Agenda for today

- **Introduction to approximate matching**
  - **Edit distance**
  - **Intro to dynamic programming**
  - **Substitution matrices and gap penalties**
    - **PAM250 and BLOSUM50**
  - **Local alignment**
  - **BLAST and FASTA**

Approximate matching

- **Allows for mismatches in string comparisons**
- **Linguistic motivation**
  - **Spell check**
  - **Morpheme sequence homology across languages**
- **Biological motivation**
  - **Sequence similarities imply functional similarities**
  - **Pairs of proteins related by common ancestry**
  - **DNA sequence homology across species**

Approximate matching on string sequences

- **Matching two strings corresponds to finding the best alignment between the strings according to some distance metric**
- **In exact matching, we searched for an alignment where the 'distance' between two strings was zero**
- **In approximate matching, we will be searching for some minimal distance between two strings**

Edit distance

- Given two strings, one can ask: how many changes to the first string would it take to yield the second?
- For example, if I typed ‘eammpld’ but meant ‘example’
  - first need to add back the ‘x’: eammpld ⟶ exammpld
  - next need to remove the extra ‘m’: exammpld ⟶ exampld
  - next need to switch the ‘d’ to an ‘e’: exampld ⟶ example
  - One insertion, one deletion and one substitution: 3 edits
- Many other ways to map ‘eammpld’ onto ‘example,’ some more reasonable than others
  - first remove all of the letters in ‘eammpld,’ then insert all of the letters in ‘example’
  - Seven deletions and seven insertions: 14 edits
- Of all possible mappings, which has the LEAST number of edits?

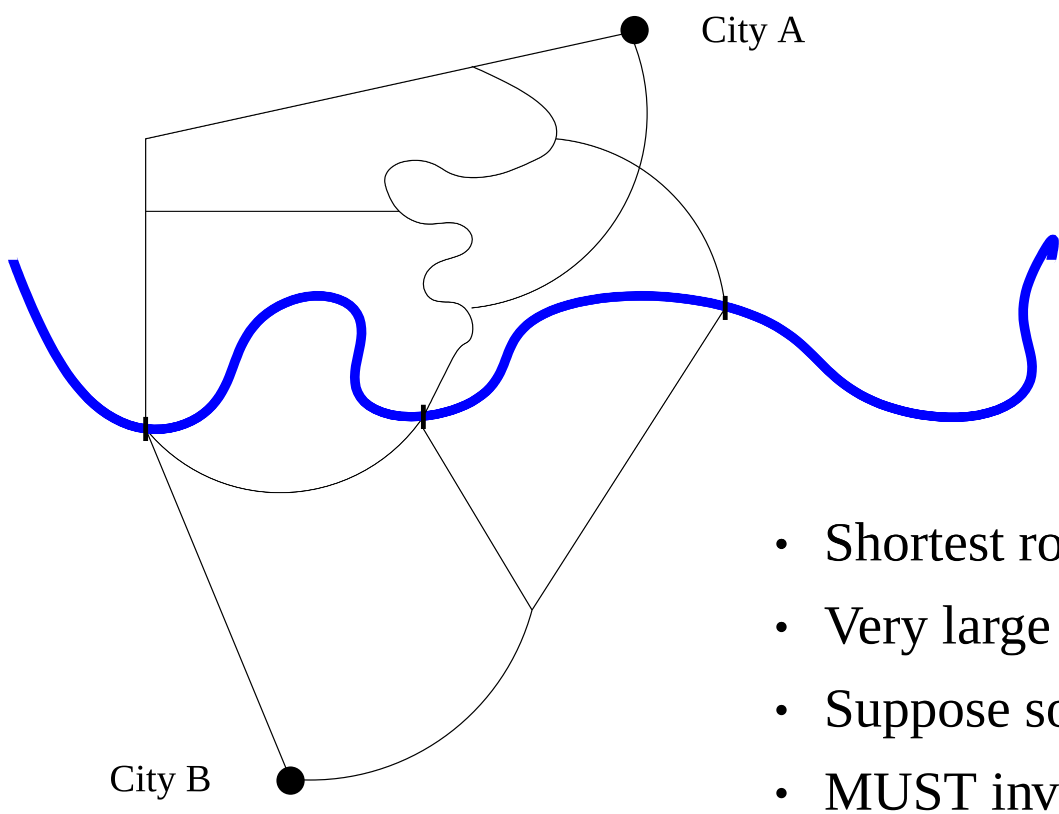
Complexity of approximate matching

- In approximate matching, the number of possible mappings between two strings is exponential in the length of the string
  - Due to allowing insertions and deletions
  - Enumerating all possible mappings with exact matching was slow, but not impossible (naive match): $O(n^2)$
  - With approximate matching, becomes computationally intractable to enumerate all possible mappings: $O(2^n)$
- To find the minimum edit distance, will need some 'trick' to make the search tractable: dynamic programming

Dynamic programming

- **General technique to find globally optimal solutions by solving a sequence of sub-problems**
- **In scenarios where searching from among very large (exponential) set of solutions, can make search tractable**
- **For example, finding the shortest route between two cities with a fixed number of mid-points (e.g., bridges)**
  - **Rather than building every route and comparing**
  - **Find shortest routes to each midpoint, then find shortest combination**

Example: shortest distance



- Shortest route from city A to city B
- Very large number of possible routes
- Suppose solution goes through middle bridge
- MUST involve shortest route from each city to middle bridge
- Break global solution into half

Edit distance dynamic programming algorithm

- Given two strings S_1 and S_2 of length m and n respectively
- Let $F(i, j)$ be the fewest edits mapping $S_1[1, i]$ to $S_2[1, j]$
- Let $F(0, j) = j$ and $F(i, 0) = i$ for all i, j
- Let $M[x, y]$ be the cost of mapping from symbol x to symbol y

$$M[x, y] = \begin{cases} 0 & \text{if } x = y \\ 1 & \text{otherwise} \end{cases}$$

- Then

$$F(i, j) = \min \left\{ \begin{array}{l} F(i, j-1) + 1, \\ F(i-1, j) + 1, \\ F(i-1, j-1) + M[S_1(i), S_2(j)] \end{array} \right\}$$

Tabular representation: 'perambulate' $\rightarrow$ 'preamble'

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0									
p	1									
e	2									
r	3									
a	4									
m	5									
b	6									
u	7									
l	8									
a	9									
t	10									
e	11									

Initialize zero positions

			p	r	e	a	m	b	l	e
	$\overset{i}{\downarrow}$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1								
e	2	2								
r	3	3								
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

Fill cell, $i = 1$, $j = 1$

			p	r	e	a	m	b	l	e
	$\overset{i}{\downarrow}\ {}_{j} \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	$\searrow\downarrow$ $\rightarrow\bullet$							
e	2	2								
r	3	3								
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(1,1) = \min \left\{ \begin{array}{l} F(1,0) + 1, \\ F(0,1) + 1, \\ F(0,0) + M[p,p] \end{array} \right\}$$

Fill cell, $i = 2$, $j = 1$

			p	r	e	a	m	b	l	e
	$\overset{i}{\downarrow}$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0							
e	2	2	$\searrow \downarrow$ $\rightarrow \bullet$							
r	3	3								
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(2,1) = \min \left\{ \begin{array}{l} F(2,0)+1, \\ F(1,1)+1, \\ F(1,0)+M[e,p] \end{array} \right\}$$

Fill cell, $i = 1$, $j = 2$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	$\searrow \downarrow$ $\rightarrow \bullet$						
e	2	2	1							
r	3	3								
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(1,2) \;=\; \min \left\{ \begin{array}{l} F(1,1)+1, \\ F(0,2)+1, \\ F(0,1)+M[p,r] \end{array} \right\}$$

Fill cell, $i = 2$, $j = 2$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1						
e	2	2	1	$\searrow\downarrow$ $\rightarrow\bullet$						
r	3	3								
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(2,2) = \min \left\{ \begin{array}{l} F(2,1)+1, \\ F(1,2)+1, \\ F(1,1)+M[e,r] \end{array} \right\}$$

Fill cell, $i = 3$, $j = 1$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1						
e	2	2	1	1						
r	3	3	$\searrow \downarrow$ $\longrightarrow \bullet$							
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(3,1) = \min \left\{ \begin{array}{l} F(3,0) + 1, \\ F(2,1) + 1, \\ F(2,0) + M[r,p] \end{array} \right\}$$

Fill cell, $i = 3$, $j = 2$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1						
e	2	2	1	1						
r	3	3	2	$\searrow \downarrow \rightarrow \bullet$						
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(3,2) = \min \left\{ \begin{array}{l} F(3,1)+1, \\ F(2,2)+1, \\ F(2,1)+M[r,r] \end{array} \right\}$$

Fill cell, $i = 1$, $j = 3$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	$\searrow\downarrow$ $\rightarrow\bullet$					
e	2	2	1	1						
r	3	3	2	1						
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(1,3) = \min \left\{ \begin{array}{l} F(1,2)+1, \\ F(0,3)+1, \\ F(0,2)+M[p,e] \end{array} \right\}$$

Fill cell, $i = 2$, $j = 3$

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2					
e	2	2	1	1	$\searrow \downarrow \; \rightarrow \bullet$					
r	3	3	2	1						
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(2,3) \;=\; \min \left\{ \begin{array}{l} F(2,2)+1, \\ F(1,3)+1, \\ F(1,2)+M[e,e] \end{array} \right\}$$

Fill cell, $i = 3$, $j = 3$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2					
e	2	2	1	1	1					
r	3	3	2	1	$\searrow \downarrow$ $\rightarrow \bullet$					
a	4	4								
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

$$F(3,3) \quad = \quad \min \left\{ \begin{array}{l} F(3,2)+1, \\ F(2,3)+1, \\ F(2,2)+M[r,e] \end{array} \right\}$$

Fill cell, $i = 4$, $j = 4$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3				
e	2	2	1	1	1	2				
r	3	3	2	1	2	2				
a	4	4	3	2	2	$\searrow \downarrow \rightarrow \bullet$				
m	5	5								
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

Fill cell, $i = 5$, $j = 5$

			p	r	e	a	m	b	l	e
	$\overset{i}{\downarrow}$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4			
e	2	2	1	1	1	2	3			
r	3	3	2	1	2	2	3			
a	4	4	3	2	2	2	3			
m	5	5	4	3	3	3	$\searrow \downarrow$ $\rightarrow \cdot$			
b	6	6								
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

Fill cell, $i = 6$, $j = 6$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5		
e	2	2	1	1	1	2	3	4		
r	3	3	2	1	2	2	3	4		
a	4	4	3	2	2	2	3	4		
m	5	5	4	3	3	3	2	3		
b	6	6	5	4	4	4	3	$\searrow \downarrow \longrightarrow \bullet$		
u	7	7								
l	8	8								
a	9	9								
t	10	10								
e	11	11								

Fill cell, $i = 7$, $j = 7$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	
e	2	2	1	1	1	2	3	4	5	
r	3	3	2	1	2	2	3	4	5	
a	4	4	3	2	2	2	3	4	5	
m	5	5	4	3	3	3	2	3	4	
b	6	6	5	4	4	4	3	2	3	
u	7	7	6	5	5	5	4	3	$\searrow \downarrow \longrightarrow \bullet$	
l	8	8								
a	9	9								
t	10	10								
e	11	11								

Fill cell, $i = 8$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	$\searrow \downarrow \rightarrow \bullet$
a	9	9								
t	10	10								
e	11	11								

Fill cell, $i = 9$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	4
a	9	9	8	7	7	6	6	5	4	$\searrow \downarrow \rightarrow \bullet$
t	10	10								
e	11	11								

Fill cell, $i = 10$, $j = 8$

			p	r	e	a	m	b	l	e
	$\overset{i}{\downarrow}$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	4
a	9	9	8	7	7	6	6	5	4	4
t	10	10	9	8	8	7	7	6	5	$\searrow \downarrow \longrightarrow \bullet$
e	11	11								

Fill cell, $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	4
a	9	9	8	7	7	6	6	5	4	4
t	10	10	9	8	8	7	7	6	5	5
e	11	11	10	9	8	8	8	7	6	$\searrow \downarrow \rightarrow \bullet$

Minimal edit distance: cell $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	4
a	9	9	8	7	7	6	6	5	4	4
t	10	10	9	8	8	7	7	6	5	5
e	11	11	10	9	8	8	8	7	6	**5**

Find the optimal alignment

- **Now we know that the lowest cost of aligning 'perambulate' to 'preamble' is 5**
- **Just knowing this cost might be useful in some cases**
- **But in general, we want to know *which* edits led to the optimal alignment**
- **Thus, backtrace to find the path(s) corresponding to the score in bottom-right cell ($i = 11$, $j = 8$)**
  - **(Why might we have more than one optimal path?)**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	4
a	9	9	8	7	7	6	6	5	4	4
t	10	10	9	8	8	7	7	6	5	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$\overset{i}{\downarrow}$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	4
a	9	9	8	7	7	6	6	5	4	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	3	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	3	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$\overset{i}{\downarrow}$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	2	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	2	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	2	3	4	5	6
m	5	5	4	3	3	3	**2**	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	2	2	3	4	5	6
a	4	4	3	2	2	**2**	3	4	5	6
m	5	5	4	3	3	3	**2**	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	1	1	2	3	4	5	6
r	3	3	2	1	**2**	2	3	4	5	6
a	4	4	3	2	2	**2**	3	4	5	6
m	5	5	4	3	3	3	**2**	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	1	2	3	4	5	6	7
e	2	2	1	**1**	**1**	2	3	4	5	6
r	3	3	2	**1**	**2**	2	3	4	5	6
a	4	4	3	2	2	**2**	3	4	5	6
m	5	5	4	3	3	3	**2**	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	0	**1**	2	3	4	5	6	7
e	2	2	**1**	**1**	**1**	2	3	4	5	6
r	3	3	2	**1**	**2**	2	3	4	5	6
a	4	4	3	2	2	**2**	3	4	5	6
m	5	5	4	3	3	3	**2**	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	0	1	2	3	4	5	6	7	8
p	1	1	**0**	**1**	2	3	4	5	6	7
e	2	2	**1**	**1**	**1**	2	3	4	5	6
r	3	3	2	**1**	**2**	2	3	4	5	6
a	4	4	3	2	2	**2**	3	4	5	6
m	5	5	4	3	3	3	**2**	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Find path(s) corresponding to score in $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	**0**	1	2	3	4	5	6	7	8
p	1	1	**0**	**1**	2	3	4	5	6	7
e	2	2	**1**	**1**	**1**	2	3	4	5	6
r	3	3	2	**1**	**2**	2	3	4	5	6
a	4	4	3	2	2	**2**	3	4	5	6
m	5	5	4	3	3	3	**2**	3	4	5
b	6	6	5	4	4	4	3	**2**	3	4
u	7	7	6	5	5	5	4	**3**	3	4
l	8	8	7	6	6	6	5	4	**3**	4
a	9	9	8	7	7	6	6	5	**4**	4
t	10	10	9	8	8	7	7	6	**5**	5
e	11	11	10	9	8	8	8	7	6	**5**

Backtrace

- Can find the path(s) corresponding to final score in $O(n+m)$
- While filling in the matrix, keep a backpointer $B(i,j)$ for each cell such that

$$B(i,j) = \operatorname{argmin} \left\{ \begin{array}{l} F(i,j-1)+1, \\ F(i-1,j)+1, \\ F(i-1,j-1)+M[S_1(i),S_2(j)] \end{array} \right\}$$

  - On a match/substitution, $B(i,j)$ will point to cell $(i-1,j-1)$
  - On an insertion, $B(i,j)$ will point to cell $(i,j-1)$
  - On a deletion, $B(i,j)$ will point to cell $(i-1,j)$
  - On a tie, $B(i,j)$ may point to multiple cells

Saving backpointers, initialize table

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	$\nwarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$
p	1	$\uparrow$								
e	2	$\uparrow$								
r	3	$\uparrow$								
a	4	$\uparrow$								
m	5	$\uparrow$								
b	6	$\uparrow$								
u	7	$\uparrow$								
l	8	$\uparrow$								
a	9	$\uparrow$								
t	10	$\uparrow$								
e	11	$\uparrow$								

Saving backpointers, $i = 1$, $j = 1$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \rightarrow$	0	1	2	3	4	5	6	7	8
	0	$\nwarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$
p	1	$\uparrow$	$\nwarrow$							
e	2	$\uparrow$								
r	3	$\uparrow$								
a	4	$\uparrow$								
m	5	$\uparrow$								
b	6	$\uparrow$								
u	7	$\uparrow$								
l	8	$\uparrow$								
a	9	$\uparrow$								
t	10	$\uparrow$								
e	11	$\uparrow$								

Saving backpointers, $i = 2$, $j = 2$

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	$\nwarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$
p	1	$\uparrow$	$\nwarrow$	$\leftarrow$						
e	2	$\uparrow$	$\uparrow$	$\nwarrow$						
r	3	$\uparrow$								
a	4	$\uparrow$								
m	5	$\uparrow$								
b	6	$\uparrow$								
u	7	$\uparrow$								
l	8	$\uparrow$								
a	9	$\uparrow$								
t	10	$\uparrow$								
e	11	$\uparrow$								

Saving backpointers, $i = 3$, $j = 3$

			p	r	e	a	m	b	l	e
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	$\nwarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$	$\leftarrow$
p	1	$\uparrow$	$\nwarrow$	$\leftarrow$	$\leftarrow$					
e	2	$\uparrow$	$\uparrow$	$\nwarrow$	$\nwarrow$					
r	3	$\uparrow$	$\uparrow$	$\nwarrow$	$\nwarrow \uparrow \leftarrow$					
a	4	$\uparrow$								
m	5	$\uparrow$								
b	6	$\uparrow$								
u	7	$\uparrow$								
l	8	$\uparrow$								
a	9	$\uparrow$								
t	10	$\uparrow$								
e	11	$\uparrow$								

Saving backpointers, $i = 11$, $j = 8$

			p	r	e	a	m	b	l	e
	$i \downarrow$ $j \rightarrow$	0	1	2	3	4	5	6	7	8
	0	↖	←	←	←	←	←	←	←	←
p	1	↑	↖	←	←	←	←	←	←	←
e	2	↑	↑	↖	↖	←	←	←	←	←
r	3	↑	↑	↖	↖↑←	↖	↖←	↖←	↖←	↖←
a	4	↑	↑	↑	↖	↖	↖←	↖←	↖←	↖←
m	5	↑	↑	↑	↖↑	↖↑	↖	←	←	←
b	6	↑	↑	↑	↖↑	↖↑	↑	↖	←	←
u	7	↑	↑	↑	↖↑	↖↑	↑	↑	↖	↖←
l	8	↑	↑	↑	↖↑	↖↑	↑	↑	↖	↖
a	9	↑	↑	↑	↖↑	↖	↑	↑	↑	↖
t	10	↑	↑	↑	↖↑	↑	↖↑	↑	↑	↖↑
e	11	↑	↑	↑	↖	↑	↖↑	↑	↑	↖

Backpointers along optimal path(s)

			p	r	e	a	m	b	l	e
	$i \downarrow \quad j \longrightarrow$	0	1	2	3	4	5	6	7	8
	0	$\nwarrow$								
p	1		$\nwarrow$	$\leftarrow$						
e	2		$\uparrow$	$\nwarrow$	$\nwarrow$					
r	3			$\nwarrow$	$\nwarrow \uparrow \leftarrow$					
a	4					$\nwarrow$				
m	5						$\nwarrow$			
b	6							$\nwarrow$		
u	7							$\uparrow$		
l	8								$\nwarrow$	
a	9								$\uparrow$	
t	10								$\uparrow$	
e	11									$\nwarrow$

Paths correspond to alignments

- Three different alignments result in edit distance of 5:

1.

p	**r**	**e**	**a**	**m**	**b**	**-**	**l**	**-**	**-**	**e**
p	**e**	**r**	**a**	**m**	**b**	**u**	**l**	**a**	**t**	**e**

2.

p	**-**	**r**	**e**	**a**	**m**	**b**	**-**	**l**	**-**	**-**	**e**
p	**e**	**r**	**-**	**a**	**m**	**b**	**u**	**l**	**a**	**t**	**e**

3.

p	**r**	**e**	**-**	**a**	**m**	**b**	**-**	**l**	**-**	**-**	**e**
p	**-**	**e**	**r**	**a**	**m**	**b**	**u**	**l**	**a**	**t**	**e**

- Can choose to slightly skew costs to avoid such ambiguities
  - e.g., score substitutions at cost 0.99

Substitution models

- For natural language sequences, typically looking for full approximate matches (e.g., spell checking)
- For protein and DNA/RNA sequences, more often looking to match subsequences (e.g., for similarity across species)
- Need some way to find "likely" related subsequences, i.e., approximate matches that probably didn't arise by chance
  - Build "random" model, whereby two sequences are modeled independently
  - Build joint model, whereby two sequences are modeled together
  - Compare likelihoods via log likelihood or log odds ratio
- This is a principled way to capture the fact that particular symbols tend to substitute for each other
  - i.e., are evolutionarily related

Substitution likelihood

- Let $q(a)$ be the probability of observing symbol a
- Let $p(ab)$ be the probability that symbols a and b are substituted
- Then, for a given ungapped alignment between S_1 and S_2, the *odds ratio* between the joint and random models is

$$\text{odds}(S_1, S_2) = \frac{\prod_i p(S_1(i)S_2(i))}{\prod_i q(S_1(i)) \prod_i q(S_2(i))} = \prod_i \frac{p(S_1(i)S_2(i))}{q(S_1(i))q(S_2(i))}$$

- Taking the log, we get

$$\text{log-odds}(S_1, S_2) = \sum_i L[S_1(i), S_2(i)]$$

where $$L[a, b] = \log p(ab) - \log q(a) - \log q(b)$$

- $L[a, b]$ will be positive for symbols with high probability of substitution
- Note that we now switch from min to max for dynamic programming

PAM250 substitution matrix

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	13	6	9	9	5	8	9	12	6	8	6	7	7	4	11	11	11	2	4	9
R	3	17	4	3	2	5	3	2	6	3	2	9	4	1	4	4	3	7	2	2
N	4	4	6	7	2	5	6	4	6	3	2	5	3	2	4	5	4	2	3	3
D	5	4	8	11	1	7	10	5	6	3	2	5	3	1	4	5	5	1	2	3
C	2	1	1	1	52	1	1	2	2	2	1	1	1	1	2	3	2	1	4	2
Q	3	5	5	6	1	10	7	3	7	2	3	5	3	1	4	3	3	1	2	3
E	5	4	7	11	1	9	12	5	6	3	2	5	3	1	4	5	5	1	2	3
G	12	5	10	10	4	7	9	27	5	5	4	6	5	3	8	11	9	2	3	7
H	2	5	5	4	2	7	4	2	15	2	2	3	2	2	3	3	2	2	3	2
I	3	2	2	2	2	2	2	2	2	10	6	2	6	5	2	3	4	1	3	9
L	6	4	4	3	2	6	4	3	5	15	34	4	20	13	5	4	6	6	7	13
K	6	18	10	8	2	10	8	5	8	5	4	24	9	2	6	8	8	4	3	5
M	1	1	1	1	0	1	1	1	1	2	3	2	6	2	1	1	1	1	1	2
F	2	1	2	1	1	1	1	1	3	5	6	1	4	32	1	2	2	4	20	3
P	7	5	5	4	3	5	4	5	5	3	3	4	3	2	20	6	5	1	2	4
S	9	6	8	7	7	6	7	9	6	5	4	7	5	3	9	10	9	4	4	6
T	8	5	6	6	4	5	5	6	4	6	4	6	5	3	6	8	11	2	3	6
W	0	2	0	0	0	0	0	0	1	0	1	0	0	1	0	1	0	55	1	0
Y	1	1	2	1	3	1	1	1	3	2	2	1	2	15	1	2	2	3	31	2
V	7	4	4	4	4	4	4	4	5	4	15	10	4	10	5	5	5	72	4	17

Blosum50 substitution matrix

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	5	-2	-1	-2	-1	-1	-1	0	-2	-1	-2	-1	-1	-3	-1	1	0	-3	-2	0
R	-2	7	-1	-2	-4	1	0	-3	0	-4	-3	3	-2	-3	-3	-1	-1	-3	-1	-3
N	-1	-1	7	2	-2	0	0	0	1	-3	-4	0	-2	-4	-2	1	0	-4	-2	-3
D	-2	-2	2	8	-4	0	2	-1	-1	-4	-4	-1	-4	-5	-1	0	-1	-5	-3	-4
C	-1	-4	-2	-4	13	-3	-3	-3	-3	-2	-2	-3	-2	-2	-4	-1	-1	-5	-3	-1
Q	-1	1	0	0	-3	7	2	-2	1	-3	-2	2	0	-4	-1	0	-1	-1	-1	-3
E	-1	0	0	2	-3	2	6	-3	0	-4	-3	1	-2	-3	-1	-1	-1	-3	-2	-3
G	0	-3	0	-1	-3	-2	-3	8	-2	-4	-4	-2	-3	-4	-2	0	-2	-3	-3	-4
H	-2	0	1	-1	-3	1	0	-2	10	-4	-3	0	-1	-1	-2	-1	-2	-3	2	-4
I	-1	-4	-3	-4	-2	-3	-4	-4	-4	5	2	-3	2	0	-3	-3	-1	-3	-1	4
L	-2	-3	-4	-4	-2	-2	-3	-4	-3	2	5	-3	3	1	-4	-3	-1	-2	-1	1
K	-1	3	0	-1	-3	2	1	-2	0	-3	-3	6	-2	-4	-1	0	-1	-3	-2	-3
M	-1	-2	-2	-4	-2	0	-2	-3	-1	2	3	-2	7	0	-3	-2	-1	-1	0	1
F	-3	-3	-4	-5	-2	-4	-3	-4	-1	0	1	-4	0	8	-4	-3	-2	1	4	-1
P	-1	-3	-2	-1	-4	-1	-1	-2	-2	-3	-4	-1	-3	-4	10	-1	-1	-4	-3	-3
S	1	-1	1	0	-1	0	-1	0	-1	-3	-3	0	-2	-3	-1	5	2	-4	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	2	5	-3	-2	0
W	-3	-3	-4	-5	-5	-1	-3	-3	-3	-3	-2	-3	-1	1	-4	-4	-3	15	2	-3
Y	-2	-1	-2	-3	-3	-1	-2	-3	2	-1	-1	-2	0	4	-3	-2	-2	2	8	-1
V	0	-3	-3	-4	-1	-3	-3	-4	-4	4	1	-3	1	-1	-3	-2	0	-3	-1	5

Gap penalties

- Not just substitution to consider – also insertion and deletion
- These are penalized as "gaps" of a certain length g
- Linear gap penalties give the same cost d to every single symbol gap
  - Thus, the penalty for a gap of length g is $\gamma(g) = -gd$
- Also, commonly, an "affine" gap penalty is used
  - A penalty for starting a gap d
  - Another penalty for continuing an already started gap e
  - Thus, the penalty for a gap of length g is $\gamma(g) = -d - (g-1)e$
- For affine gap penalties, need to keep track of whether gap is started or not
  - slightly different dynamic programming (stay tuned ...)

Protein sequence alignment

- Will use example from Durbin et al., section 2.3
  - Strings S_1 = 'HEAGAWGHEE' and S_2 = 'PAWHEAE'
  - Use BLOSUM50 substitution matrix
  - Linear gap penalty with $d = 8$
- Let $F(0, j) = -jd$ and $F(i, 0) = -id$ for all i, j
- Alignment scores are calculated

$$F(i,j) = \max \left\{ \begin{array}{l} F(i, j-1) - d, \\ F(i-1, j) - d, \\ F(i-1, j-1) + M[S_1(i), S_2(j)] \end{array} \right\}$$

Initialize zero positions

			P	A	W	H	E	A	E
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	-8	-16	-24	-32	-40	-48	-56
H	1	-8							
E	2	-16							
A	3	-24							
G	4	-32							
A	5	-40							
W	6	-48							
G	7	-56							
H	8	-64							
E	9	-72							
E	10	-80							

Fill cell, $i = 1$, $j = 1$

			P	A	W	H	E	A	E
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	-8	-16	-24	-32	-40	-48	-56
H	1	-8	$\searrow \downarrow \rightarrow \bullet$						
E	2	-16							
A	3	-24							
G	4	-32							
A	5	-40							
W	6	-48							
G	7	-56							
H	8	-64							
E	9	-72							
E	10	-80							

$$F(1,1) = \max \left\{ \begin{array}{l} F(1,0) - 8, \\ F(0,1) - 8, \\ F(0,0) + M[H,P] \end{array} \right\}$$

$$M[H,P] = -2$$

Fill cell, $i = 2$, $j = 2$

			P	A	W	H	E	A	E
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	-8	-16	-24	-32	-40	-48	-56
H	1	-8	-2	-10					
E	2	-16	-9	$\searrow\downarrow$ $\rightarrow\bullet$					
A	3	-24							
G	4	-32							
A	5	-40							
W	6	-48							
G	7	-56							
H	8	-64							
E	9	-72							
E	10	-80							

$$F(2,2) \; = \; \max \left\{ \begin{array}{l} F(2,1) - 8, \\ F(1,2) - 8, \\ F(1,1) + M[E,A] \end{array} \right\}$$

$$M[E,A] \; = \; -1$$

(skip to interesting bits) **Fill cell, $i = 5$, $j = 2$**

			P	A	W	H	E	A	E
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	-8	-16	-24	-32	-40	-48	-56
H	1	-8	-2	-10					
E	2	-16	-9	-3					
A	3	-24	-17	-4					
G	4	-32	-25	-12					
A	5	-40	-33	$\searrow\downarrow$ $\rightarrow\bullet$					
W	6	-48							
G	7	-56							
H	8	-64							
E	9	-72							
E	10	-80							

$$F(5,2) \;=\; \max \left\{ \begin{array}{l} F(5,1) - 8, \\ F(4,2) - 8, \\ F(4,1) + M[A,A] \end{array} \right\}$$

$$M[A,A] \;=\; 5$$

Fill cell, $i = 6$, $j = 3$

			P	A	W	H	E	A	E
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	-8	-16	-24	-32	-40	-48	-56
H	1	-8	-2	-10	-18				
E	2	-16	-9	-3	-11				
A	3	-24	-17	-4	-6				
G	4	-32	-25	-12	-7				
A	5	-40	-33	-20	-15				
W	6	-48	-41	-28	$\searrow \downarrow \rightarrow \cdot$				
G	7	-56							
H	8	-64							
E	9	-72							
E	10	-80							

$$F(6,3) = \max \left\{ \begin{array}{l} F(6,2) - 8, \\ F(5,3) - 8, \\ F(5,2) + M[W,W] \end{array} \right\}$$

$$M[W,W] = 15$$

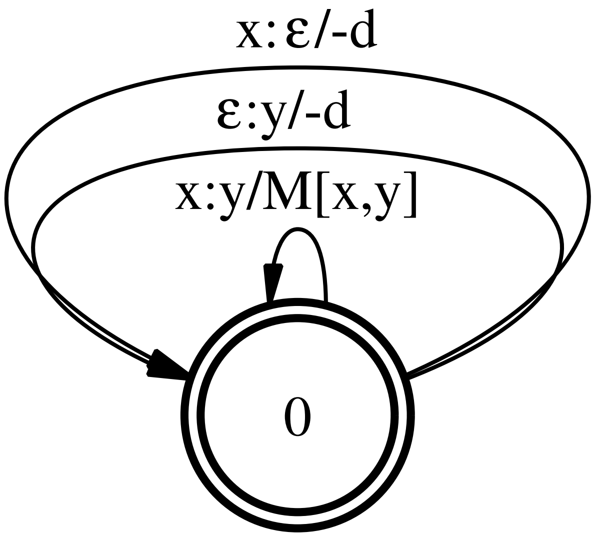
Fill cell, $i = 9$, $j = 5$

			P	A	W	H	E	A	E
	$i \downarrow$ $j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	-8	-16	-24	-32	-40	-48	-56
H	1	-8	-2	-10	-18	-14	-22		
E	2	-16	-9	-3	-11	-18	-8		
A	3	-24	-17	-4	-6	-13	-16		
G	4	-32	-25	-12	-7	-8	-16		
A	5	-40	-33	-20	-15	-9	-9		
W	6	-48	-41	-28	-5	-13	-12		
G	7	-56	-49	-36	-13	-7	-15		
H	8	-64	-57	-44	-21	-3	-7		
E	9	-72	-65	-52	-29	-11	$\searrow \downarrow \longrightarrow \bullet$		
E	10	-80							

Best path (one among many)

			P	A	W	H	E	A	E
	$\overset{i}{\downarrow}$ $j \longrightarrow$	0	1	2	3	4	5	6	7
	0	**0**	-8	-16	-24	-32	-40	-48	-56
H	1	**-8**	-2	-10	-18	-14	-22	-30	-38
E	2	-16	**-9**	-3	-11	-18	-8	-16	-24
A	3	-24	-17	**-4**	-6	-13	-16	-3	-11
G	4	-32	-25	**-12**	-7	-8	-16	-11	-6
A	5	-40	-33	**-20**	-15	-9	-9	-11	-12
W	6	-48	-41	-28	**-5**	-13	-12	-12	-14
G	7	-56	-49	-36	**-13**	-7	-15	-12	-15
H	8	-64	-57	-44	-21	**-3**	-7	-15	-12
E	9	-72	-65	-52	-29	-11	**3**	**-5**	-9
E	10	-80	-73	-60	-37	-19	-5	2	**1**

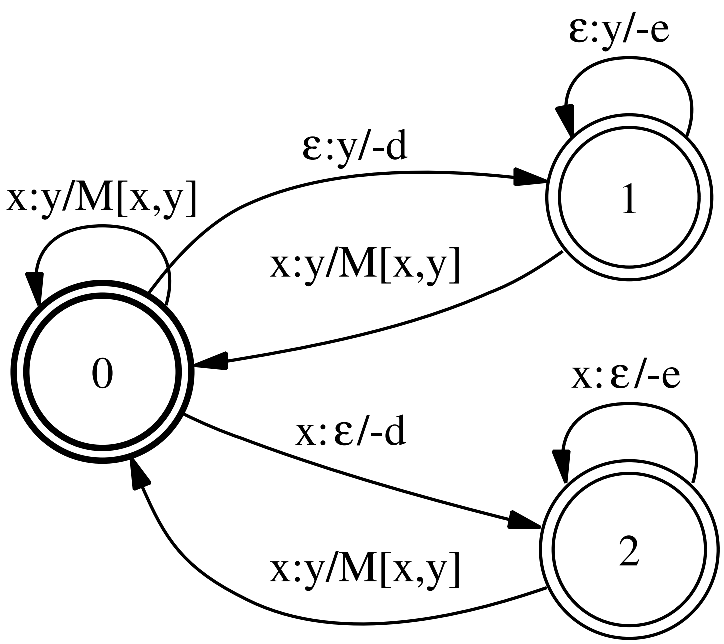
Finite-state transducer: linear gaps



	ϵ	P	A	ϵ	ϵ	W	ϵ	H	E	A	E
	H	E	A	G	A	W	G	H	E	ϵ	E
state: 0	0	0	0	0	0	0	0	0	0	0	0

- Only one state required; add scores together
- ϵ represents a gap of length 1
- gaps receive $-d$ cost for each symbol in gap
- Mapping input symbol x to output symbol y gets substitution matrix score for that pair

Finite-state transducer: affine gaps



	ϵ	P	A	ϵ	ϵ	W	ϵ	H	E	A	E
	H	E	A	G	A	W	G	H	E	ϵ	E
state: 0	1	0	0	1	1	0	1	0	0	2	0

- Three states required; add scores together
- Initial gap on input goes to state 1; initial gap on output to state 2
- gaps receive $-d$ cost to start; plus $-e$ for each additional symbol in gap
- Mapping input symbol x to output symbol y gets substitution matrix score for that pair

Larger chart required for dynamic programming

						P			A			W			H			E			A		
	i ↓ j →		0			1			2			3			4			5			6		
	state:	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0
	0	0	·	·	·	-8	·	·	-12	·	·	-16	·	·	-20	·	·	-24	·	·	-28	·	·
H	1	·	·	-8	↘	→	↓																
E	2	·	·	-12																			
A	3	·	·	-16																			
G	4	·	·	-20																			
A	5	·	·	-24																			
W	6	·	·	-28																			
G	7	·	·	-32																			
H	8	·	·	-36																			
E	9	·	·	-40																			
E	10	·	·	-44																			

State 1 only from states 0,1; State 2 from 0,2

					P			A			W			H			E			A			
	$i \downarrow$ $j \rightarrow$	0			1			2			3			4			5			6			
	state:	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0
	0	0	·	·	·	-8	·	·	-12	·	·	-16	·	·	-20	·	·	-24	·	·	-28	·	·
H	1	·	·	-8	-2	·	·	↘	→	↓													
E	2	·	·	-12																			
A	3	·	·	-16																			
G	4	·	·	-20																			
A	5	·	·	-24																			
W	6	·	·	-28																			
G	7	·	·	-32																			
H	8	·	·	-36																			
E	9	·	·	-40																			
E	10	·	·	-44																			

State 1 costs $-d$ from state 0; only $-e$ from state 1

					P			A			W			H			E			A			
	$i \downarrow$ $j \rightarrow$		0			1			2			3			4			5			6		
	state:	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0
	0	0	·	·	·	-8	·	·	-12	·	·	-16	·	·	-20	·	·	-24	·	·	-28	·	·
H	1	·	·	-8	-2	·	·	-10	-10	·	↘	→	↓										
E	2	·	·	-12																			
A	3	·	·	-16																			
G	4	·	·	-20																			
A	5	·	·	-24																			
W	6	·	·	-28																			
G	7	·	·	-32																			
H	8	·	·	-36																			
E	9	·	·	-40																			
E	10	·	·	-44																			

State 1 only from states 0,1; State 2 from 0,2

					P			A			W			H			E			A			
	i ↓ j →	0			1			2			3			4			5			6			
	state:	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0
	0	0	·	·	·	-8	·	·	-12	·	·	-16	·	·	-20	·	·	-24	·	·	-28	·	·
H	1	·	·	-8	-2	·	·	-10	-10	·	-15	-14	·										
E	2	·	·	-12	↘	→	↓																
A	3	·	·	-16																			
G	4	·	·	-20																			
A	5	·	·	-24																			
W	6	·	·	-28																			
G	7	·	·	-32																			
H	8	·	·	-36																			
E	9	·	·	-40																			
E	10	·	·	-44																			

State 2 costs $-d$ from state 0; only $-e$ from state 2

					P			A			W			H			E			A		
	$i \downarrow$ $j \rightarrow$	0			1			2			3			4			5			6		
	state:	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2
	0	0	·	·	·	-8	·	·	-12	·	·	-16	·	·	-20	·	·	-24	·	·	-28	·
H	1	·	·	-8	-2	·	·	-10	-10	·	-15	-14	·									
E	2	·	·	-12	-9	·	-10															
A	3	·	·	-16	↘	→	↓															
G	4	·	·	-20																		
A	5	·	·	-24																		
W	6	·	·	-28																		
G	7	·	·	-32																		
H	8	·	·	-36																		
E	9	·	·	-40																		
E	10	·	·	-44																		

And so on – same dynamic programming

					P			A			W			H			E			A		
	$i \downarrow \; j \rightarrow$	0			1			2			3			4			5			6		
	state:	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2
	0	0	·	·	·	-8	·	·	-12	·	·	-16	·	·	-20	·	·	-24	·	·	-28	·
H	1	·	·	-8	-2	·	·	-10	-10	·	-15	-14	·									
E	2	·	·	-12	-9	·	-10															
A	3	·	·	-16	-13	·	-14															
G	4	·	·	-20																		
A	5	·	·	-24																		
W	6	·	·	-28																		
G	7	·	·	-32																		
H	8	·	·	-36																		
E	9	·	·	-40																		
E	10	·	·	-44																		

Finite-state transducers for alignment

- Can move to arbitrarily complex finite-state transducer models
  - Durbin et al. mention 4 state model, with two match states corresponding to low and high fidelity regions
- Must keep track of scores at each state in dynamic programming
- Next lecture we will look at Hidden Markov Models
  - States represent hidden variables
  - Stochastic model conditioned on hidden state
  - Still finite-state

Local alignment

- Simple idea: allow resetting alignment at any point
- Get high quality local alignments, rather than global alignments
- Same algorithm, except now:

$$F(i,j) = \max \left\{ \begin{array}{l} 0, \\ F(i,j-1) - d, \\ F(i-1,j) - d, \\ F(i-1,j-1) + M[S_1(i), S_2(j)] \end{array} \right\}$$

- Similar modification for multi-state models
- Note: assumes scores less than zero
  - PAM250 won't work unmodified

Initialize zero positions (Global)

			P	A	W	H	E	A	E
	$\overset{i}{\downarrow}\ {}_{j} \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	-8	-16	-24	-32	-40	-48	-56
H	1	-8							
E	2	-16							
A	3	-24							
G	4	-32							
A	5	-40							
W	6	-48							
G	7	-56							
H	8	-64							
E	9	-72							
E	10	-80							

Initialize zero positions (Local)

			P	A	W	H	E	A	E
	$\overset{i}{\downarrow}\ _j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	0	0	0	0	0	0	0
H	1	0							
E	2	0							
A	3	0							
G	4	0							
A	5	0							
W	6	0							
G	7	0							
H	8	0							
E	9	0							
E	10	0							

P no matches; H 1 match

			P	A	W	H	E	A	E
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	0	0	0	0	0	0	0
H	1	0	0	0	0	10	0	0	0
E	2	0	0						
A	3	0	0						
G	4	0	0						
A	5	0	0						
W	6	0	0						
G	7	0	0						
H	8	0	0						
E	9	0	0						
E	10	0	0						

4 non-zero cells in next row

			P	A	W	H	E	A	E
	$i \downarrow \ j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	0	0	0	0	0	0	0
H	1	0	0	0	0	10	0	0	0
E	2	0	0	0	0	2	16	8	6
A	3	0	0						
G	4	0	0						
A	5	0	0						
W	6	0	0						
G	7	0	0						
H	8	0	0						
E	9	0	0						
E	10	0	0						

Great local match – not in global solutions

			P	A	W	H	E	A	E
	$i \downarrow \; j \longrightarrow$	0	1	2	3	4	5	6	7
	0	0	0	0	0	0	0	0	0
H	1	0	0	0	0	**10**	0	0	0
E	2	0	0	0	0	2	**16**	8	6
A	3	0	0	5	0	0	8	**21**	13
G	4	0	0						
A	5	0	0						
W	6	0	0						
G	7	0	0						
H	8	0	0						
E	9	0	0						
E	10	0	0						

BLAST and FASTA

- Pronounced ‘that was pretty fast, eh?’
- Widely used heuristic local match algorithms
- Begin with exact (or near exact) match seeds
  - “Diagonals” on our chart
- Grow larger matches out from these seeds
- Heuristic because they may miss some matches
- Great speedups through use of very fast exact match algorithms
- Very highly tuned to domains, but roughly speaking are instances of “exclusion” methods

Alignment: what's left to cover

- **Better space usage: current approach $O(nm)$ in space**
- **Faster approximate matching**
  - **Bounded number of differences**
  - **Exclusion methods**
- **Better models**
  - **Hidden Markov Models**
- **Multiple sequences to jointly align**
- **(In other words, today was the tip of the iceberg)**