BMEG 3105 : Data Analytics for Personalized Genomics and Precision Medicine
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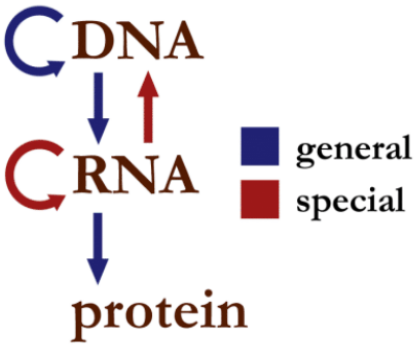
Sequence and Dynamic Programming (L3)

A) Sequence Data



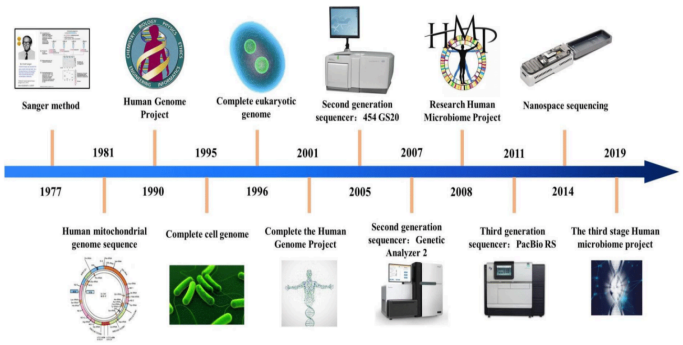
DNA store genetic information
RNA helps express information and turns to protein.

Phenotype = Genotype + Environment

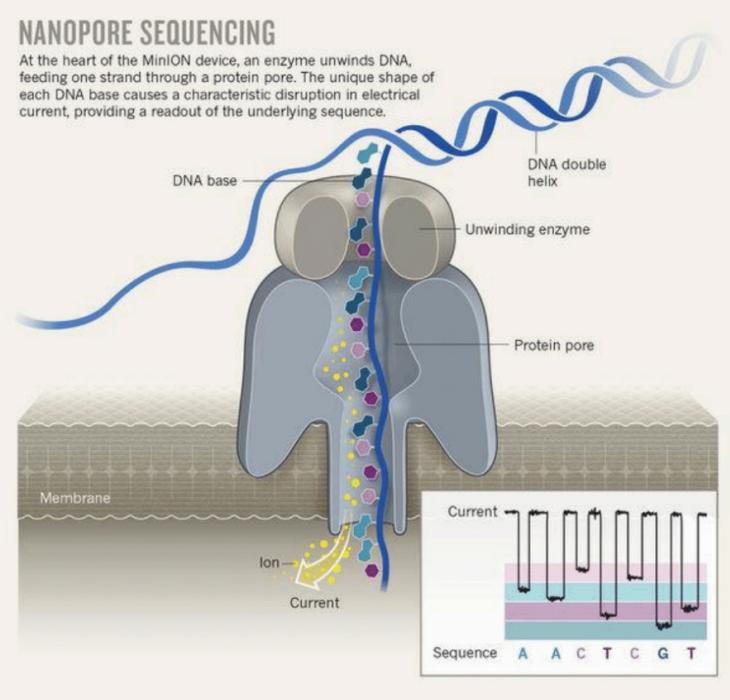
Phenotype : How we look, for example skin colours.
Genotype : DNA sequence / gene sequence. 99% dna sequence of each individuals is the same
Environment : That affect the gene expression

1) Sequence Type

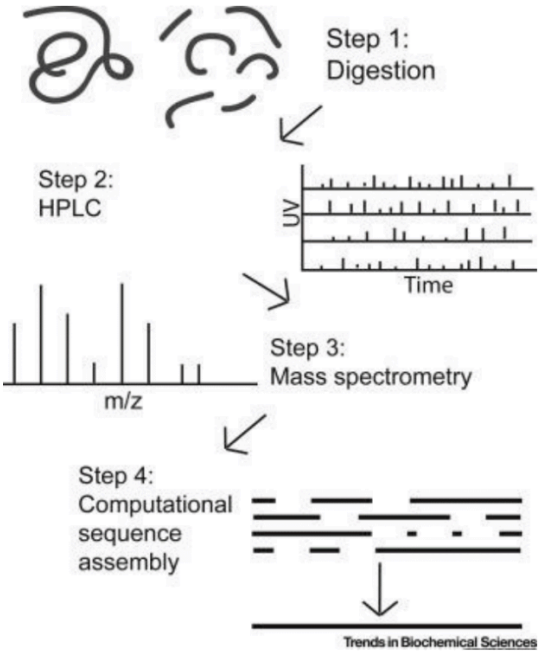
No.	Sequence		How to get the sequence
	DNA Sequence	• ATCG • Double Strand • There are 3 billions of this pair	As years go, there are more advanced ways to achieve sequence and it still under development From short read to long reads
	RNA Sequence	• AUCG • Single Strand	



- Nanopore Sequencing

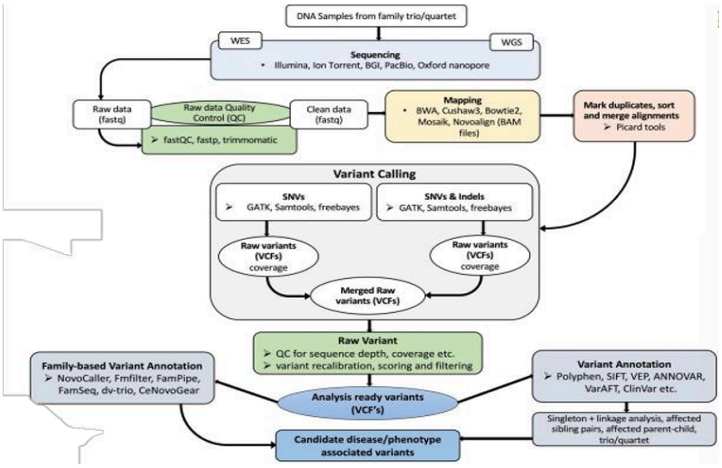


- ☐ DNA **goes through chemical pore** (like when we go through a security gate) with each **base generating electric current change**.
- ☐ Sequencing by detecting electric change from different bases (ATCG).
- ☐ Manage to sequence **long sequences up to 4 Mb** compared to the older generation that can only up to 1000 bp.
- ☐ But have a high **error rate at 5%.**
- ☐ Still under active development.

	Protein Sequence	• 20 amino acids • Multiple sequence alignment	Protein Sequencing  ☐ Based on **Mass Spectrometry (MS)** ☐ The process starts by **breaking** it down into **short pieces** then being **determined by MS** based **on weight** before being **assembled into raw sequence** (similar like a jigsaw puzzle).

2) Raw Data Handling

No.	Sequence	Process

1	DNA Sequence	 ● Quality Control Delete unneeded sequence ● Map reads to reference genome Mark duplicate, sort and merge alignment to detect mutation and variant ● Variant Calling ● Phenotype associated variants Link between genetic variant to phenotype
2	Protein Sequence	By sequence comparison such as **multiple sequence alignment** which if the sequence similar: ☐ Sequence - to Structure -to Function Paradigm Similar sequence -> Similar structure -> Similar function ☐ Homology Common ancestor

3) Sequence Alignment

To determine the similarity between sequences and identify regions of similarity

Why is it important?:
- For biomolecular function and property prediction
  Similar sequence -> Similar structure -> Similar function

- For evolution, identifying conservative region, investing mechanism
  Common ancestor

Pairwise sequence alignment

Maximise the similarity of the two sequences by inserting the gap in the sequences and score the alignments.

ATCG_ _ -> Even though its has the same formation sequence but the position of the gap
_ _ ATCG in the arrangement makes them very different if we calculated it from the alignment score directly which ended up being wrong.

How to do the scoring?

Scoring Type	Example
Match (identical bases)	• A-A • T-T • C-C • G-G
Mismatch (Substitution)	• A-T • T-G • C-A • etc…
Gap (Insertion / deletion)	• A-_ • T-_ • C-_ • G-_

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2

A G G C C G -> 2 + (-7) + 2 + 2 + (-10) +2
A T G C _ G = -9

A G G C C G -> 2 + (-7) + 2 + 2 + (-7) +(-10)
A T G C G _ = -18

Higher the alignment score means the more similarity between the sequences.

How can we find the best alignment?

- enumeration
  The straight forward solution is to **enumerate down all** the possibilities then **combine the score alignment** then find the **highest**.

  But the problem is there are too many alignments

$$\binom{2n}{n} = \frac{(2n)!}{(n!)^2}$$

If n = 300
There are 7 x 10^88 possibilities

- Dynamic Programming
  The solution to enumeration problem

B) Dynamic Programming

- Break main problems into **sub-problems**
- Solve the sub-problems optimally and **recursively**
- Utilize these optimal solutions to build the best overall solution for the initial problem

Step:

Scoring matrix:

	A	C	G	T
A	2	-7	-5	-7
C	-7	2	-7	-5
G	-5	-7	2	-7
T	-7	-5	-7	2

Gap penalty = -10

		A	C	C	G
A					
C					
G					

1) Fill the **first row and and first column** which is the **gap penalties** and in this example is (-10)

		A	C	C	G
	0	-10	-20	-30	-40
A	-10				
C	-20				
G	-30				

As you go toward the left or down side of the gap penalties , **add the gap penalties from the previous box number.**

2) Next we start to fill the box on the diagonal of the box (0)

0	-10
-10	

To fill the box, there are 3 options to be considered, **top, left, and diagonal**.

Top

Previous number + gap
-10 + (-10)
-20

Left

Previous number + gap
-10 + (-10)
-20

Diagonal

Previous number +match/mismatch
(Since in this case is A-A so is a match)
0 + 2
2

From the results, we got -20 , -20 and 2. Here we **choose the biggest number** to be put in the box which is 2. Also **put the arrow** to indicate which side the number comes from.

		A	C	C	G
	0 →	-10 →	-20 →	-30 →	-40
A	-10 ↓	2			
C	-20 ↓				
G	-30				

3) Do it to the other empty box until it fills the whole table.

		A	C	C	G
	0 →	-10 →	-20 →	-30 →	-40
A	-10 ↓	2 →	-8 →	-18 →	-28
C	-20 ↓	-8 ↓	4 →	-6 →	-16
G	-30	-18	-6	-3	-4

4) Translate the arrow into alignment starting from the bottom right. It may have more than 1 alignment. Horizontal arrow translates to a gap while diagonal arrow means both sequences proceeding by one letter.

In this case there are 2 alignment

A C C G A C C G
A _ C G A C _ G