Genome 559: Introduction to Statistical and Computational Genomics

Lecture 15a
Multiple Sequence Alignment

Larry Ruzzo

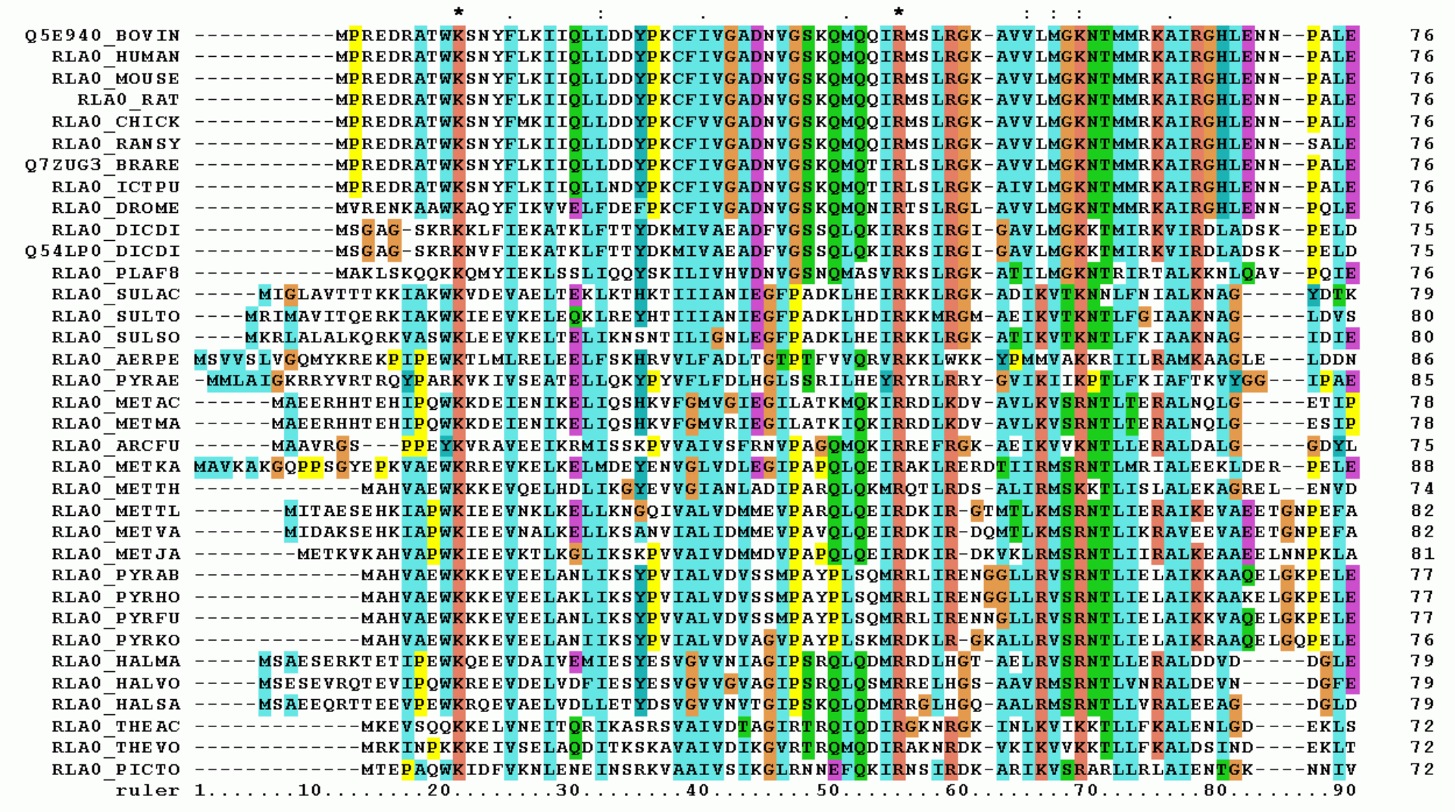
Multiple Alignment: Motivations

Common structure, function, or origin may be only weakly reflected in sequence; multiple comparisons may highlight weak signal

Major uses

- represent protein, RNA families
- represent & identify conserved seq features
- “whole genome” alignments

Ribosomal Protein L10E



First 90 Residues, Human to Archaea

Alignment of 7 globins.

```
Helix                 AAAAAAAAAAAAAAAA   BBBBBBBBBBBBBBBBCCCCCCCCCCC
HBA_HUMAN  ---------VLSPADKTNVKAAWGKVGA--HAGEYGAEALERMFLSFPTTKTYFPHF
HBB_HUMAN  --------VHLTPEEKSAVTALWGKV----NVDEVGGEALGRLLVVYPWTQRFFESF
MYG_PHYCA  ---------VLSEGEWQLVLHVWAKVEA--DVAGHGQDILIRLFKSHPETLEKFDRF
GLB3_CHITP ----------LSADQISTVQASFDKVKG------DPVGILYAVFKADPSIMAKFTQF
GLB5_PETMA PIVDTGSVAPLSAAEKTKIRSAWAPVYS--TYETSGVDILVKFFTSTPAAQEFFPKF
LGB2_LUPLU --------GALTESQAALVKSSWEEFNA--NIPKHTHRFFILVLEIAPAAKDLFS-F
GLB1_GLYDI ---------GLSAAQRQVIAATWKDIAGADNGAGVGKDCLIKFLSAHPQMAAVFG-F
Consensus            Ls....  v a W kv .  .    g . L.. f . P .   F  F

Helix          DDDDDDDEEEEEEEEEEEEEEEEEE              FFFFFFFFFFF
HBA_HUMAN  -DLS-----HGSAQVKGHGKKVADALTNAVAHV---D--DMPNALSALSDLHAHKL-
HBB_HUMAN  GDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHL---D--NLKGTFATLSELHCDKL-
MYG_PHYCA  KHLKTEAEMKASEDLKKHGVTVLTALGAILKK----K-GHHEAELKPLAQSHATKH-
GLB3_CHITP AG-KDLESIKGTAPFETHANRIVGFFSKIIGEL--P---NIEADVNTFVASHKPRG-
GLB5_PETMA KGLTTADQLKKSADVRWHAERIINAVNDAVASM--DDTEKMSMKLRDLSGKHAKSF-
LGB2_LUPLU LK-GTSEVPQNNPELQAHAGKVFKLVYEAAIQLQVTGVVVTDATLKNLGSVHVSKG-
GLB1_GLYDI SG----AS---DPGVAALGAKVLAQIGVAVSHL--GDEGKMVAQMKAVGVRHKGYGN
Consensus   .  t    .. . v..Hg kv. a   a...l   d   . a l. l   H  .

Helix         FFGGGGGGGGGGGGGGGGG     HHHHHHHHHHHHHHHHHHHHHHHHHH
HBA_HUMAN  -RVDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR------
HBB_HUMAN  -HVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH------
MYG_PHYCA  -KIPIKYLEFISEAIIHVLHSRHPGDFGADAQGAMNKALELFRKDIAAKYKELGYQG
GLB3_CHITP --VTHDQLNNFRAGFVSYMKAHT--DFA-GAEAAWGATLDTFFGMIFSKM-------
GLB5_PETMA -QVDPQYFKVLAAVIADTVAAG---------DAGFEKLMSMICILLRSAY-------
LGB2_LUPLU --VADAHFPVVKEAILKTIKEVVGAKWSEELNSAWTIAYDELAIVIKKEMNDAA---
GLB1_GLYDI KHIKAQYFEPLGASLLSAMEHRIGGKMNAAAKDAWAAAYADISGALISGLQS-----
Consensus    v.   f  l . ..  ....    f   . aa. k. .     l sky
```

Human, whale, midge, lamprey, lupin, bloodworm.

A-H mark 8 alpha helices. Consensus line: upper case = 6/7, lower = 4/7, dot=3/7.

Multiple Alignments: Key Issues

Scoring:

How to evaluate a proposed alignment

Computational demands:

How to do it in reasonable time

Multiple Alignment Scoring

A Key Issue

Varying goals, methods (& controversy)

Ideal is perhaps phylogenetic, position specific, but typically too slow, too many parameters

Most methods assume independence between columns, so you can score them separately

(Very inappropriate for RNA alignments, e.g.)

Multiple Alignment Scoring within one column

Two common ways:

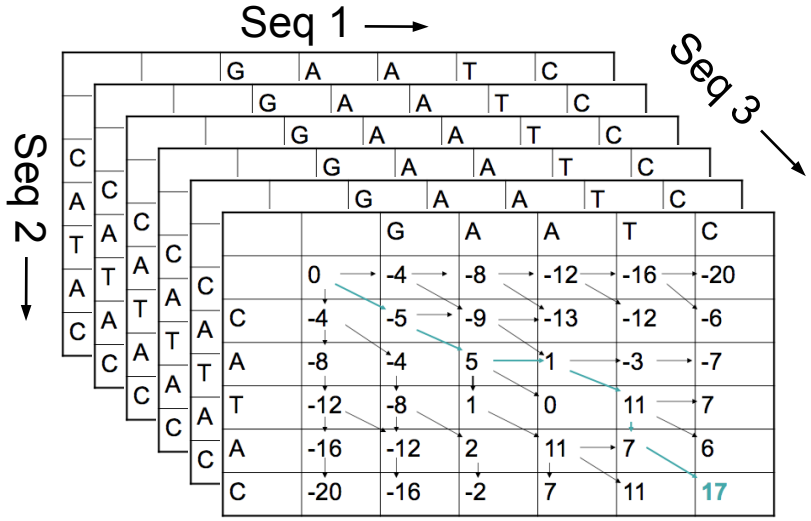
1. Min Entropy – if you assume a star phylogeny with long branches, positions in one column are independent and a proper probabilistic model reduces to per-column entropy (akin to last week). Intuitively sensible; favors alignments with less in-column variability
2. SP score: Sum of Pairs
   E.g., use BLOSUM62 score between all pairs of sequences

   abcde
   ac-de
   xccxd

   $\Sigma_{i<j} D(S_i, S_j)$

   It is *not* theoretically justifiable, but is easy, not terrible

Optimal SP Alignment via DP



k sequences of length n

(n+1) x (n+1) x ··· x (n+1) k-dim array

Max of 2^k-1 neighbors per cell; $(n+1)^k$ cells

Time: at least $(2n)^k$

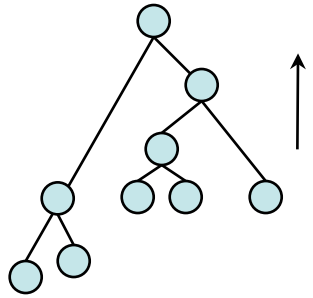
Want n, k 10's to 100's

Unlikely to do dramatically better – it's "NP-hard" Wang & Jiang, '94

E.g., n = 100
10^6 ops/sec

k	Time
2	40 ms
3	8 sec
4	.5 hr
5	100 hrs
6	2 years

Common Heuristic: Progressive Alignment



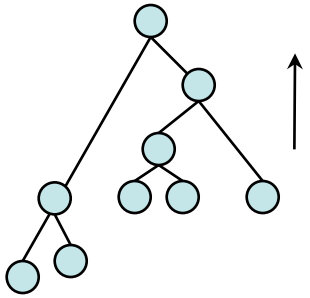
Pick a "guide tree"

- phylogeny is ideal, but expensive
- quicker alternative: get pairwise alignment scores, convert to distances, use, e.g., "neighbor joining"

Work up tree, leaves to root, doing pairwise alignments

(Many implementations, many variants, e.g. ClustalW)

Aligning Alignments



Except at leaves, progressive alignment is aligning two alignments or a sequence to an alignment

Key in pairwise alignment is scoring "x aligns with y"

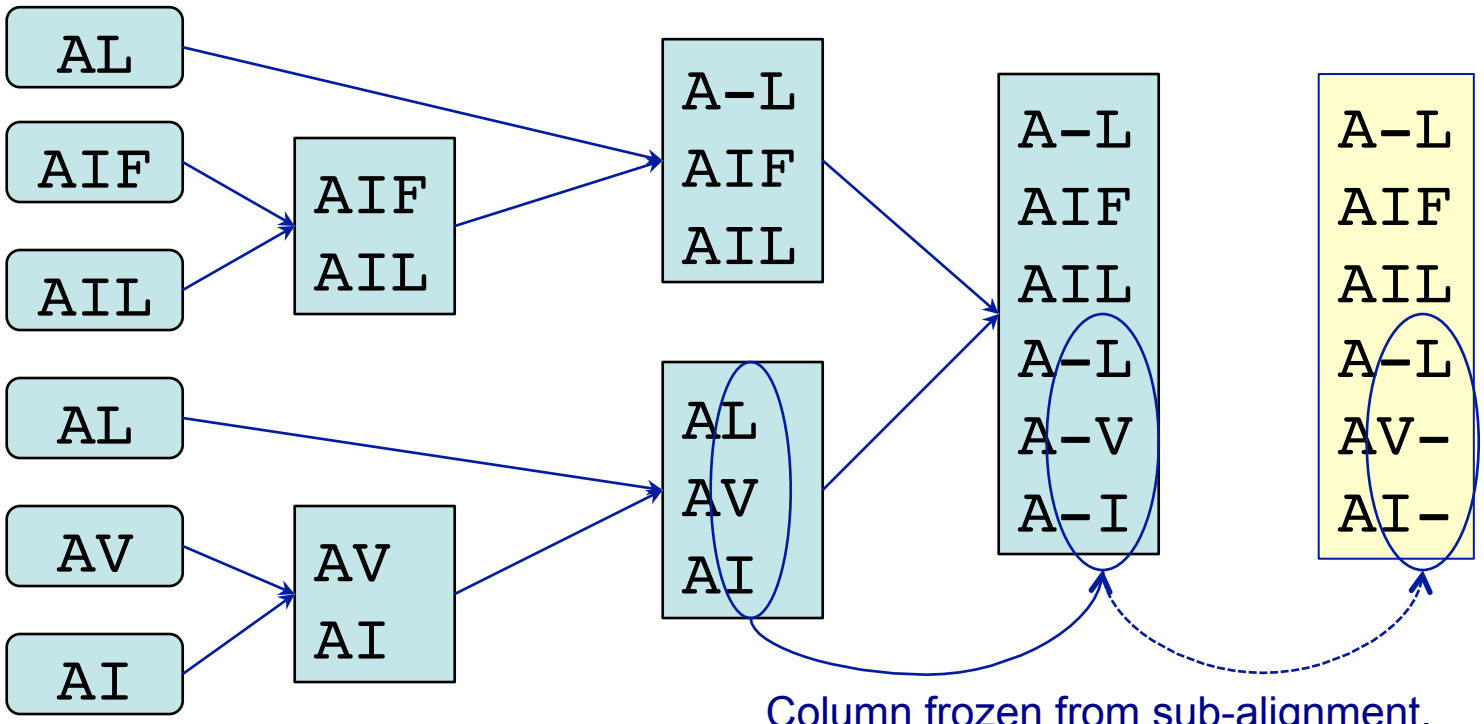
Now x, y are *columns* in the input alignments. Score?

Convenience of SP score is that you just score each letter in x vs each letter in y, say via BLOSUM62

Usual issues with gaps

Now run usual pairwise DP alignment at each step

Progressive Alignment



BLOSUM 62

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	**4**	-1	-2	-2	0	-1	-1	0	-2	-1	-1	-1	-1	-2	-1	1	0	-3	-2	0
R	-1	**5**	0	-2	-3	1	0	-2	0	-3	-2	2	-1	-3	-2	-1	-1	-3	-2	-3
N	-2	0	**6**	1	-3	0	0	0	1	-3	-3	0	-2	-3	-2	1	0	-4	-2	-3
D	-2	-2	1	**6**	-3	0	2	-1	-1	-3	-4	-1	-3	-3	-1	0	-1	-4	-3	-3
C	0	-3	-3	-3	**9**	-3	-4	-3	-3	-1	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1
Q	-1	1	0	0	-3	**5**	2	-2	0	-3	-2	1	0	-3	-1	0	-1	-2	-1	-2
E	-1	0	0	2	-4	2	**5**	-2	0	-3	-3	1	-2	-3	-1	0	-1	-3	-2	-2
G	0	-2	0	-1	-3	-2	-2	**6**	-2	-4	-4	-2	-3	-3	-2	0	-2	-2	-3	-3
H	-2	0	1	-1	-3	0	0	-2	**8**	-3	-3	-1	-2	-1	-2	-1	-2	-2	2	-3
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	**4**	2	-3	1	0	-3	-2	-1	-3	-1	3
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	**4**	-2	2	0	-3	-2	-1	-2	-1	1
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	**5**	-1	-3	-1	0	-1	-3	-2	-2
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	**5**	0	-2	-1	-1	-1	-1	1
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	**6**	-4	-2	-2	1	3	-1
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	**7**	-1	-1	-4	-3	-2
S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	**4**	1	-3	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	**5**	-2	-2	0
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	**11**	2	-3
Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	**7**	-1
V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	**4**

Summary

Very important problem

Scoring is very difficult to get right

Fast, exact solutions appear impossible (even with simple scoring schemes)

Many heuristics have been tried

Useful methods like ClustalW are available

Still an open field

- e.g., “genome scale” and RNA especially challenging

Iterative Pairwise Alignment (More Detail)

align some pair

while not done

- Pick an unaligned string "near" some aligned one(s)
- Align with the profile of the previously aligned group
- Resulting new spaces inserted in all

Many variants

Summarizing a Multiple Alignment

A *profile* of a multiple alignment gives letter frequencies per column

```
a b a
a b -
- b a
c a -
```

	col 1	col 2	col 3
a	50%	25%	50%
b	0%	75%	0%
c	25%	0%	0%
-	25%	0%	50%

Alternatively, use log likelihood ratios

$p_i(a)$ = fraction of a's in col i

$p(a)$ = fraction of a's overall

$\log p_i(a)/p(a)$

Aligning to a Phylogenetic Tree

Given a tree with a sequence at each leaf, assign labels to internal nodes so as to minimize $\Sigma_{\text{edges (i,j)}} D(S_i,S_j)$

[Note: NOT SP score]

Also NP-Complete

Poly time approximation within 2 x possible; better with more time (PTAS)

Multiple Sequence Alignment

Defn: An *alignment* of $S_1, S_2, \ldots, S_k$,
is a set of strings $S'_1, S'_2, \ldots, S'_k$, (with spaces) s.t.

(1) $|S'_1| = |S'_2| = \ldots = |S'_k|$, and

(2) removing all spaces leaves $S_1, S_2, \ldots, S_k$

```
a c b c d b      a c – – b c d b
c a d b d        – c a d b – d –
a c a b c d      a c a – b c d –
```

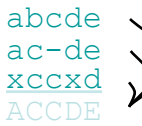
Multiple Alignment Scoring

Varying goals

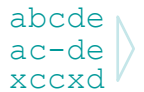
Varying methods (& controversy)

3 examples:

- Consensus string;
  sum distances to it
- Align to (evolutionary) tree;
  sum edges
- SP score:
  Sum of Pairs



$\Sigma_i D(S_i,C)$



$\Sigma_{i<j} D(S_i,S_j)$

NP-Complete Problems

A problem X is *NP-Complete* if
(1) it's in NP, and
(2) a poly time algorithm for X would give a poly time algorithm for *all* problems in NP

Thousands known; superficially very different - algebra, geometry, cs, bio, …

Smart Money betting against P = NP