

# Project 5: Statistical phylogenetics

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April 18, 2024

## Problem 12: Transition matrix, rate matrix, and stationary distribution

1. Show that  $\frac{dP(t)}{dt} = R \cdot P(t)$

*Proof.*

$$\begin{aligned}\frac{dP(t)}{dt} &= \frac{P(dt+t) - P(t)}{dt} && \text{(Definition of derivative)} \\ &= \frac{P(dt)P(t) - P(t)}{dt} && \text{(Chapman-Kolmogorov's equation)} \\ &= \frac{(I + Rdt)P(t) - P(t)}{dt} && \text{(Definition of } P(dt)) \\ &= \frac{\cancel{P(t)} + RP(t)dt - \cancel{P(t)}}{dt} \\ &= \frac{RP(t)dt}{dt} \\ &= RP(t)\end{aligned}$$

□

2. Assume that the given Markov chain is ergodic with (unique) stationary distribution  $\pi$ , show that  $R\pi = 0$

*Proof.* The stationary distribution  $\pi$  satisfies:

$$P(t)\pi = \pi$$

after a sufficiently long time  $t$  and any time point that follows. Hence, the following equation also holds:

$$P(t+dt)\pi = \pi$$

We can further re-write the left-hand side of the equation:

$$\begin{aligned}P(dt+t)\pi &= P(dt)P(t)\pi && \text{(Chapman-Kolmogorov's equation)} \\ &= (I + Rdt)P(t)\pi && \text{(Definition of } P(dt)) \\ &= P(t)\pi + R \cdot P(t)dt\pi \\ &= \pi + Rdt\pi && \text{(Plug in } P(t)\pi = \pi)\end{aligned}$$

which leads us to the following equality:

$$\begin{aligned}\pi + Rdt\pi &= \pi \\ Rdt\pi &= 0 \\ R\pi &= 0\end{aligned}$$

□

## Problem 13: Phylogenetic trees as Bayesian networks

### 1. What is the joint probability $P(X, Z|T)$ of the tree?

$$P(X, Z|T) = \pi(Z_4)P(X_5|Z_4)P(Z_3|Z_4)P(Z_2|Z_3)P(Z_1|Z_3)P(X_4|Z_2)P(X_3|Z_2)P(X_2|Z_1)P(X_1|Z_1)$$

### 2. How many summation steps would be required for the naive calculation of $P(X|T)$ via brute-force marginalization over the hidden nodes $Z$ ?

Since there are 4 possibilities (A, C, G, T) for each hidden node:

$$4 \times 4 \times 4 \times 4 = 256$$

### 3. Rearrange the expression $P(X|T)$ such that the number of operations is minimized. How many summation steps are required now for the calculation of $P(X|T)$ ?

$$\begin{aligned}P(X|T) &= \sum_{Z_4} \sum_{Z_3} \sum_{Z_2} \sum_{Z_1} \pi(Z_4)P(X_5|Z_4)P(Z_3|Z_4)P(Z_2|Z_3)P(Z_1|Z_3)P(X_4|Z_2)P(X_3|Z_2)P(X_2|Z_1)P(X_1|Z_1) \\ &= \sum_{Z_4} \pi(Z_4)P(X_5|Z_4) \sum_{Z_3} P(Z_3|Z_4) \sum_{Z_2} P(Z_2|Z_3)P(X_4|Z_2)P(X_3|Z_2) \sum_{Z_1} P(Z_1|Z_3)P(X_2|Z_1)P(X_1|Z_1) \quad (\text{distrib}) \\ &= \underbrace{\sum_{Z_4} \pi(Z_4)P(X_5|Z_4)}_4 \underbrace{\sum_{Z_3} P(Z_3|Z_4)}_{4 \times 4} \underbrace{\sum_{Z_2} P(Z_2|Z_3)P(X_4|Z_2)P(X_3|Z_2)}_{4 \times 4 (Z_2 \rightarrow X_4 \text{ branch}) + 4 \times 4 (Z_2 \rightarrow X_3 \text{ branch})} \underbrace{\sum_{Z_1} P(Z_1|Z_3)P(X_2|Z_1)P(X_1|Z_1)}_{4 \times 4 (Z_1 \rightarrow X_2 \text{ branch}) + 4 \times 4 (Z_1 \rightarrow X_1 \text{ branch})}\end{aligned}$$

In total we have  $(16 + 16) \times 2 + 16 + 4 = 52$  summations.

## Problem 14: Learning phylogenetic trees from sequence alignment data

Load the dataset ParisRT.txt.

```
data <- read.dna("ParisRT.txt", format="sequential")
data

## 17 DNA sequences in binary format stored in a matrix.
##
## All sequences of same length: 618
##
## Labels:
## B_OYI
## B_HXB2
## D_eli
## Mr_D
## Mme_L
## A_ibng
## ...
##
```

```
## Base composition:
##      a      c      g      t
## 0.404 0.162 0.195 0.239
## (Total: 10.51 kb)
```

Create initial tree topology for the alignment using neighbor joining and K80 model.

```
set.seed(42)
tree.ini <- NJ(dist.dna(data, model = "K80"))
tree.ini.TN93 <- NJ(dist.dna(data, model = "TN93"))
tree.ini.JC69 <- NJ(dist.dna(data, model = "JC69"))
```

```
tree.ini
```

```
##
## Phylogenetic tree with 17 tips and 15 internal nodes.
##
## Tip labels:
##  B_OYI, B_HXB2, D_eli, Mr_D, Mme_L, A_ibng, ...
##
## Unrooted; includes branch lengths.
```

Plot the initial trees.

```
plot.phylo(tree.ini)
```

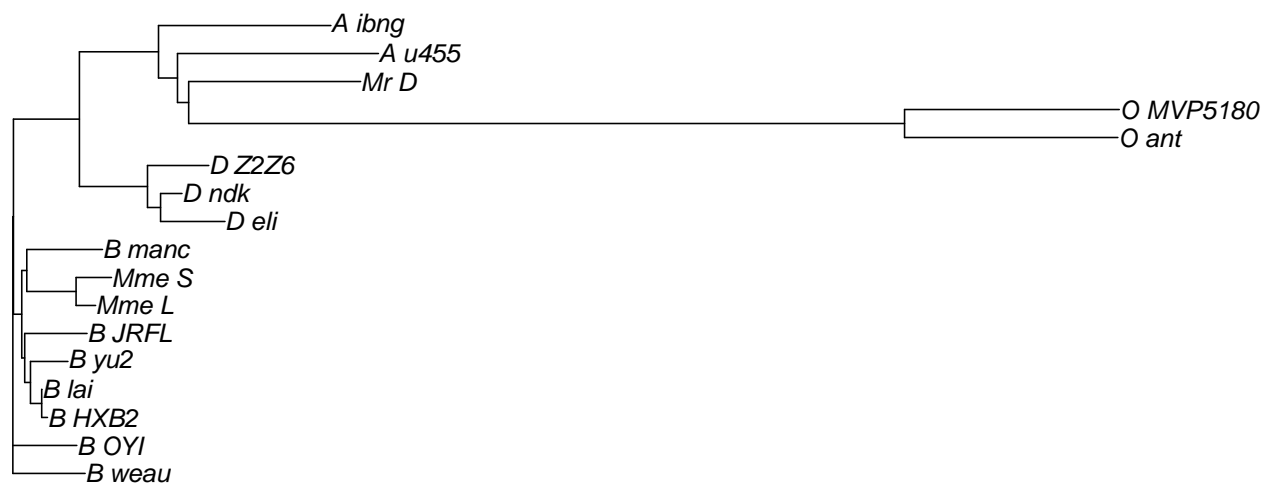


Figure 1: Initial tree with K80 model

```
plot.phylo(tree.ini.TN93)
```

```
plot.phylo(tree.ini.JC69)
```

```
tree.ML <- pml(tree.ini, phyDat(data), model = "K80")
tree.ML
```

```
## model: K80
## loglikelihood: -3003.487
## unconstrained loglikelihood: -2098.897
##
## Rate matrix:
##   a c g t
## a 0 1 1 1
```

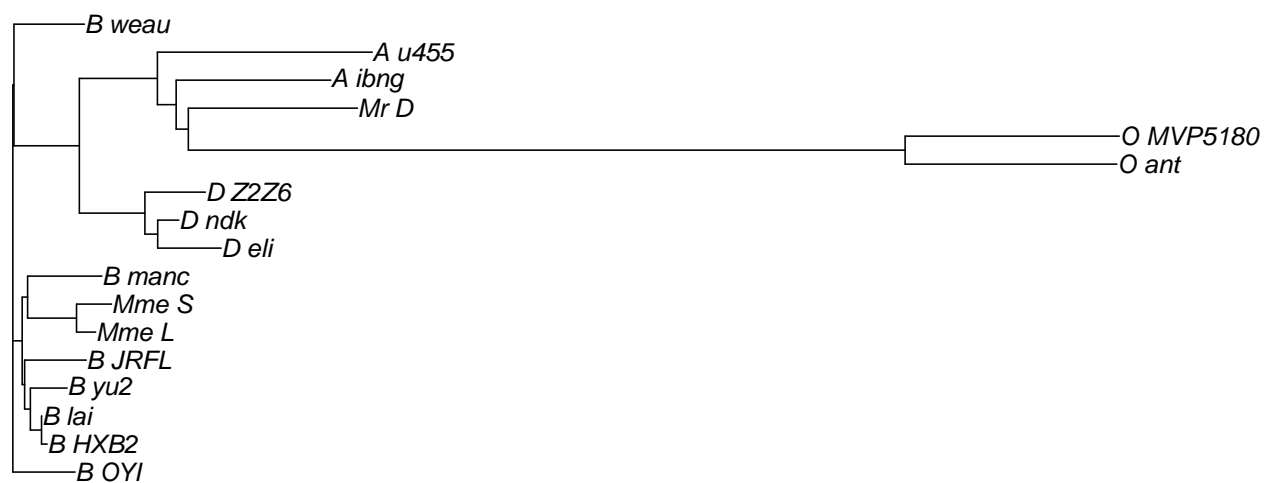


Figure 2: Initial tree with TN93 model

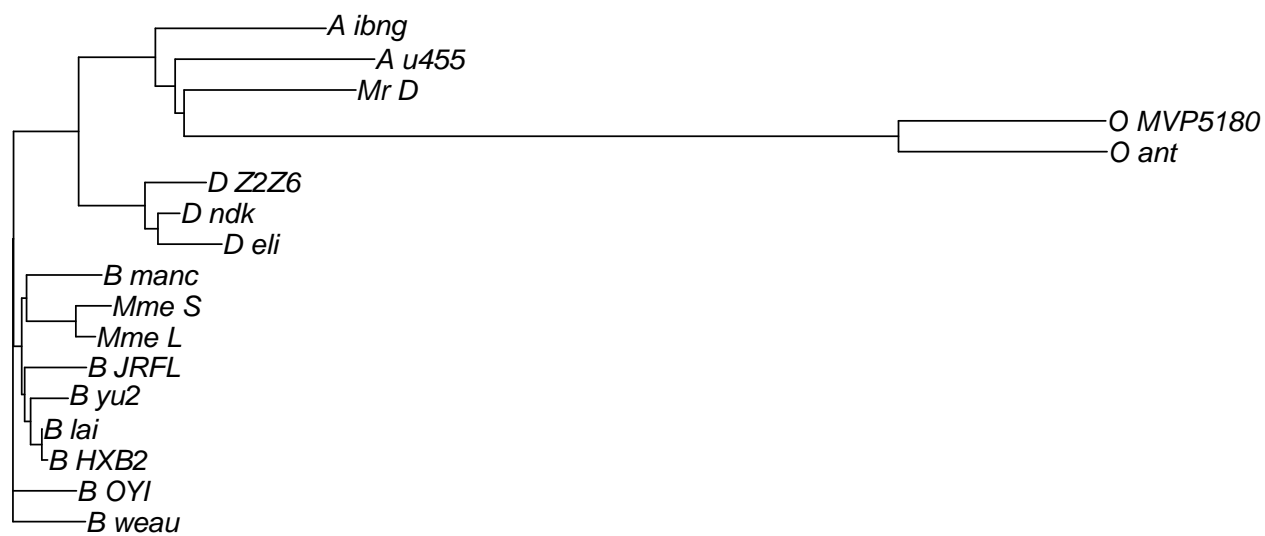


Figure 3: Initial tree with JC69 model

```
## c 1 0 1 1
## g 1 1 0 1
## t 1 1 1 0
##
## Base frequencies:
##   a   c   g   t
## 0.25 0.25 0.25 0.25
```

Find the optimal parameters of K80 model for rate matrix.

```
tree.optim.Q <- optim.pml(
  tree.ML,
  optQ = TRUE,
  optNni = FALSE,
  optBf = FALSE,
  optInv = FALSE,
  optGamma = FALSE,
  optEdge = FALSE,
  optRate = FALSE,
  optRooted = FALSE,
  model = "K80"
)
```

```
## optimize rate matrix: -3003.487 --> -2884.408
## optimize rate matrix: -2884.408 --> -2884.408
```

```
tree.optim.Q
```

```
## model: K80
## loglikelihood: -2884.408
## unconstrained loglikelihood: -2098.897
##
## Rate matrix:
##       a       c       g       t
## a 0.000000 1.000000 4.976955 1.000000
## c 1.000000 0.000000 1.000000 4.976955
## g 4.976955 1.000000 0.000000 1.000000
## t 1.000000 4.976955 1.000000 0.000000
##
## Base frequencies:
##   a   c   g   t
## 0.25 0.25 0.25 0.25
```

Optimize for branch lengths, nucleotide substitution rates and tree topology simultaneously.

```
tree.optim <- optim.pml(
  tree.ML,
  optQ = TRUE,      # rate matrix
  optNni = TRUE,    # tree topology
  optBf = FALSE,    # base frequencies
  optInv = FALSE,   # proportion of var size
  optGamma = FALSE, # gamma rate param
  optEdge = TRUE,   # edge lengths
  optRate = FALSE,  # overall rate
  optRooted = FALSE, # edge lengths of a rooted tree
  model = "K80"
)
```

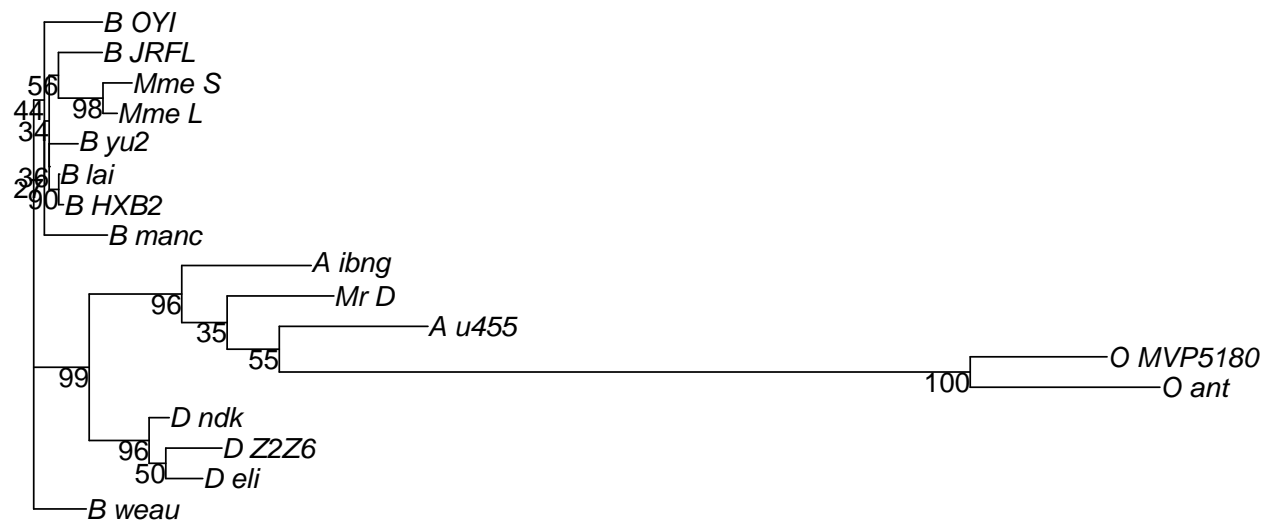
```
## optimize edge weights: -3003.487 --> -2992.981
## optimize rate matrix: -2992.981 --> -2873.703
## optimize edge weights: -2873.703 --> -2872.892
## optimize topology: -2872.892 --> -2859.775 NNI moves: 5
## optimize rate matrix: -2859.775 --> -2859.682
## optimize edge weights: -2859.682 --> -2859.681
## optimize topology: -2859.681 --> -2859.681 NNI moves: 0
## optimize rate matrix: -2859.681 --> -2859.681
## optimize edge weights: -2859.681 --> -2859.681
```

```
tree.optim
```

```
## model: K80
## loglikelihood: -2859.681
## unconstrained loglikelihood: -2098.897
##
## Rate matrix:
##      a      c      g      t
## a 0.000000 1.000000 5.262144 1.000000
## c 1.000000 0.000000 1.000000 5.262144
## g 5.262144 1.000000 0.000000 1.000000
## t 1.000000 5.262144 1.000000 0.000000
##
## Base frequencies:
##      a      c      g      t
## 0.25 0.25 0.25 0.25
```

Bootstrap on optimised model. The program resampled the nucleotides in the alignment (columns in the input matrix).

```
plotBS(tree.optim$tree, bootstrap, type = "phylogram")
```



*Mme\_S* is more likely to affect patient *Mme\_L*. The bootstrap support is 98% (in my run with seed 42), suggesting *Mme\_S* and *Mme\_L* share a more recent ancestor (closer relationship) than *Mr D*