Computational Biology

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Computational Evolution
Department of Biosystems Science and Engineering

HS 2019

The Simulation Game
Studying evolution
Simulating evolution
Initializing the starting sequence
Simulating the substitutions
Pen and paper exercise
Algorithm

How to study evolution?

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  - Allows us to:
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Today we will simulate evolution!

The tree of great apes

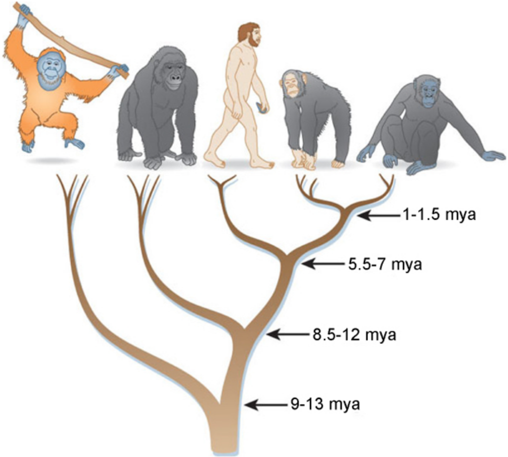
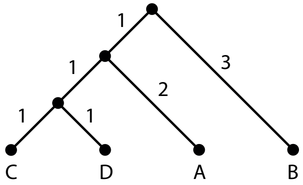


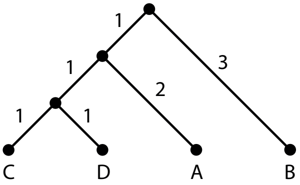
Figure adapted from [?]

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

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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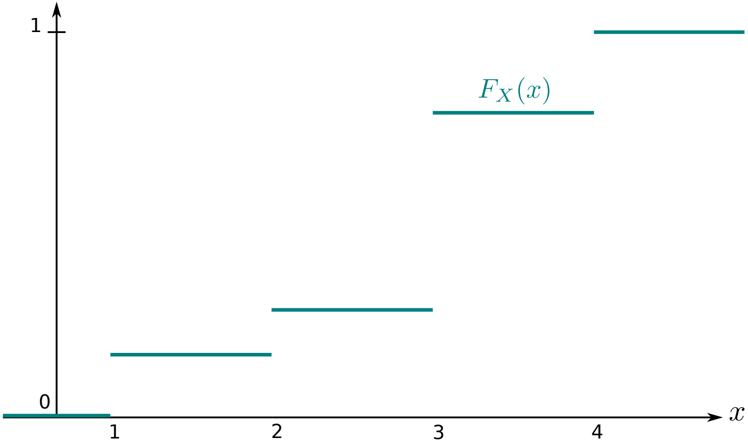
Knowing Π, how do we sample a nucleotide?

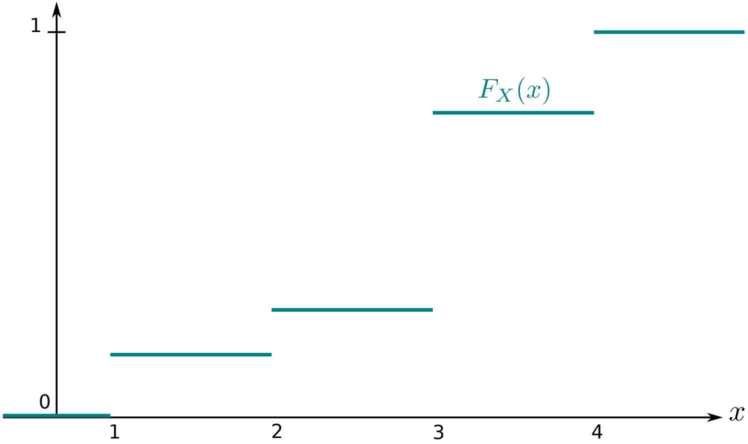
Inverse transform method

- 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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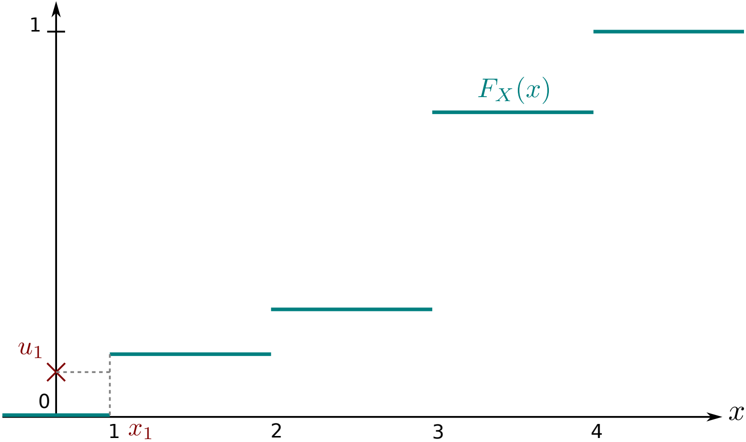

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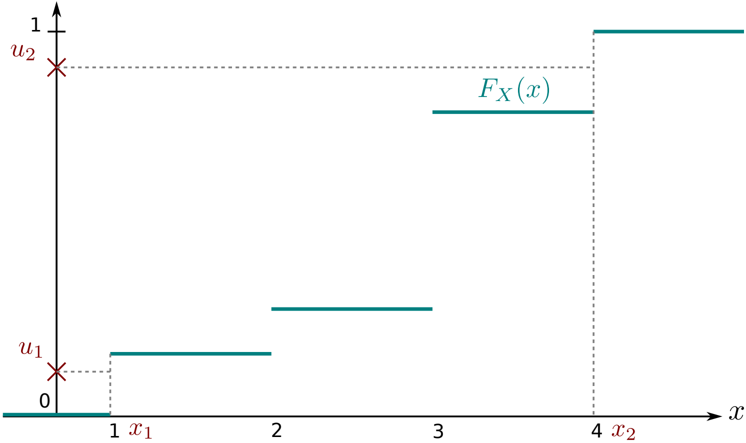

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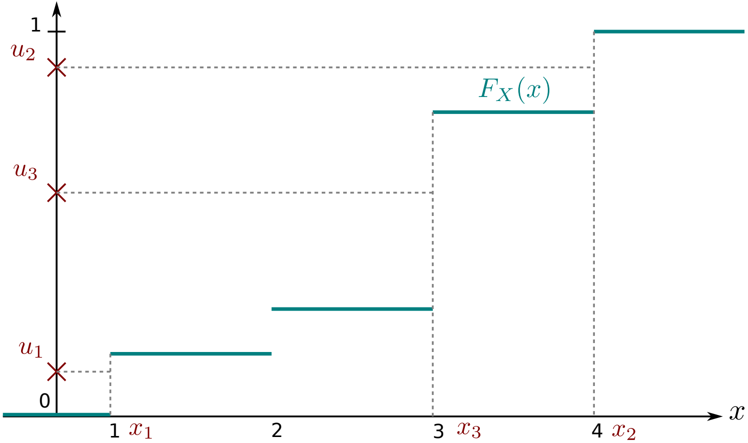
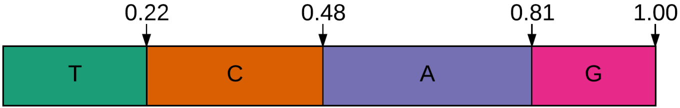


Sampling discrete random variables

	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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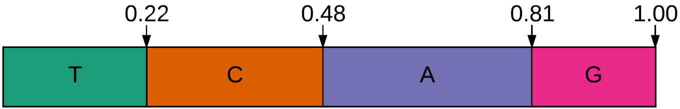

Sample u from $\mathcal{U}(0, 1)$.

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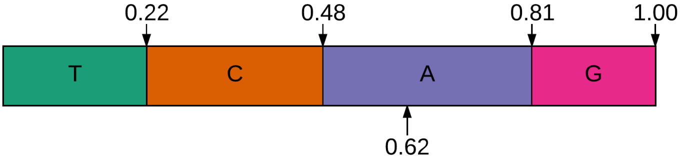
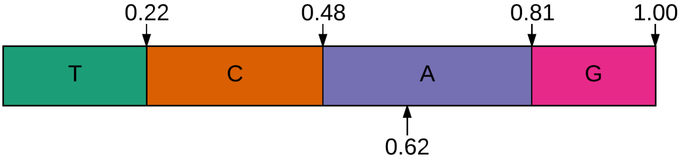


Sample u from $\mathcal{U}(0,1)$.

E.g. $u = 0.62$.

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



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

E.g. $u = 0.62$.

Select nucleotide **A**.

Sampling discrete random variables

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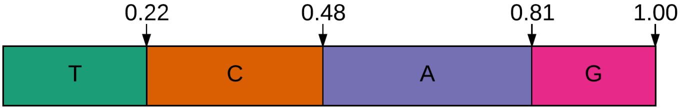

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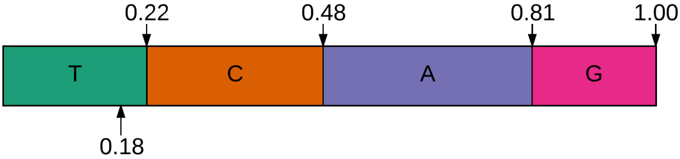

Sample u from $\mathcal{U}(0, 1)$.

E.g. $u = 0.18$.

Sampling discrete random variables

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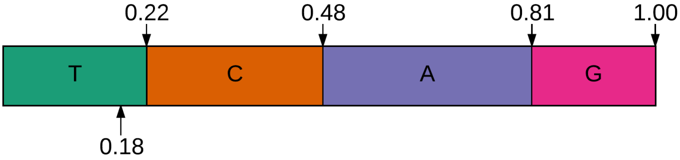
CDF	0.22	0.48	0.81	1.00



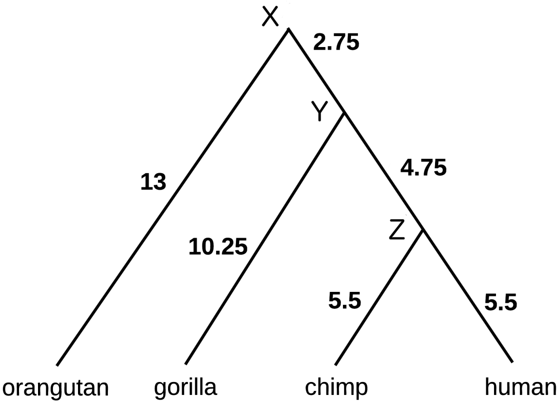
Sample u from $U(0,1)$.

E.g. $u = 0.18$.

Select nucleotide **T**.

Step 1: Initializing the starting sequence

1b. Place n on the root node;



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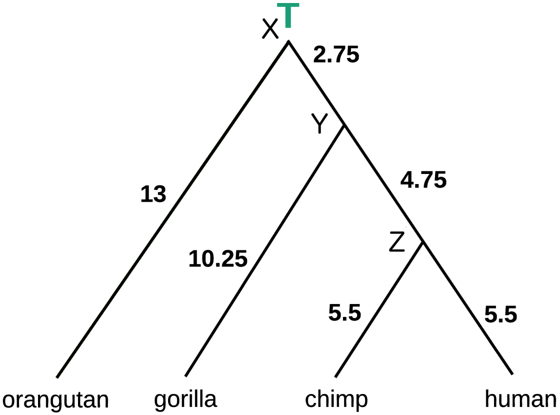
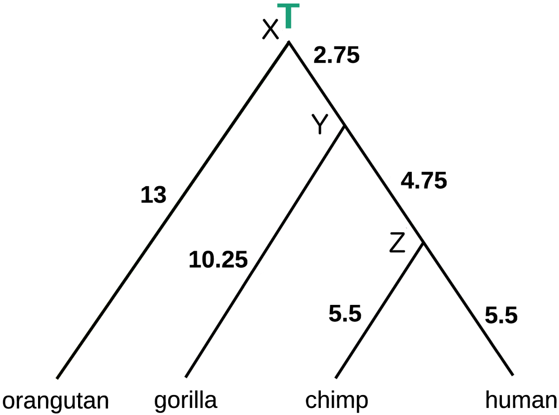


Step 2a: Choose the next branch for simulation

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



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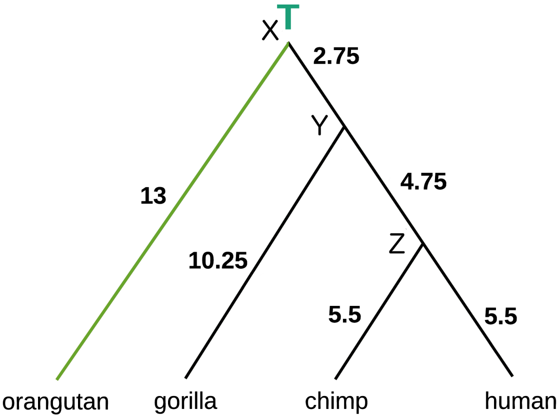

Step 2b-d: Sample the new nucleotide

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

β - transversion ratios.

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

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

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

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

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 ratios.

β - transversion ratios.

t_b - branch length

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

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 mya

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

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 $[p_{T \to T}, p_{T \to C}, p_{T \to A}, p_{T \to G}]$

Getting the substitution

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

E.g. $u = 0.81$.

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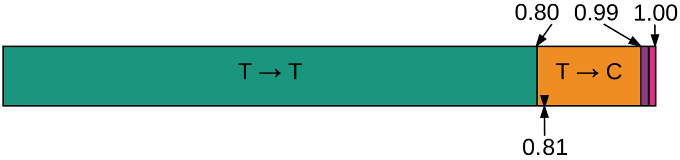
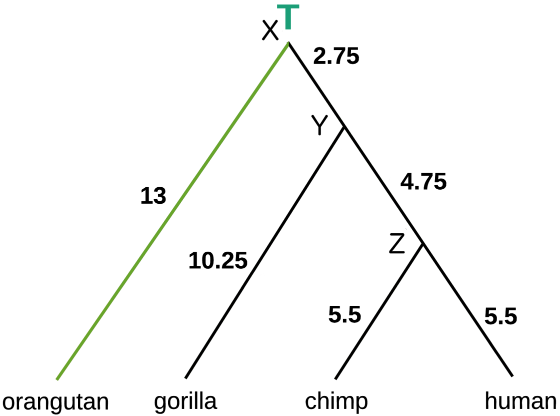


Selected substitution is T → C.

Step 2b-d: Sample the new nucleotide

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



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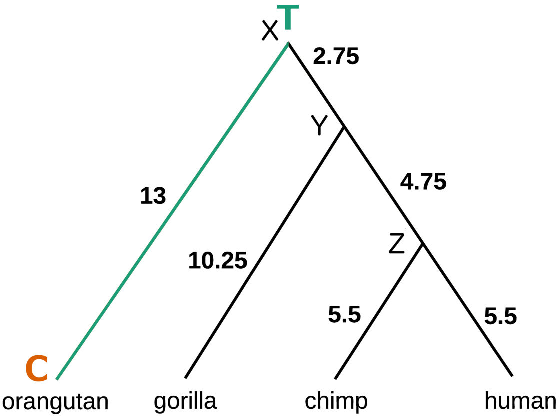
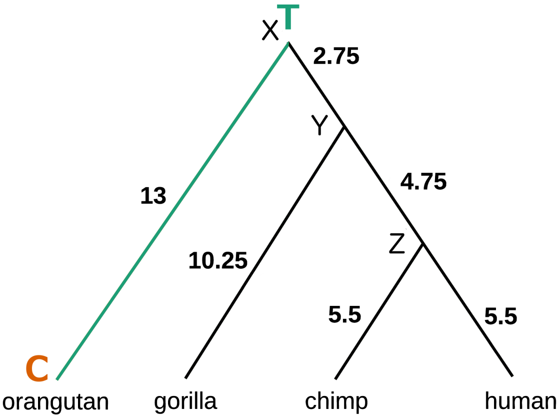


Repeat step 2

```
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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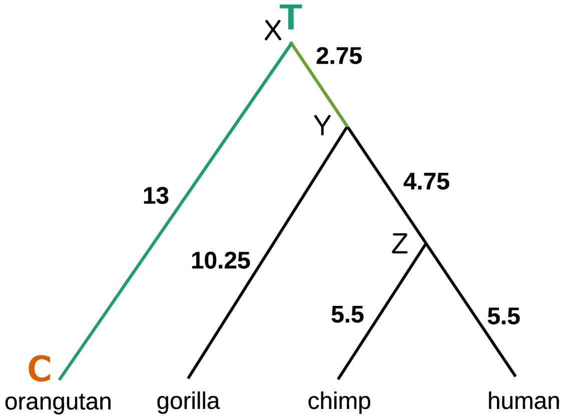

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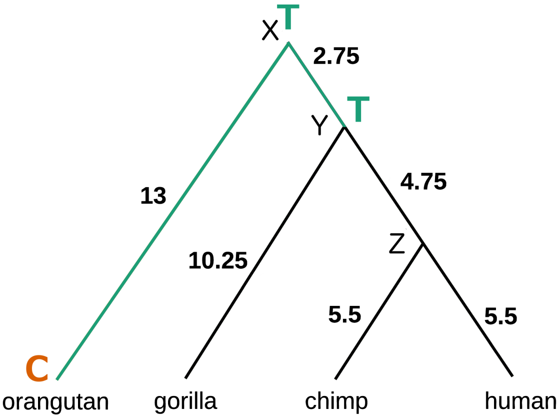

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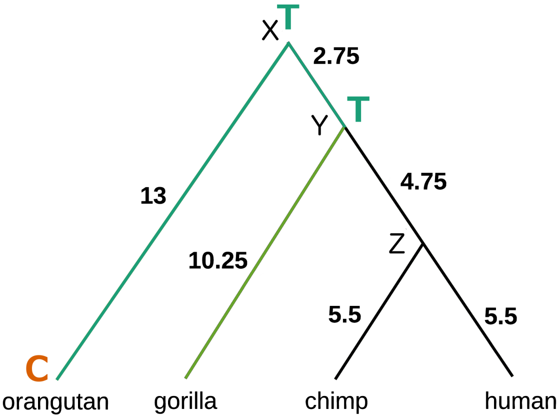

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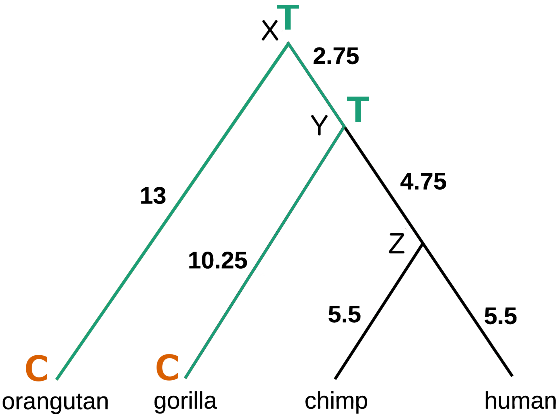

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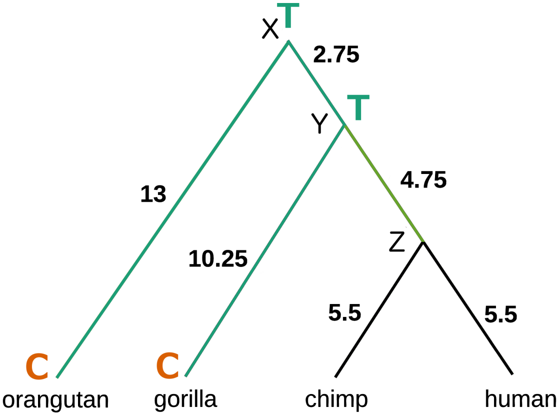

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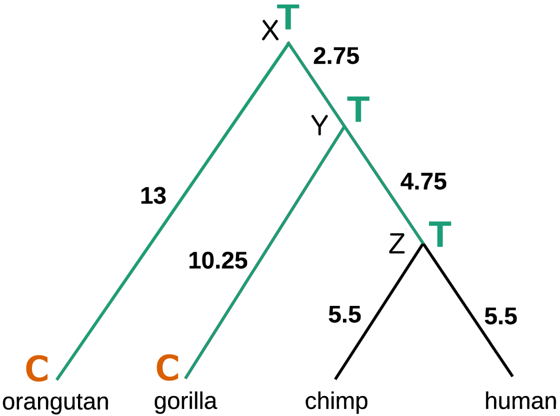
X
T
2.75
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C
C
orangutan
gorilla
chimp
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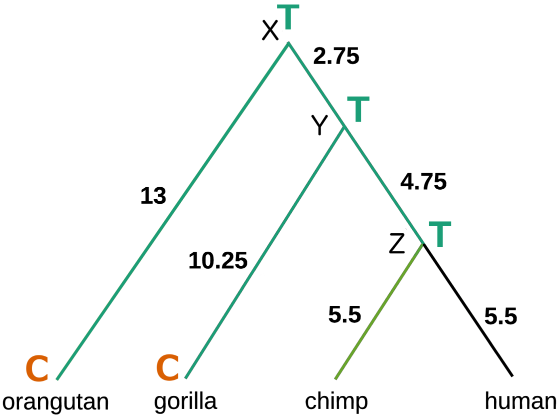
Evolution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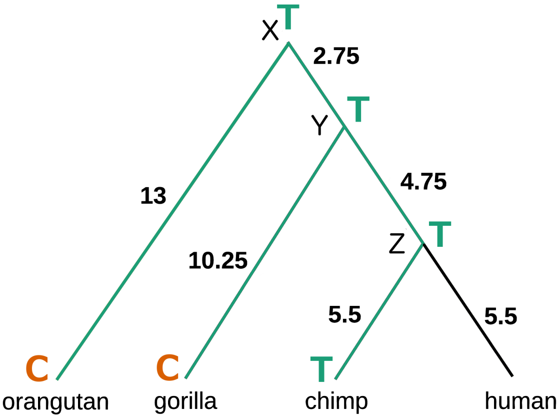
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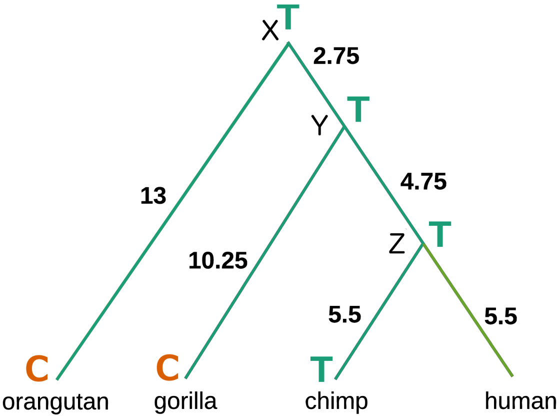
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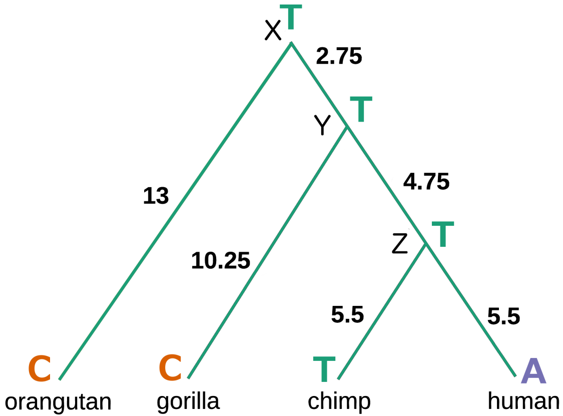
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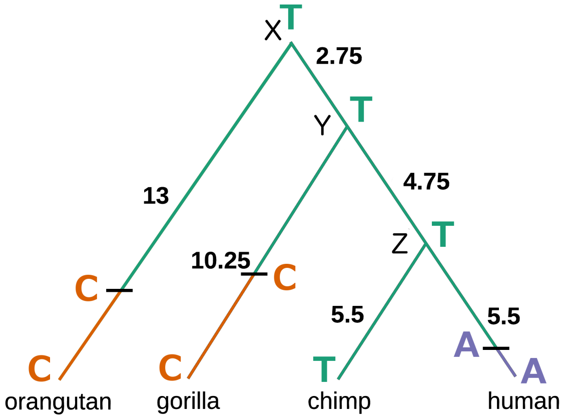
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Exercise for today

1. Split into pairs;
2. Get the materials;
3. Evolve a character along the tree;

All of the characters together will produce an alignment.

Using dice to generate random numbers

We will be using 10-sided dice for our random number generation.

Using dice to generate random numbers

We will be using 10-sided dice for our random number generation.
Samples from Unif(0,1) with 2 decimal point precision:

1. Take 2 dice of different colours;
2. Assign a fixed decimal position to each of the dice (and keep it for the whole simulation);
   - E.g. red is 1st position, blue is 2nd;
3. Roll the dice to get 2 numbers;
   - E.g. red = 5, blue = 8;
4. Combine the numbers to get a sample;
   - E.g. 0.58.

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;
    $t_b = \text{length}(b)$;
    $P(t_b) = e^{Qt_b}$;
    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
```