///PLATINUM

Version 1.0

Tutorial

Contents

0. Introduction

PLATINUM stands for <u>P</u>rotein-<u>L</u>igand <u>AT</u>tractions <u>I</u>nvestigation <u>NUM</u>erically. This web-service is designed to assist in analysis of results of molecular docking carried out by standard software packages.

The main feature of PLATINUM is calculation and comparison of hydrophobic properties of two interacting molecules (or molecular systems), which is done by application of the empirical Molecular Hydrophobicity Potential (MHP). The tutorial covers three topics:

1) Rescoring the docking poses generated using a popular docking tool GOLD;

2) Altering parameters of MHP calculations to achieve better results;

3) Exploring systems other than protein – small molecule:
   An example of membrane-active peptide binding to lipid bilayer.

PLATINUM tutorial files can be downloaded at:
http://model.nmr.ru/platinum/files/

1. Docking and rescoring

1.1. Theory: Scoring functions and consensus docking

Docking is a computational method designed to predict the mutual orientation of two molecules, usually a protein (receptor) and a small compound (ligand). This implies insertion of one of the molecules – the ligand – into the "known" 3D-structure of the receptor.

Modern docking apllications proved themselves quite effective in generating correct (native-like) orientations of ligands in receptor binding sites. However, there remains a problem of selecting these correct predictions among the great variety of misleading solutions. Sometimes this is difficult to do due to inaccuracies of scoring functions. One way to overcome this problem is to use more precise criteria or even combinations of scoring functions to re-rank the docking poses, the approach referred to as "consensus docking/scoring".

Often, hydrophobic interactions play determinitive role in receptor-ligand recognition. While some scoring functions do not account for such contacts, it would be useful to re-rank the results of docking with a criterion based on complementarity of hydrophobic (and hydrophilic) properties between the two molecules. This can easily be done through the PLATINUM web-service.

1.2. Example I: Rescoring results of docking atgatroban to Human thrombin

This exercise demonstrates how to use the basic features of PLATINUM. We will consider the complex of Human thrombin with argatroban (Banner et al., 1991; PDB-code 1DWC). Argatroban is an amphiphilic molecule (Fig. 1.1), and in complex with thrombin its properties perfectly match those of the protein-receptor.
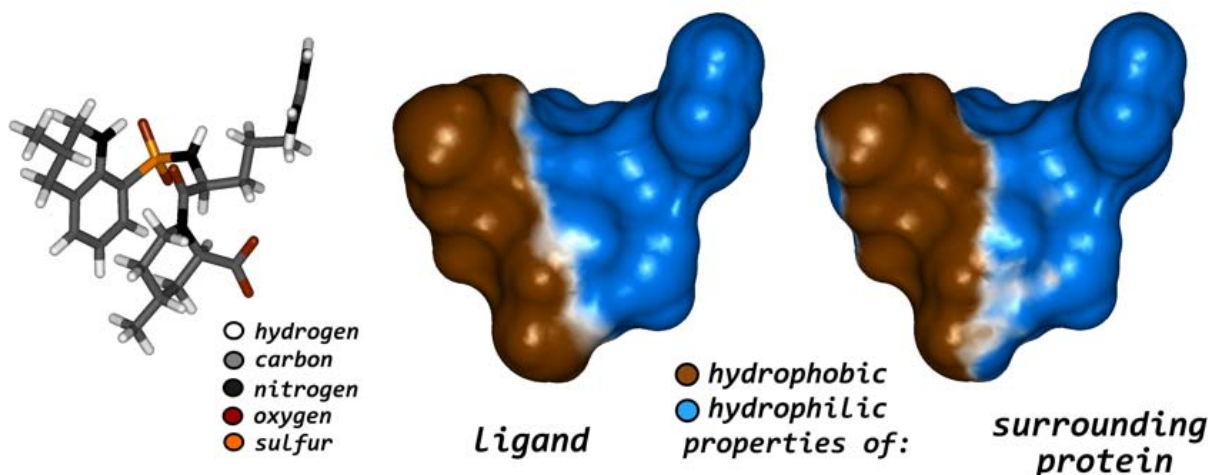

Figure 1.1. *Structure of argatroban molecule (left). Hydrophobic/hydrophilic properties of argatroban (middle) and its protein environment (right) in complex with Human thrombin (PDB-code 1DWC). The properties are expressed in terms of MHP calculated on the solvent-accessible surfase of argatroban. The picture was generated in InsightII (Molecular Simulations Inc., 2000) using MHP grids calculated with PLATINUM.*

Step 1: Upload files

Select one or more "ligand" files — if you want just to assess their hydrophobic properties — and add a single receptor file to assess ligand/receptor interactions. (File size limit: 5 Mb.)

Please note: If you don't have, or do not want to install Adobe Flash 9, you may use simple mode for uploading files.

Select a receptor file:

| ⊗ 1dwc_protein.mol2 | 547.12 KB |

Select file(s) with ligands:

Browse files

⊗ 1dwc_ligand.mol2	7.33 KB
⊗ gold_soln_argatroban_m1_1.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_2.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_3.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_4.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_5.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_6.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_7.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_8.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_9.mol2	8.66 KB
⊗ gold_soln_argatroban_m1_10.mol2	8.66 KB

Browse files

Please note: PLATINUM requires that all molecules are protonated!

Upload files

Figure 1.2. Uploading the results of docking argatroban to thrombin obtained with GOLD 2.0. Receptor structure is uploaded separately from ligands. After uploading, the file 1dwc_ligand.mol2 should be marked as "reference" because it represents orientation of the ligand in the X-ray structure.

Let us consider the results of docking of argatroban back to its binding site at thrombin. Docking was performed with GOLD 2.0 (Jones et al., 1995). Note that PLATINUM only works with the 3D molecular coordinates submitted by the user – it does not perform any geometry search or optimization. So, PLATINUM can only analyze results of docking obtained with other programs.

The first task is to submit the results of docking to the PLATINUM web-site. This can be done from the main page – just open the dialog windows and select the desired molecular files and then press the "Upload files" button (as displayed in Fig. 1.2).

Molecular files:

The receptor file is: 1dwc_protein.mol2 (560 Kb).

There are 11 ligand file(s) have been uploaded. You may also choose one of them as a "reference" one in order to compare RMSD values of other ligands with it.

1dwc_ligand.mol2 ⌄

Figure 1.3. Select file 1dwc_ligand.mol2 as "reference."

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Figure 1.4. While PLATINUM calculations are in progress, the unique task ID and its status are displayed. You can later view your results simply by URL containing this task ID: http://model.nmr.ru/platinum/?page=results&uid=example1.

On the next page you are prompted to select the reference ligand (Fig 1.3) and set the MHP calculation parameters. Generally, selecting the reference ligand is optional – it can be an X-ray pose used to test the performance of a docking/scoring method. If selected, PLATINUM will calculate RMSD and IFP (see Manual) of each ligand relative to the reference one. In this exercise, we will leave all MHP parameters as default. You may enter your e-mail to get a notification with the unique task ID to return to the results later (or remember the ID if you do not want to enter your e-mail). Click the "Launch" button.

The calculations are in progress; you can see the unique ID of your task and its current status (Fig. 1.4). The results page is refreshed every 30 seconds. The results are displayed after PLATINUM finishes (Fig. 1.5). The docking poses can be sorted by the value of interaction terms – by default Match1 and Match2 are recommended. In particular cases other terms may be useful.

Results

Receptor name: 1dwc_protein.mol2
Reference ligand: 1dwc_ligand.mol2.

Ligand name			r.m.s.d.	IFp	# H-bonds	$S_{L/L}$	$S_{H/H}$	S_{buried}	S_{total}	Match^1	Match^2	# Stack.	# Stack. Gua–π
1dwc_ligand			0.00	1	2.41	107.97	171.14	319.81	405.13	0.689	0.7481	0	0
gold_soln_argatroban_m1_9			1.24	0.75	2.50	105.89	173.42	335.19	416.84	0.6701	0.7253	0	0
gold_soln_argatroban_m1_8			6.30	0.333	0.60	73.42	217.72	356.96	448.73	0.6488	0.5648	0	0
gold_soln_argatroban_m1_7			6.28	0.444	0.40	71.65	207.34	347.97	448.67	0.6218	0.5481	0	0
gold_soln_argatroban_m1_1			6.18	0.444	0.71	64.11	180.25	317.66	435.32	0.5614	0.514	0.892	0.682
gold_soln_argatroban_m1_3			5.98	0.444	0.21	64.05	163.86	303.99	435.51	0.5233	0.5092	0.813	0
gold_soln_argatroban_m1_10			6.13	0.667	0.75	48.99	116.46	278.73	443.10	0.3734	0.364	0.772	1.124
gold_soln_argatroban_m1_5			5.70	0.444	1.28	45.51	191.01	346.14	448.29	0.5276	0.3424	0	0
gold_soln_argatroban_m1_2			3.68	0.75	1.11	40.51	159.43	261.33	434.81	0.4598	0.3049	0	0
gold_soln_argatroban_m1_4			6.53	0.5	0.10	33.35	120.63	340.89	444.18	0.3467	0.242	0	0
gold_soln_argatroban_m1_6			5.50	0.444	3.24	14.75	180.89	301.20	445.51	0.4391	0.1159	0	1.147

Save this table in tab-delimited format

Figure 1.5. Results of PLATINUM calculations for argatroban docking poses. Sorting by the value of surface area of hydrophobic contact ($S_{L/L}$) brings the lowest-RMSD pose on the top (scoring by "goldscore" function implemented in GOLD wrongly places it on the bottom of the list).

2. Optimization of scoring criteria

2.1. Theory: Hydrophobic interactions in scoring functions

Hydrophobic (lipophilic) interactions occur between apolar substancies that are incapable of making strong contacts (such as hydrogen bonds or salt bridges) with polar molecules. This type of contact is recognized as an important factor driving the interactions between biological molecules. Meanwhile, the complex nature of the hydrophobic effect prevented elaboration of a precise theory of "hydrophobic force", which gave rise to many empirical approaches.

One of the most successful is the concept of Molecular Hydrophobicity Potential – MHP (Testa et al., 1996; Efremov et al., 2007). In this method each atom in a molecule is assigned with a partial hydrophobic/hydrophilic constant, derived from experimental partition coefficients *logP* for a diverse set of organic compounds. Our investigations demonstrated that in some particular cases (i.g. nucleobase-containing ligands) more effective results in docking can be achieved when the MHP scale is shifted to more hydrophobic range. Such a "trick" leads to more realistic distribution of molecular hydrophobic/hydrophilic properties and thus, to more effective ranking of docking poses and to directly use MHP in docking.
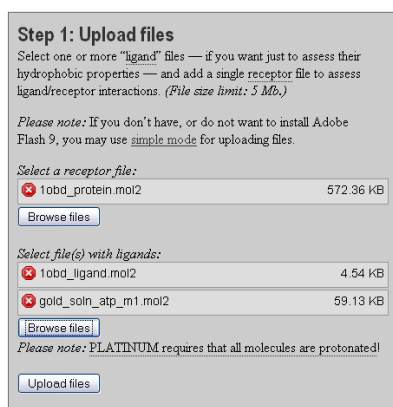
While many molecular modeling software exploit the MHP concept, the PLATINUM web-server is unique in providing the opportunity to perform such adjustment of MHP parameters.

2.2. Example II: Rescoring results of docking ATP to Saicar Synthase

This exercise demonstrates some advanced features of PLATINUM useful when re-ranking the results of docking. In our studies of binding of ATP to protein active sites (Pyrkov et al., 2007) we found that empirical MHP parameters may need some correction to better reflect the hydrophobic/hydrophilic properties of the ATP molecule. Namely, a moderate shift of MHP scale for ATP to more hydrophobic range considerably improves the overall picture as will be shown below.

Such shift of the MHP scale can be easily done using PLATINUM. Let us consider the structure SAICAR-synthase complexed with ATP (Antonyuk et al., 2001; PDB-code 1OBD). The X-ray structure of ATP has been excluded from the protein active site and re-docked using GOLD (Jones et al., 1995) software generating in total 10 ligand poses.

Upload the receptor structure, the ligand poses and the X-ray ligand structure (1obd_ligand.mol2; mark it as "reference") as described in Exercise 1 and launch the PLAINUM calculations (Fig 2.1). This time you can see that ranking by the hydrophobic match is not as good as in the previous exercise: The first structure has quite large RMSD from the reference – 3.9 Å (Fig 2.2).

Figure 2.1. *Uploading the results of docking ATP to SAICAR-synthase obtained with GOLD 2.0. Receptor structure is uploaded separately from ligands. All 10 docking solutions are written in multi-mol2 file gold_soln_atp_m1.mol2. After uploading, the file 1obd_ligand.mol2 should be marked because it represents orientation of the ligand in the X-ray structure.*

Results

Receptor name: 1obd_protein.mol2
Reference ligand: 1obd_ligand.mol2.

Ligand name			r.m.s.d.	IFp	# H-bonds	$S_{L/L}$	$S_{H/H}$	S_{buried}	S_{total}	Match[1]	Match[2]	# Stack.
gold_soln_atp_m1_10			3.91	0.294	3.18	4.18	168.86	210.32	330.13	0.5242	0.164	0
gold_soln_atp_m1_7			2.21	0.75	6.40	2.34	139.24	223.92	330.95	0.4278	0.0495	0.994
gold_soln_atp_m1_8			2.14	0.562	5.21	1.84	132.41	224.81	327.34	0.4101	0.0365	0.973
1obd_ligand			0.00	1	5.13	1.20	115.44	208.35	326.14	0.3577	0.0236	0.987
gold_soln_atp_m1_1			11.40	0.158	5.19	0.00	220.95	231.96	310.95	0.7106	0	0
gold_soln_atp_m1_2			9.60	0.235	3.96	0.00	133.86	205.19	323.29	0.4141	0	0
gold_soln_atp_m1_3			12.36	0.294	3.45	0.00	226.58	231.65	327.47	0.6919	0	0
gold_soln_atp_m1_4			10.11	0.111	3.69	0.00	222.22	223.04	323.99	0.6859	0	0
gold_soln_atp_m1_5			7.86	0.222	4.93	0.00	178.73	183.10	313.67	0.5698	0	0
gold_soln_atp_m1_6			12.23	0.188	2.07	0.00	204.81	213.16	334.62	0.6121	0	0
gold_soln_atp_m1_9			8.00	0.105	5.86	0.00	229.94	230.19	319.56	0.7195	0	0

Figure 2.2. *Results of PLATINUM calculations for ATP docking poses. Sorting by the value of surface area of hydrophobic contact ($S_{L/L}$) brings one of wrong docking solutiosn on the top (RMSD ~ 3.9 Å), while the X-ray reference structure and correct docking poses (gold_soln_atp_m1_7 and gold_soln_atp_m1_8) with RMSD < 2.5 Å have lower scores.*
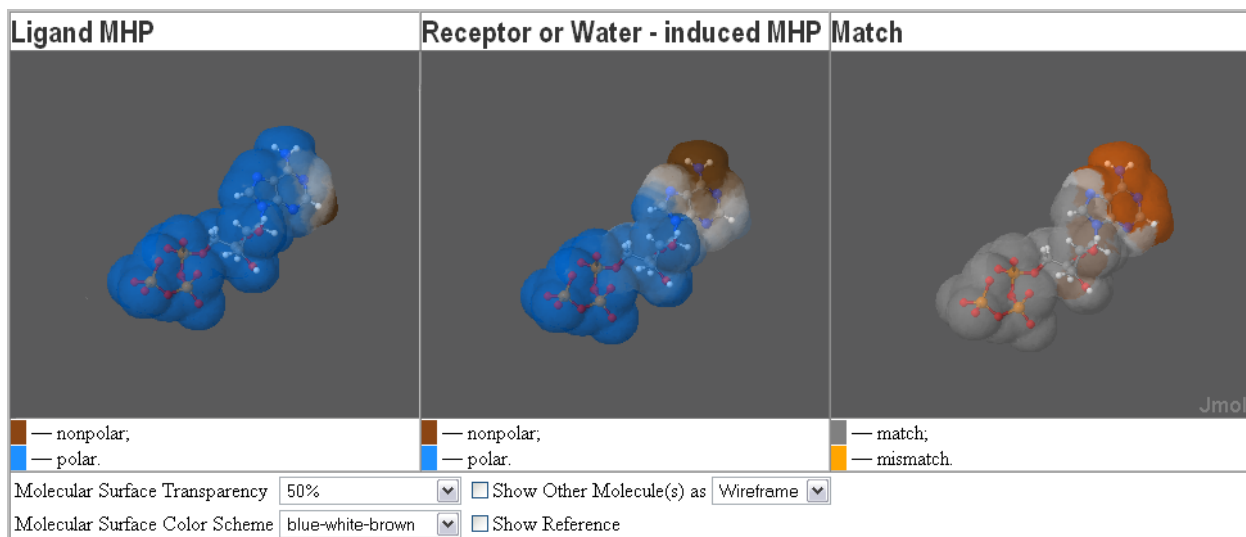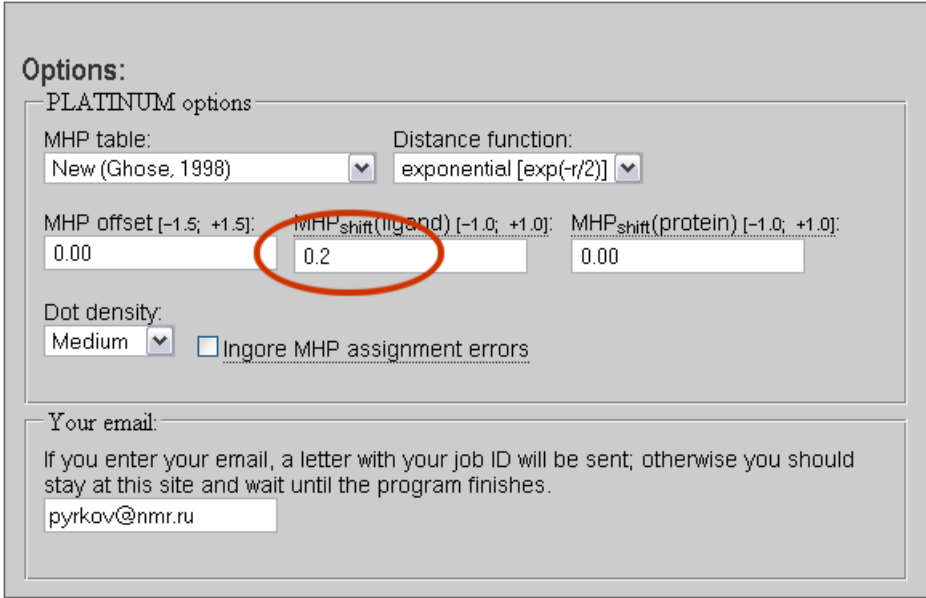

Figure 2.3. *Visualization of hydrophobic/hydrophilic properties of ATP (left) and its binding site (middle) projected onto the surface of the ligand, and their complementarity (right). The structures are the X-ray models from PDB-code 1OBD. The screenshot was produced using the online visualization Jmol applet as implemented in the PLATINMUM web-service.*

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This happened because the empirical MHP underestimated hydrophobic properties of adenine. To see more details click the molecule icon 🦋 next to "1obd_ligand". You are redirected to the visualization page (Fig. 2.3; requires javascript), where the three windows show the distribution of hydrophobic/hydrophilic properties of: ATP in X-ray position (left), exerted by protein surroundings (middle), and their complementarity (right).

You can see that the aromatic adenine moiety of ATP is less hydrophilic than the ribose and phosphates. In such representation, the hydrophobic nature of adenine is quite poor. And this does not correspond to the facts. However, this is easy to correct: Change the "MHP-shift(ligand)" parameter to 0.2 [logP units]. This will add 0.2 to the ligand hydrophobicity potential at each surface point. You will see that the ribose and phosphates remain hydrophilic as it should be. Meanwhile, adenine becomes quite more hydrophobic. (In our previous studies we have found that shift to a more hydrophobic range is likely to produce better scoring results. General MHP shifts can be found in Manual in section *3.2 Parameters of MHP Calculations*.)

Now, we will recalculate hydrophobic/hydrophilic molecular properties with new parameters. Find the "Change settings & restart" button in the upper-left corner on the results page, set the "MHP-shift(ligand)" parameter to 0.2 and restart the calculations (Fig. 2.4). This should place all correct docking poses (RMSD < 2.5 Å) with the reference structure on the top when ranked by the value of the hydrophobic match surface (Fig. 2.5). Note also that adenine participates in stacking interaction in the structure 1OBD, and therefore the term of stacking contact could be effectively used to "fish out" the correct docking poses in this case.

Figure 2.4. *Parameters of MHP calculation. Set MHP-shift(ligand) to 0.2 to better reproduce hydrophobic/hydrophilic properties of ATP.*

Results

Receptor name: 1obd_protein.mol2
Reference ligand: 1obd_ligand.mol2.

Ligand name			r.m.s.d.	IFp	# H-bonds	$S_{L/L}$	$S_{H/H}$	S_{buried}	S_{total}	Match[1]	Match[2]	# Stack.
gold_soln_atp_m1_7			2.21	0.75	6.40	62.41	125.76	223.92	330.95	0.5686	0.7163	0.994
1obd_ligand			0.00	1	5.13	60.13	106.84	208.35	326.14	0.5119	0.6832	0.987
gold_soln_atp_m1_8			2.14	0.562	5.21	59.05	118.80	224.81	327.34	0.5433	0.6719	0.973
gold_soln_atp_m1_10			3.91	0.294	3.18	40.13	148.61	210.32	330.13	0.5717	0.6015	0
gold_soln_atp_m1_6			12.23	0.188	2.07	0.44	156.27	213.16	334.62	0.4683	0.0089	0
gold_soln_atp_m1_1			11.40	0.158	5.19	0.00	173.92	231.96	310.95	0.5593	0	0
gold_soln_atp_m1_2			9.60	0.235	3.96	0.00	101.39	205.19	323.29	0.3136	0	0
gold_soln_atp_m1_3			12.36	0.294	3.45	0.00	170.25	231.65	327.47	0.5199	0	0
gold_soln_atp_m1_4			10.11	0.111	3.69	0.00	181.27	223.04	323.99	0.5595	0	0
gold_soln_atp_m1_5			7.86	0.222	4.93	0.00	147.03	183.10	313.67	0.4687	0	0
gold_soln_atp_m1_9			8.00	0.105	5.86	0.00	184.68	230.19	319.56	0.5779	0	0

Figure 2.5. *Results of PLATINUM calculations for ATP docking poses. Setting parameter MHP-shift(ligand) to 0.2 improves ranking by the value of the surface area of hydrophobic contact ($S_{L/L}$).*

3. Analysis of sytems other than protein – small molecule

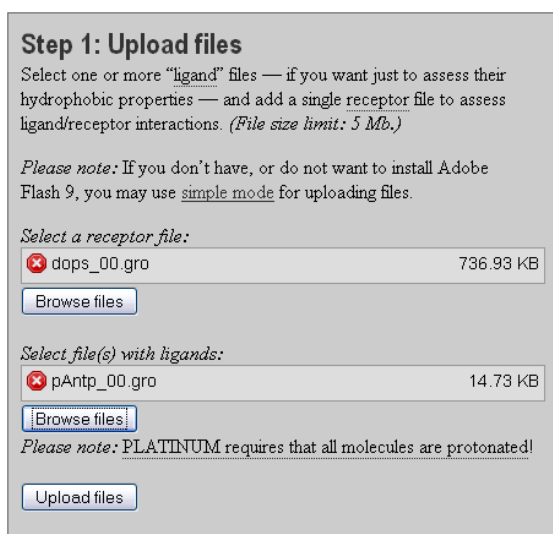#### 3.1. Theory: Hydrophobic effect in molecular biology

Apolar substancies such as aliphatic carbon chains, aromatic fragments, and so on tend to avoid contact with polar molecules of water and others. This results in effective hydrophobic interaction which plays an important role in maintenance of the spatial structure of biological macromolecules and their interactions with each other and small organic compounds. Hydrophobic contacts are ubiquitous – along with polar interactions, such as hydrogen bonds or salt bridges, they determine the recognition of proteins and some small molecules by other proteins, etc. Another prominent manifestation of hydrophobic effect is the arrangement of a great number of individual lipid molecules forming lipid membranes.

Taking all this into account, it becomes clear that study of many biomolecular systems requires investigation of distribution of molecular hydrophobic/hydrophilic properties and their complementarity (match) at the interface between interacting molecules. Considerable insight to the subject can be gained from visual inspection and quantitative estimation of molecular hydrophobic/hydrophilic properties.

3.2. Example III: Interactions of a peptide with lipid bilayer

In this exercise we will examine binding of the penetratin peptide (pAntp) to a dioleoylphosphatidylserine (DOPS) bilayer (Polyansky et al., 2008). The molecules of DOPS are distinctly amphiphilic – interacting with each other through aliphatic hydrocarbon chains and facing their polar heads to water. However, the solvent-accessible surface of a lipid bilayer is not uniform – it possesses a lot of dynamic "hydrophobic" clusters, where aliphatic chains are temporarily exposed to water. Dynamic properties of such clusters, such as, the hydrophobic surface area or characteristic lifetime, may be the factors that determine the specificity of interactions of lipid bilayers with manifold membrane-active compounds.

To demonstrate how PLATINUM can help to visualize intermolecular hydrophobic interactions, we will analyze two frames extracted from molecular dynamics simulations of pAntp with DOPS bilayer: (i) the starting structure, where pAntp is only approaching the membrane, (ii) pAntp bound to the membrane after 20 ns of simulations.

Figure 3.1. *Uploading pAntp peptide as a ligand and DOPS lipid membrane as a receptor.*

Figure 3.2. *Parameters of MHP calculation. Set MHP-offset to 0.1 to better reproduce hydrophobic/hydrophilic properties of the pAntp peptide and lipid bilayer.*
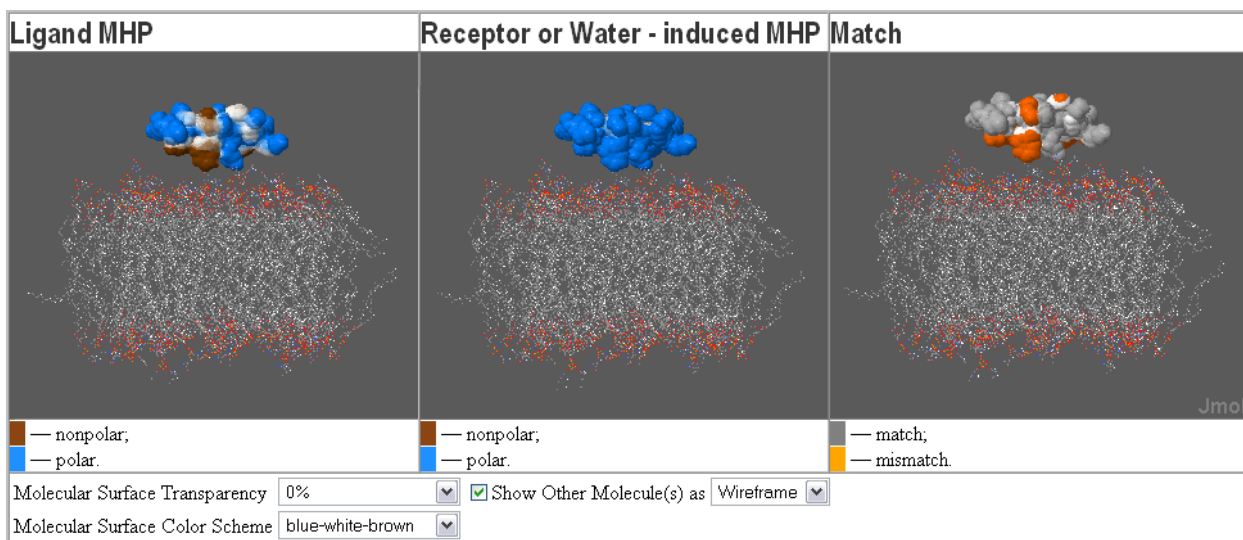

Figure 3.3. *Visualization of hydrophobic/hydrophilic properties of pAntp peptide (left) and its environment (middle) projected onto the peptide surface. The screenshot was produced using the online visualization Jmol applet as implemented in the PLATINMUM web-service.*

First, upload the structures corresponding to the starting state: lipid membrane as a receptor (*dops_00.gro*) and pAntp as a ligand (*pAntp_00.gro*) as shown in Fig. 3.1. Upload files and change parameter MHP-offset to 0.1 (Fig. 3.2) – this will better reflect the hydrophobic/hydrophilic properties of the molecules.

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When calculations are finished, you can see the results page. Above the Results table you can see a notice "There are warnings! →". Clicking on it shows a list of atoms for which PLATINUM did not assign hydrophobicity constants because their valences were not assigned correctly. This happened because some bond in the .pdb file were too long and PLATINUM did not identified them. If < 10% of receptor atoms have errors PLATINUM continues calculations. However, if more atoms of the receptor or any atom of a ligand cause errors the calculations will not proceed. The user should either correct the molecular structures or (if sure that the errors are minor) mark the "Ignore MHP assignment errors" check-box on the parameters page (Step 2).

Visualize online the hydrophobic/hydrophilic properties of pAntp and its molecular environment projected onto its surface clicking the molecule icon 🦠 as in the previous exercise (Fig. 3.3). You can see that the environmental properties are totally hydrophilic – this is because the peptide is not in contact with the membrane and is surrounded by water (S_{buried} = 0.0 Å^2). Note that the receptor file *dops_00.gro* contains only lipid molecules and waters have been removed. PLATINUM surrounds the ligand with a grid of effective hydrophilic probes, whose MHP constant was fitted to represent the hydrophilic properties of water (see Manual) – so the problem of missing water molecules does not spoil the picture.
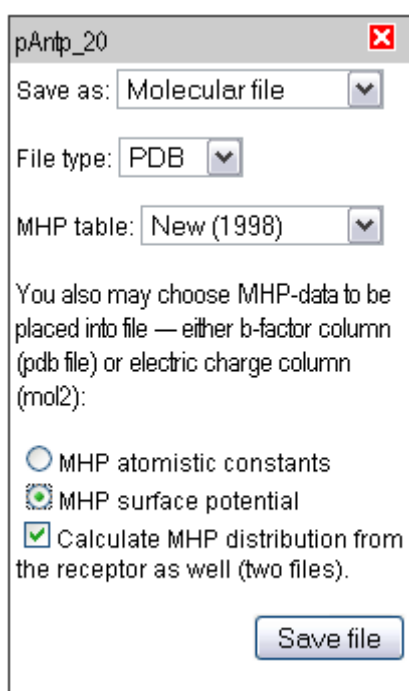

Figure 3.4. The floppy-disk menu. Here the user can select, which type of data to save for further use in a molecular visualizing software to create illustrative pictures of hydrophobic/hydrophilic molecular properties.

Next we will examine the changes in the hydrophobic/hydrophilic interactions induced by pAntp binding to the membrane surface. Click the "Start a new task" button in the upper right corner and upload *dops_20.gro* as a receptor and *pAntp_20.gro* as a ligand. Make sure that MHP-offset parameter is set to 0.1 so that we could compare the results of these two PLATINUM calculations. The area of buried surface S_{buried} = ~90 Å^2 tells us that the peptide is bound to the lipid membrane. Besides that, a hydrophobic contact between the peptide side chains and the exposed aliphatic moieties of lipids is formed. Most of the peptide hydrophobic surface is still exposed to hydrophilic environment, and PLATINUM provides a quantitative estimate of the contact and the hydrophobic match surface areas along the molecular dynamics run.

The picture on the visualization page may be of insufficient quality. There is an alternative way to produce a better picture using a standard molecular visualization software (e.g. PyMol). To do that, click the floppy-disk icon 💾. A menu appears, where you can choose the format of output data and readjust some parameters of MHP calculation (Fig. 3.4). Select the parameters as shown in the Figure 3.4: save as Molecular file; File type PDB; MHP table New (1998); MHP surface potential; Calculate MHP distribution from the receptor as well.

PLATINUM will generate two files *pAntp_20_mhplig.pdb* and *pAntp_20_mhprec.pdb* with the structure of the peptide ligand, where the B-factor column contains the hydrophobic/hydrophilic properties of the ligand (*pAntp_20_mhplig.pdb*) and those projected from its environment (*pAntp_20_mhprec.pdb*). These files can be loaded into e.g. PyMol and colored by the values written to the B-factor column (Fig. 3.5). To do that, the following command should be typed: ***cmd.spectrum("b", "green_white_yellow", selection="all")***. This will color the molecules according to the Yellow-Green color scheme (yellow and green correspond to hydrophobic and hydrophilic properties, respectively).
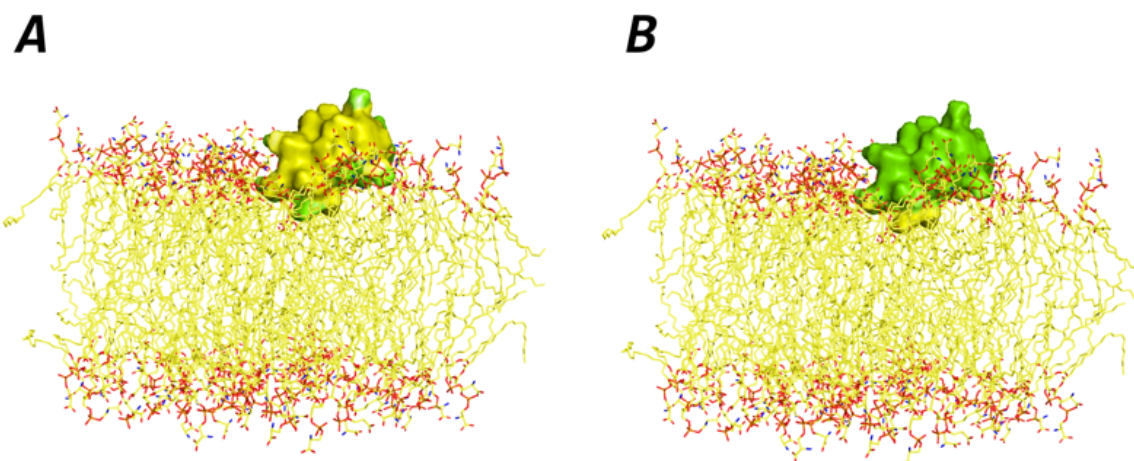

Figure 3.5. *Visualization of hydrophobic/hydrophilic properties of pAntp peptide (A) and its lipid environment projected onto the surface of the peptide (B). The molecules are colored according to the Yellow-Green color scheme (yellow and green correspond to hydrophobic and hydrophilic properties, respectively). The picture was generated in PyMol (DeLano, 2002; http://www.pymol.org) using MHP pre-calculated with PLATINUM (the structure of the lipid bilayer is not included into the PLATINUM output – it was added for better understanding the molecular system).*

4. Getting Help, Feedback and References

This web-service combines all our best results obtained in the efforts to improve the performance of standard molecular docking packages. It is absolutely free to use for Academia; commercial users must ask for a licence. We hope that PLATINUM will be useful in molecular modeling of interactions of ligands with receptors. Please, use the following reference to cite the software:

Timothy V. Pyrkov, Anton O. Chugunov, Nikolay A. Krylov, Dmitry E. Nolde, Roman G. Efremov. PLATINUM. Laboratory of Biomolecular Modeling at Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciencies, Moscow, Russia, 2008. http://model.nmr.ru/platinum.
(Article in preparation)

All questions about PLATINUM can be asked at the net forum or via e-mail to:
pyrkov@nmr.ru (Tim Pyrkov, scientific concept & programming)
volster@nmr.ru (Anton Chugunov, web-design & programming)
efremov@nmr.ru (Roman Efremov, head of the lab)

The authors will be grateful for any remarks on conceptual issues or suggestions on technical improvements of the service.

5. Cited Literature

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