Sequence vs structure comparisons

Ultimate aim

- how to find out the most about a protein
- what you can get from sequence and structure information

Sometimes you do know the structure of your protein

- what are the differences between structure and sequence similarities

Sequence and structure similarity

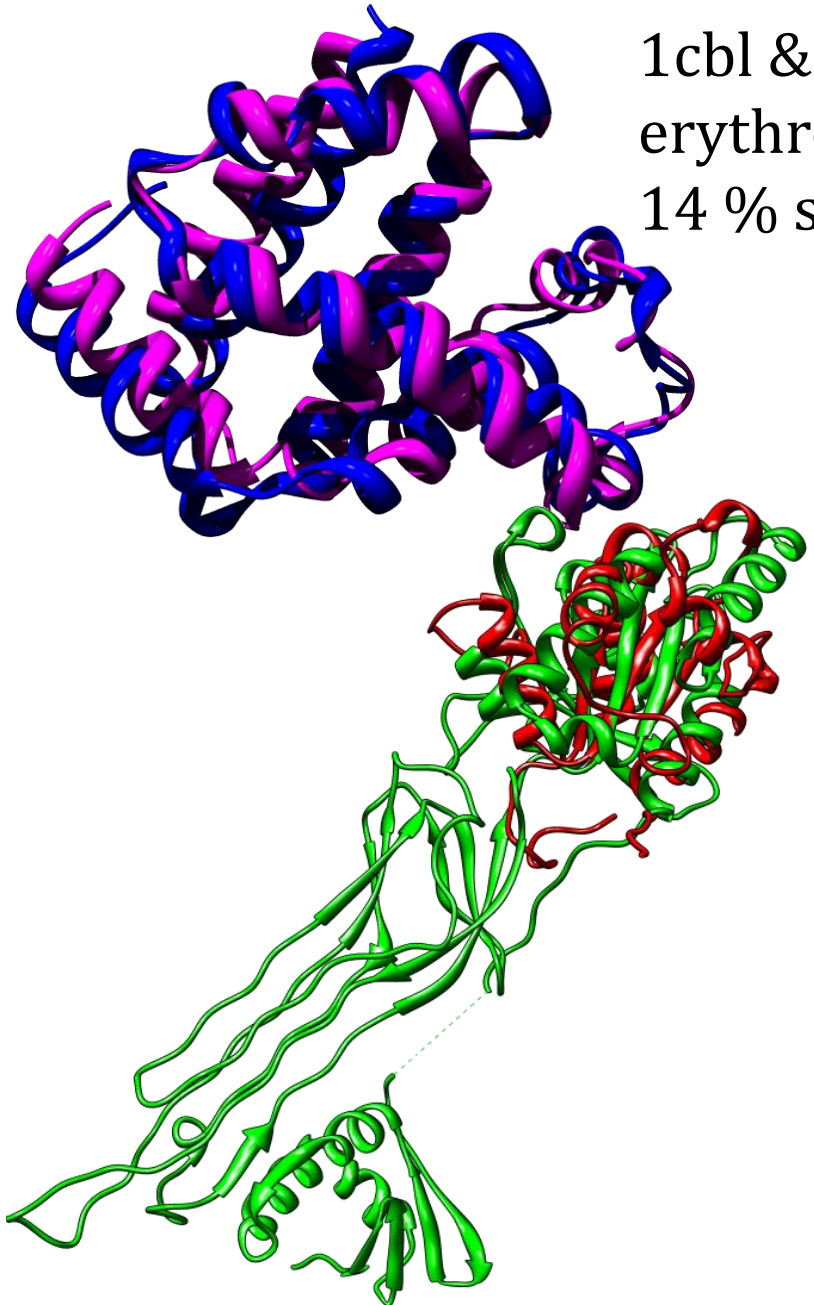
Claim from before

- if two sequences are similar
  - they are related – structures are similar

Question

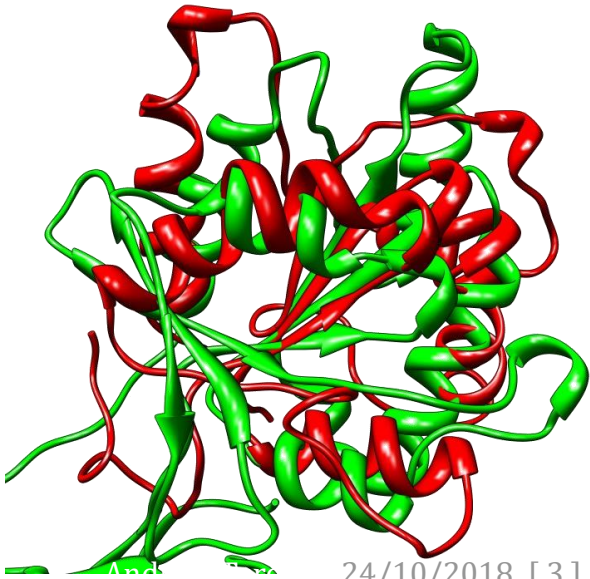
- if two sequences are different
  - are their structures different ?

Remote similarities

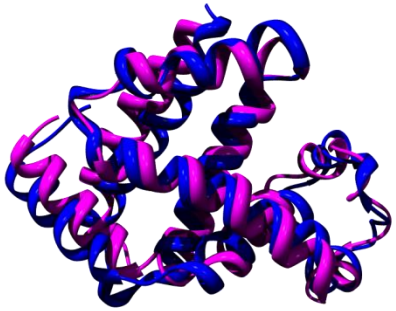


1cbl & 1eca (haemoglobin & erythrocruorin)
14 % sequence id

1fyv & 1udx, TLR receptor and nucleotide binder, 9 % sequence id



No sequence similarity – similar structures

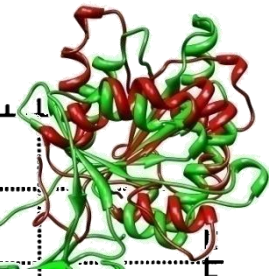


Are these rare ?

- easy to find 100s of examples

Does this agree with previous claims ?

- dot in diagram – two structures seem different



If sequences are similar

- structures will be similar

If sequences are different

- one does not know

Rost, B.Prot Eng, 12,85–94, 1999

Structure versus sequence similarity

Clear statement

- sequence changes faster than structure

Reason ? Unclear

- possibility..

- protein function depends on having groups in orientation in space

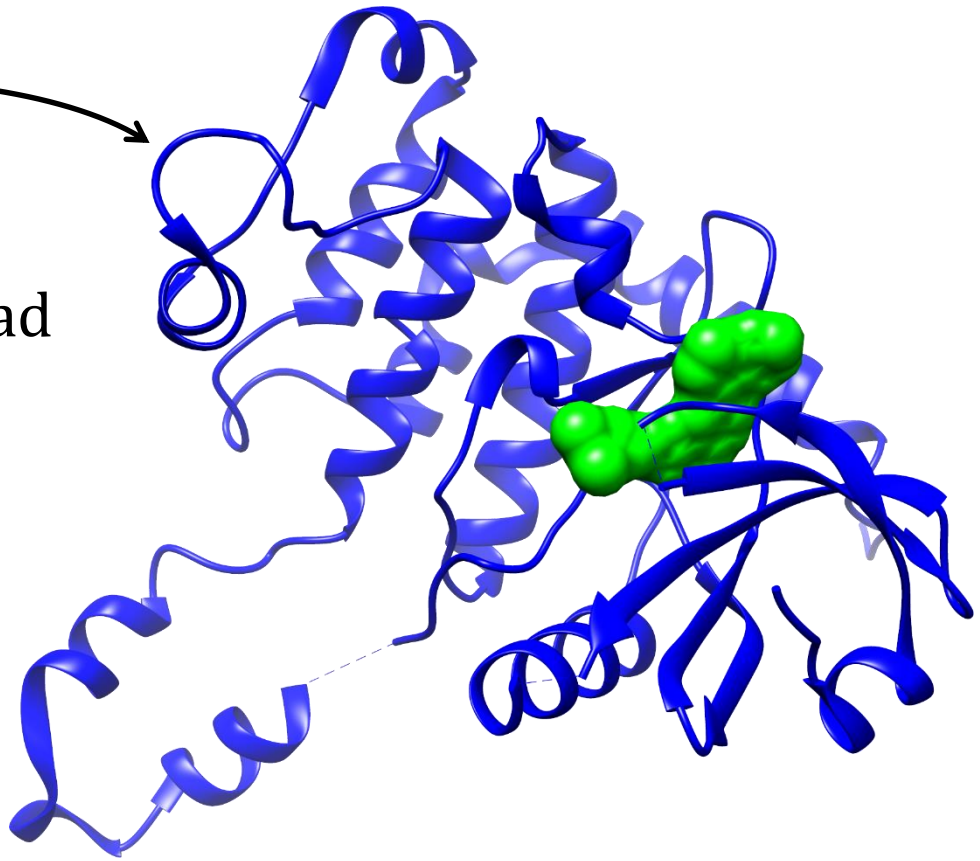
Why can sequence change

View of molecular evolution…

change here

residue changes ? OK

structure changes ? Bad

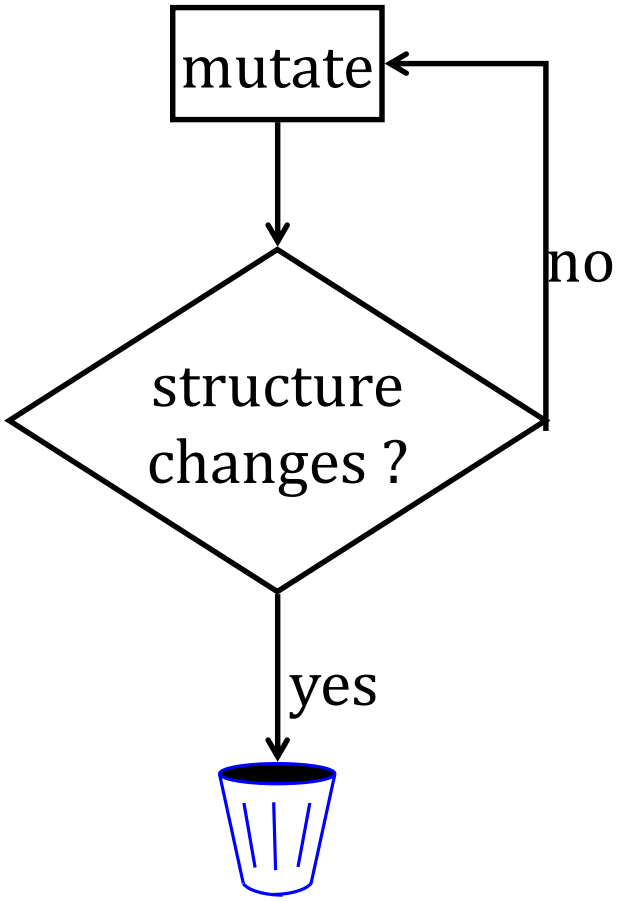


2wtj (transferase) + inhibitor

Simple view of molecular evolution

mutate continuously

- mutations which are not lethal
  - may be passed on (fixed)
- if structure changes
  - protein probably will not function
  - not passed on



Result

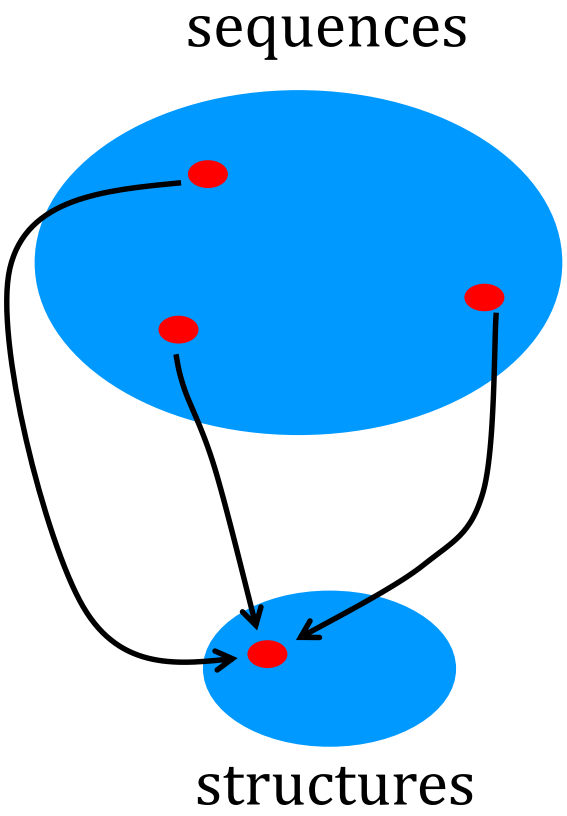
- evolution will find many sequences
  - compatible with structure
  - compatible with function
- how else would we see this ?

Sequence vs structure evolution

Sequence and structure space

- sequence space is larger
  - many different sequences map to similar structure

- sequence evolves faster than structure



Practical Consequences

Sequences of proteins are nearly always known

Similar sequence

- usually similar structure, similar function

Sequences not (obviously) related

- maybe similar structure
- maybe similar function

Sequence vs structure similarity

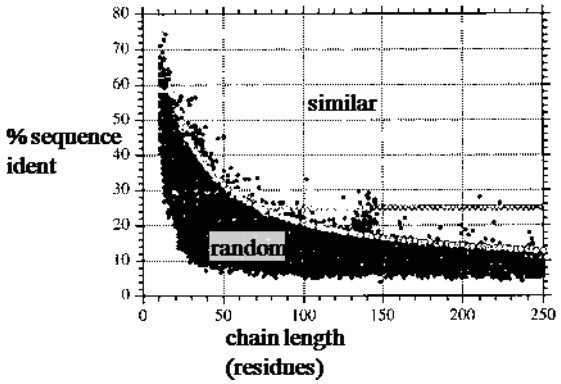
When comparing proteins

Similar sequences

- structure and function will be similar
  - remember threshold graphs from earlier

Similar structures, different sequences

- evolutionary relationship implied but
  - bigger evolutionary distance
- not enough to be confident about function



- what do we mean by similar structures ?
  - winter semester

practical consequences …

Little summary

Multiple sequence alignments

- for conservation
- first step to phylogenies

Phylogenies

- not as reliable as the pictures imply

Structure vs sequence evolution

- sequence changes faster
- sequence similarity means a closer evolutionary relationship
    - functional similarity