Molecular Modeling And Drug Discovery

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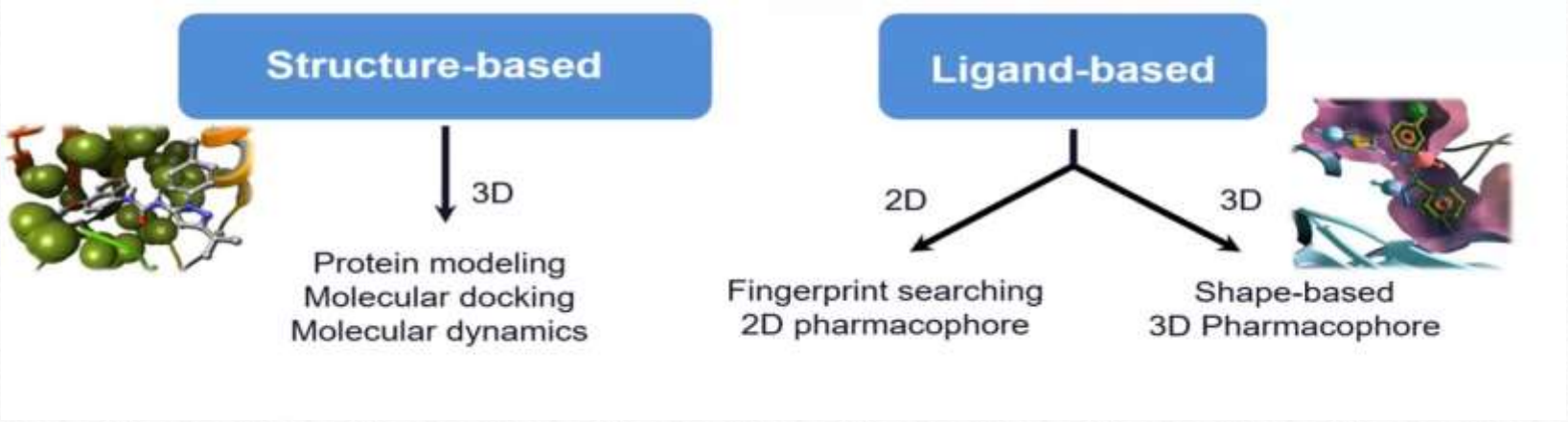
Molecular Modeling

- In silico methods to identify molecules that could bind to a target of interest
- These methods are classified as either structure-based or ligand-based.



Why molecular modeling

- Time consuming ~13 years
- Cost expensive ~ $ 2 Billion

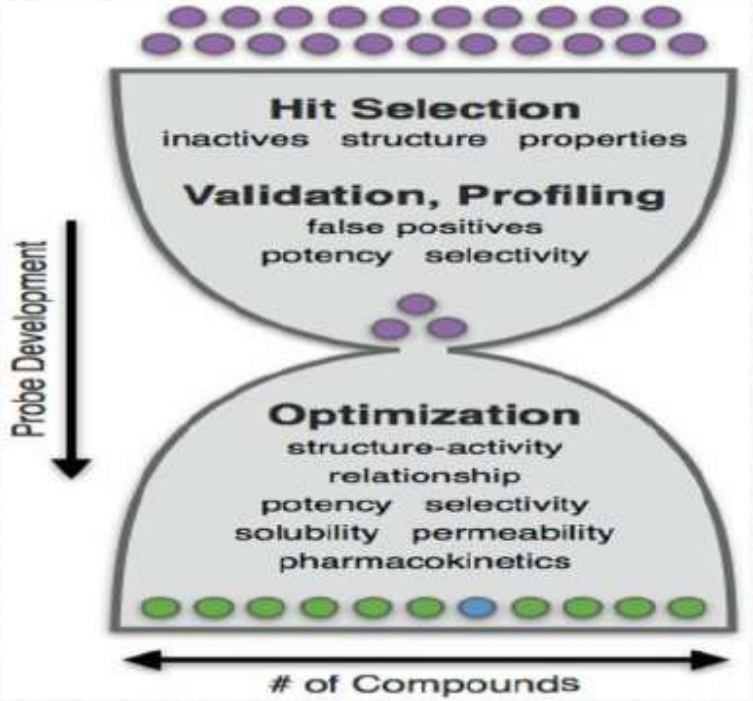
Drug discovery phases

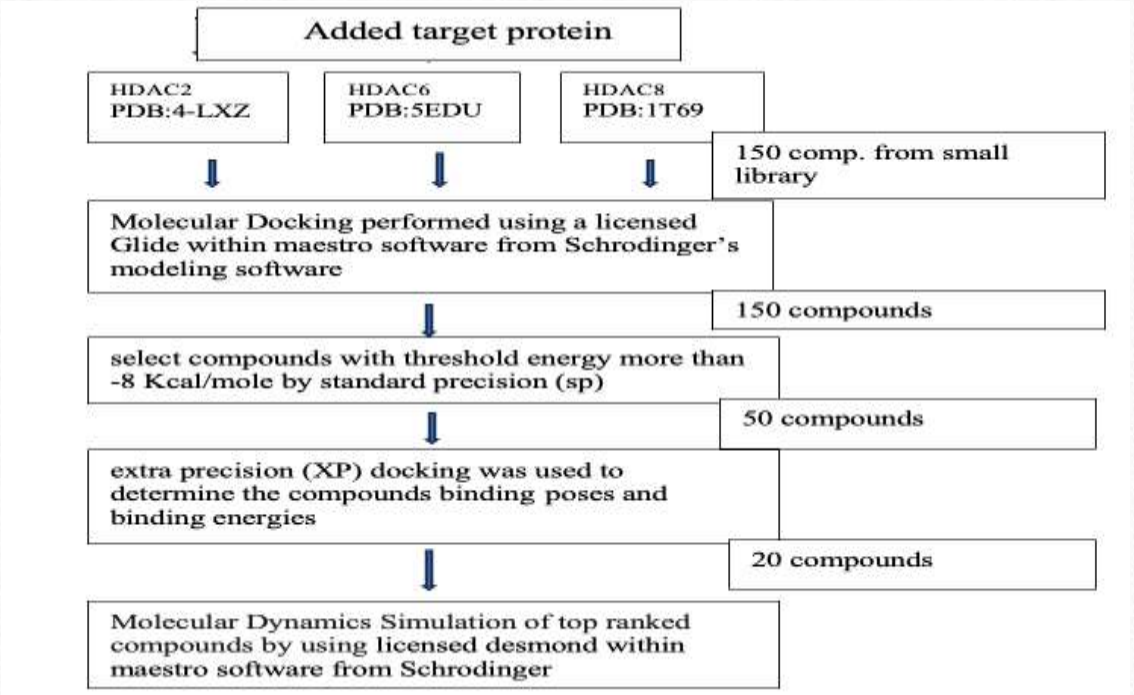
- Target: which main protein molecules for given disease
- Hit ID: molecules interact with protein for reasonable affinity i.e vertual screening depending on computing power
- Hit identification: some molecules have binding affininity.
- Lead molecules: molecules with increased binding affinity compare to the hit molecule
- then optimised lead molecules to ensure it does not have any side effect (inhance ADME)

Drug discovery phases

- This may take 6.5 year but with molecular modeling this may have less than 1 year as that made by most drug companies
- Preclinical tials: test the mol. on animal models then phase I,II and III on humans
- This whole process is time consuming it take 13 years and cost expensive it take about 2 billion $ (reagents and lab. equipment)
- Designing drugs is too hard so it take this amount of time.why?

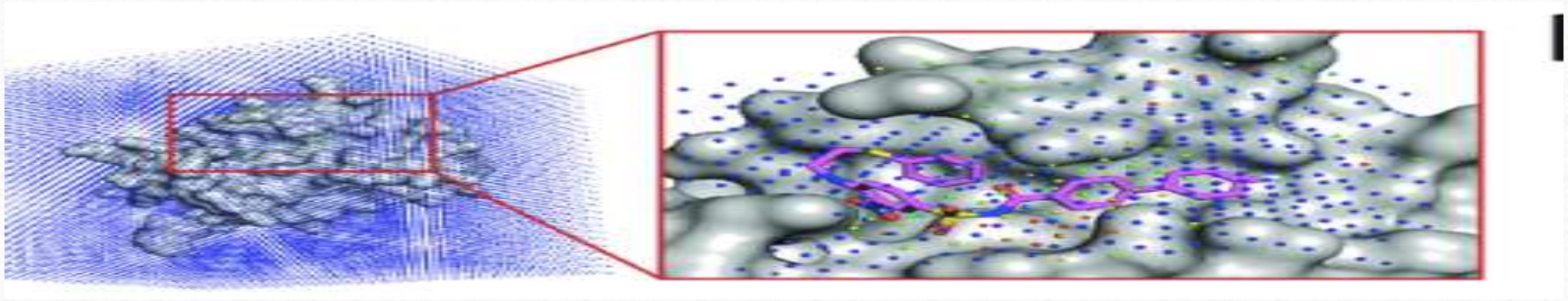
Designing of drug





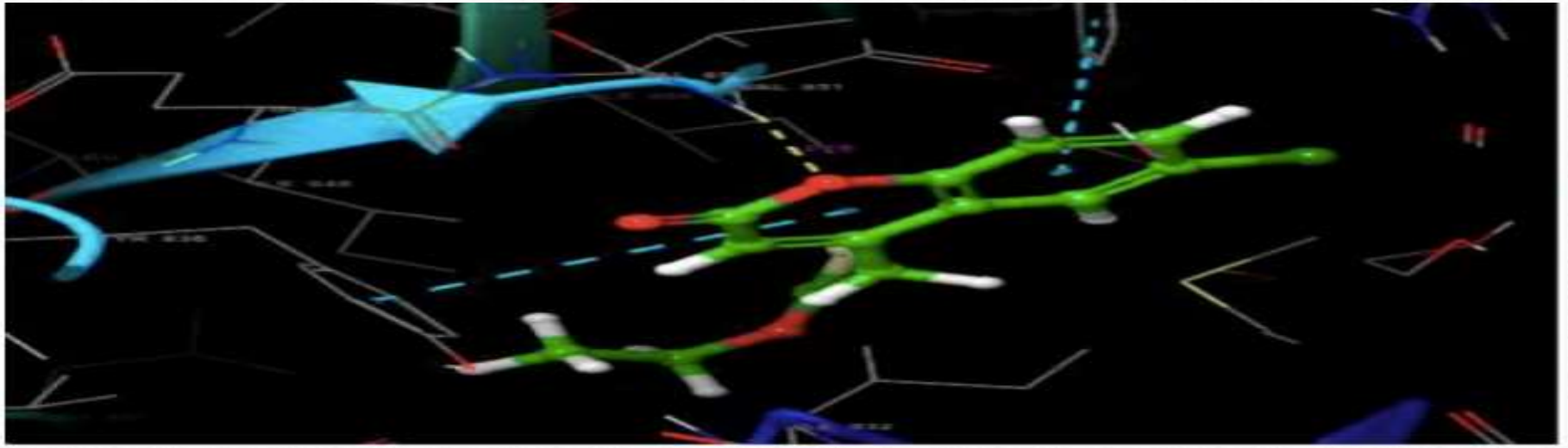
Structure based drug design

- Protein data bank (PDB) has 180000 structure of protein can be use to design our drug molecules usually 3D in nature so we can do molecular docking and dynamic on it.
- Ligand molecules must have geometric and electronic complementarity.



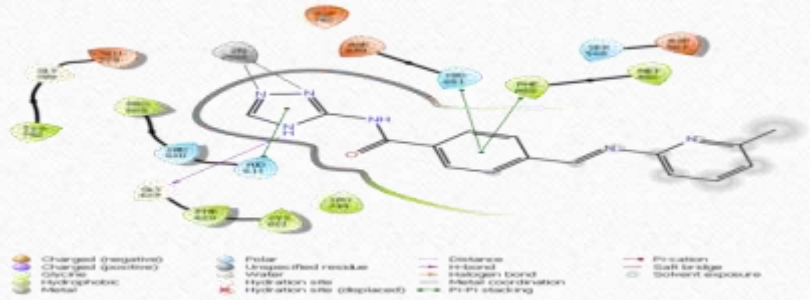
Molecular docking

- Docking is computional prediction of binding mode and binding affinity between protein and ligand



Component of molecular docking

1. Search algorithem: that can generates a large number of poses of amolecule in the binding site (fit shape)
2. Scoring function: rank orders the conformations/poses to distiguish the expermental binding pose from the rest binding affinity



Molecular dynamics MD

- is a computational tool to simulate the motions of a molecular system, it deals with the study of molecules when they are in motion when they are dynamic in nature to understand how drug molecules interact with protein when the protein is in motion.

Molecular dynamics MD

Why use molecular dynamics

- the problem with docking is the protein never static so for this reason we need MD simulation after the docking study to improve the results because ligand and protein in reality always in motion.
- Differentiate ligands with similar docking scores. Scoring function good enough to differentiate between molecules with high and low docking score as -10 kcal/mole and -5 kcal/mole but not good enough with similar docking score (faster)

Why use molecular dynamics

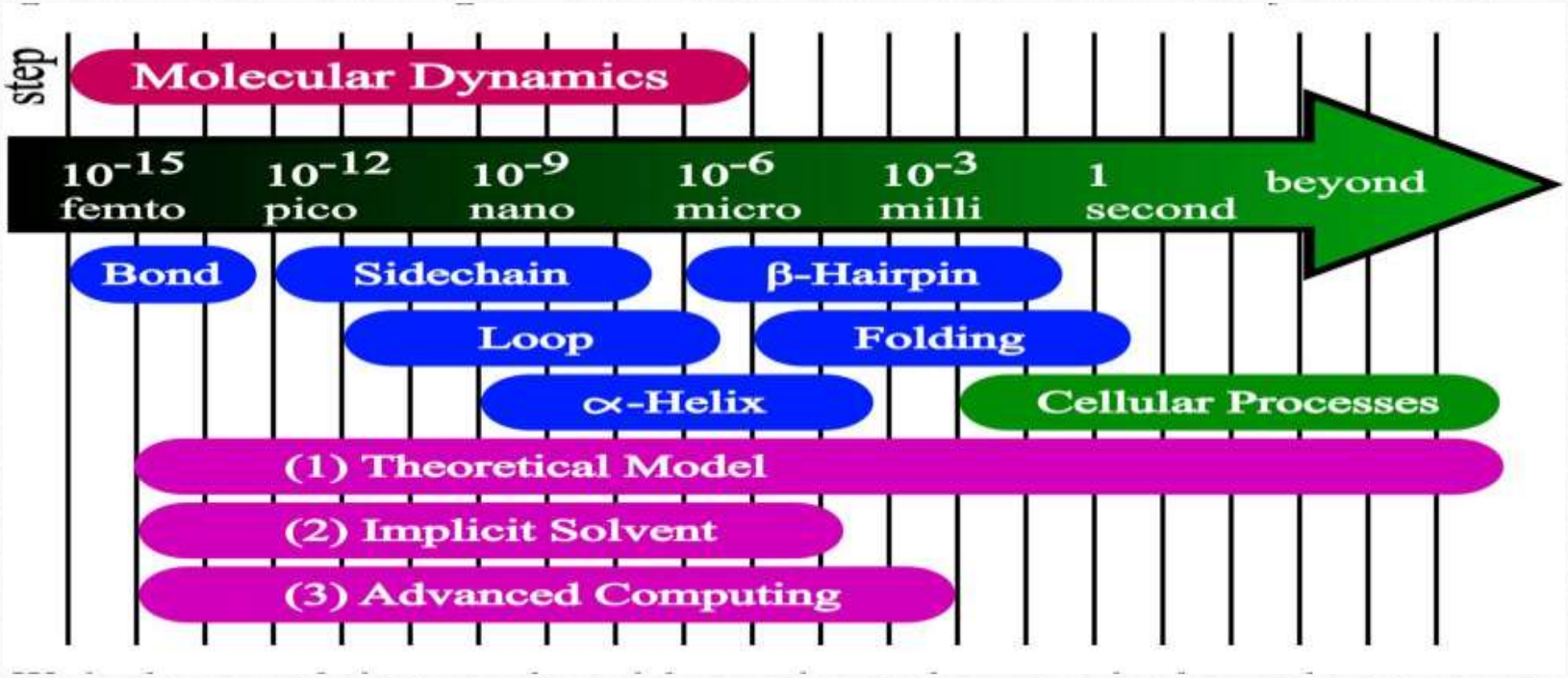
- Stability of drug binding to see how long the ligand stays in the binding pocket of protein. if dissociate out mean the ligand is not stable.
- Lastly, MD quite close to labarotory conditions through MD panel we can add water, ions and membrane also we make control to temrature and pressure

Why use molecular dynamics

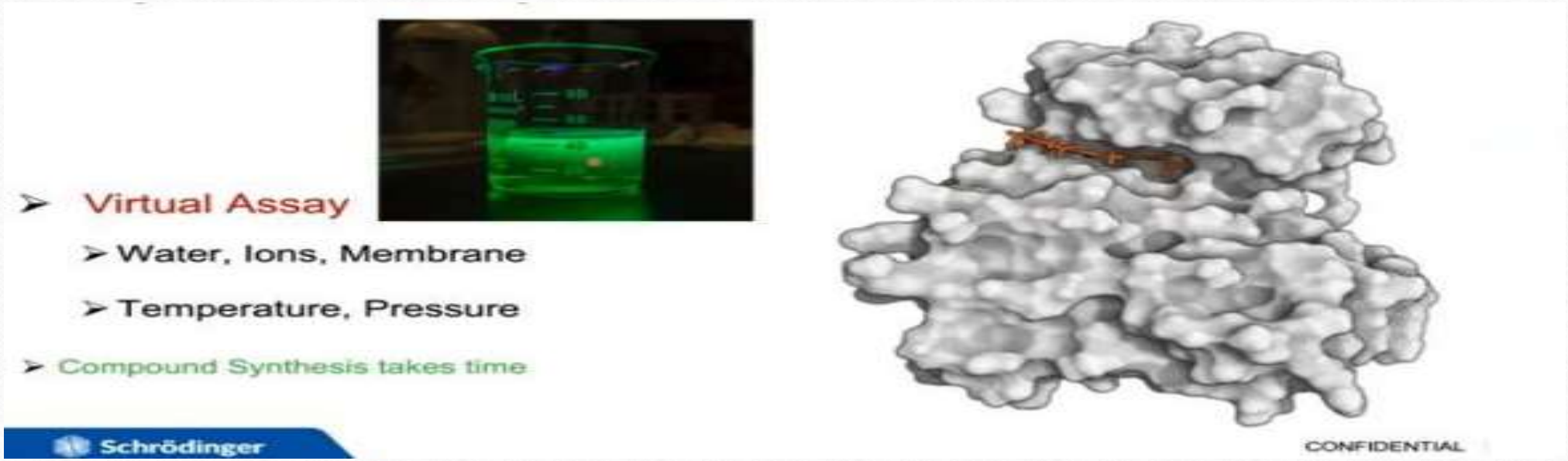
- In general major differences between molecular docking and dynamic is

Molecular docking	molecular dynamic
Rigid oprotein	flexible protein
Flexible ligand	flexible ligand
Fast/quick calculation	very slow calculation
Computionaly cheaper	expensive
Depend on scoring function	different conformation

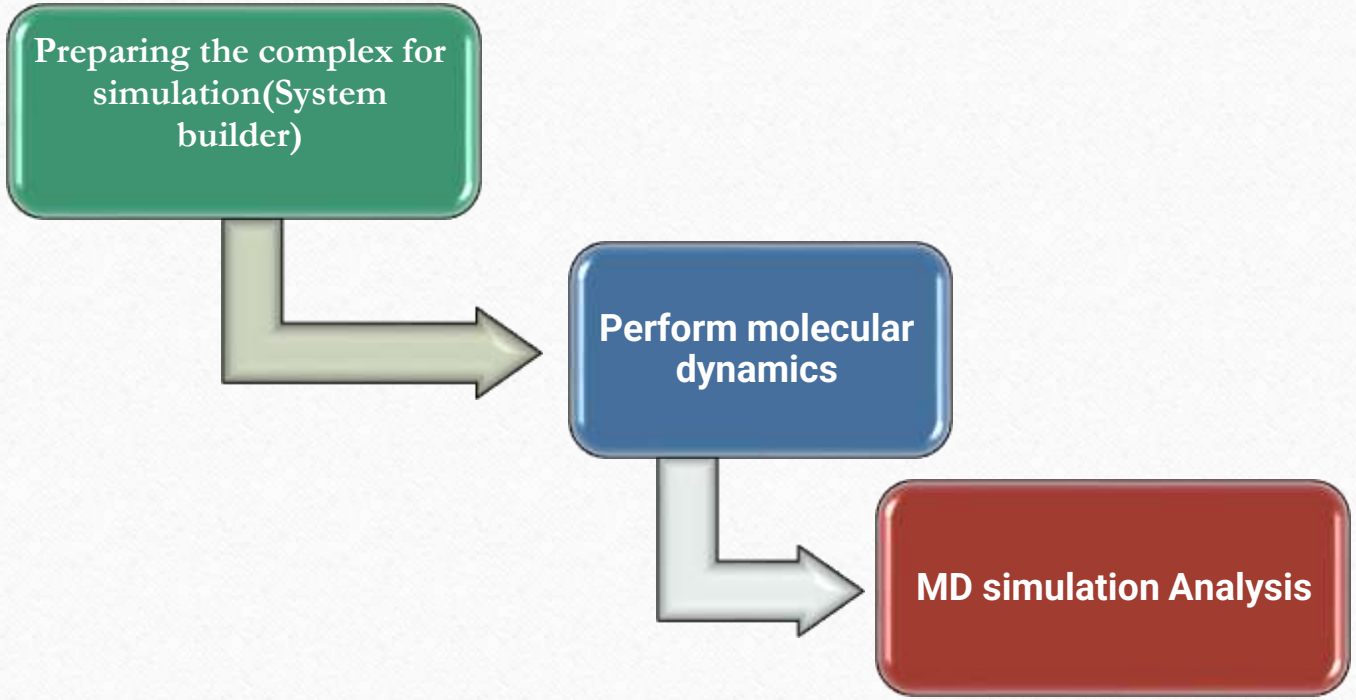
Time scale of MD running



Molecular Dynamics



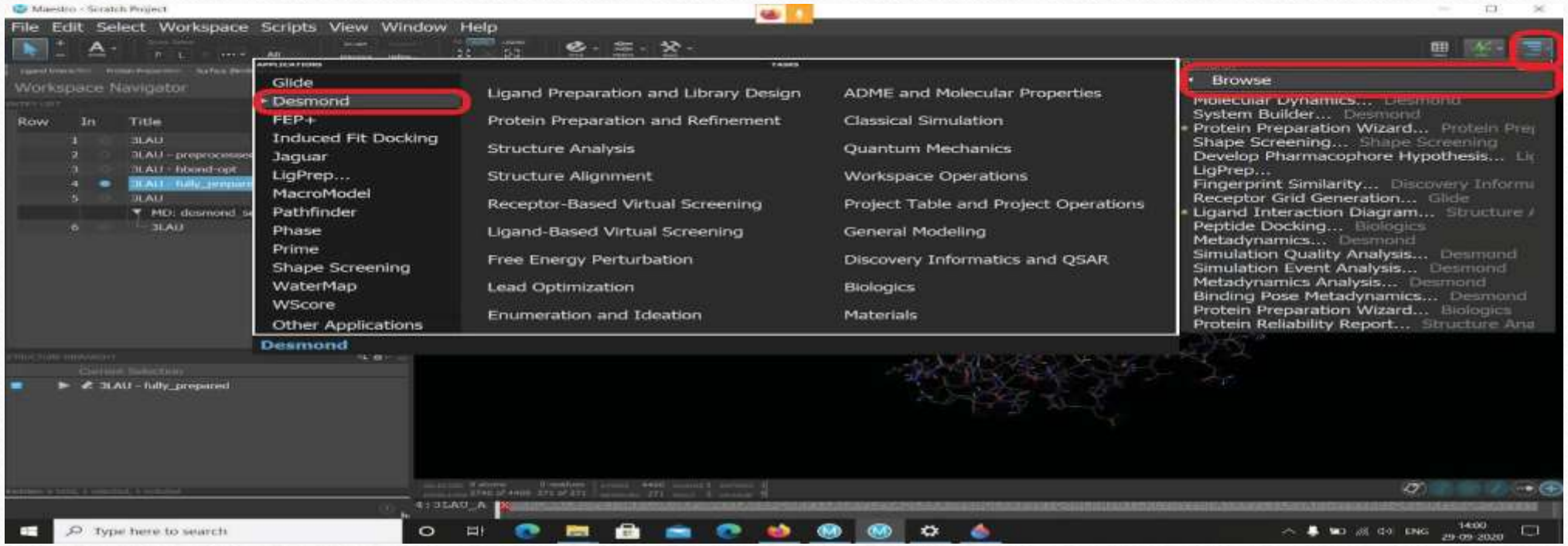
Molecular dynamics protocol



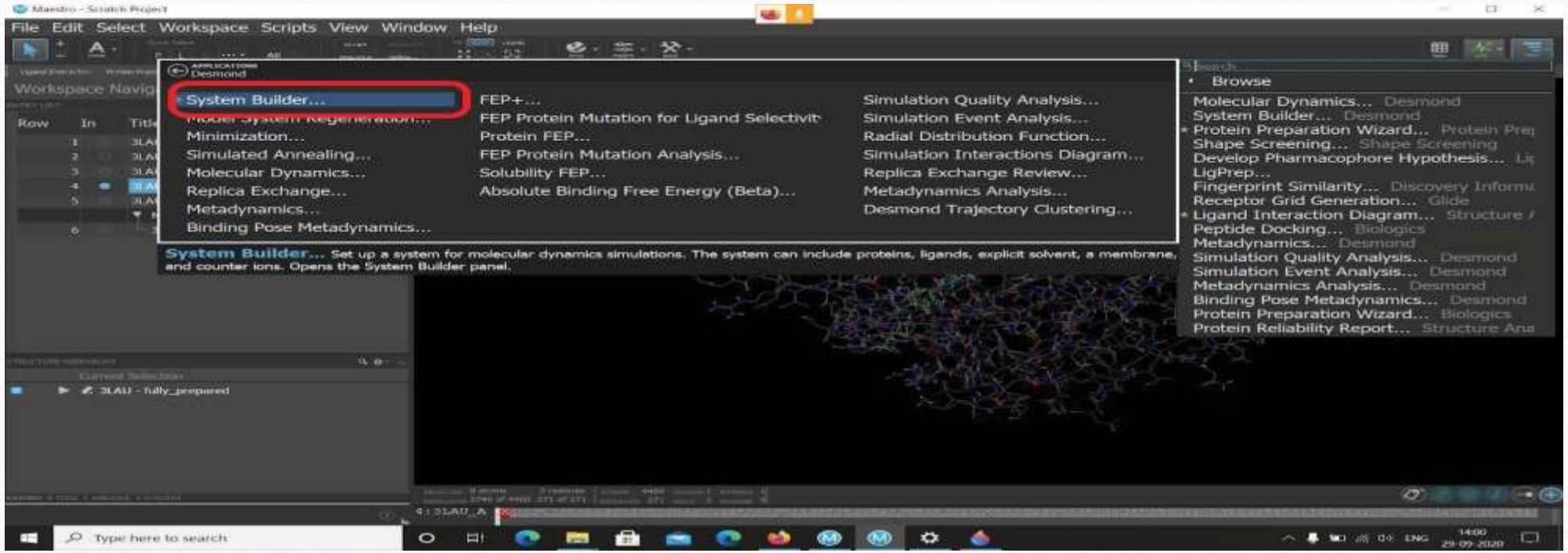
1. Preparing the complex for simulation

- Once the structure is loaded, open System Builder. To do that, go to Tasks→ Browse→ Desmond. Click on Desmond

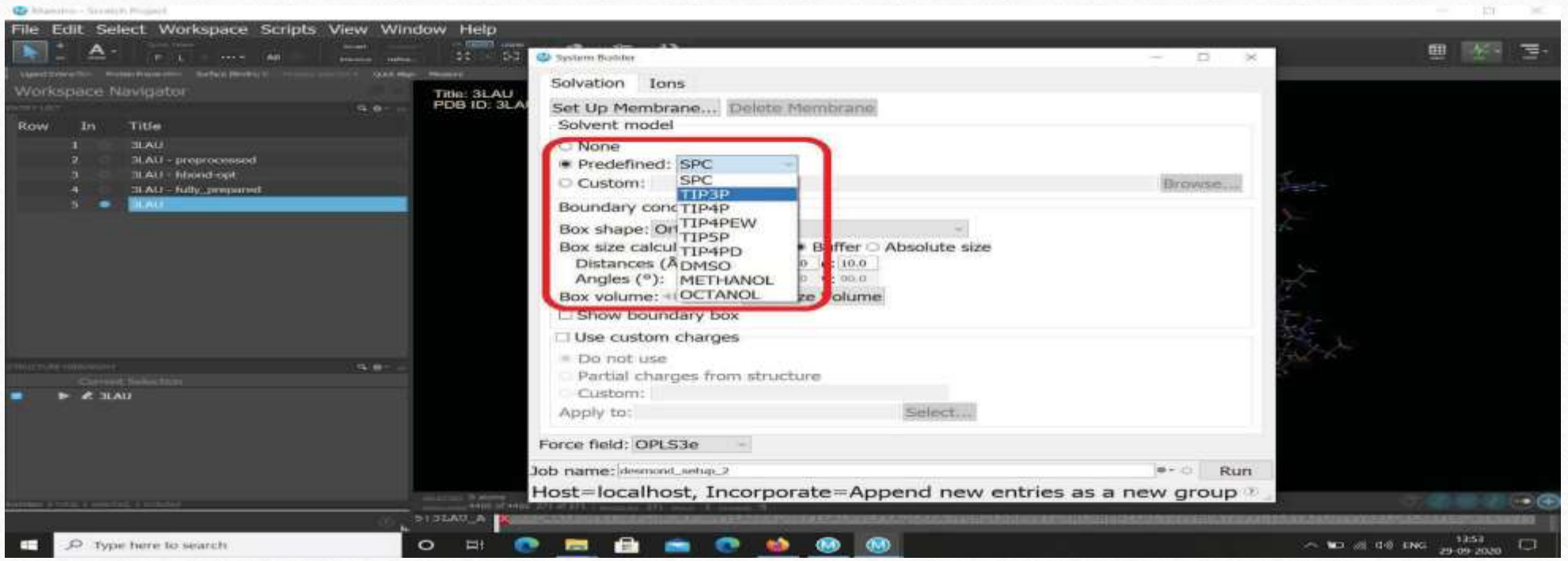
1. Preparing the complex for simulation



2- System Builder



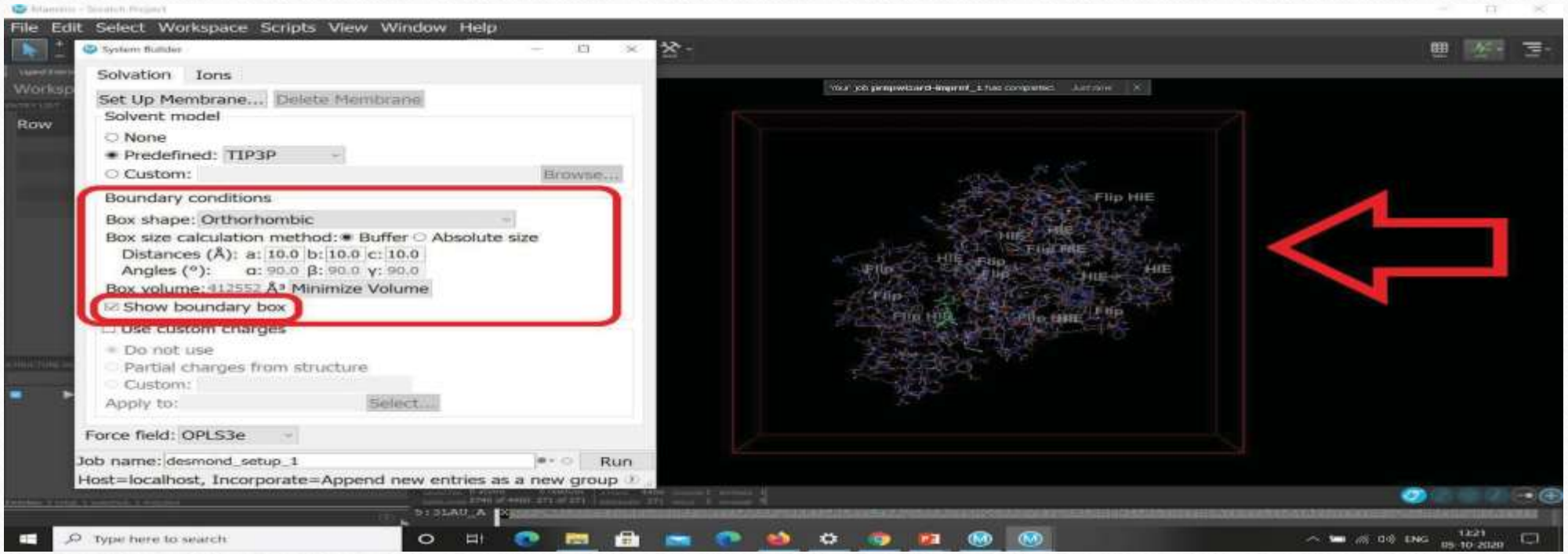
3-Select water model. Click dropdown menu and select TIP3P



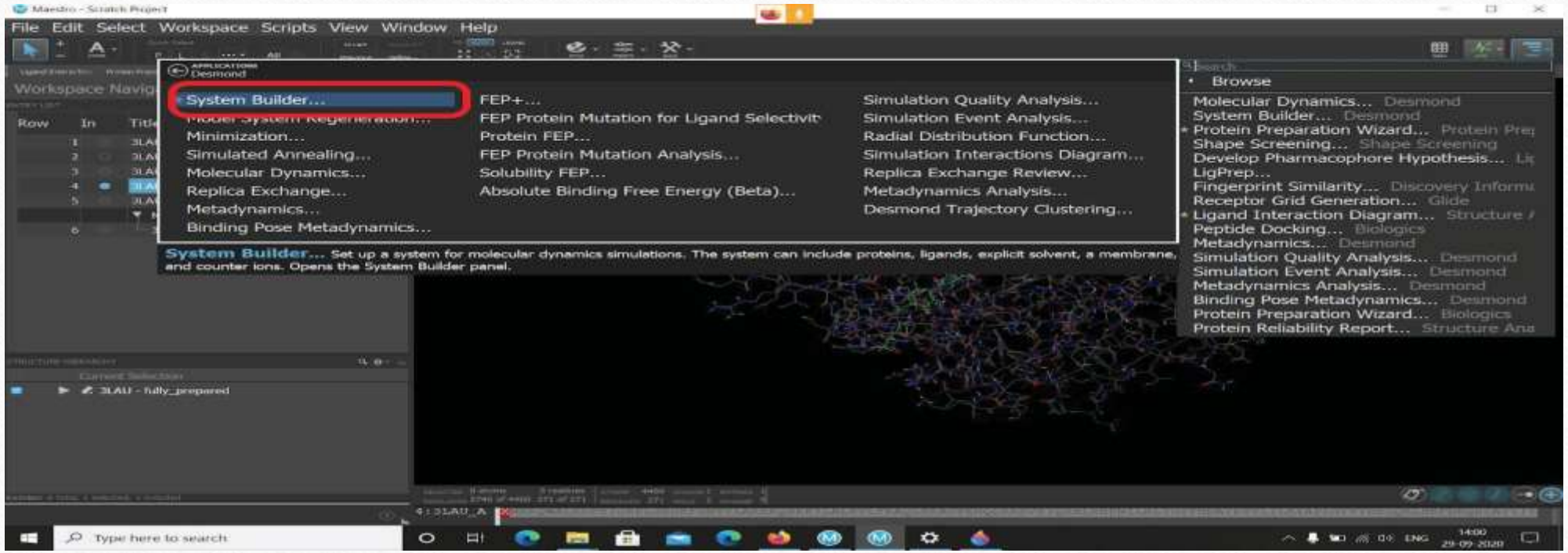
Molecular Dynamics

- For boundary conditions, click on “Show boundary box”. An orthorhombic water box should appear in the workspace, indicated by the arrow in the image below

Molecular Dynamics



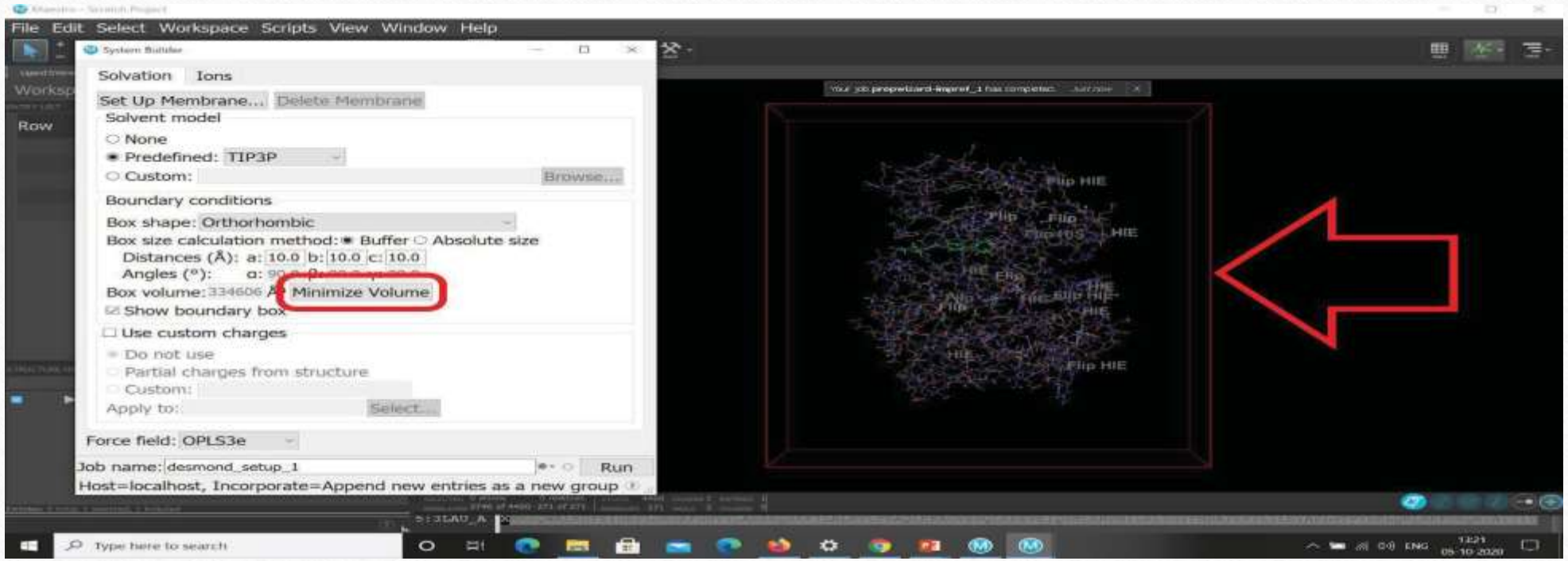
System Builder



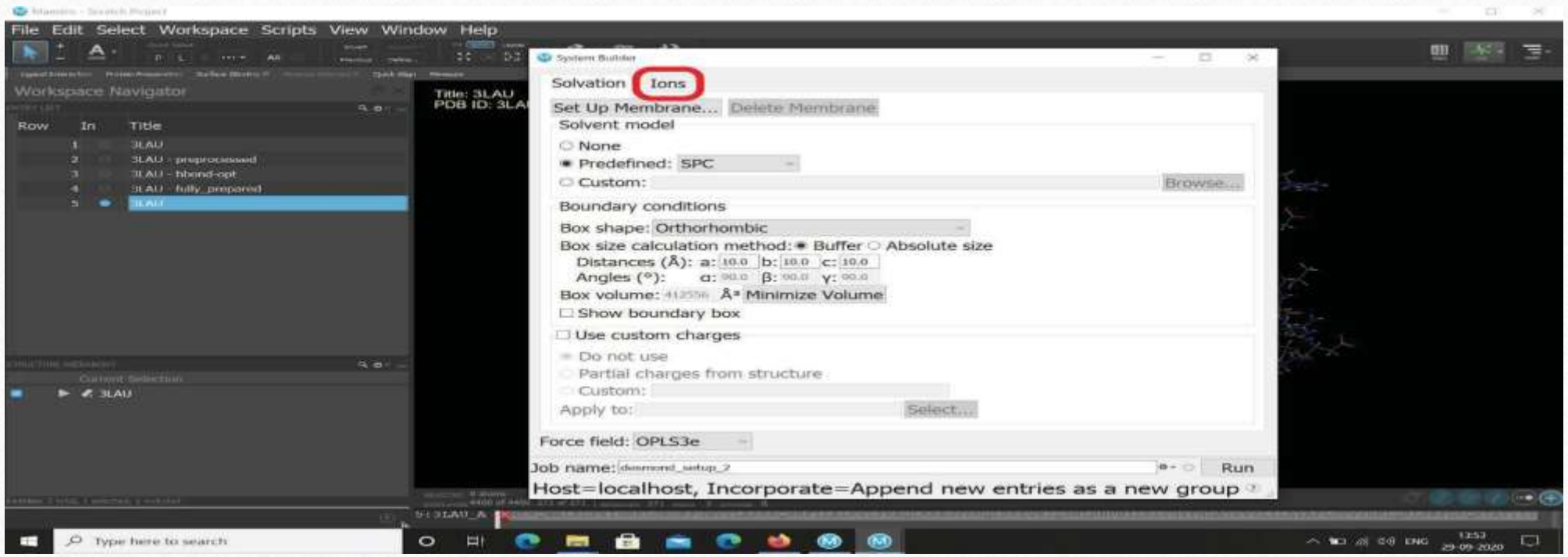
Molecular Dynamics

- Observe the shape and size of the water box. Then, click on “Minimize volume”. While clicking on “Minimize volume”, keep observing the water box and how it changes shape and size after minimization.

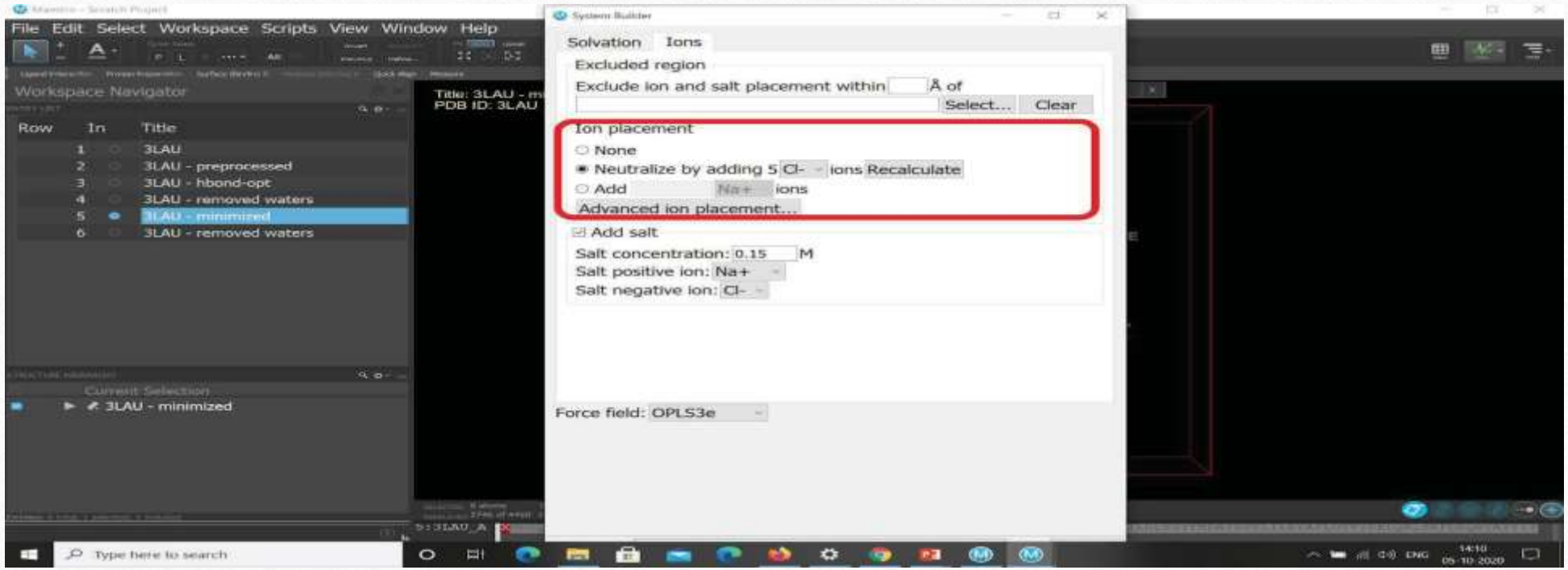
Molecular Dynamics



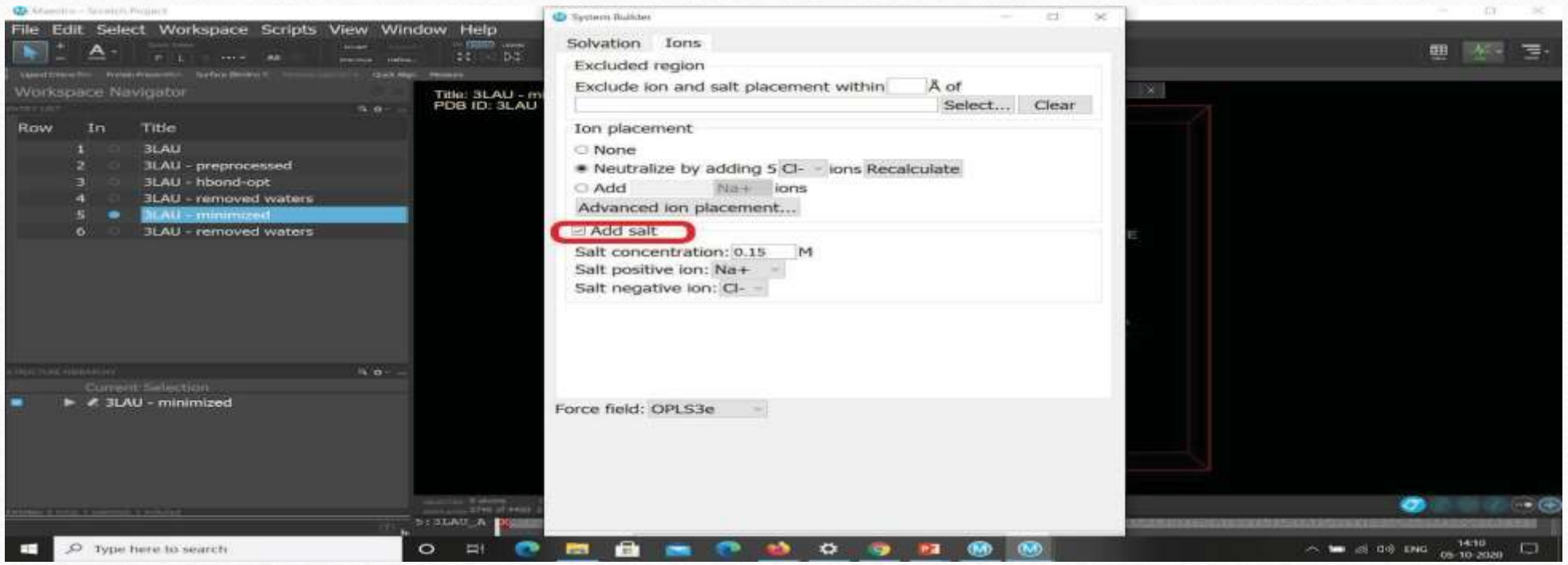
Then, Go to Ions to add ions.



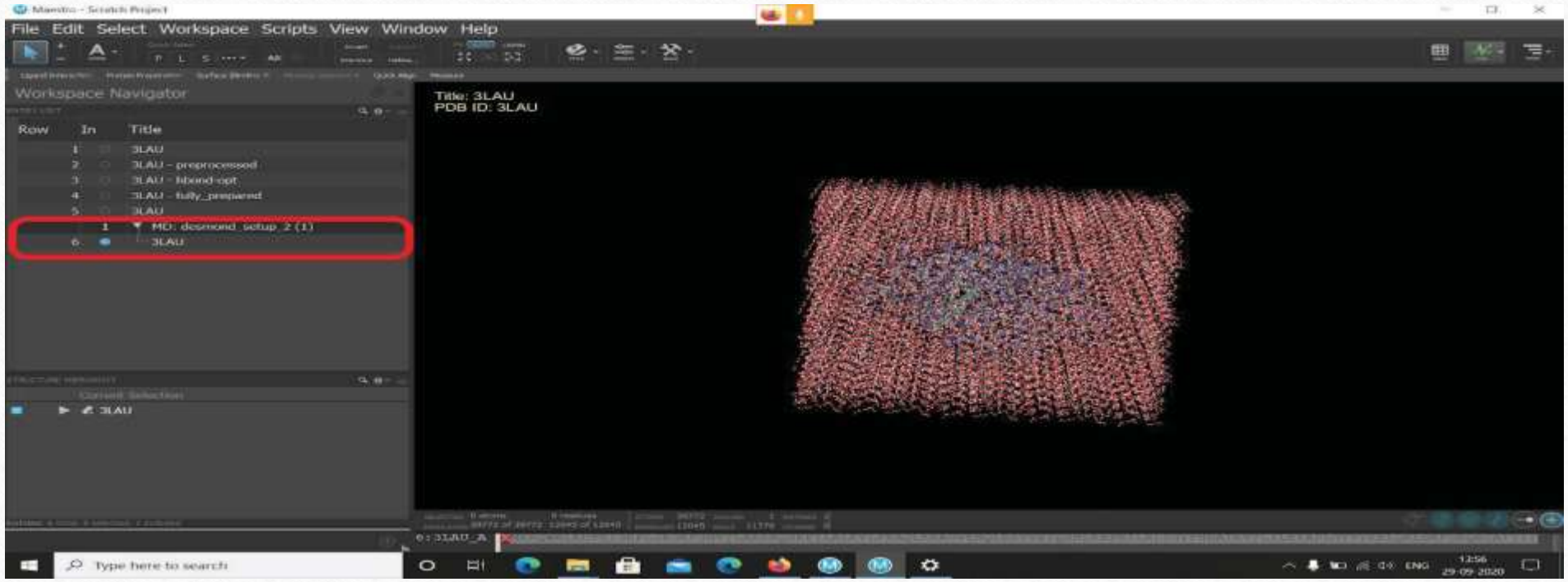
The software automatically detects the number of ions to be added. Use Default



Select Add salt and run

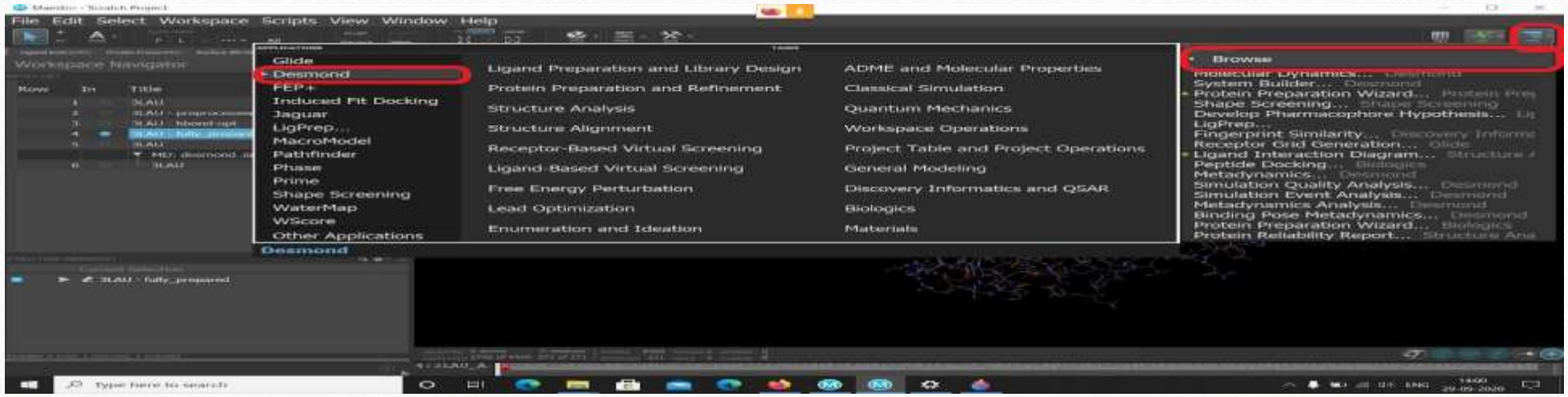


Click on the new molecule incorporated into the workspace. You should see a molecule with water and ions around it

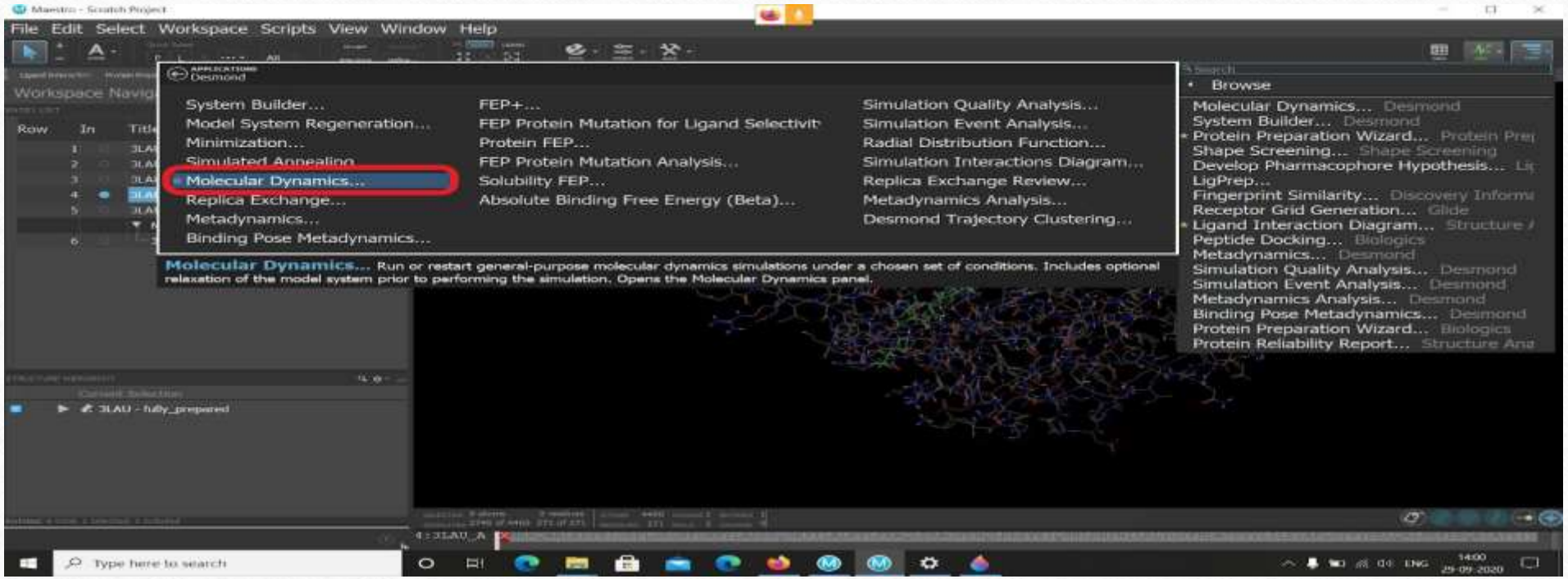


2.Perform molecular dynamics simulation

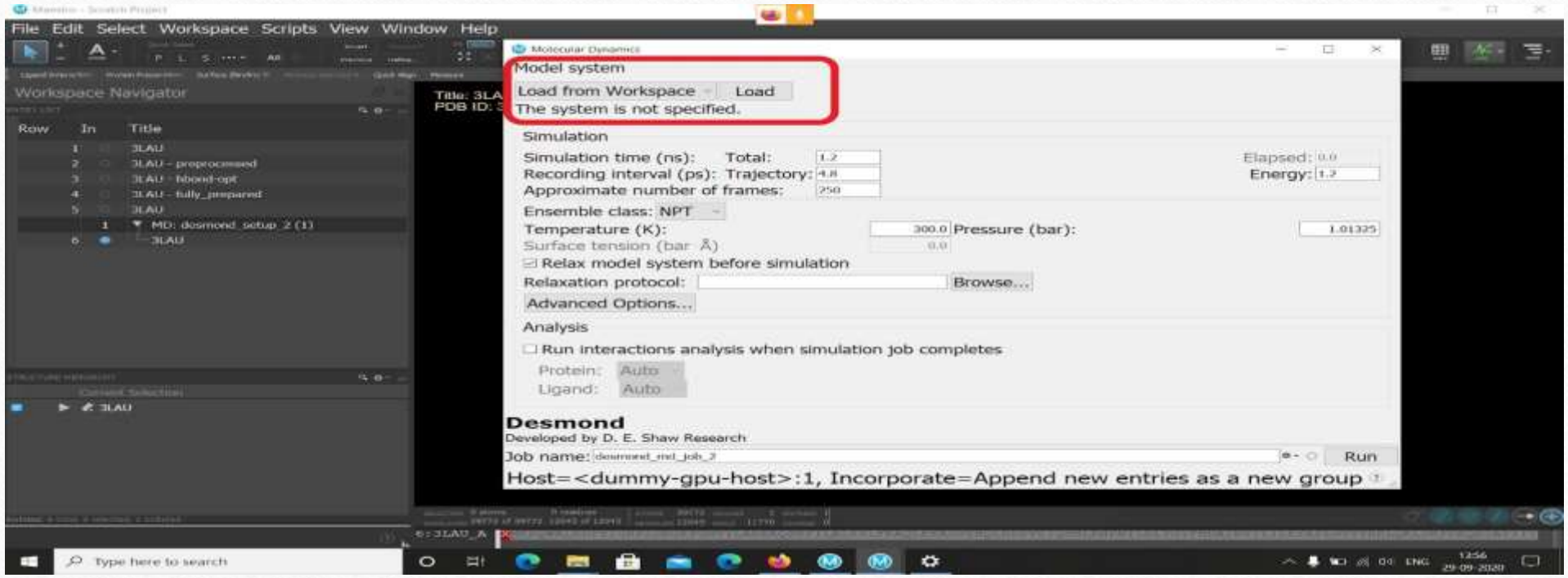
- After adding water and ions, open the Molecular Dynamics panel. To do that, go to Tasks→ Browse→ Desmond. Click on Desmond



Click on the Molecular Dynamics button

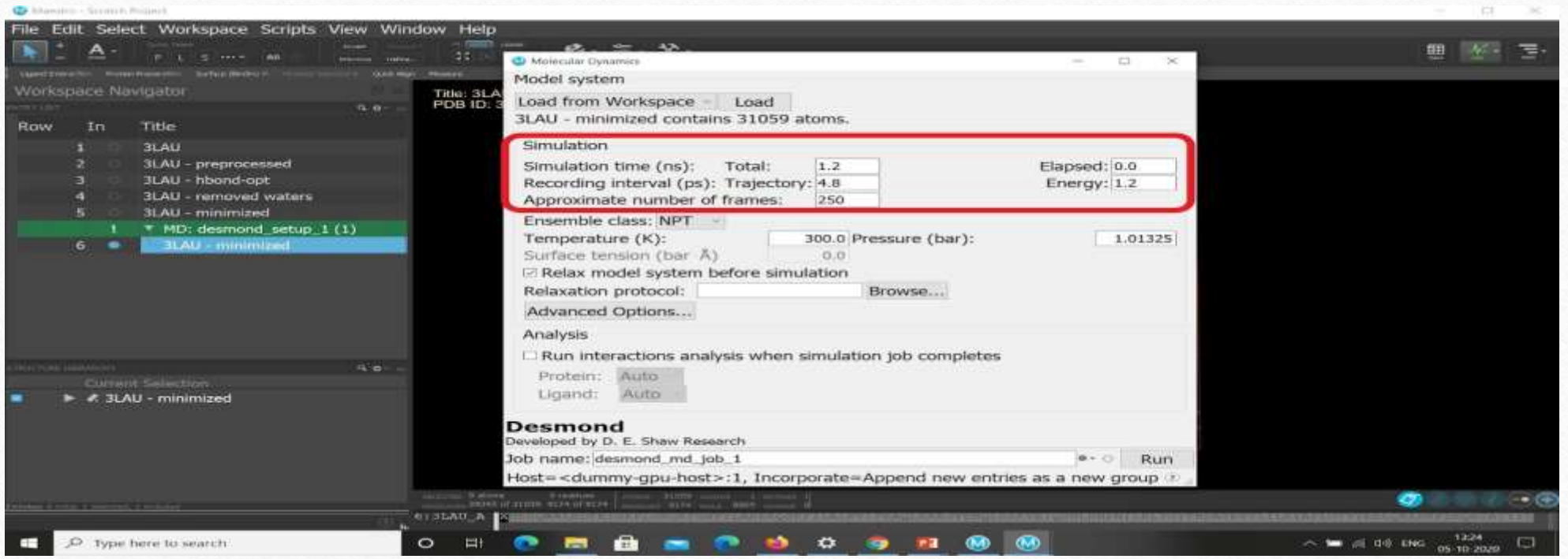


Once the Molecular Dynamics panel, load the molecule by clicking Load.



Molecular Dynamics

- The molecule should be loaded and the number of atoms in the workspace should be visible in the Molecular Dynamics panel below the Load button. After that, set the simulation timings. Use the default values and click **run**

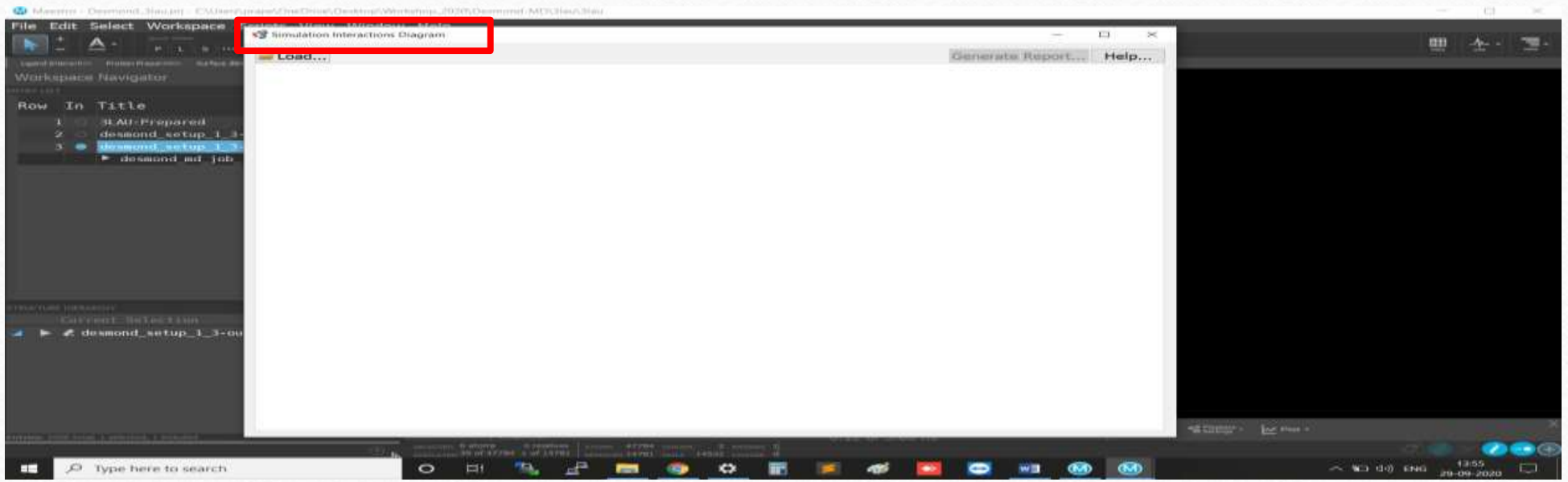

File Edit Select Workspace Scripts View Window Help
Workspace Navigator
Row In Title
1 3LAU
2 3LAU - preprocessed
3 3LAU - hbond-opt
4 3LAU - removed waters
5 3LAU - minimized
MD: desmond_setup_1 (1)
6 3LAU - minimized
Current Selection
3LAU - minimized
Molecular Dynamics
Model system
Load from Workspace
Load
3LAU - minimized contains 31059 atoms.
Simulation
Simulation time (ns): Total: 1.2
Recording interval (ps): Trajectory: 4.8
Approximate number of frames: 250
Elapsed: 0.0
Energy: 1.2
Ensemble class: NPT
Temperature (K): 300.0
Pressure (bar): 1.01325
Surface tension (bar Å) 0.0
Relax model system before simulation
Relaxation protocol:
Browse...
Advanced Options...
Analysis
Run interactions analysis when simulation job completes
Protein: Auto
Ligand: Auto
Desmond
Developed by D. E. Shaw Research
Job name: desmond_md_job_1
Run
Host=<dummy-gpu-host>:1, Incorporate=Append new entries as a new group
Type here to search

3.MD Analysis

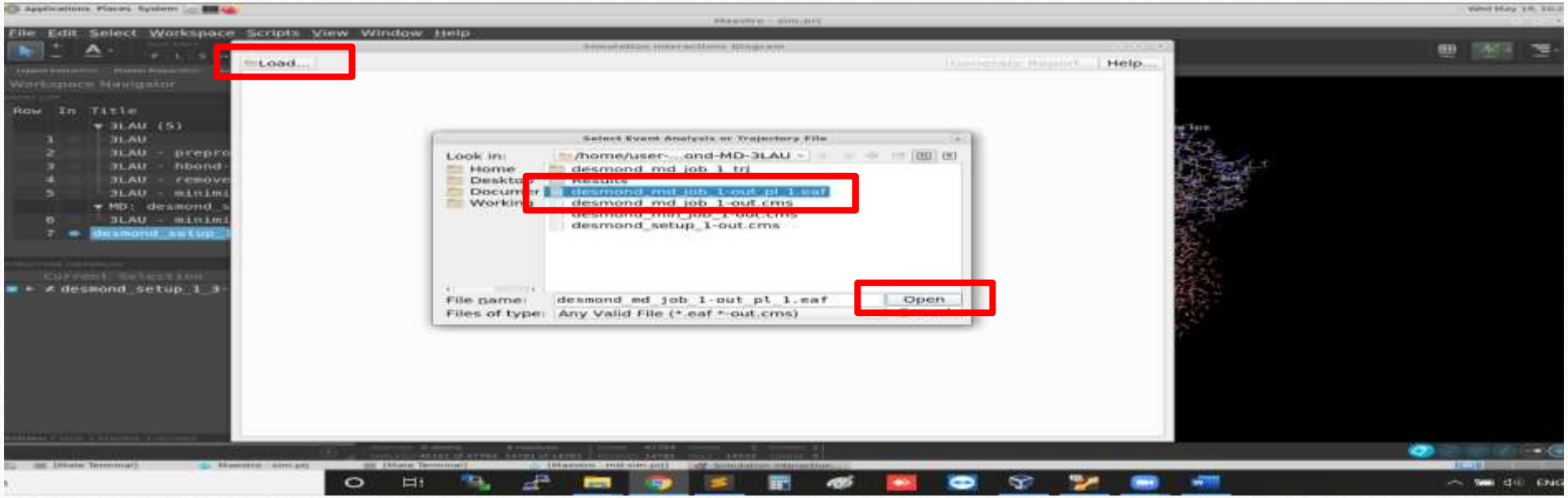
- Go to “TASKS -> Browse -> Desmond -> Simulation Interactions Diagram” and Click on it.


File Edit Select Workspace Scripts View Window Help
Desmond
System Builder...
Model System Regeneration...
Minimization...
Simulated Annealing...
Molecular Dynamics...
Replica Exchange...
Metadynamics...
Binding Pose Metadynamics...
FEP+...
FEP Protein Mutation for Ligand Selectivity...
Protein FEP...
FEP Protein Mutation Analysis...
Solubility FEP...
Absolute Binding Free Energy (Beta)...
Simulation Quality Analysis...
Simulation Event Analysis...
Simulation Interactions Diagram...
Metadynamics Analysis...
Desmond Trajectory Clustering...
Simulation Interactions Diagram... Display information on protein-ligand interactions derived from a molecular dynamics simulation, in graphical form. The diagrams show RMSD and RMSF measures for proteins, including backbone, side chain, and secondary structure changes; ligands, including internal and external motions; and protein-ligand contacts, including H-bonds, hydrophobic, ionic, and water-bridge contacts.
Opens the Simulation Interactions Diagram panel.
Workspace Navigator
Browse
Type here to search

Check the Simulation Interactions Diagram (SID) Panel

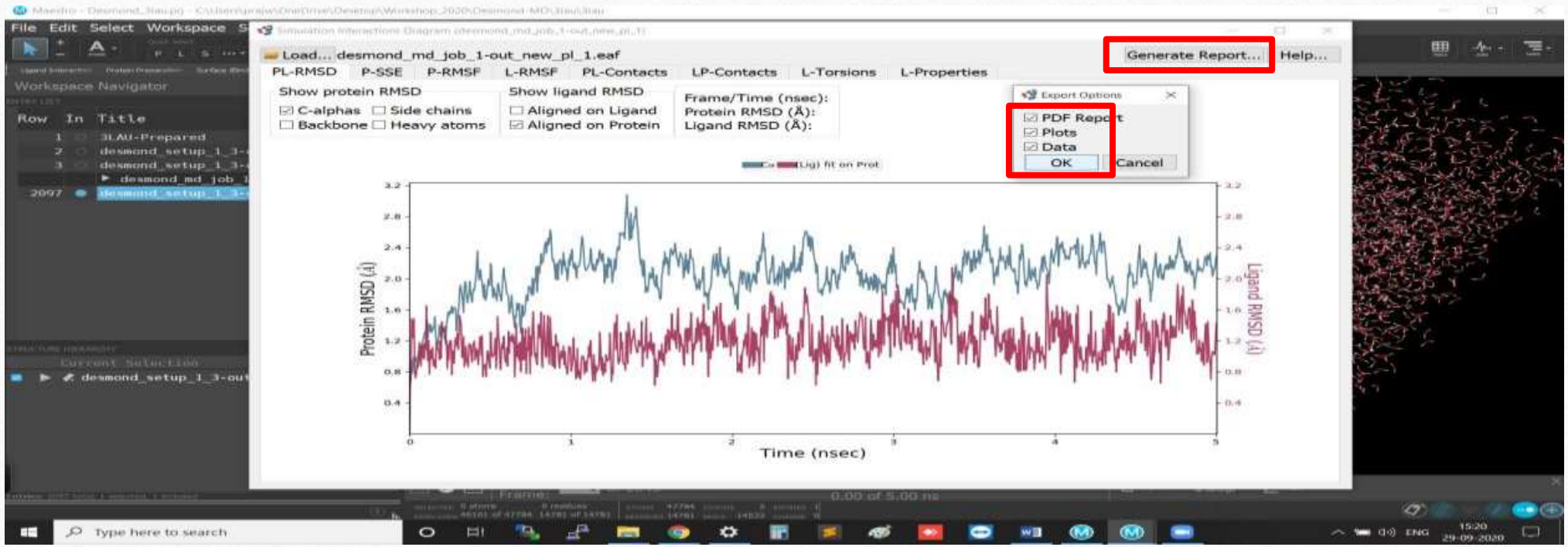


On the SID panel, Click on “Load” button and Browse for “desmond_md_job_1-out_pl_1.eaf” file

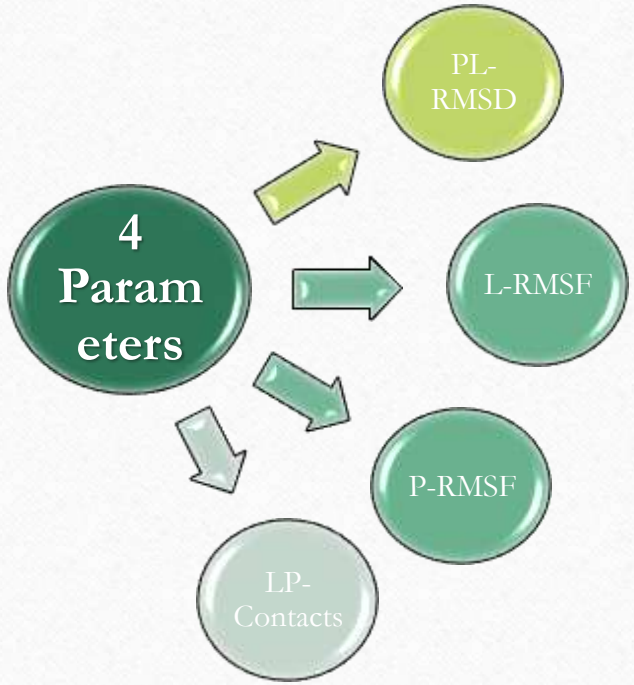


Once the file is loaded, it will automatically show all results in SID panel. Carefully. analyze all the Tabs and Plots.

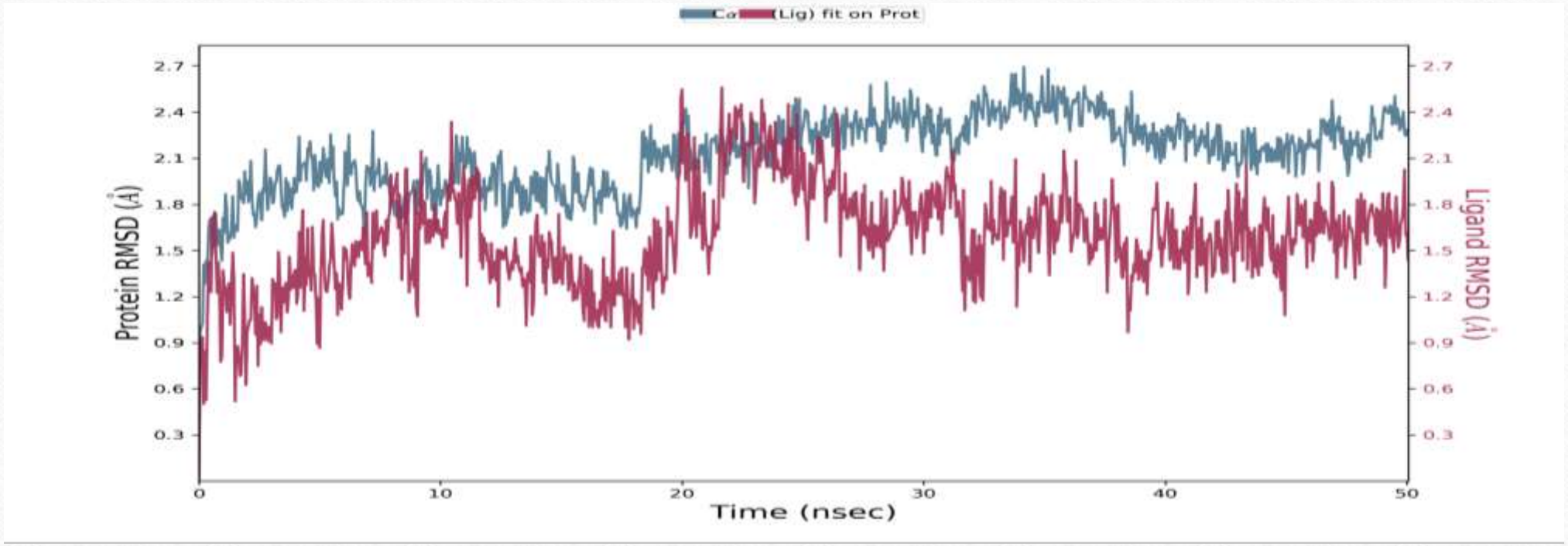
- After analyzing all the plots and data, you can generate the Report.
- Click on “Generate Report” and Tick on all options and Click on “OK”


File Edit Select Workspace
Workspace Navigator
Row In Title
1 3LAU-Prepared
Load... desmond_md_job_1-out_new_pl_1.eaf
Generate Report...
Help...
PL-RMSD
P-SSE
P-RMSF
L-RMSF
PL-Contacts
LP-Contacts
L-Torsions
L-Properties
Show protein RMSD
C-alphas
Side chains
Backbone
Heavy atoms
Show ligand RMSD
Aligned on Ligand
Aligned on Protein
Frame/Time (nsec):
Protein RMSD (Å):
Ligand RMSD (Å):
Export Options
PDF Report
Plots
Data
OK
Cancel
Protein RMSD (Å)
Ligand RMSD (Å)
Time (nsec)
Type here to search

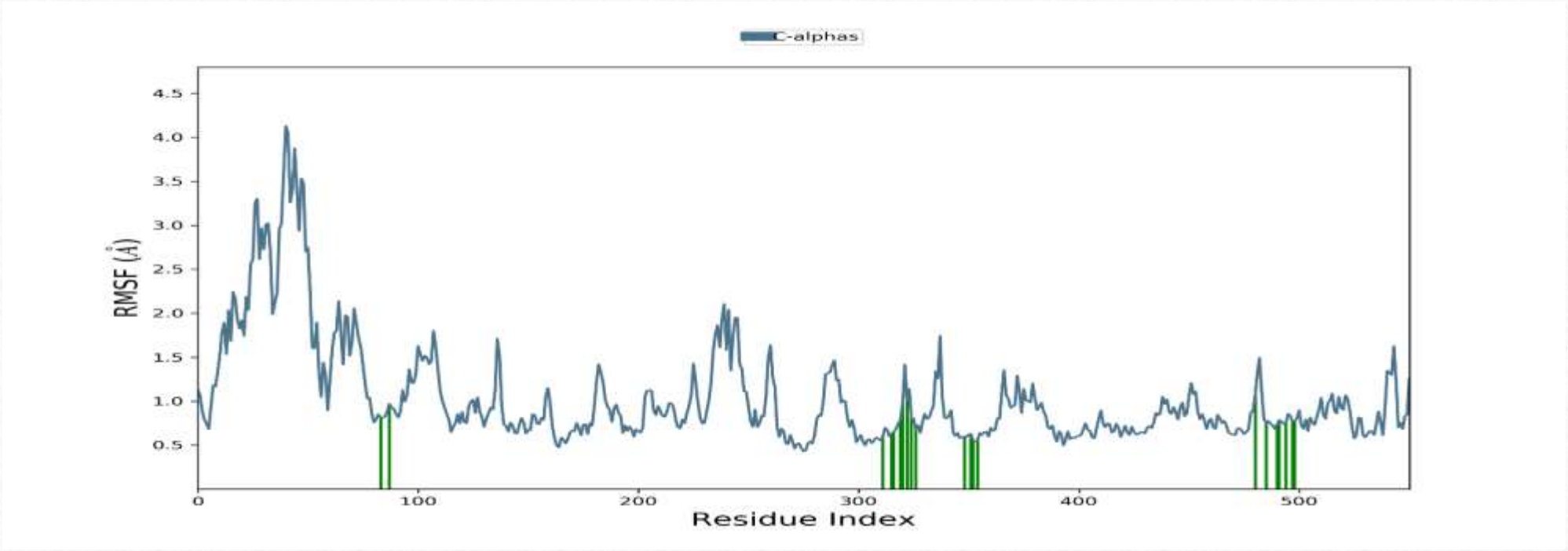
4.Discussion



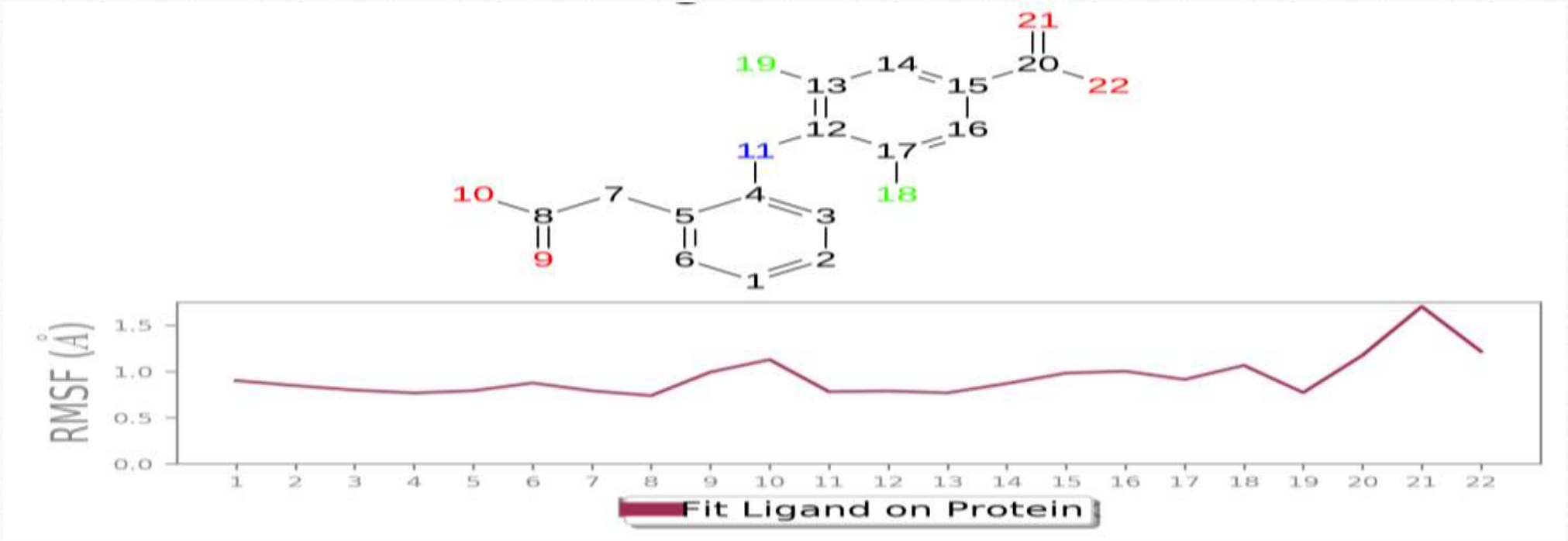
PL-RMSD


Cα (Lig) fit on Prot
Protein RMSD (Å)
Ligand RMSD (Å)
Time (nsec)
0
10
20
30
40
50
0.3
0.6
0.9
1.2
1.5
1.8
2.1
2.4
2.7

P-RMSF


C-alphas
RMSF (Å)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
100
200
300
400
500
Residue Index

L-RMSF


21
19
13
14
15
20
22
12
16
11
17
18
10
8
7
5
4
3
9
6
2
1
RMSF (Å)
1.5
1.0
0.5
0.0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Fit Ligand on Protein

PL-Contacts