Optimisation Alignment. 7.11.05 (60 minutes)

http://www.stats.ox.ac.uk/~hein/lectures.htm

Current Topics in Computational Molecular Biology

Chapter 3. 45-58 + Chapter 4.71-82

α-globin (141) and β-globin (146)

```
V-LSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHF-DLS--H---GSAQVKGHGKKVADAL
VHLTPEEKSAVTALWGKV--NVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPKVKAHGKKVLGAF

TNAVAHVDDMPNALSALSDLHAHKLRVDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR
SDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH
```

1. It often matches functional region with functional region.
2. Determines homology at residue/nucleotide level.
3. Similarity/Distance between molecules can be evaluated
4. Molecular Evolution studies.
5. Homology/Non-homology depends on it.

Evaluating alignments & choosing the best.

```
V-LSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHF-DLS--H---GSAQVKGHGKKVADAL
VHLTPEEKSAVTALWGKV--NVDEVGGEALGRLLVVYPWTQRFFESFGDLSTPDAVMGNPKVKAHGKKVLGAF
```

1. **Similarity/Distance (Parsimony):**

   a. **Similarity**

      Identity scores high – difference low.

      variable positions are scored less extreme than conserved sites.

      Used scores: identities, structural or log-odds $\log[p_{i,j}/(p_i * p_j)]$

   b. **Distance** 

      The scale is reversed: identity low – difference high.

      Used scores: identities, structural, genetic code, …

   c. **Distance is easier to interpret – similarity more flexible (+ & -, + only).**

2. **Gaps – single or many at a time.**

   Many is better, slightly more complicated

3. **Choose the alignment that optimizes the selection criteria – minimize/maximize.**

Number of alignments, T(n,m)

	1	9	41	129	321	681	
T							
	1	7	25	63	129	231	
G							
	1	5	13	25	41	61	
T							
	1	3	5	7	9	11	
T							
	1	1	1	1	1	1	
		C	T	A	G	G	

Parsimony Alignment of two strings.

Sequences: s1=CTAGG s2=TTGT.

Basic operations:

transitions 2 (C-T & A-G), transversions 5, indels (g) 10.

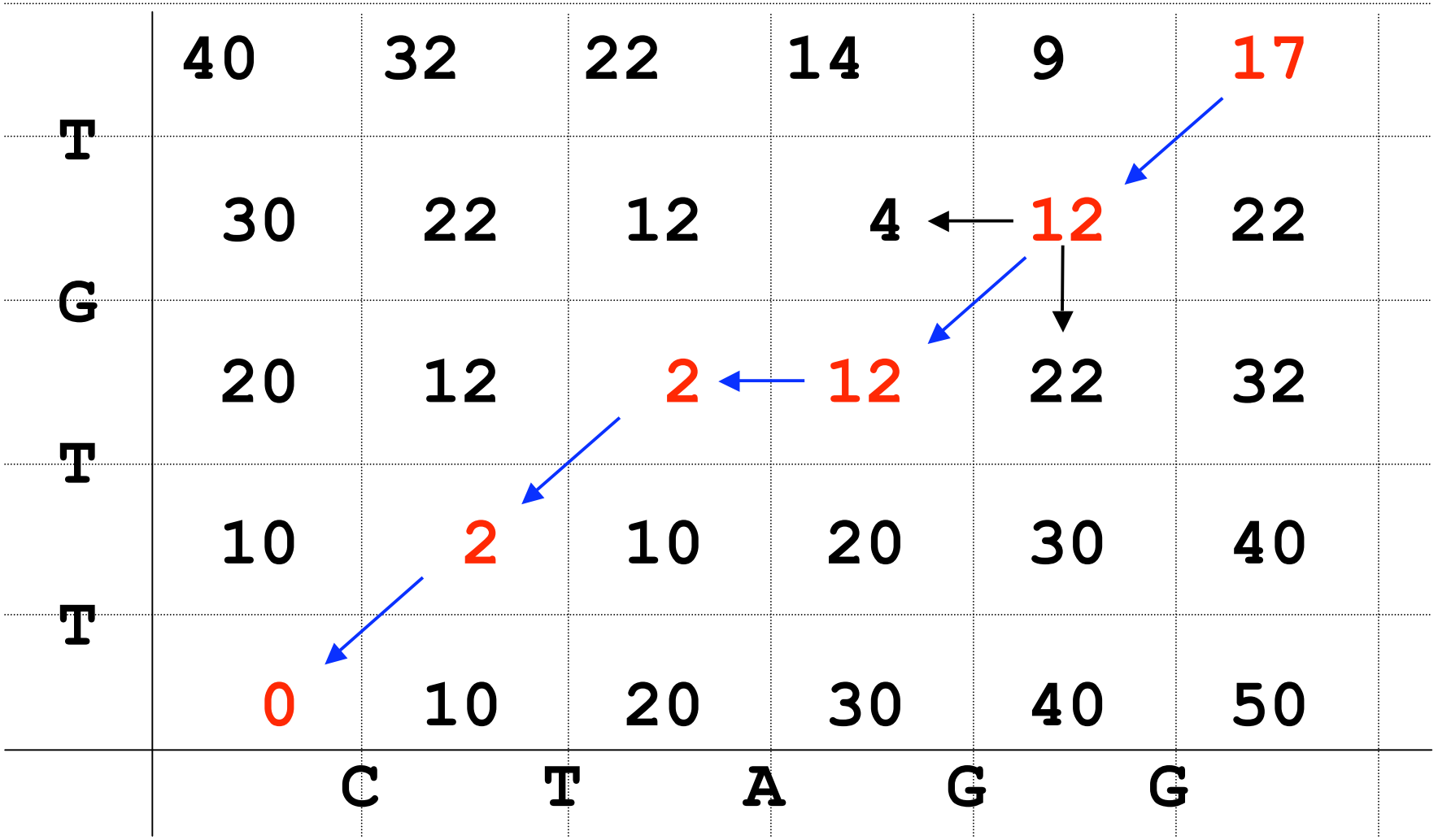
Cost Additivity

$$\begin{matrix} CTAG \\ TT\text{-}G \end{matrix} = \begin{matrix} CTA \\ TT\text{-} \end{matrix} + \begin{matrix} G \\ G \end{matrix}$$

$$\{CTAG,TTG\}_{AL} = \begin{matrix} (A) & \{CTA,TT\}_{AL} & + & GG \\ & 12 & & 0 \\ (B) & \{CTA,TTG\}_{AL} & + & G\text{-} \\ & 4 & & 10 \\ (C) & \{CTAG,TT\}_{AL} & + & \text{-}G \\ & 22 & & 10 \end{matrix}$$

Initial condition: $D_{0,0}=0$. ($D_{i,j}$:= D(s1[1:i], s2[1:j]))

$D_{i,j}=\min\{D_{i-1,j-1} + d(s1[i],s2[j]), D_{i,j-1} + g, D_{i-1,j} + g\}$



Alignment: CTAGG
i v
TT-GT

Cost 17

Complexity of Accelerations of pairwise algorithm.

Dynamical Programming: (n+1)(m+1)3=O(nm)

Backtracking: O(n+m)

Recursion without memory: T(n,m) > 3 $^{\min(n,m)}$

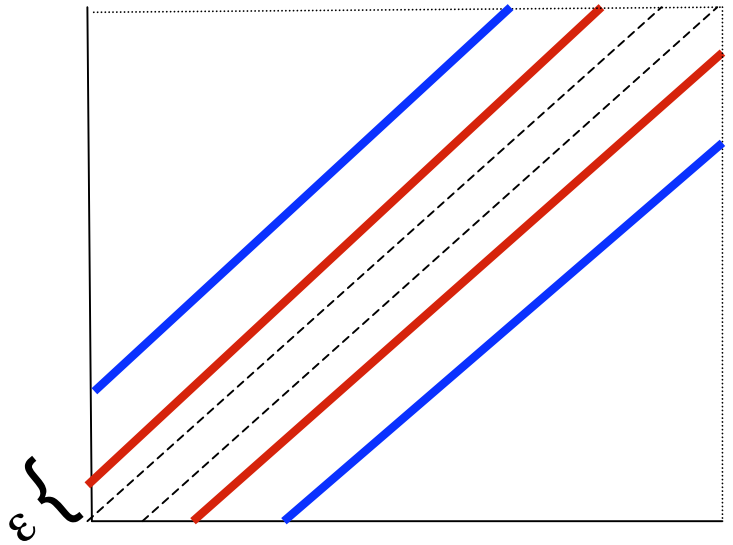
(T(n,m)=T(n-1,m)+T(n,m-1)+T(n-1,m-1), T(0,0)=1)

Exact acceleration (Ukkonen,Myers).

Assume all events cost 1.

If $d_\varepsilon(s_1,s_2) < 2\varepsilon+|l_1-l_2|$, then

$d(s_1,s_2)= d_\varepsilon(s_1,s_2)$



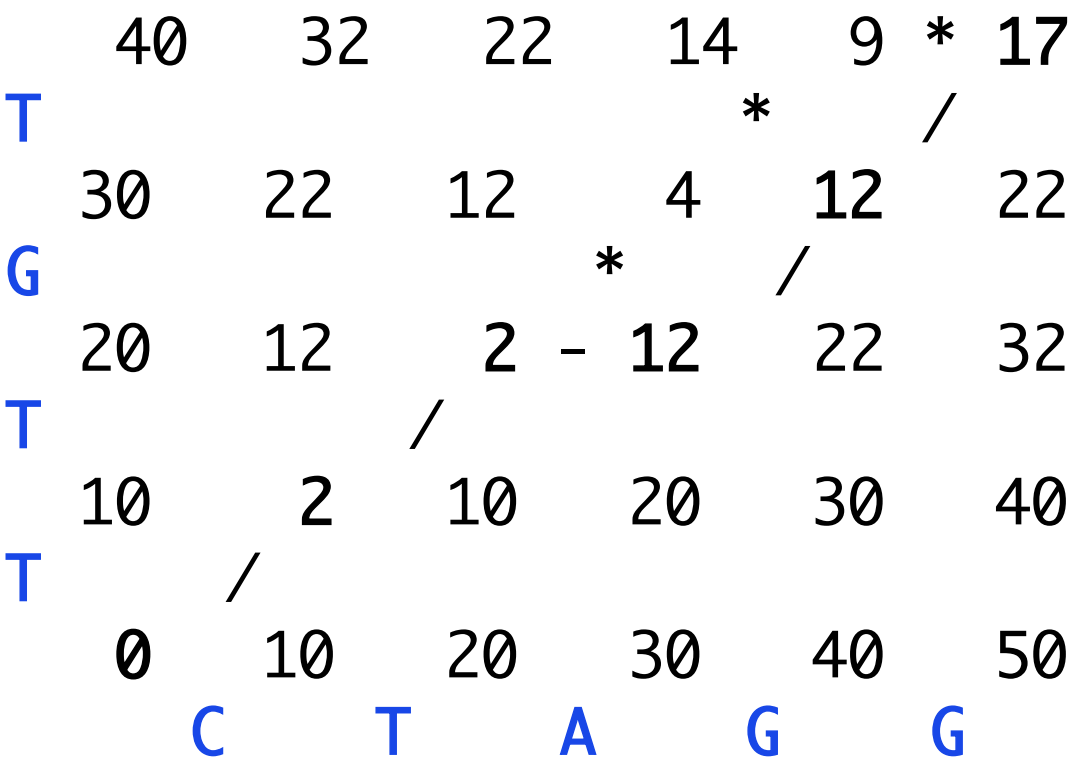
Heuristic acceleration: Smaller band & larger acceleration, but no guarantee of optimum.

Close-to-Optimum Alignments

(Waterman & Byers, 1983)

Alignments within ε of optimal

Ex. ε = 2.



C T A G G
i i v g Cost 19
T T G T -

Caveat:

There are enormous numbers of suboptimal alignments.

Hirschberg & Close-to-Optimum Alignments

(Hirschberg, 1975).

Sets of positions that are on some suboptimal alignment.
Alignments within ε of optimal. Ex. ε = 2

	40/50	32/40	22/30	14/20	9/10	17/0
T						
	30/40	22/30	12/25	4/15	12/5	22/10
G						
	20/35	12/25	2/15	12/5	22/10	32/20
T						
	10/25	2/15	10/15	20/15	30/20	40/30
T						
	0/17	10/15	20/20	30/25	40/30	50/40
		C	T	A	G	G

Mid point: (3,2) and the alignment problem is then reduced to 2 smaller alignment problems: (CTA + TT) and (GG + GT)

Longer Indels

TCATGGTACCGTTAGCGT
GCA----------GCAT

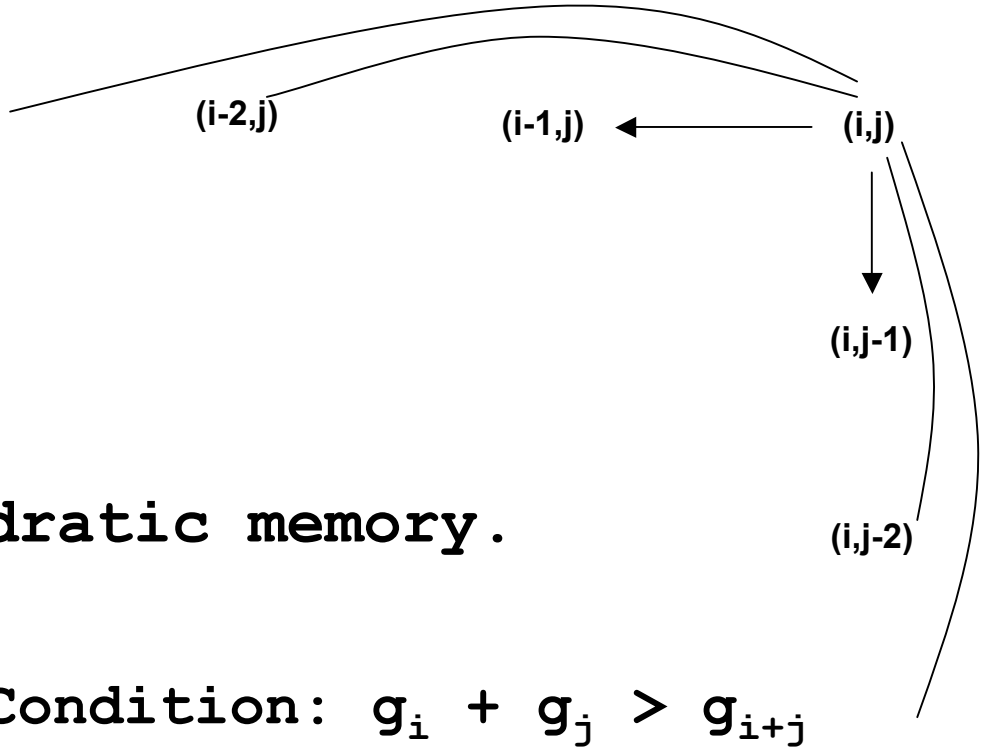
g_k :cost of indel of length k.

Initial condition: $D_{0,0}=0$

$D_{i,j}$ = min {

$D_{i-1,j-1}$ + d(s1[i],s2[j]),
$D_{i,j-1}$ + g_1,$D_{i,j-2}$ + g_2,,
$D_{i-1,j}$ + g_1,$D_{i-2,j}$ + g_2,,
}

Cubic running time. Quadratic memory.



Comment:

Evolutionary Consistency Condition: $g_i + g_j > g_{i+j}$

If $g_k = a + b*k$, then quadratic running time

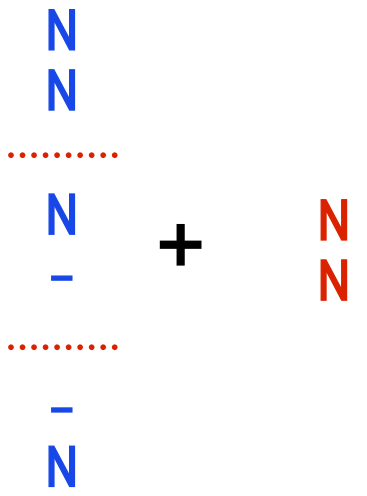
Gotoh (1982) $D_{i,j}$ is split into 3 types:

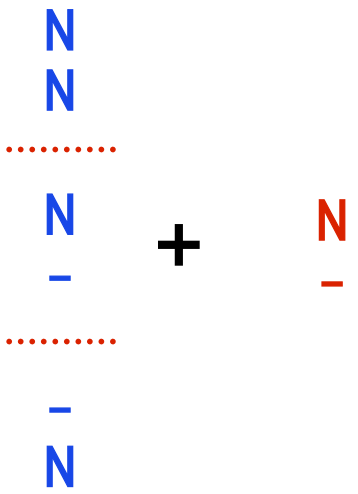
1. $D0_{i,j}$ as $D_{i,j}$, except s1[i] must mactch s2[j].
2. $D1_{i,j}$ as $D_{i,j}$, except s1[i] is matched with "-".
3. $D2_{i,j}$ as $D_{i,j}$, except s2[i] is matched with "-".

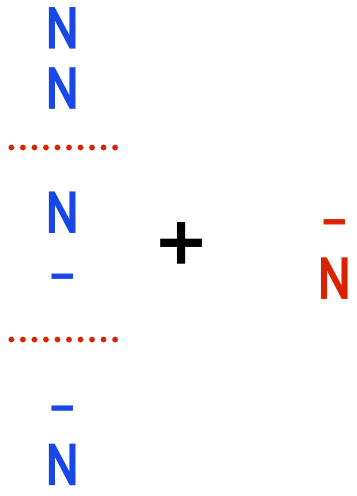
Then: $D0_{i,j} = \min(D0_{i-1,j-1},\ D1_{i-1,j-1},\ D2_{i-1,j-1}) + d(s1[i],s2[j])$

$D1_{i,j} = \min(D1_{i,j-1} + b,\ D0_{i,j-1} + a + b)$

$D2_{i,j} = \min(D2_{i-1,j} + b,\ D0_{i-1,j} + a + b)$







Distance-Similarity.

(Smith-Waterman-Fitch,1982)

$$S_{i,j}=\max\{S_{i-1,j-1} + s(s1[i],s2[j]),\ S_{i,j-1} - w,\ S_{i-1,j} - w\}$$

Similarity	Distance
s(n1,n2)	M - d(n1,n2)
w	1/(2*M) + g

Similarity: Transversions:0 Transitions:3 Identity:5 Indels: 10 + 1/10

Distance: Transitions:2 Transversions 5 Identity 0 Indels:10. M largest dist (5)

	40/-40.4	32/-27.3	22/-12.2	14/0.9	9/11.0	17/2.9
T						
	30/-30.3	22/-17.2	12/-2.1	4/11.0	12/2.9	22/-7.2
G						
	20/-20.2	12/-7.1	2/8.0	12/-2.1	22/-12.2	32/-22.3
T						
	10/-10.1	2/3.0	10/-7.1	20/-17.2	30/-27.3	40/-37.4
T						
	0/0	10/-10.1	20/-20.2	30/-30.3	40/-40.4	50/-50.5
		C	T	A	G	G

1. The Switch from Dist to Sim is highly analogous to Maximizing {-f(x)} instead of Minimizing {f(x)}.
2. Dist will based on a metric:

   i. d(x,x) =0, ii. d(x,y) >=0, iii. d(x,y) = d(y,x) &
   iv. d(x,z) + d(z,y) >= d(x,y).

   There are no analogous restrictions on Sim, giving it a larger parameter space.

Local alignment

Smith,Waterman (1981

Global Alignment: $S_{i,j}=\max\{D_{i-1,j-1} + s(s1[i],s2[j]),\ S_{i,j-1} -w,\ S_{i-1,j}-w\}$

Local: $S_{i,j}=\max\{D_{i-1,j-1} + s(s1[i],s2[j]),\ S_{i,j-1} -w,\ S_{i-1,j}-w, 0\}$

	0	1	0	.6	1	2	.6	1.6	1.6	3	2.6
C											
	0	0	1	0	1	.3	.6	0.6	2	3	1.6
A											
	0	0	0	1.3	0	1	1	2	3.3	2	1.6
G									/		
	0	0	.3	.3	1.3	1	2.3	2.3	2	.6	1.6
C								/			
	0	0	.6	1.6	.3	1.3	2.6	2.3	1	.6	1.6
U							/				
	0	0	2	.6	.3	1.6	2.6	1.3	1	.6	1
A						!					
	0	1	.6	0	1	3	1.6	1.3	1	1.3	1.6
C					/						
	0	1	0	0	2	1.3	.3	1	.3	2	.6
C				/							
	0	0	0	1	.3	0	0	.6	1	0	0
G			/								
	0	0	0	.6	1	0	0	0	1	1	2
U											
	0	0	1	.6	0	0	0	0	0	0	0
A											
	0	0	1	0	0	0	0	0	0	0	0
A											
	0	0	0	0	0	0	0	0	0	0	0
		C	A	G	C	C	U	C	G	C	U	U

Score Parameters:

Match: 1

Mismatch -1/3

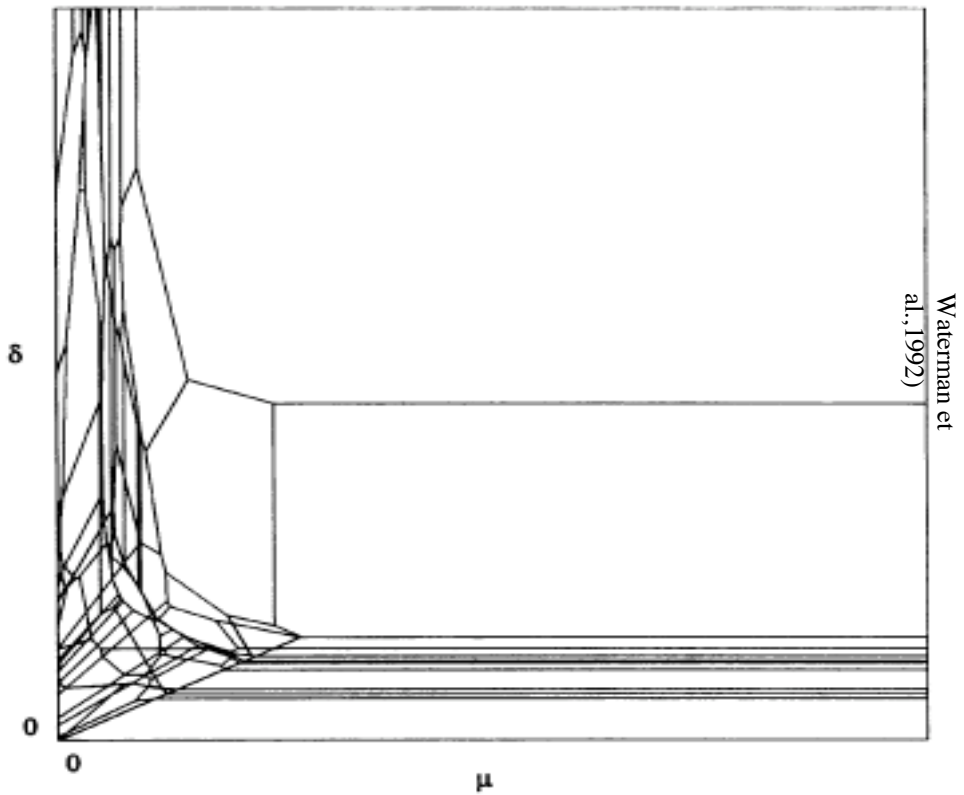
Gap 1 + k/3

GCC-UCG
GCCAUUG

Parametric Alignment

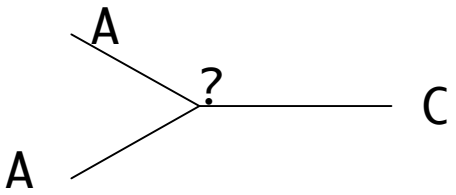
Waterman et al. 1992, Gusfield et al.,1992

- The set of alignments if finite, while parameter space is region of Euclidian Space.
- The parameter space can be tiled into areas with the same optimal alignment.



Alignment of three sequences.

s1=ATCG s2=ATGCC s3=CTCC



Alignment: AT-CG
ATGCC
CT-CC

Consensus sequence: ATCC

Configurations in an alignment column:

-	-	n	n	n	-	n	-
-	n	-	n	-	n	n	-
n	-	-	-	n	n	n	-

Recursion: $D_{i,j,k} = \min\{D_{i-i',j-j',k-k'} + d(i,i',j,j',k,k')\}$

Initial condition: $D_{0,0,0} = 0.$

Running time: $l_1*l_2*l_3*(2^3-1)$ Memory requirement: $l_1*l_2*l_3$
New phenomena: ancestral sequence.

Parsimony Alignment of four sequences

s1=ATCG s2=ATGCC s3=CTCC s4=ACGCG

Alignment:

AT-CG
ATGCC
CT-CC
ACGCG

Configurations in alignment columns:

-	-	-	n	-	-	-	n	n	n	-	n	n	n	n	-
-	-	n	-	n	n	-	n	-	-	n	-	n	n	n	-
-	n	-	-	n	-	n	-	n	-	n	n	-	n	n	-
n	-	-	-	-	n	n	-	-	n	n	n	n	-	n	-

Recursion: $D_i = \min\{D_{i-\Delta} + d(i,\Delta)\}\ \Delta\ [\{0,1\}^4 \backslash \{0\}^4]$

Initial condition: $D_0 = 0$.

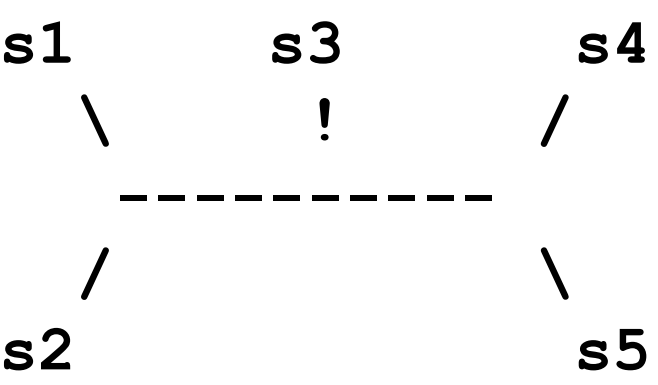
Computation time: $l_1 * l_2 * l_3 * l_4 * 2^4$ **Memory :** $l_1 * l_2 * l_3 * l_4$

Alignment of many sequences.

s1=ATCG, s2=ATGCC, ..., sn=ACGCG

Alignment:

AT-CG
ATGCC
.....
.....
ACGCG



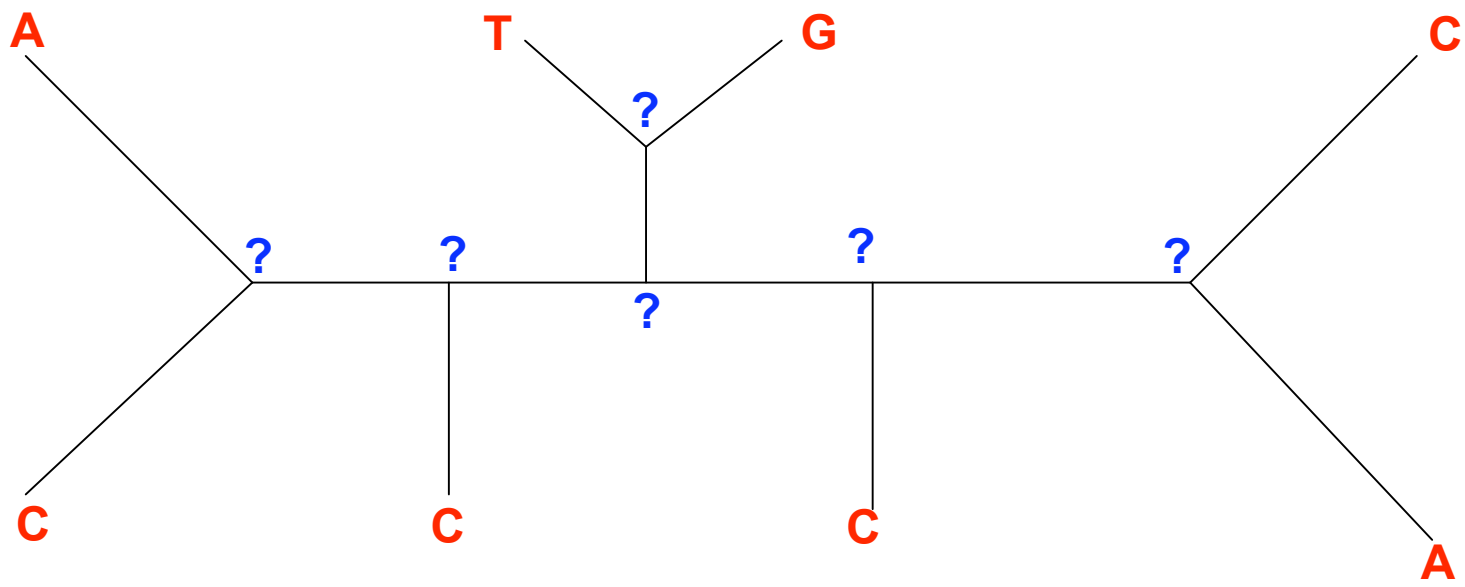
Configurations in an alignment column: 2^n-1

Recursion: $D_i=\min\{D_{i-\Delta} + d(i,\Delta)\}\ \Delta \in [\{0,1\}^n \backslash \{0\}^n]$

Initial condition: $D_{0,0,..0} = 0.$

Computation time: $l^n*(2^n-1)*n$ Memory requirement: l^n
(l:sequence length, n:number of sequences)

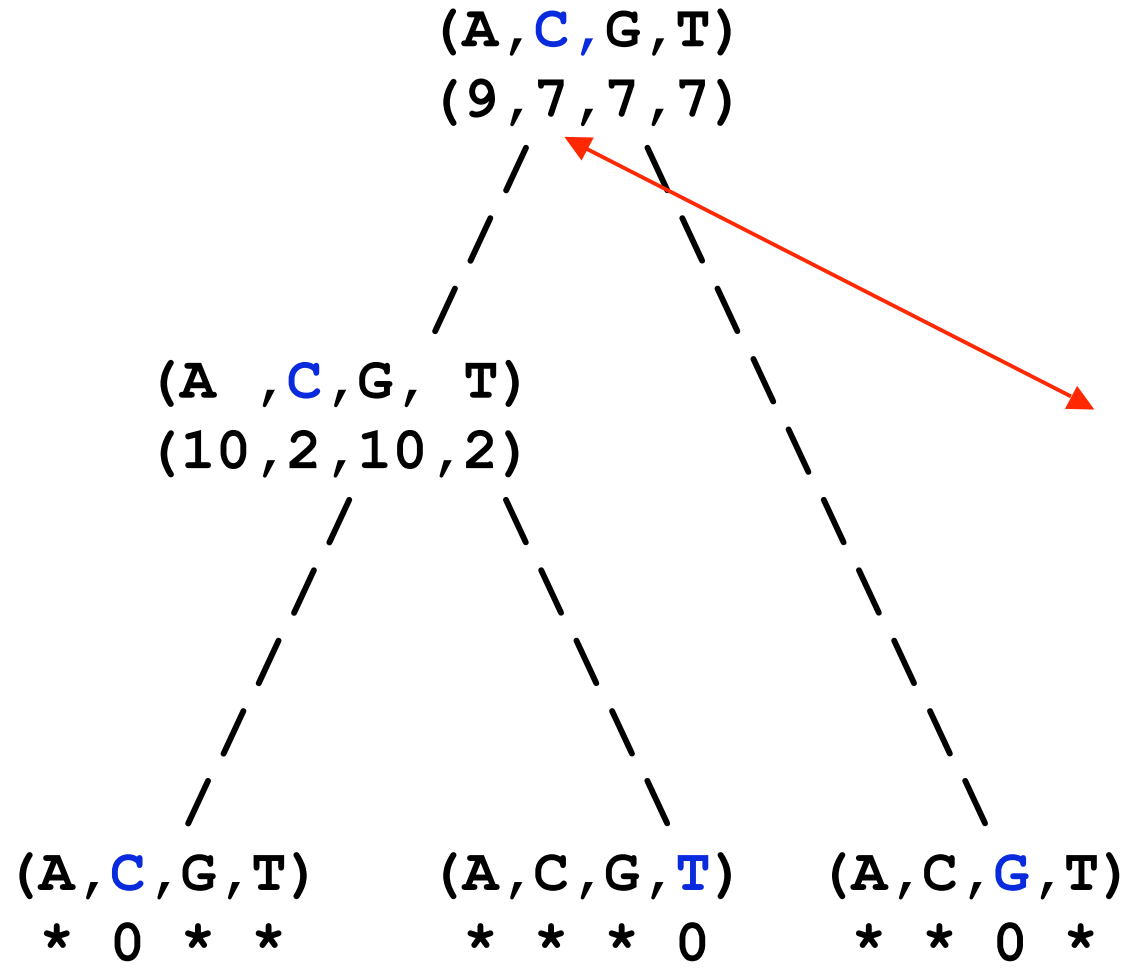
Assignment to internal nodes: The simple way.



What is the cheapest assignment of nucleotides to internal nodes, given some (symmetric) distance function $d(N_1,N_2)$??

If there are k leaves, there are k-2 internal nodes and 4^{k-2} possible assignments of nucleotides. For k=22, this is more than 10^{12}.

Fitch-Hartigan-Sankoff Algorithm

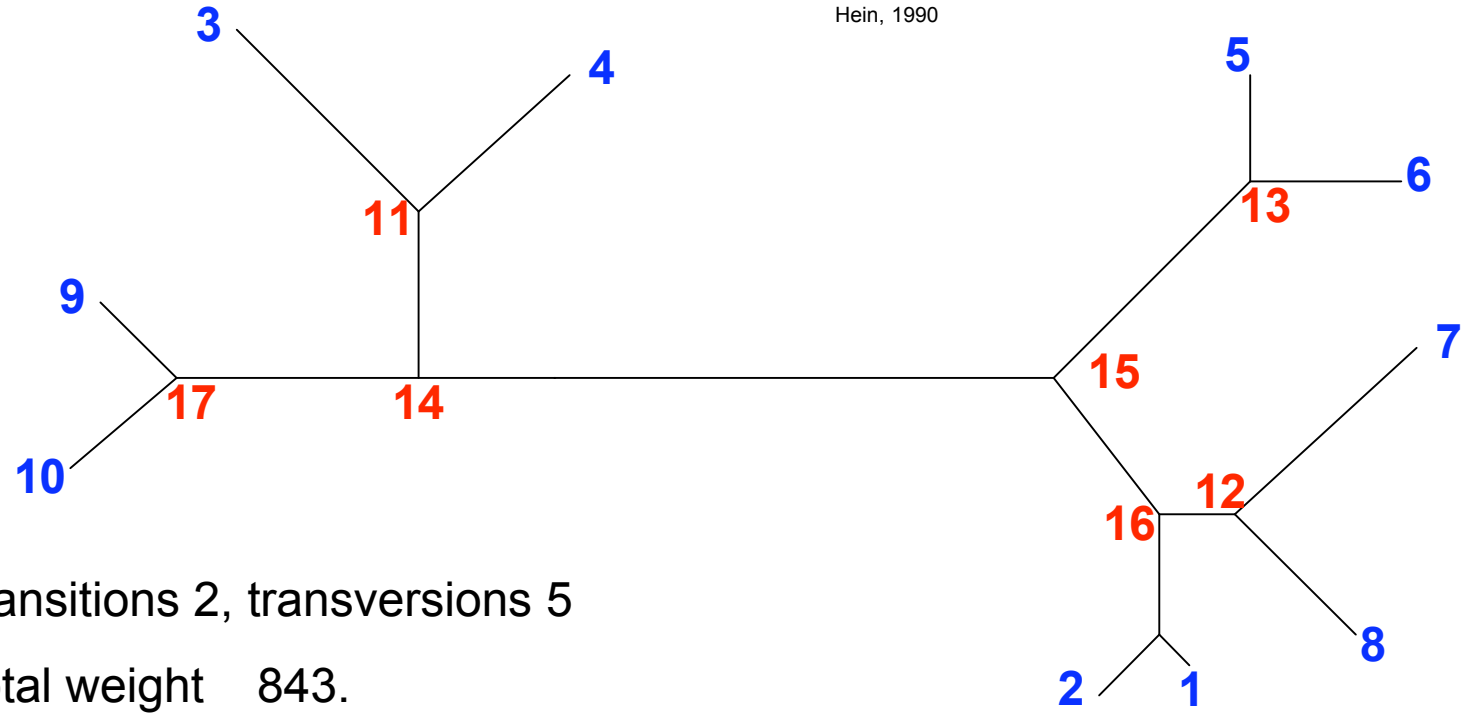


Costs: Transition 2, Transversion 5, indel 10.

The cost of cheapest tree hanging from this node given that there is a "C" at this node

Indel Constraint: Nucleotides is connected set.

5S RNA Alignment & Phylogeny



Transitions 2, transversions 5

Total weight 843.

```
10 tatt-ctggtgtcccaggcgtagaggaaccacaccgatccatctcgaacttggtggtgaaactctgccgcggt--aaccaatact-cg-gg-gggggccct-gcggaaaaatagctcgatgccagga--ta
17 t--t-ctggtgtcccaggcgtagaggaaccacaccaatccatcccgaacttggtggtgaaactctgctgcggt--ga-cgatact-tg-gg-gggagcccg-atggaaaaatagctcgatgccagga--t-
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```

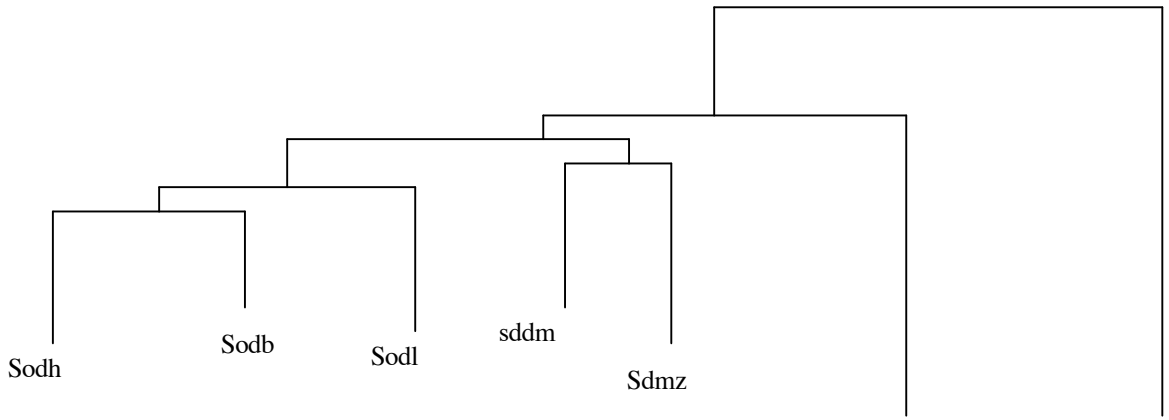
Progressive Alignment

(Feng-Doolittle 1987 J.Mol.Evol.)

Can align alignments and given a tree make a multiple alignment.

```
    *                *
alkmny-trwq       acdeqrt
akkmdyftrwq       acdehrt
kkkmemftrwq
```

$[P(n,q) + P(n,h) + P(d,q) + P(d,h) + P(e,q) + P(e,h)]/6$




```
                 *      *                          *** *   *        *            * *   *
Sodh  atkavcvlkgdgpqvqgsinfeqkesdgpvkvwgsikglte-glhgfhvhqfg----ndtagct    sagphfnp lsrk
Sodb  atkavcvlkgdgpqvqgtinfeak-gdtvkvwgsikglte--glhgfhvhqfg----ndtagct    sagphfnp lsrk
Sodl  atkavcvlkgdgpqvqgsinfeqkesdgpvkvwgsikglte-glhgfhvhqfg----ndtagct    sagphfnp lsrk
Sddm  atkavcvlkgdgpqvq -infeak-gdtvkvwgsikglte--glhgfhvhqfg----ndtagct    sagphfnp lsrk
Sdmz  atkavcvlkgdgpqvq- infeqkesdgpvkvwgsikglte-glhgfhvhqfg----ndtagct    sagphfnp Lsrk
Sods vatkavcvlkgdgpqvq- infeak-gdtvkvwgsikgltepnglhgfhvhqfg----ndtagct    sagphfnp lsrk
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```

Summary

Comparison of 2 Strings

- Minimize Distance-Maximize Similarity
- Dynamical Programming Algorithm
- Local alignment
- Close-to-Optimal Solutions
- Parametric Alignment

Comparison of many Strings

- Simultaneous Phylogeny and Alignment

History of Alignment

1953 Richard Bellman invents Dynamical Programming

1966: Levenstein formulates distance measure between sequences and instroduces dynamica programming algorithm finding the distance.

1970: Needleman and Wunch compares proteins maximising a similarity score.

1972: Sankoff & Sellers reinvents the basic algorithm.

1972: Sankoff can align subject to the constraint that there must be exactly k indels.

1973: Sankoff makes multiple alignment and phylogeny - both exact & heuristic.

1975: Hirschberg gives linear memory algorithm.

1976: Waterman gives cubic algorithm allowing for indels of arbitrary length without reference to phylogeny.

1981: Waterman, Smith and Fitch shows duality of simiarity and distance.

1981 Smith and Waterman invents similarity based local alignment.

1982: Gotoh gives quadratic algorithm if gap penalty functionen is $g_k = a + b*k$ (for indel of length k). Uses 3 matrices in stead of 1.

1983: Waterman and Byers introduces close-to-optimal alignments.

1984-5: Ukkonen, Myers, Fickett accelerates algorithmen considerably.

1984: Hogeveg and Hespers introduces heuristic multiple phylogenetic alignment.

1984: Fredman introduces triple alignment generalisation of Needleman-Wunch.

1985: Lipman & Wilbur uses hashing. 1989: Myers introduces alignment with concave gap penalty function.

1987: Feng-Doolittle introducesphylogenetisk alignment: "Once a gap always a gap".

1989: Kececioglou makes strong acceleration of Sankoff's exact algorithm.

1991: Thorne, Kishino & Felsenstein makes good model for statistical alignment, partially introduced in 1986 by Thomson & Bishop.

1991: States & Botstein compares a DNA string with a protein in search of frameshift mutations.

1993-4: Gusfield, Lander, Waterman and others introduces parametric alignment.

1994: Krogh et al & Baldi et al. introduces Hidden Markov Models for multiple alignment.

1995: Mitcheson & Durbin introduces Tree-HMMs

1999 - Resurgence of interest in statistical alignment

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