

# CSE 427 Comp Bio

## Sequence Alignment

# Sequence Alignment

What

Why

A Dynamic Programming Algorithm

# Sequence Alignment

Goal: position characters in two strings to “best” line up identical/similar ones with one another

We can do this via Dynamic Programming

# What is an alignment?

Compare two strings to see how “similar” they are  
E.g., maximize the # of identical chars that line up

But we'll see more  
subtle measures

ATGTTAT vs  
ATCGTAC

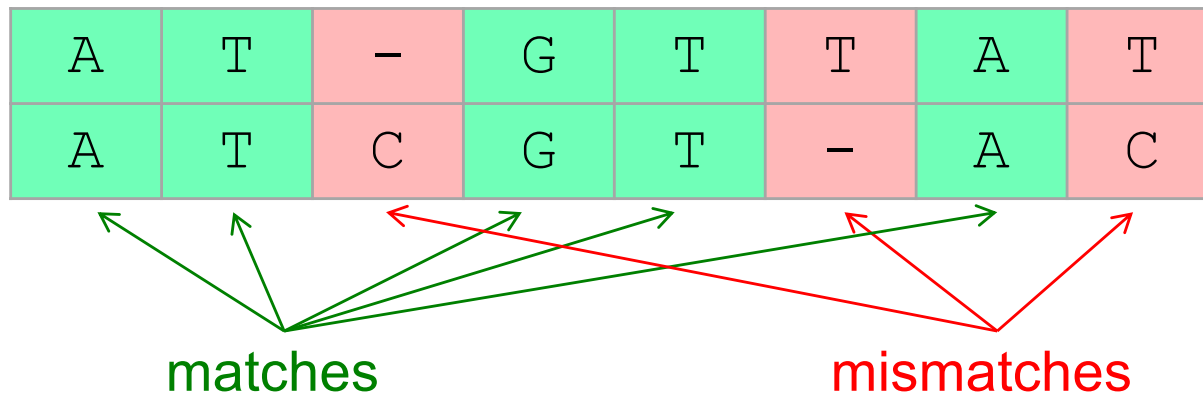
A	T	-	G	T	T	A	T
A	T	C	G	T	-	A	C

# What is an alignment?

Compare two strings to see how “similar” they are  
E.g., maximize the # of identical chars that line up

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# Sequence Alignment: Why

## Biology

Among most widely used comp. tools in biology

DNA sequencing & assembly

New sequence always compared to data bases

**Similar sequences often have similar origin and/or function**

Recognizable similarity after  $10^8 - 10^9$  yr

## Other

spell check/correct, diff, svn/git/..., plagiarism, ...

# BLAST Demo

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

click “protein blast”

[get seq from: http://www.uniprot.org/uniprot/P15172](http://www.uniprot.org/uniprot/P15172) i.e.:

```
>sp|P15172|MYOD1_HUMAN Myoblast determination protein 1 OS=Homo sapiens GN=MYOD1 PE=1 SV=3
MELLSPPLRDVDLTAPDGSLCSFATDDDFYDDPCFDSPDLRFFEDLDPRLMHVVGALLKPE
EHSHFPAAVHPAPGAREDEHVRAPSGHHQAGRCLLWACKACKRKTNNADRRKAATMRERR
RLSKVNEAFETLKRCTSSNPQRLPKVEILRNAIRYIEGLQALLRDQDAAPPAAAAFYA
PGPLPPGRGGEHYSGDSDASSPRSNCSGMMMDYSGPPSGARRRNCYEGAYYNEAPSEPRP
GKSAAVSSLDCLSSIVERISTESPAAPALLLADVPSSEPPRRQEAAAPSEGESSGDPTQS
PDAAPQCPAGANPNPIYQVL
```

in blast window, paste “P15172” (or fasta above) in “query” box

adjust “alg parameters” to get top 1000 hits (or more)

click “BLAST” button.

scrolling to bottom of hits list & click may download all alignments, (otherwise it seems to download only 4 or 5 more when you scroll to bottom)

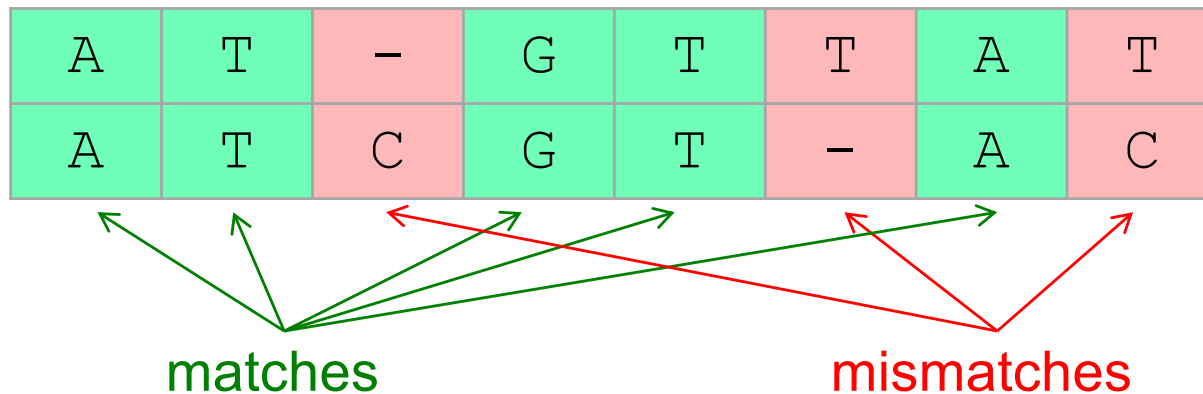
Also check out the “Graphic Summary”, “Alignments”, “Taxonomy” tabs, + “Distance tree of results”

# What is an alignment?

Compare two strings to see how “similar” they are  
E.g., maximize the # of identical chars that line up

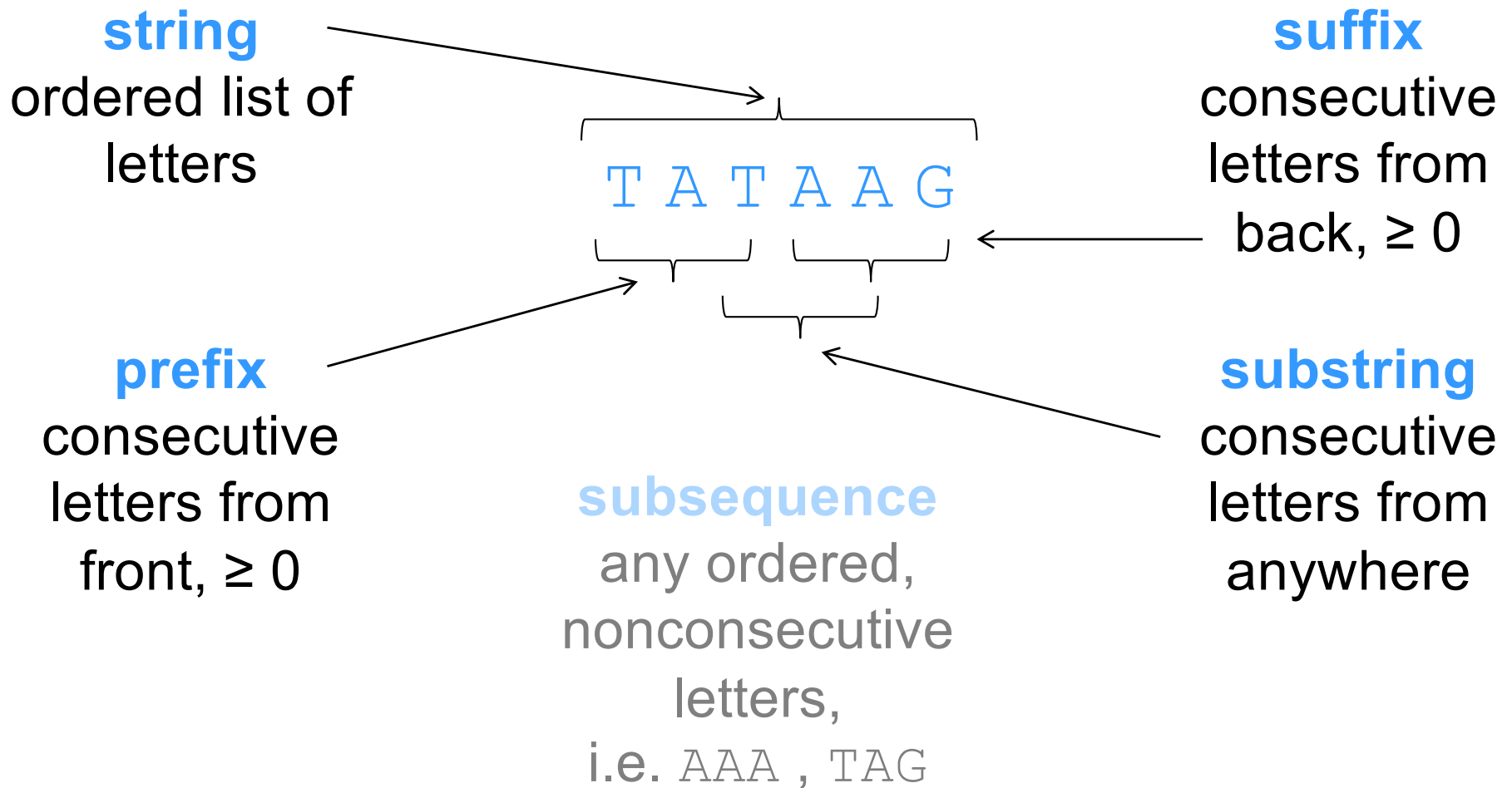
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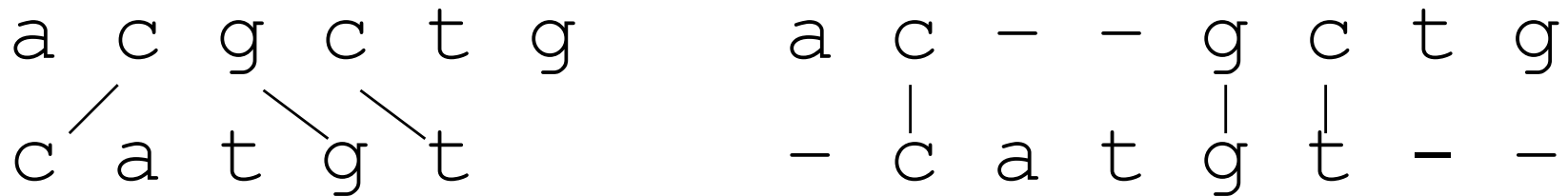




# Terminology



# Formal definition of an alignment



An **alignment** of strings  $S$ ,  $T$  is a pair of strings  $S'$ ,  $T'$  with dash characters “-” inserted, so that

1.  $|S'| = |T'|$ , and  $(|S| = \text{“length of } S\text{”})$
2. Removing dashes leaves  $S$ ,  $T$

*Consecutive* dashes are called “**a gap**.”

(NB: this is a defn for a general alignment, not necessarily optimal.)

# Scoring an arbitrary alignment

Define a score for *pairs* of aligned chars, e.g.

$$\sigma(x, y) = \begin{cases} \text{match} & 2 \\ \text{mismatch} & -1 \end{cases}$$

(Toy scores for examples in slides)

Apply that *per column*, then *add*.

a	c	-	-	g	c	t	g
-	c	a	t	g	t	-	-
-1	+2	-1	-1	+2	-1	-1	-1

Total Score = -2

# More Realistic Scores: BLOSUM 62

(the “ $\sigma$ ” scores)

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

# Optimal Alignment: A Simple Algorithm

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

$S = agct$	$A = ct$
$T = wxyz$	$B = xz$
$-agc-t$	$a-gc-t$
$w--xyz$	$-w-xyz$

# Analysis

Assume  $|S| = |T| = n$

Cost of evaluating one alignment:  $\geq n$

How many alignments are there:  $\geq \binom{2n}{n}$

pick  $n$  chars of  $S, T$  together

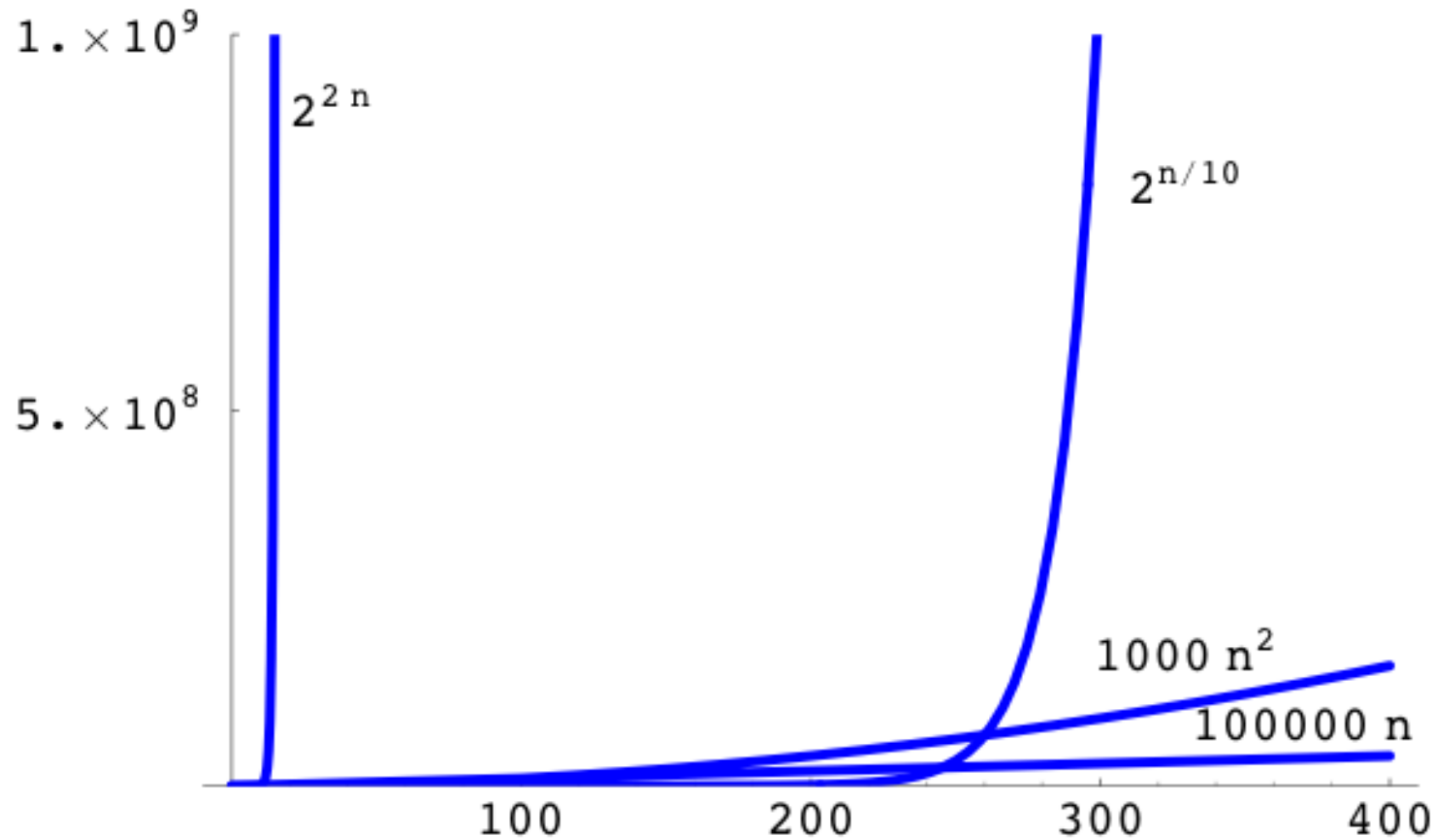
say  $k$  of them are in  $S$

match these  $k$  to the  $k$  *unpicked* chars of  $T$ , rest to -

Total time:  $\geq n \binom{2n}{n} > 2^{2n}$ , for  $n > 3$

E.g., for  $n = 20$ , time is  $> 2^{40}$  operations

# Polynomial vs Exponential Growth



# Fibonacci Numbers (recursion)

```
fibr(n) {  
  if (n <= 1) {  
    return n;  
  } else {  
    return fibr(n-1) + fibr(n-2);  
  }  
}
```

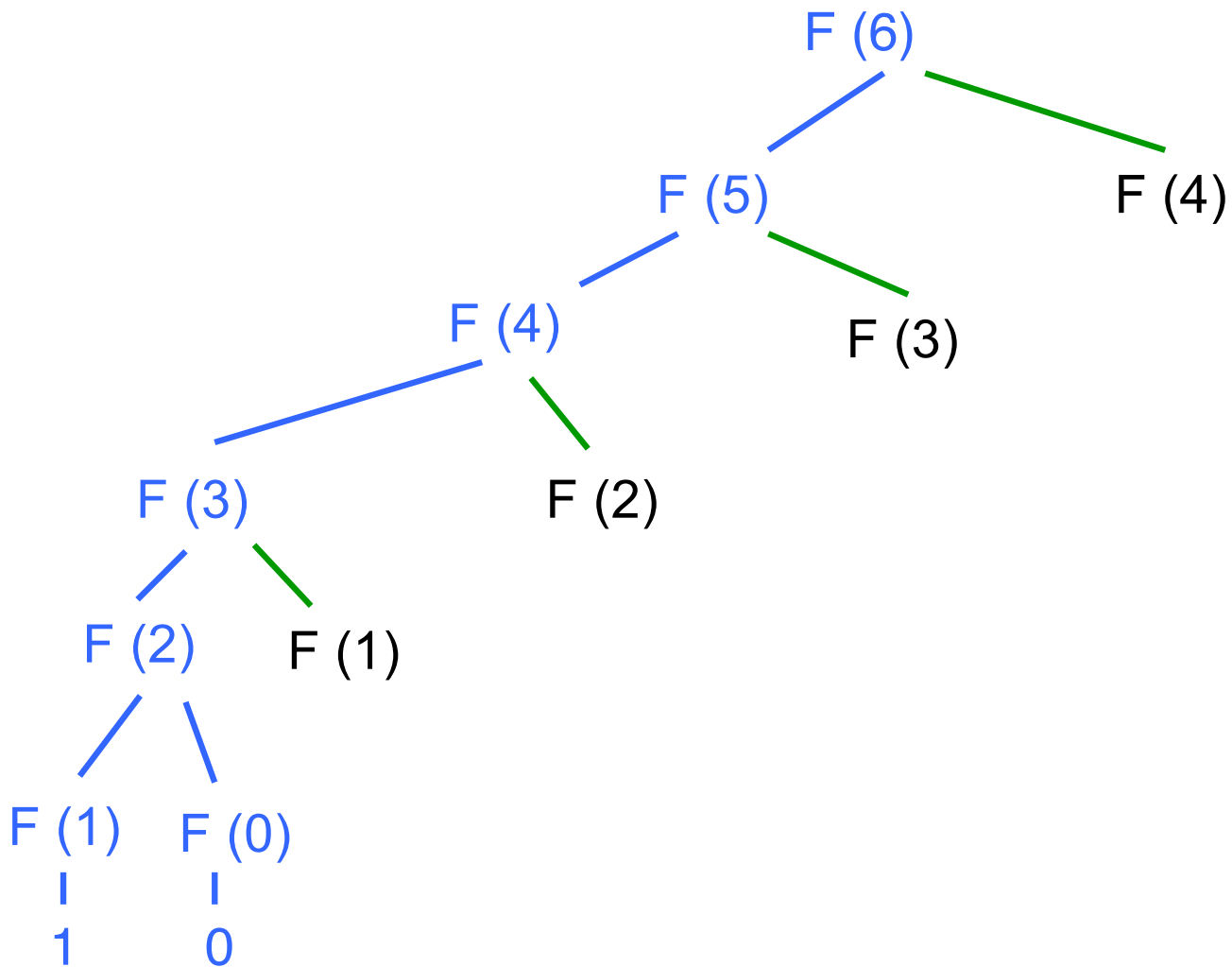
Simple recursion,  
but many  
repeated  
subproblems!!

⇒

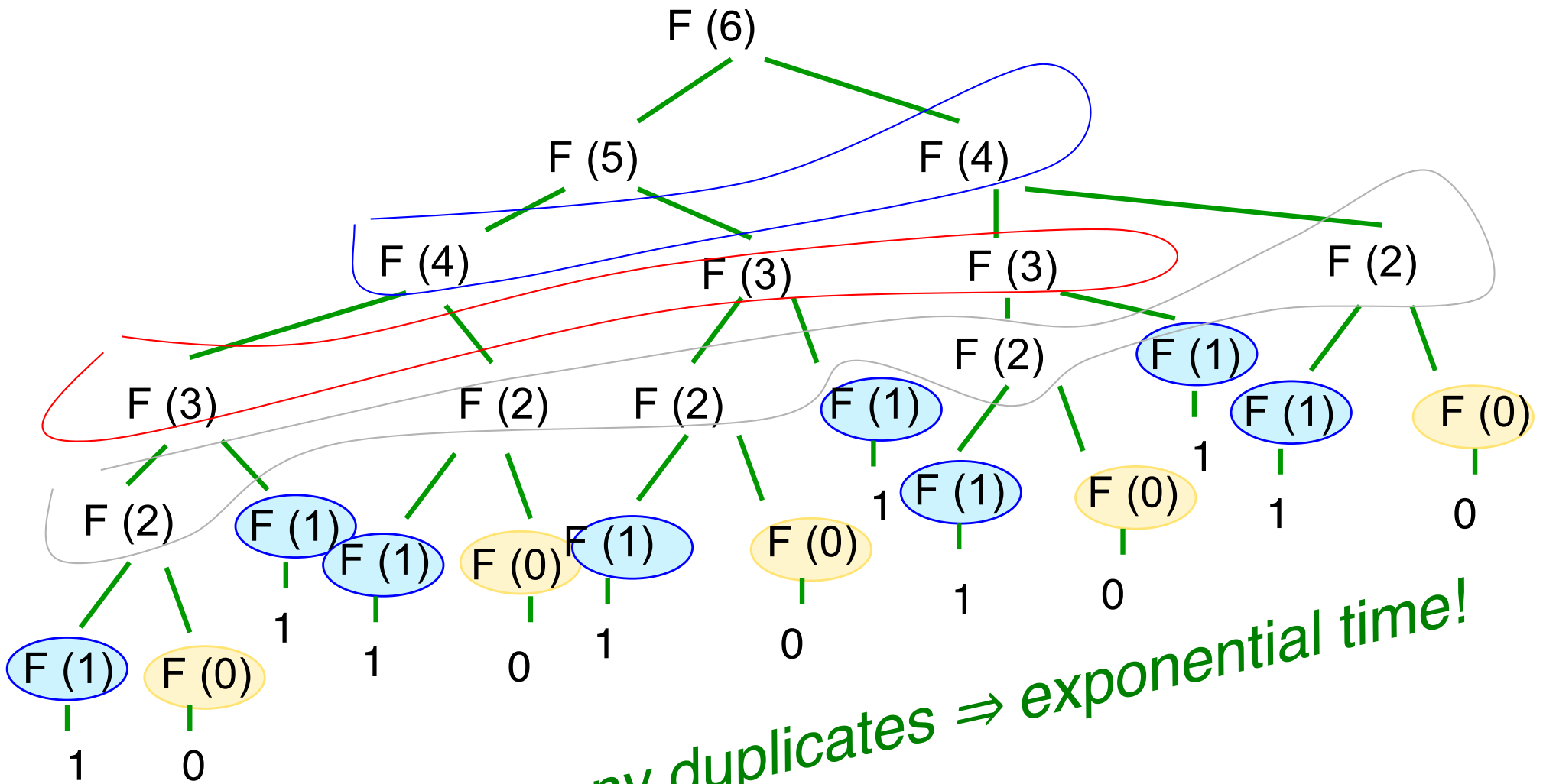
Time =  $\Omega(1.61^n)$



# Call tree - start



# Full call tree



many duplicates  $\Rightarrow$  exponential time!

# Fibonacci, II

## (dynamic programming)

```
int fibd[n];
fibd[0] = 0;
fibd[1] = 1;
for(i=2; i<=n; i++) {
    fibd[i] = fibd[i-1] + fibd[i-2];
}
return fibd[n];
```

Avoid repeated  
subproblems by  
tabulating their  
solutions

⇒

Time =  $O(n)$

(in this case)

# When can we use Dynamic Programming?

1. Can we decompose into **subproblems**?

E.g., can we align smaller substrings (say, prefix/suffix in this case), then combine them somehow?

2. Do we have **optimal substructure**?

I.e., is optimal solution to a subproblem *independent of context*? E.g., is appending two optimal alignments also optimal? Perhaps, but some changes at the interface might be needed?

# 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 dash in T

last char of T aligned with dash in S

(assume  $\sigma(-, -) < 0$ , so never align dash with dash)

*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  
 $S[1], \dots, S[i]$  with  $T[1], \dots, T[j]$   
for **all**  $0 \leq i \leq n, 0 \leq j \leq m$ .

# Base Cases

$V(i,0)$ : first  $i$  chars of  $S$  all match dashes

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

$V(0,j)$ : first  $j$  chars of  $T$  all match dashes

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

# General Case

Opt align of  $S[1], \dots, S[i]$  vs  $T[1], \dots, T[j]$ :

$$\left[ \begin{array}{c} \sim\sim\sim\sim S[i] \\ \sim\sim\sim\sim T[j] \end{array} \right], \quad \left[ \begin{array}{c} \sim\sim\sim\sim S[i] \\ \sim\sim\sim\sim - \end{array} \right], \quad \text{or} \quad \left[ \begin{array}{c} \sim\sim\sim\sim - \\ \sim\sim\sim\sim T[j] \end{array} \right]$$

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

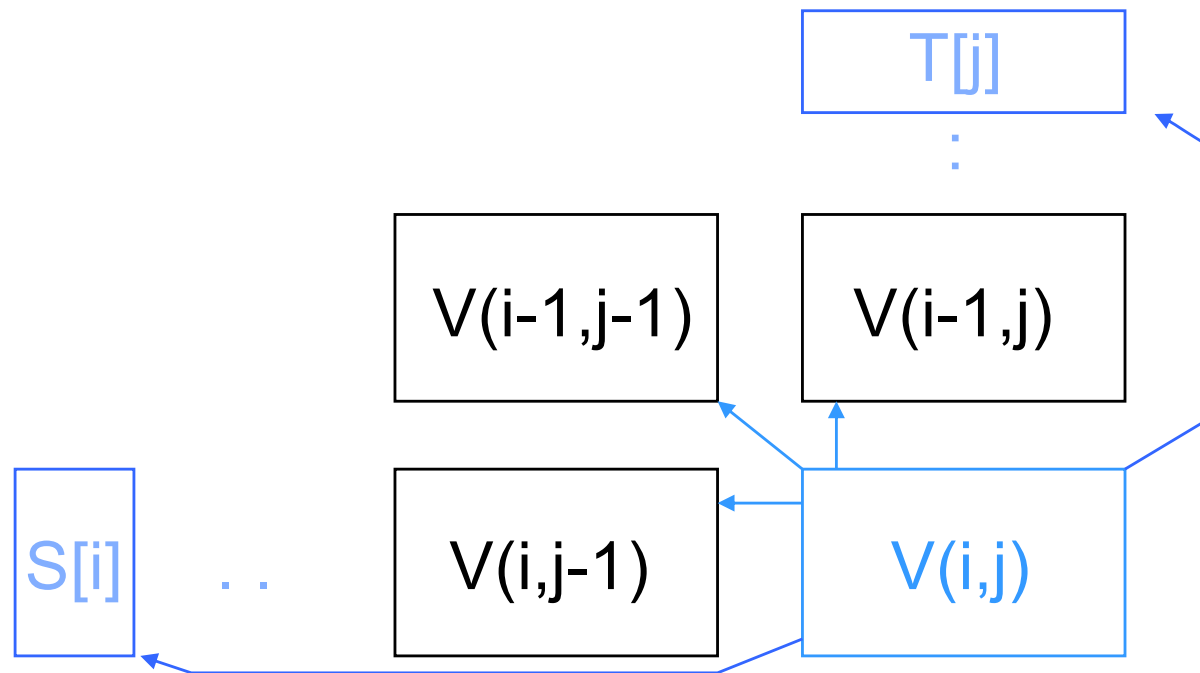
$$V(i,j) = \max \left\{ \begin{array}{l} V(i-1,j-1) + \sigma(S[i],T[j]) \\ V(i-1,j) + \sigma(S[i], -) \\ V(i,j-1) + \sigma(-, T[j]) \end{array} \right\},$$

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



# Calculating One Entry

$$V(i,j) = \max \left\{ \begin{array}{l} V(i-1,j-1) + \sigma(S[i], T[j]) \\ V(i-1,j) + \sigma(S[i], -) \\ V(i,j-1) + \sigma(-, T[j]) \end{array} \right\}$$



# Example

Mismatch = -1  
Match = 2

	j	0	1	2	3	4	5	
i			c	a	t	g	t	←T
0		0	-1	-2	-3	-4	-5	
1	a	-1						
2	c	-2						
3	g	-3						
4	c	-4						
5	t	-5						
6	g	-6						

↑S

c
-

 Score(c,-) = -1

Mismatch = -1  
Match = 2

# Example

	j	0	1	2	3	4	5
i			c	a	t	g	t
0		0	-1	-2	-3	-4	-5
1	a	-1					
2	c	-2					
3	g	-3					
4	c	-4					
5	t	-5					
6	g	-6					

←T

↑S

$\begin{matrix} - \\ a \end{matrix}$  Score(-,a) = -1

Mismatch = -1  
 Match = 2

# Example

	j	0	1	2	3	4	5
i			c	a	t	g	t
0		0	-1	-2	-3	-4	-5
1	a	-1					
2	c	-2					
3	g	-3					
4	c	-4					
5	t	-5					
6	g	-6					

← T

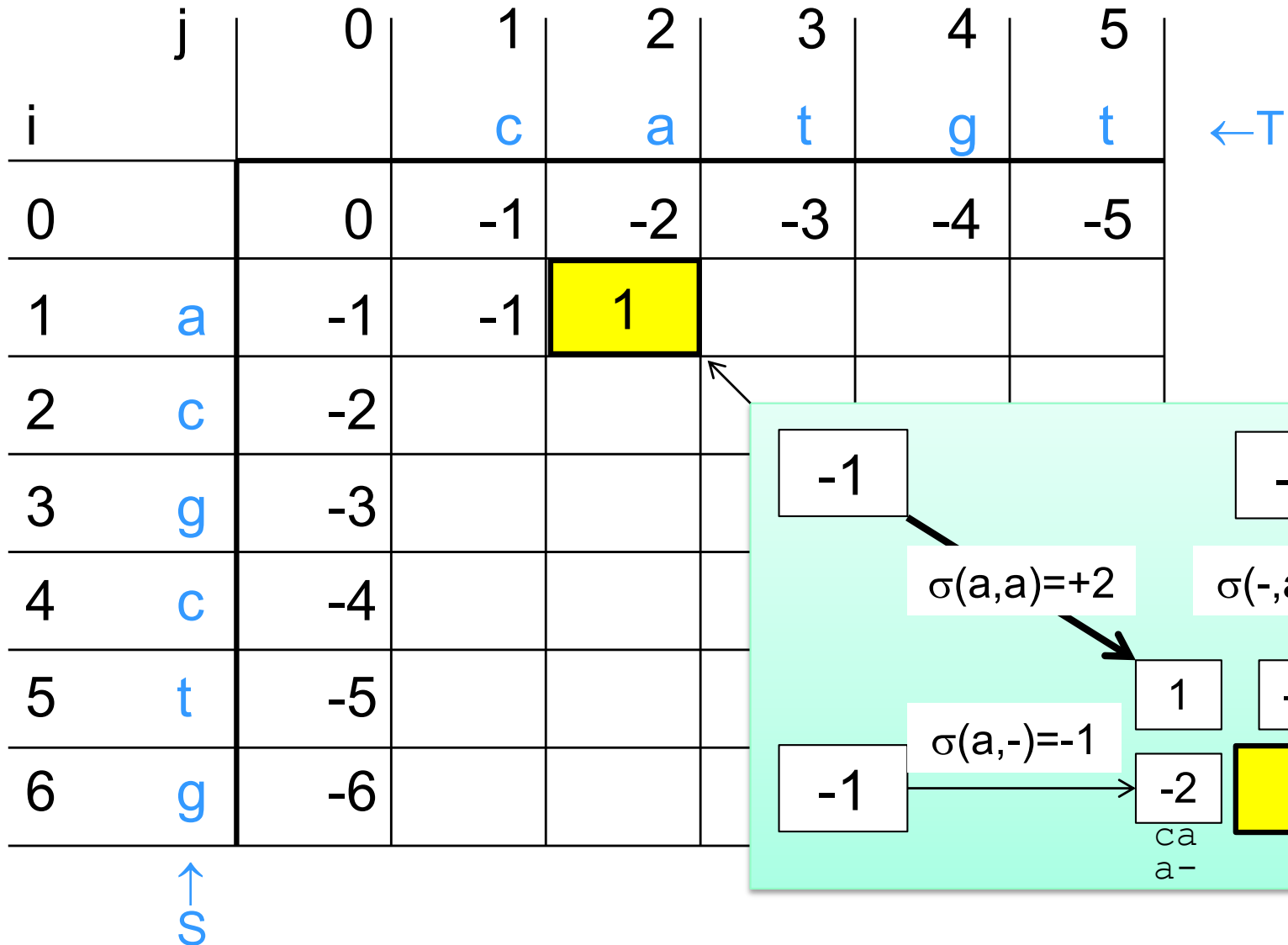
-	-
a	c
-1	

Score(-,c) = -1

↑ S

Mismatch = -1  
Match = 2

# Example



# Example

Mismatch = -1

Match = 2

	j	0	1	2	3	4	5
i			c	a	t	g	t
0		0	-1	-2	-3	-4	-5
1	a	-1	-1	1			
2	c	-2	1				
3	g	-3					
4	c	-4					
5	t	-5					
6	g	-6					

←T

Time =  
 $O(mn)$

↑  
S

Mismatch = -1  
 Match = 2

# Example

	j	0	1	2	3	4	5
i			c	a	t	g	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	g	-3	0	0	-1	2	1
4	c	-4	-1	-1	-1	1	1
5	t	-5	-2	-2	1	0	3
6	g	-6	-3	-3	0	3	2

←T

↑  
S

# Finding Alignments: Trace Back

Arrows = (ties for) max in  $V(i,j)$ ; 3 LR-to-UL paths = 3 optimal alignments

	j	0	1	2	3	4	5
i			c	a	t	g	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	g	-3	0	0	-1	2	1
4	c	-4	-1	-1	-1	1	1
5	t	-5	-2	-2	1	0	3
6	g	-6	-3	-3	0	3	2

← T

↑ S

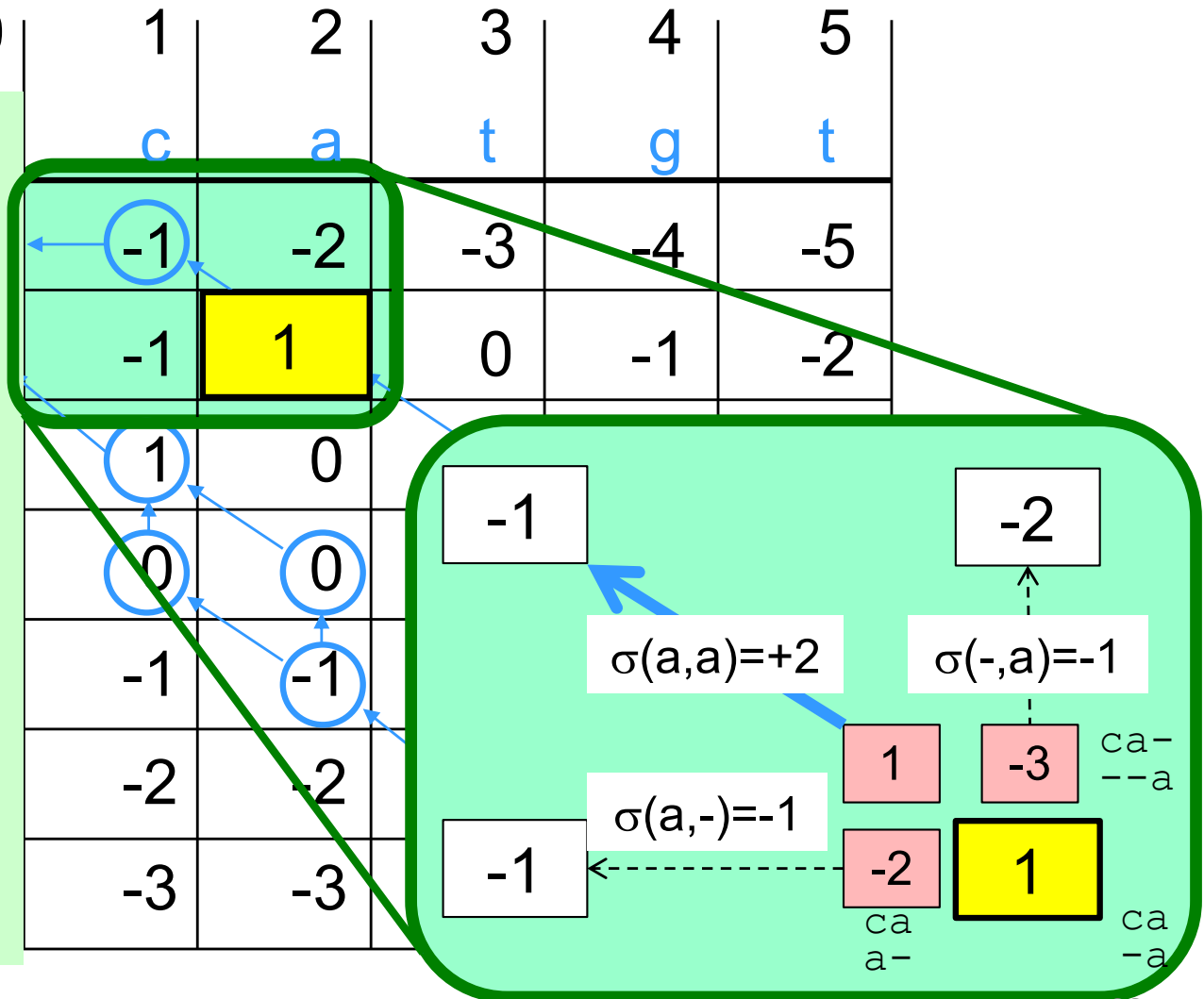
Ex: what are the 3 alignments? C.f. slide 12.



# Finding Alignments: Trace Back

Arrows = (ties for) max in  $V(i,j)$ ; 3 LR-to-UL paths = 3 optimal alignments

NB: trace back follows max *terms* (pink boxes;  $ngbr + \sigma$ ), not max neighbors (white boxes). E.g., TB from yellow cell is only *diagonal* ( $ngbr = -1$ ,  $term = 1$ ), not to the equally-good horizontal neighbor ( $term = -2$ )



# 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 =  $O(\min(m,n))$

# 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 dashes cost 10 x one dash?

Many others

Similarly fast DP algs often possible

# 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 (toy  $\sigma$ )

# Local Alignment: “Obvious” 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  $0 \leq i \leq n, 0 \leq j \leq m$  :

$V(i,j) = \mathbf{max}$  value of opt (global)  
alignment of a **suffix** of  $S[1], \dots, S[i]$   
with a **suffix** of  $T[1], \dots, T[j]$

Report best  $i,j$



# Base Cases

Assume  $\sigma(x,-) < 0$ ,  $\sigma(-,x) < 0$

$V(i,0)$ : some suffix of first  $i$  chars of  $S$ ; all match dashes in  $T$ ; best suffix is empty

$$V(i,0) = 0$$

$V(0,j)$ : similar

$$V(0,j) = 0$$

# General Case Recurrences

Opt **suffix** align  $S[1], \dots, S[i]$  vs  $T[1], \dots, T[j]$ :

$$\left[ \begin{array}{c} \sim\sim\sim\sim S[i] \\ \sim\sim\sim\sim T[j] \end{array} \right], \left[ \begin{array}{c} \sim\sim\sim\sim S[i] \\ \sim\sim\sim\sim - \end{array} \right], \left[ \begin{array}{c} \sim\sim\sim\sim - \\ \sim\sim\sim\sim T[j] \end{array} \right], \text{ or } \left[ \begin{array}{c} - \\ - \end{array} \right]$$

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

$$V(i,j) = \max \left\{ \begin{array}{l} V(i-1,j-1) + \sigma(S[i], T[j]) \\ V(i-1,j) + \sigma(S[i], -) \\ V(i,j-1) + \sigma(-, T[j]) \\ 0 \end{array} \right\},$$

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

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

# Scoring Local Alignments

i \ j	0	1	2	3	4	5	6
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					

←T

s

# Finding Local Alignments

Again, arrows follow max *term* (not max neighbor)

	j	0	1	2	3	4	5	6
i			x	x	x	c	d	e
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

← T

One alignment is:

c-de  
cxde

What's the other?

↑ 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

*A Gap:* maximal run of dashes in S' or T'

ag--ttc-t

2 gaps in S'

acag---gt

1 gap in T'

Motivations, e.g.:

mutation might insert/delete several or even many residues at once

some parts of proteins less critical

matching mRNA (no introns) to genomic DNA (exons and introns)

# A Protein Structure: (Dihydrofolate Reductase)



# Alignment of 5 Dihydrofolate reductase proteins

```

mouse P00375 ----MVRPLNCIVAVSQNMGIGKNGDLPWPPLRNEFKYFQRM TTTSSVEGKQNLVIMGRK
human P00374 ----MVGSLNCIVAVSQNMGIGKNGDLPWPPLRNEFRYFQRM TTTSSVEGKQNLVIMGKK
chicken P00378 ----VRSLSNIVAVCQNMGIGKDG NLPWPPLRNEYKYFQRM TSTSHVEGKQNAVIMGKK
fly P17719 ----MLR-FNLIVAVCENFGIGIRG DLPWR- IKSELKYFSRTTKRTSDPTKQNAVVMGRK
yeast P07807 MAGGKIPIVGIVACLQPEMGIGFRG GLPWR- LPSEMKYFRQV TSLTKDPNKKNALIMGRK

```

```

      :  . . : . . : : : * * * * * . * * * * : . * : * * : * . : * : * : : * * : *

```

```

P00375 TWFSIPEKNRPLKDRINIVLSRELKEP----PRGAHFLAKSLDDALRLIEQPELASKVDM
P00374 TWFSIPEKNRPLKGRINLVLSRELKEP----PQGAHFLSRSLDDALKLTEQPELANKVDM
P00378 TWFSIPEKNRPLKDRINIVLSRELKEA----PKG AHYLSKSLDDALALLDSPELKS KVD M
P17719 TYFGVPESKRPLPDRLNIVLSTTLQESDL--PKG-VLLCPNLETAMKILEE---QNEVEN
P07807 TWESIPPKFRPLPNRMNVIISRSFKDDFVHDKERSIVQSNLANAIMNLESN-FKEHLER

```

```

* : . : * . * * * . * : * : : * : : : . . . * * : : . . . : :

```

```

P00375 VWIVGGSSVYQEAMNQP GHLR L FVTRIMQEFESDTFFPEIDL GKYKLLPEYPG-----
P00374 VWIVGGSSVYKEAMNHP GHLK L FVTRIMQDFESDTFFPEIDL EKYKLLPEYPG-----
P00378 VWIVGGTAVYKAAMEKPINHRL FVTRILHEFESDTFFPEIDYKDFKLLTEYPG-----
P17719 IWIVGGSGVYEEAMASPRCHRL YITKIMQKFD CD TFFPAIP-DSFREVAPDSD-----
P07807 IYVIGGGEVYSQIFSI TDH WLITKINPLDKNATPAMDTFLDAKKLEEVFSEQDPAQLKEF

```

```

: : : : * * * * . : . : . . . : : . : . . : . . : .

```

```

P00375 VLSEVQ-----EEKGIKYKFEVYEKKD----
P00374 VLSDVQ-----EEKGIKYKFEVYEKND----
P00378 VPADIQ-----EEDGIQYKFEVYQKSVLAQ
P17719 MPLGVQ-----EENG I KFEYKILEKHS----
P07807 LPPKVELPETDCDQRYSL E E K G Y C F E F T L Y N R K ----

```

```

: : : * * . * : : : : :

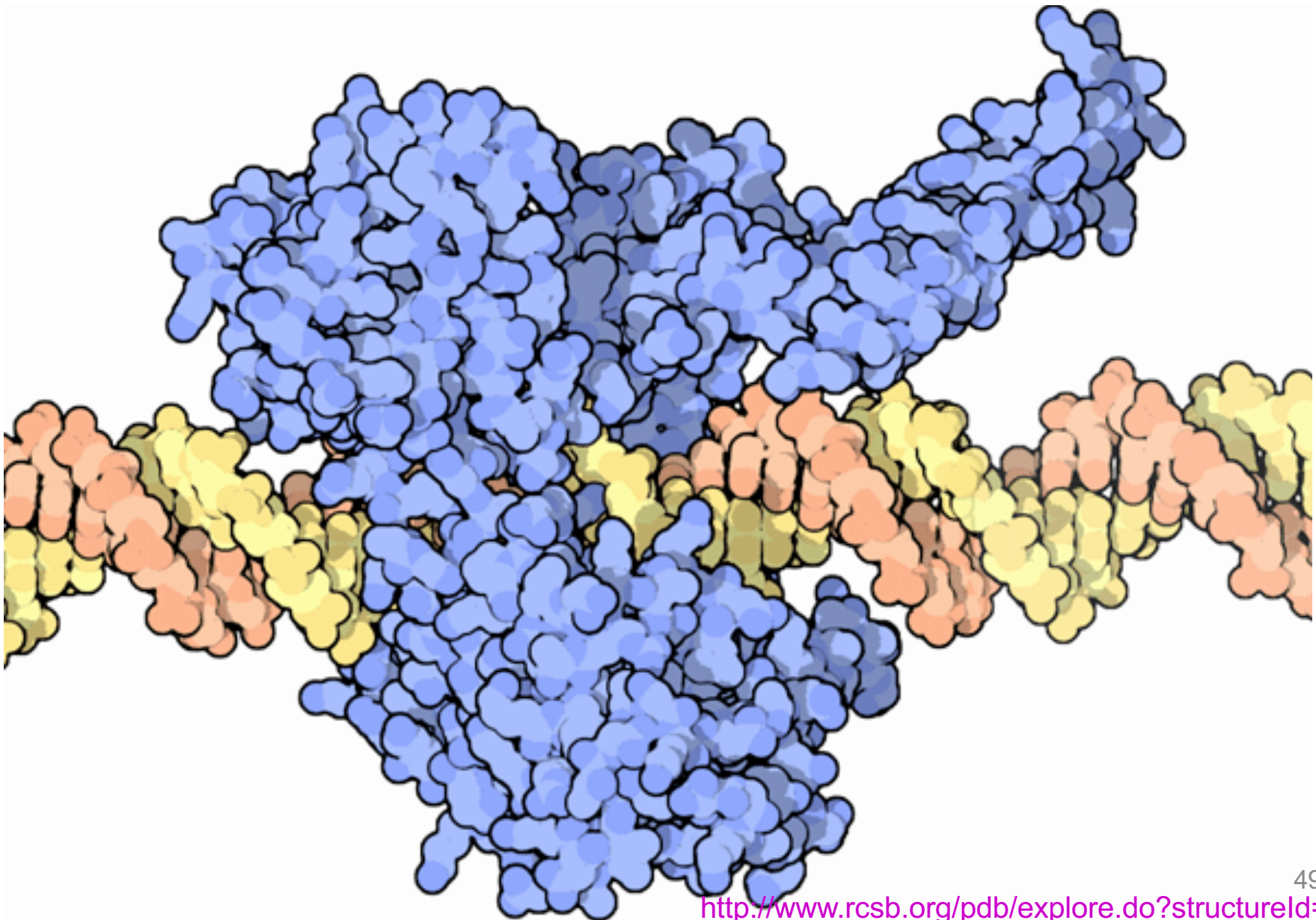
```

*CLUSTAL W (1.82) multiple sequence alignment*

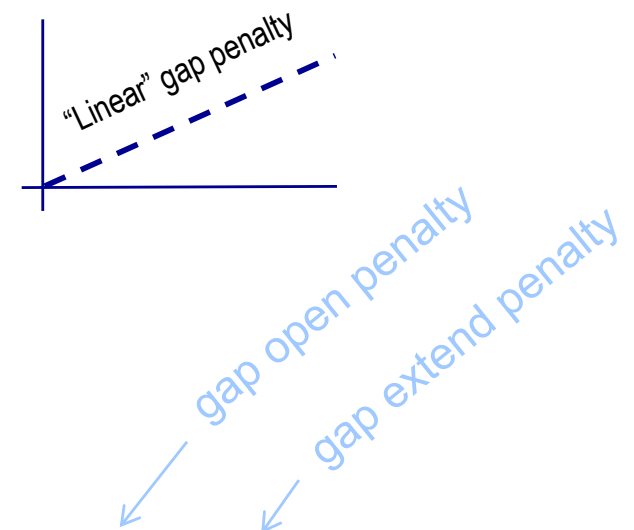
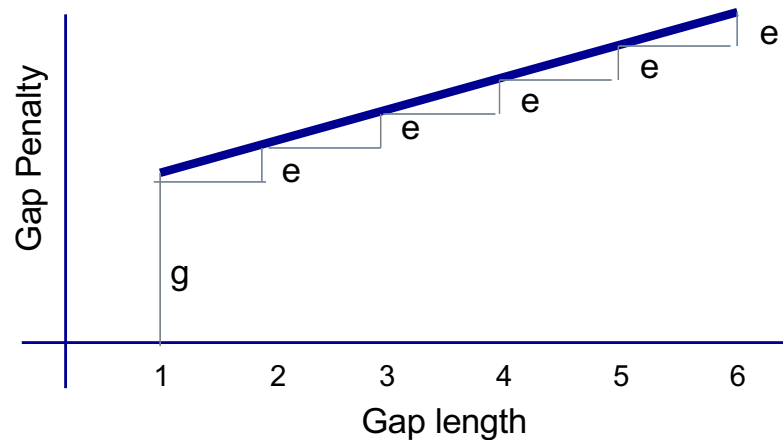
<http://pir.georgetown.edu/cgi-bin/multaln.pl> 2/11/2013



# Topoisomerase I



# Affine Gap Penalties



$$\text{Gap penalty} = g + e * (\text{gaplen} - 1), \quad g \geq e \geq 0$$

Note: no longer suffices to know just the *score* of best subproblem(s) – *state* matters: do they end with ‘-’ or not.

# Global Alignment with Affine Gap Penalties

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

$G(i,j)$  = ..., 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 – &  $T[j]$

S	T
x/	x/
–	–
x	x
x	–
–	x

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

# Affine Gap Algorithm

$$\text{Gap penalty} = g + e^*(\text{gaplen}-1), \quad g \geq e \geq 0$$

$$V(i,0) = E(i,0) = V(0,i) = F(0,i) = -g - (i-1)*e$$

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

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

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

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

old gap

new gap


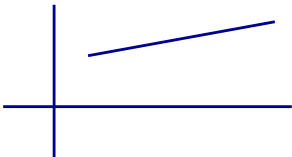
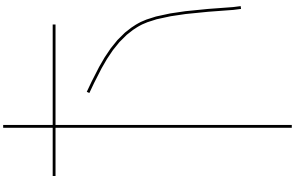
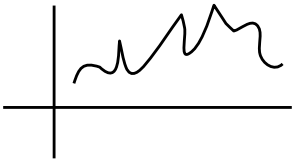
S	T
x/	x/
-	-
x	x
x	-
-	x

Q. Why is the “V” case a “new gap” when V includes E & F?

# Other Gap Penalties

Score =  $f(\text{gap length})$

Kinds, & best known alignment time

 affine		$O(n^2)$ [really, $O(mn)$ ]
convex		$O(n^2 \log n)$
general		$O(n^3)$

# Summary: Alignment

Functionally similar proteins/DNA often have recognizably similar sequences even after eons of divergent evolution

Ability to find/compare/experiment with “same” sequence in other organisms is a huge win

Surprisingly simple scoring works well in practice: score positions separately & add, usually w/ fancier affine gaps

Simple dynamic programming algorithms can 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, and elsewhere.

# Summary: Dynamic Programming

Keys to D.P. are to

- a) Identify the subproblems (usually repeated/overlapping)
- b) Solve them in a careful order so all small ones solved before they are needed by the bigger ones, and
- c) Build table with solutions to the smaller ones so bigger ones just need to do table lookups (*no* recursion, despite recursive formulation implicit in (a))
- d) Implicitly, optimal solution to whole problem devolves to optimal solutions to subproblems

*A really* important algorithm design paradigm

# Significance of Alignment Scores

Is “42” a good score?

*Compared to what?*

Usual approach: compared to a specific “null model”, such as “random sequences”

More on this later; a taste now, for use in next HW



# Overall Alignment Significance, I

## Empirical p-values (via randomization)

You just searched with  $x$ , found “good” score for  $x:y$

Generate  $N$  random “ $y$ -like” sequences (say  $N = 10^3 - 10^6$ )

Align  $x$  to each & score

If  $k$  of them have score than better or equal to that of  $x$  to  $y$ , then the (empirical) probability of a chance alignment as good as your observed  $x:y$  alignment is  $(k+1)/(N+1)$

e.g., if 0 of 99 are better, you can say “estimated  $p \leq .01$ ”

How to gen “random  $y$ -like” seqs? Scores depend on:

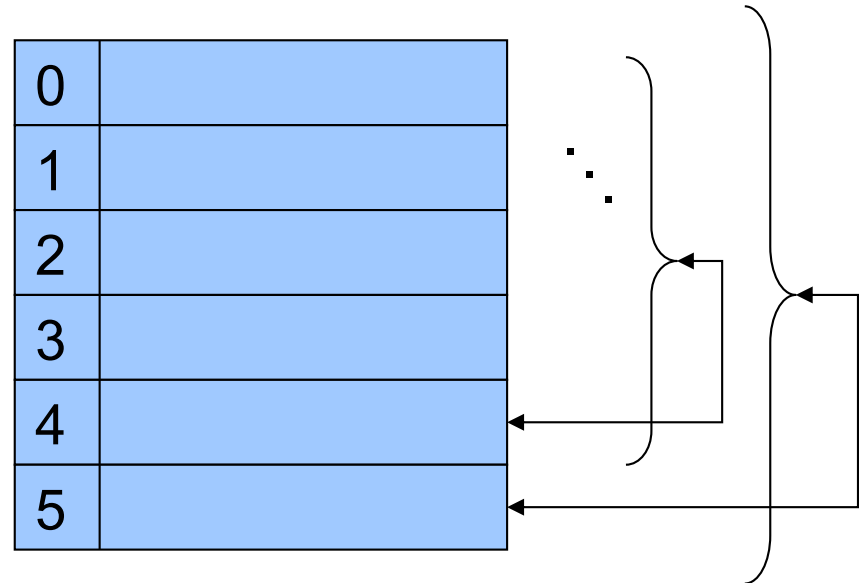
Length, so use same length as  $y$

Sequence composition, so uniform  $1/20$  or  $1/4$  is a bad idea; even background  $p_i$  can be dangerous (if  $y$  unusual)

Better idea: *permute*  $y$   $N$  times: exactly preserves len & composition

# Generating Random Permutations

```
for (i = n-1; i > 0; i--){  
    j = random(0..i);  
    swap X[i] <-> X[j];  
}
```



All  $n!$  permutations of the original data equally likely: A specific element will be last with prob  $1/n$ ; given that, another specific element will be next-to-last with prob  $1/(n-1)$ , ...; overall:  $1/(n!)$

C.f. [http://en.wikipedia.org/wiki/Fisher–Yates\\_shuffle](http://en.wikipedia.org/wiki/Fisher–Yates_shuffle) and (for subtle way to go wrong) <http://www.codinghorror.com/blog/2007/12/the-danger-of-naivete.html>