Computational Biology

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Adrian Lison & Chaoran Chen

Computational Evolution
Department of Biosystems Science and Engineering

HS 2022

How to study evolution?

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- Wetlab
  - Very realistic;
  - Time-consuming and expensive;
  - Impossible (sometimes).
- Simulation
  - A virtual experiment in which we mimic a (biological) process on a computer to study its properties
  - Not necessarily realistic
  - Allows us to:
    - generate data with given assumptions;
    - test predictive properties of models.

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Today we will simulate evolution!

The tree of great apes

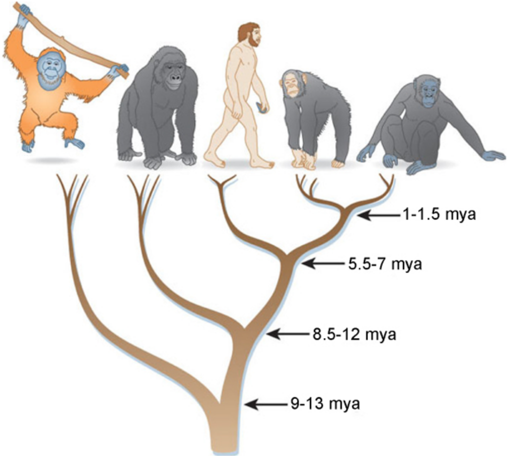
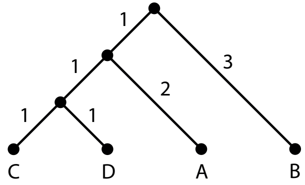


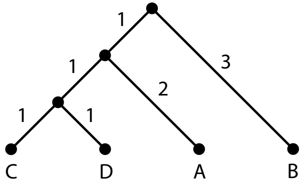
Figure adapted from [Paabo, 2003]

Storing trees: Newick format



- Format for tree representation
- To record a tree in Newick format:
  - Assign a label to each tip
  - Choose two tips that are a cherry (e.g. C and D)
  - Replace selected tips with a new tip of the form (tip1:branch1,tip2:branch2) (e.g. $(\mathrm{C}:1,\mathrm{D}:1)$)
    - Branch length to the new tip is the branch length to the cherry
  - Repeat until the full tree is rewritten
- What is the Newick format for the rooted tree above?

Storing trees: Newick format



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  - Repeat until the full tree is rewritten
- What is the Newick format for the rooted tree above? $(((\mathrm{C}:1, \mathrm{D}:1):1, \mathrm{A}:2):1, \mathrm{B}:3)$;

Storing trees: Newick format

- Draw the tree given by the newick string: $(Bovine : 7, (Gibbon : 4, (Orangutan : 3, (Gorilla : 2, (Chimp : 2, Human : 1) : 1) : 0.5) : 2) : 5, Mouse : 12);$

Storing trees: Newick format

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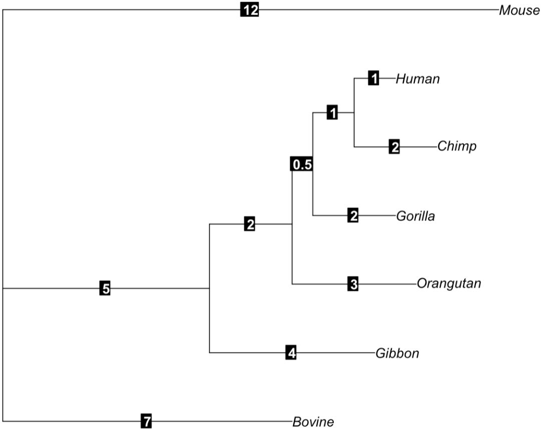

Evolution Simulation Algorithm

Steps:

1. **Initialization of the starting sequence**:
   - Sample a starting nucleotide for each position in the sequence
2. **Iterative simulation** of sequence evolution, along all branches of the tree
   - Compute the transition probability matrix $P(t_b)$.
   - Sample a new nucleotide for each position in the sequence.

Step 1: Initialization of the starting sequence

1a. Sample a starting nucleotide n

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From the vector of equilibrium frequencies of nucleotides

	T	C	A	G
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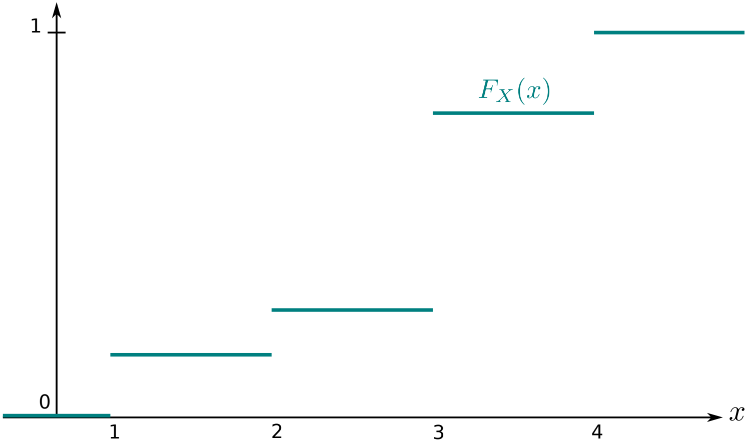
Knowing Π, how do we sample a nucleotide?

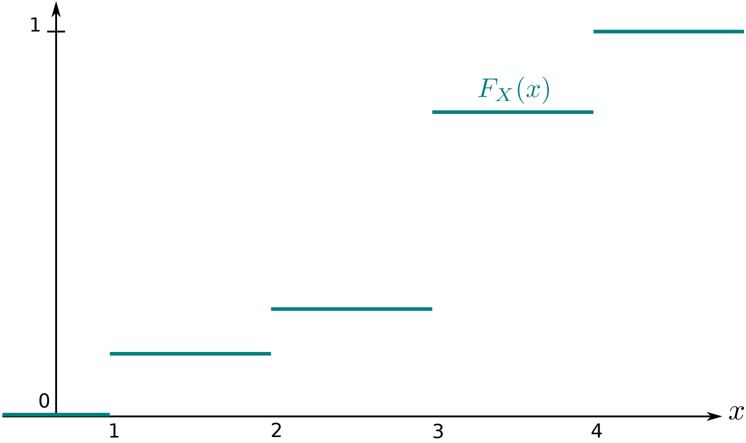
Inverse transform method

- Sample u from $U(0, 1)$;



Inverse transform method

- Sample u from $U(0,1)$;
- Transform u into a sample from the desired distribution using the **CDF** $==$ **C**umulative **D**istribution **F**unction $F_X(x) = P(X \leqslant x)$.



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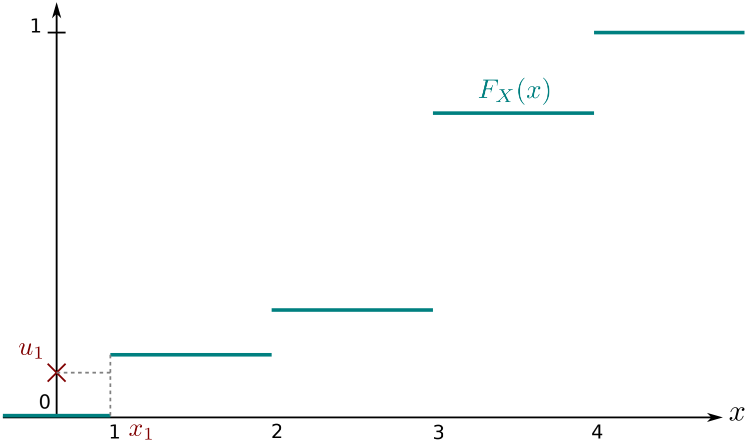

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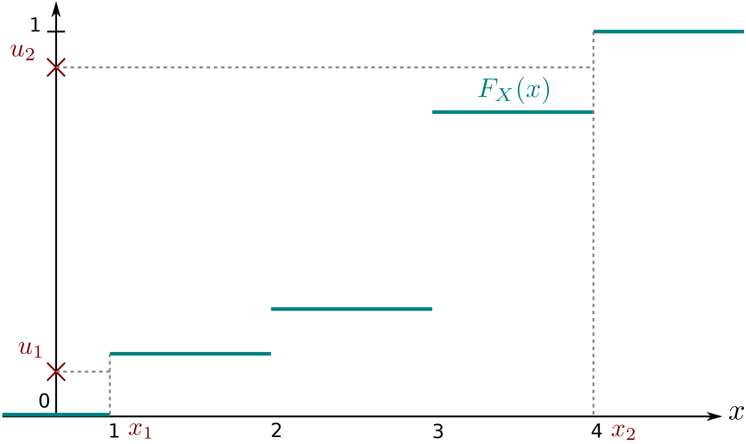

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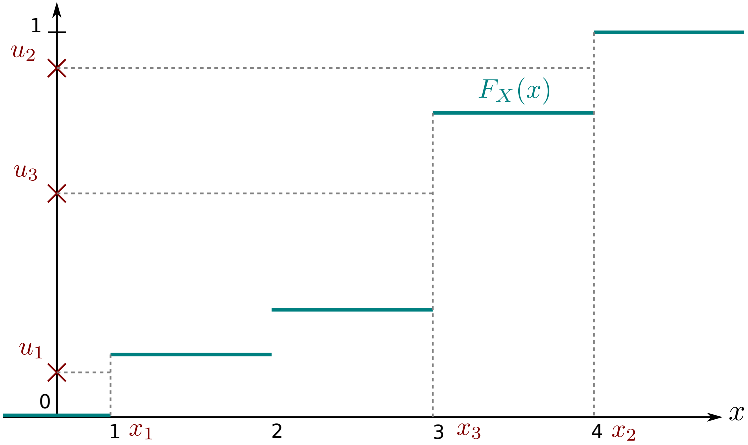
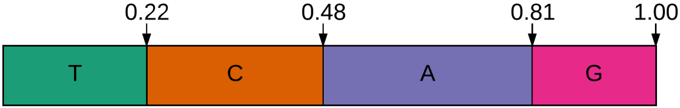


Sampling discrete random variables

	T	C	A	G
Π	0.22	0.26	0.33	0.19
CDF	0.22	0.48	0.81	1.00



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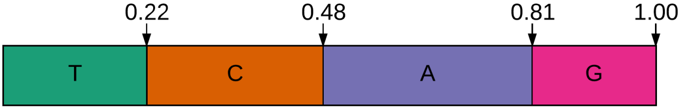

Sample u from $\mathcal{U}(0, 1)$.

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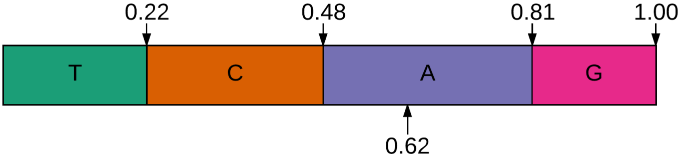

Sample u from $\mathcal{U}(0, 1)$.

E.g. $u = 0.62$.

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	T	C	A	G
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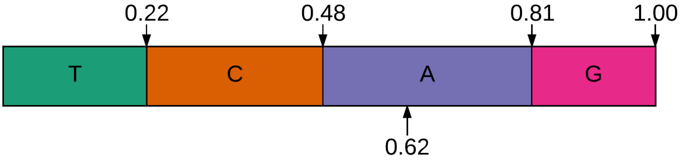

Sample u from $\mathcal{U}(0,1)$.

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Select nucleotide **A**.

Sampling discrete random variables

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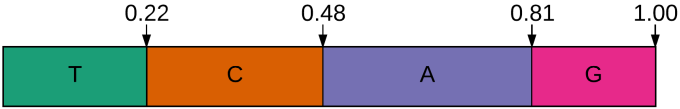
CDF	0.22	0.48	0.81	1.00



Sample u from $U(0, 1)$.

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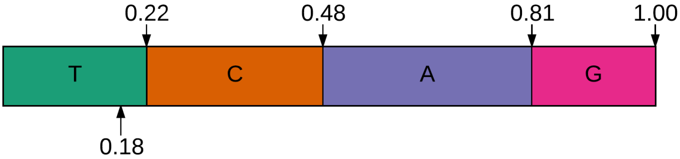

Sample u from $U(0, 1)$.

E.g. $u = 0.18$.

Sampling discrete random variables

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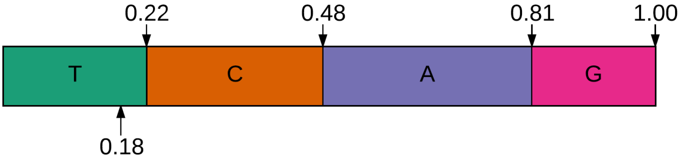
Π	0.22	0.26	0.33	0.19
CDF	0.22	0.48	0.81	1.00



Sample u from $\mathcal{U}(0, 1)$.

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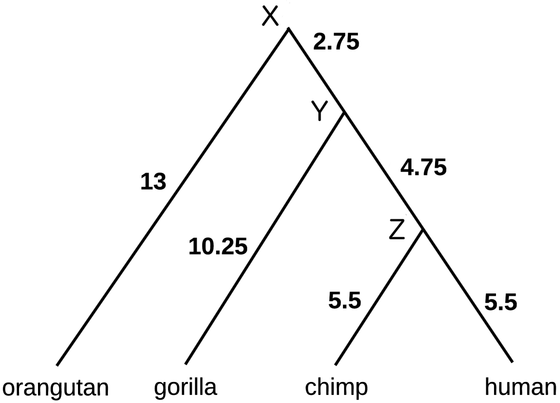
Select nucleotide **T**.

Step 1: Initializing the starting sequence

1b. Place n on the root node;



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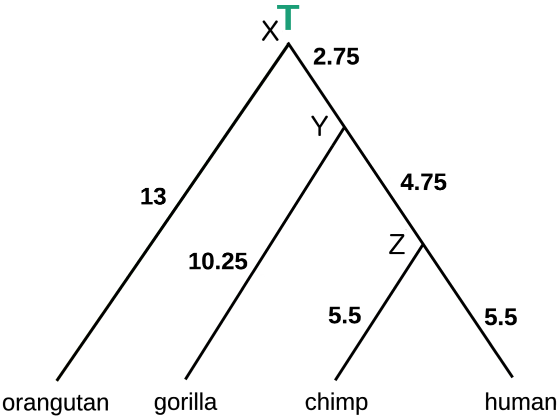
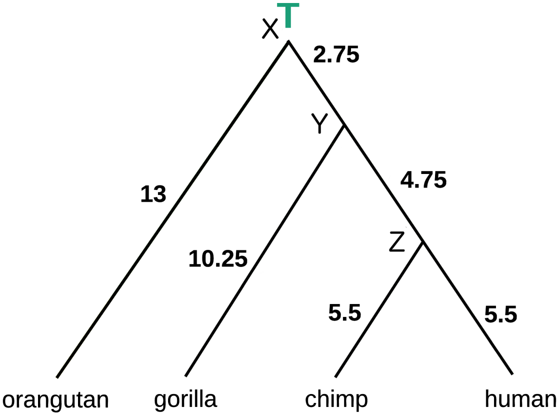


Step 2a: Choose the next branch for simulation

```
Get a branch $b$ with a nucleotide at the start;
$t_b$ = length($b$);
$n$ = nucleotide at start of branch $b$;
```



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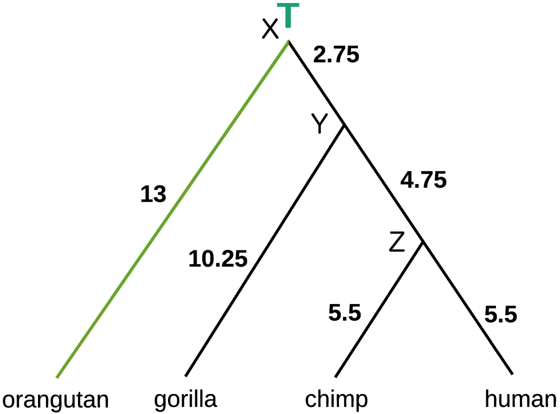

Step 2b-d: Sample the new nucleotide

$P(t_b) = e^{Qt_b}$;

Sample new nucleotide n_{new} from row n in $P(t_b)$;

Place n_{new} at the end of branch b;

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To sample new nucleotide n_{new} we will need the substitution rate matrix Q, and transition probability matrix P.

Substitution rate matrix – TN93

$\Pi = (\pi_T, \pi_C, \pi_A, \pi_G)$ - equilibrium frequencies.

α_1, α_2 - transition rates.

β - transversion rate.

$$Q_{TN93} = \begin{array}{c} \\ T \\ C \\ A \\ G \end{array} \begin{array}{c} \begin{array}{cccc} T & C & A & G \end{array} \\ \begin{pmatrix} \cdot & \alpha_1\pi_C & \beta\pi_A & \beta\pi_G \\ \alpha_1\pi_T & \cdot & \beta\pi_A & \beta\pi_G \\ \beta\pi_T & \beta\pi_C & \cdot & \alpha_2\pi_G \\ \beta\pi_T & \beta\pi_C & \alpha_2\pi_A & \cdot \end{pmatrix} \end{array}$$

The diagonals are set such that each row sums up to zero, e.g. $q_{TT} = -(\alpha_1\pi_C + \beta\pi_A + \beta\pi_G)$.

Substitution rate matrix – TN93

$$\Pi = (0.22, 0.26, 0.33, 0.19)$$
$$\alpha_1 = 44.229,\ \alpha_2 = 21.781$$
$$\beta = 1$$

$$Q_{TN93} = \begin{array}{c} \\ T \\ C \\ A \\ G \end{array} \begin{array}{c} \begin{array}{cccc} \mathrm{T} & \mathrm{C} & A & \mathrm{G} \end{array} \\ \begin{pmatrix} -0.01957 & 0.01873 & 0.00054 & 0.00031 \\ 0.01584 & -0.01669 & 0.00054 & 0.00031 \\ 0.00036 & 0.00042 & -0.00752 & 0.00674 \\ 0.00036 & 0.00042 & 0.01170 & -0.01249 \end{pmatrix} \end{array}$$

Note: the matrix is scaled to 0.0135 substitutions per mya so that we get reasonable sequences.

Transition probability matrix – TN93

$\Pi = (\pi_T, \pi_C, \pi_A, \pi_G)$ - equilibrium frequencies.

α_1, α_2 - transition rates.

β - transversion rate.

t_b - branch length.

$$\mathrm{P}(t_b) = e^{t_b \mathrm{Q}_{TN93}(\alpha_1, \alpha_2, \beta, \Pi)}$$

Substitution rate matrix – TN93

$$\Pi = (0.22, 0.26, 0.33, 0.19)$$

$$\alpha_1 = 44.229,\ \alpha_2 = 21.781$$

$$\beta = 1$$

$$t_b = 13\,\text{mya}$$

$$P_{TN93}(13\,\text{mya}) = \begin{array}{c} \\ T \\ C \\ A \\ G \end{array} \begin{array}{c} \begin{array}{cccc} T & C & A & G \end{array} \\ \begin{pmatrix} 0.795 & 0.194 & 0.007 & 0.004 \\ 0.164 & 0.824 & 0.007 & 0.004 \\ 0.005 & 0.005 & 0.913 & 0.077 \\ 0.005 & 0.005 & 0.134 & 0.856 \end{pmatrix} \end{array}$$

Sampling substitution times

We start with nucleotide **T**, so we are interested in row T:

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Sample new nucleotide n_{new} with the weights $[p_{\mathsf{T}\to\mathsf{T}}, p_{\mathsf{T}\to\mathsf{C}}, p_{\mathsf{T}\to\mathsf{A}}, p_{\mathsf{T}\to\mathsf{G}}]$

Getting the substitution

Sample u from $\mathcal{U}(0, 1)$.
E.g. $u = 0.81$.

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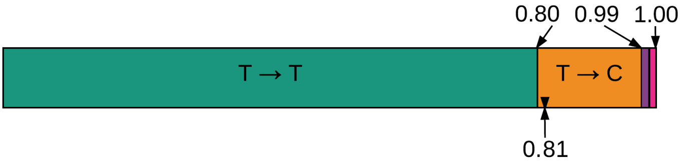
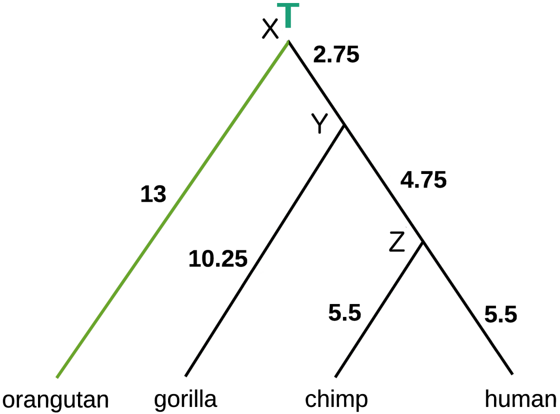


Selected substitution is T → C.

Step 2b-d: Sample the new nucleotide

$P(t_b) = e^{Qt_b}$;
Sample new nucleotide n_{new} from row n in $P(t_b)$;
Place n_{new} at the end of branch b;



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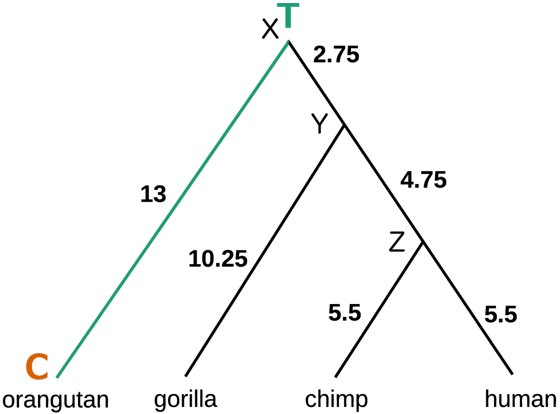
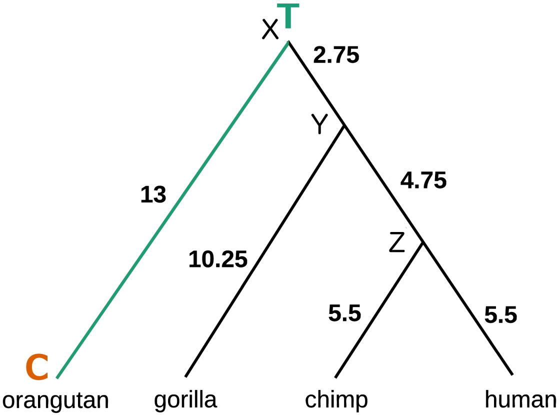


Repeat step 2

```
while not all branches are used do
    Get a branch $b$ with a nucleotide at the start;
    $t_b$ = length($b$);
    $n$ = nucleotide at start of branch $b$;
    $P(t_b) = e^{Qt_b}$;
    Sample new nucleotide $n_{new}$ from row $n$ in $P(t_b)$;
    Place $n_{new}$ at the start of the daughter branches of $b$;
end
```

Evolution



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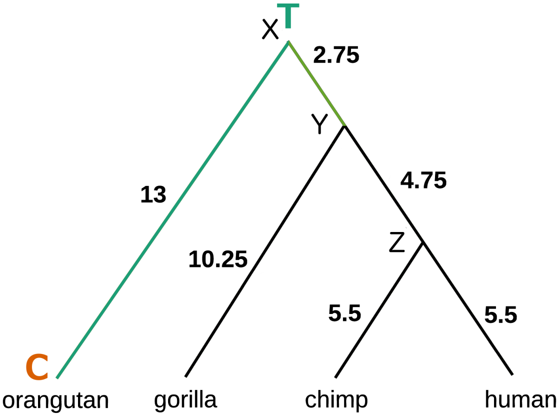

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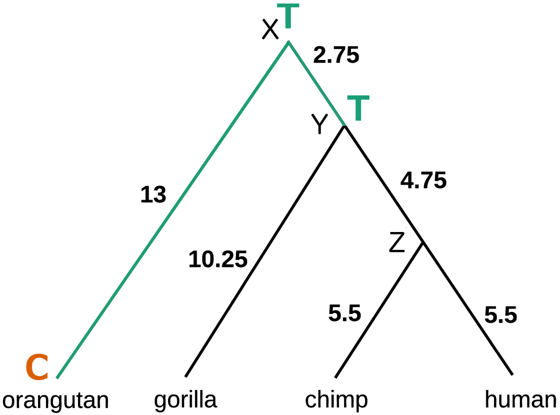

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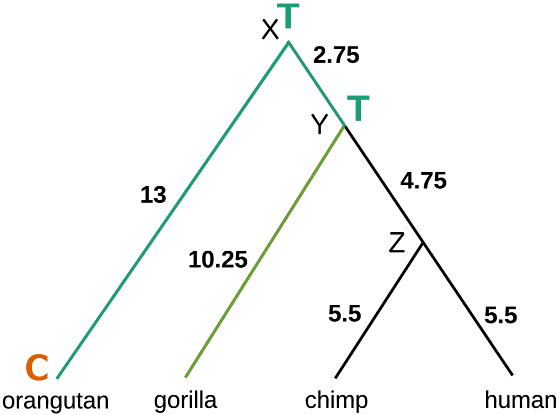

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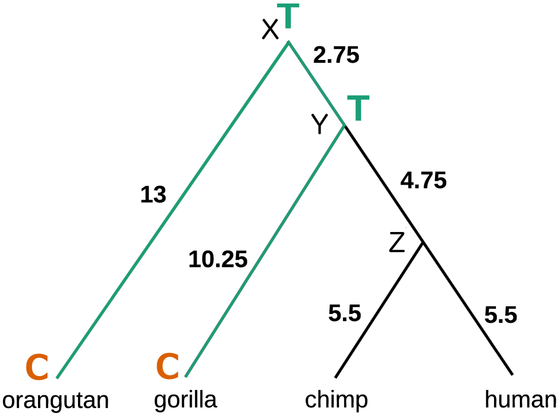

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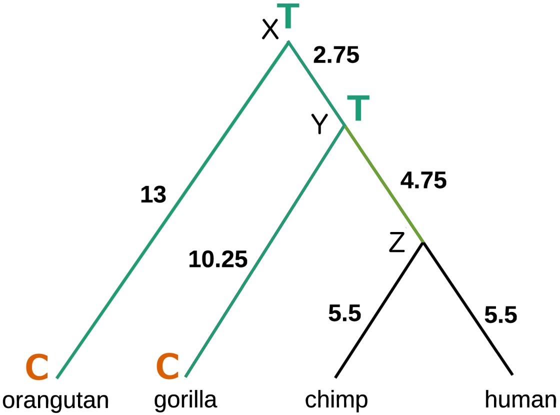

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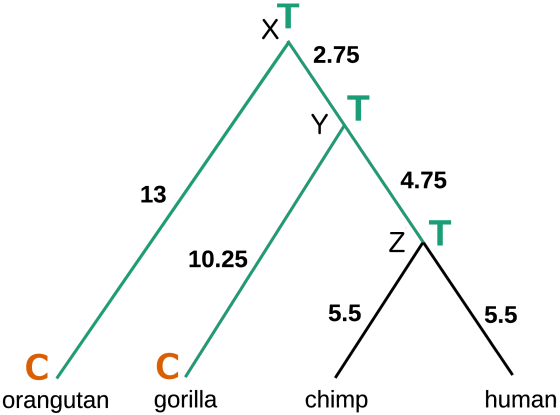
X
T
2.75
Y
T
13
4.75
Z
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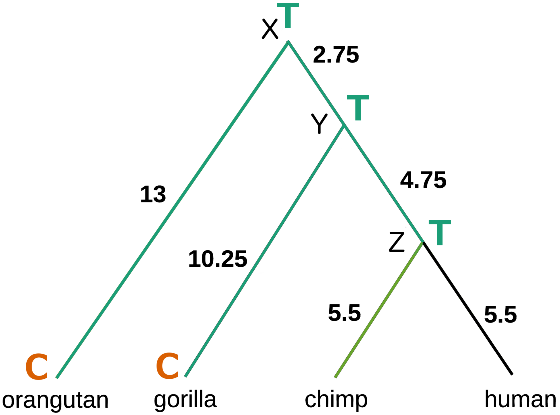
C
C
orangutan
gorilla
chimp
human

Evolution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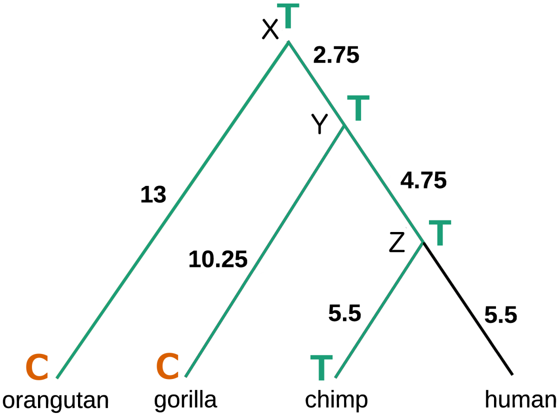
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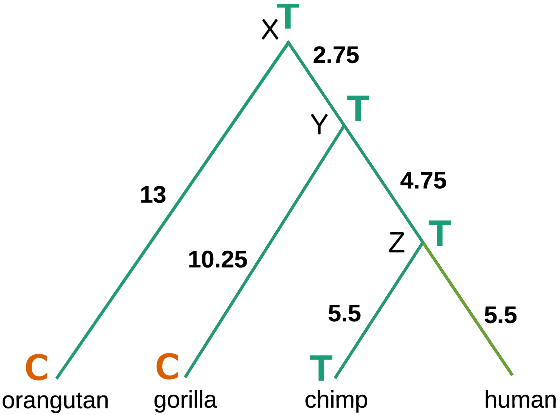
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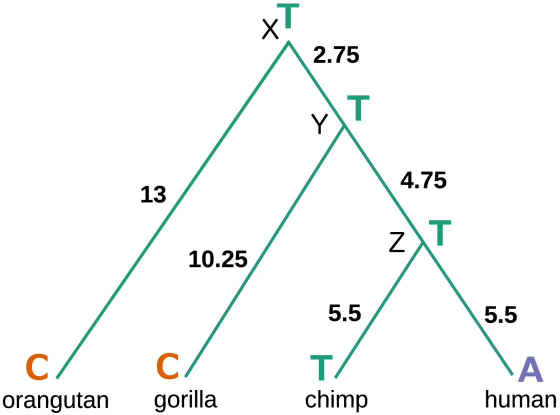
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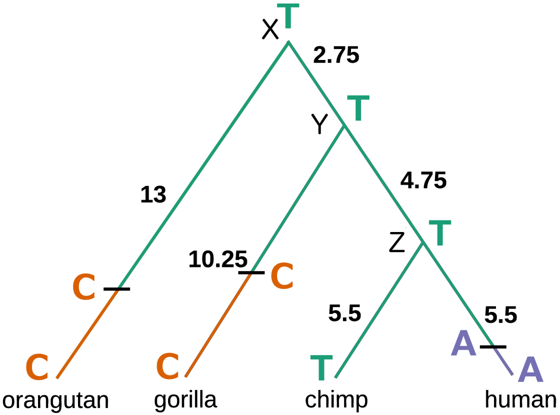
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Exercise for today

1. Use a random number generator to “roll dice”
2. Evolve a character along the tree;

All of the characters together will produce an alignment.

Algorithm

```
$N$ = number of sites in the alignment;
$Q$ = substitution rate matrix;
for $i = 1$ to $N$ do
    Sample a nucleotide $n$ from the initial distribution;
    Add $n$ to the sequence of the root node;
end
while not all branches are visited do
    Get a branch $b$ with a sequence at the start;
    $t_b$ = length($b$);
    $P(t_b) = e^{Qt_b}$;
    for $i = 1$ to $N$ do
        $n$ = nucleotide at position $i$ at the start of branch $b$;
        Sample new nucleotide $n_{new}$ from row $n$ in $P(t_b)$;
        Place $n_{new}$ at the end of sequences in the daughter
          branches of $b$;
    end
end
```

References I

- Paabo, S. (2003). The mosaic that is our genome. *Nature*, 421(6921):409–12.