Protein-Ligand Simulation

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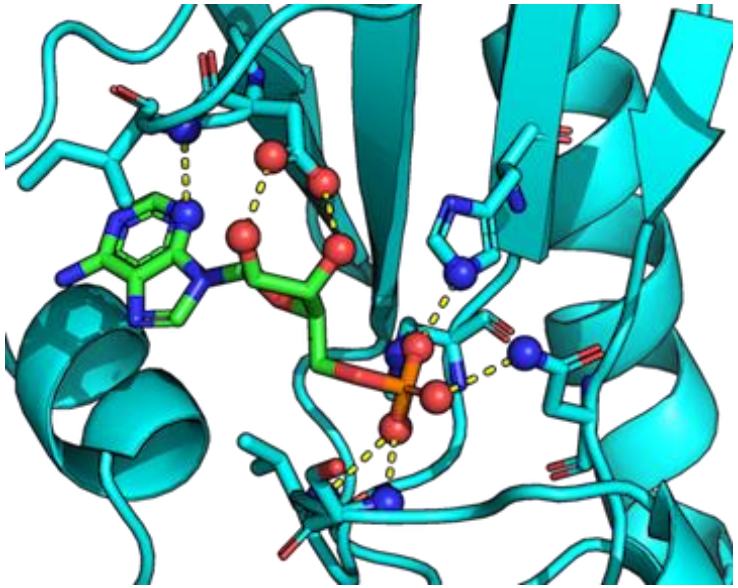
Protein-Ligand

- Complexes of proteins with small ligands are of utmost importance in biochemistry and pharmacology
- Protein-ligand interactions are a necessary prerequisite for signal transduction, immunoreaction, and gene regulation. Protein-ligand interaction studies are important for understanding the mechanisms of biological regulation, and they provide a theoretical basis for the design and discovery of new drug targets



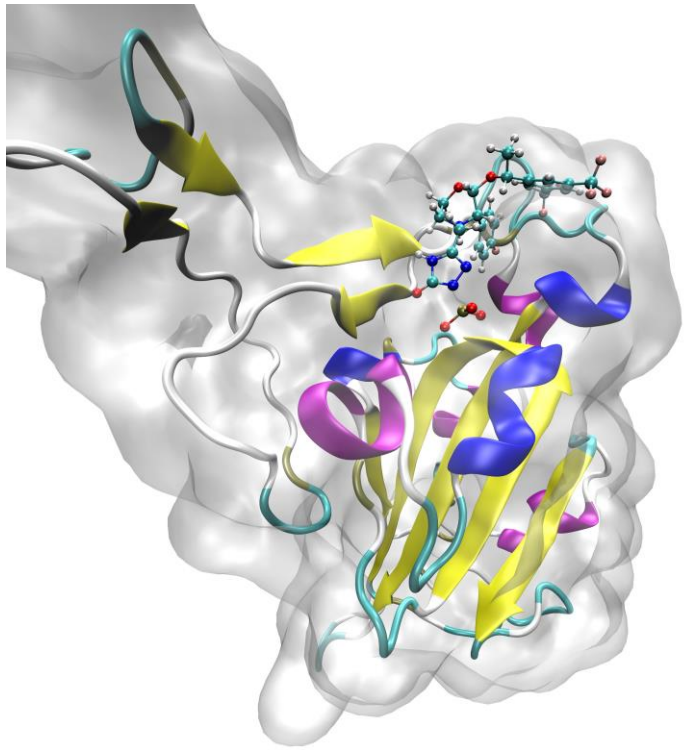
Protein-Ligand Simulation: Step by Step

STEP 1 : Force field development for ligand

1. Get the protein-ligand structure
2. Get the ligand structure separately: Either directly or from the docking program or separate it by yourself
3. We need the ligand structure file as pdb, mol, or mol2
4. Generate the force field parameters for the ligand **.str file = force field file**
5. Upload the force-field file into QwikMD plugin in VMD
6. Prepare the MD simulation

Protein-Ligand Structure

- Protein – Ligand Structure: We get the structure from
- From the Docking of ligand with the protein from a Docking Program
- From any other source, like PDB (some structure come as a protein – ligand complex from PDB database)



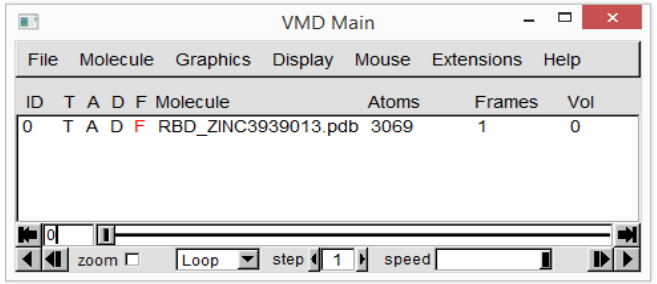
Protein-Ligand Structure in VMD

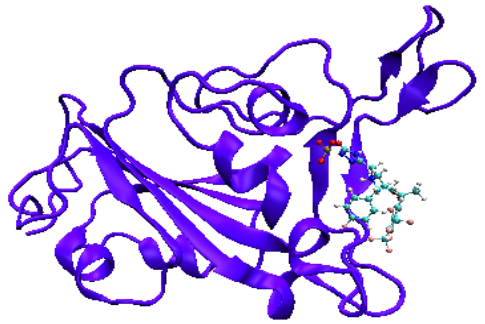
- We can view the protein-ligand complex in *VMD*, and we can specifically know the ligand part or atoms by using the *selection options*

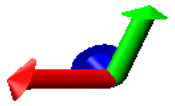
- It is also recommended to check the PDB file to make sure that the ligand we want is actually there

```
ATOM   3459  O   CYS B 525     -25.431  18.840  41.686 -0.5679  1.5000       O
ATOM   3460  N   GLY B 526     -27.018  17.888  43.011 -0.4157  1.5500       N
ATOM   3461  H   GLY B 526     -27.612  18.038  43.811  0.2719  1.3000       H
ATOM   3462  CA  GLY B 526     -27.110  16.586  42.340 -0.0252  1.7000       C
ATOM   3463  HA2 GLY B 526     -27.923  16.112  42.856  0.0698  1.2000       H
ATOM   3464  HA3 GLY B 526     -27.353  16.735  41.291  0.0698  1.2000       H
ATOM   3465  C   GLY B 526     -25.875  15.708  42.445  0.5973  1.7000       C
ATOM   3466  O   GLY B 526     -24.991  15.861  41.632 -0.5679  1.5000       O
ATOM   3467  N   PRO B 527     -25.747  14.782  43.409 -0.2802  1.5500       N
ATOM   3468  CD  PRO B 527     -26.500  14.705  44.646  0.0434  1.7000       C
ATOM   3469  HD2 PRO B 527     -27.456  14.227  44.472  0.0331  1.2000       H
ATOM   3470  HD3 PRO B 527     -26.630  15.687  45.101  0.0331  1.2000       H
ATOM   3471  CG  PRO B 527     -25.641  13.812  45.523  0.0466  1.7000       C
ATOM   3472  HG2 PRO B 527     -26.243  13.257  46.244  0.0172  1.2000       H
ATOM   3473  HG3 PRO B 527     -24.889  14.414  46.037  0.0172  1.2000       H
ATOM   3474  CB  PRO B 527     -24.973  12.903  44.547 -0.0543  1.7000       C
ATOM   3475  HB2 PRO B 527     -25.673  12.115  44.266  0.0381  1.2000       H
ATOM   3476  HB3 PRO B 527     -24.067  12.466  44.966  0.0381  1.2000       H
ATOM   3477  CA  PRO B 527     -24.645  13.836  43.380 -0.1336  1.7000       C
ATOM   3478  HA  PRO B 527     -23.681  14.332  43.506  0.0776  1.2000       H
ATOM   3479  C   PRO B 527     -24.736  13.069  42.055  0.6631  1.7000       C
ATOM   3480  O   PRO B 527     -25.756  12.483  41.857 -0.7697  1.5000       O
ATOM   3481  OXT PRO B 527     -23.767  13.009  41.301 -0.7697  1.5000       O
TER    3482       PRO B 226
ATOM      1  C1  LIG L   1     -34.929  25.432   1.483  1.00  0.00      LIG
ATOM      2  O1  LIG L   1     -36.301  25.656   1.826  1.00  0.00      LIG
ATOM      3  C2  LIG L   1     -36.511  26.373   3.049  1.00  0.00      LIG
ATOM      4  C3  LIG L   1     -35.284  27.212   3.460  1.00  0.00      LIG
ATOM      5  N1  LIG L   1     -33.990  26.403   3.491  1.00  0.00      LIG
ATOM      6  C4  LIG L   1     -34.111  25.102   2.755  1.00  0.00      LIG
ATOM      7  C5  LIG L   1     -34.658  24.102   3.777  1.00  0.00      LIG
```

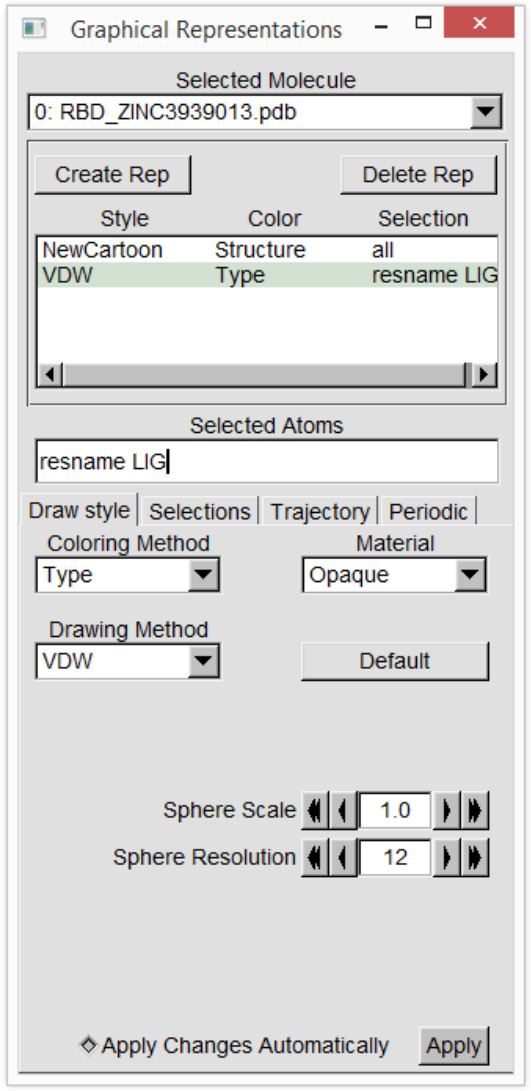
Text

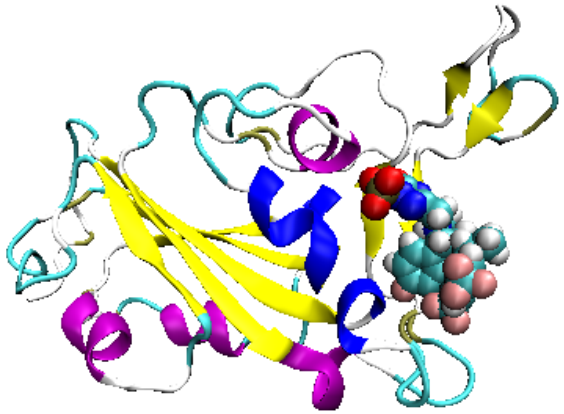






Extracting Ligand Structure by VMD





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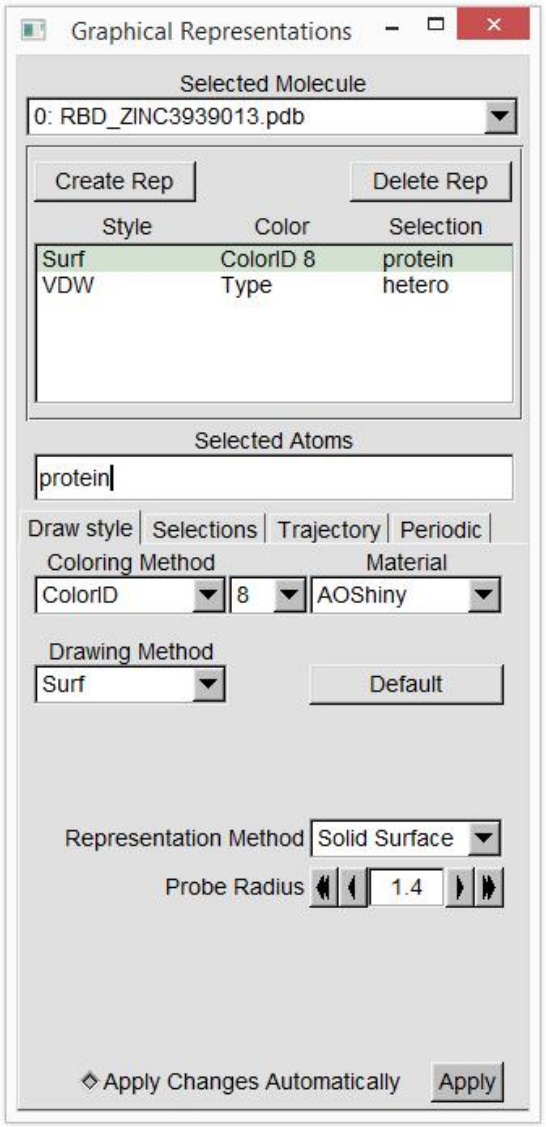
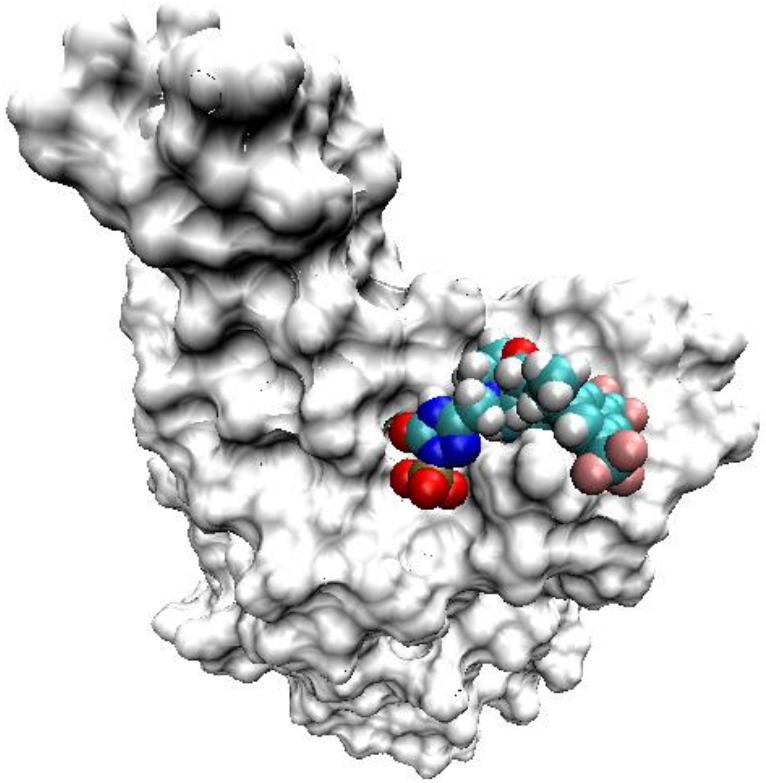
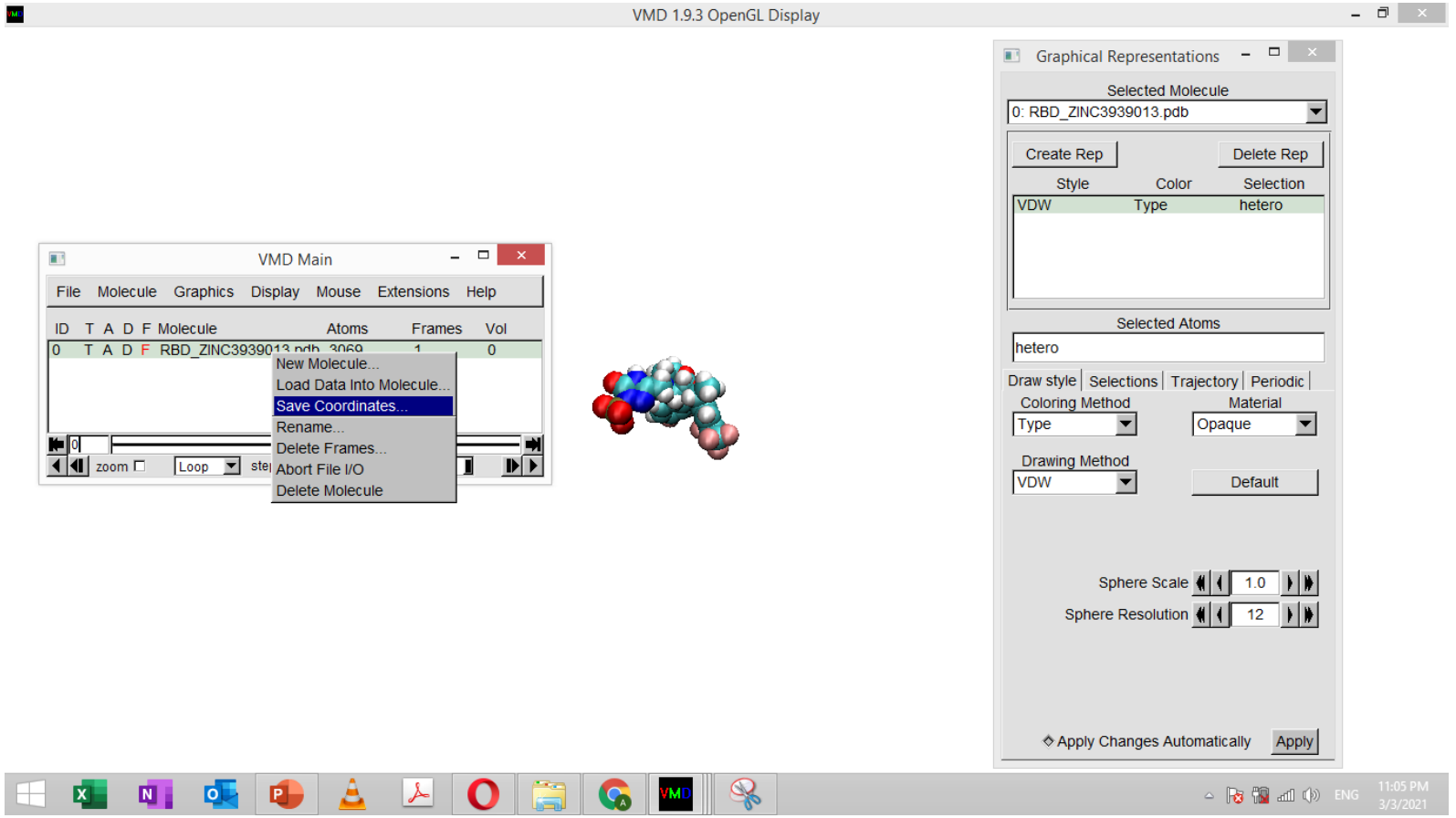




Extracting Ligand Structure by VMD

- We choose the *selection option* that only displays the ligand alone, then in the *main window*

- *Right click > Save coordinates > filename.pdb*



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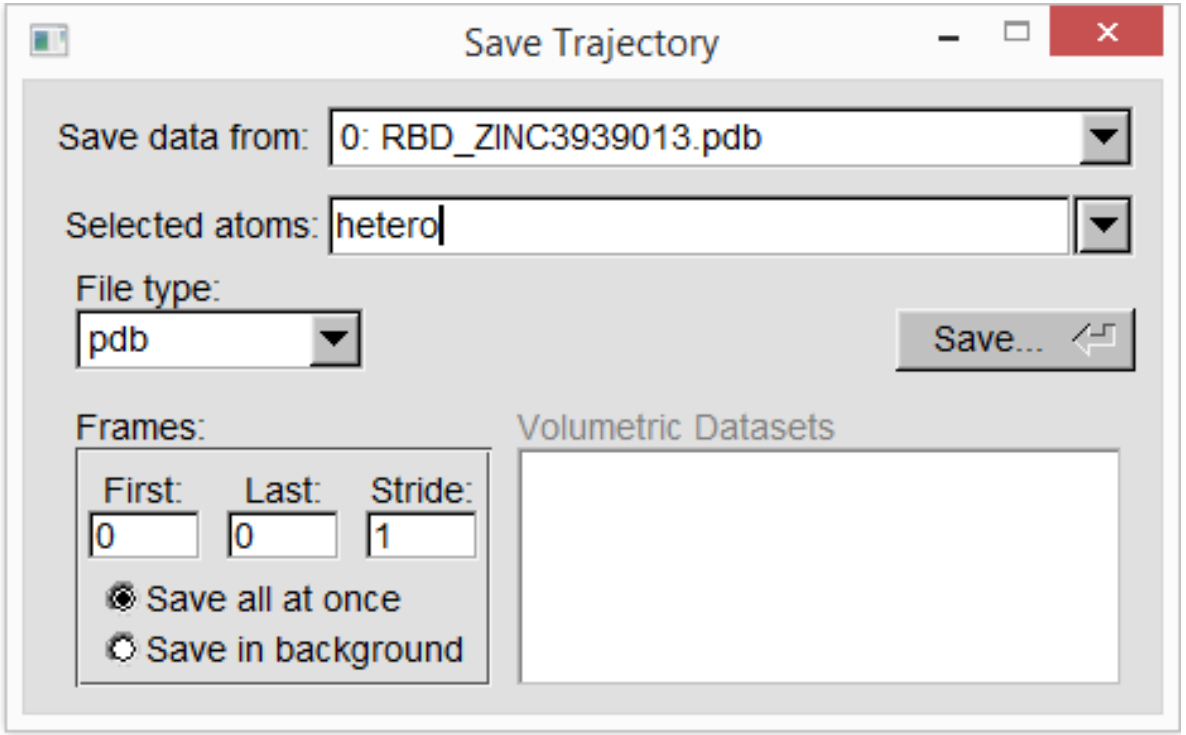

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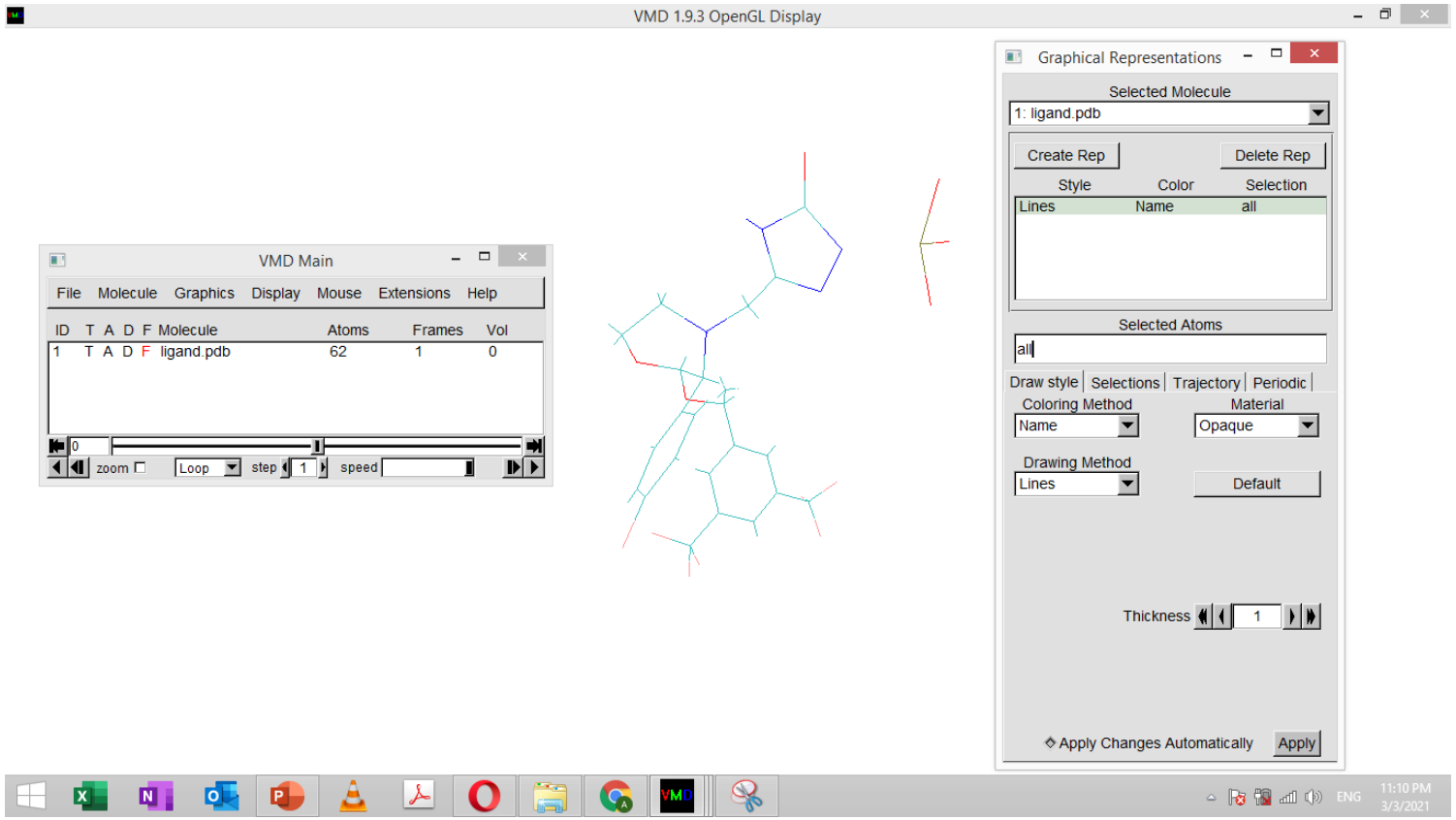


Ligand Structure

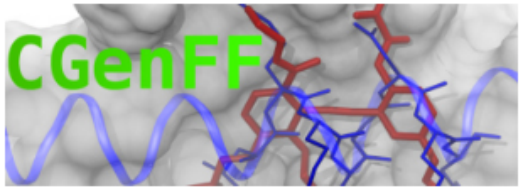
- We now need to convert the ligand pdb file to .mol or .mol2 file, because it's the most convenient format to generate the force field file not necessary
- We can do this step by using any program that is able to convert the file format, like:
- Avogadro: https://avogadro.cc/
- Open Babel: https://openbabel.org/docs/dev/Installation/install.html
- **We also need to add hydrogen atoms** with the conversion process, because the PDB file by default doesn't contain any hydrogens MUST

Generating a force field for the ligand

- NAMD program contains by default the CHARMM force field for standard structures like proteins, lipids, membranes, ….etc.
- The Ligand or chemical structure needs parametrized force field file to be added to VMD before running the simulation
- There are several websites that we can use to generate the force field file for the ligand:

- http://cgenff.umaryland.edu/
- http://www.charmm-gui.org/
- http://zarbi.chem.yale.edu/ligpargen/

Generating a force field for the ligand



New User Registration / Login

My Account | Upload molecule | More Info & Tools | About CGenFF

Welcome to CGenFF

The CHARMM General Force Field (CGenFF) program performs atom typing and assignment of parameters and charges by analogy in a fully automated fashion. Atom typing is done by a deterministic programmable decision tree. Assignment of bonded parameters is based on substituting atom types in the definition of the desired parameter. A penalty is associated with every substitution and the existing parameter with the lowest total penalty is chosen as an approximation for the desired parameter; the "penalty score" is returned to the user as a measure for the accuracy of the approximation. Charges are assigned using an extended bond-charge increment scheme that is able to capture short- and medium-range inductive and mesomeric effects.

The CGenFF program is a product of the discontinued ParamChem project. Future directions for the CGenFF program can be found at the future prospects page.

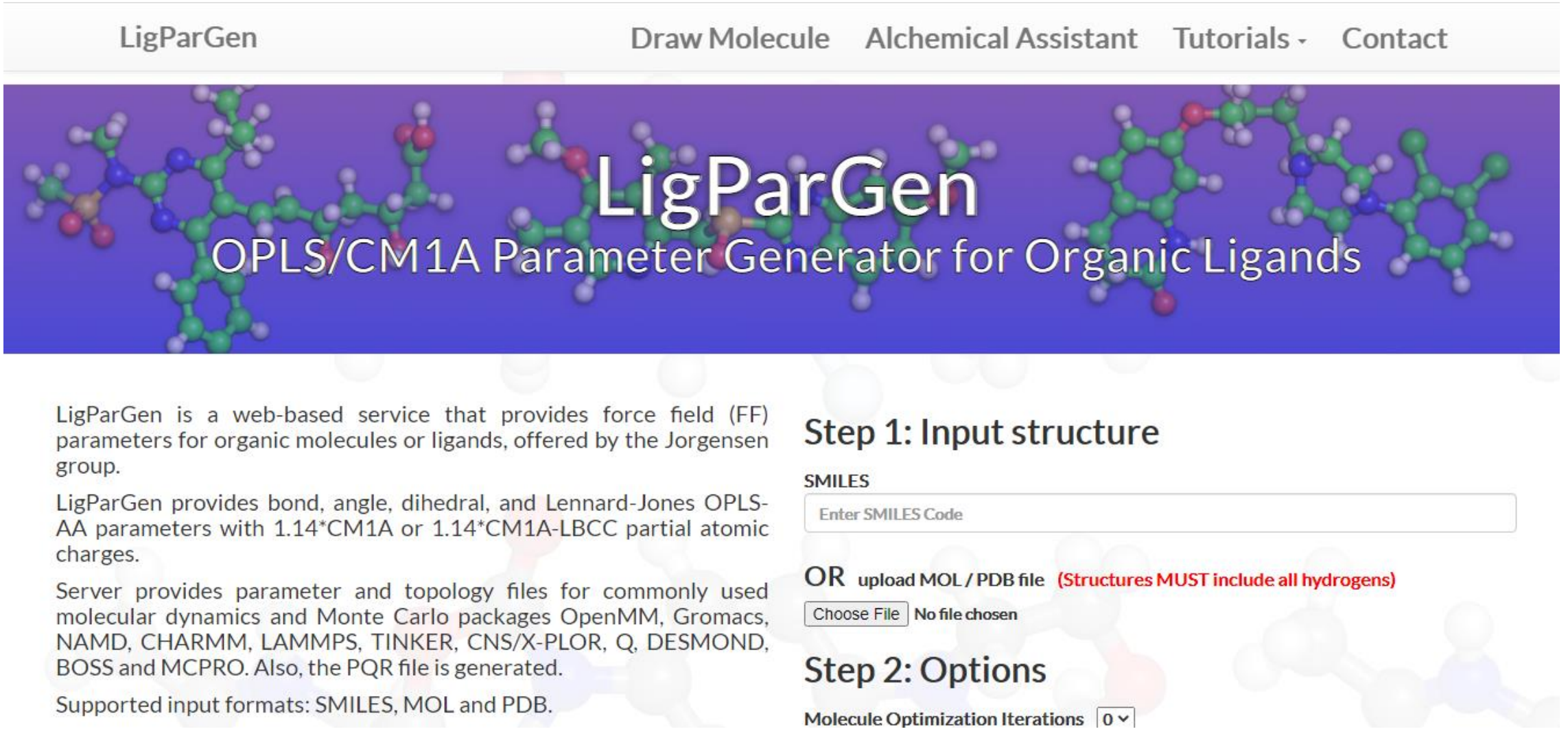
CGenFF *program* links

- Usage information.
- Summary of output data and its utilization (**required** reading).
- FAQ (read this before contacting us with questions).
- How to cite / references.

CGenFF *force field* links

- Latest CGenFF version (**required** for using the output of the CGenFF program).
- Introduction.
- FAQ.
- Parameter optimization tutorial
- How to cite / references.

Generating a force field for the ligand



Generating a force field for the ligand

CHARMM-GUI

Effective Simulation Input Generator and More

CHARMM is a versatile program for atomic-level simulation of many-particle systems, particularly macromolecules of biological interest. - M. Karplus

about us :: input generator :: Q&A :: archive :: charmm docs :: lectures :: movie gallery :: video demo :: citations :: update log :: jobs & events :: giving

Some lectures, job postings, and FAQ are now available. See upload log for update history and giving for donation. Contact info is given below.

CHARMM-GUI

- About Us
- Input Generator
- Questions & Answers
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- ST-analyzer

Geographical Visitors

Front Page

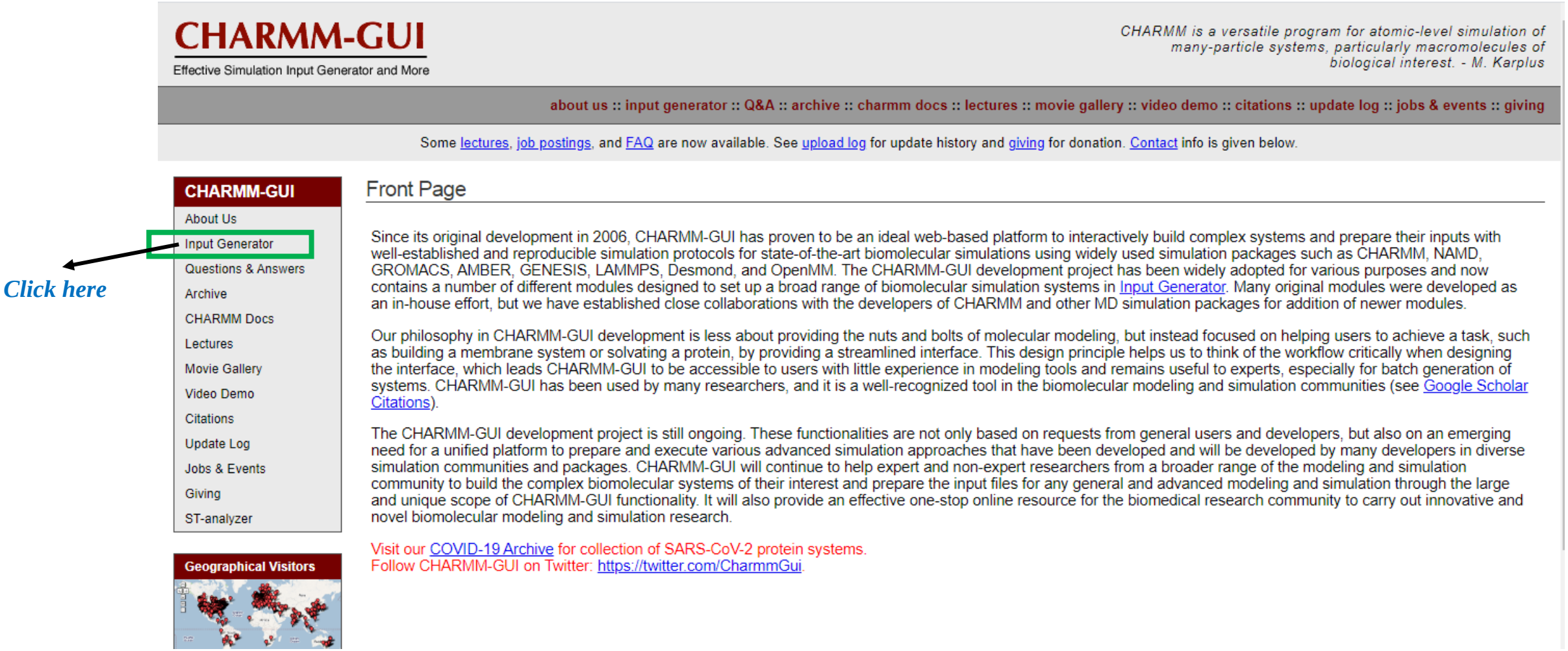
Since its original development in 2006, CHARMM-GUI has proven to be an ideal web-based platform to interactively build complex systems and prepare their inputs with well-established and reproducible simulation protocols for state-of-the-art biomolecular simulations using widely used simulation packages such as CHARMM, NAMD, GROMACS, AMBER, GENESIS, LAMMPS, Desmond, and OpenMM. The CHARMM-GUI development project has been widely adopted for various purposes and now contains a number of different modules designed to set up a broad range of biomolecular simulation systems in Input Generator. Many original modules were developed as an in-house effort, but we have established close collaborations with the developers of CHARMM and other MD simulation packages for addition of newer modules.

Our philosophy in CHARMM-GUI development is less about providing the nuts and bolts of molecular modeling, but instead focused on helping users to achieve a task, such as building a membrane system or solvating a protein, by providing a streamlined interface. This design principle helps us to think of the workflow critically when designing the interface, which leads CHARMM-GUI to be accessible to users with little experience in modeling tools and remains useful to experts, especially for batch generation of systems. CHARMM-GUI has been used by many researchers, and it is a well-recognized tool in the biomolecular modeling and simulation communities (see Google Scholar Citations).

The CHARMM-GUI development project is still ongoing. These functionalities are not only based on requests from general users and developers, but also on an emerging need for a unified platform to prepare and execute various advanced simulation approaches that have been developed and will be developed by many developers in diverse simulation communities and packages. CHARMM-GUI will continue to help expert and non-expert researchers from a broader range of the modeling and simulation community to build the complex biomolecular systems of their interest and prepare the input files for any general and advanced modeling and simulation through the large and unique scope of CHARMM-GUI functionality. It will also provide an effective one-stop online resource for the biomedical research community to carry out innovative and novel biomolecular modeling and simulation research.

Visit our COVID-19 Archive for collection of SARS-CoV-2 protein systems.
Follow CHARMM-GUI on Twitter: https://twitter.com/CharmmGui.

Generating a force field for the ligand: CHARMM-GUI



Click here

Generating a force field for the ligand: CHARMM-GUI

Some lectures, job postings, and FAQ are now available. See upload log for update history and giving for donation. Contact info is given below.

Input Generator

- Job Retriever
- Force Field Converter
- PDB Reader
- Glycan Reader & Modeler
- Ligand Reader & Modeler
- Glycolipid Modeler
- LPS Modeler
- Nanomaterial Modeler
- Multicomponent Assembler
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- Polymer Builder
- Drude Prepper
- Free Energy Calculator
- LBS Finder & Refiner
- MAP Utilizer
- DEER Facilitator
- NMR Structure Calculator
- PBEQ Solver
- Implicit Solvent Modeler

Click here

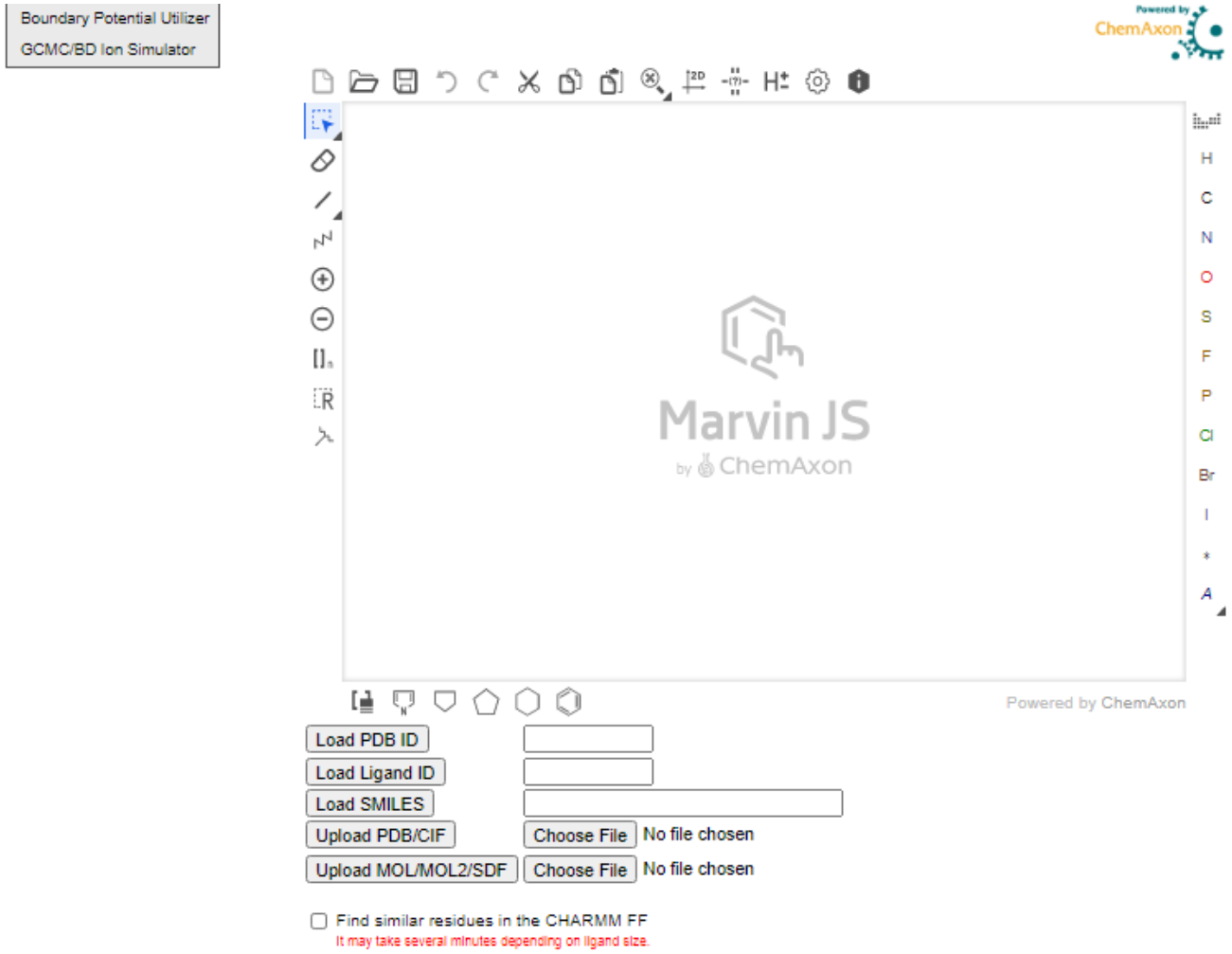
Input Generator

One easiest way to support CHARMM-GUI is to cite the CHARMM-GUI main paper as well as the papers of the modules used in users' publications. Please see Citations for details.

Since most modules start with PDB Reader, it is strongly recommended to read the PDB Reader page and to see the PDB Reader demo in Video Demo.

- Job Retriever
  Facilitates recovery of jobs, when the Job ID is known
- PDB Reader
  Read a PDB file (RCSB or CHARMM formats) into CHARMM
- Glycan Reader & Modeler
  Read carbohydrate structures from a PDB file into CHARMM and/or model user-specified N-/O-glycan or glycan-only structure(s)
- Ligand Reader & Modeler
  Generate various ligand structures using the CHARMM force field
- Glycolipid Modeler
  Provide various glycolipid structure and PSF files
- LPS Modeler
  Provide various lipopolysaccharide (LPS) structure and PSF files
- Nanomaterial Modeler
  Generate various nanomaterial systems for molecular dynamics simulation
- Multicomponent Assembler
  Combine PSF/CRD of non-membrane molecules into a heterogeneous system
- Solvator
  Solvate globular protein, or generate various shapes of water box
- Solution Builder (new Quick MD Simulator)
  Setup subsequent steps for molecular dynamics simulations of globular proteins

Generating a force field for the ligand: CHARMM-GUI



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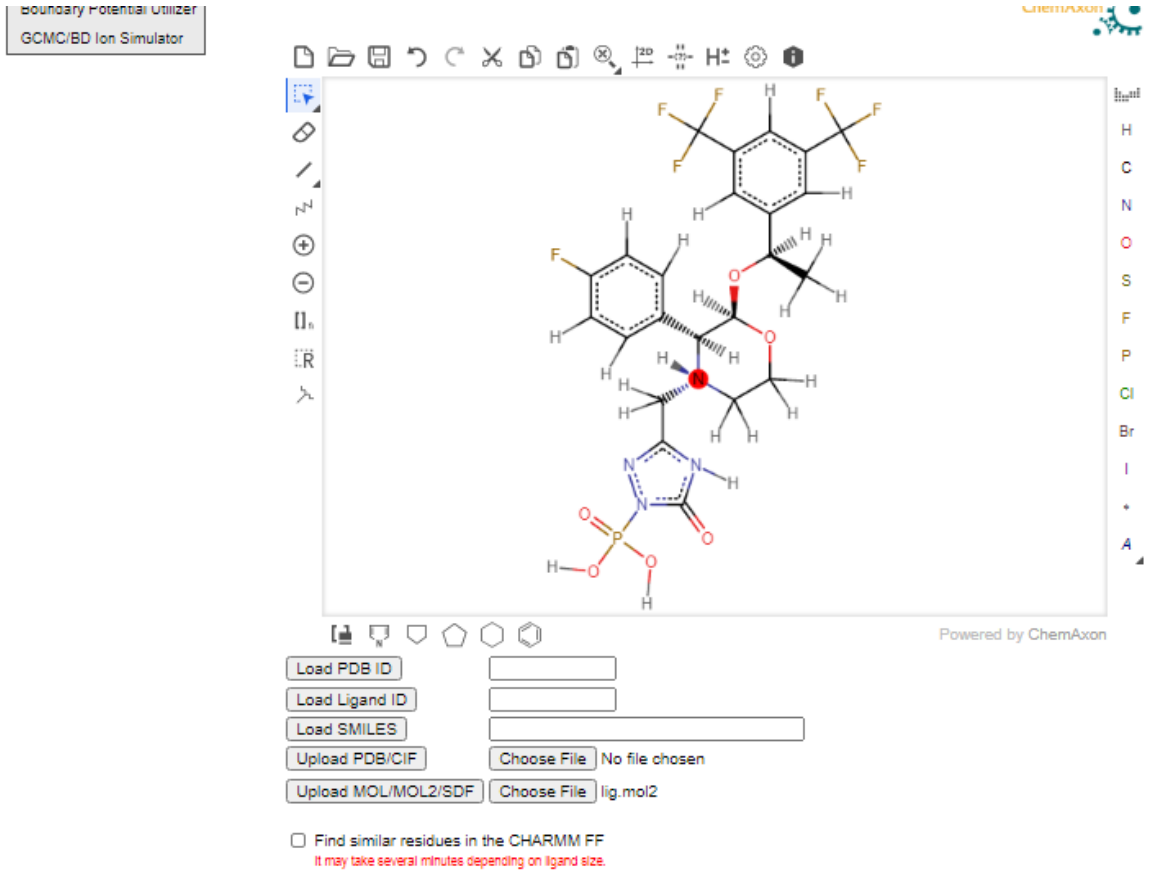
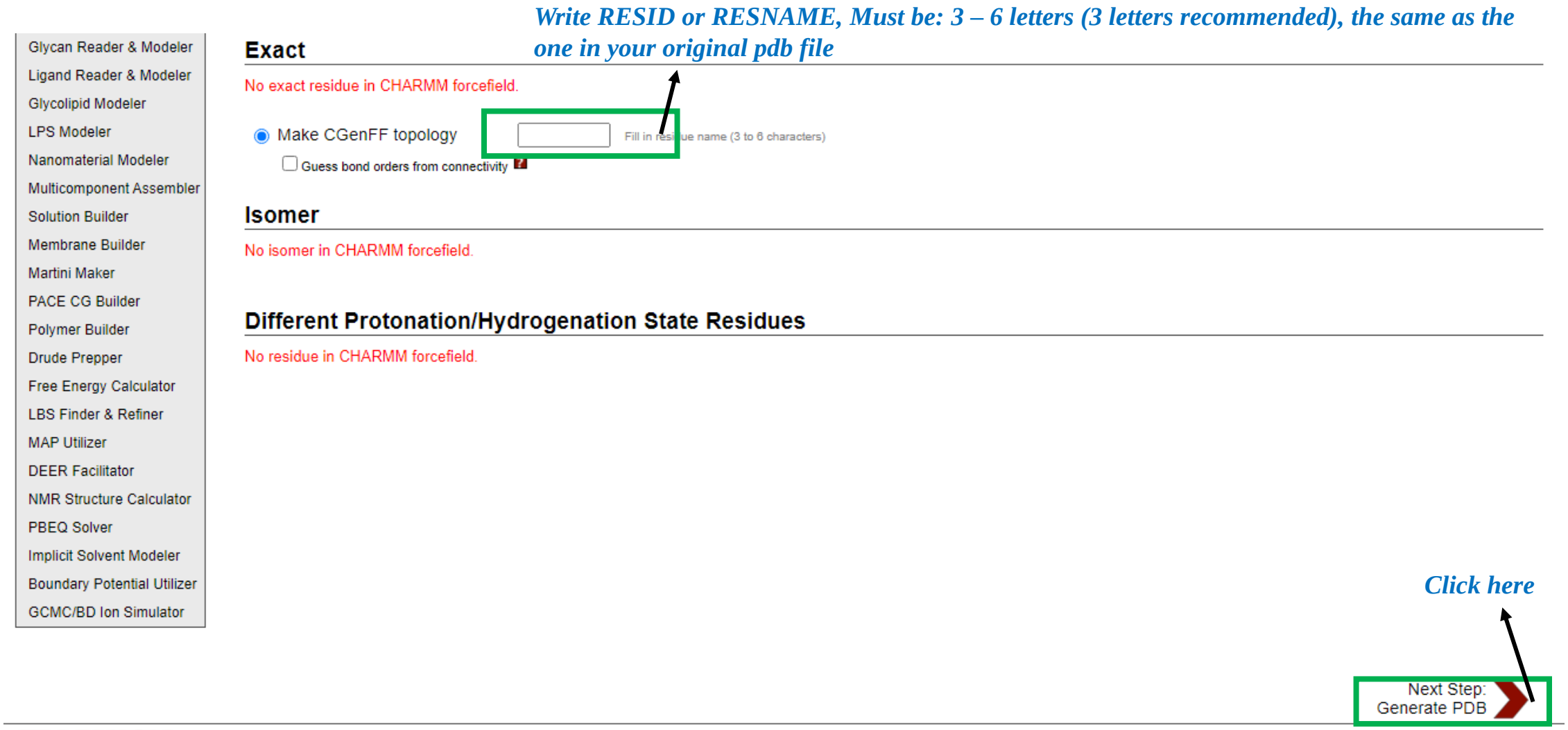


Click here

Next Step:
Search ligand

Generating a force field for the ligand: CHARMM-GUI



Generating a force field for the ligand: CHARMM-GUI

Click here

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- DEER Facilitator
- NMR Structure Calculator
- PBEQ Solver
- Implicit Solvent Modeler
- Boundary Potential Utilizer
- GCMC/BD Ion Simulator

Bookmark this link, if you want to comeback to this page

JOB ID: 1567440399

PDB Info

download.tgz

CHARMM Input: ligandrm.inp
CHARMM Output: ligandrm.out
CHARMM PDB: ligandrm.pdb (view structure)
CHARMM CRD: ligandrm.crd
CHARMM PSF: ligandrm.psf

Computed Energy:

Please beware of that the computed energy is CHARMM single-point energy and is displayed to make sure all the coordinates are defined.

```
ENER ENR:  Eval#     ENERgy      Delta-E         GRMS
ENER INTERN:          BONDs       ANGLes       UREY-b    DIHEdrals    IMPRopers
ENER EXTERN:         VDWaals         ELEC       HBONds          ASP         USER
 ----------       ---------    ---------    ---------    ---------    ---------
ENER>        0     72.40708      0.48025      0.85781
ENER INTERN>        8.71880     17.47988      8.89140     51.29718      0.00720
ENER EXTERN>       26.19974    -40.18713      0.00000      0.00000      0.00000
 ----------       ---------    ---------    ---------    ---------    ---------
```

Topology and Parameter Files:

Below is the topology and parameter files that are generated by automatic method.

LIG
Topology: lig.rtf
Topology: lig_g.rtf
Parameter: lig.prm

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We need these files

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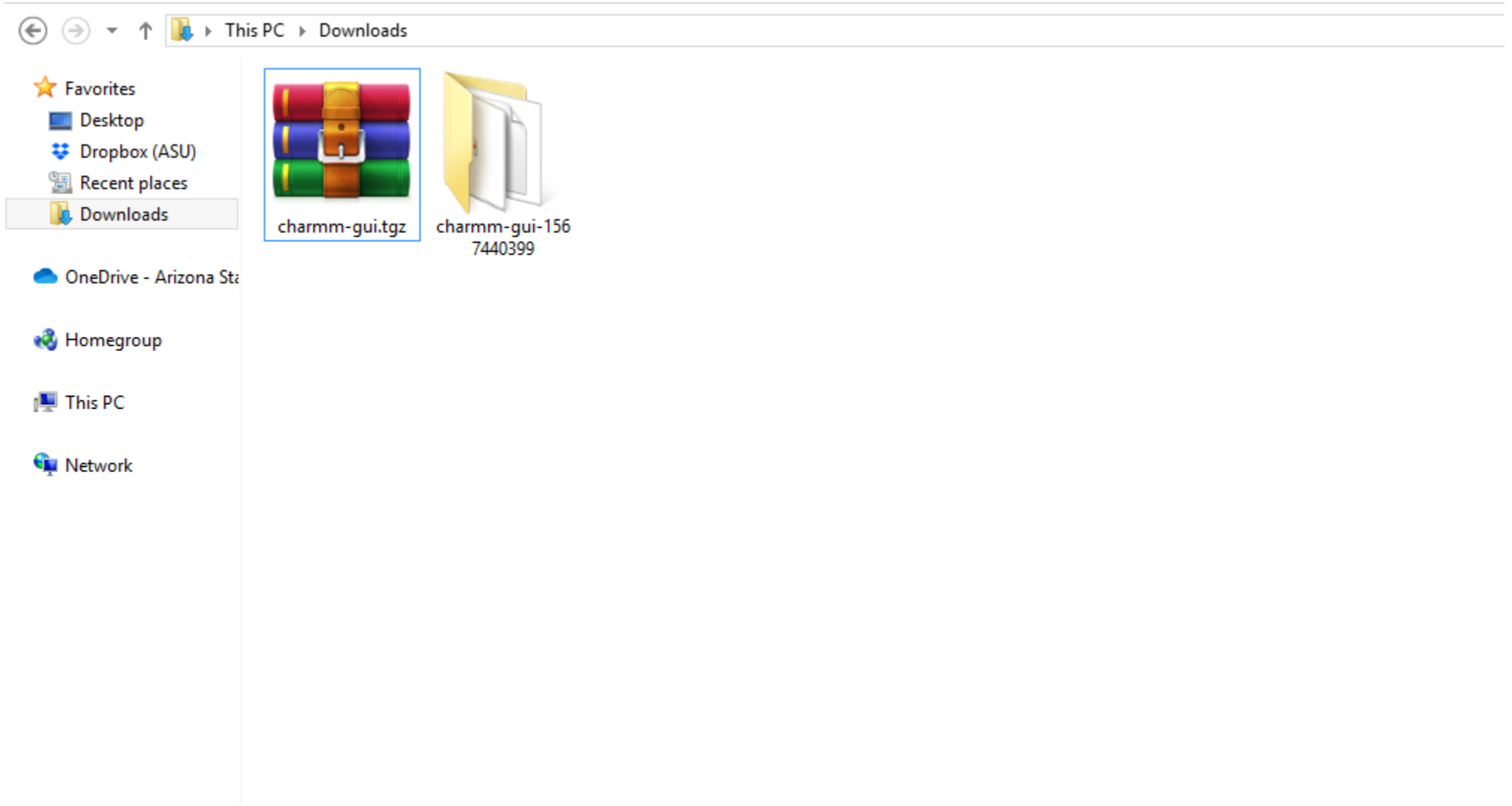

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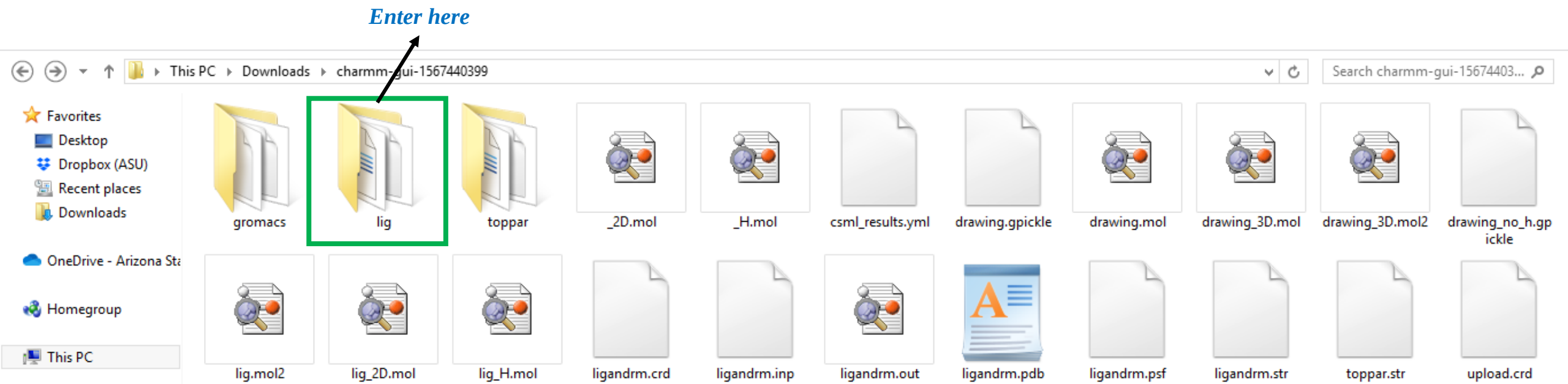
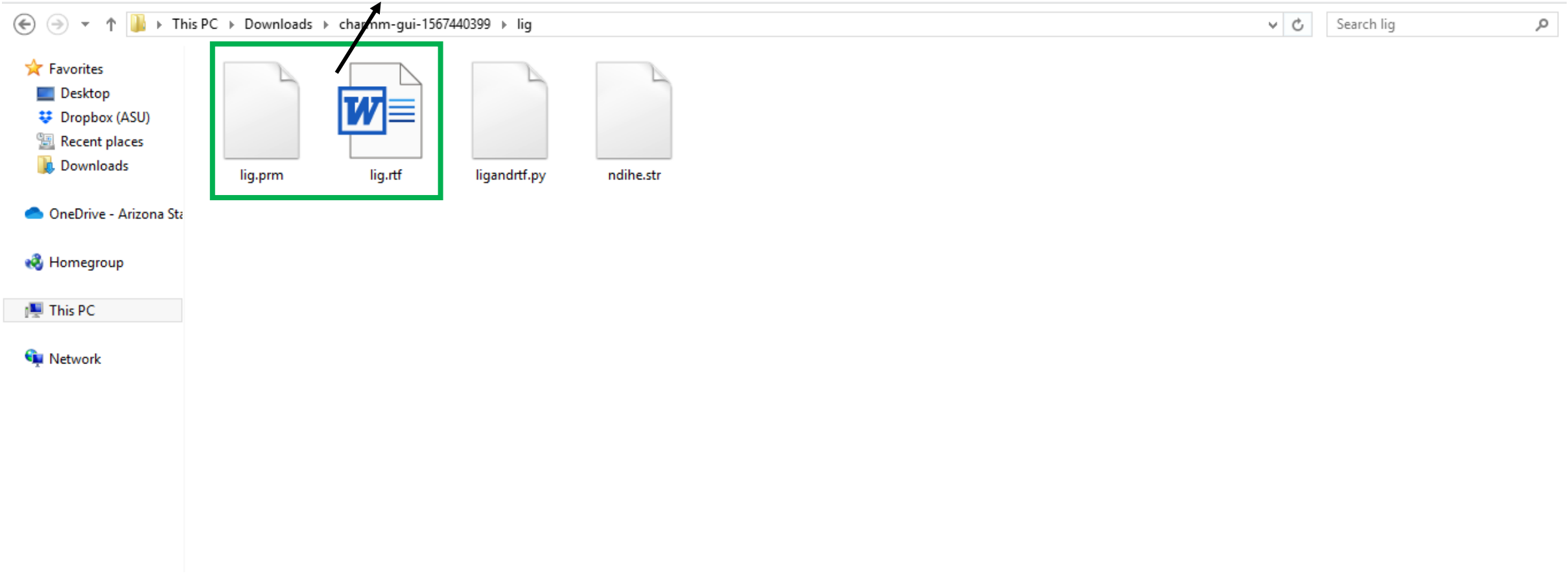
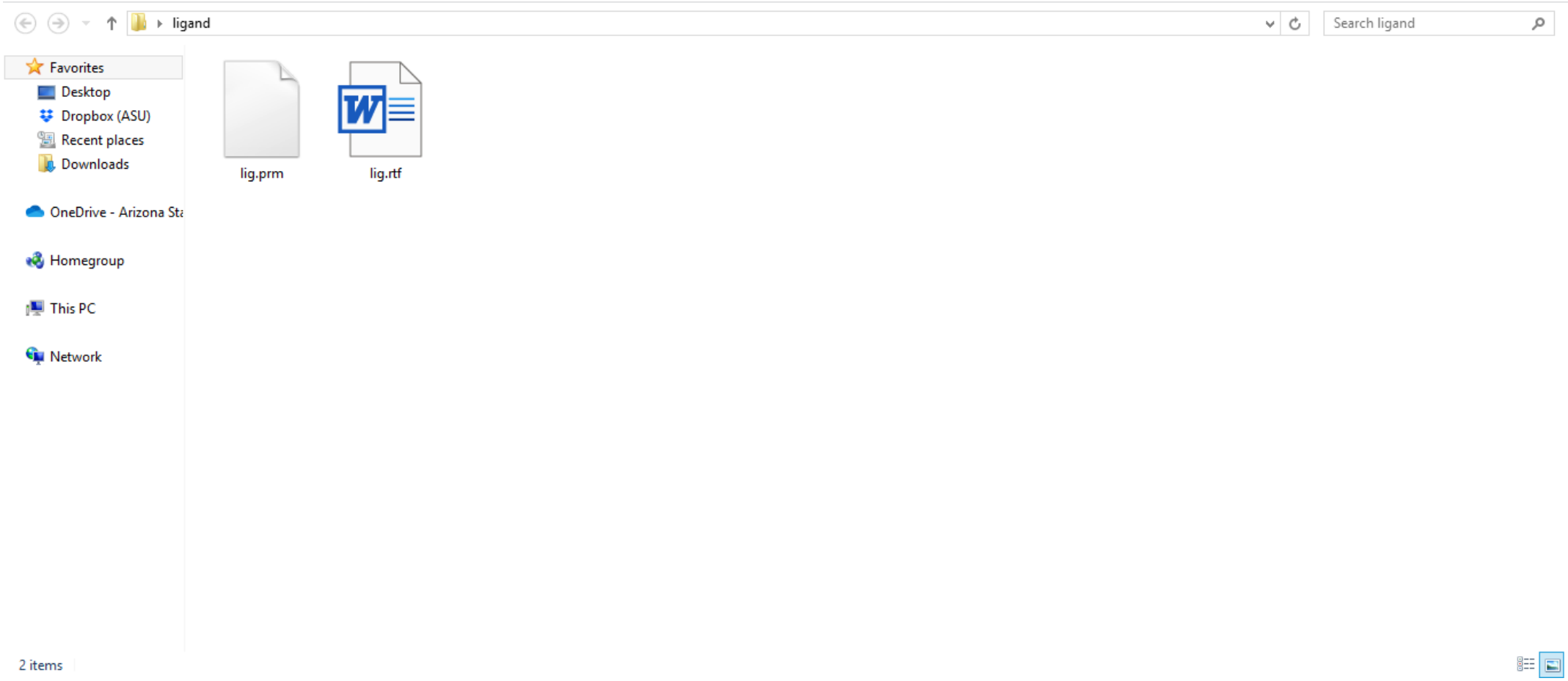


Generating a force field for the ligand: CHARMM-GUI

We want these two files

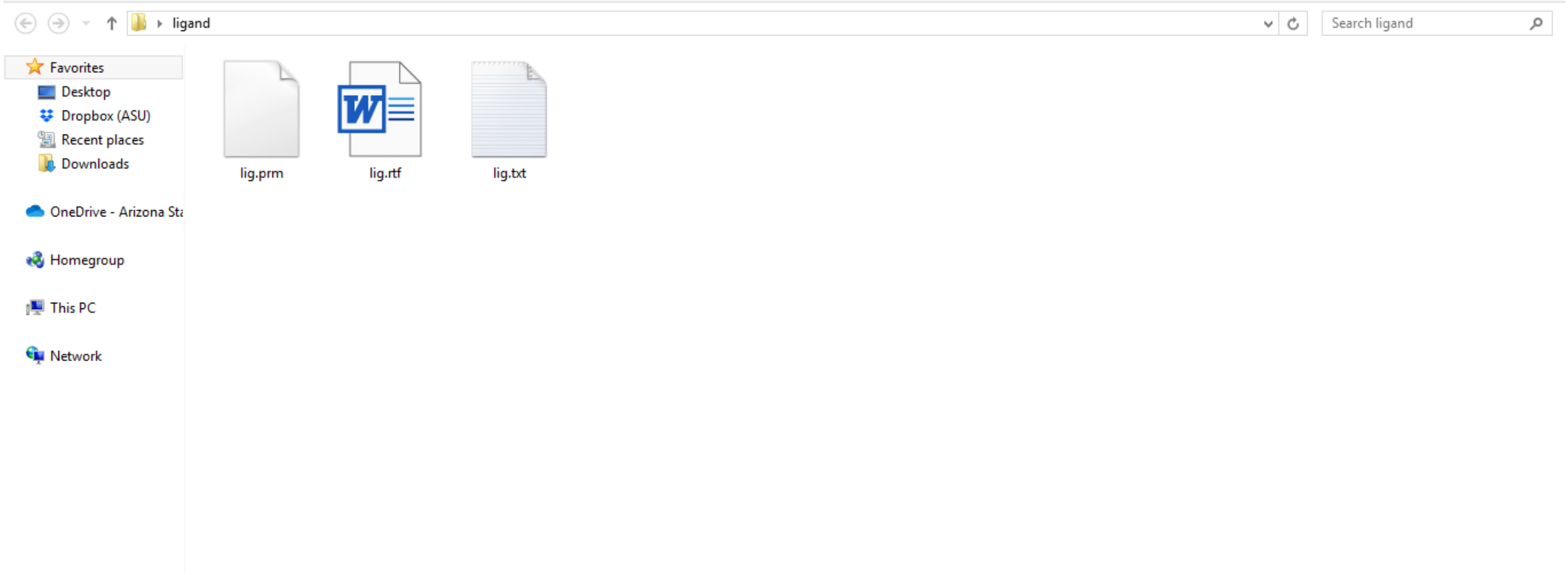


Generating a force field for the ligand: CHARMM-GUI



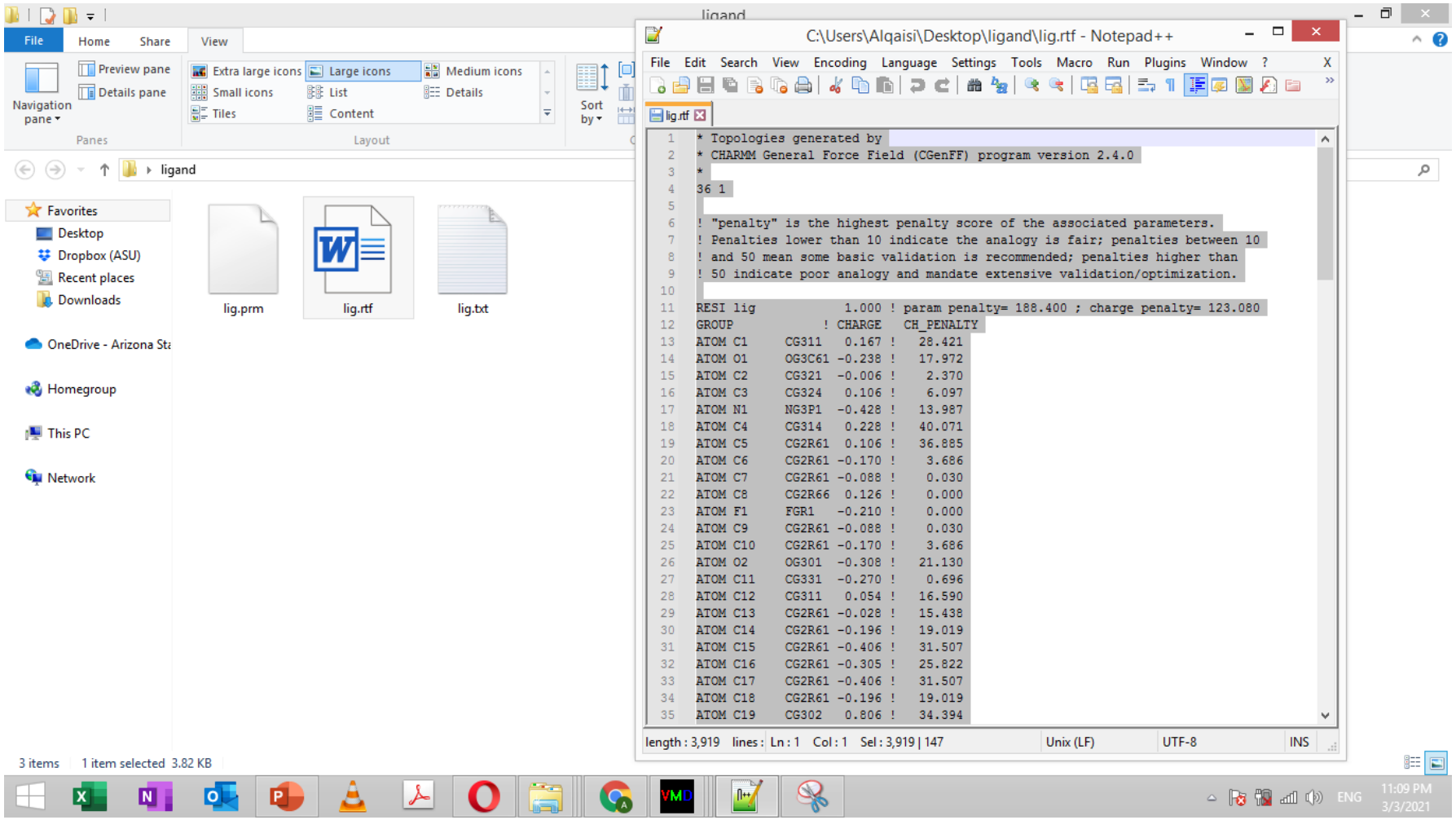
Generating a force field for the ligand: CHARMM-GUI

- Create new text file



Generating a force field for the ligand: CHARMM-GUI

- Copy the content of the lig.rtf after it lig.prm into the text file



Generating a force field for the ligand: CHARMM-GUI

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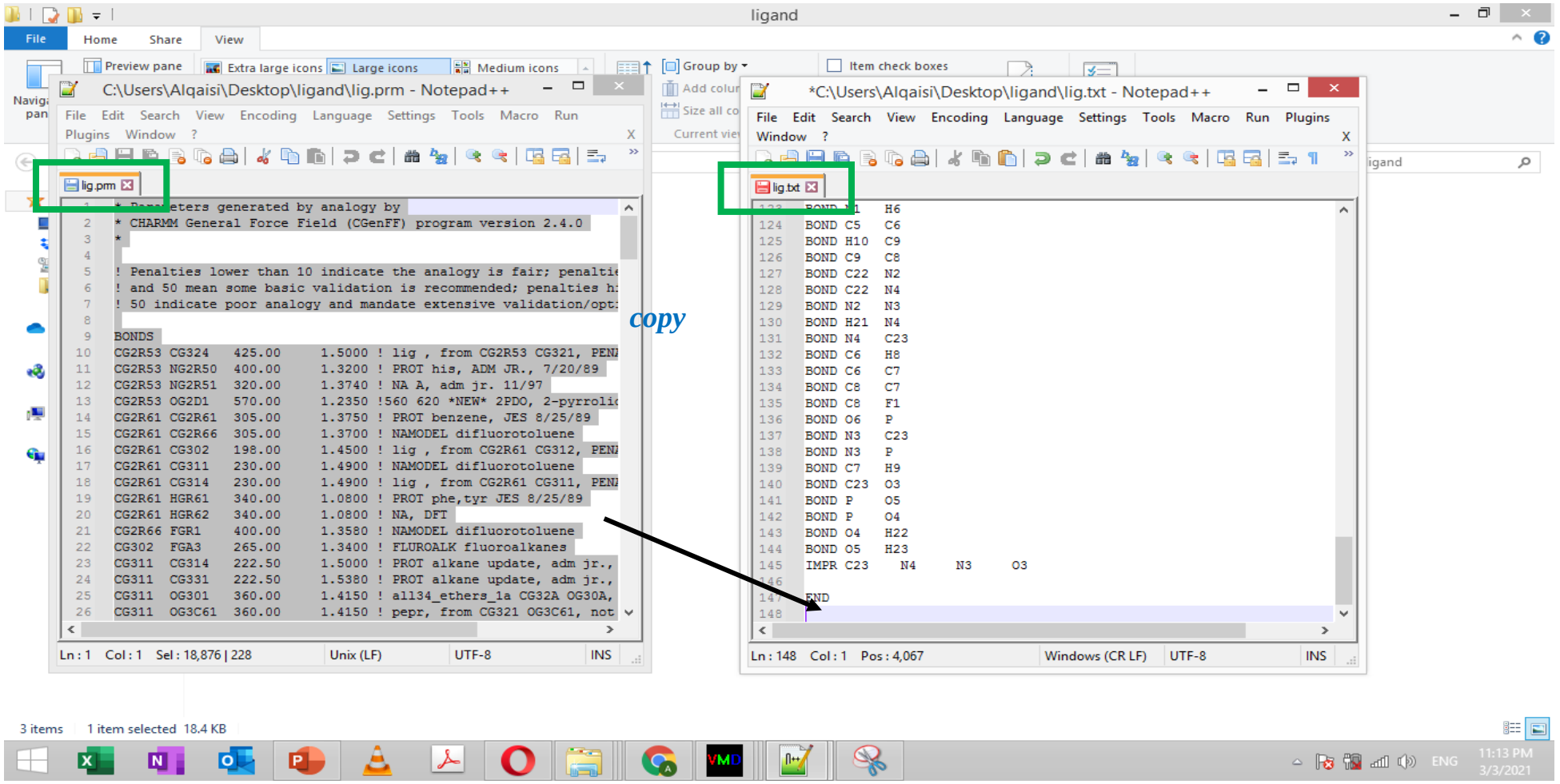

Generating a force field for the ligand: CHARMM-GUI

- Add these two lines into the text file, in there certain places
- ***"read rtf card append"*** *before the line 36.1*
- ***"read param card flex append"*** *after the first END word*

```
* Toppar stream file generated by
* CHARMM General Force Field (CGenFF) program version 2.4.0
* For use with CGenFF version 4.4
*

read rtf card append
* Topologies generated by
* CHARMM General Force Field (CGenFF) program version 2.4.0
*
36 1

! "penalty" is the highest penalty score of the associated parameters.
! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

RESI lig          1.000 ! param penalty= 188.400 ; charge penalty= 123.080
GROUP            ! CHARGE   CH_PENALTY
ATOM C1     CG311   0.167 !   28.421
ATOM O1     OG3C61 -0.238 !   17.972
ATOM C2     CG321  -0.006 !    2.370
ATOM C3     CG324   0.106 !    6.097
ATOM N1     NG3P1  -0.428 !   13.987
ATOM C4     CG314   0.228 !   40.071
```

```
BOND C7   H9
BOND C23  O3
BOND P    O5
BOND P    O4
BOND O4   H22
BOND O5   H23
IMPR C23    N4     N3     O3

END

read param card flex append
* Parameters generated by analogy by
* CHARMM General Force Field (CGenFF) program version 2.4.0
*

! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

BONDS
CG2R53 CG324   425.00     1.5000 ! ***** , from CG2R53 CG321, penalty= 1
CG2R61 CG302   198.00     1.4500 ! ***** , from CG2R61 CG312, penalty= 6
CG2R61 CG314   230.00     1.4900 ! ***** , from CG2R61 CG311, penalty= 1
CG314  NG3P1   200.00     1.4800 ! ***** , from CG324 NG3P1, penalty= 4
NG2R51 PG0     180.00     1.7920 ! ***** , from NG2S3 PG1, penalty= 70
```

Generating a force field for the ligand: CHARMM-GUI

- Change the RESI to CAPITAL LETTERS

```
* CHARMM General Force Field (CGenFF) program version 2.4.0
* For use with CGenFF version 4.4
*

read rtf card append
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ATOM C5     CG2R61  0.106 !   36.885
ATOM C6     CG2R61 -0.170 !    3.686
ATOM C7     CG2R61 -0.088 !    0.030
ATOM C8     CG2R66  0.126 !    0.000
```
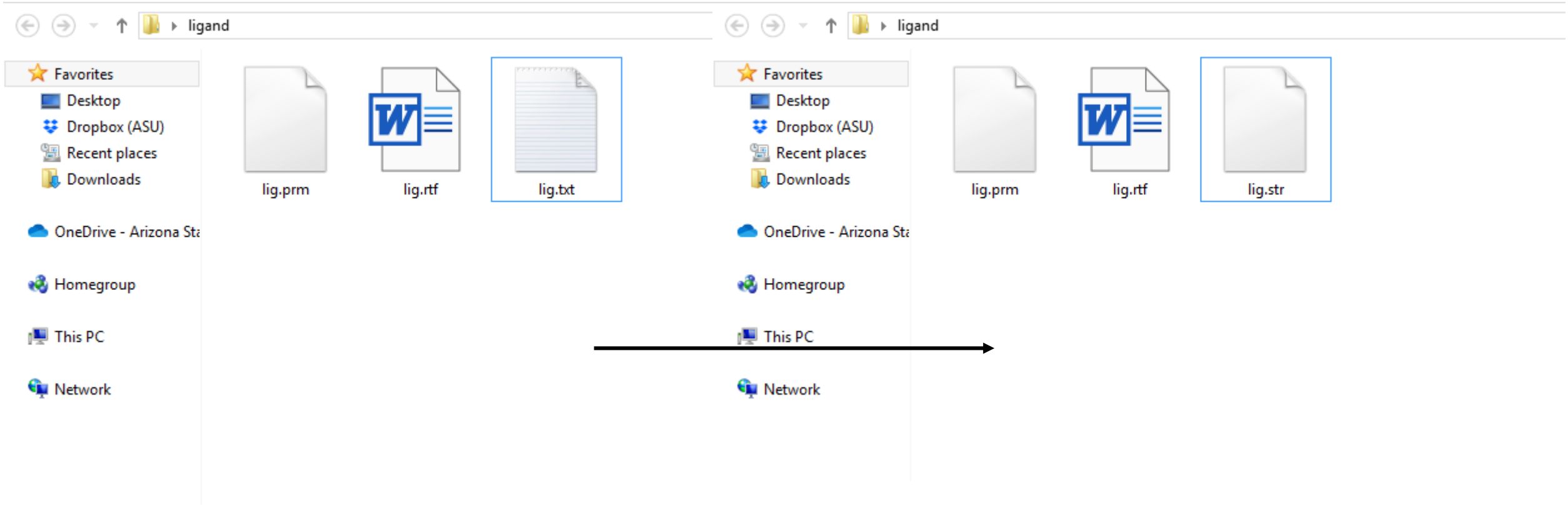
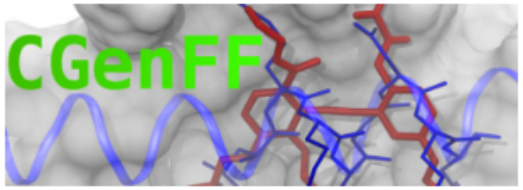

Generating a force field for the ligand: CHARMM-GUI

- Save file
- Change file extension to *.str*



Generating a force field for the ligand: CGenFF



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Welcome to CGenFF

The CHARMM General Force Field (CGenFF) program performs atom typing and assignment of parameters and charges by analogy in a fully automated fashion. Atom typing is done by a deterministic programmable decision tree. Assignment of bonded parameters is based on substituting atom types in the definition of the desired parameter. A penalty is associated with every substitution and the existing parameter with the lowest total penalty is chosen as an approximation for the desired parameter; the "penalty score" is returned to the user as a measure for the accuracy of the approximation. Charges are assigned using an extended bond-charge increment scheme that is able to capture short- and medium-range inductive and mesomeric effects.

The CGenFF program is a product of the discontinued ParamChem project. Future directions for the CGenFF program can be found at the future prospects page.

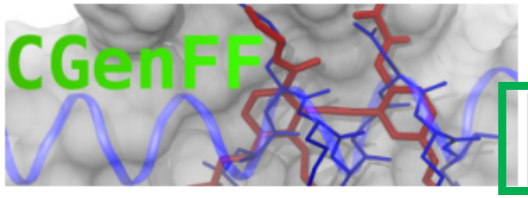
CGenFF *program* links

- Usage information.
- Summary of output data and its utilization (**required** reading).
- FAQ (read this before contacting us with questions).
- How to cite / references.

CGenFF *force field* links

- Latest CGenFF version (**required** for using the output of the CGenFF program).
- Introduction.
- FAQ.
- Parameter optimization tutorial
- How to cite / references.

Generating a force field for the ligand: CGenFF



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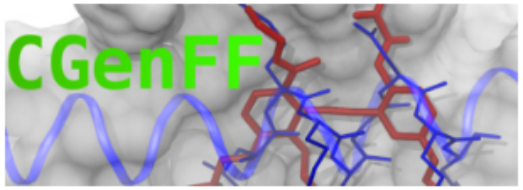
Generating a force field for the ligand: CGenFF



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Generating a force field for the ligand: CGenFF

Upload Molecule

THIS SITE IS VERIFIED TO WORK WITH FIREFOX 17 AND NEWER, CHROME 23 AND NEWER, AND INTERNET EXPLORER 10 AND NEWER. INTERNET EXPLORER 9 AND OLDER ARE KNOWN NOT TO WORK.

RESTRICTIONS

Please upload your molecule in mol2 format. It is important that all hydrogens are present, in **the correct protonation and tautomeric states**, and that the **bond orders** are correct. The xyz coordinates are not critical. The maximum number of atoms is 384, and there is a limit of 100 molecules per user per week.

Important notes:

** CGenFF should **NOT** be used for biological macromolecules! Only use CGenFF for small organic molecules; the highly optimized CHARMM force field for **Proteins, Nucleic Acids, Carbohydrates and Lipids** can be downloaded freely from the CHARMM Force Field page and can readily be combined with CGenFF.

** Apart from the mol2 format, it is also possible to upload files in pdb format. Such files are internally converted to mol2 using Open Babel 2.3.0. However, we cannot guarantee the correctness of this conversion; therefore, it is highly recommended to download the intermediary mol2 file and carefully inspect its connectivity and bond orders for errors.

** For more info, see the summary of output data and its utilization, the usage information for the CGenFF program and the FAQ.

Total number of files uploaded: 10 of 150 for the week ending March 14, 2021

Filename:

Choose File No file chosen

Click here, to choose the .mol2 file

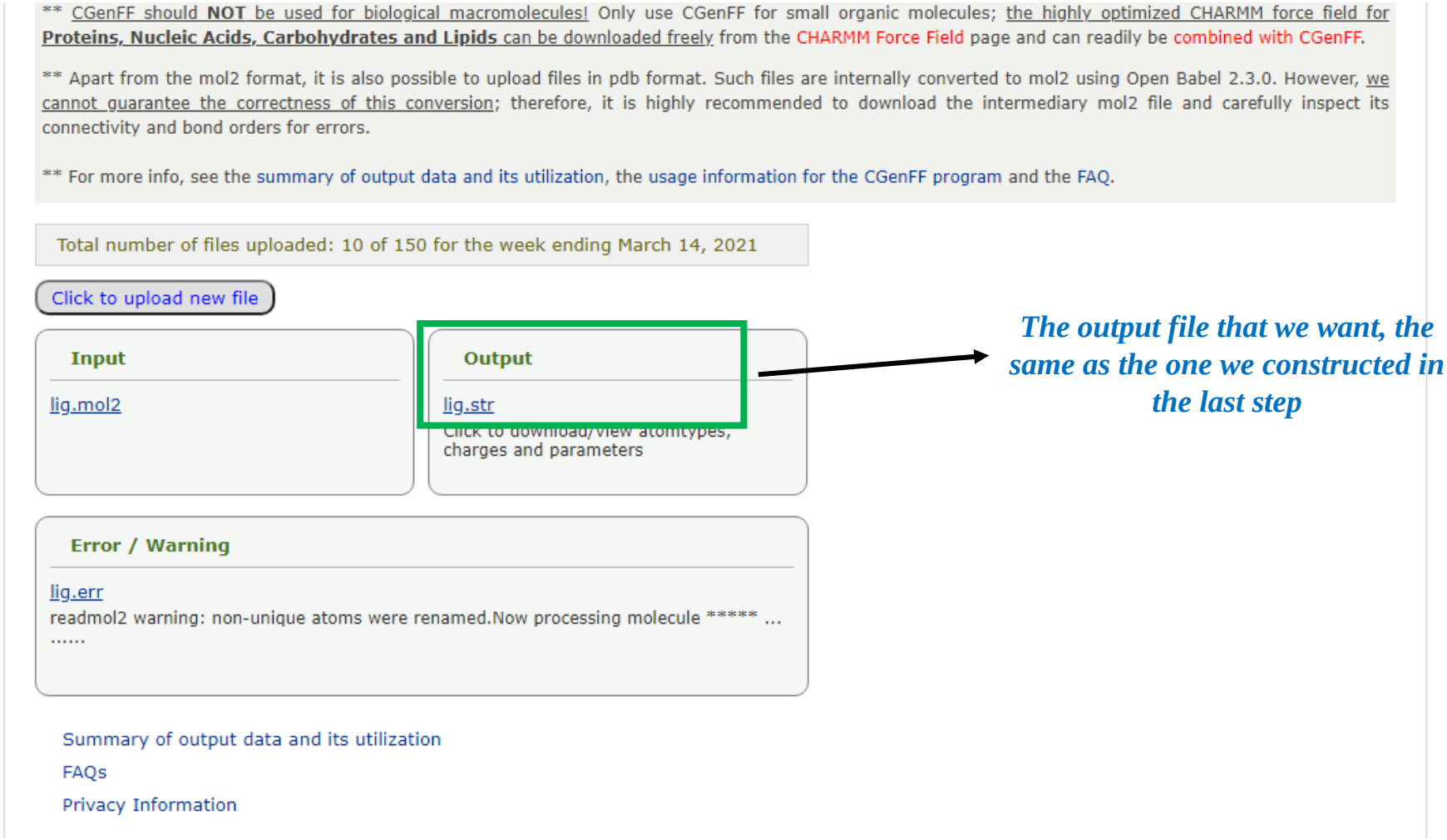
Note: Please click on the Upload File button to obtain your .str file

- [ ] Guess bond orders from connectivity
- [ ] Include parameters that are already in CGenFF
- [ ] Use CGenFF legacy v1.0

Upload File

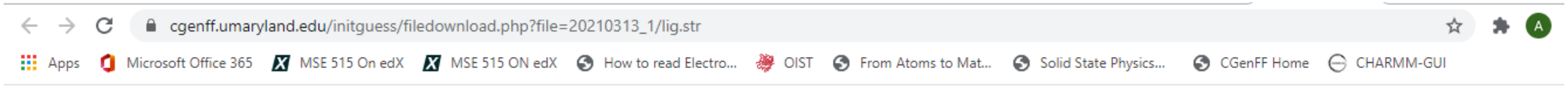
Click here, to generate the force field file

Generating a force field for the ligand: CGenFF



The output file that we want, the same as the one we constructed in the last step

Generating a force field for the ligand: CGenFF



No RESID

```
* Toppar stream file generated by
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read rtf card append
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ATOM C7     CG2R61 -0.088 !    0.030
ATOM C8     CG2R66  0.126 !    0.000
ATOM F1     FGR1   -0.210 !    0.000
ATOM C9     CG2R61 -0.088 !    0.030
ATOM C10    CG2R61 -0.170 !    3.686
ATOM O2     OG301  -0.308 !   21.130
ATOM C11    CG331  -0.270 !    0.696
ATOM C12    CG311   0.054 !   16.590
ATOM C13    CG2R61 -0.028 !   15.438
ATOM C14    CG2R61 -0.196 !   19.019
ATOM C15    CG2R61 -0.406 !   31.507
ATOM C16    CG2R61 -0.305 !   25.822
ATOM C17    CG2R61 -0.406 !   31.507
ATOM C18    CG2R61 -0.196 !   19.019
```
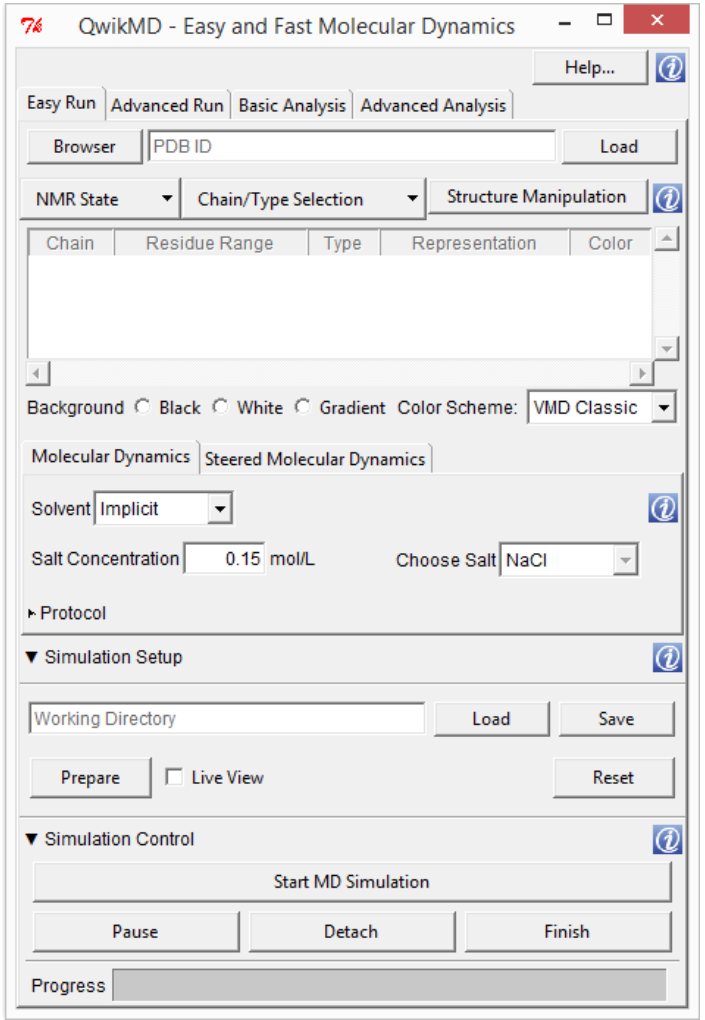
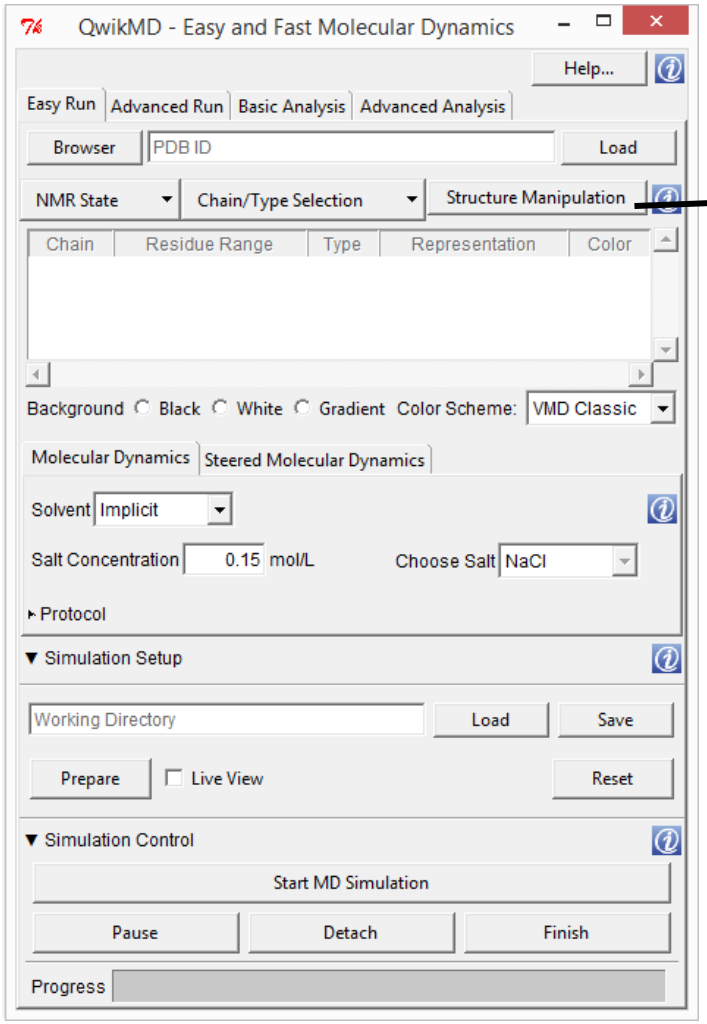

Protein-Ligand Simulation

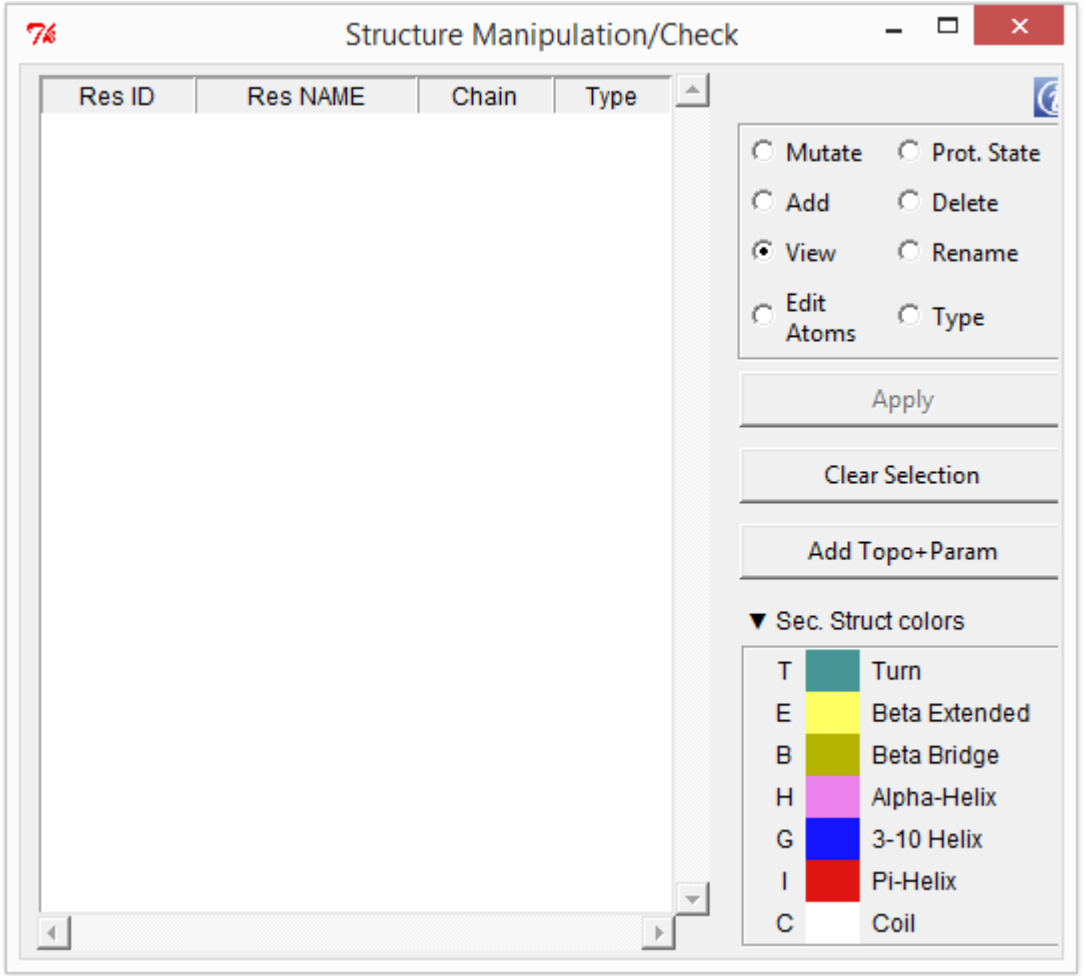
- Now we return and open QwikMD in VMD program



Protein-Ligand Simulation

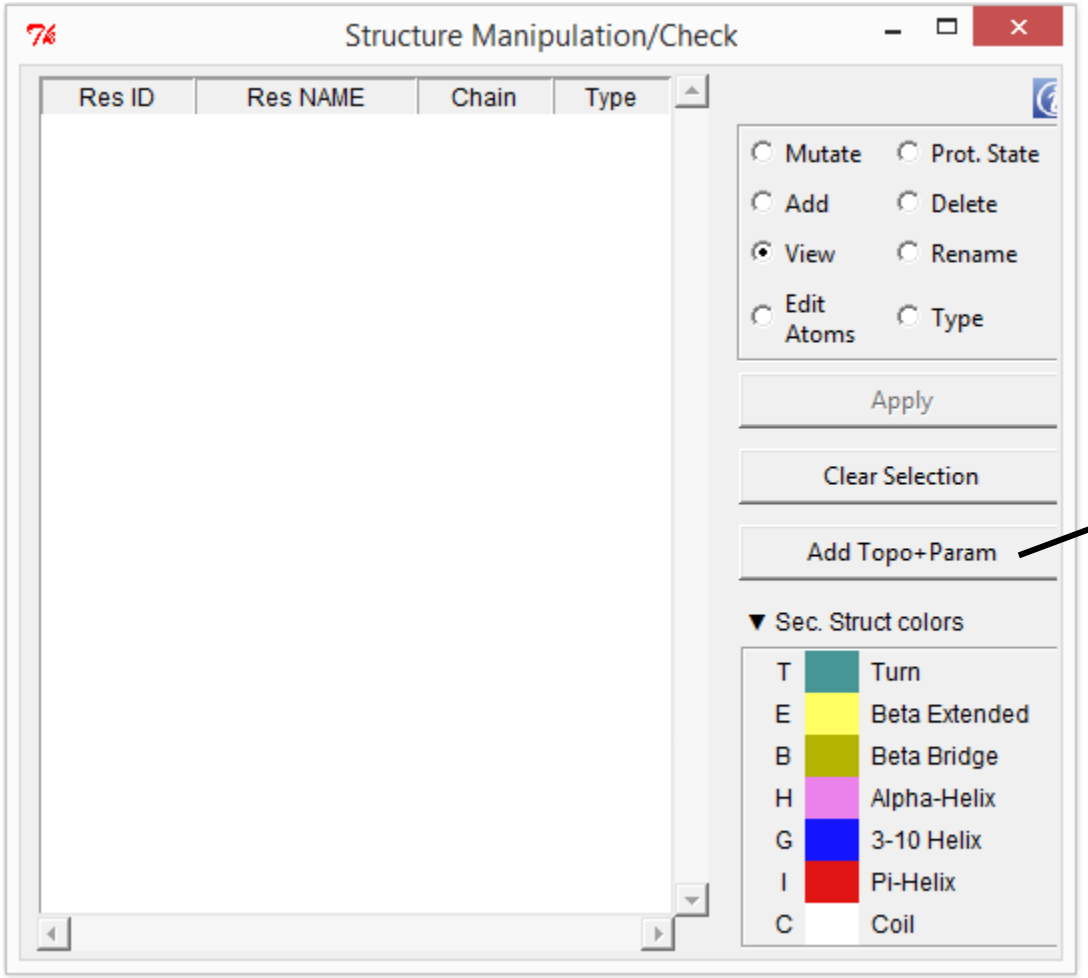
- Open *Structure Manipulation* > Add *Topo+Param*

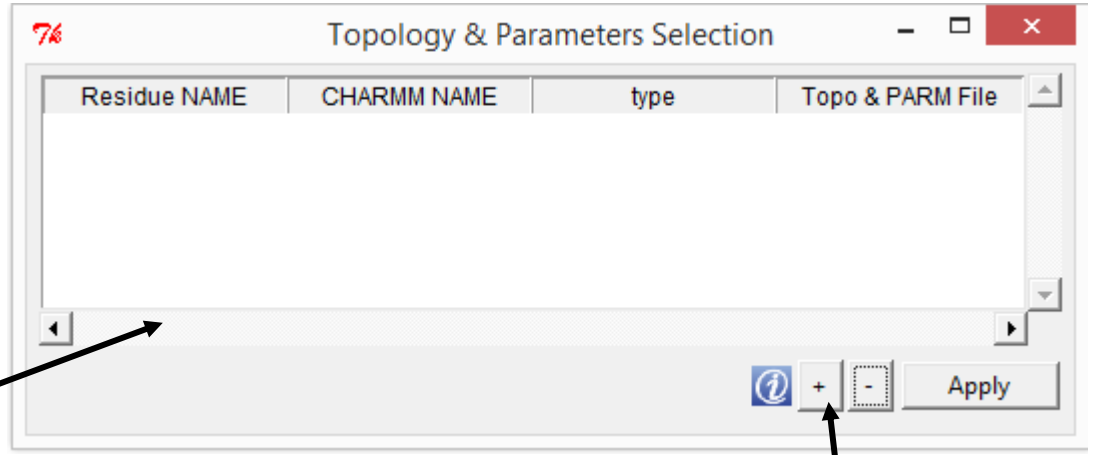




Protein-Ligand Simulation

- Open *Structure Manipulation* > Add *Topo+Param*

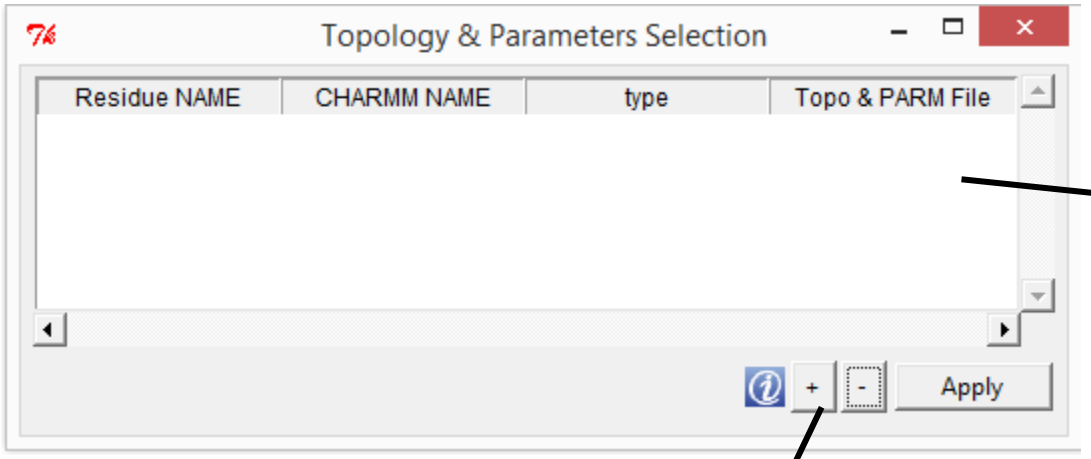




Click here to add the force field file

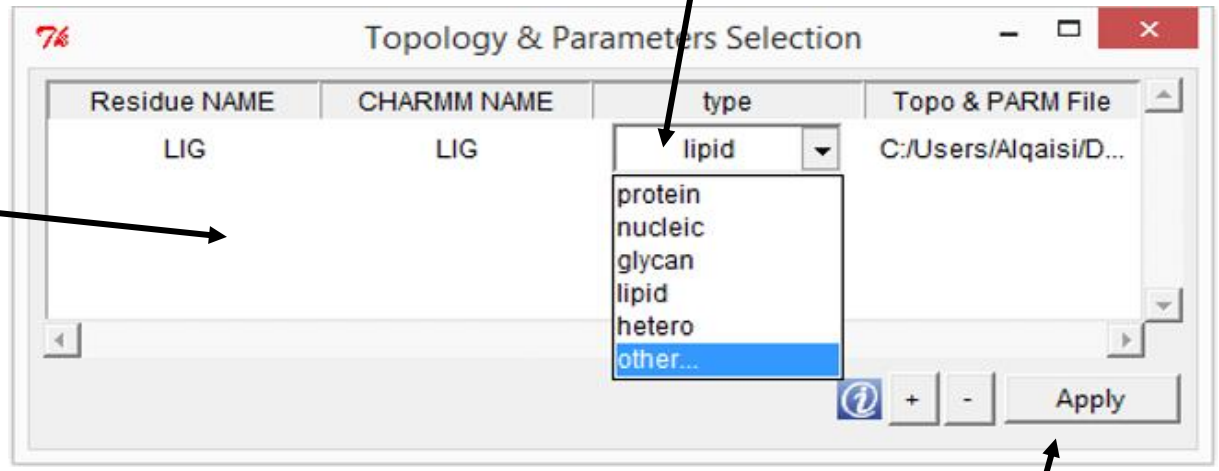
Protein-Ligand Simulation

- Open *Structure Manipulation* > Add *Topo+Param*



Click here to add the force field file

Choose then type of structure that you are adding



Click here to apply

Protein-Ligand Simulation