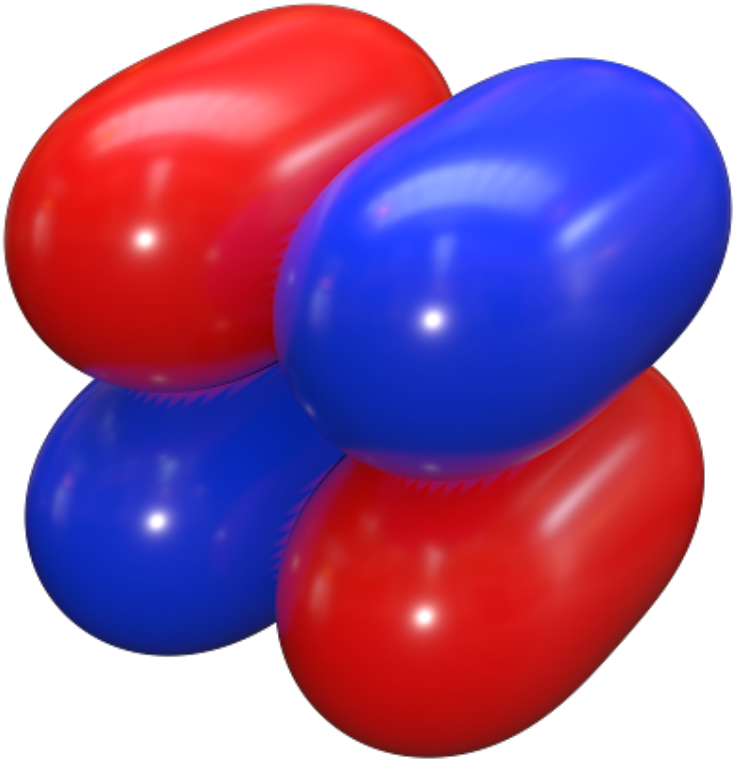
Sakura Science Computational Chemistry Workshop Series:

Non-Covalent Interaction for Polymers

February 11, 2025



1 Introduction

In this workshop, we will learn more about the fundamental aspect of non-covalent interactions (NCI) between polymer and smaller organic molecules. Due to a long polymer chain, the NCI between polymer and any molecules has a larger degree of freedom. As a result, a simple geometry optimization to find the global minimum will never work. Therefore, in the present workshop, we utilize the conformer-rotamer ensemble sampling tool (CREST) to search for the global minimum of the non-covalent interactions. The conformer sampling will be performed by employing the general force field developed based on the quantum mechanical method, namely, the GFN-FF[1]. Herein, GFN stands for geometry, frequency, and non-covalent interactions. The force field was developed by Stefan Grimme as an extension of his work in developing the semi-empirical extended tight-binding (xTB) methods[2]. The GFN-FF method is not only quick but also has been claimed as the most flexible non-reactive force field that has a high accuracy in describing the non-covalent interaction. However, it is highly recommended that in a more comprehensive research, the GFN1-xTB, GFN2-xTB, or even the extension to the density-functional theory (DFT) levels are necessary. Our work utilized CREST for searching for capsanthin-based organic molecules at GFN2-xTB level and further extended in the DFT as well as TD-DFT calculations[3].

The current workshop is structured as follows:

- Performing a **short quantum mechanical docking** between two adopted molecules. In this short docking, the intention is guessing the initial interaction between two molecules. It is a better approach than initializing the molecules at a faraway distance. The docking will be performed by using the computational molecular and material design environment (CMMDE) program that interfaces ORCA 6 code. Therefore, in other words, we will perform the docking by using the new ORCA 6 feature. More details on this new feature will be discussed in the last session of our workshop series as an advanced computational method.

- **Conformation sampling** of the interacting molecules by using CREST at GFN-FF level. In this case, we will be taking the last frame of docking trajectories by simply downloading the last optimized structures from the docking simulation. Note that in this case, you will need to kill your docking simulation beforehand.

- **Classifying the type of molecular interactions** via the reduced density gradient (RDG) calculations along the second eigenvalue of the density matrix ($sign(\lambda_2)$). In this case, we will use an approach developed in the previous works[4, 5]. It is highly recommended to learn more from their works since the interpretation of the obtained results will depend on the understanding of the density matrices and molecular interactions. This procedure will be facilitated by the CMMDE program. Thus, the user just needs to provide the atomic coordinates of the best conformation obtained from CREST.

2 Quantum Mechanical Docking between Two Molecules

1. Open the Termius application and access the workstation with the following details:

```
Address: catalyst.compscience.app
User: ssc
Password: sakura
```

2. Upon a successful login, make your personal directory by typing:

```
mkdir yourname; cd yourname
```

   replace `yourname` by your own name. Note that you should skip this step if you had created your directory in the previous workshop session.

3. Make the docking directory by typing:

```
mkdir Day2/docking -p
```

   Enter to the docking directory by typing:

```
cd Day2/docking
```

4. Copy the necessary molecules from the main workshop material directory,

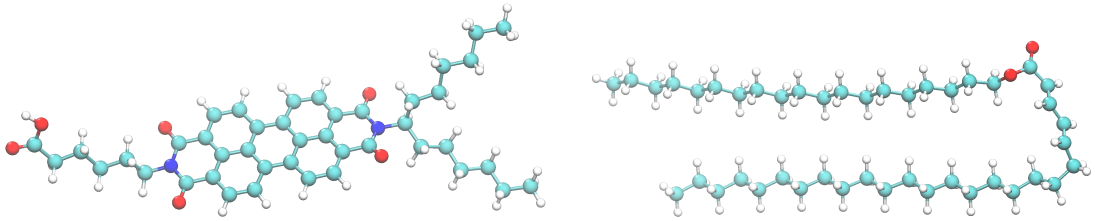
```
cp /home/ssc/SSC_Workshop/Day2/dock1/XTB2/TDA1.xyz .
```

```
cp /home/ssc/SSC_Workshop/Day2/dock1/XTB2/C5_Pe.xyz .
```

   You can also download the `TDA1.xyz` and `C5_Pe.xyz` structures to your computer by opening the **SFTP** window of the Termius and simply dragging those xyz files to the left column of the SFTP window. View your structure by using the VMD or Avogadro program, the structures are shown in Figs. 1(a) and (b).

5. Performing a docking simulation by typing:

```
cmmde.py -j docker -i C5_Pe.xyz -guest TDA1.xyz -np 8
```



(a) (b)

Figure 1: Adopted molecules in the present workshop, namely, (a) asphaltene and (b) a polymer.

In this case, you are using 8 CPUs to perform the docking simulation between the asphaltene (`C5_Pe.xyz`) and a polymer model (`TDA1.xyz`). The `-j docker` option is used to define that you are performing the docking simulation by using the ORCA 6 program. Always take a note on your job ID as it appears on your screen upon typing the above command.

6. Check your simulation gradually by typing:

```
squeue
```

The ST column shows the status of your job submission. The values should be **R** or **PD**, which indicates running and pending, respectively.

7. After ensuring that you have the **R** status and it has been approximately 3 minutes since then, you can kill your simulation by typing:

```
scancel YourJobID
```

Replace `YourJobID` by your job ID. It is why you will need your job ID; thus, as previously mentioned, do not forget to take note of it. Even in your real research, it is not necessary to wait for the normal termination of this docking.

8. Download (by using SFTP) the resulted docked molecule. Since it is an ongoing simulation, the filename will vary depending on when you kill it. However, the filename should be something like:

```
cmmd.docker.struct1.ev4_trj.xyz
```

The `ev4` in the filename denotes the number of docking poses search has been performed. Since you perhaps kill with different timing than this tutorial, you may have different filename. It can be `ev1`, `ev2`, `ev3`, etc. Visualize your structure by using VMD or other software. The docked structure is shown in Fig. 2.

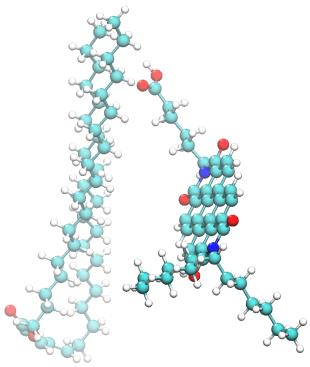


Figure 2: The docked asphaltene-polymer complex obtained from the preliminary quantum mechanical docking at GFN2-XTB level.

3 Non-Covalent Interaction Sampling from Metadynamics Simulations

1. Assuming that you took a note of your docked structure filename and you are still inside the **Docking** directory, create the **NCI** directory by typing:

```
cd ../;mkdir NCI; cd NCI
```

2. Copy the previous docked structure and rename it as `geom.xyz` by typing:

```
cp ../Docking/cmmd.docker.struc1.ev4.xyz geom.xyz
```

3. Copy the running CREST running script from the workshop source directory:

```
cp /home/ssc/SSC_Workshop/Day2/nci_quick/run.sh .
```

Note that even though it is said therein as `nci_quick`, in fact, it is not quick at all. It maybe the quickest that we can get for this approach. You may see the `run.sh` script for a more detailed CREST setup that we will perform, by typing:

```
less run.sh
```

The following content will appear on your screen:

```
#!/bin/bash
```

```
#SBATCH --nodes=1
#SBATCH --ntasks=1
#SBATCH --cpus-per-task=1
#SBATCH --time=168:0:0
#SBATCH --job-name=nci_quick
export OMP_NUM_THREADS=8
export OMP_STACKSIZE=16G
cd $PWD
crest geom.xyz --nci --gfnff -mquick -ewin 3.0 -bconst 1.5 -cinp
```

The `--nci` option denotes that we will perform the non-covalent interaction sampling by using the CREST program. The `--gfnff` and `--mquick` options denote the GFN-FF method and very quick algorithm are employed, respectively. The `-ewin` option represents the energy window for the conformational search. In this case, we limit our conformational search to 3.0 kcal/mol. The larger value you specified leads to a more exhaustive search, and thus, you will obtain more interacted conformers. Depending on your aim, one would usually like to have only the most possible interacted conformer.

4. Submit your job by typing:

```
sbatch run.sh
```

This simulation will take about **6 to 7 hours**. Thus, once you submit the simulation, you can visit the workstation tomorrow to check and download your conformers. In this tutorial, we will discuss the obtained results.

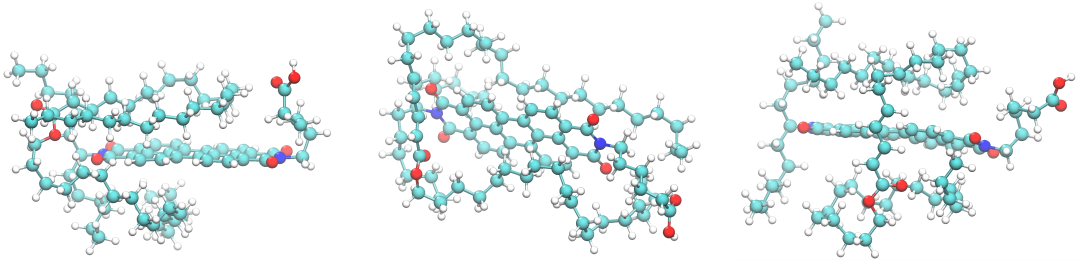
5. You can preliminarily copy the finished NCI sampling from the workshop resource directory by typing:

```
cp /home/ssc/SSC_Workshop/Day2/nci_quick/crest_conformers.xyz .
```

```
cp /home/ssc/SSC_Workshop/Day2/nci_quick/slurm-9905.out .
```

```
cp /home/ssc/SSC_Workshop/Day2/nci_quick/crest_best.xyz .
```

6. Check the `slurm-9905.out` for more detailed output and `crest_conformers.xyz` for the obtained conformers from a series of metadynamics simulations. The `crest_best.xyz` file contains the most stable conformer obtained from the NCI sampling. The example of conformers that were obtained from the NCI sampling are shown in Figs. 3 (a), (b), and (c).



Top #1 Top #2 Top #3

Figure 3: Resulted conformers from non-covalent interaction sampling at GFN-FF level.

4 Investigation of Non-Covalent Interactions via Reduced Density Gradient Approach

1. Make a new directory and enter into it by typing:

```
mkdir plot; cd plot
```

2. Copy the `crest_best.xyz` file from your previous NCI sampling simulation by typing:

```
cp ../crest_best.xyz .
```

3. Perform the 2-dimensional NCI analysis by typing:

```
cmmdepost.py -j nci2d -i crest_best.xyz -np 2
```

Herein, you are using 2 CPUs for investigating the type of non-covalent interactions. You will obtained the following files at the end of calculation:

- **crest_best-dens.cube, crest_best-grad.cube** ⇒ The electronic densities and gradients, respectively. These files can be visualized by a certain type of visualization software, such as Avogadro and VMD.
- **crest_best.vmd** ⇒ A series of vmd command line that allows you to visualize the above-mentioned cube files by using VMD.

- **crest_best.dat** ⇒ The two-columns data file that contains the RDG (denoted as s in atomic units) and $sign(\lambda_2)$. The mathematical formalism on how to obtain those values are available in the previous works[4, 5].

4. Plot the obtained `crest_best.dat` by using CMMDEPOST program.

```
cmmdepost.py -j nciplot -i crest_best.dat
```

This command will generate `nci.png` file that can be downloaded and visualized by using any image viewer. The NCI plot for the interaction between asphaltene and the adopted polymer model is shown in Fig. 4.

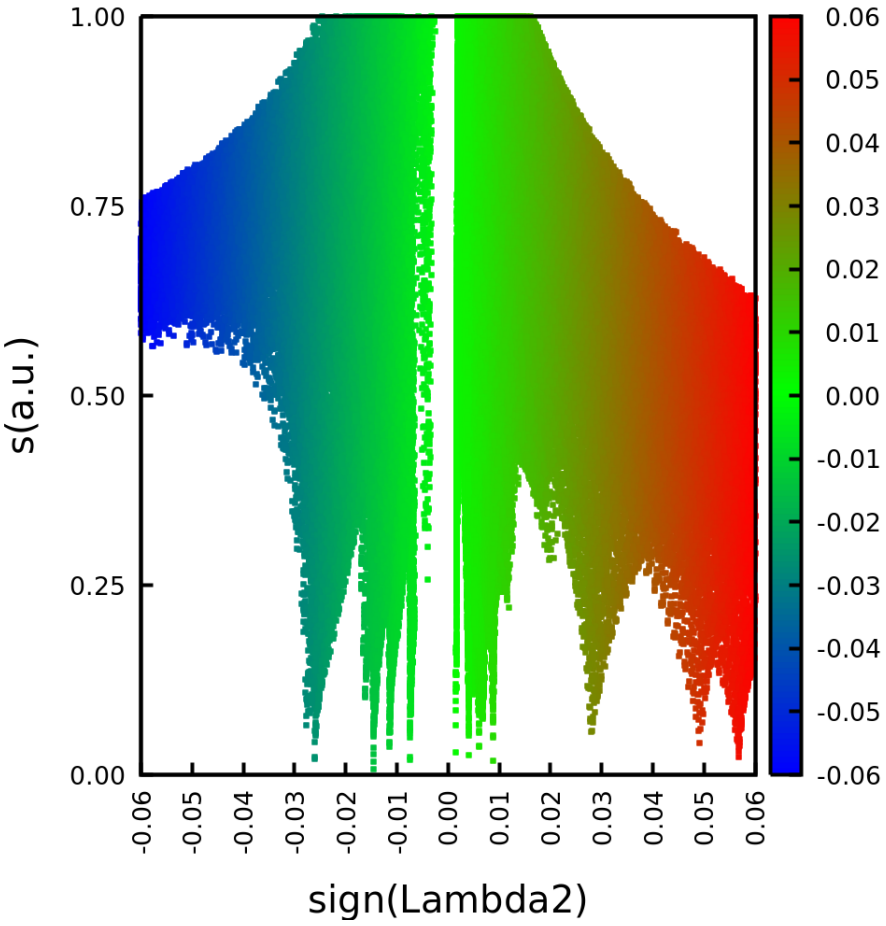


Figure 4: Plot of the reduced density gradient (s) against the $sign(\lambda_2)$ values. The blue and green colors represent the strong attractive and van der Waals interactions, respectively. On the other hand, the red color represents the steric hindrance between two interacting instances.

Further work that we can elaborate from this workshop is calculating the interaction energies between polymer and asphaltene. It will be demonstrated in the workshop, and the participants will be asked to perform themselves either during the workshop or by watching our recorded workshop video.

References

[1] Julian D. Gale et al. "A Universal Force Field for Materials, Periodic GFN-FF: Implementation and Examination". In: *Journal of Chemical Theory and Computation* 17.12 (Dec. 2021), pp. 7827–7849. ISSN: 1549-9618. DOI: 10.1021/acs.jctc.1c00832. URL: https://doi.org/10.1021/acs.jctc.1c00832 (visited on 03/14/2024).

[2] Stefan Grimme, Christoph Bannwarth, and Philip Shushkov. "A Robust and Accurate Tight-Binding Quantum Chemical Method for Structures, Vibrational Frequencies, and Noncovalent Interactions of Large Molecular Systems Parametrized for All spd-Block Elements (Z = 1–86)". In: *Journal of Chemical Theory and Computation* 13.5 (May 2017), pp. 1989–2009. ISSN: 1549-9618. DOI: 10.1021/acs.jctc.7b00118. URL: http://dx.doi.org/10.1021/acs.jctc.7b00118 (visited on 10/10/2017).

[3] Permono Adi Putro et al. "Quantum mechanical assessment on the optical properties of capsanthin conformers". en. In: *Journal of Computational Chemistry* 44.30 (2023), pp. 2319–2331. ISSN: 1096-987X. DOI: 10.1002/jcc.27199. (Visited on 02/27/2024).

[4] Rubén Laplaza et al. "NCIPLOT and the analysis of noncovalent interactions using the reduced density gradient". en. In: *WIREs Computational Molecular Science* 11.2 (2021), e1497. ISSN: 1759-0884. DOI: 10.1002/wcms.1497. URL: https://onlinelibrary.wiley.com/doi/abs/10.1002/wcms.1497 (visited on 11/15/2022).

[5] Julia Contreras-García et al. "NCIPLOT: A Program for Plotting Noncovalent Interaction Regions". In: *Journal of Chemical Theory and Computation* 7.3 (Mar. 2011), pp. 625–632. ISSN: 1549-9618. DOI: 10.1021/ct100641a. URL: https://doi.org/10.1021/ct100641a (visited on 12/04/2022).