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Recent methods in identifying drug targets using *in silico* methods – Review

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ABSTRACT

Bioinformatics tools and insilico methods considered as a function of ligand- receptor concept, in which correct adaptability of ligand binding to receptor will enhance the secondary functions within cell. In such type of studes of molecular interactins, secondary bonding of two proteins play an important role in this association and initial cellular functions. The molecular interaction can be described as optimization problem, giving details of best interaction of ligand and receptor. In such molecular interactin, the ligand and the receptor may undergo structural changes and resulting in stronger interaction which is called as induced-fit. In silico methods in drug designing is a bioinformatic tool stimulate the interaction between the biomolecules.

KEY WORDS: protein ligand docking, pdb viewr, sequence alignment, docking score.

1. INTRODUCTION

There are several methods available in insilico drug designing analysis. One method utilizes as match finding method which will exhibit complementary surfaces between ligand and receptor. The second approach simulates the actual docking process in which the ligand-protein pairwise interaction energies are calculated. Geometric matching/ shape complementarity tools explain about protein-protein interactions which explains the induced fit models. The receptor's molecular surface is explained based on solvent accessible surface area and the ligand's external morphology is explained by severl other methods. The matching compatibility between two ligands results in shape matching description giving details of complementarity docking on target and ligand molecules.

Another technique is to use Fourier shape descriptor, which tells about hydrophobic features on ligands or receptor in main chain atoms. In other words, structural relationship based analysis are rapid and highly efficient, this method cannot ordinarily simulate changes in ligand or receptor complimentarity exactly. The structural suitability techniques can rapidly look through many hundreds of ligands in seconds and find out the adaptability in ligand binding site and generally upscalable to ligand protein interactions.

Simulation: Another important in silico method is more complicated, in which the ligand-receptor are kept apart and this ligand finds the place into protein binding site by adjusting through movements in molecular docking. In such process there will be rotatins and translations leading to transformation in rigid body and intromolecular alterations to protein structuresin torsion angle rotations. Every movement in the structural rotaions of the ligand creates a total energenetic cost of system, which enables to calculate total energy of the system. The advantage of the method is adaptability of ligand in structural simulations whereas shape structural similiratiy methods will utilize a few internal techniques to include adaptability in ligands. The disadvantage of this method is that it is more time consuming to calculate the ideal location of binding site as they have to search large energy landscape.

Mechanics of docking: To evaluate structural adaptability evaluation, the initial necessity is ligand interest. In general, the structure was found utilizing biophysical method such as X-ray crystallography or to lesser extend NMR spectroscopy. This structural tool of actual receptors serve as inputs to strucutural algorhythms and the scoring function.

Search algorithm: Looking at spatial organization compose of all possible orientations and similiarities of the protein paired with receptor or ligand. With the currently availability bioinformatics tools, it is not feasible to extensively find the search space- this bring all possible distortions in every molecule and all rotational and translational orientatins of the protein similar to the ligand at a given level of granularity. In a number of bioinformatics adaptability software tools for flexible ligand, many of them model a flexible protein receptor. The pictures are obtained as "snapshot" which is is described to a pose. Literature has described several methods for finding the search space and we have listed below a few examples.

Scoring function: The scoring function takes a pose as input and returns a number indicating the likelihood that the pose represents a favorable binding interaction. Most scoring functions are physics-based molecular mechanics force fields that estimate the energy of the pose; a low (negative) energy indicates a stable system and thus a likely binding interaction. An alternative approach is to derive a statistical potential for interactions from a large database of protein-ligand complexes, such as the Protein Data Bank, and evaluate the fit of the pose according to this inferred potential.

GOLD - Protein-Ligand Docking: GOLD is bioinformtaics tool in computing the adaptability modes of compounds in ligand receptor binding and for post-processing (GoldMine) and obtaining interaction outcomes. Which is very highly considered as a bioinformatics modeling tool for exact molecular analysis and dependability.

GOLD features include:

- A genetic algorithm (GA) for protein-ligand docking
- An easy to use interface with interactive docking set-up via Hermes
- A comprehensive docking set-up wizard
- Full ligand flexibility
- Partial protein flexibility, including protein side chain and backbone flexibility for up to ten user-defined residues.

Gold has been reported valided variety of protein ligands complexes and leading resolutions leads to exact use of success criteria. GOLD's genetic algorithm readings are well suited for bioinformtaics drug designing and screening applications. GOLD is well developed for parallel execution on processor networks; another model of GOLD is suitable in commercial PC GRID systems.

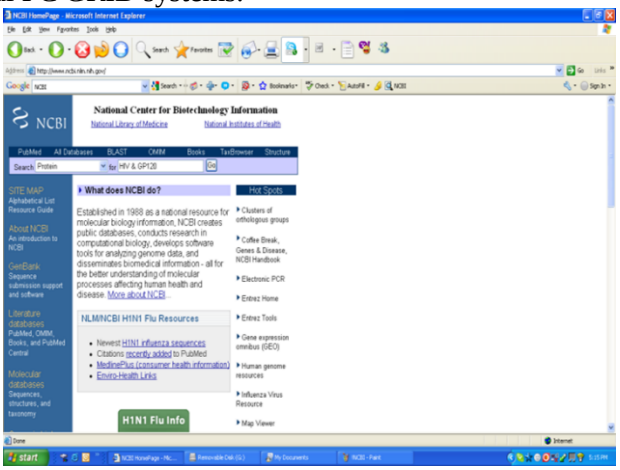

Figure.1. NCBI Homepage for protein sequence search. Go to the drop down menu and select the protein option. Type the required search in the search box. The window displaying the search results for the required protein

Figure.2.Result of protein sequence search in NCBI site for gp120 Copy the resulting sequence. Paste the sequence on a notepad and save it. Open the swiss pdb viewer homepage Load the raw sequence from the notepad. Select the sequence file from the list

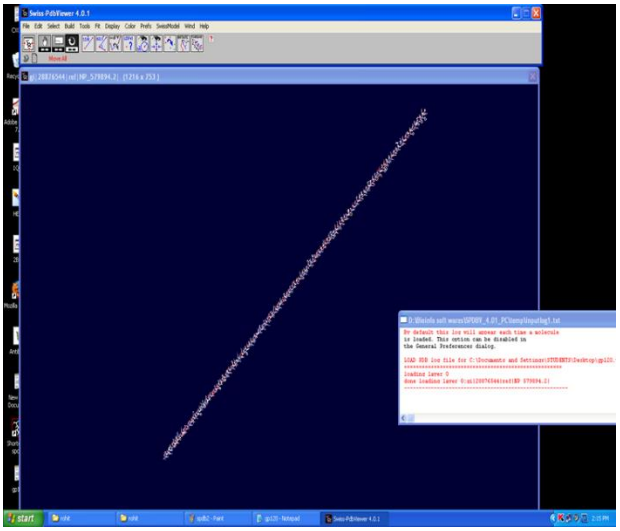

Figure.3.Image of the raw sequence Select all of the atoms in the structure. Save the current selectionSelect the swissmodel option in tools menu. Enter your e-mail id and name. Load the PDB file of the TEMPLATE sequence Select the pdb file from the list. Image of the pdb file inserted. Go to the WIND menu and select the Alingment

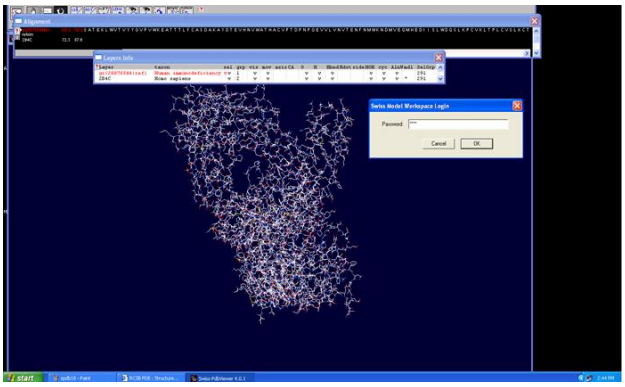

Figure.4.Type in your password in the pop up menu. Go to the WIND menu and select the LAYERS INFO option. Image displaying the layers info window. Go to the FIT menu and select the Magic fit. Image displaying the stucture after magic fit. Go to swissmodel menu and select the submit template search option

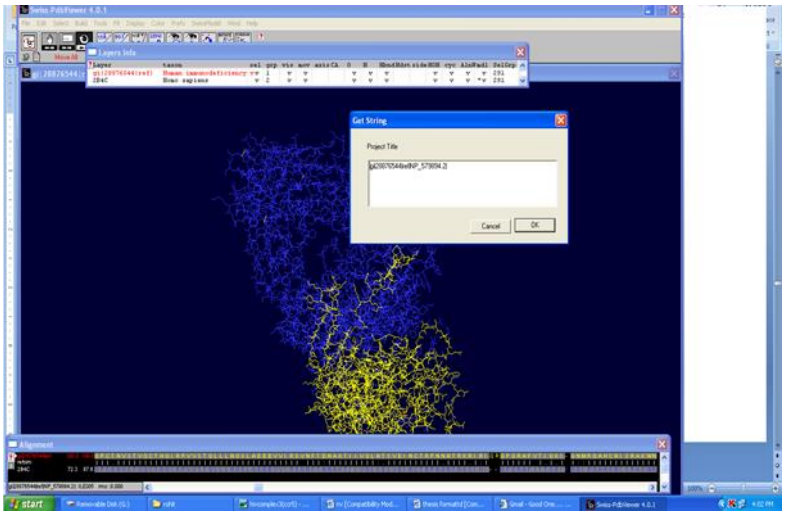

Figure.5.Pop up window which shows the project title and then we select ok.. Window displaying job completion. Graphical representaion of the required template. Go to controls menu and select docking option. Activate the docking from the sub menu appearing. Image displayin the progress of docking for the given molecules. Image displaying the final structure of the complex consisting of GP120 and CD4+. found 1419 clusters from 2000 docking solutions in 2.47 seconds

Discussion: Anticipation of structural organization of ligand protein interactions from primary protein sequence of a homologous ligand for which an X-ray or NMR structure is provided. A method is required when either of these techniques fail to determine the spatial configuration of ligand. The well-developed model gives a lot of information

of how the ligand reaction with information at primary sequence or residue property level. However such type of results or methods cannot be applied for genetic sequence alternation evaluation or drug designing.

As per the protein structure prediction methods like Homology Modeling, Threading and Ab initio methods, we are supposed to find the template for our sequence of interest. While finding the template we have looked for the % identity or similarity between the sequence of interest and template (Figure 5). As per the modeling scenario, if the % identity is more than 60%, we should go for Homology modeling, if is in the range of 25-60%; should go for threading method and if it is below 20-25%; should go for Ab Initio method. As per the % identity we have got from template after sending template selection request either through Swiss PDB viewer or directly through the online Swiss model server, we have chosen the homology modeling method for structure prediction. Modeling for the Sequences of interest has done by Swiss PDB Viewer offline tool or by directly the automated mode for structure prediction available online on Swiss-Model Server. It has given us with the final predicted structure based on the template structure so as to predict the function of the sequence of interest. Here we have got the structures of HIV1 gp120 on the basis of template 2B4C. And Human CD4+ structure on the basis of the template.

In docking, we are supposed to manipulate the receptor and ligand molecules before we will be going for docking. Manipulations are to be done according to the Tool which we are going to use for docking purpose. Here we have used Hex docking platform which has manipulating criteria in terms of enabling solvent, enabling hetero and enabling Arg/Lysine. This has to be done by the enabling all this options so as to create the live environment for docking as that of in vivo process of ligand and receptor binding. When we have started with the docking, first thing we considered is Estart and then simultaneously Emin and Emax. The results of data are reported energy has to be reduced to stabilize more movable bonds in ligand receptor binding and had in finding better developed modes in repeated bioinformatics ligand interactaction studies. Thus final result that is the Etotal should lie in between Emin and Emax. ETotal should be always less so as to get the maximum stability to docking complex for perfect merge and also less than Estart.

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