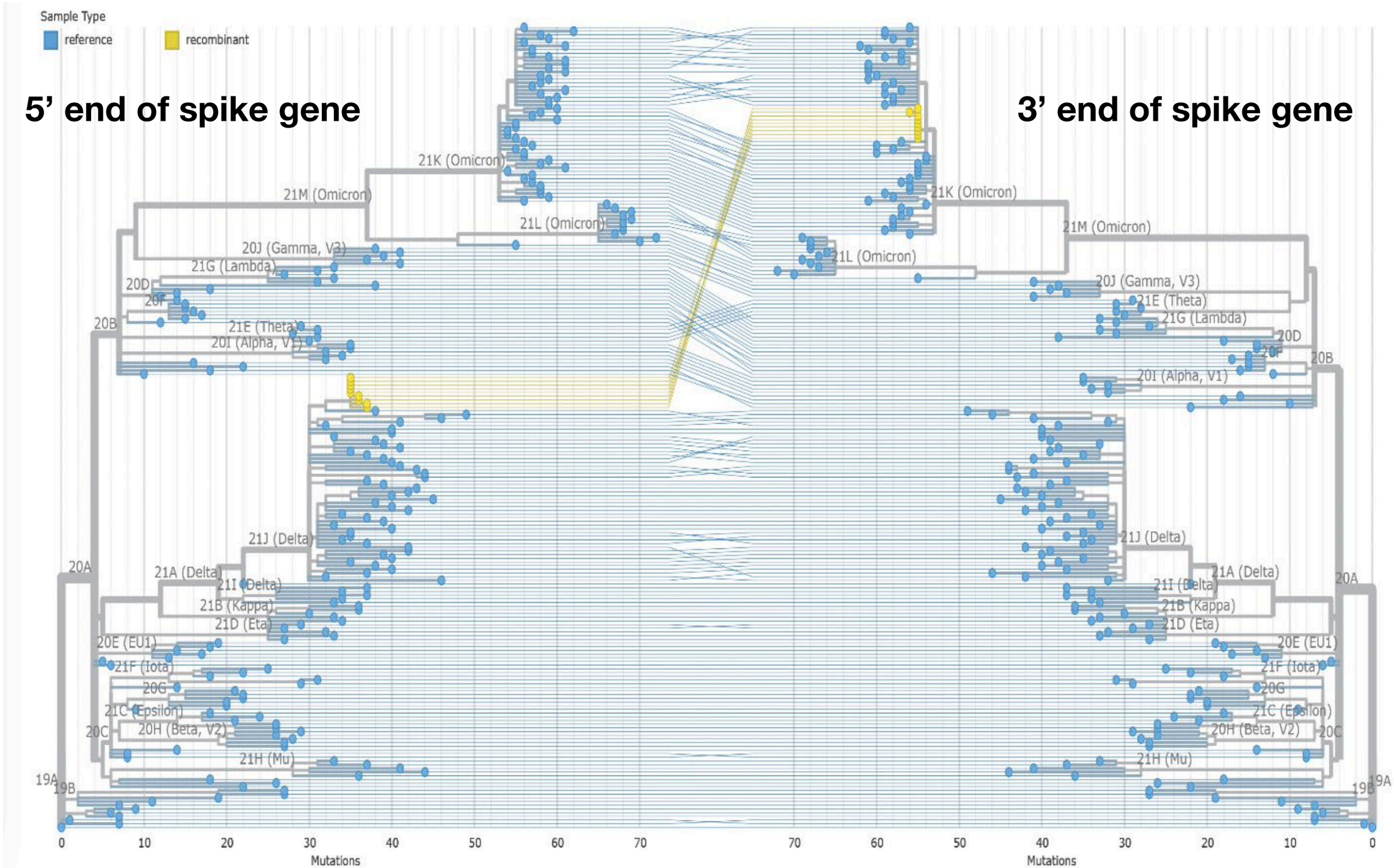


Trees are fundamental in comparing & analysing genetic sequences…

from: SARS-CoV-2 Delta–Omicron Recombinant Viruses, United States (Lacek *et al.*, Emerg Infect Dis. 2022: https://doi.org/10.3201/eid2807.220526)

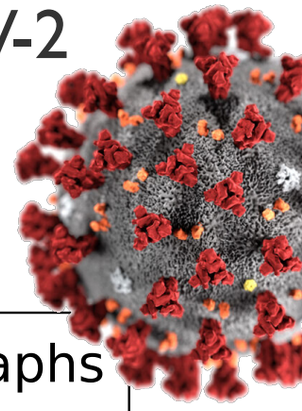


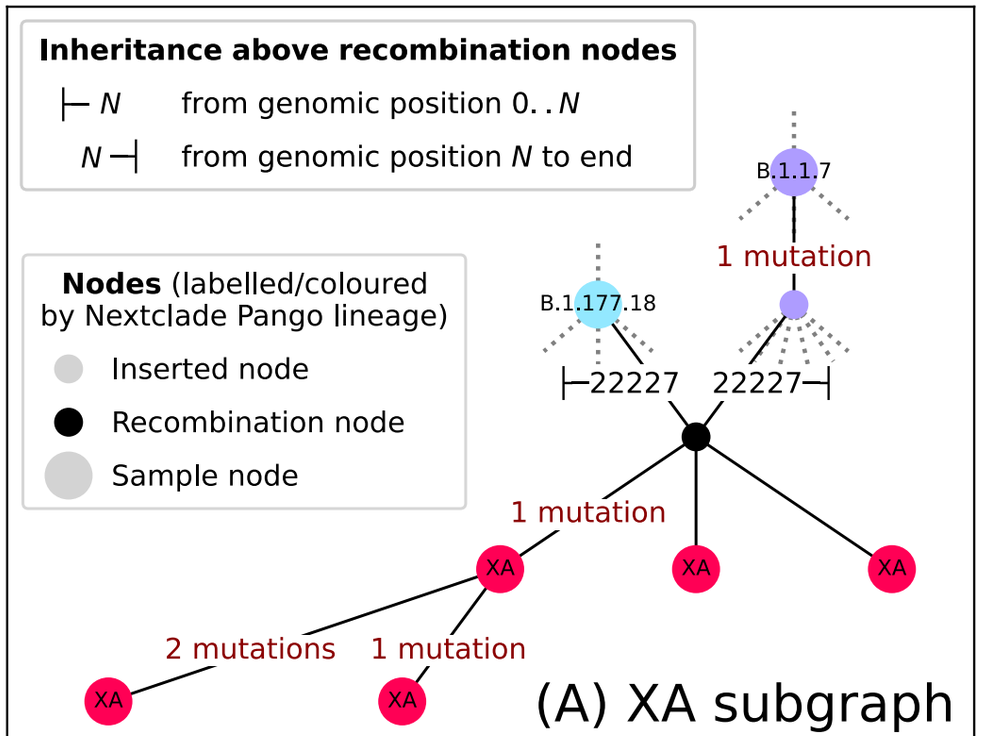
… but recombination causes different genetic regions to have different trees

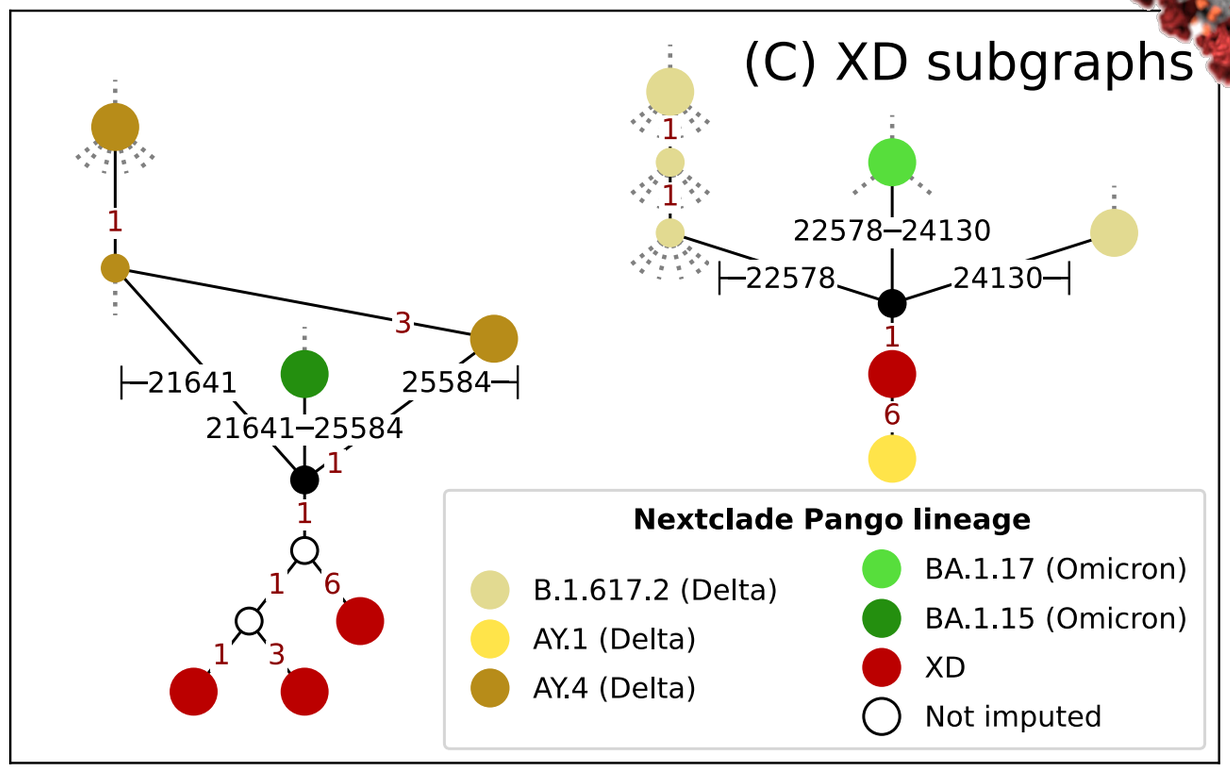


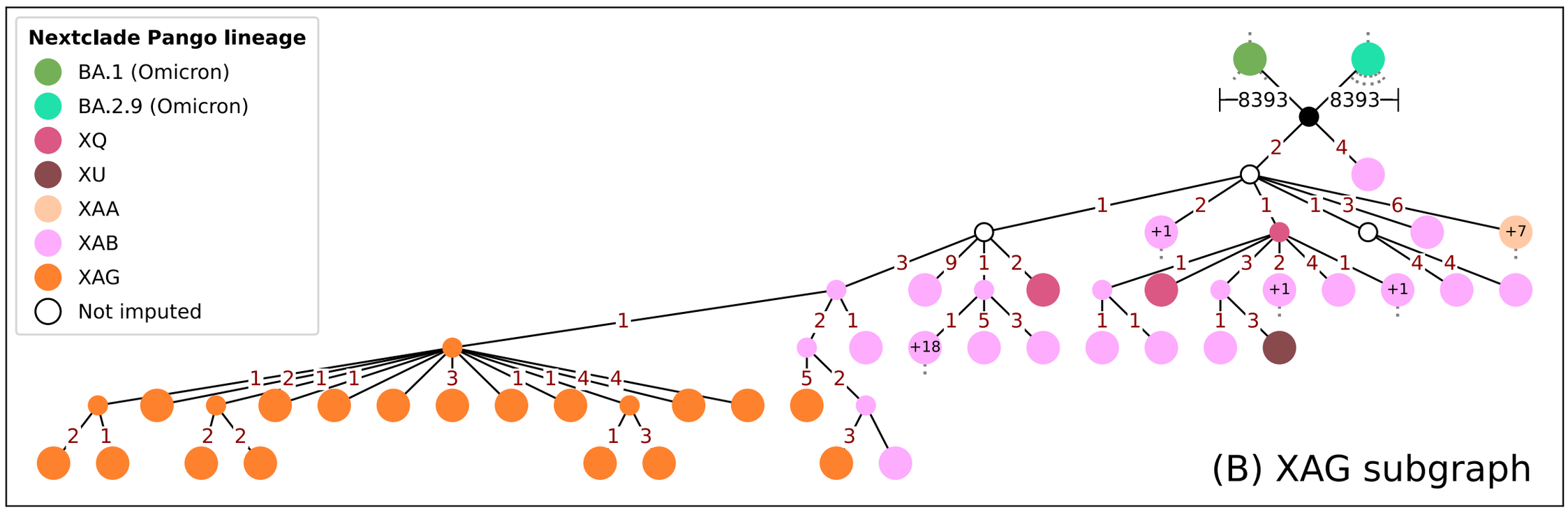
Towards Pandemic-Scale Ancestral Recombination Graphs of SARS-CoV-2

Zhan *et al.* (2023): https://doi.org/10.1101/2023.06.08.544212



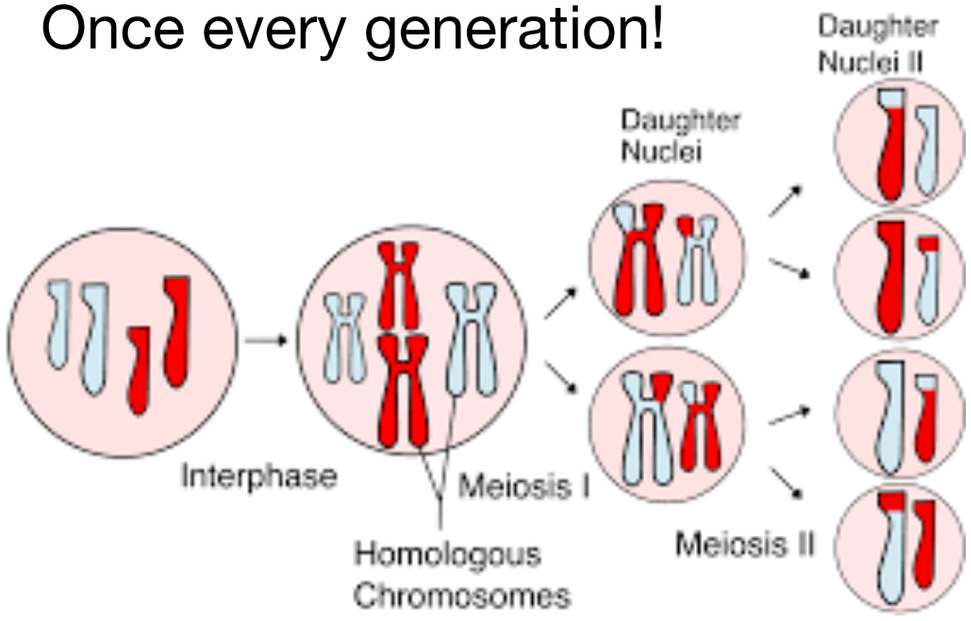






Problem: most organisms (including ourselves) recombine much *more* that coronaviruses

Once every generation!



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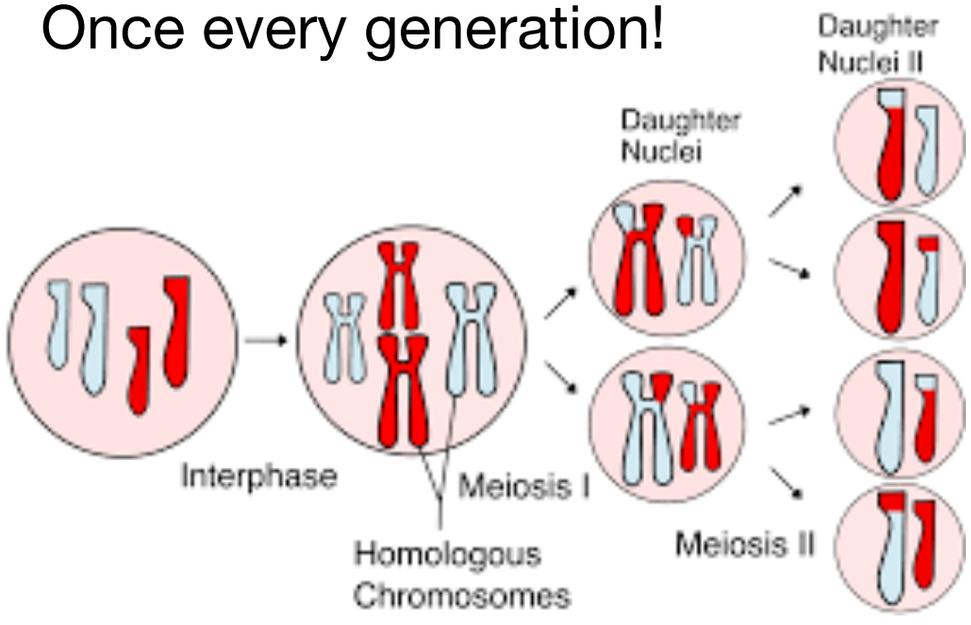
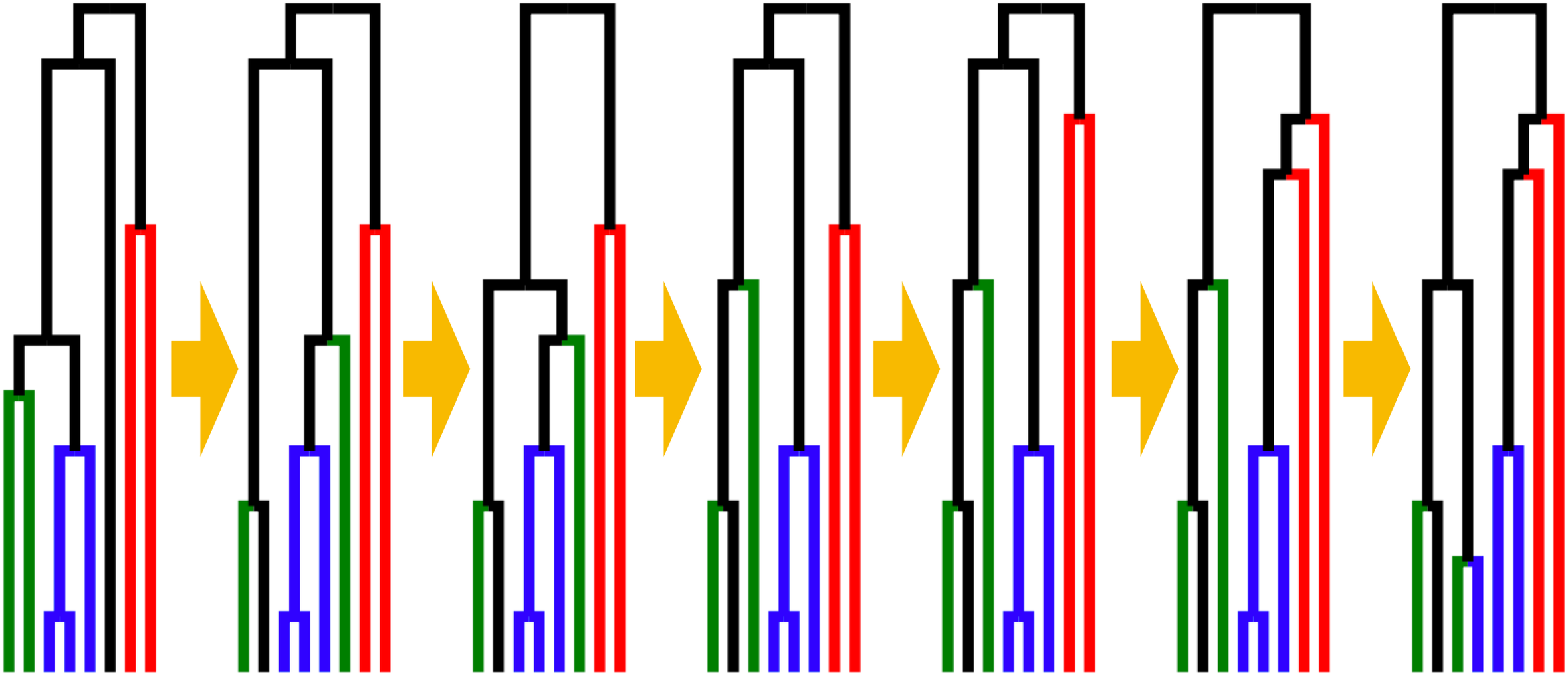
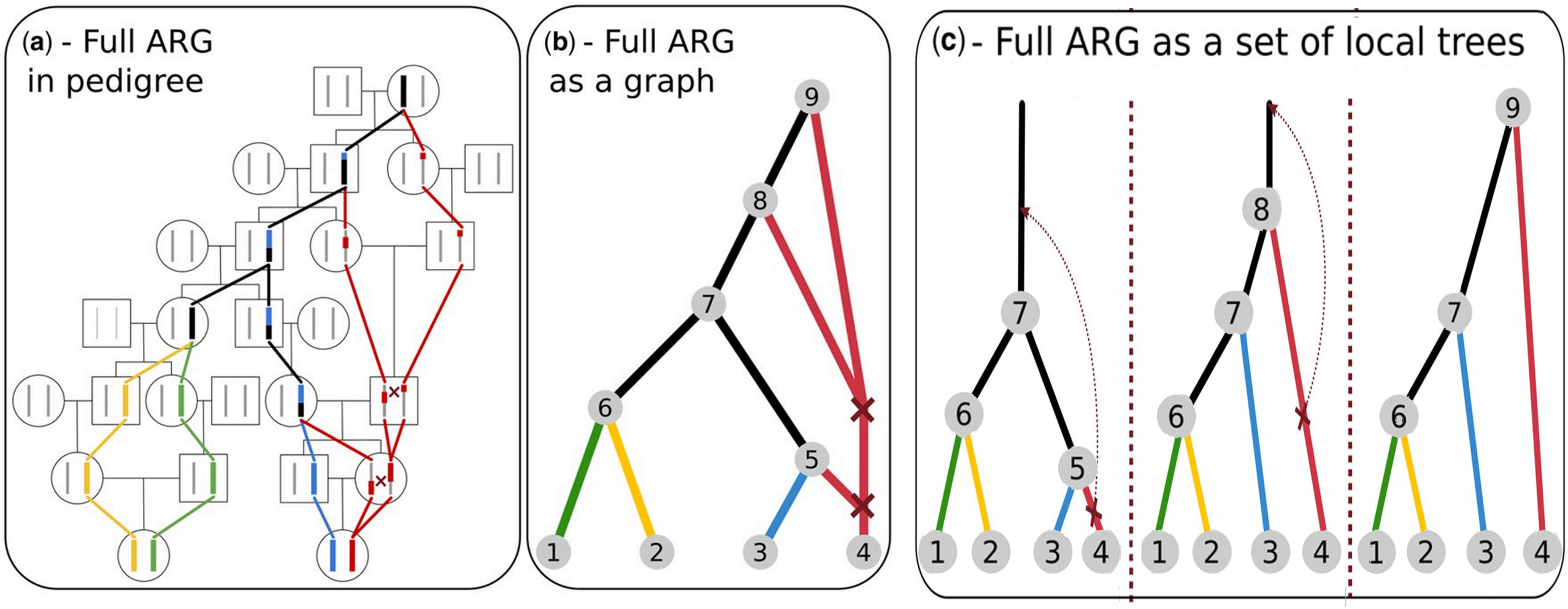




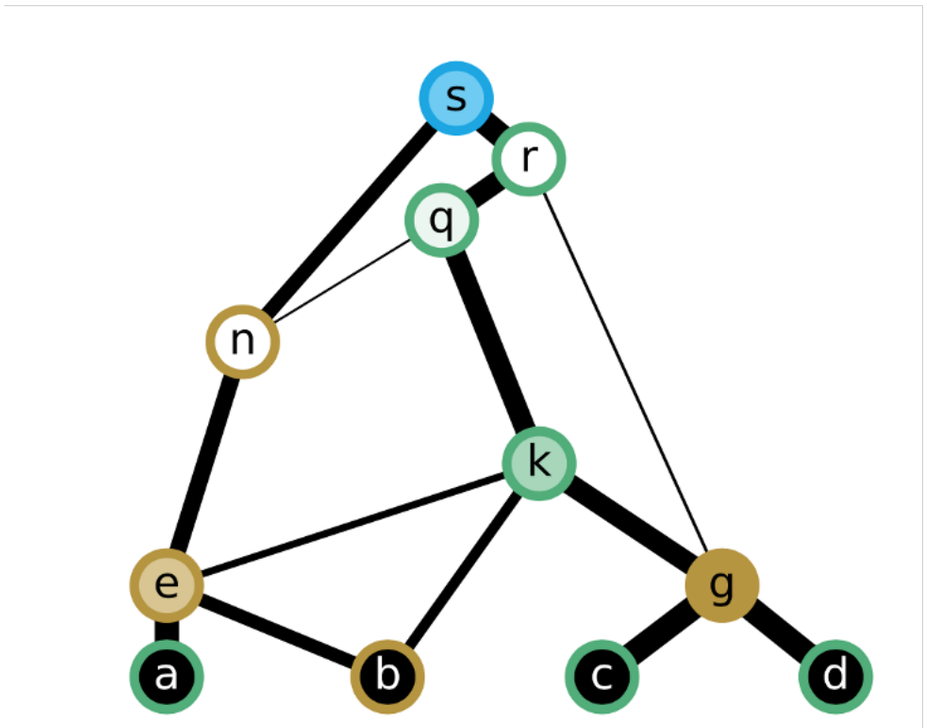
A “genetic genealogy” tracks genome-wide inheritance paths

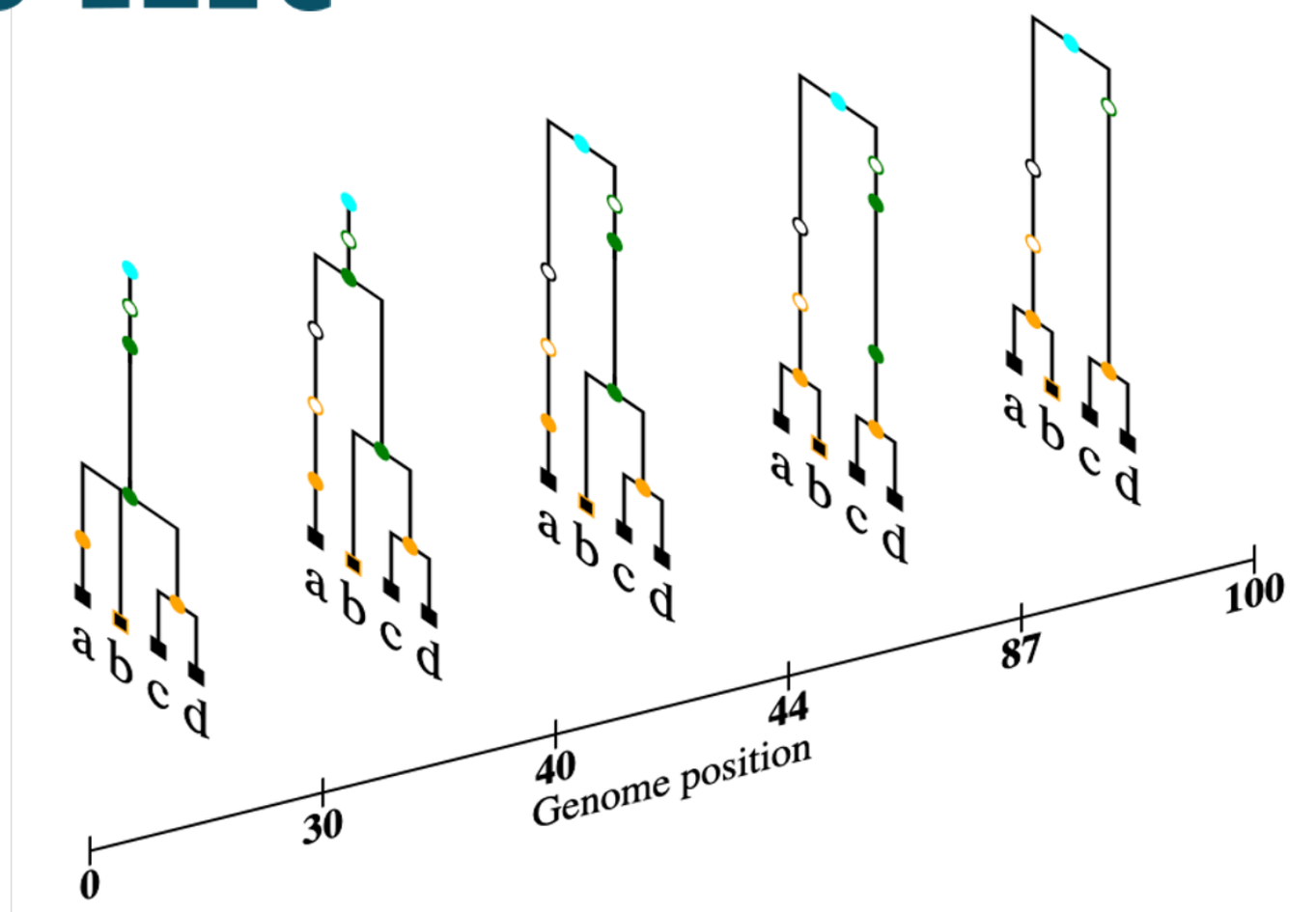


“succinct tree sequence format”

from: Evaluation of methods for estimating coalescence times using ancestral recombination graphs (Brandt *et al.*, **Genetics.** 2022: https://doi.org/10.1093/genetics/iyac044)

ts kit





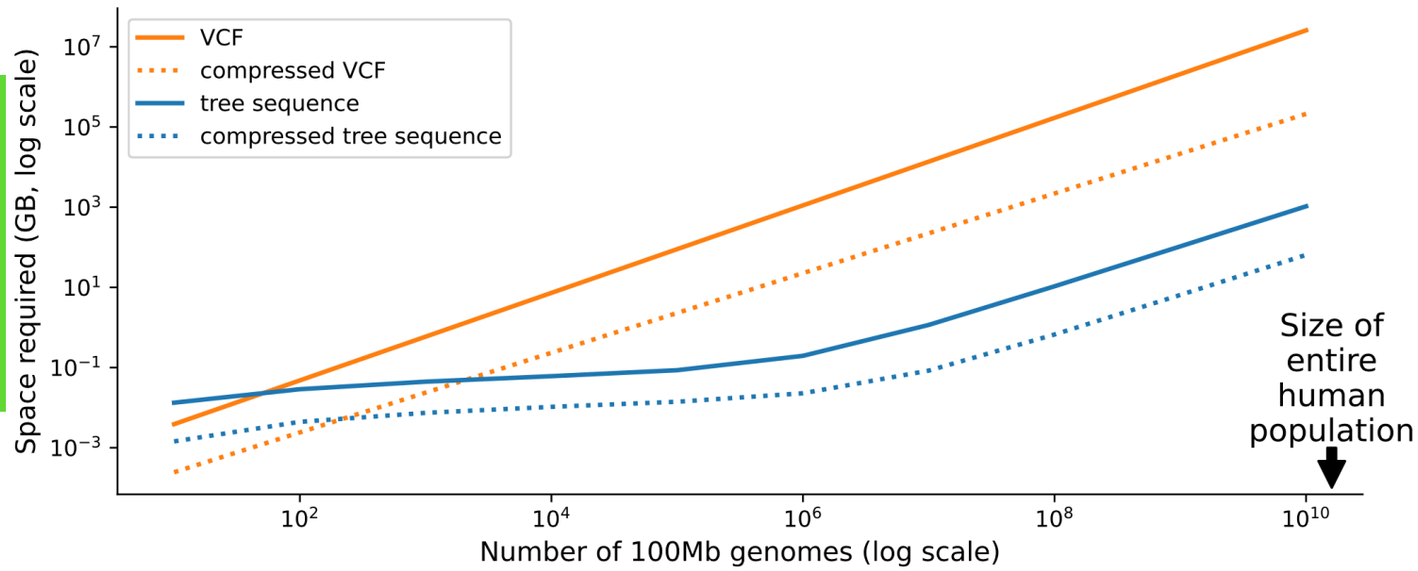
Graph representation

Local tree representation

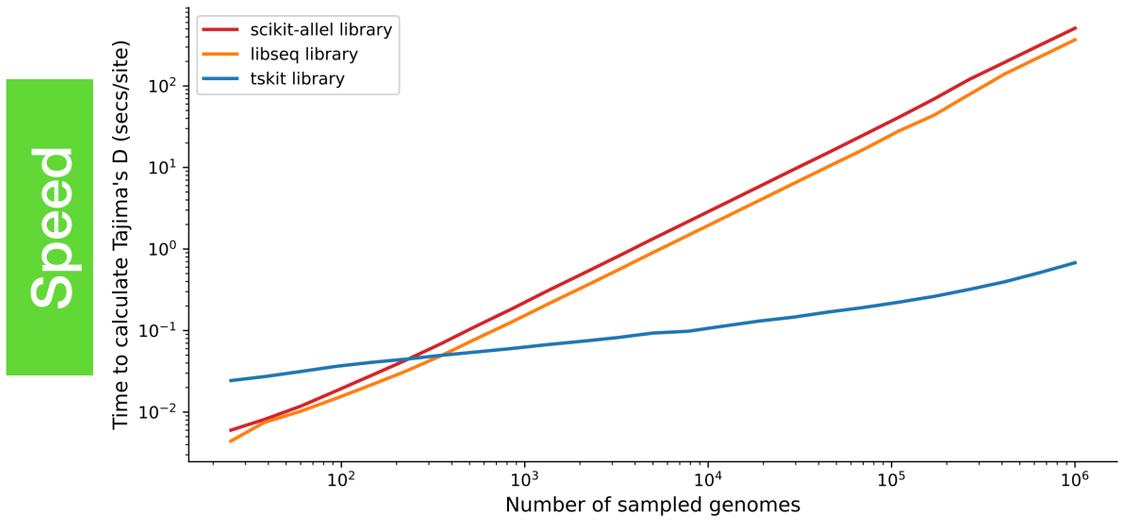
Storing a genetic genealogy in the (succinct) tree sequence format has many benefits

- **Compact storage** ("domain specific compression")
- **Fast, efficient analysis** (a "succinct" structure)
- **Well tested, open source** (active dev community)
- **Built-in functionality** (well documented: http://tskit.dev)

File size



Speed



…but limited support for major genomic rearrangements (e.g. inversions, large indels): genomes should be (reasonably) aligned => current primary focus = **population genetics**

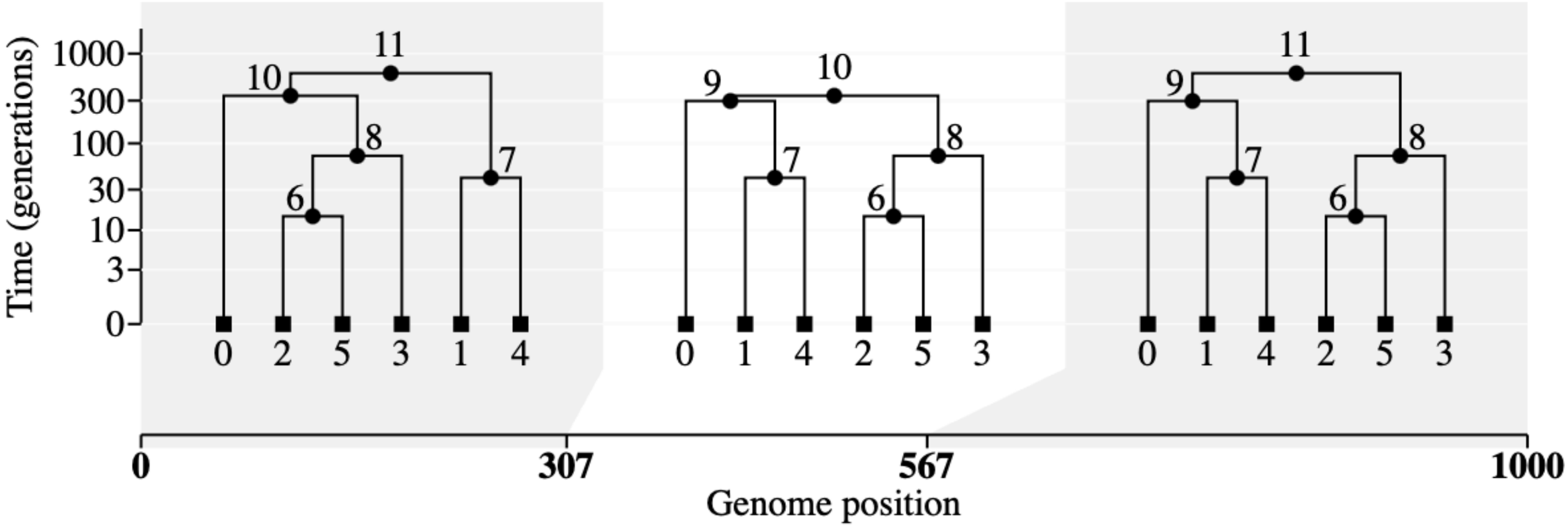
Images from online tutorials: "What is a tree sequence": https://tskit.dev/tutorials/what_is.html

How do we get hold of a tree sequence?

- **Simulation**
  - Forwards-time: **SLiM**
  - Backwards-time: **msprime**
- **Inference from real data**
  - Topology only: **tsinfer** — With branch lengths (dated): **tsdate**
  - **Relate** (but this tree seq is more like a sequence of separate trees)

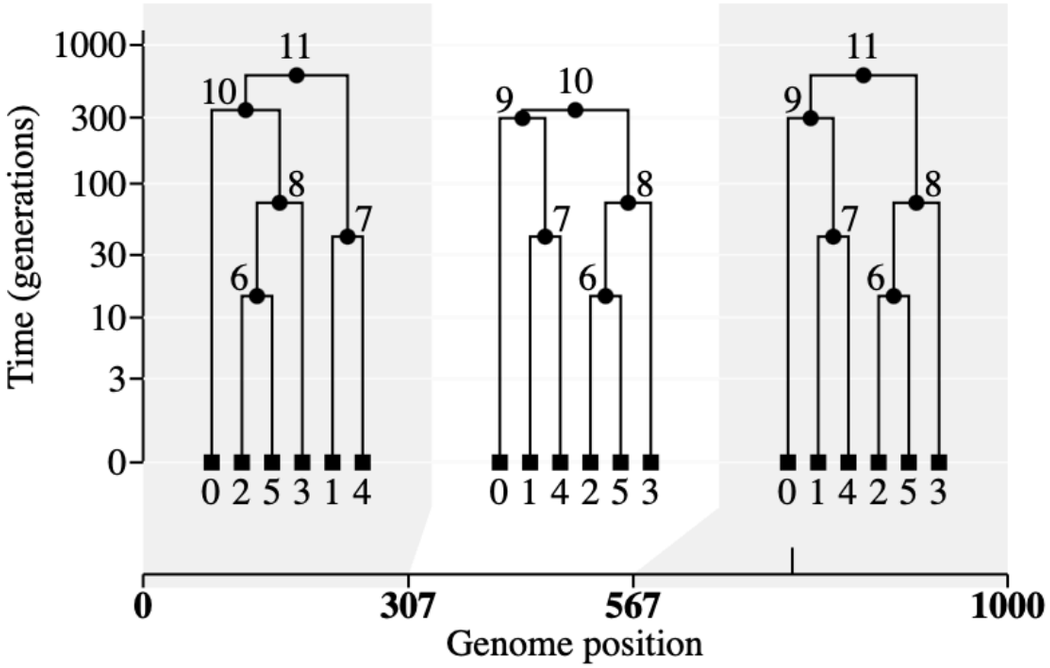
Also other inference programs that don't output in the tree sequence format by default (ARGweaver, Argneedle)

Tskit terminology: the basics

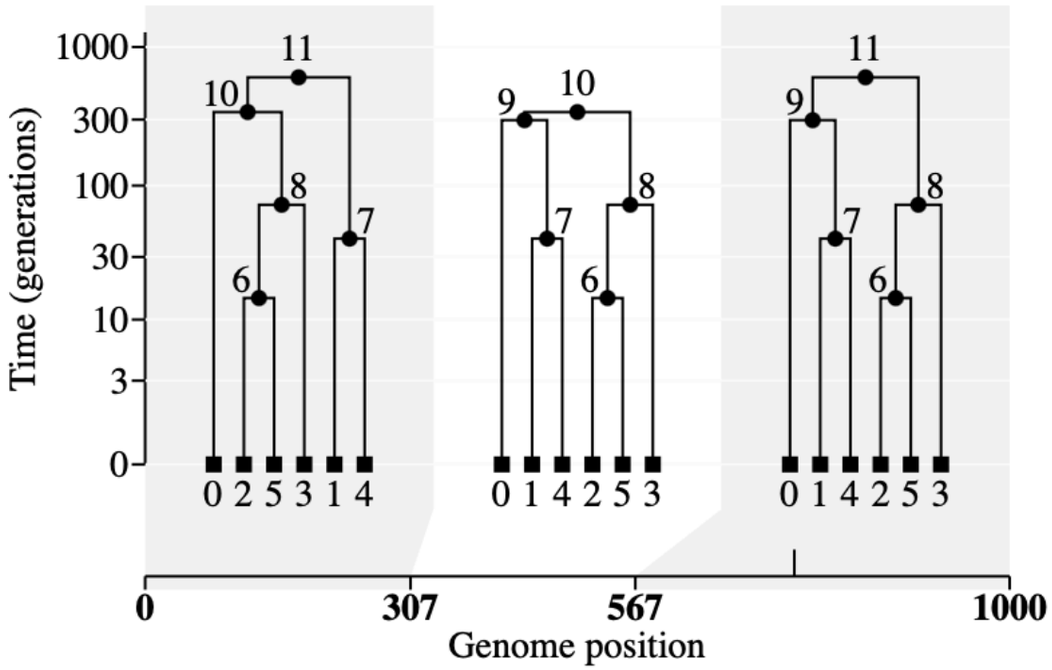


- Multiple **local trees** exist along a genome of fixed length
  (by convention measured in base pairs)
- Genomes exist at specific times, and are represented by **nodes**
  (the same node can persist across many local trees
- Some nodes are most recent common ancestors (MRCAs) of other nodes
- Entities are zero-based: the first node has id 0, the second id 1, …

Images from online tutorials: “Terminology & concepts”:
https://tskit.dev/tutorials/terminology_and_concepts.html



Tskit terminology: nodes and edges



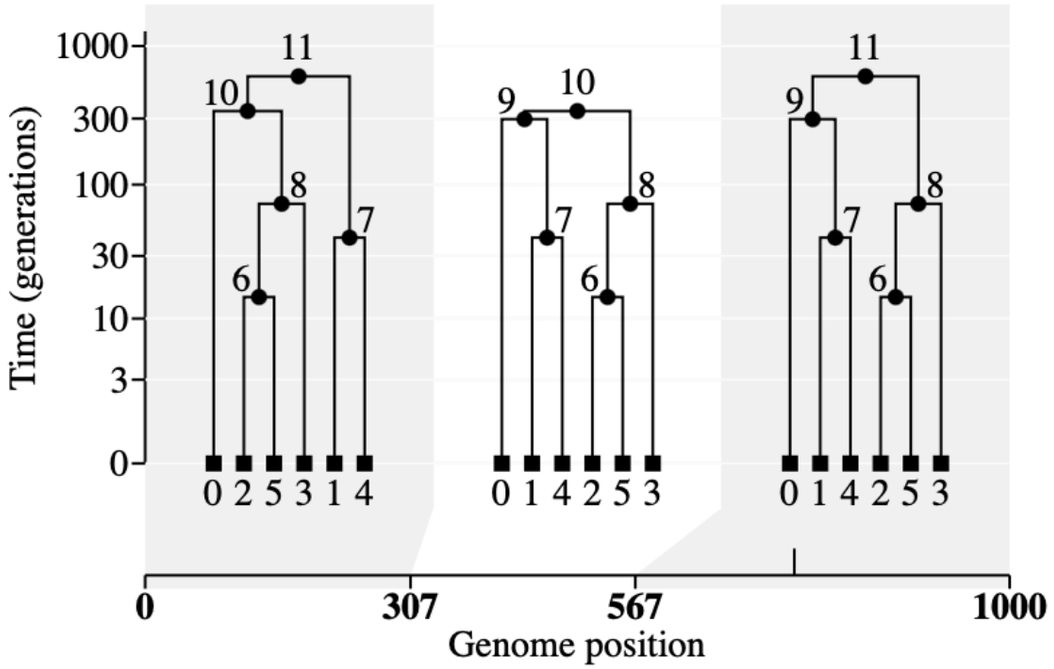
Tskit terminology: nodes and edges

Nodes (=genomes)

- exist at a specific *time*
- can be flagged as "*samples*"
- can belong to "*individuals*" (e.g. 2 nodes per individual in humans) and, if useful, "*populations*"

id	flags	population	individual	time
0	1	0	0	0.00000000
1	1	0	0	0.00000000
2	1	0	1	0.00000000
3	1	0	1	0.00000000
4	1	0	2	0.00000000
5	1	0	2	0.00000000
6	0	0	-1	14.70054184
7	0	0	-1	40.95936939
8	0	0	-1	72.52965866

Tskit terminology: nodes and edges



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Edges

Connect a *parent & child*

Have a *left & right* genomic coordinate

And usually *span* multiple trees,
(e.g. edges connecting nodes 1+7 and 2+7)

id	left	right	parent	child
0	0	1000	6	2
1	0	1000	6	5
2	0	1000	7	1
3	0	1000	7	4
4	0	1000	8	3
5	0	1000	8	6
6	307	1000	9	0
7	307	1000	9	7
8	0	307	10	0
9	0	567	10	8
10	307	567	10	9

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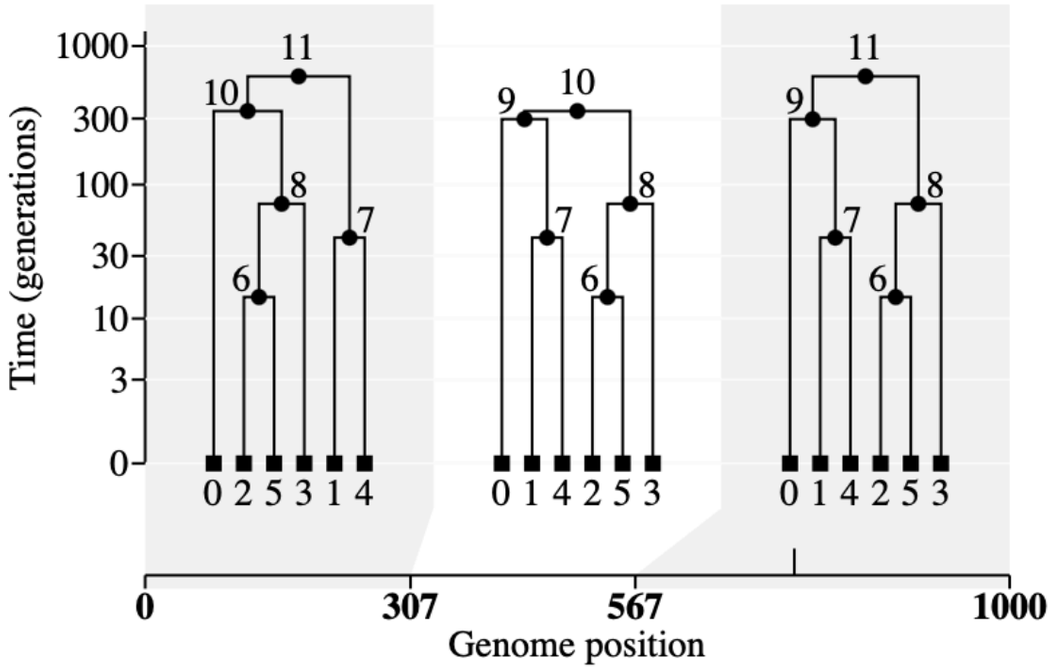

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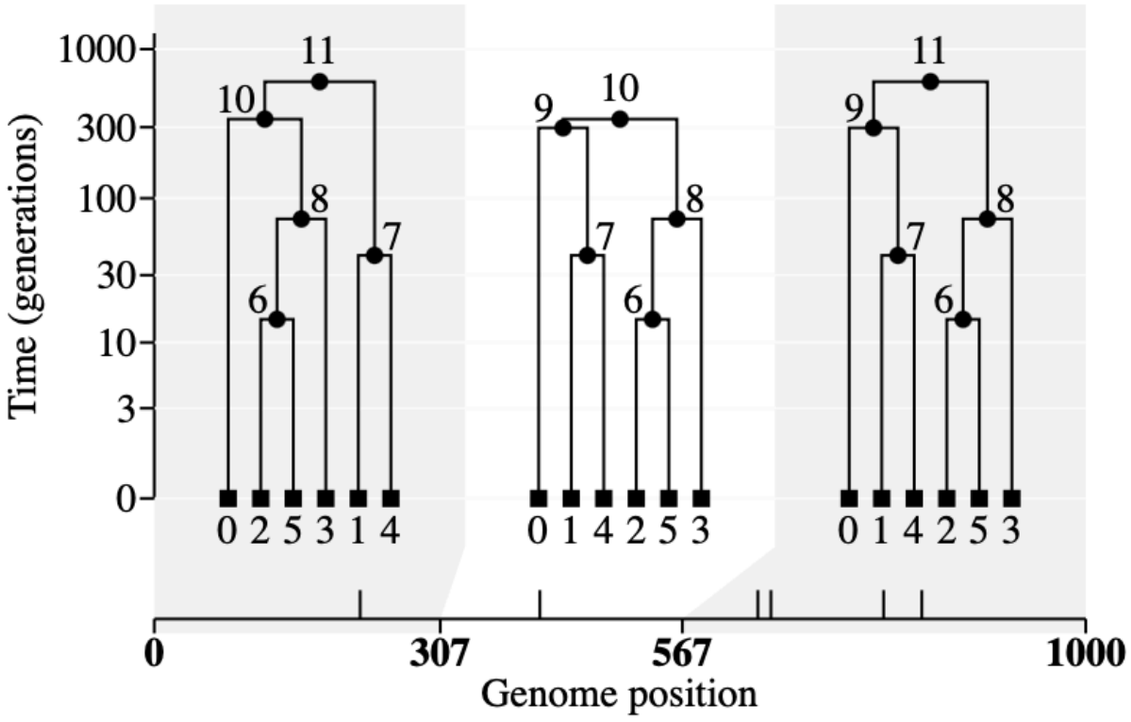
Number of edges = primary determinant of tree sequence filesize, and processing efficiency

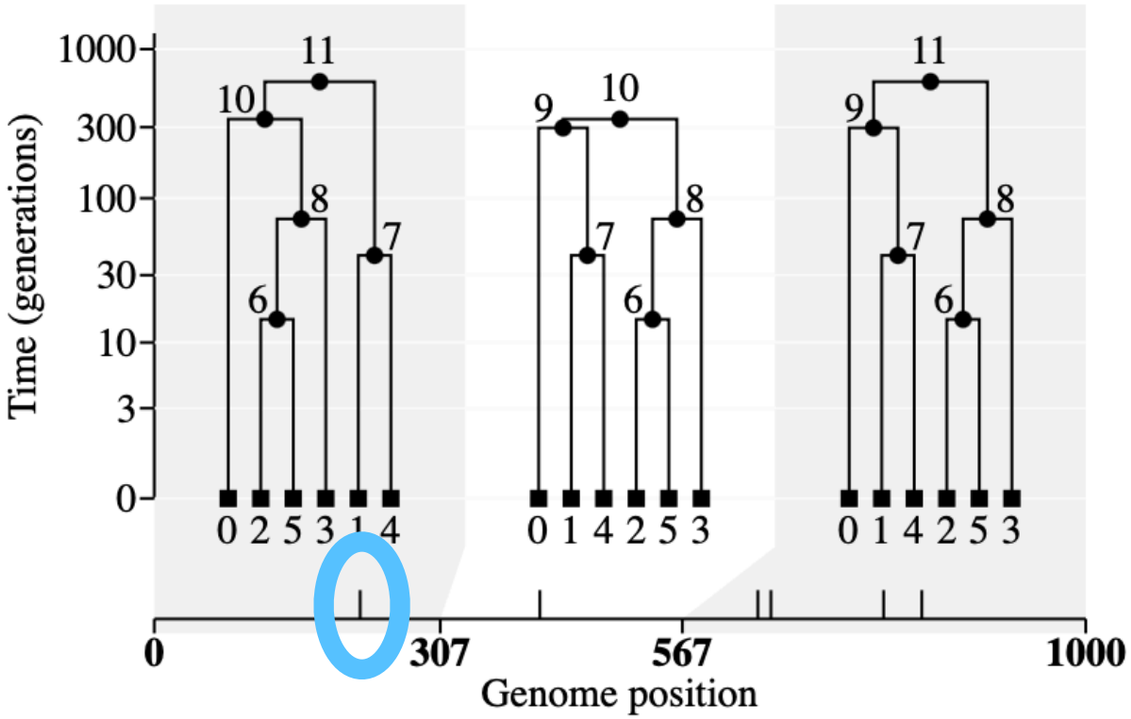
(e.g UKBB chr20 ~ 1M sample nodes, 62 M edges, tree iteration ~ 5secs)



Tskit terminology: sites & mutations

This is how we can encode genetic variation

Most genomic positions do not vary between genomes: usually we don't bother tracking these



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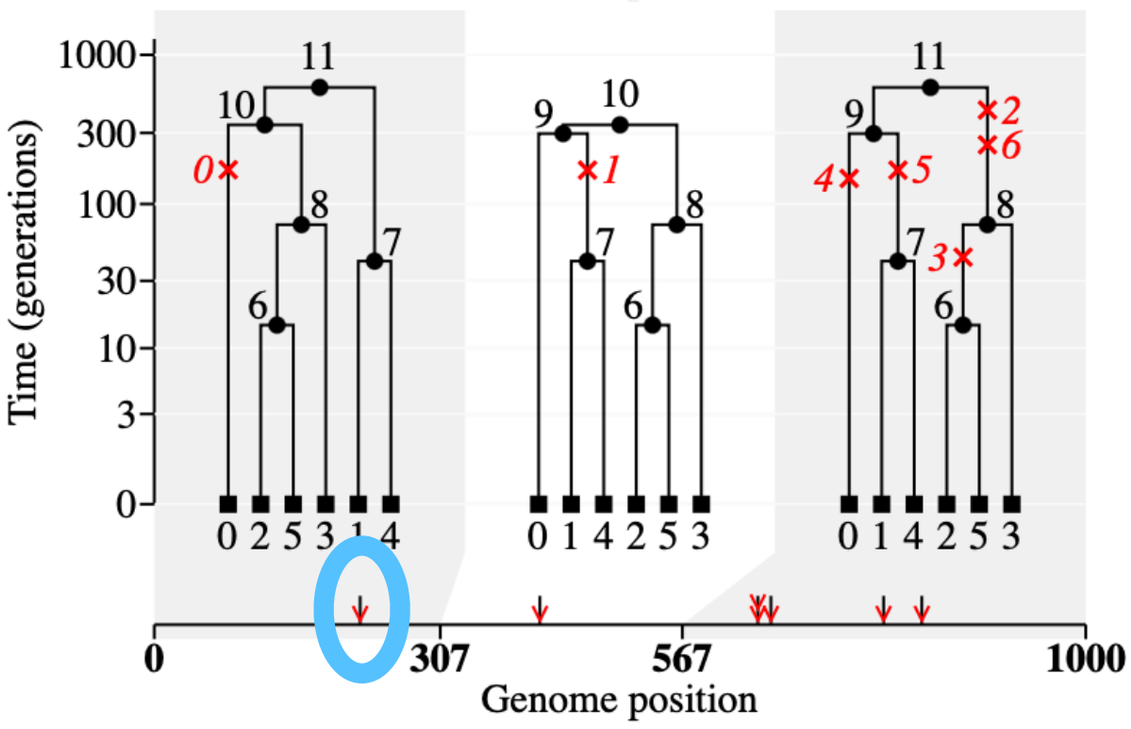
We can create a **site** at a given genomic **position** with a fixed **ancestral state**.

id	position	ancestral_state
0	221	T
1	414	G
2	648	A
3	662	G
4	783	T
5	824	C

Sites table



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Normally, a site is created in order to place one or more **mutations** at that site

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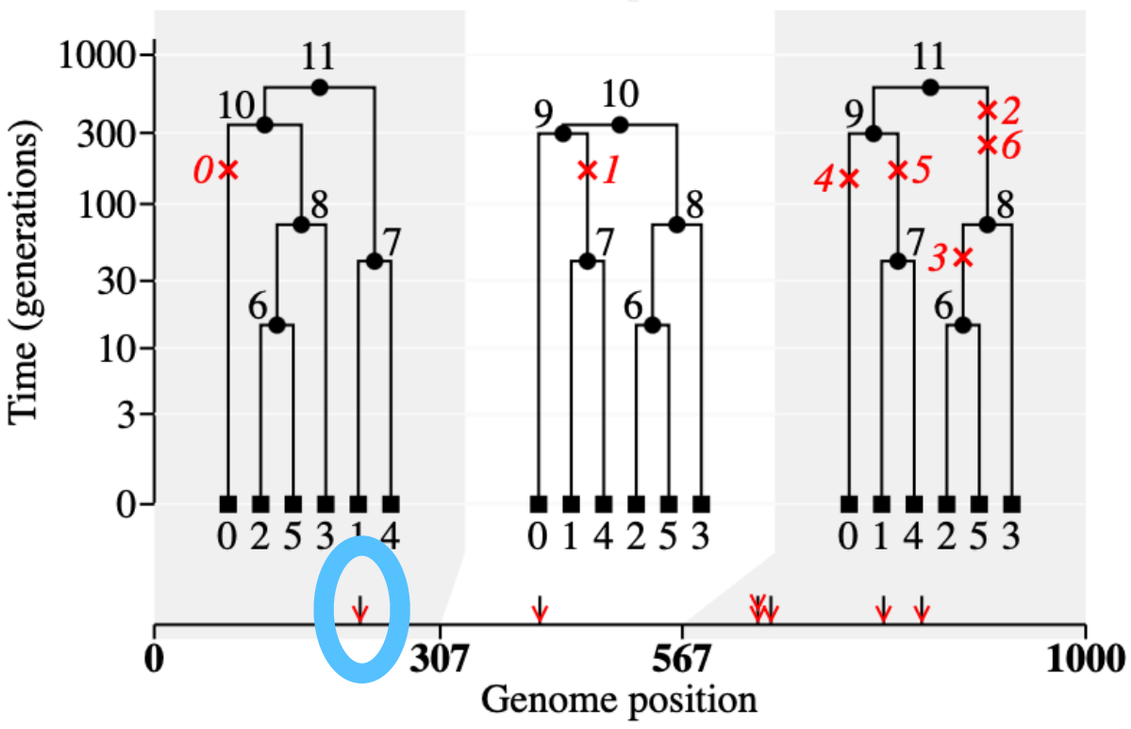
2	648	A
3	662	G
4	783	T
5	824	C

Sites table

id	site	node	time	derived_state	parent
0	0	0	nan	A	-1
1	1	7	nan	T	-1
2	2	8	nan	T	-1
3	2	6	nan	C	2
4	3	0	nan	C	-1
5	4	7	nan	C	-1
6	5	8	nan	T	-1

Mutations table



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2	2	8	nan	T	-1
3	2	6	nan	C	2
4	3	0	nan	C	-1
5	4	7	nan	C	-1
6	5	8	nan	T	-1

Mutations table

But actually you can do lots of analysis even if you don't have sites & mutations: https://tskit.dev/tutorials/no_mutations.html)

Using tskit

Using tskit

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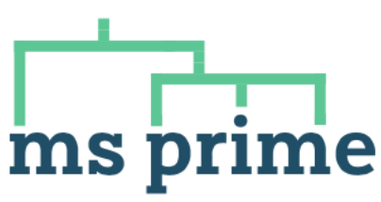

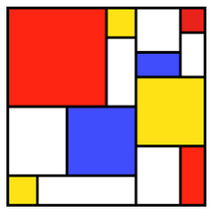

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