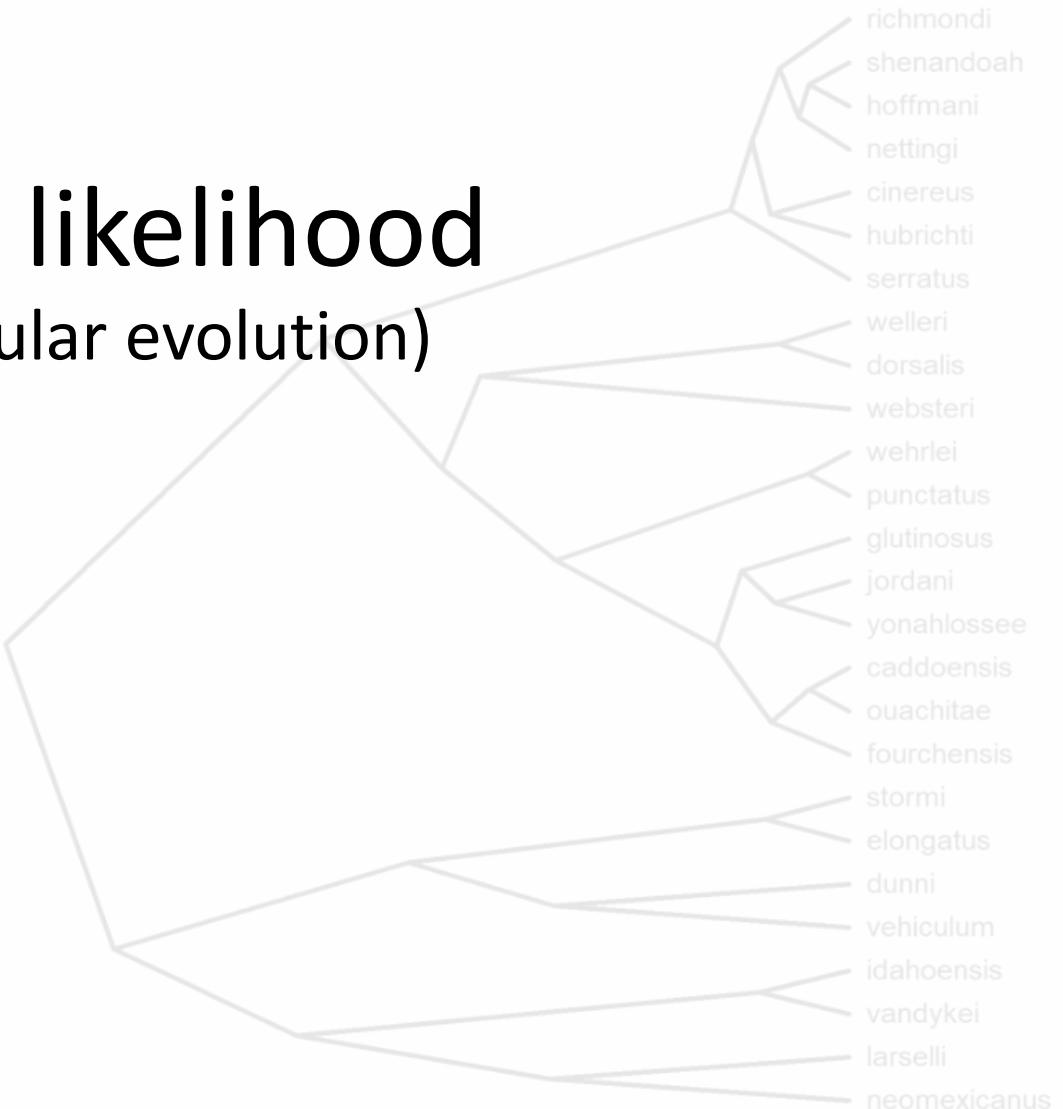


```
exercise5.R <--> exercise5.R
Source on Save | Run | Source | Environment | History | Connections | Tutorial
40 pp<-get("last_plot.phylo",envir=.PlotPhyloEnv)
41 for(i in 1:nrow(pp$edge)){
42   lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
43 }
44 for(i in 1:length(vert.tree$tip.label)){
45   text(pp$xx[i],pp$yy[i],vert.tree$tip.label[i],
46     pos=4)
47 }
48 slantyTree<-function(phy){
49   plotTree(phy,plot=FALSE)
50   pp<-get("last_plot.phylo",envir=.PlotPhyloEnv)
51   for(i in 1:nrow(pp$edge)){
52     lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
53   }
54   for(i in 1:length(phy$tip.label)){
55     text(pp$xx[i],pp$yy[i],phy$tip.label[i],
56       pos=4)
57   }
58 }
59 data(salamanders)
60 slantyTree(salamanders)
61
62 (Top Level) <--> R Script
```

Console Terminal Background Jobs

```
R 4.2.2 --> ~/...
+ pp<-get("last_plot.phylo",envir=.PlotPhyloEnv)
+ for(i in 1:nrow(pp$edge)){
+   lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],
+     lwd=3)
+ }
+ for(i in 1:length(phy$tip.label)){
+   text(pp$xx[i],pp$yy[i],phy$tip.label[i],
+     pos=4)
+ }
+ }
> data(salamanders)
> slantyTree(salamanders)
> |
```

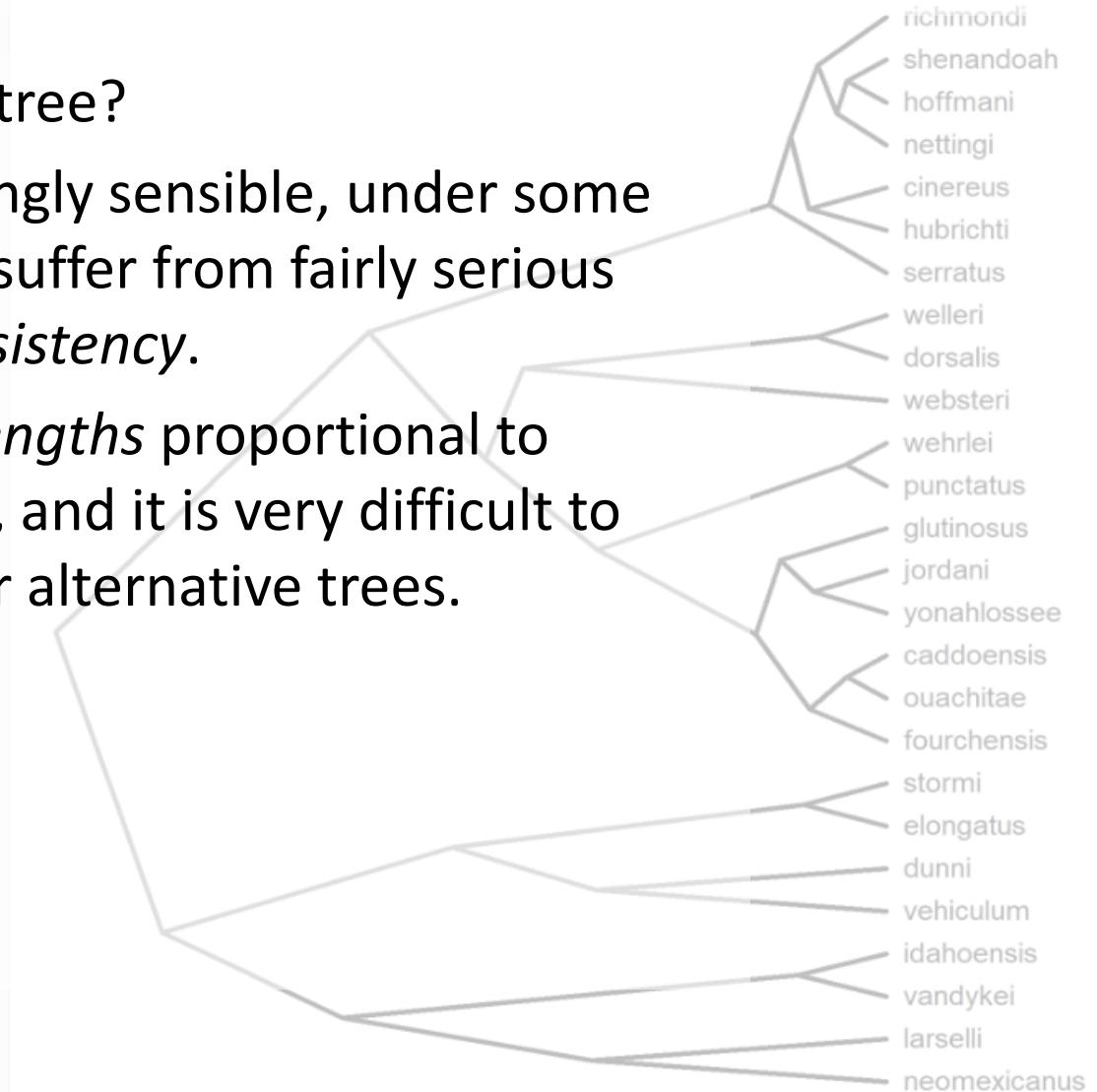
# Introduction to likelihood (and models of molecular evolution)



# Phylogenetic inference (and why it matters)

## How do we *estimate* a phylogenetic tree?

- Although highly intuitive & seemingly sensible, under some important circumstances MP can suffer from fairly serious statistical problems such as *inconsistency*.
  - It also does not result in *branch lengths* proportional to elapsed time or character change, and it is very difficult to evaluate the *degree of support* for alternative trees.



# Phylogenetic inference (and why it matters)

# How do we *estimate* a phylogenetic tree?

- Most contemporary phylogenetic inference studies use model-based statistical methods to estimate trees.
  - Among these are **Maximum Likelihood** (ML) and **Bayesian inference** (BI).
  - According to the statistical inference method of ML we should prefer the model to explain our data that makes having obtained the data we've observed most probable.
  - ML estimators tend to be *statistically consistent* and *efficient* (and this has been shown for phylogeny inference).
  - To estimate phylogeny using ML we need a model for our data.

RStudio

File Edit Code View Plots Session Build Debug Profile Tools Help

Go to file/function Addins

exercise5.R

```
40 pp<-get("last_plot.phylo",envir=.PlotPhyloEnv)
41 for(i in 1:nrow(pp$edge)){
42   lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
43 }
44 for(i in 1:length(vert.tree$tip.label)){
45   text(pp$xx[i],pp$yy[i],vert.tree$tip.label[i],
46     pos=4)
47 }
48 slantyTree<-function(phy){
49   plotTree(phy,plot=FALSE)
50   pp<-get("last_plot.phylo",envir=.PlotPhyloEnv)
51   for(i in 1:nrow(pp$edge)){
52     lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
53   }
54   for(i in 1:length(phy$tip.label)){
55     text(pp$xx[i],pp$yy[i],phy$tip.label[i],
56       pos=4)
57   }
58 }
59 data(salamanders)
60 slantyTree(salamanders)
```

Environment History Connections Tutorial

Zoom Export

richmondi  
shenandoah  
hoffmani  
nettingi  
cinereus  
hubrichti  
serratus  
welleri  
dorsalis  
websteri  
wehrlei  
punctatus  
glutinosus  
jordani  
yonahlossee  
caddoensis  
ouachitae  
fourchensis  
stormi  
elongatus  
dunni  
vehiculum  
idahoensis  
vandykei  
larselli  
neomexicanus

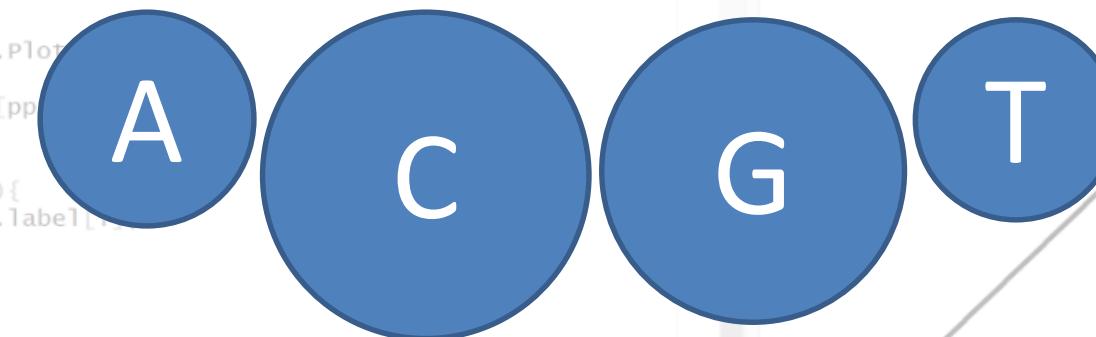
# The structure of a substitution model

## Part 1: transition rates between states, i.e., nucleotides.

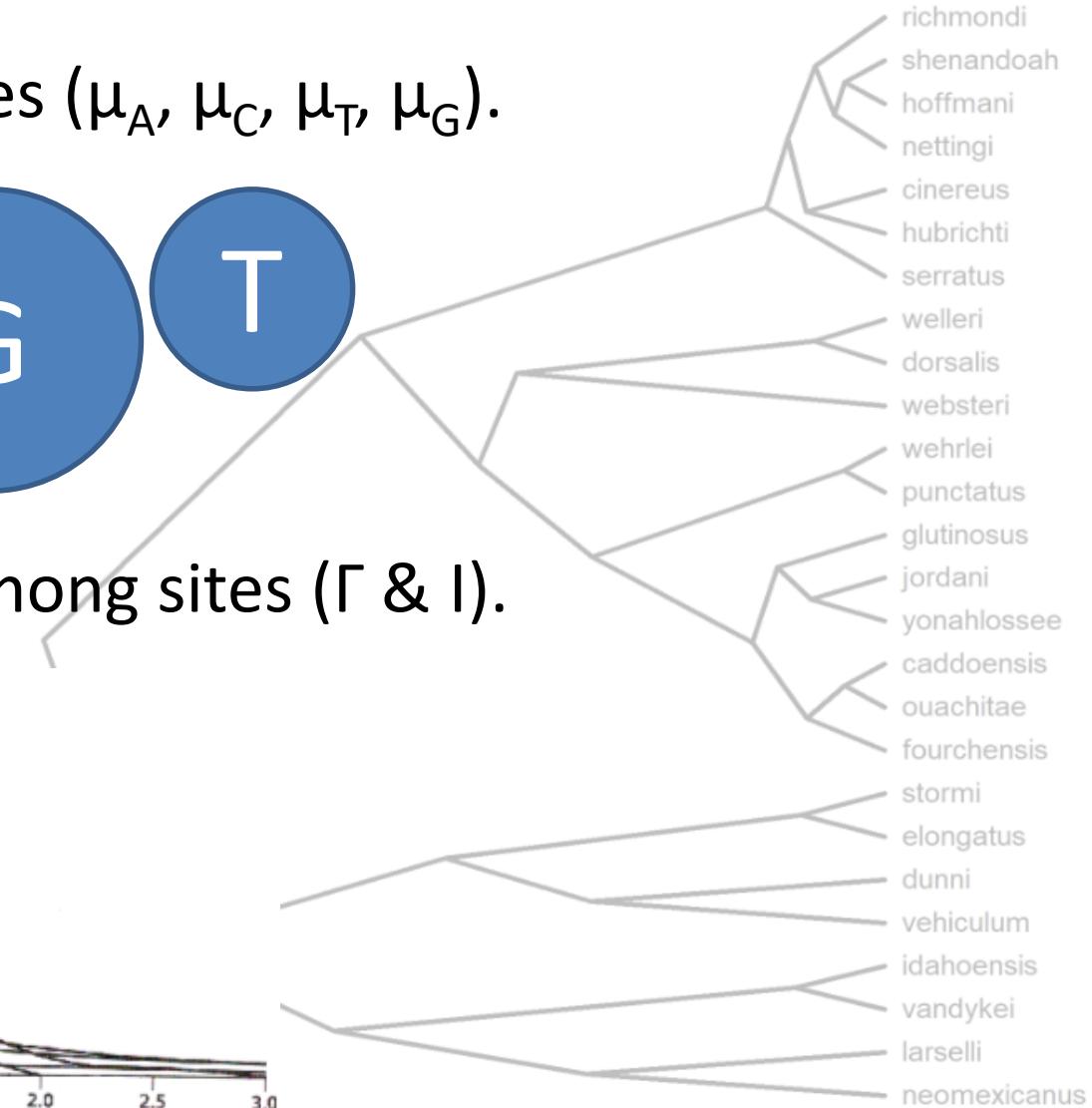
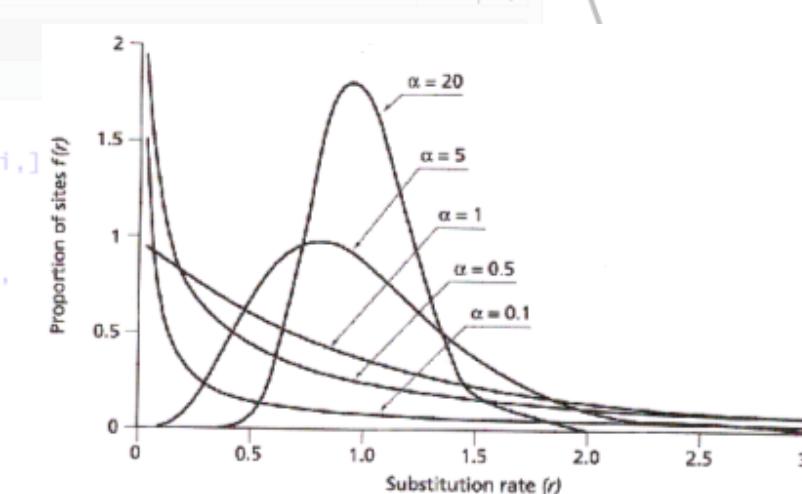
```
graph TD; T((T)) <--> C((C)); T <--> G((G)); T <--> A((A)); A <--> C; A <--> G; A <--> T;
```

# The structure of a substitution model

Part 2: nucleotide frequencies ( $\mu_A$ ,  $\mu_C$ ,  $\mu_T$ ,  $\mu_G$ ).



## Part 3: rate heterogeneity among sites ( $\Gamma$ & I).



RStudio  
File Edit Code View Plots Session Build Debug Profile Tools Help

Go to file/function Addins

exercise5.R

```
40 pp<-get("last_plot.phylo")
41 for(i in 1:nrow(pp$edge)){
42   lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
43 }
44 for(i in 1:length(vert.tree$tip.label)){
45   text(pp$xx[i],pp$yy[i],vert.tree$tip.label[i],
46     pos=4)
47 }
48 slantyTree<-function(phy){
49   plotTree(phy,plot=F)
50   pp<-get("last_plot.phylo",envir=.GlobalEnv)
51   for(i in 1:nrow(pp$edge)){
52     lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
53   }
54   for(i in 1:length(phy$tip.label)){
55     text(pp$xx[i],pp$yy[i],phy$tip.label[i],
56       pos=4)
57   }
58 }
59 data(salamanders)
60 slantyTree(salamanders)
```

Environment History Connections Tutorial

Zoom Export

richmondi  
shenandoah  
hoffmani  
nettingi  
cinereus  
hubrichti  
serratus  
welleri  
dorsalis  
websteri  
wehrlei  
punctatus  
glutinosus  
jordani  
yonahlossee  
caddoensis  
ouachitae  
fourchensis  
stormi  
elongatus  
dunni  
vehiculum  
idahoensis  
vandykei  
larselli  
neomexicanus

Project: (None)

Console Terminal Background Jobs

R 4.2.2 ~/ ~

```
pp<-get("last_plot.phylo")
for(i in 1:nrow(pp$edge)){
  lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
}
for(i in 1:length(phy$tip.label)){
  text(pp$xx[i],pp$yy[i],phy$tip.label[i],pos=4)
}
> data(salamanders)
> slantyTree(salamanders)
>
```

# Phylogenetic inference (and why it matters)

## How do we estimate a phylogenetic tree?

- The other major advantage of ML (and BI) is that it leads to an inferred tree in which branch lengths are *proportional to accrued evolutionary change or time.*
- Finally, ML (and BI) allow us to easily compare among alternative trees.
- Most trees estimated via statistical methods have branch lengths that are proportional to accrued change in the molecular characters used to estimate the tree. However, most phylogenies used in ecology are *ultrametric*. An ultrametric tree has branch lengths that are *proportional to time.*

RStudio  
File Edit Code View Plots Session

Project: (None)

exercise.R

```

40 pp<-get("las")
41 for(i in 1:nrc)
42   lines(pp$xx[i])
43 }
44 for(i in 1:ler)
45   text(pp$xx[i]
46     pos=4)
47 }
48 slantyTree<-fl
49 plotTree(phy
50 pp<-get("las
51 for(i in 1:r
52   lines(pp$xx
53     lwd=3)
54 }
55 for(i in 1:l
56   text(pp$xx
57     pos=4)
58 }
59 data(salamande
60 slantyTree(sal
61 |
62 (Top Level) ▾

```

Console Terminal Bac

```

R 4.2.2 · ~/r
+ pp<-get("las
+ for(i in 1:r
+   line
+   }
+   for(i in 1:l
+     text
+   }
+   }
+ data(salamanders)
> slantyTree(salamard
>

```

# Jukes-Cantor model (JC69)

The Jukes-Cantor model is the simplest model of DNA substitution.

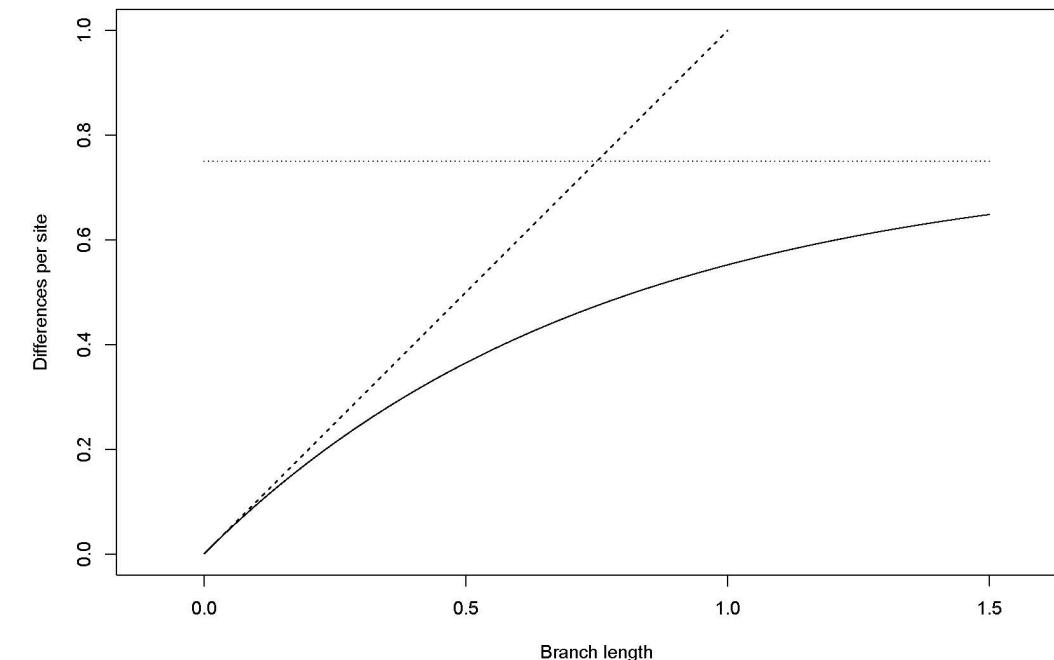
According to this model, base frequencies are equal, substitution rates among nucleotides are equal.

The diagram illustrates the Jukes-Cantor model with four nucleotides (A, T, C, G) represented as blue circles. Each nucleotide has a self-loop arrow labeled  $\lambda$ . Between any two nucleotides, there are two crossing arrows forming an X, also labeled  $\lambda$ , indicating that transitions between all pairs of bases occur at the same rate.

## Jukes-Cantor model (JC69)

The distance between sequences accrues non-linearly under the JC model.

Here is a plot showing the expected number of differences plotted by elapsed time.



RStudio  
File Edit Code View Plots Session

Project: (None)

```

exercise5.R
Source
40 pp<-get("las")
41 for(i in 1:nrc)
42 lines(pp$xx)
43 }
44 for(i in 1:ler)
45 text(pp$xx[i
46 pos=4]
47 }
48 slantyTree<-fl
49 plotTree(phy
50 pp<-get("las
51 for(i in 1:r
52 lines(pp$>
53 lwd=3)
54 }
55 for(i in 1:l
56 text(pp$x
57 pos=4)
58 }
59 slantyTree<-
60 plotTree(phy
61 pp<-get("las
62 for(i in 1:r
63 lines(pp$>
64 lwd=3)
65 }
66 for(i in 1:l
67 text(pp$x
68 pos=4)
69 }
70 data(salamande
71 slantyTree(sal
72
72:1 (Top Level) +

```

Console Terminal Bac

```

R 4.2.2 · ~/ →
+ pp<-get("las
+ for(i in 1:r
+ lines(
+ }
+ for(i in 1:l
+ text(
+ }
+ }
> data(salamanders)
> slantyTree(salamard
>

```

# Jukes-Cantor model (JC69)

First set the instantaneous substitution rate between all letters to  $\lambda = \frac{u}{3}$ . This is because if mutation away from each state occurs with rate  $u$ ; mutation to any of the remaining 3 states must occur with rate  $\frac{u}{3}$ .

From the zero-term of the **Poisson distribution**, the probability of no event occurring after time,  $t$ , is given by:

$$e^{-\frac{4}{3}ut}$$

Thus, the probability of any event is just:  $1 - e^{-\frac{4}{3}ut}$

From this we can get:

$$P(C|A, u, t) = \frac{1}{4}(1 - e^{-\frac{4}{3}ut})$$

(we have the  $\frac{1}{4}$  because there are four sites into which A could have changed).

- richmondi
- shenandoah
- hoffmani
- nettingi
- cinereus
- hubrichti
- serratus
- welleri
- dorsalis
- websteri
- wehrlei
- punctatus
- glutinosus
- jordani
- yonahlossee
- caddoensis
- ouachitae
- fourchensis
- stormi
- elongatus
- dunni
- vehiculum
- idahoensis
- vandykei
- larselli
- neomexicanus

## Jukes-Cantor model (JC69)

Ok, so, from before

$$P(x = C|x = A, u, t) = \frac{1}{4} \left(1 - e^{-\frac{4}{3}ut}\right)$$

Now, if we add up all the sites that A can change to that result in a difference between sequences, i.e.:

$$P(x \neq A | x = A, u, t) = \frac{3}{4} \left(1 - e^{-\frac{4}{3}ut}\right)$$

Of course, this is just the same as the raw difference between sequences – since the expected distance is just the long run probability of a site having changed state in the time interval separating the sequences, i.e.:

$$D_s = \frac{3}{4} \left( 1 - e^{-\frac{4}{3}ut} \right)$$

```
exercise5.R x
Source
40 pp<-get("las")
41 for(i in 1:nrc)
42   lines(pp$xx|
43 }
44 for(i in 1:ler)
45   text(pp$xx[i]
46     pos=4)
47 }
48 slantyTree<-fu
49 plotTree(phy
50 pp<-get("las
51 for(i in 1:r
52   lines(pp$>
53     lwd=3)
54 }
55 for(i in 1:l
56   text(pp$>
57     pos=4)
58 }
59 data(salamande
60 slantyTree(sal
61 |
62 (Top Level) ▾
```

```
R 4.2.2 · ~/r
+ pp<-get("las
+ for(i in 1:r
+   line
+
+   }
+ for(i in 1:l
+   text
+
+   }
+
> data(salamanders)
> slantyTree(salamar
> |
```

# Jukes-Cantor model (JC69)

Now defining:

$$D_{JC} = \hat{u}t \text{ (expected value of D)}$$

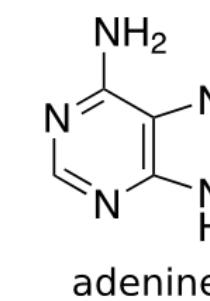
Let's solve for  $D_{JC}$ :

$$D_{JC} = -\frac{3}{4} \ln \left( 1 - \frac{4}{3} D_s \right)$$

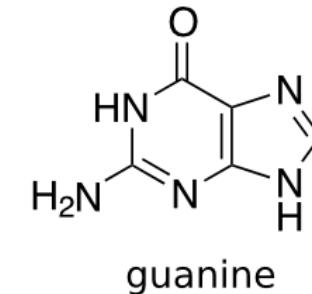


```
exercise5.R
Source on Save
40 pp<-get("last_plot.phylo", envir=.
41 for(i in 1:nrow(pp$edge)){
42   lines(pp$xx[pp$edge[i,]],pp$yy[.
43 }
44 for(i in 1:length(vert.tree$tip.l.
45   text(pp$xx[i],pp$yy[i],vert.tre.
46   pos=4)
47 }
48
49 slantyTree<-function(phy){
50   plotTree(phy,plot=FALSE)
51   pp<-get("last_plot.phylo",envir=
52   for(i in 1:nrow(pp$edge)){
53     lines(pp$xx[pp$edge[i,]],pp$yy[.
54     lwd=3)
55   }
56   for(i in 1:length(phy$tip.label)
57     text(pp$xx[i],pp$yy[i],phy$tip.
58     pos=4)
59   }
60 }
61 data(salamanders)
62 slantyTree(salamanders)
63
64
65
66
67
68
69
70
71
72
72:1 (Top Level) ▾
```

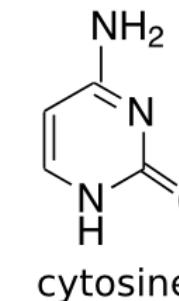
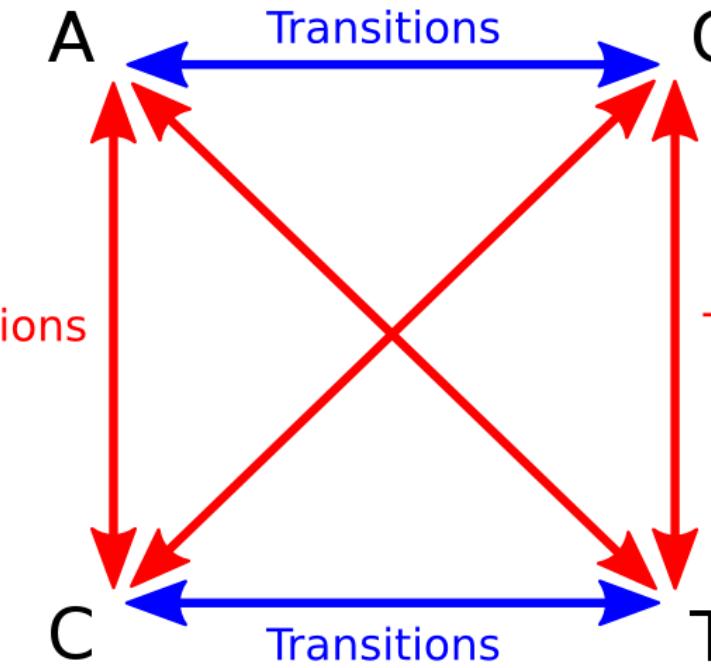
```
R 4.2.2 · ~/r/
+ pp<-get("last_plot.phylo", envir=.
+ for(i in 1:nrow(pp$edge)){
+   lines(pp$xx[pp$edge[i,]],pp$yy[.
+ }
+ for(i in 1:length(phy$tip.label)
+   text(pp$xx[i],pp$yy[i],
+     pos=4)
+ }
>
> data(salamanders)
> slantyTree(salamanders)
>
```



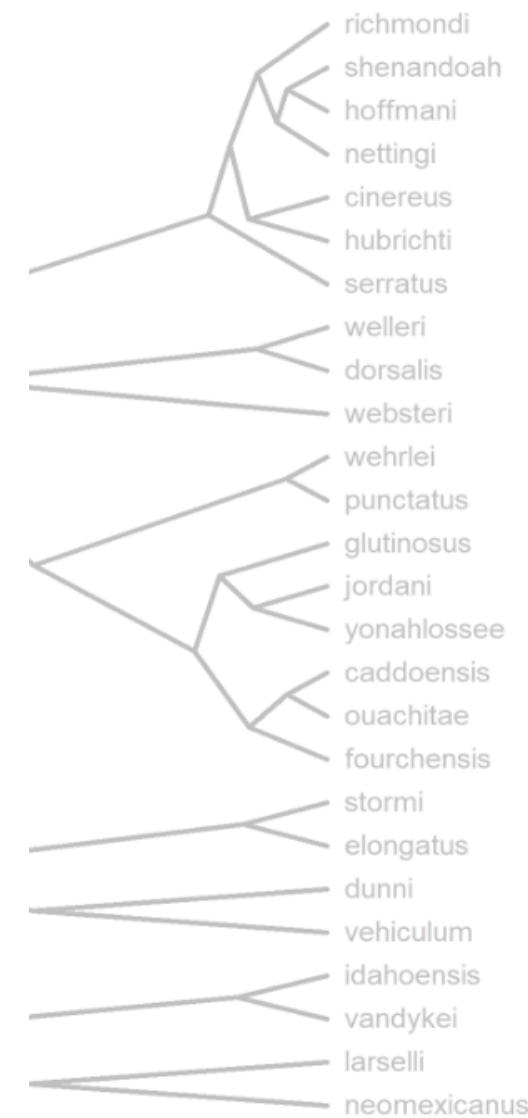
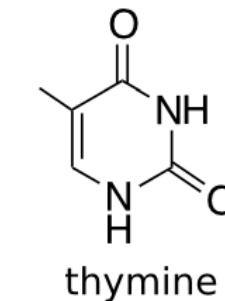
purines



Transversions



pyrimidines



# Other models of DNA substitution

Before learning other models, we review a technique for computing the transition probabilities between nucleotides. To explore this technique, let's first write down our transition matrix for the JC69 model.

This matrix contains the instantaneous transition rates between states in off-diagonal position. We then put  $-3\lambda$  in the diagonal to ensure that rows sum to zero:

$$Q = q_{ij} = \begin{pmatrix} -3\lambda & \lambda & \lambda & \lambda \\ \lambda & -3\lambda & \lambda & \lambda \\ \lambda & \lambda & -3\lambda & \lambda \\ \lambda & \lambda & \lambda & -3\lambda \end{pmatrix}$$

RStudio  
 File Edit Code View Plots Session

Project: (None)

```

exercise.R
Source
40 pp<-get("las")
41 for(i in 1:nrc
42   lines(pp$xx|
43 }
44 for(i in 1:ler
45   text(pp$xx[i
46   pos=4)
47 }
48
49 slantyTree<-f
50 plotTree(phy
51 pp<-get("las
52 for(i in 1:r
53   lines(pp$>
54   lwd=3)
55 }
56 for(i in 1:l
57   text(pp$x>
58   pos=4)
59 }
60
61 data(salamande
62 slantyTree(sal
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70 data(salamanders)
71 slantyTree(salamard
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79
72:1 (Top Level) ▾
```

Console Terminal Bac

```

R 4.2.2 · ~/r
+ pp<-get("las
+ for(i in 1:r
+   line
+
+   }
+   for(i in 1:l
+     text
+
+   }
+
+ }
>
> data(salamanders)
> slantyTree(salamard
>
```

The neat thing about this matrix  $Q$ , is that [matrix exponentiation](#) gives us the transition probabilities between all states.

$$P(t) = p_{ij}(t) = e^{Qt} = \begin{pmatrix} p_0(t) & p_1(t) & p_1(t) & p_1(t) \\ p_1(t) & p_0(t) & p_1(t) & p_1(t) \\ p_1(t) & p_1(t) & p_0(t) & p_1(t) \\ p_1(t) & p_1(t) & p_1(t) & p_0(t) \end{pmatrix},$$

,

where  $\begin{cases} p_0(t) = \frac{1}{4} + \frac{3}{4}e^{-4\lambda t} \\ p_1(t) = \frac{1}{4} - \frac{1}{4}e^{-4\lambda t} \end{cases}$

In this matrix,  $p_{ij}(t)$  is the probability that, given  $i$  at the start of a time interval,  $j$  is the state at the end of the interval  $t$ .

- richmondi
- shenandoah
- hoffmani
- nettingi
- cinereus
- hubrichti
- serratus
- welleri
- dorsalis
- websteri
- wehrlei
- punctatus
- glutinosus
- jordani
- yonahlossee
- caddoensis
- ouachitae
- fourchensis
- stormi
- elongatus
- dunni
- vehiculum
- idahoensis
- vandykei
- larselli
- neomexicanus

```
Console Terminal ✘ Basic  
R 4.2.2 · ~/  
+ pp<-get("las  
+ for(i in 1:r  
+           line  
+  
+           }  
+           for(i in 1:l  
+             text  
+           }  
+           }  
+         }  
>  
> data(salamanders)  
> slantyTree(salamander  
> |
```

K80 (Kimura 1980)

The K80, K2P, or Kimura two parameter model (Kimura 1980). This model has a different rate  $\alpha$  for transitions ( $C \longleftrightarrow T$  and  $A \longleftrightarrow G$ ) and transversions  $\beta$  (all other substitutions).

$$Q = \begin{pmatrix} -(\alpha + 2\beta) & \alpha & \beta & \beta \\ \alpha & -(\alpha + 2\beta) & \beta & \beta \\ \beta & \beta & -(\alpha + 2\beta) & \alpha \\ \beta & \beta & \alpha & -(\alpha + 2\beta) \end{pmatrix}$$

- richmondi
- shenandoah
- hoffmani
- nettingi
- cinereus
- hubrichti
- serratus
- welleri
- dorsalis
- websteri
- wehrlei
- punctatus
- glutinosus
- jordani
- yonahlossee
- caddoensis
- ouachitae
- fourchensis
- stormi
- elongatus
- dunni
- vehiculum
- idahoensis
- vandykei
- larselli
- neomexicanus

# General time-reversible model (GTR)

The most general model used is the general time-reversible model (GTR)(Tavare 1986). The rate matrix can be represented the following way:

$$Q = \begin{pmatrix} \pi_A & 0 & 0 & 0 \\ 0 & \pi_C & 0 & 0 \\ 0 & 0 & \pi_G & 0 \\ 0 & 0 & 0 & \pi_T \end{pmatrix} \begin{pmatrix} . & r_{AC} & r_{AG} & r_{AT} \\ r_{CA} & . & r_{CG} & r_{CT} \\ r_{GA} & r_{GC} & . & r_{GT} \\ r_{TA} & r_{TC} & r_{TG} & . \end{pmatrix}$$

where  $\pi_i$  are the equilibrium frequencies of the bases and  $r_{ij}$  are rate parameters.

# Overview over common models

Model	Summary
JC69 (Jukes & Cantor 1969)	Equal rates; equal nucleotide frequencies (bf)
K80 (Kimura 1980)	Different rates for transitions (ts) and transversions (tv).
F81 (Felsenstein 1981)	Equal rates; different nucleotide frequencies.
HKY85 (Hasegawa et al. 1985)	Different rate for ts and tv; unequal base frequencies.
F84 (Felsenstein 1984)	Similar to HKY85, different rates (for pyrimidines and purines).
TN93 (Tamura & Nei 1993)	Two types of tv; one type of ts; unequal base frequencies.
GTR (Tavare 1986)	All rates different; unequal base frequencies.

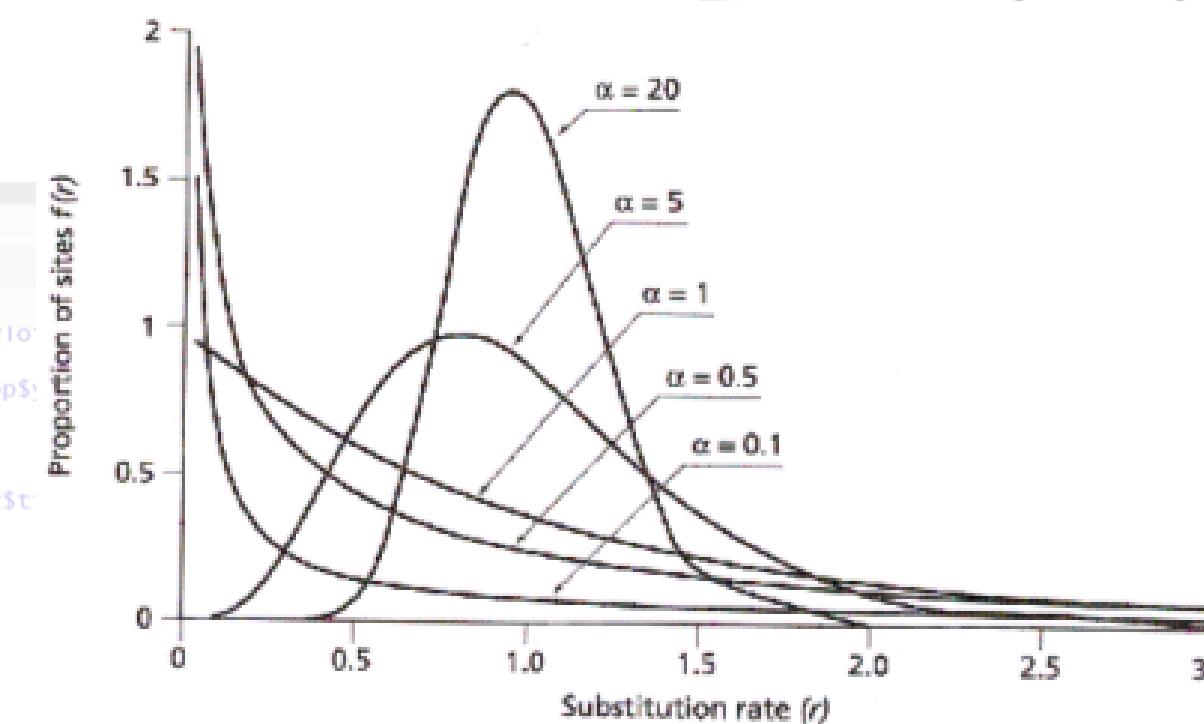
```
exercise5.R
40 pp<-get("last_plot.phylo",envir=.PlotPhylo)
41 for(i in 1:nrow(pp$edge)){
42   lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],lwd=3)
43 }
44 for(i in 1:length(vert.tree$tip.label)){
45   text(pp$xx[i],pp$yy[i],vert.tree$tip.label[i],
46     pos=4)
47 }
48 slantyTree<-function(phy){
49   plotTree(phy,plot=FALSE)
50   pp<-gpar("last.plot.phylo",envir=.PlotPhylo)
51   for(i in 1:nrow(pp$edge)){
52     lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],
53       lwd=3)
54   }
55   for(i in 1:length(phy$tip.label)){
56     text(pp$xx[i],pp$yy[i],phy$tip.label[i],
57       pos=4)
58   }
59 }
60 data(salamanders)
61 slantyTree(salamanders)
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72
```

Console Terminal × Background Jobs ×

```
R 4.2.2 · ~/r ·
+ pp<-get("last_plot.phylo",envir=.PlotPhylo)
+ for(i in 1:nrow(pp$edge)){
+   lines(pp$xx[pp$edge[i,]],pp$yy[pp$edge[i,]],
+     lwd=3)
+ }
+ for(i in 1:length(phy$tip.label)){
+   text(pp$xx[i],pp$yy[i],phy$tip.label[i],
+     pos=4)
+ }
+
> data(salamanders)
> slantyTree(salamanders)
>
```

# Other model complexity

- Invariant sites.
- Gamma ( $\Gamma$ ) distributed rate heterogeneity among sites.



RStudio

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Project: (None)

exercise5.R

```
40 pp<-get("las")
41 for(i in 1:nrc)
42   lines(pp$xx|
43 }
44 for(i in 1:ler
45   text(pp$xx[i
46     pos=4)
47 }
48
49 slantyTree<-fu
50 plotTree(phy
51 pp<-get("las
52 for(i in 1:r
53   lines(pp$>
54     lwd=3)
55 }
56 for(i in 1:l
57   text(pp$>
58     pos=4)
59 }
60
61 data(salamande
62 slantyTree(sal
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72 | (Top Level) ▾
```

Console Terminal Bac

```
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+ pp<-get("las
+ for(i in 1:r
+   line
+
+ }
+ for(i in 1:l
+   text
+
+ }
+
+ }
>
> data(salamanders)
> slantyTree(salamar
> |
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richmondi  
shenandoah  
hoffmani  
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cinereus  
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jordani  
yonahlossee  
caddoensis  
ouachitae  
fourchensis  
stormi  
elongatus  
dunni  
vehiculum  
idahoensis  
vandykei  
larselli  
neomexicanus

# Other models of DNA substitution

- ▶ A notable aspect of all of these models is that simpler models tend to be special cases of more complex ones.
- ▶ That means that we should be able to compare nested models using standard statistical methods (which we will revisit later).



exercise5.R x

Source

40 pp&lt;-get("las")

49 for(i in 1:nrc)

50 lines(pp\$xx)

51 }

52 for(i in 1:ler)

53 text(pp\$xx[i

54 pos=4)

55 }

56

57 slantyTree&lt;-fu

58 plotTree(phy

59 pp&lt;-get("las")

60 for(i in 1:r)

61 lines(pp\$

62 lwd=3)

63 }

64 for(i in 1:l)

65 text(pp\$x)

66 pos=4)

67 }

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70 data(salamanders)

71 slantyTree(sal

72

&lt; (Top Level) &gt;

Console Terminal Bac

R 4.2.2 · ~/

+ pp&lt;-get("las")

+ for(i in 1:r)

+ line

+ }

+ for(i in 1:l)

+ text

+ }

+ }

&gt;

&gt; data(salamanders)

&gt; slantyTree(salamar

&gt; |

# Overview over common models

Model	Summary
JC69 (Jukes & Cantor 1969)	Equal rates; equal nucleotide frequencies (bf)
K80 (Kimura 1980)	Different rates for transitions (ts) and transversions (tv).
F81 (Felsenstein 1981)	Equal rates; different nucleotide frequencies.
HKY85 (Hasegawa et al. 1985)	Different rate for ts and tv; unequal base frequencies.
F84 (Felsenstein 1984)	Similar to HKY85, different rates (for pyrimidines and purines).
TN93 (Tamura & Nei 1993)	Two types of tv; one type of ts; unequal base frequencies.
GTR (Tavaré 1986)	All rates different; unequal base frequencies.

```

richmondi
shenandoah
hoffmani
nettingi
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hubrichti
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yonahlossee
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dunni
vehiculum
idahoensis
vandykei
larselli
neomexicanus

```

Project: (None)

Publish



```
exercise5.R x
Source
40 pp<-get("las
41 for(i in 1:nrc
42   lines(pp$xx|
43 }
44 for(i in 1:ler
45   text(pp$xx[i
46     pos=4)
47 }
48
49 slantyTree<-f
50 plotTree(phy
51 pp<-get("las
52 for(i in 1:r
53   lines(pp$|
54     lwd=3)
55 }
56 for(i in 1:l
57   text(pp$xx|
58     pos=4)
59 }
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61 data(salamande
62 slantyTree(sal
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```

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R 4.2.2 · ~/r
+ pp<-get("las
+ for(i in 1:r
+   line
+
+ }
+ for(i in 1:l
+   text
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+ }
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+ }
+
> data(salamanders)
> slantyTree(salamard
> |
```

# Other models of DNA substitution

- ▶ A notable aspect of all of these models is that simpler models tend to be special cases of more complex ones.
- ▶ That means that we should be able to compare nested models using standard statistical methods (which we will revisit later).

```
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neomexicanus
```



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exercise5.R x
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40 pp<-get("las
41 for(i in 1:nrc
42   lines(pp$xx|
43 }
44 for(i in 1:ler
45   text(pp$xx[i
46   pos=4)
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49 plotTree(phy
50 pp<-get("las
51 for(i in 1:r
52   lines(pp$>
53   lwd=3)
54 }
55 for(i in 1:l
56   text(pp$x>
57   pos=4)
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59 data(salamande
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```

# Some probability basics

Probabilities of discrete events must add to 1.0.

For instance, in a 6 sided dice, the probability of rolling a I, a II, a III,..., VI must sum to 1.0:

$$P(I) + P(II) + P(III) + P(IV) + P(V) + P(VI) = 1.0$$

The probability of not an event is simply 1.0 minus the probability of the event.

For instance, the probability of not rolling I, is merely 1.0 minus the probability of rolling I.

$$P(x \neq I) = 1 - P(I)$$

Project: (None)

Publish

- richmondi
- shenandoah
- hoffmani
- nettingi
- cinereus
- hubrichti
- serratus
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- vandykei
- larselli
- neomexicanus

RStudio  
File Edit Code View Plots Session

Project: (None)

exercise5.R

```
40 pp<-get("las")
41 for(i in 1:nrc)
42   lines(pp$xx[i])
43 }
44 for(i in 1:ler)
45   text(pp$xx[i]
46     pos=4)
47 }
48 slantyTree<-function()
49   plotTree(phy)
50   pp<-get("las")
51   for(i in 1:r)
52     lines(pp$xx[i]
53       lwd=3)
54   }
55 for(i in 1:l)
56   text(pp$xx[i]
57     pos=4)
58 }
59 data(salamanders)
60 slantyTree(salamanders)
61 }
62 (Top Level) <-->
```

Console Terminal Bac

R 4.2.2 · ~ / →

```
pp<-get("las")
for(i in 1:r)
  lines(pp$xx[i])
}
for(i in 1:l)
  text(pp$xx[i]
    pos=4)
}
data(salamanders)
slantyTree(salamanders)
>
```

# Some probability basics

**Probabilities of independent observations are multiplicative.**

For instance, if  $P(H) = 0.6$  (i.e., a slightly biased coin), the probability of the observed sequence  $HHH$  is simply:

$$P(HHH) = 0.6 \times 0.6 \times 0.6 = 0.6^3 = 0.216$$

**Probabilities of mutually exclusive possibilities are additive.**

For instance, if  $P(H) = 0.6$ , the probability of a sequence of 4 tosses that begin and end with  $H$  is simply:

$$P(HxxH) = P(HHHH) + P(HHTH) + P(HTTH) + P(HTHH)$$
$$P(HxxH) = 0.6^4 + 0.6^3 \times 0.4 + 0.6^2 \times 0.4^2 + 0.6^3 \times 0.4 = 0.36$$

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RStudio  
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Project: (None)

exercise5.R

```
40 pp<-get("las")
41 for(i in 1:nrc)
42   lines(pp$xx[i])
43 }
44 for(i in 1:ler)
45   text(pp$xx[i]
46     pos=4)
47 }
48 slantyTree<-fun
49 plotTree(phy
50 pp<-get("las")
51 for(i in 1:r
52   lines(pp$xx[i]
53     lwd=3)
54 }
55 for(i in 1:l
56   text(pp$xx[i]
57     pos=4)
58 }
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# Maximum likelihood phylogeny inference

The famous statistician Neyman (1971) first used likelihood to on molecular sequences. Felsenstein developed an much faster algorithm (pruning algorith) which made the inference computational feasible.

## Why maximize the likelihood?

The likelihood is not only used as an objective function, but also to compare tree and evolutionary models in a probabilistic framework.

Intuition: If we pick the tree topology and branch lengths that maximize the likelihood, we are effectively choosing the tree under which our data have the highest probability of having arisen. Since we know our data exist (i.e., they did arise), this seems reasonable.

# Maximum likelihood phylogeny inference

## Why maximize the likelihood?

*Statistical properties:* Maximum likelihood parameter estimates tend to have good statistical properties. For instance, MLEs are typically consistent, minimum variance, and asymptotically normal.

*Statistical consistency:* The estimate of  $\theta$  approaches its true value as  $n \rightarrow \infty$ . This should not be confused with unbiased; sometimes statistically consistent estimators are biased.

*Minimum variance (efficiency):* Lower variance than other estimators. This means, that for a given amount of data we will tend have a closer estimate of  $\theta$  to the true value by using ML.

*Asymptotic normality:* Error approaches normality as more data is obtained (i.e., as  $n \rightarrow \infty$ ).

The good statistical properties of ML have been shown to have been inherited by phylogeny inference.

# The pruning algorithm

Felsenstein (1981) introduced the pruning algorithm which made the computation of the likelihood feasible. Let nodes  $j$  and  $k$  have a direct ancestor  $i$ . We can estimate the conditional likelihood

$$L_i(x_i) = \left( \sum_{x_j} p_{x_i, x_j}(t_j) L_j(x_j) \right) \times \left( \sum_{x_k} p_{x_i, x_k}(t_k) L_k(x_k) \right) \quad (1)$$

The likelihood of the tree is evaluated by traversing the tree in postorder fashion from the tips towards the root. For unrooted trees, a root can be chosen arbitrarily as our models are time-reversible. We get the likelihood of the tree if we multiply the conditional likelihood of the root node  $r$  with the base composition  $\pi$ , as

$$L = \sum_{x \in A, C, G, T} \pi_x L_0(x), \quad (2)$$



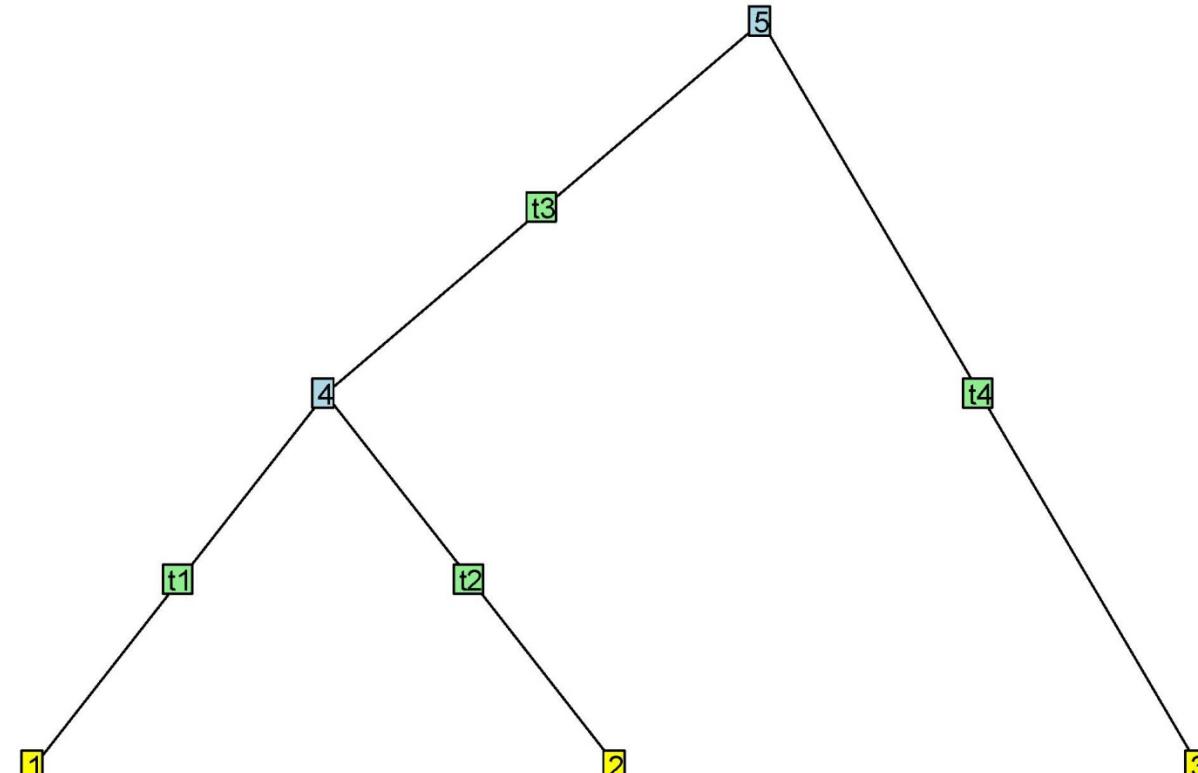
```
exercise5.R x
40 pp<-get("las
41 for(i in 1:r
42   lines(pp$xx|
43 }
44 for(i in 1:le
45   text(pp$xx[i
46     pos=4)
47 }
48 slantyTree<-
49 plotTree(phy
50 pp<-get("la
51 for(i in 1:r
52   lines(pp$>
53     lwd=3)
54 }
55 for(i in 1:l
56   text(pp$xx|
57     pos=4)
58 }
59 data(salamande
60 slantyTree(sal
61 }
62 < (Top Level) >
```

Console Terminal × Bac

```
R 4.2.2 · ~/r
+ pp<-get("la
+ for(i in 1:r
+   line
+
+   }
+ for(i in 1:l
+   text
+
+   }
+
+ }
> data(salamanders)
> slantyTree(salamar
> |
```

# The pruning algorithm

## A simple example (it can't get much smaller)



- richmondi
- shenandoah
- hoffmani
- nettingi
- cinereus
- hubrichti
- serratus
- welleri
- dorsalis
- websteri
- wehrlei
- punctatus
- glutinosus
- jordani
- yonahlossee
- caddoensis
- ouachitae
- fourchensis
- stormi
- elongatus
- dunni
- vehiculum
- idahoensis
- vandykei
- larselli
- neomexicanus

# The pruning algorithm

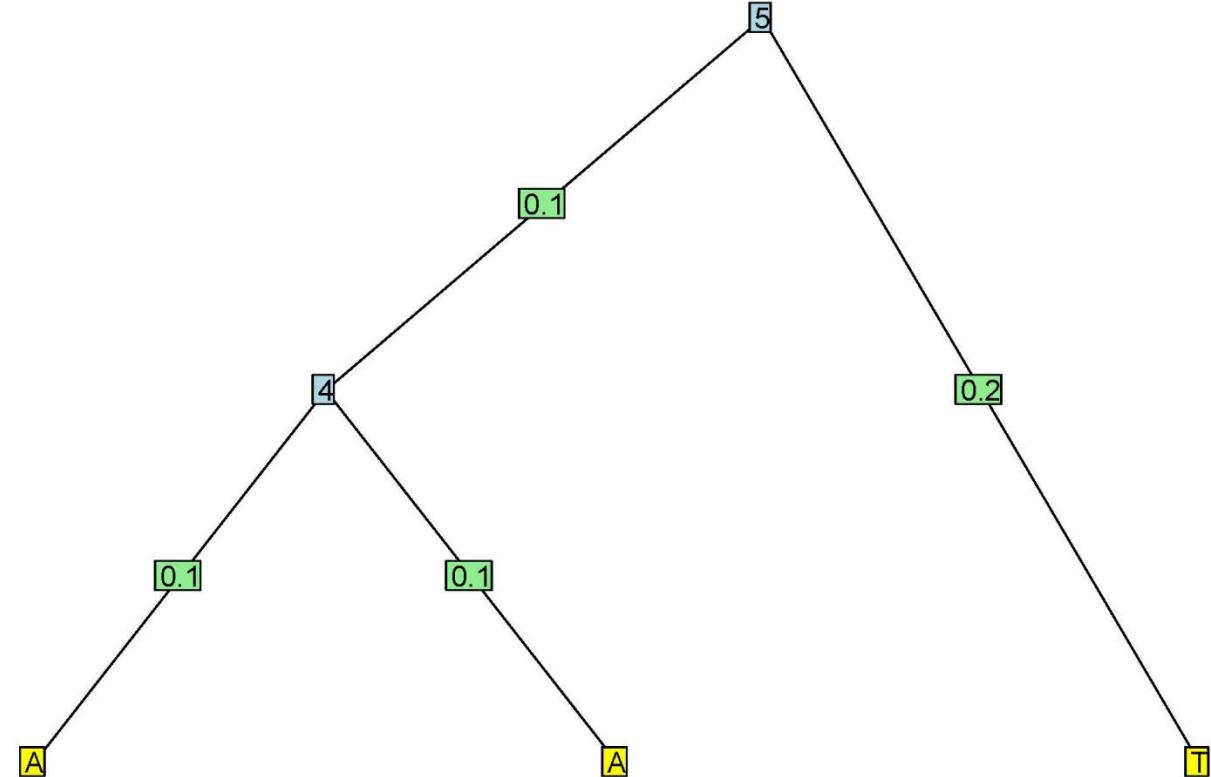
If we use equation (1) to expand equation(2) for our tree we get:

$$L = \sum_{x \in A, C, G, T} \left( \pi_x P(T|x, t_3) \left( \sum_{y \in A, C, G, T} L_4(y) P(y|x, t_4) \right) \right) = \\ \sum_{x \in A, C, G, T} \left( \pi_x P(T|x, t_3) \left( \sum_{y \in A, C, G, T} P(A|x, t_1) P(A|x, t_2) P(y|x, t_4) \right) \right)$$

Don't run away!!!

```
Console Terminal ✘ Basic  
R 4.2.2 · ~/Documents  
+ pp<-get("las  
+ for(i in 1:r  
+     line  
+  
+     }  
+     for(i in 1:l  
+         text  
+     }  
+ }  
>  
> data(salamanders)  
> slantyTree(salamanders)  
> |
```

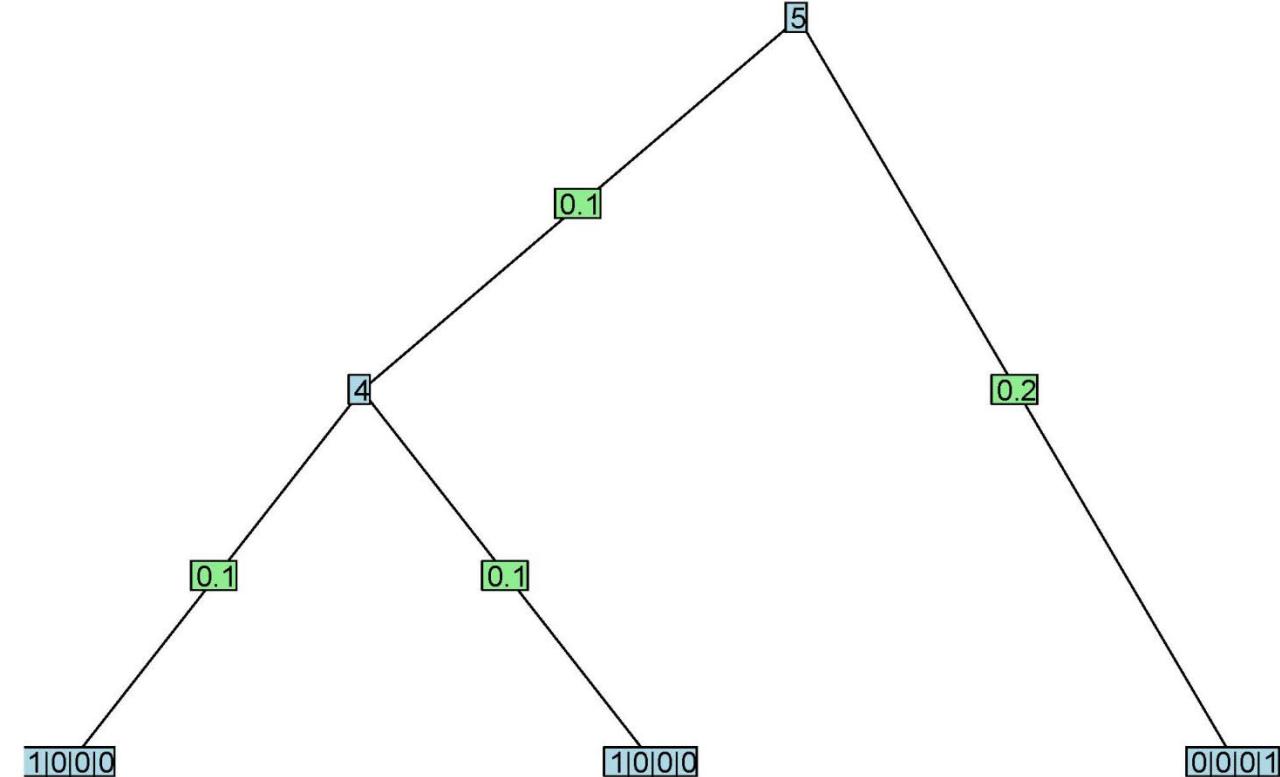
## The pruning algorithm



- richmondi
- shenandoah
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- nettingi
- cinereus
- hubrichti
- serratus
- welleri
- dorsalis
- websteri
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- punctatus
- glutinosus
- jordani
- yonahlossee
- caddoensis
- ouachitae
- fourchensis
- stormi
- elongatus
- dunni
- vehiculum
- idahoensis
- vandykei
- larselli
- neomexicanus

```
Console Terminal ✘ Basic  
R 4.2.2 · ~/○  
+ pp<-get("las  
+ for(i in 1:r  
+     line  
+  
+     }  
+     for(i in 1:l  
+         text  
+     }  
+     }  
>  
> data(salamanders)  
> slantyTree(salamander  
> |
```

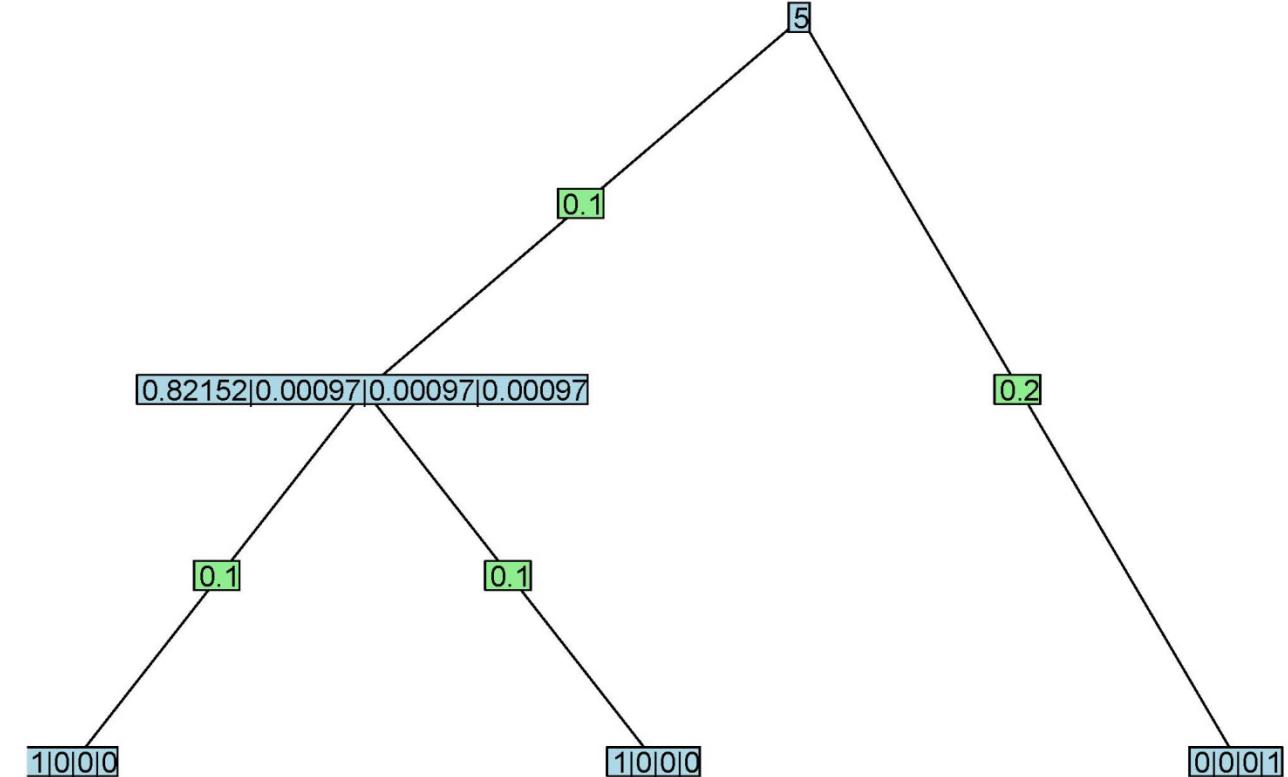
## The pruning algorithm



- richmondi
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- larselli
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```
Console Terminal ✘ Basic  
R 4.2.2 · ~/  
+ pp<-get("las  
+ for(i in 1:r  
+           line  
+  
+           }  
+           for(i in 1:l  
+             text  
+           }  
+           }  
+         }  
>  
> data(salamanders)  
> slantyTree(salamander  
> |
```

# The pruning algorithm



```
exercise5.R x
Source
40 pp<-get("las
41 for(i in 1:nrc
42 lines(pp$xx|
43 }
44 for(i in 1:ler
45 text(pp$xx[i
46 pos=4)
47 }
48
49 slantyTree<-f
50 plotTree(phy
51 pp<-get("la
52 for(i in 1:r
53 lines(pp$xx|
54 lwd=3)
55 }
56 for(i in 1:l
57 text(pp$xx|
58 pos=4)
59 }
60
61 data(salamande
62 slantyTree(sal
63 }
64
65 richmondi
66 shenandoah
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85 dunnii
86 vehiculum
87 idahoensis
88 vandykei
89 larselli
90 neomexicanus
```

# The pruning algorithm

And we can finally compute out likelihood: 0.01715091  
and log-likelihood: -4.065704

