

Biosequence Algorithms, Spring 2005

Lecture 11: Introduction to Multiple Alignments

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Multiple String Alignments

In this section:

(~ Sections 14.1–14.3 in Gusfield)

1. Definition of multiple alignment
2. Biological motivation
3. Aligning strings with a profile

Definition

A **(global) multiple alignment** (*(globaali) monirinnastus*) of $k > 2$ strings is an obvious generalization of two-string alignments:

Insert spaces into the strings to make them equally long (say, l chars), and arrange them in k rows and l columns, each character or space in a unique column

Example: A multiple alignment of strings
 $\{abca, ababa, accb, cbbc\}$

```

a b c _ a
a b a b a
a c c b _
c b _ b c
    
```

Local Multiple Alignments

There are also *local* multiple alignments

A **local multiple alignment** of strings S_1, \dots, S_k consists of selecting a *substring* S'_i of each S_i , and aligning these k substrings globally

We restrict to considering *global* multiple alignments only

Motivation

Multiple alignment is a specific formalization of *multiple string comparison*, which is one of the most important methodologies and active research areas in bio-sequence analysis; It is used for

- ⑥ extracting and representing biologically important commonalities from a set of strings
 - ▲ which might go unnoticed if only two strings were compared
- ⑥ inferring evolutionary history from DNA or protein sequences

Family Representations

Found commonalities are used to characterize (and to understand) families of proteins

- ⑥ **family:** set of proteins related by structure, function, or evolutionary history, e.g., *globins* and *immunoglobulins*

“This classification is central to our understanding of how life has evolved, and makes elucidation and definition of such families one of the principal concerns of molecular biology”
 (Cyrus Chothia, *Nature*, 1992)

Usefulness of Compact Representations

Family representations are useful: It's been estimated that the ~ 100,000 human proteins could be organized in about thousand families (or even a few hundred only)

A new sequence can be tested for potential membership in a family by comparing it with a family *representation*

Commonly used forms: *profiles*, *consensus sequences*, and *signatures*

- ⑥ all derived from multiple string comparison

Profiles as Family Representations

A **profile** of a multiple alignment \mathcal{M} with row-length l is a $|\Sigma'| \times l$ matrix p , where $p(y, j)$ is the *occurrence frequency* that char y occurs in column j of \mathcal{M} . ($\Sigma' = \Sigma \cup \{_ \}$)

Example: The profile of the previous multiple alignment:

p	1	2	3	4	5
a	.75	.00	.25	.00	.50
b	.00	.75	.00	.75	.00
c	.25	.25	.50	.00	.25
$_$.00	.00	.25	.25	.25

How to compare a string and a profile?

Aligning a String to a Profile

A profile p is a sequence of columns \rightsquigarrow we can align a string S with p , by inserting spaces in them:

Example: A string/profile alignment:

p' :	1	–	2	3	4	5
a	.75		.00	.25	.00	.50
b	.00		.75	.00	.75	.00
c	.25		.25	.50	.00	.25
–	.00	1.0	.00	.25	.25	.25
S' :	a	a	b	–	b	c

How to score a string/profile alignment?

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Scoring a String/Profile Alignment

Common approach: (1) The score $S(x, j)$ of a char x aligned with a column j is the average of the pair-wise character scores btw x and any character at col j :

$$S(x, j) = \sum_{y \in \Sigma'} [s(x, y) \times p(y, j)]$$

(2) score of the full alignment = sum of column scores

Example: Assume character scores $s(a, a) = 2$, $s(a, b) = s(a, -) = -1$, and $s(a, c) = -3$

The first column of the previous alignment adds $S(a, 1) = 0.75 \times 2 + 0.25 \times (-3)$ to the total score, and the second $S(a, -) = 1.0 \times (-1)$

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Computing an Optimal String/Profile Alignment

An optimal string/profile alignment can be computed as a straight-forward extension of string/string alignments

Let $V(i, j)$ denote the value of an optimal alignment of prefix $S[1 \dots i]$ with columns $1, \dots, j$ of profile p

Recurrences:

Base cases:

$$V(0, j) = \sum_{k=1}^j S(-, k) \quad (\leftarrow \text{'-'} \text{ against } j \text{ first columns of } p)$$

$$V(i, 0) = \sum_{k=1}^i s(S_1[k], -) \quad (\leftarrow S_1[1 \dots i] \text{ against spaces})$$

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Computing a String/Profile Alignment

Inductive cases for $i, j > 0$:

$$V(i, j) = \max \begin{cases} V(i-1, j-1) + S(S_1[i], j) \\ V(i-1, j) + s(S_1[i], -) \\ V(i, j-1) + S(-, j) \end{cases}$$

With these recurrences an optimal string/profile alignment can be computed, similarly to a string/string alignment, in time $O(|\Sigma|nm)$

Factor $|\Sigma|$ comes from considering all characters of column j for computing the score of aligning a character at column j

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