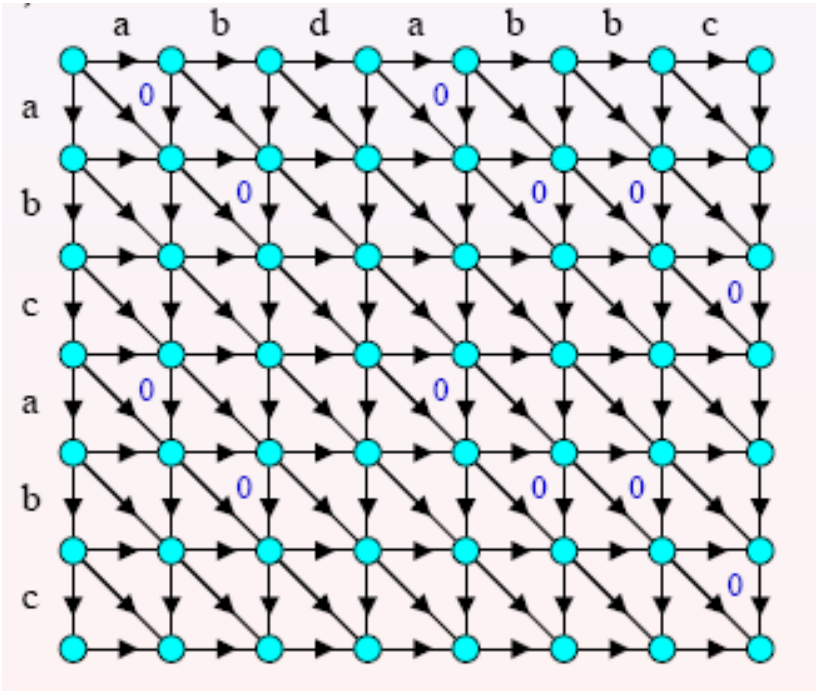
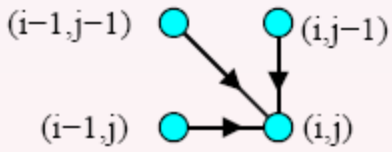
Alignment Graph



Alignment Matrix

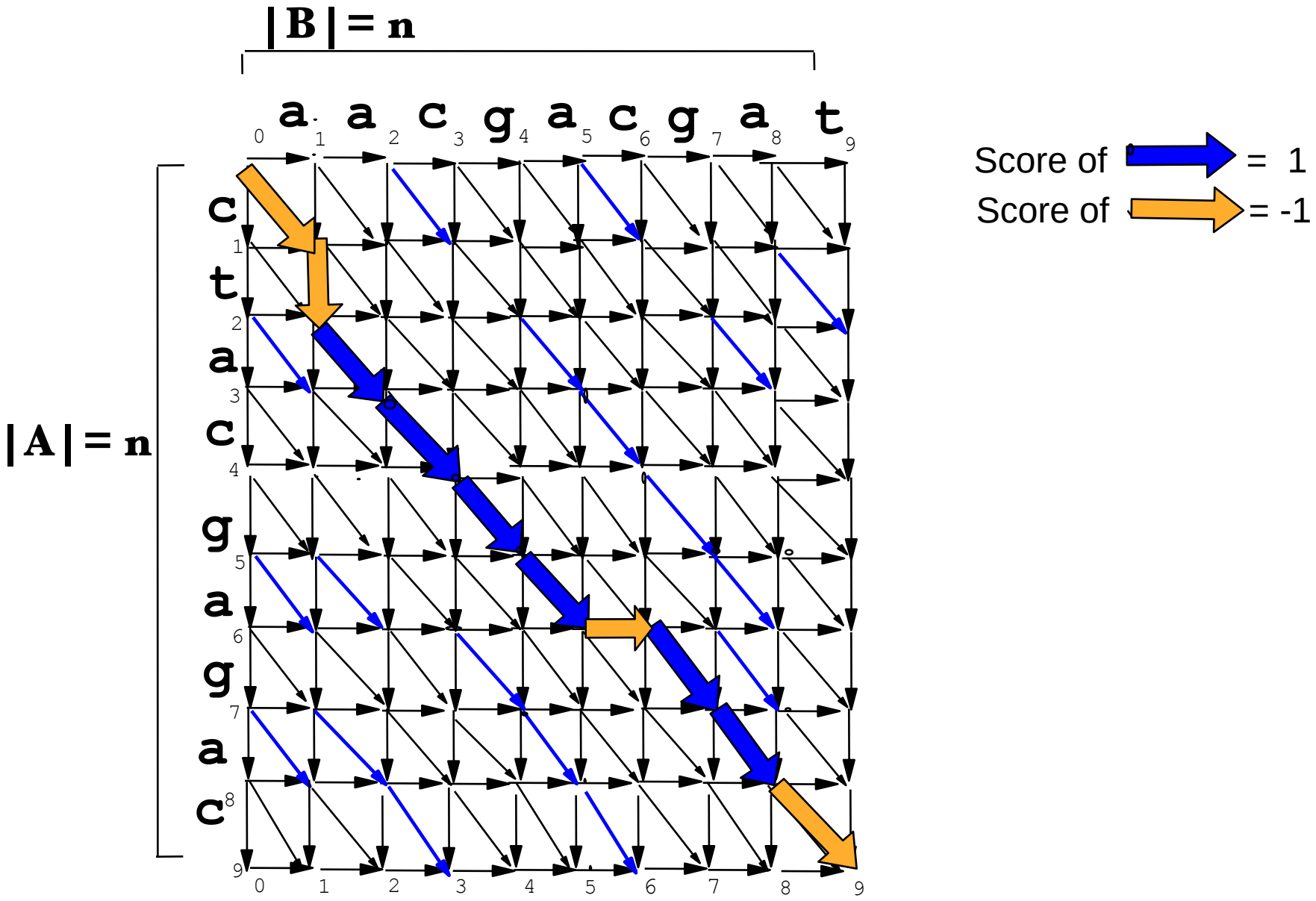
		a	b	d	a	b	b	c
	0	1	2	3	4	5	6	7
a	1	0	1	2	3	4	5	6
b	2	1	0	1	2	3	4	5
c	3	2	1	1	2	3	4	4
a	4	3	2	2	1	2	3	4
b	5	4	3	3	2	1	2	3
c	6	5	4	4	3	2	2	2

- For $i,j > 0$:



$$F(i,j) = \min \begin{cases} F(i-1,j)+1, \\ F(i,j-1)+1, \\ F(i-1,j-1)+w(i,j) \end{cases}$$

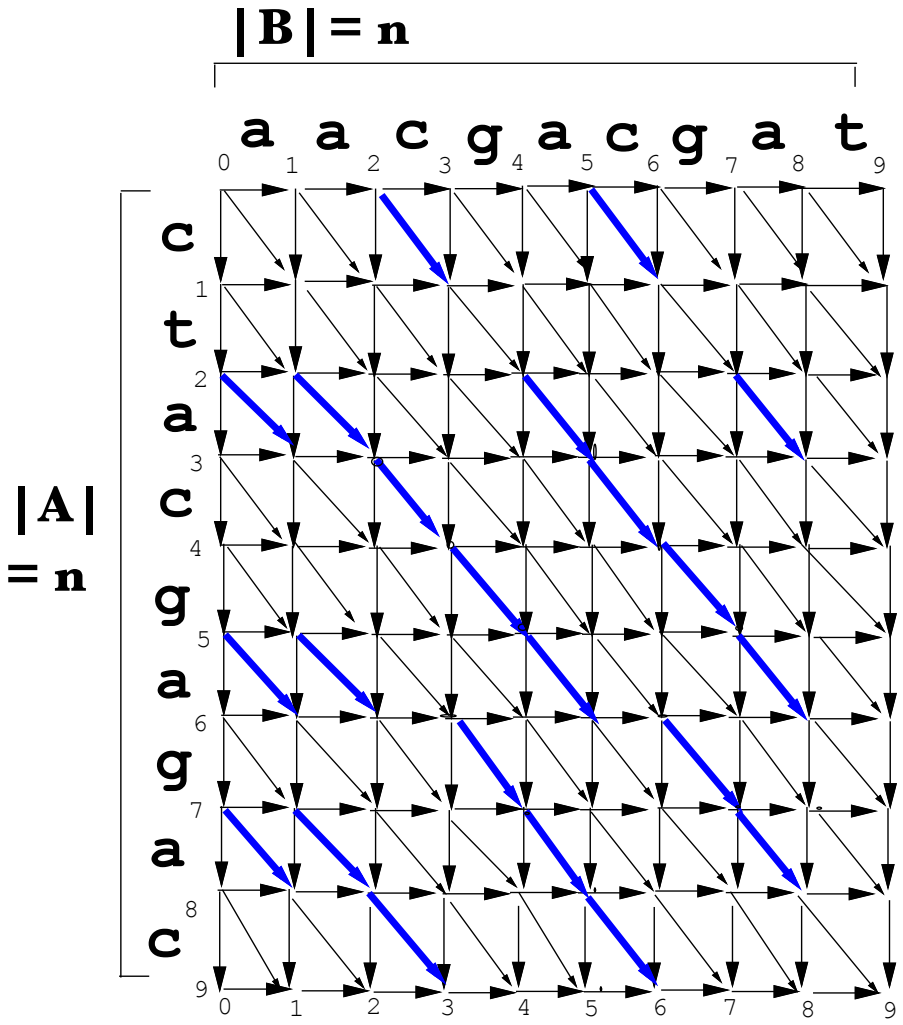
Computing the Optimal Global Alignment Value

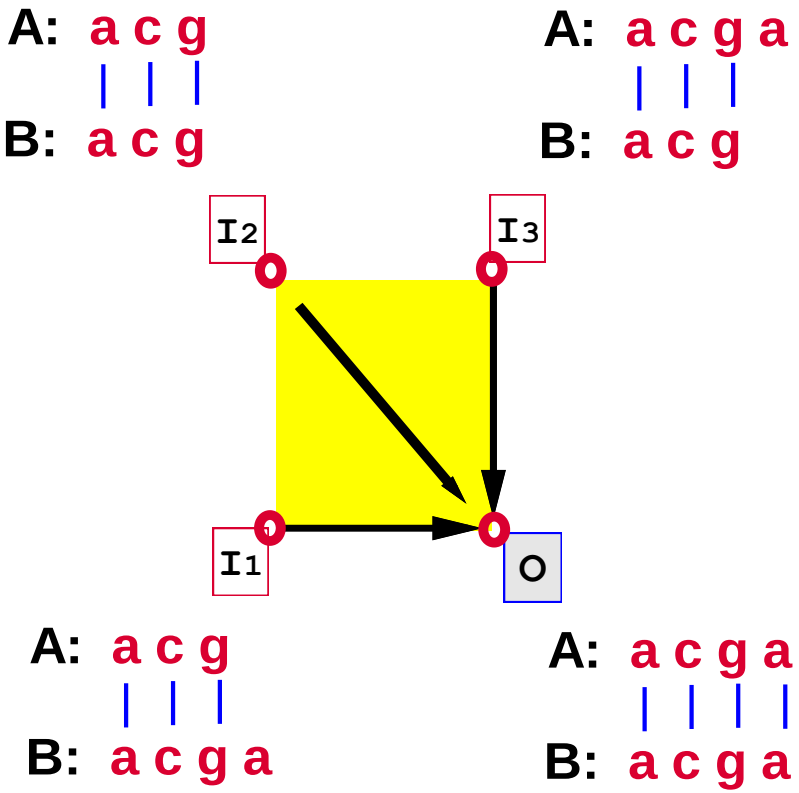


Classical Dynamic Programming: $O(n^2)$

The O(n^2) time, Classical Dynamic Programming Algorithm

The Alignment Graph





$$O = \max_{x=1}^{3}(I_x + edge[I_x, O])$$

Can the quadratic complexity of the optimal alignment value computation be reduced without relaxing the problem?

Is it Possible to Align Sequences in Subquadratic Time?

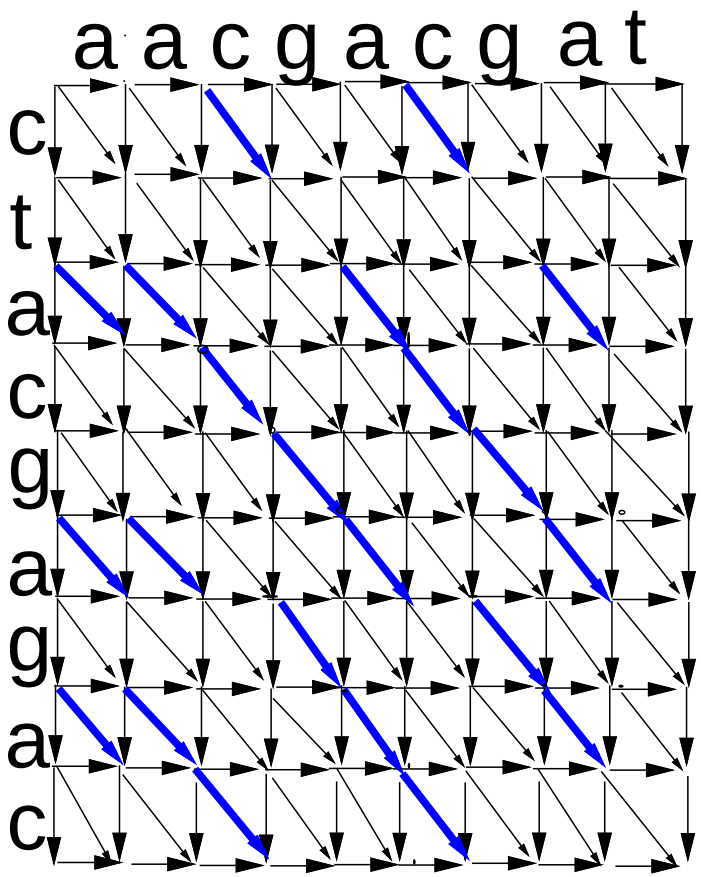
- Dynamic Programming takes O(n^2) for global alignment
- Can we do better? O (h n^2 /log n), h <= 1.

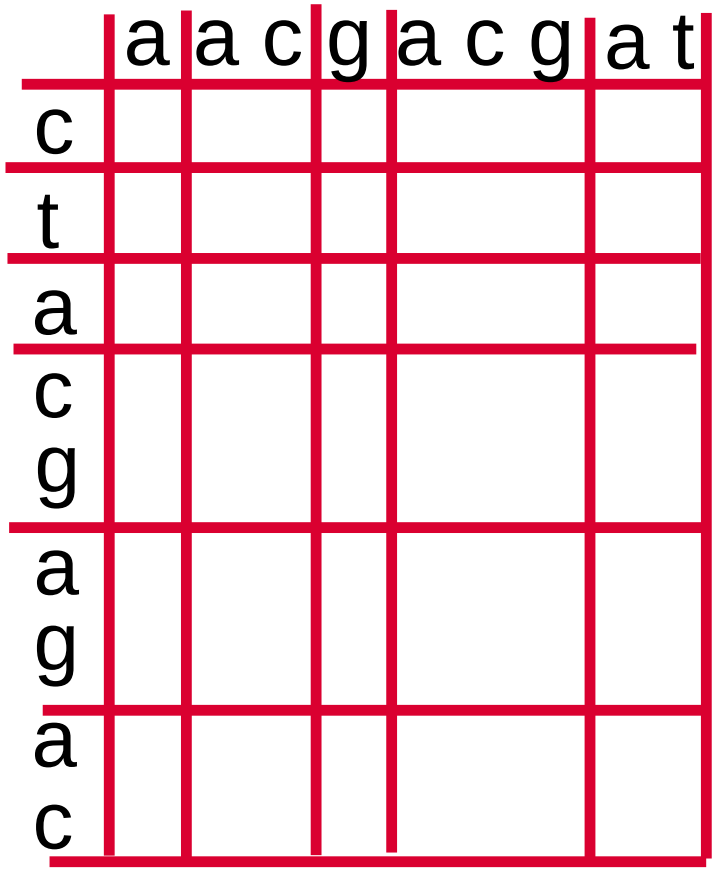
  Landau,Crochemore&Ziv-ukelson 2003

  Techniques:

  (1) **Compress** the sequences.

  (2) Utilize the **Total Monotonicity** of DIST.

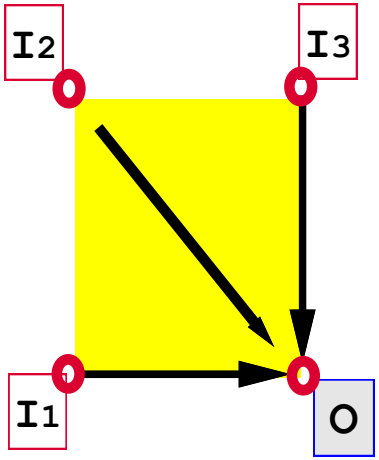




$O(n^2)$ vertices

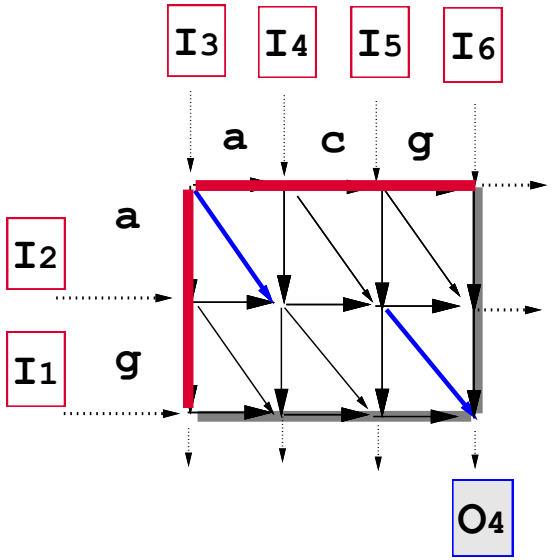
O(h n / log n) rows of n vertices +
O(h n / log n) columns of n vertices

Standard, single-cell DP



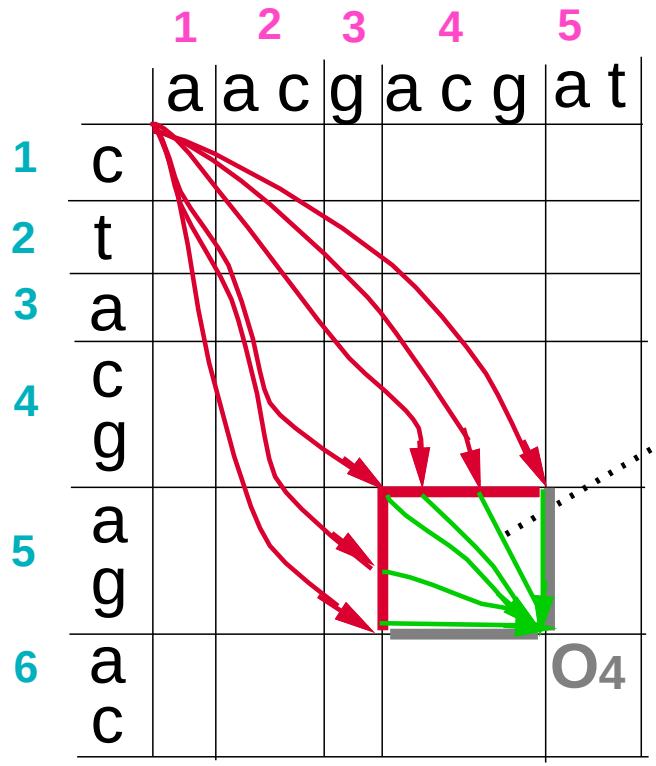
$$O = \max_{x=1}^{3}(I_x + edge[I_x, O])$$

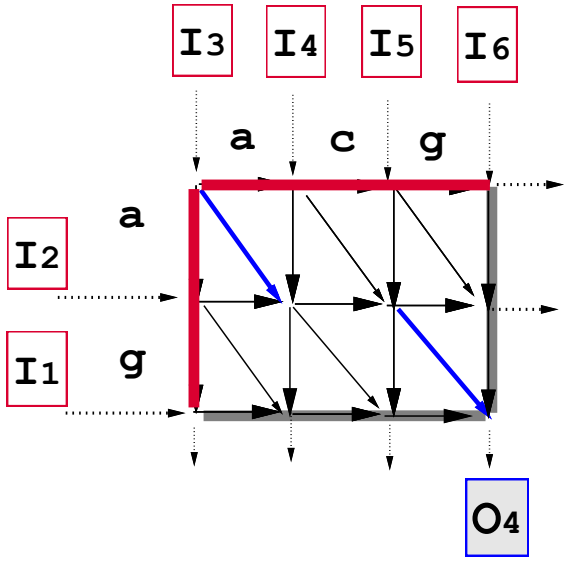
New, extended-cell DP



$$O_4 = \max_{x=0}^{6}(I_x + DIST[x,3])$$

Computing the score for Output Border Vertex O_4





I_1	DIST[1,4]	I_1+DIST[1,4]
I_2	DIST[2,4]	I_2+DIST[2,4]
I_3	DIST[3,4]	I_3+DIST[3,4]
I_4	DIST[4,4]	I_4+DIST[4,4]
I_5	DIST[5,4]	I_5+DIST[5,4]
I_6	DIST[6,4]	I_6+DIST[6,4]

$$O_4 = \max_{x=0}^{6}(I_x + DIST[x,3])$$

	1	2	3	4	5	6
Input I\ DIST Matrix						
I1 = 1	0	−1	−2	−3	□	□
I2 = 2	−1	−1	−2	−1	−3	□
I3 = 3	−2	0	0	1	−1	−3
I4 = 2	□	−2	−2	0	−2	−2
I5 = 1	□	□	−2	0	−1	−1
I6 = 3	□	□	□	−2	−1	0

OUT[x,j] = Ix + DIST[x,j]

1	0	−1	−2	□	□
1	1	0	1	−1	□
(1)	(3)	(3)	(4)	2	0
□	0	0	2	0	0
□	□	−1	1	0	0
□	□	□	1	(2)	(3)

Output vector O

1	3	3	4	2	3

The Main Challenges

How to obtain the DIST for G in O(t) time ?

(Take advantage of the incremental nature of LZ78 parsing).

How to compute the column maxima of OUT in O(t) time ?

(Utilize the Total Monotonicity Property of OUT).

How does Total Monotonicity affect Column Maxima behavior?

For all a <b and c < d, OUT[a,c] <= OUT[b,c] ⇒ OUT[a,d] <= OUT[b,d]

OUT Matrix

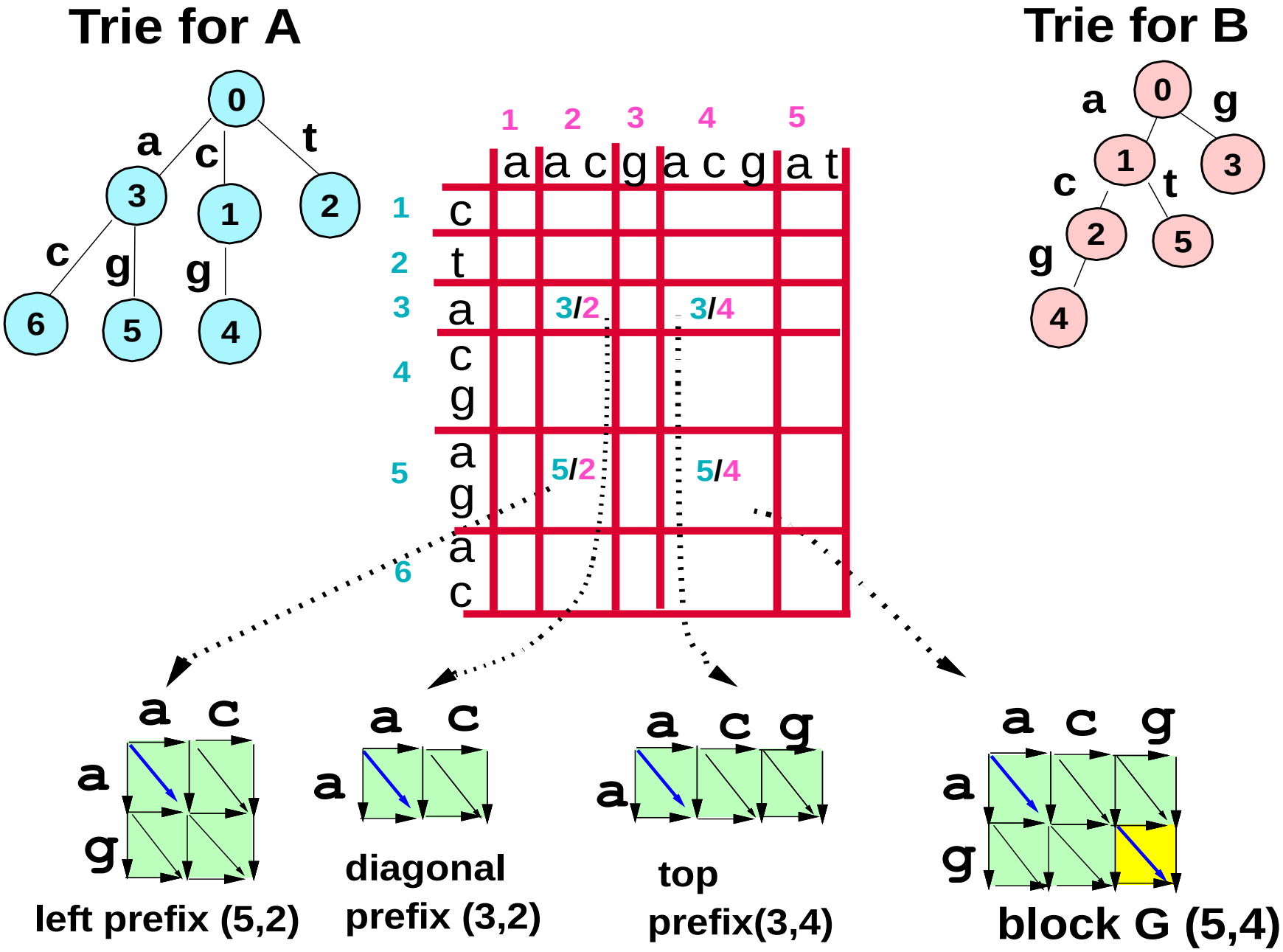
				c	d	
a	1	0	−1	−2	$-\omega$	$-\omega$
	1	1	0	1	−1	$-\omega$
b	1	3	3	4	2	0
	−12	0	0	2	0	0
	−13	−13	−1	1	0	0
	−14	−14	−14	1	2	3

Column maxima row indices are monotonically non-decreasing.

SMAWK Matrix Searching[Aggarwal et-al 87] .

The **t** column maxima of a Totally Monotone array can be computed in O(**t**) time, by querying only O(**t**) elements.

Accessing a Prefix Block in Constant time.

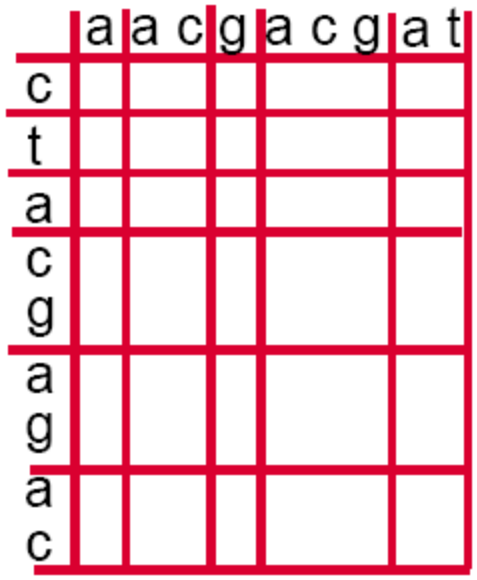


Another technique to Align Sequences in Subquadratic Time?

- For limited edit scoring schemes, such as LCS, use "*Four-Russians" Speedup*

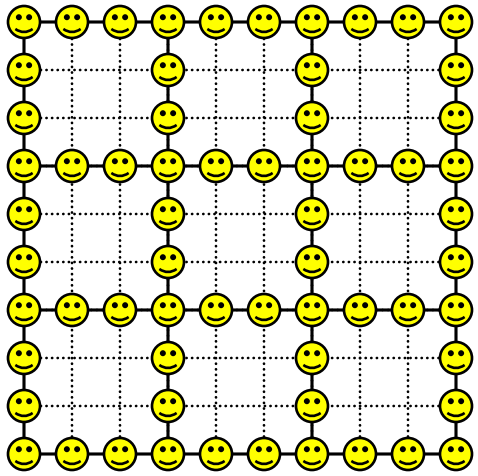
How Many Points Of Interest?

LZ-78 compression



O(h n / log n) rows of n vertices +
O(h n / log n) columns of n vertices

blocks of size t



How many points of interest? $O(n^2/t)$

n/ t rows with n vertices each

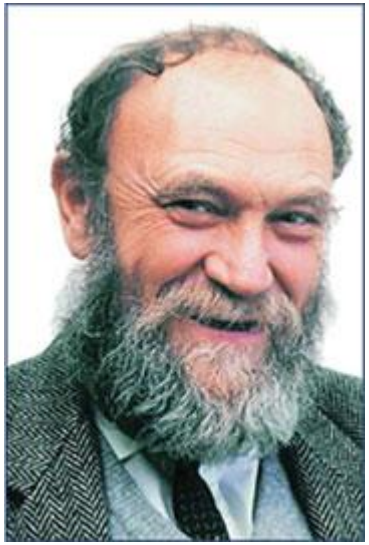
n/ t columns with n vertices each

The "*Four-Russians" technique for speeding up for dynamic programming*

Dan Gusfield: The idea, comes from a paper by four authors … concerning boolean matrix multiplication.

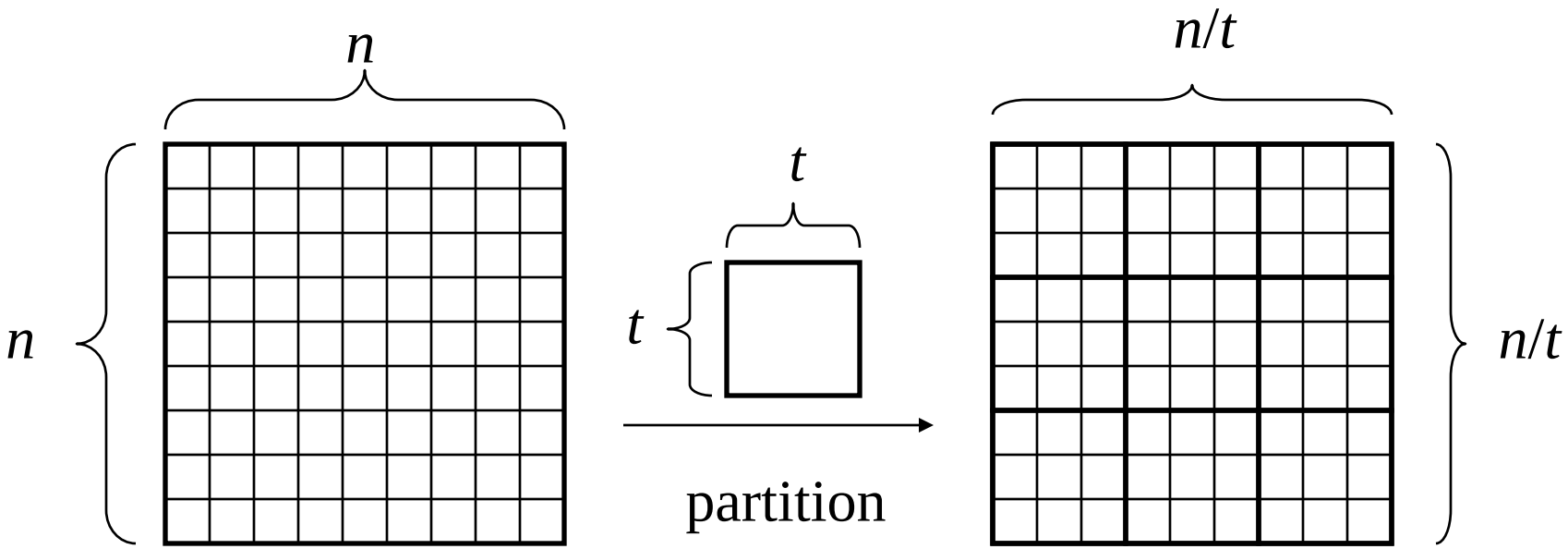
The general idea taken from this paper has come to be known in the West as The Four-Russians technique, even though only one of the authors is Russian.

Arlazarov, Dinic, Kronrod and Faradzev



Masek & Paterson applied the "Four Russians" to the string edit problem

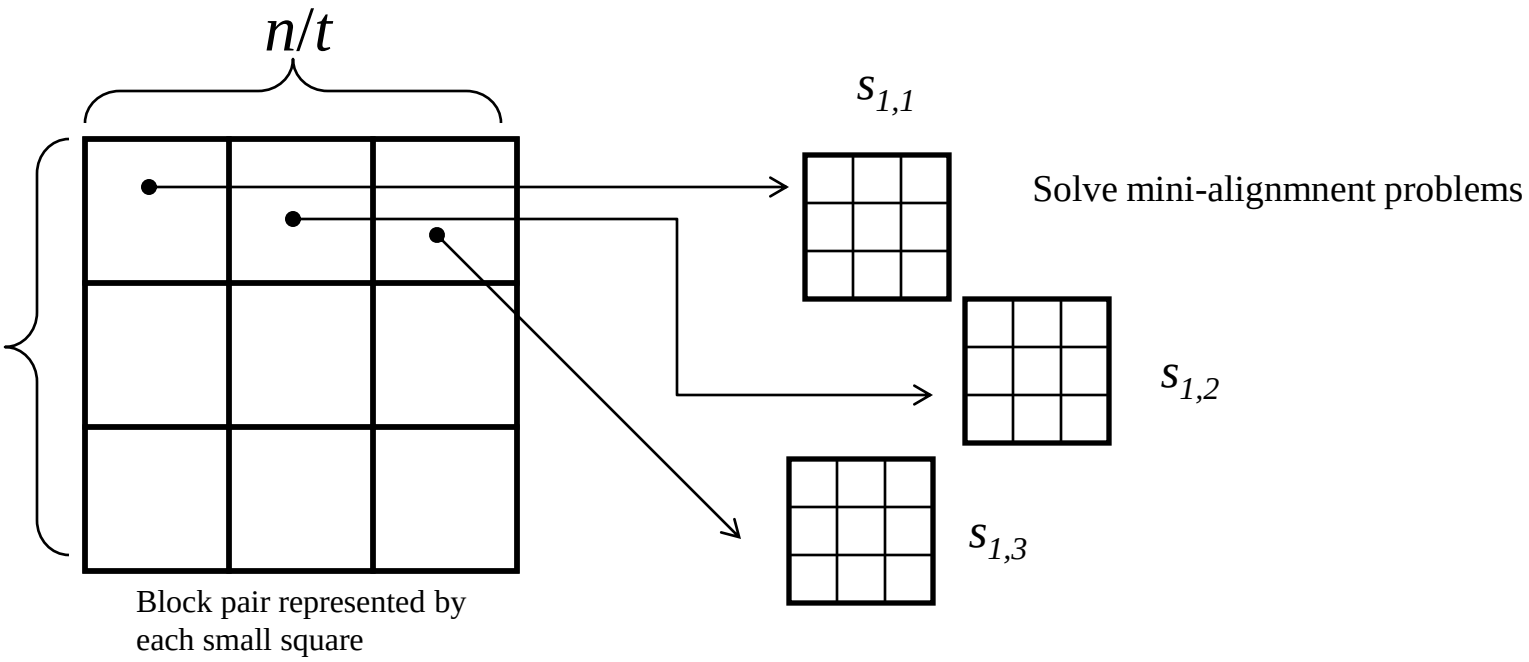
Partitioning Alignment Grid into Blocks of equal size t



Block Alignment Problem

- Goal: Find the longest block path through an edit graph
- Input: Two sequences, ***u*** and ***v*** partitioned into blocks of size *t*. This is equivalent to an *n* x *n* edit graph partitioned into *t* x *t* subgrids
- Output: The block alignment of ***u*** and ***v*** with the maximum score (longest block path through the edit graph)

Stage 1: compute the mini-alignments



How may blocks?

$(n/t)*(n/t) = (n^2/t^2)$

Stage 2: dynamic programming

- Let $s_{i,j}$ denote the optimal block alignment score between the first *i* blocks of ***u*** and first *j* blocks of ***v***

$$s_{i,j} = \max \begin{cases} s_{i-1,j} - \sigma_{\text{block}} \\ s_{i,j-1} - \sigma_{\text{block}} \\ s_{i-1,j-1} + \beta_{i,j} \end{cases}$$

σ_{block} is the penalty for inserting or deleting an entire block

$\beta_{i,j}$ is score of pair of blocks in row *i* and column *j*.

Block Alignment Runtime

- Indices *i*,*j* range from *0* to *n*/*t*

- Running time of algorithm is

$$O([n/t]*[n/t]) = O(n^2/t^2)$$

if we don't count the time to compute each $\beta_{i,j}$

Block Alignment Runtime (cont'd)

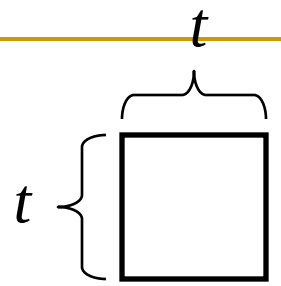
- Computing all $\beta_{i,j}$ requires solving

  $(n/t)*(n/t) = n^2/t^2$ mini block alignments,

  each of size $(t*t) = t^2$
- So computing all $\beta_{i,j}$ takes time

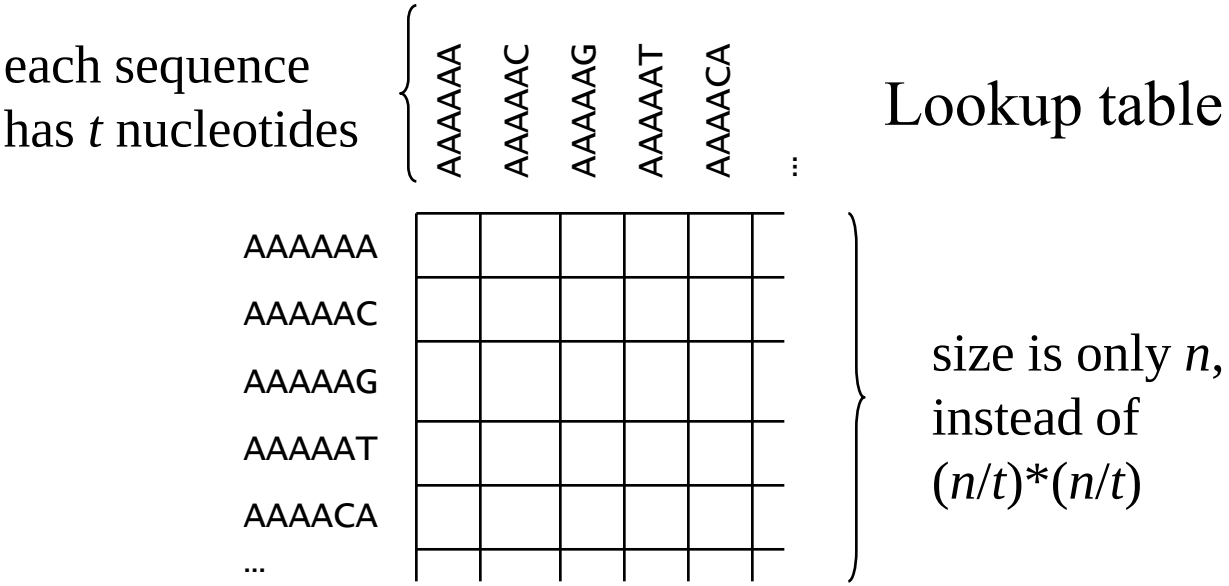
  $$O(n^2/t^2 * t^2) = O(n^2)$$
- This is the same as dynamic programming
- How do we speed this up?

Four Russians Technique



- Let $t = \log(n)$, where t is block size, n is sequence size.
- Instead of having $(n/t)*(n/t)) = n^2/t^2$ mini-alignments, construct $4^t \times 4^t$ mini-alignments for all pairs of strings of t nucleotides (huge size), and put in a lookup table.
- However, size of lookup table is not really that huge if t is small. Let $t = (\log n)/4$. Then $4^t \times 4^t = 4^{(\log n)/4} \times 4^{(\log n)/4} = 4^{(\log n)/2} = 2^{(\log n)} = n$

Look-up Table for Four Russians Technique



Let $t = (\log n)/4$. Then the number of entries
In the lookup table: $4^t \times 4^t = n$

Computing the scores for each entry in the table requires dynamic programming for a (log n) by (log n) alignment: $(\log n)^2$

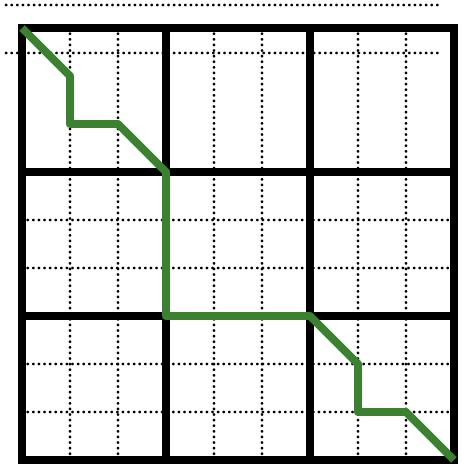
Altogether: $n\ (\log n)^2$

New Recurrence

- The new lookup table *Score* is indexed by a pair of *t*-nucleotide strings, so

$$s_{i,j} = \max \begin{cases} s_{i-1,j} - \sigma_{\text{block}} \\ s_{i,j-1} - \sigma_{\text{block}} \\ s_{i-1,j-1} + Score(i^{\text{th}} \text{ block of } \boldsymbol{v}, j^{\text{th}} \text{ block of } \boldsymbol{u}) \end{cases}$$

O(log*n*) time



Four Russians Speedup Runtime

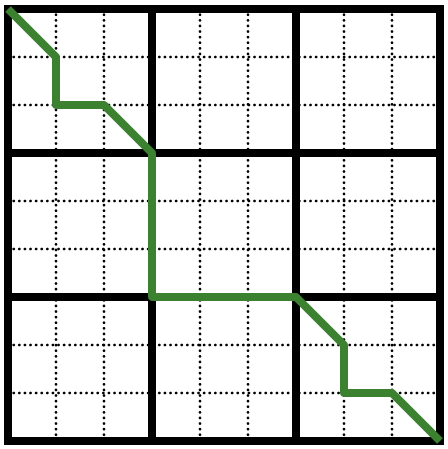
- Since computing the lookup table *Score* of size n takes $O(n (\log n)^2)$ time, the running time is mainly limited by the n^2/t^2 accesses to the lookup table
- Each access takes $O(\log n)$ time
- Overall running time: $O([n^2/t^2]*\log n)$
- Since $t = \log n$, substitute in:
- $O([n^2/\{\log n\}^2]*\log n) = O(n^2/\log n)$

So Far… (restriced to block alignment)

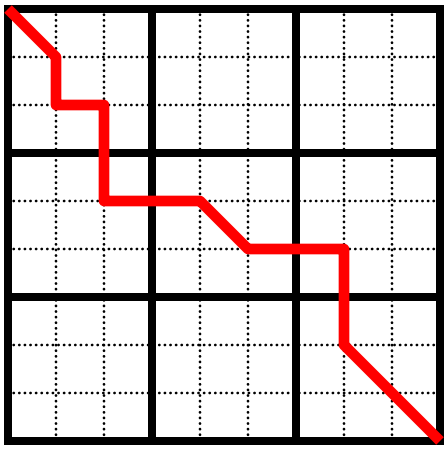
- We can divide up the grid into blocks and run dynamic programming only on the corners of these blocks
- In order to speed up the mini-alignment calculations to under n^2, we create a lookup table of size n, which consists of all scores for all t-nucleotide pairs
- Running time goes from quadratic, $O(n^2)$, to subquadratic: $O(n^2/\log n)$

Four Russians Speedup for LCS

- Unlike the block partitioned graph, the LCS path does not have to pass through the vertices of the blocks.



block alignment



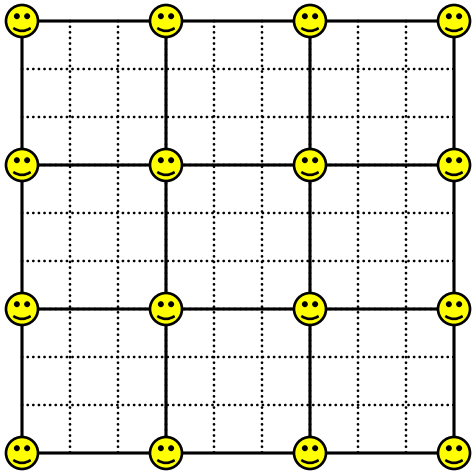
longest common subsequence

Block Alignment vs. LCS

- In block alignment, we only care about the corners of the blocks.
- In LCS, we care about all points on the edges of the blocks, because those are points that the path can traverse.
- Recall, each sequence is of length *n*, each block is of size *t*, so each sequence has (*n*/*t*) blocks.

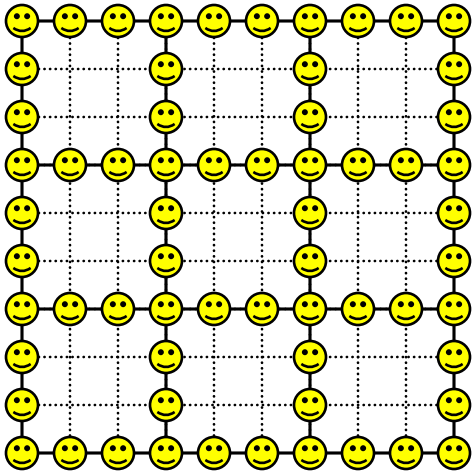
How Many Points Of Interest?

block alignment



How may blocks?
$(n/t)*(n/t) = (n^2/t^2)$

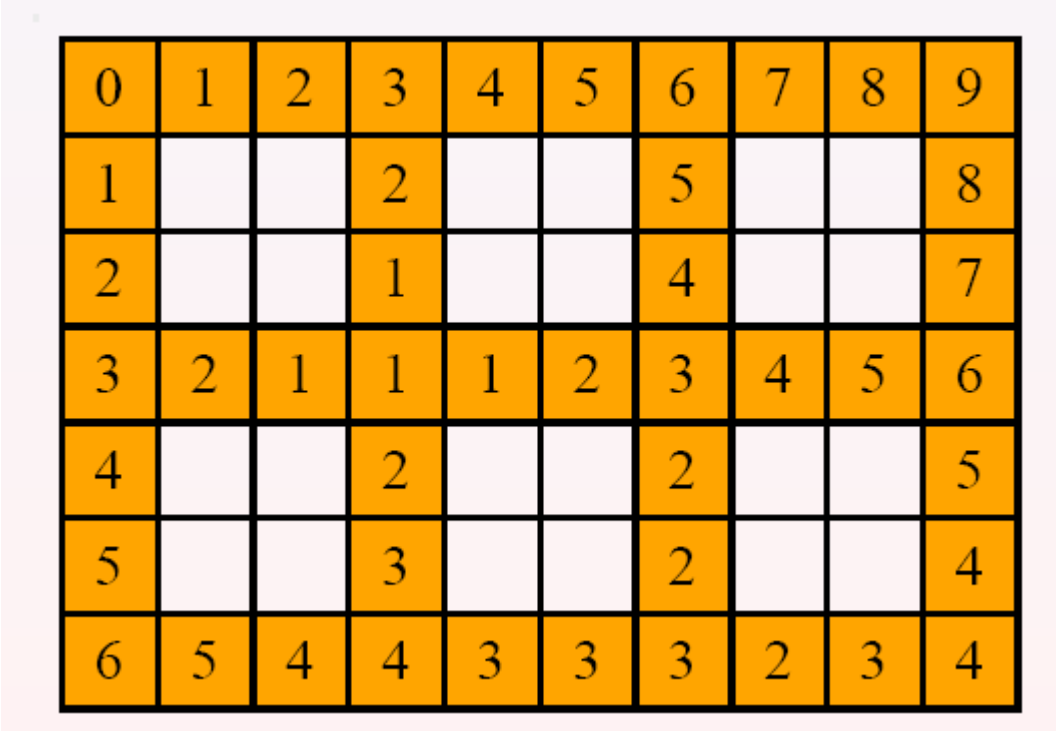
longest common subsequence



How many points of interest? $O(n^2/t)$

n/t rows with n vertices each

n/t columns with n vertices each


0 1 2 3 4 5 6 7 8 9
1 2 5 8
2 1 4 7
3 2 1 1 1 2 3 4 5 6
4 2 2 5
5 3 2 4
6 5 4 4 3 3 3 2 3 4

0	1	2	3	4	5	6	7	8	9
1									
2									
3									
4									
5									
6									

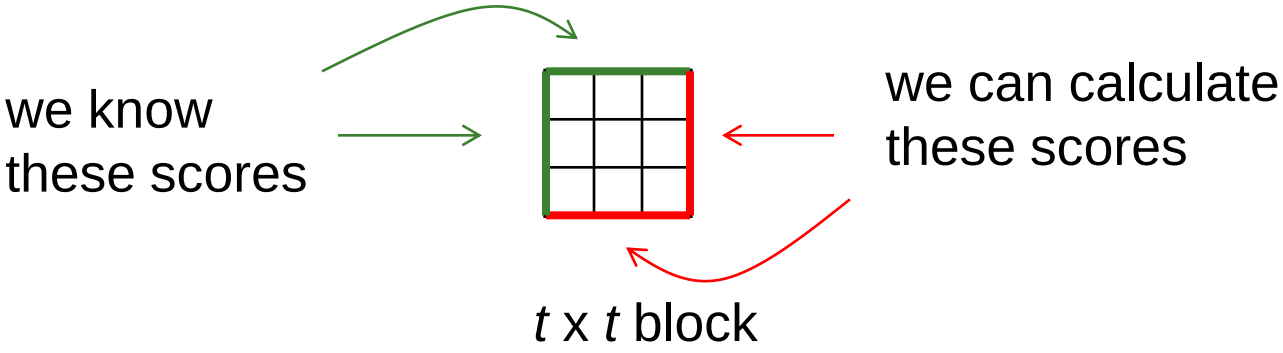
0	1	2	3	4	5	6	7	8	9
1			2						
2			1						
3	2	1	1						
4									
5									
6									

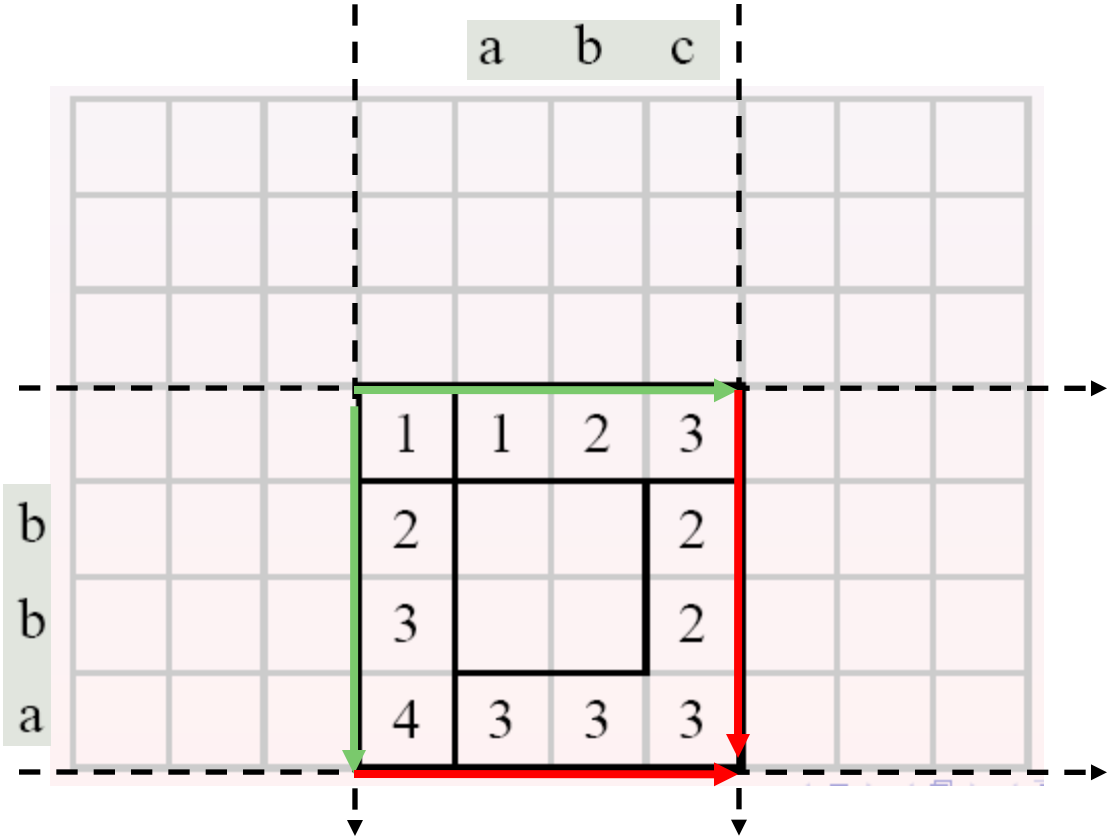
0	1	2	3	4	5	6	7	8	9
1			2						
2			1						
3	2	1	1						
4			2						
5			3						
6	5	4	4						

0	1	2	3	4	5	6	7	8	9
1			2			5			
2			1			4			
3	2	1	1	1	2	3			
4			2						
5			3						
6	5	4	4						

Traversing Blocks for LCS (cont'd)

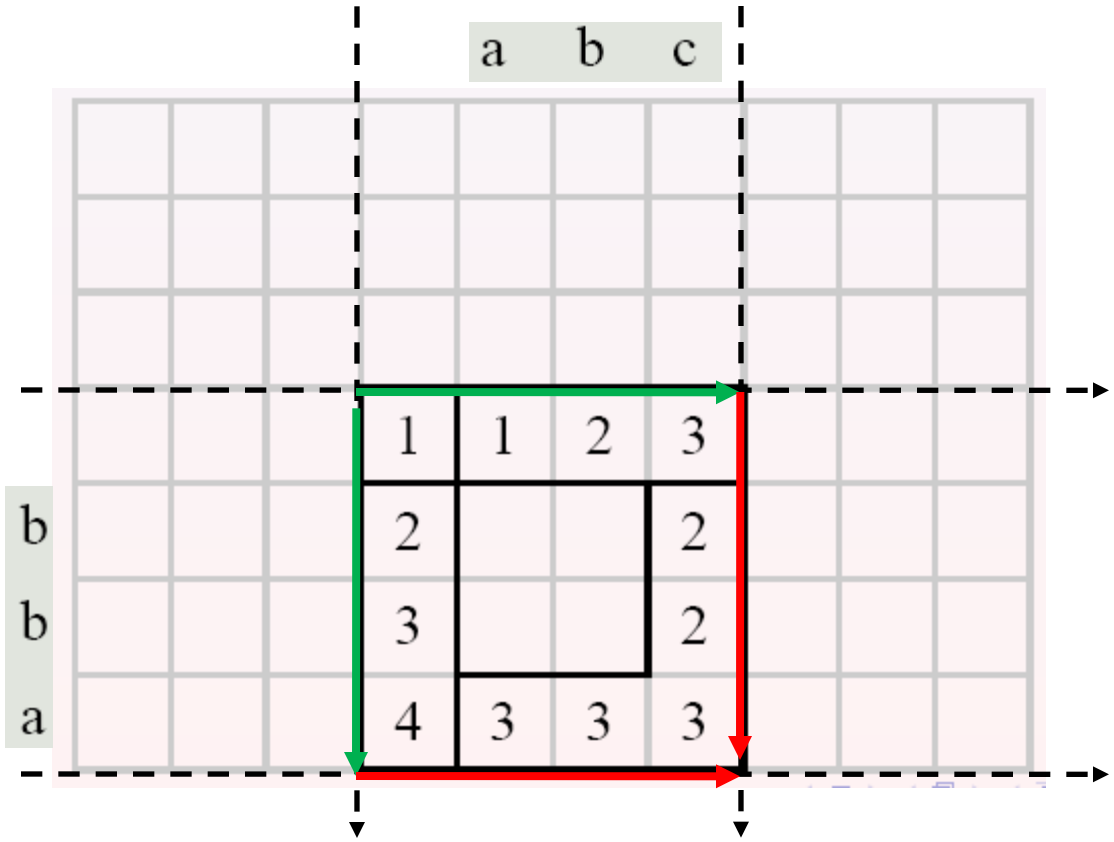
- If we used regular dynamic programming to compute the grid, it would take quadratic, $O(n^2)$ time, but we want to do better.
- Use the "Four Russians" Tabulation!





I = ((1, 2, 3), (2, 3, 4), abc, bba)

O = (4, 3, 3, 3, 2, 2, 3)



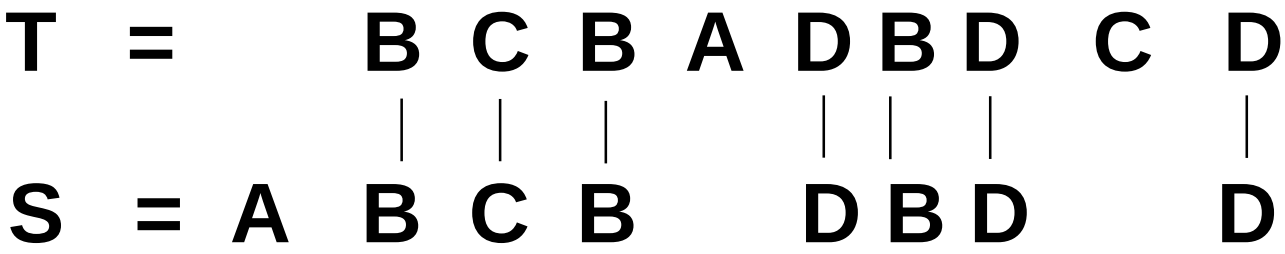
I = (1,1, 2, 3), (1, 2, 3, 4), abc, bba)

n^t * n^t * 4^t * 4^t = $(4n)^{2t}$

This will be a huge table!
we need another trick…

O = (4, 3, 3, 3, 2, 2, 3)

The Longest Common Subsequence



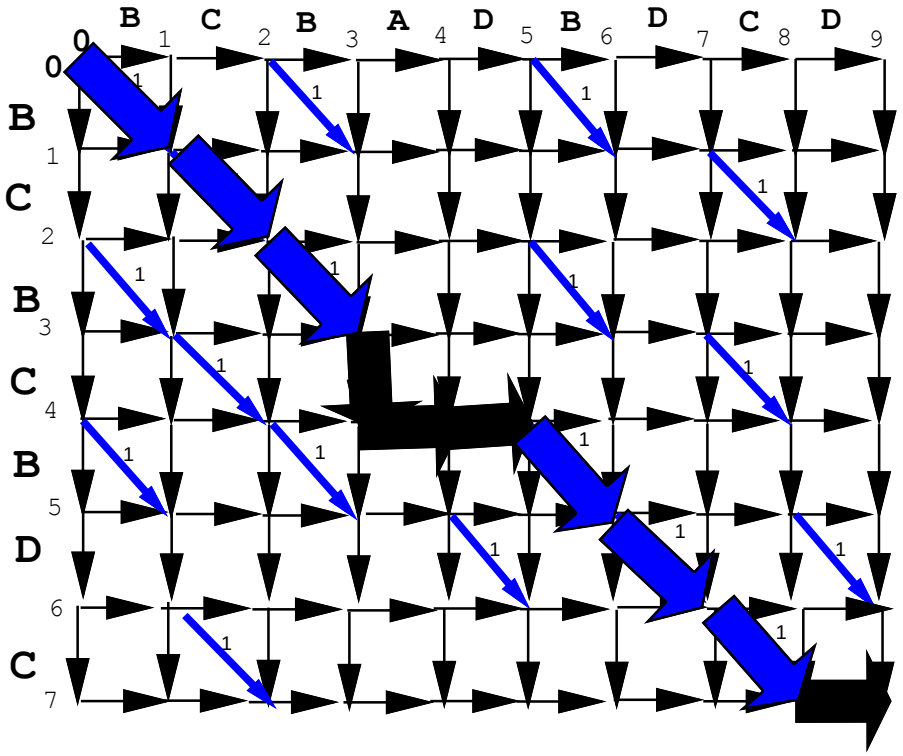
X = LCS(S,T) = BCBDBDD

L = |LCS(S,T)| = |BCBDBDD| = 7

The LCS Alignment Graph

|T| = n

|S| = m



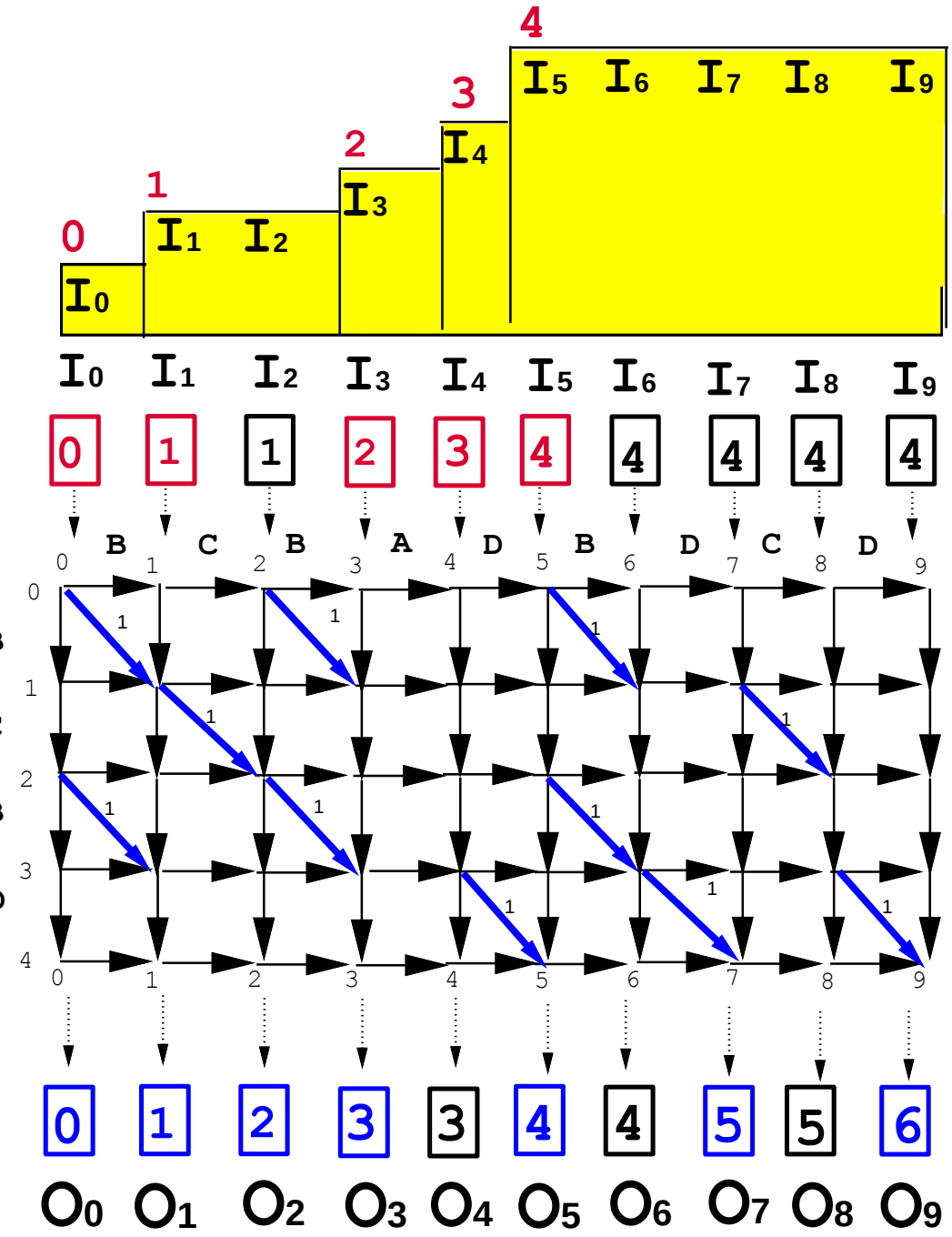
Diagonal blue arrows are match points {(i,j)| S[i] = T[j] Assigned a score of 1.

Horizontal black arrows are deletions from T. Assigned a score of 0.

Vertical black arrows are deletions from S Assigned a score of 0.

Classical Dynamic Programming: O(n m)

(Crochemore, Landau, Ziv-Ukelson O(n m/ log m))



Observation. Due to the unit-step properties of LCS, both **I** and **O** are monotonically non-decreasing series, and their values go up by unit steps. **[Hunt-Szymanski-77].**

Input row I

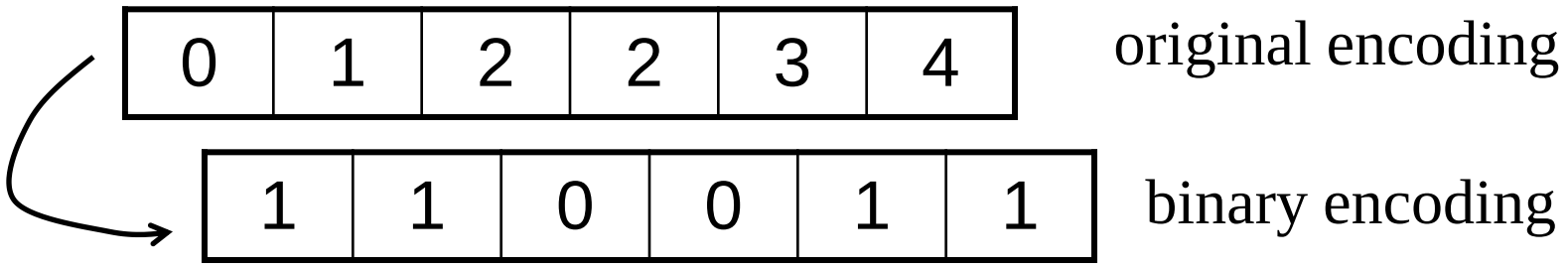
Output row O

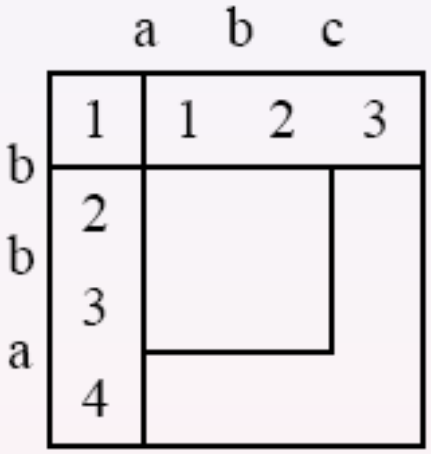
Reducing Table Size

- Alignment scores in LCS are monotonically increasing, and adjacent elements can't differ by more than 1
- Example: 0,1,2,2,3,4 is ok; 0,1,**2,4**,5,8, is not because 2 and 4 differ by more than 1 (and so do 5 and 8)
- Therefore, we only need to store quadruples whose scores are monotonically increasing and differ by at most 1

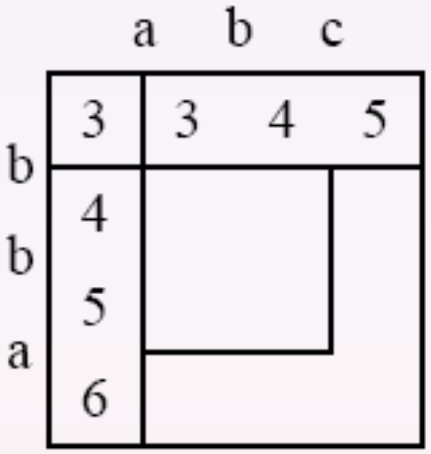
Efficient Encoding of Alignment Scores

- Instead of recording numbers that correspond to the index in the sequences *u* and *v*, we can use binary to encode the differences between the alignment scores





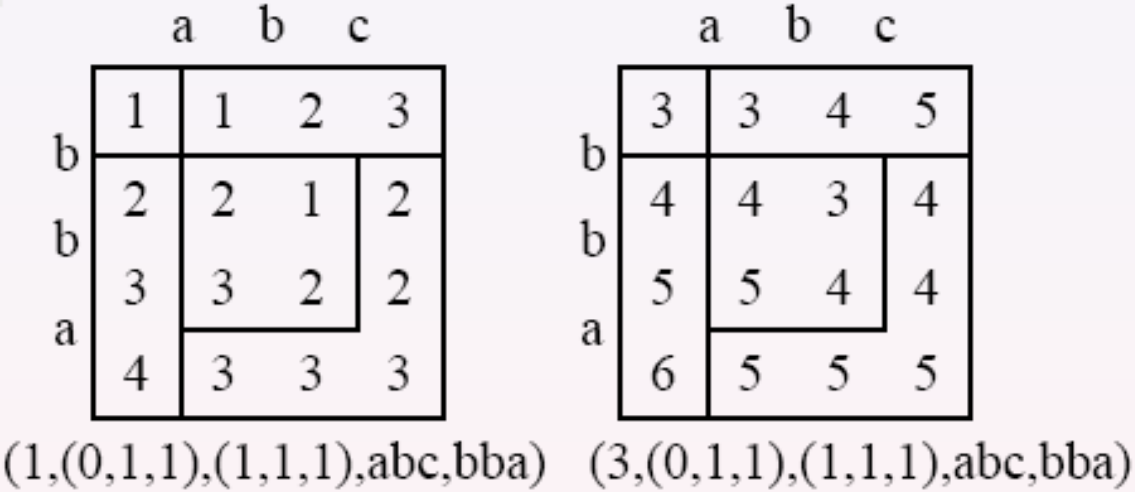
(1,(0,1,1),(1,1,1),abc,bba)



(3,(0,1,1),(1,1,1),abc,bba)

If we have two blocks with representations (a, b, c, s, t) and (a', b, c, s, t),then the blocks are "equivalent":

We need to precompute only (0,(0,1,1),(1,1,1), abc, bba)



If we have two blocks with representations (a, b, c, s, t) and (a', b, c, s, t),then the blocks are "equivalent": The value of each cell in the 2nd block is equal to the value of the corresponding cell in the 1st block plus $a' - a$.

Reducing Lookup Table Size

(1,(0,1,1),(1,1,1),abc,bba)

- 2^t possible "steps" (t = size of blocks)
- 4^t possible strings
  - Lookup table size is $(2^t * 2^t)*(4^t * 4^t) = 2^{6t}$
    - Computing each entry in the table: t^2
    - Total Table Construction Time: $2^{6t}\, t^2$
- Let $t = (\log n)/6$;
  - Table construction time is:
    - $2^{6((\log n)/6)}\, (\log n)^2 = n\, (\log n)^2$

Reducing Lookup Table Size

- Let $t = (\log n)/6$;

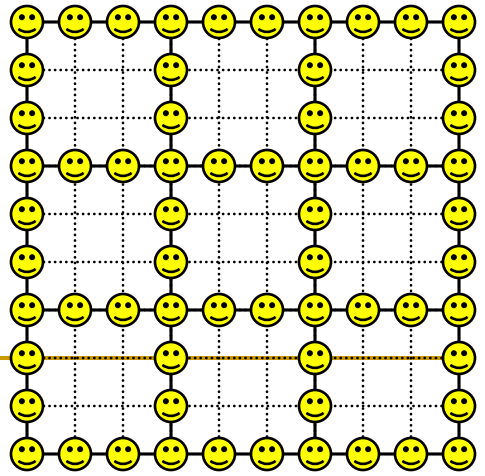
  Stage 1: Table construction time is:

$$2^{6((\log n)/6)} (\log n)^2 = n (\log n)^2$$

  Stage 2: alignment graph computation time is:

$$O([n^2/t^2]*t) = O([n^2/\{\log n\}^2]*\log n)$$

$$= O(n^2/\log n)$$



Summary

- We take advantage of the fact that for each block of $t = O(\log n)$, we can pre-compute all possible scores and store them in a lookup table of size n, *whose values can be computed in time* $O(n (\log n)^2)$.
- We used the Four Russian speedup to go from a quadratic running time for LCS to subquadratic running time: $O(n^2/\log n)$