CMSC 423: Sequence Alignment

Part5

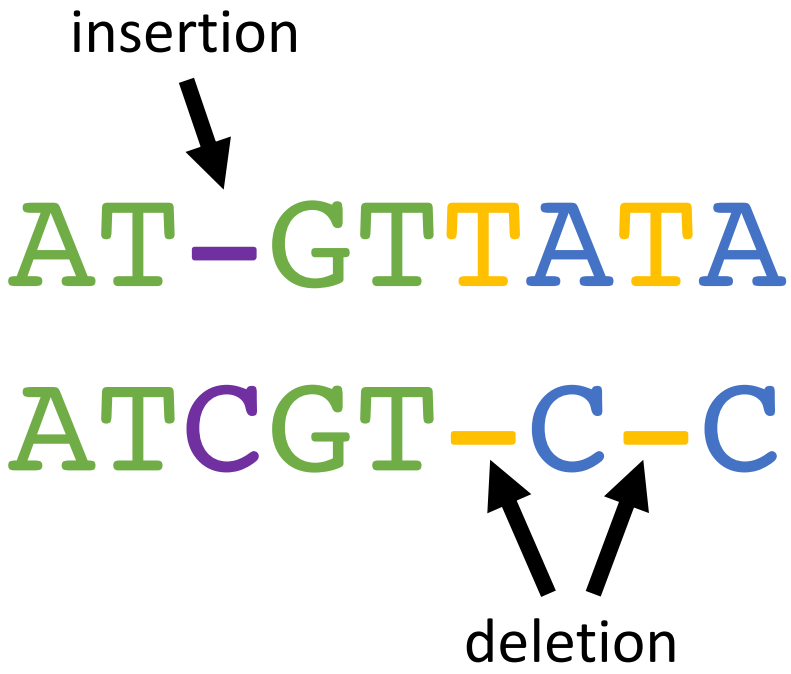
Inexact matching: why?

- Redundancy in the genetic code: nucleotide sequence may differ, but proteins are the same
- Different amino-acid sequences can still fold the same way: function is unchanged
- Aligning RNA sequences to DNA- need to account for gaps corresponding to exons
- Sequencing errors

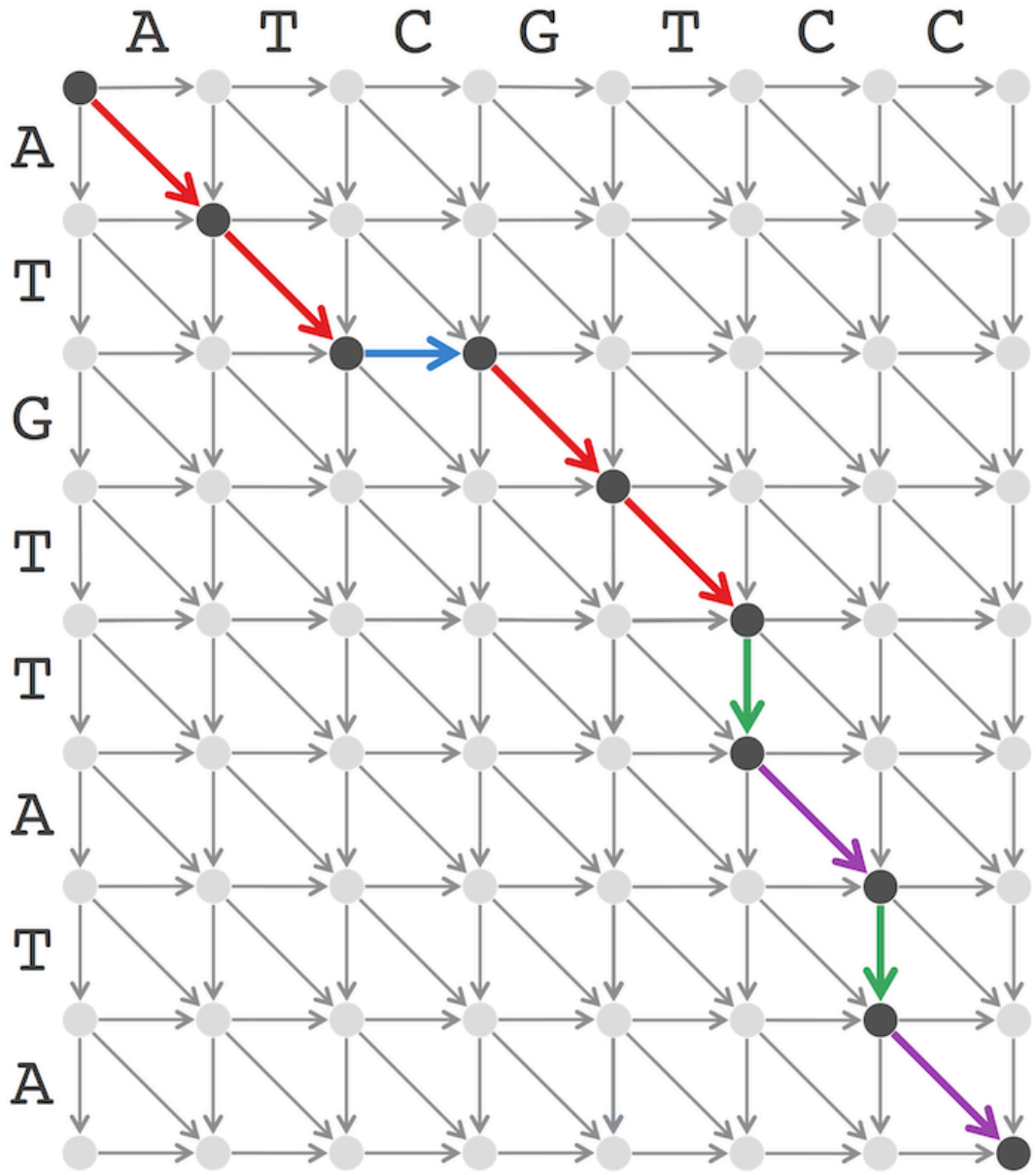
Alignment of sequences *v* and *w*

v = ATGTTATA

w = ATCGTCC



Sequence Alignment is the Manhattan Tourist Problem in Disguise



i

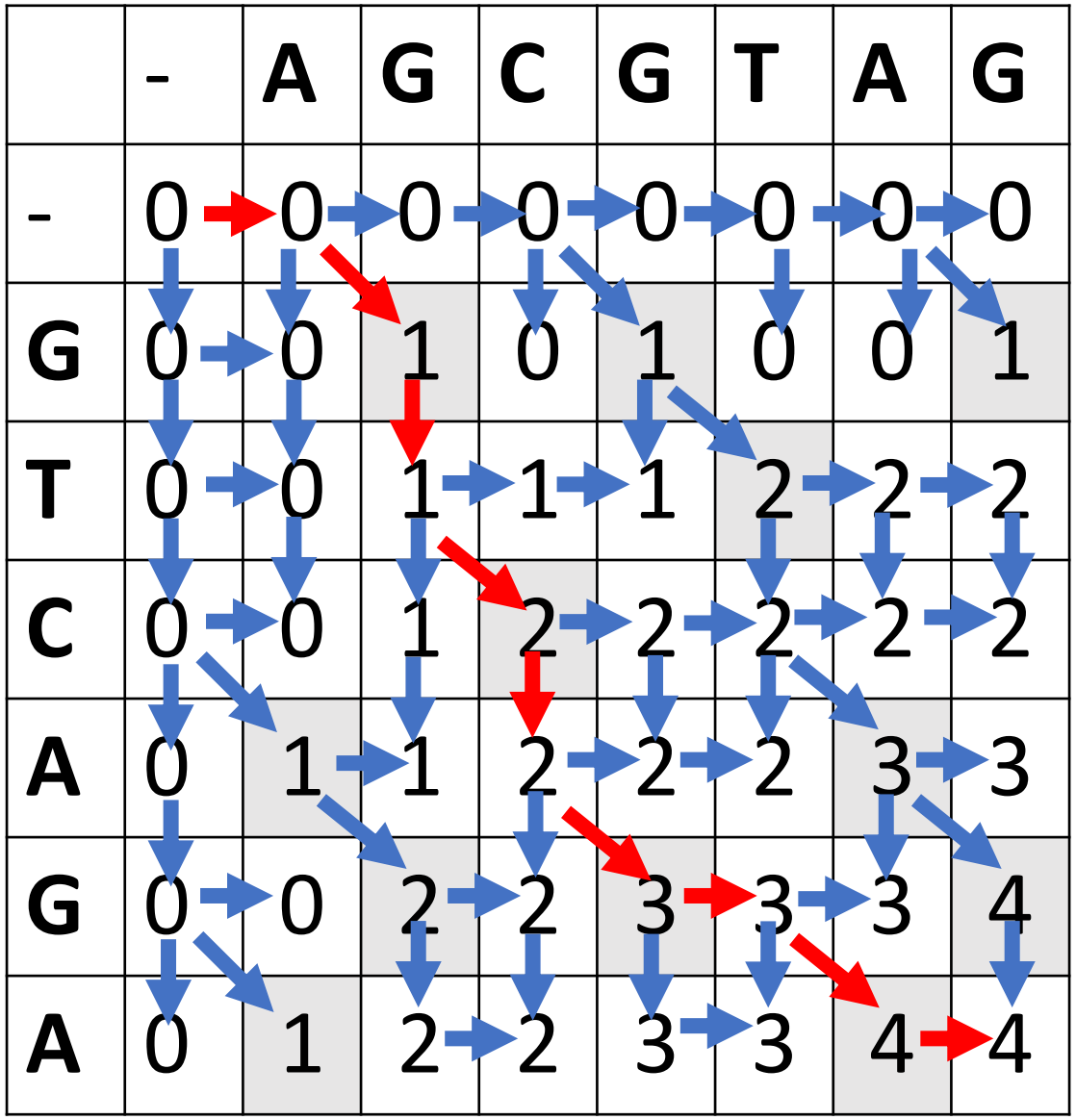
	-	**A**	**G**	**C**	**G**	**T**	**A**	**G**
-	0							
G								
T								
C								
A								
G								
A								

j

v = AGCGTAG

w = GTCAGA

$$s_{i,j} = \max \begin{cases} s_{i-1,\,j-1} + 1, & \text{if } v_i = w_j \\ s_{i-1,\,j} + 0 \\ s_{i,\,j-1} + 0 \end{cases}$$



v = AGCGTAG

w = GTCAGA

A G – C – G T A G

– G T C A G – A –

Local alignment

- What if we just want a region of similarity?
- Change the first row and column in the dynamic programming table to 0s
- Allow the alignment to start anywhere

  Score[i,j] = max{0, case 1, case 2, case 3}

- Answer is the location in the matrix with the highest score

Extending to sequence alignment

- When solving for the LCS, mis-alignments are free
- What happens if we pay for our "mistakes"? (this also allows us to account for "similar" amino acids)

Value[Match] = 10

Value[Mismatch] = -5

Value[Gap] = -2

Match = [A,A], [C,C], [G,G], [T,T]

Mismatch = [A,G], [A,C], [A,T], …

Gap = [A,-], [-,A], …

The same dynamic programming algorithm works!

Penalizing insertions and Deletions

- Linear scoring model
  - σ = penalty for insertion or deletion of a single simple
  - σ · *k* = penalty for insertion or deletion of *k* symbols

```
GATCCAG        GATCCAG
GA-C-AG        GA--CAG
```

Penalizing insertions and Deletions

Mutations are often caused by errors in DNA replication that insert or delete an entire interval of *k* nucleotides as a single event (instead of *k* independent insertions or deletions)

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Affine gap penalties

$$\text{Cost}(k \text{ gaps in a row}) = \text{Cost}(\text{gap open}) + (k-1)^* \text{Cost}(\text{gap})$$

$$= \sigma + (k-1) \cdot \varepsilon$$

Gap opening penalty is high and gap extension penalty is low (once we start a gap we might as well pile more gaps on top)

and Think

How are the following alignments penalized using the new affine gap penalties?

```
GATCCAG
GA-C-AG
```

```
GATCCAG
GA--CAG
```

and Think

How are the following alignments penalized using the new affine gap penalties?

Cost(k gaps in a row) = Cost(gap open) + (k-1)* Cost(gap)

$= \sigma + (k-1) \cdot \varepsilon$

GATCCAG

GA–C–AG

$= \sigma + (1-1) \cdot \varepsilon + \sigma + (1-1) \cdot \varepsilon$

$= 2\sigma$

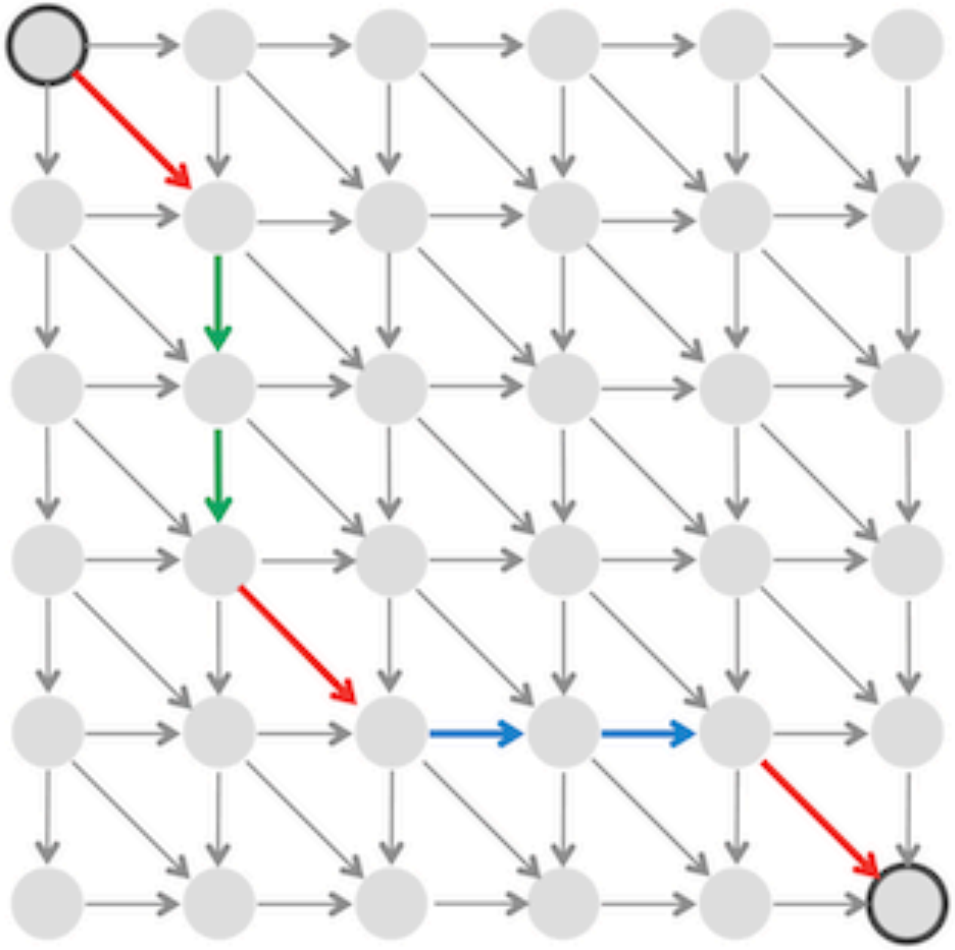
GATCCAG

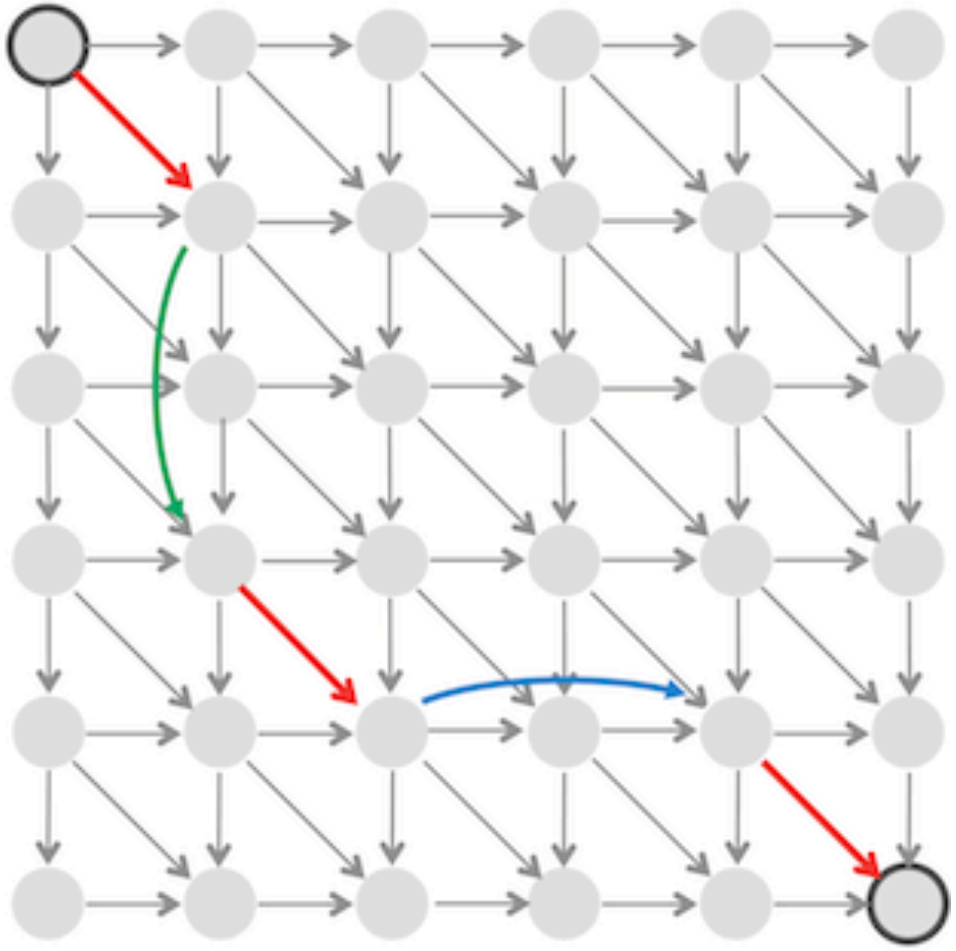
GA––CAG

$= \sigma + (2-1) \cdot \varepsilon$

$= \sigma + \varepsilon$

Adding Affine Gap Penalties to the Alignment Graph





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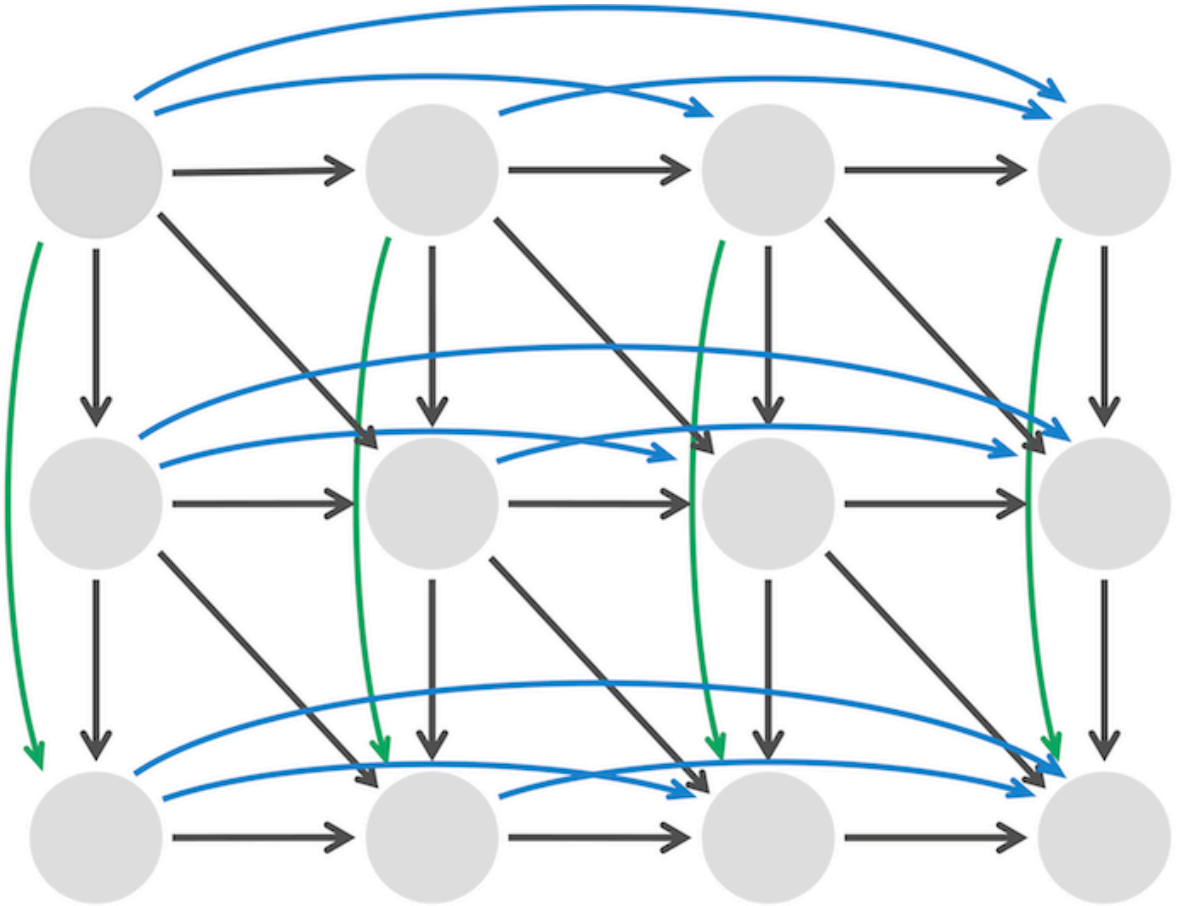

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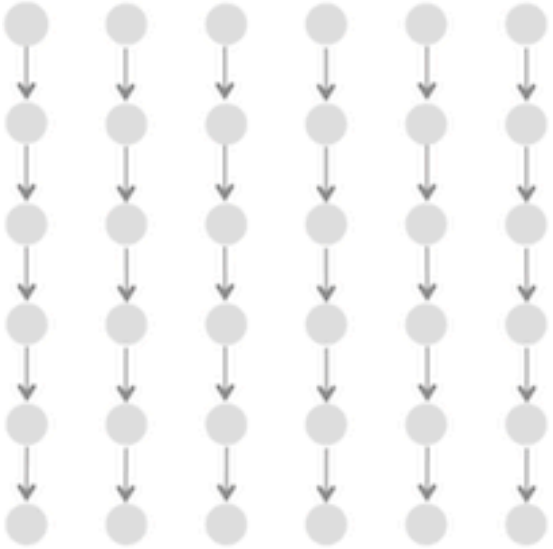

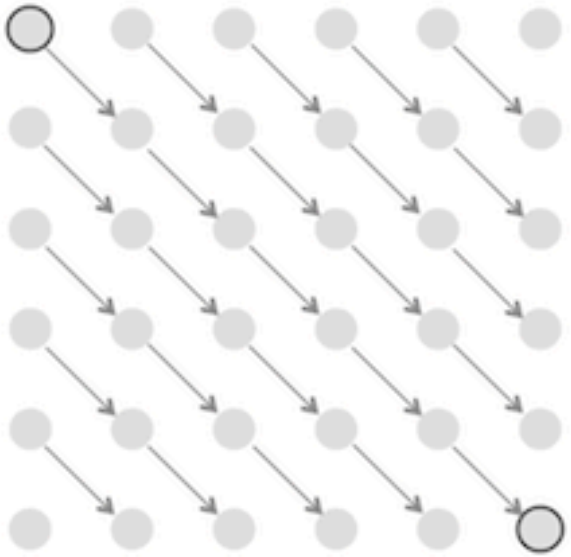

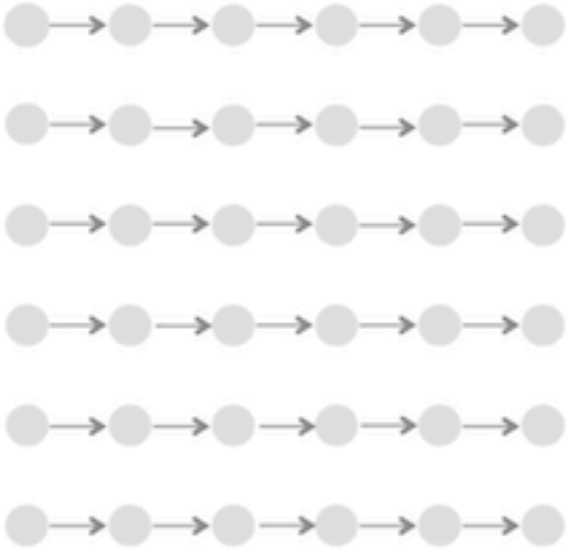

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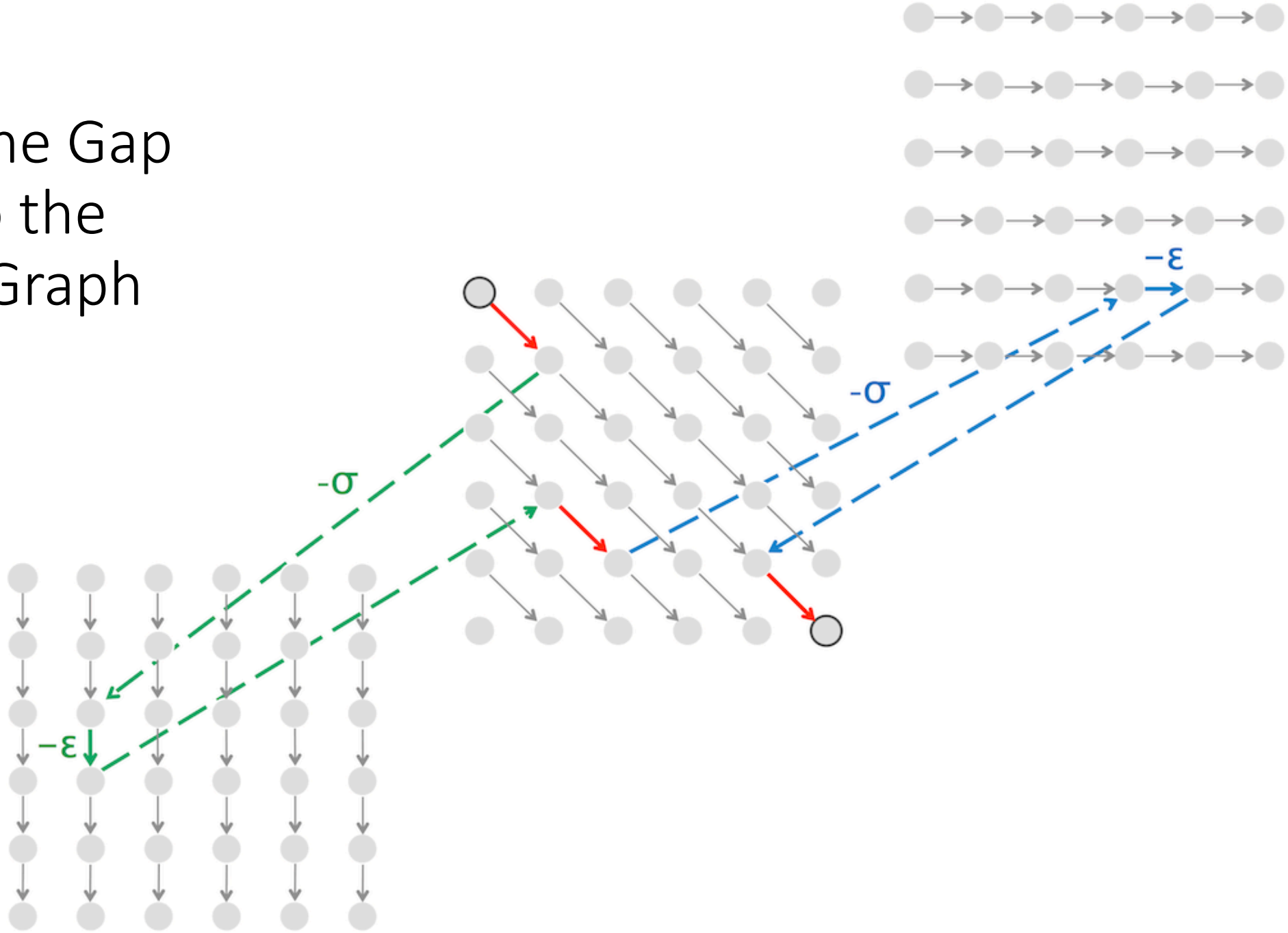

Where do the alignment scores come from?

- PAM matrices –
  - PAM1 – based on frequency of mutations between closely related proteins (within 1 "evolutionary step")
  - PAM 2 - ... within 2 evolutionary steps – ...
  - PAM 250 – commonly used
- BLOSUM matrices – Frequency of mutations between proteins that are x% similar
  - BLOSUM100 – based on proteins that are exactly the same (e.g. score(A,A) is defined but not score(A,G))
  - BLOSUM62 – commonly used
- gap scores usually determined empirically

BLOSUM62

	Ala	Arg	Asn	Asp	Cys	Gln	Glu	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val
Ala	4																			
Arg	−1	5																		
Asn	−2	0	6																	
Asp	−2	−2	1	6																
Cys	0	−3	−3	−3	9															
Gln	−1	1	0	0	−3	5														
Glu	−1	0	0	2	−4	2	5													
Gly	0	−2	0	−1	−3	−2	−2	6												
His	−2	0	1	−1	−3	0	0	−2	8											
Ile	−1	−3	−3	−3	−1	−3	−3	−4	−3	4										
Leu	−1	−2	−3	−4	−1	−2	−3	−4	−3	2	4									
Lys	−1	2	0	−1	−3	1	1	−2	−1	−3	−2	5								
Met	−1	−1	−2	−3	−1	0	−2	−3	−2	1	2	−1	5							
Phe	−2	−3	−3	−3	−2	−3	−3	−3	−1	0	0	−3	0	6						
Pro	−1	−2	−2	−1	−3	−1	−1	−2	−2	−3	−3	−1	−2	−4	7					
Ser	1	−1	1	0	−1	0	0	0	−1	−2	−2	0	−1	−2	−1	4				
Thr	0	−1	0	−1	−1	−1	−1	−2	−2	−1	−1	−1	−1	−2	−1	1	5			
Trp	−3	−3	−4	−4	−2	−2	−3	−2	−2	−3	−2	−3	−1	1	−4	−3	−2	11		
Tyr	−2	−2	−2	−3	−2	−1	−2	−3	2	−1	−1	−2	−1	3	−3	−2	−2	2	7	
Val	0	−3	−3	−3	−1	−2	−2	−3	−3	3	1	−2	1	−1	−2	−2	0	−3	−1	4

https://en.wikipedia.org/wiki/BLOSUM#/media/File:BLOSUM62.png