State-space exploration of Tajima Trees

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Motivation: Estimation of Effective Population Size

Effective Population Size Trajectory $Ne(t)$

$N_e(t)$ is a measure of relative genetic diversity over time.

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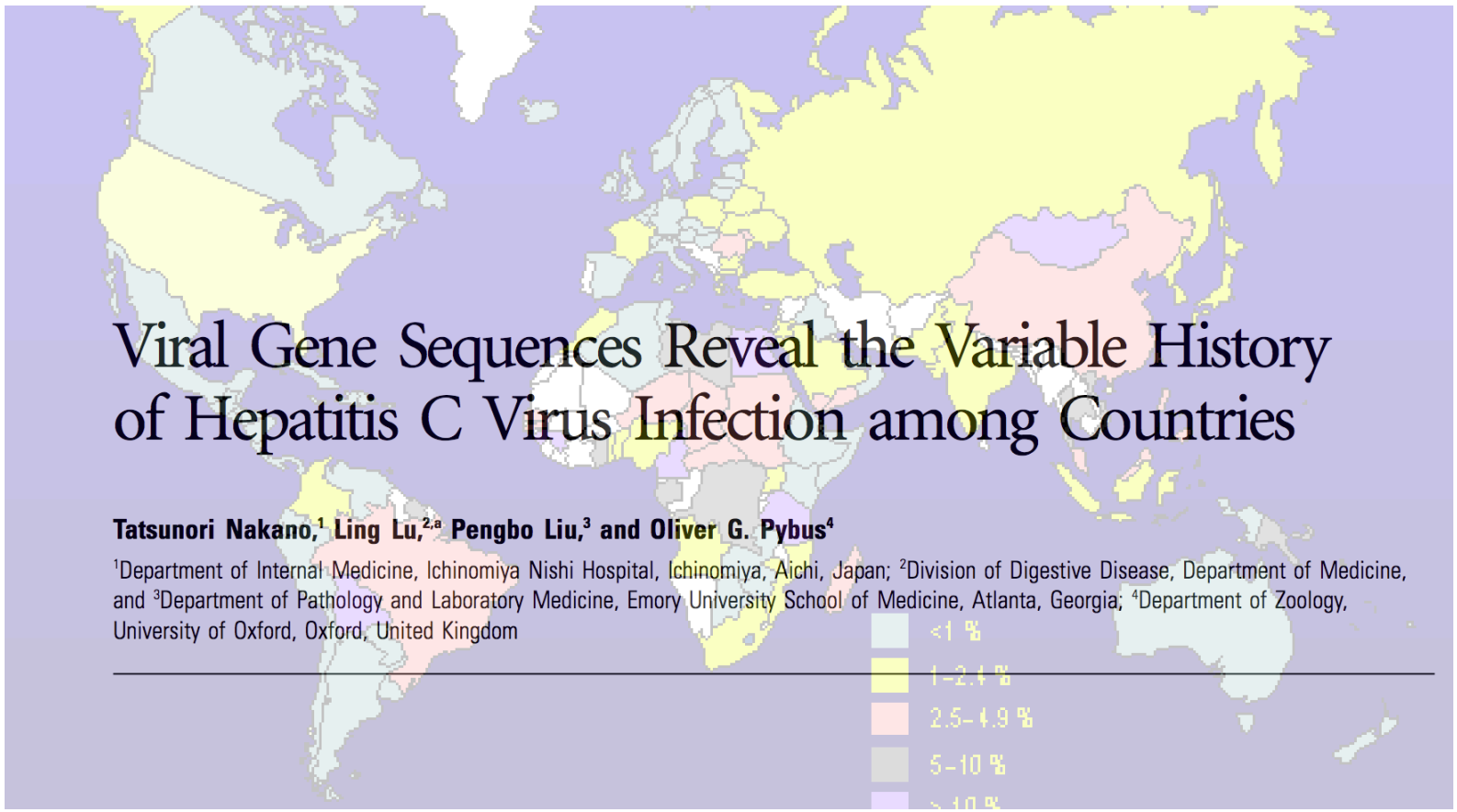
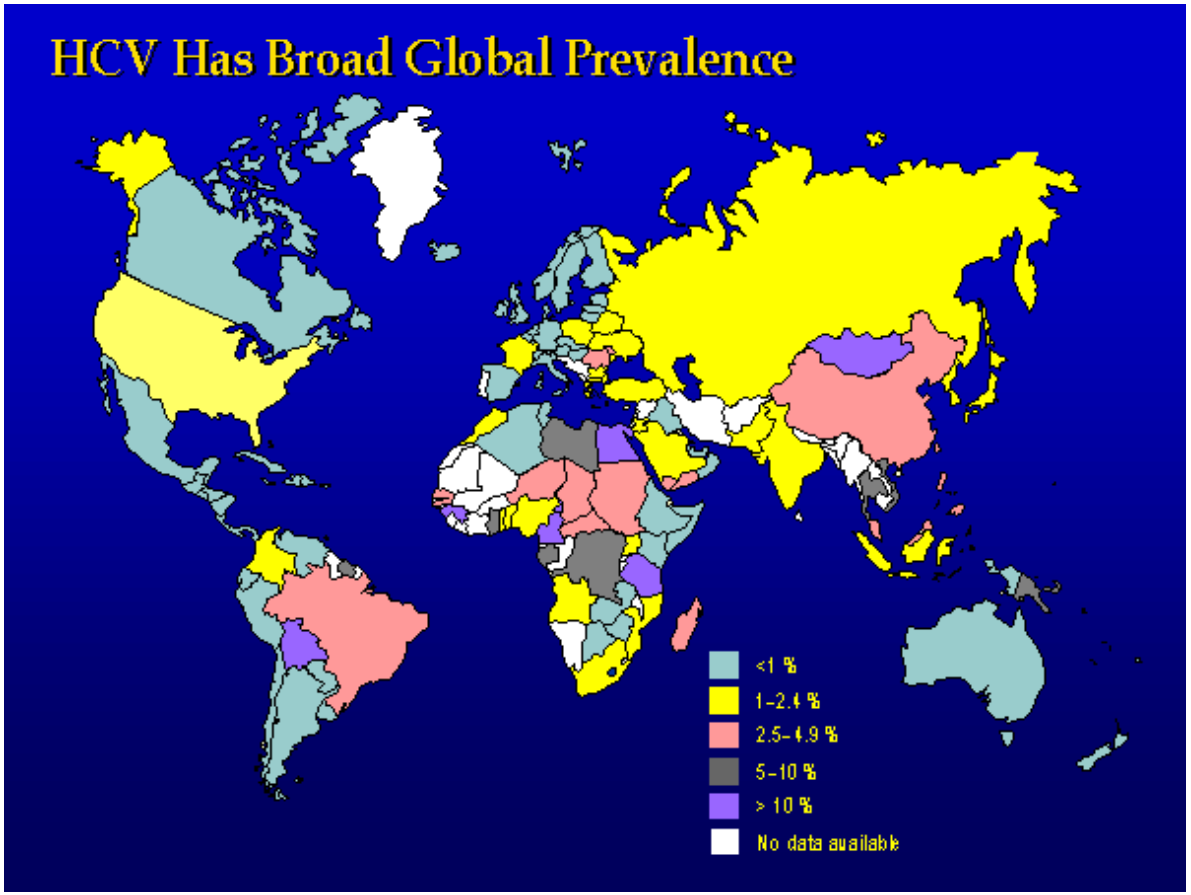


Example 1: Hepatitis C Virus



Prevalence of HCV - WHO 1999

- Identified in 1989
- Spread by blood to blood contact
- $\approx$3% of infected population worldwide
- 8,000 - 10,000 deaths per year in the USA
- Egypt has the highest prevalence

Example 1: Hepatitis C Virus

- 62 samples in 1993 from the E1 gene (411bp)
- Parenteral antischistosomal therapy (PAT) was practiced from 1920s to 1980s
- In the 1970s started a transition from the intravenous to the oral administration of the PAT

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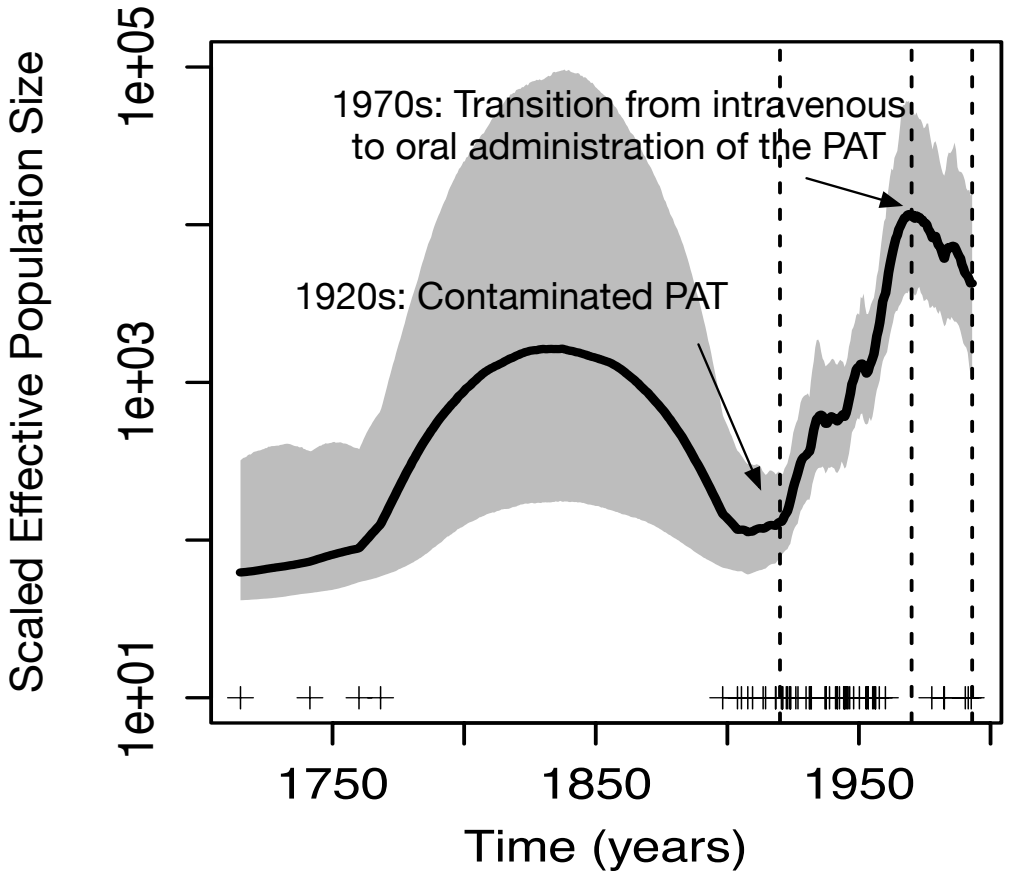

[Palacios and Minin, Biometrics 2013]

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Present-day DNA data inform us about the past

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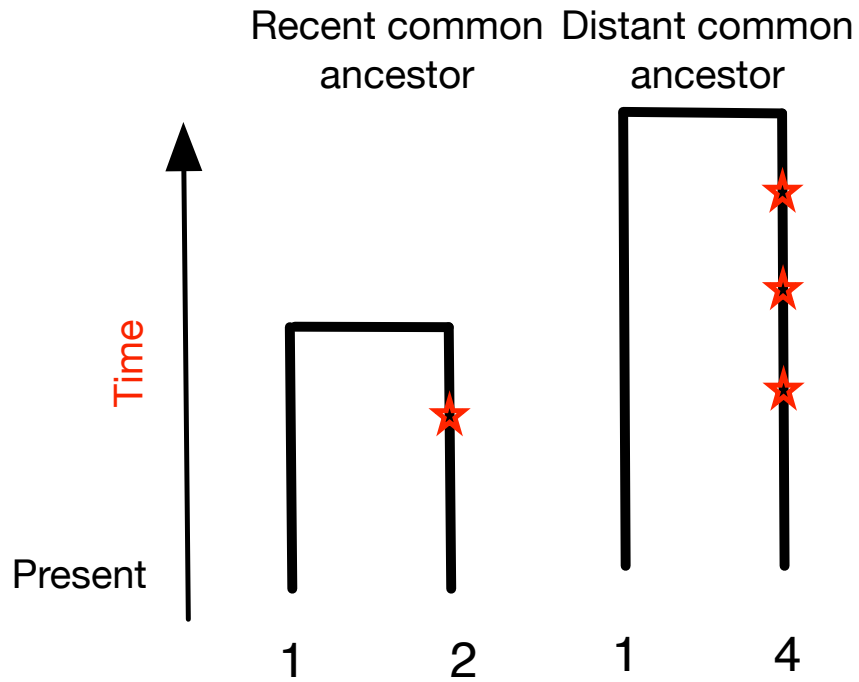
2	A T T C A A C C T G
3	T T C C A A C C T G
4	A T T C A C G C T G



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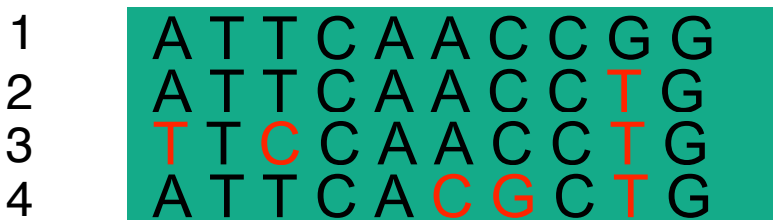

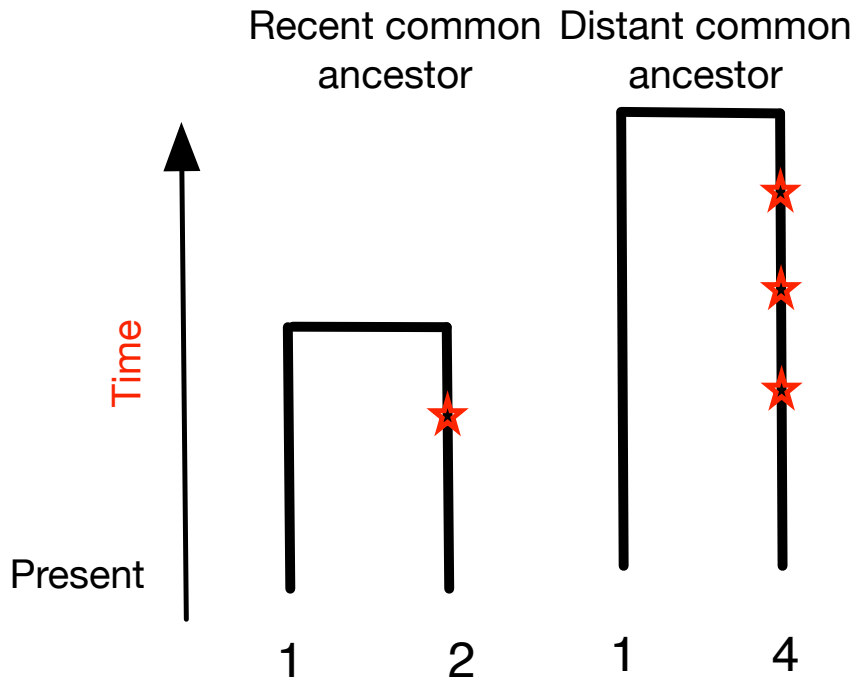

- In humans, mutation rate is estimated to be $\approx 10^{-8}$ per base per generation.

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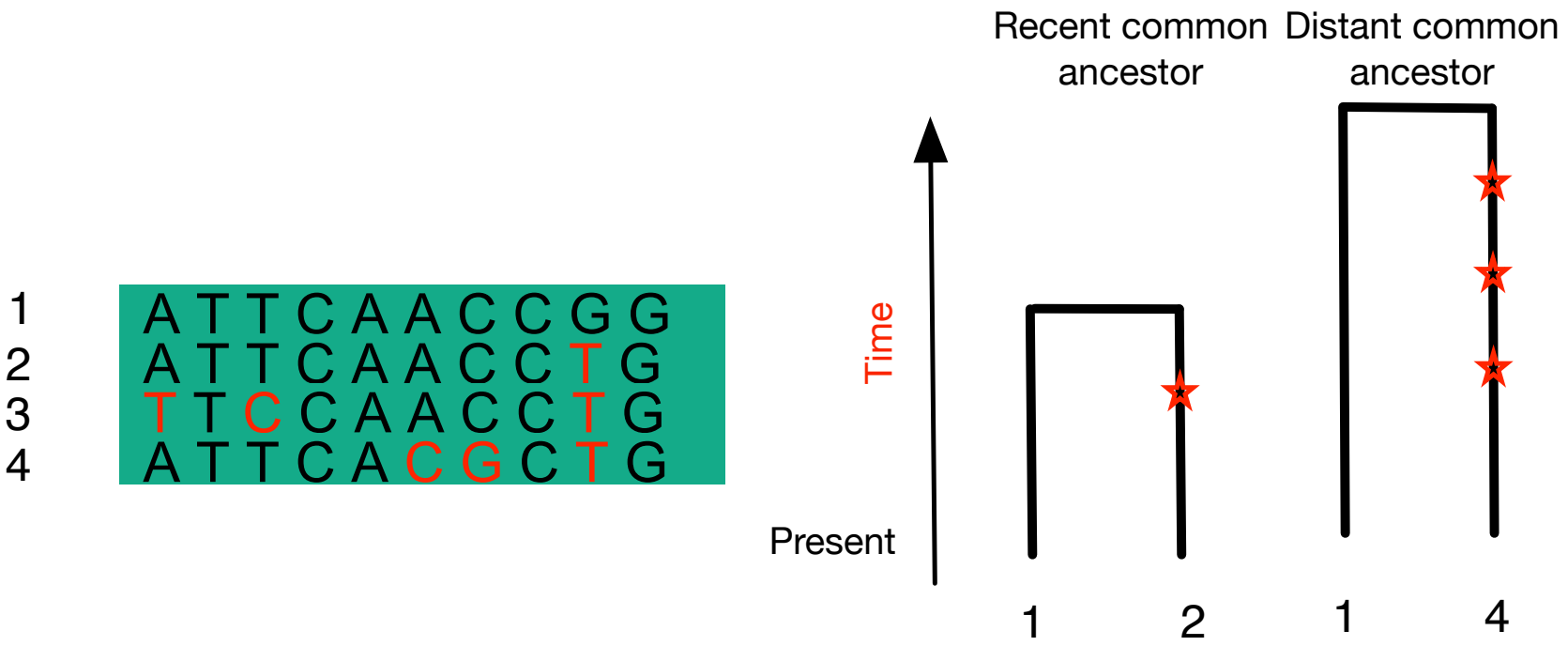
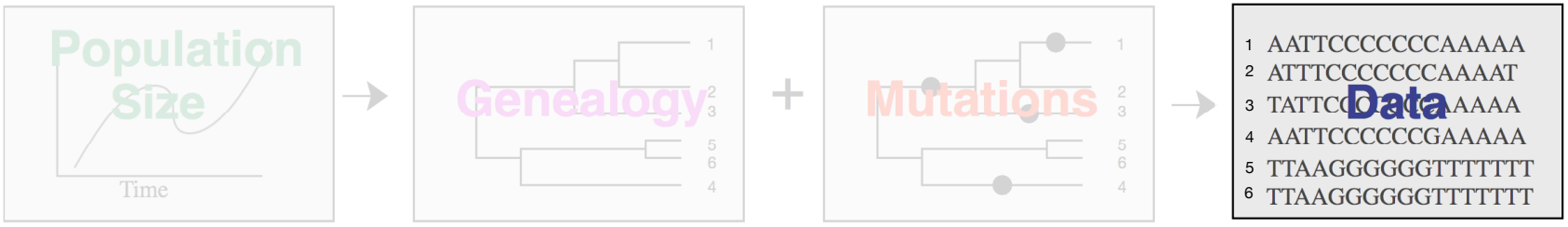


- In humans, mutation rate is estimated to be $\approx 10^{-8}$ per base per generation.
- Recent ancestry indicates small population sizes.

Goal: Estimation of Effective Population Size

Coalescent-based model



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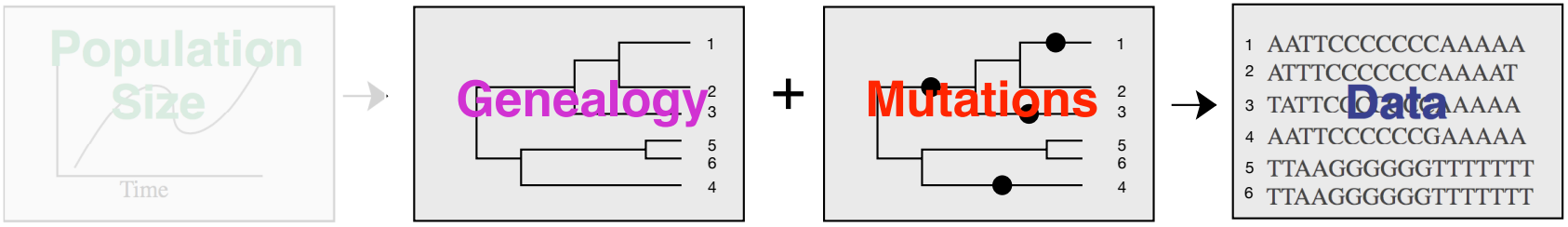

- Ancestral process: coalescent process of genealogies
- Mutation process: Poisson process along the branches of the genealogy

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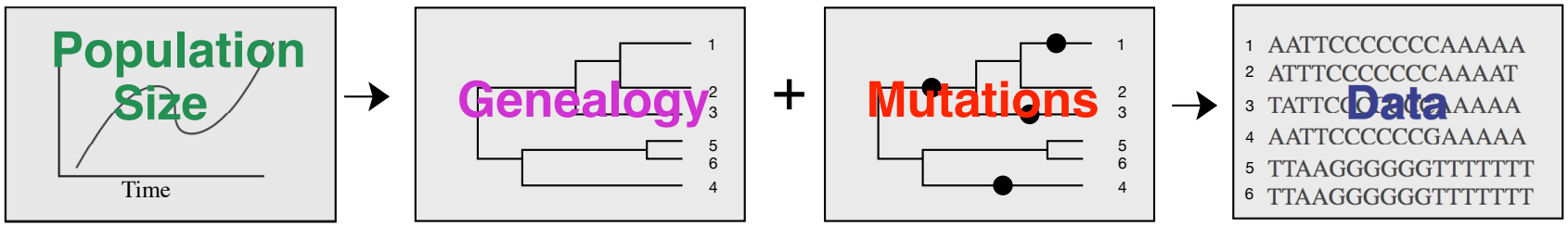
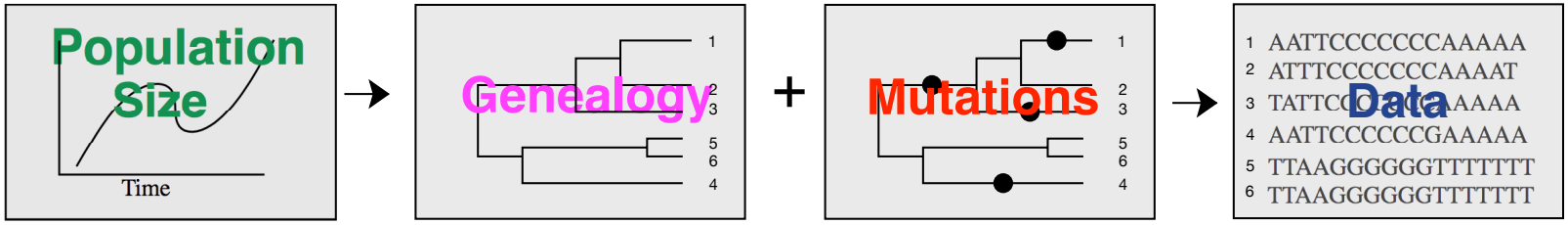


- Ancestral process: coalescent process of genealogies.
- Mutation process: Poisson process along the branches of the genealogy.
- Population process: Effective population size trajectory over time.

Challenging inference from data



$N_e(t)$ $\mathbf{G}$ $\mathbf{Q}$ $\mathbf{Y}$

$$P\left(N_e(t), \mathbf{G}, \mathbf{Q}, \tau \mid \mathbf{Y}\right) \propto \underbrace{P\left(\mathbf{Y} \mid \mathbf{G}, \mathbf{Q}\right)}_{\text{Likelihood}} \underbrace{P\left(\mathbf{G} \mid N_e(t)\right)}_{\text{Coalescent prior}} P\left(\mathbf{Q}\right) \underbrace{P\left(N_e(t) \mid \tau\right)}_{\log \text{GP}(0, \mathbf{C}(\tau))} P\left(\tau\right)$$

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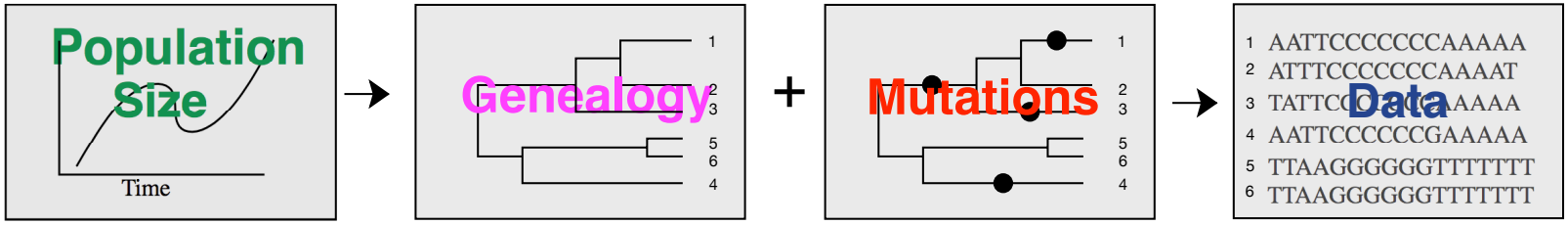

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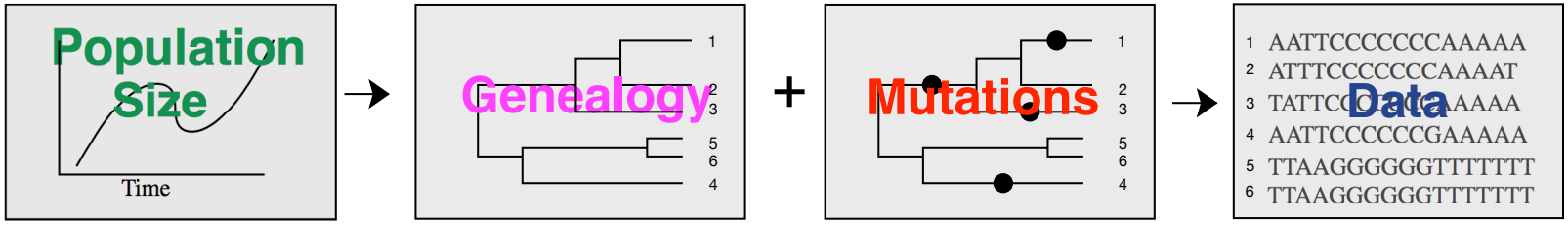

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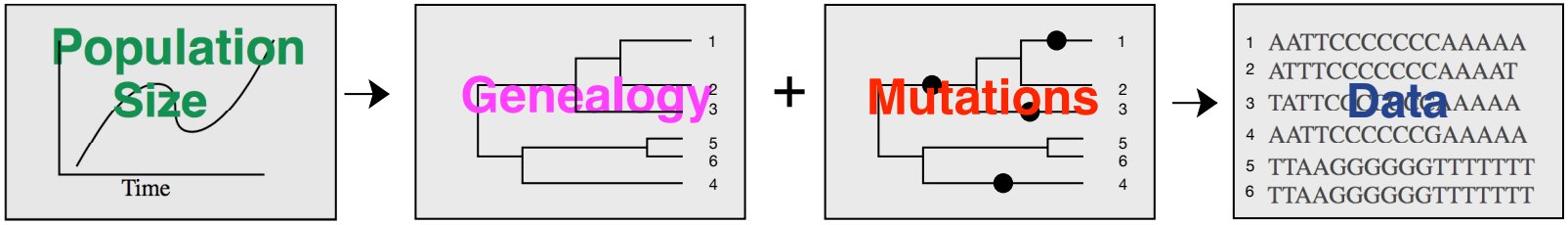

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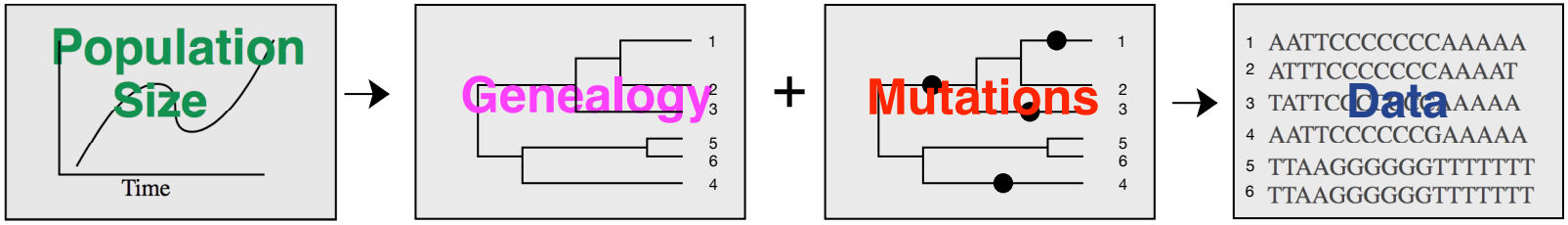
- $\mathcal{G} = \mathcal{T}_n \otimes \mathbb{R}^{+n-1}$
- $|\mathcal{T}_n| = n!(n-1)!/2^{n-1}$
- $|\mathcal{T}_{100}| \approx 10^{284}$

Challenging inference from data



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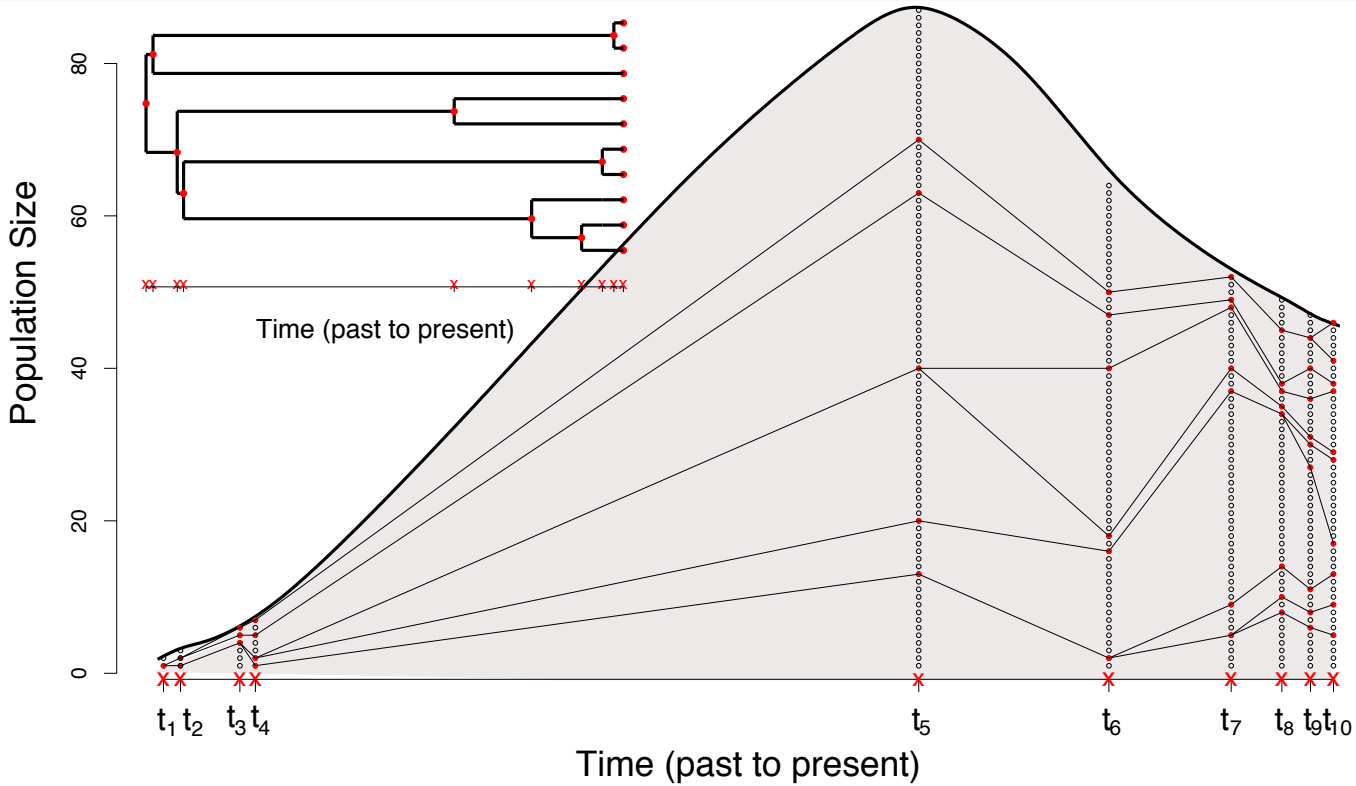
- $|\mathcal{T}_n| = n!(n-1)!/2^{n-1}$
- $|\mathcal{T}_{100}| \approx 10^{284}$
- $\approx 10^{80}$ atoms in the universe
- $\approx 4.4 \times 10^{17}$ seconds since the Big Bang

Coalescent times alone are sufficient statistics for $N(t)$

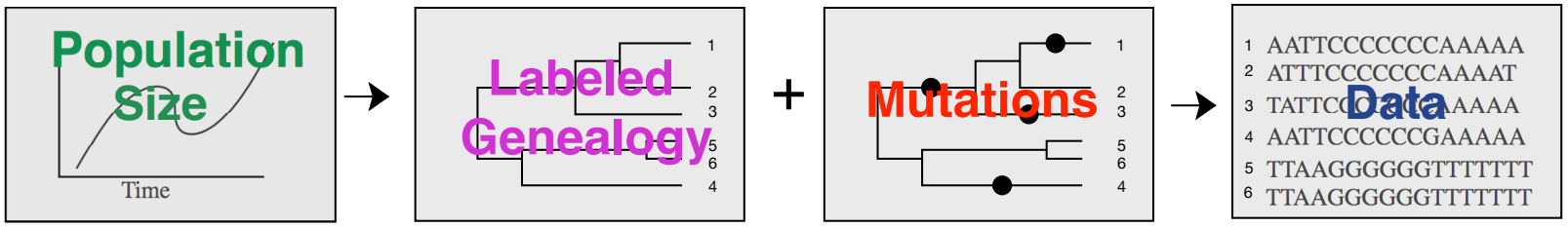


Coalescent Density:

$$P\left(\mathbf{G}|N_e(t)\right) \propto \prod_{k=2}^{n} P[t_{k-1}|t_k, N_e(t)].$$

$\mathbf{t} = (t_2, t_3, \ldots, t_n)$ are sufficient statistics for inferring $N_e(t)$

An alternative coalescent model?



What if we replace $\mathbf{G}$ with $\mathbf{t}$, the vector of coalescent times?
Posteriors:

$$P\left(N_e(t), \mathbf{G}, \mathbf{Q}, \tau \mid \mathbf{Y}\right) \text{ vs } P\left(N_e(t), \mathbf{t}, \mathbf{Q}, \tau \mid \mathbf{Y}\right)$$

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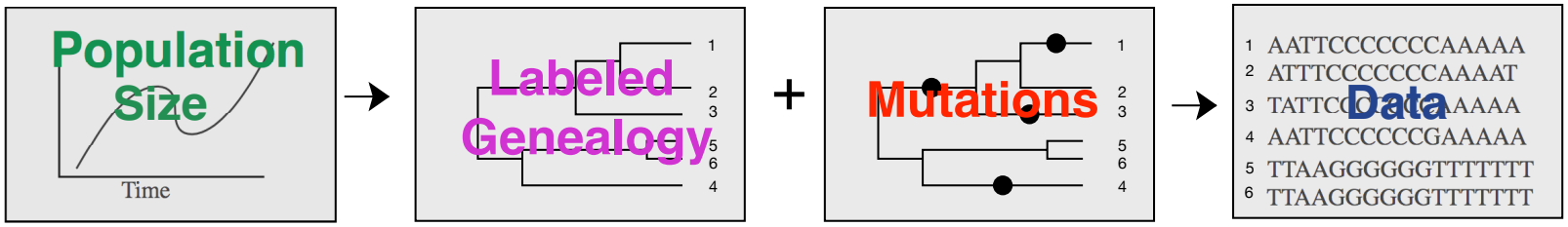

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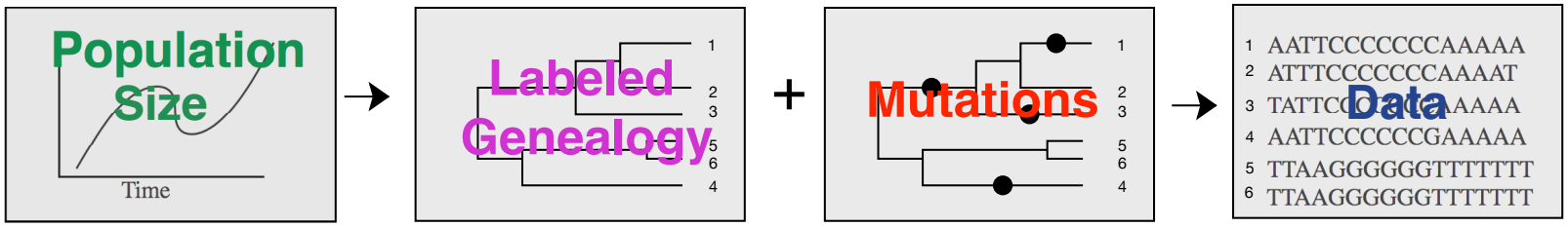

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- $P\left(\mathbf{Y} \mid \mathbf{t}, \mathbf{Q}\right) = \sum_{\mathcal{T}} P\left(\mathbf{Y}, \mathcal{T} \mid \mathbf{t}, \mathbf{Q}\right)$ is not “practical" since we need to sum over all possible topologies.

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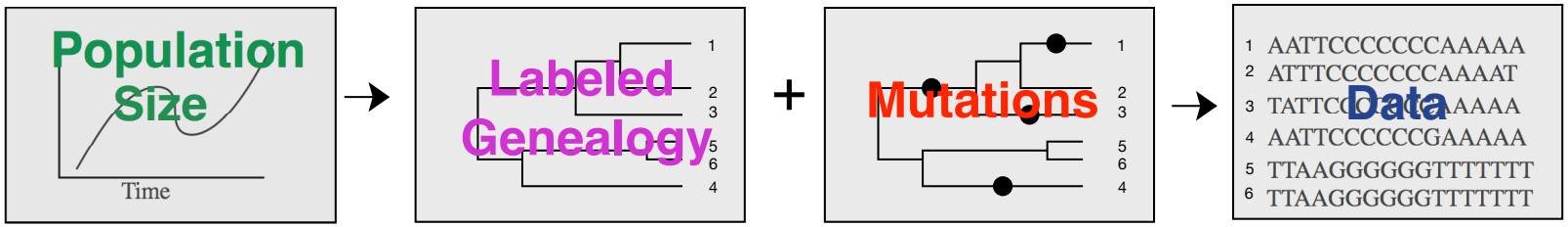

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- The times alone $\mathbf{t}$ are not sufficient for inferring $N_e(t)$ for whole genomes [Palacios et al., 2015]

An alternative coalescent model?

Different resolutions of the coalescent:

Finding the best resolution for the Kingman-Tajima coalescent: theory and applications

R. Sainudiin · T. Stadler · A. Véber

[J. Math. Biol, 2015]
“ considering the optimal resolution with respect to a given statistic can (i) lead to significant computational savings in terms of time complexity by directly sampling from a much smaller hidden space and (ii) help generate samples from the conditional hidden space (given the observed statistics) by controlling the sampling in such a way that only trees or shapes in the hidden space that are compatible with the observed statistics are drawn"

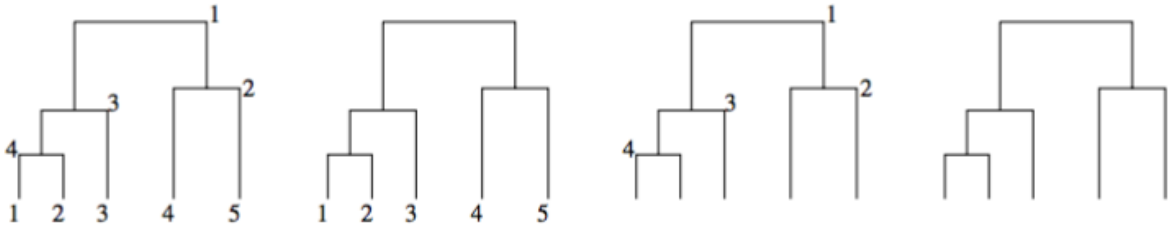
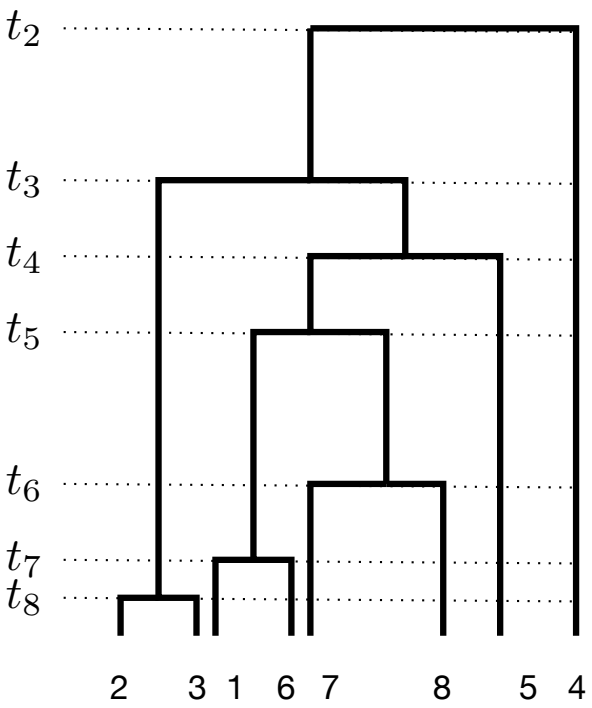


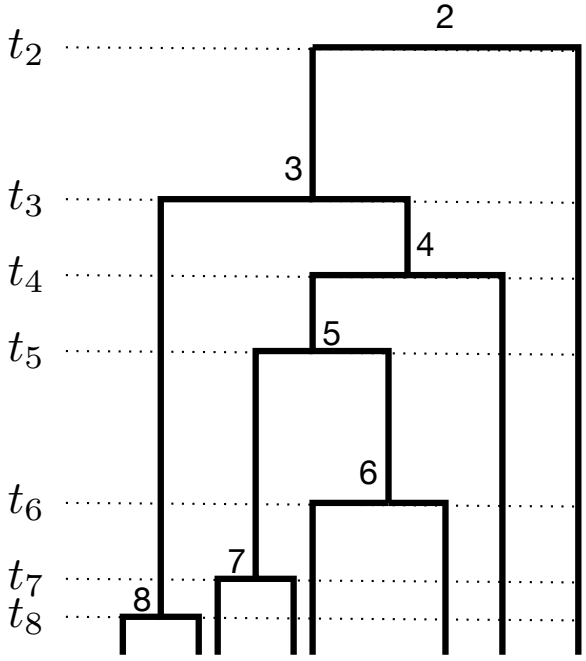
Fig. 2 Example for a ranked labeled tree with leaf label set $\mathfrak{L} = \{1,2,3,4,5\}$, a labeled tree with $\mathfrak{L} = \{1,2,3,4,5\}$, a ranked tree shape and a tree shape (from left to right).

Kingman's genealogies vs Tajima's genealogies

Kingman's genealogy



Tajima's genealogy



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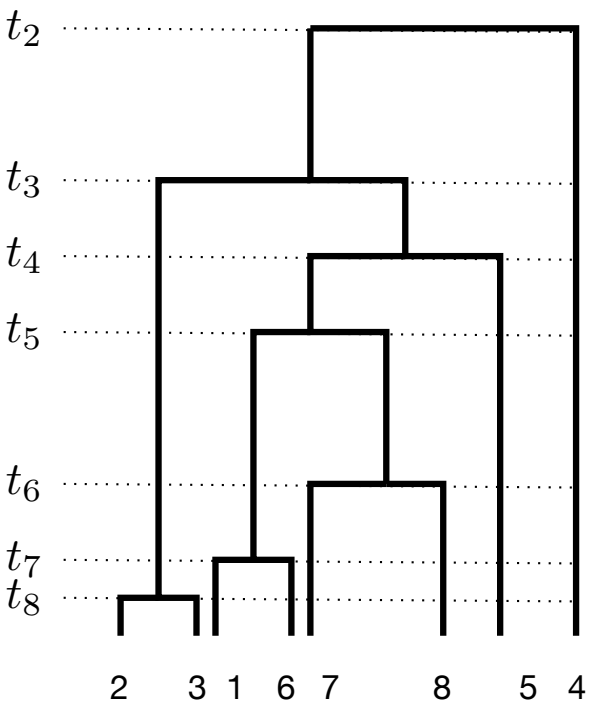

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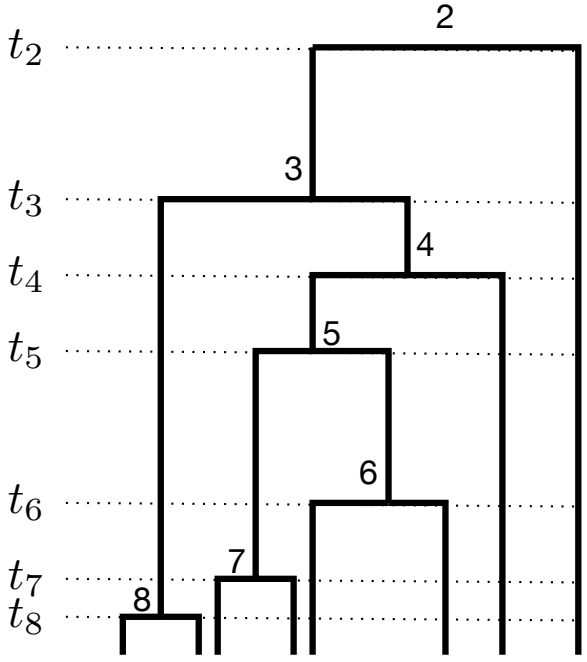
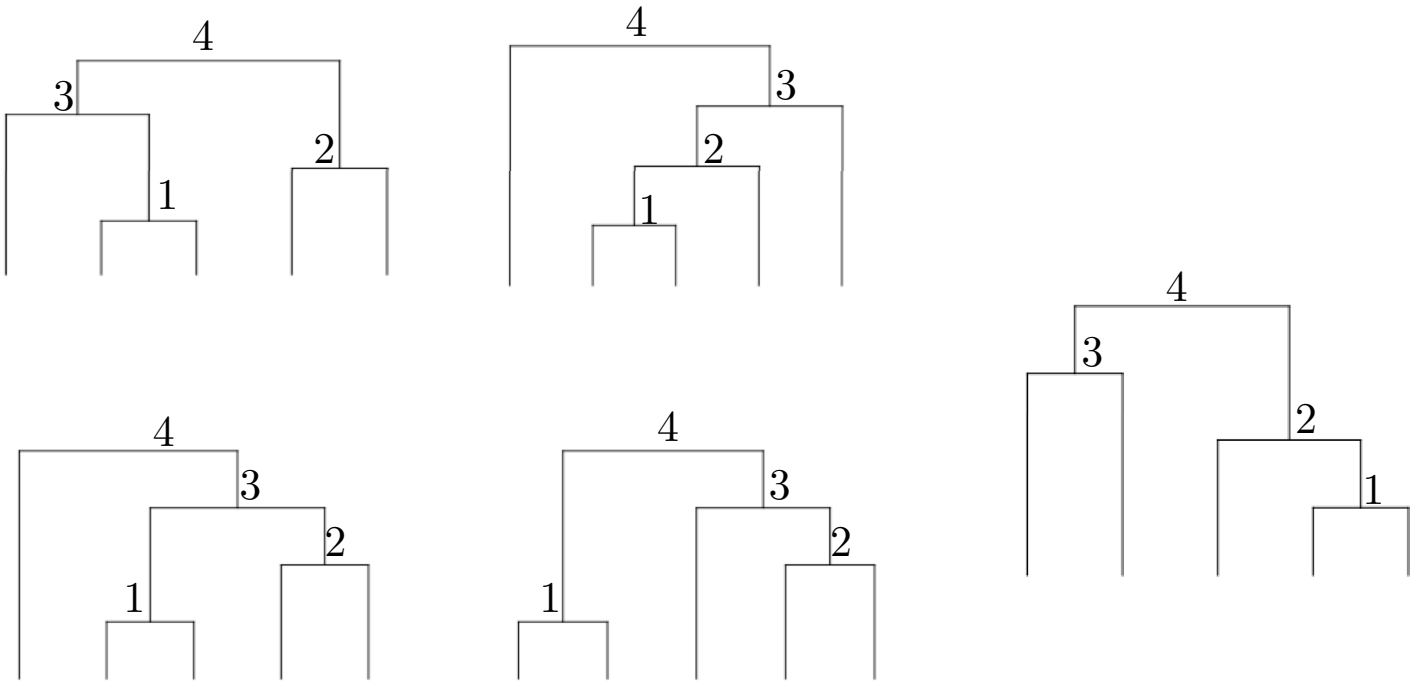


n	labeled topologies	ranked tree shapes
3	3	1
5	180	5
10	2.5×10^9	7936
20	5.64×10^{29}	2.9×10^{13}
50	3.28×10^{112}	1.9×10^{53}

Ranked tree shapes

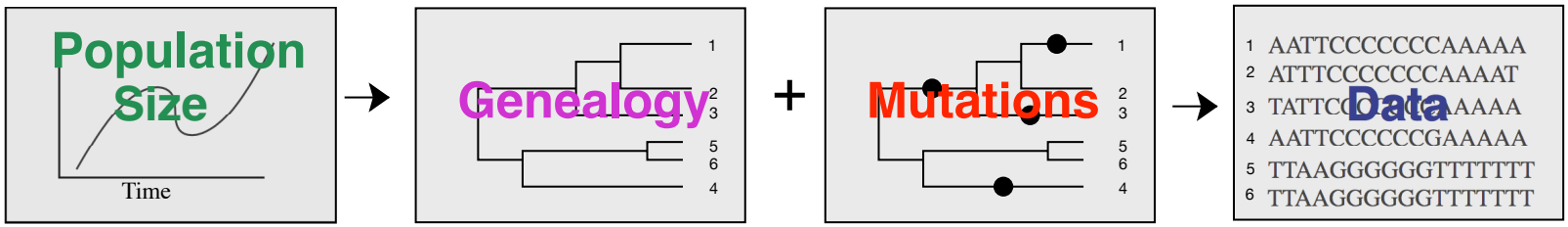
For $n = 5$



In parenthetical notation, the first tree would be represented by

$$4 : (3 : (1 : (,),),2 : (,)) \tag{1}$$

Inference with Tajima's coalescent



With Kingman's coalescent:

- Goal: $P\left(N_e(t), \mathbf{G}, \mathbf{Q}, \tau \mid \mathbf{Y}\right)$
- The state space of genealogies $\mathcal{G}$
  $\mathcal{G} = \mathcal{T}_n \otimes \mathbb{R}^{+n-1}$
- The likelihood $P\left(\mathbf{Y} \mid \mathbf{G}, \mathbf{Q}\right)$ is tractable.

With Tajima's coalescent:

- Goal: $P\left(N_e(t), \mathbf{G}^{\mathbf{T}}, \mathbf{Q}, \tau \mid \mathbf{Y}\right)$
- The state space of Tajima's genealogies $\mathcal{G}^T$
  $\mathcal{G}^T = \mathcal{R}_n \otimes \mathbb{R}^{+n-1}$
- $P\left(\mathbf{Y} \mid \mathbf{G}^{\mathbf{T}}, \mathbf{Q}\right)$ directly with infinite sites mutations model

Outline

Inference with Tajima's coalescent:

- Felsenstein-Tajima conditional likelihood
- Bayesian model for inferring $N(t)$
- MCMC Algorithm for Posterior inference
  - Sampling of ranked tree shapes (F)
  - Sampling of coalescent times (t)
  - Sampling of $N(t)$
- Results
- Summary and future directions

Felsenstein-Tajima conditional likelihood

Goal:

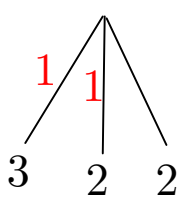
$$P(\mathbf{Y} \mid G^T = \{\mathbf{F}, \mathbf{t}\}, \mu)$$

Assumptions:

- We assume the infinite-sites mutation model
- We know the ancestral state at each polymorphic site
- Our data can be represented as sequences of 0s and 1s
- There is a one-to-one correspondence between data consistent with ISM and a perfect phylogeny (gene tree)

$$P(\mathbf{Y} \mid G^T = \{\mathbf{F}, \mathbf{t}\}, \mu) = P(PP \mid G^T = \{\mathbf{F}, \mathbf{t}\}, \mu)$$

1	A	C
2	A	C
3	A	C
4	T	C
5	T	C
6	T	G
7	T	G
ancestral:	T	C



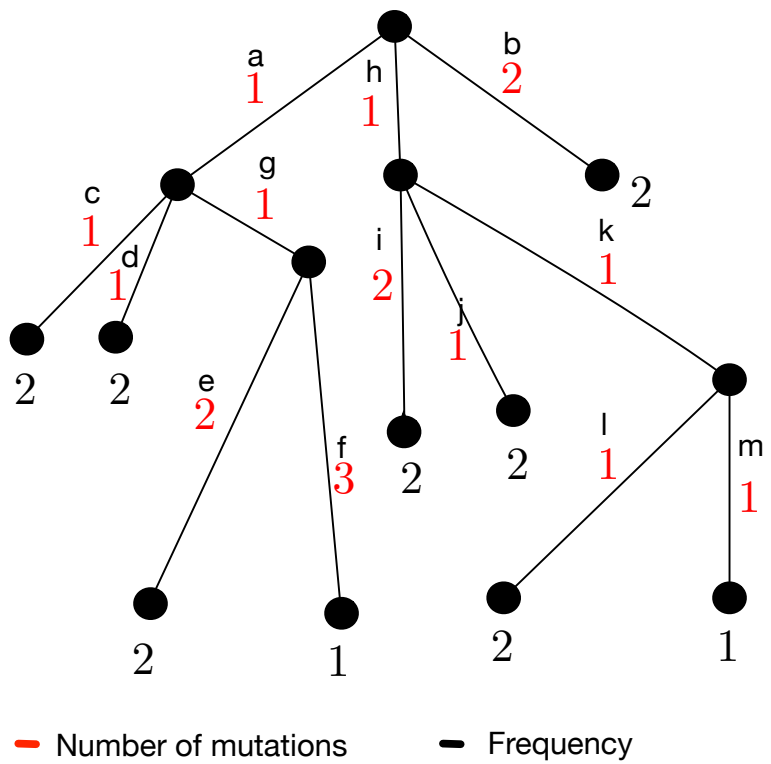
Data as perfect phylogeny (gene tree)

A bigger example (Dan Gusfield, 1991):

A Data $(\mathbf{Y})$

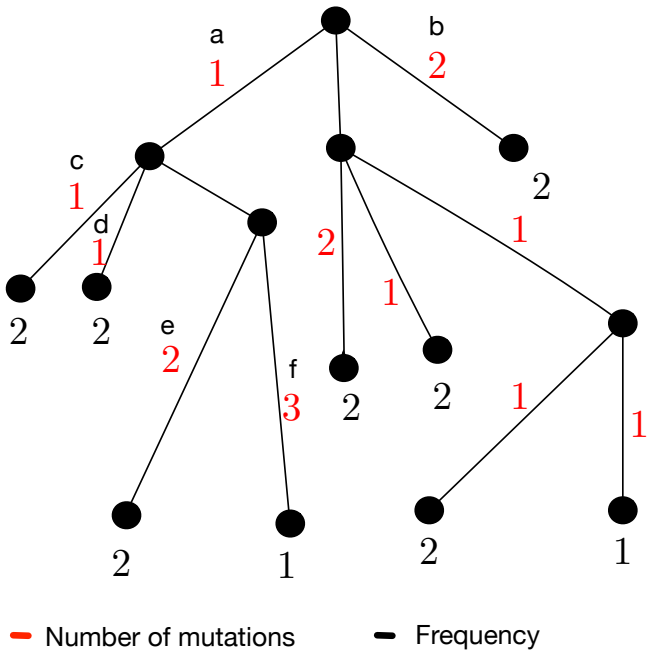
Haplotype	Frequency	a	b	b	c	d	e	e	f	f	f	...
1	2	1	0	0	1	0	0	0	0	0	0	
2	2	1	0	0	0	1	0	0	0	0	0	
3	2	1	0	0	0	0	1	1	0	0	0	
4	1	1	0	0	0	0	0	0	1	1	1	
5	2	0	0	0	0	0	0	0	0	0	0	
6	2	0	0	0	0	0	0	0	0	0	0	
7	2	0	1	1	0	0	0	0	0	0	0	
8	2	0	0	0	0	0	0	0	0	0	0	
9	1	0	0	0	0	0	0	0	0	0	0	
	16											

B Perfect Phylogeny $(\mathcal{T})$

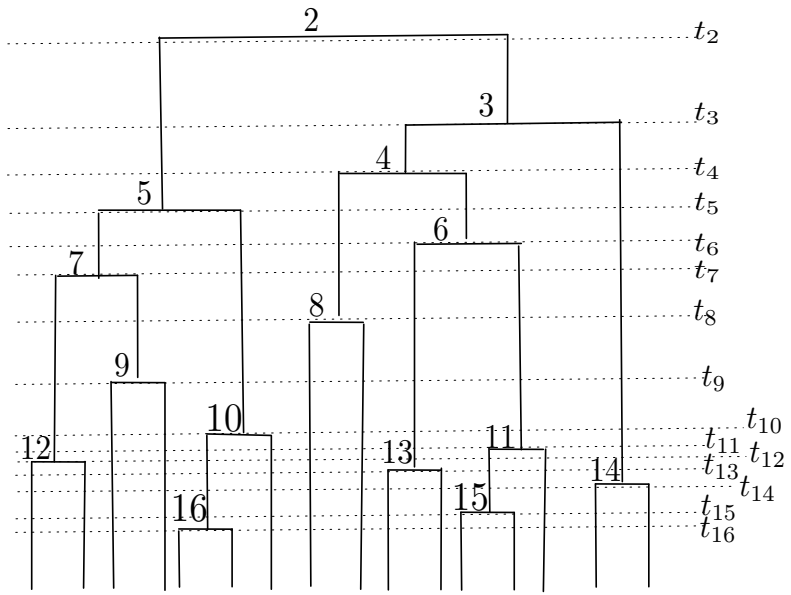


Felsenstein-Tajima conditional likelihood

Perfect Phylogeny $(\mathbf{Y})$



Tajima's genealogy (g^T)



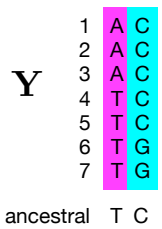
Goal:

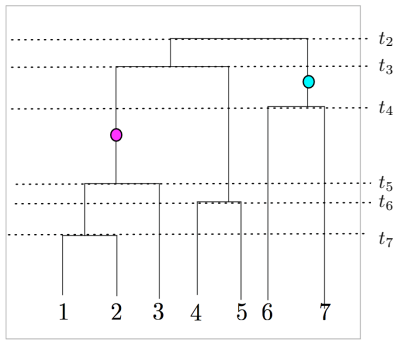
$$P(\mathbf{Y} \mid G^T = \{\mathbf{F}, \mathbf{t}\}, \mu)$$

Felsenstein-Tajima conditional likelihood

The tricky part: once we remove the labels, we can have more than one assignment of mutations to branches

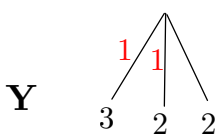
With Kingman's coalescent

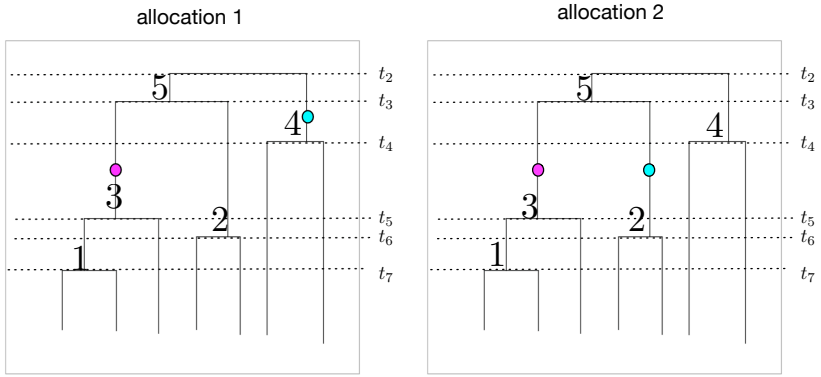




$$\mathrm{P}\left(\mathbf{Y} \mid \mathbf{G}, \mu\right) = \mathrm{P}\left(\text{●},\text{●} \mid \mathbf{G}, \mu\right)$$

With Tajima's coalescent

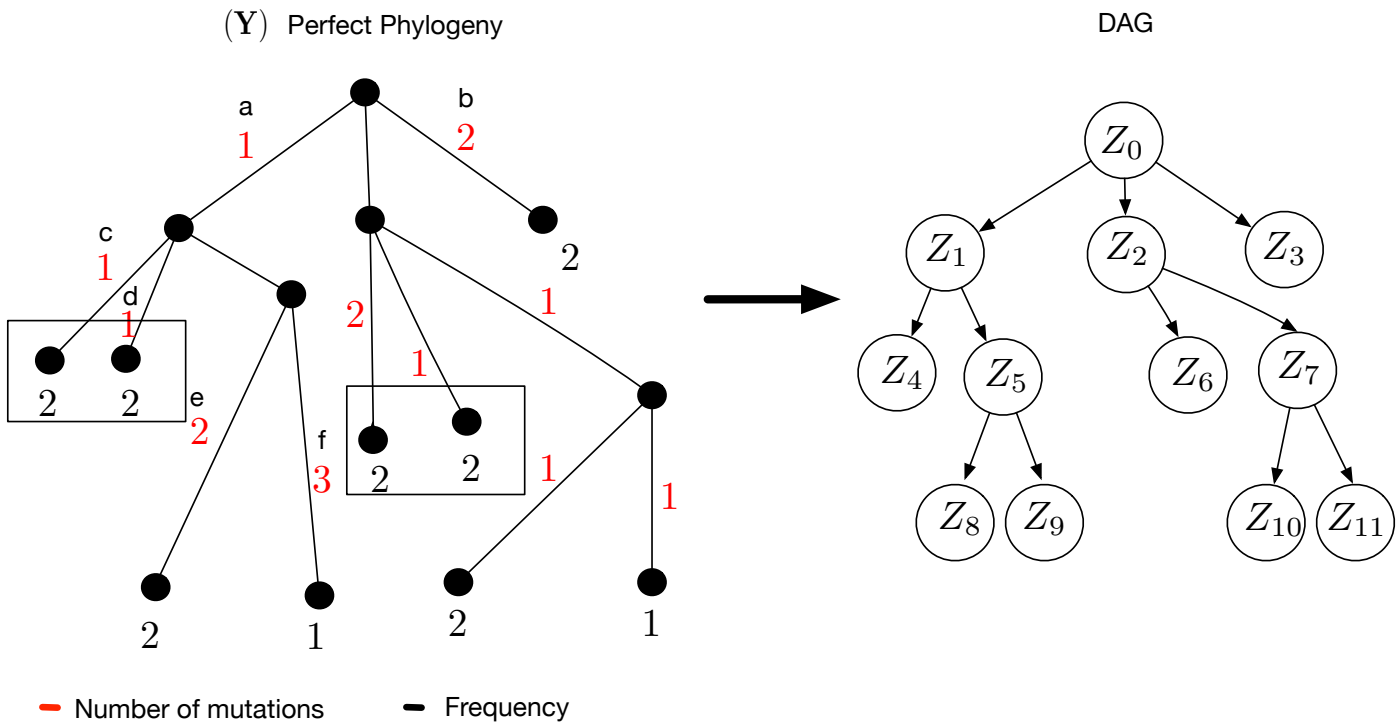




$$\mathrm{P}\left(\mathbf{Y} \mid \mathbf{G}^T, \mu\right) = \mathrm{P}\left(\text{●},\text{●}\text{in allocation 1 or allocation 2} \mid \mathbf{G}^T, \mu\right)$$

Felsenstein-Tajima conditional likelihood

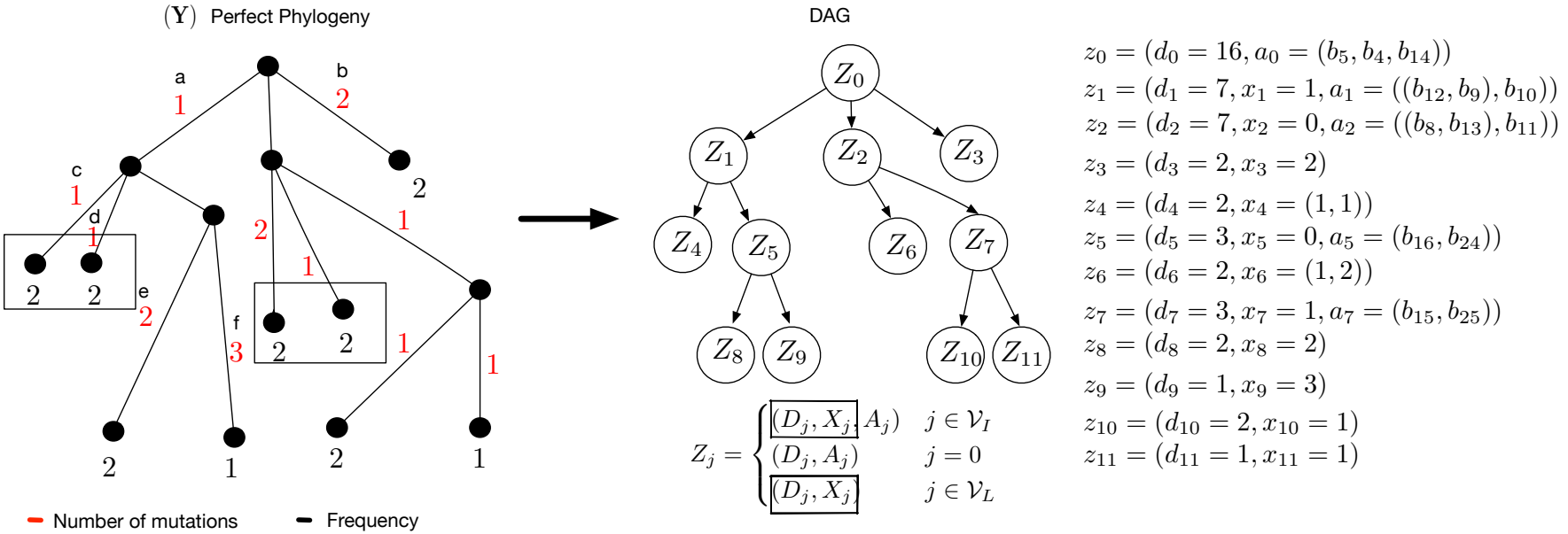
The computational helper: We use the structure of the perfect phylogeny to generate a probabilistic DAG model (Bayes network, Bayes nets, belief networks, Bayesian graphical model)



We merge sister leaves with the same number of descendants into a single leaf in the DAG.

Felsenstein-Tajima conditional likelihood

We equip the DAG with mutations ...

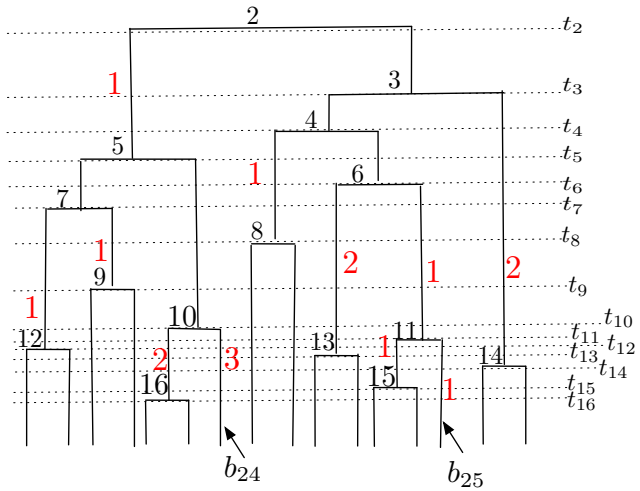


We merge sister leaves with the same number of descendants into a single leaf in the DAG.

Felsenstein-Tajima conditional likelihood

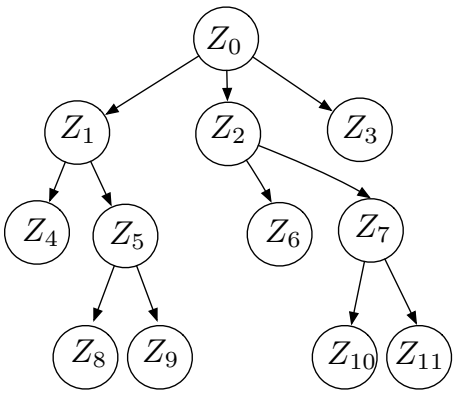
We augment the DAG with allocation of mutations (A_j) along $\mathbf{G}^T$

A Tajima's genealogy and a possible allocation of the mutations observed in the data



Number of mutations

B DAG corresponding to **A**



$$Z_j = \begin{cases} (D_j, X_j, A_j) & j \in \mathcal{V}_I \\ (D_j, A_j) & j = 0 \\ (D_j, X_j) & j \in \mathcal{V}_L \end{cases}$$

$$z_0 = (d_0 = 16, a_0 = (b_5, b_4, b_{14}))$$
$$z_1 = (d_1 = 7, x_1 = 1, a_1 = ((b_{12}, b_9), b_{10}))$$
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$$z_3 = (d_3 = 2, x_3 = 2)$$
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$$z_8 = (d_8 = 2, x_8 = 2)$$
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$$z_{10} = (d_{10} = 2, x_{10} = 1)$$
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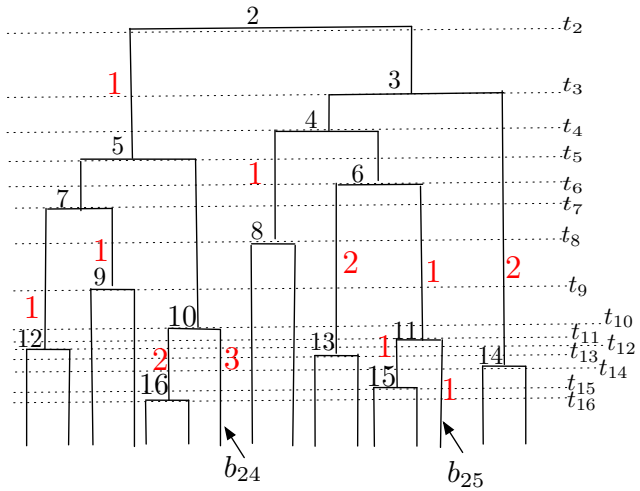

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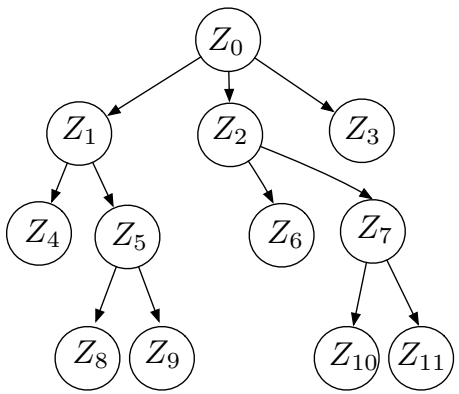

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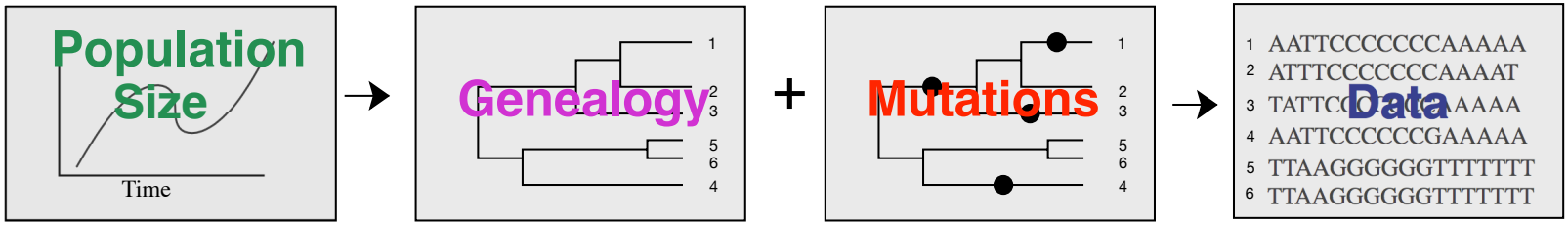
$$\begin{aligned} P(\mathbf{Y} \mid G^T, \mu) \propto & \sum_{A_0} \sum_{A_1} \cdots \sum_{A_{n_I}} P(\mathbf{D} \mid G^T, \mu) e^{-\mu \mathcal{L}} \\ = & \; e^{-\mu \mathcal{L}} \sum_{A_0} \sum_{A_1} \cdots \sum_{A_{n_I}} P(Z_0, \ldots, Z_{n_I+n_L} \mid G^T, \mu) \\ = & \; e^{-\mu \mathcal{L}} \sum_{A_0} \sum_{A_1} \cdots \sum_{A_{n_I}} \prod_{i=1}^{n_I+n_L} P(Z_i \mid Z_{pa(i)}, G^T, \mu) \end{aligned}$$

Bayesian model for inferring $N(t)$



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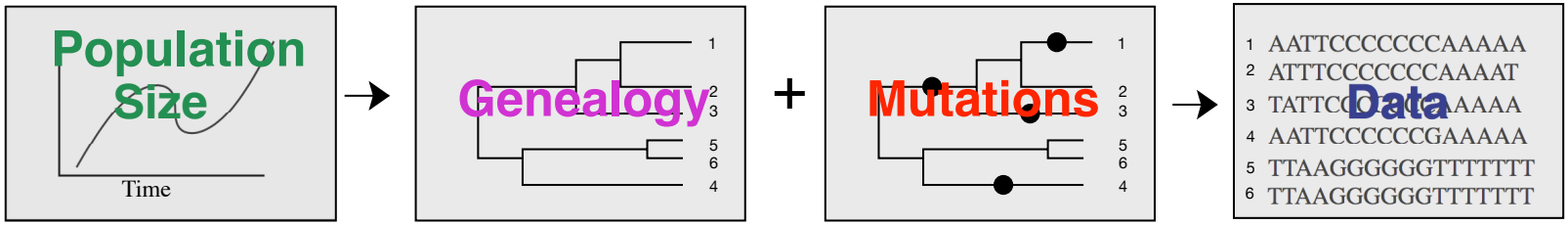


- $\gamma = \log N(t) \sim GP(0, C(\tau))$, $\tau \sim Gamma(\alpha, \beta)$
- Tajima coalescent prior

$$P[G^T = \{\mathbf{F}, \mathbf{t}\} \mid N_e(t)] = P(\mathbf{F}) \prod_{k=2}^{n} P[t_k \mid t_{k+1}, N_e(t)], \quad (2)$$

and

$$P(\mathbf{F}) = \frac{2^{n-c-1}}{(n-1)!}, \quad (3)$$

$$P[t_{k-1} | t_k, N_e(t)] = \frac{C_{k-1}}{N_e(t_{k-1})} \exp\left[- \int_{t_k}^{t_{k-1}} \frac{C_{k-1} dt}{N_e(t)} \right], \quad (4)$$

where $C_k = \binom{k}{2}$ is the coalescent factor that depends on the number of lineages $k = 2, ..., n$.

MCMC Algorithm for Posterior inference

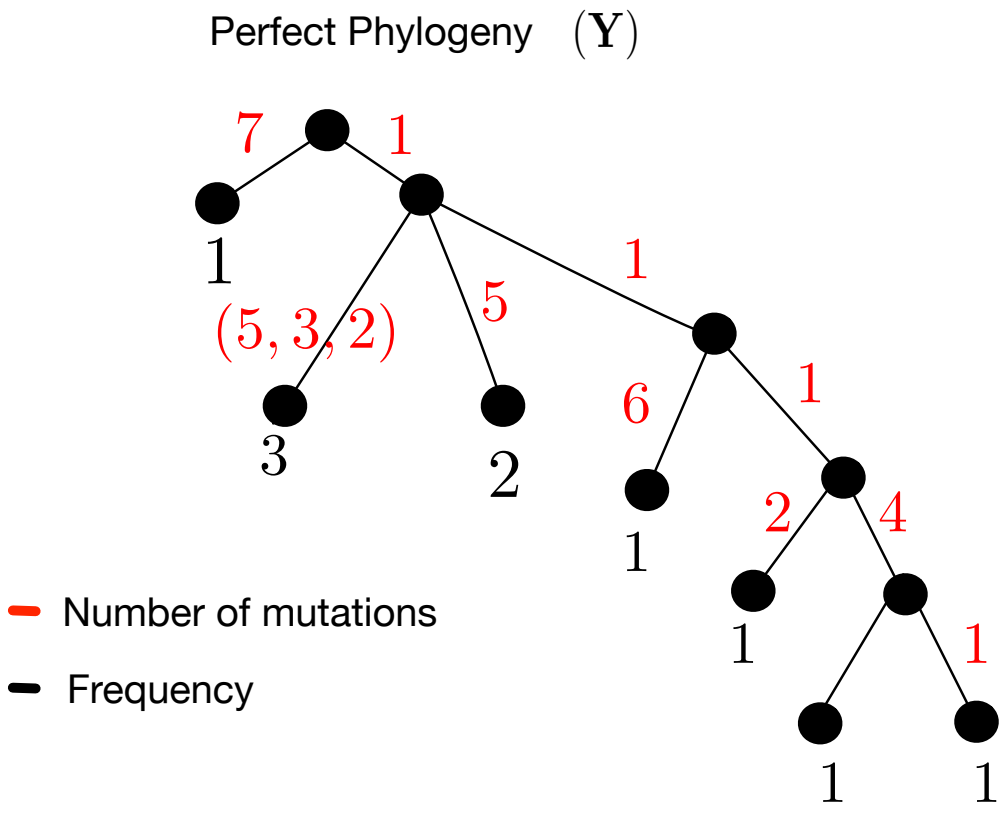
Goal:

$$P[\boldsymbol{\gamma}, G^T, \tau \mid \mathbf{Y}, \mu] \propto P(\mathbf{Y} \mid G^T, \mu) P[G^T \mid \boldsymbol{\gamma}] P[\boldsymbol{\gamma} \mid \tau] P(\tau) \qquad (5)$$

Metropolis-Hastings

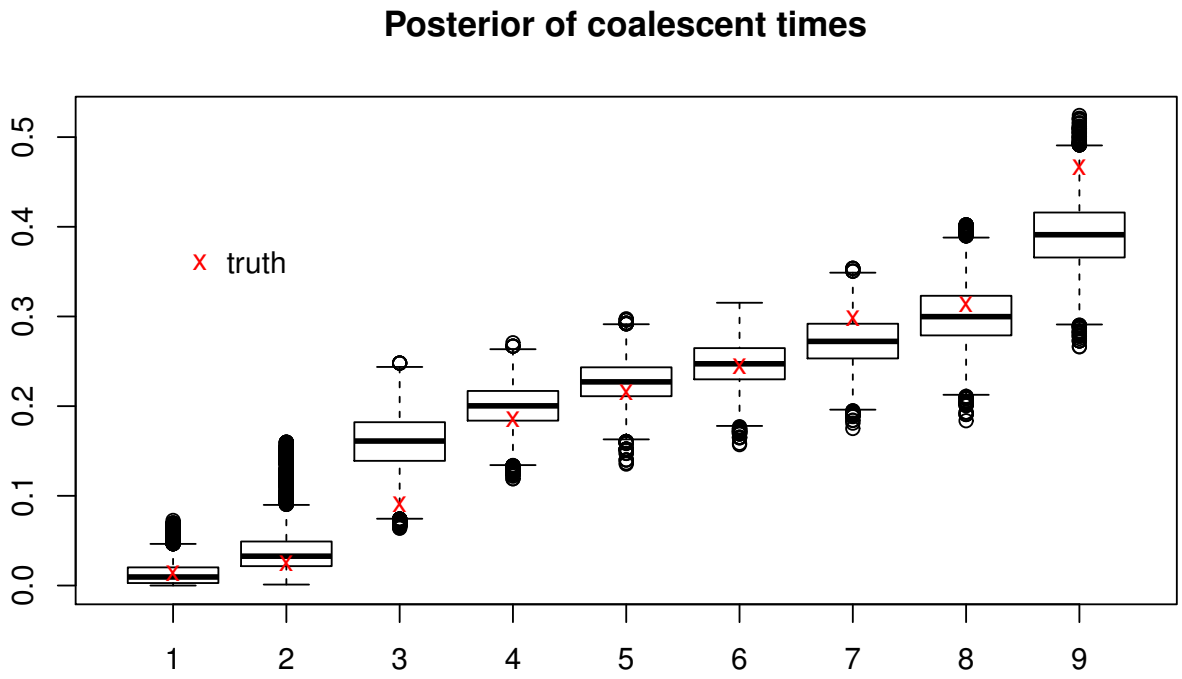
- splitHMC [Lan et al., Bioinformatics 2015] to sample $\boldsymbol{\gamma}, \tau$
- HMC to sample $\mathbf{t}$
- $q(F \mid \mathbf{Y})$ proposal for ranked tree shapes exploiting the DAG representation of perfect phylogeny

Simulation

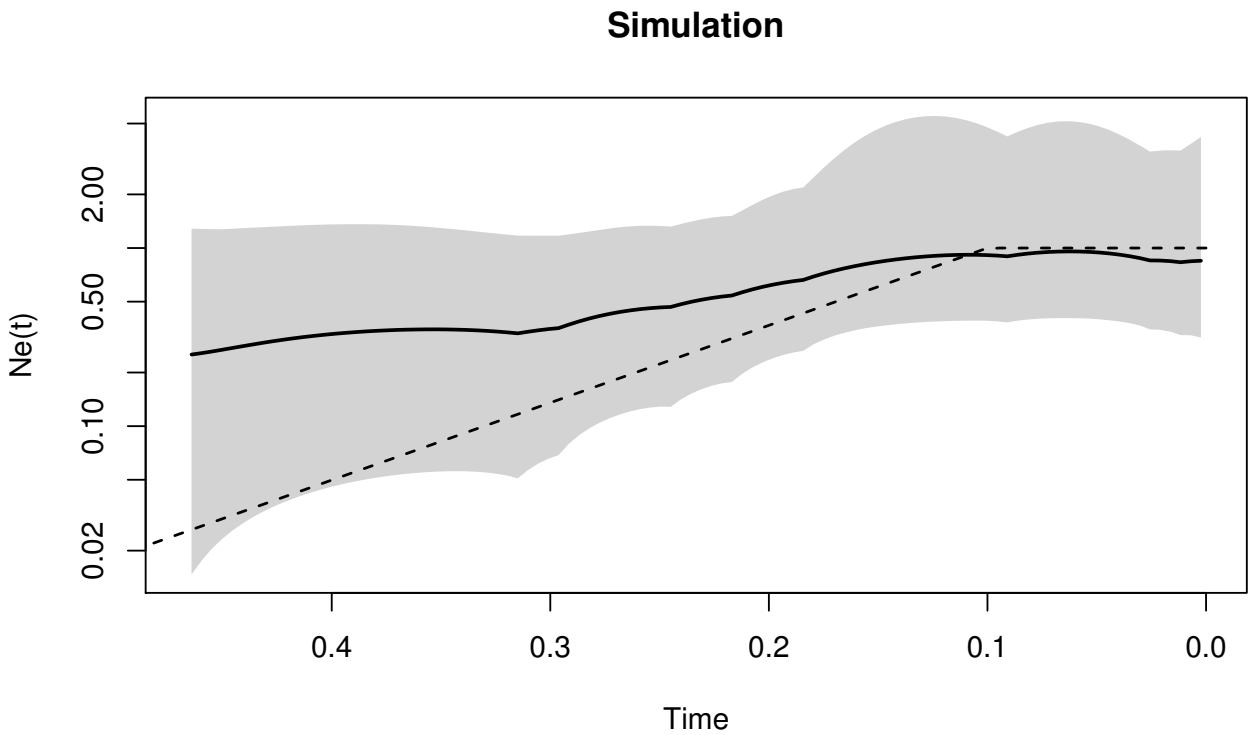


- Only 548 ranked tree shapes are compatible with the data

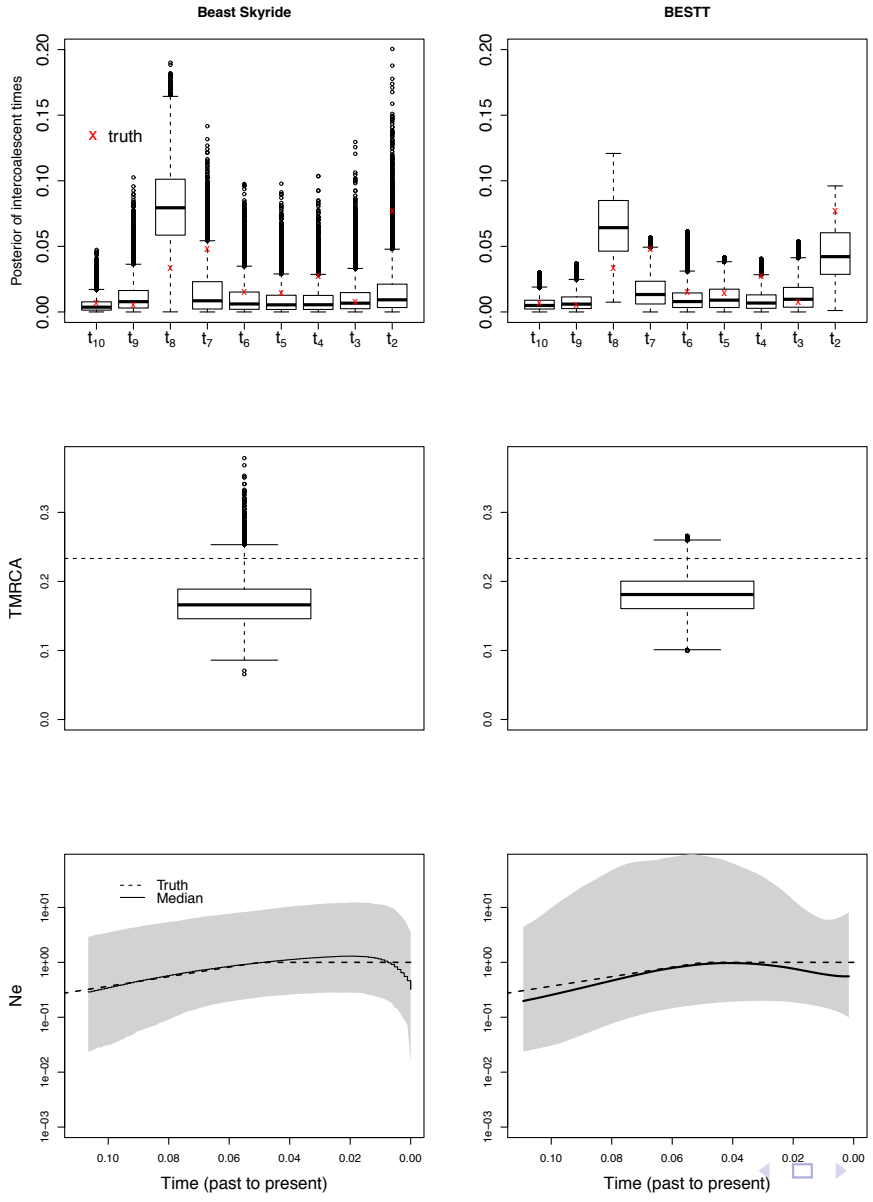
Simulation: Sampling coalescent times



Simulation: Sampling Ne



Comparison with BEAST [Suchard et al (2018)]



Summary

- Tajima's coalescent is a more **efficient** lower resolution model for inference of effective population sizes.
- A priori, the hidden state space of ranked tree shapes is much **smaller** than the **space** of labeled topologies.
- Current implementation (in R `phylodyn`) is **limited to the infinite-sites** mutation model.
- Tajima's inference can be extended for modeling recombination under the sequential Markovian coalescent.
- The Felsenstein-Tajima conditional likelihood calculation can be extended for tree shapes.

Size of ranked tree shapes

- The cardinality of the hidden space of ranked tree shapes depends on your observed data.
- For our simulation example ($n = 10$ samples)
  - $|\mathcal{T}_{10}| = 2.5 \times 10^9$ labeled topologies

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- Let $\beta_x = (x+1, n-x+1)$ be a binary perfect phylogeny with two leaves with $x+1$ leaves on one side and $n-x+1$ on the other side.
- The set of unlabeled histories (ranked tree shapes) compatible with β_x, assuming $x < n/2$ is

$$|R_{n+2} \mid \beta_x| = e_x \cdot e_{n-x} \cdot \binom{n}{x}, \tag{6}$$

where e_i is the number of unlabeled histories with i internal nodes. The integer e_i is the ith Euler number:

$$\sum_{i=0}^{\infty} \frac{e_i z^i}{i!} = \frac{1}{\cos(z)} + \tan(z) \tag{7}$$

Size of ranked tree shapes

Theorem

The maximum number of ranked tree shapes of n leaves compatible with the perfect phylogeny occurs when the perfect phylogeny is a multifurcating phylogeny of degree n or $n-1$.

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Theorem

The maximum number of ranked tree shapes of n leaves compatible with a binary perfect phylogeny occurs when there is a single bifurcation event dividing the samples in two groups of sizes $(n-2)$ and (2).

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- Amandine Veber (Ecole Polytechnique)
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