

Bioinformatics Topics

Informatics

Biology

Operating
Systems



Windows, Macintosh both offer an intuitive GUI ... familiarity can be assumed?

Linux with a Windows like GUI interface ... also, familiarity can be assumed?

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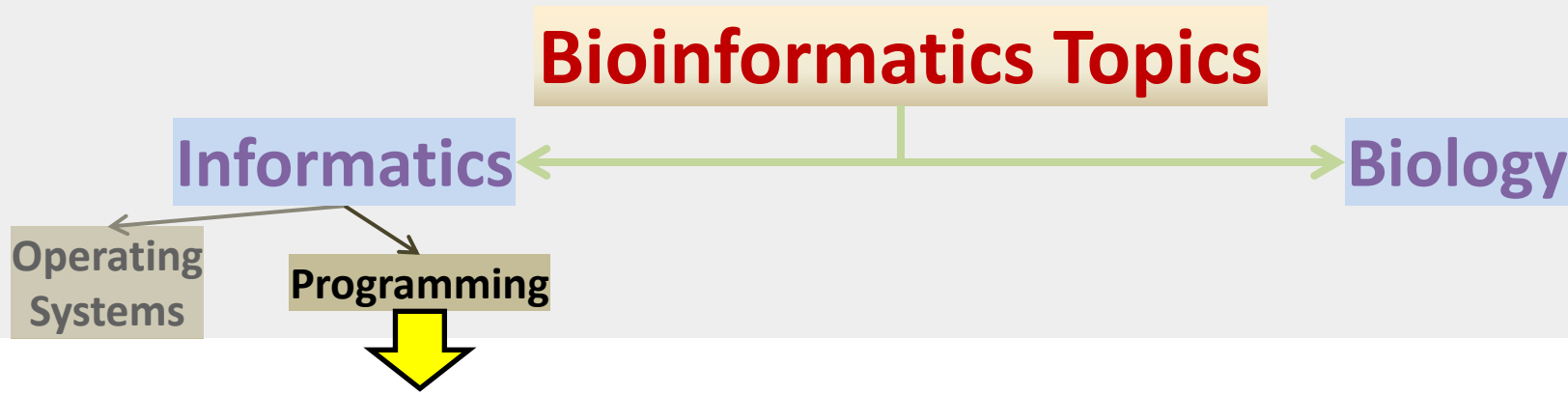
Operating
Systems



Linux command line! ... complexity is overstated, but some instruction is required.

All OS options are conceptually identical ... enabling control over files, folders, and programs.

Linux command line! ... **the only option** for compute intense software.



Rarely is there a need to become a truly proficient programmer.

BUT - Sufficient skill to affect basic management of large datasets is important.

AS IS - Sufficient skill to construct simple customised [pipelines](#).

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Python is currently the most popular Programming Language for Bioinformatics.

Minimal programming skill levels
would allow:

The construction of small programs.
The understanding of slightly larger programs.
Ability to convey program specifications to a specialist.

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A basic understanding of Statistics is just as vital when designing an experiment.



“To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he may be able to say what the experiment died of.”

As it is when large datasets need to be interpreted, which sensibly demands a working familiarity with a quality Statistical Package.

Bioinformatics software commonly employs statistics to select the most probable answer from a set of many possible answers to a given question.

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Experimental Data types include :

Sequences

- Typically [Next-Generation DNA Sequencing \(NGS\)](#).

3D Protein Structures - [X-ray crystallography](#) or
[Nuclear magnetic resonance spectroscopy \(NMR\)](#)

Gene Expression Data - [Microarrays](#)

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The Alignment of Pairs of Homologous DNA/Protein sequences.

Fundamental to most forms of DNA/Protein Sequence analysis

Substitution

Deletion

Conservation

Insertion

Putative
Ancestor Sequence

... ACYG-QWRWDVI-S...
... ACFGHQWRWDVI-S...
... ACFGHQWRWDVILS...

Sequences of
Homologous Proteins

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The Alignment of Families of Homologous sequences.

First, find a family of Homologous sequences.

```
... APFELVISWKLIVESPAINCDWRTENGLANDSGMLVNOWPAI ...
... APYELVISQWKLIVESNPAINKDWRITYENGLANDSGMLVNOWAI ...
... APFELVISWKLIVESNPAINCDWRTENGLANDSGMLVNOWAI ...
... APFELVISQWKLIVESNPAINCDWRTENGLANDSGMLVNOWAI ...
... APYELVISWKLIVESNPINCDWRTENGLANDRSGMLINOWAI ...
... APFELVISQWKLIVESNPAINCDWRTENGLANDSGMLVNOWLI ...
... APFELVISQWKLIVESNPAINCDWRTENGLANDSGMLVNOWAI ...
... APYELVISWKLIVESNPAINCDWRTENGLANDSGMLLNOWMI ...
```


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The Alignment of Families of Homologous sequences.

Then, align by inserting “-”s representing InDels, in each sequence.

```
... APFELVIS-WKLIVES-PAINCDWRT-ENGLANDSGMLV-NOWPAI ...
... APYELVISQWKLIVESNPAINKDWRITYENGLANDSGMLV-NOW-AI ...
... APFELVIS-WRLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNP-INCDWRT-ENGLANDRSGMLINOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-LI ...
... APFELVISQWKLIVESNPAIN-DWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNPAINCDWRT-ENGLANDSGMLL-NOW-MI ...
```

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The Alignment of Families of Homologous sequences.

Next, identify the columns where **Substitutions** and/or **InDels** have been predicted.

```
... APFELVIS-WKLIVES-PAINCDWRT-ENGLANDSGMLV-NOWPAI ...
... APYELVISQWKLIVESNPAINKDWRITYENGLANDSGMLV-NOW-AI ...
... APFELVIS-WRLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNP-INCDWRT-ENGLANDRSGMLINOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-LI ...
... APFELVISQWKLIVESNPAIN-DWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNPAINCDWRT-ENGLANDSGMLL-NOW-MI ...
```

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The Alignment of Families of Homologous sequences.

Then, identify the columns where full **Conservation** has been predicted.

```
... APFELVIS-WKLIVES-PAINCDWRT-ENGLANDSGMLV-NOWPAI ...
... APYELVISQWKLIVESNPAINKDWRTYENGLANDSGMLV-NOW-AI ...
... APFELVIS-WRLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNP-INCDWRT-ENGLANDRSGMLINOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-LI ...
... APFELVISQWKLIVESNPAIN-DWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNPAINCDWRT-ENGLANDSGMLL-NOW-MI ...
```

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The Alignment of Families of Homologous sequences.

Finally ... Identify the Glorious Message!!!!.

```
... APFELVIS-WKLIVES-PAINCDWRT-ENGLANDSGMLV-NOWPAI ...
... APYELVISQWKLIVESNPAINKDWRTYENGLANDSGMLV-NOW-AI ...
... APFELVIS-WRLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNP-INCDWRT-ENGLANDRSGMLINOW-AI ...
... APFELVISQWKLIVESNPAINCDWRT-ENGLANDSGMLV-NOW-LI ...
... APFELVISQWKLIVESNPAIN-DWRT-ENGLANDSGMLV-NOW-AI ...
... APYELVIS-WKLIVESNPAINCDWRT-ENGLANDSGMLL-NOW-MI ...
```

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Searching for Homologous Sequences in a Sequence Database.

Database searching is the most common Bioinformatics process by far.

Database searching is pairwise comparison repeated many times.

Non-optimal comparison methods are essential for practical reasons.

A list of matches, ordered by the improbability of occurring just by chance is generated.

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Searching for Homologous Sequences in a Sequence Database.

Database searching seeks “Similarity”. Users seek “Homology”.

Query

KLYPLRPQTPEPPPPPPPPPLPAAPPQP

Similarity

+L P +P P P PP P PP PP+P

Database Entry

RLTPPQPLMMPPRPPTPPTPLPPATLTVPPRP

Homology?

Or 2 proteins including a
lot of Prolines??

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Searching for Homologous Sequences in a Sequence Database.

Database searching seeks “Similarity”. Users seek “Homology”.

Query

TTAGCAAGATCAGCCCTAACTCGGCATCTT

Similarity

| | | | | | | | | |

Database Entry

CTTGCGCGCTCTGTCTTGACGAGACACTTA

Homology?

A very unconvincing
alignment!!

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Searching for Homologous Sequences in a Sequence Database.

Database searching seeks “Similarity”. Users seek “Homology”.

Query

TTAGCAAGATCAGCCCTAACTCGGCATCTT

Similarity

L A R S C L T R H L

Database Entry

L A R S C L T R H L

CTTGCGCGCTCTGTC TTGACGAGACACTTA

Homology?

Probable --- a perfect
protein match??

In all circumstances – always align at the protein level wherever possible.

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Searching for simple sequence patterns Sequences in DNA.

Largely a matter of finding short sequences within longer ones.

Computationally trivial.

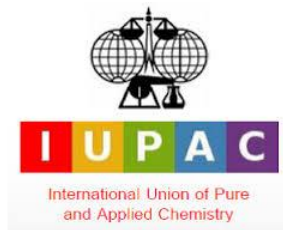
A concrete example is required:

Restriction Mapping

Detecting Restriction Enzyme Recognition Sites
is complicated by their redundancy.

Few Recognition Sites can be simply defined
using only the codes **A**, **C**, **G** and **T**.

The solution is to use the [Nucleotide Ambiguity Codes](#) defined by [IUPAC](#).



Unambiguous site (EcoRI):

G/AATC

Ambiguous site (PpuMI):

RG/GWCCY

Cut here

And here

TTAGCAAGATCAGGACCTACTCGGCATCTTCCTGGGTCCC

RGGWCCY

IUPAC DNA Alphabet

<u>Code</u>		<u>Meaning</u>
A		A
C		C
G		G
T/U		T/U
M	`aMino`	A C
R	`puRine`	A G
W	`Weak`	A T
S	`Strong`	C G
Y	`pYrimidine`	C T
K	`Keto`	G T
V	`not T`	A C G
H	`not G`	A C T
D	`not C`	A G T
B	`not A`	C G T
N	`aNy`	A C G T

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Searching for simple sequence patterns Sequences in Proteins.

Patterns can be derived manually to represent conserved regions of MSAs

Simple where conservation is 100%

```
... CQVLNPYYHWGQCGGIGWSGPTVCASGTT ...  
... CQYSNDYYHWGQCGGIGWSGCKTCTSGTT ...  
... CHVLNPYYQWGQCGGIGWTPSTTCASPYT ...  
... CSTLNPYYVWGQCGGIGWSGPTNCAPGSA ...  
... CVYSNDYYVWGQCGGIGWSGPTCCASGST ...
```

WGQCGGIGW

Pattern

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Searching for simple sequence patterns Sequences in Proteins.

Not so easy where conservation is
less than perfect

An Amino Acid Alphabet including
all ambiguities is not practical!

The solution is a simple syntax for
ambiguous amino acid sequences.

```
... CQVLNPYYHWKQCGGLGWSGPTVCASGTT ...  
... CQYSNDYYHWGQCPGIGWSGCKTCTSGTT ...  
... CHVLNPYYQW AQC FGVGWTPSTTCASPYT ...  
... CSTLNPYYVW LQCYGIGWSGPTNCAPGSA ...  
... CVYSNDYYVW AQC GG VGWSGPTCCASGST ...
```

W{P}QCxG[LIV]GW

Pattern

NOT a P

Anything

L or I or V

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Searching for simple sequence patterns Sequences in Proteins.

Match Here
Feature Site?



... GGSKFAWD GMYDKLRMLMRLWLQCKGVGWRTSFTQEQIEALEKEFERRQASNTPSHPI ...

W{P}QCxG[LIV]GW

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Searching for simple sequence patterns Sequences in Proteins.

Simple Protein patterns are of limited precision.

Only highly conserved regions can be described usefully.

Patterns cannot weight possibilities by frequency.

F
F
F
Y
F
F
F
F

[FY] --- or --- [F_Y] ?

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Searching for simple sequence patterns Sequences in Proteins.

Simple Protein patterns are of limited precision.

Patterns do not reflect commonly accepted substitutions.

F
F
F
F
F
F
F
F
F
F

--- or ---

[F_Y] ?

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Searching for Protein properties with better models.

Again, start with an MSA of instances of the feature to be modelled.

Create a “suitable” representation of the relevant portion of MSA

Compare the model along other protein sequences was illustrated for simple patterns.

Where matches are detected, the corresponding protein property is likely to occur.

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Searching for Protein properties with better models.

A variety of simple models have been developed (e.g. [Position Weight Matrices](#)) for a number of purposes, including:

- Gene discovery in bacteria genomes (DNA)
- Early versions of 2D protein Structure Prediction
- [Transmembrane Alpha Helix prediction](#)
- [TATA box Detection](#) (DNA)
- [Helix-Turn-Helix \(HTH\) Prediction](#)
- [Prediction of Coiled Coils](#)

The most powerful and prolific current profiles are [Hidden Markov Models](#) (HMMs)

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Estimating evolution - [Phylogeny](#).

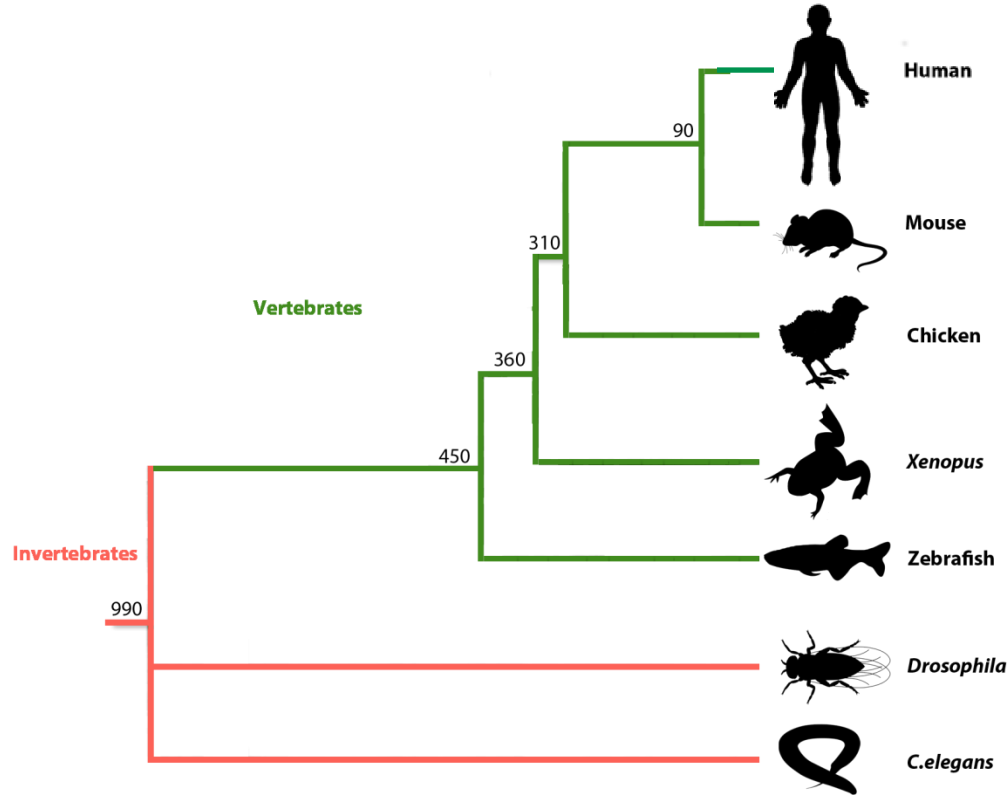
Broadly, the estimation of evolutionary history from available evidence.

“Evidence” does not have to be a carefully crafted MSA of Orthologous sequences from a range of organisms.

However, in the context of Bioinformatics, it invariably is.

Typically, conclusions of Phylogenetic analysis are represented as Evolutionary Trees.

Which are very Beautiful!!



My personal preference is for trees that place ME as far away from a MOUSE as possible!!!!

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Estimating evolution - [Phylogeny](#).

Phylogeny is another example of an analysis based on MSAs.

One very effective Phylogenetic strategy is to seek an answer to the question:

“What is the most probable Evolutionary Tree, given I believe this MSA to be perfect?”

Reinforcing how central is the role of Statistics in Bioinformatics.

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Protein structure prediction. Secondary Structure.

Essentially predicting the locations of Alpha Helices, Beta Sheets and Turns.

Modern methods employ Machine Learning to generate Artificial Neural Networks.

That is profiles computed by “learning” from observation of examples.

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Protein structure prediction. Secondary Structure.

Better predictions are obtained from MSA data than from individual protein sequences.

General principle being, the more information offered, the more reliable the prediction.

Some systems will automatically generate an MSA if offered a solitary protein sequence.

Prediction will be based on the MSA, computed by iterative database searching.

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Protein structure prediction. Tertiary Structure.

Predicting Tertiary Structure directly from Primary Structure is not currently practical.

De novo protein structure prediction requires better algorithms and more computing power.

Homology modelling requires a reliable Tertiary Structure for a homologous protein.

Tertiary Structure for a protein is predicted by comparison with the homologous structure.

Homology modelling is hampered by low volumes and uneven spread of available structures.

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Overview.

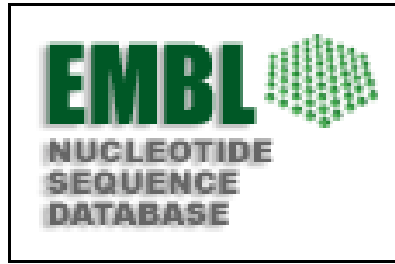
Raw Experimental Data, can next be Annotated in the light of analytical revelation.

Data + Annotation = Information.

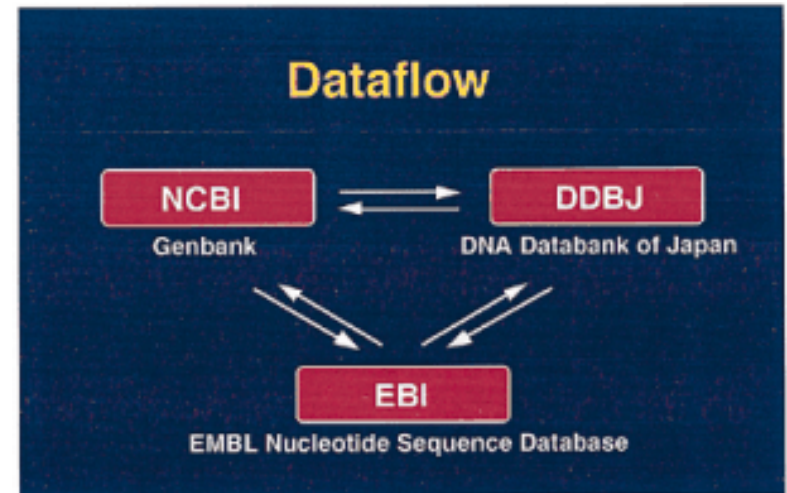
Information can now be stored in Databases that allow users easy and unrestricted access.

Primary DNA Sequence Databases

Original submission by experimentalists
Content controlled by the submitter



NCBI
GenBank



Primary Protein Sequence Databases



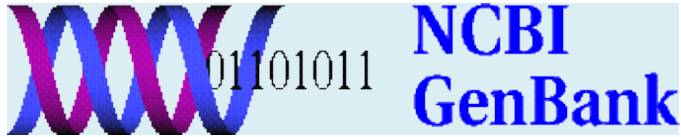
UniProtKB

an encyclopedia on proteins

- ★ composed of 2 sections ★
 - UniProtKB/TrEMBL and UniProtKB/Swiss-Prot
 - unreviewed and reviewed
 - automatically annotated and manually annotated

Derivative Sequence Databases

Built from primary data



RefSeq

Submission by experimentalists
Significant redundancy
Annotation inconsistent
DNA and RNA only

non-redundant
richly annotated
DNA, RNA, protein
diverse taxa

akin to the primary
research literature

akin to the review
literature

Derivative Databases for Protein Features

Collections of HMMs representing [Protein Domains](#) and/or [Motifs](#) derived from Protein sequence Databases.

Derivative Databases for Protein Features

It is generally wise to use more than one Feature Searching service.

This can be tedious, involving many websites and different search tools.

is a consortium of member databases.

defines protein families, domains, regions, repeats and sites according to matches against member databases

enables any subset of member databases to be searched together



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Genome Databases.

Genome Databases store entire genome sequence(s) AND their interpretation.

Each new sequenced genome or significantly re-assembled existing genome is fully analysed.

The individual processes for manual analysis are the same as those for automatic analysis.
Most have been mentioned in this simple talk.

Analysing an individual gene can be done manually.

Analysing an entire genome is only practical using automated strategies.

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e!Ensembl

The Three foremost Genome Database options



NCBI Map Viewer



Genome Browser

Ensembl and UCSC Browser software can be downloaded and used for private datasets.

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Protein Structure Databases.

RCSB **PDB**
PROTEIN DATA BANK



Worldwide
Protein Data Bank
Foundation

PDBj
Protein Data Bank Japan

PDBe
Protein Data Bank in Europe

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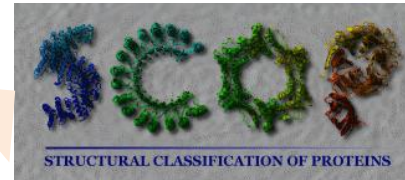
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Protein Structure Databases.



Worldwide
Protein Data Bank
Foundation



Superfamily

HMM library and genome assignments server



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Genetic Variation Databases.

Databases storing the many genetic variations that occur between individuals and species.

Widely incorporated into Genome Databases, such as Ensembl.

Since High Throughput Sequencing (HTS) has become standard, variation detection has become easier. Databases have developed dramatically.

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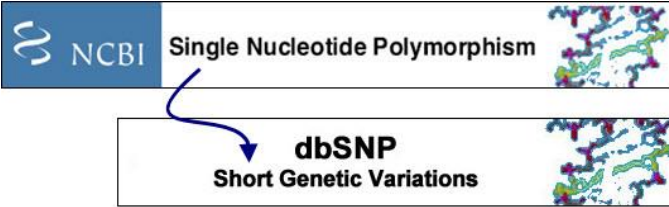
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Genetic Variation Databases.



dbSNP is the largest general database for genetic variations.
Originally just Single Nucleotide Polymorphisms (SNPs).
Now includes other types of Short Genetic Variation.

dbSNP, originally focused on human variations, now covers many organisms.

dbSNP now records relationships between variation and phenotype.

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Other relevant databases include:

Microarray databases

There are a considerable number, both commercial and public domain.

Two major Public Domain Microarray Databases are:

The Gene Expression Omnibus (GEO), maintained in America.



ArrayExpress, maintained in Europe.



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Other relevant databases include:

Microarray databases

High Throughput Sequencing (HTS) has become a viable option to the use of Microarrays.

Accordingly, both GEO and ArrayExpress now manage HTS data sets.

ArrayExpress regularly imports data from GEO.

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Other relevant databases include:

Literature databases

Many free literature search/access services are available via the INTERNET.

You will be introduced to, arguably, the best and most famous as a part of this course.

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Other relevant databases include:

[Gene Ontology Database](#)



Early Primary Database annotation was poor.

Annotation was left to the submitted and then not curated .

In consequence, Database Searching just by Keyword was far from reliable.

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Other relevant databases include:

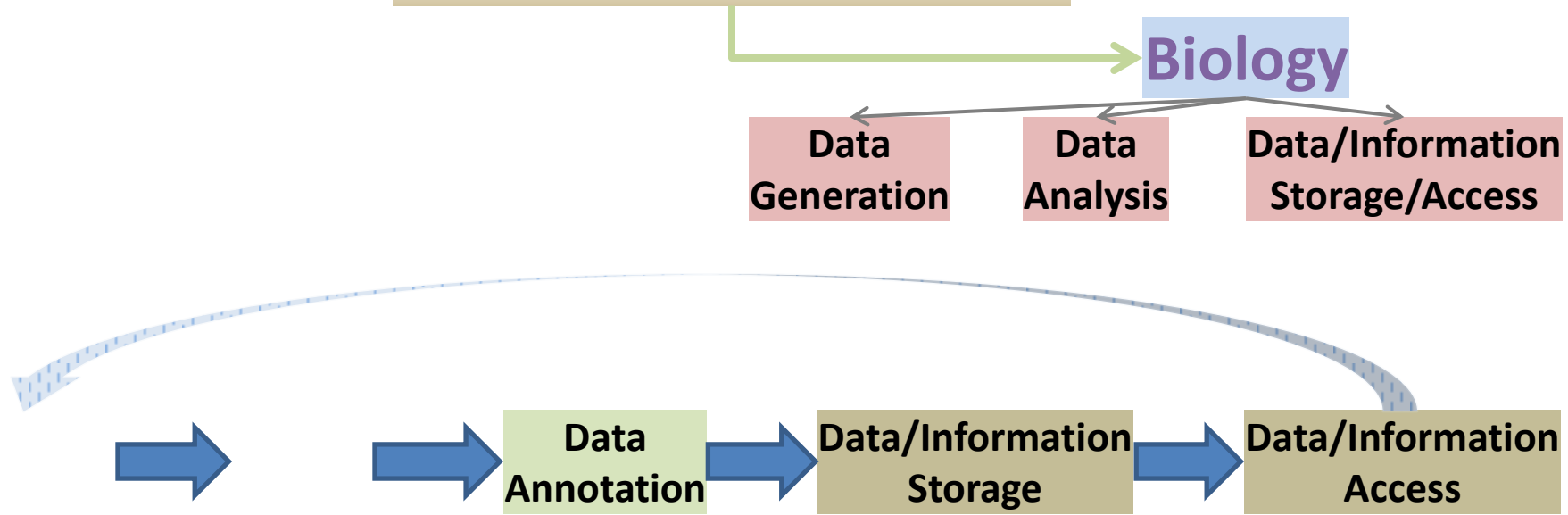
[Gene Ontology Database](#)



The [Gene Ontology](#) (GO) database provides a hierarchy of formally agreed terms to describe gene products accurately and unambiguously.

Searching with these terms radically improves the efficacy of annotation searching.

Bioinformatics Topics



A simplistic ordering for the **Bioinformatics Topics** discussed here

And now ... Once again ... Your turn!
Some issue for consideration, discussion and reaction

The Bioinformatics topics mentioned here do not constitute a comprehensive list. What would suggest is missing ... in order of importance?

The term algorithm was mentioned once or twice. There are slightly differing definitions. Pick the one you like best and justify your selection.

Define the three terms Homologue, Paralogue and Orthologue, being ever assiduous to ignore offensive American misspellings!

The is but one basic strategy for computing Pairwise Alignments that is considered optimal. However, this strategy can be implemented to compute either [Global Alignments](#) or [Local Alignments](#).

Just informally, [how do these two possibilities differ?](#)

Generally speaking, would you compute MSAs using a Global or a Local approach? Briefly justify your choice.

Generally speaking, would you conduct Database Similarity searches using a Global or a Local approach? Briefly justify your choice.

“Sequence alignment only makes sense for sequences representing Homologous entities”

A profound observation made by the ever sagacious David Philip Judge whilst sipping an eventide cup of [Tesco](#)’s very cheapest tea in the penthouse suite of his Ivory Tower (personal communication, 2016.06.10).

Consider and comment upon this fundamental truth.

“A Multiple Alignment of Homologous sequences which were a mixture of Orthologues and Paralogues would not be suitable as input data for [Phylogenetic](#) analysis ”

Another deep one from DPJ

Consider and comment upon this further pearl of enlightenment.

In the course of the dialogue for this presentation, there was mention of “Accepted Substitutions”, more formally referred to as “Accepted Point Mutations”, or ... if you enjoy clumsy for the sake of a pronounceable acronym, “[Point Accepted Mutation](#)” (PAM).

How would you informally define an “Accepted Point Mutation”?

The [Extended syntax for ScanProsite](#) is the most common syntax used for protein pattern definition. [ScanProsite](#) being the program for searching the of the [Prosite database](#). Prosite was first created way back in the 1980s and, initially, was composed exclusively of protein patterns.

There is no great value, at this stage, to be entirely familiar with this very simple syntax. However, from the hints in this presentation and a quick glance at the appropriate web pages, can you interpret the pattern?

`C{P}x(3,7)[FY](2)Wx(2)[VIL]`

In the slides preceding, [Protein Domains](#) and [Protein Sequence Motifs](#) were mentioned with rather sparse explanation.

Define both of these terms and describe simply the [difference between them](#).

In the slide notes, there is mention of Position Weight Matrices (PWMs).

Can you say, simply, what a Position Weight Matrix might be and how it might be used?

What obvious property does a PWM possess that is lacking in a simple sequence pattern (or consensus sequence)?

The best secondary structure programs are reckoned to be around 80% accurate.

It is further suggested that 80% is about as good as it is possible to achieve.

Stated simply, why would you suppose that 100% accuracy might be unobtainable?

Hint: Do you think that two human experts, given the very best evidence of Tertiary Structure, would also agree upon the exact amino acid positions where an Alpha Helix starts and finishes?

Homology Modelling is mentioned in the slides as a method for predicting tertiary structure when structure(s) of protein(s) homologous to the query protein are available. The process involves aligning the query protein with the known structure, using the known sequence as a guide.

It is also possible to predict Tertiary Structure when, known structures thought to be appropriate exist, but only for sequences that **ARE NOT HOMOLOGOUS**. In such cases, the Primary Sequence corresponding to the known structure will be of little assistance.

Tricky eh!? What are the name(s) for those types of method? **ONLY** if you can do so **VERY** simply. Say a few words to say how they over come the lack of a homologous sequence.

It was noted in the slides that often different Protein Feature searches often do not exactly agree.

It is common for two services to agree upon the presence of a domain, but not upon its precise start and end positions within a protein.

Would you find this to be worrying? Surprising? If not, why not?

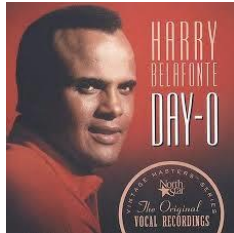
THE END

BREAK!

More to come I fear ... but time for a swift cup of tea perchance?

Maybe time for a short jig? The whistling of a merry tune?

Or, mayhap, a delving into the melodic possibilities of youtube?
There be much good stuff there ... I offer you a few of my favourites.



Once fully refreshed Click on mon braves!

