Sequence Alignment

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4/12/2018

Exercise: Scoring an ungapped alignment

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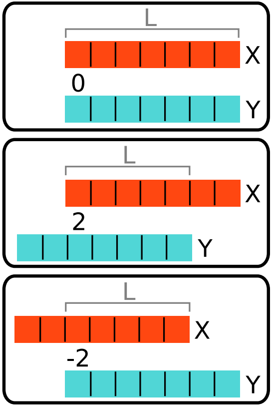
Given two sequences and a scoring matrix, find the offset that yields the best scoring ungapped alignment.

```
def score(S,x,y):
    assert(len(x) == len(y))
    s = 0
    for (i,j) in zip(x,y):
        s += S[i][j]
    return s
```

Exercise: Scoring an ungapped alignment

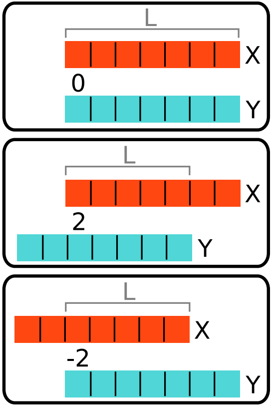
Given two sequences and a scoring matrix, find the offset that yields the best scoring ungapped alignment.

```
def subseqs(x,y,i):
    if(i > 0):
        y = y[i:]
    elif(i < 0):
        x = x[-i:]
    L = min(len(x),len(y))
    return x[:L],y[:L]
```



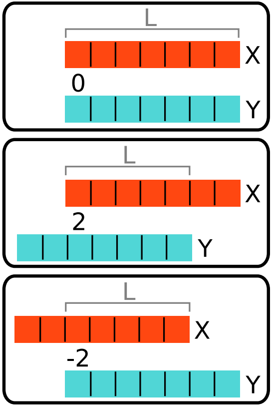
Given two sequences and a scoring matrix, find the offset that yields the best scoring ungapped alignment.

```
def alignment(x,y,i):
    if(i > 0):
        x = "-"*i+x
    elif(i < 0):
        y = "-"*(-i)+y
    L = len(y) - len(x)
    if(L > 0):
        x += "-"*L
    elif(L < 0):
        y += "-"*(-L)
    return x,y
```



Given two sequences and a scoring matrix, find the offset that yields the best scoring ungapped alignment.

```
def ungapped(S,x,y):
    best = None
    best_score = None
    for i in range(-len(x)+1,len(y)):
        (sx,sy) = subseqs(x,y,i)
        s = score(S,sx,sy)
        if((best_score is None) or (s > best_score)):
            best_score = s
            best = i
    return best, best_score, alignment(x,y,best)
```



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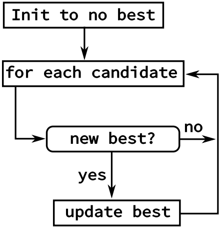

Exercise: Scoring a gapped alignment

Write a new scoring function with separate penalties for opening a zero length gap (*e.g.*, G = -11) and extending an open gap by one base (*e.g.*, E = -1).

$$S_{gapped}(x, y) = S(x, y) + \sum_{i}^{gaps} (G + E * len(i))$$

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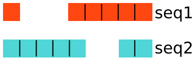
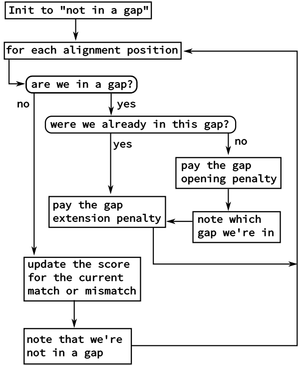
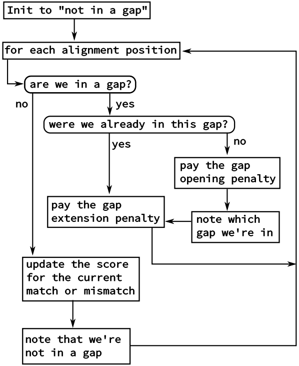




Exercise: Scoring a gapped alignment

$$S_{gapped}(x,y) = S(x,y) + \sum_{i}^{gaps} (G + E * len(i))$$

```python
def gapped_score(seq1, seq2,
                 s, g = 0, e = -1):
    gap = None
    score = 0
    for pair in zip(seq1,seq2):
        assert(pair != ("-","-"))
        try:
            curgap = pair.index("-")
        except ValueError:
            score += s[pair[0]][pair[1]]
            gap = None
        else:
            if(gap != curgap):
                score += g
                gap = curgap
            score += e
    return score
```



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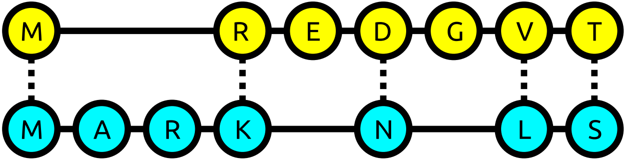
            gap = None
        else:
            if(gap != curgap):
                score += g
                gap = curgap
            score += e
    return score
```

```
def gapped_score(seq1, seq2,
                 s, g = 0, e = -1):
    gap = None
    score = 0
    for (c1,c2) in zip(seq1,seq2):
        if((c1 == "-") and (c2 == "-")):
            raise ValueError
        elif(c1 == "-"):
            if(gap != 1):
                score += g
                gap = 1
            score += e
        elif(c2 == "-"):
            if(gap != 2):
                score += g
                gap = 2
            score += e
        else:
            score += s[c1][c2]
            gap = None
    return score
```

How many ways can we align two sequences?



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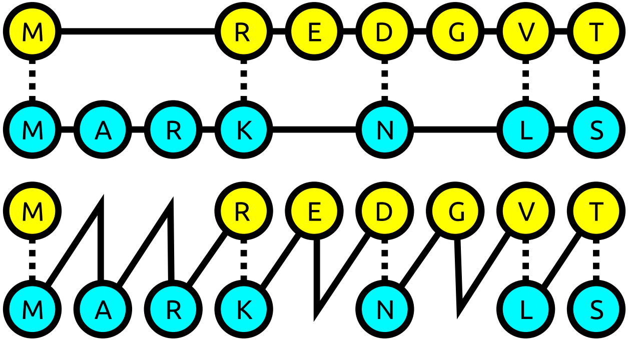

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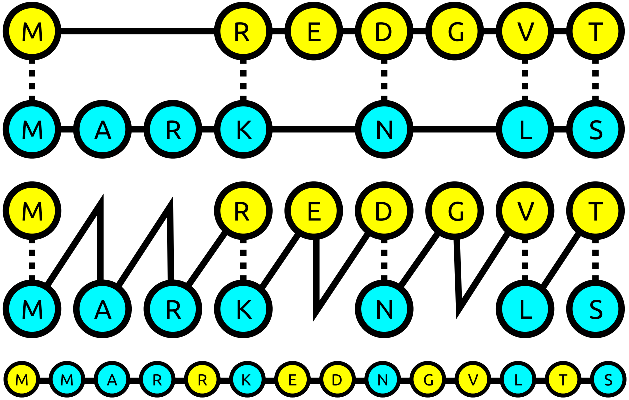

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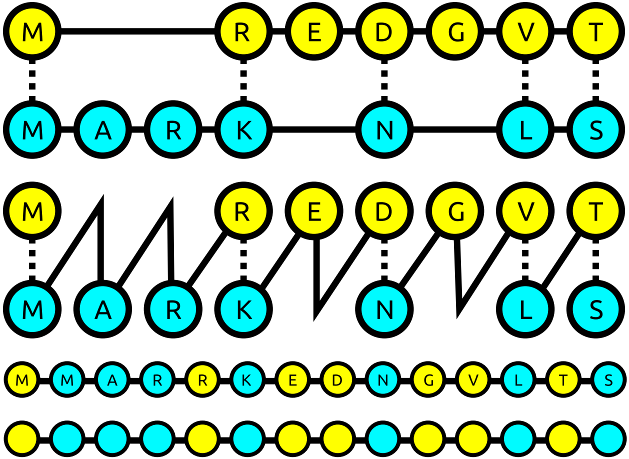

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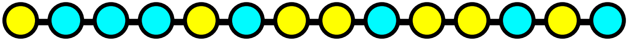

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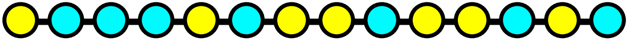

Binomial formula:

$$\binom{k}{r} = \frac{k!}{(k-r)!r!}$$

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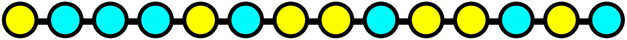

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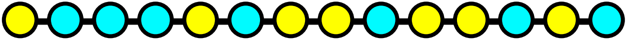

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$$x! \approx \sqrt{2\pi}\left(x^{x+\frac{1}{2}}\right)e^{-x}$$

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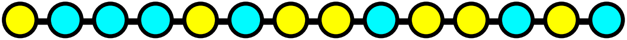

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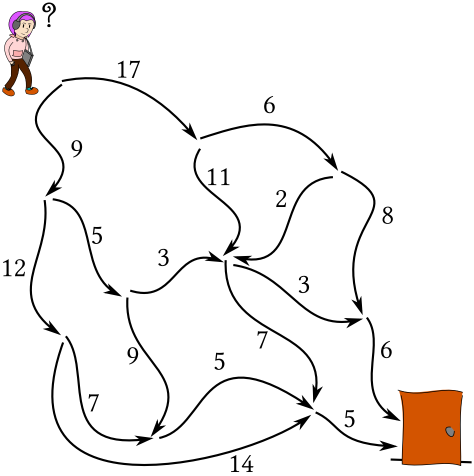
$$x! \approx \sqrt{2\pi}\left(x^{x+\frac{1}{2}}\right)e^{-x}$$

$$\binom{2n}{n} \approx \frac{2^{2n}}{\sqrt{\pi n}}$$

Dynamic Programming



Needleman-Wunsch

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

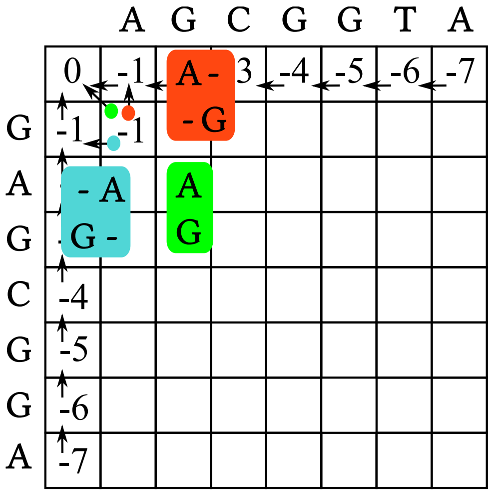
Needleman-Wunsch

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

Needleman-Wunsch

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1							
A	-2							
G	-3							
C	-4							
G	-5							
G	-6							
A	-7							

Needleman-Wunsch



		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1						
A	-2							
G	-3							
C	-4							
G	-5							
G	-6							
A	-7							

Needleman-Wunsch

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0					
A	-2							
G	-3							
C	-4							
G	-5							
G	-6							
A	-7							

Needleman-Wunsch

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0	-1				
A	-2							
G	-3							
C	-4							
G	-5							
G	-6							
A	-7							

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0	-1	-2			
A	-2							
G	-3							
C	-4							
G	-5							
G	-6							
A	-7							

Needleman-Wunsch

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0	-1	-2	-3		
A	-2							
G	-3							
C	-4							
G	-5							
G	-6							
A	-7							

Needleman-Wunsch

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0	-1	-2	-3	-4	-5
A	-2							
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A	-7							

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		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0	-1	-2	-3	-4	-5
A	-2	0						
G	-3							
C	-4							
G	-5							
G	-6							
A	-7							

Needleman-Wunsch

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0	-1	-2	-3	-4	-5
A	-2	0	-1	-1	-2	-3	-4	-3
G	-3	-1	1	0	0	-1	-2	-3
C	-4	-2	0	2	1	0	-1	-2
G	-5	-3	-1	1	3	2	1	0
G	-6	-4	-2	0	2	4	3	2
A	-7	-5	-3	-1	1	3	3	4

Needleman-Wunsch

		A	G	C	G	G	T	A
	0	-1	-2	-3	-4	-5	-6	-7
G	-1	-1	0	-1	-2	-3	-4	-5
A	-2	0	-1	-1	-2	-3	-4	-3
G	-3	-1	1	0	0	-1	-2	-3
C	-4	-2	0	2	1	0	-1	-2
G	-5	-3	-1	1	3	2	1	0
G	-6	-4	-2	0	2	4	3	2
A	-7	-5	-3	-1	1	3	3	4

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

Smith-Waterman

The implementation of local alignment is the same as for global alignment, with a few changes to the rules:

- Initialize edges to 0 *(no penalty for starting in the middle of a sequence)*
- The maximum score is never less than 0, and no pointer is recorded unless the score is greater than 0 *(note that this implies negative scores for gaps and bad matches)*
- The trace-back starts from the highest score in the matrix and ends at a score of 0 *(local, rather than global, alignment)*

Because the naive implementation is essentially the same, the time and space requirements are also the same.

Smith-Waterman

		A	G	C	G	G	T	A
	0	0	0	0	0	0	0	0
G	0	0	1	0	0	1	0	0
A	0	1	0	0	0	0	0	1
G	0	0	2	1	1	1	0	0
C	0	0	1	3	2	1	0	0
G	0	0	0	2	4	3	2	1
G	0	0	1	1	3	5	4	3
A	0	1	0	0	2	4	4	5

Final Homework

Implement Needleman-Wunsch global alignment with zero gap opening penalties. Try attacking the problem in this order:

1. Initialize and fill in a dynamic programming matrix by hand (*e.g.*, try reproducing the example from my slides on paper).
2. Write a function to create the dynamic programming matrix and initialize the first row and column.
3. Write a function to fill in the rest of the matrix
4. Rewrite the *initialize* and *fill* steps to store pointers to the best sub-solution for each cell.
5. Write a *backtrace* function to read the optimal alignment from the filled in matrix.

If that isn't enough to keep you occupied, try implementing Smith-Waterman local alignment and/or non-zero gap opening penalties.