CSE 421 Intro Algorithms Summer 2007

Sequence Alignment

Sequence Alignment

- What
- Why
- A Simple Algorithm
- Complexity Analysis
- A better Algorithm:
  "Dynamic Programming"

Sequence Similarity: What

G G A C C A

T A C T A A G

T C C A A T

Sequence Similarity: What

```
G G A C C A

T A C T A A G
|  :  |  :  |  |  :
T C C – A A T
```

Sequence Similarity: Why

- Most widely used comp. tools in biology
- New sequence always compared to sequence data bases

Similar sequences often have similar origin or function

- Selection operates on system level, but mutation occurs at the sequence level
- Recognizable similarity after $10^8 – 10^9$ yr

BLAST Demo

http://www.ncbi.nlm.nih.gov/blast/

Taxonomy Report

```
root ................................   64 hits   16 orgs
. Eukaryota .........................   62 hits   14 orgs [cellular organisms]
. . Fungi/Metazoa group .............   57 hits   11 orgs
. . . Bilateria .....................   38 hits    7 orgs [Metazoa; Eumetazoa]
. . . . Coelomata ...................   36 hits    6 orgs
. . . . . Tetrapoda .................   26 hits    5 orgs [;;; Vertebrata;;;; Sarcopterygii]
. . . . . . Eutheria ................   24 hits    4 orgs [Amniota; Mammalia; Theria]
. . . . . . . Homo sapiens ..........   20 hits    1 orgs [Primates;; Hominidae; Homo]
. . . . . . . Murinae ...............    3 hits    2 orgs [Rodentia; Sciurognathi; Muridae]
. . . . . . . . Rattus norvegicus ....    2 hits    1 orgs [Rattus]
. . . . . . . . Mus musculus ........    1 hits    1 orgs [Mus]
. . . . . . . Sus scrofa ............    1 hits    1 orgs [Cetartiodactyla; Suina; Suidae; Sus]
. . . . . . Xenopus laevis ..........    2 hits    1 orgs [Amphibia;;;;;; Xenopodinae; Xenopus]
. . . . . Drosophila melanogaster ....   10 hits    1 orgs [Protostomia;;;; Drosophila;;;]
. . . . Caenorhabditis elegans .......    2 hits    1 orgs [; Nematoda;;;;;; Caenorhabditis]
. . . Ascomycota ....................   19 hits    4 orgs [Fungi]
. . . . Schizosaccharomyces pombe ....   10 hits    1 orgs [;;;; Schizosaccharomyces]
. . . . Saccharomycetales ...........    9 hits    3 orgs [Saccharomycotina; Saccharomycetes]
. . . . . Saccharomyces .............    8 hits    2 orgs [Saccharomycetaceae]
. . . . . . Saccharomyces cerevisiae .    7 hits    1 orgs
. . . . . . Saccharomyces kluyveri ...    1 hits    1 orgs
. . . . . Candida albicans ..........    1 hits    1 orgs [mitosporic Saccharomycetales;]
. . Arabidopsis thaliana ............    2 hits    1 orgs [Viridiplantae; …Brassicaceae;]
. . Apicomplexa .....................    3 hits    2 orgs [Alveolata]
. . . Plasmodium falciparum .........    2 hits    1 orgs [Haemosporida; Plasmodium]
. . . Toxoplasma gondii .............    1 hits    1 orgs [Coccidia; Eimeriida; Sarcocystidae;]
. synthetic construct ...............    1 hits    1 orgs [other; artificial sequence]
. lymphocystis disease virus ........    1 hits    1 orgs [Viruses; dsDNA viruses, no RNA …]
```

Terminology

- *String*: ordered list of letters TATAAG
- *Prefix:* consecutive letters from front

  empty, T, TA, TAT, ...
- Suffix: … from end

  empty, G, AG, AAG, ...
- *Substring:* … from ends or middle

  empty, TAT, AA, ...
- *Subsequence:* ordered, nonconsecutive

  TT, AAA, TAG, ...

Sequence Alignment

```
a c b c d b          a c – – b c d b
 /    \   |            |     |   |
c a d b d            – c a d b – d –
```

Defn: An *alignment* of strings S, T is a pair of strings S’, T’ (with spaces) s.t.

(1) |S’| = |T’|, and (|S| = “length of S”)

(2) removing all spaces leaves S, T

Alignment Scoring

Mismatch = -1
Match = 2

```
a c b c d b        a  c  -  -  b  c  d  b
c a d b d          -  c  a  d  b  -  d  -
                   -1 2  -1 -1 2  -1 2  -1
                   Value = 3*2 + 5*(-1) = +1
```

- The *score* of aligning (characters or spaces) x & y is $\sigma(x,y)$.
- *Value* of an alignment $\sum_{i=1}^{|S'|} \sigma(S'[i], T'[i])$
- An *optimal alignment:* one of max value

Optimal Alignment: A Simple Algorithm

```
for all subseqs A of S, B of T s.t. |A| = |B| do
    align A[i] with B[i], 1 ≤ i ≤ |A|
    align all other chars to spaces
    compute its value
    retain the max
end
output the retained alignment
```

S = abcd   A = cd
T = wxyz   B = xz

```
-abc-d    a-bc-d
w--xyz    -w-xyz
```

Analysis

- Assume |S| = |T| = n
- Cost of evaluating one alignment: ≥ n
- How many alignments are there: $\geq \binom{2n}{n}$

  pick n chars of S,T together

  say k of them are in S

  match these k to the k *un*picked chars of T
- Total time: $\geq n \binom{2n}{n} > 2^{2n}, \text{ for } n > 3$
- E.g., for n = 20, time is > 2^{40} operations—bad!

Candidate for Dynamic Programming?

- Common Subproblems?
  - Plausible: probably re-considering alignments of various small substrings unless we're careful.
- Optimal Substructure?
  - Plausible: left and right "halves" of an optimal alignment probably should be optimally aligned (though they obviously interact a bit at the interface).
- (Both made rigorous below.)

Optimal Substructure
(In More Detail)

- Optimal alignment ends in 1 of 3 ways:
  - last chars of S & T aligned with each other
  - last char of S aligned with space in T
  - last char of T aligned with space in S
  - (never align space with space; $\sigma(-, -) < 0$)
- In each case, the rest of S & T should be optimally aligned to each other

Optimal Alignment in $O(n^2)$ via “Dynamic Programming”

- Input: S, T, |S| = n, |T| = m
- Output: value of optimal alignment

Easier to solve a “harder” problem:

V(i,j) = value of optimal alignment of S[1], …, S[i] with T[1], …, T[j] for all $0 \le i \le n$, $0 \le j \le m$.

Base Cases

- V(i,0): first i chars of S all match spaces

$$V(i,0) = \sum_{k=1}^{i} \sigma(S[k],-)$$

- V(0,j): first j chars of T all match spaces

$$V(0,j) = \sum_{k=1}^{j} \sigma(-,T[k])$$

General Case

Opt align of S[1], …, S[i] vs T[1], …, T[j]:

$$\begin{bmatrix} \sim\sim\sim\sim & S[i] \\ \sim\sim\sim\sim & T[j] \end{bmatrix}, \quad \begin{bmatrix} \sim\sim\sim\sim & S[i] \\ \sim\sim\sim\sim & - \end{bmatrix}, \text{ or } \begin{bmatrix} \sim\sim\sim\sim & - \\ \sim\sim\sim\sim & T[j] \end{bmatrix}$$

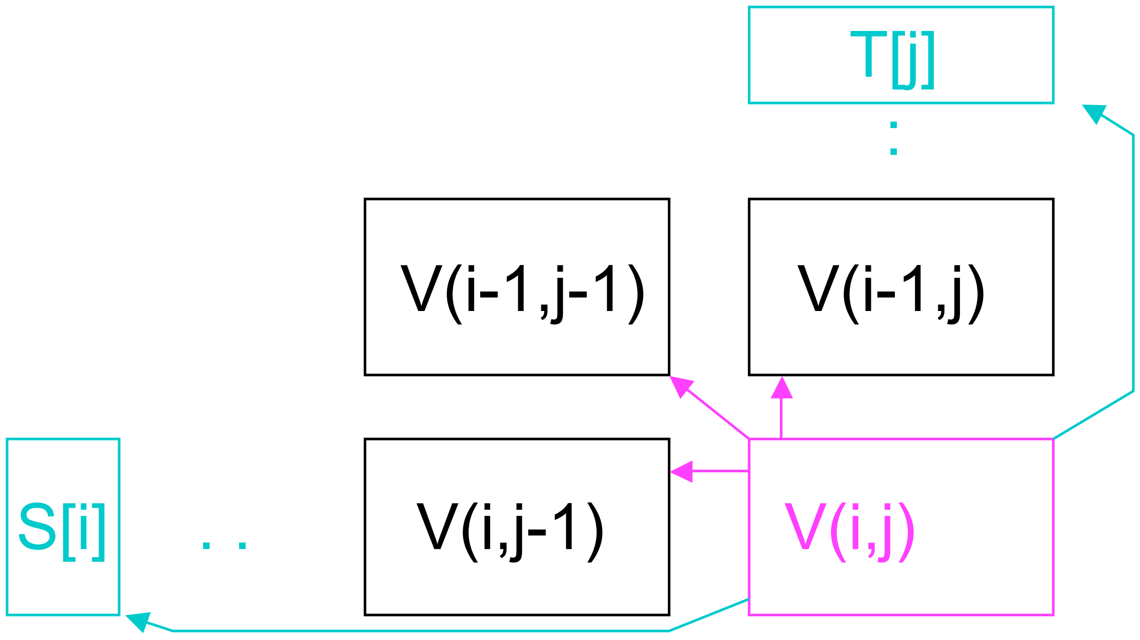
Opt align of $S_1 \ldots S_{i-1}$ & $T_1 \ldots T_{j-1}$

$$V(i,j) = \max \begin{Bmatrix} V(i\text{-}1,j\text{-}1) + \sigma(S[i],T[j]) \\ V(i\text{-}1,j) + \sigma(S[i], -) \\ V(i,j\text{-}1) + \sigma(-, T[j]) \end{Bmatrix},$$

for all $1 \le i \le n,\ 1 \le j \le m.$

Calculating One Entry

$$V(i,j) = \max \begin{cases} V(i\text{-}1,j\text{-}1) + \sigma(S[i],T[j]) \\ V(i\text{-}1,j) \quad + \sigma(S[i],\ -\ ) \\ V(i,j\text{-}1) \quad + \sigma(\ -\ ,\ T[j]) \end{cases}$$



Example

Mismatch = -1
Match = 2

	j	0	1	2	3	4	5
i			c	a	d	b	d
0		0	-1	-2	-3	-4	-5
1	a	-1	-1	1			
2	c	-2	1				
3	b	-3					
4	c	-4					
5	d	-5					
6	b	-6					$\boxed{}$

←T

↑
S

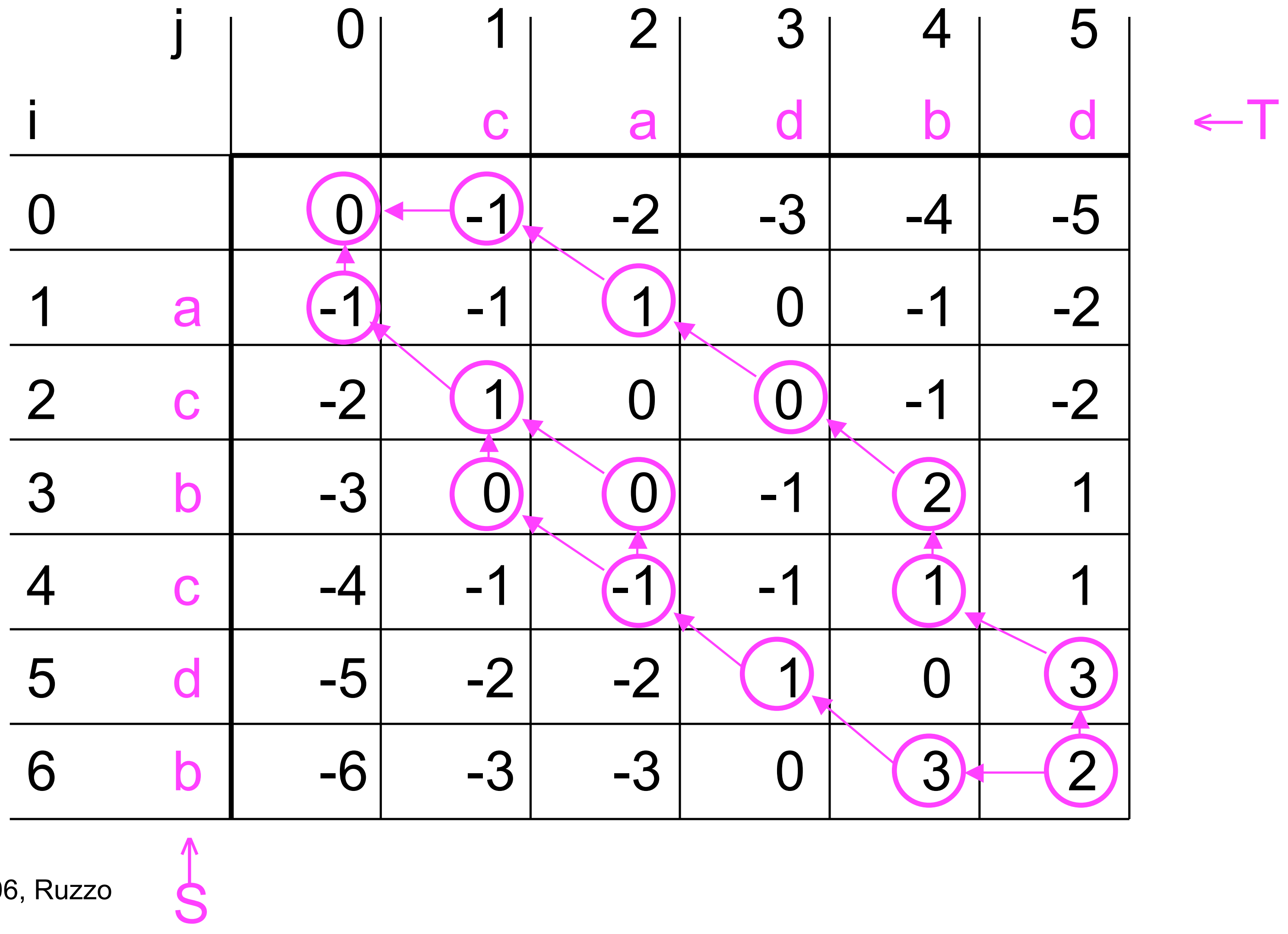
Time =
O(mn)

Example

Mismatch = -1
Match = 2

	j	0	1	2	3	4	5	
i			c	a	d	b	d	←T
0		0	-1	-2	-3	-4	-5	
1	a	-1	-1	1	0	-1	-2	
2	c	-2	1	0	0	-1	-2	
3	b	-3	0	0	-1	2	1	
4	c	-4	-1	-1	-1	1	1	
5	d	-5	-2	-2	1	0	3	
6	b	-6	-3	-3	0	3	↑2	
	↑S							

Finding Alignments: Trace Back



j		0	1	2	3	4	5
i			c	a	d	b	d
0		0	-1	-2	-3	-4	-5
1	a	-1	-1	1	0	-1	-2
2	c	-2	1	0	0	-1	-2
3	b	-3	0	0	-1	2	1
4	c	-4	-1	-1	-1	1	1
5	d	-5	-2	-2	1	0	3
6	b	-6	-3	-3	0	3	2

←T

↑
S

Complexity Notes

- Time = O(mn), (value and alignment)
- Space = O(mn)
- Easy to get value in Time = O(mn) and Space = O(min(m,n))
- Possible to get value *and alignment* in Time = O(mn) and Space = O(min(m,n)) but tricky.

Sequence Alignment

Part II

Local alignments & gaps

Variations

- Local Alignment
  - Preceding gives *global* alignment, i.e. full length of both strings;
  - Might well miss strong similarity of part of strings amidst dissimilar flanks
- Gap Penalties
  - 10 adjacent spaces cost 10 x one space?
- Many others

Local Alignment:Motivations

- “Interesting” (evolutionarily conserved, functionally related) segments may be a small part of the whole
  - “Active site” of a protein
  - Scattered genes or exons amidst “junk”, e.g. retroviral insertions, large deletions
  - Don’t have whole sequence
- Global alignment might miss them if flanking junk outweighs similar regions

Local Alignment

Optimal *local alignment* of strings S & T: Find substrings A of S and B of T having max value global alignment

S = abcxdex	A = c x d e	
T = xxxcde	B = c - d e	value = 5

The “Obvious” Local Alignment Algorithm

```
for all substrings A of S and B of T
    Align A & B via dynamic programming
    Retain pair with max value
end ;
Output the retained pair
```

Time: $O(n^2)$ choices for A, $O(m^2)$ for B, $O(nm)$ for DP, so $O(n^3m^3)$ total.

[Best possible? Lots of redundant work…]

Local Alignment in O(nm) via Dynamic Programming

- Input: S, T, |S| = n, |T| = m
- Output: value of optimal local alignment

Better to solve a "harder" problem
for all $0 \le i \le n$, $0 \le j \le m$:

  V(i,j) = max value of opt (global)
    alignment of a suffix of S[1], …, S[i]
    with a suffix of T[1], …, T[j]

  Report best i,j

Base Cases

- Assume $\sigma(x,-) \le 0$, $\sigma(-,x) \le 0$
- V(i,0): some suffix of first i chars of S; all match spaces in T; best suffix is empty

  $V(i,0) = 0$
- V(0,j): similar

  $V(0,j) = 0$

General Case Recurrences

Opt suffix align S[1], …, S[i] vs T[1], …, T[j]:

$$\begin{bmatrix} \boxed{\sim\sim\sim\sim} & S[i] \\ \sim\sim\sim\sim & T[j] \end{bmatrix}, \begin{bmatrix} \sim\sim\sim\sim & S[i] \\ \sim\sim\sim\sim & - \end{bmatrix}, \begin{bmatrix} \sim\sim\sim\sim & - \\ \sim\sim\sim\sim & T[j] \end{bmatrix}, \text{or} \begin{bmatrix} \ \\ \ \end{bmatrix}$$

Opt align of suffix of $S_1 \ldots S_{i-1}$ & $T_1 \ldots T_{j-1}$

$$V(i,j) = \max \begin{Bmatrix} V(i\text{-}1,j\text{-}1) + \sigma(S[i],T[j]) \\ V(i\text{-}1,j) \quad + \sigma(S[i], \ - \ ) \\ V(i,j\text{-}1) \quad + \sigma(- \ , \ T[j]) \\ 0 \end{Bmatrix},$$

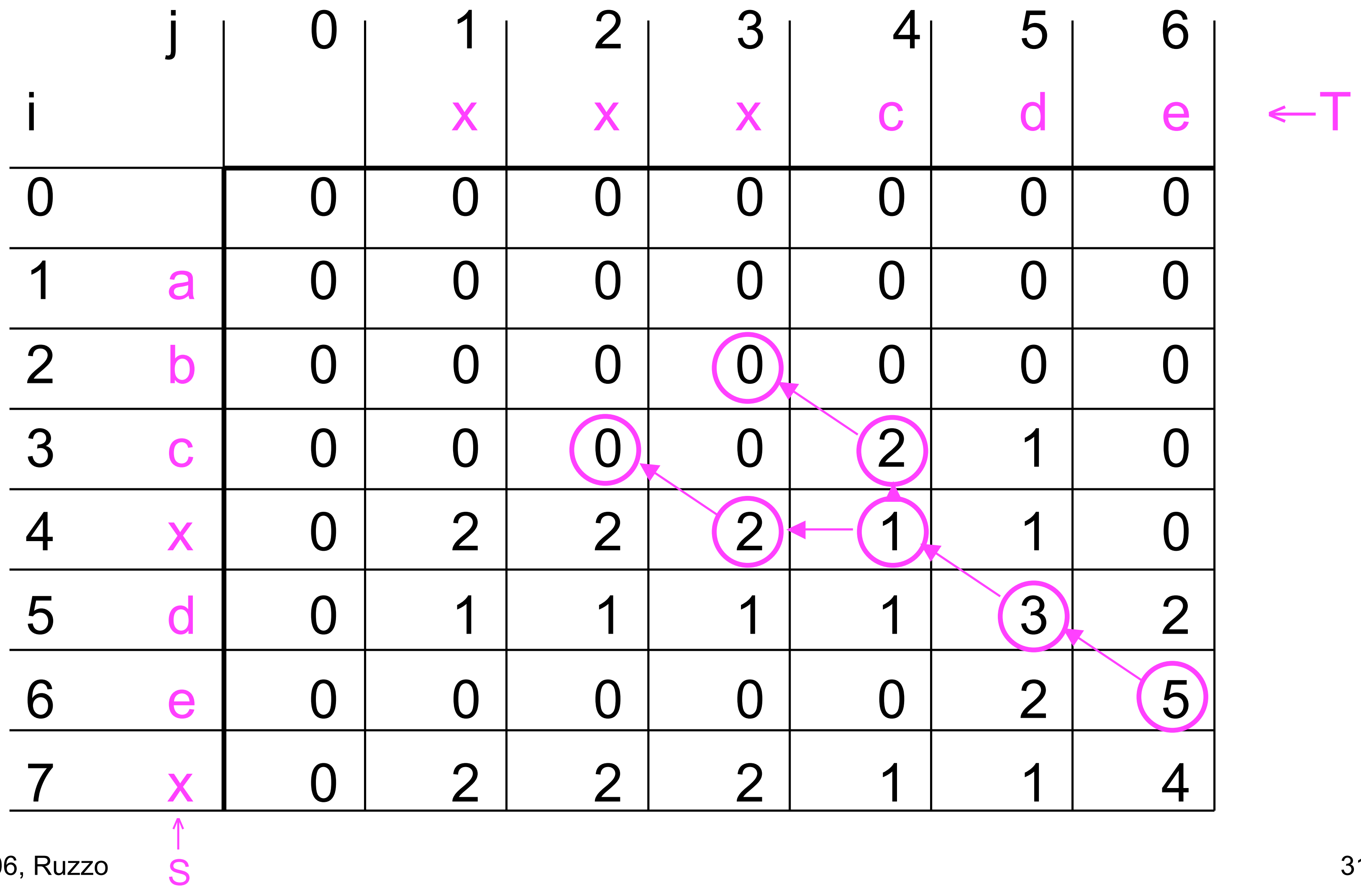
opt suffix alignment has: 2, 1, 1, 0 chars of S/T

$$\text{for all } 1 \le i \le n, \ 1 \le j \le m.$$

Scoring Local Alignments

j		0	1	2	3	4	5	6	
i			x	x	x	c	d	e	←T
0		0	0	0	0	0	0	0	
1	a	0							
2	b	0							
3	c	0							
4	x	0							
5	d	0							
6	e	0							
7	x	0							
	↑S								

Finding Local Alignments



	j	0	1	2	3	4	5	6	
i			x	x	x	c	d	e	←T
0		0	0	0	0	0	0	0	
1	a	0	0	0	0	0	0	0	
2	b	0	0	0	0	0	0	0	
3	c	0	0	0	0	2	1	0	
4	x	0	2	2	2	1	1	0	
5	d	0	1	1	1	1	3	2	
6	e	0	0	0	0	0	2	5	
7	x	0	2	2	2	1	1	4	
	↑ S								

Notes

- Time and Space = O(mn)
- Space O(min(m,n)) possible with time O(mn), but finding alignment is trickier

- Local alignment: “Smith-Waterman”
- Global alignment: “Needleman-Wunsch”

Alignment With Gap Penalties

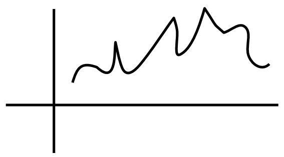
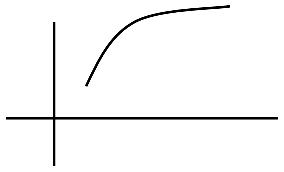
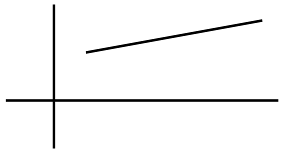
- *Gap:* maximal run of spaces in S' or T'

```
ab----c-d
a-ddddcbd          2 gaps in S', 1 in T'
```

- Motivations, e.g.:
  - mutation might insert/delete several or even many residues at once
  - matching cDNA (no introns) to genomic DNA (exons and introns)

Gap Penalties

- Score = f(gap length)
- Kinds, & best known alignment time

general		O(n^3)
convex		O(n^2log n)
affine		O(mn)

Global Alignment with Affine Gap Penalties

V(i,j) = value of opt alignment of
S[1], …, S[i] with T[1], …, T[j]

G(i,j) = …, s.t. last pair matches S[i] & T[j]

F(i,j) = …, s.t. last pair matches S[i] & –

E(i,j) = …, s.t. last pair matches – & T[j]

Time: O(mn) [calculate all, O(1) each]

Affine Gap Algorithm

Gap penalty = g + s*(gap length), g,s ≥ 0

$V(i,0) = E(i,0) = V(0,i) = F(0,i) = -g-i*s$

$$V(i,j) = \max(G(i,j), F(i,j), E(i,j))$$

$$G(i,j) = V(i-1,j-1) + \sigma(S[i],T[j])$$

$$F(i,j) = \max(\,\boxed{F(i-1,j)-s}\,,\ \boxed{V(i-1,j)-g-s}\,)$$

$$E(i,j) = \max(\,\underbrace{\boxed{E(i,j-1)-s}}_{\text{old gap}}\,,\ \underbrace{\boxed{V(i,j-1)-g-s}}_{\text{new gap}}\,)$$

Summary

- In bio, similar sequences usually => same function
  (even after eons of divergent evolution)
- Surprisingly simple scoring model works well in practice: score each position separately & add,
  (possibly w/ fancier gap model like affine)
- Simple "dynamic programming" algorithms find *optimal* alignments under these assumptions in poly time (product of sequence lengths)
- This, and heuristic approximations to it like BLAST, are workhorse tools in molecular biology
- Many applications outside bio, too. (Spelling correction, spam detection, unix "diff", CVS compression,…)