Molecular Evolution

A Statistical Approach

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CHAPTER 3

Phylogeny reconstruction: overview

3.1 Tree concepts

This chapter introduces basic concepts related to phylogenetic trees and discusses general features of tree reconstruction methods. Distance and parsimony methods are described in this chapter as well, while likelihood and Bayesian methods are discussed later in Chapters 4 and 6–8.

3.1.1 *Terminology*

3.1.1.1 *Trees, nodes (vertexes), and branches (edges)*

A phylogeny or phylogenetic tree is a representation of the genealogical relationships among species, among genes, among populations, or even among individuals. Mathematicians define a *graph* as a set of *vertexes* and a set of *edges* connecting the vertexes, and a tree as a connected graph without loops (see, e.g. Tucker 1995, p. 1). Biologists instead use *nodes* for vertexes and *branches* for edges. Here we consider trees for species, but the description also applies to trees of genes or individuals. The *tips*, *leaves*, or *external nodes* represent present-day species, while the *internal nodes* usually represent extinct ancestors for which no sequence data are available. The ancestor of all sequences is the *root* of the tree.

3.1.1.2 *Root of the tree and rooting the tree*

A tree with the root specified is called a *rooted tree* (Figure 3.1a), while a tree with the root unknown or unspecified is called an *unrooted tree* (Figure 3.1b). If the evolutionary rate is constant over time, an assumption known as the *molecular clock*, distance matrix, maximum likelihood (ML) and Bayesian methods can identify the root and produce rooted trees. Such use of the clock assumption to determine the root of the tree is known as *molecular clock rooting*.

Another related rooting method, often used in the analysis of population data, is *midpoint rooting*. First, an unrooted tree is inferred without the clock assumption. Then the most distant pair of sequences is identified, with the distance calculated as the sum of branch lengths connecting the two sequences. The root is then placed at the midpoint between the two sequences. Midpoint rooting also relies on the molecular clock assumption.

When the species are distantly related or the sequences are fairly divergent, the clock assumption is most often violated. Incorrectly assuming the clock then can cause serious

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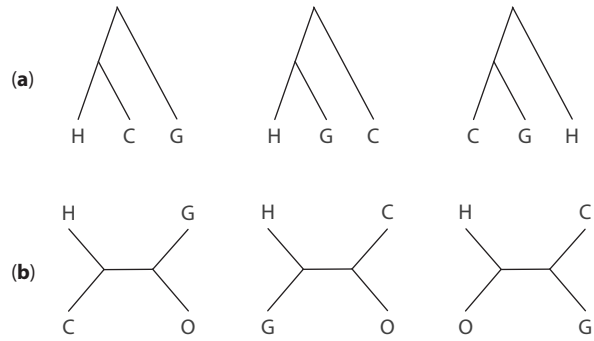


Fig. 3.1 Outgroup rooting. To infer the relationships among human (H), chimpanzee (C), gorilla (G), represented by the three rooted trees in (**a**), we use orangutan (O) as the outgroup. Tree reconstruction methods allow us to estimate an unrooted tree, i.e. one of the trees in (**b**). As the root is along the branch leading to the outgroup, these three unrooted trees for all four species correspond to the three rooted trees for the ingroup species H, C, and G.

errors in phylogeny reconstruction and in rooting. Without the clock and with independent rates for branches on the tree, most tree reconstruction methods are unable to identify the root of the tree and instead produce unrooted trees. Then the commonly used approach to rooting the tree is *outgroup rooting*. Distantly related species, called the *outgroups*, are included in tree reconstruction, while in the reconstructed unrooted tree for all species, the root is placed on the branch leading to the outgroups, so that the subtree for the *ingroups* is rooted. In the example of Figure 3.1, the orangutan is used as the outgroup to root the tree for the ingroup species: human, chimpanzee, and gorilla. In general, outgroups closely related to the ingroup species are better than distantly related outgroups.

In the universal tree of life, no outgroup species exist. Then a strategy is to root the tree using ancient gene duplications that occurred prior to the divergence of all existing life forms (Gogarten et al. 1989; Iwabe et al. 1989). The subunits of ATPase arose through a gene duplication before the divergence of eubacteria, eukaryotes, and archaebacteria. Protein sequences from both paralogues were used to construct a composite unrooted tree, and the root was placed on the branch separating the two duplicates (Gogarten et al. 1989). Elongation factors Tu and G constitute another ancient duplication, and were used in rooting the universal tree of life (Iwabe et al. 1989).

One should note that the output from a tree reconstruction program may look like a rooted tree. The user of the program is expected to know whether the analysis should produce rooted or unrooted trees and to interpret the tree accordingly.

3.1.1.3 *Tree topology, branch lengths, and the parenthesis notation*

The branching pattern of a tree is called the tree structure or *topology*. The length of a branch may represent the amount of sequence divergence or the time period covered by the branch. A tree showing only the topology without the branch length information is

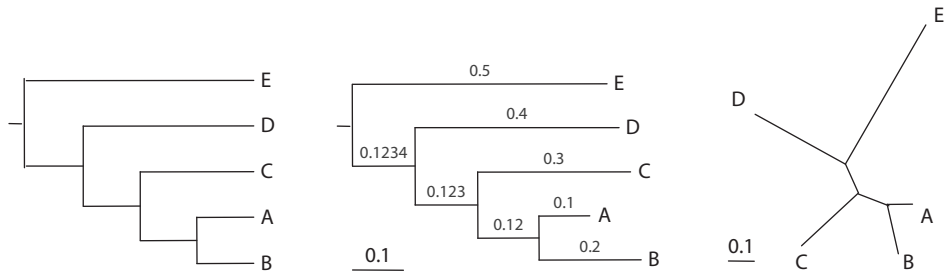


Fig. 3.2 The same tree shown in different styles. (**a**) The cladogram shows the tree topology without branch lengths or with branch lengths ignored. (**b**) In a phylogram, branches are drawn in proportion to their lengths. Here the branch lengths are shown along the branches. (**c**) In an unrooted tree, the location of the root is unknown or ignored.

sometimes called a *cladogram* (Figure 3.2a), while a tree showing both the topology and branch lengths is called a *phylogram* (Figure 3.2b).

For use in computer programs, trees are often represented using the nested parenthesis format or the *Newick format*, named after a lobster restaurant in Dover, New Hampshire, where the format was proposed (Felsenstein 2004, p. 590). For example, the trees in Figure 3.2 may be represented as:

a and **b**: ((((A, B), C), D), E);
b: ((((A: 0.1, B: 0.2): 0.12, C: 0.3): 0.123, D: 0.4): 0.1234, E: 0.5);
c: (((A, B), C), D, E);
c: (((A: 0.1, B: 0.2): 0.12, C: 0.3): 0.123, D: 0.4, E: 0.6234);.

Each internal node is represented by a pair of parentheses, which groups its daughter nodes, while the order of the daughter nodes is arbitrary. The outmost pair of parentheses groups the daughter nodes of the root. Tip nodes are represented by their names. A node can be followed by a semicolon together with a number that is the length of the branch ancestral to the node. Branch lengths here are measured by the expected number of nucleotide substitutions per site, like the sequence distance discussed in Chapter 1.

This format is natural to represent rooted trees. Unrooted trees are represented by placing the root at an arbitrary internal node and by having a trifurcation at the root. The representation is not unique, as the root can be placed anywhere on the tree. For example, the unrooted tree of Figure 3.2c can also be represented as '(A, B, (C, (D, E)));'.

Just as the Newick format does not represent the same tree in a unique way, there is much arbitrariness when a tree is drawn. For example, the root can be on the top, at the bottom, or on the side. To decide whether the different trees are equivalent, think about whether they represent the same evolutionary/genealogical relationships: for example, the three trees shown in Figure 3.3 are identical.

Because of different rates of evolution in different lineages, there may not be direct correspondence between evolutionary *relatedness* and sequence *distance* between two species: two closely related species may not have the smallest sequence distance. The distance is the amount of sequence evolution and is equal to the sum of branch lengths on the paths connecting the two species, while the relatedness is measured by the time of divergence between the two species (see Problem 3.3).

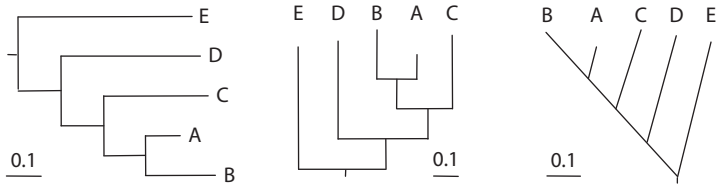


Fig. 3.3 All three trees are identical as they represent the same genealogical relationships among A, B, C, D, and E. This is the same tree of Figure 3.2b: ((((A: 0.1, B: 0.2): 0.12, C: 0.3): 0.123, D: 0.4): 0.1234, E: 0.5).

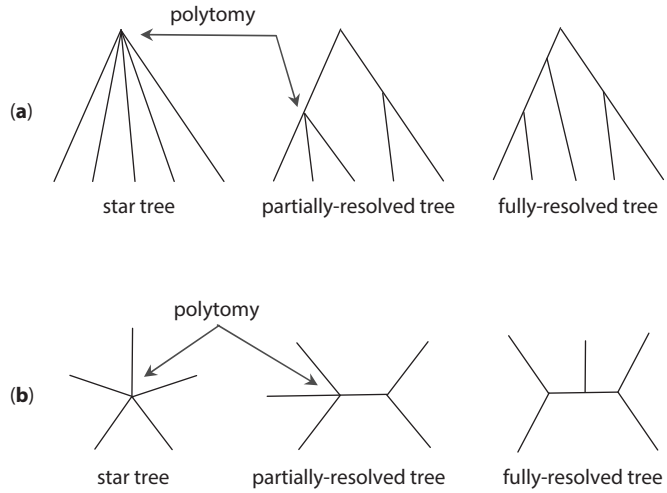


Fig. 3.4 Unresolved and resolved phylogenetic trees. (**a**) Rooted trees. (**b**) Unrooted trees.

3.1.1.4 *Bifurcating and multifurcating trees*

The number of branches connected to a node is called the *degree* of the node. Leaves have a degree of 1. If the root node has a degree greater than 2 or a non-root node has a degree greater than 3, the node represents a *polytomy* or *multifurcation*. A tree with no polytomies is called a *binary tree*, *bifurcating tree*, or *fully resolved tree*. The most extreme unresolved tree is the *star* or *big-bang* tree, in which the root is the only internal node (see Figure 3.4 for example). A polytomy representing truly simultaneous species divergences is sometimes called a *hard polytomy*. It would seem extremely unlikely for one species to diverge into several at exactly the same time, and it may be argued that hard polytomies do not exist. Most often the polytomy represents lack of information in the data to resolve the relationships within a clade (a group of species). Such polytomies are called *soft polytomies*.

3.1.1.5 *The number of trees*

We can work out the total number of unrooted trees by the following *stepwise addition algorithm* (Cavalli-Sforza and Edwards 1967) (Figure 3.5). We start with the single tree for the first three species. This has three branches to which the fourth species can be added. Thus there are three possible trees for the first four species. Each four-species tree has

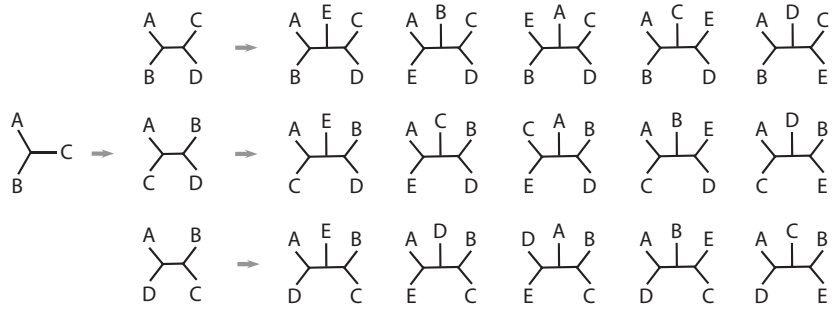


Fig. 3.5 Enumeration of all trees for five taxa A, B, C, D, and E using the stepwise addition algorithm.

five branches, to which the fifth species can be added, resulting in five different five-species trees for each four-species tree. There are thus 3×5 possible trees for five species. In general, a tree of the first $n-1$ species has $(2n-5)$ branches, to which the nth species can be added, so that each of the $(n-1)$-species trees generates $(2n-5)$ distinct n-species trees. Thus the total number of unrooted bifurcating trees for n species is

$$U_n = U_{n-1} \cdot (2n-5) = 3 \cdot 5 \cdot 7 \cdot \cdots \cdot (2n-5) = \frac{1 \cdot 2 \cdot 3 \cdot 4 \cdot 5 \cdot \cdots \cdot (2n-5)}{2 \cdot 4 \cdot \cdots \cdot (2n-6)} = \frac{(2n-5)!}{2^{n-3}(n-3)!}. \tag{3.1}$$

To work out the number of rooted trees for n species, note that each unrooted tree has $(2n-3)$ branches, and the root can be placed on any of those branches, generating $(2n-3)$ rooted trees from each unrooted tree. Thus the number of rooted trees for n species is

$$R_n = U_n \times (2n-3) = U_{n+1} = \frac{(2n-3)!}{2^{n-2}(n-2)!}. \tag{3.2}$$

In certain applications, we also need the concept of *labelled histories*. For example, under the coalescent model, the Yule model of pure birth, or the birth-death process model, all possible labelled histories have the same probability (Aldous 2001). A labelled history is a rooted tree with the internal nodes rank-ordered according to their ages (Edwards 1970). Thus a rooted tree may correspond to several labelled histories. For example, the symmetrical rooted tree for four species $((a, b), (c, d))$ corresponds to two labelled histories, depending on whether or not the common ancestor of a and b is older than the common ancestor of c and d. The asymmetrical rooted tree $(((a, b), c), d)$ corresponds to a single labelled history since there is only one ordering of the internal nodes. The number of possible labelled histories for n sequences is

$$H_n = \frac{n(n-1)}{2} \times \frac{(n-1)(n-2)}{2} \times \cdots \times \frac{2 \cdot 1}{2} = \frac{n!(n-1)!}{2^{n-1}}. \tag{3.3}$$

The counting is done by the so-called coalescent process, which traces the genealogy backwards in time to find common ancestors. Initially there are n lineages, so there are $\binom{n}{2} = \frac{1}{2}n(n-1)$ possible ways of choosing two lineages to join (to coalesce). After the first coalescent event, there will be $n-1$ lineages left so there are $\frac{1}{2}(n-1)(n-2)$ possible ways of choosing two lineages to join, and so on. The last coalescence joins two lineages at the root of the tree. Obviously this coalescent process of joining lineages respects the order of

Table 3.1 The numbers of unrooted trees (U_n), rooted trees (R_n), and labelled histories (H_n) for n species

n	Unrooted trees (U_n)	Rooted trees (R_n)	Labelled histories (H_n)
3	1	3	3
4	3	15	18
5	15	105	180
6	105	945	2,700
7	945	10,395	56,700
8	10,395	135,135	1,587,600
9	135,135	2,027,025	57,153,600
10	2,027,025	34,459,425	2,571,912,000
20	$\sim 2.22 \times 10^{20}$	$\sim 8.20 \times 10^{21}$	$\sim 5.64 \times 10^{29}$
50	$\sim 2.84 \times 10^{74}$	$\sim 2.75 \times 10^{76}$	$\sim 3.29 \times 10^{112}$

coalescent events or the ranking of node ages on the tree; it thus enumerates the labelled histories correctly. The coalescent process is discussed in detail in Chapter 9.

As we can see from Table 3.1 , the number of unrooted trees U_n increases explosively with the number of species n. The number of rooted trees R_n and the number of labelled histories H_n rise even faster.

3.1.1.6 *Distance between trees*

Sometimes we would like to measure how different two trees are. For example, we may be interested in how different the trees estimated from different genes are, or how different the estimated tree is from the true tree in a computer simulation conducted to evaluate a tree reconstruction method. A commonly used measure of topological distance between two trees is the *partition distance* defined by Robinson and Foulds (1981) (see also Penny and Hendy 1985). We give the definition for unrooted trees first. Note that each branch on the tree defines a *bipartition* or *split* of the species; if we chop the branch, the species will fall into two mutually exclusive sets. For example, branch b in tree T_1 of Figure 3.6 partitions the eight species into two sets: (1, 2, 3) and (4, 5, 6, 7, 8). This partition is also present on tree T_2. Partitions defined by terminal branches are in all possible trees and are thus not informative for comparisons between trees. Thus we focus on internal branches only. Partitions defined by branches b, c, d, and e of tree T_1 are the same as partitions defined by branches b', c', d', and e' of tree T_2, respectively. The partition defined by branch a of tree T_1 is not in tree T_2, nor is the partition defined by branch a' of tree T_2 in tree T_1. The partition distance is defined as the total number of bipartitions that exist in one tree but not in the other. Thus T_1 and T_2 have a partition distance of 2. As an unrooted binary tree of n species has $(n-3)$ internal branches, the partition distance ranges from 0 (if the two trees are identical) to $2(n-3)$ (if the two trees do not share any bipartition).

The partition distance can be equivalently defined as the number of contractions and expansions needed to transform one tree into the other. Removing an internal branch by reducing its length to zero is a contraction, while creating an internal branch is an expansion. Trees T_1 and T_2 of Figure 3.6 are separated by a contraction (from T_1 to T_0) and an expansion (from T_0 to T_2), so that their partition distance is 2.

For rooted trees, we use the same definition as for unrooted trees, but imagine the existence of an outgroup species attached to the root. As a rooted binary tree of n species

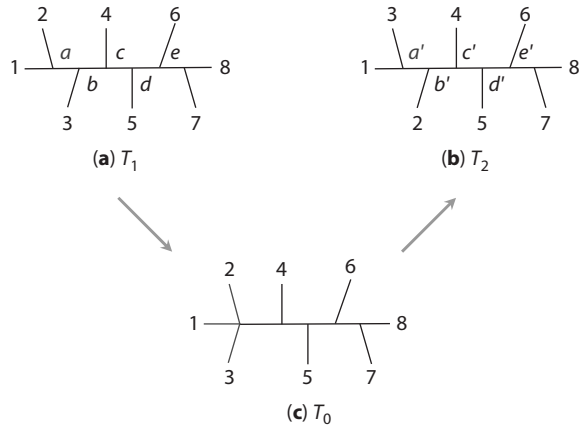


Fig. 3.6 The partition distance between two trees T_1 and T_2 is the total number of bipartitions that are in one tree but not in the other. It is also the number of contractions and expansions needed to change one tree into another. A contraction converts T_1 into T_0 and an expansion converts T_0 into T_2, so the distance between T_0 and T_1 is 1 while the distance between T_1 and T_2 is 2.

has $(n-2)$ internal branches, the partition distance ranges from 0 (if the two trees are identical) to $2(n-2)$ (if the two trees do not share any bipartition).

The partition distance has limitations. First, the distance does not recognize certain similarities between trees. The three trees in Figure 3.7 are identical concerning the relationships among species 2–7 but do not share any bipartitions, so that the partition distance between any two of them is the maximum possible. Indeed, the probability that a random pair of unrooted trees achieve the maximum distance is 70–80% for n = 5–10, and is even greater for larger n. Figure 3.8 shows the distribution of partition distance between two random unrooted trees for the case of n = 10. Second, the partition distance ignores branch lengths in the tree. Intuitively, two trees that are in conflict around short internal branches are less different than two trees that are in conflict around long internal branches. It is unclear how to incorporate branch lengths in a definition of tree distance. One such measure has been suggested by Kuhner and Felsenstein (1994), and is defined as the sum of squared differences between branch lengths in the two trees

$$B_s = \sum\nolimits_i (b_i - b'_i)^2, \tag{3.4}$$

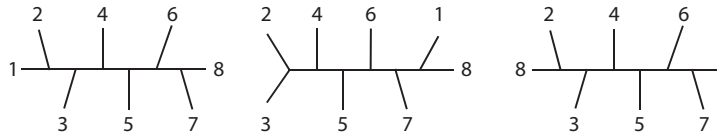


Fig. 3.7 Three trees that do not share any bipartitions and thus achieve the maximum partition distance.

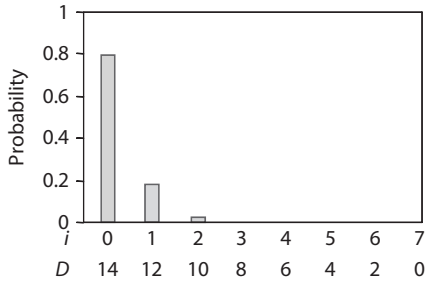


Fig. 3.8 The probability that two random trees from all possible unrooted trees of ten species share i bipartitions or have partition distance D. Note that $D = 2 \times (10 - 3 - i)$.

where b_i and b'_i are branch lengths in the two trees, respectively. If a branch exists in one tree but not in the other, the missing branch has length 0 in the calculation. Third, the partition distance may be misleading if either of the two trees has multifurcations. Suppose we conduct a computer simulation to compare two tree reconstruction methods, using an unrooted binary tree to simulate datasets, and use the partition distance to measure performance: $P = 1 - D/D_{\max}$, where $D_{\max} = 2(n-3)$ is the maximum distance and D is the distance between the true tree and the estimated tree. When both the true tree and the estimated tree are binary, P is the proportion of bipartitions in the true tree that are recovered in the estimated tree. Suppose that with no information in the data, one method returns the star tree as the estimate while the other method returns an arbitrarily resolved binary tree. Now for the first method, $D = (n-3) = 1/2D_{\max}$, so that $P = 50\%$, which may seem very impressive. The second method has a performance of $P = 1/3$ when $n = 4$ or nearly 0 for large n, since a random tree is very unlikely to share any bipartition with the true tree. However, the two methods clearly have the same performance, and the measure based on the partition distance is unreasonable for the first method.

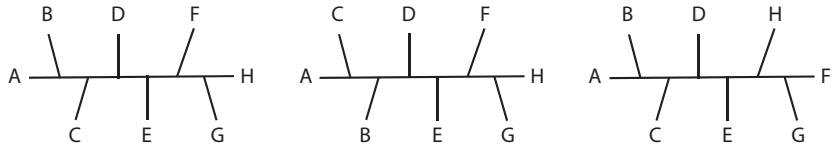
3.1.1.7 *Consensus trees*

While the partition distance measures how different two trees are, a consensus tree summarizes common features among a collection of trees. Many different consensus trees have been defined; see Bryant (2003) for a comprehensive review. Here we introduce two of them.

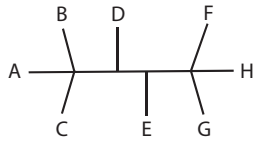
The *strict consensus tree* shows only those branches (partitions or splits) that are shared among all trees in the set, with those not supported by all trees collapsed into polytomies. Consider the three trees in Figure 3.9a. The strict consensus tree is shown in Figure 3.9b. The group (A, B) is in the first and third trees but not in the second, while (A, B, C) is in all three trees. Thus the strict consensus tree shows (A, B, C) as a trichotomy, as well as (F, G, H). The strict consensus tree is a conservative way of summarizing the trees and may not be very useful as it often produces the star tree.

The *majority-rule consensus tree* shows branches or splits that are supported by at least half of the trees in the set. It is also common practice to show the percentage of trees that support every node on the consensus tree (Figure 3.9c). For example, the group (A, B) is in two out of the three trees and is thus shown in the majority-rule consensus tree as resolved, with the percentage of support (2/3) shown next to the node. It is known that all groups that occur in more than half of the trees in the set can be shown on the same consensus tree without generating any conflict.

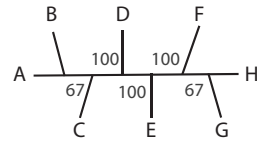
Like the partition distance, the majority-rule consensus tree, as a summary of trees in the set, has limitations. Suppose that there are only three distinct trees in the set, which



(**a**) Three trees for eight species



(**b**) Strict consensus tree



(**c**) Majority-rule consensus tree

Fig. 3.9 Three trees for eight species (**a**) and their strict consensus tree (**b**) and majority-rule consensus tree (**c**).

are the trees of Figure 3.7, each occurring in proportions around 33%. Then the majority-rule consensus tree will be the star tree. In such cases, it appears more informative to report the first few whole trees with the highest support values.

It may be fitting to emphasize here that polytomies in a consensus tree are a heuristic way of summarizing (or visualizing) phylogenetic uncertainties, and do not represent simultaneous speciation events. The consensus tree may thus be unsuitable for use in downstream phylogenetic analyses, such as molecular clock dating, because used in such an analysis, the consensus tree with polytomies is treated as an exact mathematical model of simultaneous speciation. Instead one should use a fully resolved tree inferred from the data, such as the ML tree or the neighbour-joining (NJ) tree.

3.1.1.8 *Monophyly, paraphyly, clade, and clan*

While phylogenetics is concerned with inference of the phylogeny or reconstruction of the evolutionary relationships of the species, classification or taxonomy is the science of describing, naming, and classifying organisms. It is now widely accepted that phylogeny should be the basis of taxonomic classifications. While classification is beyond the scope of this book, some terms are commonly used in molecular phylogenetic analysis, and will be described here.

A monophyletic group includes all the descendants of a common ancestor. Such a group is also called a *clade*. Taxa in a monophyletic group are more *closely related*; i.e. they have more recent common ancestors than those outside the group. We also use the term *sister species* when two species are each other's closest relatives. A group that includes some descendants of a common ancestor but excludes some others is *non-monophyletic*. Some authors distinguish two types of non-monophyly: paraphyly and polyphyly. A *paraphyletic* group does not include all of the descendants of a single common ancestor. For example, 'apes' include chimpanzees, gorillas, orangutans, and gibbons but exclude humans. Apes are thus a paraphyletic group. Similarly 'reptiles' are a paraphyletic group (Figure 3.10). Reptiles include crocodiles, lizards, and turtles but exclude birds (because birds have novel anatomy and behaviour), but crocodiles are more closely related to birds than they are to other reptiles. A *polyphyletic* group includes species that have multiple common ancestors but excludes some other descendants of those ancestors so that the last common ancestor

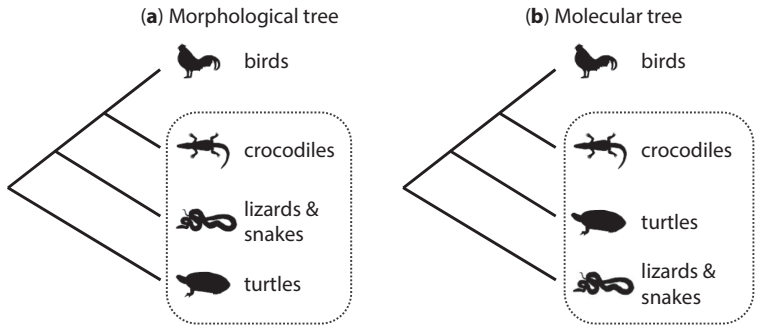


Fig. 3.10 Traditional morphological tree (**a**) and recent molecular tree (**b**) for birds, crocodiles, lizards, and turtles (e.g. Iwabe et al. 2005; Crawford et al. 2012). No matter which of those two trees is correct, 'reptiles' (circled) are a paraphyletic group.

of the group is not a member of the group. A polyphyletic group is often the result of erroneous taxonomic classification based on morphological similarities that are the result of convergent evolution. For example, 'pachyderms' include elephants, rhinoceroses, hippopotamuses, etc. Those mammals all have thick skins but belong to different orders and are a polyphyletic group. 'Vultures' are another polyphyletic group. The Old and New World vultures have striking similarities (such as bald heads) due to convergent evolution. However, the Old World vultures evolved from birds of prey (such as eagles, kites, hawks) while the New World vultures evolved from storks.

Use of terms such as monophyly and clade implies a knowledge of the root of the tree. As most phylogeny reconstruction methods produce unrooted trees, those terms are sometimes applied to unrooted trees as well, with the assumption that the root is in a place such that the use of those terms would be sensible. Wilkinson et al. (2007) recommend the use of the term *clan* (instead of clade) to mean a group of species identified on an unrooted tree. When we cut an internal branch on an unrooted tree, the species will fall into two groups (partitions or splits). These are two clans, and one of them must be a clade.

3.1.2 *Species trees and gene trees*

The phylogeny representing the relationships among a group of species is called the *species tree* or *organismal* tree. The phylogeny for sequences at a particular gene locus from those species is called the *gene tree*. A number of factors may cause the gene tree to differ from the species tree.

First, phylogeny reconstruction errors may cause the estimated gene tree to be different from the species tree even if the true gene tree agrees with the species tree. The estimation errors may be either random, due to the limited amount of sequence data, or systematic, due to deficiencies of the tree reconstruction method or serious violations of its assumptions. One such case is convergent evolution. For example, the lysozyme has apparently undergone convergent evolution in ruminants (e.g. the cow) and the leaf-eating colobine monkeys (e.g. the langur), as it is recruited as a bacteriolytic enzyme in the fermentative foreguts of those animals (Stewart et al. 1987). As a result, the stomach lysozymes of mammals from those two groups share some physico-chemical and catalytical

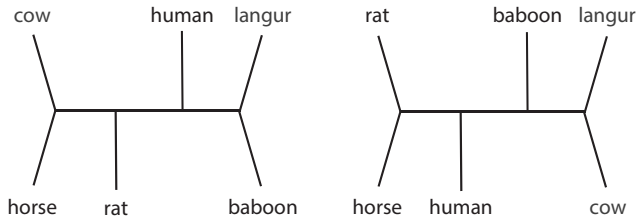


Fig. 3.11 Convergent evolution in the stomach lysozyme of the cow and the langur misleads phylogeny reconstruction methods to infer an incorrect gene tree. The organismal tree for six species of mammals is the one in (**a**), and this should also be the true gene tree for the lysozyme. However, the parsimony (and ML) methods incorrectly infer the gene tree to be the one in (**b**), grouping the cow and the langur together. Drawn following Stewart et al. (1987).

properties as well as certain key amino acids. When the protein sequences are used in tree reconstruction, an incorrect tree is inferred, grouping the cow and the langur together (Figure 3.11).

Second, during the early stages of evolution near the root of the universal tree of life, there appears to have been substantial lateral (horizontal) gene transfer (LGT). As a result, different genes or proteins may have different gene trees, in conflict with the species tree. The LGT appears to be so extensive that some researchers question the concept of a universal tree of life (see, e.g. Doolittle 1998). Third, gene duplications, especially if followed by gene losses, can cause the gene tree to be different from the species tree if paralogous copies of the gene are used for phylogeny reconstruction (Figure 3.12a). Note that

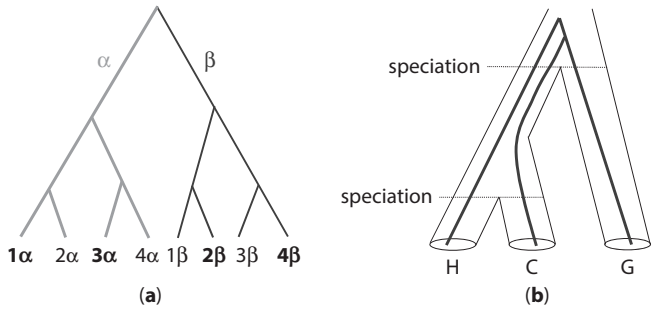


Fig. 3.12 Conflict between species tree and gene tree can be due to gene duplication (**a**) or ancestral polymorphism (**b**). In (**a**), a gene duplicated in the past, creating paralogous copies α and β, followed by divergences of species 1, 2, 3, and 4. If we use gene sequences 1α, 3α, 2β, 4β for phylogeny reconstruction, the true gene tree is $((1\alpha, 3\alpha), (2\beta, 4\beta))$, different from the species tree $((1, 2), (3, 4))$. In (**b**), the species tree is ((human, chimpanzee), gorilla). However, due to ancestral polymorphism and incomplete lineage sorting, the true gene tree is (human, (chimpanzee, gorilla)).

paralogues are genes that originated from gene duplications and may not reflect species relationships, while orthologues are genes that originated from species divergences and thus track speciation events (Fitch 1970). Fourth, *ancestral polymorphism* or polymorphism in ancestral species means that gene sequences in different modern species may be descendants of different ancestral sequences, so that the gene genealogy may fail to track the species phylogeny, a phenomenon called *incomplete lineage sorting*. An example is shown in Figure 3.12b. Here the species tree for human, chimpanzee, and gorilla is ((H, C), G). However, because of sequence variations (polymorphisms) in the extinct ancestral species, the true gene tree is (H, (C, G)). The probability that the gene tree differs from the species tree is greater if the speciation events are closer in time (i.e. if the species tree is almost a star tree) and if the population size of the H-C common ancestor is greater. Such information concerning the gene tree-species tree conflict can be used to estimate the effective population sizes of extinct common ancestors and to infer phylogeographic processes. We will discuss modern computational approaches to such inference using multiple-locus sequence data later, in Chapter 9.

3.1.3 *Classification of tree reconstruction methods*

Here we consider some overall features of phylogeny reconstruction methods. First, some methods are *distance based*. In those methods, distances are calculated from pairwise comparisons of sequences, and the resulting distance matrix is used in subsequent analysis. A cluster algorithm is often used to convert the distance matrix into a phylogenetic tree (Everitt et al. 2001). The most popular methods in this category include UPGMA (Unweighted Pair-Group Method using Arithmetic Averages, Sneath 1962) and NJ (neighbour-joining, Saitou and Nei 1987). Other methods are *character based*, which attempt to fit the characters (nucleotides or amino acids, say) observed in all species at every site to a tree. Maximum parsimony (Fitch 1971b; Hartigan 1973), ML (Felsenstein 1981), and Bayesian methods (Rannala and Yang 1996; Mau and Newton 1997; Li et al. 2000) are all character based. Distance methods are often computationally faster than character-based methods, and can be easily applied to analyse different kinds of data as long as pairwise distances can be calculated.

Tree reconstruction methods can also be classified as being either *algorithmic* (cluster methods) or *optimality* based (search methods). The former include UPGMA and NJ, which use cluster algorithms to arrive at a single tree from the data as the best estimate of the true tree. Optimality-based methods use an optimality criterion (objective function) to measure a tree's fit to data, and the tree with the optimal score is the estimate of the true tree (Table 3.2). In the maximum parsimony method, the tree score is the minimum number of character changes required for the tree, and the *maximum parsimony tree* or *most parsimonious tree* is the tree with the smallest tree score. The ML method uses the log

Table 3.2 Optimality criteria used for phylogeny reconstruction

Method	Criterion (tree score)
Maximum parsimony	Minimum number of changes, minimized over ancestral states
Maximum likelihood	Log likelihood score, optimized over branch lengths and model parameters
Minimum evolution	Tree length (sum of branch lengths, often estimated by least squares)
Bayesian	Posterior probability, calculated by integrating over branch lengths and substitution parameters

likelihood value of the tree to measure the fit of the tree to the data, and the *maximum likelihood tree* is the tree with the highest log likelihood value. In the Bayesian method, the posterior probability of a tree is the probability that the tree is true given the data. The tree with the maximum posterior probability is the estimate of the true tree, known as the maximum *a posteriori* (MAP) *tree*. In theory, methods based on optimality criteria have to solve two problems: (i) calculation of the criterion (tree score) for a given tree and (ii) search in the space of all trees to identify the tree with the best score. The first problem can be expensive if the tree is large, but the second is much worse when the number of sequences is greater than 20 or 50 because of the huge number of possible trees. As a result, heuristic algorithms are used for tree searches. Optimality-based search methods are usually much slower than algorithmic cluster methods.

Some tree reconstruction methods are model based. Distance methods use nucleotide or amino acid substitution models to calculate pairwise distances. Likelihood and Bayesian methods use substitution models to calculate the likelihood function. These methods are clearly model based. Parsimony does not make explicit assumptions about the evolutionary process. Opinions differ as to whether the method makes any implicit assumptions, and, if so, what they are. We will return to this issue in Chapter 5.

3.2 Exhaustive and heuristic tree search

3.2.1 *Exhaustive tree search*

For parsimony and likelihood methods of tree reconstruction, which evaluate trees according to an optimality criterion, one should in theory calculate the score for every possible tree and then identify the tree having the best score. Such a strategy is known as *exhaustive search* and is guaranteed to find the best tree. As mentioned above, the stepwise addition algorithm provides a way of enumerating all possible trees for a fixed number of species (Figure 3.5).

An exhaustive search is, however, computationally unfeasible except for small datasets with, say, fewer than ten taxa. For the parsimony method, a branch-and-bound algorithm has been developed to speed up the exhaustive search (Hendy and Penny 1982). Even so, the computation is feasible for small datasets only. For the likelihood method, such an algorithm is not available. Thus computer programs use heuristic algorithms to search in the tree space, which are not guaranteed to find the optimal tree.

3.2.2 *Heuristic tree search*

Heuristic search algorithms may be grouped into two categories. The first includes hierarchical *cluster algorithms*. These may be subdivided into *agglomerative* methods, which proceed by successive fusions of the n species into groups, and *divisive* methods, which separate the n species successively into finer groups (Everitt et al. 2001). Whether each step involves a fusion or fission, the algorithm involves choosing one out of many alternatives, and the optimality criterion is used to make that choice. The second category of heuristic tree search algorithms includes *tree-rearrangement* or *branch-swapping* algorithms. They propose new trees through local perturbations to the current tree, and the optimality criterion is used to decide whether or not to move to a new tree. The procedure is repeated until no improvement can be made in the tree score. We describe two cluster algorithms in this subsection and a few branch-swapping algorithms in the next.

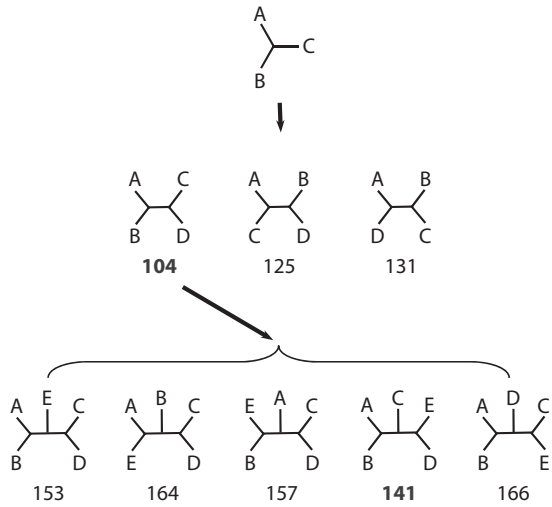


Fig. 3.13 Stepwise addition algorithm under the maximum parsimony criterion. The tree score is the minimum number of changes required by the tree.

Stepwise addition or *sequential addition* is an agglomerative algorithm. It adds sequences one by one, until all sequences are in the tree. When each new sequence is added, all the possible locations are evaluated and the best is chosen using the optimality criterion. Figure 3.13 illustrates the algorithm for the case of five sequences, using the parsimony score as the optimality criterion. Note that this algorithm of heuristic tree search is different from the stepwise addition algorithm for enumerating all possible trees explained in Figure 3.5. In the heuristic search, the locally best subtree is selected at each step, and trees that can be generated from the suboptimal subtrees are ignored. In our example, the ten five-species trees on the second and third rows of Figure 3.5 are never visited in the heuristic search. Thus the algorithm is not guaranteed to find the globally optimal tree. It is less clear whether one should add the most similar sequences or the most divergent sequences first. A common practice is to run the algorithm multiple times, adding sequences in a random order.

Star decomposition is a divisive cluster algorithm. It starts from the star tree of all species, and proceeds to resolve the polytomies by joining two taxa at each step. From the initial star tree of n species, there are $n(n-1)/2$ possible pairs, and the pair that results in the greatest improvement in the tree score is grouped together. The root of the tree then becomes a polytomy with $(n-1)$ taxa. Every step of the algorithm reduces the number of taxa connected to the root by one. The procedure is repeated until the tree is fully resolved. Figure 3.14 shows an example of five sequences, using the log likelihood score for tree selection.

For n species, the stepwise addition algorithm evaluates three trees of four species, five trees of five species, seven trees of six species, with a total of $3+5+7+\cdots+(2n-5) = (n-1)(n-3)$ trees. In contrast, the star decomposition algorithm evaluates $n(n-1)/2 + (n-1)(n-2)/2+\cdots+3 = \frac{1}{6}n(n^2-1)-7$ trees in total, all of which are for n species. Thus for $n > 4$, the star decomposition algorithm evaluates many more and bigger trees than the stepwise addition algorithm and is expected to be much slower. The scores for trees constructed during different stages of the stepwise addition algorithm are not directly

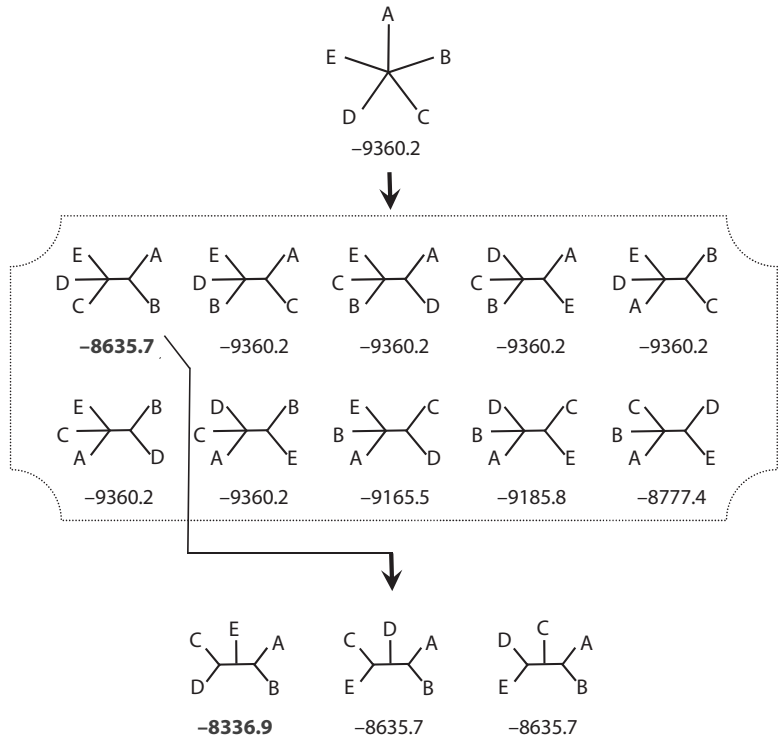


Fig. 3.14 Star decomposition algorithm under the likelihood criterion. The tree score is the log likelihood value calculated by optimizing branch lengths on the tree.

comparable as the trees are of different sizes. Trees evaluated in the star decomposition algorithm are all of the same size and their tree scores are comparable.

Both the stepwise addition and star decomposition algorithms produce resolved trees of all *n* species. If we stop at the end of either algorithm, we have an algorithmic cluster method for tree reconstruction based on the optimality criterion. However, in most programs, trees generated from these algorithms are treated as starting trees and subjected to local rearrangements. Below are a few such algorithms.

3.2.3 *Branch swapping*

Branch swapping or tree rearrangements are heuristic algorithms of hill climbing in the tree space. An initial tree is used to start the process. This can be a random tree, or a tree produced by stepwise addition or star decomposition algorithms, or by other faster tree reconstruction methods such as NJ. The branch-swapping algorithm generates a collection of neighbour trees around the current tree. The optimality criterion is then used to decide which neighbour to move to. The branch-swapping algorithm affects our chance of finding the best tree and the amount of computation it takes to do so. If the algorithm generates too many neighbours, each step will require evaluation of too many candidate trees. If the algorithm generates too few neighbours, we do not have to evaluate many trees at each step, but there may be many local peaks in the tree space (see below), and the search can easily get stuck at a local peak.

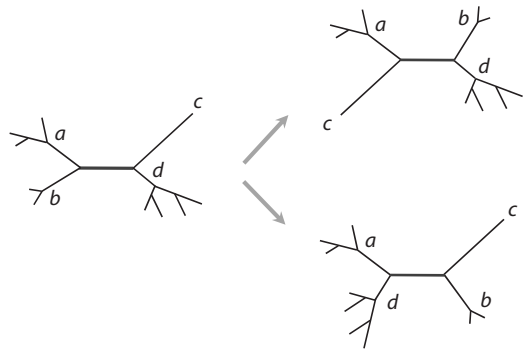


Fig. 3.15 The NNI algorithm. Each internal branch in the tree connects four subtrees or nearest neighbours (*a*, *b*, *c*, *d*). Interchanging a subtree on one side of the branch with another on the other side constitutes an NNI. Two such rearrangements are possible for each internal branch.

Nearest neighbour interchange (NNI). Each internal branch defines a relationship among four subtrees, say, *a*, *b*, *c*, and *d* (Figure 3.15). Suppose the current tree is $((a, b), c, d)$ and the two alternative trees are $((a, c), b, d)$ and $((a, d), b, c)$. The NNI algorithm allows us to move from the current tree to the two alternative trees, by swapping a subtree on one side of the branch with a subtree on the other side. An unrooted tree for n species has $n - 3$ internal branches. The NNI algorithm thus generates $2(n - 3)$ immediate neighbours. The neighbourhood relationships among the 15 trees for five species are illustrated in Figure 3.17.

Two other commonly used algorithms are *subtree pruning and regrafting* (SPR) and *tree bisection and reconnection* (TBR) (Swofford et al. 1996). In the former, a subtree is pruned and then reattached to a different location on the tree (Figure 3.16a). In the latter, the tree

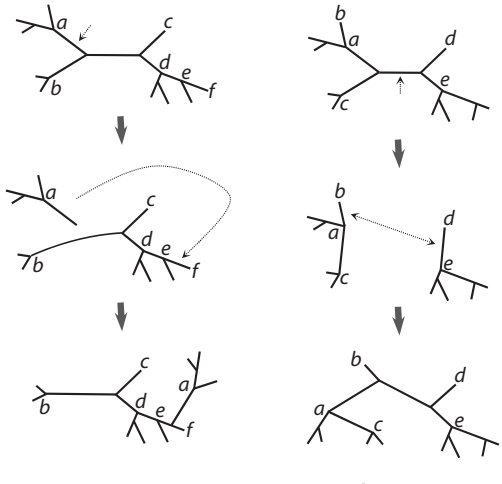


Fig. 3.16 (**a**) Branch swapping by SPR. A subtree (for example, the one represented by node *a*) is pruned, and then reattached to a different location on the tree. (**b**) Branch swapping by TBR. The tree is broken into two subtrees by cutting an internal branch. Two branches, one from each subtree, are then chosen and rejoined to form a new tree.

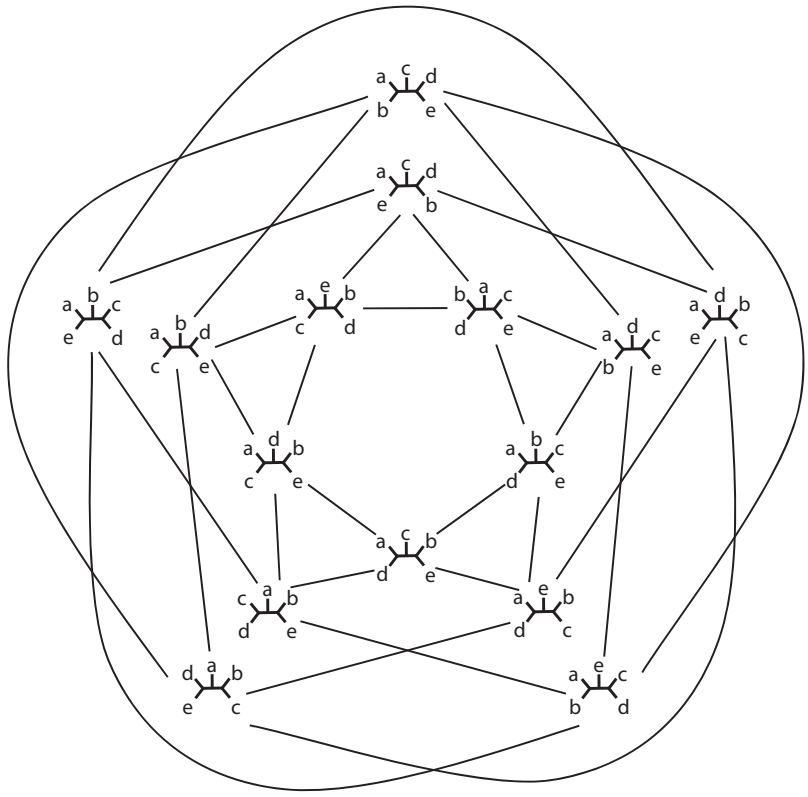


Fig. 3.17 The 15 trees for five species, with neighbourhood relationships defined by the NNI algorithm. Trees that are neighbours under NNI are connected. Note that this visually appealing representation has the drawback that trees close by may not be neighbours. Drawn following Felsenstein (2004).

is cut into two parts by chopping an internal branch and then two branches, one from each subtree, are chosen and rejoined to form a new tree (Figure 3.16b). TBR generates more neighbours than SPR, which in turn generates more neighbours than NNI.

3.2.4 *Local peaks in the tree space*

Maddison (1991) and Charleston (1995) discussed local peaks or tree islands in the tree space. Figure 3.18 shows an example for five species and 15 trees. The neighbourhood relationship is defined using the NNI algorithm (see Figure 3.17). Each tree has four neighbours, while the ten other trees are two NNI steps away. The parsimony tree lengths for the two trees on the top of the graph, T_1 and T_2, are 1366 and 1362. T_1 is the best tree by the likelihood and Bayesian methods, while T_2 is the most parsimonious tree. Other trees are much worse than those two trees by both the likelihood and parsimony criteria. The eight trees that are neighbours of T_1 or T_2 have tree lengths ranging from 1406 to 1438, while the five trees that are two steps away from T_1 and T_2, have tree lengths ranging from 1488 to 1500. Trees T_1 and T_2 are separated from each other by other trees of much poorer scores and are thus local peaks. They are local peaks for the SPR and TBR algorithms as well. Also T_1 and T_2 are local peaks when the data are analysed under

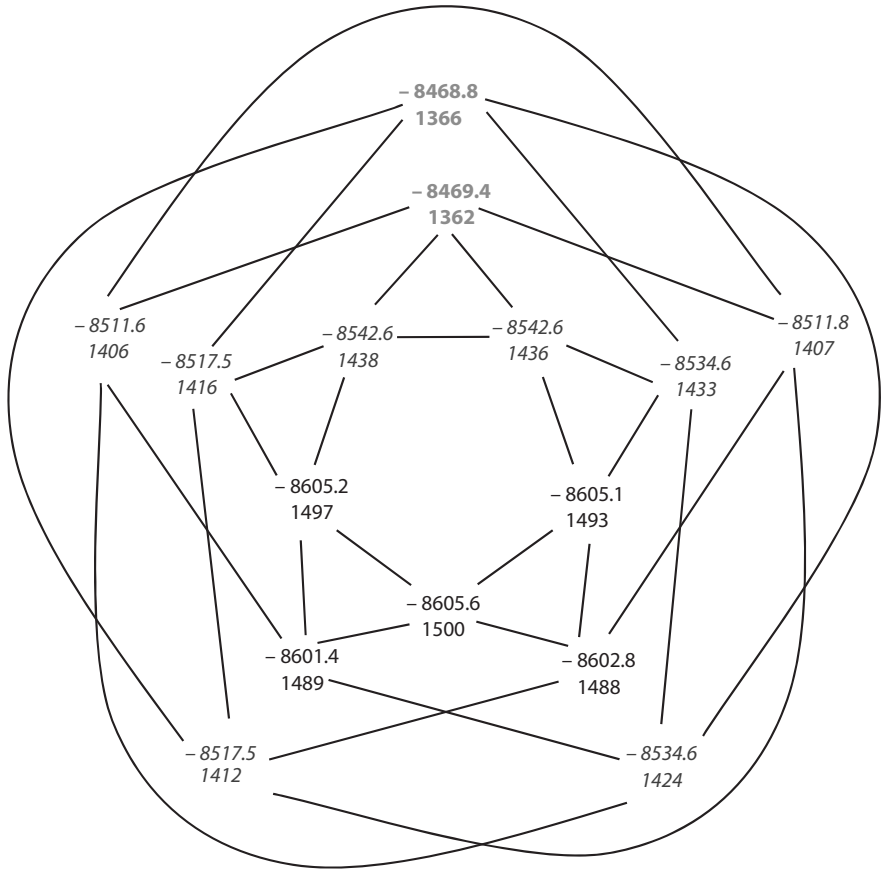


Fig. 3.18 Local peaks in the tree space. The log likelihood values (above) and parsimony scores (below) for the 15 trees of Figure 3.17, shown in the same locations. The dataset was simulated following the construction of Mossel and Vigoda (2005). It consists of 2,000 nucleotide sites simulated under JC69 using the top two trees in Figure 3.17: T_1: ((*a*, *b*), *c*, (*d*, *e*)) and T_2: ((*a*, *e*), *c*, (*d*, *b*)), with 1,000 sites from each tree. All branch lengths are fixed at 0.1. Trees T_1 and T_2 are two local optima under both parsimony and likelihood criteria. The posterior probabilities for T_1 and T_2 are ~0.64 and ~0.36, respectively.

ML. Indeed for this dataset, the rank order of the 15 trees is almost identical under the likelihood and parsimony criteria. Similarly the dataset may pose serious computational problems for Bayesian Markov chain Monte Carlo algorithms, as discussed by Mossel and Vigoda (2005).

One can design a branch-swapping algorithm under which trees T_1 and T_2 are neighbours. However, such an algorithm will define a different neighbourhood relationship among trees, and may have different local peaks or may have local peaks for different datasets. The problem should be more serious for larger trees with more species, as the tree space is much larger. Similarly, in larger sequence datasets with more sites, the peaks tend to be higher and the valleys deeper, making it very difficult to traverse between peaks (Salter 2001).

3.2.5 *Stochastic tree search*

An optimization algorithm that always goes uphill may get stuck at a local peak. Some algorithms attempt to overcome the problem of local peaks by allowing downhill moves. They can work under either parsimony or likelihood criteria.

The first such algorithm is *simulated annealing* (Metropolis et al. 1953; Kirkpatrick et al. 1983). This is inspired by annealing in metallurgy, a technique involving heating and controlled cooling of a metal to reduce defects. The heat causes the atoms to move at random, exploring various configurations, while the slow cooling allows them to find configurations with low internal energy. In a simulated annealing algorithm of optimization, the objective function is modified to have a flattened surface during the early (heating) stage of the search, making it easy for the algorithm to move between peaks. At this stage downhill moves may be accepted nearly as often as uphill moves. The 'temperature' is gradually reduced as the simulation proceeds, according to some 'annealing schedule'. At the final stage of the algorithm, only uphill moves are accepted, as in a greedy algorithm. Simulated annealing algorithms are highly specific to the problem, and their implementation is more art than science. The efficiency of the algorithm is affected by the neighbourhood function (branch-swapping algorithms) and the annealing schedule. Implementations in phylogenetics include Goloboff (1999) and Barker (2004) for parsimony, and Salter and Pearl (2001) for likelihood. Fleissner et al. (2005) used simulated annealing for simultaneous sequence alignment and phylogeny reconstruction.

A second stochastic tree search algorithm is the *genetic algorithm*. A 'population' of trees is kept in every generation; these are allowed to 'breed' to produce trees of the next generation. The algorithm uses operations that are similar to mutation and recombination in genetics to generate new trees from the current ones. The 'survival' of each tree into the next generation depends on its 'fitness', which is the optimality criterion. Lewis (1998), Katoh et al. (2001), and Lemmon and Milinkovitch (2002), among others, have implemented genetic algorithms to search for the ML tree.

A third stochastic tree search algorithm is the Bayesian Markov chain Monte Carlo (MCMC) algorithm. This is a statistical approach and produces not only a point estimate (the tree with the highest likelihood or posterior probability) but also a measure of uncertainty in the point estimate through posterior probabilities estimated during the search. While MCMC algorithms allow downhill as well as uphill moves, high peaks and deep valleys in the search space can cause serious computational problems. In this regard, we note that both simulated annealing and genetic algorithms have been used to design advanced MCMC algorithms for Bayesian computation. We will discuss Bayesian phylogenetic methods in Chapters 7 and 8.

3.3 Distance matrix methods

Distance methods of phylogeny reconstruction involve two steps: (i) calculation of the distance between every pair of species and (ii) reconstruction of a phylogenetic tree from the distance matrix. The first step has been discussed in Chapters 1 (for nucleotide sequence data) and 2 (for amino acid and codon sequence data). Here we discuss the second step. We describe two optimality-based methods (least-squares and minimum evolution) and one cluster algorithm (neighbour-joining). All distance methods treat the matrix of pairwise distances as observed data. Some of them in addition make use of the variances (and even the covariances) of the estimated distances. After the distance matrix is calculated, the original sequence alignment is no longer used.

3.3.1 *Least-squares method*

The least-squares (LS) method takes the pairwise distances as observed data and estimates branch lengths on any given tree by trying to match those distances as closely as possible, i.e. by minimizing the sum of squared differences between the observed and expected distances. The expected distance between two species is calculated as the sum of branch lengths along the path on the tree connecting the two species. The minimum sum of squared differences achieved on the tree then measures the fit of the tree to the distance data and is used as the tree score. The tree with the best (least) score is the LS tree, which is the estimate of the true tree. This method was proposed by Cavalli-Sforza and Edwards (1967; see also Edwards and Cavalli-Sforza 1963b), who called it the *additive-tree method*.

More formally, let the observed (calculated) distance between species i and j be d_{ij} and the expected distance be δ_{ij}, which is the sum of branch lengths along the path from species i to j on the tree. Their difference is the error $e_{ij} = d_{ij} - \delta_{ij}$. The closer the errors are to zero, the better the tree and branch lengths fit the data. The LS method estimates the branch lengths by minimizing the sum of the squared errors:

$$S = \sum_{i<j} (d_{ij} - \delta_{ij})^2. \tag{3.5}$$

For example, the pairwise distances (d_{ij}) calculated under the K80 model for the mitochondrial data of Brown et al. (1982) are shown in Table 3.3. These are taken as observed data. Now consider the tree ((human, chimpanzee), gorilla, orangutan), with its five branch lengths $t_0, t_1, t_2, t_3,$ and t_4 (Figure 3.19). The expected distances in the tree are thus $\delta_{12} = t_1 + t_2$ between the human and the chimpanzee, $\delta_{13} = t_1 + t_0 + t_3$ between the human and the gorilla, and so on. The sum of squared differences is then

$$S = (d_{12} - \delta_{12})^2 + (d_{13} - \delta_{13})^2 + (d_{14} - \delta_{14})^2 + (d_{23} - \delta_{23})^2 + (d_{24} - \delta_{24})^2 + (d_{34} - \delta_{34})^2. \tag{3.6}$$

In this setup, the distances (d_{ij}) are the observed data and the δs (or more precisely, the five branch lengths $t_0, t_1, t_2, t_3,$ and t_4) are the unknown parameters to be estimated. The

Table 3.3 Pairwise distances for the mitochondrial DNA sequences

1. Human				
2. Chimpanzee	0.0965			
3. Gorilla	0.1140	0.1180		
4. Orangutan	0.1849	0.2009	0.1947	
	1. Human	2. Chimpanzee	3. Gorilla	4. Orangutan

Note: The distance matrix is symmetrical so that only the lower-triangular part is shown. The diagonals are zero.

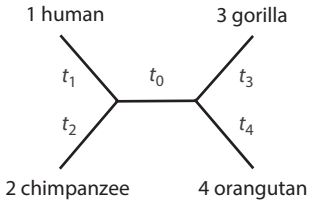


Fig. 3.19 A tree to demonstrate the LS criterion for estimating branch lengths.

Table 3.4 LS branch lengths under K80 for the distance matrix of Table 3.3

Tree	t_0 for internal branch	t_1 for H	t_2 for C	t_3 for G	t_4 for O	S_j
τ_1: ((**H**, **C**), **G**, **O**)	**0.008840**	**0.043266**	**0.053280**	**0.058908**	**0.135795**	**0.000035**
τ_2: ((H, G), C, O)	0.000000	0.046212	0.056227	0.061854	0.138742	0.000140
τ_3: ((C, G), H, O)						
τ_0: (H, C, G, O)						

values of branch lengths that minimize S are the LS estimates. These can be found numerically to be $\hat{t}_0 = 0.008840$, $\hat{t}_1 = 0.043266$, $\hat{t}_2 = 0.053280$, $\hat{t}_3 = 0.058908$, and $\hat{t}_4 = 0.135795$, with the corresponding tree score $S = 0.00003547$. Similar calculations can be done for the other two trees. Indeed, the other two binary trees both converge to the star tree, with the internal branch length estimated to be 0; see Table 3.4. Here we assumed that the branch lengths are estimated under the nonnegative constraint. The tree ((human, chimpanzee), gorilla, orangutan) has the smallest S and is called the LS tree. It is the LS estimate of the true phylogeny. Note that two optimizations are involved: the optimization of branch lengths to calculate the tree score S, and the search in the space of trees for the one with the best tree score, i.e. the LS tree.

Estimation of branch lengths on a fixed tree by the LS criterion uses the same principle as calculating the line of best fit $y = a + bx$ on a scatter plot. If there are no constraints on the branch lengths, the solution is analytical and can be obtained by solving a set of linear equations (Cavalli-Sforza and Edwards 1967). Efficient algorithms that require less computation and less space have also been developed by Rzhetsky and Nei (1993) and Bryant and Waddell (1998). Those algorithms may produce negative branch lengths, which are not meaningful biologically. If the branch lengths are constrained to be nonnegative (as in the above example), the problem becomes one of constrained optimization, which is expensive. However, if we ignore the interpretation of branch lengths, the unconstrained LS is at least consistent: when more and more data are available and the distances approach their true values, the LS tree converges to the true tree. Simulation studies suggest that constraining branch lengths to be nonnegative leads to improved performance in tree reconstruction (e.g. Kuhner and Felsenstein 1994; Gascuel 1997). However, most computer programs implement the LS method without the constraint. It is noted that when the estimated branch lengths are negative, they are most often close to zero.

The LS method described above (i.e. the criterion S of equation (3.5)) uses equal weights for the different pairwise distances and is known as the ordinary least squares (OLS). As in the case of fitting a straight line to a scatter plot, OLS is based on the assumptions that the errors are independent and have equal variance, or equivalently that the (observed) distances are independent and have equal variance. These assumptions are incorrect in the case of pairwise distances. First, larger distances tend to have larger variances. Second, the distances may be correlated because they share branch lengths on the tree. For example, in the tree of Figure 3.19 the distances d_{12} and d_{13} involve the same branch length t_1 so that they both tend to be larger if t_1 is larger: indeed d_{12} and d_{13} have a positive covariance that is equal to the variance of branch length t_1 (Nei and Jin 1989).

The standard approach to dealing with unequal variances is weighted least squares (WLS), which minimizes

$$S = \sum_{i<j} w_{ij}(d_{ij} - \delta_{ij})^2, \tag{3.7}$$

where the weight $w_{ij} = 1/\text{var}(d_{ij})$ (Bulmer 1990). In the method of Fitch and Margoliash (1967), $w_{ij} = 1/d_{ij}^2$ is used. Note that OLS is a special case of WLS with $w_{ij} = 1$. A further extension to WLS that accommodates the correlations (covariances) between the distances, as well as the unequal variances, is the generalized least squares (GLS). While computer simulations suggest that WLS works better than OLS in tree reconstruction, WLS, and especially GLS, involve more computation and are not commonly used.

3.3.2 *Minimum evolution method*

In the LS method discussed above, the LS criterion is used both to estimate the branch lengths on a given tree and to search for the best tree in the tree space. The minimum S for a tree achieved by optimizing its branch lengths is the score for that tree, and at least in theory all possible trees should be compared to find the one with the best score, the LS tree.

In the minimum evolution (ME) method, the LS criterion is usually used to estimate the branch lengths, but tree selection relies on the sum of branch lengths (the tree length). This is based on the plausible but heuristic idea that the true tree is most likely to be the one that involves the minimum amount of evolutionary change. A number of researchers had the same idea at about the same time, including Edwards and Cavalli-Sforza (1963a), Camin and Sokal (1965), and Eck and Dayhoff (1966) (see Edwards 1996, 2009a; Felsenstein 2004). In their analysis of blood group allele frequencies to reconstruct the human population relationships, Edwards and Cavalli-Sforza (1963a) arrived at the *principle of minimum evolution*, which states that 'The most plausible estimate of the evolutionary tree is that which invokes the minimum net amount of evolution'. While the word 'principle' was used, it was intended from the start to be an approximation to the ML method (Edwards 1996). Also it was intended to apply to both continuous and discrete characters. For discrete characters, the amount of evolutionary change should be the minimum number of character changes; so this ME method is now known as parsimony (Camin and Sokal 1965) (see §3.4). For distance data, the amount of evolutionary change is the sum of branch lengths on the tree. Phylogeny reconstruction under the ME criterion based on distances is studied in detail by Kidd and Sgaramella-Zonta (1971) and Rzhetsky and Nei (1993). Gascuel et al. (2001) and Desper and Gascuel (2005) provided excellent reviews of this class of methods.

Variations exist in the practical implementation of the ME principle. First, branch lengths are usually estimated using LS, but as discussed above, variations exist concerning whether the variances and covariances of the observed distances are taken into account and whether the branch lengths are optimized under the nonnegative constraint. Second, several definitions of the tree length exist, differing in their treatment of negative branch lengths. Gascuel et al. (2001) analysed the consistency properties of those variations, and the results are summarized in Table 3.5. A further definition (or estimation method) of tree length is described by Pauplin (2000). This will be described in the next subsection in our discussion of the NJ method.

3.3.3 *Neighbour-joining method*

The simplest distance method is perhaps UPGMA (Sneath 1962). This is a cluster algorithm based on the molecular clock assumption and generates rooted trees. It is thus applicable to population data or closely related species but is not suitable for inferring species phylogenies in general, as the clock is often violated when the sequences are divergent.

Table 3.5 Consistency status of minimum evolution method for phylogeny reconstruction

	Tree length			
Method	All-BL	Positive-BL	Absolute-BL	Nonnegative-BL
Ordinary LS	Consistent	Consistent	Consistent	Unknown
Weighted LS	Inconsistent	Inconsistent	Inconsistent	Inconsistent
Generalized LS	Inconsistent	Inconsistent	Inconsistent	Inconsistent

Note: Branch lengths are estimated using Ordinary LS, Weighted LS, or Generalized LS. They are then summed to give the tree length, which is minimized according to the ME criterion. All-BL means that the tree length is calculated as the sum of all branch lengths (both positive and negative) (Rzhetsky and Nei 1993); Positive-BL means the sum of the positive branch lengths, ignoring the negative ones (Swofford and Olsen 1990); Absolute-BL means the sum of the absolute values of the branch lengths (Kidd and Sgaramella-Zonta 1971); and Nonnegative-BL means the sum of the (nonnegative) branch lengths estimated under the nonnegative constraint. For any of the method for estimating branch lengths and for calculating tree length, the ME method selects the shortest tree as being the estimate of the true phylogeny. From Gascuel et al. (2001).

Here we discuss NJ, which is a divisive cluster algorithm proposed by Saitou and Nei (1987). See §3.2.2 for a discussion of divisive and agglomerative cluster algorithms. NJ does not require the clock assumption and produces unrooted trees. It is widely used because it is computationally fast, produces reasonable trees, and has easy-to-use software implementations (Tamura et al. 2011). It starts with a star tree and then chooses a pair of nodes (neighbours) to join (Figure 3.20). A new node is then created to replace the two joined nodes, reducing the number of nodes connected to the root by one and reducing the dimension of the distance matrix by one. The procedure is repeated until the tree is fully resolved. The branch lengths are updated during every step of the algorithm.

Suppose at the current stage of the algorithm, there are r nodes connected to the root (node o). Out of the $r(r-1)/2$ possible pairs of nodes, the pair that minimizes the following Q criterion is chosen to be neighbours for joining:

$$Q_{ij} = (r-2)d_{ij} - \sum_{k=1}^{r}(d_{ik} + d_{jk}), \text{ for } i < j \le r. \tag{3.8}$$

Suppose nodes i and j are the selected nodes and they are joined to form node u. NJ estimates the length of the branch i–u as

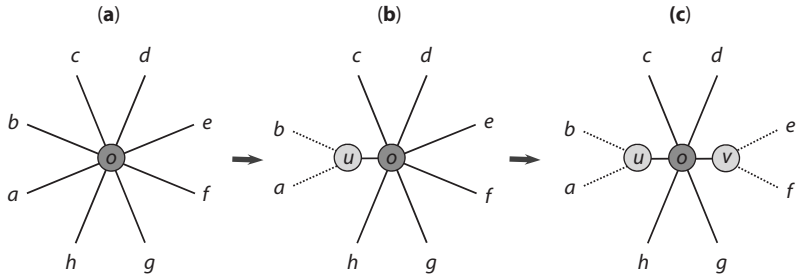


Fig. 3.20 The neighbour-joining method of tree reconstruction is a divisive cluster algorithm. It starts with the star tree (**a**), and chooses a pair of nodes (say, *a* and *b*) to join. The two joined nodes are replaced by a new node (node *u*), reducing the number of nodes connected to the root (node *o*) by one (**b**). The process is repeated until the tree is fully resolved.

$$d_{iu} = \frac{1}{2}d_{ij} + \frac{1}{2(r-2)}\left[\sum_{k=1}^{r} d_{ik} - \sum_{k=1}^{r} d_{jk}\right]. \tag{3.9}$$

The branch length d_{ju} is calculated similarly. Finally, NJ replaces i and j by u in the distance matrix, using the reduction formula

$$d_{uk} = \frac{1}{2}(d_{ik} - d_{iu}) + \frac{1}{2}(d_{jk} - d_{ju}), \tag{3.10}$$

where k is any node connected to the root (o) other than i and j. Equations (3.8)–(3.10) are due to Studier and Keppler (1988). They are equivalent to and computationally more efficient than those given by Saitou and Nei (1987), according to Gascuel (1994). The two versions always construct the same tree, both in terms of topology and branch lengths.

While good performance of NJ was noted early in computer simulations, its assumptions were not well understood until after mathematical analysis several years later. The discussion below draws heavily on Gascuel and Steel (2006).

Saitou and Nei (1987; see also Nei and Kumar 2000) provided a proof of the consistency of NJ. They showed that pair selection using their equivalent of equation (3.8) minimizes the OLS estimate of the tree length. Accordingly, they considered NJ to be an ME method, minimizing the OLS tree length. However, this proof is not strictly correct because it applies only to the first step of the algorithm, when all the nodes connected to the root are tips, but does not apply to the later steps, when some nodes are interior nodes resulting from joining early neighbours (Gascuel and Steel 2006). Also the consistency of the ME method under OLS tree lengths was not established until Rzhetsky and Nei (1993), later than Saitou and Nei (1987).

Nevertheless, NJ is based on an ME criterion, but the tree length is estimated using a different method from OLS (Gascuel and Steel 2006). Pauplin (2000) studied a method for calculating the tree length directly using the distance matrix. Note that for the example tree of four tips of Figure 3.21a, the tree length is given as

$$l = \frac{1}{2}(d_{ac} + d_{cd} + d_{db} + d_{ba}). \tag{3.11}$$

The rule here is to traverse the tree by visiting pairs of tips in the clockwise direction, i.e. in the order a, c, d, and b, as indicated by the dashed lines. This way each branch on the tree is passed twice, hence the factor $\frac{1}{2}$. If the tree is perfectly additive with the distances to be the true values, equation (3.11) will give the true tree length. Otherwise if the distances are estimates, equation (3.11) will give an estimate of the true tree length. However, the same tree can be drawn in different ways, so that this estimate of tree length is not unique. Then it is natural, as suggested by Pauplin (2000), to average over all possible ways of drawing the same tree. In our example, there is a second way of drawing the same tree, shown in Figure 3.21b, and this gives $l = \frac{1}{2}(d_{ad} + d_{dc} + d_{cb} + d_{ba})$. Averaging over the two ways gives

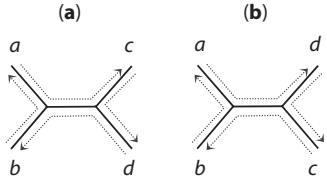


Fig. 3.21 Two different ways of drawing the same tree for four tips to explain Paulin's (2000) direct calculation of tree length from the distance matrix.

$$l = \frac{1}{2}(d_{ab} + d_{cd}) + \frac{1}{4}(d_{ac} + d_{ad} + d_{bc} + d_{bd}). \tag{3.12}$$

In general, Pauplin's (2000) estimate of tree length on a binary tree is

$$l = \sum_{i<j} w_{ij} d_{ij}, \tag{3.13}$$

which averages over all pairwise distances d_{ij}, with the weight w_{ij} to be $\frac{1}{2}$ raised to the power of the number of interior nodes on the path between i and j. This estimate was extended to multifurcating trees by Semple and Steel (2003), in which case the weight w_{ij} is calculated as follows. Consider the directed path from i to j, and for each interior node on the path, count the number of outgoing branches. Multiply those numbers and the reciprocal of the product will be w_{ij}. For example, with the tree of Figure 3.20c, we have $w_{ab} = 1/2$, $w_{cd} = 1/5$, $w_{ae} = 1/(2 \times 5 \times 2)$, and so on. For w_{ae}, note that the path from a to e passes three interior nodes (u, o, v), and the numbers of outgoing branches at those nodes are 2, 5, and 2 respectively. Semple and Steel showed that with this redefinition of w_{ij}, the tree length estimate of equation (3.13) gives exactly the average of estimates of the form of equation (3.11) over all possible ways of drawing the same tree.

Going back to our discussion of NJ, Gascuel and Steel (2006) showed that pair selection in the NJ algorithm by equation (3.8) is equivalent to minimizing the tree length defined in equation (3.13). Of course NJ is a cluster algorithm and does not search for the globally optimal tree under the criterion. One may wonder whether an exhaustive search or a more thorough search than NJ can lead to better performance. The answer to this question is 'Yes'. Indeed this ME method, based on the tree length of equation (3.13), was proposed by Pauplin (2000) and implemented by Desper and Gascuel (2002) as the *balanced ME* method in their FASTME program. Desper and Gascuel's (2002) simulations suggest that FASTME performs better than NJ and other available distance methods (see also Vinh and von Haeseler 2005). Note that equation (3.13) has some flavour of WLS, because a large distance d_{ij} tends to be separated by more interior nodes so that the weight w_{ij} will tend to be smaller (Desper and Gascuel 2004). Desper and Gascuel (2004) also showed that the balanced ME method is consistent.

In summary, NJ is an ME method, but it minimizes the tree length of equation (3.13), not the OLS estimate of tree length. Furthermore the tree length of equation (3.13) is better than the OLS estimate. This explains some counterintuitive results observed in several simulation studies (Gascuel 1997, 2000; Nei et al. 1998). Nei et al. (1998) found that minimizing the OLS tree length leads to poorer performance than NJ. The results prompted the authors to question the optimization principle. The result is unusual, as NJ was justified on the ground that it was based on the ME principle but a more correct implementation (by a more thorough search in the tree space) of the ME principle actually leads to poorer performance than NJ. The optimization principle is justified, but the criterion being optimized is important.

As implied above, a major concern with any distance matrix method is that large distances are poorly estimated, and it is important to take into account their large variances, for example, by using WLS. Besides WLS, Gascuel (1997) modified the formula for updating branch lengths in the NJ algorithm to incorporate approximate variances and covariances of distance estimates. This method, called BIONJ, is close to WLS, and was found to outperform NJ, especially when substitution rates are high and variable among lineages. Another modification is the weighted NJ or WEIGHBOR method of Bruno et al. (2000). This uses an approximate likelihood criterion for joining nodes to accommodate the fact that large distances are poorly estimated. Computer simulations suggest that

WEIGHBOR produces trees similar to ML, and is more robust to the problem of long-branch attraction (see §3.4.5) than NJ (Bruno et al. 2000). Another idea, due to Ranwez and Gascuel (2002), is to improve distance estimates. When calculating the distance between a pair of sequences, those authors used a third sequence to break the long distance into two parts and used ML to estimate three branch lengths on the tree of the three sequences; the pairwise distance is then calculated as the sum of the two branch lengths. Simulations suggest that the improved distance, when combined with the NJ, BIONJ, and WEIGHBOR algorithms, led to improved topological accuracy.

3.4 Maximum parsimony

3.4.1 *Brief history*

Felsenstein (2004) and Edwards (2009a) have published accounts of the early history of phylogeny reconstruction methods. Edwards and Cavalli-Sforza (1963a) suggested the *minimum evolution principle* (later renamed the minimum evolution method) as an approximation to the ML solution. For discrete characters, the amount of evolution should be measured by the minimum number of character changes on the tree. In modern terminology, the method applied to discrete data is known as parsimony, while ME refers to methods minimizing the sum of branch lengths after correcting for multiple hits, as discussed in last section. For discrete morphological characters, Camin and Sokal (1965) suggested the use of the minimum number of changes as a criterion for tree selection, justifying it by arguing that evolution follows the shortest paths, a view sharply criticized by Edwards (1996, 2009a). For molecular data, minimizing changes on the tree to infer ancestral proteins appears most natural and was practised by many pioneers in the field, for example, by Pauling and Zuckerkandl (1963) and Zuckerkandl (1964) as a way of 'restoring' ancestral proteins for 'paleogenetic' studies of their chemical properties, and by Eck and Dayhoff (1966) to construct empirical matrices of amino acid substitution rates. Fitch (1971b) was the first to present a systematic algorithm to enumerate all and only the most parsimonious reconstructions. Fitch's algorithm works on binary trees only. Hartigan (1973) considered multifurcating trees as well and provided a mathematical proof for the algorithm. Since then, much effort has been made to develop fast algorithms for the parsimony analysis of large datasets; see, e.g. Ronquist (1998), Nixon (1999), and Goloboff (1999).

3.4.2 *Counting the minimum number of changes on a tree*

The minimum number of character changes at a site on a given tree is often called the *character length* or *site length*. The sum of character lengths over all sites in the sequence is the minimum number of required changes for the entire sequence and is called the *tree length*, *tree score*, or *parsimony score*. The tree with the smallest tree score is the estimate of the true tree, called the *maximum parsimony tree* or the *most parsimonious tree*. It is common, especially when the sequences are very similar, for multiple trees to be equally best; i.e. they have the same minimum score and are all shortest trees.

Suppose the data for four species at a particular site are AAGG, and consider the minimum number of changes required by the two trees of Figure 3.22. We calculate this number by assigning character states to the extinct ancestral nodes. For the first tree, this is achieved by assigning A and G to the two nodes, and one change (A $\leftrightarrow$ G on the internal branch) is required. For the second tree, we can assign either AA (shown) or

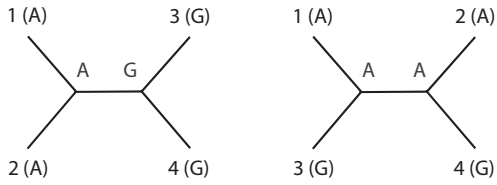


Fig. 3.22 Data AAGG at one site for four species mapped onto two alternative trees ((1, 2), 3, 4) and ((1, 3), 2, 4). The tree on the left requires a minimum of one change while the tree on the right requires two changes to explain the data.

GG (not shown) to the two internal nodes; in either case, a minimum of two changes is required. Note that the set of character states (nucleotides) at a site assigned to ancestral nodes is called an *ancestral reconstruction*. The total number of reconstructions at each site is thus $4^{(n-2)}$ for nucleotides or $20^{(n-2)}$ for amino acids as a binary unrooted tree of n species has $n-2$ interior nodes. The reconstruction that achieves the minimum number of changes is called the *most parsimonious reconstruction*. Thus, for the first tree, there is one single most parsimonious reconstruction, while for the second tree, two reconstructions are equally parsimonious. The algorithm of Fitch (1971b) and Hartigan (1973) calculates the minimum number of changes and enumerates all the most parsimonious reconstructions at a site. We will not describe this algorithm here. Instead we describe in the next subsection a more general algorithm due to Sankoff (1975), which is very similar to the likelihood algorithm to be discussed in Chapter 4.

Some sites do not contribute to the discrimination of trees and are thus noninformative. For example, a constant site, at which the different species have the same nucleotide, requires no change for any tree. Similarly a *singleton* site, at which two states are observed but one is observed only once (e.g. TTTC or AAGA), requires one change for every tree and is thus not informative. Perhaps more strikingly, a site with data AAATAACAAG (for ten species) is not informative either, as a minimum of three changes are required by any tree, which is also achieved by every tree by assigning A to all ancestral nodes. For a site to be a *parsimony-informative* site, at least two characters have to be observed, each at least twice. Note that the concepts of informative and noninformative sites apply to parsimony only. In distance and likelihood methods, all sites including the constant sites affect the calculation and should be included.

We often refer to the observed character states in all species at a site as a *site configuration* or *site pattern*. The above discussion means that for four species, only three *site patterns* are informative: *xxyy*, *xyxy*, and *xyyx*, where x and y are any two distinct states. It is obvious that those three site patterns 'support' the three trees T_1: $((1,2),3,4)$; T_2: $((1,3),2,4)$; and T_3: $((1,4),2,3)$, respectively. Suppose the numbers of sites with those site patterns are $n_1, n_2,$ and n_3, respectively. Then $T_1, T_2,$ or T_3 is the most parsimonious tree if $n_1, n_2,$ or n_3 is the greatest among the three.

3.4.3 *Weighted parsimony and dynamic programming*

The algorithm of Fitch (1971b) and Hartigan (1973) assumes that every change has the same cost. In weighted parsimony, different weights are assigned to different types of character changes. Rare changes are penalized more heavily than frequent changes. For example, transitions are known to occur at a higher rate than transversions and can be assigned a lower cost (weight). Weighted parsimony uses a *step matrix* or *cost matrix* to specify the cost of every type of change. An extreme case is *transversion parsimony*, which gives a penalty of 1 for a transversion but no penalty for a transition. Below we describe Sankoff's (1975) dynamic programming algorithm, which calculates the minimum cost at

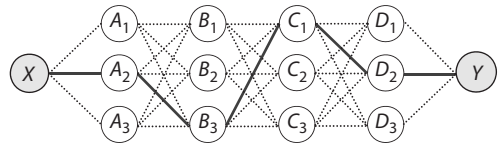


Fig. 3.23 Caravan travelling example used for illustrating the dynamic programming algorithm. It is required to determine the shortest route from *X* to *Y*, through four countries A, B, C, and D. Stops between neighbouring countries are connected, with their distances known.

a site and enumerates the reconstructions that achieve this minimum given any arbitrary cost matrix.

We first illustrate the basic idea of dynamic programming algorithms using a fictitious example of a caravan travelling on the silk route. We start from the source city *X*, Chang-an in central China, to go to the destination *Y*, Baghdad in Iraq (Figure 3.23). The route goes through four countries *A*, *B*, *C*, and *D*, and has to pass one of three caravan stops in every country: $A_1, A_2,$ or A_3 in country *A*; $B_1,$ $B_2,$ or B_3 in country *B*; and so on. We know the distance between any two stops in two neighbouring countries, such as XA_2 and A_1B_2. We seek to determine the shortest distance and the shortest route from *X* to *Y*. An obvious strategy is to evaluate all possible routes, but this can be expensive as the number of routes (3^4 in the example) grows exponentially with the number of countries. A dynamic programming algorithm answers many smaller questions, with the new questions building on answers to the old ones. First we ask for the shortest distances (from *X*) to stops $A_1, A_2,$ and A_3 in country *A*. These are just the given distances. Next we ask for the shortest distances to stops in country *B*, and then the shortest distances to stops in country *C*, and so on. Note that the questions at every stage are easy given the answers to the previous questions. For example, consider the shortest distance to C_1, when the shortest distances to $B_1, B_2,$ and B_3 are already determined. This is just the smallest among the distances of the three routes going through $B_1,$ $B_2,$ or B_3, with the distance through B_j $(j = 1,\ 2,\ 3)$ being the shortest distance (from *X*) to B_j plus the distance between B_j and C_1. After the shortest distances to $D_1, D_2,$ and D_3 are determined, it is easy to determine the shortest distance to *Y* itself. It is important to note that adding another country to the problem will add another stage in the algorithm, so that the amount of computation grows linearly with the number of countries.

We now describe Sankoff's algorithm. We seek to determine the minimum cost for a site on a given tree as well as the ancestral reconstruction that achieves that minimum. We use the tree of Figure 3.24 as an example. The observed nucleotides at the site at the six tips are CCAGAA. Let $c(x, y)$ denote the cost of change from state x to state y, so $c(x, y) = 1$ for a transitional difference and $c(x, y) = 1.5$ for a transversion (Figure 3.24).

Instead of the minimum cost for the whole tree, we calculate the minimum costs for many subtrees. We refer to a branch on the tree by the node it leads to or by the two nodes it connects. For example, branch 10 is also branch 8–10 in Figure 3.24. We say that each node *i* on the tree defines a subtree, referred to as subtree *i*, which consists of branch *i*, node *i*, and all its descendant nodes. For example, subtree 3 consists of the single tip branch 10–3 while subtree 10 consists of branch 8–10 and nodes 10, 3, and 4. Define $S_i(x)$ as the minimum cost incurred on subtree *i*, given that the mother node of node *i* has

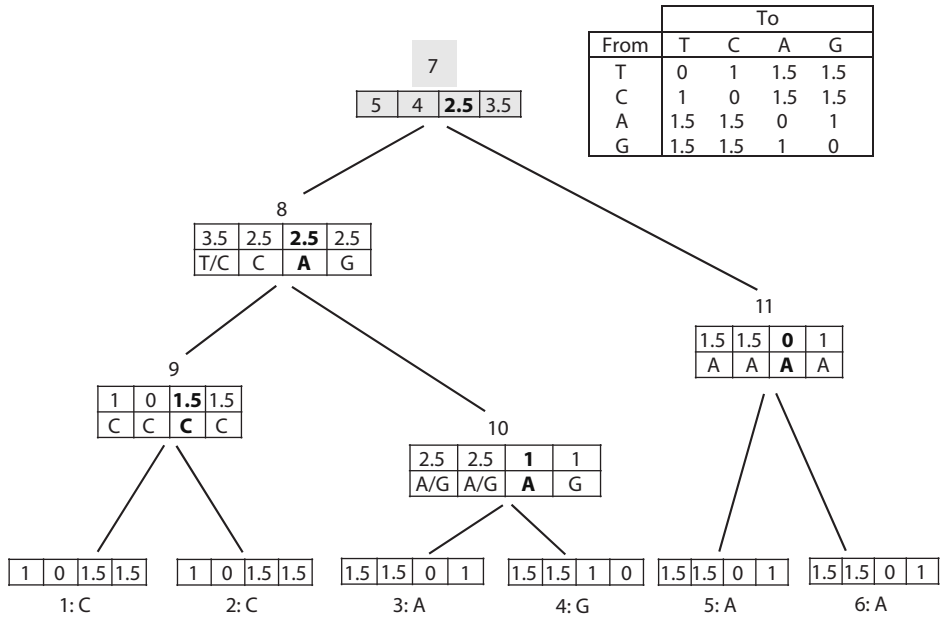


Fig. 3.24 Dynamic programming algorithm for calculating the minimum cost and enumerating the most parsimonious reconstructions using weighted parsimony. The site has observed data CCAGAA. The cost vector at each node gives the minimum cost of the subtree induced by that node (which includes the node itself, its mother branch and all its descendants), given that the mother node has nucleotides T, C, A, or G. The nucleotides at the node that achieved the minimum cost are shown below the cost vector. For example, the minimum cost of the subtree induced by node 3 (including the single branch 10–3) is 1.5, 1.5, 0, or 1, if node 10 has T, C, A, or G, respectively. The minimum cost of the subtree induced by node 10 (including branches 8–10 and nodes 10, 3 and 4) is 2.5, 2.5, 1, or 1, if node 8 has T, C, A, or G, respectively; the said minimum is achieved by node 10 having A/G, A/G, A, or G, respectively. The cost vectors are calculated for every node, starting from the tips and proceeding towards the root. At the root (node 7), the cost vector gives the minimum cost of the whole tree as 5, 4, 2.5, or 3.5, if the root has T, C, A, or G, respectively.

state x. Thus $\{S_i(\mathrm{T}), S_i(\mathrm{C}), S_i(\mathrm{A}), S_i(\mathrm{G})\}$ constitutes a cost vector for subtree i at node i. They are like the shortest distances to stops in a particular country in the caravan example. We calculate the cost vectors for all nodes on the tree, starting with the tips and visiting a node only after we have visited all its descendant nodes. For a tip node i, the subtree is just the tip branch and the cost is simply read from the cost matrix. For example, tip 3 has the cost vector $\{1.5, 1.5, 0, 1\}$, meaning that the (minimum) cost of subtree 3 is 1.5, 1.5, 0, or 1, if mother node 10 has T, C, A, or G, respectively (Figure 3.24). If the nucleotide at the tip is undetermined, the convention is to use the minimum cost among all compatible states (Fitch 1971b). For an interior node i, suppose its two daughter nodes are j and k. Then

$$S_i(x) = \min_y [c(x, y) + S_j(y) + S_k(y)]. \tag{3.14}$$

Note that subtree i consists of branch i plus subtrees j and k. Thus the minimum cost of subtree i is the cost along branch i, $c(x, y)$, plus the minimum costs of subtrees j and k, minimized over the state y at node i. We use $C_i(x)$ to record the state y that achieved the minimum.

Consider node 10 as an example, for which the cost vector is calculated to be $\{S_{10}(\mathrm{T}), S_{10}(\mathrm{C}), S_{10}(\mathrm{A}), S_{10}(\mathrm{G})\} = \{2.5, 2.5, 1, 1\}$. Here the first entry, $S_{10}(\mathrm{T}) = 2.5$, means that the minimum cost of subtree 10, given that mother node 8 has T, is 2.5. To see this, consider the four possible states at node 10: y = T, C, A, or G. The (minimum) cost on subtree 10 is 3 = 0 + 1.5 + 1.5, 4, 2.5, or 2.5, if node 10 has the state y = T, C, A, or G, respectively (and if node 8 has T). Thus the minimum is 2.5, achieved by node 10 having y = A or G; i.e. $S_{10}(\mathrm{T}) = 2.5$ and $C_{10}(\mathrm{T})$ = A or G (Figure 3.24). This is the minimization over y in equation (3.14). Similarly, the second entry in the cost vector at node 10, $S_{10}(\mathrm{C}) = 2.5$, means that the minimum cost for subtree 10, given that node 8 has C, is 2.5. This minimum is achieved by having $C_{10}(\mathrm{C})$ = A/G at node 10.

Similar calculations can be done for nodes 9 and 11. We now consider node 8, which has daughter nodes 9 and 10. The cost vector is calculated to be $\{3.5, 2.5, 2.5, 2.5\}$, meaning that the minimum cost of subtree 8 is 3.5, 2.5, 2.5, or 2.5, if mother node 7 has T, C, A, or G, respectively. Here we derive the third entry $S_8(\mathrm{A}) = 2.5$, with mother node 7 having A. By using the cost vectors for nodes 9 and 10, we calculate the minimum cost on subtree 8 to be 5 = 1.5 + 1 + 2.5, 4, 2.5, or 4.5, if node 8 has T, C, A, or G, respectively (and if mother node 7 has A). Thus $S_8(\mathrm{A}) = 2.5$ is the minimum, achieved by node 8 having $C_8(\mathrm{A}) = \mathrm{A}$.

The algorithm is applied successively to all nodes in the tree, starting from the tips and moving towards the root. This upper pass calculates $S_i(x)$ and $C_i(x)$ for all nodes i except the root. Suppose the root has daughter nodes j and k and note that the whole tree consists of subtrees j and k. The minimum cost of the whole tree, given that the root has y, is $S_j(y) + S_k(y)$. This cost vector is $\{5, 4, 2.5, 3.5\}$, for y = T, C, A, G at the root (Figure 3.24). The minimum is 2.5, achieved by having A at the root. In general, if j and k are the daughter nodes of the root, the minimum cost for the whole tree is

$$S = \min_{y}[S_j(y) + S_k(y)]. \tag{3.15}$$

After calculation of $S_i(x)$ and $C_i(x)$ for all nodes through the upper pass, a down pass reads out the most parsimonious reconstructions. In our example, given A for the root, node 8 achieves the minimum for subtree 8 by having A. Given A at node 8, nodes 9 and 10 should have C and A, respectively. Similarly given A for the root, node 11 should have A. Thus the most parsimonious reconstruction at the site is $y_7y_8y_9y_{10}y_{11}$ = AACAA, with the minimum cost 2.5.

3.4.4 *Probabilities of ancestral states*

Obviously the ancestral states reconstructed by parsimony may not always be the true states. Many authors thus recognized the desirability of calculating the probability that the parsimony reconstructions are the true states (Fitch 1971b; Maddison and Maddison 1982). This can only be achieved by the use of a character evolution model. Unfortunately most of those calculations do not appear to be correct (e.g. Fitch 1971b; Schluter 1995; Pagel 1999) or relevant (e.g. Maddison 1995). We defer the discussion of such calculations to §4.4, where the correct approach is described.

3.4.5 *Long-branch attraction*

Felsenstein (1978b) demonstrated that the parsimony method can be statistically inconsistent under certain combinations of branch lengths on a four-species tree. When the

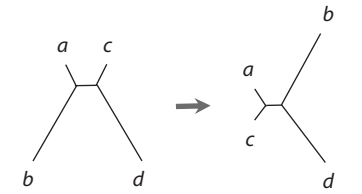


Fig. 3.25 Long-branch attraction. When the correct tree (T_1) has two long branches separated by a short internal branch, parsimony tends to recover a wrong tree (T_2) with the two long branches grouped together.

amount of data (the number of sites) increases to infinity, it becomes more and more certain that the most parsimonious tree is an incorrect tree.

The tree Felsenstein used has the characteristic shape shown in Figure 3.25a, with two long branches separated by a short internal branch. The estimated tree by parsimony, however, tends to group the two long branches together (Figure 3.25b). This phenomenon is now known as 'long-branch attraction'. Using a simple model of character evolution, Felsenstein calculated the probabilities of observing sites with the three site patterns *xxyy*, *xyxy*, *xyyx*, where *x* and *y* are any two distinct characters, and found that Pr(*xyxy*) > Pr(*xxyy*) when the two long branches are much longer than the three short branches. This calculation will be described later in Chapter 4 (see Problem 4.3). Thus with more and more sites in the sequence, it will be increasingly certain that more sites will have pattern *xyxy* than pattern *xxyy*, and that parsimony will recover the wrong tree T_2 instead of the true tree T_1. The phenomenon has been demonstrated in many simulated and real datasets (see, e.g. Huelsenbeck 1998) and is due to the failure of parsimony to correct for parallel changes on the two long branches. Likelihood and distance methods using simplistic and unrealistic evolutionary models show the same behaviour.

3.4.6 *Assumptions of parsimony*

A discussion of the assumptions underlying the parsimony method of phylogeny reconstruction is provided in Chapter 5. Here we comment on a few obvious concerns on the parsimony reconstruction of ancestral states. First, the method ignores branch lengths. Some branches on the tree are longer than others, meaning that they have accumulated more evolutionary changes than other branches. It is thus illogical to assume that a change is as likely to occur on a long branch as on a short one, as parsimony does, when character states are assigned to ancestral nodes on the tree. Second, the simple parsimony criterion ignores different rates of changes between nucleotides. Such rate differences are taken into account by weighted parsimony through the use of a step matrix, although determining the appropriate weights may be nontrivial. In theory, how likely a change is to occur on a particular branch should depend on the length of the branch as well as the relative rate of the change. If one attempts to derive appropriate weights from the observed data, one will naturally be led to the likelihood method, which uses a Markov chain model to describe the nucleotide substitution process, relying on probability theory to accommodate unequal branch lengths, unequal substitution rates between nucleotides, and any other features of the evolutionary process. This is the topic of next chapter.

3.5 Problems

3.1 Draw the tree

(((human: 0.040, chimpanzee: 0.052): 0.016, gorilla: 0.059) : 0.047, orangutan: 0.090, gibbon: 0.125);

The branch lengths are the MLEs under JC69 obtained from the mitochondrial data of Brown et al. (1982). Identify the most distant pair of species and use midpoint rooting to root the tree. Draw the resulting rooted tree.

3.2 Write two equivalent Newick representations of the tree in Figure 3.9b.

3.3 The following rooted tree is shown in Figure 3.26:

(a:0.05, (c: 0.07, ((b:0.015, f:0.12) :0.01, (d:0.01, e:0.4) :0.005) :0.03) :0.025);

Which of the following statements are incorrect?
(a) Species d and e are most closely related.
(b) Sequences b and d are most similar.
(c) Species b is more closely related to d than to e.
(d) Species d is more closely related to c than to f.

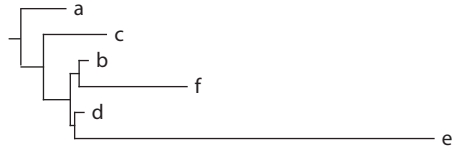


Fig. 3.26 A tree showing branch lengths for Problem 3.3.

3.4 Calculate the partition distance between the two trees of Figure 3.11.

3.5 Use the three trees of Figure 3.27 to construct the majority-rule consensus tree, and show the support values for the nodes on it.

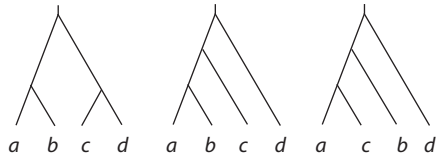


Fig. 3.27 Three rooted trees for constructing the majority-rule consensus tree in Problem 3.5.

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