CHEMICAL COMPUTING GROUP

Molecular Operating Environment
One fully integrated drug discovery software package

Generously supported by Chemical Computing Group, Montreal, QC, Canada, who provided teaching licences for MOE (Molecular Operating Environment) software package.

Seminar 1

Basic orientation in the environment MOE

Table 1: basic window in a graphical interface (GUI) MOE.

MOE	MOE Window , which is the primary interface window of the graphical MOE, containing the 3D rendering area.
DBV	Database Viewer , used for examining the contents of MOE databases. More than one can be open at any given time.
SEQ	Sequence Editor , which provides sequence-only view of molecules currently loaded in MOE.
SVL	SVL Commands window , in which output from applications is displayed, and where SVL commands can be entered.

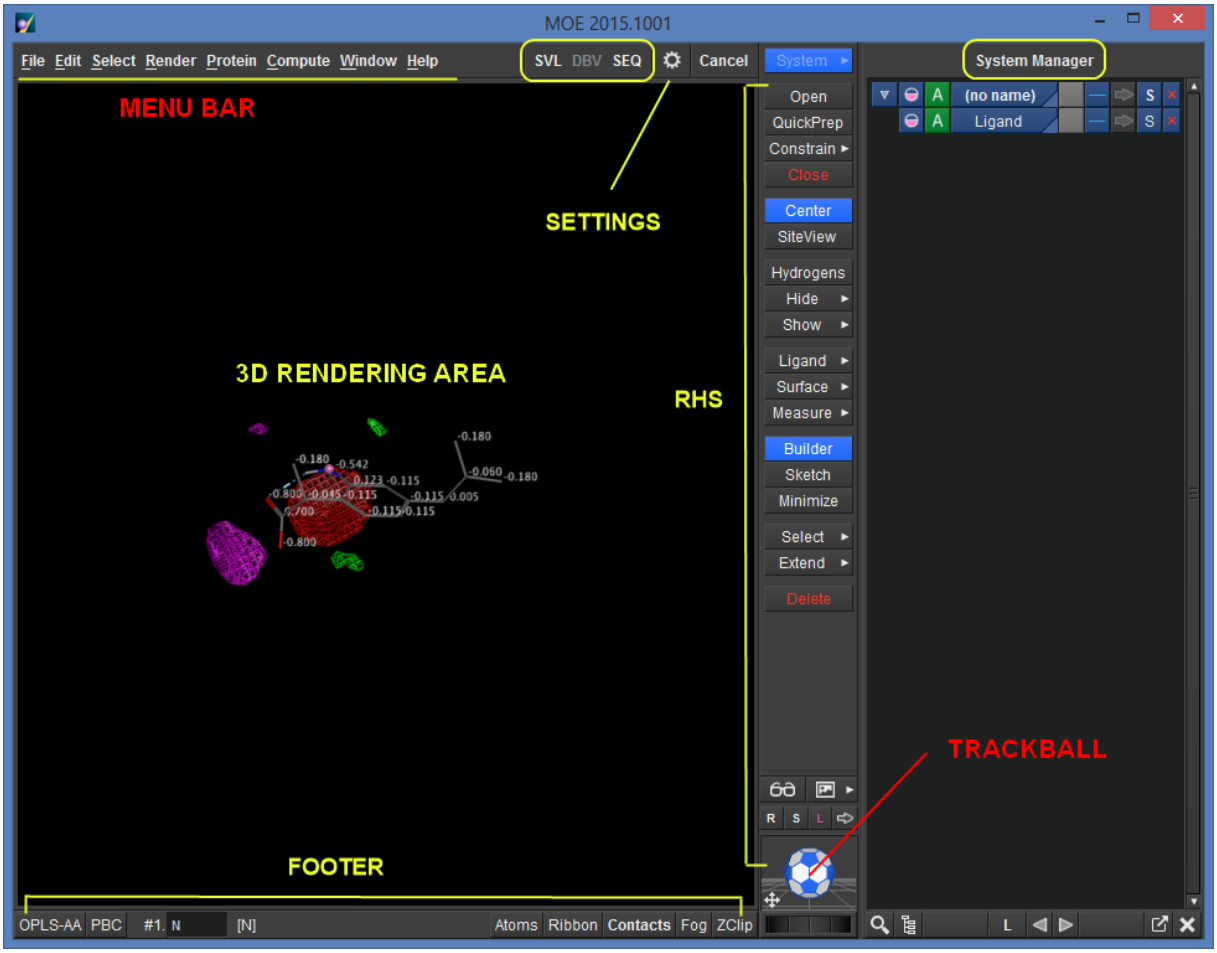

Fig. 1. Basic Graphical User Interface of MOE

Manipulation of the molecule

Rotation: press the middle mouse button in the MOE Window and move the mouse. Alternatively, you can use the **MOE | Footer | Trackball**.

The molecule (or system of molecules) rotates around its centre. If you selected atom (left-click with mouse), the system will rotate around the selected atom. If you want to rotate the molecule again around its centre, left-click outside the molecule to deselect any atoms.

Translation: press the SHIFT key and move the molecule with the middle mouse button. Alternatively, you can use the Trackball to move the molecules, after activating this feature by clicking the button in the lower left corner of the Trackball.

Zoom in/out: press the CTRL key, press the middle mouse button and pull to zoom in or out from each other. The alternative is to roll the middle button. Another option is to use the wheel under the Trackball.

Preparation of small molecule (ligand)

1. Getting a molecule to the main window of MOE. This can be achieved in many ways:
    - Open from file **MOE | File | Open**
    - Build using the **RHS | Builder**
    - Draw using the **RHS | Sketch –** starts the pre-set program for drawing 2D structures, such as ChemDraw
    - Insert the molecule via **Ctrl + C**, **Ctrl + V**
    - Insert SMILES to the **RHS | Builder**

2. Revision of the structure, bonds, errors, etc. You can use the **MOE | Compute | 2D Molecules** for visualisation.

3. Selection of protonation state and/or tautomer- **MOE | Compute | Prepare | Protomers**

4. Check of the stereochemical aspects, *R*/*S*, *cis/trans*. Application of stereochemical constraint. **RHS | Builder**

5. Calculation of partial charges. **MOE | Compute | Prepare | Partial charges**

6. Energy minimization according to the selected force field (Force Field). **MOE | Compute | Energy Minimize** (or with the basic setting **RHS | Minimize)**

Task 1

Using the procedure described above, prepare the molecule of ibuprofen (construct with **RHS | Builder**). At the centre of chirality set tight constraints on the *S*-isomer (the effective isomer, eutomer). Save the prepared molecule in a MOE format (ibuprofen_minim.moe) and SDF format (ibuprofen_minim.sdf). (**MOE | File | Save | Molecule**). Open the SDF file with Notepad and observe its structure (it is human readable).

Task 2

According to the instructions of a teacher, experiment with the options to display molecules. A good starting point are the check boxes in the **System Manager,** next to the name of a ligand. Hide/display the hydrogen atoms (repeat **RHS | Hydrogens**), alternatively **RHS | Show |** ...; **RHS | Hide |** ...

Task 3

Visualize the ibuprofen molecule using the Sticks model. Label the atoms of the carboxylic functional group with the calculated partial charges (**Footer | Atoms | Label | Charges**). Measure (**RHS | Measure**) the bond length and angle between two neighbouring sp^2 carbon atoms of the benzene ring. Save as a picture. **MOE | File | Save | Picture**.

Task 4

Clear the working area of the MOE window (**RHS | Close**). By putting SMILES into the **Builder,** construct the assigned molecule and prepare it following the standard procedure. How many protomers / tautomers MOE offers and what is their abundance at pH = 7? Select the most abundant protomer / tautomer form.

Working with surfaces

Types of surfaces

- **van der Waals surface (VWS)** – on the basis of van der Waals radii of individual atoms (Fig**.** 2, VWS, red dotted)
- **solvent excluded surface (SES) = molecular surface = Connolly surface –** (Fig. 2, SES, blue)
- **solvent accessible surface (SAS)** (Fig. 2, SAS, purple)

SAS and SES are defined based on the probe rolling over the molecule. The probe is a sphere representing the effective volume of a molecule of the chosen solvent. The most common probe is the molecule of water, that is, the sphere with van der Waals radius of oxygen.

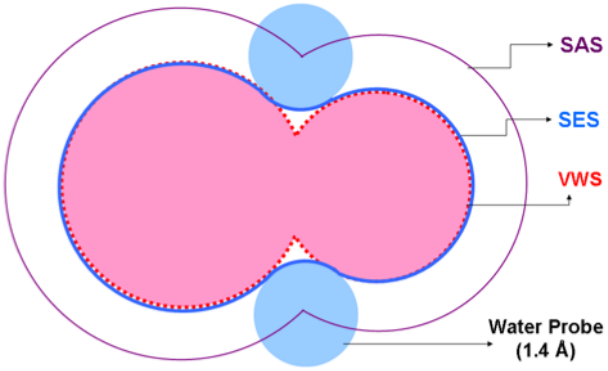

Fig. 2. Schematic representation of surfaces

Task 5

Visualize the assigned molecule in MOE and experiment with different types of surfaces. The basic surfaces are created in **System Manager** by using buttons **S** (such as Surface). Advanced management of surfaces can be accomplished in **MOE | Compute | Surfaces and Maps.**

Working with MDB databases

MDB database is used to store a large number of molecules in one file (tens to hundreds of thousands). Each row (**Entry**) in the database represents a single molecule and must contain at least the column (**Field**) with the name **mol**, which stores the structure of the molecule (2D, 3D, or e.g. only SMILES). Additional fields (can contain any information (text and numerical values of several data types).

MDB databases in MOE are used as:

- input database (e.g. databases of ligands to be docked to a receptor, or molecular fragments for Fragment Based Drug Design - FBDD)
- output database (e.g. results of docking, database of generated conformers)

Basic operations on MDB databases:

- creating a new database – **MOE | File | New | Database**
- adding a molecule from MOE window to the database- **DBV | Edit | New | Entry**
- sending a molecule from database to the MOE window - **DBV | Molecule | Send to MOE**
- sequential viewing of individual records from database in the MOE main window **– DBV | File | Browse**

The great advantage of databases is that it is possible to perform selected operation on the whole database, it means on all molecules present in the database. Generation of tautomers, deprotonation of strong acids, protonation of strong bases, discarding small salt ion counterparts from the structure, generating 2D or the 3D coordinates from SMILES, generation of conformers, energy minimization. These bulk operations are applied mainly in the preparation of input data for molecular modelling.

Task 6

Open file cox-2-inhibitors-pdb-smiles.smi (download from the Moodle course) with Notepad and observe its structure (human readable). Open this file from MOE and import the structures into a new database named cox-2-inhibitors.pdb. Work according to the teacher's instructions.

- Open file - import into database
- Clean up the structures, generate tautomers, protomers - **DBV | Compute | Molecule | Wash**
- Calculation of partial charges - **DBV | Compute | Molecule | Partial Charges**
- Energy minimization- **DBV | Compute | Molecule | Energy Minimize**