Universität Basel

Cost Partitioning Techniques for Multiple Sequence Alignment

Mirko Riesterer, 10.09.18

Agenda.

Introduction

Multiple Sequence Alignment

- Biological sequences mutate during evolution
- Insertion, deletion, substitution
- Some mutations are more likely (A↔G / C↔T)
- Observe phylogenetic relationships

Introduction

Multiple Sequence Alignment

– Insert gaps within sequences
– Maximize correspondence between letters in columns

Sequences		Alignment
ACGTG		ACGT-G
ACTAG	→	AC-TAG
CGTAG		-CGTAG

Introduction

Judging the alignment quality

- Count matches/mismatches
- Score matrix
  - Point accepted mutation (PAM_n) matrix (Dayhoff et al., 1978)
  - Blocks substitution matrix (BLOSUM) (Henikoff and Henikoff, 1992)

```
Score matrix:

  A C T G –
A 0 4 2 2 3
C   1 4 3 3
T     0 6 3
G       1 3
-         0
```

Agenda.

1	Introduction
2	Formal Definition
3	Solving MSA
4	Combining Multiple Pattern Databases
5	Cost Partitioning
6	Experiments
7	Conclusion

Formal Definition

Family of sequences $S = \{s_1, \ldots, s_n\}$ over alphabet Σ and $\Sigma' = \Sigma \cup \{-\}$

Alignment

Matrix $A^{n \times m} = (\mathrm{a_{ij}})$, where

- $a_{ij} \in \Sigma'$
- a_i without $\{-\}$ is exactly s_i
- No column contains only $\{-\}$

Score matrix:

	A	C	T	G	-
A	0	4	2	2	3
C		1	4	3	3
T			0	6	3
G				1	3
-					0

Sequences:

```
ACT
CTG
```

Alignment A:

```
A C T _
_ C T G
```

$C^A = 3 + 1 + 0 + 3 = 7$

Formal Definition

Score matrix can be viewed as function $sub : \Sigma' \times \Sigma' \rightarrow \mathbb{N}$

Given alignment A and score matrix sub.

Pair score

$$\boldsymbol{C_{ij}^{A} = \sum_{k=1}^{m} sub(a_{ik}, a_{jk})}$$

Sum of pairs score

$$\boldsymbol{C^{A} = \sum_{1 \leq i < j \leq n} C_{ij}^{A}}$$

Formal Definition

Shortest Path Problem

Directed acyclic graph $G = (V, E)$

$$V = \{(x_1, \dots, x_n) |\ x_i = 0, \dots, l_i\}$$
$$E = \cup_{e \in \{0,1\}^n} \{(v, v+e) |\ v, v+e \in V, e \neq 0\}.$$

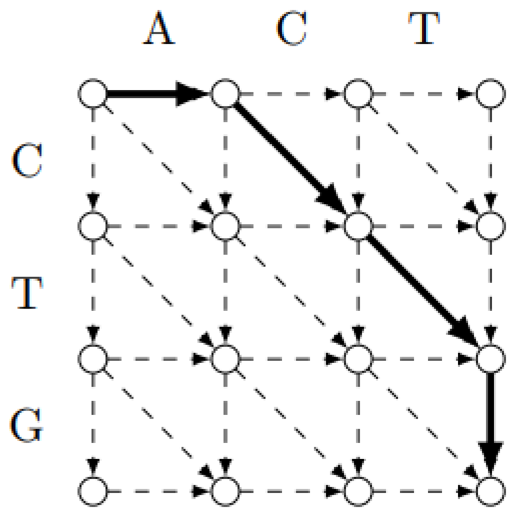

Figure: 2D graph alignment

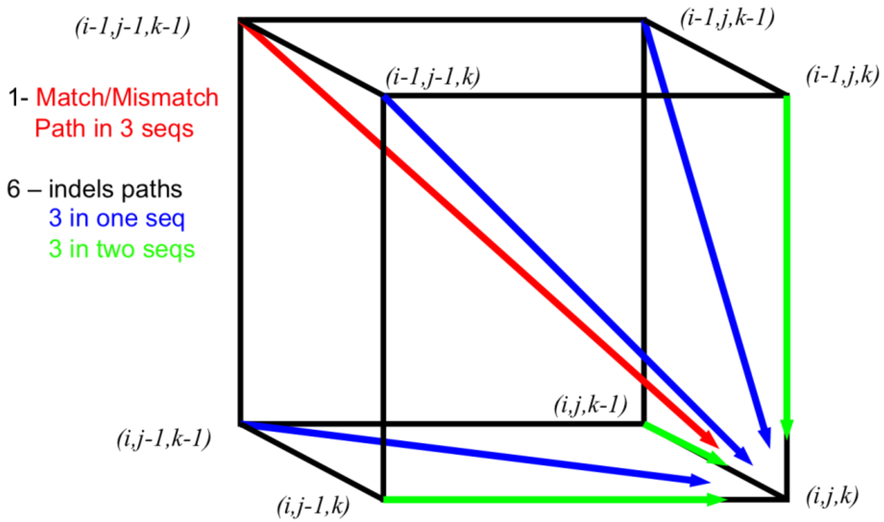

Figure: 3D edge structure

(http://www.csbio.unc.edu/mcmillan/Comp555S16/Lecture14.html)

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Solving MSA

Needleman-Wunsch algorithm
Dynamic programming approach

Generates zero-based index table with optimal scores

Dim n, lengths l: Complexity $O(l^n)$

	A	C	T	
C	7	4	6	9
T	8	6	3	6
G	8	6	6	3
	9	6	3	0

Score matrix:

	A	C	T	G	_
A	0	4	2	2	3
C		1	4	3	3
T			0	6	3
G				1	3
_					0

Figure 2: Needleman-Wunsch score table using a score matrix

Solving MSA

Pattern databases

Family of sequences $S = \{s_1, \dots, s_n\}$.

A *pattern* is a subset $P \subseteq S, |P| \geq 2$.

A *pattern database* (PDB) is the perfect heuristic h^*
for the subproblem induced by pattern P.

Solving MSA

Heuristic search estimators

Family of sequences $S = \{s_1, \ldots, s_n\}$.

$\boldsymbol{h_{pair}}$ (Ikeda and Imai, 1994):

$$h_{pair}(v) = \sum_{1 \le i < j \le n} h^{ij}(v)$$

– Uses the information of every 2-dimensional PDB

Solving MSA

Heuristic search estimators

Family of sequences $S = \{s_1, \ldots, s_n\}$.

$\boldsymbol{h_{all,k}}$ (Kobayashi and Imai, 1998):

$$h_{all,k}(v) = \frac{1}{\binom{n-2}{k-2}} \sum_{1 \le x_1 < \cdots < x_k \le n} h^{x_1,\ldots,x_k}(v)$$

- Uses the information of every 3-dimensional PDB
- Every pair of sequences appears $\binom{n-2}{k-2}$ times → normalize
- If $k = 3$, lenghts ~ 500, each PDB contains 10^8 vertices!
- Branching factor $2^n - 1$

Solving MSA

Heuristic search estimators

Family of sequences $S = \{s_1, \dots, s_n\}$.

$\boldsymbol{h_{one,k}}$ (Kobayashi and Imai, 1998):

$$h_{one,k}(v) = h^{x_1,\dots,x_k}(v) + h^{x_{k+1},\dots,x_n}(v) + \sum_{i=1}^{k} \sum_{j=k+1}^{n} h^{x_i,x_j}(v)$$

- 1 or 2 higher-dimensional PDBs + *remaining* 2-dimensional PDBs
- Avoids normalization by choosing PDBs carefully

$$\boldsymbol{h_{pair} \le h_{one,k} \le h_{all,k}}$$

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Combining Multiple Pattern Databases

Additivity

- A pattern collection of $S = \{s_1, \dots, s_n\}$ is a collection $P = \{P_1, \dots, P_m\}, \mathrm{P_i} \subseteq S$.
- P is non-conflicting, if no pair of elements of P conflict.
- Then the sum of PDBs is additive

Pattern collection heuristic

$$h^P(v) = \sum_{i=1}^{m} h^{P_i}(v)$$

- Admissible, if P is non-conflicting

Combining Multiple Pattern Databases

- Conflicting pattern collections may violate admissibility
- Parts may still be useful?

Canonical PDB heuristic (Haslum et al., 2007)

$$h^{\mathrm{CAN}}(\mathrm{v}) = \max_{s \in MNS} \sum_{P \in S} h^{P}(v)$$

Combining Multiple Pattern Databases

Post-hoc optimization (Pommerening et al., 2013)

- Use linear programming to solve constrained problem
- Pattern collection is *strictly conflicting* if $|\cap_{i=0}^{m} P_i| > 1$

Let $\langle w_1, \dots, w_m \rangle$ be the solution to the linear program that maximizes

$$h^{PHO}(v) = \sum_{i}^{m} w_i \, h^{P_i}(v)$$

$$s.t. \sum_{i:P_i \in S'} w_i \leq 1 \text{ for all strictly conflicting pattern collections } S' \subseteq P$$

$$s.t. \, 0 \leq w_i \leq 1 \text{ for all } \mathrm{P_i}$$

Combining Multiple Pattern Databases

Post-hoc optimization (Pommerening et al., 2013)

$h_{all,k}$ equals h^{PHO} if we choose the *same patterns*

Proof sketch:

Four sequences $S = \{s_1, s_2, s_3, s_4\}$ of length 1

Score matrix:

	A	C	T	G	–
A	1	1	1	0	1
C		1	1	0	1
T			1	0	1
G				1	1
-					1

$$s_1 = A, s_2 = C, s_3 = T, s_4 = G$$

$$P = \{P_1 = \{s_1, s_2, s_3\}, P_2 = \{s_1, s_2, s_4,\}, P_3 = \{s_1, s_3, s_4,\}, P_4 = \{s_2, s_3, s_4\}\}$$

$$h^{P_1}(s) = 3$$

$$h^{P_2}(s) = h^{P_3}(s) = h^{P_4}(s) = 1$$

→ $h^{PHO}(s) = 1 * 3 + 0 * 1 + 0 * 1 + 0 * 1 = \mathbf{3} = \frac{3+1+1+1}{2} = h_{all,3}$

Combining Multiple Pattern Databases

A factored representation of MSA with operators

$$O = \left\{ o^{i,j}_{\langle x,y \rangle \to \langle x',y' \rangle} \middle| \, 1 \leq i < j \leq n, 0 \leq x \leq l_i, 0 \leq y \leq l_j \right\}$$

An operator $o^{i,j}_{\langle x,y \rangle \to \langle x',y' \rangle}$ *affects* heuristic h^P if $s_i, s_j \in P$

Example:

e.g. edge $\langle 3,3,5 \rangle \to \langle 4,3,6 \rangle$ is factored into 3 operators:

$$\{ o^{1,2}_{\langle 3,3 \rangle \to \langle 4,3 \rangle}, o^{1,3}_{\langle 3,5 \rangle \to \langle 4,6 \rangle}, o^{2,3}_{\langle 3,5 \rangle \to \langle 3,6 \rangle} \}$$

- Basic factors for opreators in higher dimensions
- Less operators than defining all operators

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Cost Partitioning

Better estimates than using max. among available?

- Patterns only consider parts of the problem
- Combine multiple heuristic values
- Distribute operator costs among them

Formal (Seipp et al., 2017)

Given a pattern collection of size m
Cost partitioning is a tuple $C = \langle c_1, \ldots, c_m \rangle$ $s.t. \sum_{i=1}^{m} c_i(o) \leq c(o)$
CP heuristic is $h^C(v) \coloneqq \sum_{i=1}^{m} h^{P_i, c_i}(v)$

Cost Partitioning

Greedy zero-one cost partitioning (Haslum et al. 2005; Edelkamp, 2006)

- Assign full costs to at most one PDB
- Multiple PDBs affected? Greedily chose from ordering

- Assign full costs to $\mathrm{c_i}(o)$ if $o \in aff(h^{P_i})$ and $o \notin \cup_{j=1}^{i-1} aff(h^{P_j})$

Cost Partitioning

Saturated cost partitioning (Seipp and Helmert, 2014)

- Assign exploitable parts of the costs to components
- Remainder can contribute to other components

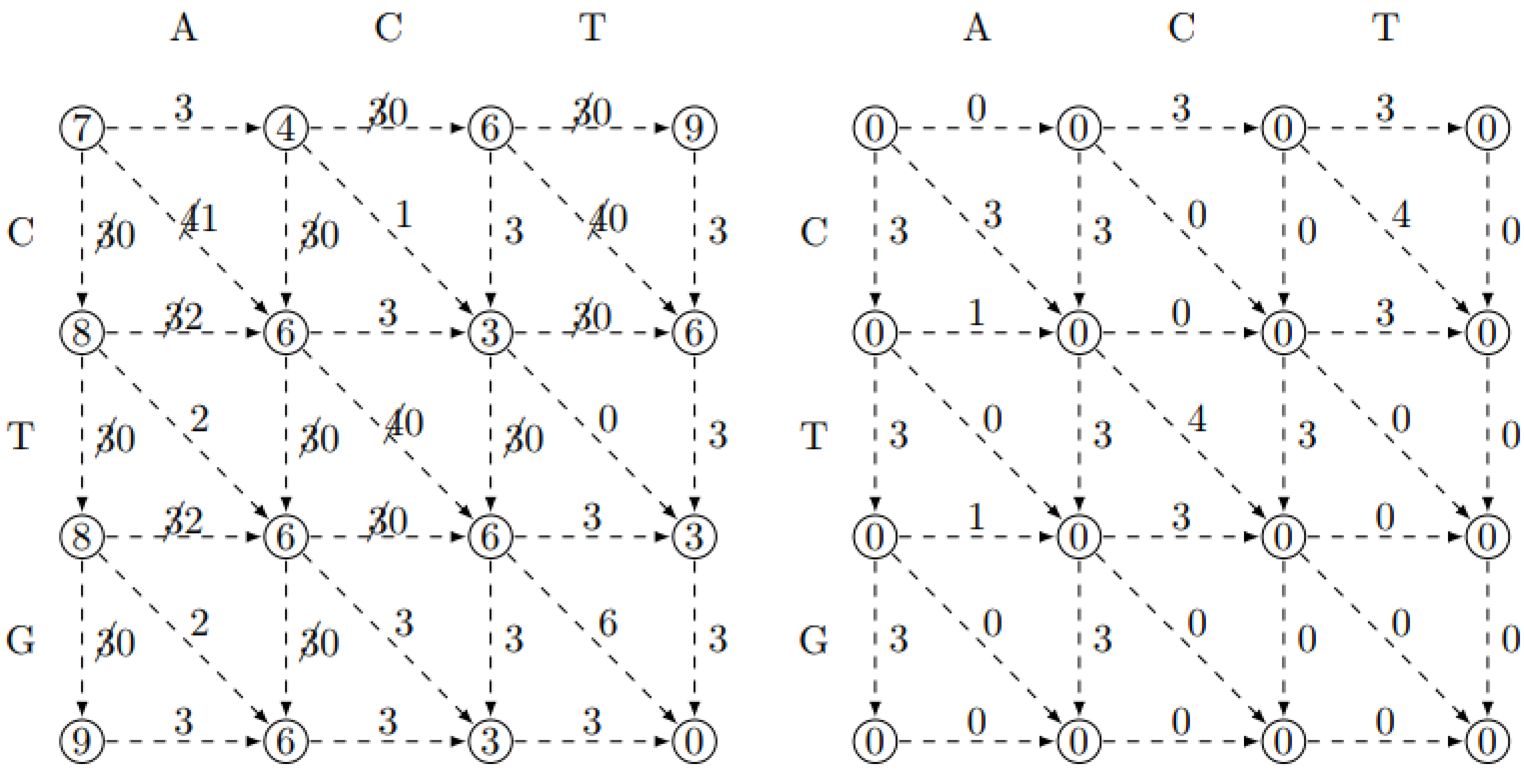
Saturated cost function
Assigns the least possible cost without changing outcome

Formal:
$saturate(h^P, c)$ is the minimal cost function $c' \leq c$ with $h^{P,c'}(v) = h^{P,c}(v)$

Saturated cost partitioning $C = \langle c_1, \ldots, c_m \rangle$
remaining cost functions $\langle \bar{c}_0, \ldots, \bar{c}_m \rangle$

$$\bar{c}_0 = c$$
$$c_i = saturate(h^{P_i}, \bar{c}_{i-1})$$
$$\bar{c}_i = \bar{c}_{i-1} - c_i$$

Cost Partitioning



(a) Saturated operator costs (b) Remaining operator costs

Figure 4.1: Saturated and remaining operator costs for a two-dimensional PDB.

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Experiments

- Using MSASolver Java program by Matthew Hatem
- BAliBASE Benchmark Reference Set 1 (Thompson et al., 1999)

1aab_ref1.seq (4 sequences)					
Pattern collection in order ω	$h_{pair}(s)$	$h_{one,3}(s)$	$h_{all,3}(s)$	$h^{PHO}(s)$	$h_{\omega}^{GZOCP}(s)$
$\{0,1\},\{0,2\},\{0,3\},\{1,2\},\{1,3\},\{2,3\}$	14179	-	-	14179	14179
$\{0,1,2\},\{0,3\},\{1,3\},\{2,3\}$	-	14199	-	14199	14199
$\{0,1,2\},\{0,1,3\},\{0,2,3\},\{1,2,3\}$	-	-	14302	14302	14199

Table 5.1: Initial heuristic estimate comparison for the instance 1aab_ref1.seq

Experiments

1aab_ref1.seq (4 sequences)		
#3-fold	Pattern collection	$h^{PHO}(s)$
1	$\{0,1,2\}, \{0,3\}$	9466
	$\{0,1,2\}, \sout{\{0,1\}}, \sout{\{0,2\}}, \sout{\{1,2\}}, \{0,3\}, \{1,3\}, \{2,3\}$	14199
	$\{0,1,2\}, \{0,3\}, \{1,3\}, \{2,3\}$	14199
2	$\{0,1,2\}, \sout{\{0,1,3\}}, \sout{\{0,1\}}$	7186
	$\{0,1,2\}, \sout{\{0,1,3\}}, \{2,3\}$	9466
	$\sout{\{0,1,2\}}, \{0,1,3\}, \{1,2\}, \sout{\{1,3\}}, \{2,3\}$	11849
	$\{0,1,2\}, \sout{\{0,1,3\}}, \{0,3\}, \{1,3\}, \{2,3\}$	14199
3	$\{0,1,2\}, \{0,1,3\}, \{0,2,3\}, \{1,2\}$	11951
	$\{0,1,2\}, \{0,1,3\}, \{0,2,3\}, \{1,2\}, \{1,3\}$	13119
	$\{0,1,2\}, \{0,1,3\}, \{0,2,3\}, \sout{\{0,1\}}, \sout{\{0,2\}}, \sout{\{0,3\}}, \{1,2\}, \{1,3\}, \{2,3\}$	14259
	$\{0,1,2\}, \{0,1,3\}, \{0,2,3\}, \{1,2\}, \{1,3\}, \{2,3\}$	14259
4	$\{0,1,2\}, \{0,1,3\}, \{0,2,3\}, \{1,2,3\}$	14302

Table 5.2: Initial heuristic estimates of h^{PHO} for the instance 1aab_ref1.seq. Crossed out patterns are assigned weights of 0 by the linear program

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Conclusion

GZOCP

- No benefit over existing heuristics

PHO

- LP Solver in every search step
- Expensively computed PDB may be left unused

Future Work

- Implement other cost partitioning techniques
- Generate PDBs automatically e.g. like Haslum et al. (2007)
- M&S heuristics (Dräger et al., 2009; Helmert et al., 2014)

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Thank you
for your attention.

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