Melbourne Bioinformatics

BIOINFORMATICS + DATA SERVICES + INFRASTRUCTURE, FOR LIFE SCIENCES TODAY

THE UNIVERSITY OF MELBOURNE

COMP90014

Algorithms for Bioinformatics

Week 5A - Evolutionary Trees I

生物学中的一种图形表示，用于展示不同物种或生物体之间的进化关系和演化历史

系统发育学）是研究生物种类之间的演化关系

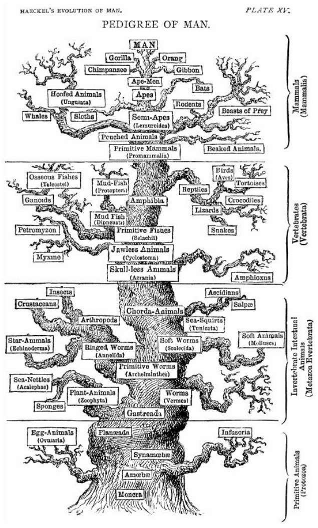
Evolutionary Trees I

Phylogenetics

How do we build trees?

Building trees (distance methods)
- UPGMA algorithm
- Neighbor Joining algorithm

Phylogenetic trees



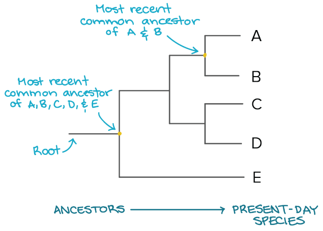
Ernst Haeckel (public domain)

- approaches for phylogenetic reconstruction
  - distance-based methods
  - character-based methods
- assessing reliability/robustness

系统发育学）是研究生物种类之间的演化关系和分类学的科学领域。系统发育学的主要目标是通过分析不同物种的遗传信息、形态特征以及其他演化信息，来构建进化树，从而揭示生物种类的进化历程和亲缘关系。系统发育学在研究生物分类学、进化过程以及物种多样性的形成等方面发挥着重要作用。

Phylogenetics

分类学
系统发育学
物种形成


Most recent common ancestor of A & B
A
B
C
D
E
Most recent common ancestor of A, B, C, D, & E
Root
ANCESTORS
PRESENT-DAY SPECIES

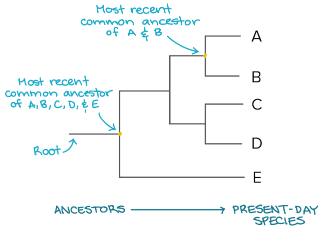
Taxonomy:	the science of classifying organisms
Phylogenetics:	describes the evolutionary relationship between species
Speciation:	A population of organisms becomes separated. Over time, these evolve into separate species that do not cross-breed.

Robert Bear via Khan Academy

Phylogenetic tree

图的右侧说明了构建系统发生树的两种主要方法：

经典系统发生分析：基于形态学特征，如动物的腿的数量、鸟的喙形状等。
分子系统发生学：基于DNA、RNA或蛋白质序列的比较，特别是在不同物种中相同（同源）的序列。


Most recent common ancestor of A & B
Most recent common ancestor of A, B, C, D, & E
Root
A
B
C
D
E
ANCESTORS
PRESENT-DAY SPECIES

Classical phylogenetic analysis:

- 🌲 number of legs, beak shape, etc.

Molecular phylogenetics:

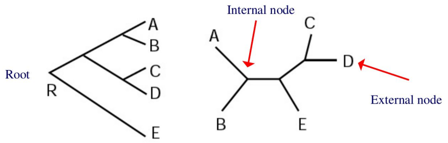
- 🌲 sequences
- 🌲 **homologous** sequences in different species

同源序列 不同物种

Robert Bear via Khan Academy

What is a tree, mathematically?

- connected, acyclic graph 无环图
- graph: a pair $G = (V, E)$, consisting of:
  - a set V of vertices (or nodes)
  - and a set E of edges (or branches) that connect nodes
- acyclic: there is no path where the first and last vertices are the same
- unrooted
- rooted



What information is encoded on the tree?

External nodes (leaves): Taxonomic unit, *e.g.* different current day species.

外部节点：代表分类单元，例如不同的现代物种。每个外部节点仅与树上的一个其他节点相连。

Only connected to one other node.

Internal nodes: **Hypothetical** most recent common ancestors (MRCA).

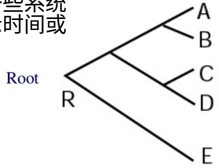
代表假设的最近共同祖先（MRCA，Most Recent Common Ancestor）树的分支点，代表了一次分化事件，即两个或多个物种分开的地方

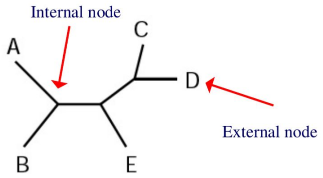
Node degree? 假设的最近的共同祖先（MRCA）

Edge length: Distance between leaves, *e.g.* time since divergence.

Topology: Relationship between leaves and nodes.

边长：表示叶子（物种）之间的距离，例如自从分歧以来的时间。在一些系统发生树中，分支的长度可以表示时间或遗传变异的量。





Evolutionary Trees I

Phylogenetics

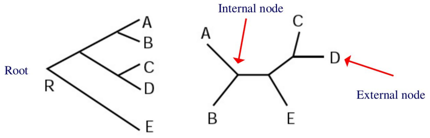
How do we build trees?

Building trees (distance methods)
- UPGMA algorithm
- Neighbor Joining algorithm

How many different trees can we construct with *n* sequences?

Sequences	Unrooted trees
3	1
4	3
5	15
10	$> 2\,000\,000$

Unrooted: $\prod_{i=3}^{n} (2i - 5)$

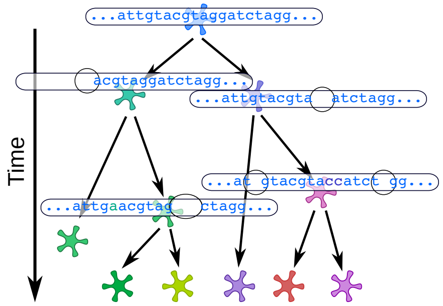


Rooted: (more or less?)

列举所有可能的树来找到最好的树不是可行的优化方法：哪棵树最小化了解释数据所需的变化数量（简约性）？?是减少类群之间距离的？

- enumerating all possible trees to find the best one is not feasible
- optimisation approach:
  - which tree minimises number of changes needed to explain data (parsimony)?
  - which minimises the distance between taxa?

Inferring a phylogenetic tree: workflow



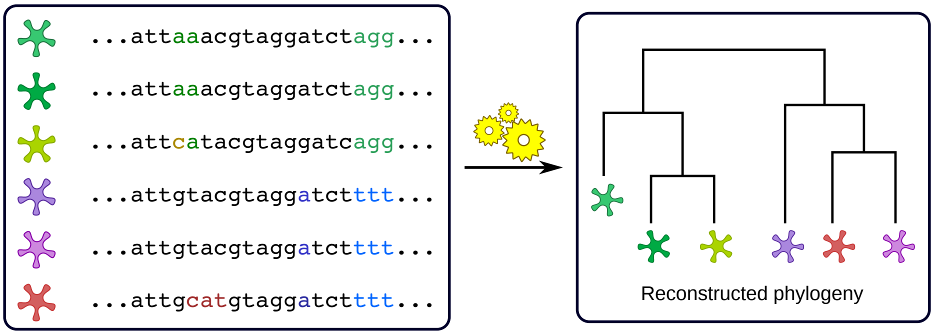
1. **data preparation**:
   multiple sequence alignment
2. **tree inference/reconstruction methods**:
   different algorithmic approaches
3. **tree analysis**:
   assess robustness/reliability

🌲 Substitutions accumulated over time tell us about evolution/genealogy

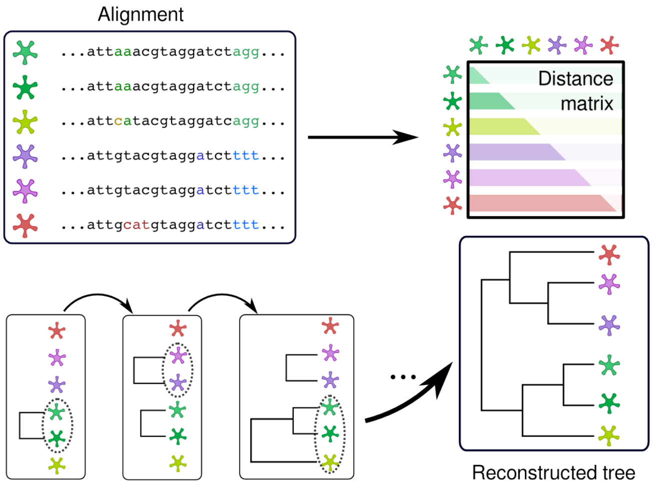
评估稳健性/可靠性

Thibaut Jombart, Introduction to phylogenetics

Inferring a phylogenetic tree


...attaaacgtaggatctagg...
...attaaacgtaggatctagg...
...attcatacgtaggatcagg...
...attgtacgtaggatctttt...
...attgtacgtaggatctttt...
...attgcatgtaggatctttt...
Reconstructed phylogeny

Agglomerative clustering


Alignment
...attaaacgtaggatctagg...
...attaaacgtaggatctagg...
...attcatacgtaggatcagg...
...attgtacgtaggatctttt...
...attgtacgtaggatctttt...
...attgcatgtaggatctttt...
Distance matrix
...
Reconstructed tree

Thibaut Jombart, Introduction to phylogenetics

Phylogeny reconstruction algorithms

系统发育重建算法

Two types of reconstruction:

Distance-based

- A tree is built based on the distance between items
- Closer taxa should be more evolutionarily related

  更近的类群应该在进化上更相关
- UPGMA
- neighbour-joining

Character-based

- Every taxon is described by a number of characters
  e.g. number of fingers, protein sequence.
- each has a finite number of states.
- Goal: build the tree that best explains the character matrix
  - Optimise a objective function

- Maximum Parsimony
- Maximum Likelihood

Evolutionary Trees I

Phylogenetics

How do we build trees?

<u>Building trees (distance methods)</u>

- UPGMA algorithm
- Neighbor Joining algorithm

Distance metrics

用于比较基因序列的两种主要的距离度量方法：基于多序列比对（MSA）的方法和无需比对的方法。

Scores from multiple sequence alignments (MSA)

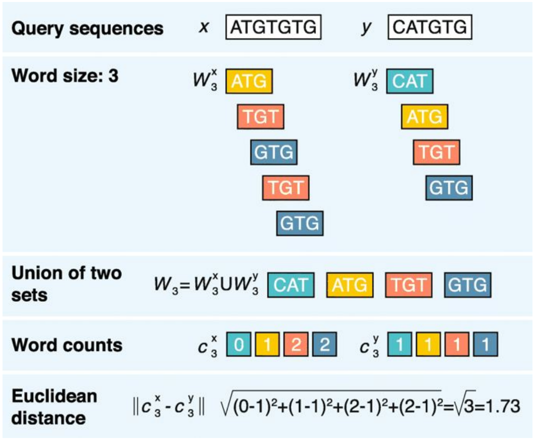
- 🌲 progressive (ClustalW)
- 🌲 iterative (MAFFT, MUSCLE)
- 🌲 probabilistic (Hidden Markov Models)

Alignment-free alternatives

- 🌲 *k*-mer count (substring/word of length *k*)
- 🌲 usually much faster than alignment but much less sensitive

k-mer计数（k-mer count，即长度为k的子串/单词）：这种方法通过计算序列中所有可能的k长子串的出现频率来估算序列之间的差异，不需要进行序列比对。
通常比比对方法要快得多（usually much faster than alignment），但是灵敏度要低得多（but much less sensitive），这意味着k-mer方法可能无法检测到微小的差异，因此在需要高精确度的情况下可能不太适用。

k-mers



- 🌲 all possible substrings of length *k*
  - *e.g.* $k = 3$
- 🌲 sliding window

1. generate the set of unique *k*-mers
2. count *k*-mer frequency in each sequence
3. calculate distance

- 🌲 time complexity?
  - how many *k*-mers of size *k* are there in a sequence of length *L*?
  - how many times do we move the sliding window for a sequence of length *L*?

Zielezinski *et al.*, 2017. 10.1186/s13059-017-1319-7

Distance-based methods

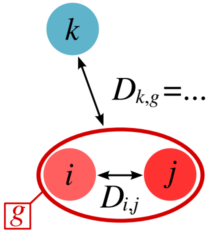
Start with each data point as a single cluster, then iteratively join clusters into bigger clusters until we reach a single cluster with all the data points

- 🌲 which are the next clusters to merge?
  - *e.g.* single linkage,
    complete linkage,
    average linkage (UPGMA),
    neighbour-joining

Agglomerative clustering:

1. Compute pairwise distances into a distance matrix D;
2. Find the two clusters i and j with the smallest distance d_{ij};
3. Create a new cluster u that joins clusters i and j;
4. Define the height (*i.e.* distance from leaves) of u to be $\frac{d_{ij}}{2}$;
5. Update D (d_{ku} for each $k \neq \{i, j\}$, replace i and j by new cluster u);
6. Go back to 2 until all items are grouped.

Which are the next clusters to merge?



- Cluster $g = (i, j)$
- Recalculate the distance matrix ($D_{k,g}$, where k are items still in individual clusters)

Single linkage: $D_{k,g} = \min(D_{k,i}, D_{k,j})$

Complete linkage: $D_{k,g} = \max(D_{k,i}, D_{k,j})$

Average linkage: $D_{k,g} = \dfrac{D_{k,i} + D_{k,j}}{2}$

UPGMA: Unweighted Pair Group Method with Arithmetic Mean

Branches have the same evolutionary rate (molecular clocks)

Neighbour joining: Transforms original distances to account for heterogeneous rates of evolution

Thibaut Jombart, Introduction to phylogenetics

Evolutionary Trees I

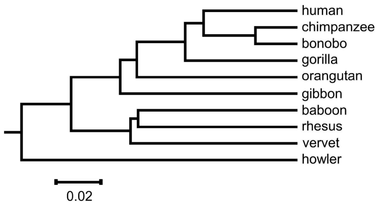
Phylogenetics

How do we build trees?

Building trees (distance methods)
<u>- UPGMA algorithm</u>
- Neighbor Joining algorithm

UPGMA

Unweighted Pair Group Method with Arithmetic Mean



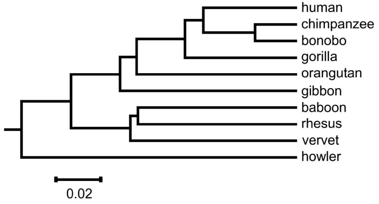
$$\frac{1}{|\mathbb{A}| \cdot |\mathbb{B}|} \sum_{x \in \mathbb{A}} \sum_{y \in \mathbb{B}} d(x, y)$$

- 🌲 average linkage: mean distance between elements of each group
- 🌲 generates ***rooted*** trees
- 🌲 generates ***ultrametric*** trees:
  - distances from the root to every branch tip are equal
- 🌲 $O(n^3)$ unoptimized

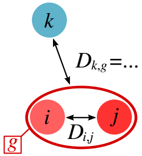
UPGMA assumes a molecular clock

ultrameric: distances from the root to every branch tip are equal

- 🌲 for this to be true, mutation rate along each branch would have to be the same
- 🌲 this is called a ***molecular clock***
- 🌲 the rate of the molecular clock is ***definitely not constant*** in nature!
- 🌲 UPGMA still has some applications, but not in phylogenetics



UPGMA algorithm



Consider a distance matrix D, and n groups containing one item/leaf each:

1. Choose the i and j with the smallest D_{ij}
2. Create a new group ij
3. Connect i and j to a new node in the tree that correspond to the new group
4. Set the branch length to $\frac{D_{ij}}{2}$ (ultrametric)
5. Calculate the distance between the group and all existing groups (n_i = number of elements):

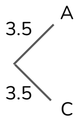
$$D_{(ij),k} = (\frac{n_i}{n_i + n_j})D_{ik} + (\frac{n_j}{n_i + n_j})D_{jk}$$

6. Replace the i and j columns with the new group
7. If there is only one item left stop, otherwise go to 1

Thibaut Jombart, Introduction to phylogenetics

Example

	A	B	C	D
A	0			
B	8	0		
C	7	9	0	
D	12	14	11	0



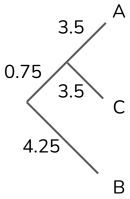
UPGMA algorithm

1. Choose smallest D_{ij}
2. Create a new group *ij*
3. Set the branch length to $\frac{D_{ij}}{2}$
4. Update distance matrix
5. Replace the *i* and *j* columns with the new group

$M_{B(AC)} = (M_{BA} + M_{BC}) / 2 = (8 + 9) / 2 = 8.5$
$M_{D(AC)} = (M_{DA} + M_{DC}) / 2 = (12 + 11) / 2 = 11.5$

Example

	AC	B	D
AC	0		
B	8.5	0	
D	11.5	14	0



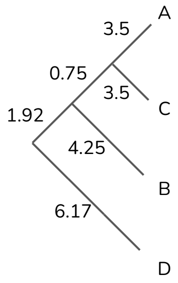
UPGMA algorithm

1. Choose smallest D_{ij}
2. Create a new group ij
3. Set the branch length to $\frac{D_{ij}}{2}$
4. Update distance matrix
5. Replace the i and j columns with the new group

$$M_{D(ABC)} = (M_{AD} + M_{BD} + M_{CD}) / 3 = (12 + 14 + 11) / 3 = 12.33$$

Example

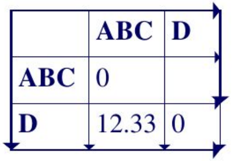
	ABC	D
ABC	0	
D	12.33	0



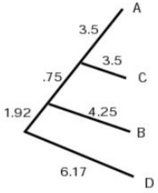
UPGMA algorithm

1. Choose smallest D_{ij}
2. Create a new group *ij*
3. Set the branch length to $\frac{D_{ij}}{2}$
4. Update distance matrix
5. Replace the *i* and *j* columns with the new group

Example



	ABC	D
ABC	0	
D	12.33	0



UPGMA algorithm

1. Choose smallest D_{ij}
2. Create a new group ij
3. Set the branch length to $\frac{D_{ij}}{2}$
4. Update distance matrix
5. Replace the i and j columns with the new group

- 🌲 UPGMA assumes that the rates of evolution are the same among different items
- 🌲 We don’t use this method for phylogenetic tree reconstruction (unless we believe the assumption...!)

Evolutionary Trees I

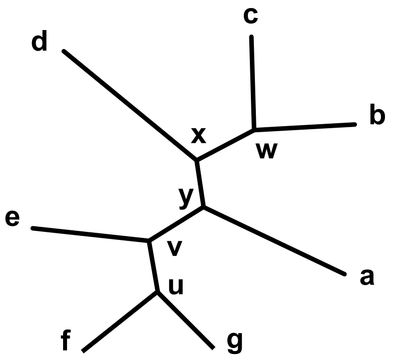
Phylogenetics

How do we build trees?

Building trees (distance methods)
- UPGMA algorithm
- Neighbor Joining algorithm

Neighbour joining

即不假设不同物种的进化速率一致。
超度树是指树中所有叶节点到根节点的路径长度相等。



- most widely-used distance based method for phylogenetic reconstruction
- trees are unrooted
- does not assume a molecular clock
- does not produce ultrametric trees

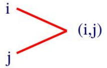
- UPGMA: constructs a larger cluster C by merging two nearest clusters A and B
- neighbour joining: distance from A and B to other clusters should be as large as possible
  - look for nodes that are ***close to each other*** and ***far from everything else***
    - subtract the averaged distances to all other leaves
    - compensate for long edges
- $O(n^3)$ unoptimized

在选择合并的节点时，寻找彼此距离最近且与其他所有节点的距离都较远的节点对。
在这个过程中，会从每个节点到其他所有节点的平均距离中减去这个平均值，以此来补偿边的长度。

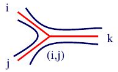
Tomfy via WikiMedia Commons

Neighbour joining algorithm

$$u_i = \sum_{j:j\neq i}^{n} \frac{D_{ij}}{n-2}$$



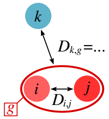
$$v_i = \frac{1}{2}D_{ij} + \frac{1}{2}(u_i - u_j)$$
$$v_j = \frac{1}{2}D_{ij} + \frac{1}{2}(u_j - u_i)$$



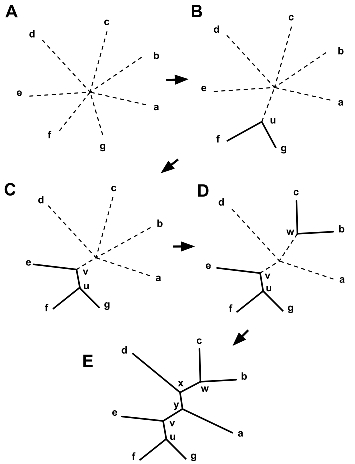
$$D_{(ij)k} = \frac{D_{ik} + D_{jk} - D_{ij}}{2}$$

Consider a distance matrix D:

1. Calculate the “average” distance to other nodes/clusters for each leaf
2. Choose i and j to minimize $D_{ij} - u_i - u_j$
   (Nodes that are close to each other, and far from everything else)
3. Join i and j to create a new node (i, j) and calculate the new branch lengths
4. Compute distance between leaves and the new group
5. Replace the i and j leaves with the new node (i, j)
6. Continue until two nodes remain



Neighbour joining, graphically



Tomfy via WikiMedia Commons

1. begin with a star tree
2. minimise $D_{ij} - u_i - u_j$
3. resolve pairs
4. update distance matrices
5. go to 2

🌲 neighbour joining does not assume all sequences evolve at the same rate

Distance-based methods

Advantages

- simple
- flexible
- fast and scalable

Limitations

- sensitive to distance method
- evolutionary rates are not estimated
- no measure of uncertainty for the tree obtained

Melbourne Bioinformatics
BIOINFORMATICS + DATA SERVICES + INFRASTRUCTURE, FOR LIFE SCIENCES TODAY

THE UNIVERSITY OF MELBOURNE

Thank you!

Today: Evolutionary Trees I

Next time: Evolutionary Trees II