GUIDE User Manual

ORCA and MOPAC are popular tools used for quantum mechanical (QM) calculations of molecules. However, inexperienced users often struggle with developing input files in the correct atom order. Additionally, the lack of a clear protocol and a graphical user interface (GUI) for these software applications can discourage users from initiating and analyzing calculations.

To address these challenges and enhance the usability of ORCA and MOPAC, a Python-based plugin called GUIDE has been developed for the YASARA View and YASARA Structure suites. This plugin offers a GUI within YASARA, allowing users to perform QM calculations on any molecule using ORCA and MOPAC. By providing a user-friendly interface, GUIDE simplifies the process of running calculations that are typically executed through a command-line interface.

GUIDE offers unique advantages compared to other available tools. It allows users to launch quantum mechanical (QM) calculations directly within YASARA's graphical environment, eliminating the need to open or edit input files. The results of the calculations can be displayed directly on the screen, taking advantage of YASARA's visualization capabilities.

Furthermore, GUIDE seamlessly integrates with YAMACS, enabling users to launch calculations and interactively display results from GROMACS, ORCA, or MOPAC without leaving the graphical environment. This integration provides a streamlined workflow for users.

Another notable feature of GUIDE is its ability to select regions for applying restraints or launching QM calculations using the mouse. This intuitive interface allows users to easily define specific areas of interest.

In terms of result visualization, GUIDE simplifies repetitive tasks. The coordinates are dynamically updated on the screen, providing real-time feedback. Important information such as the energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) is displayed on the screen. Additionally, atomic results like the Fukui function are written into the molecule itself, allowing users to view them as color gradients and access them directly on the screen using the mouse. This enhances the analysis and interpretation of results.

Overall, GUIDE enhances the usability and efficiency of QM calculations by providing a user-friendly interface, seamless integration with other tools, and intuitive result visualization within YASARA's graphical environment.

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1 INSTALLATION

The GUIDE plugin was developed using the Python programming language. To install the plugin, users are required to have YASARA (Structure), ORCA (version 5.0 or later), MOPAC (MOPAC2016), and Python (3.8 or higher) installed on their system. Below is the step-by-step installation process for the GUIDE plugin:

1. Download and install ORCA and MOPAC for your system.
   ORCA: https://orcaforum.kofo.mpg.de/app.php/portal
   MOPAC: http://openmopac.net/Download_MOPAC_Executable_Step2.html
2. Download and install YASARA View suite (free) or YASARA Structure* suite from YASARA official page: http://www.yasara.org/downloads.htm
3. From the GitHub page https://github.com/YAMACS-SML/GUIDE download the Guide files
   a. If you have YASARA View installed, download the file GUIDE_YASARA_view.py
   b. If you have YASARA Structure installed, download the file GUIDE_YASARA_structure.py
4. Place the .py file in the plg folder inside YASARA installation path (...yasara/plg). For more information, please watch the video: https://github.com/YAMACS-SML/GUIDE/blob/main/video_tutorials/1_GUIDE_installation.mp4.
5. Launch the GUIDE plugin from the YASARA toolbar.
   a. The YASARA window will display the YASARA python path information.
   b. A file named **module_command.txt** will be generated in the specific directory.
   c. Additionally, the YASARA python path information will be written in the *module.txt* file located in the YASARA /plg folder.
   d. The **module_command.txt** file will provide installation instructions for the required Python modules. Follow the instructions to install the necessary modules.

For further details, refer to section 2.1 of the manual.

*Unlike YASARA View (free version), YASARA Structure suite has some extra features like energy minimization, charge calculation, fixing of atoms etc., allowing several advanced-level QM calculations using GUIDE.

2 DESCRIPTION OF THE PLUGIN

2.1 GUIDE.py

When you click on the GUIDE plugin, a window will appear, as shown in Figure 1. In this window, the user will be prompted to provide the path of the working directory. Additionally, they will need to select either ORCA or MOPAC from the provided list to specify the method of density functional theory (DFT) calculation. It is important for users to understand that ORCA performs ab initio level quantum calculations, while MOPAC conducts semiempirical quantum calculations.

By entering the working directory path and selecting the appropriate calculation method, users can proceed with their QM calculations using the chosen software. This user-friendly interface simplifies the process of specifying calculation parameters and enhances the overall usability of the GUIDE plugin.

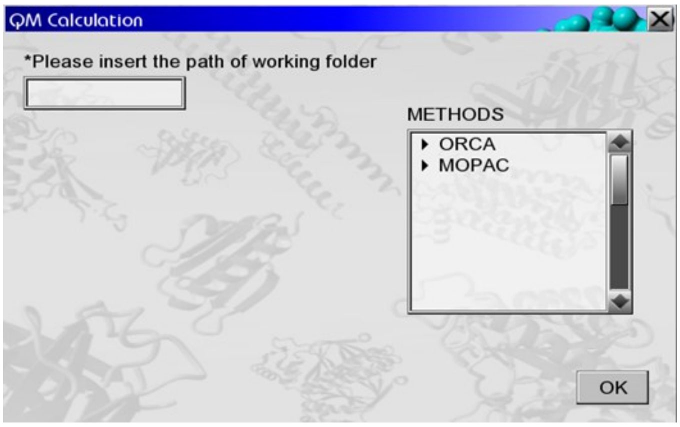
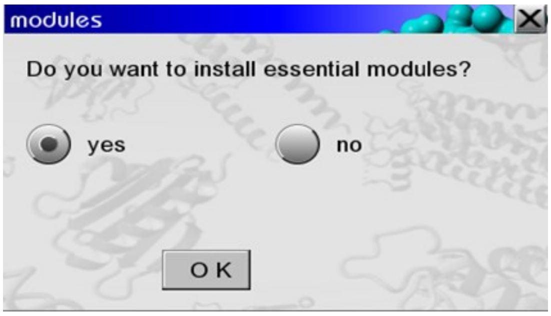


Figure 1:YASARA plugin window to define the working path and method.

After providing the working directory information, a small window will appear on the YASARA screen, prompting the user to install essential Python modules. If the user clicks Yes, they will be directed to the Python environment, and the plugin will automatically generate a module installation instruction file called **module_command.txt**. This file contains detailed instructions for manually installing the required modules. The user should carefully follow the instructions provided in the **module_command.txt** file to install the modules. This window for module installation (Figure 2) will appear the first time the plugin is used.

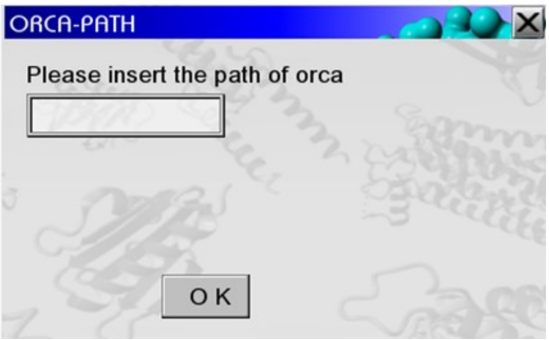


Do you want to install essential modules?

● yes ○ no

Figure 2: YASARA plugin window to install essential modules.

After providing the working directory and method of calculation information, a small window (Figure 3) will appear. In this window, the user needs to specify the installation path of ORCA or MOPAC. For ORCA, the path should point to the folder containing the **orca.exe** file, and for MOPAC, the path should point to the folder containing the **MOPAC2016.exe** file. This window will only appear the first time the plugin is run. Once the user provides the path information, the plugin will store it and automatically recall it for subsequent calculations.



Please insert the path of orca

Figure 3: YASARA plugin window to define the installation path of ORCA.

Next, another window will appear for selecting the type of calculation. If the user chooses **ORCA**, they will be prompted to select the type of experiment from options shown in Figure 4. The plugin currently supports the following calculations: Single point, Geometry optimization, Transition state, UV-Vis spectroscopy, Vibrational frequencies, HOMO-LUMO energy gap, Fukui function, Constraining QM, and multilevel DFT calculations.

If the user wishes to provide their own ORCA input file for the calculation, they should select the '**None of these**' option.

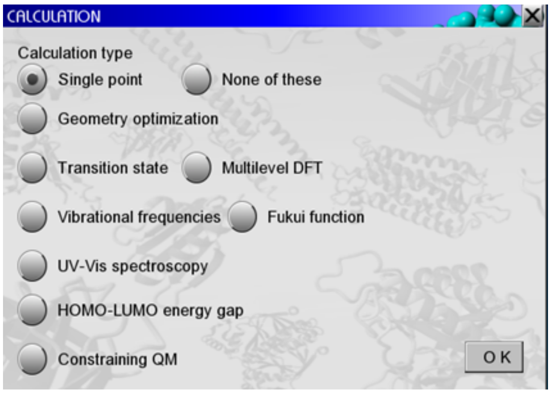


Figure 4: YASARA plugin window to select the experiment for ORCA.

If the user chooses a **MOPAC** semiempirical calculation, another window will appear, prompting the user to select the type of calculation from the options shown in Figure 5. For semiempirical calculations in MOPAC, the user must specify the specific theory (such as AM1, PM3, etc.), as well as the method (restricted or unrestricted Hartree–Fock, RHF or UHF) and the desired type of calculation.

If the user wants to provide their own input file for the calculation, they should select the '**None**' option from the list.

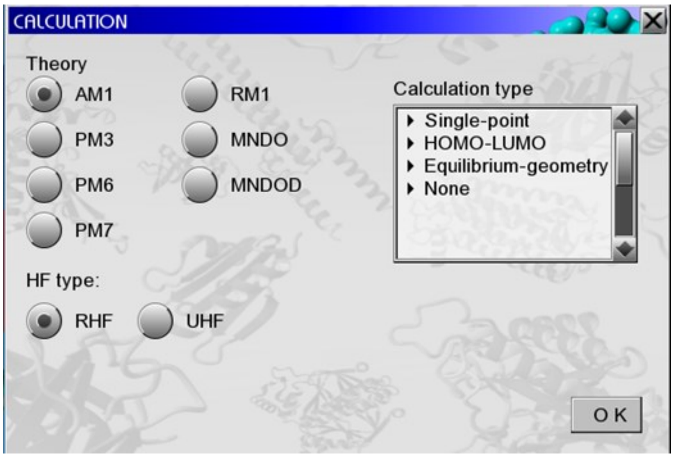


Figure 5: YASARA plugin window to select the experiment for MOPAC.

2.2 ORCA calculation

For calculations such as **Single point**, **Geometry optimization**, **Vibrational frequencies**, **UV-Vis spectroscopy**, **HOMO-LUMO energy gap**, **Fukui function**, **multilevel QM-QM2**, and **QM-MM** calculations using ORCA, the user needs to select the respective options from the calculation window. Additionally, they must choose a specific functional set and basis set for the calculation, as shown in Figure 6.

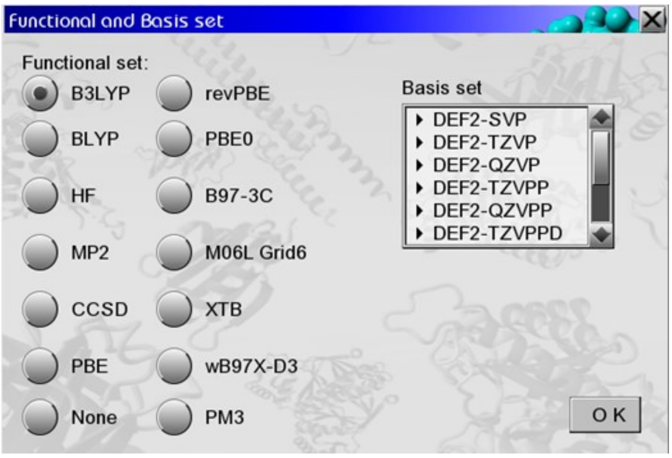


Figure 6: YASARA plugin window to select the functional set and basis set.

If the user wants to define their own functional and basis set keywords, they should select the '**None of these**' option for the functional set and '**None**' option for the basis set. They can then click **OK**. This action will trigger a new window (Figure 7) where the user can enter their own functional and basis set keywords. It is important to select a DFT functional and basis set for Fukui function calculations on any molecule.

Afterward, the user will be prompted to either build or select an experimental object (if more than one object is present in the structure) for further analysis and calculation. This will initiate the ORCA calculation, and the results of the calculation will be stored in the path provided by the user.

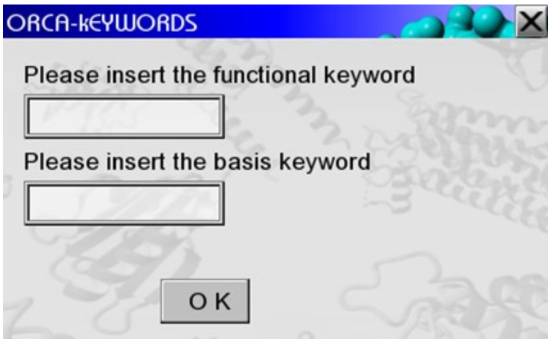
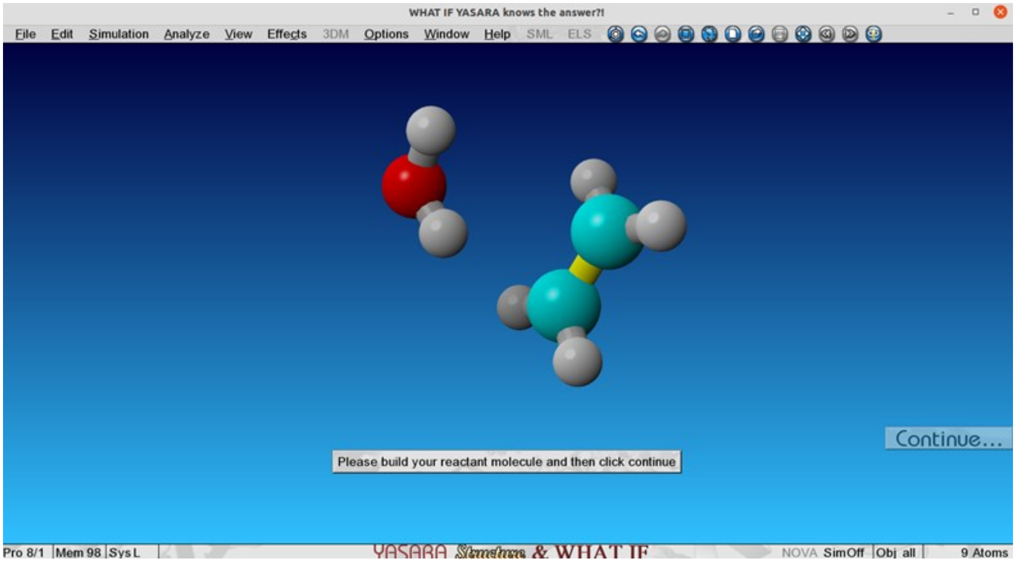

ORCA-KEYWORDS
Please insert the functional keyword
Please insert the basis keyword
O K

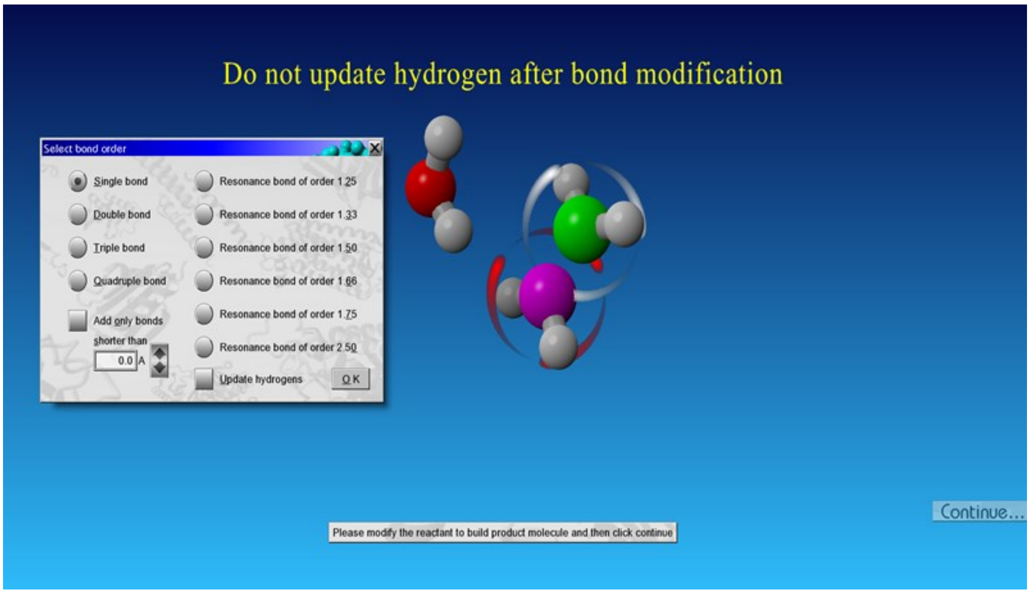
Figure 7: YASARA plugin window to define functional set and basis set keywords by user.

For a **Transition state calculation**, the user will be prompted by the plugin to build the reactant molecule(s) (as shown in Figure 8). After constructing the reactant molecule, the user should click to continue and proceed to build the product molecule(s). To build the product molecule, the user needs to modify the reactant molecule by adding or deleting bonds. During this bond modification process, **it is important for the user not to update the hydrogens** (as illustrated in Figure 9). By disabling the '**update hydrogens**' checkbox while adding bonds, the user can ensure that the hydrogens are not updated. It is important to note that the user cannot add, delete, or swap any atoms during the development of the product molecules.


WHAT IF YASARA knows the answer?!
File Edit Simulation Analyze View Effects 3DM Options Window Help SML ELS
Continue...
Pro 8/1 Mem 98 SysL
YASARA Structure & WHAT IF
NOVA SimOff Obj all
9 Atoms

Please build your reactant molecule and then click continue

Figure 8: Development of reactant molecules.


Do not update hydrogen after bond modification

Select bond order

- ● Single bond
- ○ Double bond
- ○ Triple bond
- ○ Quadruple bond
- □ Add only bonds shorter than 0.0 A
- ○ Resonance bond of order 1.25
- ○ Resonance bond of order 1.33
- ○ Resonance bond of order 1.50
- ○ Resonance bond of order 1.66
- ○ Resonance bond of order 1.75
- ○ Resonance bond of order 2.50
- □ Update hydrogens

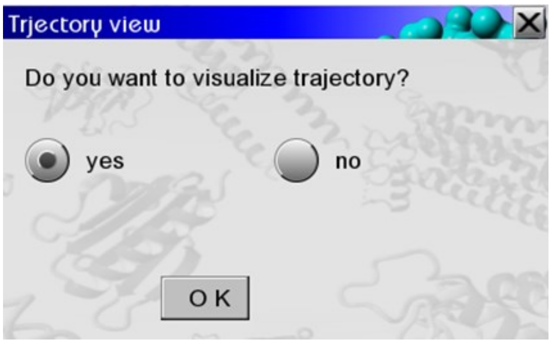
Please modify the reactant to build product molecule and then click continue

Figure 9: Development of product molecules.

After developing the reactant and product molecules, another window will appear where the user must select a specific functional set and basis set to initiate the geometry optimization of both the reactant and product molecules (Figure 6).

Using the user-provided input information, the plugin will automatically optimize the geometry of the reactant and product molecule(s). Subsequently, it will initiate the **Transition State** (TS) calculation using the Nudged Elastic Band method (NEB-TS).

Once the TS calculation is complete, another window will appear, allowing the visualization of the TS trajectory (Figure 10). By selecting **yes**, the minimum energy pathway (MEP) trajectory will be displayed in YASARA, providing a visual representation of the TS.



Trjectory view

Do you want to visualize trajectory?

● yes ○ no

Figure 10: YASARA plugin window to visualize the MEP trajectory.

Upon successful completion of the TS calculation, the user can access all the results in the **ts.out** and **ts.log** files. These files are generated and provide comprehensive information about the TS calculation.

To perform a Constraining QM calculation, the user needs to load a complex structure (e.g., protein-ligand complex) into the YASARA window. After loading the structure, the user must select specific objects or residues by using the selection box. This allows the user to choose the regions of interest for the QM calculation (Figure 11).

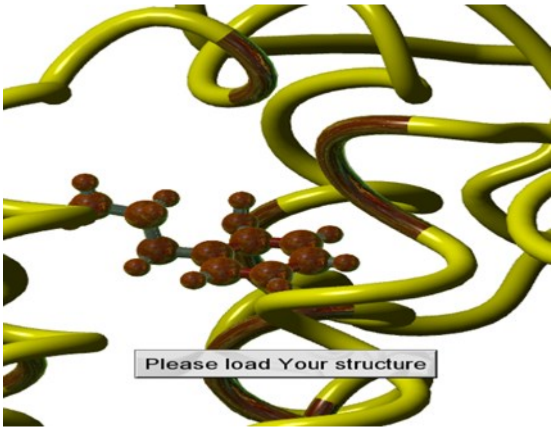


Figure 11: Selection of QM objects (in red) from a complex structure.

After selecting the QM objects, the plugin will prompt the user to additionally select the residues they wish to restrain during the calculation. In Figure 11, the QM objects are represented by the red-colored atoms, while the yellow-colored residues are chosen for additional restraint.

In biological systems, it is unrealistic for a molecule to exist in isolation. It is typically surrounded by other atoms or residues that impose constraints on its movement. In the QM calculation, the plugin will ask the user to restrain the positions of atoms that may influence the movement of the quantum objects. This restraint aids in achieving more accurate and precise calculations.

The plugin will automatically apply restraints to the selected residues and perform a geometry optimization of the QM objects. Following this, the user needs to modify the QM object for the transition state calculation while avoiding any updates to the hydrogen positions or adding new atoms (Figure 9). Subsequently, the plugin will initiate another geometry optimization of the modified structure and carry out the transition state calculation. The results of this calculation will be saved in the working directory in the **ts.out** file format.

The plugin also offers the capability to perform a **Multilevel DFT calculation** for receptor-ligand complex systems. To initiate this calculation, the user needs to select the **Multilevel DFT calculation** option from the plugin interface. Subsequently, the user will be prompted to select the basis set for the first level QM atoms (QM region). Then, they will be asked to select the basis set for the second level QM atoms (QM2 region). It is important to note that currently, **the plugin supports the use of XTB functional for the QM2 region specifically on Linux systems**. To download XTB please visit the following link:

https://github.com/grimme-lab/xtb/releases/tag/v6.5.1.

For performing a Multilevel DFT calculation on a Windows system, the user has the option to select PM3 as an alternative functional to XTB. It is important to note that both XTB and PM3 are semiempirical methods and do not require additional basis set information for the calculation. Therefore, the user can select the '**None**' option from the basis set list in the plugin.

After selecting the basis sets for the QM and QM2 regions, the user will be prompted to select the QM atoms and additionally the QM2 atoms from the structure. The plugin will automatically execute the multilevel DFT calculation, and the results will be stored in the working directory in the 'ts.out' file format. The trajectory can be visualized by analyzing the **ts_MEP_trj.xyz** file.

The plugin includes the capability to calculate the **condensed Fukui function** for any given molecule. The process begins with performing a geometry optimization of the molecule using the user provided DFT basis set. Following this, the plugin conducts separate geometry optimizations for the anion and cation structures by removing and adding one electron, respectively.

For each atom in the molecule, the **Hirshfeld charge** is computed for both the anion and cation structures. By averaging the Hirshfeld charges of the anion and cation, the condensed Fukui function is calculated. The calculated condensed Fukui function values are then displayed and labeled on each atom of the molecule within the YASARA window.

2.3 MOPAC calculation

To start a semiempirical calculation, the user needs to select the desired type of calculation from the list of experiments in MOPAC (Figure 5). Following this, the user will be prompted to either build a specific object or select an existing object for the calculation. Once the selection is made, the calculation will be initiated and the results will be stored in the path specified by the user.

3 APPENDIX

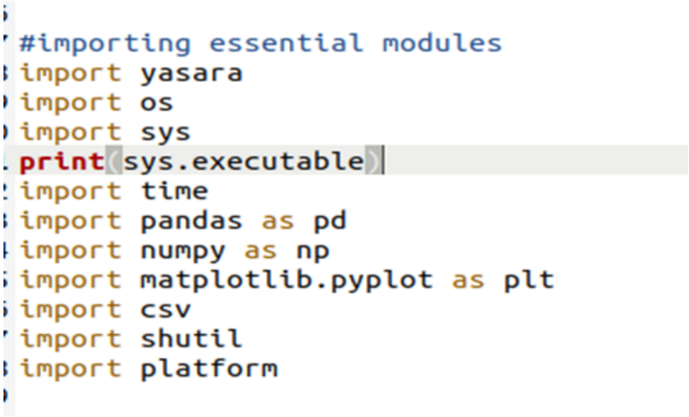
3.1 YASARA missing package installation

To run the GUIDE plugin and install any missing Python modules, follow these steps:

1. In the plugin code, after line number 39 in the DFT calculation plugin (Figure 12), add the following two commands:

```
import sys
print(sys.executable)
```

These commands will print the path of the Python executable being used by YASARA in the YASARA terminal. For example: **C:\python33\yasaraw.exe**.



```
#importing essential modules
import yasara
import os
import sys
print(sys.executable)
import time
import pandas as pd
import numpy as np
import matplotlib.pyplot as plt
import csv
import shutil
import platform
```

Figure 12: Importing sys module and executing the Python path.

2. Open a command prompt (CMD) in Windows or a shell window in Linux and navigate to the Python installation directory. In this case, it would be **C:\python33** based on the example path mentioned above.

3. Verify the version of the Python interpreter used by YASARA. Run the following command in the terminal window:

```
python -V
```

If the Python version is greater than or equal to 3.7, you can proceed to steps 4 and 5. If the Python version is lower than 3.7, you will need to force the switch to Python 3.7 (or a higher version) by following the instructions in the ***How to force version switch*** section below.

4. To install the missing package (e.g., Pandas), run the following command in the terminal:

```
python -m pip install pandas
```

Replace **pandas** with the name of the actual missing package if it is different.

5. Repeat step 4 for each missing package. For example, if you also need to install **NumPy**, run:

```
python -m pip install numpy
```

6. Once all the missing packages are installed, you can continue running the GUIDE plugin in YASARA.

How to force version switch

To switch from Python 3.3 (or the default Python interpreter used by YASARA) to Python 3.7, you can follow these methods:

1. Install Python 3.7 (or a higher version) into a different folder: Download and install Python 3.7 or a higher version from the official Python website (https://www.python.org/downloads/). During the installation, make sure to select a different folder for the installation (e.g., **C:\python37**).

2. Rename the default Python directory: Open the command prompt (CMD) or shell window and navigate to the Python installation directory (e.g., **C:\**). Rename the default directory (e.g., **C:\python33**) to a different name (e.g., **C:\python33.backup**).

3. Change the correct version directory to the previous default directory name: If you installed Python 3.7 (or a higher version) into a different folder (e.g., **C:\python37**), navigate to that directory in the command prompt (CMD) or shell window. Rename the directory to match the previous default directory name (e.g., **C:\python37** renamed to **C:\python33**).

Once you have completed the version switch, repeat the installation steps mentioned above to install the missing packages for YASARA.