barryus@gmail.com
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Summary

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jcrilly
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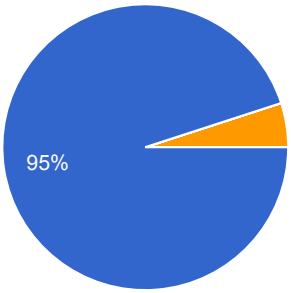
malrayya
anabelf
ashergal
nragazzo
nlesniak
mirogers
katiephd

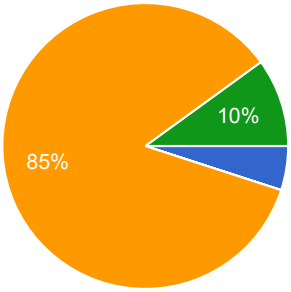
Which of the following databases is NOT primarily protein structure related?

PFAM	**19**	95%
PDB	**0**	0%
CATH	**1**	5%



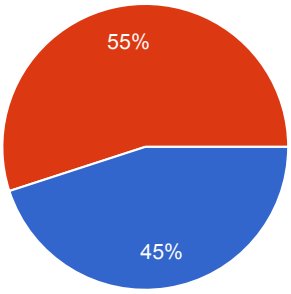
SCOP	**0**	0%

which structure determination



CryoEM	**1**	5%
NMR	**0**	0%
X-ray crystallography	**17**	85%
Molecular Dynamics	**2**	10%

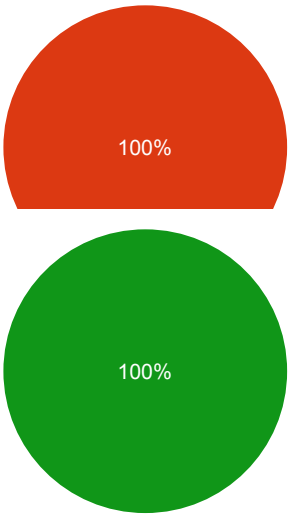
True or False: Protein structure databases are much larger than protein sequence databases in terms of number of entries?



TRUE	**9**	45%
FALSE	**11**	55%

True or False: Proteins have only one unique structure conformation?

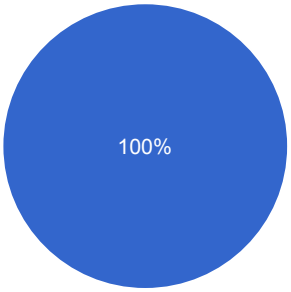
TRUE	**0**	0%
FALSE	**20**	100%



in the most common form of

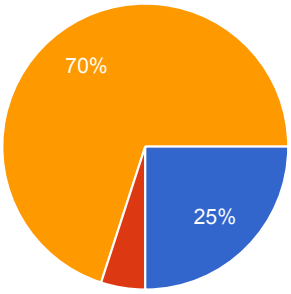
i and i+1	**0**	0%
i and i+2	**0**	0%
i and i+3	**0**	0%
i and i+4	**20**	100%
i and i+5	**0**	0%

True or False: Structure knowledge can facilitate the identification of more distant evolutionary relationships



TRUE	**20**	100%
FALSE	**0**	0%

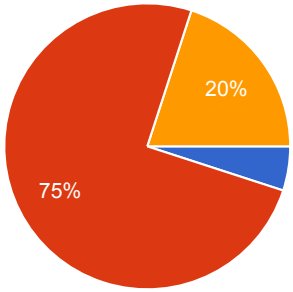
Conformational change is a dynamic characteristic intrinsic to many proteins, in many cases essential for function. Conformational change often needs to be taken into account in docking calculations (prediction of ligand binding). What is the most widely used approach for predicting conformational changes?



Normal mode analysis	**5**	25%
Dynamic programming	**1**	5%
Molecular Dynamics	**14**	70%

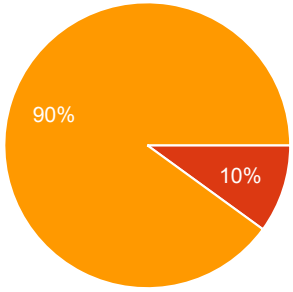
Monto Carlo	**0**	0%

Which is the most reliable method for structure prediction?



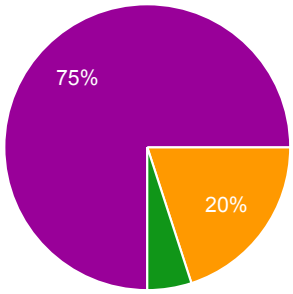
Threading	**1**	5%
Homology modeling	**15**	75%
Ab initio folding	**4**	20%

The hydrogen bond is a weak interaction between two polar atoms. Its strength depends on:



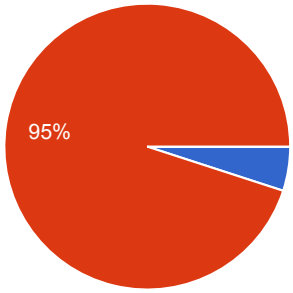
Distance between atoms only	**0**	0%
The angle between atoms only	**2**	10%
Both the distance and bond angle	**18**	90%

Which is the longest range force typically included in a physics based potential for protein structure modeling?



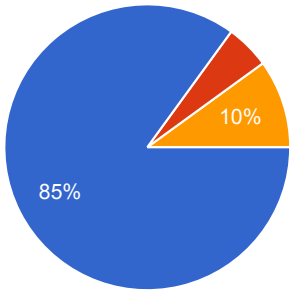
van der Waals interactions	4	20%
Hydrogen bonds	1	5%
Electrostatics	15	75%

Which pairs below are orthologues?



Human hemoglobin alpha and human hemoglobin beta	1	5%
Human hemoglobin alpha and horse hemoglobin alpha	19	95%
Human hemoglobin alpha and horse hemoglobin beta	0	0%

Which pairs below are paralogues?



Human hemoglobin alpha and human hemoglobin beta	17	85%
Human hemoglobin alpha and horse hemoglobin alpha	1	5%
Human hemoglobin alpha and horse hemoglobin beta	2	10%

Many proteins from pathogens have human homologues. Suppose you had a method for comparing the determinants of specificity in the binding sites of two homologous proteins. How could you use this method to select propitious targets for drug design?

I would want to select targets that only bind pathogen proteins and not their human homologues.

Fragmental structure-based screening would work. Find fragments that bind specifically in pocket at a particular sites. Then design the compound from the fragments.

~~You could find which sites are conserved in the orthologues and try to target those regions for therapy.~~

You can compare the binding site between the pathogen protein and the human protein to determine differences. If residues are different then you can design a drug that is specific for the pathogen site that won't be able to bind to the human site. For example, the pathogen binding site could contain a charged residue like aspartic acid that isn't present in the human homolog that can hydrogen bond with a potential drug.

~~You can design drugs for different proteins from pathogens without having to know their structure.~~

Receptor-target based drug discovery - can perform fragment structural based screening, identify multiple non active-site pockets, ensemble docking and candidate inhibitor testing

you can use what you know about the determinants of specificity of the first protein to design a drug that would block/inhibit the binding site of that homologous protein. If you know a certain amino acid in a binding site is important (for example a lysine) and that amino acid is conserved in the homologous human protein, then you can design a drug to interact with that lysine to get the desired result.

If I had a model that could determine the specificity in binding sites of two homologous protein, I would study/analyze the surrounding structure of those binding sites and make some educated guesses about what properties (hydrophilic, hydrophobic, etc) of the ligand that would induce some sort of conformational change that would hinder the pathogenic protein's ability to function. Then test which potential drug may work best with the highest level of specificity.

Virtual docking of drug molecule in homologues

Look for structural differences that could be explored for developing a compound/drug specific for the pathogen structure

Receptor/Target Based Method: You could use a fragment library along with the 3D structure of the target and preform fragment docking and see which fragments bound to the pathogen rather than the human. You then could design a compound, run some experiments to check

the specificity and then create drug candidates.

Design a small molecule that has higher affinity for the pathogen protein than the human homolog. Preferably, generate a small molecule that does not interfere with the human homolog protein function whatsoever while inhibiting the function of the homologous pathogen protein. If there are molecules known to bind the human homolog, use similar compounds to determine structure activity relationships, and hopefully find a similar compound specific to the pathogen.

Molecular dynamics/Monte Carlo based methods have been previously used in Ligand-based approaches. I can use simulations similar to those that can identify both potential ligands and their binding sites on the drug target. In essence, the target is flooded with ligands, or more typically small fragments, which are then slowly “evaporated,” leaving behind only the most tightly bound ligands. Computer simulations have shown to be successful in drug discovery, for example in the design of novel nanomolar inhibitors of p38 kinase. Essentially run two simulations, in where one simulation you find the potential drug/ligand that has more specificity for the pathogen protein versus the human protein. The use of computer simulations reduced the use of time consuming and money hungry in vitro based assays like HTS screens, inhibition assays, and generating IC50 for every drug to find the one that has the best inhibition and selectivity for the pathogen protein.

If you find similar sequences or binding sites between the two proteins you can use that to compare binding sites that have changed between the homologs. When you find these differences then you can use those sites on the pathogens to design drugs that can make the protein inactive. The comparing method will allow you to decrease the sites that you have to test for binding of drugs.

Since the pathogen have human homologues, that means you have the sequence alignment for both of the proteins. Aside from the alignment, I will obtain the structure of the protein by either modeling or x-ray crystallography. From the structure, you will able to identify "pocket sites", in which you could be able to create a highly specific ligand that will target the pocket of the protein of interest. You can identify the pocket site by looking a the sequence alignment so that can help you in synthesizing a ligand. I will make sure its specific for one protein and not the homologous protein. To be safe, I will create multiple ligands with different "R" groups, to detect which one of those is more specific.

Search for a small molecule that is capable of binding specifically and strictly the pathogenic homologue

If you were able to find differences between the pathogen protein and homologous human protein you would be able to specifically target the pathogen protein. Binding differences between the two proteins can allow specific targeting. You would want to target the pathogen protein to in the end kill the pathogen vs disrupting the normal human protein.

Because proteins from pathogens are homologous to some proteins in humans you can

assume that their structures are relatively conserved. Using the method that was developed to assess binding specificity in each of the proteins, you can select for a drug that specifically binds to distinct regions of the pathogen protein (more divergent regions) and not in the human version (more conserved regions).

We can use docking software to see which ligands bind to the protein pathogen and not the human protein. This allows us to virtually screen for possible ligands to use (receptor-based drug discovery). Further wet lab studies can be done (experimental assays) to verify these candidate drugs.

Number of daily responses