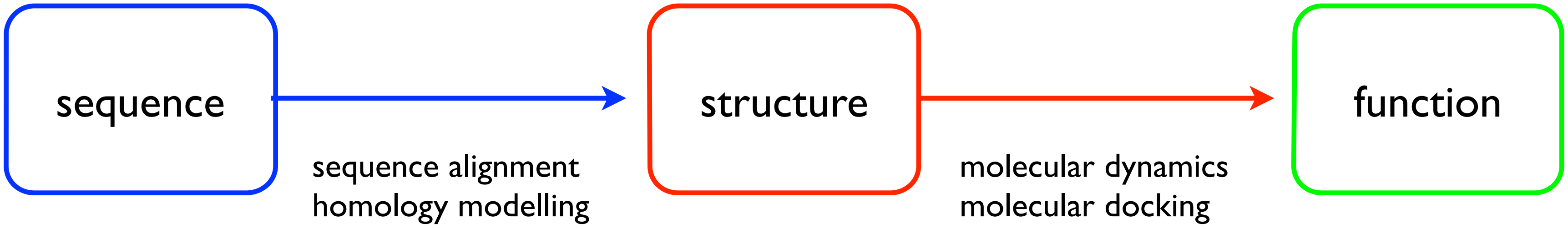
CHEM 498Q / 630Q

Molecular modelling of proteins

Fall 2015 Term

Instructor:
Guillaume Lamoureux
Concordia University, Montréal, Canada

Overview of the course



sequence

sequence alignment
homology modelling

structure

molecular dynamics
molecular docking

function

Sources of information	**UniProt, PDB, etc.**	**CHARMM ff, Molecular libraries, etc.**
Algorithms	**BLAST, MODELLER, etc.**	**NAMD, AutoDock, etc.**

Comparing protein sequences : Similarity *versus* Homology

Identity
Proteins have the same amino acid sequence.

→ Yes or no.
(Easy to check.)

Similarity
Protein sequences have "similar" amino acids.

Nonpolar : Gly (G), Ala (A), Val (V), Leu (L), etc.
Polar : Asn (N), Ser (S), etc.
Acidic : Asp (D), Glu (E)
Basic : His (H), Lys (K), Arg (R)
etc.

→ Something we can quantify.

(We have to decide on a similarity measure, though, which has a certain degree of arbitrariness.)

Homology
Proteins are related to a common ancestor.

→ Either true or false.
(We may or may not know.)

Comparing protein sequences : Similarity *versus* Homology

Homologous proteins very often have similar structures.

Rost, *Protein Eng.* 1999, **12**, 85-94.
http://dx.doi.org/10.1093/protein/12.2.85

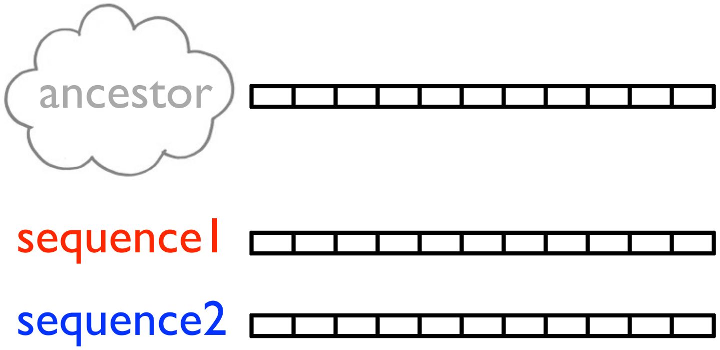
sequence identity > 30% means prob(homology) > 90%
sequence identity < 25% means prob(homology) < 10%
25% < identity < 30% means that you are in the "twilight zone"…

Homologous proteins don't necessarily have the same function.

Hegyi & Gertstein, *J. Mol. Biol.* 1999, **288**, 147-164.
http://dx.doi.org/10.1006/jmbi.1999.2661

Russell, Sasieni, Sternberg, *J. Mol. Biol.* 1998, **282**, 903-918.
http://dx.doi.org/10.1006/jmbi.1998.2043

Sequence alignment



“Hypothesis about which pairs of residues have evolved from the same ancestral residue”

(Zvelebil & Baum, p.74)

Similarity matrix
What are the odds that a certain amino acid X in one sequence is the homolog of amino acid Y in another?

Similarity matrices *S*(X,Y) are usually obtained from the “log odd ratios” observed in a large number of “reference” alignments :

$$S(\mathrm{X},\mathrm{Y}) = \log_{10}\left(\frac{\#\text{ of X-to-Y transitions } / \text{ }\#\text{ of transitions}}{2f(\mathrm{X})f(\mathrm{Y})}\right)$$

20×20 matrix

frequency of amino acid X

frequency of amino acid Y

The odds are high if a large number of X-to-Y transitions is observed in those alignments (relative to the total number of transitions).

```
PQPLEQIKISESQLAGRVGYVEMDLASGRTLAAWRASERFPLMSTFKVLLCGAVLARVDA
GDEQLDRRIHYRQQDLVDYSPVSEKHLADGMTVGELCAAAITMSDNTAGNLLLKIVGGPA
GLTAFLRQIGDNVTRLDRWETELNEALPGDVRDTTTPASMATTLRKLLTTPSLSARSQQQ
LLQWMVDDRVAGPLIRAVLPAGWFIADKTGAGERGSRGIVALLGPDGKAERIVVIYLRDT
AATMAERNQQIAGIGAALIEHWQR
```

```
PQPLEQVTRSESQLAGRVGYVEMDLASGRTLAAWRASERFPLMSTFKVLLCGAVLARVDA
GDEQLDRRIRYRQQDLVDYSPVSEKHLADGMTVGELCAAAITMSDNSAGNLLLKSVGGPA
GLTAFLRQIGDNVTRLDRWETELNEALPGDVRDTTTPASMAATLRKLLTSHALSARSQQQ
LLQWMVDDQVAGPLIRAVLPAGWFIADKTGAGERGSRGIVALLGPNGKAERIVVIYLRDT
PATMAERNQQIARIGAALIEHWQR
```

PQPLEQVTRSESQLAGRVGYVEMDLASGRTLAAWRASERFPLMSTFKVLLCGAVLARVDA
GDEQLDRRIRYRQQDLVDYSPVSEKHLADGMTVGELCAAAITMSDNSAGNLLLKSVGGPA
GLTAFLRQIGDNVTRLDRWETELNEALPGDVRDTTTPASMAATLRKLLTSHALSARSQQQ
LLQWMVDDQVAGPLIRAVLPAGWFIADKTGAGERGSRGIVALLGPNGKAERIVVIYLRDT
PATMAERNQQIARIGAALIEHWQR

PAM1 matrix ("point accepted mutation")

Built from alignments of very similar sequences (identity > 85%, therefore likely evolutionarily related) and normalized so that they describe the probability of having 1 point mutation per 100 amino acids.

Describes in statistical terms a certain "unit" of molecular evolution.

PAM2 = PAM1 × PAM1

PAM3 = PAM2 × PAM1

etc.

Margaret Dayhoff

Source: **Wikipedia**
http://en.wikipedia.org/wiki/Margaret_Dayhoff

BLOSUM matrices

Built from *ungapped* alignments of sequences (mostly from core regions of proteins, where few loops are found).

BLOSUM80
Using only alignments that have more than 80% sequence identity

The NCBI-BLAST server uses **BLOSUM62** (by default), but also **BLOSUM80** and **BLOSUM45**.

It can also use **PAM30** and **PAM70**.

In principle, similar sequences should be aligned based on “low” **PAM** matrices (small evolutionary distances) or “high” **BLOSUM** matrices (highly similar sequences).

BLOSUM62 matrix

	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

Source: **Wikipedia**
http://en.wikipedia.org/wiki/BLOSUM

The alignment problem

To align a sequence of length *N* with a sequence of length *M* :

1. Build the *N* × *M* "scoring table" according to the chosen similarity matrix.

2. Find the top-scoring path across that table, which corresponds to the best alignment.

   This can in principle be done systematically (by trying all possible alignments and comparing their scores, using the *Needleman–Wunsch algorithm*), but most useful software use a *heuristic approach*.

To align two sequences of different lengths, we may have to introduce **gaps**. These gaps carry a penalty.

In BLAST using BLOSUM62, there is a default penalty of 11 units to open a gap, and of 1 unit to extend it by one amino acid.

We quantify the statistical significance of a given alignment using the ***E*-value**, which is the number of sequences one can expect to match the query sequence with a score ***S*** (or higher) due to chance alone.

In other words, the ***E*-value** is the number of alignments that may be as good or better as the one found using the heuristic method.

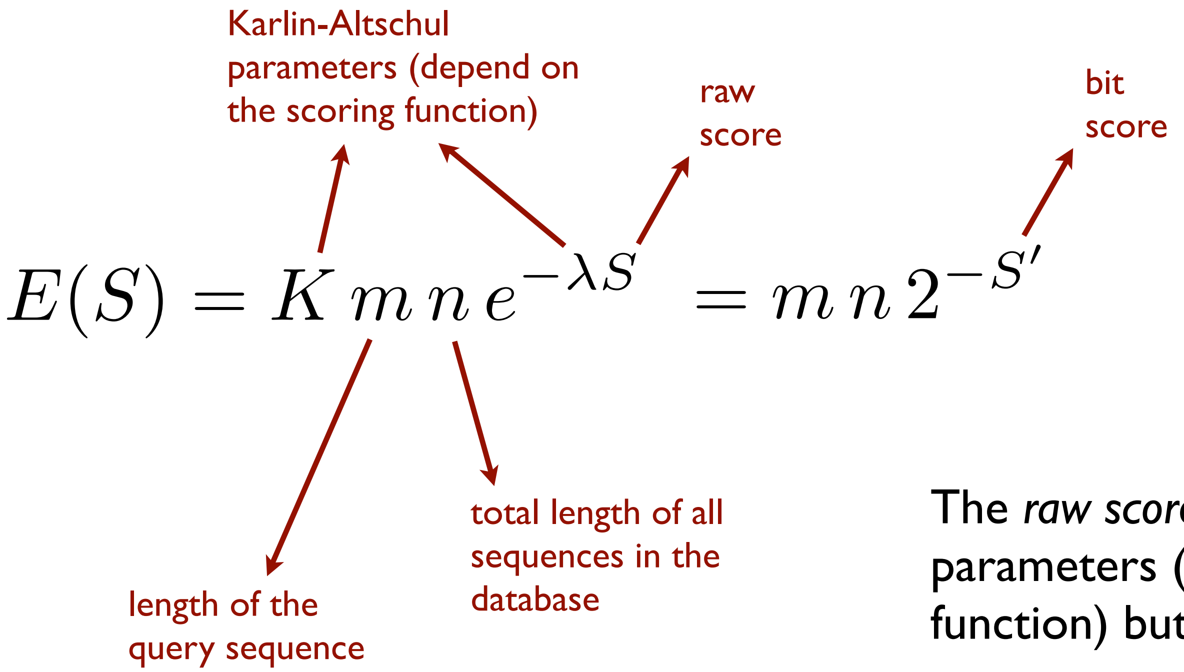
G	D	N	V	T	R	Score
D	V	R	D			
	D	V	R	D		
		D	V	R	D	
D	V	R		D		
	D	V	R		D	
D	V		R	D		
	D	V		R	D	
D		V	R	D		
	D		V	R	D	
D	V	R			D	
D	V			R	D	
D			V	R	D	

Don’t forget
the gap penalty!

Example:
–11 for gap existence
–1 for gap extension

E-value in BLAST

The maximum score found from aligning a sequence to a *database* of sequences is presumed to follow an "extreme value distribution" :



Karlin-Altschul parameters (depend on the scoring function)

raw score

bit score

$$E(S) = K\,m\,n\,e^{-\lambda S} = m\,n\,2^{-S'}$$

length of the query sequence

total length of all sequences in the database

$$S' = \frac{\lambda S - \ln K}{\ln 2}$$

The *raw score* depends on the K-A parameters (therefore, on the scoring function) but the *bit score* does not.

The *bit score* still depends on the size of the database into which the query sequence is searched, though.

For more information:
http://www.ncbi.nlm.nih.gov/BLAST/tutorial/Altschul-1.html

To get started with BLAST

BLAST Help :
http://blast.ncbi.nlm.nih.gov/Blast.cgi?CMD=Web&PAGE_TYPE=BlastDocs