Models of Sequence Evolution with Selection

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\end{aligned}$$

- Similar equations can be written for $\Pr(X(t) = C)$, $\Pr(X(t) = G)$ and $\Pr(X(t) = T)$.

Matrix notation

- We can gather all equations in a more compact form. We note

$$x(t) = \begin{pmatrix} X(t) = A & X(t) = C & X(t) = G & X(t) = T \end{pmatrix}$$

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- 'P' defines the *substitution process.*

A few more considerations

- We have

$$\forall i, \sum_j p_{i,j} = 1$$

that is

$$\Pr(A \to A) + \Pr(A \to C) + \Pr(A \to G) + \Pr(A \to T) = 1$$

- If we assume that all types of mutations are equi-probable (Jukes and Cantor, 1969), we can simplify:

$$P_{(JC69)} = \begin{pmatrix} 1-3r & r & r & r \\ r & 1-3r & r & r \\ r & r & 1-3r & r \\ r & r & r & 1-3r \end{pmatrix}$$

Continuous time

We assume that the process does not change over time, so we can write the equations for any time t:

$$t = t_0 + dt_0, \quad r = \alpha \cdot dt_0$$

$$x(t_0 + dt_0) = x(t_0) \times \begin{pmatrix} 1 - 3\alpha dt_0 & \alpha dt_0 & \alpha dt_0 & \alpha dt_0 \\ \alpha dt_0 & 1 - 3\alpha dt_0 & \alpha dt_0 & \alpha dt_0 \\ \alpha dt_0 & \alpha dt_0 & 1 - 3\alpha dt_0 & \alpha dt_0 \\ \alpha dt_0 & \alpha dt_0 & \alpha dt & 1 - 3\alpha dt_0 \end{pmatrix}$$

$$x(t_0 + dt_0) = x(t_0) + x(t_0) \cdot Q dt_0$$

$$\frac{x(t_0 + dt_0) - x(t_0)}{dt_0} = x(t_0) \cdot Q$$

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$$Q_{(JC69)} = \begin{pmatrix} -3\alpha & \alpha & \alpha & \alpha \\ \alpha & -3\alpha & \alpha & \alpha \\ \alpha & \alpha & -3\alpha & \alpha \\ \alpha & \alpha & \alpha & -3\alpha \end{pmatrix}$$

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- This resolves into

$$x(t) = x(t_0) \cdot \exp(Q \cdot t)$$

Conclusion

We can compute the probability that a certain sequence ($x(t_0)$) transforms into another given sequence ($x(t)$) after a known time (t) and given a certain substitution process specified by its generator (Q).

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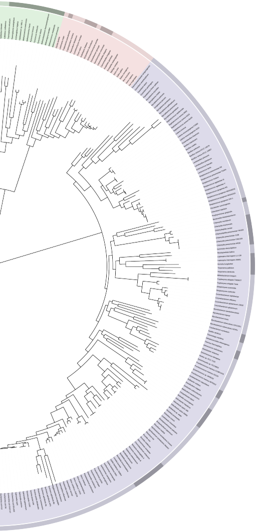
So what???

If we have two sequences and Q, we can compute t which maximizes this probability $\rightarrow$ unbiased estimate of the divergence between the two sequences!

Evolution along a tree



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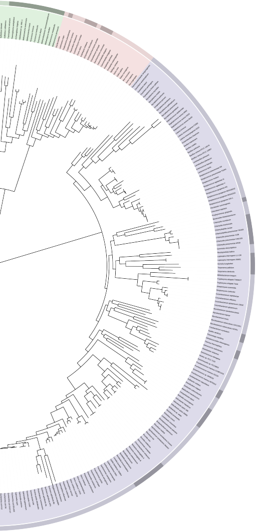

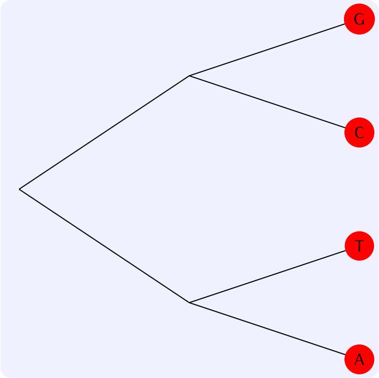

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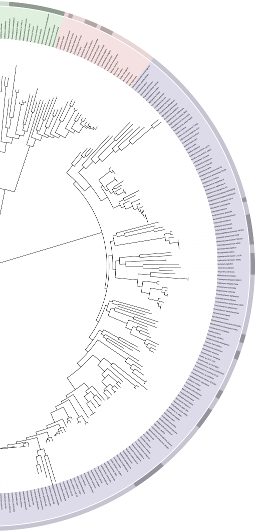

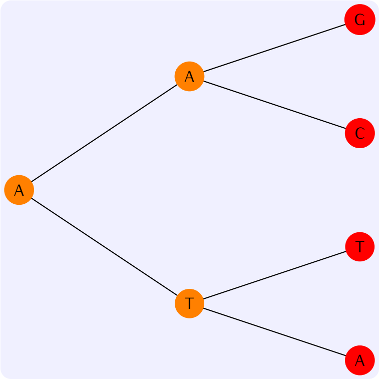

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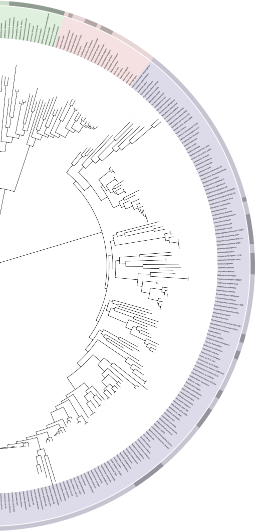

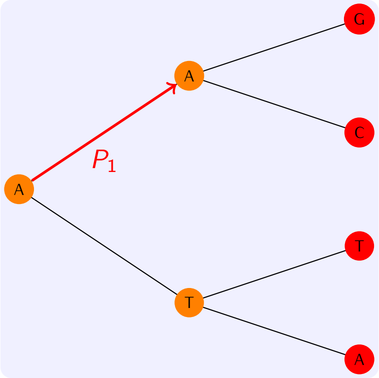

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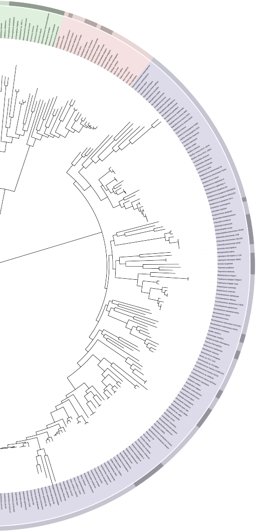

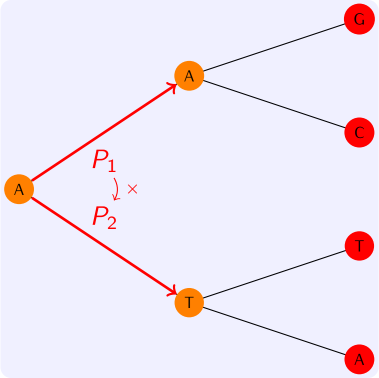

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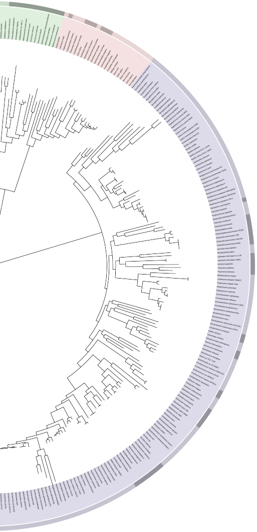

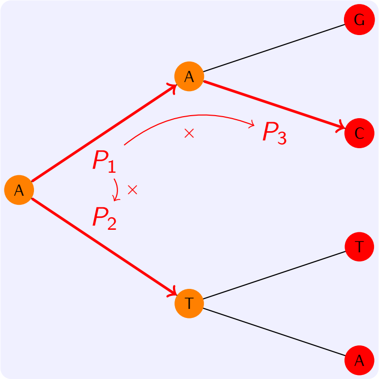

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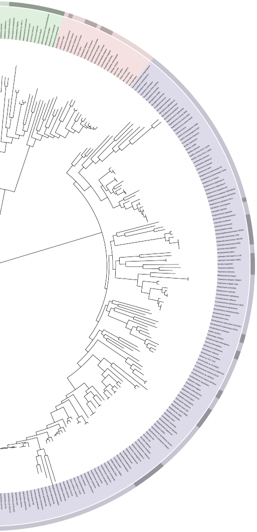

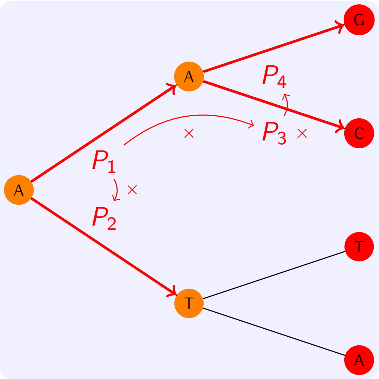

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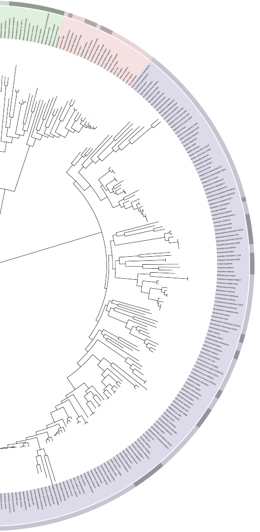

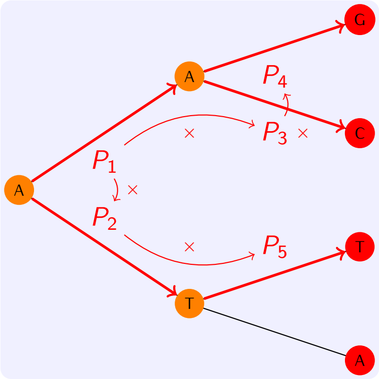

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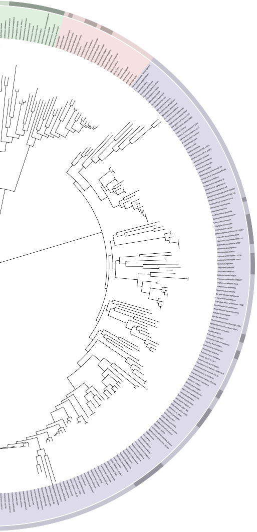

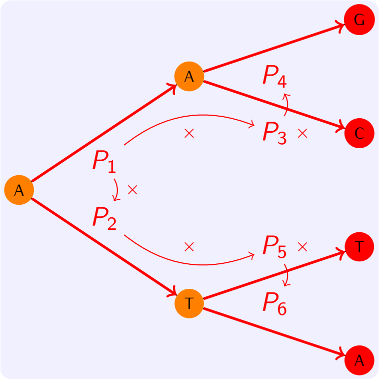

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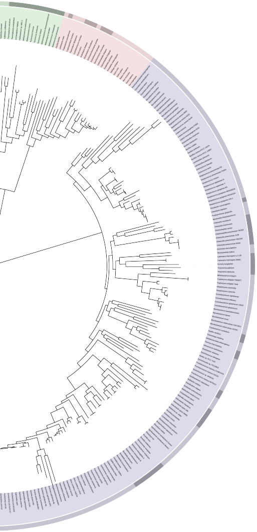

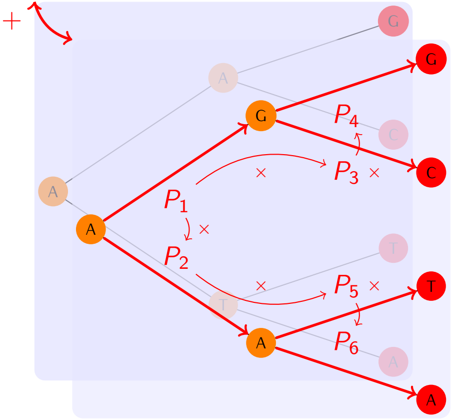

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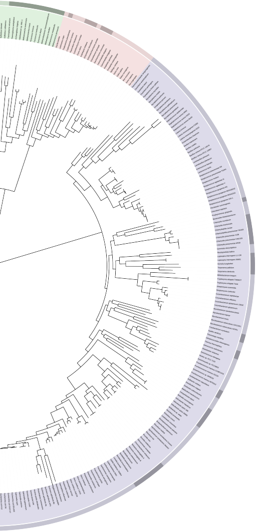

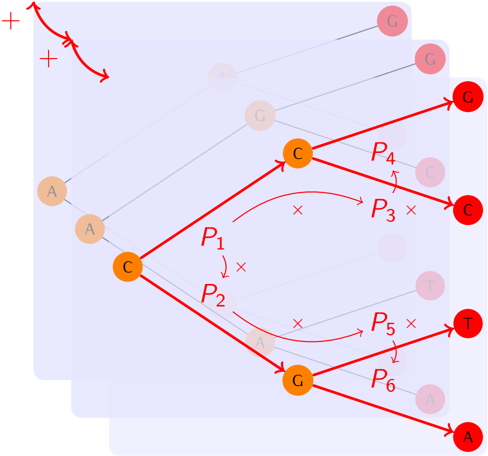

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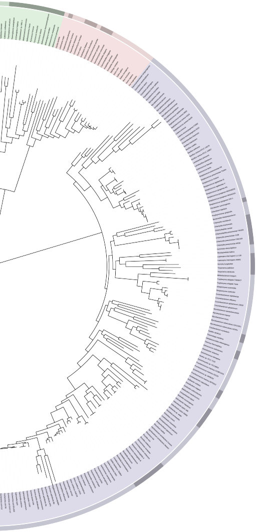

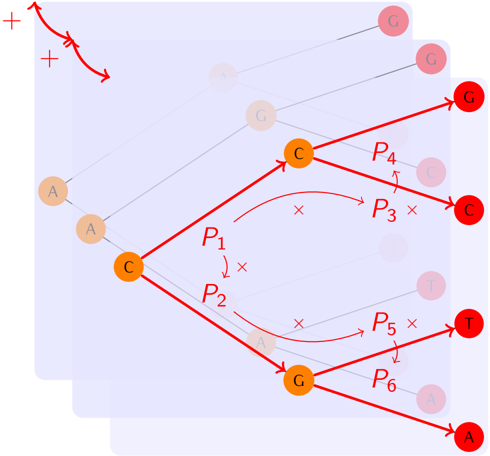

$$L_i = \sum_{\text{Ancestors}} P_1 \times P_2 \times P_3 \times P_4 \times P_5 \times P_6$$

Common nucleotide substitution models

Model	Authors	Parameters
JC69	Jukes Cantor	1 substitution rate
K80	Kimura	1 transition rate, 1 transversion rate
K81	Kimura	1 transition rate, 2 transversion rates
F81 = TN84	Felsenstein, Tajima et Nei	1 substitution rate and 3 frequencies
HKY85	Hasegawa, Kishino et Yano	1 transition rate, 1 transversion rate and 3 frequencies
TN93	Tamura et Nei	1 transition rate, 2 transversion rates and 3 frequencies
Z94	Zharkikh	6 substitution rates
T92	Tamura	1 transition rate, 1 transversion rate and 1 GC rate
GTR	"General time reversible"	6 substitution rate and 3 frequencies

Common nucleotide substitution models

$$\begin{tikzcd}
 & \begin{array}{c} v_1 = v_2 = v_3 = v_4 \\ s_1 = s_2 \end{array} & \begin{array}{c} v_1 = v_4 \\ v_2 = v_3 \\ s_1 = s_2 \end{array} & \begin{array}{c} v_1, v_2, v_3, v_4 \\ s_1, s_2 \end{array} & \\
\begin{array}{c} \text{JC69} \\ \text{1 parameter} \end{array} \arrow[r] \arrow[d] & \begin{array}{c} \text{K80} \\ \text{2 parameters} \end{array} \arrow[r] \arrow[d] & \begin{array}{c} \text{K81} \\ \text{3 parameters} \end{array} \arrow[r] \arrow[d] & \begin{array}{c} \text{Z94} \\ \text{6 parameters} \end{array} \arrow[d] & \begin{array}{l} \pi_{\mathtt{A}} = \pi_{\mathtt{U}} \\ = \pi_{\mathtt{G}} = \pi_{\mathtt{C}} \end{array} \\
\begin{array}{c} \text{TN84} \\ \text{4 parameters} \end{array} \arrow[r] & \begin{array}{c} \text{HKY85} \\ \text{5 parameters} \end{array} \arrow[r] \arrow[d] & \begin{array}{c} \text{TN93} \\ \text{6 parameters} \end{array} \arrow[r] & \begin{array}{c} \text{GTR} \\ \text{9 parameters} \end{array} & \pi_{\mathtt{A}}, \pi_{\mathtt{U}}, \pi_{\mathtt{G}}, \pi_{\mathtt{C}} \\
 & \begin{array}{c} \text{T92} \\ \text{3 parameters} \end{array} & \begin{array}{l} \pi_{\mathtt{A}} = \pi_{\mathtt{U}} \\ \pi_{\mathtt{G}} = \pi_{\mathtt{C}} \end{array} & &
\end{tikzcd}$$

Probability of an alignment

Site independence

If sites evolve independently:

$$\begin{aligned}\Pr(D|\Theta) &= \prod_i \Pr(D_i|\Theta) \\ L &= \prod_i L_i\end{aligned}$$

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Parameters

- Branch lengths
- Entries in the substitution matrix
- Tree topology

Maximum likelihood

Maximum-likelihood estimation (MLE)

MLE is a method of estimating the parameters of a statistical model. For a given dataset and underlying statistical model, the maximum likelihood estimator corresponds to the set of values of the model parameters that maximizes the likelihood function. (The method was initially proposed by statistician Ronald Aylmer Fisher in 1922.)

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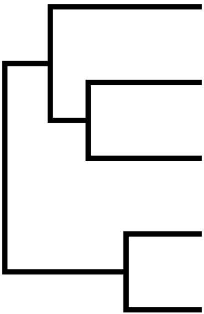
- General statistical framework
- Allows to perform model comparisons
- Allows to get confidence intervals of estimates

Modelling the evolution of a codon sequence alignment



ATG TGG CGT CGC TAT CCT ...

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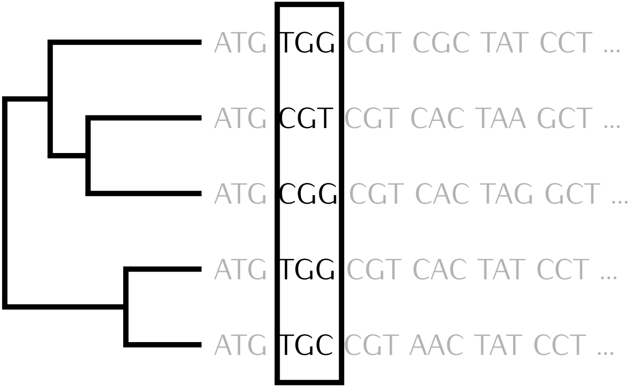
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- We assume that all columns (sites) are independent

Modelling the evolution on a branch

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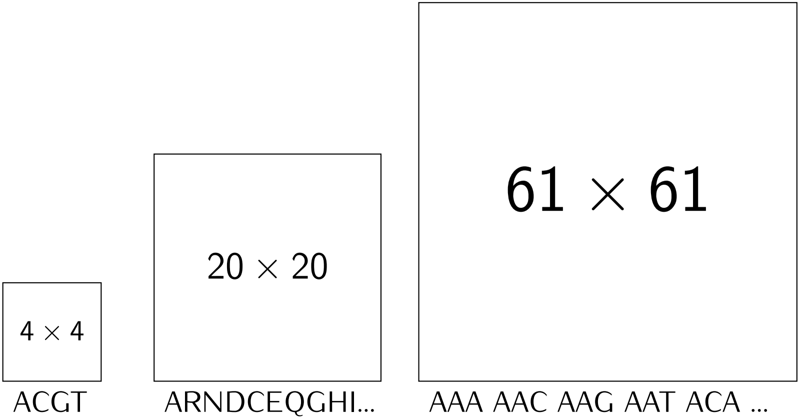
- The probability of each type of mutation is given by a matrix:



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- We can therefore express all mutation probabilities with only two parameters

Models for codon evolution

Muse and Gaut (1994), Goldman and Yang (1994)

Instantaneous substitution rate

$$q_{ij} = \begin{cases} 0 & \text{if } i \text{ and } j \text{ differ at more than one position} \\ \pi_j & \text{if } i \text{ and } j \text{ differ by one synonymous transversion} \\ \kappa \cdot \pi_j & \text{if } i \text{ and } j \text{ differ by one synonymous transition} \\ \omega \cdot \pi_j & \text{if } i \text{ and } j \text{ differ by one nonsynonymous transversion} \\ \omega \cdot \kappa \cdot \pi_j & \text{if } i \text{ and } j \text{ differ by one nonsynonymous transition} \end{cases}$$

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✍ Frequencies can be estimated, or fixed to their observed values

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2. Multiplying all probabilities for all branches for one site
3. Summing over all possible ancestral states
4. Multiplying for all sites in the alignment

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  - $\omega_2 > 1$ positive selection
- Each site can therefore "chose" between several omegas
- The likelihood of site i becomes

$$L_i = \sum_{\omega} L_i(\omega) \times \Pr(\omega)$$

where $L_i(\omega)$ is the likelihood for site i for a given value of ω, and $\Pr(\omega)$ is the probability of this given ω (the frequency of sites in the alignment which evolve with this particular ω).

Some site-heterogeneous codon models

Yang, Nielsen, Goldman and Pedersen (2000)

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M9 (variable selective pressure) some positions with $\omega \circlearrowleft \beta(p, q)$ and some with $\omega \circlearrowleft \Gamma(a, b) + 1$, where $\Gamma(a, b) + 1$ is the gamma distribution between 1 and $+\inf$.

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4. If significant, use a Bayesian approach to identify positions where M2a/M8/M9 has a higher posterior probability than M1a/M7