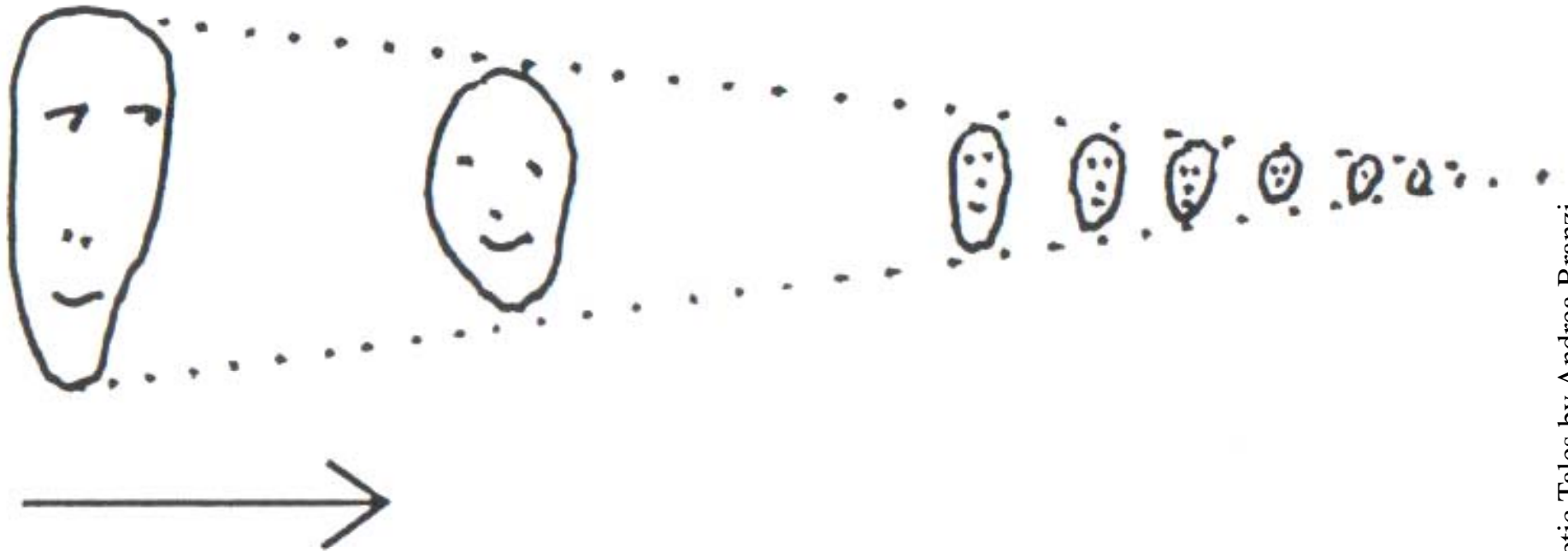


Molecular Clocks



Genetic Tales by Andrea Branzi

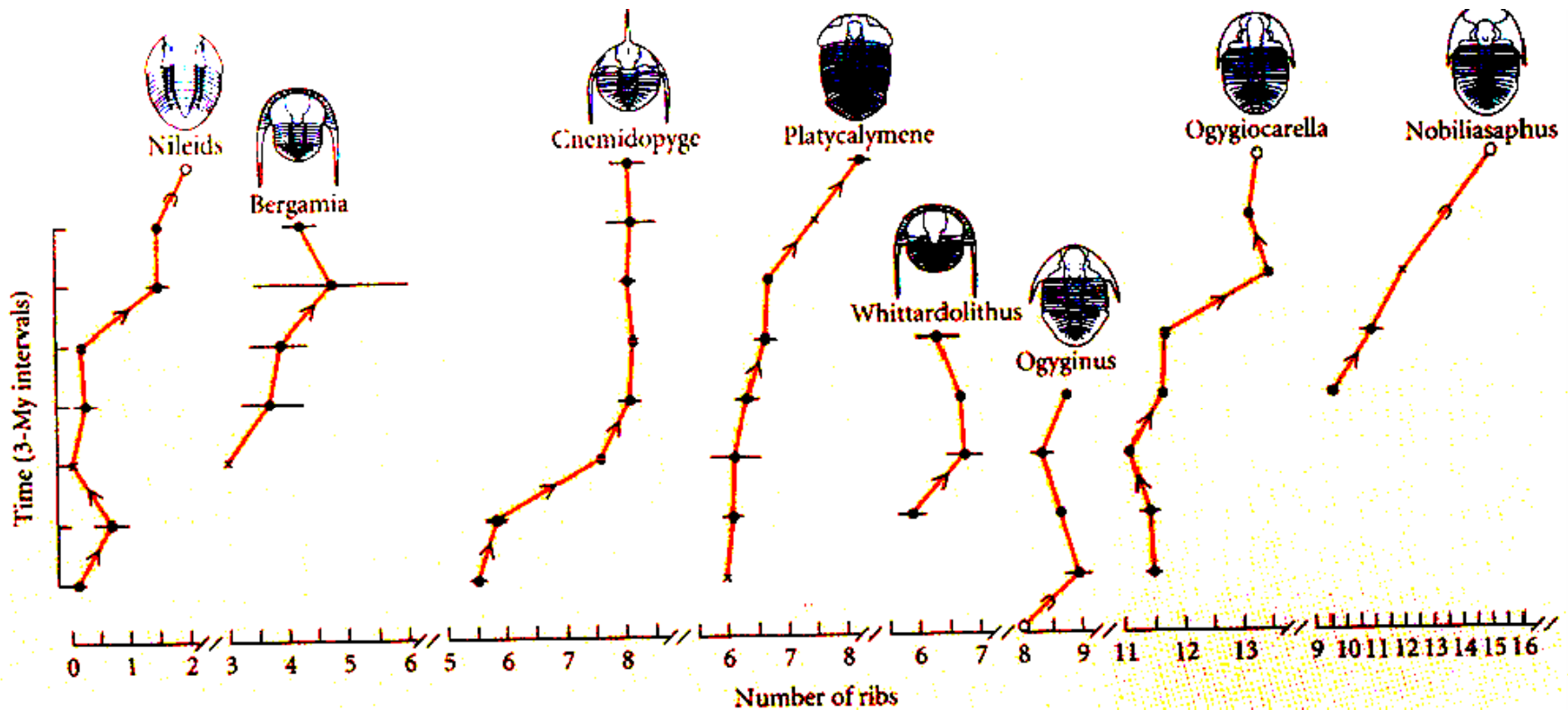
3rd Lecture, November 1st, 2009

Itai Yanai

Department of Biology

Technion – Israel Institute of Technology

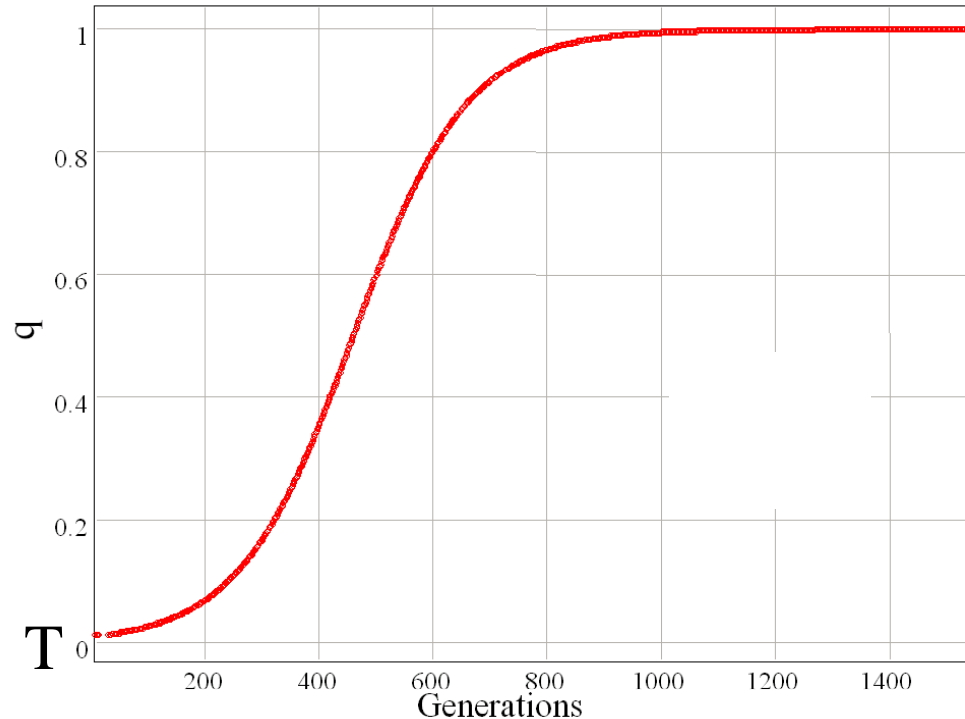
Evolution at the molecular level is radically different from evolution at the morphological level



Changes in the mean number of ribs in eight lineages of trilobites.
Irregular but mostly gradual changes are seen in most of the lineages

From population genetics to molecular evolution

Population genetics deals with allele frequencies within populations



Molecular evolution deals with evolving sequences by units of substitutions

CAGTTTATTTTCTTTTTTTCTGAGAGAGAGGGTCTTATTTTGTTGCCCAG
CAGTTTATTTTCTTTTTTTCTGAGTGAGAGGGTCTTATTTTGTTGCCCAG

Molecular Clocks

- The biological concept of homology
- Molecular clocks
 - Zuckerkandl and Pauling christen the molecular clock
 - Local clocks
 - Testing the molecular clock hypothesis with a relative rate test
 - Deviations from the molecular clock
- Estimating evolutionary distance between biological sequences
 - Simulation of the accumulation of mutations to a sequence
 - Jukes-Cantor and Kimura model
- A new time scale for hominid evolution

ATCTACCATGAAAGACTTGTGAATCCAGGAAGAGAGACTGACTGGGCAACATGTTATTC/

ACAAAAAGATTTGGACTGTAACTTAAAAATGATCAAATTATGTTTCCCATGCATCAGGTGC

GGGAAGCTCTTCTGGAGAGTGAGAGAAGCTTCCAGTTAAGGTGACATTGAAGCCAAGTC

AAAGATGAGGAAGAGTTGTATGAGAGTGGGGAGGGAAGGGGGAGGTGGAGGGGATGGG

GGGCCGGGATGGGATAGCGCAAACCTGCCCCGGGAAGGGAAACCAGCACTGTACAGACCT/

CAACGAAGATGGCATATTTTGTTCAGGGAATGGTGAATTAAGTGTGGCAGGAATGCTTTC

ACACAGTAATTTGCTTGTATGGAATTTTGCCTGAGAGACCTCATTGCAGTTTCTGATTTTT

GTCTTCATCCATCACTGTCCTTGTCAAATAGTTTGGAACAGGTATAATGATCACAATAACC

AGCATAATATTTTCGTTAATTCTCACAGAATCACATATAGGTGCCACAGTTATCCCCATTTTA

ATGGAGT**The Biological Concept of Homology**GATGAAAACCTTAGGAATAATGAATC

TGCGCAGGCTCACCTGGATATTAAGACTGAGTCAAATGTTGGGTCTGGTCTGACTTTAAT/

GCTTTGTTCATGAGCACCATATTGCCTCTCCTATGCAGTTAAGCAGGTAGGTGACAGAA

CCCATGTTTGTCTCTACTCACACACTTCCGACTGAATGTATGTATGGAGTTTCTACACCAG

TTCAGTGCTCTGGATATTAACCTGGGTATCCCATGACTTTATTCTGACACTACCTGGACCTT/

AATAGTTTGGACCTTGTCAAATAGTTTGGAGTCCTTGTCAAATAGTTTGGGGTTAGCACA/

CCCACAAGTTAGGGGCTCAGTCCCACGAGGCCATCCTCACTTCAGATGACAATGGCAAG

AAGTTGTCACCATACTTTTGACCAACCTGTTACCAATCGGGGGTTCCCGTAACTGTCTTCT

GTTTAATAATTTGCTAGAACAGTTTACGGAACCTCAGAAAAACAGTTTATTTTCTTTTTTTC

GAGAGAGGGTCTTATTTTGTGCCCAGGCTGGTGTGCAATGGTGCAGTCATAGCTCATTG

CCTTGATTGTCTGGGTTCAGTGGTTCTCCACCTCAGCCTCCCTAGTAGCTGAGACTAC/

CTGCACCACCACATCTGGCTAGTTTCTTTTATTTTTTGTATAGATGGGGTCTTGTGTGTT/

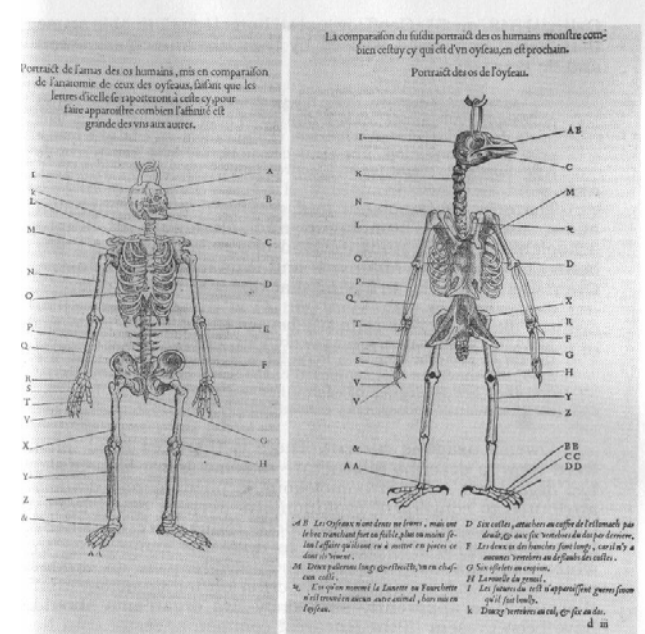
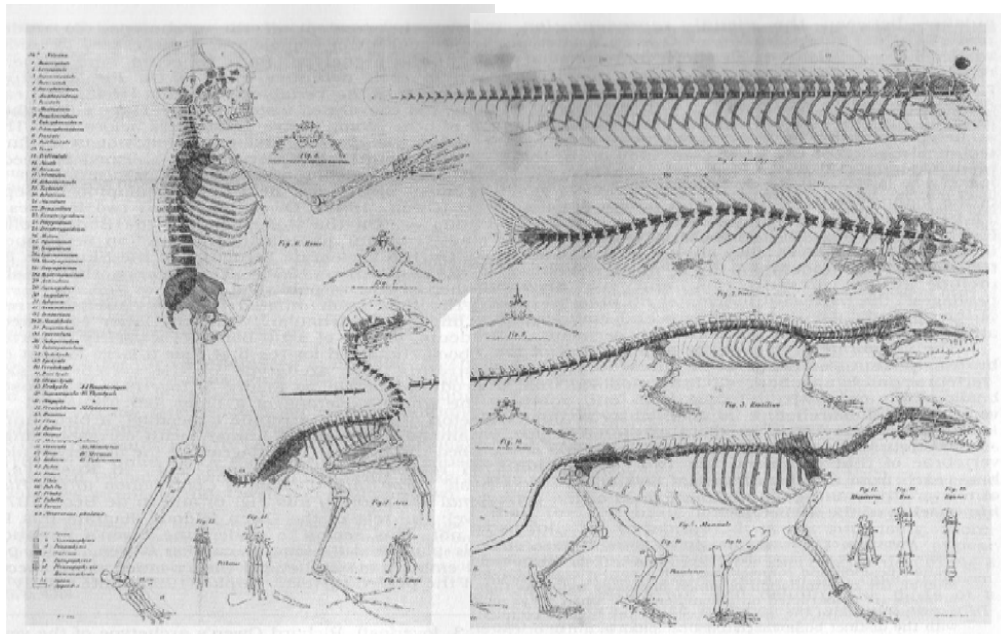
AGGCTGGCCACAAATCCTGGTCTCAAGTGATCCTCCACCTCAGCCTCTGAAAGTGCTC

TTACAGATGTGAGCCACCACATCTGGCCAGTTCATTTCCCTATTACTGGTTCATTGTGAAGG

CATCTCAGAAACAGTCAATGAAAGAGACGTGCATGCTGGATGCAGTGGCTCATGCCTGT/

TCAGCACTTTCCAGCCCAACCTCCAGCCATCCCTTAACCTCAGCACTTTTCACAGCCAG

Richard Owen (1804-1892)

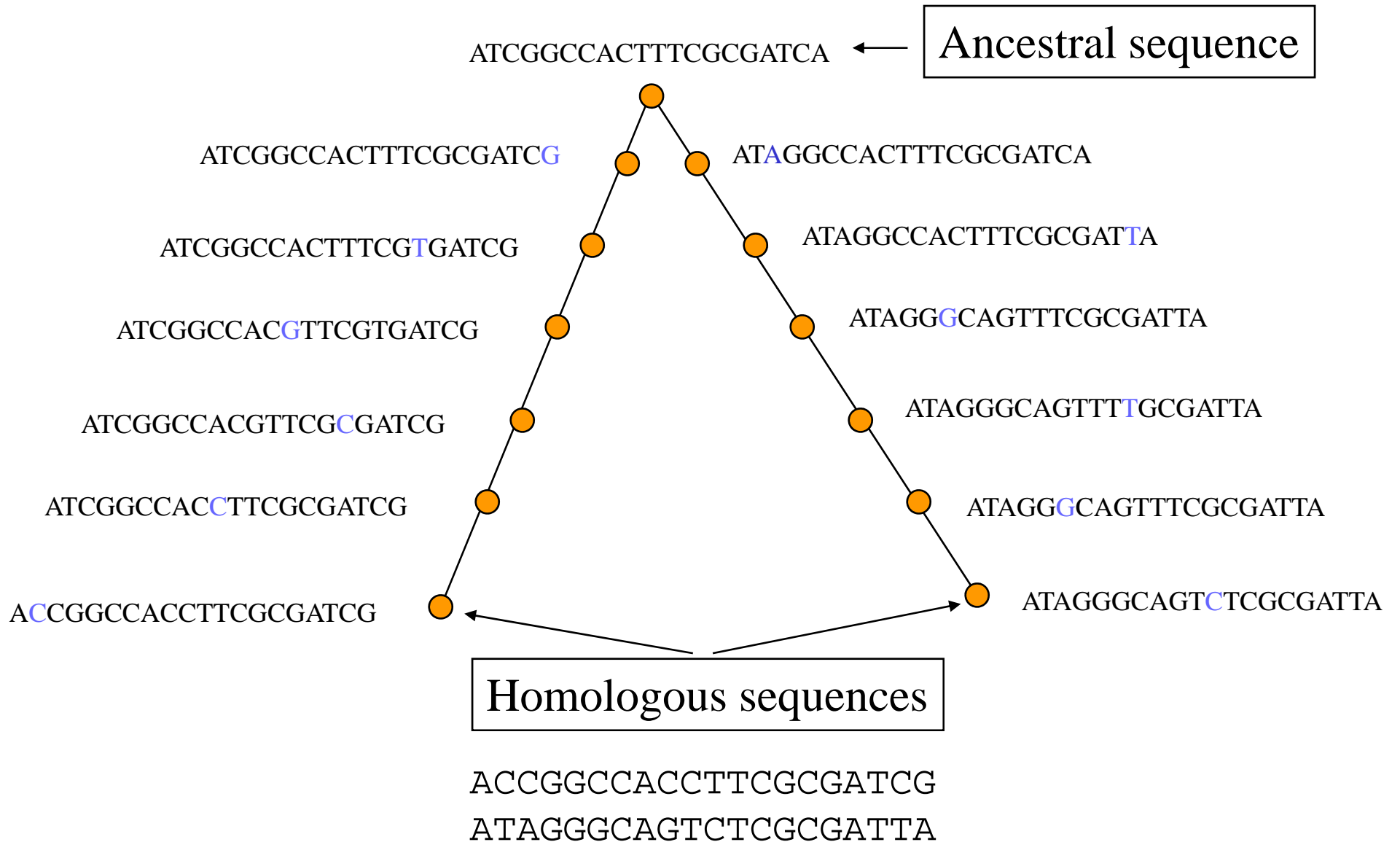


- Owen defined homology as "the same organ in different animals under every variety of form and function." – 1843
- Postulated a common structural plan (“archetype”) exists for all vertebrates.

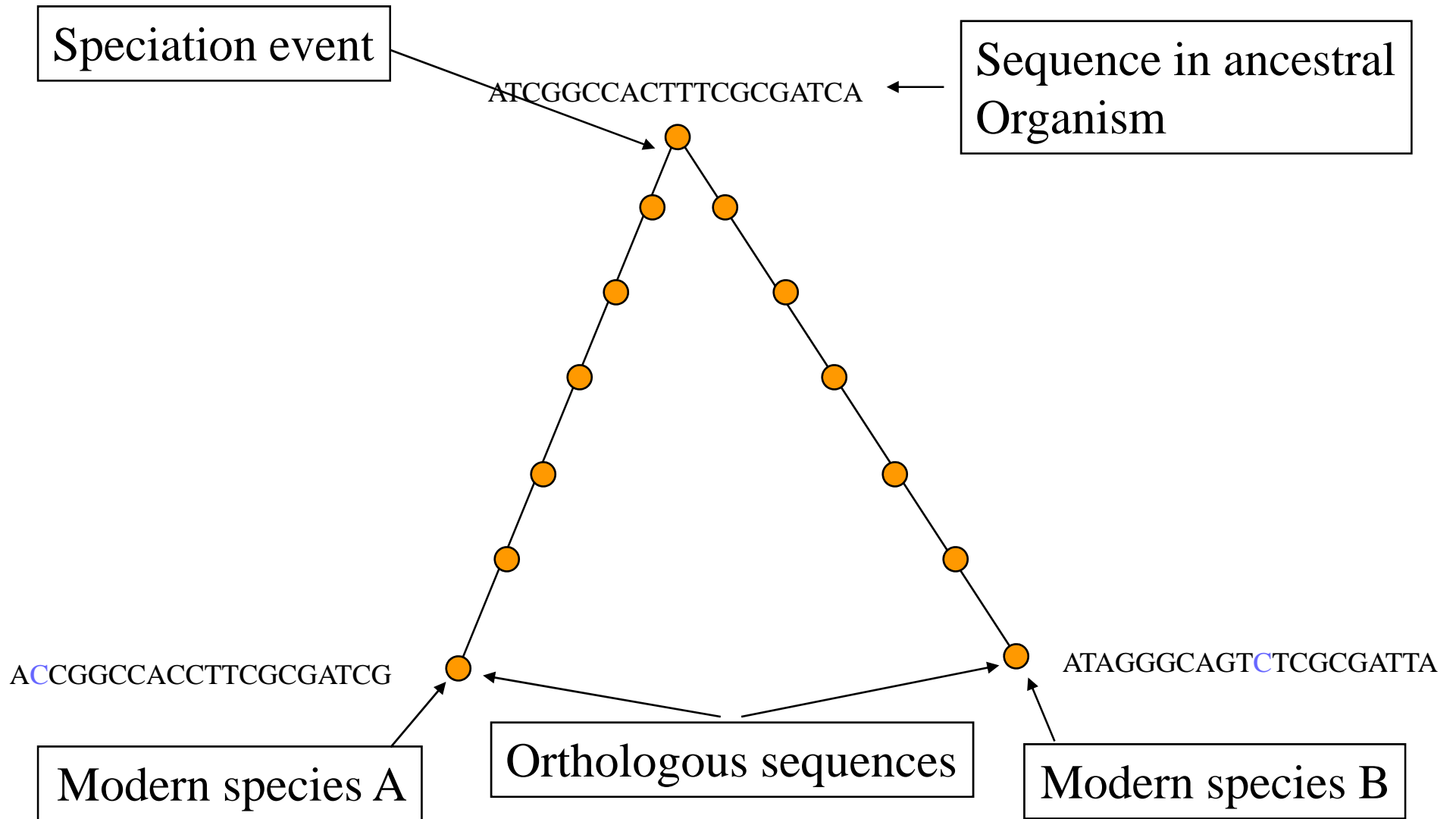


Owen, 1848

Darwin's theory reinterpreted **homology** as *common ancestry*.

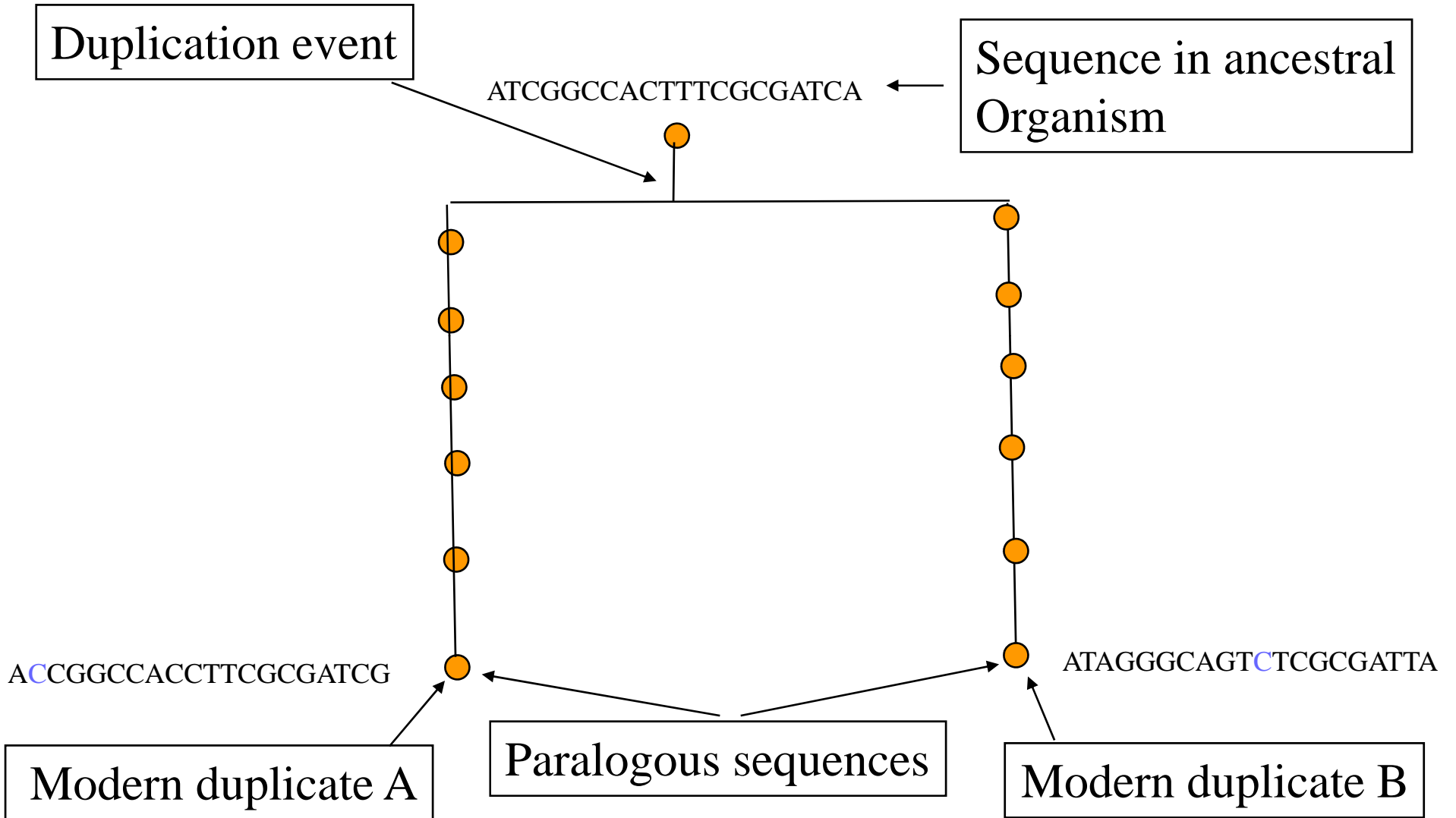


Orthologs arise by speciation

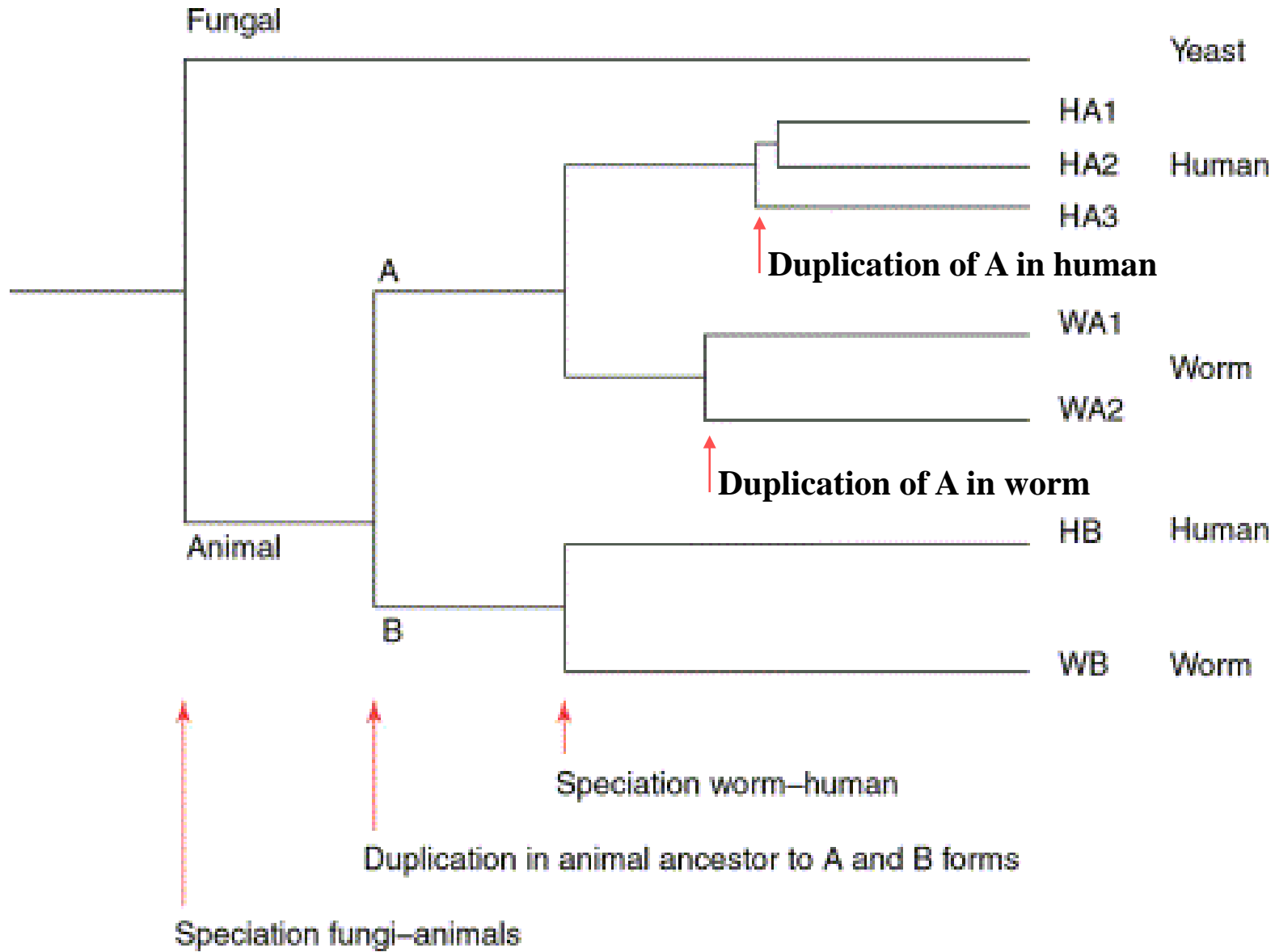


Orthologs are “evolutionary counterparts” – Koonin (2001)

Paralogs arise by duplications



An evolutionary tale...

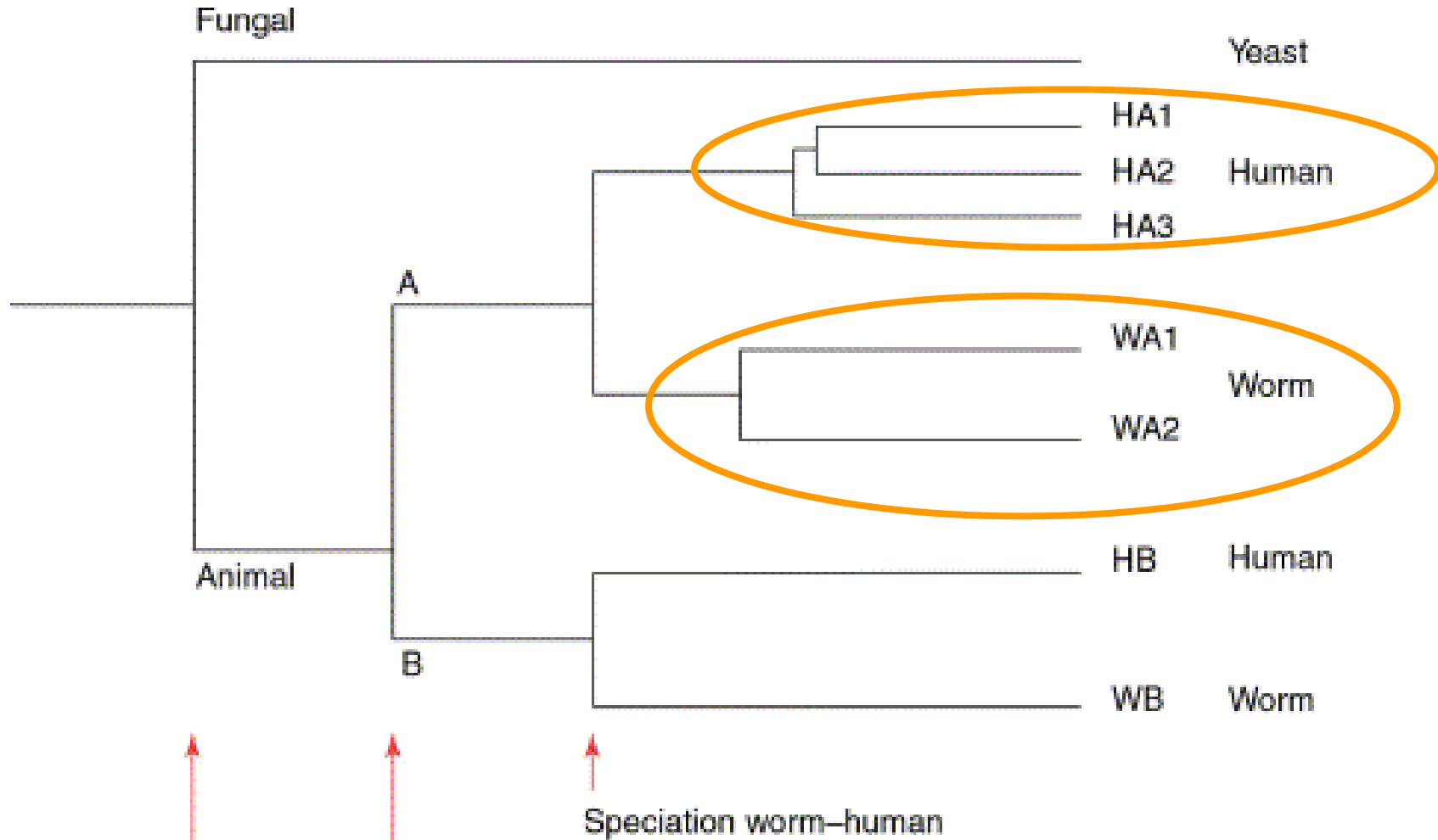


Evolutionary Relationships



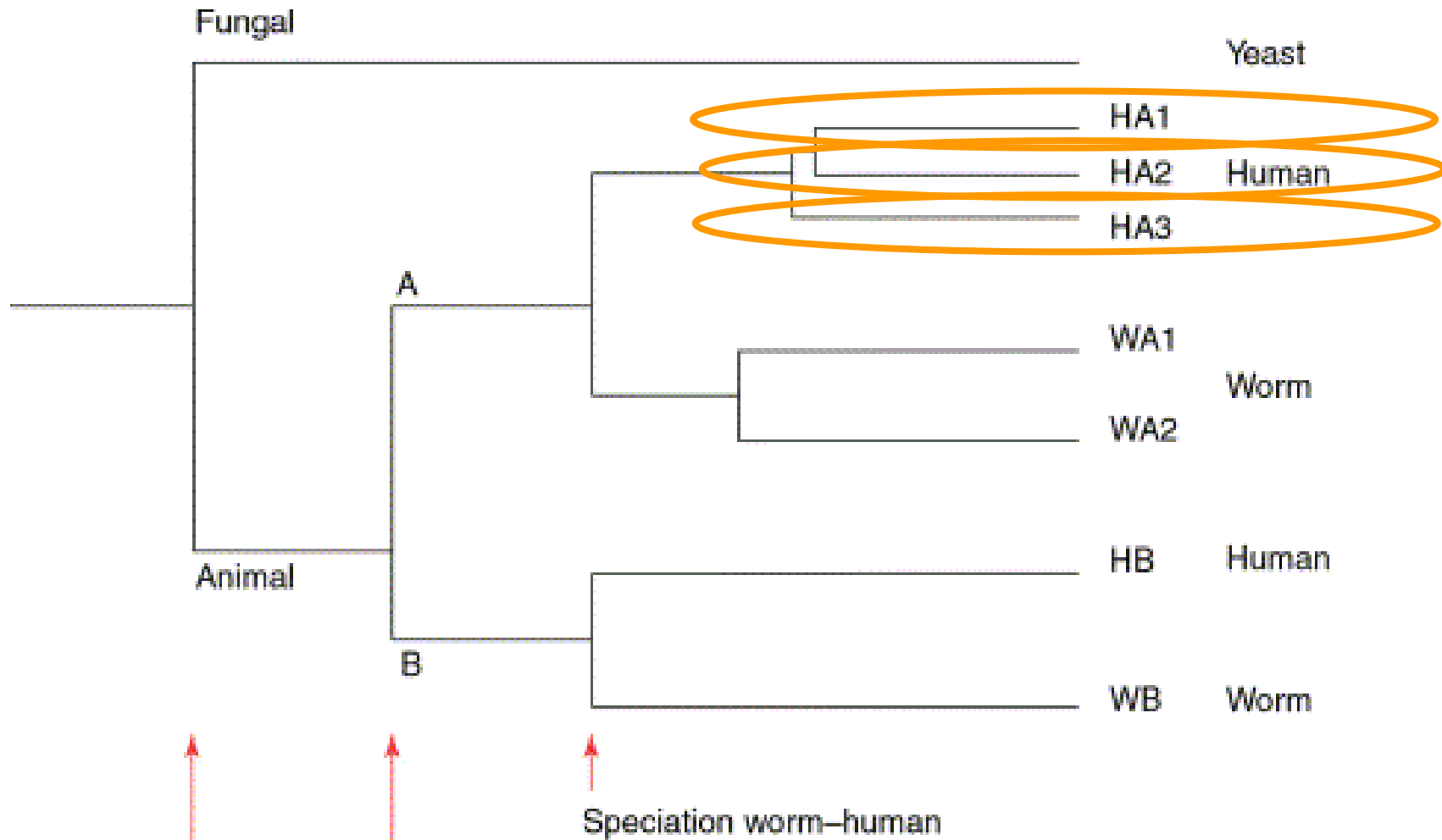
The yeast gene is orthologous to all worm and human genes, which are all co-orthologous to the yeast gene

Evolutionary Relationships



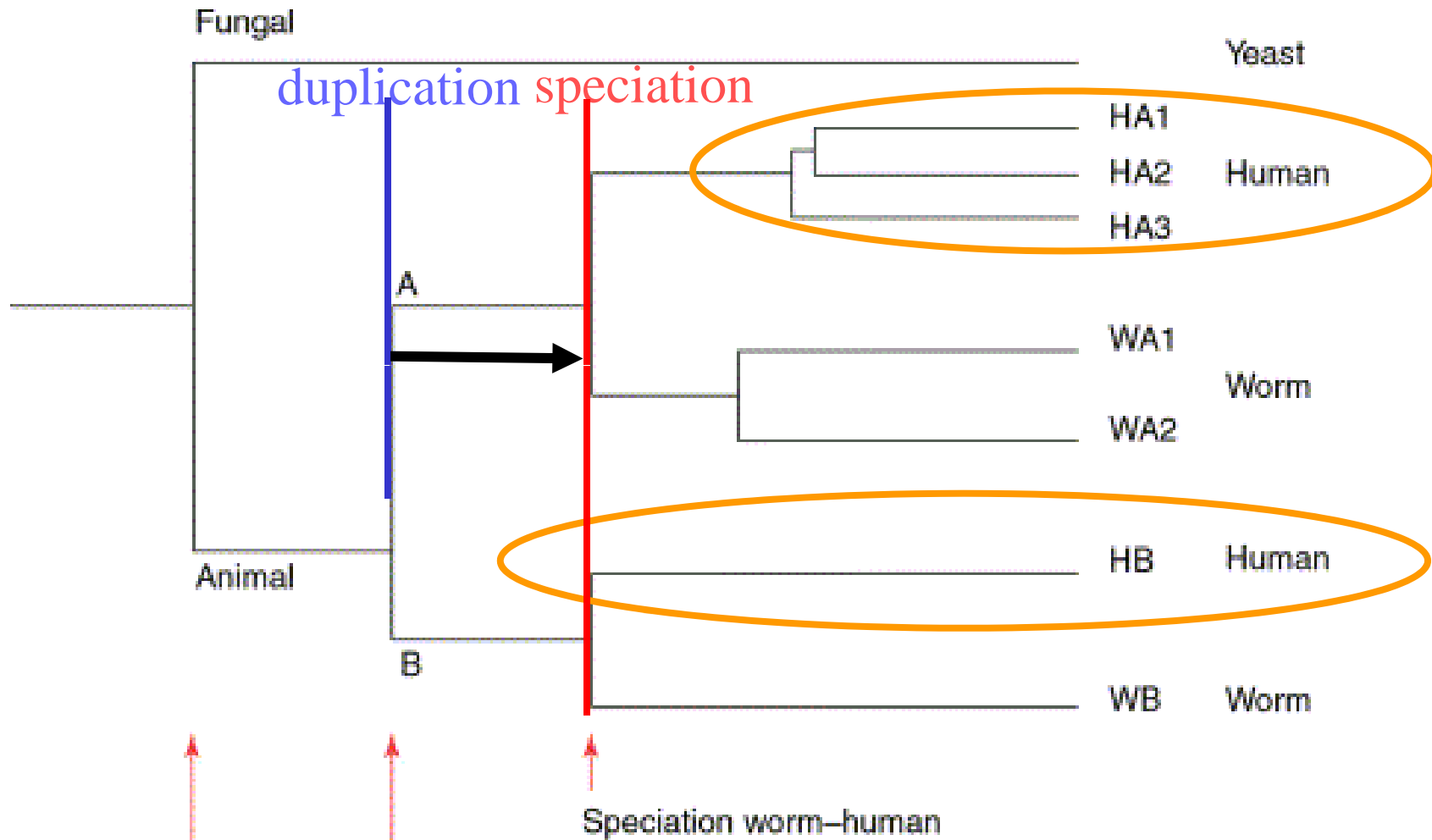
all genes in the HA* set are co-orthologous to all genes in the WA* set

Evolutionary Relationships



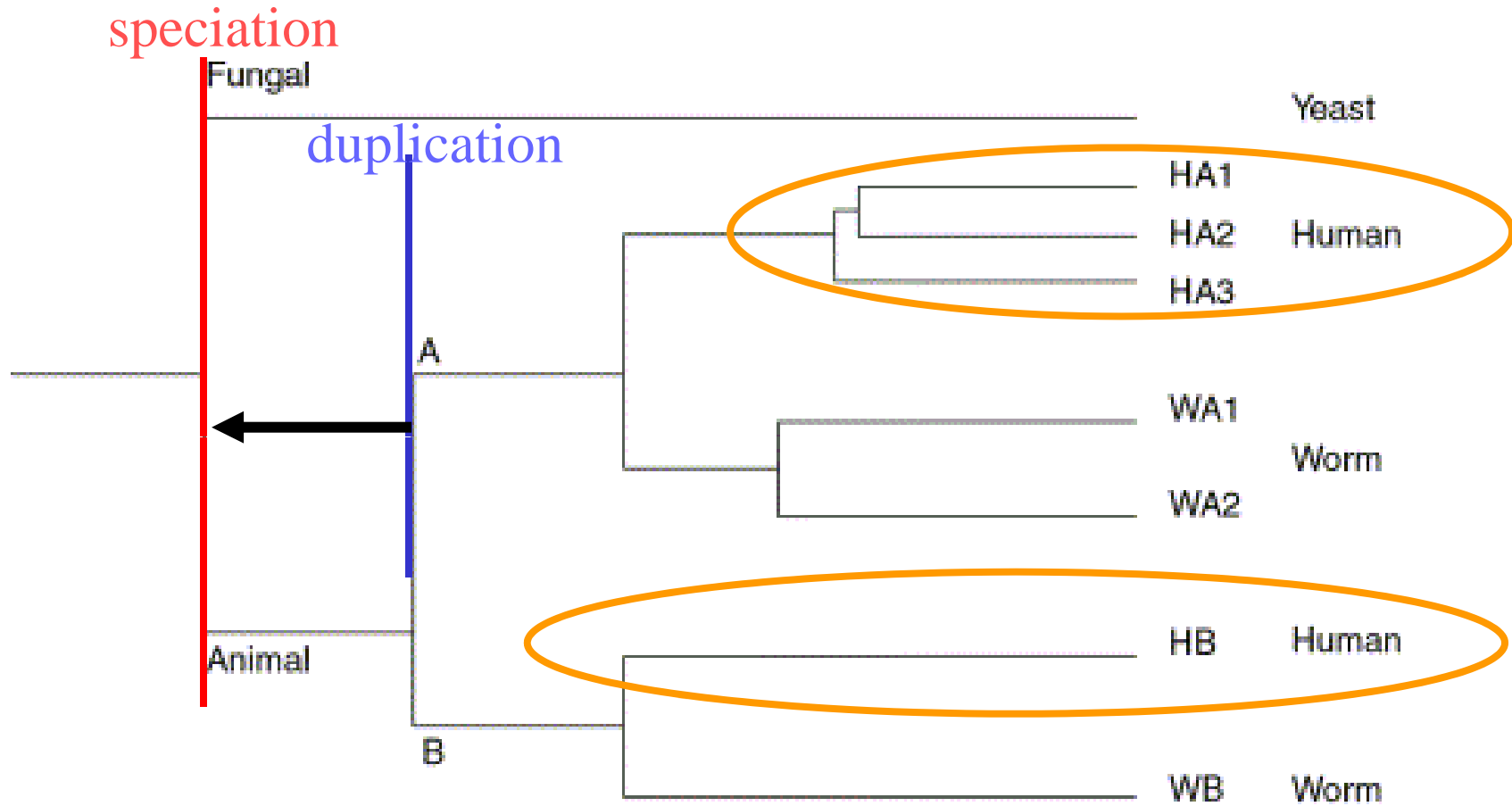
The genes HA* are hence 'inparalogs' to each other when comparing human to worm.

Evolutionary Relationships



By contrast, the genes HB and HA* are 'outparalogs' when comparing human with worm

Evolutionary Relationships



HB and HA*, and WB and WA* are inparalogs when comparing with yeast, because the animal-yeast split pre-dates the HA*-HB duplication

ATCCATGAAAGACTCTGTAATCCAGGAAAGAGAGACTGACTGGCCAAACATGTTATTC
ACAAAAGATTTGGACTGTA ACTTAAAAATGATCAAATTATGTTTCCCATGCATCAGGTGC
GGGAAGCTCTTCTGGAGAGTGAGAGAAGCTTCCAGTTAAGGTGACATTGAAGCCAAGTC
AAAGATGAGGAAGAGTTGTATGAGAGTGGGGAGGGAAGGGGGAGGTGGAGGGATGGGC
GGCCGGGATGGGATAGCGCAA ACTGCCCGGGAAGGGAAACCAGCACTGTACAGACCTC
CAACGAAGATGGCATATTTTGTTCAGGGAATGGTGAATTAAGTGTGGCAGGAATGCTTTG
ACACAGTAATTTGCTTGTATGGAATTTTGCCTGAGAGACCTCATTGCAGTTTCTGATTTT
TCTTTCATCCATCACTGTCCTTGTCAAATAGTTTGGAACAGGTATAATGATCACAATAACC
AGCATAATATTTTCGTTAATTCTCACAGAATCACATATAGGTGCCACAGTTATCCCCATTTA
ATGGAGT **MolecularClocks** GATGAAAACCTTAGGAATAATGAATGATTTGCGCAGGCTC
CTGGATATTAAGACTGAGTCAAATGTTGGGTCTGGTCTGACTTTAATGTTTGGCTTTGTTCA
GCACCACATATTGCCTCTCCTATGCAGTTAAGCAGGTAGGTGACAGAAAAGCCCATGTTT
TCTACTCACACACTTCCGACTGAATGTATGTATGGAGTTTCTACACCAGATTCTTCAGTGC
GGATATTA ACTGGGTATCCCATGACTTTATTCTGACACTACCTGGACCTTGTCAAATAGTTT
CTTGTCAAATAGTTTGGAGTCCTTGTCAAATAGTTTGGGGTTAGCACAGACCCCAACAAG
GGGCTCAGTCCCACGAGGCCATCCTCACTTCAGATGACAATGGCAAGTCCTAAGTTGTC
TACTTTTGACCAACCTGTTACCAATCGGGGGTTCCCGTAACTGTCTTCTTGGGGTTTAATA
CTAGAACAGTTTACGGAACTCAGAAAAACAGTTTATTTTCTTTTTTTCTGAGAGAGAGG
TATTTTGTGGCCAGGCTGGTGTGCAATGGTGCAGTCATAGCTCATTGCAGCCTTGATTG
GGTTCAGTGGTTCTCCACCTCAGCCTCCCTAGTAGCTGAGACTACATGCCTGCACCA
CATCTGGCTAGTTTCTTTTATTTTTTTGTATAGATGGGGTCTTGTGTGTTGGCCAGGCTGGC
AAATTCCTGGTCTCAAGTGATCCTCCACCTCAGCCTCTGAAAGTGCTGGGATTACAGAT
AGCCACCACATCTGGCCAGTTCATTTCTTACTGGTTCATTGTGAAGGATACATCTCAG
CAGTCAATGAAAGAGACGTGCATGCTGGATGCAGTGGCTCATGCCTGTAATCTCAGCACT
GGAGGCCAAGGTGGGAGGATCGCTTAAACTCAGGAGTTTGAGACCAGCCTGGGGCAACA

We have different types of hemoglobins



The major adult hemoglobin is composed of 2 α chains and 2 β chains.
The major fetal hemoglobin is composed of 2 α chains and 2 γ chains.

Emile Zuckerkandl and Linus Pauling,
 "Evolutionary Divergence and Convergence in Proteins,"
 in *Evolving Genes and Proteins*, eds. V. Bryson and H. Vogel (New York: Academic Press, 1965). pp. 97-
 166.

Comparing Hemoglobin Sequences

TABLE VIII
 NUMBER OF DIFFERENCES BETWEEN SOME MAMMALIAN HEMOGLOBIN CHAINS^a

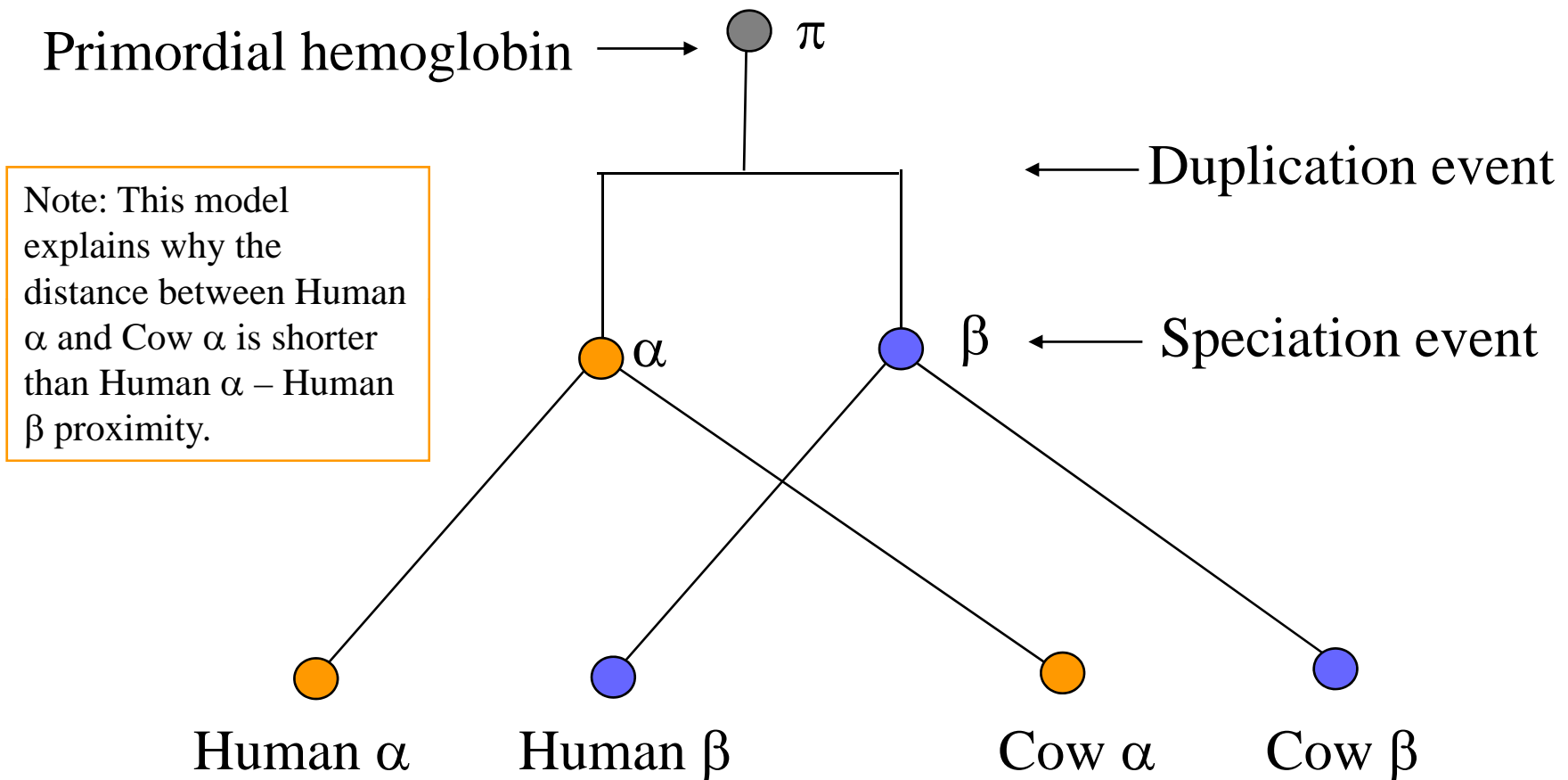
	α man	α horse	α cattle	β man	" β " horse	" β " cattle ^b	γ man	" γ " cattle
α man	0	17	~27	74	81	~75	79	82
α horse	17	0	~38	77	75	~77	77	77
α cattle	~27	~38	0	~81	~83	~83	~81	~88
β man	74	77	~81	0	26	~27	39	32
" β " horse	81	75	~83	26	0	~35	43	33
" β " cattle ^b	~75	~77	~83	~27	~35	0	~45	~28
γ man	79	77	~81	39	43	~45	0	~40
" γ " cattle	82	77	~88	32	33	~28	~40	0

^a Differences due to deletions are not counted.

^b Estimated on the basis of 65% of the cattle β chain (composition of tryptic peptides).

α vs. non- α sequences are equally distant regardless of organism

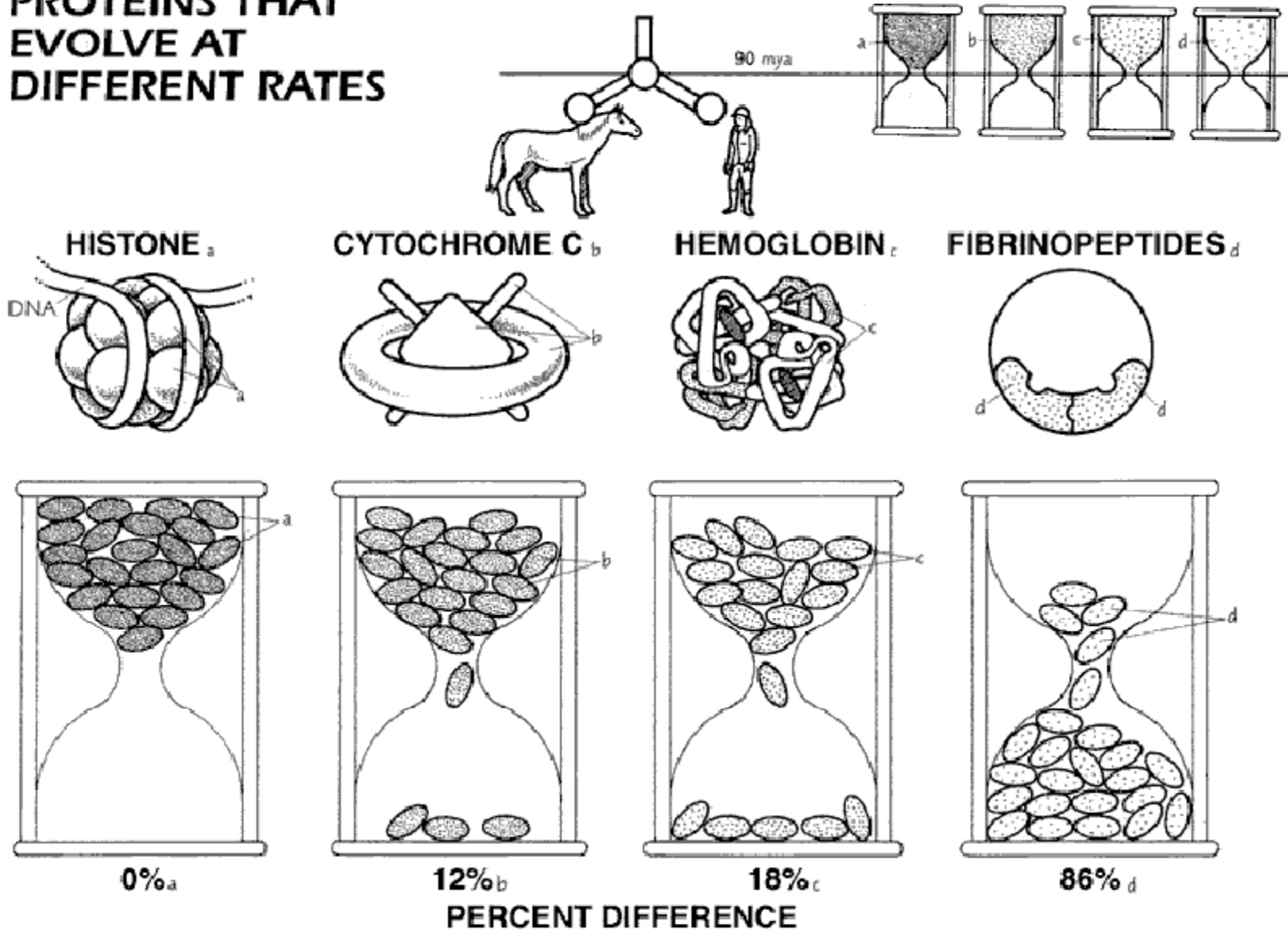
“There may thus exist a
Molecular Evolutionary Clock”
Zuckerkandl & Pauling (1965)



A model of sequence divergence can be used to extract the duplication dates of the different hemoglobin chains

Different clocks keep different times

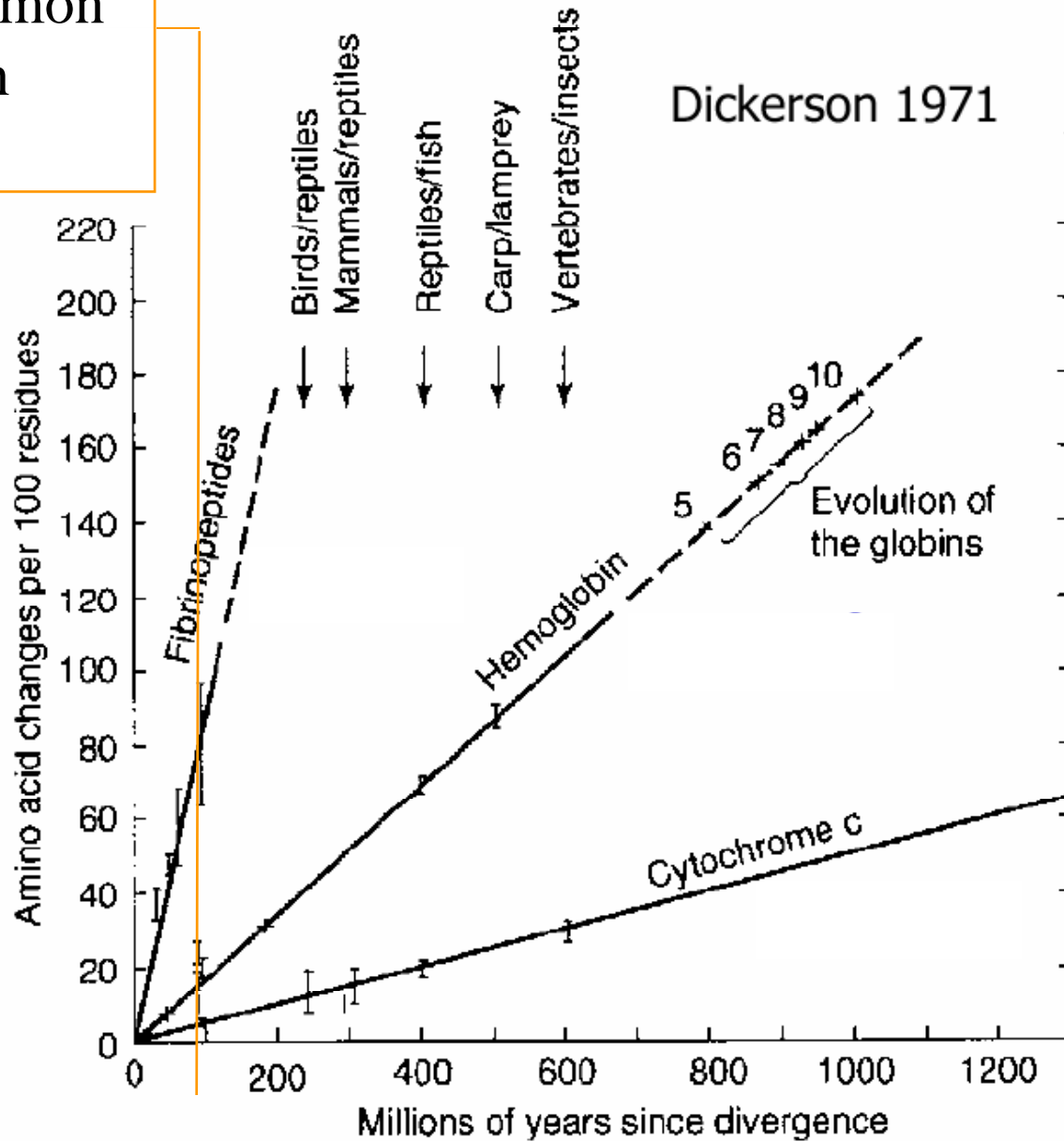
PROTEINS THAT EVOLVE AT DIFFERENT RATES



Between horse and man

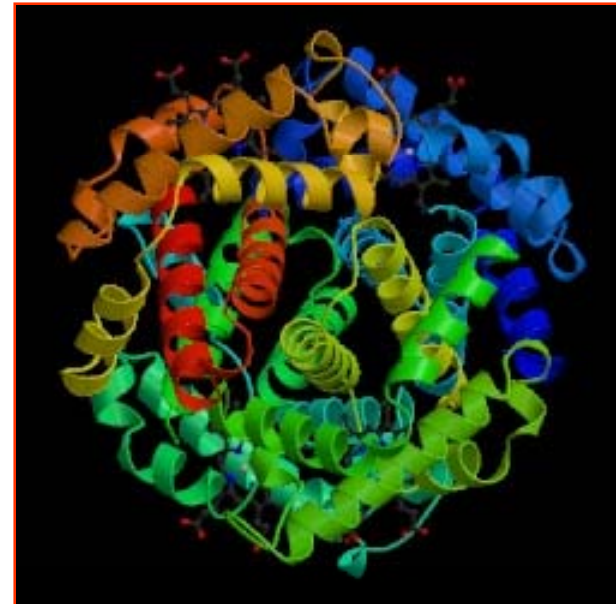
Different proteins evolve at different rates

Most recent common ancestor between Man-horse

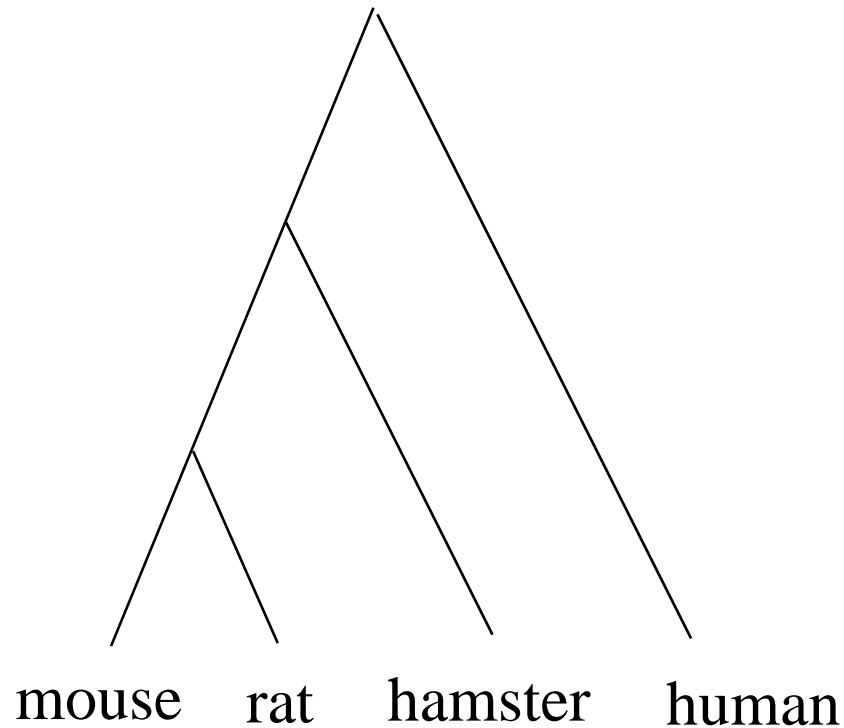


The clock varies for different regions of the protein

For example, locations on the exterior of the protein may change at a different rate than those on the interior.



Local Clock – a clock between a particular group of organisms



Distance from mouse to hamster should be same as
Distance from rat to hamster.

Distance from mouse to human should be same as
Distance from rat to human which should also be same as
Distance from hamster to human

The Molecular Clock Ticks Regularly in Muroid Rodents and Hamsters

TABLE 8.1 Numbers of nucleotide substitutions per 100 sites between species^a

Species pair	Synonymous sites		Nonsynonymous sites	
	K_S	L^b	K_A	L^b
Mouse-rat	18.0 ± 0.7	4,229	1.8 ± 0.1	15,217
Mouse-hamster	30.3 ± 1.0	4,229	2.9 ± 0.1	15,217
Rat-hamster	31.3 ± 1.0	4,229	2.7 ± 0.1	15,217
Mouse-human	53.4 ± 1.5	4,229	5.2 ± 0.2	15,217
Rat-human	51.6 ± 1.5	4,229	5.0 ± 0.2	15,217
Hamster-human	52.3 ± 1.5	4,229	5.1 ± 0.1	15,217

From O'hUigin and Li (1992).

^aComputed by Li et al.'s (1985b) method.

^bNumber of sites compared.

Very close!

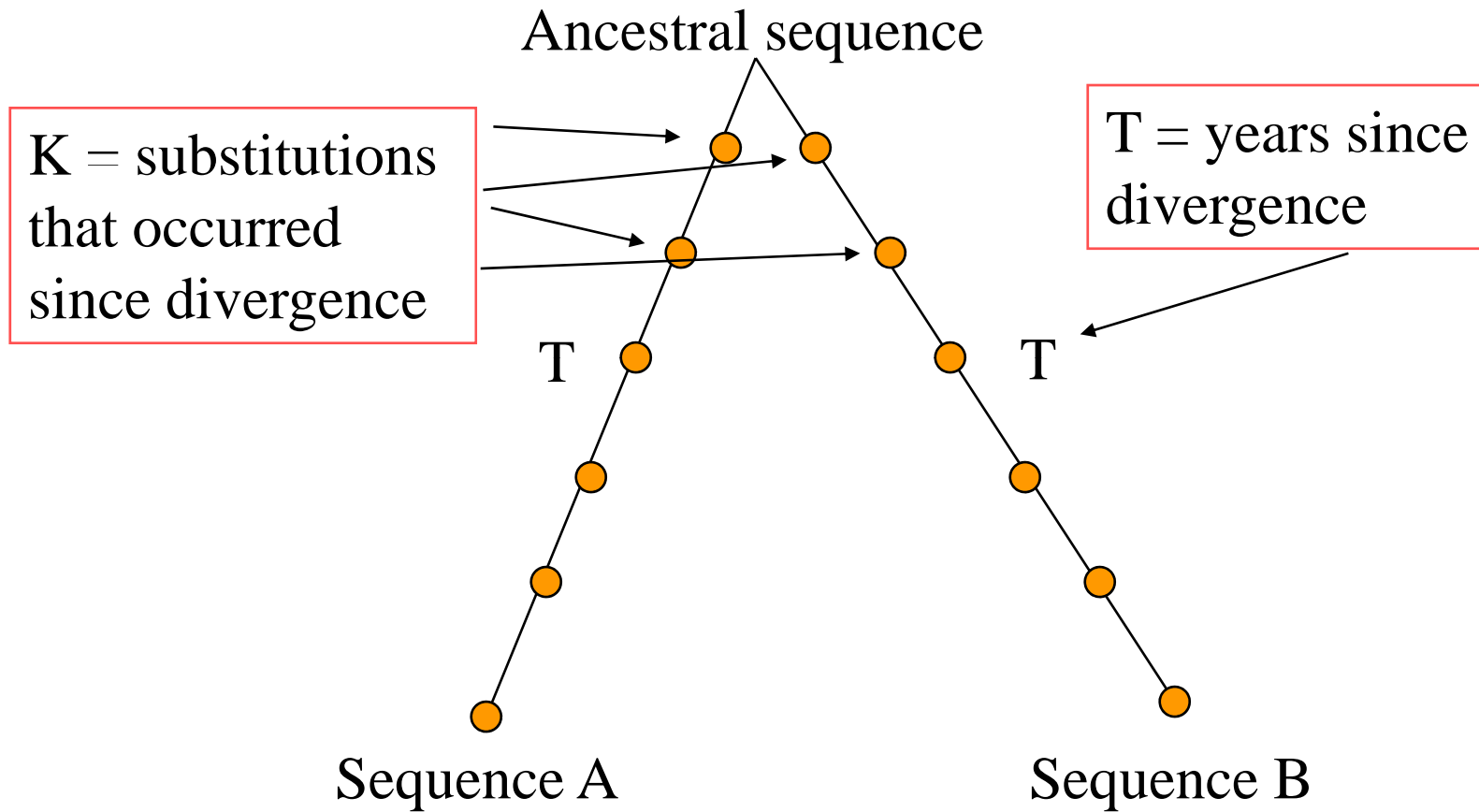
Also very close!

From Li, W-H Molecular Evolution who took it from:
Oh'Uigin and Li. JME 1992 35: 377-384

There are two reasons for being interested in the molecular clock:

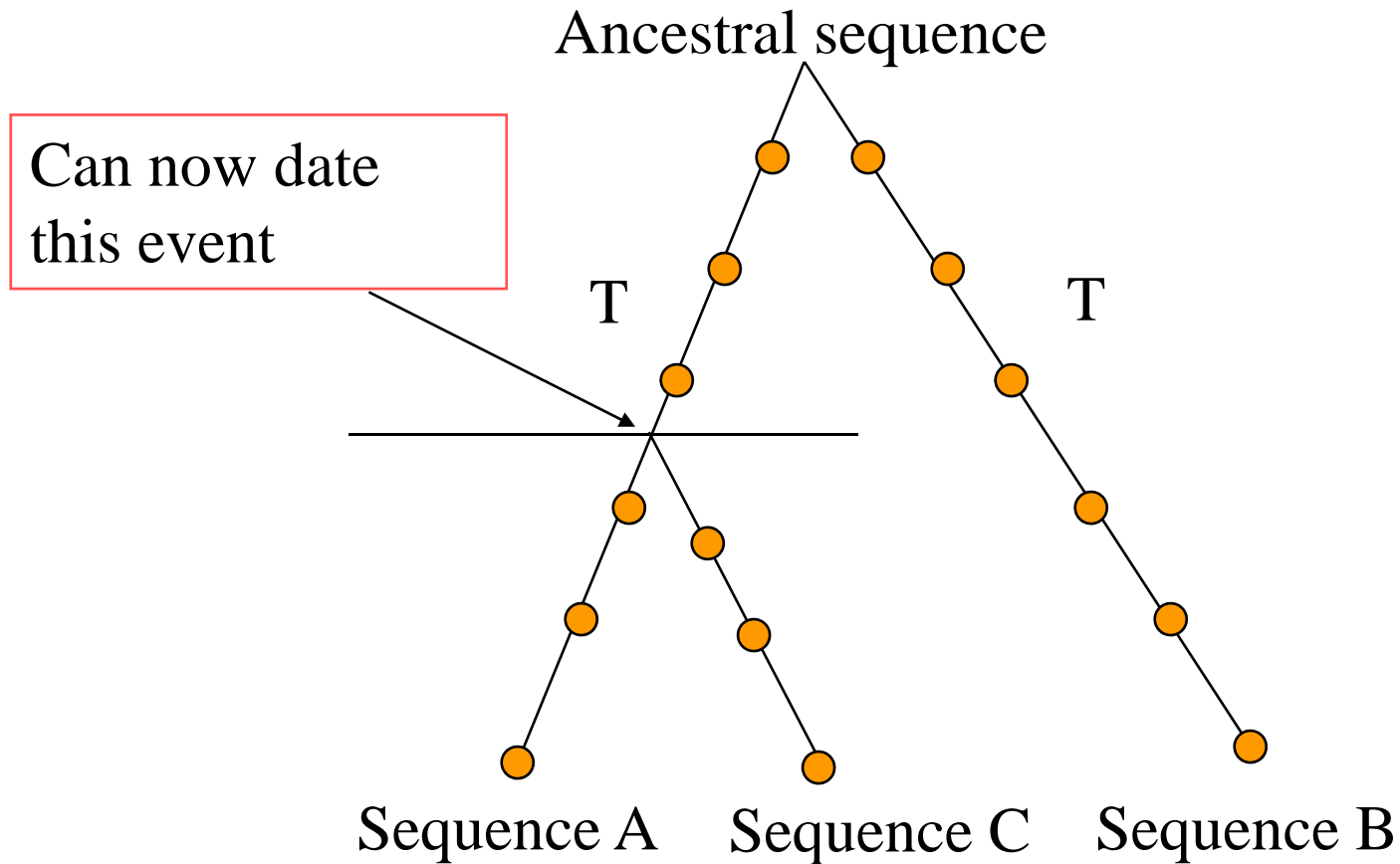
- (1) The clock has important implications for our understanding of the mechanisms of molecular evolution.
(What does the existence of a clock signify? – We will address this point in detail at the next lecture.)
- (2) The clock can help establish a time scale for evolution.
(What happened when?)

Calculating the rate of nucleotide substitution (r)



$$r = K/2T$$

Once the molecular clock is calibrated it can date other events

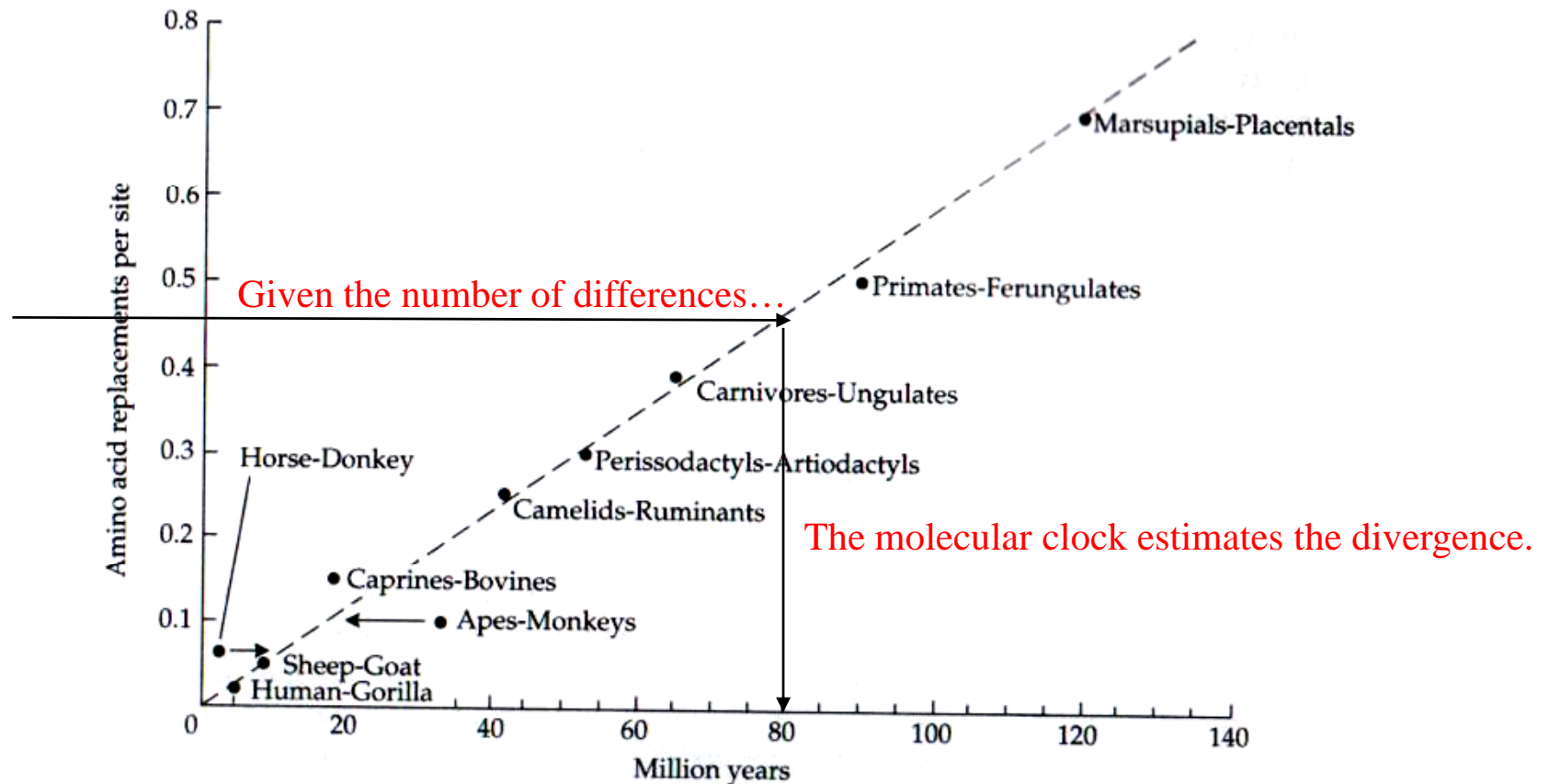


$$T = K/2r$$

Properties of the Molecular Clock

1. Clock is stochastic: large variance is expected when the number of amino acids examined is small. [metronome vs. stochastic]
2. There are many exceptions even considering the stochastic nature (selection, mutation rates, etc.)
3. In clock calibrations, geological times are necessary which are often inaccurate.

Dating events with the molecular clock



- Comparisons between a combined sequence of hemoglobins alpha and beta, cytochrome c, and fibrinopeptide A among mammalian groups
- Find a slow-down in apes and monkeys and speed up in horse-monkey

Molecular clock does not hold for Guinea pig insulin

Comparison	Observed differences
<i>Insulin A and B (except for guinea pig insulin): 51 amino acids; 510 comparisons of homologous sites</i>	
Human: horse	2
Human: rabbit	1
Human: sei whale	3
Human: bovine	3
Horse: rabbit	3
Horse: sei whale	3
Horse: bovine	3
Rabbit: sei whale	3
Rabbit: bovine	3
Bovine: sei whale	1
<i>Guinea pig insulin (51 amino acids) compared with other mammalian insulins; 255 comparisons of homologous sites</i>	
Guinea pig: human	18
Guinea pig: horse	17
Guinea pig: rabbit	18
Guinea pig: whale	16
Guinea pig: bovine	17

Unbelievably fast!



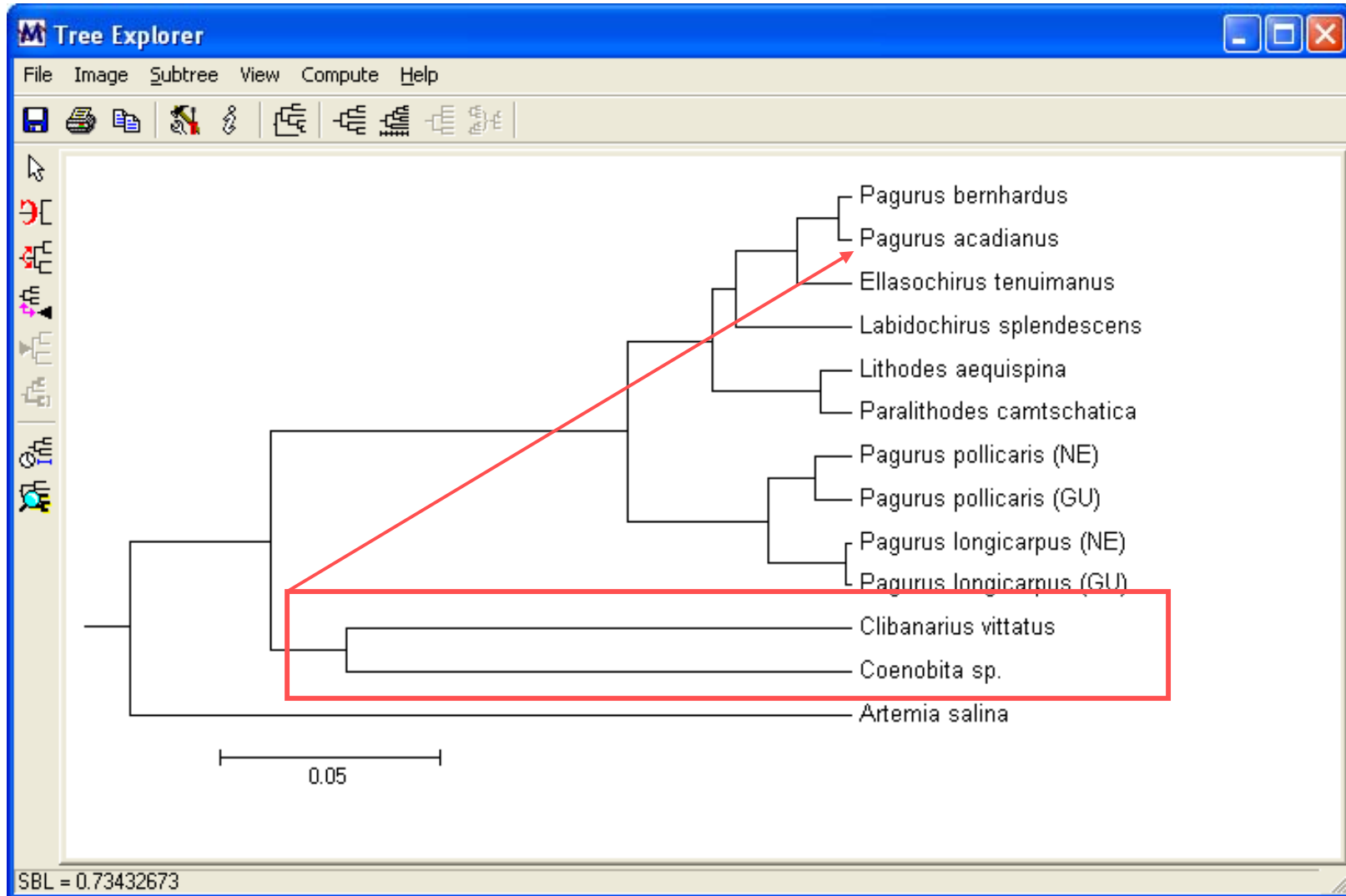
Testing the Molecular Clock



<http://www.megasoftware.net/>

Recommendation: Download this free software and learn to use it!

Tajima's relative rate test



The same number of lineage specific mutations are expected to have occurred in both lineages

Tajima's relative rate test

Clibanarius vittatus	A	A	T	G	A	A	T	G	G	T	T	G	G	A	C	G	A	A	A	A	A	C	A	C	A	C	T	G	T	T	T	C
Coenobita sp.	T	A	T	G	A	A	A	G	G	T	C	G	A	A	C	G	A	G	T	G	A	T	A	G	A	C	T	G	T	C	T	C
Pagurus acadianus	A	A	T	G	A	A	A	G	G	T	T	G	G	A	C	A	A	A	G	T	A	T	C	A	T	C	T	G	T	T	T	C

m_{jij} : ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑ = 5
 m_{ijj} : _____ = 2

$$m_1 = \sum m_{jij} = n_{AGA} + n_{ACA} + n_{ATA} + n_{GAG} + n_{GCG} + n_{GTG} + n_{CAC} + n_{CGC} + n_{CTC} + n_{TAT} + n_{TGT} + n_{TCT}$$

$$m_2 = \sum m_{ijj} = n_{AGG} + n_{ACC} + n_{ATT} + n_{GAA} + n_{GCC} + n_{GTT} + n_{CAA} + n_{CGG} + n_{CTT} + n_{TAA} + n_{TGG} + n_{TCC}$$

$$E(m_1) = E(m_2)$$

$$\chi^2 = (m_1 - m_2)^2 / (m_1 + m_2)$$

Tajima's relative rate test

```
Text File Editor and Format Converter
File Edit Search Display Utilities
Tajima's test
Computation : Tajima's relative rate test
Gaps/Missing data : Complete Deletion
Mode : Nucleotides
Data Info : (All)
Changes considered : All
Sequence A : Clibanarius vittatus
Sequence B : Coenobita sp.
Sequence C : Pagurus acadianus
Test type : Rooted on Seq C
No. of Sites : 397

m_iii = 272 (identical sites in all three sequences)
m_ijk = 22 (divergent sites in all three sequences)
m_ijj = 30 (unique differences in SeqA)
m_iji = 29 (unique differences in SeqB)
m_iij = 44 (unique differences in SeqC)
Chi-square= 0.02 with 1 degree of freedom (p=0.896)

3:39 modified Insert
```

P is not significant so we cannot rule out the molecular clock

$$E(m_1) = E(m_2)$$
$$\chi^2 = (m_1 - m_2)^2 / (m_1 + m_2)$$
$$\chi^2 = (30 - 29)^2 / (30 + 29) = 0.0169$$

What causes deviations from the clock?

1. **Generation time:** Shorter generation time will accelerate the clock because it shortens the time to fix new mutations.
2. **Mutation rate:** Species-characteristic differences in polymerases or other biological properties that affect the fidelity of DNA replication, and hence the incidence of mutations.
3. **Gene function:** Changes in the function of a protein as evolutionary time proceeds. This might particularly be expected in the case of gene duplication.
4. **Natural selection:** Organisms are continually adapting to the physical and biotic environments, which change endlessly in patterns that are unpredictable and differently significant to different species.

Generation Time effect

1. A higher rate of evolution takes place in organisms with a short generation time than in organisms with a long generation time
2. The rate of substitution is higher in monkeys than in humans and is even higher in rodents. These observations are consistent with the generation time effect hypothesis

Mutation Rate effect

1. Efficiency of the DNA repair system may differ among lineages
2. Use to explain difference between the primate and rodent lineages
3. Evidence from cultured cells support this hypothesis

How long does it take to drive from Rehovot to Tel Aviv?

Normally: $25\text{km} / 60\text{km/hr} = 0.42$ hours

But!

1. No traffic at all? Much faster (a non-functional sequence)
2. A lot of traffic? Slower (different mutation rates)
3. Overturned truck? Much slower (strong purifying selection)

ACAAAAAGATTTGGACTGTA ACTTAAAAATGATCAAATTATGTTTCCCATGCATCAGGTGC
GGGAAGCTCTTCTGGAGAGTGAGAGAAGCTTCCAGTTAAGGTGACATTGAAGCCAAGTC
AAAGATGAGGAAGAGTTGTATGAGAGTGGGGAGGGGAAGGGGGAGGTGGAGGGATGGG
GGGCCGGGATGGGATAGCGCAA ACTGCCCGGGAAGGGAAACCAGCACTGTACAGACCT
CAACGAAGATGGCATATTTTGTTCAGGGAATGGTGAATTAAGTGTGGCAGGAATGCTTTC
ACACAGTAATTTGCTTGTATGGAATTTTGCCTGAGAGACCTCATTGCAGTTTCTGATTTTT
GTCTTCATCCATCACTGTCCTTGTCAAATAGTTTGGAACAGGTATAATGATCACAATAACC
AGCATAATATTTTCGTTAATTCTCACAGAATCACATATAGGTGCCACAGTTATCCCCATTTA
ATGGAGT **What is the distance between two sequences?** GATGAAAACCTTAGGAATA/
ATGATTTGCGCAGGCTCACCTGGATATTAAGACTGAGTCAAATGTTGGGTCTGGTCTGAC
ATGTTTGCTTTGTTCATGAGCACCACATATTGCCTCTCCTATGCAGTTAAGCAGGTAGGTG
GAAAAGCCCATGTTTGTCTCTACTCACACACTTCCGACTGAATGTATGTATGGAGTTTCTA
CAGATTCTTCAGTGCTCTGGATATTA ACTGGGTATCCCATGACTTTATTCTGACACTACCTC
CTTGTCAAATAGTTTGGACCTTGTCAAATAGTTTGGAGTCCTTGTCAAATAGTTTGGGGT
ACAGACCCCAAGTTAGGGGCTCAGTCCCACGAGGCCATCCTCACTTCAGATGACAAT
AAGTCCTAAGTTGTCACCATACTTTTGACCAACCTGTTACCAATCGGGGGTTCCCGTAAC
TTCTTGGGTTTAATAATTTGCTAGAACAGTTTACGGA ACTCAGAAAAACAGTTTATTTTCT
TTTCTGAGAGAGAGGGTCTTATTTTGTGCCCAGGCTGGTGTGCAATGGTGCAGTCATAG
TTGCAGCCTTGATTGTCTGGGTTCAGTGGTTCTCCACCTCAGCCTCCCTAGTAGCTGA
ACATGCCTGCACCACCACATCTGGCTAGTTTCTTTTATTTTTTGTATAGATGGGGTCTTGTT
TTGGCCAGGCTGGCCACAAATCCTGGTCTCAAGTGATCCTCCCACCTCAGCCTCTGAA/
CTGGGATTACAGATGTGAGCCACCACATCTGGCCAGTTCATTTCTTACTGGTTCATTG
AGGATACATCTCAGAAACAGTCAATGAAAGAGACGTGCATGCTGGATGCAGTGGCTCAT
GTAATCTCAGCACTTTGGGAGGCCAAGGTGGGAGGATCGCTTAAACTCAGGAGTTTGAG
AGCCTGGGC A A C ATGGGTG A A A A CCTGTCTCTATA A A A A ATTA A A A A ATA ATA ATA ATA A C

Simulating a changing sequence

1. Begin with a sequence of 10,000 nucleotides.

AAACAGTTTATTTTCTTTTTTTTCTGAGAGAGAGGGTCTTATTTTGTTGCC

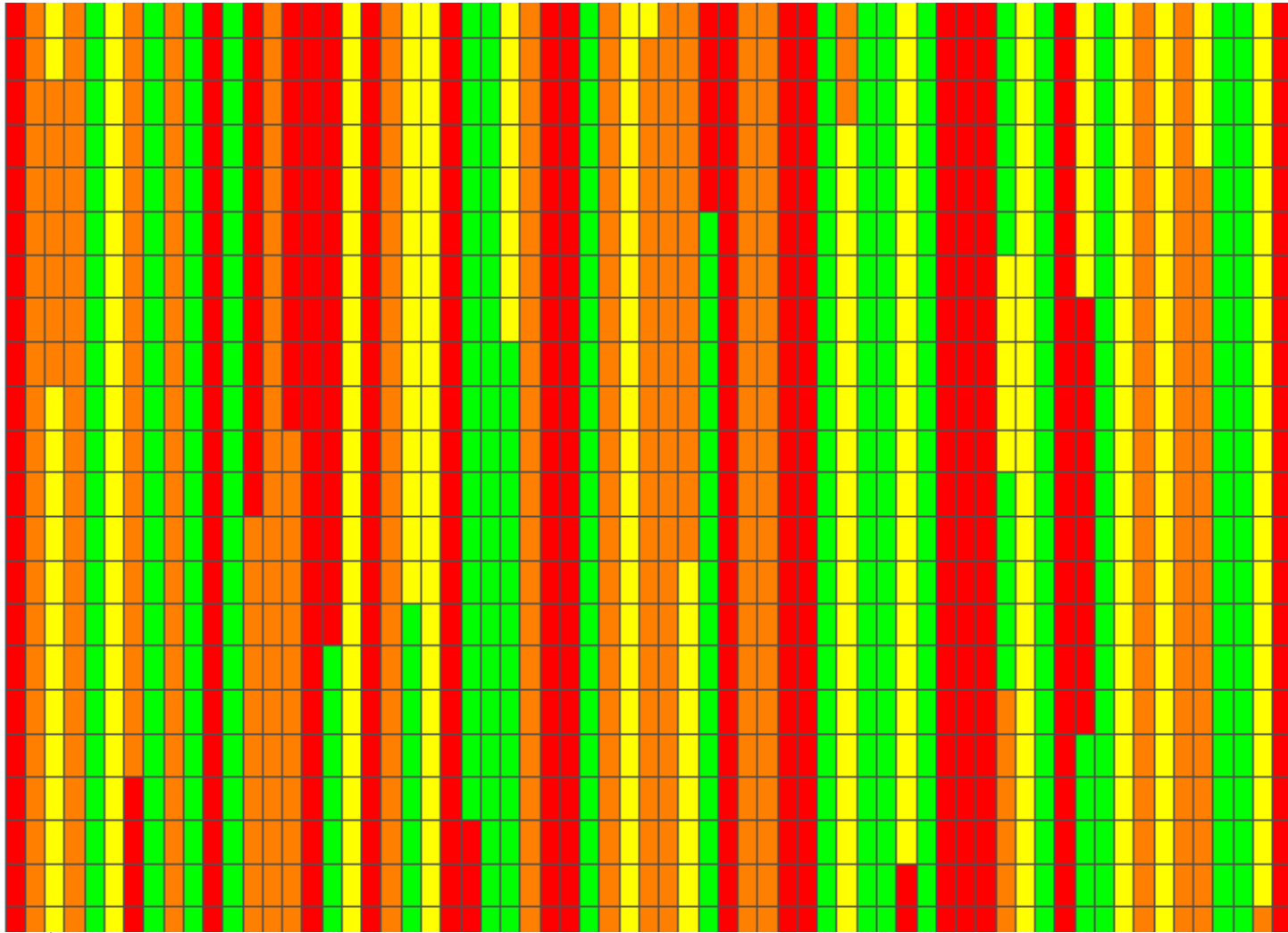
2. Choose a nucleotide at random and mutate it to another nucleotide.

AAACAGTTTATTTTCTTTTTTTTCTGAGAGAGAGGGTCTTATTTTGTTGCC

AAACAGTTTATTTTCTTTTTTTTCTGAGTGAGAGGGTCTTATTTTGTTGCC

3. Repeat 10,000 times. How many differences accumulate?

A sequence mutating at random



Back substitution

Substitution

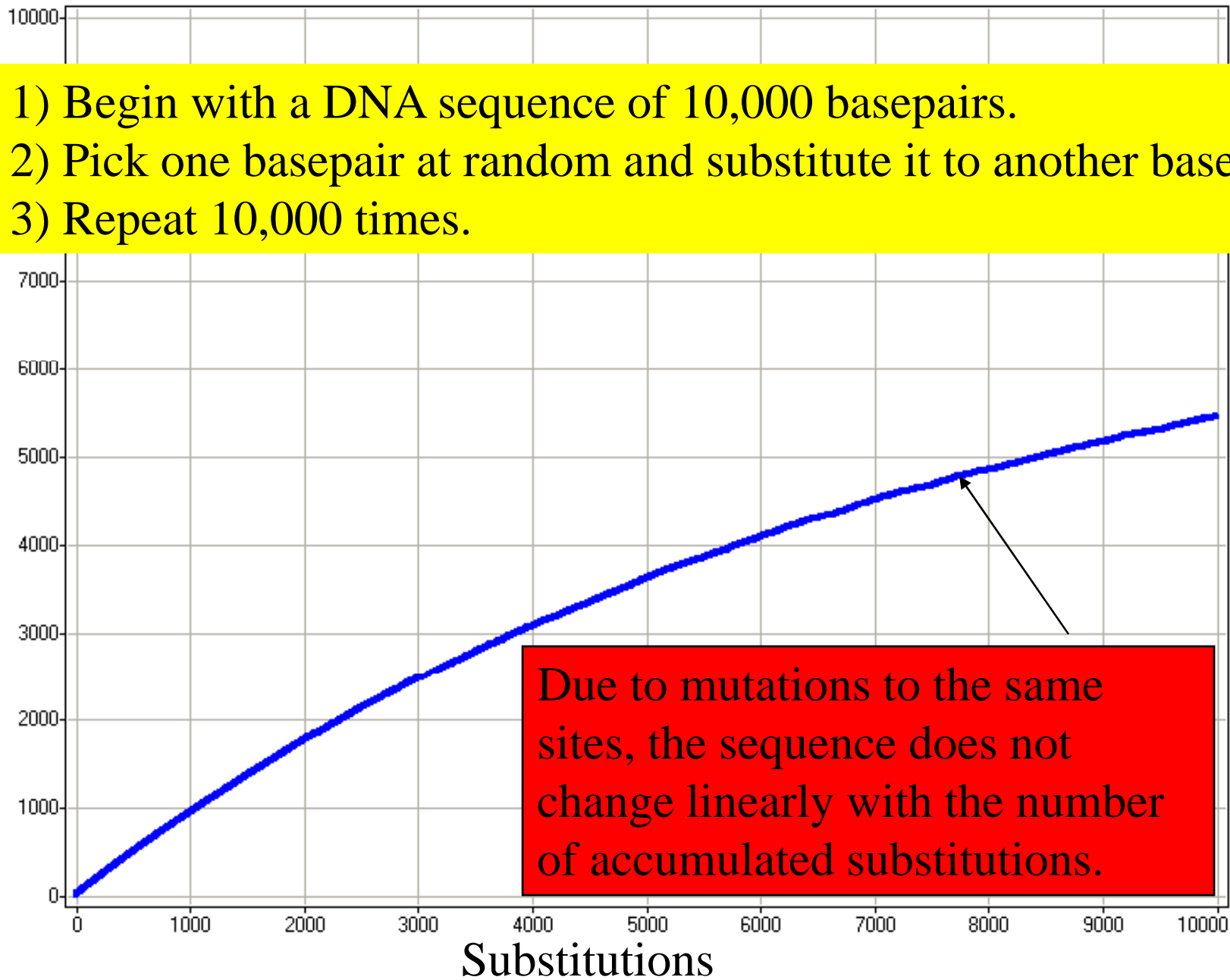
Multiple hits

21 changes but only 17 differences

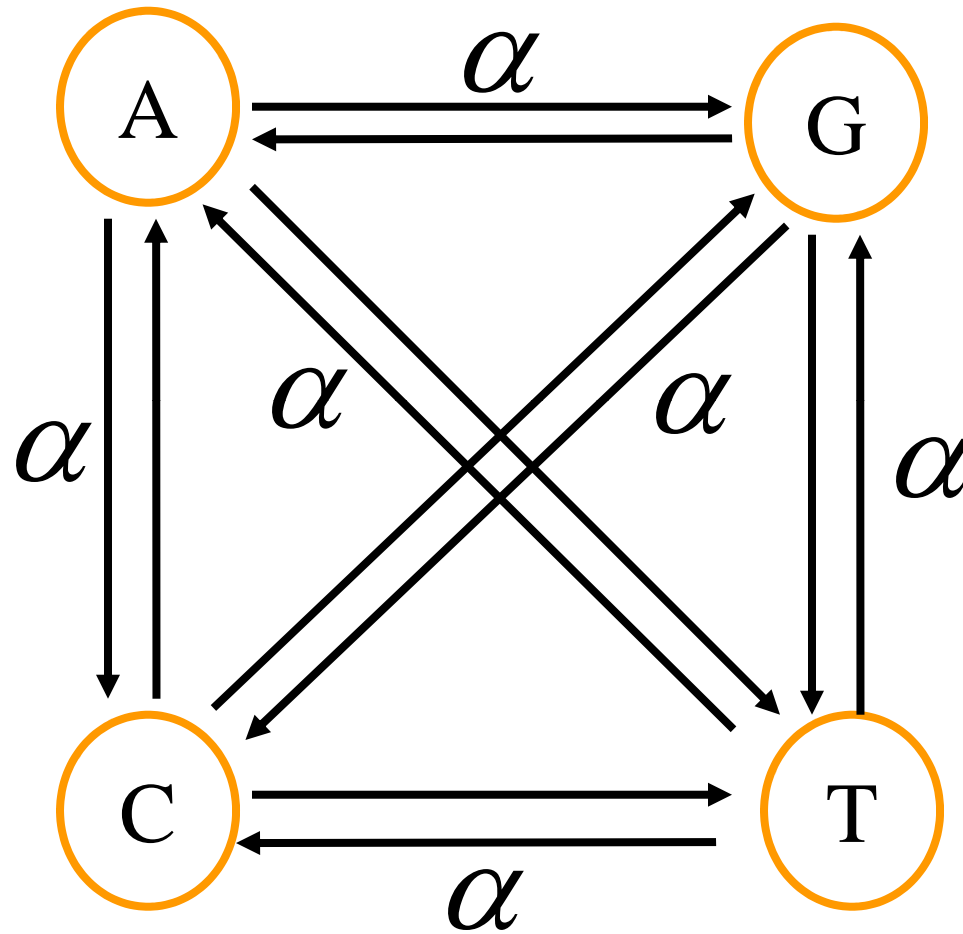
Simulating a changing sequence

- 1) Begin with a DNA sequence of 10,000 basepairs.
- 2) Pick one basepair at random and substitute it to another basepair.
- 3) Repeat 10,000 times.

Sequence Distance $\times 10,000$

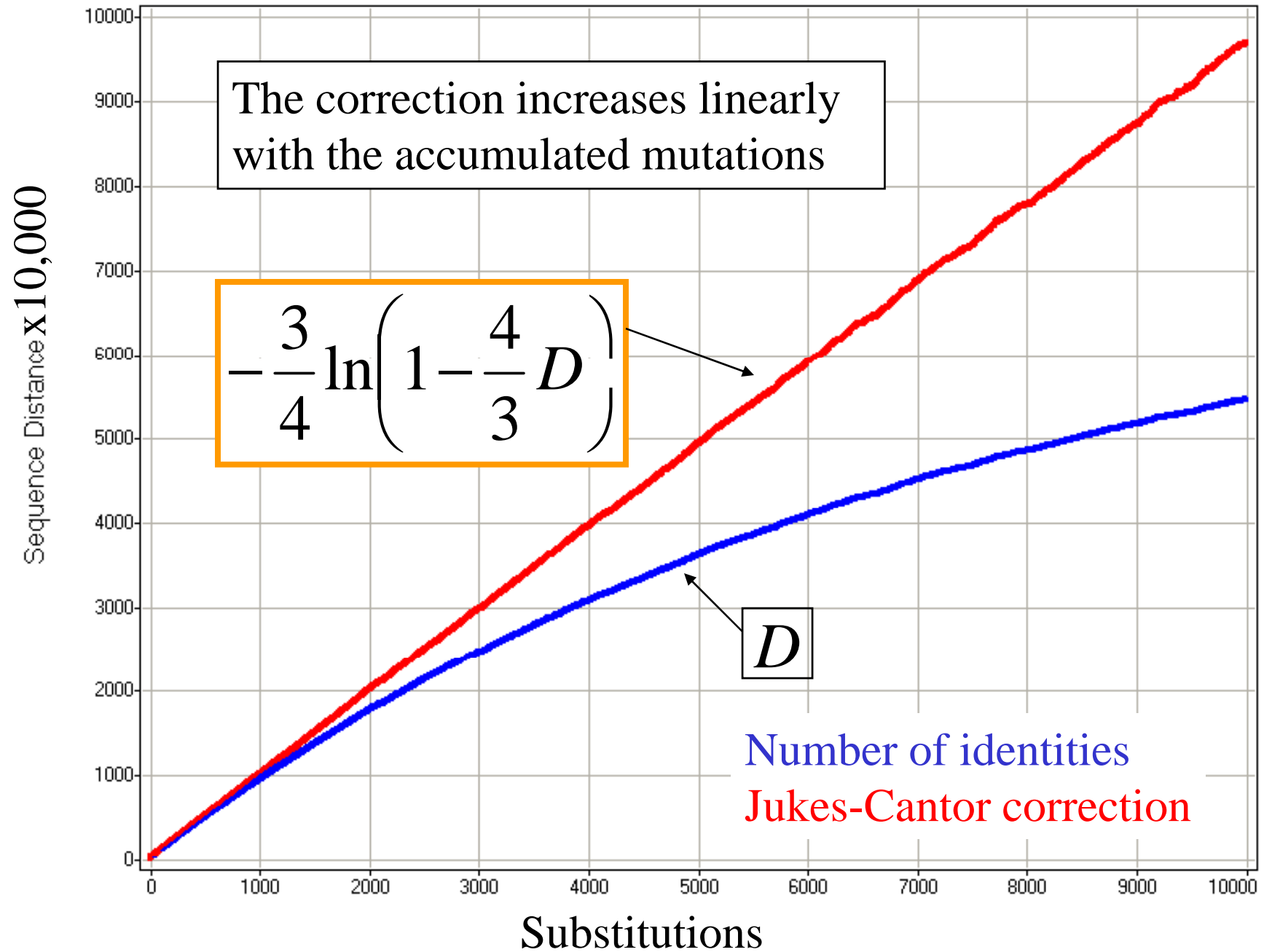


Jukes-Cantor model



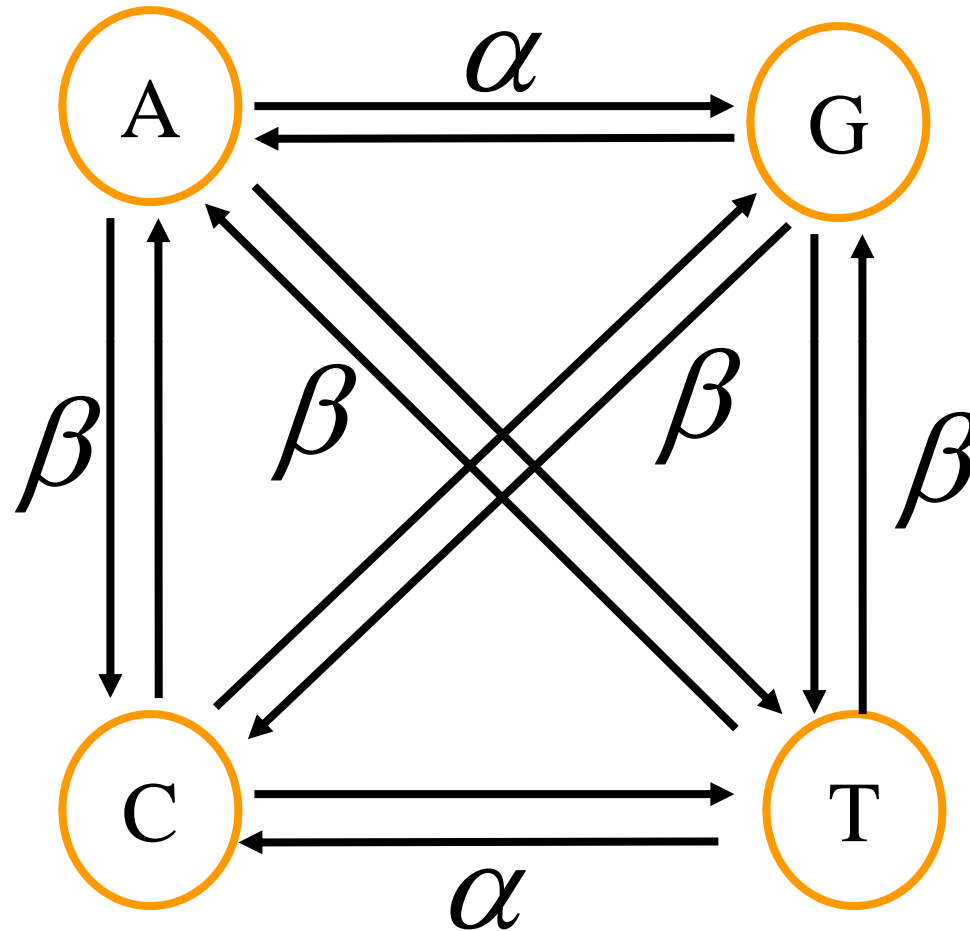
In this simulation we assumed that all changes occur at equal probabilities

The Jukes-Cantor correction



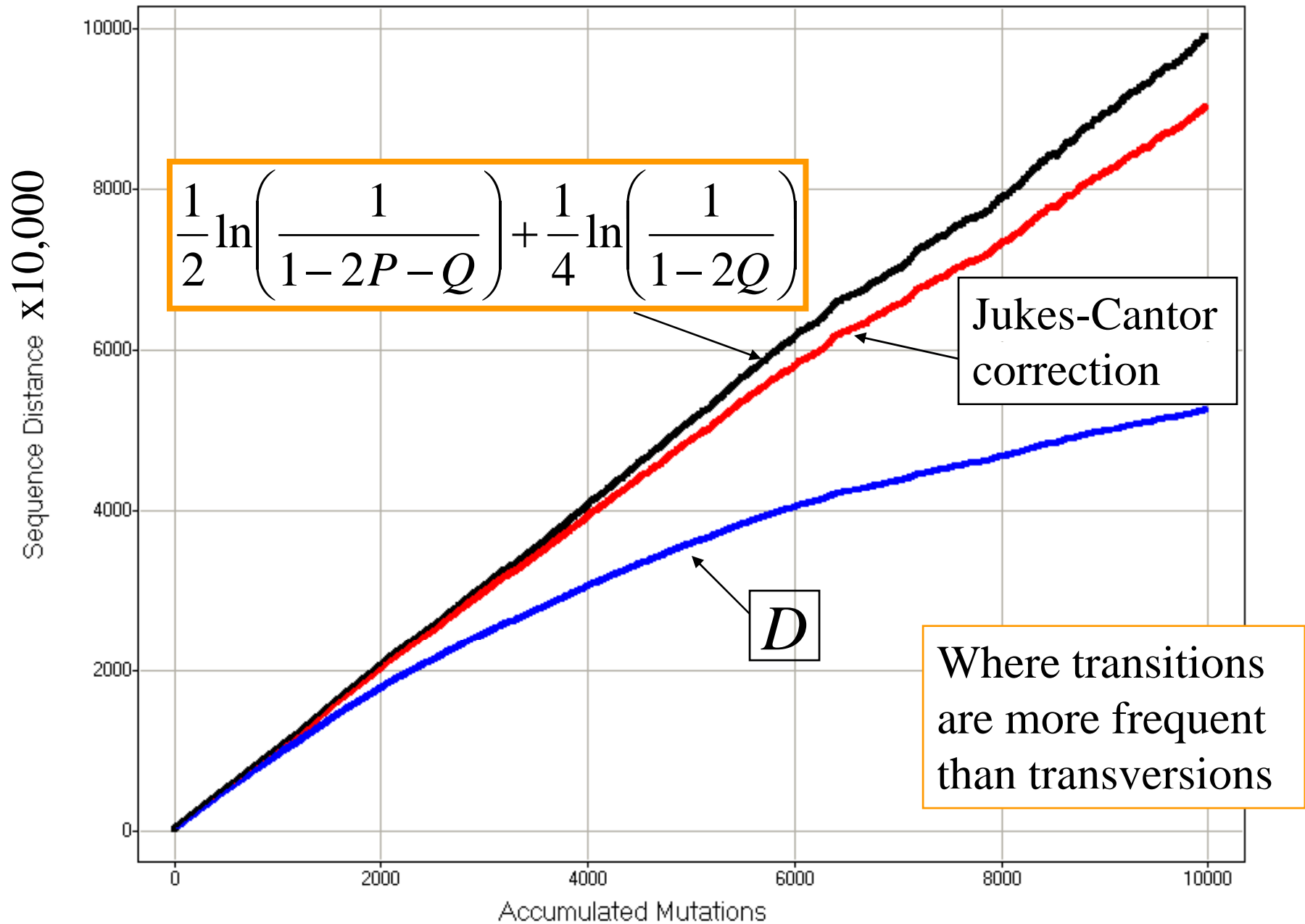
Kimura model

A more realistic simulation represents different probabilities for transitions than to transversions



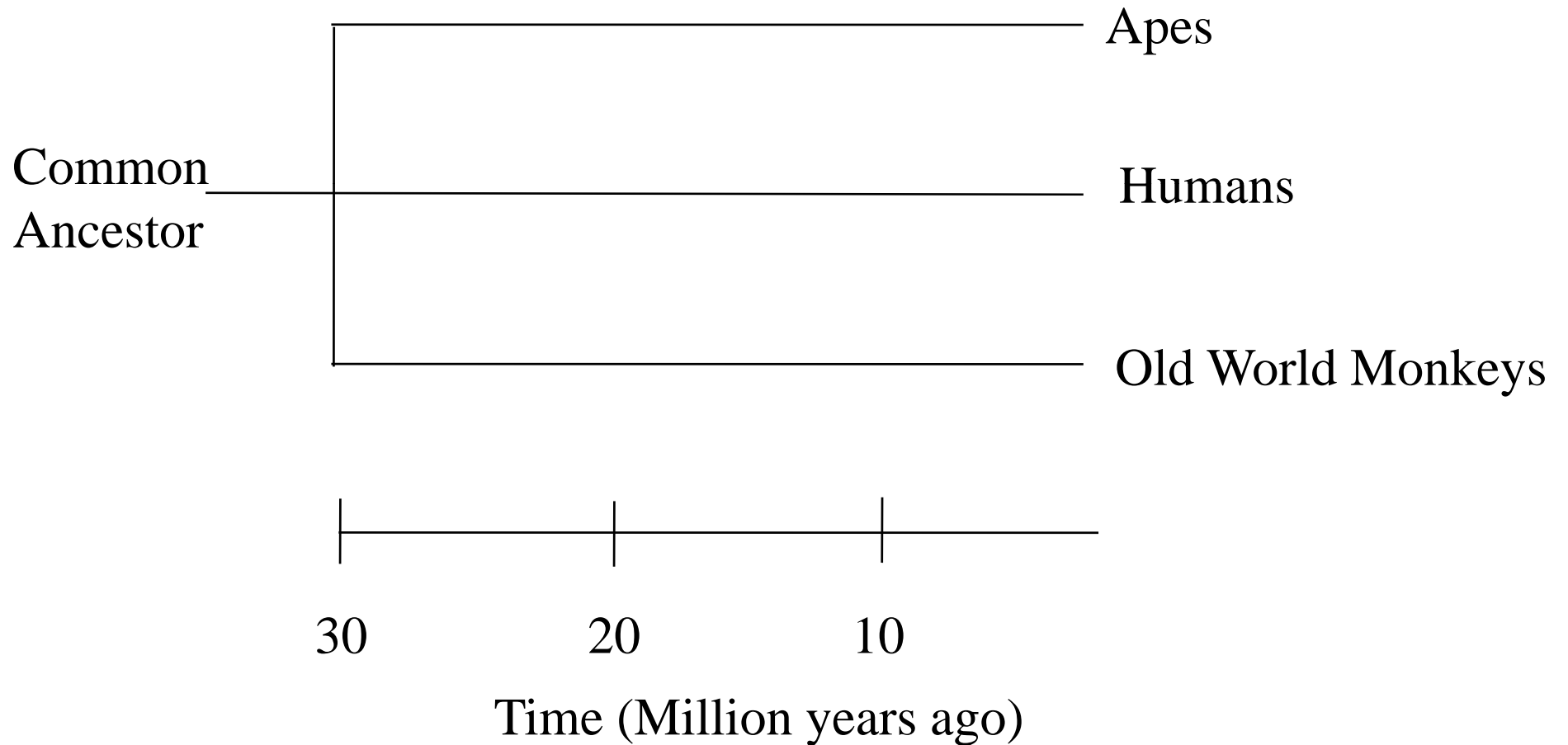
α = transitions β = transversions

The Kimura correction



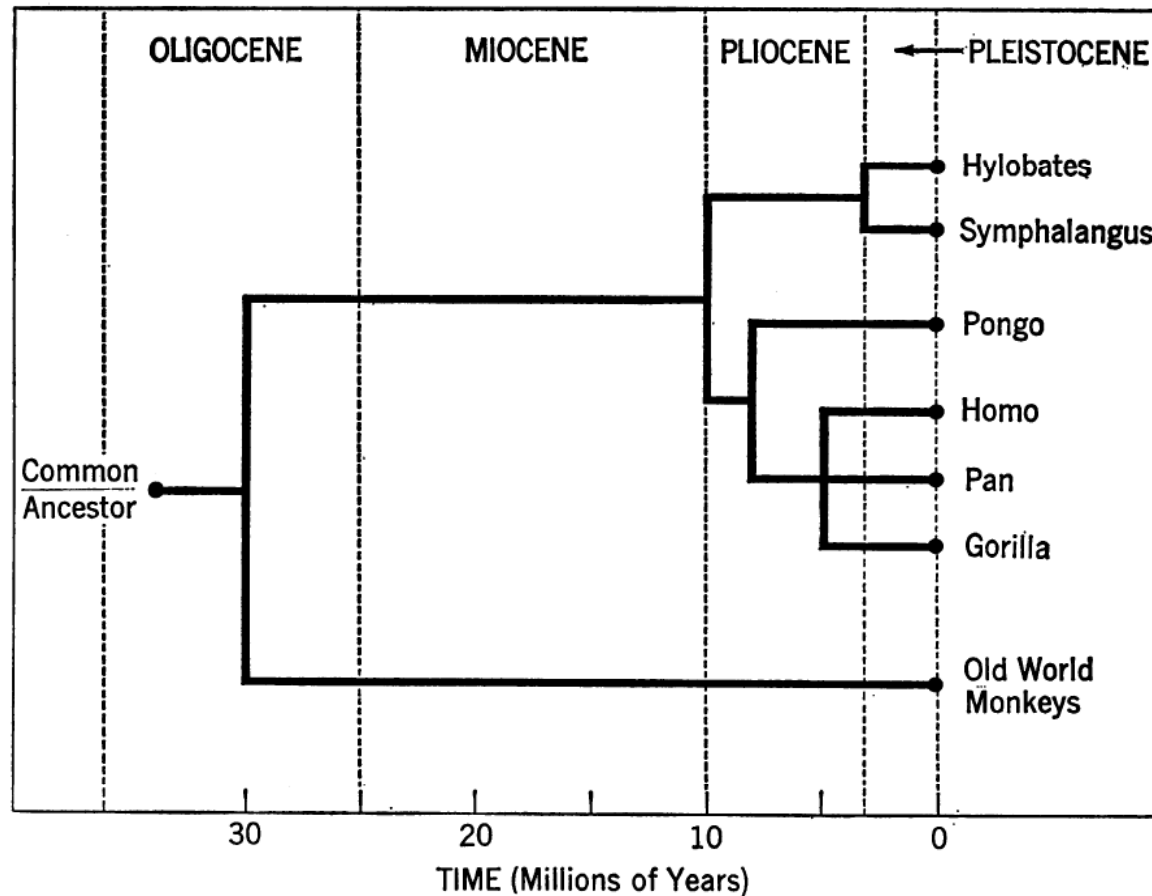
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AGCATAATATTTTCGTTAATTCTCACAGAATCACATATAGGTGCCACAGTTATCCCCATTTA
ATGGAGT **How Many Millions Of Years Separate Us From The Apes?** GATGAAAAC
GGAATAATGAATGATTTGCGCAGGCTCACCTGGATATTAAGACTGAGTCAAATGTTGGGT
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GCTCATGCCTGTAATCTCAGCACTTTGGGAGGCCAAGGTGGGAGGATCGCTTAAACTCA
TTTGAGACCAGCCTGGGCACCATGGTGA Δ Δ Δ CCTGTCTCTATA Δ Δ Δ Δ ATTA Δ Δ Δ Δ ATA ΔT

The Paleontological View of Human and Primate evolution in 1967



As drawn in Sean Carroll's "Remarkable Creatures" 2009

A new time scale for hominid evolution



Gibbon
Siamang
Orangutan
Human
Chimp
Gorilla

Fig. 1. Times of divergence between the various hominoids, as estimated from immunological data. The time of divergence of hominoids and Old World monkeys is assumed to be 30 million years.

Initial sequence of the chimpanzee genome and comparison with the human genome

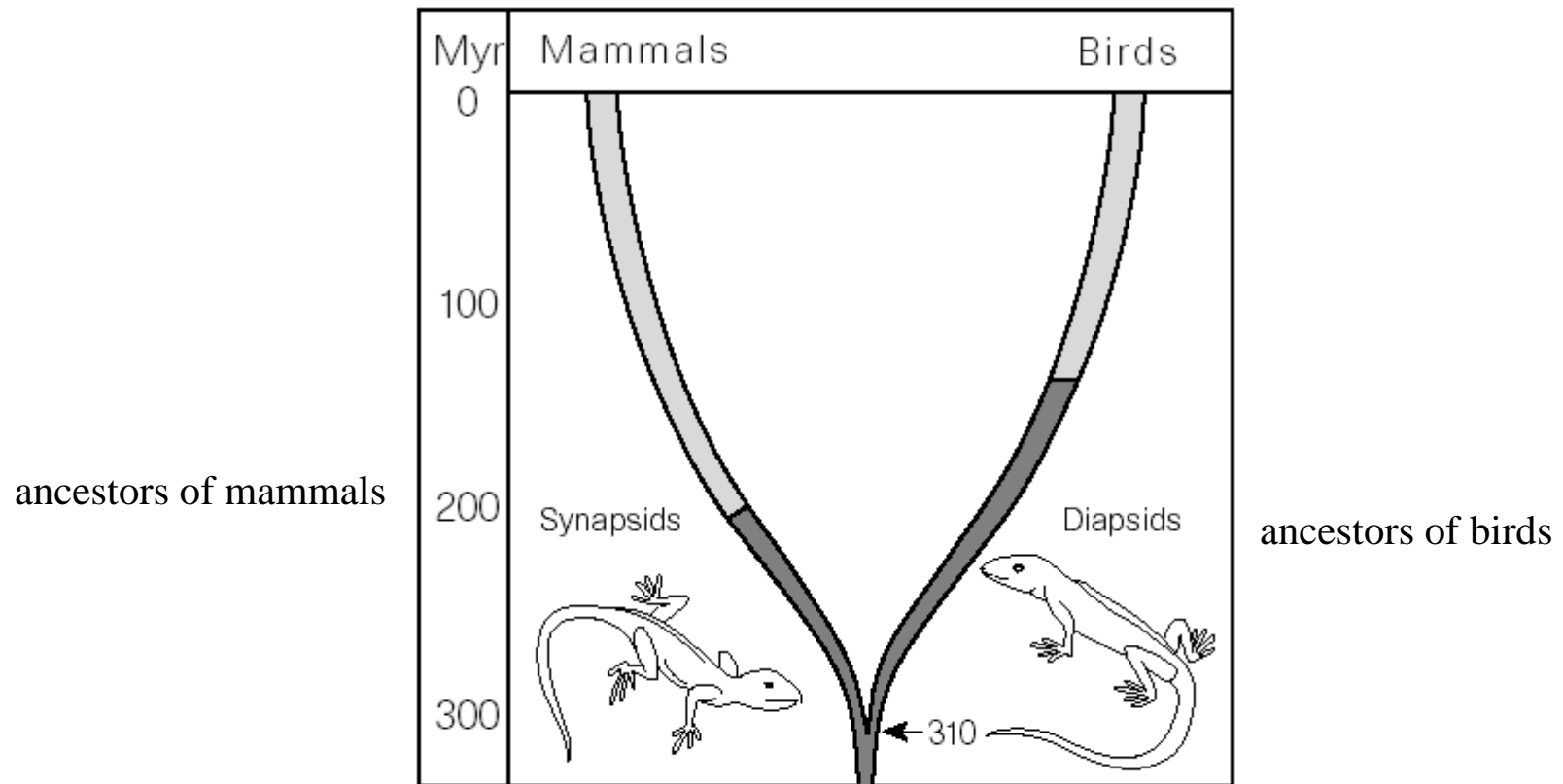
The Chimpanzee Sequencing and Analysis Consortium*



Figure 1 | Human-chimpanzee divergence in 1-Mb segments across the genome. **a**, Distribution of divergence of the autosomes (blue), the X chromosome (red) and the Y chromosome (green). **b**, Distribution of variation by chromosome, shown as a box plot. The edges of the box correspond to quartiles; the notches to the standard error of the median; and the vertical bars to the range. The X and Y chromosomes are clear outliers, but there is also high local variation within each of the autosomes.

- Single-nucleotide substitutions occur at a mean rate of 1.23% between copies of the human and chimpanzee genome.
- Orthologous proteins in human and chimpanzee are extremely similar, with, 29% being identical and the typical ortholog differing by only two amino acids, one per lineage.

Calibrating the vertebrate clock

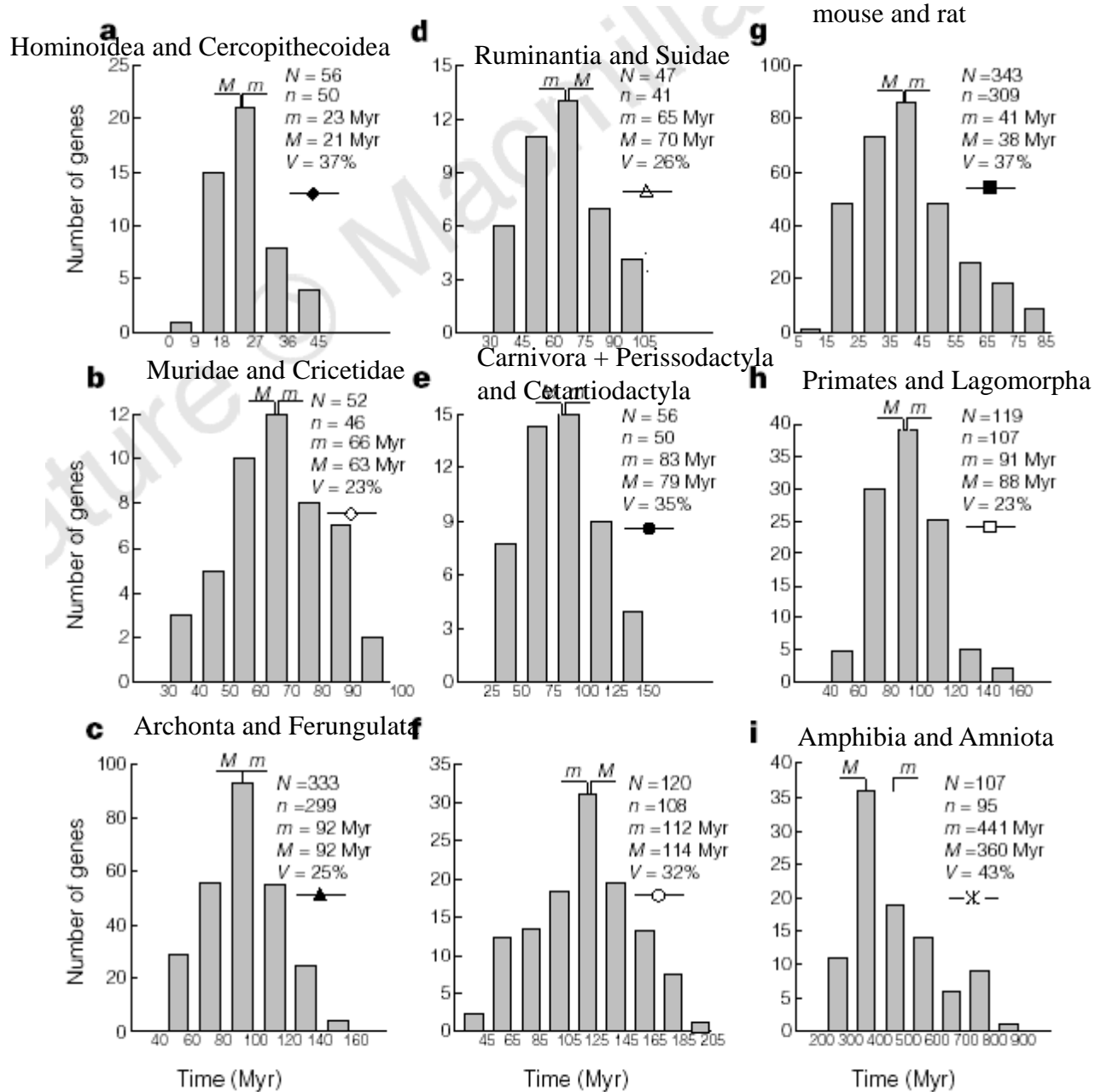


Based upon a detailed analysis of the fossil record, estimate that birds and mammals diverged 310 million years ago

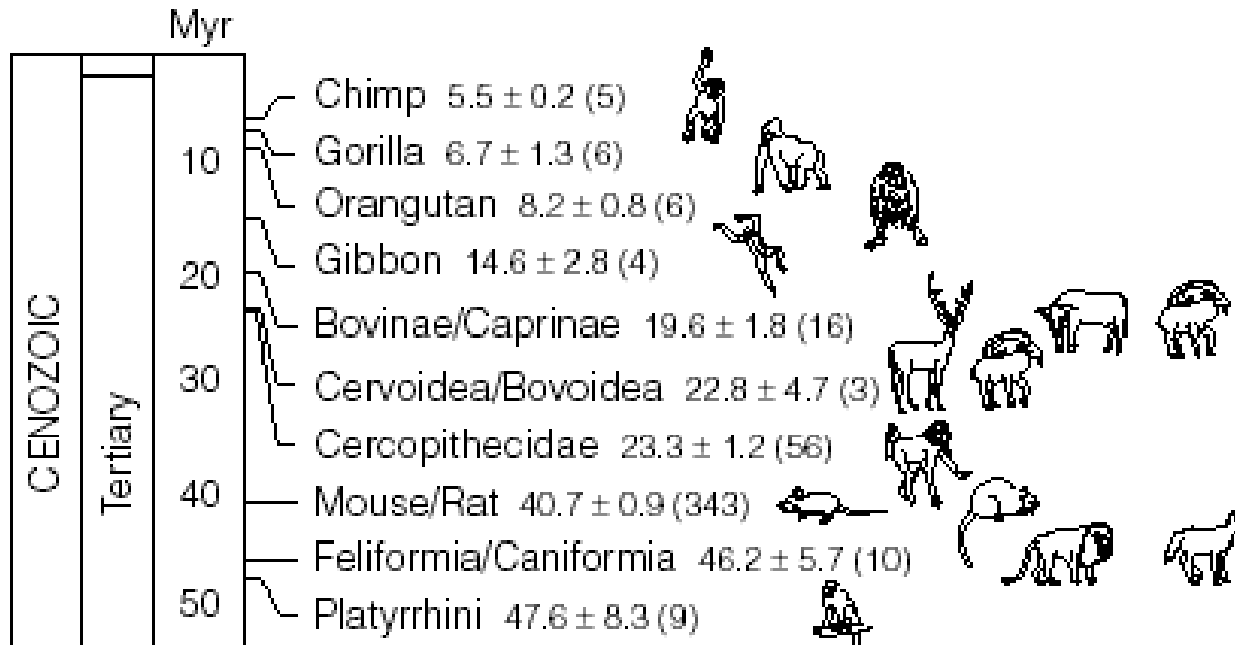
The arrow marks the first appearance of synapsids and diapsids in the fossil record at 310 Million years ago. Reconstructions of an early synapsid (*Varanosaurus*) and stem diapsid (*Hylonomus*) are shown. The dark shading represents the reptilian portion and the lighter shading represents the avian and mammalian portion of the phylogeny.

Kumar & Hedges. *Nature* (1998) **392** 917-920

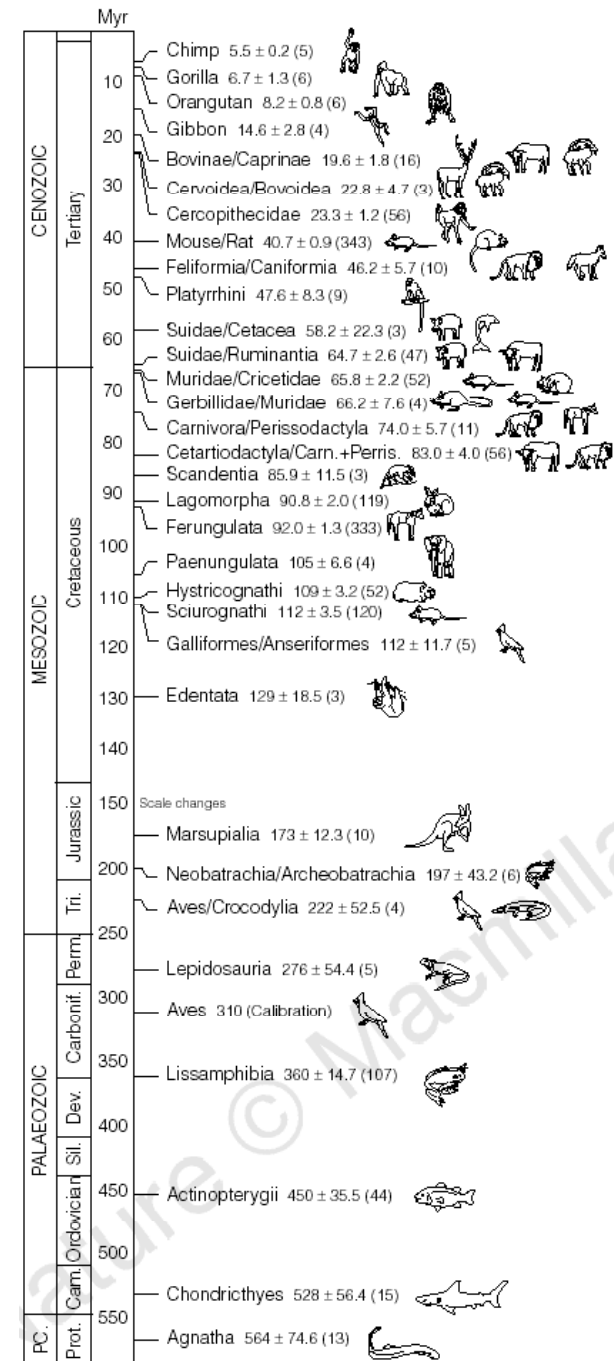
Distributions of gene divergences for nine time estimates



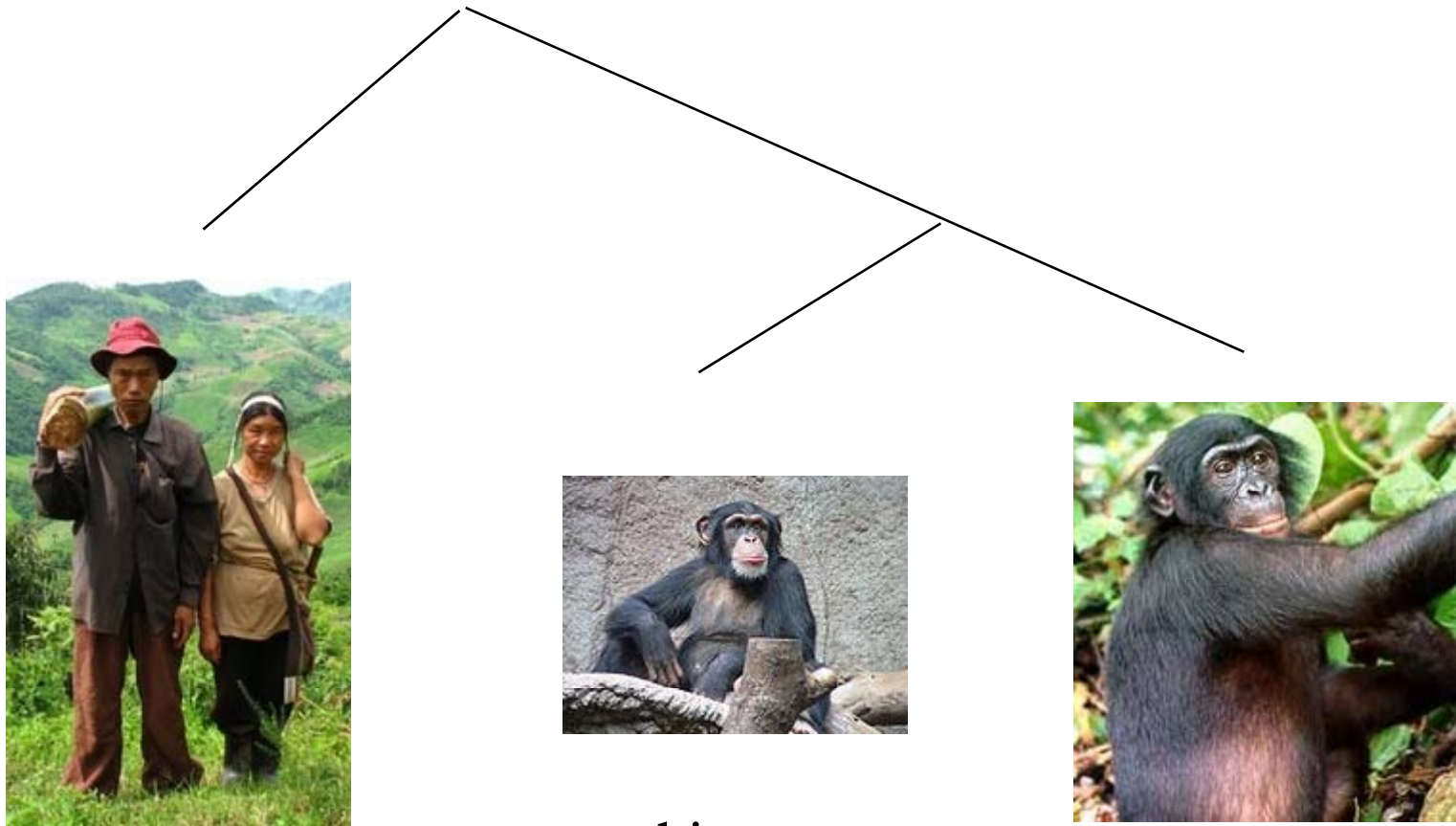
A molecular timescale for vertebrate evolution



Times indicate Million years divergence from human



The chimpanzee and bonobos are our closest living species relatives



human



chimp



bonobo

images from Wikipedia