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Molecular interaction analysis and visualization of protein-ligand docking using Biovia Discovery Studio Visualizer

Umi Baroroh[1,2,*], Zahra Silmi Muscifa[2], Wanda Destiarani[2], Fauzian Giansyah Rohmatulloh[2], Muhammad Yusuf[2,3]

1. Biotechnology Pharmacy, Indonesian School of Pharmacy, Jl. Soekarno Hatta no.354, Bandung, Indonesia.

2. Research Center for Molecular Biotechnology and Bioinformatics, Universitas Padjadjaran Jl. Singaperbangsa 2, Bandung, Indonesia

3. Department of Chemistry, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km 21, Jatinangor, Sumedang, Indonesia.

**Corresponding author: umibaroroh@stfi.ac.id*

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Molecular docking interpretation is one of the crucial parts before determining the result. Docking is commonly used to study biomolecular interaction, usually for protein-ligand interaction, and to study the molecular mechanism. This protocol aims to provide a detailed procedure for analyzing and interpreting molecular docking results using Biovia Discovery Studio (BDS). Analysis of molecular interaction can help users to determine the strengthened docking results, besides free energy of binding. In this protocol, the analysis of molecular interaction as well as the surface characteristic of receptors was discussed in detail. In addition, the docking visualization to obtain suitable pictures for publications was also included. Protein-ligand docking of the crystal structure of human folate receptor and alpha in complex with folic acid was used as a model study. The redocking method was applied and compared with the crystal structure. The entire protocol will spend more or less 2 hours. This protocol offers a comprehensive approach to analyzing molecular interactions in docking results and provides guidance on visualizing the data to generate high-quality images using BDS.

Keywords: docking visualization | protein-ligand docking| molecular interaction | BDS, autodock

Molecular docking and visualization are vital in drug discovery and molecular biology research. Docking predicts ligand-protein binding, aiding in identifying drug candidates and optimizing their properties. Visualization creates graphical representations of molecular structures and interactions, enhancing understanding of biomolecule relationships and docking simulation outcomes[1]. Docking saves time and resources by reducing the need for experimentation. Moreover, docking quickly screens numerous compounds, while visualization helps prioritize promising candidates. They also provide insights into drug mechanisms and disease pathology[2].

It is important to have clear and informative visual representations to effectively interpret and communicate the docking simulations' results. To address this requirement, several software tools have been developed. PyMOL[3] offers features to visualize protein structure and protein-ligand interactions effectively. VMD[4] (Visual Molecular Dynamics) provides powerful flexibility in analyzing and visualizing biomolecules. UCSF Chimera[5] has a special focus on identifying relevant non-covalent interactions. Additionally, Biovia Discovery Studio[6] (BDS), a comprehensive software, includes special modules for visualizing protein-ligand interactions and performing in-depth analysis of protein-ligand complexes. Furthermore, BDS is also compatible to visualize all molecular docking results. This protocol describes the steps for visualizing docking analysis results using BDS visualizer software[7]. BDS is a suite of visualization tools for effectively interpreting and communicating the results of molecular simulations and analysis. Some of the key visualization tools include: 1.) 3D Structure Viewer: Viewing and analyzing protein and small molecule structures in 3D., 2.) Ligand Explorer: for visualizing the interactions between a ligand and a protein, 3.) Complex Viewer: for visualizing protein-protein and protein-ligand complexes, 4.) Electrostatic Potential Map: Visualizing electrostatic potential distribution on a protein surface, and 5.) Surface and Volume Rendering: creating detailed and interactive visual representations of molecular structures [8]. These tools allow users to quickly assess the results of molecular simulations and make informed decisions about the next steps in drug discovery.

Application of Protocol

Biovia Discovery Studio (BDS) refers to using the software's tools to create graphical representations of molecular structures and simulation results. The visualization tools in BDS are designed to help researchers understand and communicate the results of molecular simulations, docking studies, and other molecular analyses[9]. This protocol can give guidelines to display molecular structures in 3D and highlight specific interactions between proteins and ligands, including hydrogen bonding and hydrophobic interactions[10].

These interactions determine the stability of the complex and the binding affinity between the protein and ligand[11]. Other BDS visualization capabilities include electrostatic potential mapping, surface and volume rendering, and complex visualization. The visualizations generated by BDS can be customized by adjusting settings such as color, transparency, and labels. They can be saved or exported for use in presentations, publications, or other applications.

BDS has an integrated platform integrating a wide range of molecular modeling and simulation tools, providing a comprehensive drug discovery and molecular biology research solution. BDS provides an intuitive and user-friendly interface, making it accessible to researchers with various expertise levels and advanced visualization capabilities. BDS can also provide customizable output allowing users to customize their visualization output, including adding annotations and labels and creating custom views. Robust data management.

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About Protocol

After performing molecular docking, various poses and conformations of the ligands bound to the target molecule can be generated[12]. Various software tools can be used to analyze and visualize these results, including Biovia Discovery Studio. This tool allows for creating images and animations of the docking poses and conformations, which can help understand the binding interactions and produce figures for publication. Other analysis tools can also be used to evaluate the binding free energy, binding affinity, and other properties of the ligand-target complex[13].

This protocol uses the Folic Acid and Folate Receptor Alpha complex structures from the results of molecular dynamics simulations previously carried out by Yusuf et al.[14].

Materials

Coordinate files for receptor and ligan were extracted from PDB (https://www.rcsb.org/) with the code 4LRH and docking result file with the extension .dlg. While hardware and software used in this protocol are:

Computer: Windows PC

BIOVIA Discovery Visualizer[7]: https://discover.3ds.com/discovery-studio-visualizer-download

AutoDock[15]: http://autodock.scripps.edu (the installation procedure is available at http://autodock.scripps.edu/downloads/autodock-registration/autodock-4-2-download-page/)

AutoDockTools (part of MGLTools): http://mgltools.scripps.edu (the installation procedure is available at http://mgltools.scripps.edu/downloads).

The hardware requirements for running BDS are as follows: a laptop or desktop computer compatible with Intel x86_64 or equivalent, with higher compatibility being preferable. A minimum of 4 GB of memory is recommended, although a higher capacity is preferred. The operating system should be Windows 10 64-bit.

Procedure

File Preparation of Molecular Docking Results

The output of molecular docking, .dlg files, are transformed to PDBQT format using software like AutoDock Tools. PDBQT files take a lot of information, such as partial charge, atom type and radius, and 3D coordinates of atoms. The prepared PDBQT file usually corresponds to the binding pose with the least energy value, which is the most stable and favorable binding configuration. Open docking result (.dlg) **by clicking 'Analyze → Docking → Open'.**

Read the atomic coordinates of ligand and receptor. First, read the atomic of the ligand by clicking **'Ligand → Input → Open' and for receptor, click 'File → Read Molecule'** and choose the receptor file.

Generate the coordinate file for docking results. To open the results file and sort by the energy**, click 'Analyze → Conformations → Play, ranked by energy'.** After that, click 'opens panel to change play options', and a new pop-up will appear. Click 'Write Complex', and save the file with the preference name, for example, **"dock_1.pdbqt"**

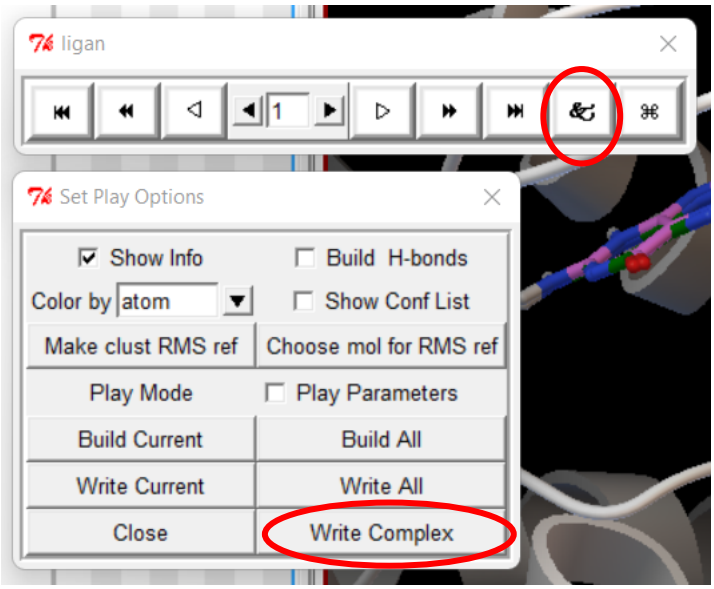

Figure 1. AutoDockTools (ADT). ADT commands for coordinate preparation and analyze the docking result.

Introduction to Biovia Discovery Studio Visualizer

BIOVIA Discovery Studio is a software tool that can be used to visualize and analyze the results of molecular docking. Additionally, BIOVIA Discovery Studio provides various analysis tools to evaluate the ligand-target complex's binding free energy, binding affinity, and other properties. The software also has an easy-to-use interface, allowing users to customize the appearance of the images and animations, making it easy to create high-quality figures for publication.

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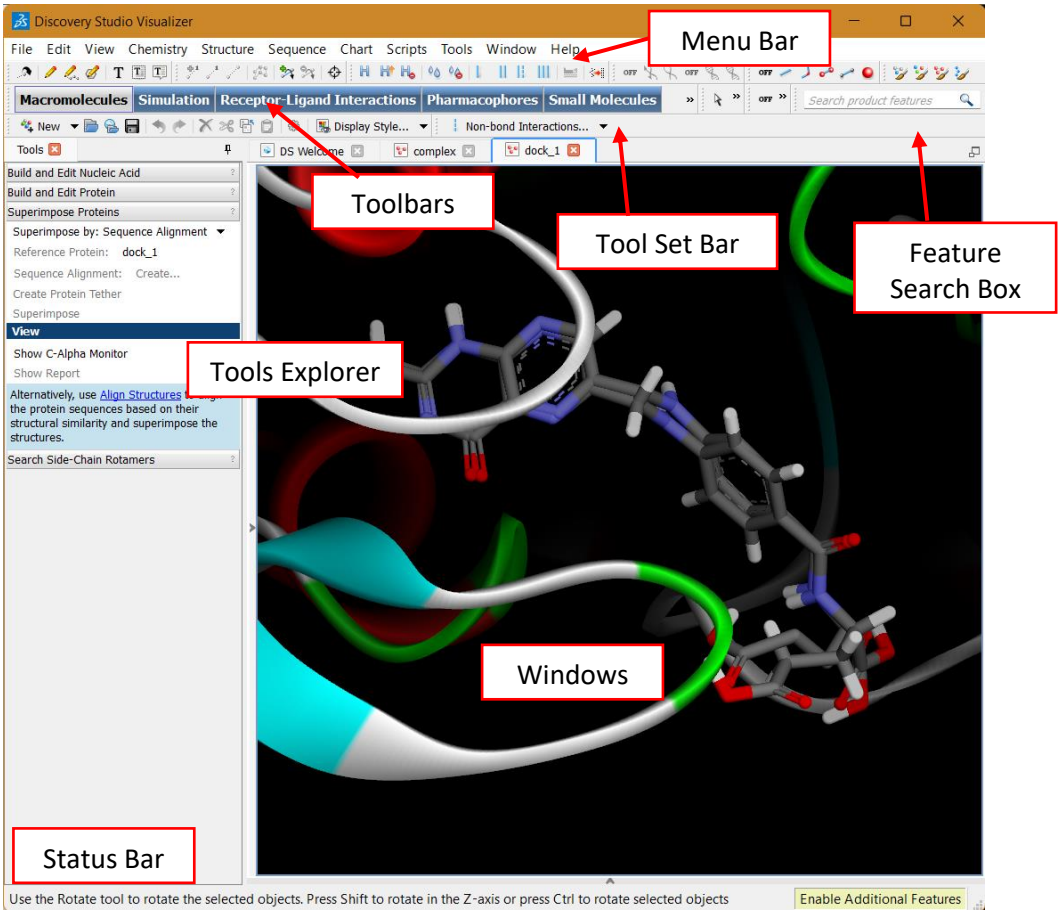

Figure 2. Biovia Discovery Studio interface. It includes many tools for modifying and viewing data, and analyzing the results. The major feature of the client is depicted in this illustration and the description of some features is explained in the following table.

Feature	Description
Feature Search Box	Use this to search and open functionality
Menu Bar	Select menu items to access commonly used tools, such as file access, editing, and viewing commands
Toolbars	Click buttons to gain access to commonly used tools for viewing and editing data
Tool Set Bar	Click buttons in the tool set bar to display different groups of related analysis tools in the Tools Explorer
Windows	The Discovery Studio Visualizer allows you to work with data in a variety of windows, including: • Molecule Window: Edit and view molecular structures and property data. • Sequence Window: Edit and view sequences and sequence alignments. • Script Window: Create, edit, and execute Perl scripts within the Visualizer.
Status Bar	Displays information about the current application activity
Files Explorer	Explore the file system to locate and open data files

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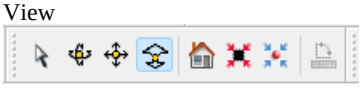
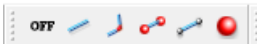
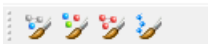
Useful toolbars that are usually used are in the following table.

Name	Description
View 	The View toolbar provides tools that manipulate the Molecule Window or edit molecules in the document.
Protein Structure Display 	The Protein Structure Display toolbar provides shortcuts to commands in the Protein tab of the Graphics View Display Style dialog.
Atom Display 	The Atom Display toolbar contains buttons allowing easy access to the commands on the Atom tab of the Graphics View Display Style dialog.
Atom Colors 	The Atom Colors toolbar contains buttons that allow you quickly change the coloring schemes used to display atoms. The change is applied to selected atoms, or all atoms if nothing is selected.
Chemistry 	The Chemistry toolbar provides shortcuts to commands in the Chemistry menu that assist you in building molecules.

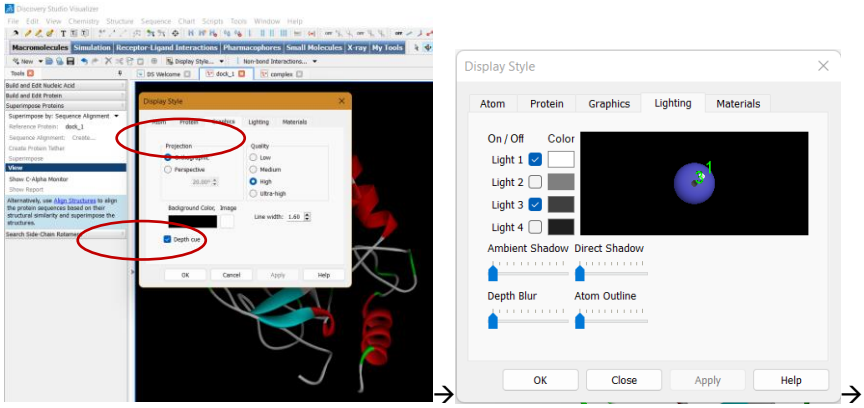
Docking Results Visualization

3D Visualization

Open the receptor file (4lrh.pdb) **by clicking 'File → Open' and choose 4lrh.pdb.** Open hierarchy to view the receptor file component, for example chain, amino acid, and atom**. Click 'View → Hierarchy' or by using the shortcut 'ctrl + H'.** Open the sequence by **clicking 'Sequence → Show Sequence' or by typing 'ctrl + Q'.**

Change Display Style

Click **'Display Style'** on the top or right-click on the windows to customize the display. To change the graphic, lighting, and material can follow this instruction. In the graphic menu, the projection of orthographic or perspective can be chosen, including background color, and the quality of the graphic. In the lighting menu, there are four lighting that can be used and can be customized by color. To make a clear visualization, the adjustment is according to the user. In this menu, the shadow, atom outline, and blur can be adjusted. The result can be seen in Figure 3.



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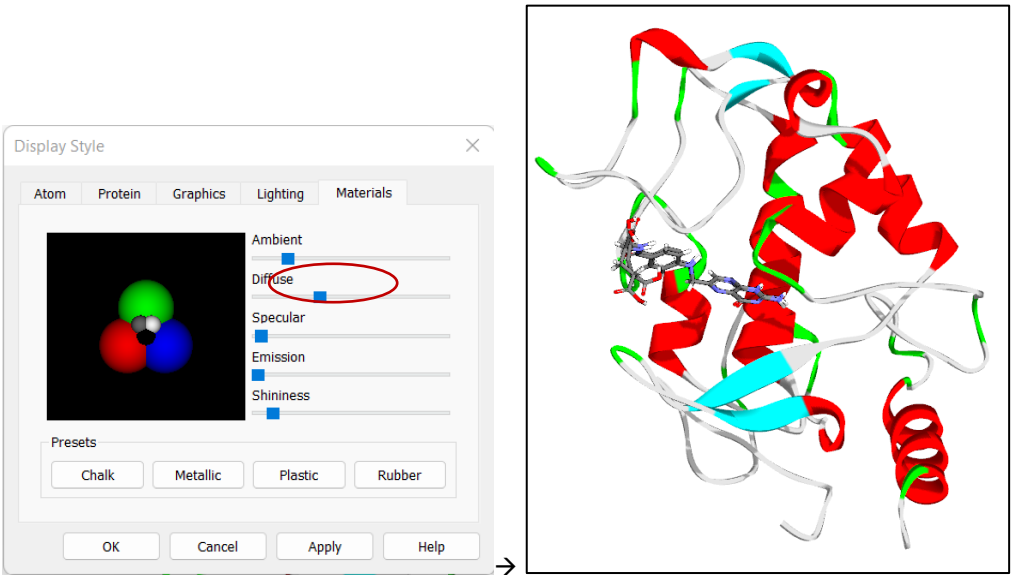

Figure 3. Step by step in display style to change the graphic, lighting, and material of molecule.

Change the protein style by clicking icon  on Toolbars, or **click 'Display Style' → Protein.** There are a lot of type of protein display and can be adjusted according to user needed.

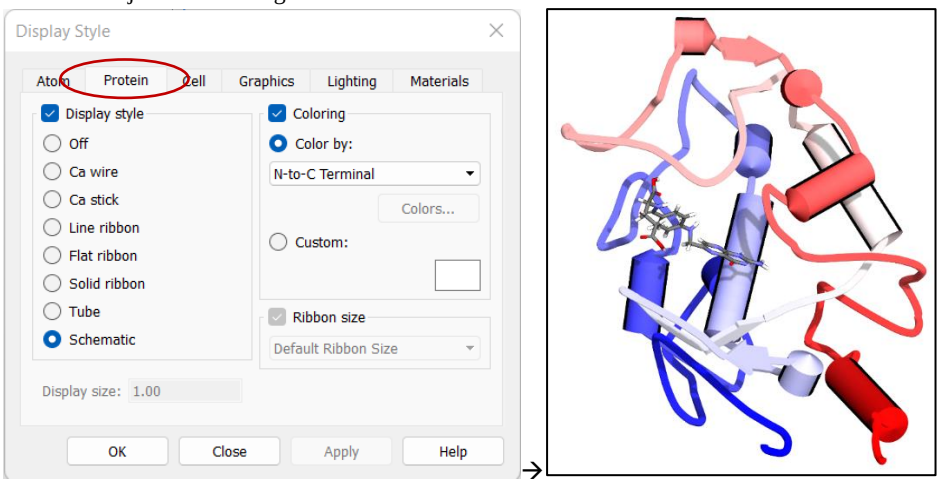

Figure 4. Menu to change protein display.

Redocking Analysis

To analyze docking results, first, open the previous file of **dock_1.pdbqt** by clicking **'File → Insert From File → click dock_1.pdbqt'.** To differentiate the coordinate of the docking result and pdb file, the color of both ligands can be changed

by 'double click on ligand or click on ligand's chain → Display Style → Atom'. In color by or custom option the color can be changed. To avoid confusion about atom color, prefer to change only in carbon atom by thickening 'Carbon atoms only'

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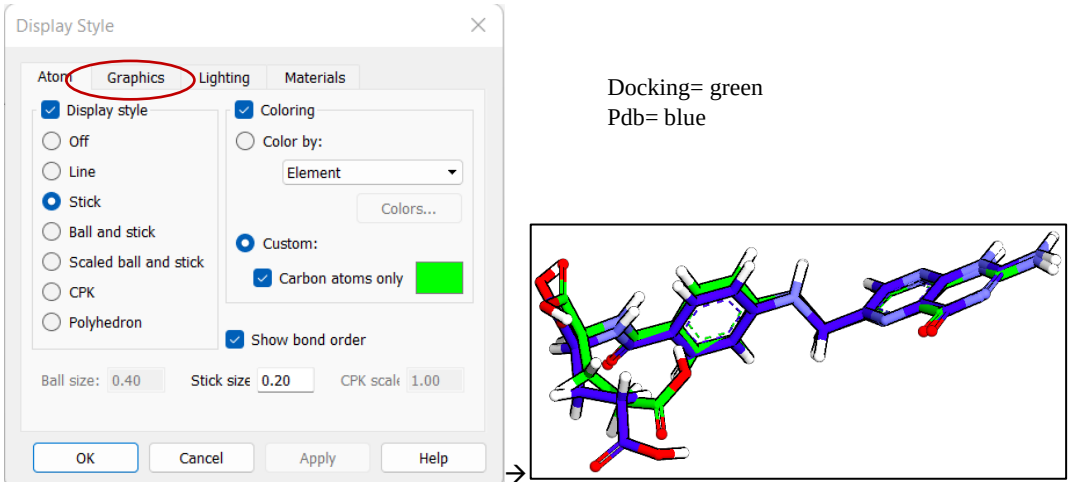


Figure 5. Menu to change atom color

Non-bond Interaction Analysis

Before carrying out this analysis, we have to define ligand and receptor. Choose **'dock_1 and 4LRH'** respectively for ligand and receptor. And then, click **"Ligand Interaction"** To make it clear, show only the polar hydrogen. Click on the **"Chemistry Toolbars"**

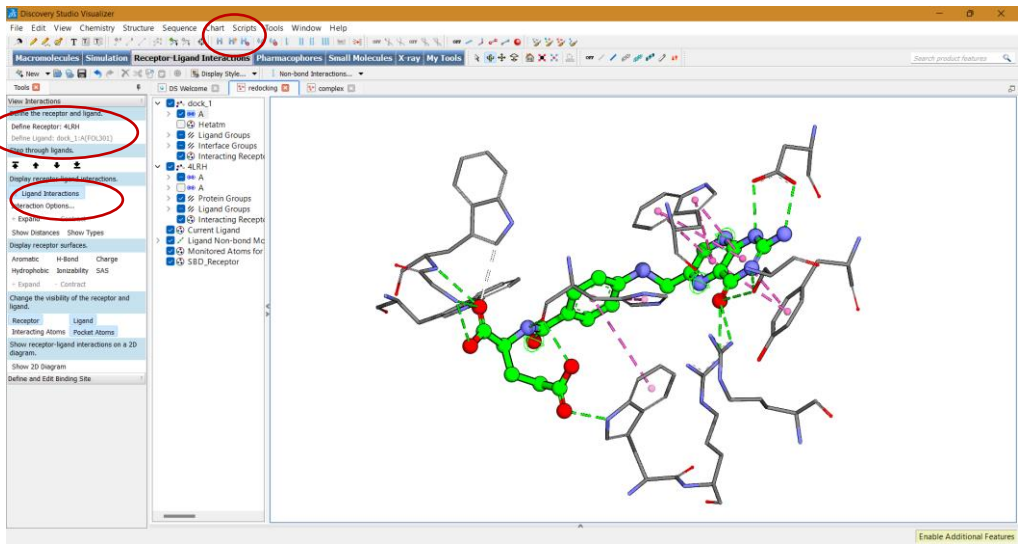
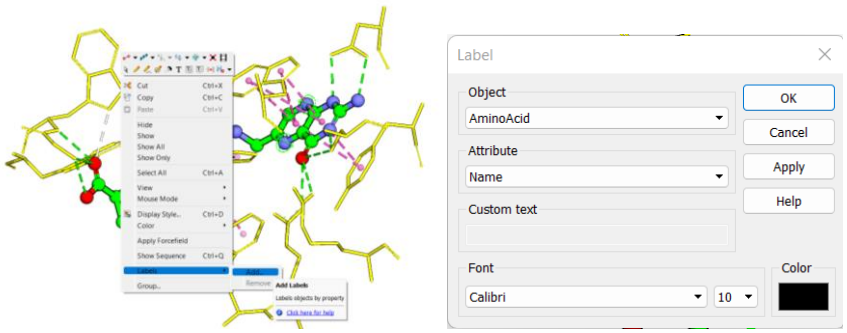


Figure 6. Step to view the interaction of ligand and receptor with polar hydrogen only.

Add label to the amino acid. **'Right click on window → Labels → Add'**



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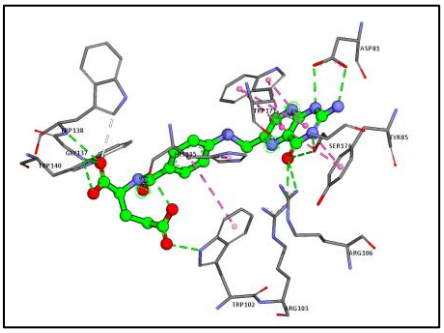


Figure 7. Labeling amino acid.

To show the interaction on the table. Click **'View → Data Table' or using short cut 'ctrl +T and click "Non-bond"**

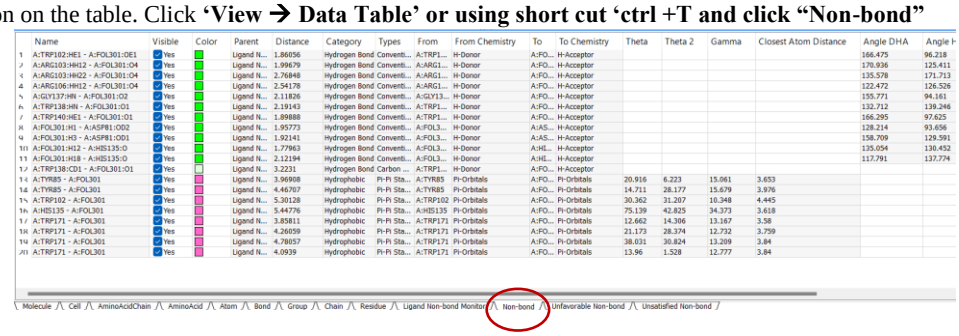
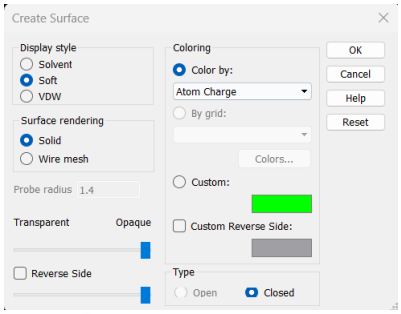


Figure 8. Table of non-bond interaction between ligand and receptor

Surface Structure

'Double click on the receptor or click on receptor's chain → Structure → Surface → add'. There are three display styles of surface, solvent, soft, and VDW. The coloring also can be customize as same as before by clicking on **'color by' or 'custom'.** The transparency also can be adjusted.



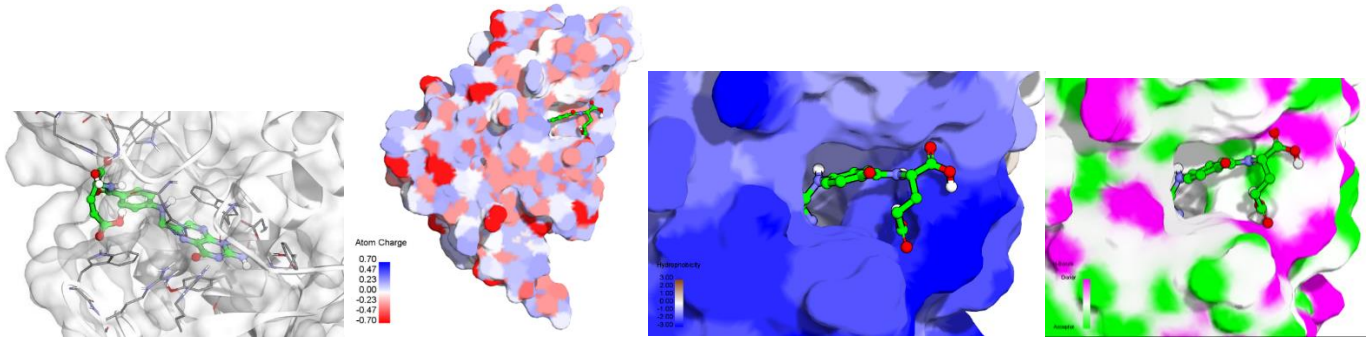


Figure 9. Surface structure colored by custom and transparent, atom charge, hydrophobicity, and hydrogen bond donor/acceptor.

Clipping Plane

Click View menu bar and choose **'Clipping Planes → Add Custom Clipping Plane',** then click Close. Adjust the clipping plane by pressing Ctrl and view toolbar, such as Translate and Rotate Cursor 

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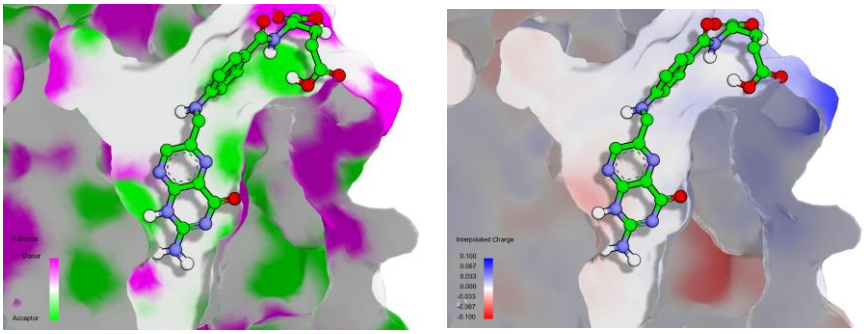

Figure 10. Clipping plane to view the interaction

2D Visualization

To create 2D visualization of protein-ligand docking complex structure, click **'Show 2D diagram'** on Receptor-Ligand Interactions menu. The 2D visualization is used to display the interactions in 2D format and view the interactions that occurred in the ligand. This visualization commonly used in conjunction with 3D visualization.

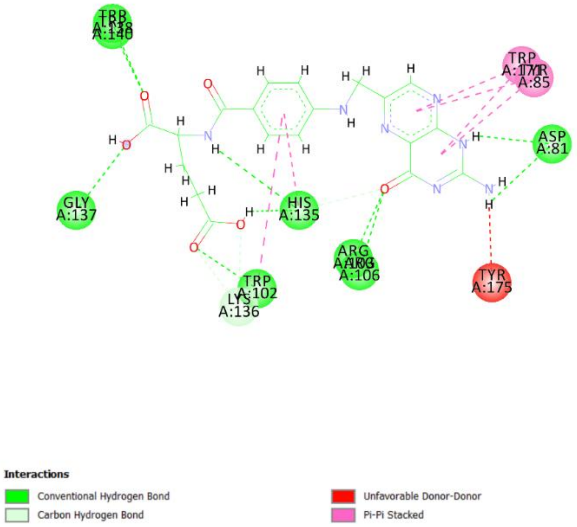

Figure 11. 2D visualization of receptor-ligand interactions

Save pictures

Place the screen in a location that corresponds with the content that will be displayed. Click **'File → Save As → Save as type : Image Files → Save → set the size → OK'.** Set the size to generate good resolution picture more than 2048 width pixels.

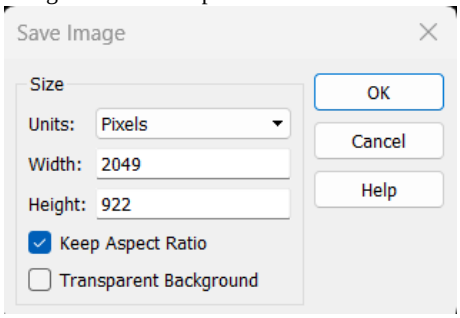

Figure 12. Save image

Conclusion

This protocol covers the molecular interaction analysis of docking results as well as the visualization to obtain good-quality pictures using BDS. It helps the user to understand how to interpret docking results and provides step-by-step how to do it. Visualization of results also one of the crucial parts that can help people to understand the meaning of our study. A good quality of pictures will represent how well the study was performed.

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