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In silico Analysis of Gestational Trophoblastic Disease Molecular Docking and Modelling

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Abstract

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization. The setting up of the input structures for the docking is just as important as the docking itself, and analyzing the results of stochastic search methods can sometimes be unclear. This chapter discusses the background and theory of molecular docking software, and covers the usage of some of the most-cited docking software.

Homology modeling is one of the computational structure prediction methods that are used to determine protein 3D structure from its amino acid sequence. It is considered to be the most accurate of the computational structure prediction methods. It consists of multiple steps that are straightforward and easy to apply. There are many tools and servers that are used for homology modeling. There is no single modeling program or server which is superior in every aspect to others. Since the functionality of the model depends on the quality of the generated protein 3D structure, maximizing the quality of homology modeling is crucial. Homology modeling has many applications in the drug discovery process. Since drugs interact with receptors that consist mainly of proteins, protein 3D structure determination, and thus homology modeling is important in drug discovery.

Keywords: GTD Drug discovery, Argus lab, Docking and Homology modelling,QED.

Introduction

The prognosis for patients with choriocarcinoma and related gestational diseases has improved dramatically since the 1950s. Cure rates now exceed 90%, even in patients with metastases. Although systemic chemotherapy has provided the major breakthrough in treatment of these neoplasms, more recent investigators indicate combination chemotherapy and adjunctive use of surgery and irradiation are useful. More data have accrued to suggest chemotherapeutic toxicity can be dramatically reduced by new drug regimens. Finally, new agents and approaches are being used with some success in patients whose disease is resistant to more traditional therapy.

This presentation deals with trophoblastic diseases of gestational origin only. Histologically similar tumors of nongestational origin, such as primary ovarian or testicular tumors, are omitted because of differences in derivation, treatment, and prognosis. *Gestational trophoblastic diseases* is used to define the spectrum of disease that has at one extreme "benign" hydatidiform mole (even prior to evacuation) and at the other, the highly malignant choriocarcinoma. Such diseases indeed form a spectrum, and to understand and adequately manage a patient with one of these conditions requires knowledge of the entire group.

Drug discovery:

Drug discovery is a process of finding a new medicine for a therapeutic use. One of the most capable methods to find out the new drug is to find out the target protein interactions with randomly chosen compounds that are the part of compound libraries. Thus, the accurate prediction of the binding modes between the ligand and protein is of fundamental importance in modern structure-based drug design. Computer-based molecular modeling aims to speed up drug discoveries by predicting potential effectiveness of ligand-protein interactions. Molecular docking is one such method of a structural based drug design. [1]

Molecular docking:

Molecular dockingis performed with **AutoDock** [6]. The protein molecules were was processed by adding all hydrogen, merging non-polar hydrogen atoms using AutoDock Tools. [4] Molecular docking is a computational procedure that aims to predict the favored orientation of a ligand to its macromolecular target (receptor), when these are bound to each other to form a stable complex. Although each docking program operates slightly differently, they share common features that involve ligand and receptor, sampling, and scoring. Sampling entails conformational and orientation location of the ligand within the constraints of the receptor-site binding. A scoring function selects the best ligand conformation, orientation, and translation (referred to as poses), and classifies ligands in rank order. A successful docking exercise must accurately predict either or both ligand structure (pose prediction) and its binding propensity (affinity prediction). Available docking programs differ essentially in ligand placement in the "combining" site, exploration of conformational space, and scoring or binding estimate. The interaction with the ligand relies both on the protein backbone fold in the region of the binding site and on the orientation of the side chains in that binding site. One of the most significant limitations in docking is that it is typically performed while keeping the protein surface rigid, which prevents consideration of the effects of induced-fit within the binding site.[3]

Molecular Modelling:

Molecular modelling is a collection of (computer based) techniques for deriving, representing and manipulating the structures and reactions of molecules, and those properties that are dependent on these three dimensional structures. This lecture course aims to introduce in a simple way the hierarchy of computational modelling methods used nowadays as standard tools by organic chemists for searching for, rationalising and predicting structure and reactivity of organic, bio-organic and organometallic molecules. The emphasis will be on helping to develop a feel for

the correct "tool" to use in the context of a typical problem in structure, activity or reactivity, by describing the limitations and strengths of each method.[7]

Molecular modelling (MM) is yet another approach providing valuable insight into the mechanism of ion–mineral surface interactions on an atomistic level. Molecular dynamics (MD), Monte-Carlo and geometry optimisation are the most commonly used simulation techniques . In these methods equilibrium structures of sorbed species and their energies are derivsed based on inter-atomic interaction energy calculations according to the laws of statistical mechanics .[5]
The interatomic energies are calculated either directly using methods of quantum mechanics or by means of empirical interaction parameters which are in turn calibrated based on quantum-mechanical calculations or experimental data for simplified model systems. The major limitations of MM simulations are related to the system size and the time scale which can be addressed in the modelling. [2]

Materials and Methods

Materials:

NCBI:

NCBI is database which is used to charged with creating automated systems for storing and analyzing knowledge about molecular biology, biochemistry, and genetics.NCBI is now a leading source for public biomedical databases, software tools for analyzing molecular and genomic data, and research in computational biology.

PUBCHEM:

PUBCHEM is the database which is used to drug discovery and many aspects such as lead identification and optimization, compound-target profiling, polypharmacology studies and unknown chemical identity elucidation. **PubChem** has also become a valuable resource for developing secondary databases, informatics tools and web services.

PDB:

PROTEIN DATA BANK is the database which is used find 3D structure of the protein.The PDB is a key in areas of structural biology, such as structural genomics. Most major scientific journals and some funding agencies now require scientists to submit their structure data to the PDB. Many other databases use **protein** structures deposited in the PDB.

UNIPROT

UNIPROT also called as SWISSPROT It provides an up-to-date, comprehensive body of **protein** information at a single site.It aids scientific discovery by collecting, interpreting and organising this information so that it is easy to access and use.

SWISS MODEL

SWISSMODEL is the online web server dedicated to homology modeling of 3D protein structures. Homology modeling is currently the most accurate method to generate reliable three-dimensional protein structure models and is routinely used in many practical applications.

PYMOL

PYMOL is a software.PyMOL can produce high-quality movies and images of macromolecules in different representations including ribbons, cartoons, dots, surfaces, spheres, sticks, and lines At present, PyMOL is one of the most widely used macromolecular visualization tools.

CASTp

CASTp can be used to study surface features and functional regions of proteins. CASTp includes a graphical user interface, flexible interactive visualization, as well as on-the-fly calculation for user uploaded structures

ARGUS LAB

ArgusLab is a molecular modeling, graphics, and drug design program for Windows operating systems which is used to binding site of protein and ligand. It can be predict binding energy.

QED

Quod erat Demonstrandum is known as QED. Which tool can be find drug likeness of given molecule. It is online web server.

CHEMSPIDER

ChemSpider is a free chemical structure database providing fast text and structure search access to over 100 million structures from hundreds of data sources.

Methods:

1. Target- Template sequence Alignment:

The Experimental crystal of structure pfADSL is not available in protein data bank (PDB). Hence the 3D structure was modelled. The protein ID of the target (NACHT, LRR and PYD domains-containing protein 7) was retrieved from Uniprot Knowledgebase (UNIPROT KB) with accession number Q8WX94.Afterwards the protein id was submitted to SWISSMODEL web server to develop a model with sufficient query sequence and sequence identity. The most reliable 3D structure was selected based on GLOBAL MODEL QUALITY ESTIMATION (GMQE) and QUANTITATIVE MODEL ENERGY ANALYSIS (QMEAN). The GMQE values are usually between 0 to -7. And the higher number and the higher the number, the higher the reliability of the predicted structure, while for QMEAN, a value below 4.0 shows reliability. The similarity identity between the amino acid sequences of the homology model of PfADSL and the template structure used for the homology model were confirmed using Clustal Omega.

2. Structure validation of Modelled protein:

The SWISS-MODEL web server automatically calculates the QMEAN scoring function for the estimation of the local and the global model quality based on the geometry, the interactions and the solvent potential of the protein model.

It also provides the z-score ranging from 0 to 1, which are compared with the expected value for any structure. PROCHECK was used to check for the quality of the modelled 3D structure of PfADSL generated via SWISS-MODEL. For this structure validation the .pdb file format of the modelled PfADSL was uploaded on the PDBsum web server30 of European Bioinformatics Institute. The .pdb file format of the modelled PfADSL was uploaded on the server to obtain both theRamachandran plot and the Ramachandran plot statistics. While the Ramachandran plot is used in accessing the quality of a modelled protein or an experimental structure, the Ramachandran plot statistics provides information on the totalnumber of amino acid residues found in the favourable, allowed and disallowed regions.31 Also, Verify 2WV4 was used to validate the structure of the modelled protein, determine how compatible a 3D structure is to its own amino acids and compare the result with that of good-known structures.[4]

3. Alignment of the PfADSL model and the template structure

The Alignment of pfADSL model and template structure was carried out using PYMOL molecular viewer. to show how closely related the carbon atoms are. This is derived from the root mean square deviation (RMSD) between the positioning of the carbon atoms of both the template and the model that is obtained from the alignment. The lower the RMSD the more closely related the structures are.[3]

4. Ligand Modelling

AICAR analogues is inhibitor of pfADSL is good and similar to vincristine as shown in figure 1, Therefore vincristine derivatives were built as ligands to function as potential inhibitors of PfADSL, Vincristine sulfate were built using ChemSpider is a free chemical structure database providing fast text and structure search access to over 100 million structures from hundreds of data sources. Chem spider was generate simplified molecular into line entry system(SMILES) that were converted to corresponding 3D structure using Chemspider online Tool. And saved in .pdb format In addition open babel software used to convert .sdf format to .mol format. And the files to Molecular docking in Arguslab. Which is a docking simulation.

5. Structre validation of modelled protein

The SWISS-MODEL web server automatically calculates the QMEAN scoring function for the estimation of the local and the global model quality based on the geometry, the interactions and the solvent potential of the protein model. It also provides the z-score ranging from 0 to 1, which are compared with the expected value for any structure. PROCHECK was nused to check for the quality of the modelled 3D structure of PfADSL generated via SWISS-MODEL. For this structure validation, the .pdb file format of the modelled PfADSL was uploaded on the PDBsum web server30 of European Bioinformatics Institute. The .pdb file format of the modelled PfADSL was uploaded on the server to obtain both the Ramachandran plot and the Ramachandran plot statistics. While the Ramachandran plot is used in accessing the quality of a modelled protein or an experimental structure, the Ramachandran plot statistics provides information on the total number of amino acid residues found in the favourable, allowed and disallowed regions.31 Also, Verify3D32 was used to validate the structure of the modelled protein, determine how compatible a 3D structure is to its own amino acids and compare the result with that of good-known structures.

6. Inslico drug likeness and toxicity of the protein

The concept of drug-likeness, established from the analyses of the physiochemical properties or/and structural features of existing small organic drugs or/and drug candidates, has been widely used to filter out compounds with undesirable properties, especially poor ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles. Here, we summarize various approaches for drug-likeness evaluations, including simple rules/filters based on molecular properties/structures and quantitative prediction models based on sophisticated machine learning methods, and provide a comprehensive review of recent advances in this field. Moreover, the strengths and weaknesses of these approaches are briefly outlined. Finally, the drug-likeness analyses of natural products and traditional Chinese medicines (TCM) are discussed.

7. Protein preparation

The homology modelled 3D structure of the target protein, PfADSL, was downloaded from SWISS-MODEL in its .pdb format. The Modelled protein structure was defined as receptor while the complexed ligand were removed using PYMOL.

8. Prediction of activesites of modelled protein

The Computer Atlas of Surface Topography of proteins(CASTp) 3.0was used to predict activesites that were present in the modelled protein structure. CASTp is a online server that is applied in the identification and measurement of void 3D structure. The modelled 3D protein was submitted on the server, and the nessasary aminoacids for binding interactions were predicted.

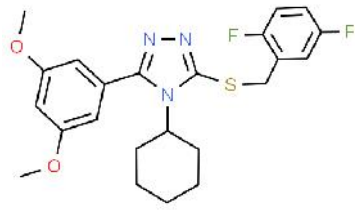


Fig1: The structure is showing regions of similarity

9. Molecular docking analysis

Argus lab is a molecular modelling,graphics and drug design program. The program contains two docking engines and simple scoring function based on an enhancement of the X-Score method. The molecular docking studies were carried out using ARGUSLAB. Which is free graphic using interface(GUI).for the arguslab programme. In the 2WV4 protein's aminoacids were selected from CASTp result and the alignment of 3D structure to the template structure. The Binding energy of the proein 2WV4 and chloridimeform is -7.37kcal/mol.

S.NO	PROTEIN NAME	LIGAND NAME	BINDING ENERGY (Kcal/mol)
1	2WV4	Hymenolane	-6.30329
2		2-Pyrrolidione	-5.87619
3		Edrela odorata	-4.76206
4		Sesmolin	-1.07411
5		Glycerric aicd	69.4078
6		Barleionoside	35.2532
7		L-colitase	-3.11361
8		Vicristine sulfate	-4.43562
9		Spongia	-2.95646
10		Chloridimeform	-7.37

Results and Discussion

Homology modelling of pfADSL and the target template sequence alignment

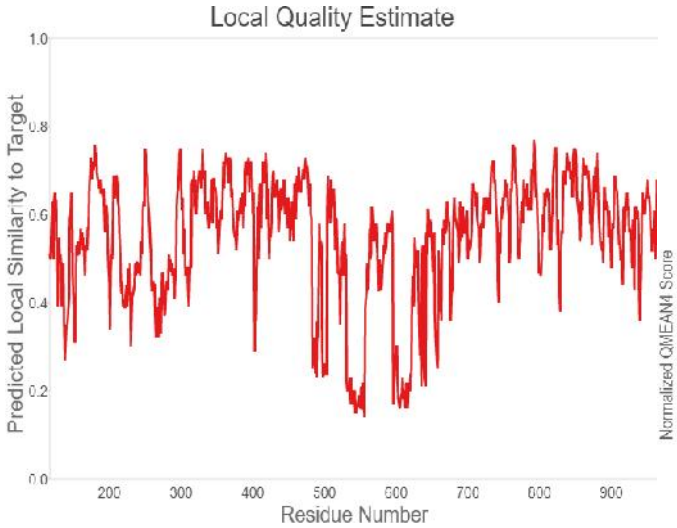
A 3D structure of pfADSL build using SWISS-MODEL with GMQE of 0.53 and QMEAN is -7.77.Also, Gestational trophoblastic ADSL Q8WX94 with AMP bound (PDB ID: 2WV4) was identified to have the closest templateto PfADSL with a similarity identity of 31.98% and sequence similarity of 0.50. The GMQE value of 0.53 and QMEAN score of -7.77bindicate that the modelled structure is reliableand has a good quality.

The multiple sequence alignment of the amino acidsequences56 of the PfADSL (UniProtKB ID: Q8WX94) and Gestational trophoblstic ADSL with AMP bound (PDB ID: 2WV4) is shown inFigure 2. A percentage identity matrix of 31.98%was obtained, which confirms the similarity identity of 31.98% obtained from the homology modelling.

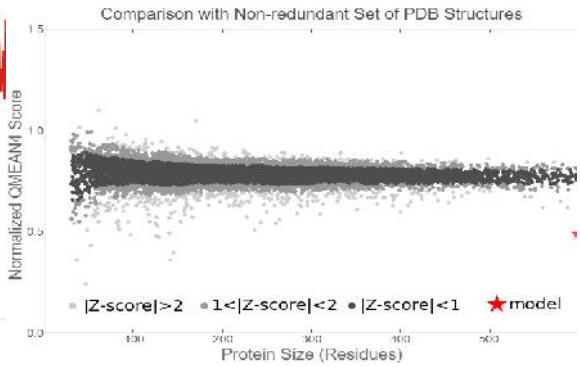
Structure validation of moelled protein

The plot of the predicted local similarity to target against the residue number of the predicted 3D structure of the modelled protein was graphically represented (Figure 3A). The value of most of the residues was close to 1, indicating that the local quality estimate of the residues of the predicted model is good. The residues with values lower than 0.6 were considered to be of low quality. The modelled protein structure also lies within the range of other protein structures in PDB, which confirms its reliability.

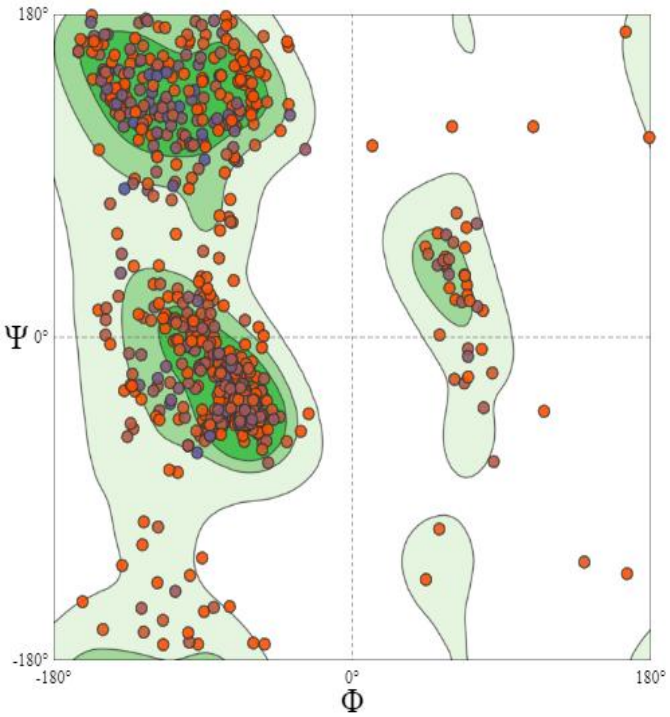
A



B



The Ramachandra plot were obtained from PDB sum web server. The Ramachandran plot statistics implied that the modelled 3D structure of PfADSL has 83.49% of its residues in the most favoured regions, 4.25% of its residues inadditional allowed regions, 2.47% of its residues in the generously allowed regions and 2.77% of its residues in disallowed regions of the Ramachandran plot.



RAMACHANDRAN PLOT

Conclusion

The molecular docking study of chlodime derivatives with GTD protein revealed that chlodime form are having good interaction in favourabformle pose with GTD which was explained by lowest binding energy, strong bond length and -7.37 no of interactions with active site of GTD molecule Thus it can be concluded that some chlodime form derivatives could be used as a template for the future development through modification or derivatization to design more potent therapeutic agents. Compounds synthesized if properly changed into therapeutic agent can be used for Gestational trophoblastic Disease.

Structure-based drug design techniques were hampered in the past by the lack of a crystal structure for the target protein. In this instance, now a day the best option is building a homology model of the entire protein. The main aim of homology modeling is to predict a structure from its sequence with an accuracy that is similar to the results obtained experimentally. Homology modeling provides a feasible cost-effective alternative method to generate models. Homology modeling studies are fastened through the use of visualization technique, and the differential properties of the proteins can be discovered. The role and reliability of homology model building will continue to grow as the number of experimentally determined structures increases.

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