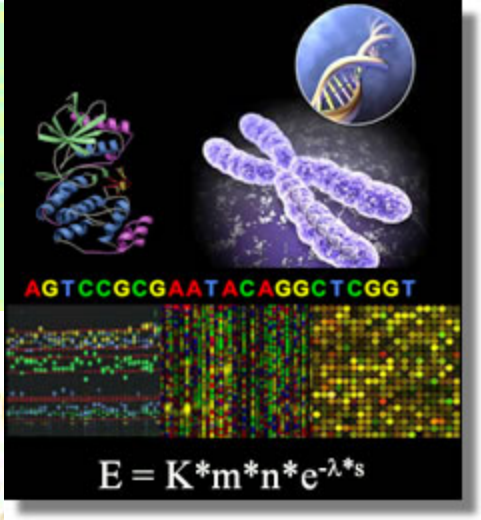
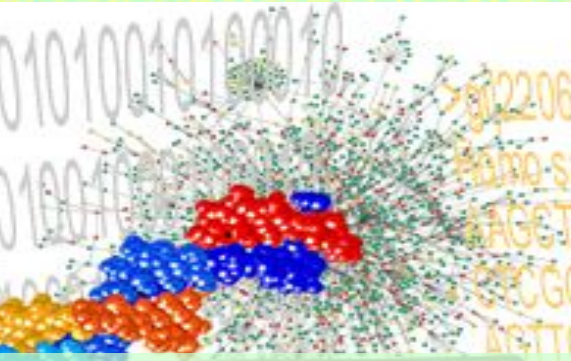
Introduction to





Bioinformatics

Introduction to Bioinformatics.

LECTURE 7: Phylogenetic Trees

* **Chapter 7: SARS, a post-genomic epidemic**

7.1 *SARS: the outbreak*

* February 28, 2003, Hanoi, the Vietnam French hospital called the WHO with a report of an influenza-like infection.

* Dr. Carlo Urbani (WHO) came and concluded that this was a new and unusual pathogen.

* Next few days Dr. Urbani collected samples, worked through the hospital documenting findings, and organized patient quarantine.

* Fever, dry cough, short breath, progressively worsening respiratory failure, death through respiratory failure.

7.1 *SARS: the outbreak*

* Dr. Carlo Urbani was the first to identify *Severe Acute Respiratory Syndrome: SARS*.

* In three weeks Dr. Urbani and five other healthcare professionals from the hospital died from the effects of *SARS*.

* By March 15, 2003, the WHO issued a global alert, calling *SARS* a worldwide health threat.

Introduction to Bioinformatics
LECTURE 7: PHYLOGENETIC TREES

Dr. Carlo Urbani (1956-2003)
WHO

Hanoi, the Vietnam French hospital, March 2003

Origin of the SARS epidemic

* Earliest cases of what now is called *SARS* occurred in November 2002 in Guangong (P.R. of China)

* Guangzhou hospital spread 106 new cases

* A doctor from this hospital visited Hong Kong, on Feb 21, 2003, and stayed in the 9th floor of the Metropole Hotel

* The doctor became ill and died, diagnozed pneumonia

* Many of the visitors of the 9th floor of the Metropole Hotel now became disease carriers themselves

Origin of the SARS epidemic

* One of the visitors of the 9th floor of the Metropole Hotel was an American business man who went to Hanoi, and was the first patient to bring *SARS* to the Vietnam French hospital of Hanoi.

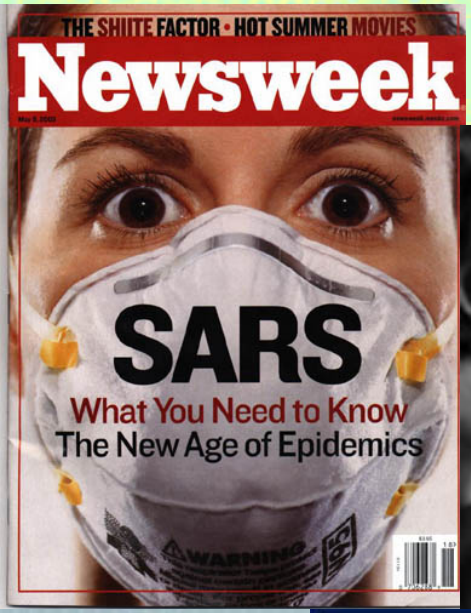
* He infected 80 people before dying

* Other visitors of the 9th floor of the Metropole Hotel brought the diesease to Canada, Singapore and the USA.

* By end April 2003, the disease was reported in 25 countries over the world, on 4300 cases and 250 deaths.

Introduction to Bioinformatics
LECTURE 7: PHYLOGENETIC TREES

SARS panic & Mediahype, April-June 2003



The SARS corona virus

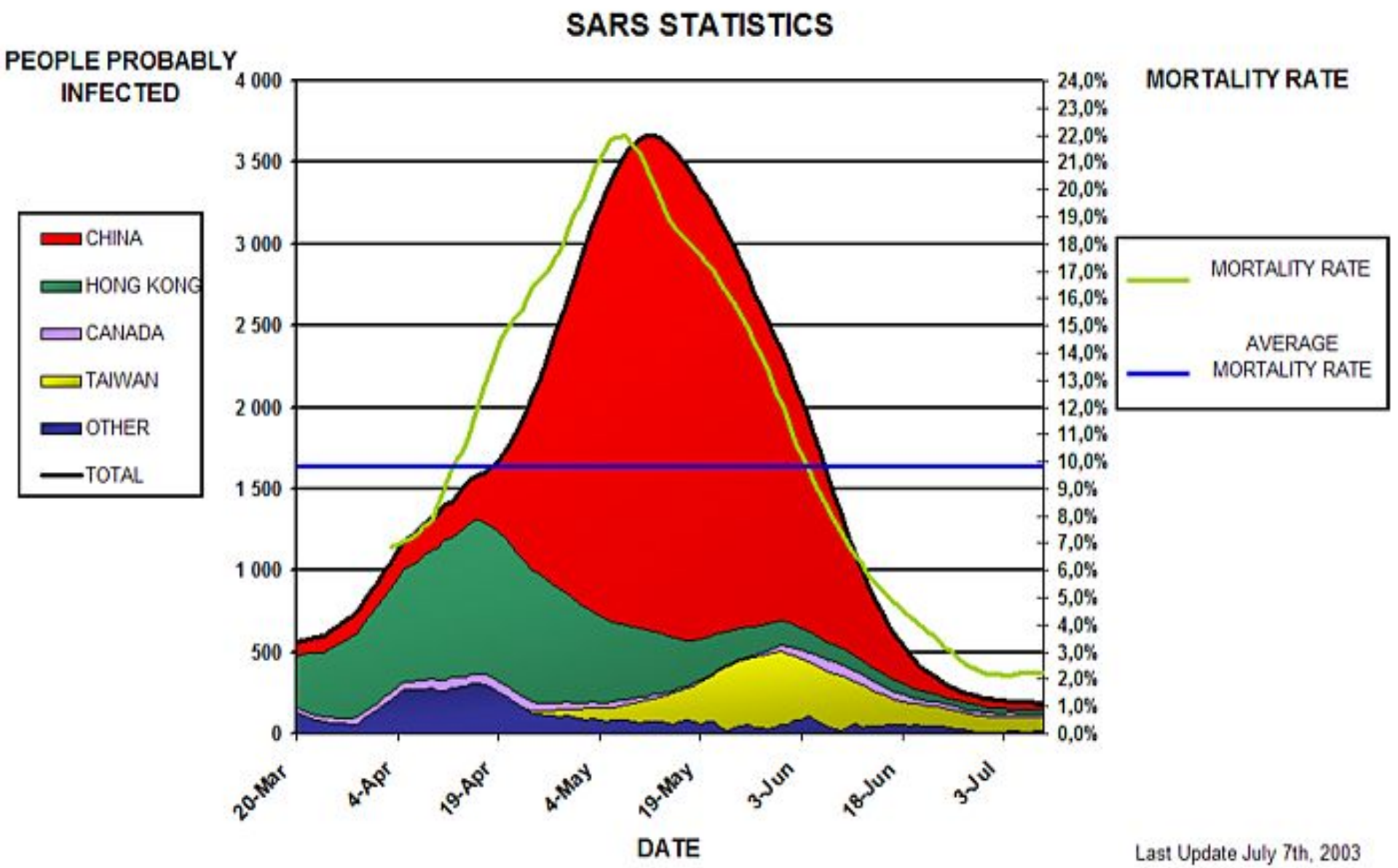
* Early March 2003, the WHO coordinated an international research .

* End March 2003, laboratories in Germany, Canada, United Staes, and Hong Kong independently identified a novel virus that caused *SARS*.

* The *SARS* corona virus (SARS-CoV) is an RNA virus (like HIV).

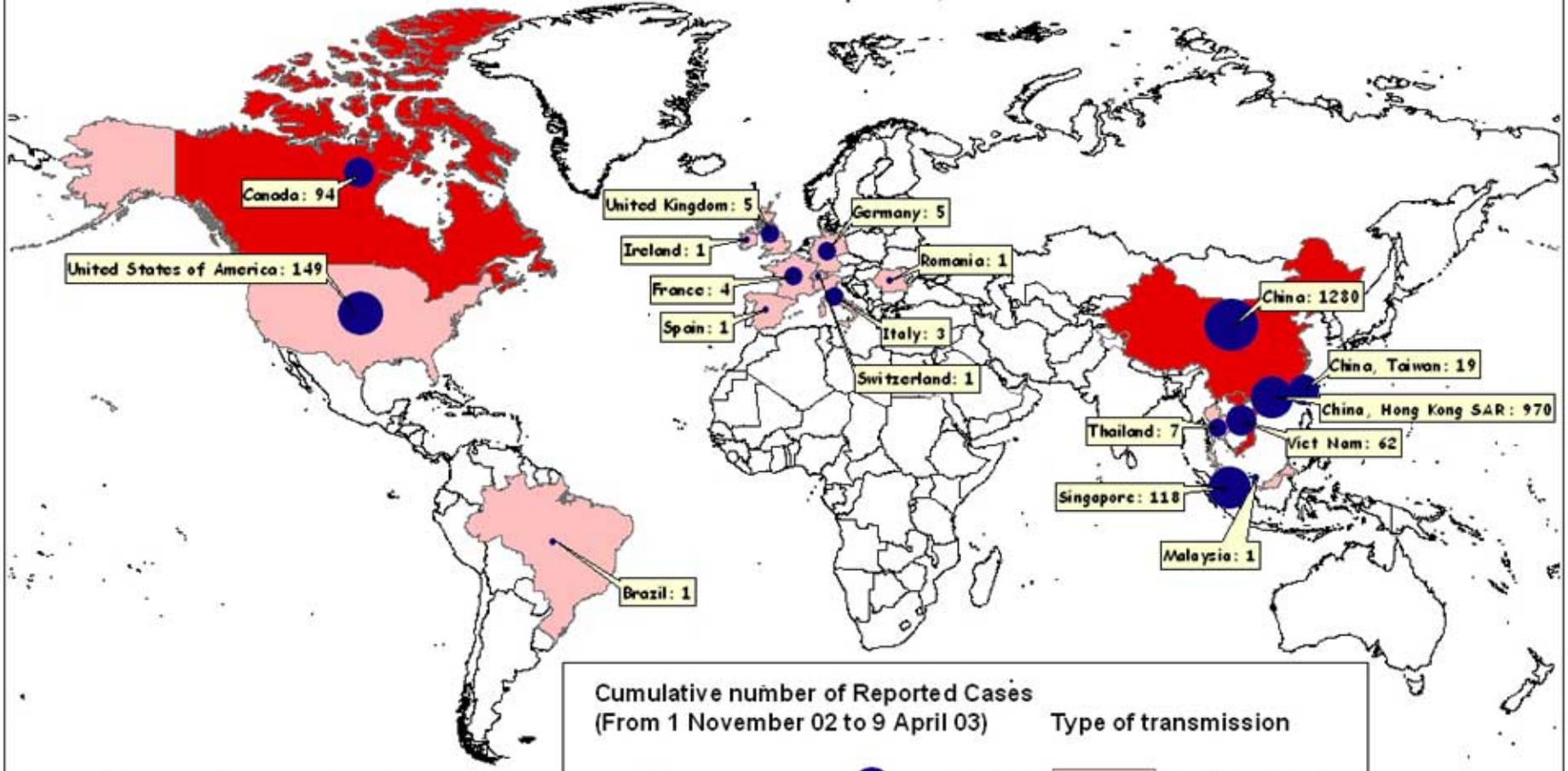
* Corona viruses are common in humans and animals, causing ~25% of all upper respiratory tract infections (e.g. common cold) .

Introduction to Bioinformatics
7.1 SARS: the outbreak



SARS : Cumulative Number of Reported Probable* Cases

Total number of cases: 2722 as of 9 Apr 2003,15:00 GMT+2



Cumulative number of Reported Cases (From 1 November 02 to 9 April 03)

1
2 - 10
11 - 100
101 - 1000
>1000

Type of transmission

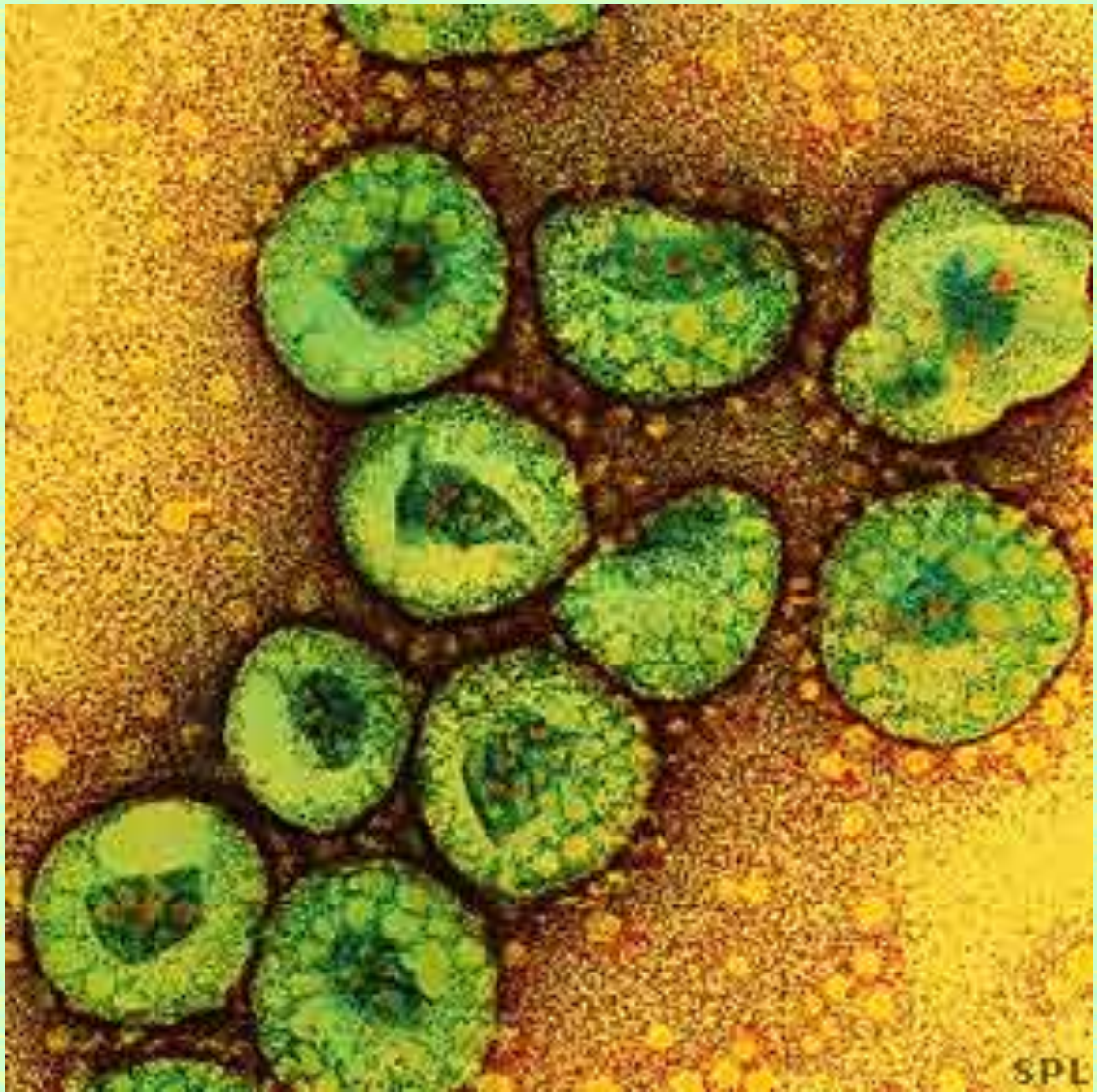
no local transmission
local transmission

*Due to differences in the case definitions being used at a national level, probable cases are reported by all countries except the United States of America, which is reporting suspect cases under investigation.

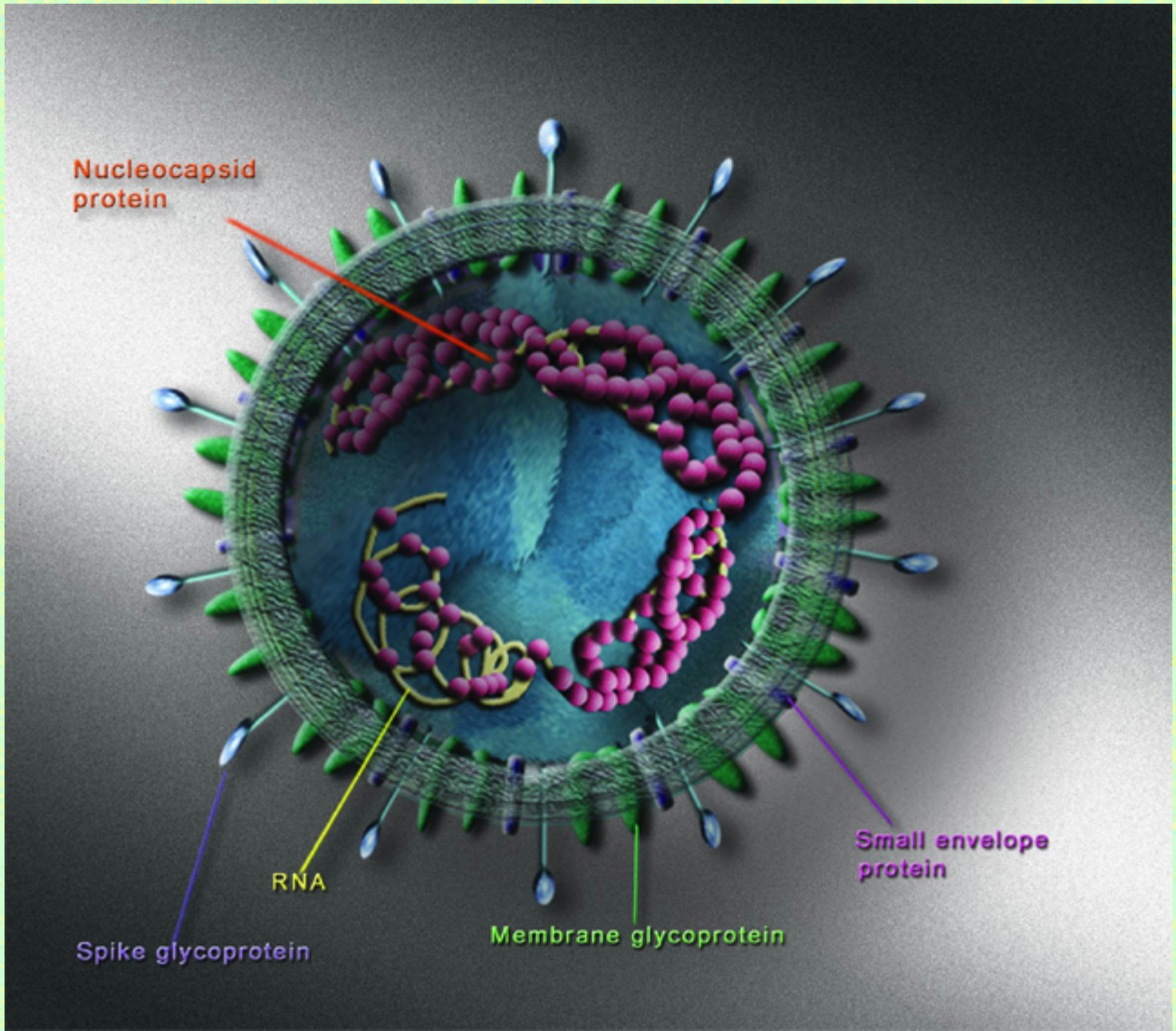
The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Data Source: World Health Organization
Map Production: Public Health Mapping Team
Communicable Diseases (CDS)
©World Health Organization, April 2003

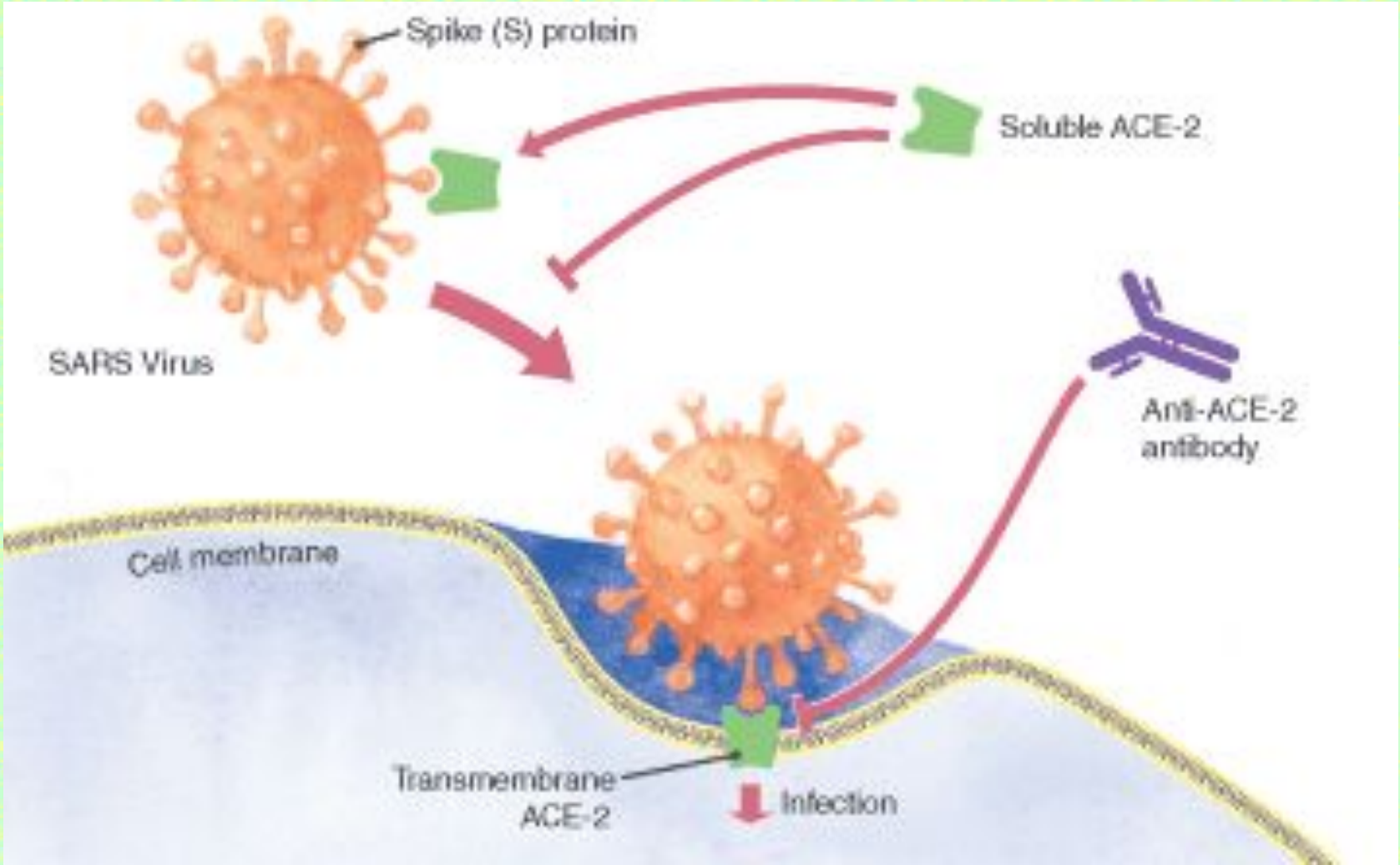
The SARS corona virus



The SARS corona virus



The SARS corona virus



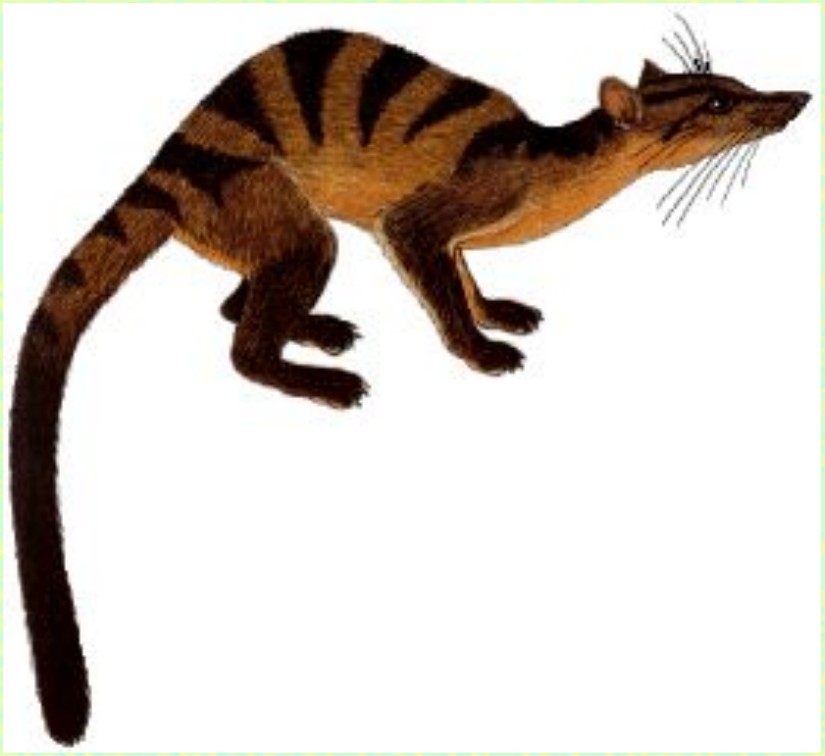
The SARS corona virus

* April 2003, a laboratory in Canada announced the entire RNA genome sequence of the *SARS* CoV virus.

* Phylogenetic analysis of the *SARS* corona virus showed that the most closely related CoV is the *palm civet*.

* The palm civet is a popular food item in the Guangdong province of China.

Introduction to Bioinformatics
7.1 SARS: the outbreak



Palm civet *alive*

Palm civet *as Chinese food*

Phylogenetic analysis of SARS CoV

* May 2003, 2 papers in Science reported the full genome of *SARS* CoV.

* Genome of *SARS* CoV contains 29,751 bp.

* Substantially different from all human CoVs.

* Also different from bird CoVs – so no relation to bird flue.

* End 2003 *SARS* had spread over the entire world

Phylogenetic analysis of SARS CoV

Phylogenetic analysis halps to answer:

* What kind of virus caused the original infection?

* What is the source of the infection?

* When and where did the virus cross the species border?

* What are the key mutations that enabled this switch?

* What was the trajectory of the spread of the virus?

7.2 *On trees and evolution*

* The trajectory of the spread of SARS can be represented by a tree

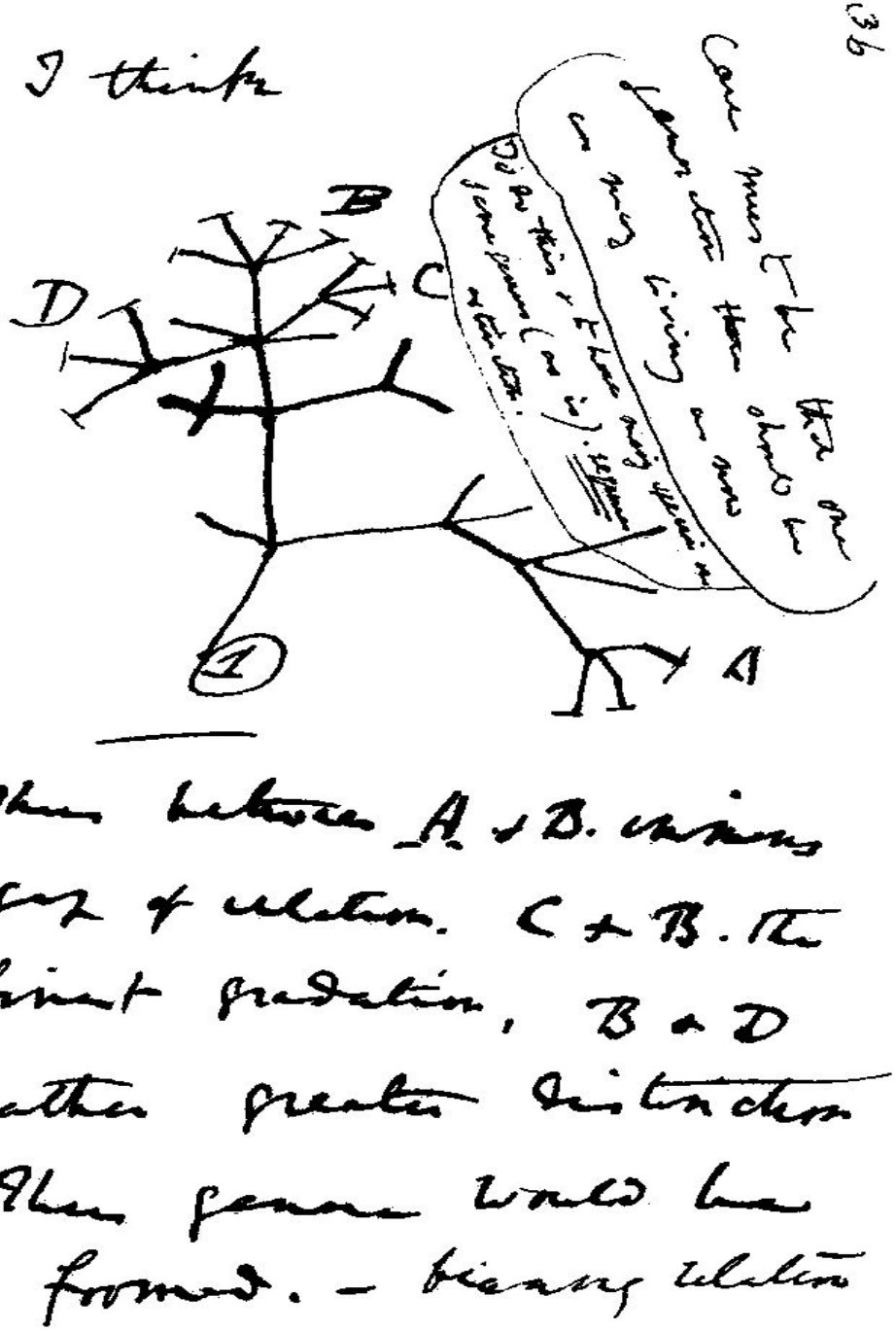
* The network of relation ships branched over and over as SARS spread over the world.

* Traditionally, the evolutionary history connecting any group of species has been represented by a tree

* The only figure in Darwin's "On the origin of species" is a tree.

Introduction to Bioinformatics
LECTURE 7: PHYLOGENETIC

The only figure in Darwin's "On the origin of species" is a tree.

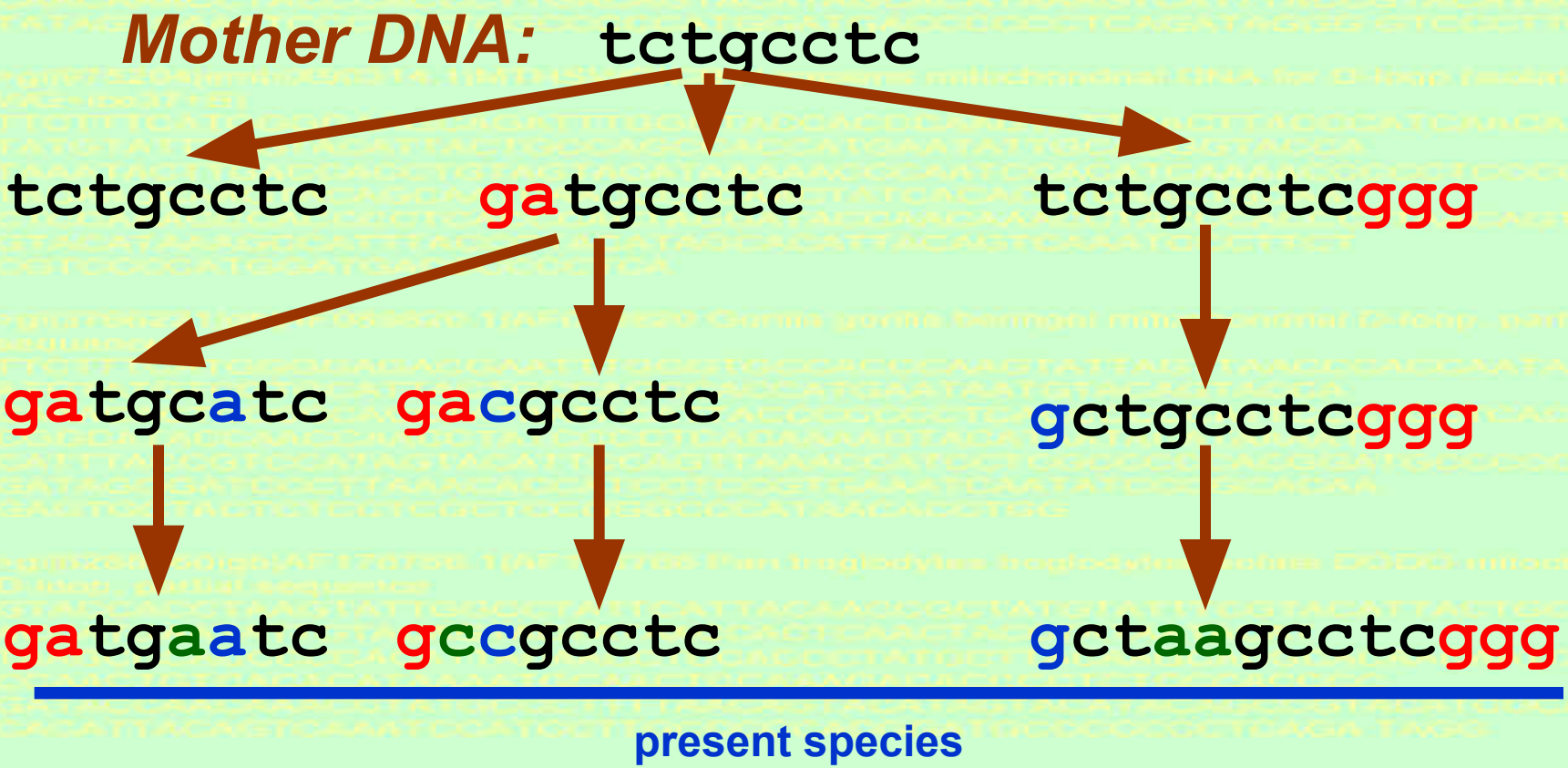


7.2 *On trees and evolution*

* Normal procreation of individuals is via a tree

* In case of e.g. horizontal gene transfer a phylogenetic network is more appropriate

The biological basis of evolution



Phylogenetics

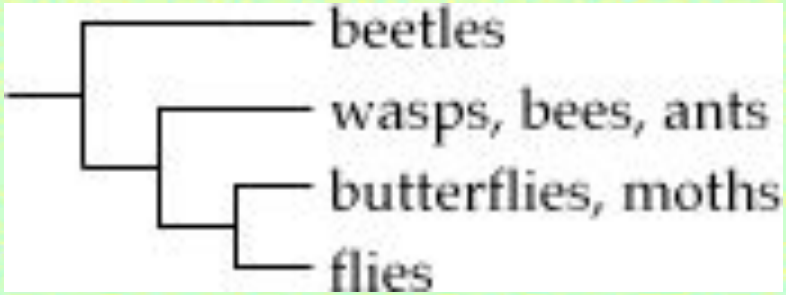
phylogenetics is the study of evolutionary relatedness among various groups of organisms (e.g., species, populations).

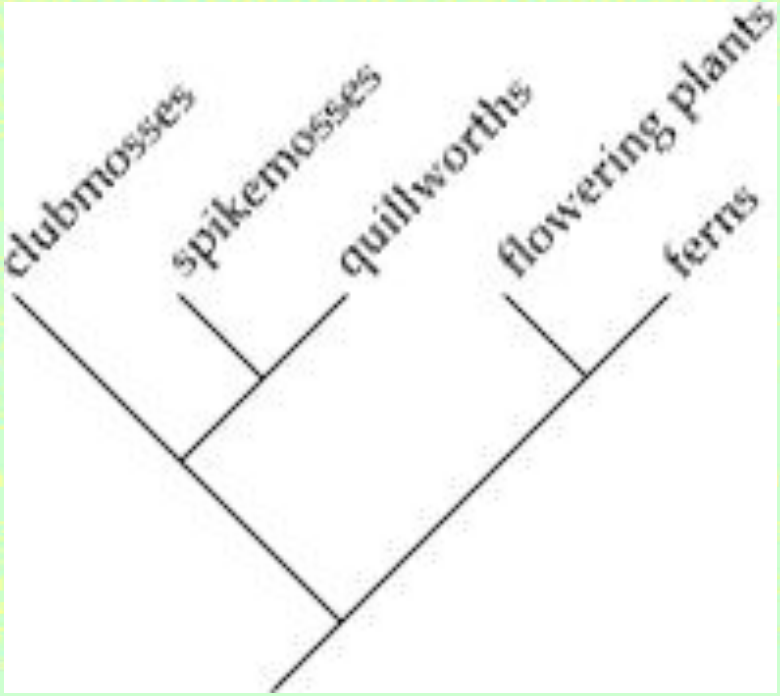
Cladistics

As treelike relationship-diagrams called "cladogram" is drawn up to show different hypotheses of relationships.

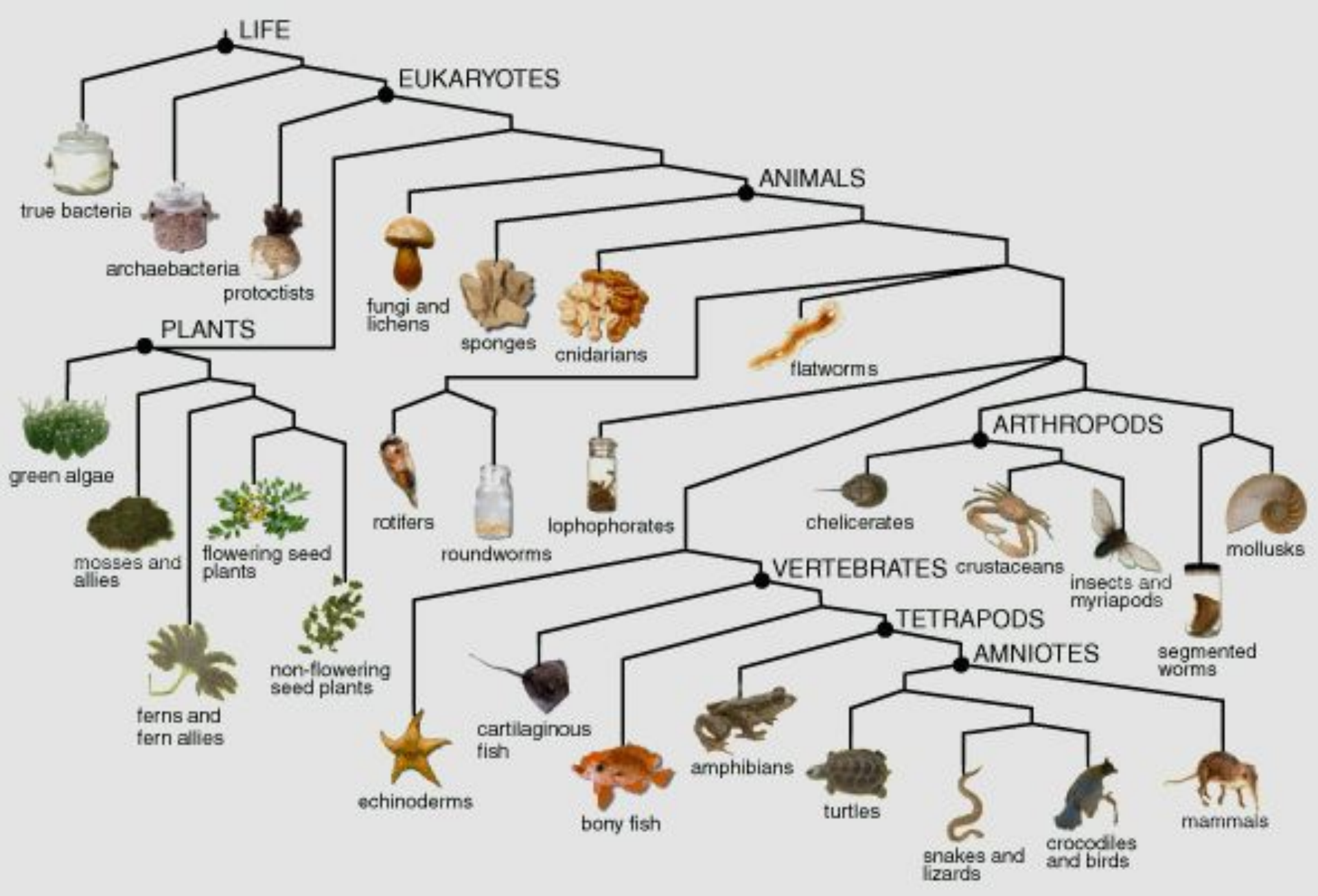
A cladistic analysis is typically based on morphological data.

Cladistics


beetles
wasps, bees, ants
butterflies, moths
flies


clubmosses
spikemosses
quillworths
flowering plants
ferns

Cladistics : *tree of life*



Phylogenetic Trees

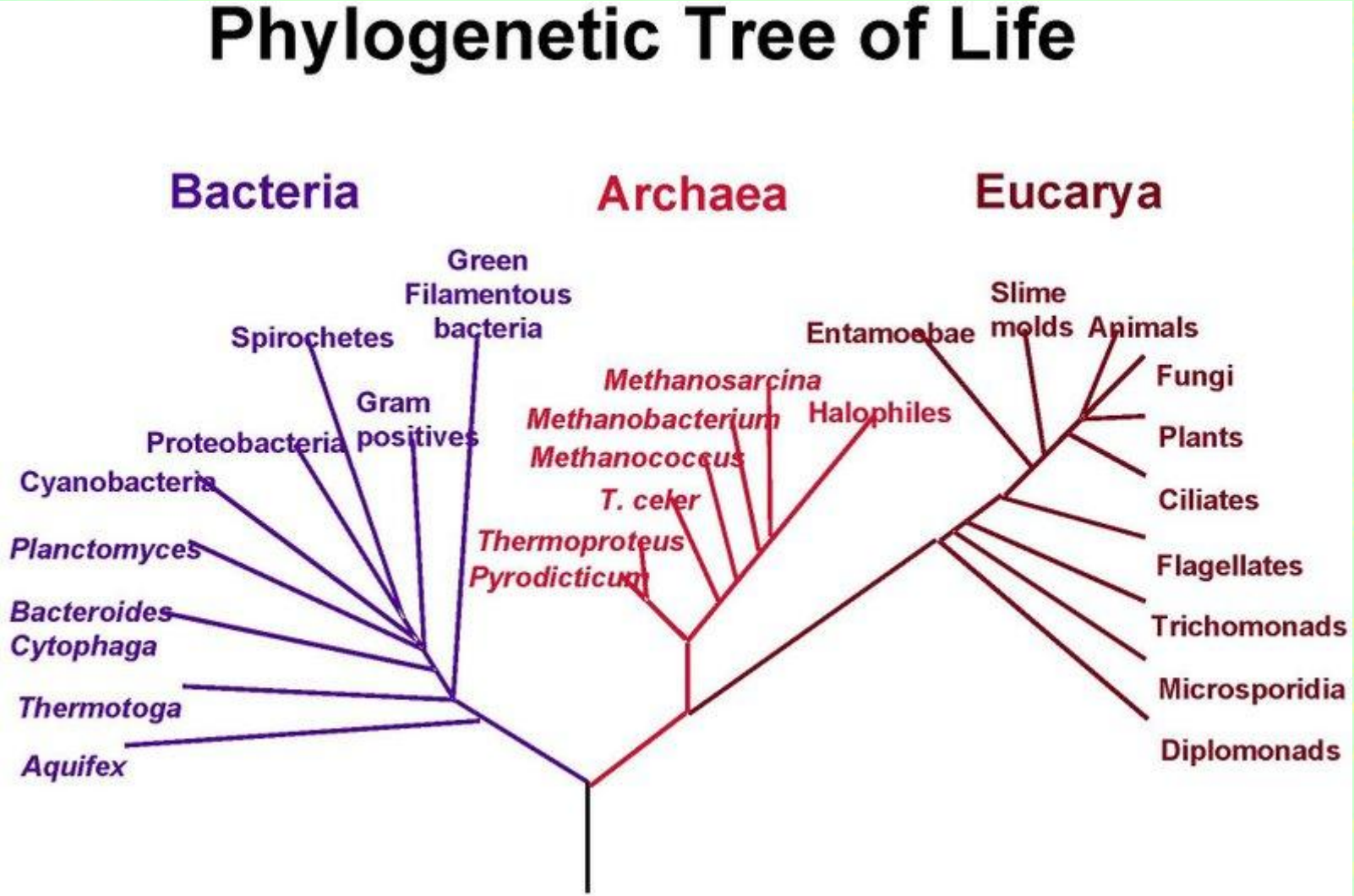
A phylogenetic tree is a tree showing the evolutionary interrelationships among various species or other entities that are believed to have a common ancestor. A phylogenetic tree is a form of a cladogram. In a phylogenetic tree, each node with descendants represents the most recent common ancestor of the descendants, and edge lengths correspond to time estimates.

Each node in a phylogenetic tree is called a taxonomic unit. Internal nodes are generally referred to as Hypothetical Taxonomic Units (HTUs) as they cannot be directly observed.

Rooted and Unrooted Trees

A **rooted phylogenetic tree** is a directed tree with a unique node corresponding to the (usually imputed) most recent common ancestor of all the entities at the leaves of the tree. Figure 1 depicts a rooted phylogenetic tree, which has been colored according to the three-domain system (Woese 1998). The most common method for rooting trees is the use of an uncontroversial outgroup - close enough to allow inference from sequence or trait data, but far enough to be a clear outgroup.

Rooted Phylogenetic Tree

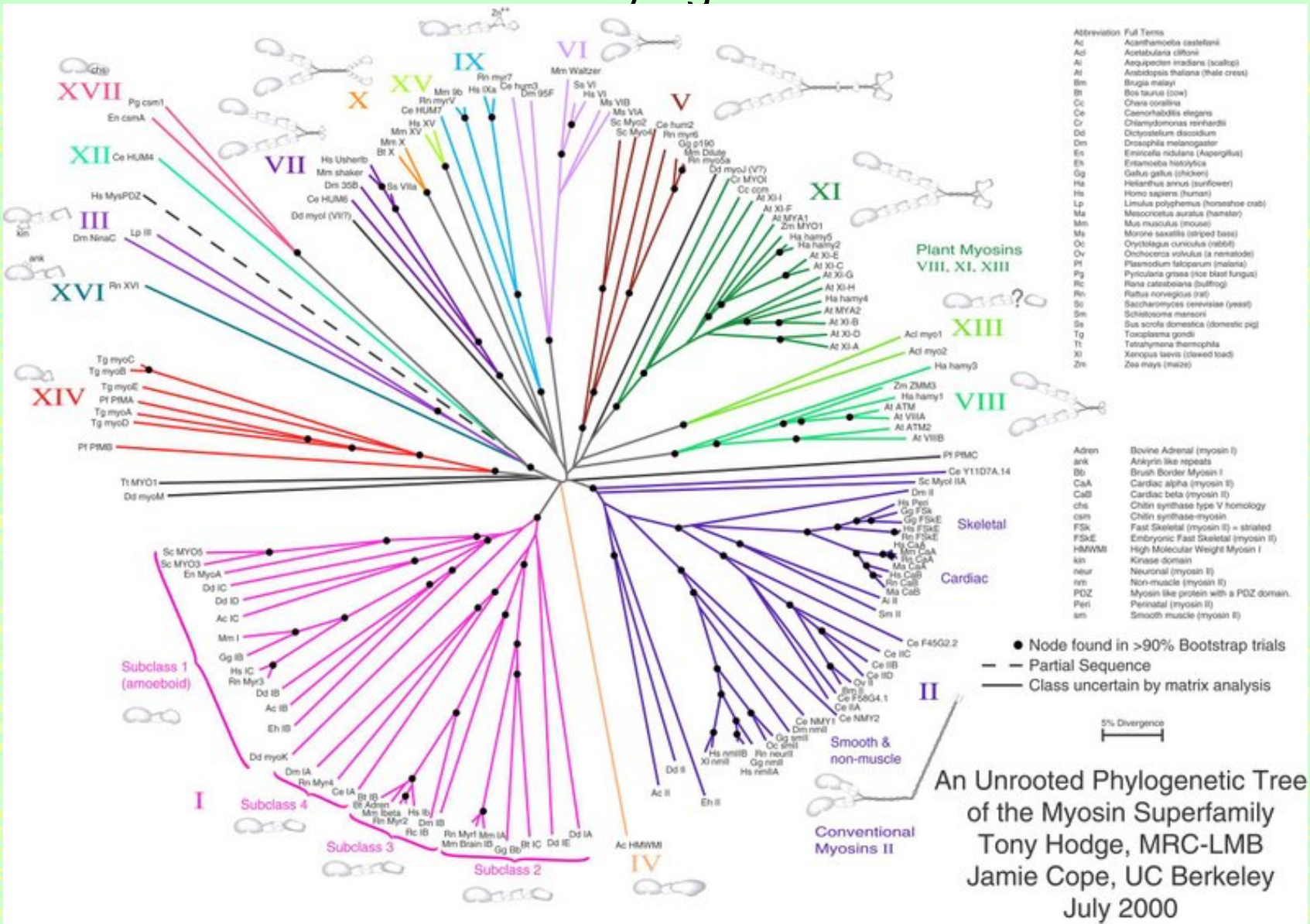


Rooted and Unrooted Trees

Unrooted phylogenetic trees can be generated from rooted trees by omitting the root from a rooted tree, a root cannot be inferred on an unrooted tree without either an outgroup or additional assumptions (for instance, about relative rates of divergence). Figure 2 depicts an unrooted phylogenetic tree[1] for myosin, a superfamily of proteins. Links to other pictures are given in the pictures on the web subsection below.

Introduction to Bioinformatics
LECTURE 7: PHYLOGENETIC TREES

Unrooted Phylogenetic Tree



Distance and Character

A tree can be based on

1. **quantitative measures** like the **distance** or **similarity** between species, or

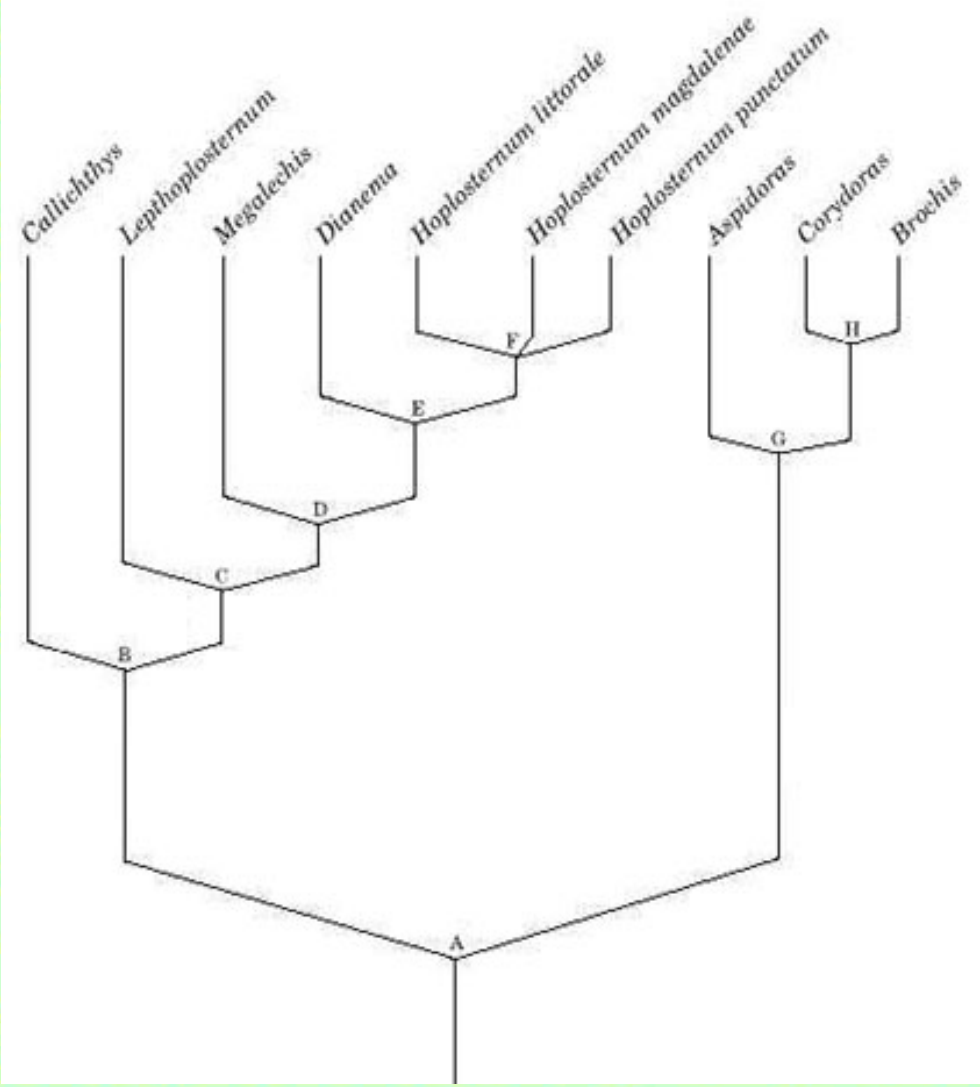
2. based on **qualitative aspects** like **common characters**.

Trees and Branch Length

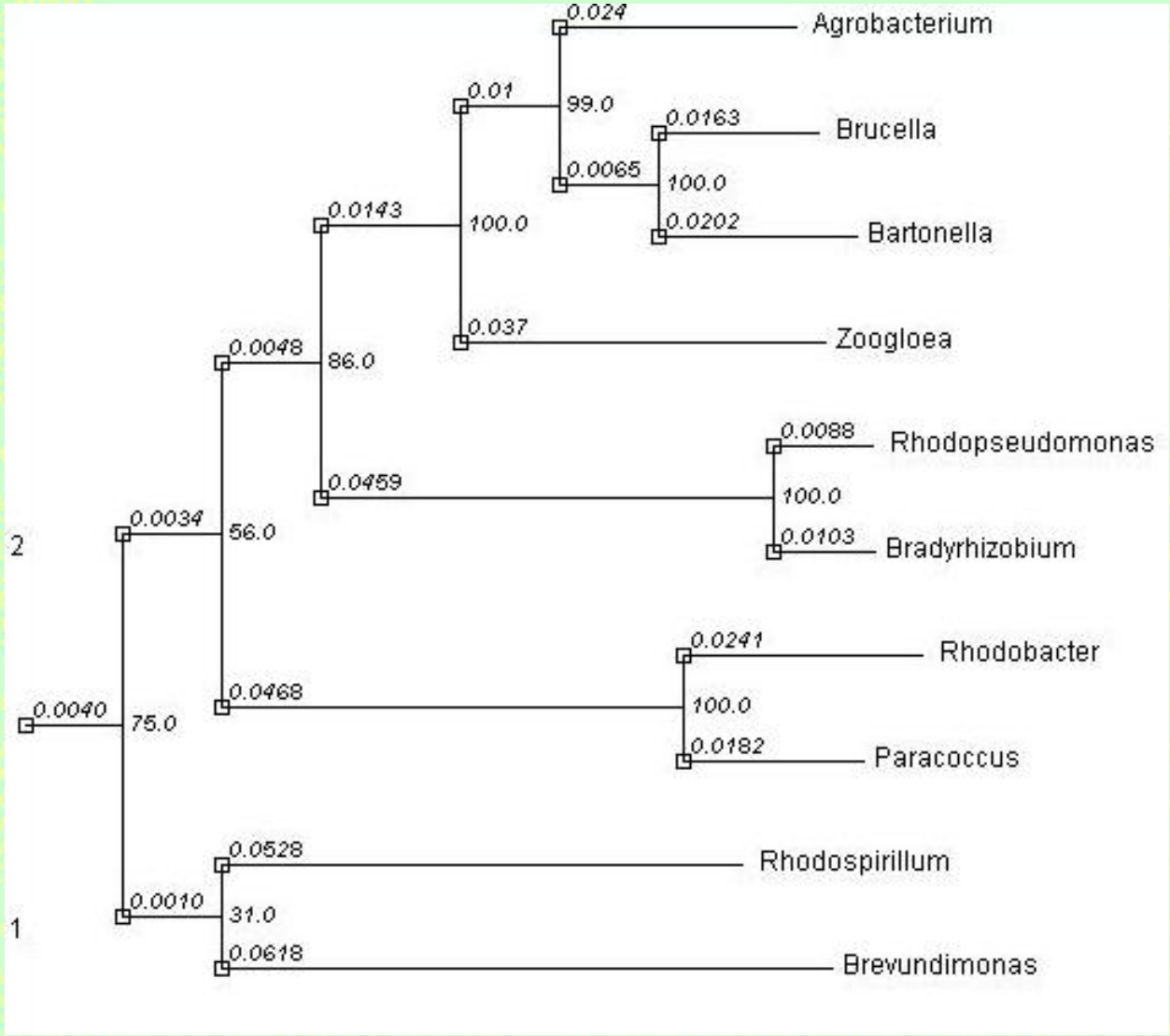
A tree can be a branching tree-graph where branches indicate close phylogenetic relations.

Alternatively, branches can have length that indicate the phylogenic closeness.

Tree without Branch Length



Tree with Branch Length



Constructing Phylogenetic Trees

There are three main methods of constructing phylogenetic trees:

* **distance-based methods** such as UPGMA and neighbour-joining,

* **parsimony-based methods** such as maximum parsimony, and

* **character-based methods** such as maximum likelihood or Bayesian inference.

Parsimony is a 'less is better' concept of frugality, economy, stinginess or caution in arriving at a hypothesis or course of action. The word derives from Latin *parsimonia*, from *parcere*: **to spare**.

7.2 *On trees and evolution*

* Relation between “taxa”

* Internal nodes and external nodes (leafs)

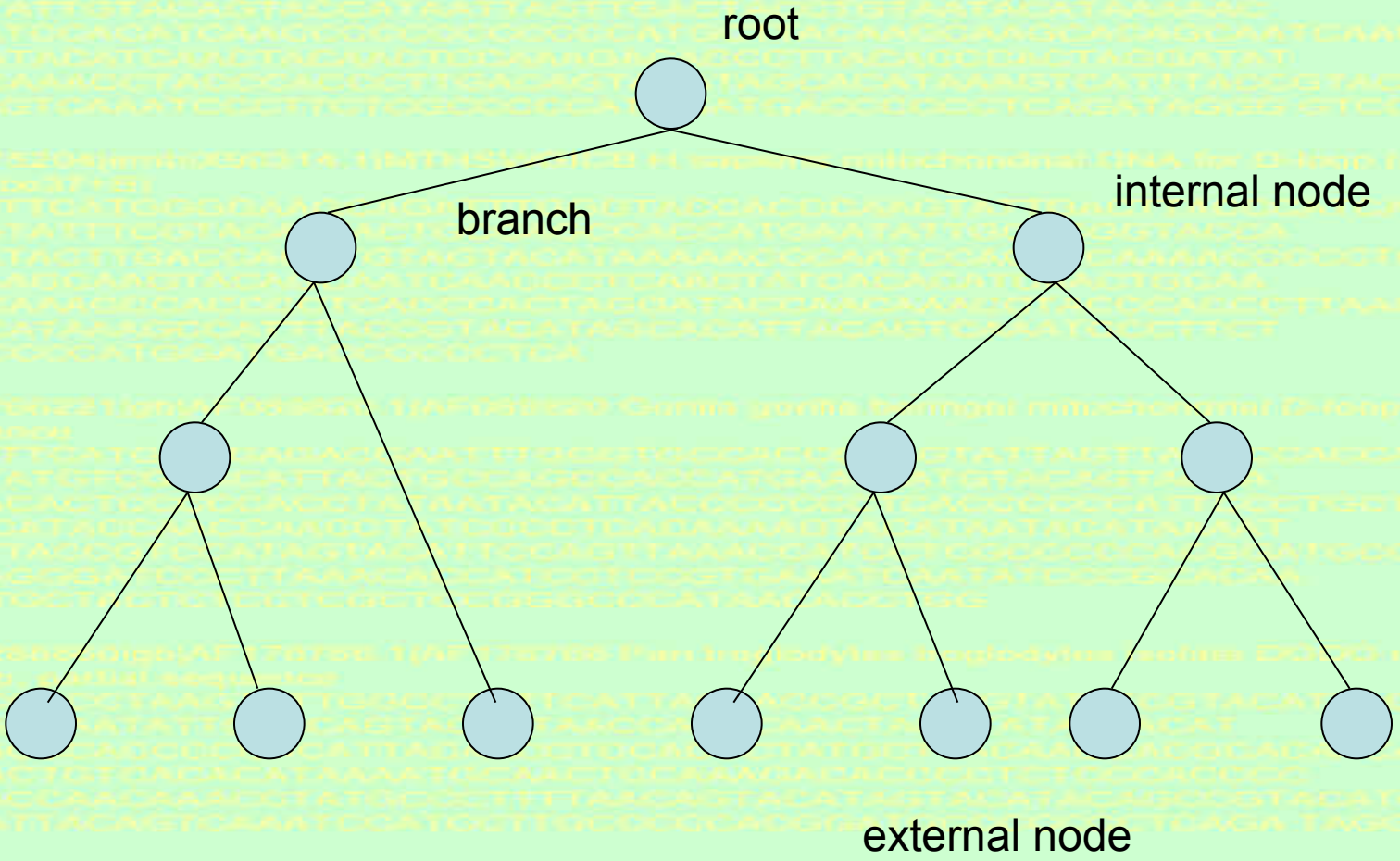
* Branches connects nodes

* Bifurcating tree: **internal** nodes have **degree**: **3**, **external** nodes degree: **1**, root **degree**: **2.**

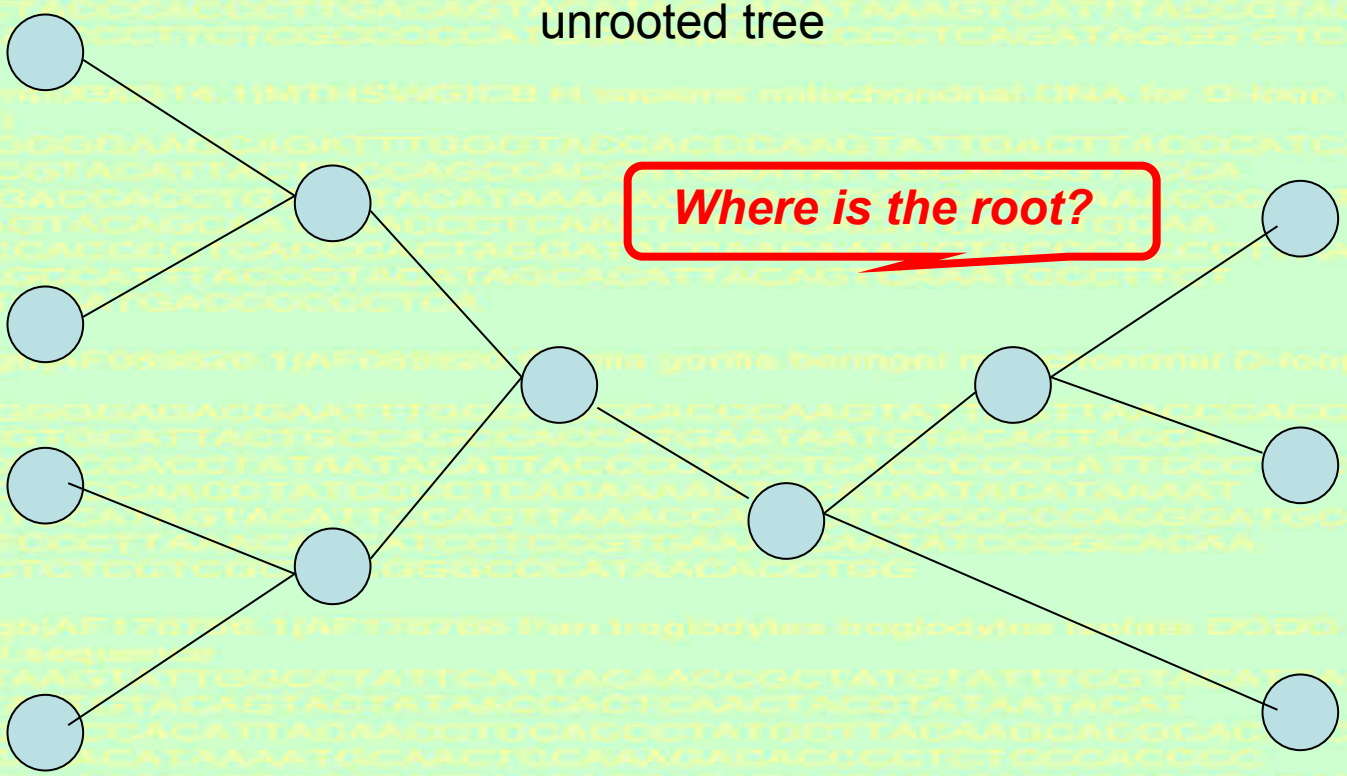
* Root connects to ‘outgroup’

* Multifurcating trees

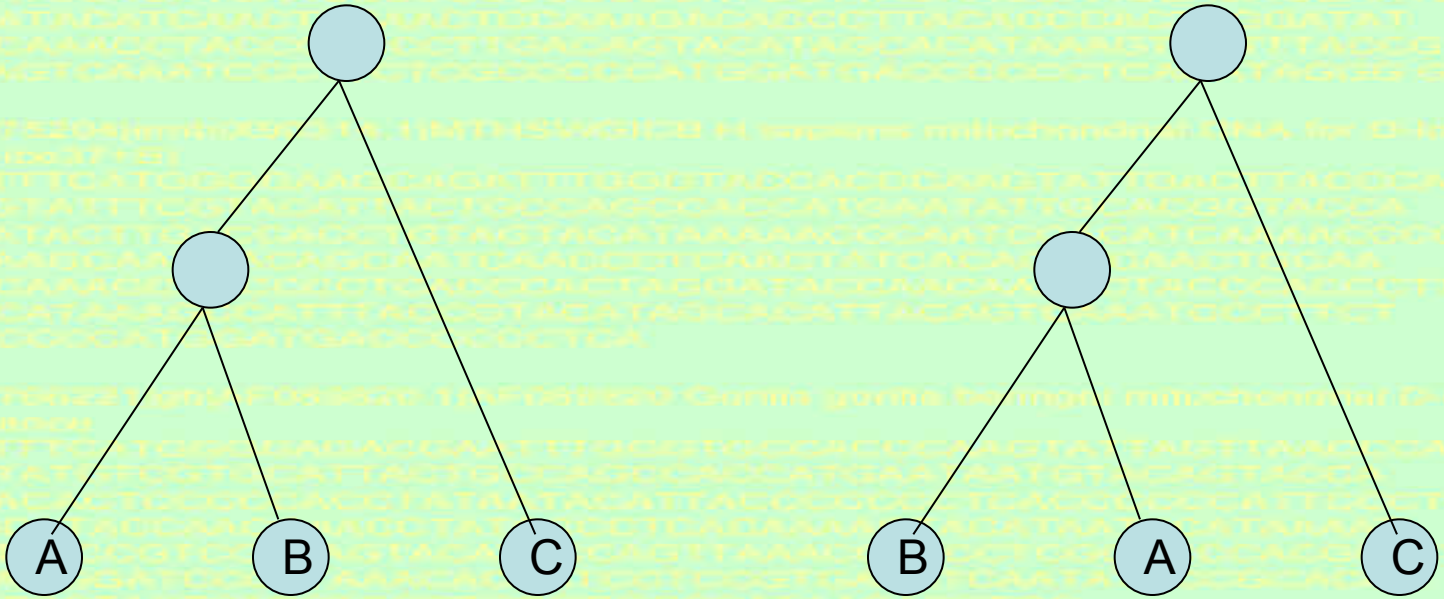
7.2 - ON TREES AND EVOLUTION



unrooted tree



* Any rotation of the internal branches of a tree keeps the the phylogenetic relations intact



rotation invariant

Number of possible trees

* n is number of taxa

* # unrooted trees for $n > 2$: $(2n - 5)!/(2n - 3(n-3)!)$

* # rooted trees for $n > 1$: $(2n - 3)!/(2n - 2(n-2)!)$

* $n = 5$: #rooted trees = 105

* $n = 10$: #rooted trees = 34,459,425

Representing trees

* Various possibilities

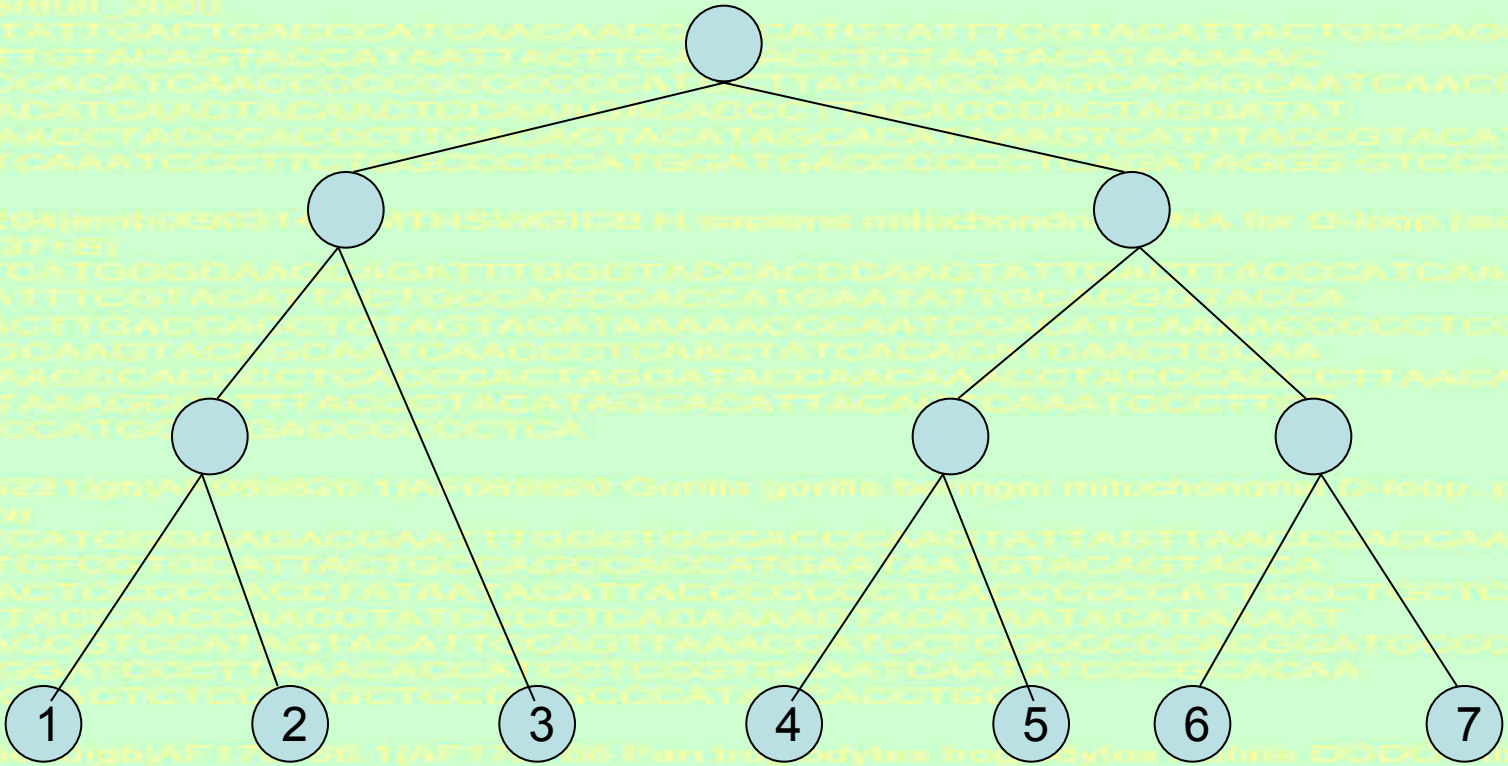
* Listing of nodes

* *n* taxa = *n* external nodes: (*n* -1) internal nodes

* internal nodes with childeren: (*n* – 1)x3 matrix

* (internal node, daughter_1, daughter_2)

* Newick format: see next slide for example



Newick format: (((1,2),3),((4,5),(6,7)))

7.3 *Inferring trees*

* n taxa $\{t_1,\ldots,t_n\}$

* D matrix of pairwise genetic distances + JC-correction

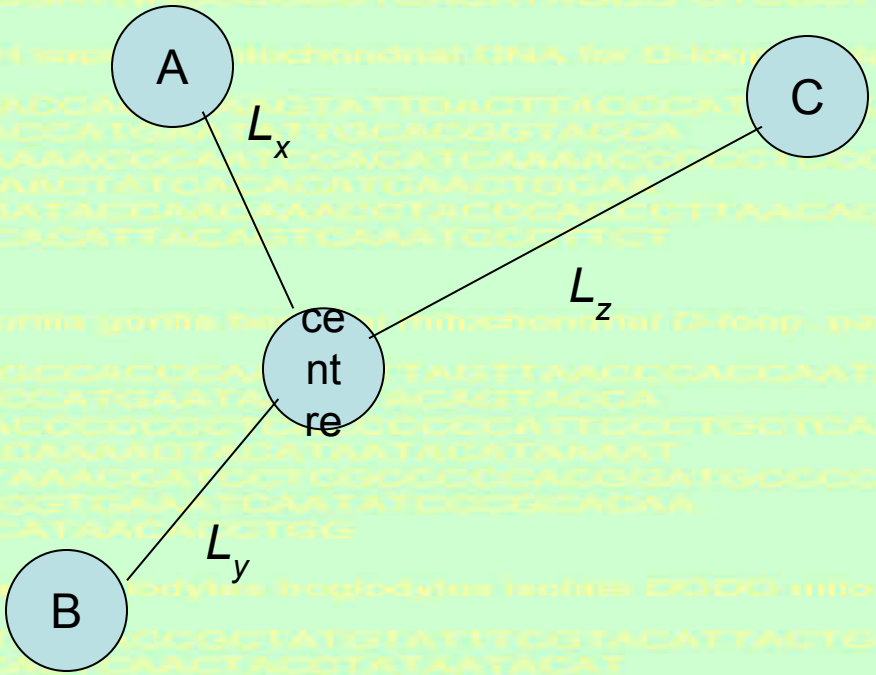
* **Additive** distances: distance over path from $i \rightarrow j$ is: $d(i,j)$

* (total) length of a tree: sum of all branch lengths.

Finding Branche lengths:

Three-point formula:

$L_x + L_y = d_{AB}$
$L_x + L_z = d_{AC}$
$L_y + L_z = d_{BC}$



$L_x = (d_{AB}+d_{AC}-d_{BC})/2$
$L_y = (d_{AB}+d_{BC}-d_{AC})/2$
$L_z = (d_{AC}+d_{BC}-d_{AB})/2$

7.3 INFERRING TREES

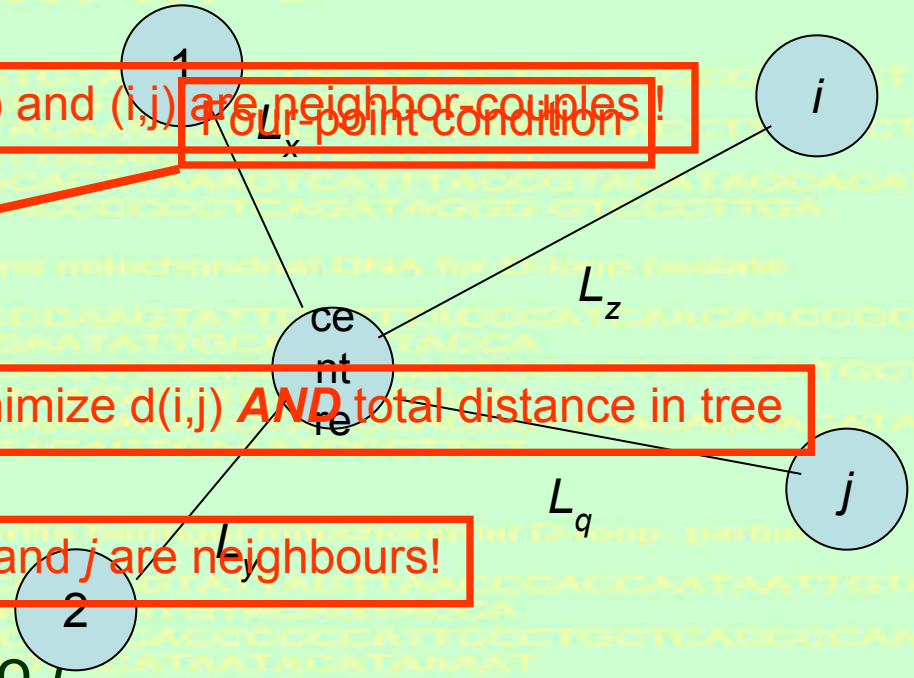
Four-point formula:

$d(1,2) + d(i,j) < d(i,1) + d(2,j)$

$R_i = \sum_j d(t_i,t_j)$

$M(i,j) = (n\text{-}2)d(i,j) - R_i - R_j$

$M(i,j) < M(i,k)$ for all k not equal to j



when (1,2) and (i,j) are neighbor-couples ! Four-point condition !

NJ algorithm:

Input: *nxn* distance matrix *D* and an outgroup
Output: rooted phylogenetic tree *T*

Step 1: Compute new table *M* using *D* – select smallest value of *M* to select two taxa to join

Step 2: Join the two taxa t_i and t_j to a new vertex *V* - use 3-point formula to calculate the updates distance matrix *D'* where t_i and t_j are replaced by *V* .

Step 3: Compute branch lengths from t_k to *V* using 3-point formula, $T(V,1) = t_i$ and $T(V,2) = t_j$ and $TD(t_i) = L(t_i,V)$ and $TD(t_i) = L(t_i,V)$.

Step 4: The distance matrix *D*' now contains *n – 1* taxa. If there are more than 2 taxa left go to step 1. If two taxa are left join them by an branch of length $d(t_i,t_j)$.

Step 5: Define the root node as the branch connecting the outgroup to the rest of the tree. (Alternatively, determine the so-called "**mid-point**")

UPGMA and ultrametric trees:

If the distance from the root to all leafs is equal the tree is **ultrametric**

In that case we can use *D* instead of *M* and the algorithm is called UPGMA (Unweighted Pair Group Method)

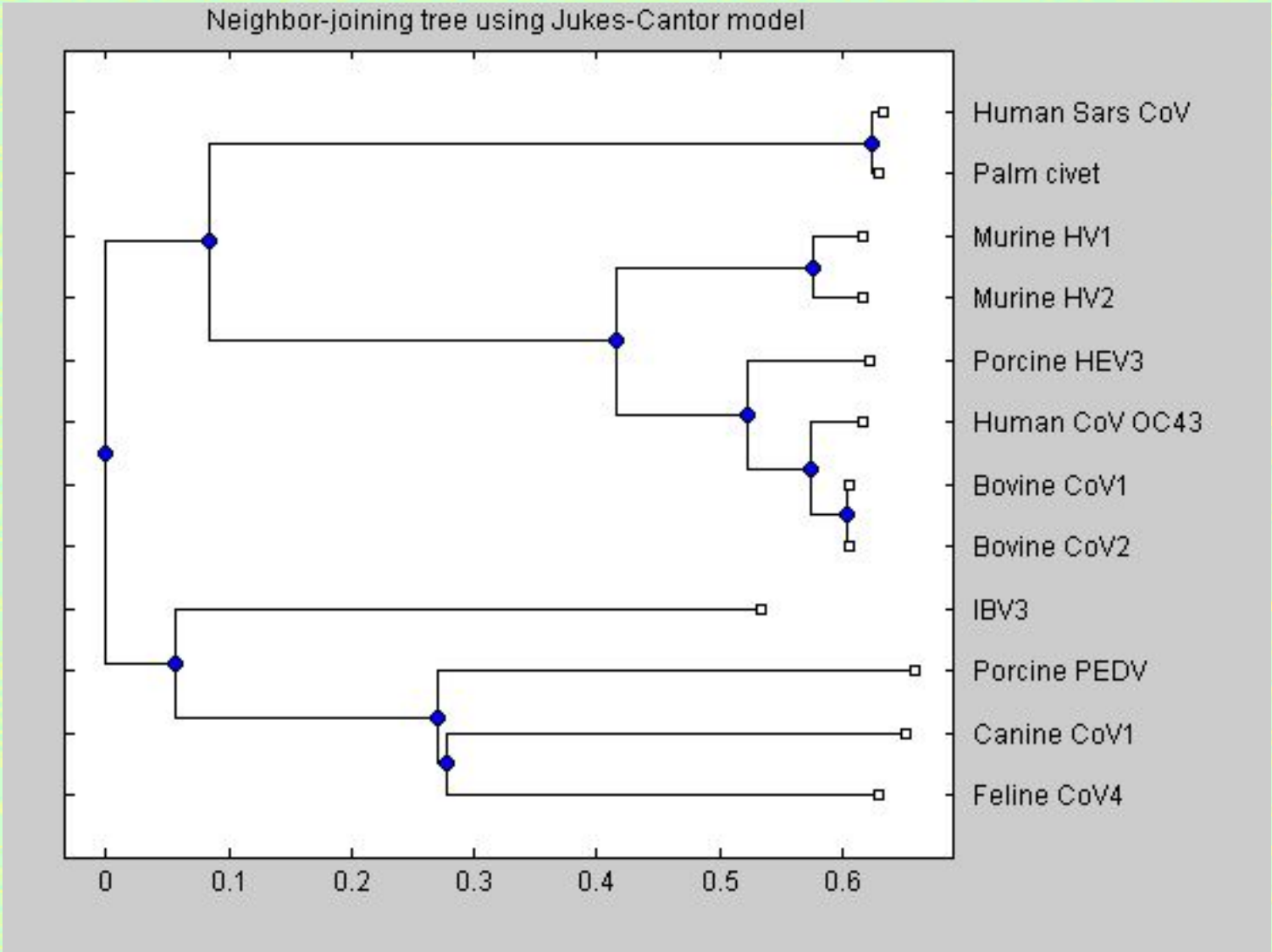
Ultrametricity must be valid for the real tee, bur due to noise this condition will in practice generate erroneous trees.

7.4 *Case study: phylogenetic analysis of the SARS epdemic*

* Genome of SARS-CoV: 6 genes
* Identify host: Himalayan Palm Civet
* The epidemic tree
* The date of origin
* Area of Origin

Introduction to Bioinformatics
LECTURE 7: PHYLOGENETIC TREES

phylogenetic analysis of SARS : Identifying the Host



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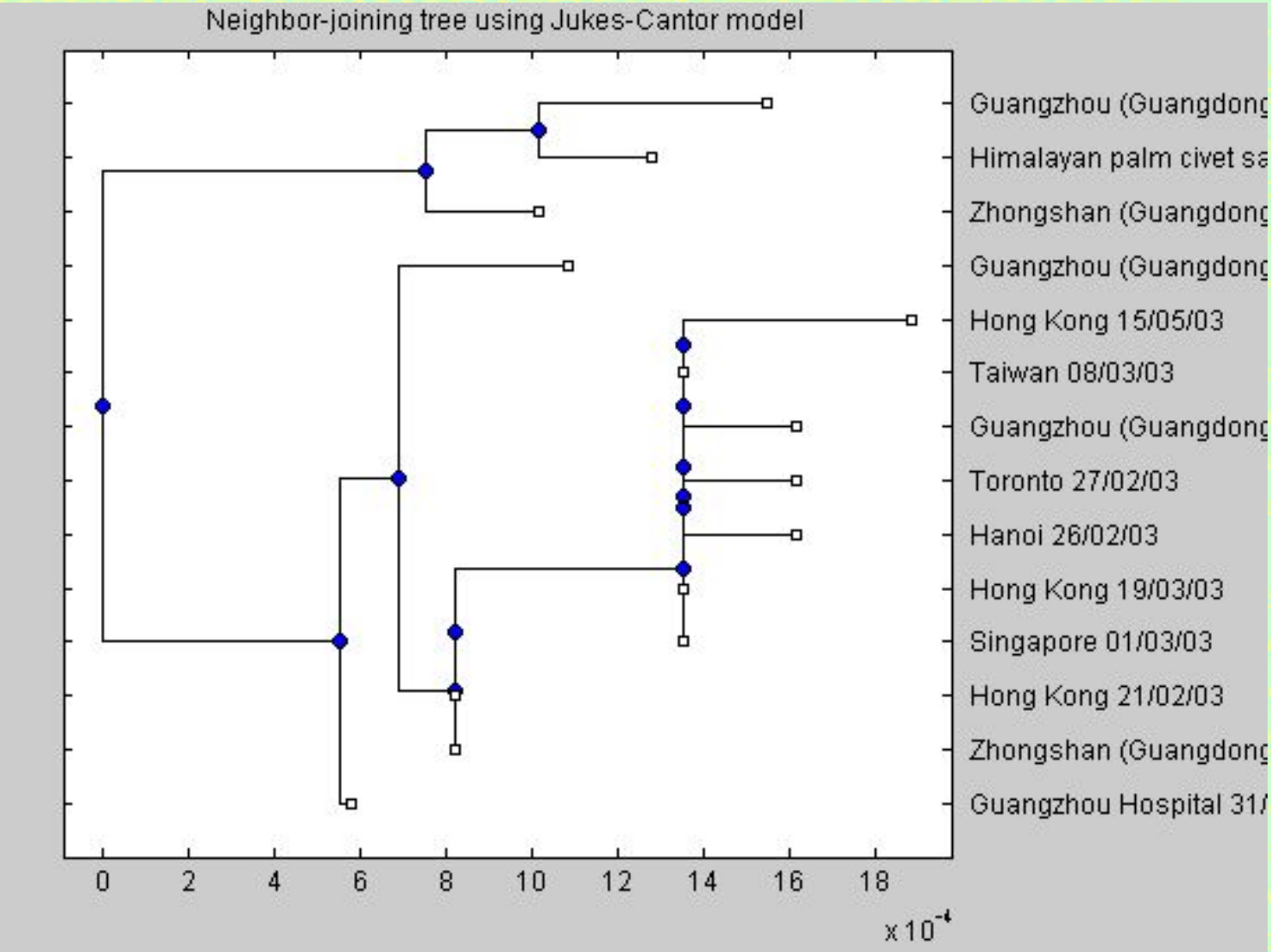
LECTURE 7: PHYLOGENETIC TREES

phylogenetic analysis of SARS : The epidemic tree



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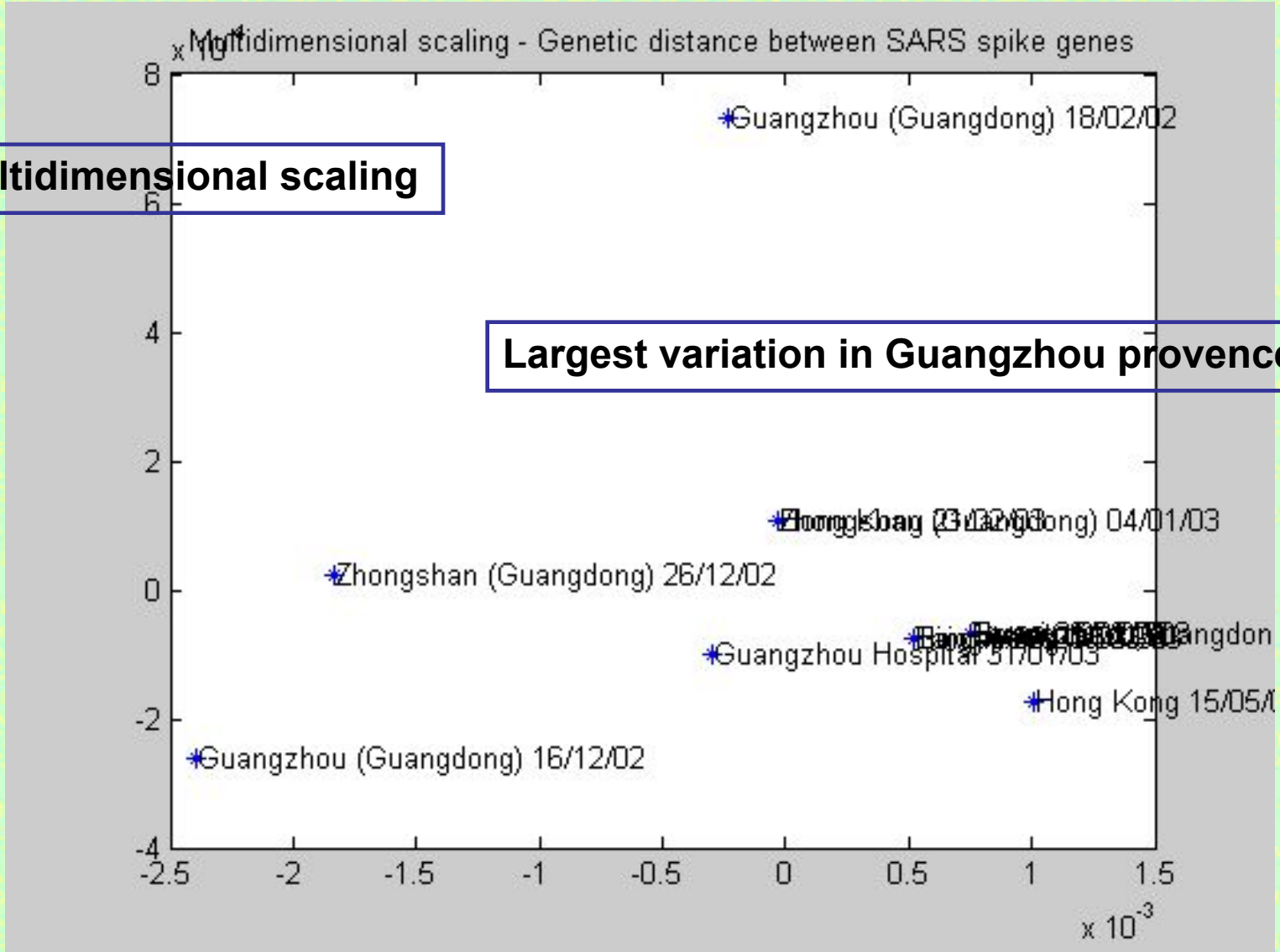
LECTURE 7: PHYLOGENETIC TREES

phylogenetic analysis of SARS : Area of origin



multidimensional scaling

Largest variation in Guangzhou provence

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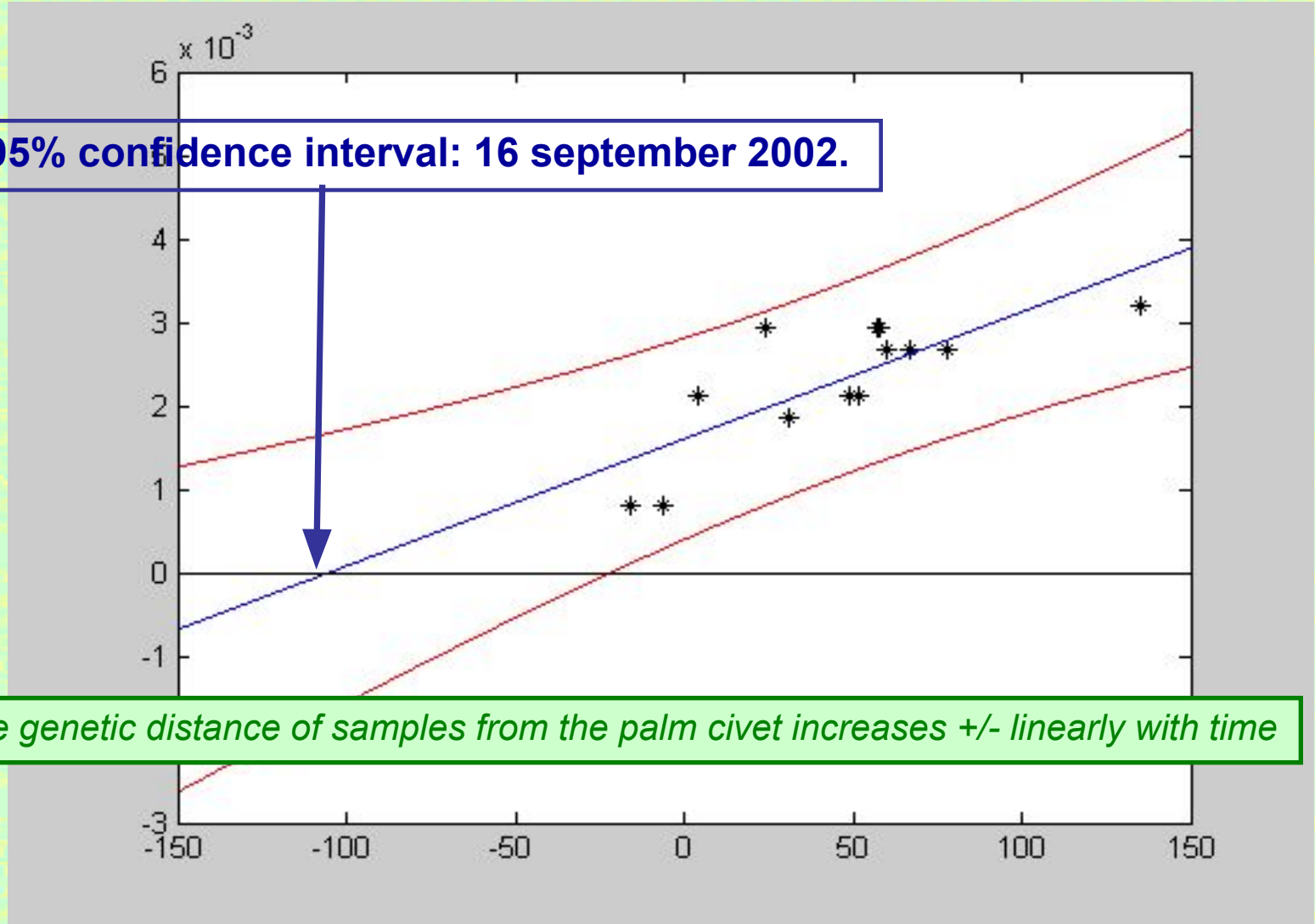
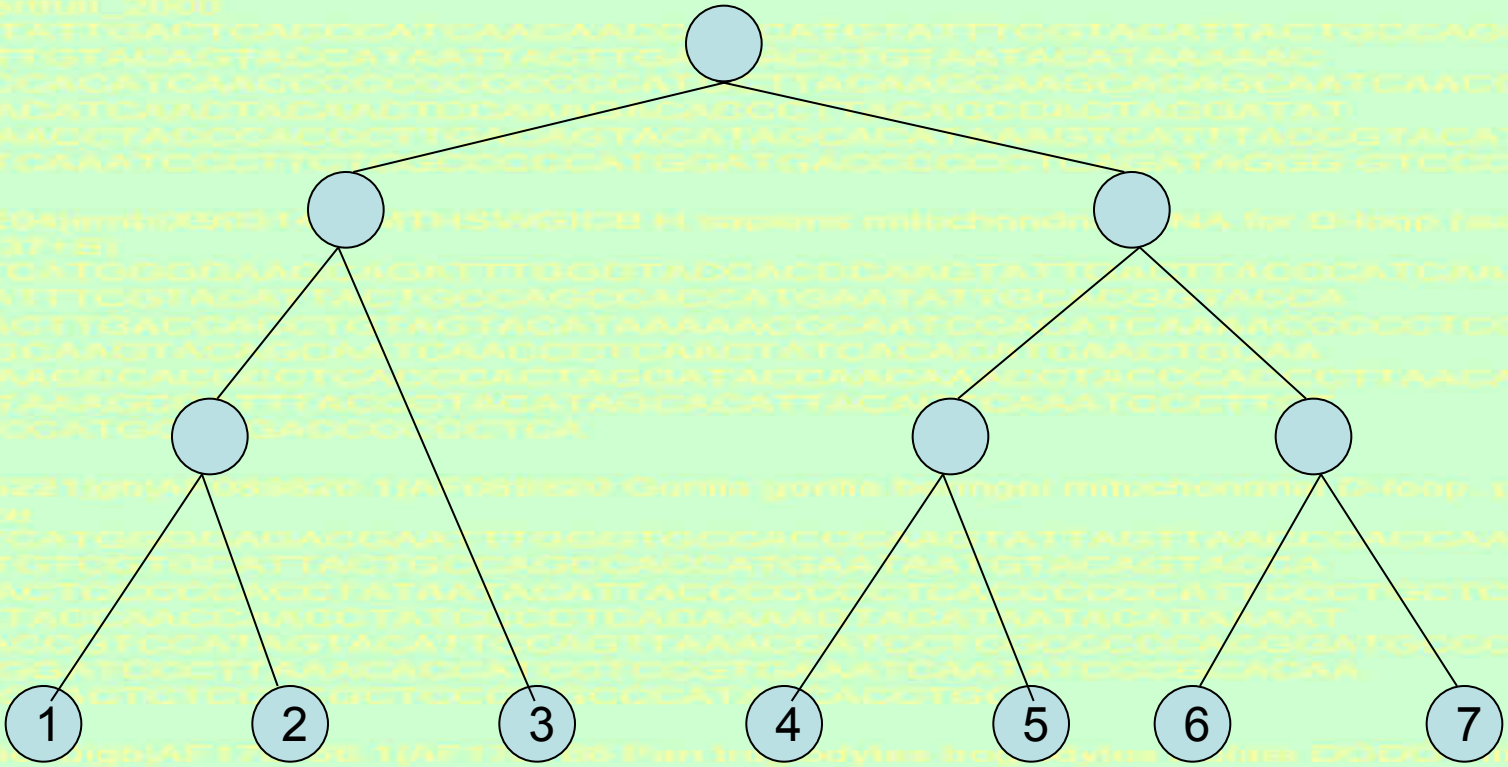
LECTURE 7: PHYLOGENETIC TREES

phylogenetic analysis of SARS : Date of origin



The genetic distance of samples from the palm civet increases +/- linearly with time

Introduction to Bioinformatics
7.5 – THE NEWICK FORMAT



Newick format: (((1,2),3),((4,5),(6,7)))


Introduction to Bioinformatics

END of LECTURE 7