# Insertion-deletion models for sequence evolution and Bayesian sampling methods for multiple alignment

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# Outline

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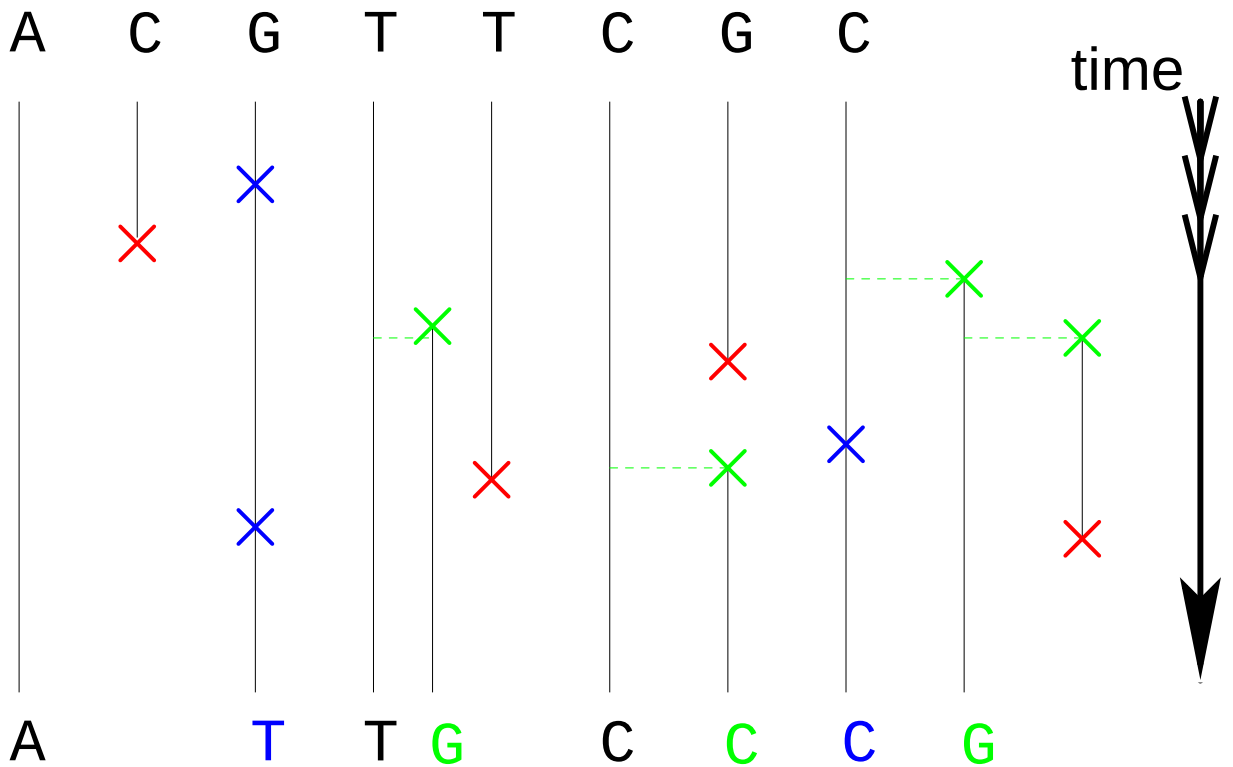
Model of Sequence Evolution
Thorne, Kishino, Felsenstein (1991):

Deletions with rate $\mu$ at each site.
Insertions with rate $\lambda$ right of each site & at the very left.
Substitutions with Rate $s$ at each site.



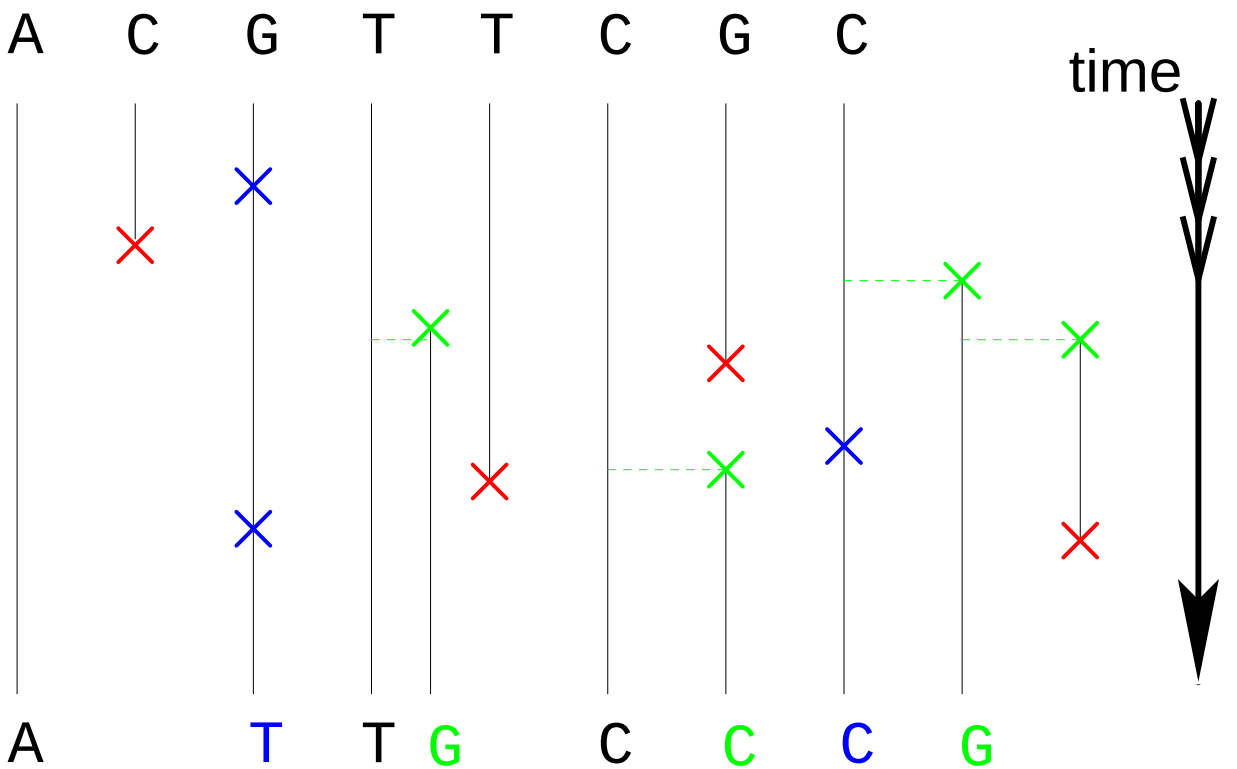
TKF alignment convention:

like this:

```
ACGT_TC_GC_
A_TTG_CC_CG
```

not like this:

```
ACGT_TCG_C_
A_TTG_C_CCG
```

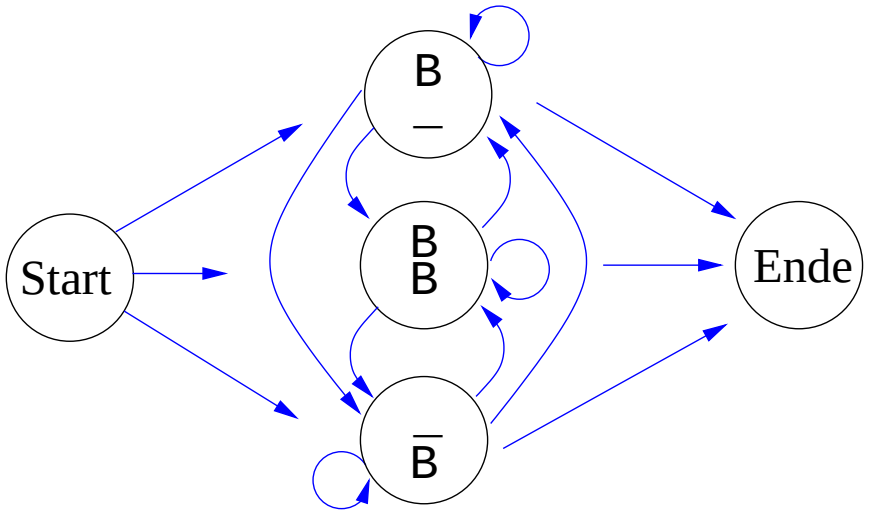


# Consequence of TKF convention

The bare alignment

BBBB_BB_BB_
B_BBB_BB_BB

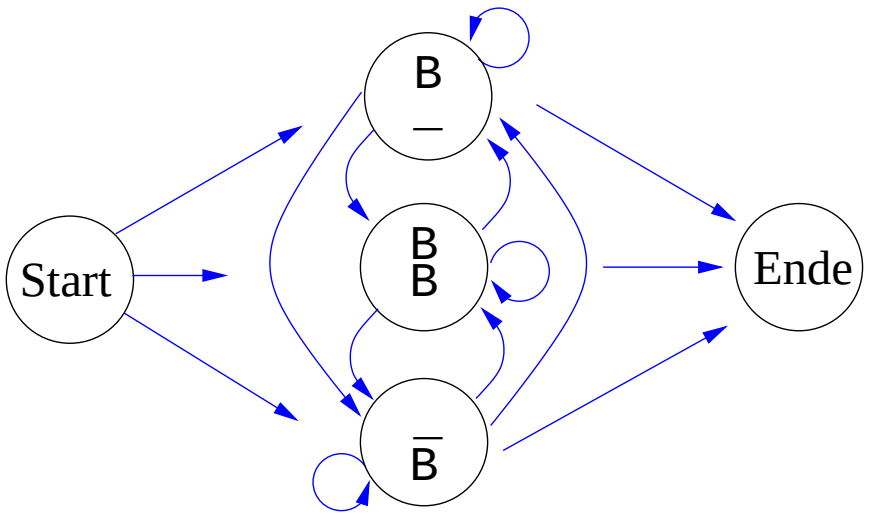
is generated by a Markov chain:



# Consequence of TKF convention

The bare alignment

BBBB_BB_BB_
B_BBB_BB_BB

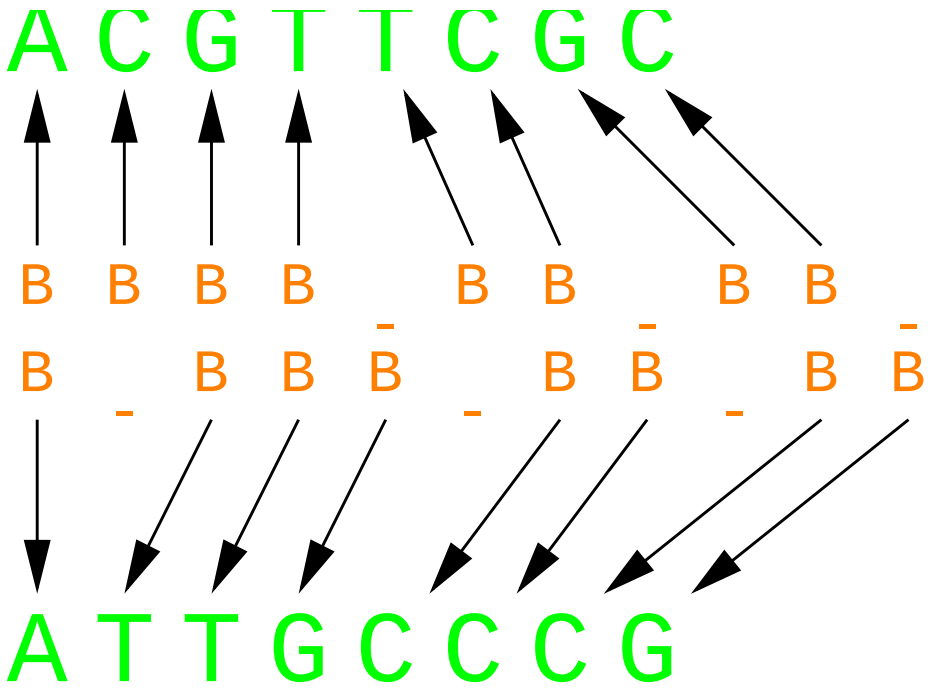



is generated by a Markov chain:

| from \ to | $\begin{smallmatrix}\mathrm{B}\\ \mathrm{B}\end{smallmatrix}$ | $\begin{smallmatrix}\mathrm{B}\\ -\end{smallmatrix}$ | $\overline{\mathrm{B}}$ |
|---|---|---|---|
| $\begin{smallmatrix}\mathrm{B}\\ \mathrm{B}\end{smallmatrix}$ | $(1-\lambda\beta)\frac{\lambda}{\mu}e^{-\mu}$ | $(1-\lambda\beta)\frac{\lambda}{\mu}(1-e^{-\mu})$ | $\lambda\beta$ |
| $\begin{smallmatrix}\mathrm{B}\\ -\end{smallmatrix}$ | $\lambda\beta\frac{e^{-\mu}}{1-e^{-\mu}}$ | $\lambda\beta$ | $\frac{1-e^{-\mu}-\mu\beta}{1-e^{-\mu}}$ |
| $\overline{\mathrm{B}}$ | $(1-\lambda\beta)\frac{\lambda}{\mu}e^{-\mu}$ | $(1-\lambda\beta)\frac{\lambda}{\mu}(1-e^{-\mu})$ | $\lambda\beta$ |

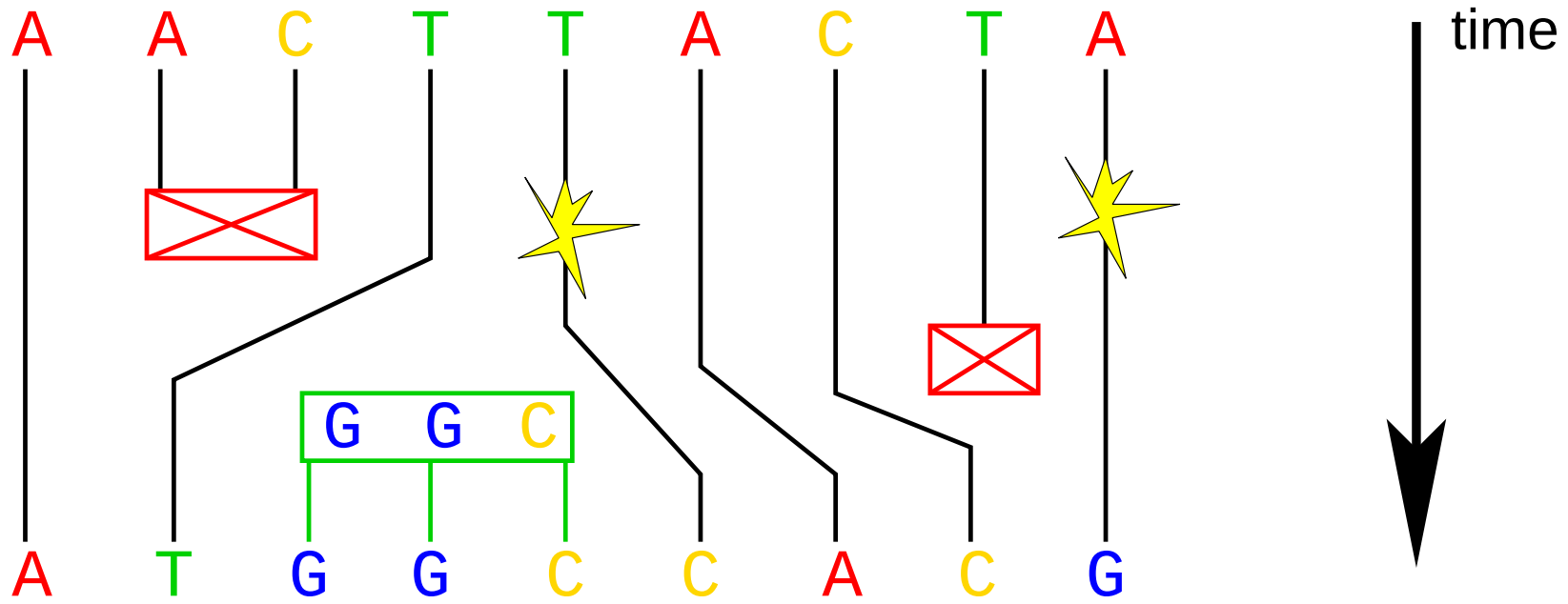
transition probabilies im (model: TKF'91), $\beta = \frac{1-e^{\lambda-\mu}}{\mu-\lambda e^{\lambda-\mu}}$

The Markov chain (the alignment) is hidden, observable is the pair of sequences emitted by the alignment.




*pair Hidden Markov Model (pair HMM)*

# InDels are usually longer than 1 position



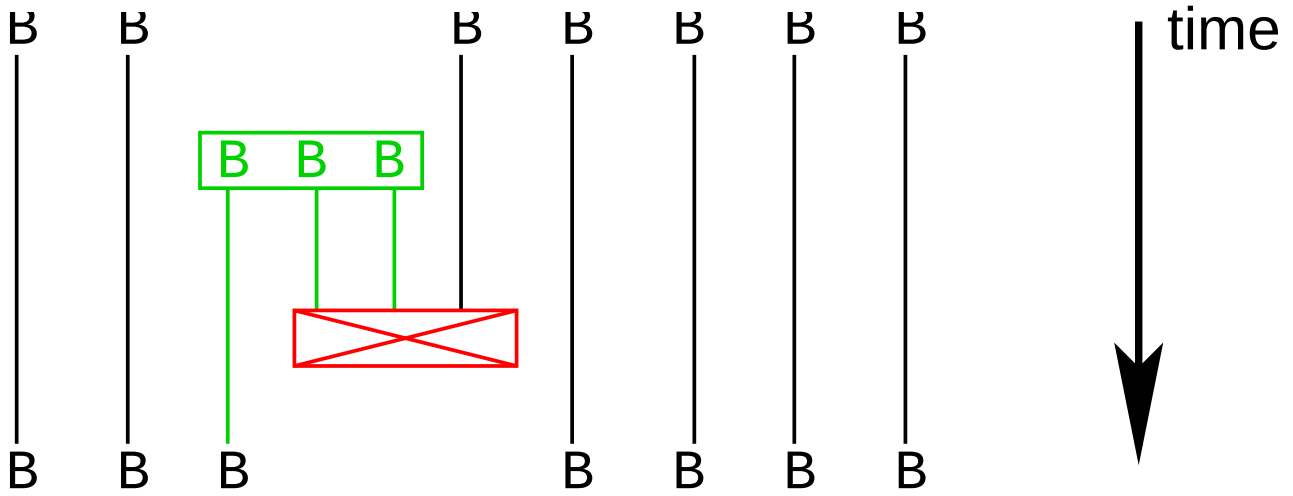
J.L. Thorne, H. Kishino, J. Felsenstein (1992) Inching towards reality: an improved likelihood model for sequence evolution. *J. Mol. Evol.*, **34**, 3-16.
D. Metzler (2003) Statistical alignment based on fragment insertion and deletion models, *Bioinformatics* 19:490-499.

FID Model (also a pairHMM):

- instead of single nucleotides, fragments are inserted an deleted with rate $\lambda$.
- Length of the fragments: geometrically distributed, mean length: $\gamma$.

$$\Pr(L = k) = \frac{1}{\gamma}\left(1 - \frac{1}{\gamma}\right)^k$$

forbidden in TKF92 and FID:




GID Model:

- ↑ this is allowed
- **no** *hidden Markov* structure

Use GID to simulate data
and test robustness of FID

How good are FID-based methods when GID/“Long Indel Model” is true?

- no problem for parameter estimations (Metzler, 2003)
- alignment accuracy can be decreased (Miklos, Lunter, Holmes, 2004)

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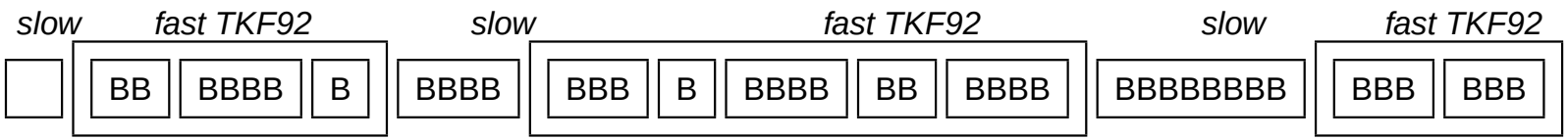
Maybe generate mixed-geometric gap-length with two types of fragments

# InDel Model for detecting conserved regions

A. Arribas-Gil, D. Metzler, J.-L. Plouhinec (2007)



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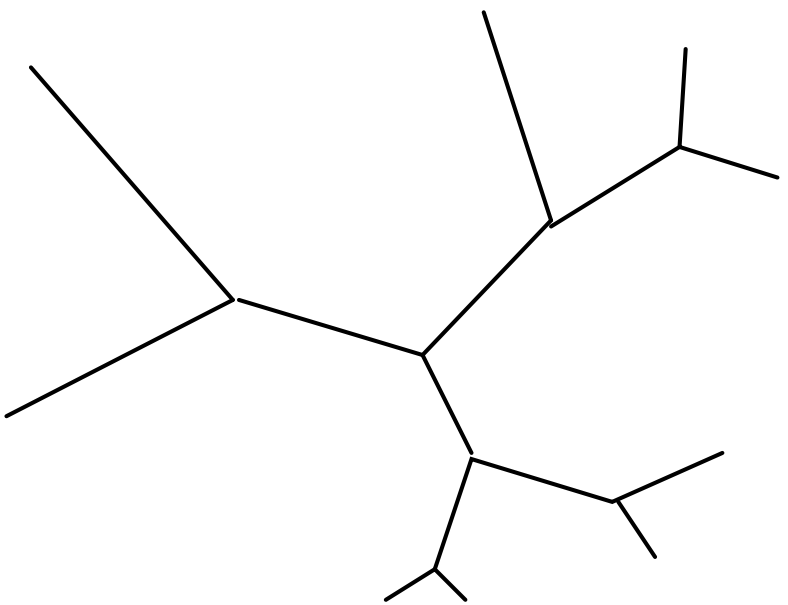
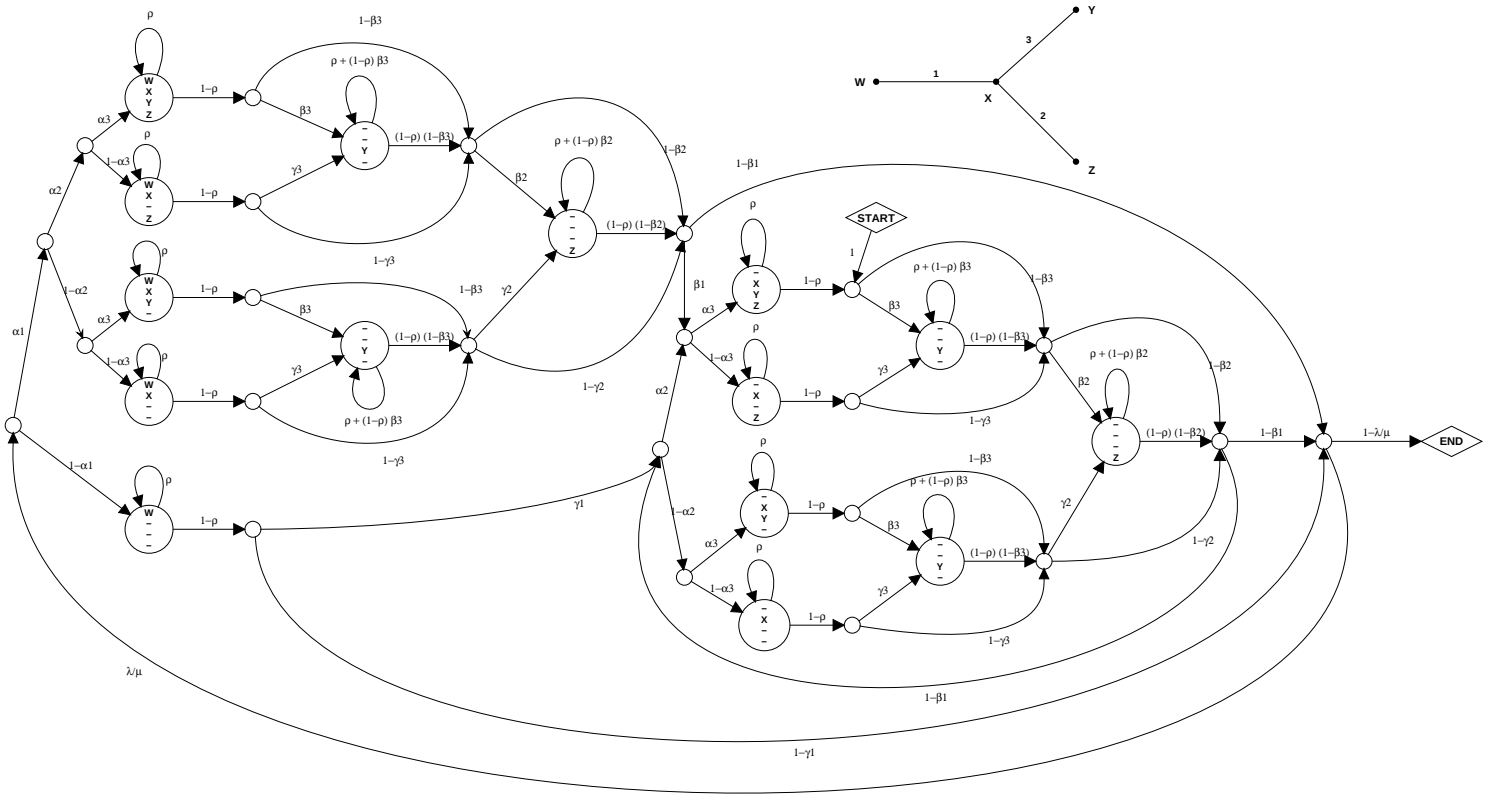
I. Holmes, W. J. Bruno (2001) Evolutionary HMMs: a Bayesian approach to multiple alignment, *Bioinformatics* 17:803-820.

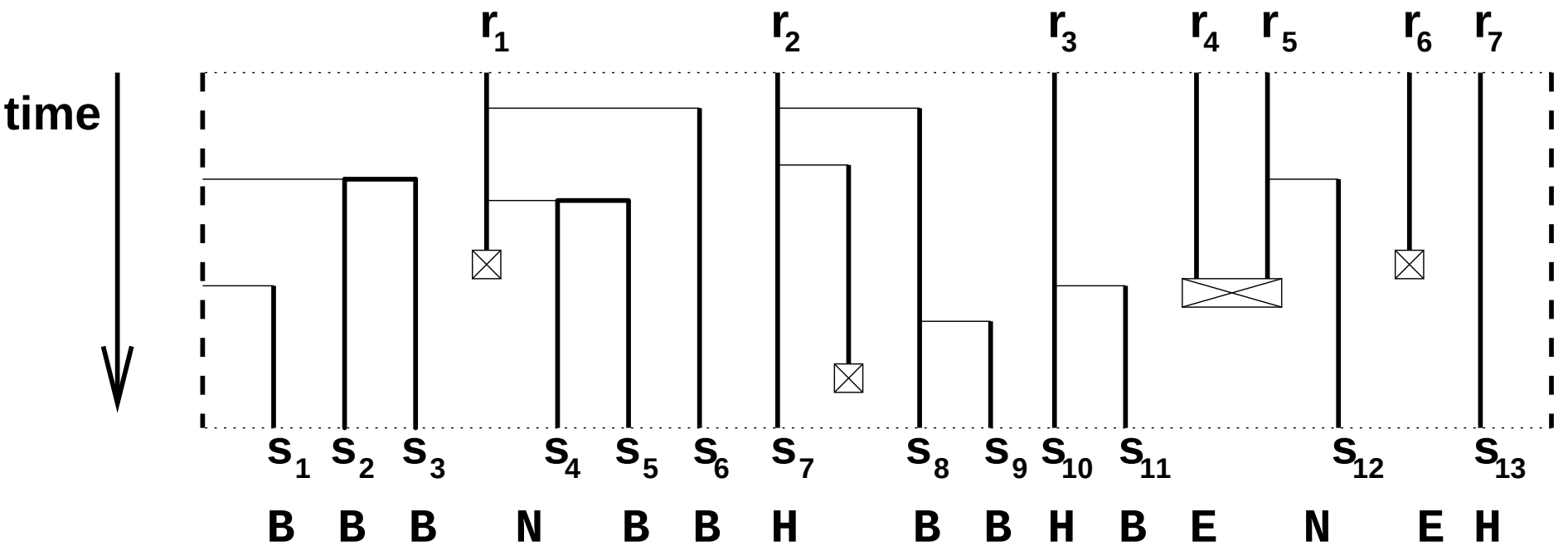
R. Fleißner, D. Metzler, A. von Haeseler (2005) Simultaneous statistical multiple alignment and phylogeny reconstruction. *Systematic Biology* 54(4):548-61.

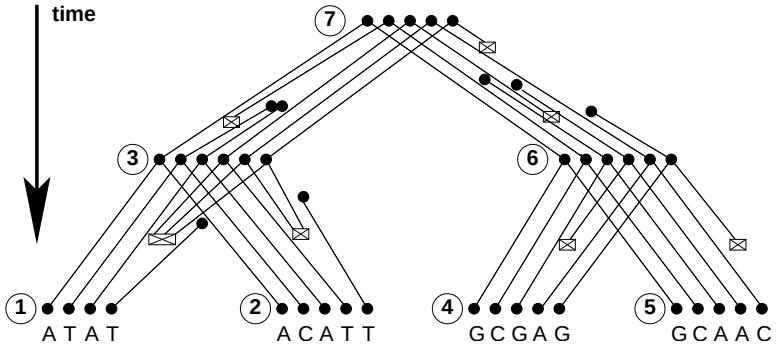


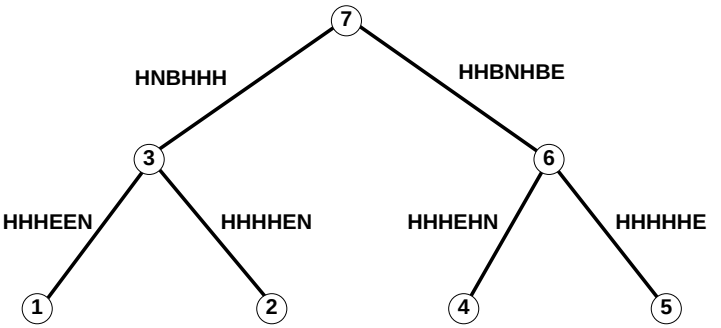
# multiple HMM for sampling a sequence given its neighbours

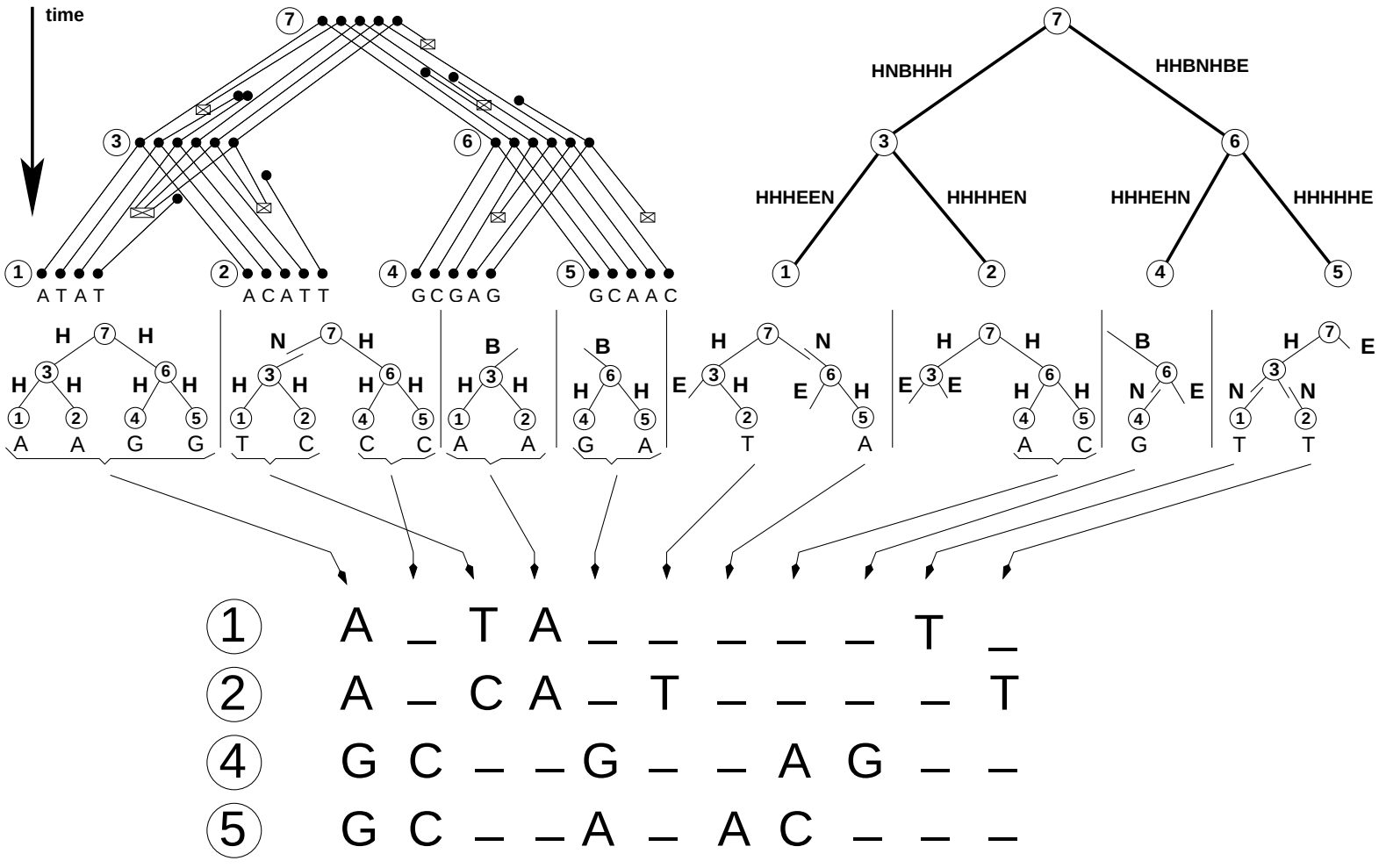


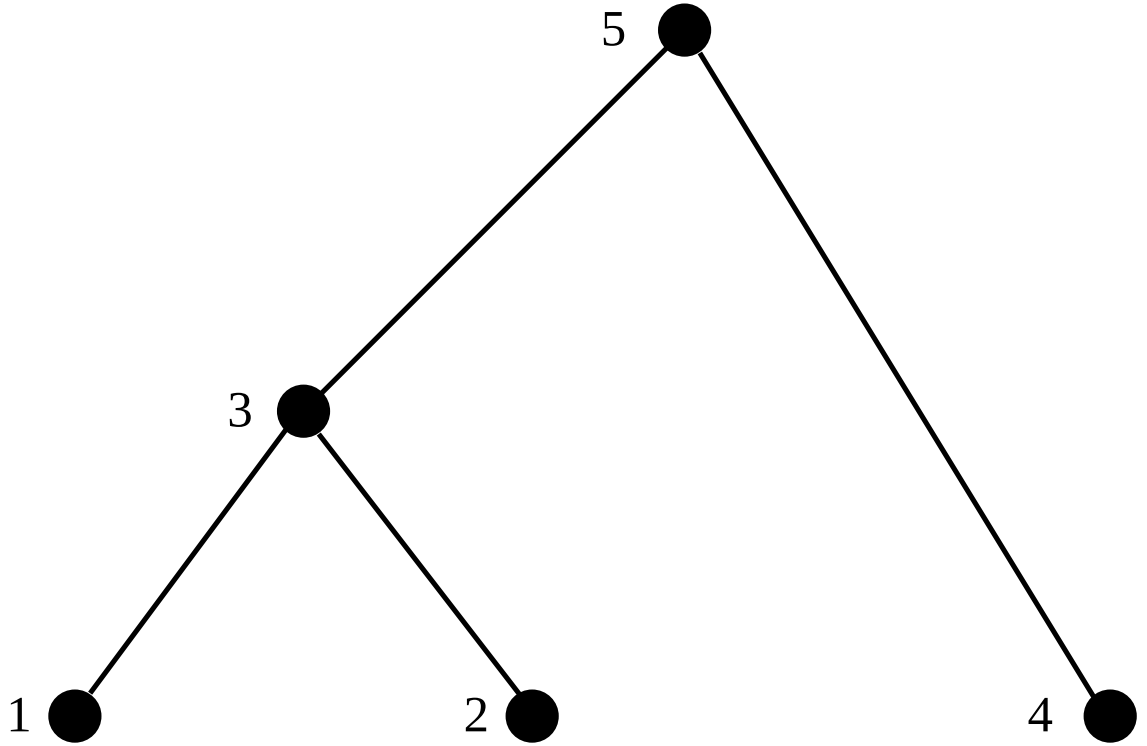
G.A. Lunter, I. Miklós, Y.S. Song, J. Hein (2003) An efficient algorithm for statistical multiple alignment on arbitrary phylogenetic trees. *J. Comp. Biol.* 10(6):869-889.

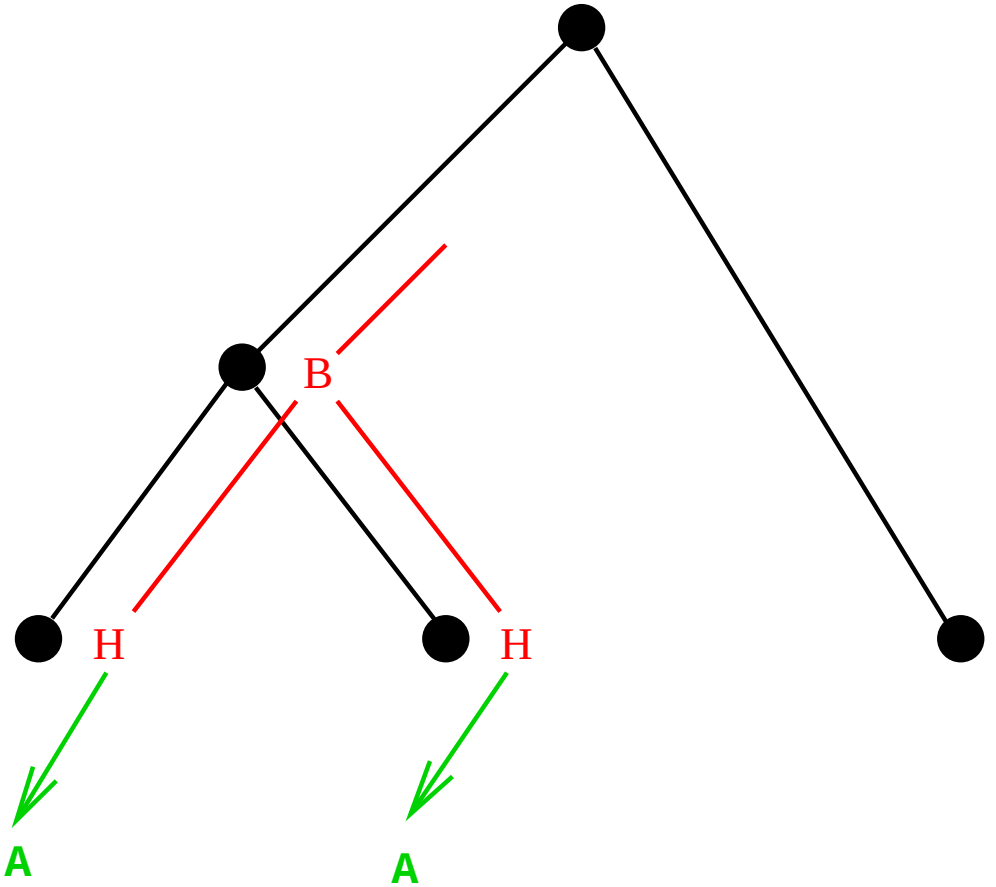



time
7
3
6
1
2
4
5
A T A T
A C A T T
G C G A G
G C A A C

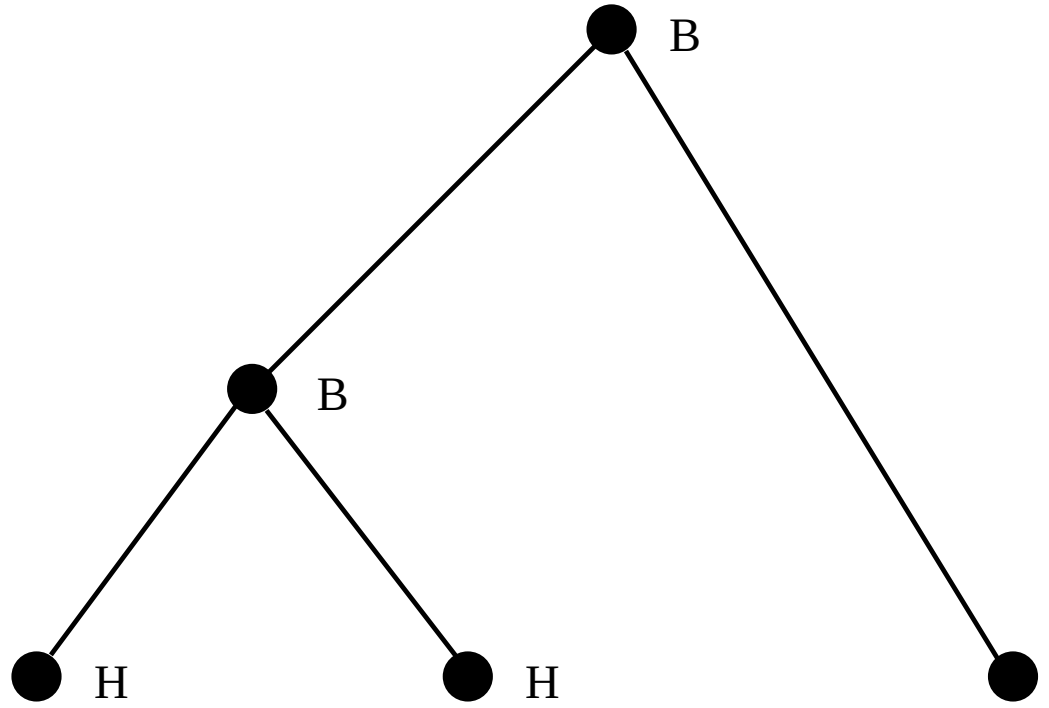

7
HNBHHH
HHBNHBE
3
6
HHHEEN
HHHHEN
HHHEHN
HHHHHE
1
2
4
5


time
A T A T
A C A T T
G C G A G
G C A A C
HNBHHH
HHBNHBE
HHHEEN
HHHHEN
HHHEHN
HHHHHE
1 A _ T A _ _ _ _ _ T _
2 A _ C A _ T _ _ _ _ T
4 G C _ _ G _ _ A G _ _
5 G C _ _ A _ A C _ _ _


5
3
1
2
4



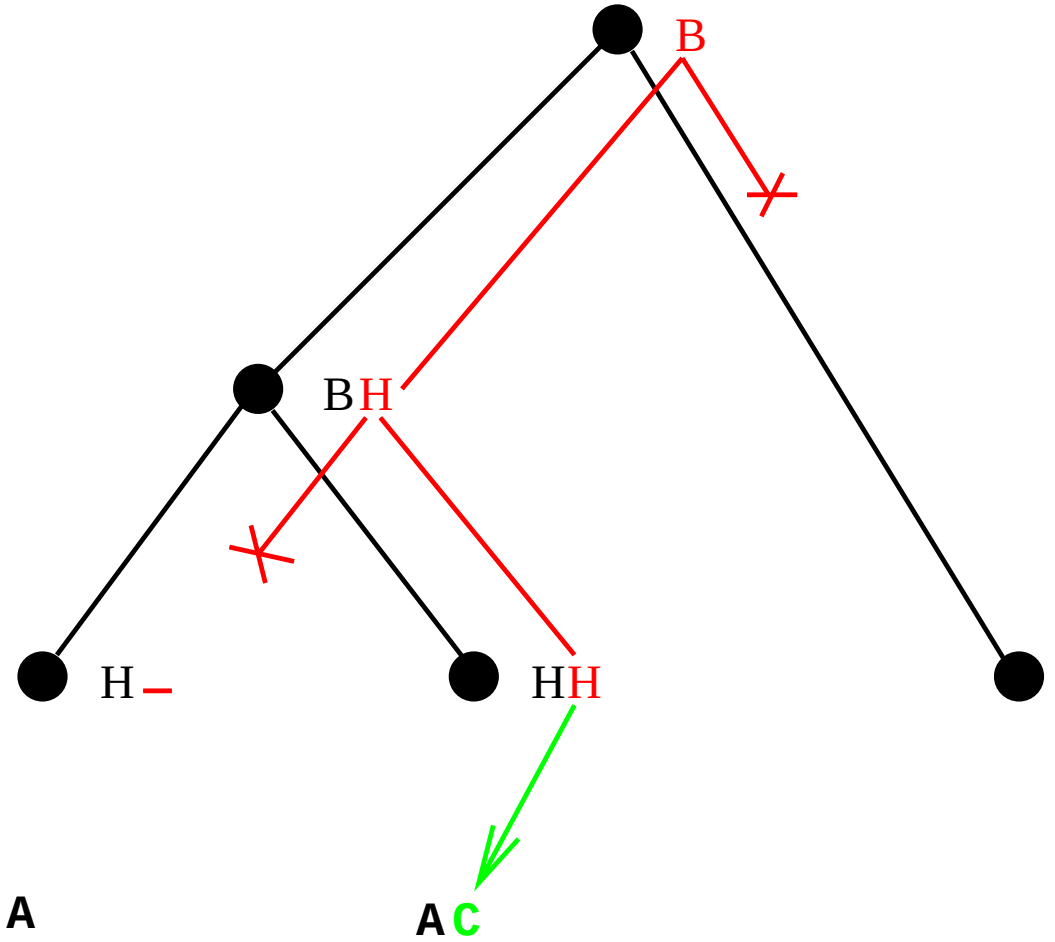

A
A
–



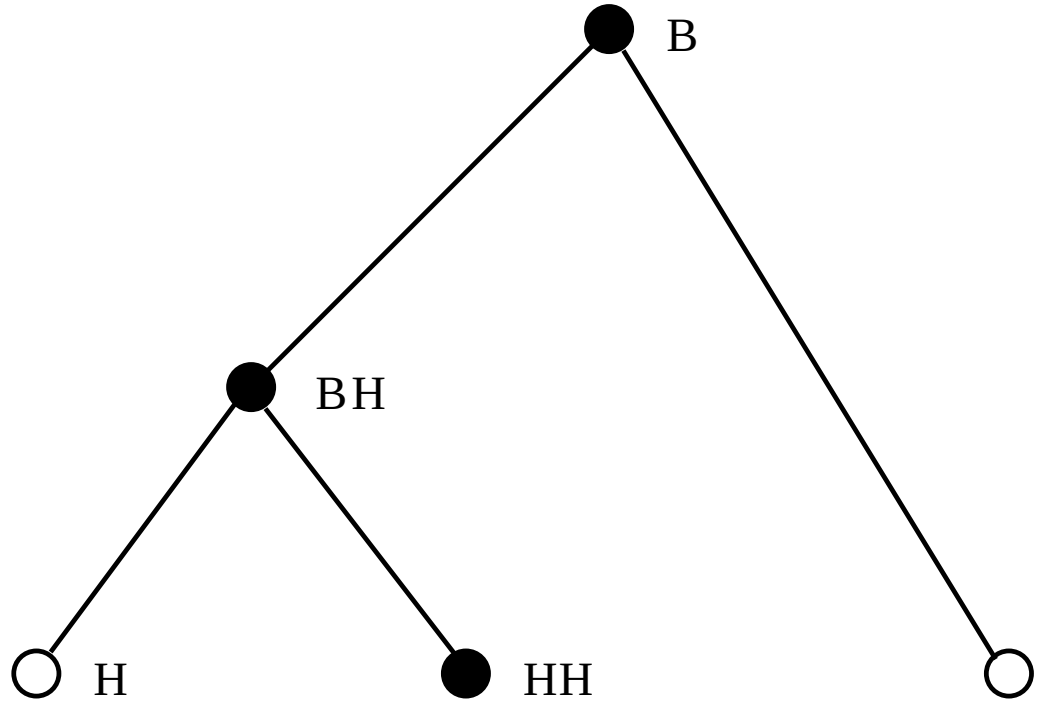

**A**

**A**

**A**
**A**
**–**



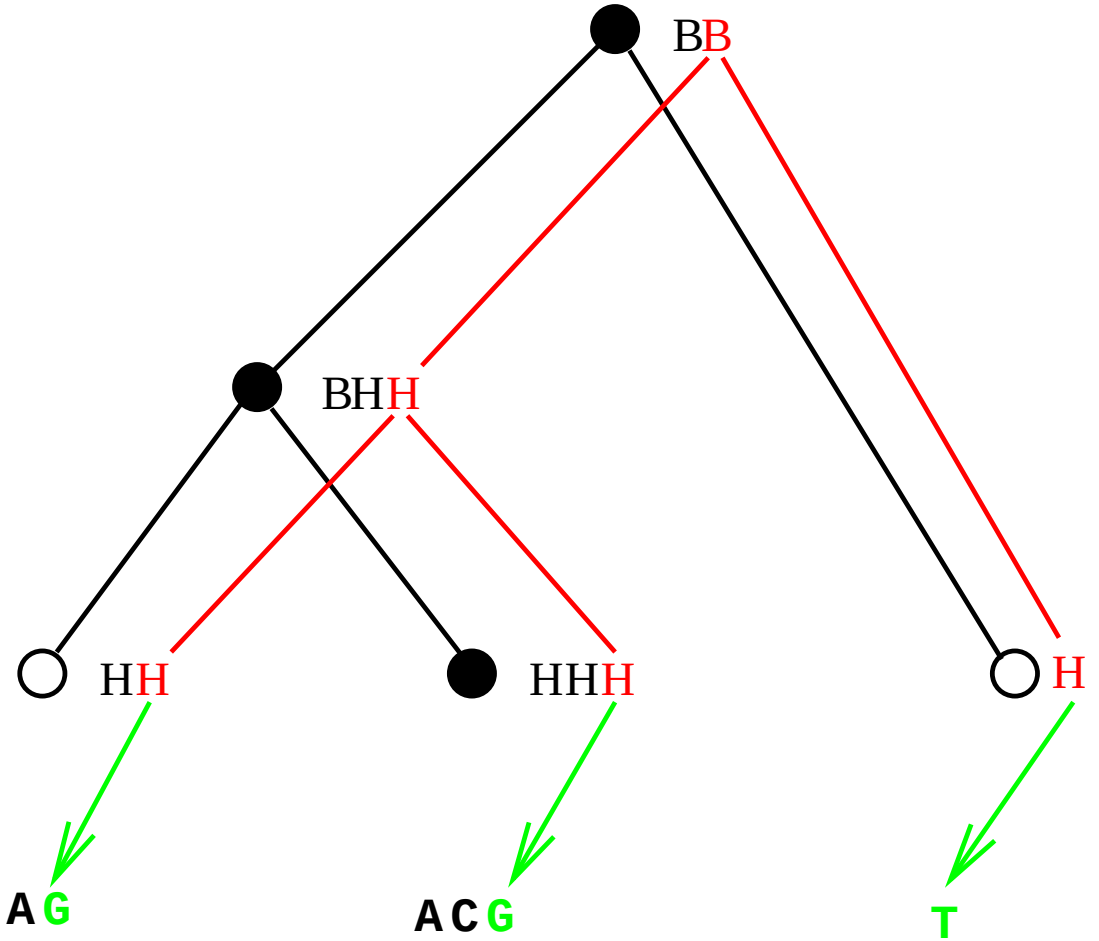

A –
A C
– –



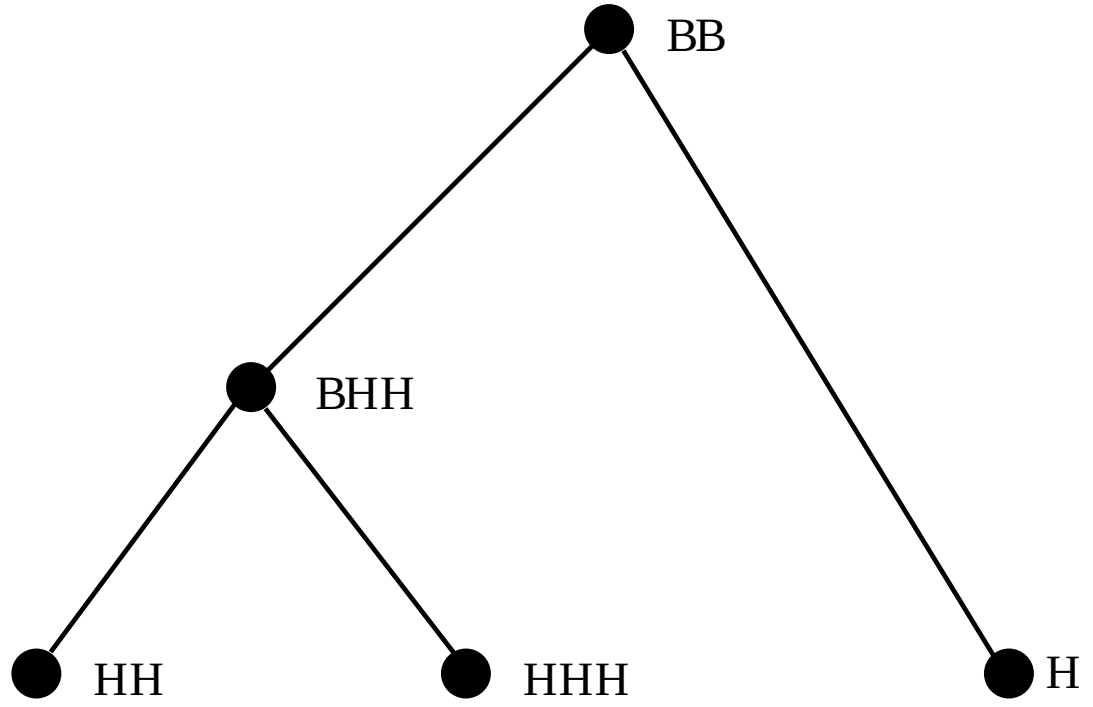

**A**

**AC**

**A –**
**A C**
**– –**

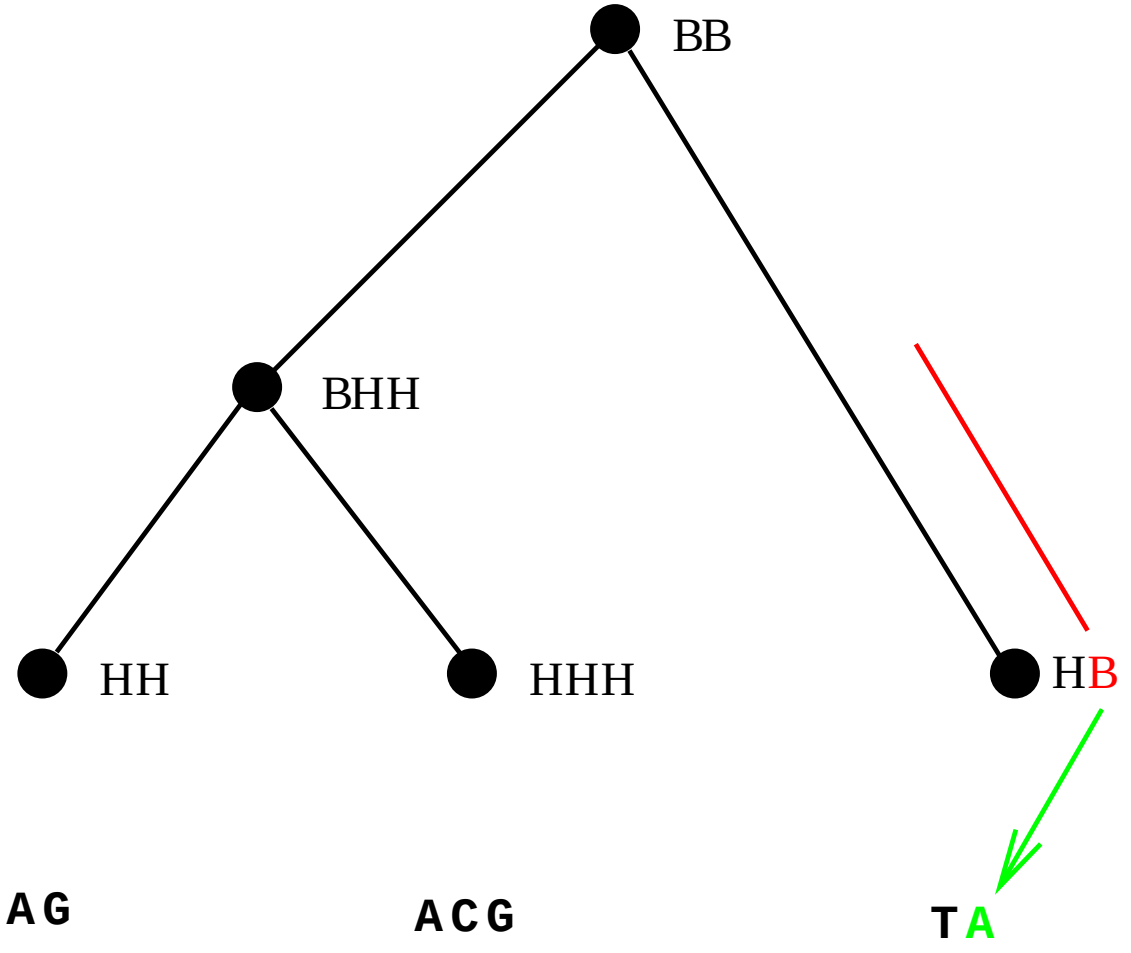



A – G
A C G
– – T

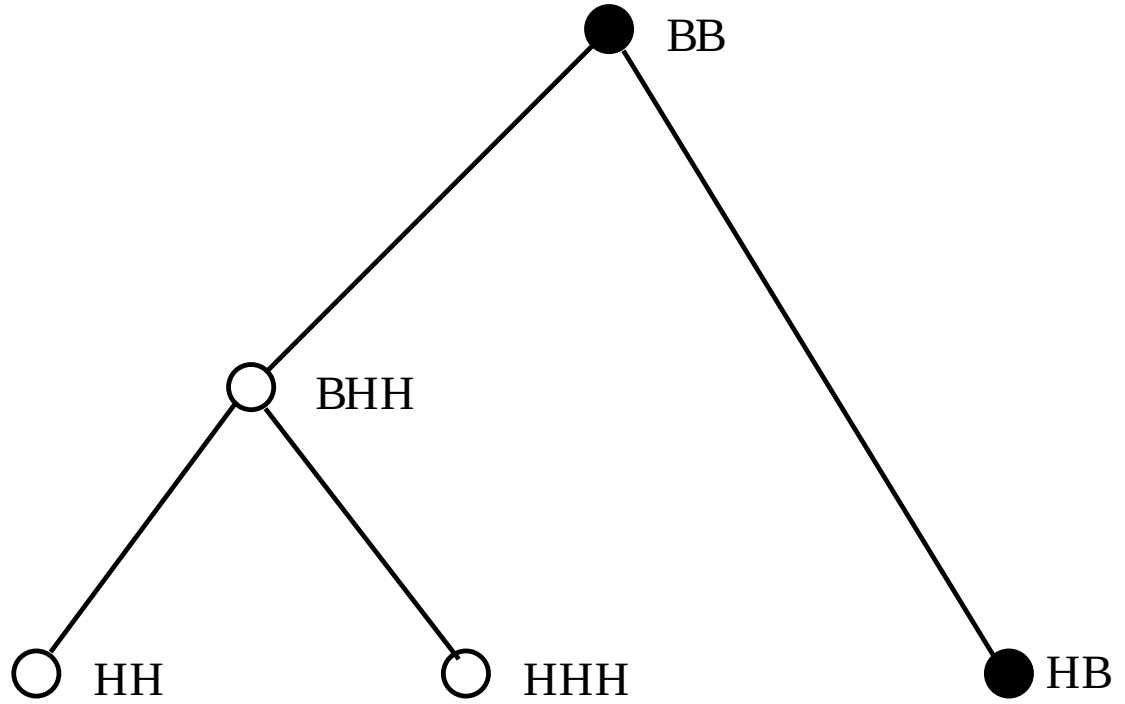



**AG** **ACG** **T**

**A – G**
**A C G**
**– – T**




A – G A
A C G –
– – T –

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**A – G A**
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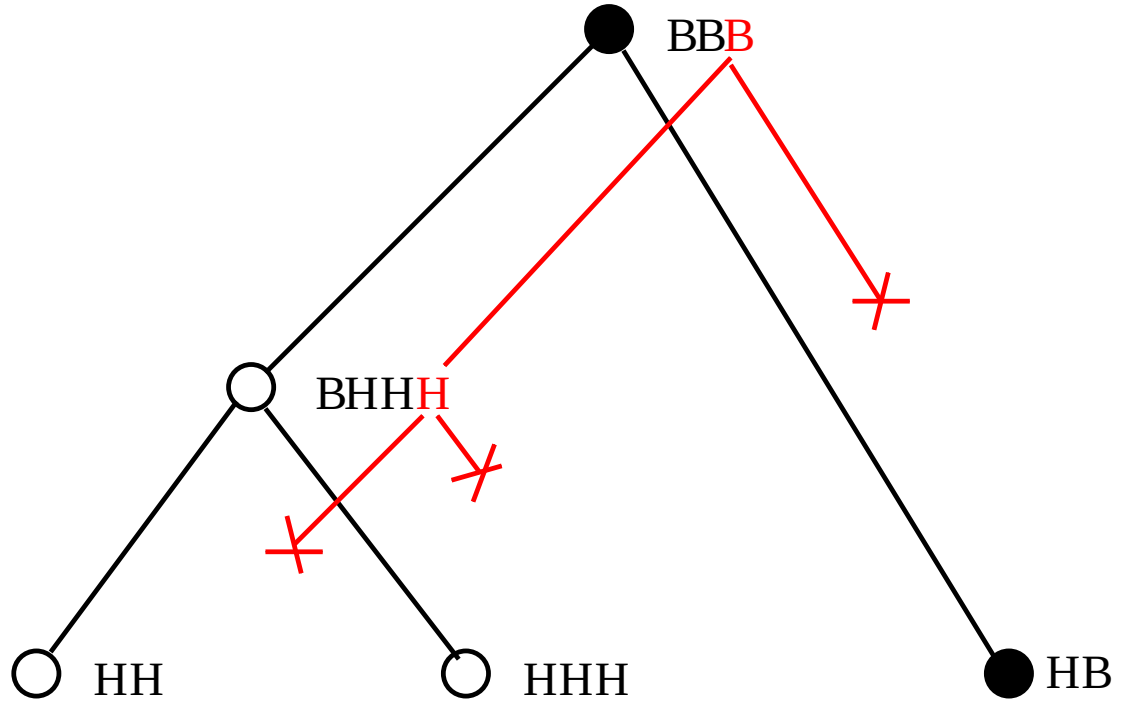
**– – T –**

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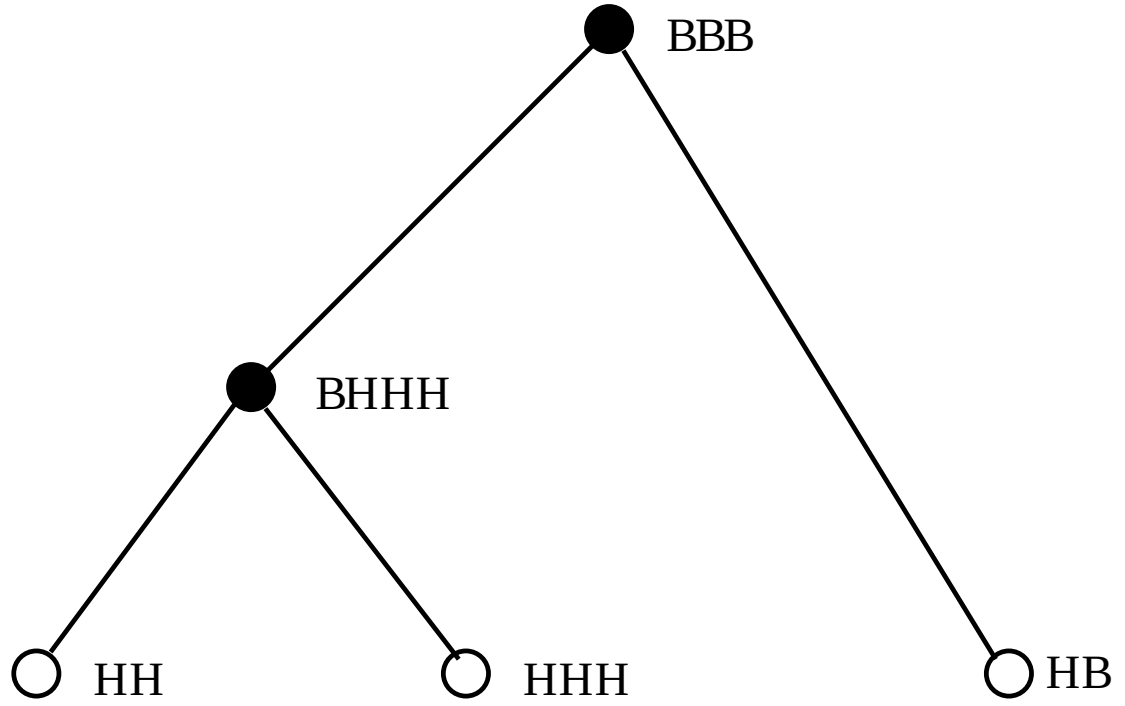
**A – G A**
**A C G –**
**– – T –**

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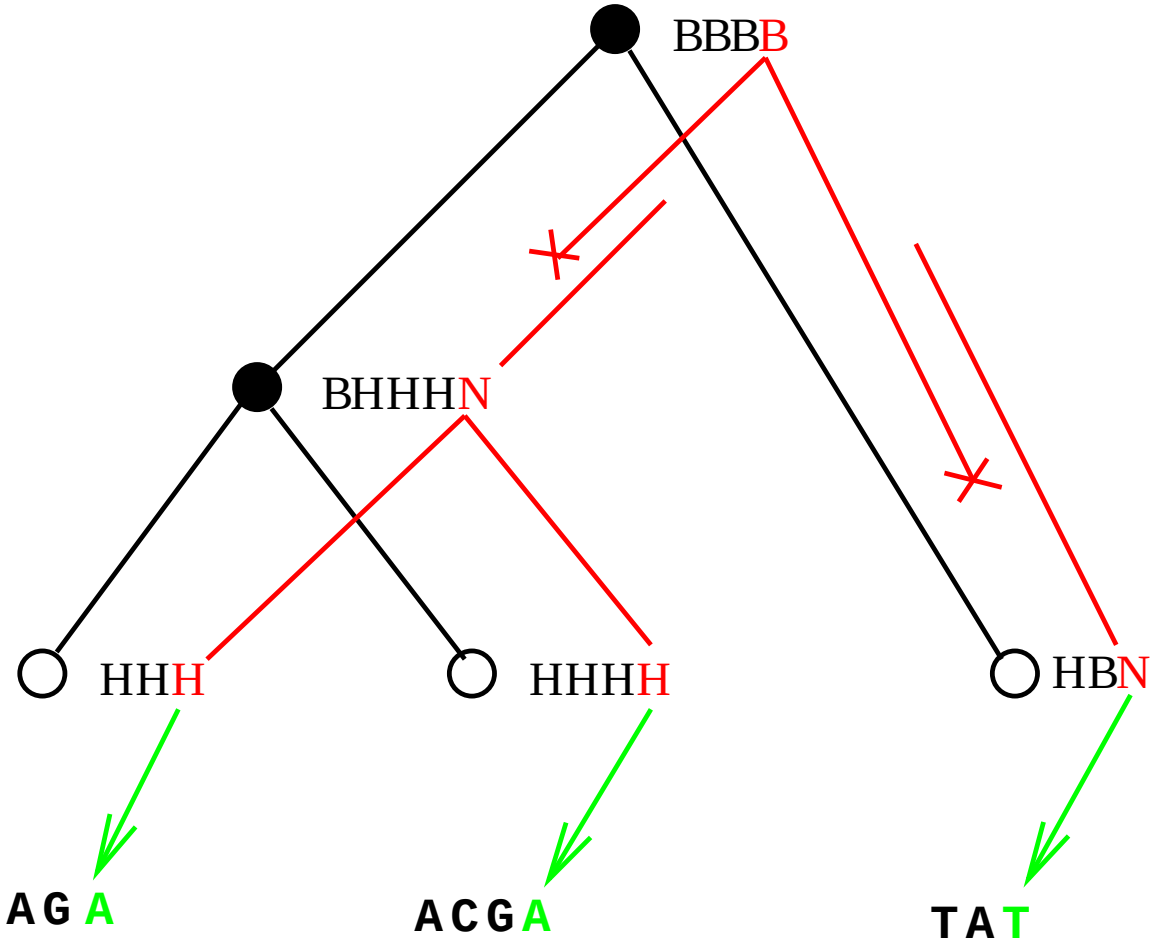
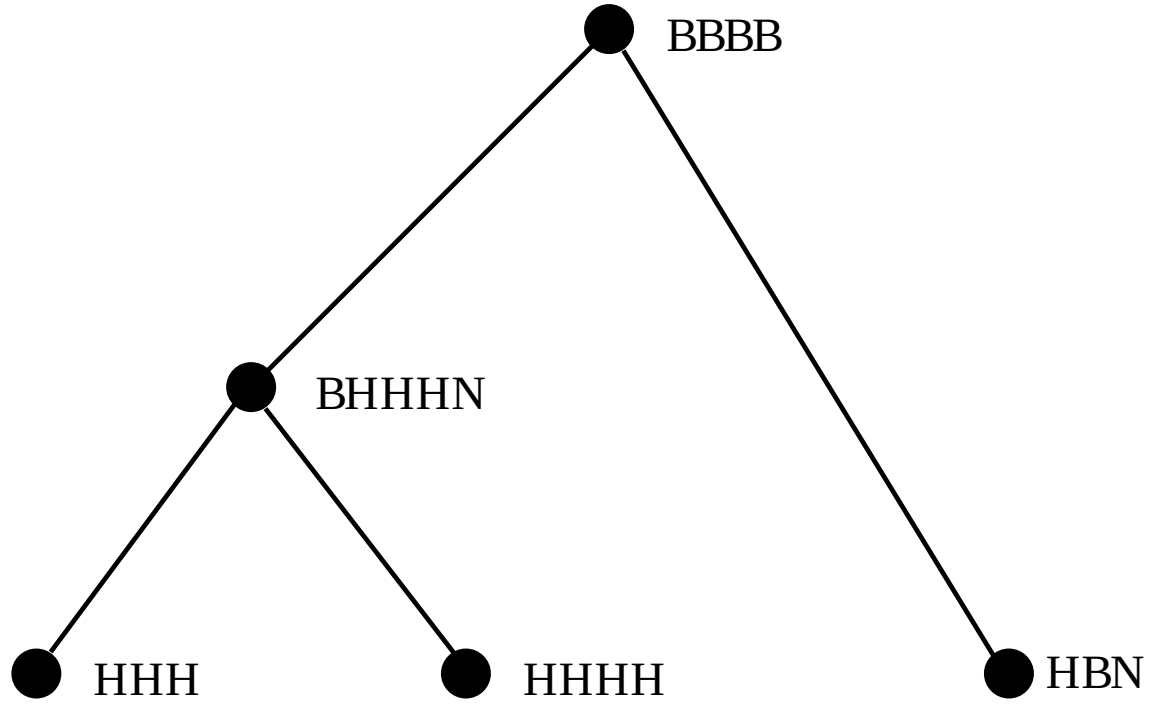
**A – G A**
**A C G –**
**– – T –**

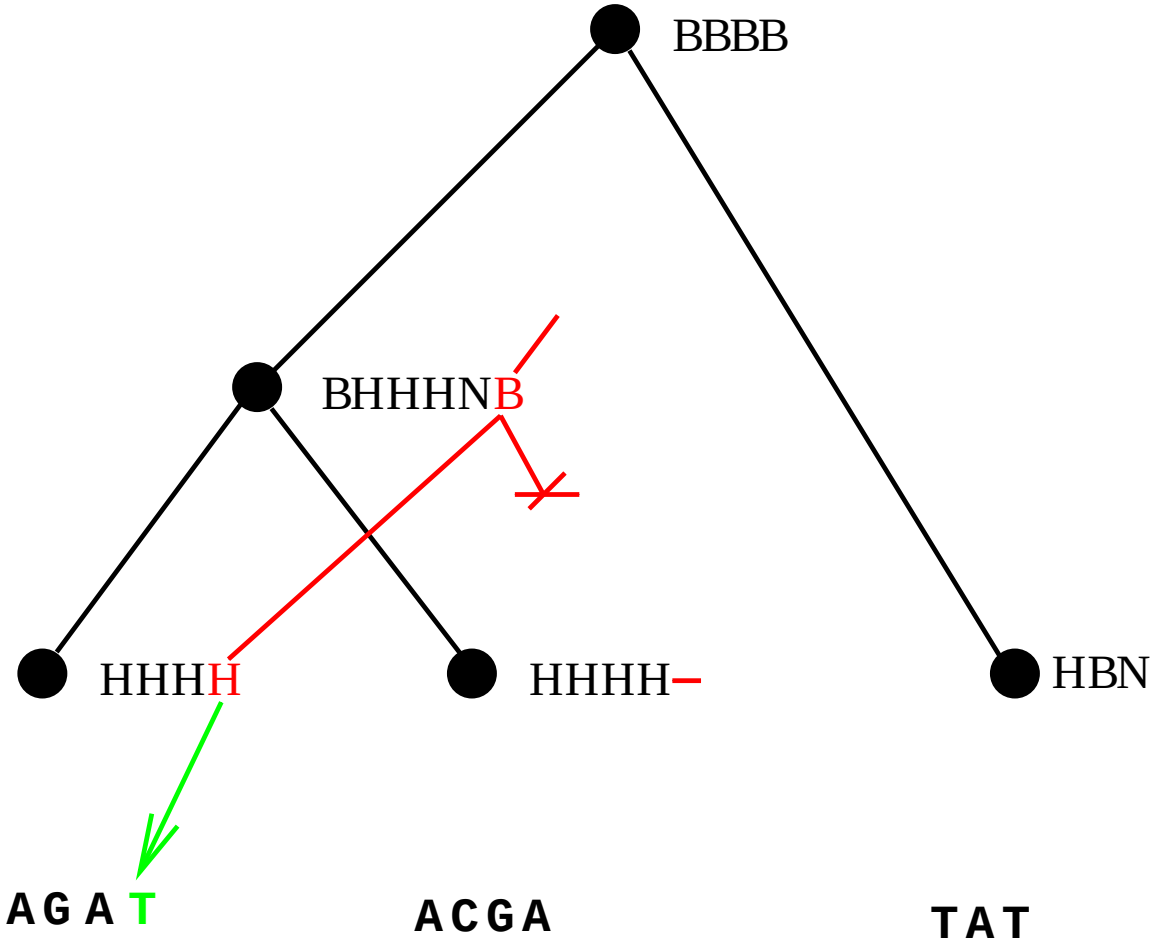



A – G A A –
A C G – A –
– – T – – T

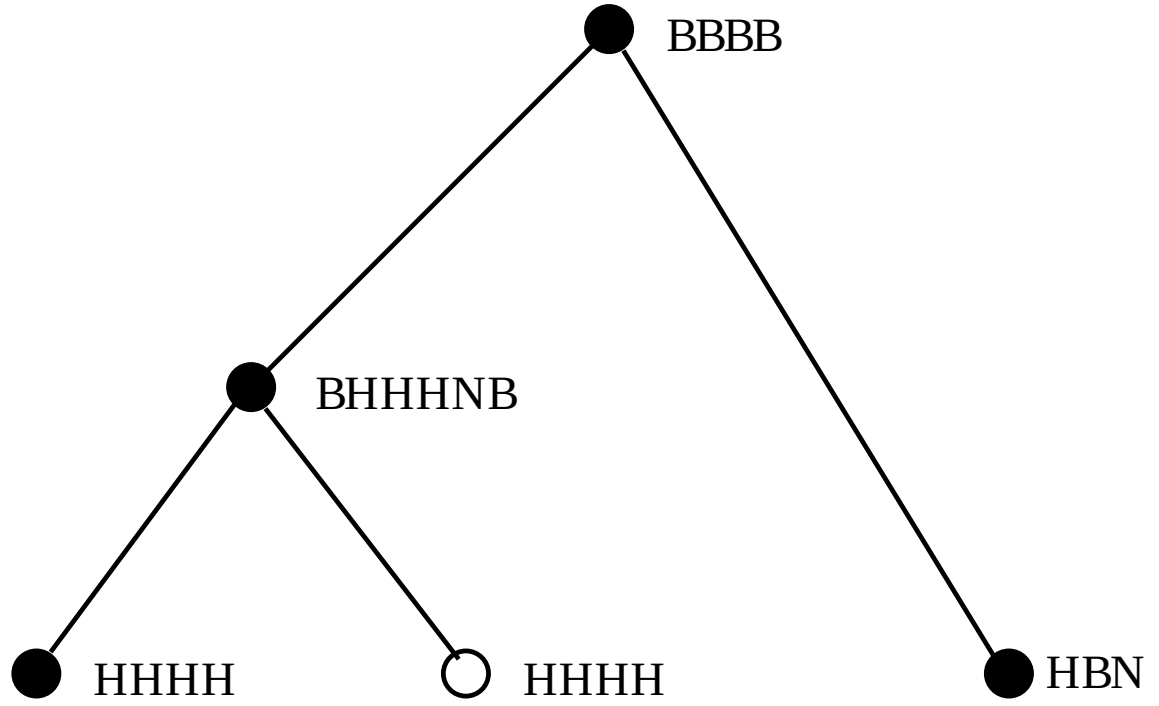



**AGA** **ACGA** **TAT**

**A – G A A –**
**A C G – A –**
**– – T – – T**




A – G A A _ T
A C G – A – –
– – T – – T –




**AGAT** **ACGA** **TAT**

**A – G A A _ T**
**A C G – A – –**
**– – T – – T –**

TKF91: states of hidden Markov chain are the Sets Of Active Nodes (soans).

$$P_{\mathcal{S}}(k) = \sum_{(\mathcal{R},e)\ :\ \mathcal{S}=[\mathcal{R},e]} p(e)q(e)P_{\mathcal{R}}(k - v_e)\vartheta(e,k)$$

where

$k$ : Multi-index of Positions in sequences at leaves

$\mathcal{S} = [\mathcal{R}, e]$ : tihl $e$ turns soan $\mathcal{S}$ into soan$\mathcal{R}$

$P_{\mathcal{S}}(k)$ : Pr(sequences up to $k$ are generated and end there)

$p(e) =$ Pr(indel history of $e$)

$q(e) =$ Pr(no inserts at nodes in $e$)

$\vartheta(e,k) =$ Pr($e$ emits base given in data types at $k$)

$v_e \in \{0,1\}^n$ : indicates postions in leaf-sequences to which $e$ emit

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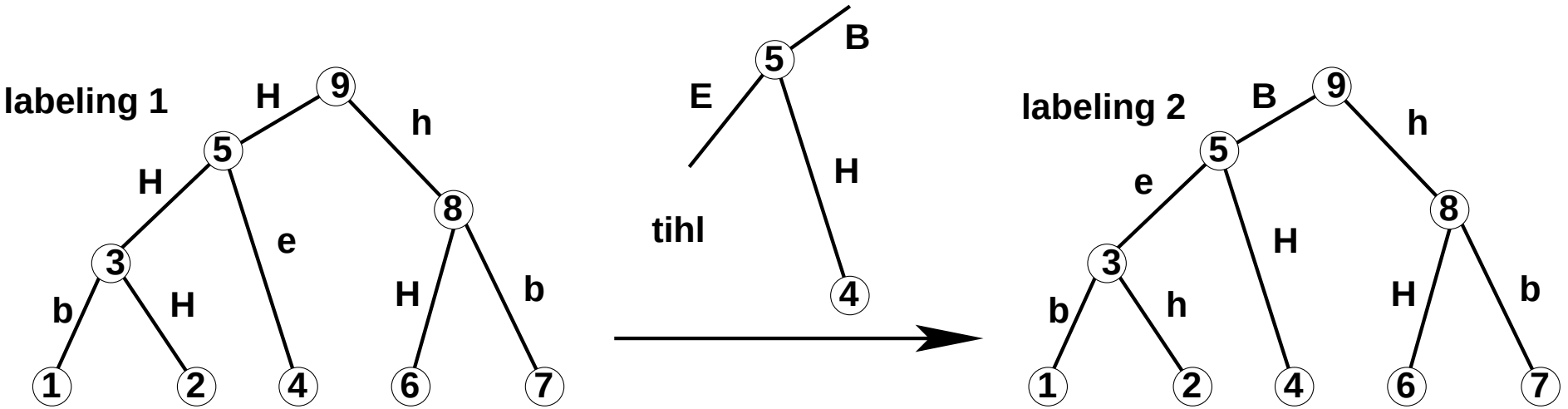
Transfer this to FID or TKF92 (fragmentation may change from edge to edge)

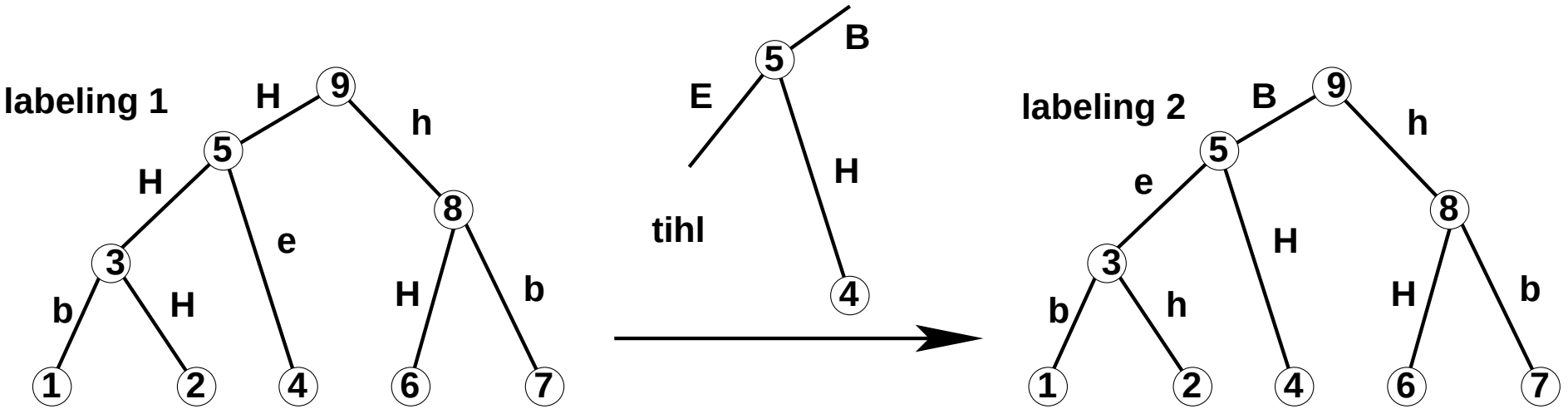
- D. Metzler, R. Fleißner, A. Wakolbinger, A. von Haeseler (2005) Stochastic insertion-deletion processes and statistical sequence alignment.
- D. Metzler, R. Fleißner (2007) Sequence Evolution Models for Simultaneous Alignment and Phylogeny Reconstruction.

state space: edge-labellings with $\{B, H, e, b, h\}$.




tihl = tree indexed heirs line

state space: edge-labellings with $\{B, H, e, b, h\}$.




tihl = tree indexed heirs line

Example: 3-leaved tree
TKF91: $2^3 = 8$ possible sets of active nodes
TKF92/FID: $5^3 = 125$ possible labellings, 41 of them are relevant

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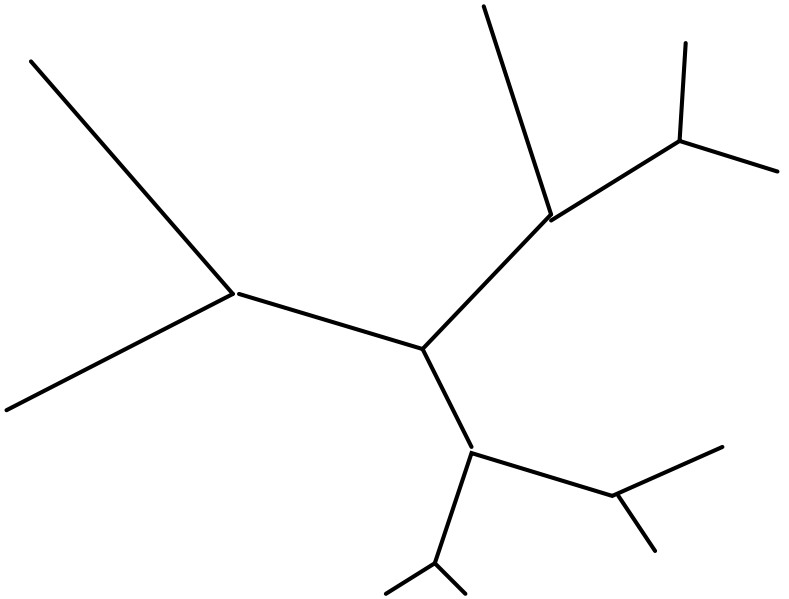
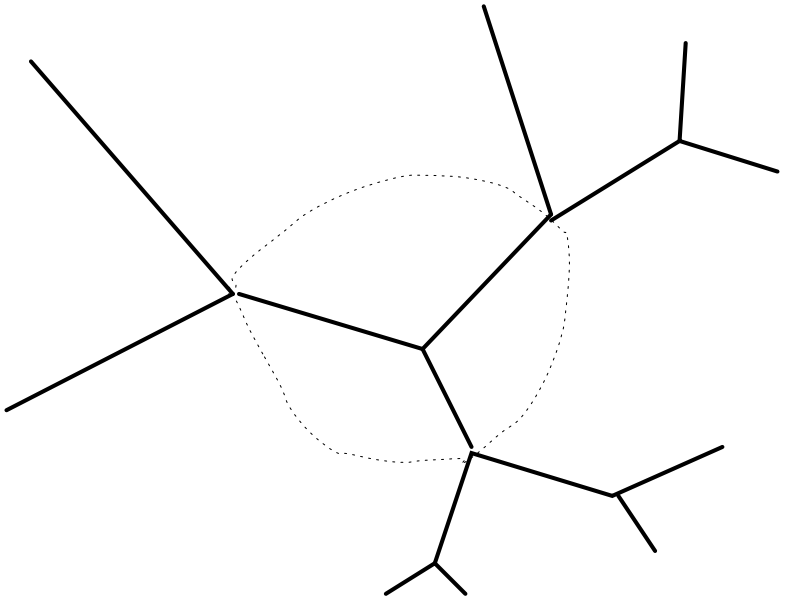


- re-sample alignments of 3-star subtrees (like J.L. Jensen and J. Hein, 2005, do for TKF91)
- do this only for limited parts of the sequences
- Can non-emitting tihls be ignored?
- assing sequences to internal nodes or use nucleotide (or AA) distributions?



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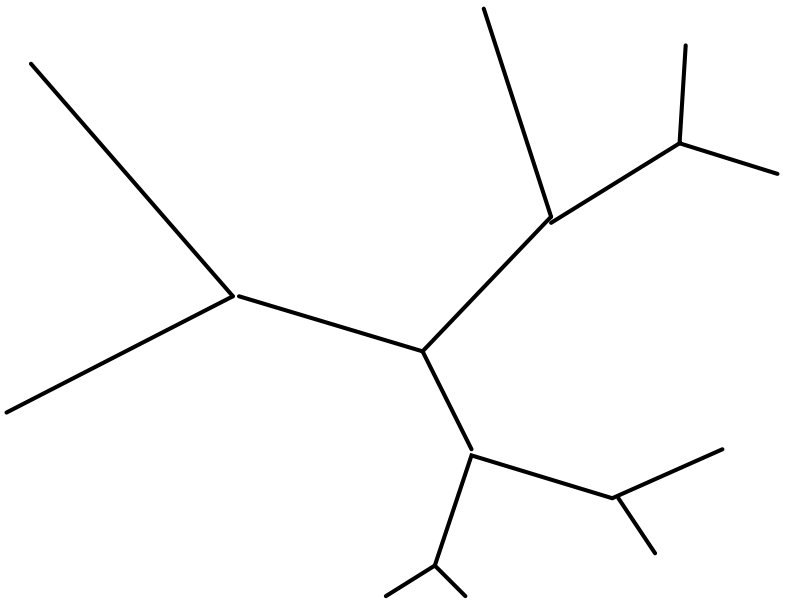
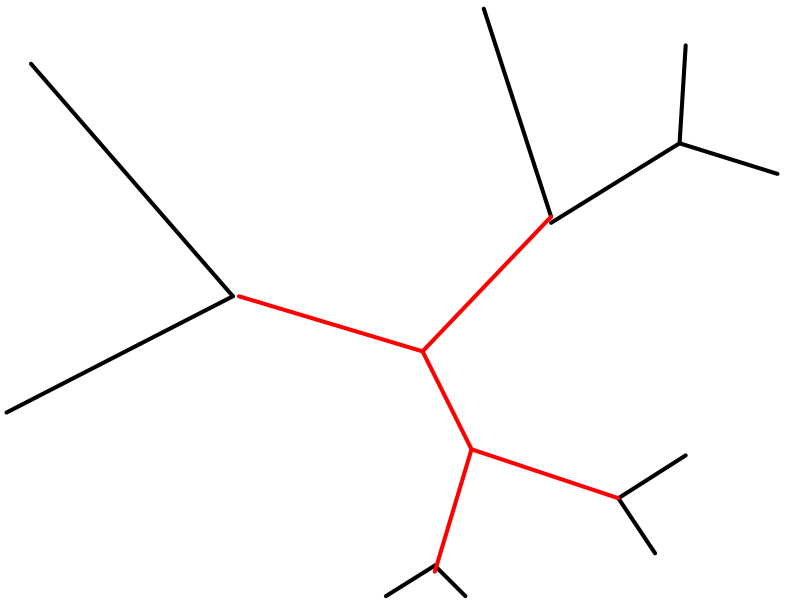
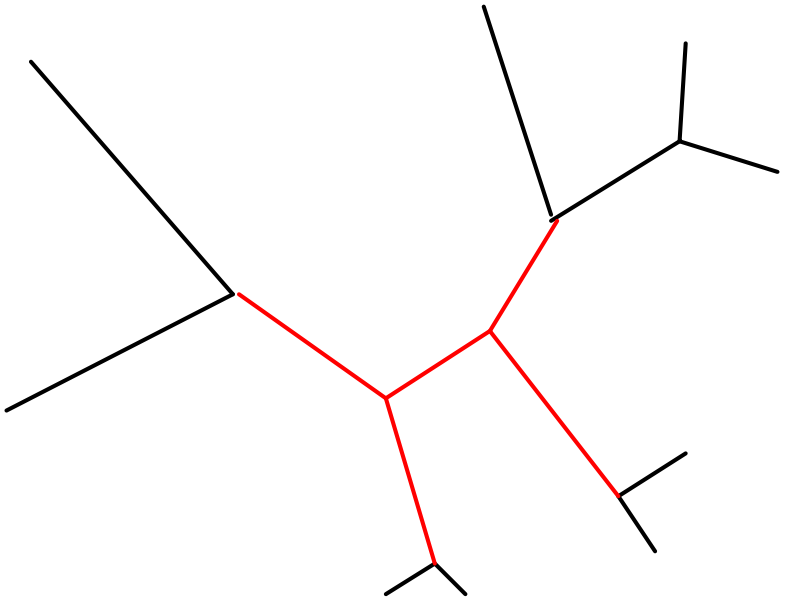
When changing the tree topology...



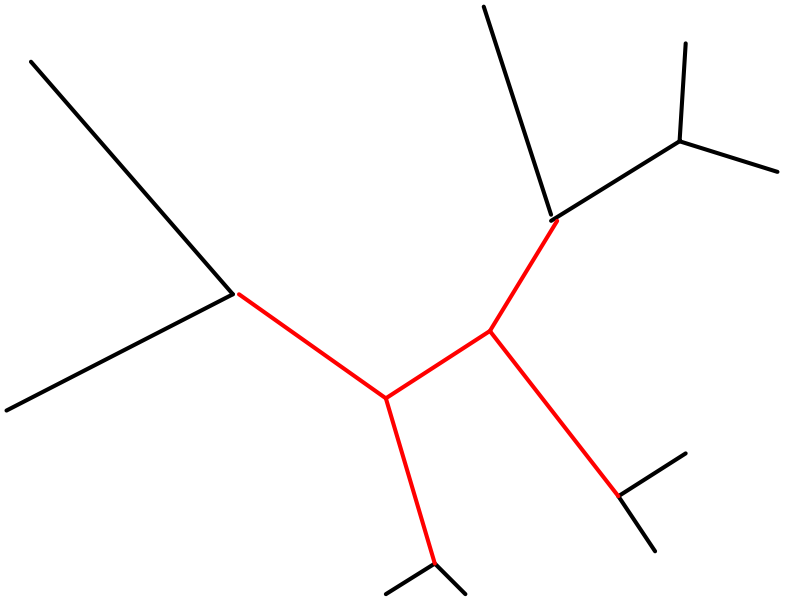
When changing the tree topology...



When changing the tree topology...



When changing the tree topology...



...keep alignments of exterior sequences fixed.
(TKF91: 32 SOANS; FID: 437 relevant lablellings)

# Conclusions

- We need multiple-alignment sampling to assess the full uncertainty in phylogeny estimation
- Let's get the software ready and try if it works!
- THANK YOU!

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