

COMENIUS UNIVERSITY IN BRATISLAVA
FACULTY OF MATHEMATICS, PHYSICS AND INFORMATICS

**SOFTWARE FOR ISOMETRIC GENE
TREE RECONCILIATION**

Master's thesis

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1 Overview

In this chapter, we introduce basic information and define essential terminology from the field of bioinformatics. We describe the problem of gene tree reconciliation in more details and present existing software for solving this problem.

1.1 Background

Every organism has its complete set of genetic information encoded in a genome. A genome consists of several DNA (deoxyribonucleic acid) molecules and contains all the information, which are required for the organism to function.

DNA is a long molecule composed of two complementary strands. Each strand is made up of four chemical bases: adenine, guanine, cytosine and thymine, and connected to its complementary strand by pairing rules, where adenine is paired up with thymine and cytosine is paired up with guanine. Sequence of these bases encodes the genetic information important for building and maintaining an organism. Specific parts of DNA are called genes.

A gene is a subsequence of a DNA strand that contains information for synthesis of a specific molecule, usually a protein. It is basic unit of heredity.

Basis of heredity is genetic variation, which allows small changes in DNA of organisms that refers to differences between individuals within a population. Genetic variation is necessary for evolution and multiple evolutionary events are known such as duplication, deletion, speciation and others.

Duplication is a type of mutation where one or more genes are copied and inserted to some other position in the same genome. A duplicated gene sometimes develops a new function. [7]

The opposite of duplication is deletion (gene loss). It is a type of mutation in which

some part of DNA sequence containing a gene is left out from the genome during DNA replication or it loses its function.

Speciation is an evolutionary process of in which a single population evolves populations into two distinct species. It can happen for various reasons, for example, when a group separates from other members of its species to different a geographical area. Members of a new group develop own unique characteristics due to the demands of another environment and this process will differentiate the new species.

Duplications and speciations result in formation of groups of similar genes, called gene families, from a single gene. A gene family consists of evolutionarily related genes from one or multiple species, which are structurally and usually functionally similar.

Evolutionary relationships formed by evolutionary events are represented in a form of graph called phylogenetic tree, which is a branching diagram that shows evolutionary relationships between organisms. A phylogenetic tree is a tree T with nodes $V(T)$, edges $E(T)$ and leaves $L(T)$. It is called weighted when branch length $w(u, v)$ is defined for each edge (u, v) .

Phylogenetic trees can be either rooted or unrooted (Fig. 1.1). A rooted tree is a phylogenetic tree T where for $(u, v) \in E(T)$: node u is the parent of node v , node v is the children of node u , $root(T)$ does not have parent and leaves $L(T)$ do not have children. An ancestor of node v is any node of tree T on the path from node v to $root(T)$. Every ancestor have at least one descendant. A descendant of node v is any node of tree T of which v is an ancestor [6]. We will denote for $u, v \in V(T)$ that $v <_T u$ if u is ancestor of v and v is descendant of u .

For group of nodes in a rooted tree, their lowest common ancestor (LCA) is the farthest node from root that has all nodes in the group as descendants.

An unrooted tree is a phylogenetic tree without root. Unrooted tree can be rooted by placing a root r on some edge (u, v) . The original edge (u, v) is subdivided into two edges (u, r) and (r, v) . If edge (u, v) is weighted, then $w(u, r) + w(r, v) = w(u, v)$.

We will be using two types of phylogenetics trees for showing evolutionary relationships: species trees (to describe the evolution of a set of species) and gene trees (to describe evolution of a particular gene).

A species tree is a phylogenetic tree S where $L(S)$ represent present-day species and internal nodes from $V(S)$ represent speciation events in the history.

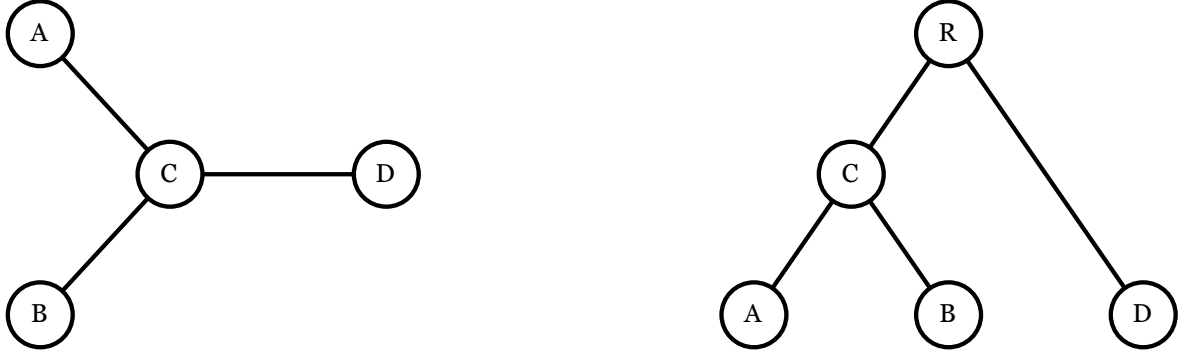


Figure 1.1: Unrooted tree(left) and its rooted version (right) tree. We placed the root R on the edge (C, D) replacing it with two new edges (C, R) and (R, D) .

A gene tree is a phylogenetic tree G where $L(G)$ represent present-day copies of the gene and internal nodes from $V(S)$ represent duplication and deletion events in the history.

Phylogenetic trees are reconstructed from a multiple alignment of the DNA sequences of present-day species by various methods [4] to find the most likely phylogenetic tree to given DNA sequences.

1.2 Different approaches to gene tree reconciliation

An evolutionary history is a possible sequence of evolutionary events that lead to an observed members of a gene family in present-day species is shown by evolutionary history (Fig. 1.2). It illustrates how many duplications and deletions happened during an evolution of one or more genes inside the evolution of a group of species.

The problem of gene tree and species tree reconciliation was introduced in 1979 by Goodman et al. [5] as a method to infer evolutionary history of duplications and deletions in a gene family to decode evolutionary relationships between copies of gene. The goal of reconciliation consists in mapping nodes of a gene tree into a species tree and thus inducing evolution of a gene family in terms of speciations, duplications and deletions. An important prerequisite for reconciliation is to have a gene tree without errors as a misplaced leaves can lead to a different history of the gene family.

Let $\mu : L(G) \rightarrow L(S)$ be leaf mapping of each leaf of G to the unique leaf of S with the same label. The LCA-mapping $\sigma : V(G) \rightarrow V(S)$ maps each node $u \in V(G)$ to the unique node $\sigma(u) = LCA(\mu(v) | \forall v \in L(G), v <_G u)$.

Definition 1 A reconciliation between gene tree G and species tree S is mapping $\phi : V(G) \rightarrow V(S)$ such that:

1. $\forall u \in L(G) : \phi(u) = \mu(u)$
2. $\forall u \in V(G) : \phi(u) = \sigma(u)$
3. $\forall u, v \in V(G)$ such that $v <_G u$: $\phi(v) <_S \phi(u)$

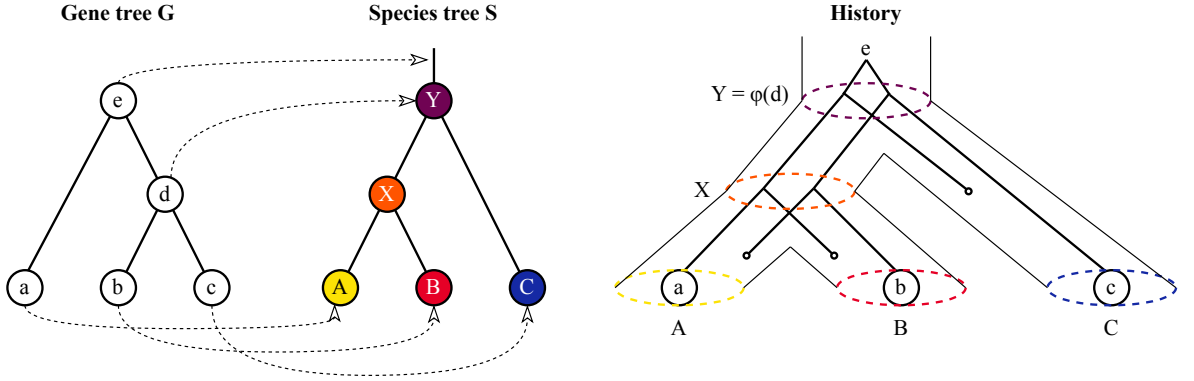


Figure 1.2: Reconciliation and evolutionary history. On the left, the gene tree G is mapped to the species tree S , where leaves are mapped to leaves, node d is mapped to node Y (because Y is LCA of mapping b and c) and node e is mapped above node Y (because $d <_G e$). On the right, we can see the evolutionary history implied by this reconciliation. This history contains one duplication e , two speciations Y and X and three deletions (empty circles).

Different approaches to gene tree reconciliation will be shown with presented examples of software that have implemented gene tree reconciliation.

1.2.1 Scoring gene tree reconciliation

Several software for gene tree reconciliation are known such as Notung [3], TreeBeST [10] or TreeFix [11]. They look for reconciliation that infer duplications and deletions with minimal duplication-deletion score depending on given species tree.

The difference between these software is in input gene tree. TreeFix requests a rooted gene tree while TreeBeST wants an unrooted gene tree (it will be rooted during the reconciliation) on input. Notung takes both, rooted or unrooted gene tree, as input.

1.2.2 Probabilistic gene tree reconciliation

Probabilistic methods have been designed to increase accuracy of reconciled trees. Here, we introduce two software tools that use probabilistic methods to reconcile gene

trees: SPIMAP and PhylDog.

SPIMAP software [9] reconciles a rooted gene tree in the presence of a known rooted species tree with given duplication and deletion rates that are estimated by Bayes approach. The model infers duplication and deletion using the birth-death process. The birth-death process is continuous-time process that generates a gene tree according to constant birth rate (representing duplication) and death rate (representing deletion). After running it for a time that represent branch length, all branches that exist at the time are "surviving" and others are "extinct". To initialize, they reconcile a single gene node to the root of S and mark it as speciation. For every speciation, they run the birth-death process to generate a gene tree.

Another software is PhylDog[1], which uses method composed from computing maximum likelihood of possible gene tree reconciliation to given species tree according to duplication and deletion rates that are estimated for each branch separately. This model also uses the birth-death process, but birth and death rates are different for each branch.

They differ in two aspects. First, while SPIMAP assumes duplication and deletion rates to be constant for all branches in the species tree, PhylDog choose to use particular pair of duplication and deletion rates to each branch of the species tree. Second, SPIMAP requires time-anchored species tree (branch length shows amount of time between two nodes) to compute likelihood of a gene family. Alternately, PhylDog calculate likelihood from the expected numbers of duplications and deletions.

1.2.3 Isometric gene tree reconciliation

Another variant of reconciliation is isometric gene tree reconciliation, where branch lengths are known and taken into account while reconciling a gene tree and a species tree. The branch length may express the expected number of substitution per site between two nodes. This problem was introduced by Ma et al. [8] in 2008. They presented an algorithm with $O(N^2)$ running time, where N stands for the total number of nodes in the gene tree and the species tree. They considered a rooted species tree and an unrooted gene tree, where both input trees have exact branch lengths.

This algorithm was later corrected and modified by Brejová et al. [2] to an efficient algorithm with $O(N \log N)$ running time. They also proposed two extensions

of the problem. In the first extension, they considered both input trees (gene tree and species tree) unrooted and designed an algorithm with $O(N^5 \log N)$ running time. The second extension presents an algorithm, where both input trees are rooted, but branch lengths are assumed to be scaled by unknown scaling factor.

Definition 2 *An isometric reconciliation between gene tree G and species tree S with branch lengths w , which are strictly positive, is mapping $\phi : V(G) \rightarrow V(S) \cup E(S)$ such that:*

1. $\forall u \in L(G) : \phi(u) = \sigma(u) = \mu(u)$
2. $\forall u, v \in V(G)$ such that $v <_G u$: $\phi(v) <_S \phi(u)$ and $w(u, v) = d(\phi(u), \phi(v))$, where d is the length of path between u and v in reconciled gene tree.

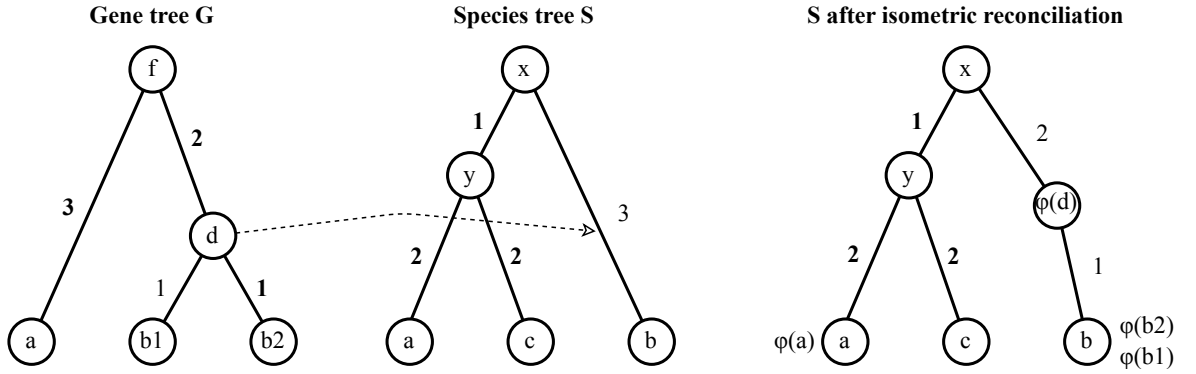


Figure 1.3: Isometric reconciliation. On the left is mapping of the node d of the gene tree G to the edge (x, b) of the species tree S . The result of the isometric reconciliation with mapped node d is on the right.

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