Importance of Protein Structure Prediction

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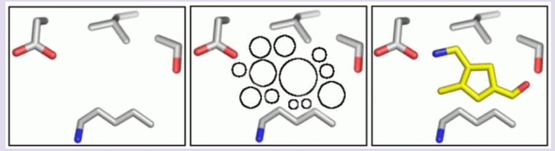
Before Protein Modeling

Initially, drugs were discovered by either chance or by trial and error through screening methods. Because scientists did not have the ability to model protein structures, drug discovery was a very expensive process. Currently, researchers are working on technologies to determine protein ligands and potential drugs through the usage of predicted protein structures.

Docking for Determining Ligands[1]

One method for structure-based drug design is docking. By using the structure of the protein's activation site, a program can determine the ligand shape needed.



Breda, A., Valadares, N.F., de Souza, O.N., Garratt, R.C. (14 September 2007) "Protein Structure, Modelling and Applications" Bioinformatics in Tropical Disease Research: A Practical and Case-Study Approach [Internet]. Retreived from http://www.ncbi.nlm.nih.gov/books/NBK6824/

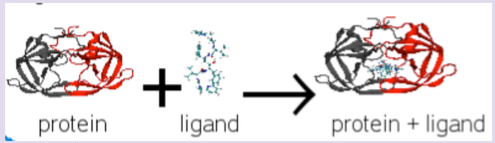
Figure 1. Representation of how a docking program called DOCK determines the ligand. After determining the binding site, the program calculates spheres to associate with the binding site. Ligand atoms later replace the spheres.

Characteristics of a Good Docking Program

- Takes in count of flexibility of the protein, ligand, and binding site
- has good scoring functions
  - enables the docking program to quickly sort through ligand positions that do not work
- Fast virtual screening for large drug analyses

Ligand-Steering Model[2]

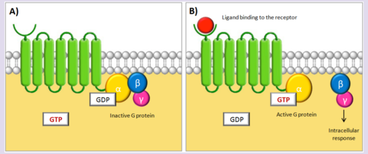
Docking for determining ligands experimentally models a protein structure without the presence of ligands. However, the Ligand-Steering Model (LSM) incorporates the structures of ligands into the predicted protein structure. Addition of ligands, to complete a protein structure, are modeled after preexisting proteins. Compared to other traditional methods of determining similarities, such as homology modeling, the LSM is shown to be more accurate in its protein prediction in its unliganded state.



"About the Docking@Home Science," (2009). Docking Home. Retrieved from http://docktest.cis.udel.edu/about/science/

Figure 2. Ligand and protein structures are combined in order to create a more accurate protein model.

Modeling G-Protein Coupled Receptors (GPCRs)[1]



"Biodetection of hCG Hormone," (2012). iGEM. Retrieved from http://2012.igem.org/Team:Chalmers-Gothenburg/Theory

Figure 3. GPCR in its inactive and active states.

Background Information:

- Over a third of all FDA-approved drugs target GPCRs.
- There are more than 800 GPCR genes expressed in humans
- Modeling GPCRs has been challenging through x-ray crystallography.
  - only 16 unique class A GPCRs have been modeled so far

Advances in Modeling

- Can now model complexes between small molecules and GCPRs if the transmembrane domain of the GPCR is mover 35% homologous to another GPCR.
  - This means that researchers are able to model around 20% of nonolfactory class A GPCRs.
- Protein-ligand modeling has also been advancing.
  - For example, the binding between the H4 receptor and its ligand has successfully been modeled.
  - Modeling protein-ligand interactions can enable researchers to better understand the effects of ligand mutations.

Structure Prediction to Target Parasitic Diseases[1]

- The main difficulty in creating drugs for parasitic diseases is developing a drug that will target parasitic proteins without affecting host proteins.
- Protein structure prediction can help ease this issue. By determining structural differences between active enzymes in the parasite and host, researchers can create inhibitors that specifically target the parasite's proteins.
- This idea has been implemented for targeting the dihydrofolate reductase-thymidylate synthase (DHFR-TS) enzyme which is present in 6 different types of parasites. (See Figure 4).

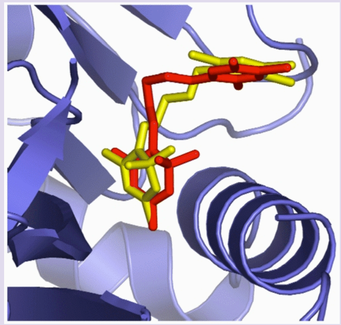


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Figure 4. In blue is the protein DHFR. In yellow is the ligand for the protein, and in red is the ligand created by a program called GOLD.

Bibliography

1. Breda, A., Valadares, N.F., de Souza, O.N., Garratt, R.C. (14 September 2007) "Protein Structure, Modelling and Applications" Bioinformatics in Tropical Disease Research: A Practical and Case-Study Approach [Internet]. Retreived from http://www.ncbi.nlm.nih.gov/books/NBK6824/
2. Schmidt, T., Bergner, A., Schwede, T. (July 2014) "Modelling three-dimensional protein structures for applications in drug design. Drug Discovery Today. 19(7), 890-897. Retrieved from http://www.sciencedirect.com/science/article/pii/S1359644613003942