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

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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 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