

MOLS v2.0

Software package for Peptide Modelling and Protein - Ligand Docking

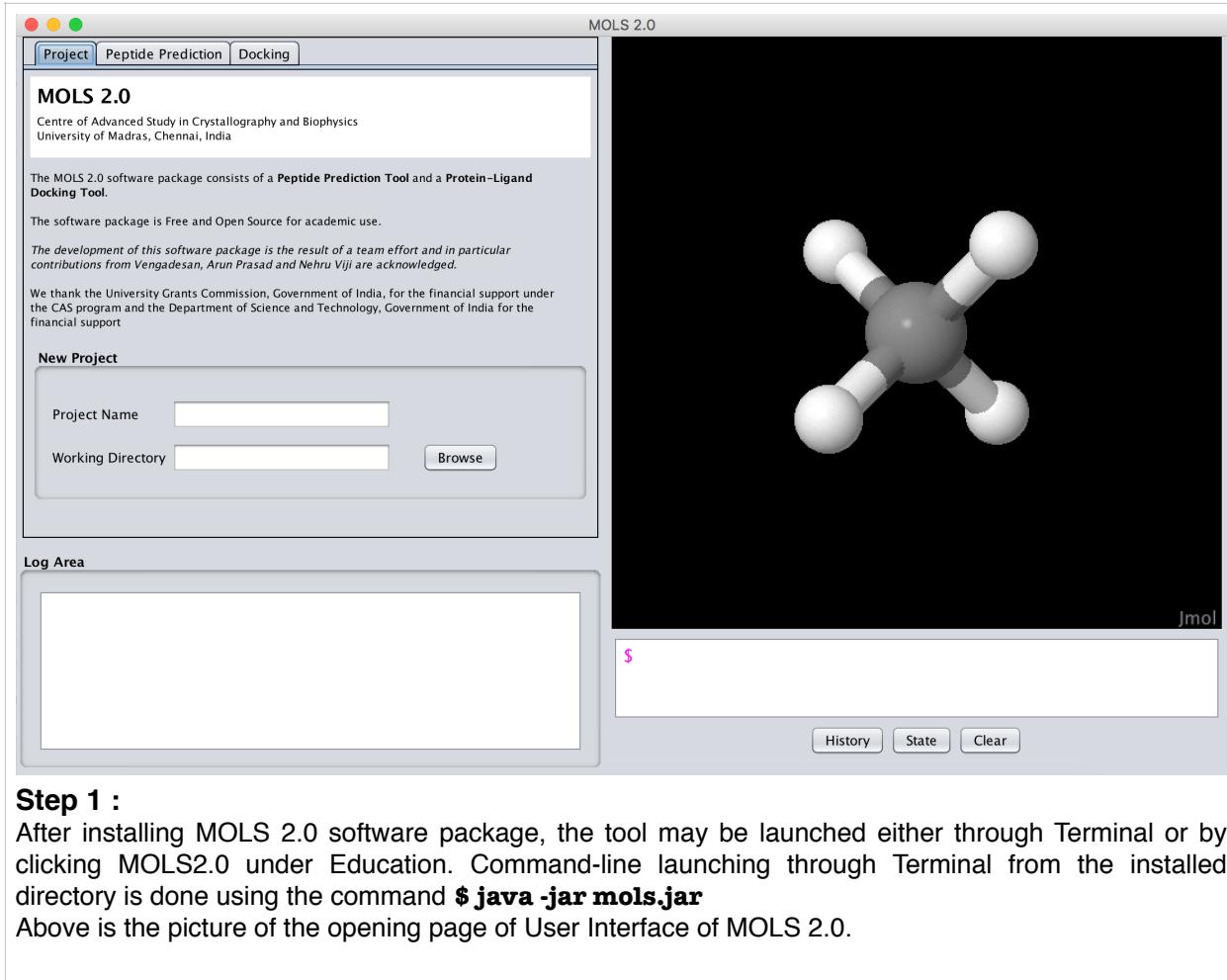
TUTORIAL

Centre of Advanced Study in Crystallography and Biophysics

University of Madras, Tamil Nadu, INDIA.

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Tutorial 1 : Peptide Prediction in MOLS 2.0



MOLS 2.0

Project Peptide Prediction Docking

MOLS 2.0

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The MOLS 2.0 software package consists of a **Peptide Prediction Tool** and a **Protein-Ligand Docking Tool**.

The software package is Free and Open Source for academic use.

The development of this software package is the result of a team effort and in particular contributions from Vengadesan, Arun Prasad and Nehru Vijji are acknowledged.

We thank the University Grants Commission, Government of India, for the financial support under the CAS program and the Department of Science and Technology, Government of India for the financial support

New Project

Project Name

Working Directory

Log Area

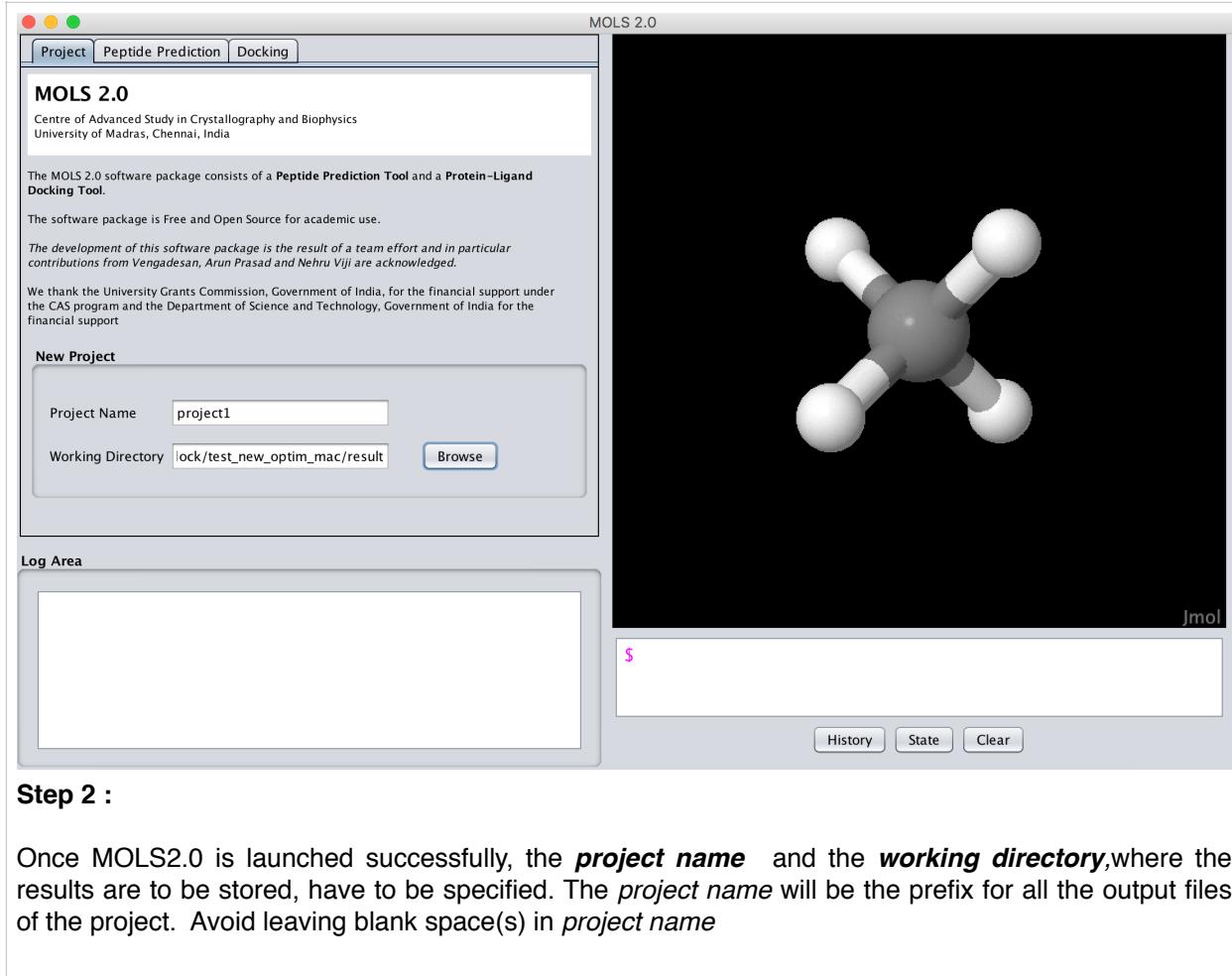
Jmol

\$

History State Clear

Step 2 :

Once MOLS2.0 is launched successfully, the **project name** and the **working directory**, where the results are to be stored, have to be specified. The *project name* will be the prefix for all the output files of the project. Avoid leaving blank space(s) in *project name*



The screenshot shows the MOLS 2.0 software interface. On the left, a 'New Project' dialog is open, prompting for a 'Project Name' (set to 'project1') and a 'Working Directory' (set to 'lock/test_new_optim_mac/result'). On the right, a large 3D molecular model is displayed in a Jmol viewer, consisting of a central grey carbon atom bonded to four white hydrogen atoms. Below the viewer is a log area with a single '\$' character. At the bottom of the interface are three buttons: 'History', 'State', and 'Clear'. The overall layout is clean and functional, typical of scientific software.

The screenshot shows the MOLS 2.0 software interface. At the top, there are three colored circles (red, yellow, green) followed by the text "MOLS 2.0". Below this is a navigation bar with tabs: Project, Peptide Prediction, Docking, Sequence, Force Field, Clustering, and Run Prediction. The "Peptide Prediction" tab is currently selected.

In the main area, there is a "Peptide Sequence" input field containing "YGGFM". Below it is a "Search Option" section with three radio button options: "BackBone" (unchecked), "BackBone + SideChain" (checked), and "Rotamer" (unchecked). To the right of this is a 3D ball-and-stick model of the peptide structure YGGFM, showing a central carbon atom bonded to four amino acid residues (alanine, glycine, glycine, and methionine).

At the bottom left is a "Log Area" which is currently empty. On the far right, the word "Jmol" is visible. Below the Log Area is a command-line interface window containing a single dollar sign (\$) symbol. At the very bottom of the interface are three buttons: History, State, and Clear.

Step 3:
After specifying the *project name* and *working directory*, click **Peptide Prediction** tab.

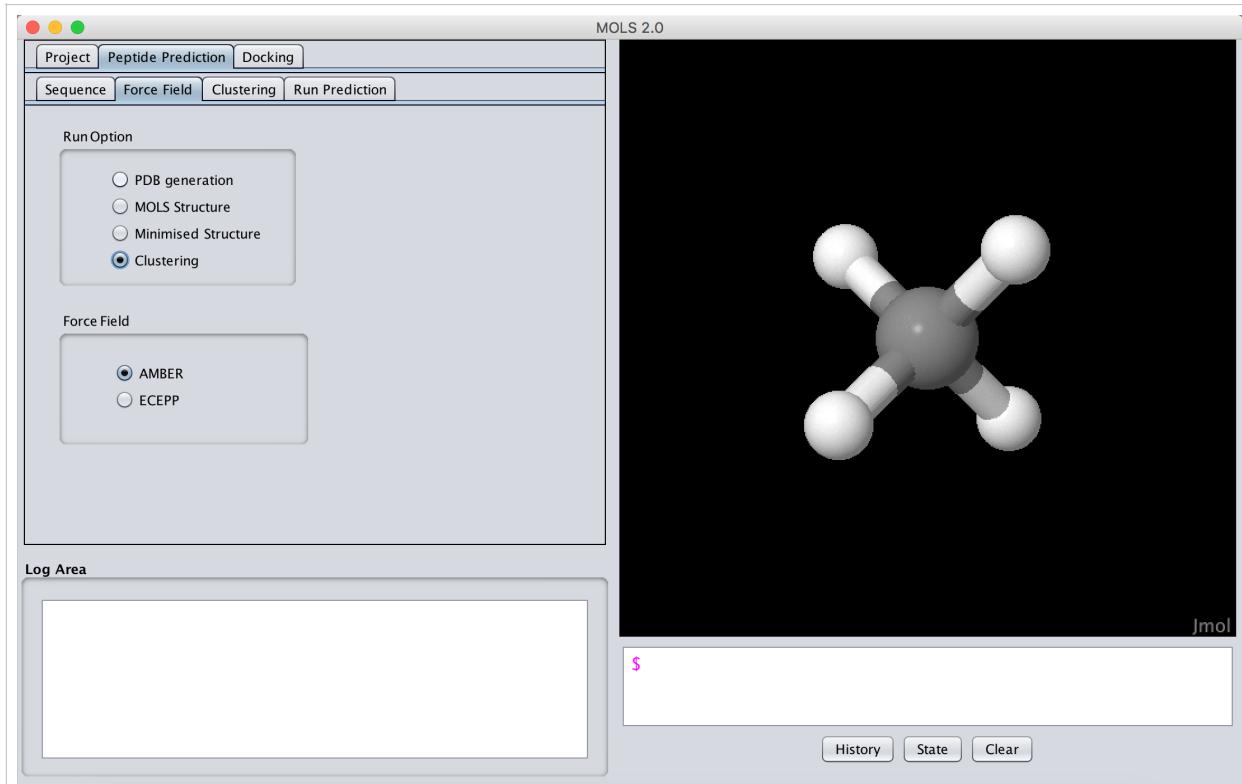
Peptide Sequence: The *peptide sequence* may be specified by single letter code in either small or capital letters.

Search Option : Based on the selection, the tool will search the conformation of the peptide structure in the torsion angle space.

Backbone: This option will take only the backbone for the conformational search and side chains are fixed at amino acid (Insight II) library value.

Backbone + Side chain: This option will take both backbone and side chains for the conformational search

Rotamer: This option will take backbone and side chain for conformational search. However, side chain conformations will be chosen from a rotamer library.



Step 4:

Click the **Force Field** Tab

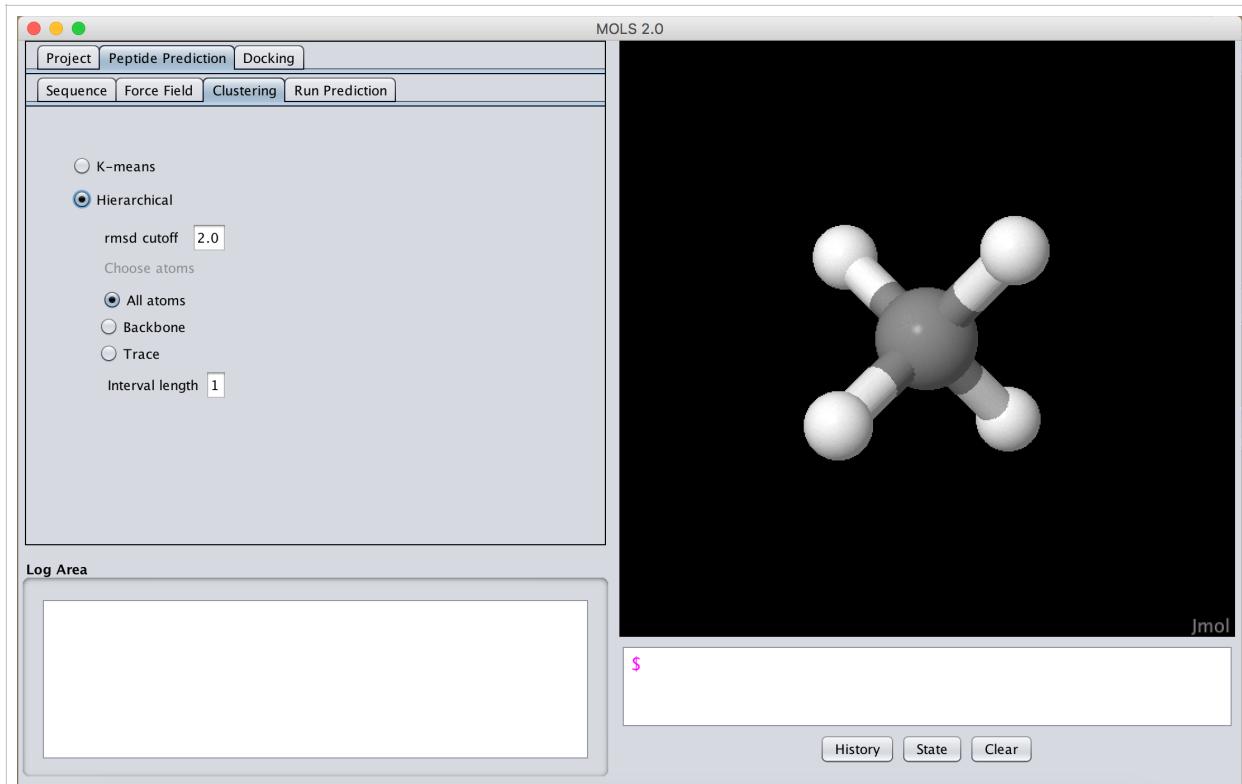
Run Option:

PDBgen option will build an initial model for the given amino acid sequence, with an extended conformation for the backbone, and maximally extended side chain conformations.

MOLS structure option generates the specified number of low energy structures using the MOLS technique.

Minimized structures option will move each structure from the discrete grid on which it is generated to the nearest local minimum using conjugate gradient minimization.

Clustering option will cluster together similar conformations among those generated and minimized.

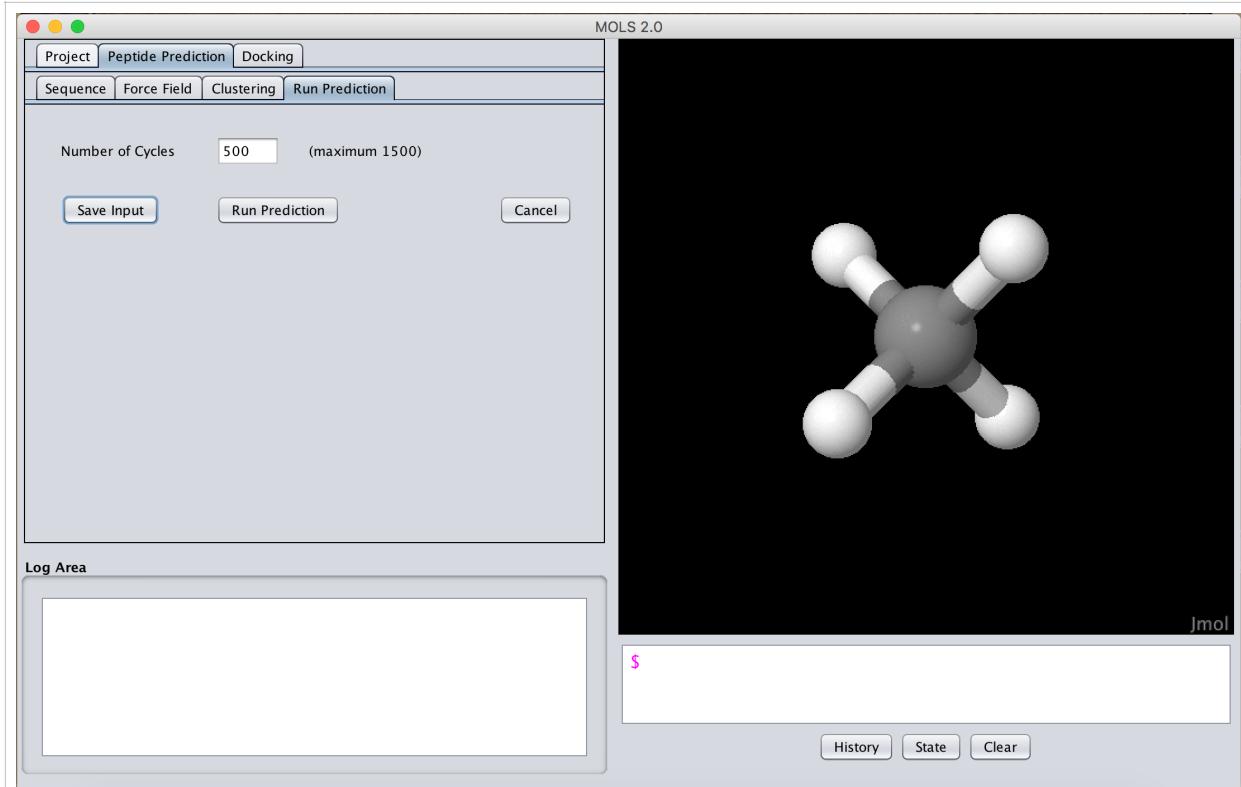


Step 5:

After clicking **Clustering** Tab, Choose either **K-means** or **Hierarchical** clustering algorithm.

If **Hierarchical clustering** algorithm is selected then the user has to specify RMSD cutoff value and select the mode of superimposition(all atom/backbone/C-Alpha trace atoms).

Interval length has to be mentioned for drawing the ‘cluster plot’. This plot gives the relationship between the new clusters discovered versus the structure number.

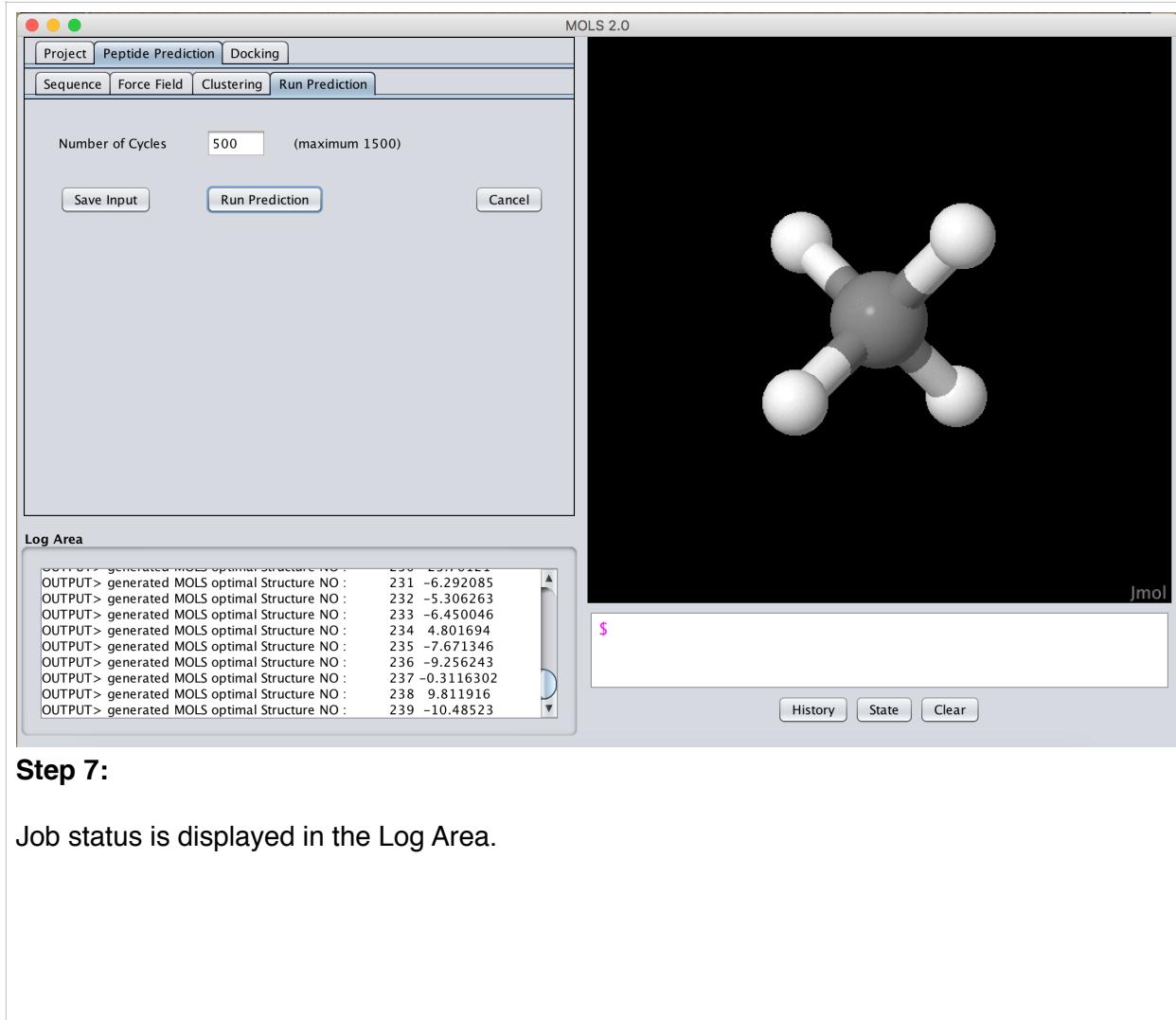


Step 6:

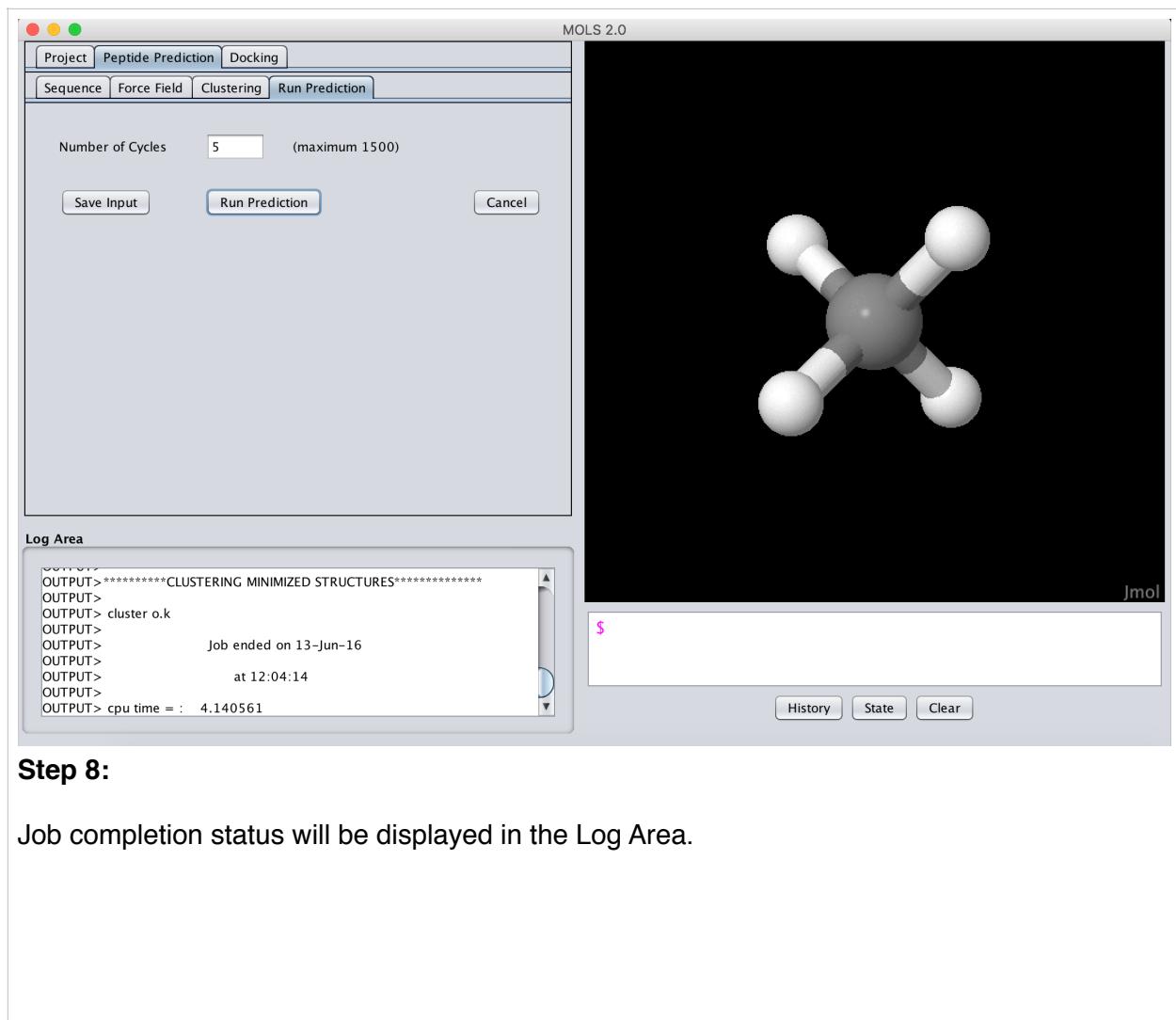
Click **Run Prediction** Tab and mention the number of optimal conformations.

Click 'Save Input' to save all the given inputs. After all the inputs are supplied, click 'Run Prediction' button to start the peptide structure prediction.

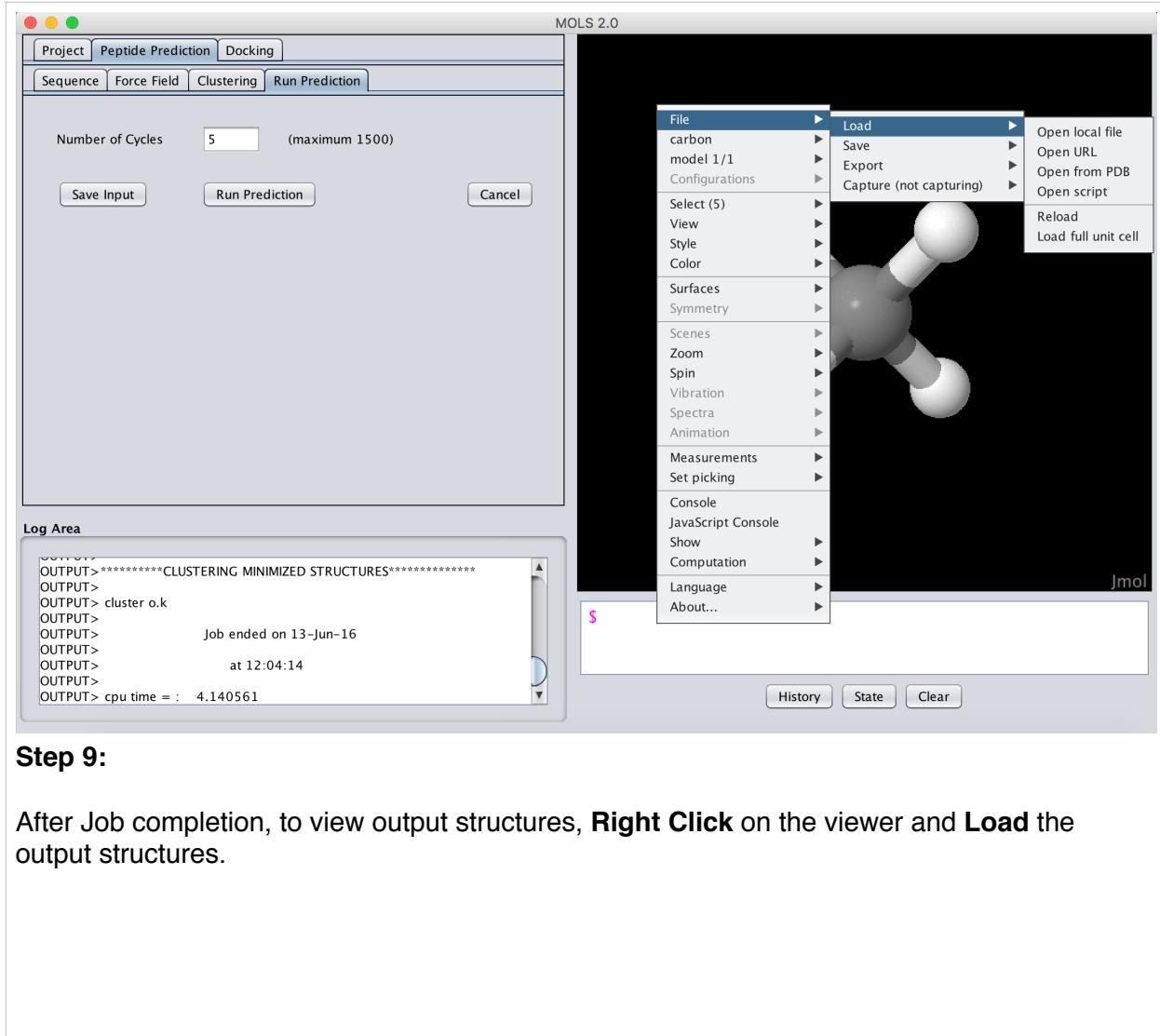
Note: After saving the inputs, If any input is updated/edited then *Save Input* must be clicked again before clicking *Run Prediction*

**Step 7:**

Job status is displayed in the Log Area.

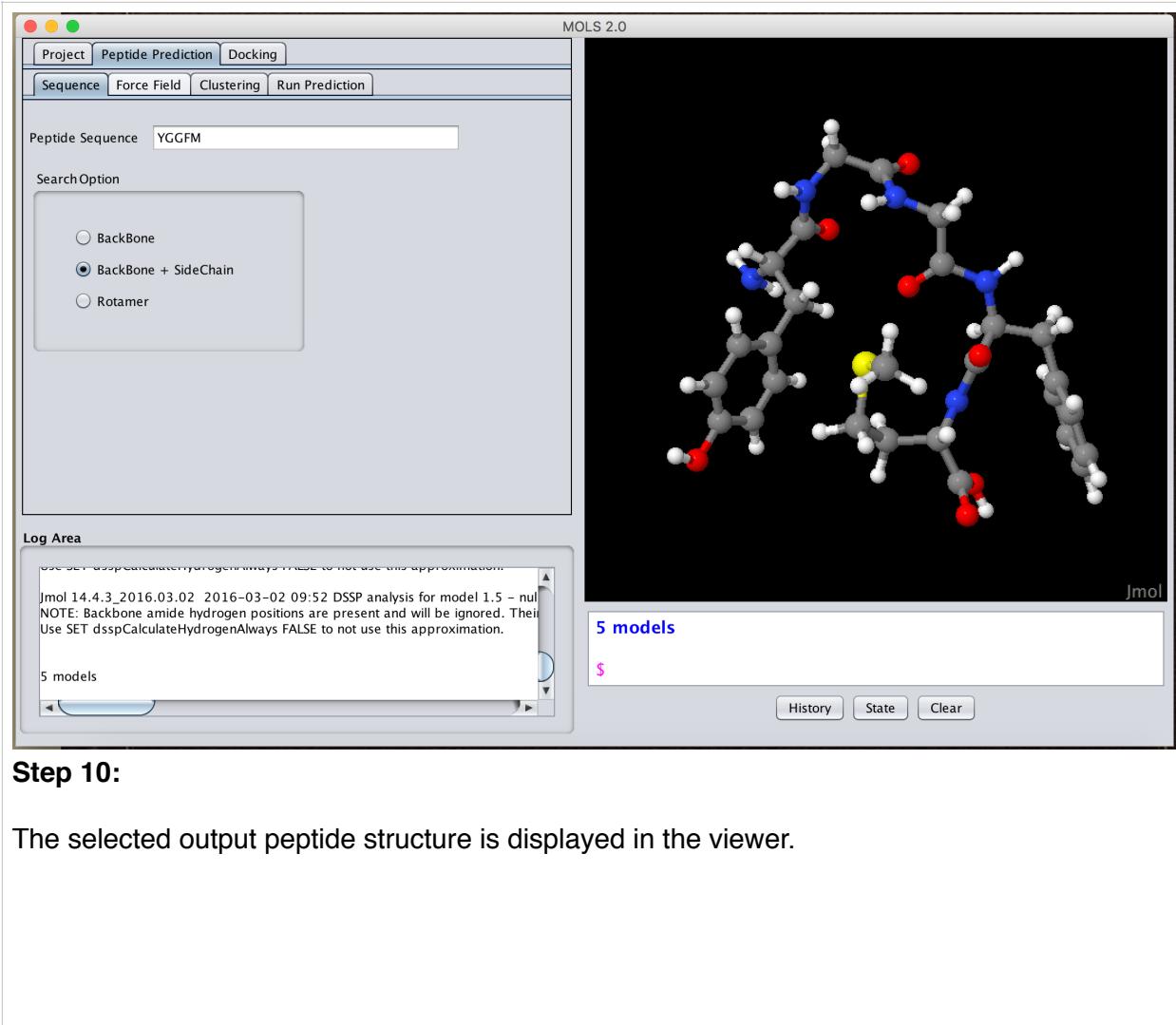
**Step 8:**

Job completion status will be displayed in the Log Area.



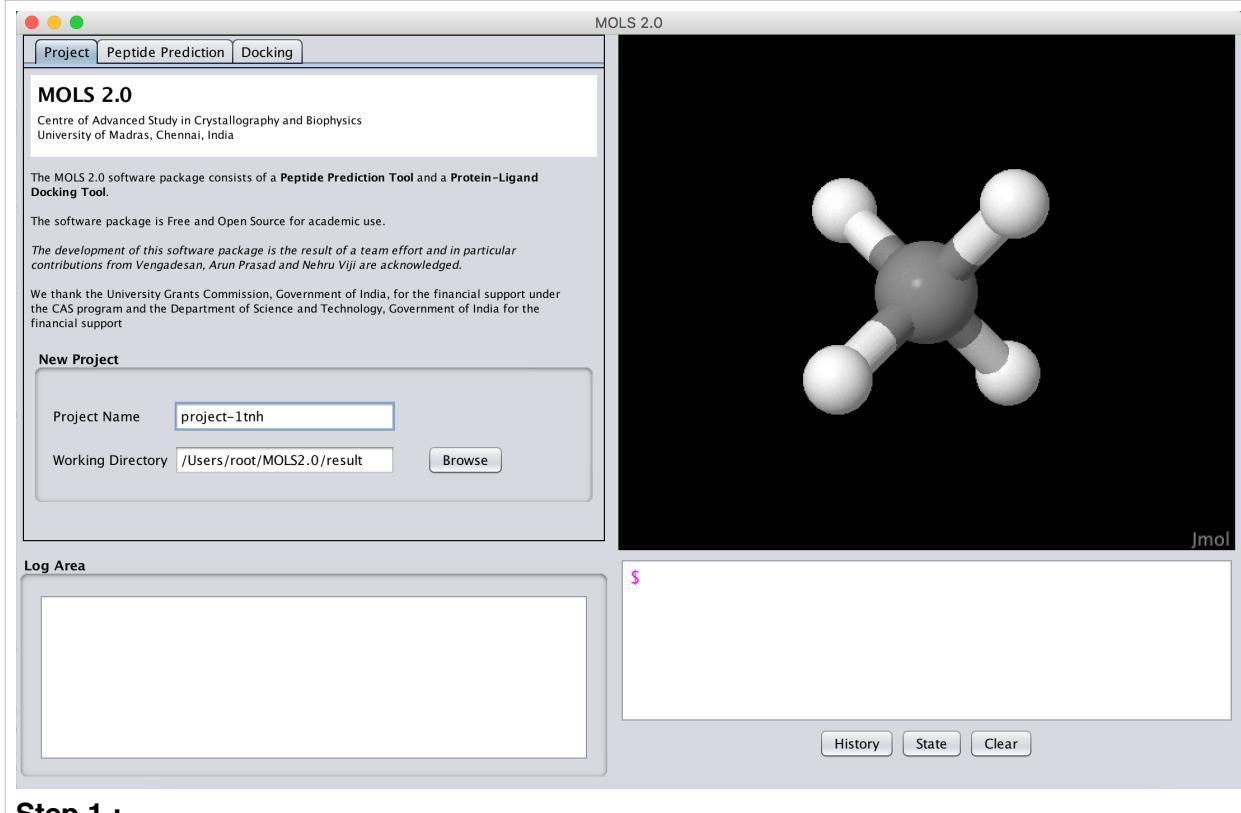
Step 9:

After Job completion, to view output structures, **Right Click** on the viewer and **Load** the output structures.

**Step 10:**

The selected output peptide structure is displayed in the viewer.

Tutorial 2.1 : Rigid Protein - Flexible Ligand Docking in MOLS 2.0



Step 1 :

After installing MOLS 2.0 software package, the tool may be launched either through Terminal or by clicking MOLS2.0 under Education. Command-line launching through Terminal from the installed directory is done using the command **\$ java -jar mols.jar**

Above is the picture of the opening page of User Interface of MOLS 2.0.

Before beginning a project, the Project name and the Working Directory has to be specified.

MOLS 2.0

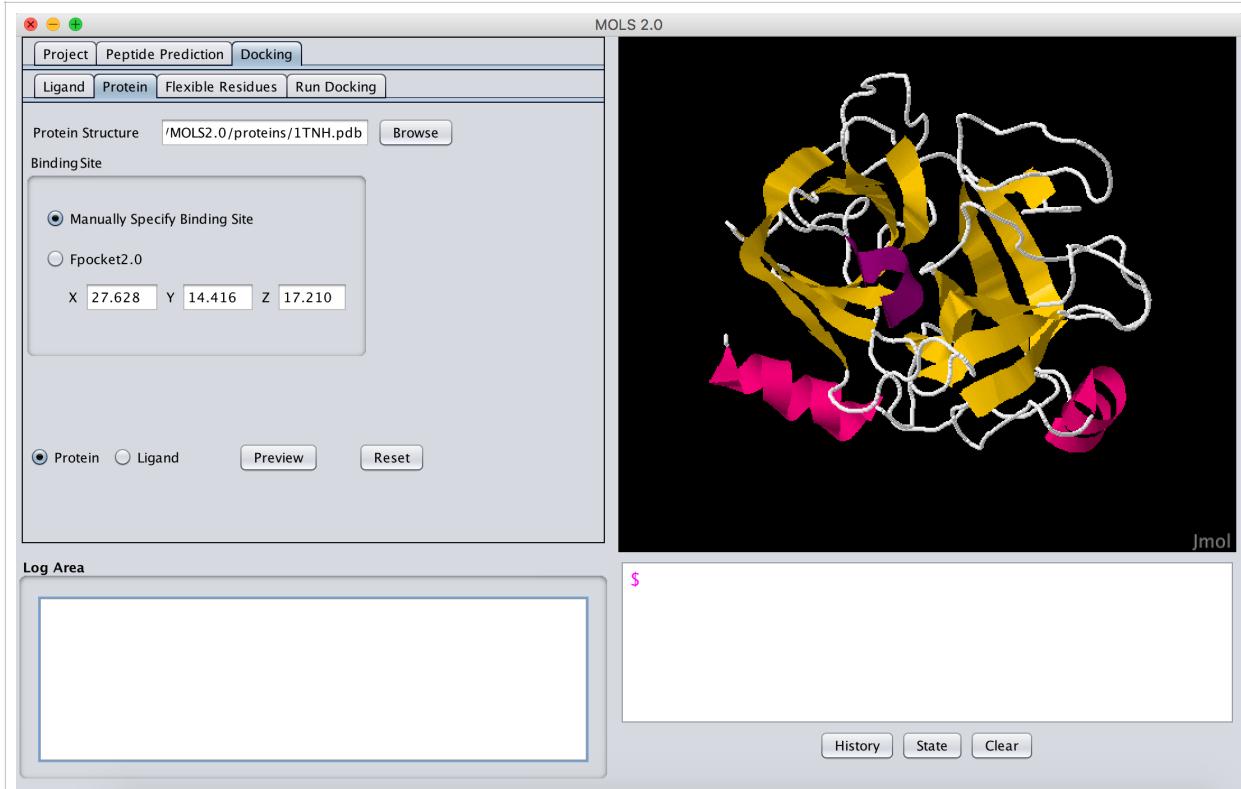
Step 2 :

After mentioning the Project name and Working Directory in the Project Tab, click **Docking Tab**.

The Ligand can be any organic chemical compound.

If the structure of the ligand to be docking is available in MDL Molfile (.mol) format then that may be selected by clicking the Browse button.

If the ligand is not available then the organic small molecule may be built using the built-in Molecule Builder (Right-Click on the viewer and select 'Model Kit' option to build the small molecule).



Step 3 :

The above options will appear when you **Click** Protein tab.

After specifying the protein structure (.pdb), the structure may be viewed on the viewer by choosing Protein option in **Preview** section. The Ligand structure also may be viewed in the viewer choosing Ligand in **Preview** section.

Binding site specification:

If the ligand binding site in the receptor protein is known then select ***Manually specify binding site*** option and specify the cartesian co-ordinates of the centre of the box and its dimensions in the X, Y and Z boxes.

If the ligand binding site is not known then select **Fpocket2.0** to automatically find the best binding pocket.

MOLS 2.0

Project Peptide Prediction Docking

Ligand Protein Flexible Residues Run Docking

Rigid Receptor Flexible Receptor

Flexible Receptor Options

Manually specify flexible residues
 Auto find flexible residues

Protein residues within 4.0 Å Show

Flexible residues (format: ASP A 29,SER B 30,TYR C 312)

Save flexible residues after add/remove flexible residues Save flexible residues

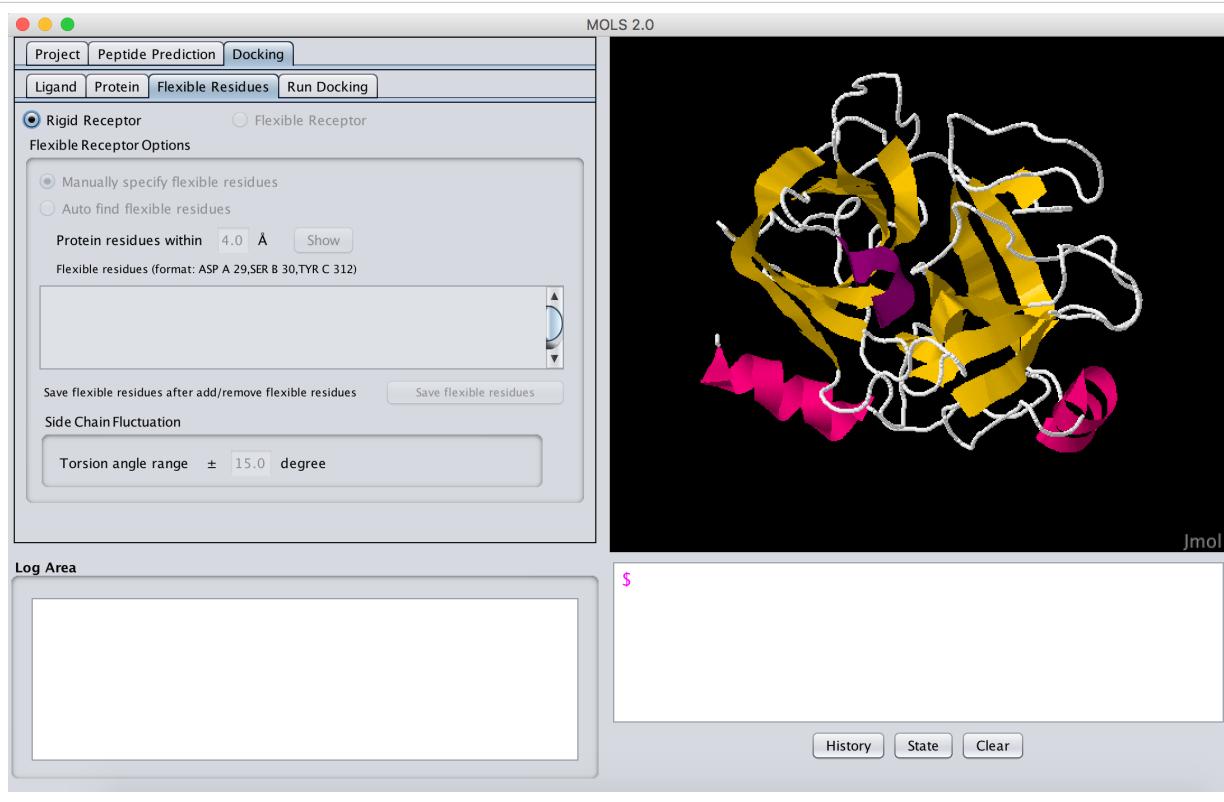
Side Chain Fluctuation

Torsion angle range ± 15.0 degree

Log Area

\$

History State Clear



Step 4 :
Only Rigid Receptor flexibility is allowed for Protein - Ligand docking. Therefore 'Flexible Receptor' option will remain disabled.

MOLS 2.0

The screenshot shows the MOLS 2.0 software interface for protein docking. The top menu bar includes Project, Peptide Prediction, Docking, Ligand, Protein, Flexible Residues, and Run Docking. The main window has tabs for Number of Structures, Log Area, and Docking Status. In the Number of Structures tab, the 'Starting' value is set to 1 and the 'Ending' value is set to 150 (maximum 1500 structures). Below these fields are Save Input, Start Docking, and Cancel buttons. To the right is a 3D ribbon model of a protein-ligand complex, with the ligand shown in yellow and magenta. The bottom right corner of the 3D view is labeled 'Jmol'. The Log Area and Docking Status tabs are currently empty. At the bottom right of the Log Area are History, State, and Clear buttons.

Step 5 :

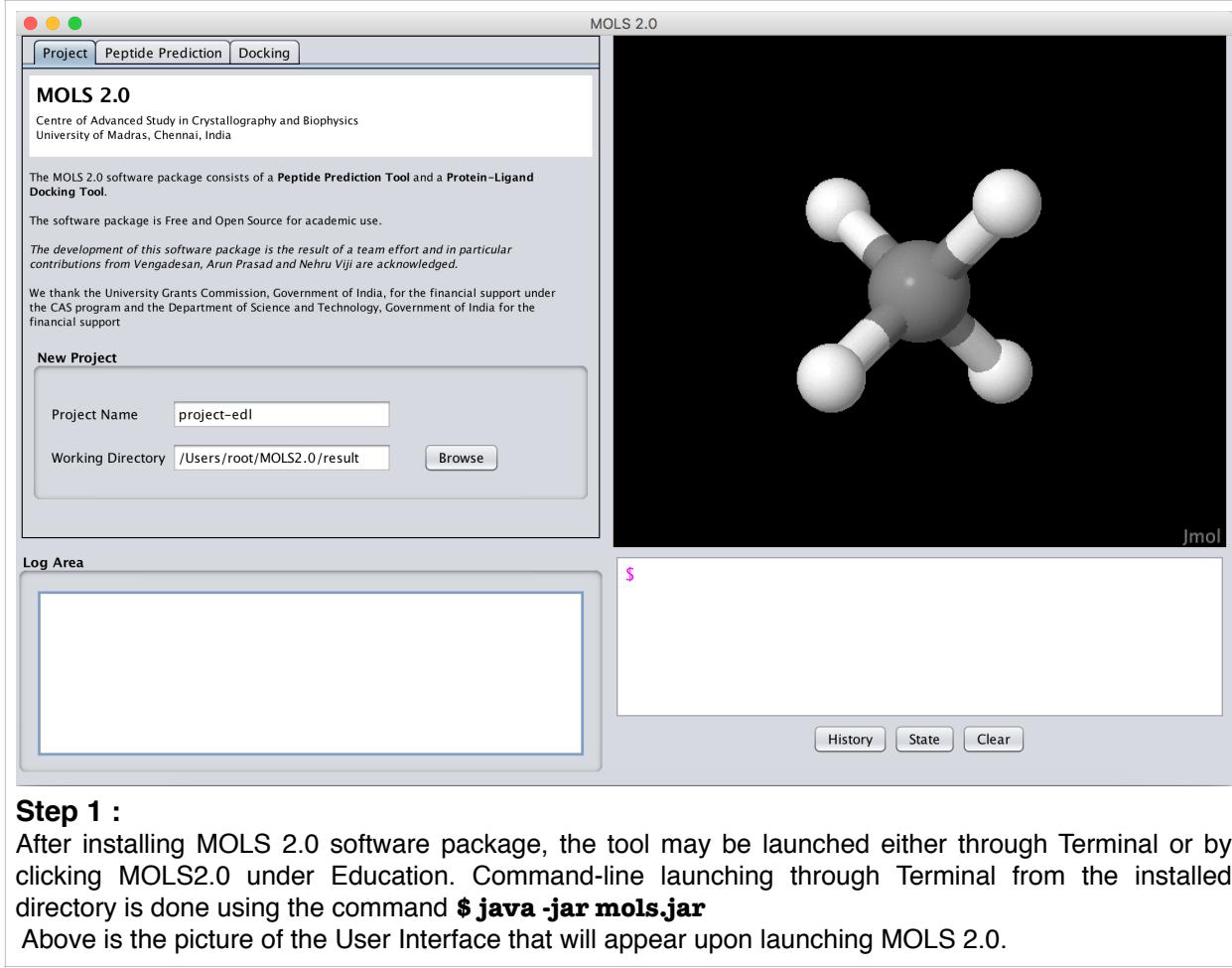
After supplying all the inputs under **Ligand**, **Protein** and **Flexible Residues** section, mention the number of docking structures to be generated.

The starting and the ending conformation number has to be specified. [Note that for technical reasons, the *starting* and *ending* are cardinal numbers]

Click Save Input to save the inputs. If all the required inputs are supplied then *Start Docking* button will get enabled (If any of the required input is missing the *Start Docking* button will remain disabled)

After the docking starts, click *Docking Status* to monitor the current project's status.

Tutorial 2.2 : Protein - Peptide Docking in MOLS 2.0



MOLS 2.0

Project Peptide Prediction Docking

Ligand Protein Flexible Residues Run Docking

Peptide

Peptide Sequence EDL
(example sequence: YGGFM)

Small Molecule

Ligand Structure Browse
(*mol structures only)

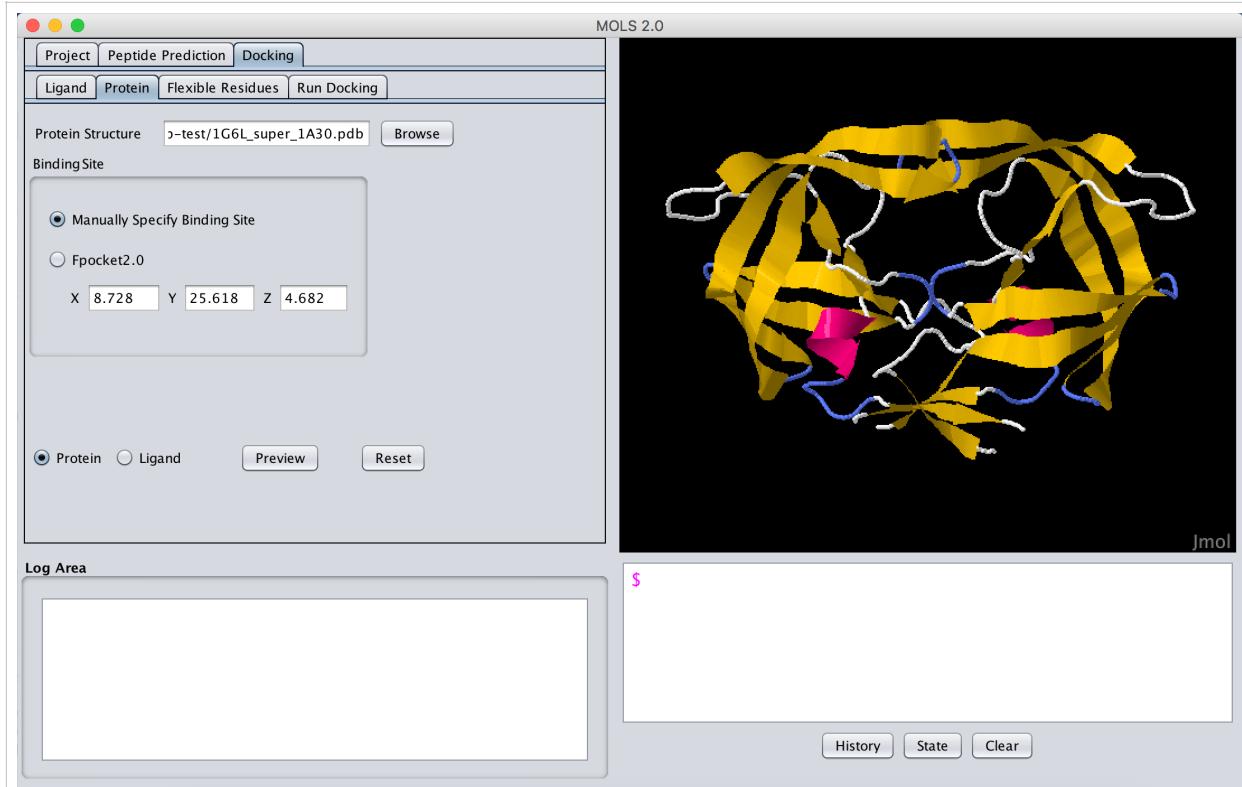
Log Area

Jmol

\$

History State Clear

Step 2 :
After mentioning the Project name and Working Directory in the Project Tab, click **Docking Tab**.
Select Peptide option and specify the peptide ligand sequence.
The amino acid sequence of the peptide ligand has to be given by single letter code.



Step 3 :

The above options will appear when you **Click** Protein tab.

After specifying the protein structure (.pdb), the structure may be viewed on the viewer by choosing Protein option in **Preview** section. The Ligand structure also may be viewed in the viewer choosing Ligand in **Preview** section.

Binding site specification:

If the ligand binding site in the receptor protein is known then select ***Manually specify binding site*** option and specify the cartesian co-ordinates of the centre of the box and its dimensions in the X, Y and Z boxes.

If the ligand binding site is not known then select **Fpocket2.0** to automatically find the best binding pocket.

MOLS 2.0

Project Peptide Prediction Docking

Ligand Protein Flexible Residues Run Docking

Rigid Receptor Flexible Receptor

Flexible Receptor Options

Manually specify flexible residues
 Auto find flexible residues

Protein residues within 4.0 Å Show

Flexible residues (format: ASP A 29,SER B 30,TYR C 312)

ASP A 29,ASP A 30

Save flexible residues after add/remove flexible residues Save flexible residues

Side Chain Fluctuation

Torsion angle range ± 15.0 degree

Log Area

Jmol

\$

History State Clear

Step 4 :

Induced fit docking is available for protein-peptide docking. To enable receptor flexibility, choose '**Flexible Receptor**' option.

- If the flexible residues are known then click the **Manually specify flexible residues** option and specify the flexible residues in the Text Area. There **Residues name**, **Chain ID** and **residue number** of the flexible residues have to be written in the following format:

ASP A 29,ASP A 30,ILE B 41

- If the flexible residues are not known, click the **Auto find flexible residues** option and click **show** button. The neighboring residues in the given 4.0 Å distance cutoff will be shown. Add/remove the flexible residues and click **Save flexible residues** to update the flexible residues list.

By default, side-chains of the selected flexible residues will fluctuate between ± 15.0 degree from their crystal position.

MOLS 2.0

The screenshot shows the MOLS 2.0 software interface for protein docking. The top menu bar includes Project, Peptide Prediction, Docking, Ligand, Protein, Flexible Residues, and Run Docking. The main window has sections for Number of Structures (Starting 1, Ending 150), Save Input, Start Docking, Cancel, Docking Status, Log Area, and a Jmol viewer showing a protein structure with a ligand docked. A log area at the bottom right shows a single character '\$'.

Step 5:
After supplying all the inputs under **Ligand**, **Protein** and **Flexible Residues** section, mention the number of docking structures to be generated.

The starting and the ending conformation number has to be specified. [Note that for technical reasons, the *starting* and *ending* are cardinal numbers]

Click *Save Input* to save the inputs. If all the required inputs are supplied then *Start Docking* button will get enabled (If any of the required input is missing the *Start Docking* button will remain disabled)

After the docking starts, click *Docking Status* to monitor the current project's status.