A short introduction to multiple sequence alignments

Jean-Baka Domelevo Entfellner

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Why do we align sequences?

The rationale for sequence alignments:

1. biological sequences have evolved in many different ways (insertions, deletions, inversions, translocations, etc)
2. yet, *homologous* sequences derive from a common *ancestral sequence*
3. to investigate evolution, we first have to *align* (i.e. put in the same column) characters that (are believed to) descend from a common ancestor

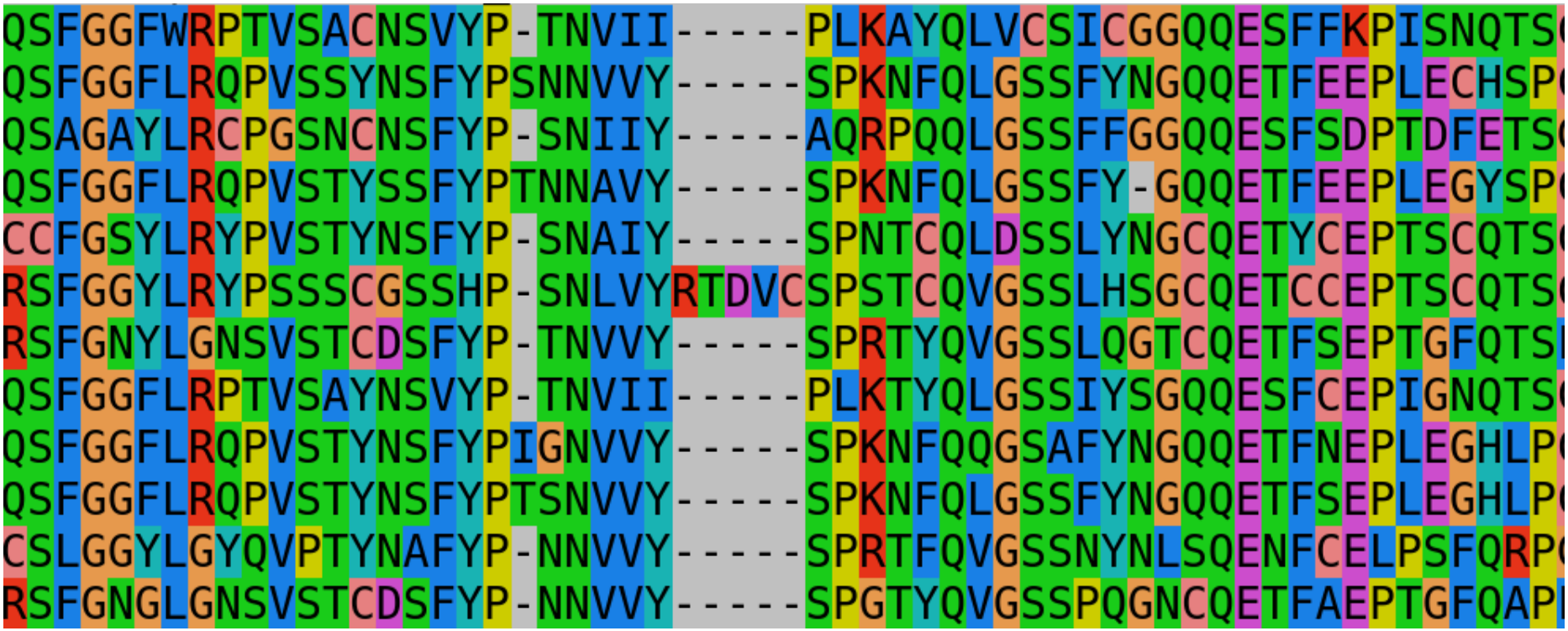
Caveat #1

Characters are often aligned based on **sequence similarity**, but the alignment with highest conservation scores is not necessarily the one depicting the true **evolutionary history**.

Some vocabulary

- **MSA**: **M**ultiple **S**equence **A**lignment
- **character**: the atomic component of a sequence (nucelotide, amino acid or quantitative trait)
- **homologous** sequences have evolved from a common ancestral sequence. Often, they still share the same function.
- **site**: a column in a multiple sequence alignment
- **gap**: a placeholder, *virtual* character ('-') used when displaying an MSA, to preserve the alignment within previous or subsequent sites (no "empty space" in an alignment)
- **indels** are insertions or deletions of one or several consecutive characters in a subset of the sequences. Whether they are called "insertions" or "deletions" only depends on the choice of a reference sequence.
- **conserved** sites are those where all taxa share the same character

Example of a proteic alignment



How do computers build MSA?

To align n sequences together, most automatic aligners use a **progressive alignment** greedy heuristic:

1. determine a **guide tree** using a quick, distance-based tree inference
   1. calculate all $n(n-1)/2$ pairwise alignments (easy: Needleman-Wunsch)
   2. determine the half-matrix of pairwise distances
   3. use some quick inference method (e.g. Neighbour-Joining) to get the guide tree
2. use a modified N-W algorithm to **perform successive** seq-to-seq, seq-to-group and group-to-group **"pairwise" alignments**
   1. pick the closest 2 sequences in the tree and align them
   2. go up into the guide tree, iteratively aggregating sequences or groups of sequences (consensus) to the alignment. Partial alignments are never un-done.
3. once no sequence remains unaligned, return the resulting alignment

Scoring schemes for pairwise alignments

Total score of a pairwise alignment made of:

1. match score: a positive number (reward) when aligning identical or similar characters
2. mismatch penalty: penalty when aligning discordant characters. Either fixed cost, or higher penalty for more dissimilar chars
3. gap opening penalty: a negative number (penalty) when opening a gap
4. gap extending penalty: a negative number (penalty) when extending a gap (usually penalized less than opening a new one)

Caveat # 2

Most aligners will prefer to "align garbage" than open several gaps.

Exercises: pairwise alignments

Let us use the following scoring scheme:

- match: +8
- mismatch: -3
- gapopen: -5
- gapextend: -3

Exercise 1

Calculate the alignment score for:

```
ATGGTT-TGA
A-TGTTTGA-
```

Can one find a better alignment (yielding a better score)?

Exercise 2

Align CATTGTGGA and CTTGTGA, and give (best) score.

Popular aligners

- Clustal, ClustalW, **ClustalΩ** (Des Higgins, Julie Thompson et al., 1988, 1994, 2011): the historical assembler. Thompson et al. 1994 (NAR) ranking #10 in *Nature*'s Top100
- **Muscle** (RC Edgar, 2004): fast and efficient
- **Mafft** (Katoh et al., 2002): very efficient, especially for protein sequences. Based on quick Fast Fourier Transforms on recoded data.
- **T-Coffee** (Notredame et al., 2010): interesting approach using aligned pairs from pairwise alignments
- **Prank** (Löytynoja & Goldman, 2008): attempt to take better care of inferred evolutionary events. Tends to insert more gaps.

Visualizing alignments: Seaview

Seaview's homepage:
`http://doua.prabi.fr/software/seaview`

Visualizing and editing alignments: Jalview

Jalview's homepage: `http://www.jalview.org/`