Exercise 1: Let nucleotide frequencies \( \pi_A, \pi_C, \pi_G, \pi_T \) and mutation rates \( \alpha \) and \( \beta \) of the HKY model be given. Under which conditions can you find rates \( \lambda \) and \( \mu \) of the Felsenstein 84 model, such that the transition matrices of the two models are the same, and which are the appropriate values for \( \lambda \) and \( \mu \)? Discuss also the opposite direction. The F84 rate matrix is:

\[
\begin{pmatrix}
-\lambda(1 - \pi_A) - \frac{\mu\pi_G}{\pi_A + \pi_G} & \lambda\pi_C & \lambda\pi_G + \frac{\mu\pi_G}{\pi_A + \pi_G} & \lambda\pi_T + \frac{\mu\pi_T}{\pi_C + \pi_T} \\
\lambda\pi_A + \frac{\mu\pi_A}{\pi_A + \pi_G} & -\lambda(1 - \pi_C) - \frac{\mu\pi_T}{\pi_C + \pi_T} & -\lambda(1 - \pi_G) - \frac{\mu\pi_A}{\pi_A + \pi_G} & \lambda\pi_T + \frac{\mu\pi_T}{\pi_C + \pi_T} \\
\lambda\pi_C + \frac{\mu\pi_C}{\pi_C + \pi_T} & -\lambda(1 - \pi_G) - \frac{\mu\pi_A}{\pi_A + \pi_G} & -\lambda(1 - \pi_T) - \frac{\mu\pi_C}{\pi_C + \pi_T} & \lambda\pi_T \\
\lambda\pi_T & -\lambda(1 - \pi_T) - \frac{\mu\pi_C}{\pi_C + \pi_T} & \lambda\pi_T & \lambda\pi_T + \frac{\mu\pi_T}{\pi_C + \pi_T}
\end{pmatrix}
\]

You can insert positive values for the F84 parameters.

Exercise 2: Calculate the equilibrium distributions of the Markov process with rate matrix \( Q \) and check whether the processes are reversible:

\[
Q = \begin{pmatrix}
-1.0 & 0.4 & 0.6 \\
0.6 & -0.9 & 0.3 \\
1.5 & 0.5 & -2.0
\end{pmatrix}
\]

Exercise 3: Based on the fossil record for lizards it is claimed that the most recent common ancestor (MRCA) of \textit{Sphenodon punctatus} and \textit{Cnemidophorus tigris} is at least 228.0 Mya old, the MRCA of \textit{Cnemidophorus tigris} and \textit{Rhineura floridana} is at least 113 Mya old, the MRCA of \textit{Rhineura floridana} and \textit{Gallotia galloti} at least 64.2 Mya, and the MRCA of \textit{Timon lepidus} and \textit{Dalmatolacerta oxycephala} at least 5.3 Mya.

(a) Use this information to estimate the phylogeny of lizards with time calibration.

(b) How does this result depend on the choice of model for the relaxed clock?

(c) How does the result change if you use only two or three of the given calibration points?

(d) How well are the given calibration points supported by fossils documented in the following references?

- Science (1990) 249:1020-1023,
- J Vertebr Paleontol (2006) 26:795-800,
- J Paleontol (1985) 59:1481-1485
Exercise 4:

(a) Implement Felsenstein’s pruning algorithm in R as a function that reads a tree in newick format, a sequence alignment and parameters of the F84 model and returns the log-likelihood of the tree. You can use the R script pruning.R as a starting point.

(b) Discuss how your implementation can be made more efficient.

Exercise 5: Compute the stationary distributions of the pfold rate matrix and the PAM substitution rate matrix. Are these evolutionary dynamics (almost) reversible? (You can use R or a similar program to solve this exercise. In R the function eigen may be helpful.)

Exercise 6: In the lecture we will discuss four different methods to compute a substitution matrix $S(t)$ from a rate matrix $R$. Investigate for the PAM rate matrix for amino acids, for the pfold rate matrix for RNA stem basepairs and for the following F84 rate matrix how efficient and how accurate and numerically stable these methods are. The PAM rate matrix and the pfold rate matrix will be available from the website of the lecture. (Note that the conventions about matrix notation are not always strictly followed in Bioinformatics. Sometimes transposed matrices are given, i.e. the roles of rows and columns are interchanged. You should always check for this with any matrix that is given to you!)