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Receptor Interactions of Transpeptidase Involved in Peptidoglycan Biosynthesis

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Abstract

Analyse the various docking modes of peptidoglycan formation and inhibition is by selecting the test sets from PDB. These test sets were docked by Hex and the resulting docking complex submitted to Spdbv. Distance of the residues in three different states viz. interface area, contact surface area and near native area. The results revealed that ARG 642 (1.33 Å) is found to be the best fit for peptidoglycan formation, GLN 422 (1.45 Å) and TYR 423 (2.15Å) are found to be the best fit for peptidoglycan inhibition using penicillin G and penicillin V respectively. Based on our study it is concluded that penicillin G has the best interacting activity as compared to penicillin V.

Keywords: Docking, Peptidoglycan, Penicillin, Interactions.

Introduction

Proteins are members of a large family of biological macromolecules and their structural, catalytic and transportation properties make them essential to all living organisms. The biochemistry of proteins has been studied experimentally for many years and with recent advances in X-ray Crystallography and nuclear magnetic resonance techniques, relationship between their function and their molecular structure are beginning to be inferred and predicted (Ritchie, 1998). A protein is a collection of atoms. The interactions between the atoms create a unique state of maximum stability

A vast number of the essential roles that proteins play require small molecules to bind to specific spots in the protein structure. For instance the small molecules can act as switches to turn on or off a protein function, or are the substrates for the particular chemical reaction that a protein enzyme catalyzes. Obtaining the atomic level details of the Protein–Ligand interactions is a valuable tool in the development of novel pharmaceuticals. As conventional experimental techniques are time and resource intensive much research effort has been focused on computational methods for the prediction of this difficult to obtain structural information. In general this process is called docking (Taufer *et al.,* 2004).

An important example of molecular recognition is the antibiotic penicillin that selectively binds with transpeptidase in bacterial cells. This antibiotic is lethal to the bacteria because once it has bound to these transpeptidase they are unable to be used to construct the bacteria's cell wall.

The current study is therefore aimed at understanding the process of computational docking. This involves the selection of proper receptor and ligand and selection of proper packages/tools. In docking, molecular recognition plays an important role and is observed in between receptor-ligand, antigen-antibody, DNA-protein etc. Molecular recognition is achieved through the complementarity of molecular surface structure and energetic with, most commonly, associated minor conformational changes. This complemetarity can take many forms: charge-charge interaction, hydrogen bonding, van der waals interaction and the size and shape of surfaces (Jiang and Kim, 1991).The details regarding computational docking as applied to the enzyme (protein) involved in peptidoglycan biosynthesis are presented and discussed.

Materials and Methods

Software packages

To perform docking computationally, algorithms are needed. Various docking algorithms are implemented in various software packages. One such software package is Hex. To evaluate the accuracy of binding, another appropriate tool viz. Deepview-Swiss-pdb viewer can be used.

Selection of test set

The test set which act as receptor and ligand includes the following biomolecules involved in peptidoglycan biosynthesis/inhibition viz. transpeptidase (Protein Enzyme), NAM (Precursor for Peptidoglycan biosynthesis), Penicillin G & V– antibiotics which act as competitive inhibitor. The test sets viz. transpeptidase, NAM were downloaded from Protein Data Bank. Entry formats of Penicillin G and Penicillin V were downloaded from Drug Bank and fed into the software Hex.

Hex software performs molecular matching and docking and Swiss pdb viewer helps to analyse the docked complex and mention the distance information in Å (RMSD).

Table: 1 List of Receptor and Ligand.

Type of activity	Receptor	Ligand
Peptidoglycan formation	Transpeptidase (2c5w.pdb)	NAM (9lyz.pdb)
Peptidoglycan inhibition	1.Transpeptidase (2c5w.pdb) 2.Transpeptidase (2c5w.pdb)	Penicillin G (APRDOO646.pdb) Penicillin V (APRDOO423.pdb)

Results and Discussions

The bacterial cell wall is a biochemically unique structure (Atlas, 1984). The principal component of the cell walls of both Gram-positive and Gram-negative bacteria is a peptidoglycan layer. Peptioglycan is composed of a backbone of alternatively repeating units of two polysaccharide or carbohydrate derivatives viz. NAM and NAG. This linear polysaccharide chains NAM and NAG are cross-linked by short tetrapeptides. Without the cross-linkage of peptide chains, the peptidoglycan layer would not be rigid and would not protect the cell against osmotic shock. Understanding this function of the cell wall very well, drug industry tries several types of drugs which are having the capacity to disrupt the cross-linkage of the peptidoglycan layer (Talaro, 2005**)** The penicillins is widely used classes of antibiotics that contain a β-lactam ring, which is primarily responsible for peptidoglycan layer inhibition (Atlas, 1984).

Docking

An analysis of conformational changes on Protein-Protein association and its implications for predictive docking was discussed by Betts and Sternberg (Betts and Sternberg, 1999). Recently, experimental and computational efforts have increasingly been devoted to the investigations of Protein-Protein interactions, which is very significant for understanding biochemical processes. Given the difficulties in experimentally determining the structures of protein complexes, the docking method to predict potential binding modes computationally is currently of great interest. The principles of docking and the progress that has been made during the last decade have been described (Cherfils and Janin, 1993; Lengauer and Rarey, 1996; Sotriffer *et al.*, 2000; Halperin *et al.,* 2002).

Matching in HEX

Prior to docking, matching was performed to find out the maximum similarity rather than maximum complementarity between the receptor and ligand. Hex matches the complexes and the matching time was calculated for all the three.

It is observed that Hex performs matching in a few seconds by using the default settings. The best matching solutions were presented by Hex in the Hex messages.

Table 2: Matching time of the complexes.

Receptor	Ligand	Matching time
2c5w(transpeptidase)	9lyz (NAM)	39 seconds
2c5w(transpeptidase)	APRDOO646 (penicillin G)	38 seconds
2c5w(transpeptidase)	APRDOO423 (penicillin V)	37 seconds

Docking in Hex

Similar to matching, docking was performed by using the same receptor and ligand (Figure: 1, 2, 3). Docking time was calculated by keeping the default settings (Table: 3).

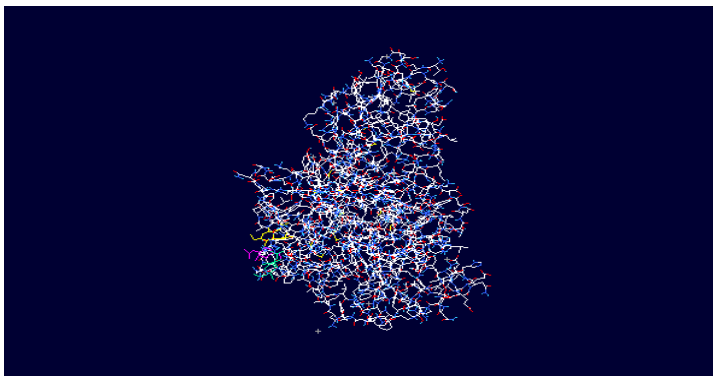

Figure 1: Docked complex structure of receptor transpeptidase (2c5w) and ligand NAM (9LYZ).

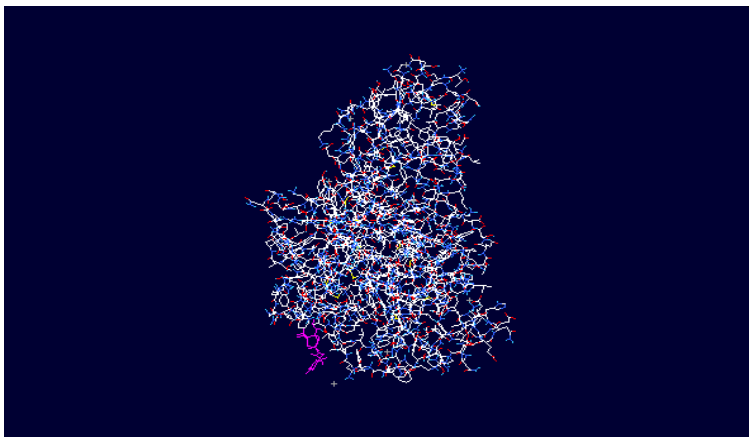

Figure 2: Docked complex structure of receptor transpeptidase (2c5w) and ligand Penicillin G (APRDOO646).

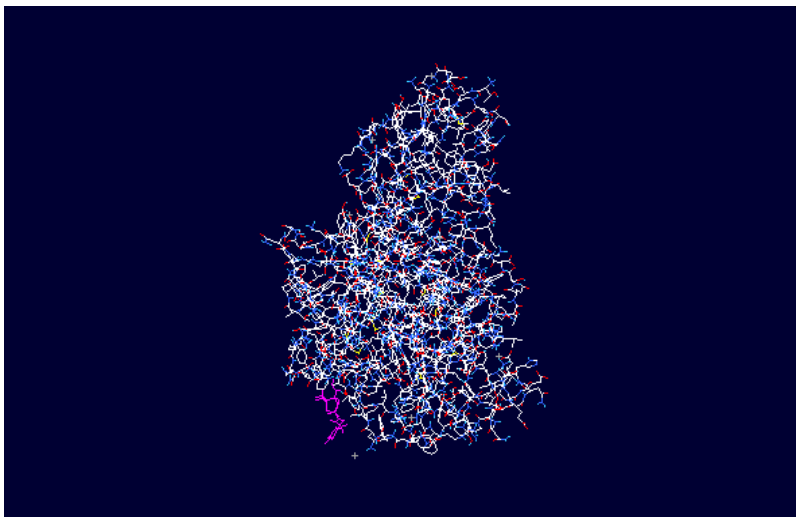

Figure 3: Docked complex structure of receptor transpeptidase (2c5w) and ligand Penicillin V (APRDOO423).

Table 3: Docking time of the complexes.

Receptor	Ligand	Matching time
2c5w(transpeptidase)	9lyz (NAM)	2 minutes
2c5w(transpeptidase)	APRDOO646 (penicillin G)	2 minutes
2c5w(transpeptidase)	APRDOO423 (penicillin V)	3 minutes

The above data suggests that docking time can be minimized by using the default settings. In other words default settings helps to find out the best fit in a minimum time (2-3minutes).

Distance Calculation in Spdbv

The output-docked structures were submitted to spdbv. The contact surfaces of docked ligand to receptor were clearly distinct from the non-contact surface. To facilitate distance calculation between the docked structures the non-contact residues were allowed to disappear. The distance between the receptor and ligand surface in contact were calculated.

Peptidoglycan Formation

Table 4: Distance measurement between the receptor transpeptidase (2c5w) and ligand NAM (9lyz)

Atomic residues	Angstrom value
ARG 642	1.33Å
TYR 548	2.97 Å
VAL 647	16.14Å
PHE 646	12.06Å
GLU 645	10.04Å
ASN 650	25.55

Peptidoglycan inhibition

Table 5: Distance measurement between the receptor transpeptidase (2c5w) and ligand penicillin G (APRDOO646).

Atomic residues	Angstrom value
TYR 423	4.61Å
GLU 645	4.35 Å
ILE 393	9.67Å
GLN 422	1.45Å
ALA 391	8.60Å
PHE646	5.19Å
ILE 393	4.34Å

Table 6: Distance measurement between the receptor transpeptidase (2c5w) and ligand penicillin V (APRDOO423**).**

Atomic residues	Angstrom value
TYR 423	2.15Å
GLN 422	8.47 Å
ALA 391	8.08Å
PHE 646	3.23Å
THR 420	6.62Å
GLN 426	4.73Å
THR 392	9.74Å

A residue is said on the interface if any of its atoms is within 10Å of an atom on the other protein (Morelli *et al.,* 2000; Wenfen, 2005). A pair of residues on different sides of Protein-Protein interface is considered to be in contact if any of their atoms were within 5Å (Wenfen, 2005). Every docked configuration is considered a near native structure if its RMS deviation from the crystallographic structure of the complex is less than 4Å (Palma *et al.,* 2000; Li *et al.,* 2003).

Table 7: Classification of the docked complexes.
a). Peptidoglycan formation Receptor transpeptidase (2c5w) and ligand NAM (9LYZ)

Angstrom value (RMSD)	**Interface area (≤10Å)**	**Contact area (≤5Å)**	**Near native structure (<4Å)**
25.55	_	_	_
16.14	_	_	_
12.06	_	_	_
10.04	_	_	_
1.33	_	_	ARG 642
2.97	_	_	TYR 548

Thus the residue in the docked complex can be classified as those found to occupy the interface area (within 5-10Å), contact area (within 4-5Å) and near native structure (less than 4Å). Based on this, the residues in the docked complexes of the present study can be grouped as follows, (Table: 7a, 7b)

Peptidoglycan Inhibition

Table 7.(b): Receptor transpeptidase (2c5w) and ligand penicillin G (APRDOO646).

Angstrom value (RMSD)	**Interface area (≤10Å)**	**Contact area (≤5Å)**	**Near native structure (<4Å)**
4.61	_	TYR 423	_
4.35	_	GLU 645	_
9.67	ILE 393	_	_
1.45	_	_	GLN 422
8.60	ALA 391	_	_
5.19	PHE 646	_	_
4.34	_	ILE 393	_

Table 7 (c): Receptor transpeptidase (2c5w) and ligand penicillin V (APRDOO423).

Angstrom value (RMSD)	Interface area (≤10Å)	Contact area (≤5Å)	Near native structure (<4Å)
2.15	_	_	TYR 423
8.47	GLN 422	_	_
8.08	ALA 391	_	_
3.23	_	_	PHE 646
6.62	THR 420	_	_
4.73	_	GLN 426	_
9.74	THR 392	_	_

Native state is the state where the interacting amino acid produces well-defined shape. By keeping this into consideration, in peptidoglycan formation two residues ARG 642 and TYR 548 were falling under this category. Of this ARG 642 was found to be the best since its Å value is 1.34. In peptidoglycan inhibition, the native state of penicillin G (APRDOO646) ligand is GLN 422 and its Å value is 1.45. Whereas the other ligand penicillin V (APRDOO423) produce two native state solution TYR 423 and PHE 646. Its Angstrom values were 2.15 and 3.23 respectively. The lowest Angstrom value 2.15 showing TYR 423 was found to be the best fit residues.As peptidoglycan inhibition is concerned the lowest RMSD value was observed in penicillin G (1.45) rather than on penicillin V (2.15,3.23). This suggests that penicillin G has well defined interacting activity than penicillin V.

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