18.417 Introduction to Computational Molecular Biology	
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Evolutionary Trees

Evolution

Evolution is a fundamental random model in population genetics. One of the examples of evolutionary models is **Moran's model**. It describes the process of genotype variation in a population of individuals under the following assumptions:

1. Individuals in population reproduce
2. The size of population is constant, i.e. the number of deaths and births is matched.
3. Mutations are allowed.

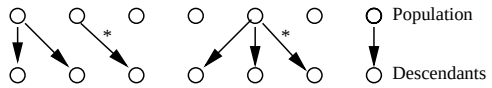


Figure 15.1: Reproduction under Moran model.

The figure depicts two generation of some population. The birth are denoted by arrows. Mutations are denoted by stars.

Reiteration of reproduction under Moran model leads to the assorted population of distinct individuals. The fundamental question in this respect is the distribution of certain characteristics of individuals among population.

In the absence of mutations we can end up with the population homogeneous with respect to some trait:

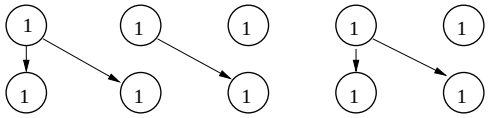


Figure 15.2: No mutations.

When some mutation occur, we can describe them by bit flipping. After certain amount of time we get a random distribution of a trait.

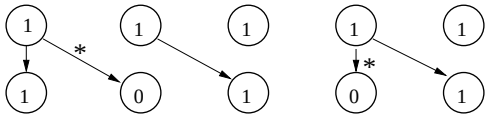


Figure 15.3: Mutations allowed.

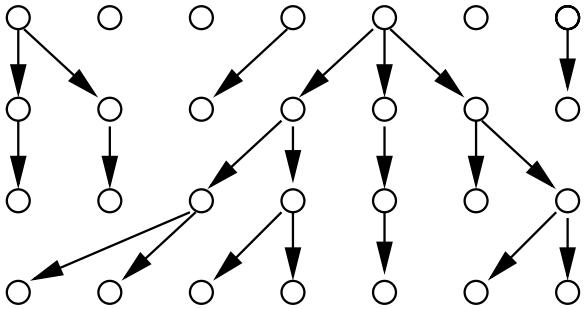


Figure 15.4: Moran model.

Coalescent

There are different probabilistic models that deal with above situation. One of them is the **coalescent** analysis.

We use simplified, modified Moran model. Based on the present data it analyzes retrospectively the past events. Based on the present generation it deduces what past events might be and what are relations with ancestors.

We start with the present time population and reverse the process of reproduction in Moran model. We randomly pick ancestors to the current individuals, keeping the size of population constant. We the repeat the process. This way we build a Moran

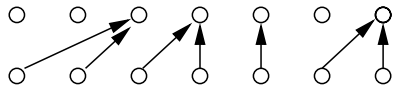


Figure 15.5: Going backwards.

model with some random topology.

Fix a subset of individuals and select a random topology. If we go farther and farther back in time we get a tree.

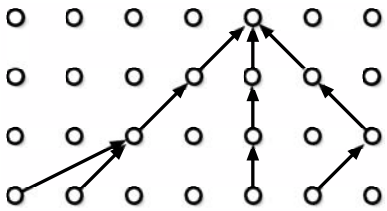


Figure 15.6: A tree.

The coalescent has some limitations because in real world:

- Parents can be mixed.
- There can be more complicated modifications.
- Genetic recombination can occur.

Building trees

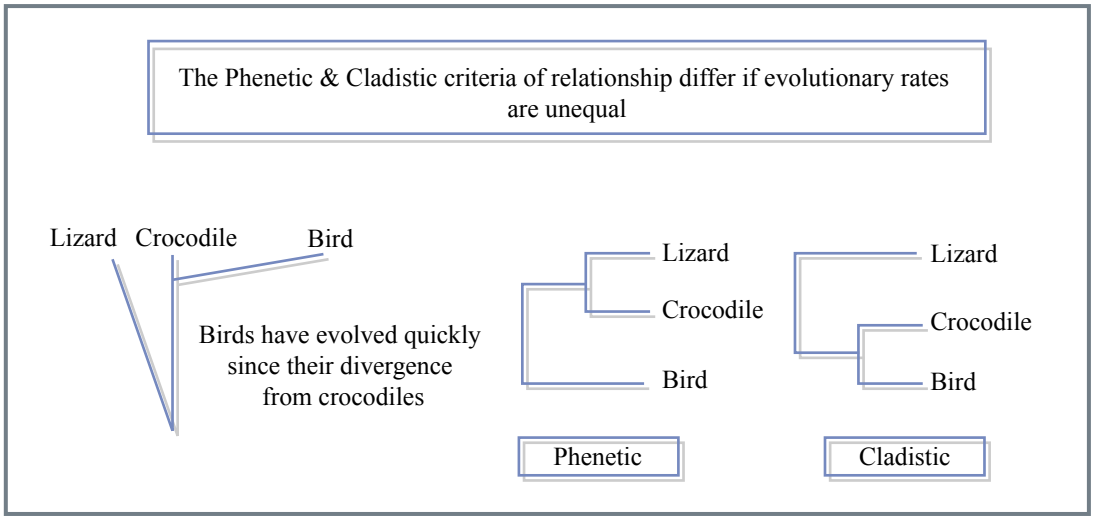
Definition 1 ***Taxonomy*** *is the science of classification of organisms.*

There are two main approaches to taxonomy.

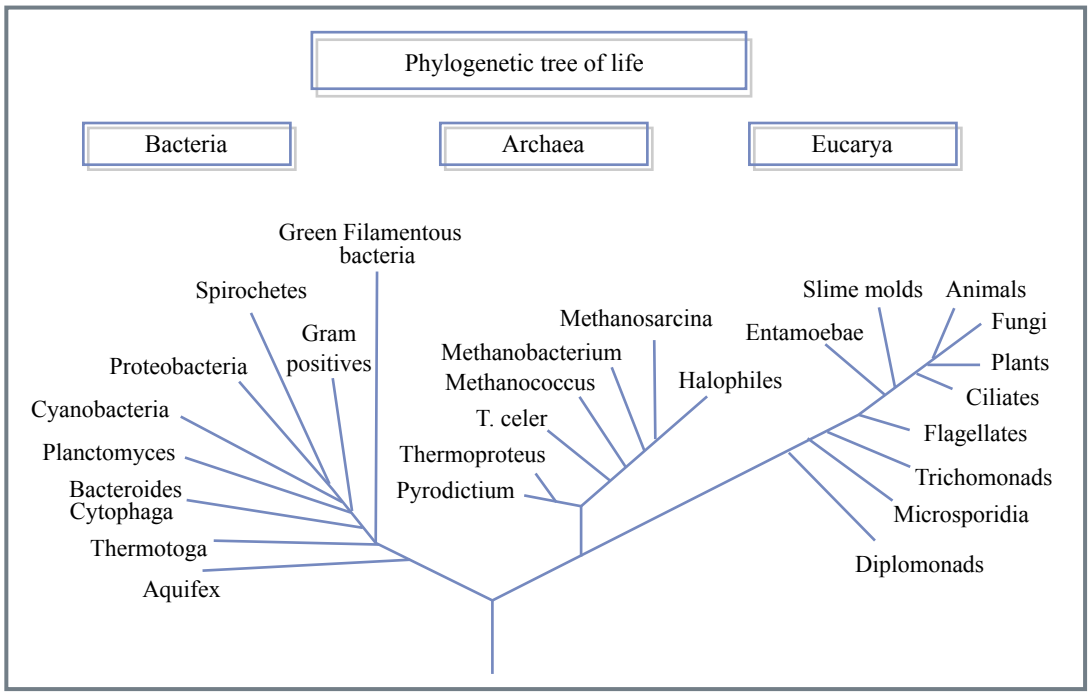
Phenetic Phenetics approach is based on the overall similarity between organisms. The main criterion for clustering species is the *current* similarity according to all possible traits.

Cladistics Considers the various possible phylogenetic trees and chooses from among these the best possible tree.

The two approaches can give different phylogenetic trees:



Adapted from Figure 15.7: Phenetic vs Cladistic.

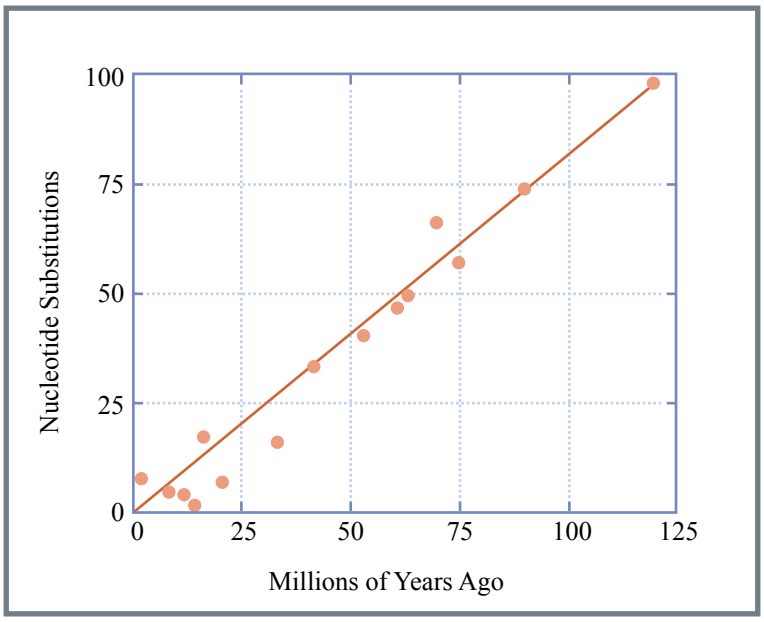


Adapted from Figure 15.8: Phylogenetic Tree of Life.

Molecular Clock Hypothesis

Introduced by Pauling and Zuckerkandl, the Molecular Clock Hypothesis states that mutations in certain regions of genome accumulate at a rate linearly proportional to time.

The diagram below shows the difference in DNA between some species versus time starting from millions years ago when organisms first were found in fossils. Compare



Adapted from Figure 15.9: Mutations allowed.

DNA of today's organisms with ancient. This means that the amount of molecular change between two species measures how long ago they shared a common ancestor. Molecular differences between species are therefore used to infer phylogenetic relations.

There are several ways to observe molecular clock.

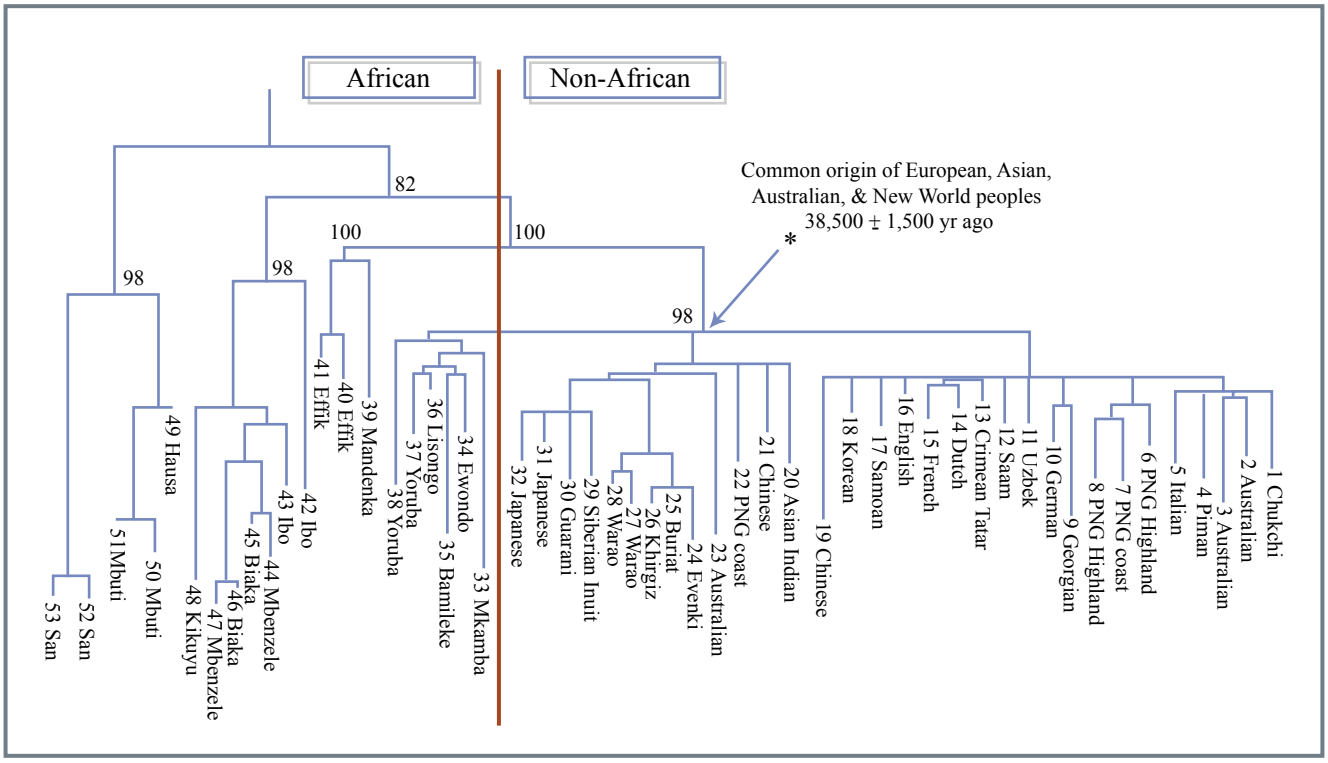
1. Mutations in mitochondrial DNA (mtDNA) are used as molecular clock in many systematic studies.

2. Neutral mutation in the noncoding region of gene.

3. Mutations in ribosomal DNA (rDNA).

Trees in biology

Phylogenetic trees illustrate the evolutionary relationship between species. We consider trees whose nodes have degree 3 each. Each node represents some species.



Adapted from Figure 15.10: Human mtDNA tree.

External nodes correspond to present time species. Internal nodes represent their ancestors. External nodes called *leaves* represent the present time species. Each node represents an even of splitting one species from another.

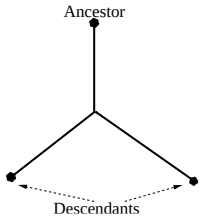


Figure 15.11: Tree node

Multiple splitting can also be thought of as single splitting in a short time interval.

Unrooted tree is a tree without a specified root. An unrooted phylogenetic tree is a reflection of our ignorance as to where the common ancestor lies.

Given a tree we can form a distance matrix whose entries are distances between pairs of leaves. Distance function on the tree should satisfy the triangle inequality

$$d(A, B) + d(B, C) \geq d(A, C).$$

Distance based tree reconstruction

The problem of reconstructing a tree from its distance matrix naturally arises. Given all pairwise distances in the tree we need to reconstruct the tree.

Input Distance matrix from some unknown tree.

Output Tree compatible with a given distance matrix.

This problem is solved using **additive tree reconstruction**. One way to do this is to find a pair of *neighboring* leaves, that is leaves that have the common parent vertex.

If i and j are neighboring leaves and k is their parent, then for any other leave m we have:

$$d(k,m) = \frac{d(i,m) + d(j,m) - d(i,j)}{2}.$$

Having found neighboring pair i, j we replace them by their parent k. Then we update the distance matrix using the above formula. Hence if we had sequence of neighbors relations, we could reconstruct the tree. Determining which leaves are neighbors is however a nontrivial task.

Another approach to tree reconstruction is shortening of edges. We choose a small number x, for example $x = 1$. If we decrease the length of each edge leaving to leaves[1] by x, then all distances will decrease by $2x$.

Updating the distance matrix according to rule $d \to d - 2x$, we obtain a new matrix corresponding to a tree with shorter hanging edges.

If there is a triple of leaves i, j, k such that $d(i,j) + d(j,k) = d(i,k)$ in the updated distance matrix, then leaves i, j, k lie on the single path. Hence j is attached by an edge of length 0 to the path from i to k. We can then throw out vertex j and continue.

The algorithm which is based on above analysis is presented in [1][p. 364].

To discern additive distance matrix from non-additive ones we use

Test for additiveness [Bunneman].

Given any four points we can rename them A, B, C, D so that:

$$d(A,B) + d(C,D) = d(A,C) + d(B,D) \geq d(A,D) + d(B,C).$$

[1]such edges are called *hanging*

Figure 15.12: Tree node

15.0.1 Approximate additive tree reconstruction

But it is a fact, that the evolutionary clock is running differently for different species and even for different regions in a protein sequence. Hence some distances matrices we obtain are not additive.

Since not all distance matrices turn out to be additive, we are facing the following problem:

Given a distance matrix, find the nearest additive tree?

This problem is NP-complete. However, there are also several algorithms that deal with above problem.

UPGMA Algorithm (Unweighted Pair Group Method with Arithmetic mean).

UPMGA is a variant of Hierarchical Clustering. It assigns heights to vertices of constructed trees. The leave with the most mutations (the oldest) has the highest height. The height serves as a molecular clock in this case.

Neighbor Joining

Intuition behind this algorithm was mentioned above: if we identify two neighbors in a tree, join them together. Then repeat until done.

We're interested in pairs, for which not only the distance between them is smallest, but also the distance to the rest points is largest.

The algorithm is following:

1. For each i define
$$u_i = \frac{\sum_{k \neq i} d(i,k)}{n-2}.$$

2. Now take the pair i, j for which $d(i, j) - u_i - u_j$ is minimal. Designate i, j to be neighbors and join them in a cluster n.

3. Recompute the distance matrix:

$$d(n, k) = \frac{d(i, k) + d(j, k) - d(i, j)}{2}.$$

4. Repeat until finished.

Character-based methods

Character-based methods take as input an $n \times m$ matrix where n is the number of species and m is the number of *characters*. The goal is a tree whose leaves correspond to n rows. The *parsimony* problem, which arises in this respect, is to minimize the number of evolutionary events to put on the tree.

Large Parsimony Problem[2]

Input An $n \times m$ matrix M describing n species, each representing by an m-character string.

Output A tree T with n leaves labeled by n rows of M, and a labeling of the internal vertices of T such that the parsimony score is minimized over all possible trees and all labelings.

References

[1] N.C. Jones, P.A. Pevzner, *Introduction to Bionformatics Algorithms*, A Bradford Book, The MIT Press, Cambridge, 2004.

[2][1][p. 374]