

GPU-CAPABLE SOFTWARE FOR STATISTICAL PHYLOGENETICS

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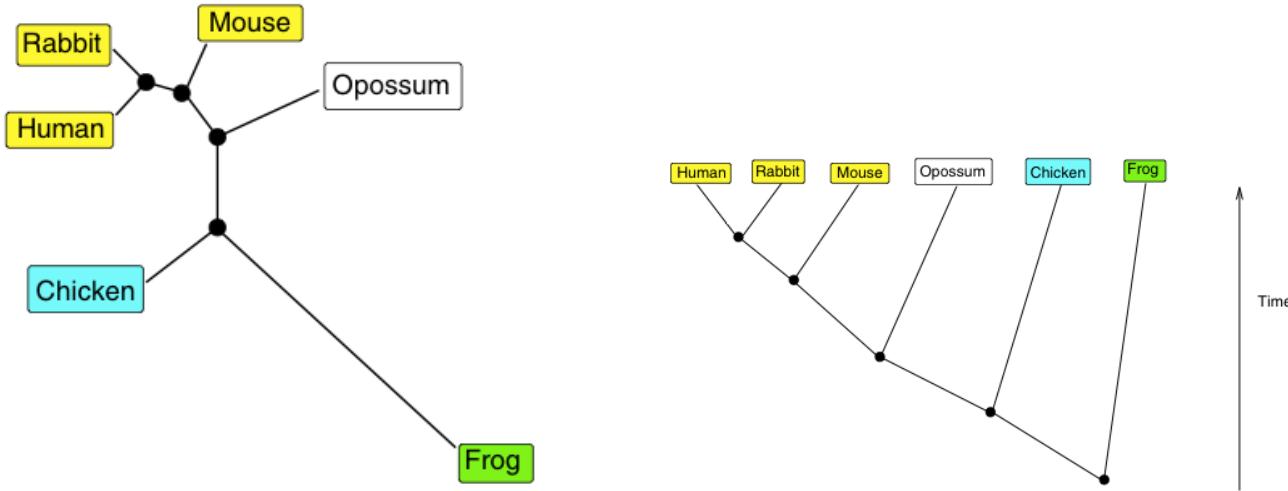
INTRODUCTION TO PHYLOGENETICS

Phylogenetics: The study of evolutionary relationships among different species or strains of organisms.

Given a set of species, the goal is to construct a model that describes:

1. Lineage and ancestry.
2. The relative degree of genetic similarity between and among the different organisms.

PHYLOGENETIC TREES

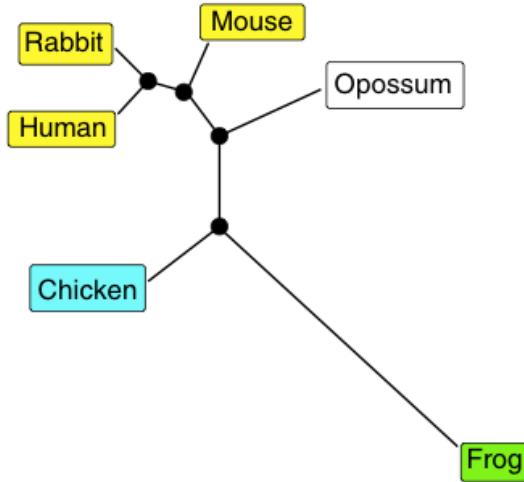


- The leaf nodes are the known, contemporary species that we care about
- The inner nodes are hidden (possibly unknown) ancestors
- An edge identifies a pair of nodes in which one member evolved directly from the other.

In general, a **phylogenetic tree** is an acyclic graph. The following properties have explicit phylogenetic meaning.

- **topology**: the branching structure: i.e., which nodes are connected to which. Topology depicts ancestry.
- **branch lengths**: how long each edge is. Branch lengths are proportional to genetic distance as measured in phylogenetic time, $\lambda \cdot t$, where λ is the genetic mutation rate and t is physical time.

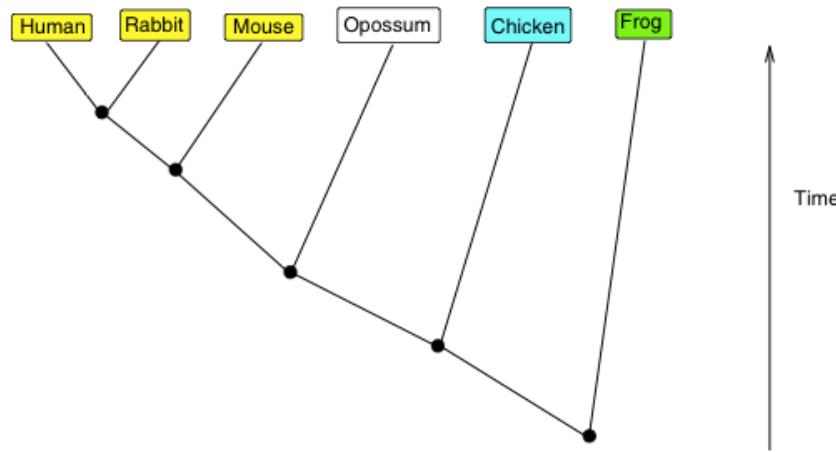
UNROOTED TREES



An **unrooted tree** is an UNDIRECTED acyclic graph that indicates no common ancestor.

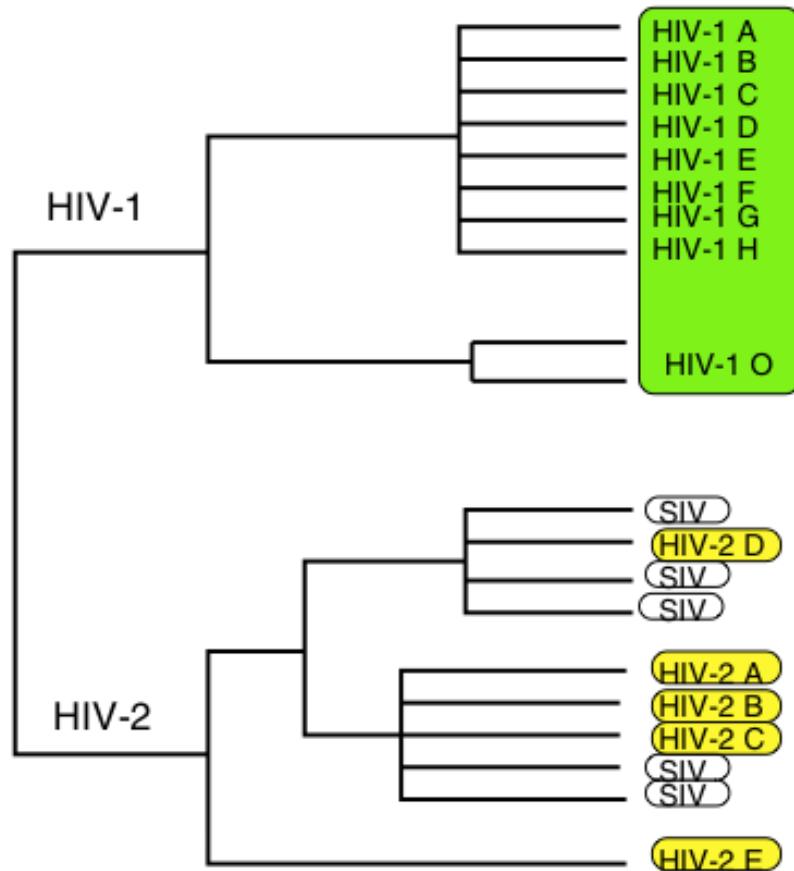
We add the additional assumption that the leaves evolved from the inner nodes, but otherwise, we don't know what evolved from what.

UNROOTED TREES

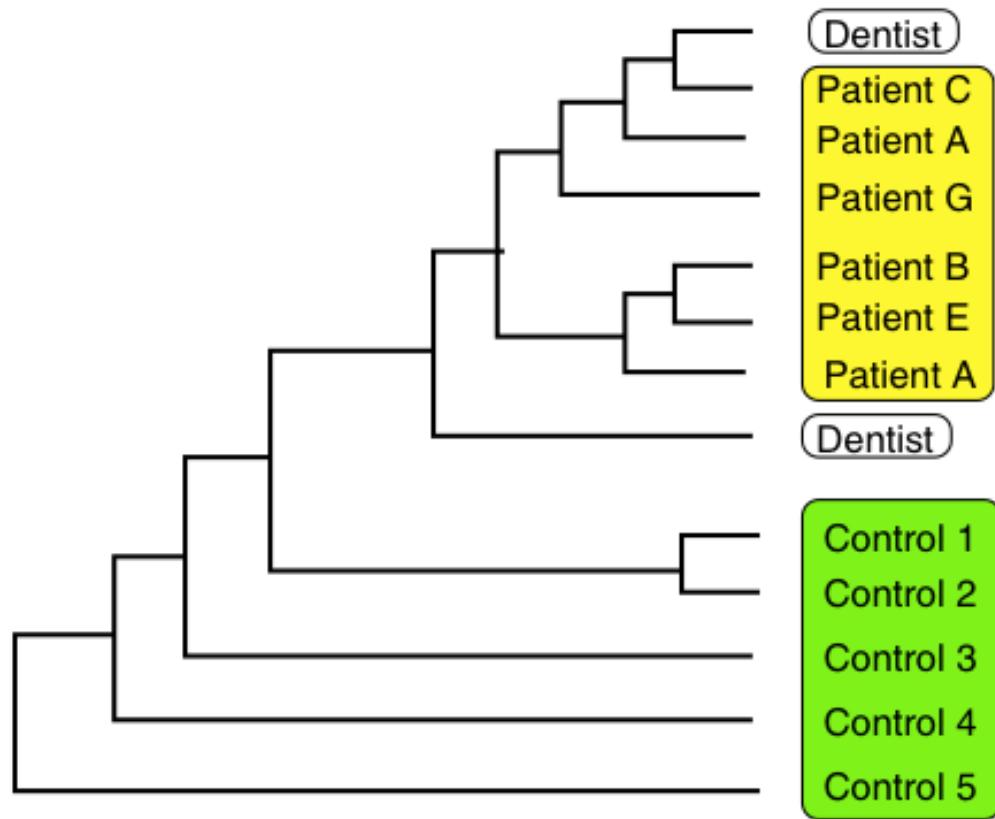


An **rooted tree** is a DIRECTED acyclic graph that indicates no common ancestor.

The time axis indicates the direction of the edges (the direction of evolution).

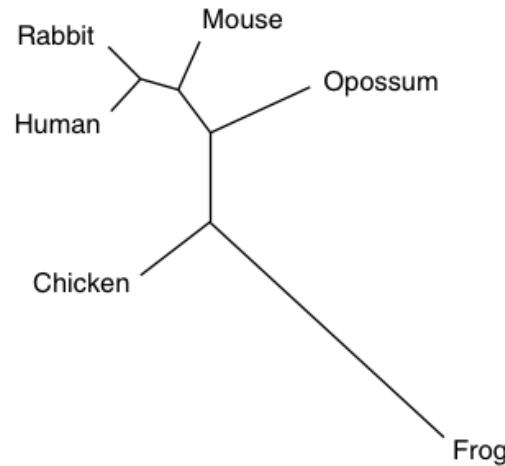


Some phylogenetic trees are displayed as cladograms like this one. The horizontal edge lengths convey phylogenetic distance, and the vertical lines are meaningless.



This one revealed that a Florida dentist infected several of his patients with HIV around 1990.

Frog	G	C	T	T	G	A	C	T	T	C	T	G	A	G	G	T	T
Chicken	G	C	G	T	A	A	C	T	T	C	A	C	A	T	G	A	T
Human	G	C	G	T	C	A	C	T	T	G	A	G	A	C	G	C	T
Rabbit	G	C	G	T	C	A	C	T	T	G	A	G	A	C	G	C	T
Mouse	G	C	G	T	C	A	C	T	T	G	A	C	A	G	G	C	T
Opossum	G	C	G	T	C	A	C	T	T	G	A	G	A	C	G	C	T

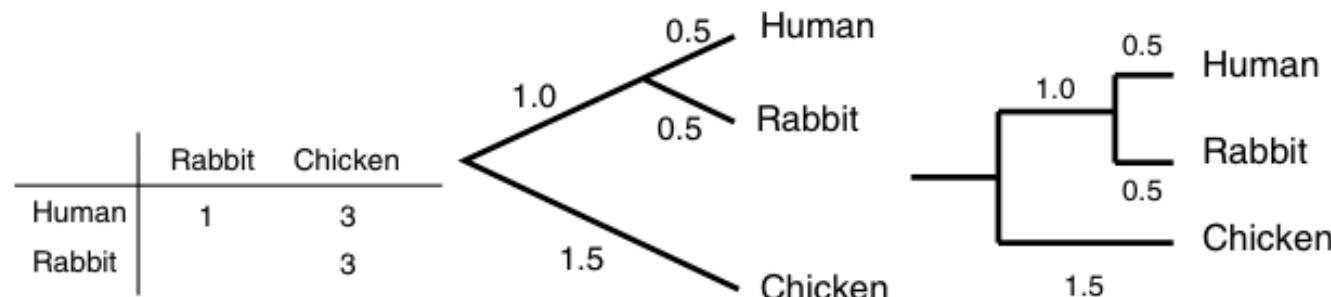


Topologies and branch lengths are inferred by sequencing DNA from each of the contemporary organisms and determining the degree of similarity from DNA sequence alignment.

Human ... T G T **A** T C G C T C ...
 Rabbit ... T G T **G** T C G C T C ...

Human ... **T** G T **A** T C G **C** T C ...
 Chicken ... **A** G T **C** T C G **T** T C ...

Rabbit ... **T** G T **G** T C G **C** T C ...
 Chicken ... **A** G T **C** T C G **T** T C ...



Use of genetic distances: one simple and naive way to put together a phylogenetic tree.

WAYS TO INFER PHYLOGENETIC TREES FROM GENOMIC DATA

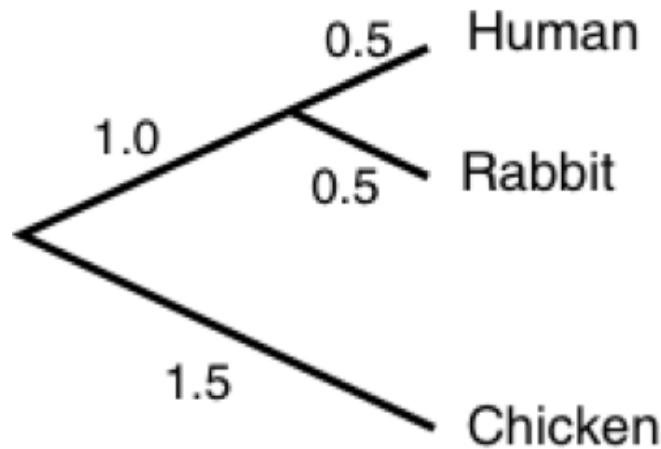
- Use of genetic distances
- UPGMA Clustering (Unweighted Pair Group Method using Arithmetic averages)
- Clustering via neighbor joining
- Parsimony
- **MAXIMUM LIKELIHOOD USING CONTINUOUS TIME MARKOV CHAINS TO MODEL GENETIC SEQUENCE MUTATION OVER TIME**

RECAP: WE CARE ABOUT SEQUENCE ALIGNMENT FOR CONSTRUCTING TREES

Human ... T G T A T C G C T C ...
Rabbit ... T G T **G** T C G C T C ...

Human ... T G T A T C G **C** T C ...
Chicken ... **A** G T C T C G T T C ...

Rabbit ... T G T **G** T C G **C** T C ...
Chicken ... **A** G T C T C G T T C ...



BY WHAT PROCESS DID THE RABBIT
AND THE CHICKEN EACH DESCEND
FROM THEIR MOST RECENT COMMON
ANCESTOR?

Rabbit ... **T** G T **G** T C G **C** T C ...
Chicken ... **A** G T **C** T C G **T** T C ...

Use a continuous time Markov process to model the genetic mutations from ancestor to rabbit and ancestor to chicken.

Sequence alignment data $\mathbf{D} =$

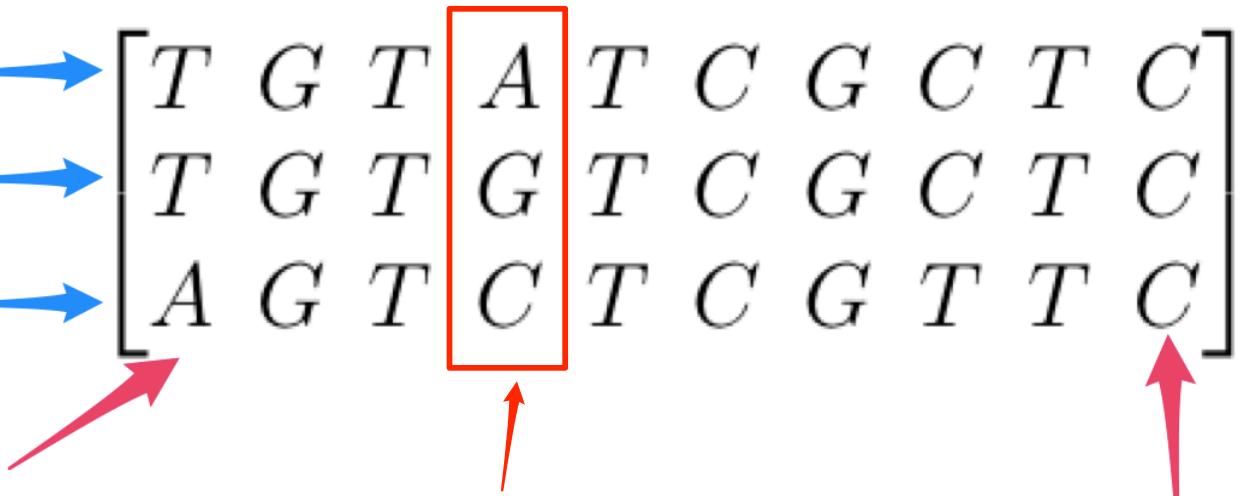
$$\begin{array}{l} \text{Human} \rightarrow [T \ G \ T \ A \ T \ C \ G \ C \ T \ C] \\ \text{Rabbit} \rightarrow [T \ G \ T \ G \ T \ C \ G \ C \ T \ C] \\ \text{Chicken} \rightarrow [A \ G \ T \ C \ T \ C \ G \ T \ T \ C] \end{array}$$

DNA Locus 1

$$= \begin{bmatrix} D_{1,1} & \cdots & D_{C,1} \\ \vdots & & \vdots \\ D_{1,n} & \cdots & D_{C,n} \end{bmatrix}$$

DNA Locus n

$$= [D_1 \ \cdots \ D_C]$$

Human	\rightarrow	T G T A T C G C T C
Rabbit	\rightarrow	T G T G T C G C T C
Chicken	\rightarrow	A G T C T C G T T C
DNA Locus 1		

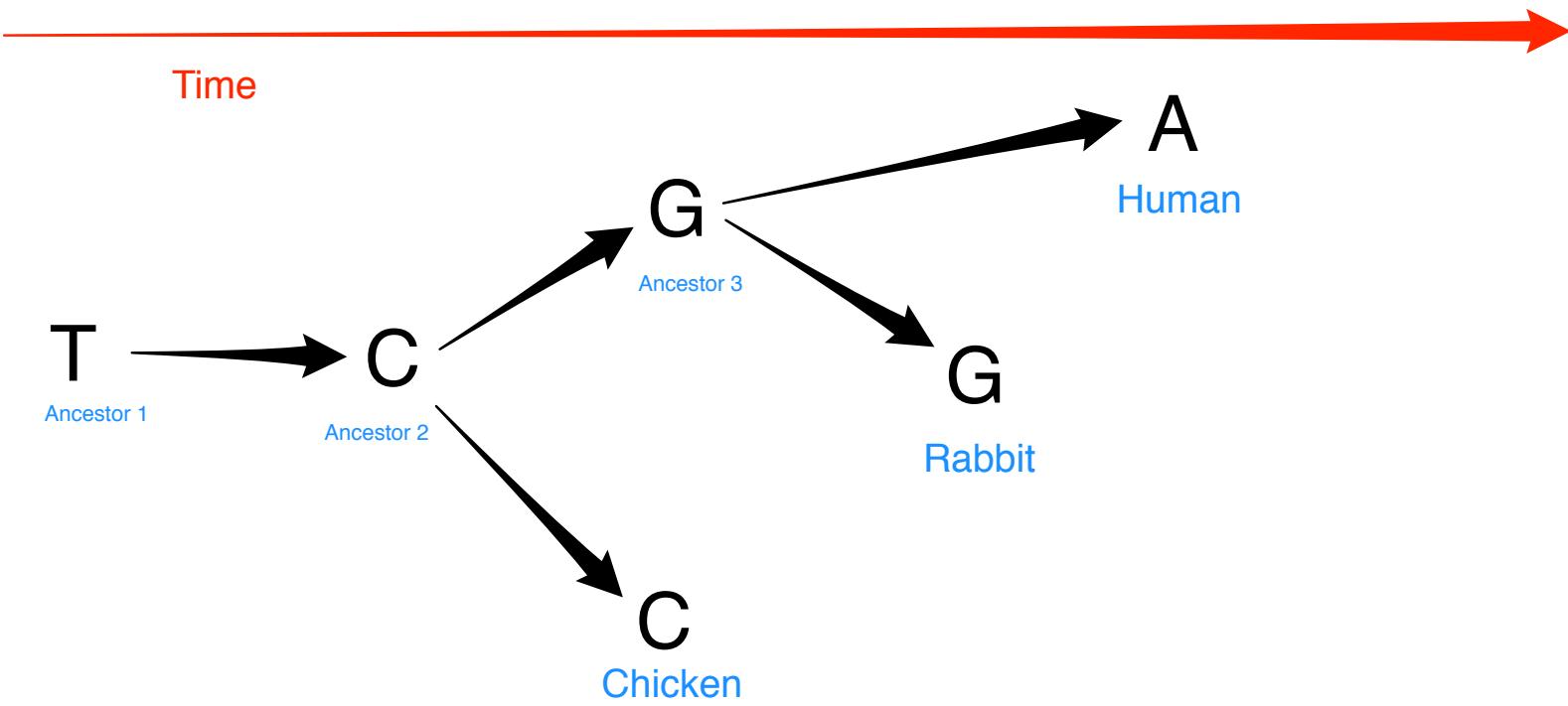
Each column was drawn
independently of the others.

DNA
Locus n

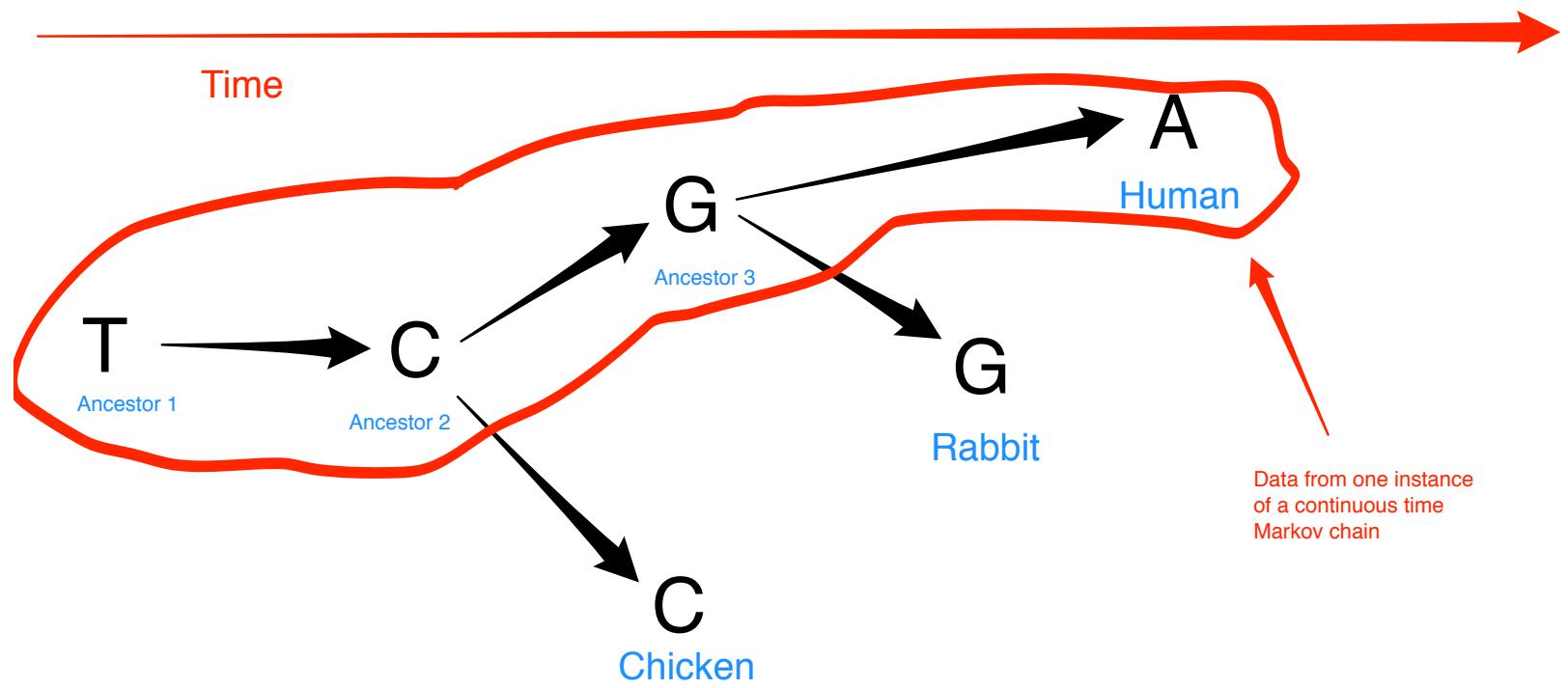
We assume that mutations in different loci are independent.

Consider locus 4...

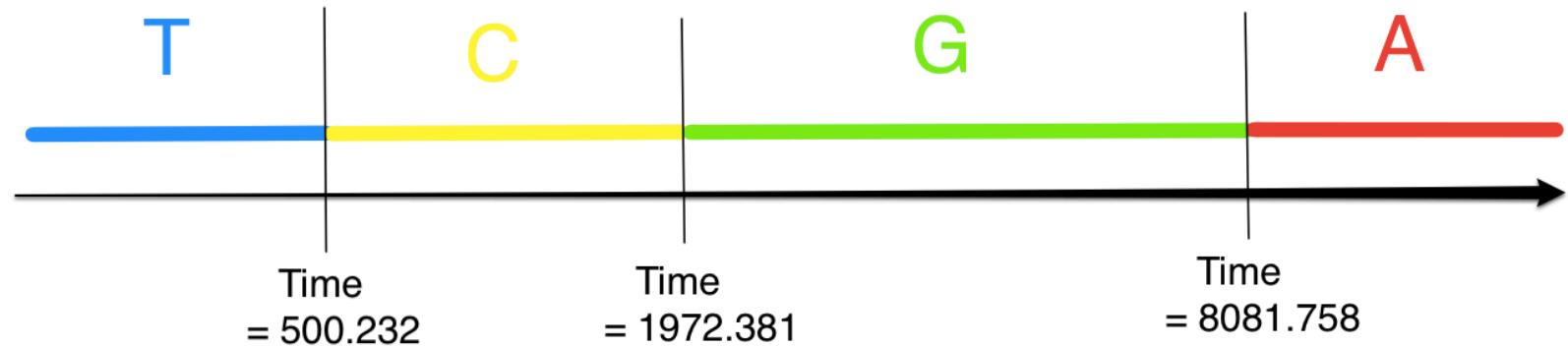
The nucleotide base in locus 4
might have changed over time in the following way:



We assume each path along the tree, or line of speciation, happens as a continuous time Markov chain:



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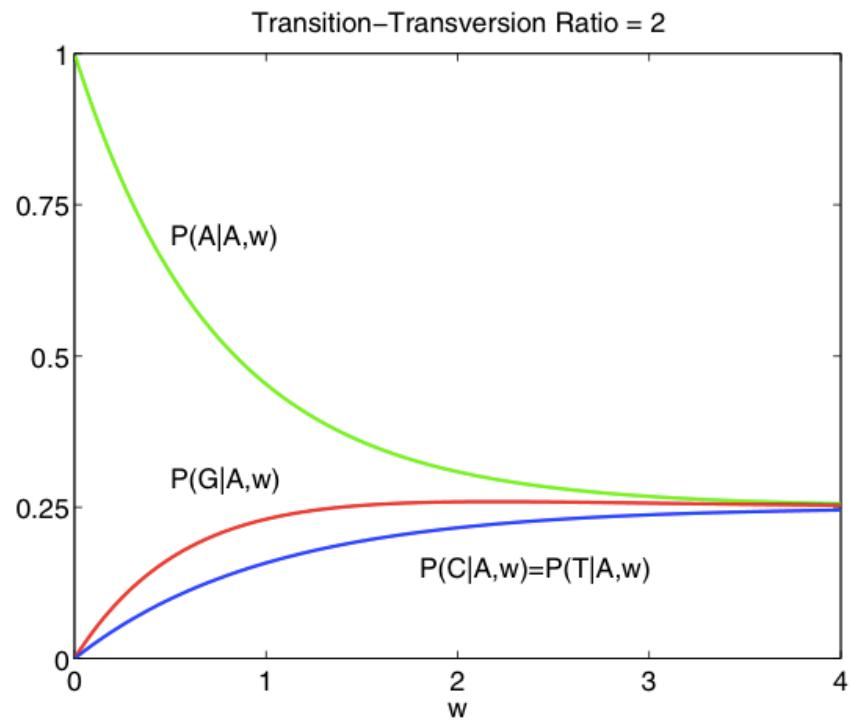
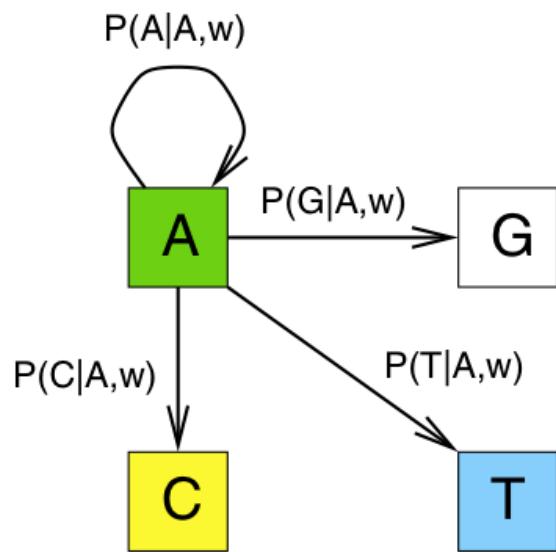


Fig. 4.17. Mathematical model of nucleotide substitution. *Left:* Nucleotide substitutions are modelled as transitions in a 4-element state space. The transition probabilities depend on the phylogenetic time $w = \lambda t$, where t is physical time, and λ is an unknown nucleotide substitution rate. *Right:* Dependence of the transition probabilities (vertical axis) on w (horizontal axis). The graphs were obtained from the Kimura model (4.16) with a transition–transversion ratio of 2.

Each physical time length t gives us a 4×4 transition matrix:

$$\mathbf{P}(t) = \begin{pmatrix} P(y(t) = A | y(0) = A) & \dots & P(y(t) = A | y(0) = T) \\ P(y(t) = G | y(0) = A) & \dots & P(y(t) = G | y(0) = T) \\ P(y(t) = C | y(0) = A) & \dots & P(y(t) = C | y(0) = T) \\ P(y(t) = T | y(0) = A) & \dots & P(y(t) = T | y(0) = T) \end{pmatrix}$$

Using calculus and some extra assumptions, we can describe $\mathbf{P}(t)$ by :

$$\mathbf{P}(t) = \exp(\mathbf{R}t)$$

where \mathbf{R} is the **rate matrix**.

A possible design for \mathbf{R} , the so-called Kimura model:

$$\mathbf{R} = \begin{pmatrix} -2\beta - \alpha & \beta & \alpha & \beta \\ \beta & -2\beta - \alpha & \beta & \alpha \\ \alpha & \beta & -2\beta - \alpha & \beta \\ \beta & \alpha & \beta & -2\beta - \alpha \end{pmatrix}$$

where α and β are parameters that make the columns sum to zero.