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Molecular Dynamics Simulation by GROMACS Using GUI Plugin for PyMOL

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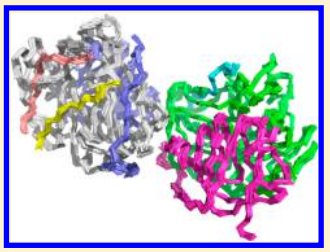
ABSTRACT: The molecular models stored as PDB formatted files are static, but most of the biomolecular systems display a dynamic behavior, in other words their conformations depend on time. To get the dynamic model from the static one, one needs to perform the molecular dynamics (MD) simulation using tools like GROMACS. This paper describes functionality of the newly created plugin for PyMOL (the popular and easy to use program for displaying and manipulating molecule models). This plugin enables the easy use of molecular dynamics simulations using GROMACS through a graphic interface. It transfers the results of those calculations and displays them back in PyMOL. All the components of the stack are open source and are available free of charge. This strategy gives researchers easy access to the molecular dynamics PYMOL plugin and creates an opportunity to modify its source when needed.



INTRODUCTION

Molecular structures, which were solved by X-ray crystallography,[1] nuclear magnetic resonance,[2] or in any other way[3] are stored in the Protein Data Bank.[4] To make those data easily accessible to researchers, the PDB file format had been developed. This type of file contains information about atom names, their positions in the Cartesian coordinate system, bindings to other atoms, and some other auxiliary information such as locations of the secondary structure elements. The PDB formatted files are plain text, so they can be easily read and manipulated by most programs dedicated to molecular structure analysis. They can also be directly read by any text viewing program.

PyMOL[5] is a powerful and widely adopted tool for biomolecular visualization, which is distributed as open source under the terms of the CNRI Python license.[6] It utilizes a general purpose and object-oriented programming language, Python.[7] Thanks to its easy to use API capabilities, its functionality can be extended by third party plugins.[5] One of PyMOL's primary uses is to view the molecular models stored in PDB formatted files. Most of those files, obtained from data centers, contain a single static model. However, molecules in the real world are not static; they display dynamic behavior. To convert a static model into a dynamic one, one needs to perform molecular dynamics simulation. This procedure requires specific tools and a lot of scientific knowledge to use. There are some other PyMOL plugins developed,[8] which are able to perform molecular dynamics simulation, but they use proprietary, and sometimes expensive, software such as the AMBER package.

There are quite a few advanced tools for performing molecular dynamics simulations. The most popular ones are AMBER,[9,10] CHARMM,[11−13] and GROMACS.[14−18] Both AMBER and CHARMM packages are closed source, and they need to be bought by the researcher. However, GROMACS was developed as an open source project under the terms of GPL.[19] It can be used and modified by the researcher without restrictions. Even an inexperienced user can install it easily on a given Unix-like operating system, for example, via a repository system. GROMACS also includes a wide range of AMBER and CHARMM force fields. While developers of tools for molecular dynamics simulation focus on scientific aspects, they often neglect usability. Unfortunately, GROMACS, like the rest of the tools for biomolecular simulations, lacks a true graphical user interface (GUI). This shortcoming can deter some researchers interested in studying the dynamic behavior of (bio)molecules from using GROMACS. This is an intentional feature of GROMACS because, in most cases, it is used on HPC machines and mostly screen-less clusters, where a GUI is not desired. This approach allows for separating the preparation step from the sometimes very long simulation. Also people, who are used to working with AMBER, might find it hard to switch to GROMACS.

These are the reasons why we developed an open source plugin for PyMOL, which combines easy to use and intuitive graphical PyMOL capabilities with advanced tools like GROMACS for performing molecular dynamics simulations. All the components of the stack are open source, while plugin is specifically distributed under the terms of GPLv3.[20]

METHODS

Our software, the so-called plugin, which is interfacing PyMOL with molecular dynamics tool GROMACS, was developed using the Python programming language. This language is also an essential part of PyMOL, and using it fits into PyMOL's development philosophy. Python is a language well known for its object-oriented programming model. Its primary aim is to keep its syntax clean in such a way that the developers browsing

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the source code can easily understand and modify it. Despite being a high-level language, it works surprisingly fast. It helps also that the Python interpreter is an essential part of almost all Unix-like operating systems, for which our software is developed.

The plugin can be installed by the PyMOL built-in plugin installation tool (*menu bar→Plugin→Manage Plugins→Install...*) and is added to the *Plugin* submenu in the menu bar. On Ubuntu Linux, the latest stable version of the plugin is also available from the PPA repository[21] and can be installed by a simple standard command "*sudo apt-get install dynamics-pymol-plugin*". The PyMOL and GROMACS programs need to be installed or compiled separately. On the Ubuntu platform, those components can be installed as easily as using a standard Ubuntu repositories with the command "*sudo apt-get install pymol gromacs*". To draw its GUI, our plugin utilizes the Tkinter[22] graphics library. It is a standard Python library and is also used by PyMOL itself, so the plugin looks native to this software and does not provide any further dependencies. Our plugin also uses the Tix[23] program (for some advanced Tk capabilities). Tix is not required by the PyMOL program, and it might not be available by default. Therefore, it needs to be additionally installed in the system. Our software also requires an Unix-like operating system to work properly.

Plugin Workflow. Figure 1 shows the workflow implementation of GROMACS in the PyMOL plugin needed to perform a molecular dynamics simulation. First, a protein structure file (usually a PDB file[4,24]) is loaded into PyMOL. When the plugin is started, it will allow the user to select one of the PyMOL loaded proteins. This may be any previous work, like an already loaded structure or any other arbitrary PDB file. After changing default configuration (using the GUI) to suit the researcher's needs, the molecular dynamics simulation could be performed. First, the plugin's logic will use GROMACS pdb2gmx[25] tool to convert the PDB formatted file to the format required by GROMACS, which is suitable for further calculations. Then, editconf[26] and genbox[27] tools will add a box of water around the solute molecule using the chosen water model. Grompp[28] and mdrun[29] GROMACS tools will perform minimization of energy, an optional MD simulation with positional restraints, and the final molecular dynamics simulation. If some restraints were selected, the genrestr[30] tool will take care of them. Finally, the trjconv[31] tool will convert results into a multimodel PDB file, which will be displayed in the PyMOL viewer. All the files, configuration, and progress status are stored and processed in the "~/.dynamics" directory. As our software development is progressing, other GROMACS tools are being implemented such as x2top.[32]

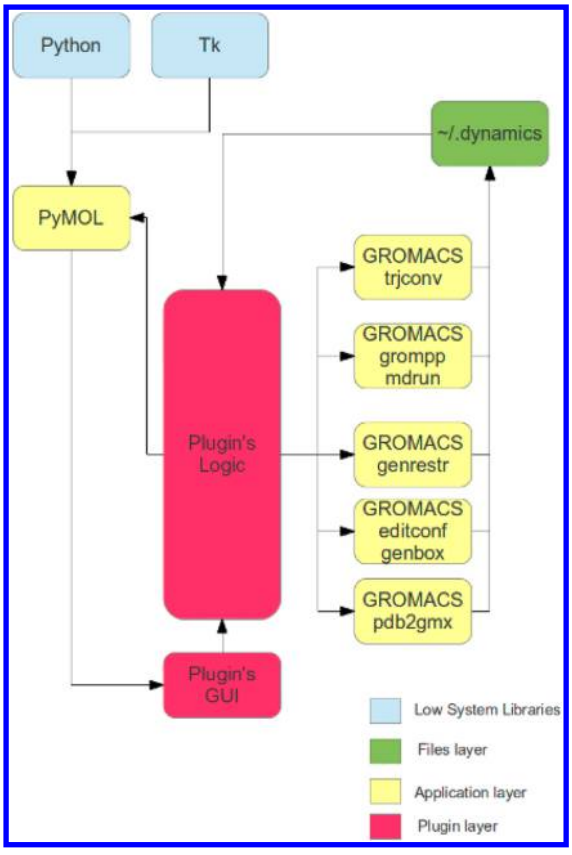

Figure 1. Workflow of communication between PyMOL and GROMACS modules using the plugin.

Graphical User Interface: Configuration. Figure 2 displays the main GUI window of the plugin. In the left column, one can select the molecule that is needed to proceed and the group of atoms for final display. In the middle column, one can select the force field type available in the GROMACS package for performing the molecular dynamics simulation. In this column, one can also configure the water molecule model and parameters of a water box. In the right column, one can configure more advanced options. See the plugin's manual[33] for more specific information. On the bottom of a window, there are a few buttons. Pressing the "Cancel" button will quit plugin. "Clean" will delete all files in the "~/.dynamics" directory. "Help" will display brief help information. "Save and Load" can be used to transfer project files to other machine. "OK" will start the molecular dynamics simulation.

RESULTS

The dynamics PyMOL plugin is meant to be as easy to use as possible. It takes, as an input, a PDB formatted molecule model. It creates, as an output, a PDB formatted multimodel molecule file, which can be easily stored and viewed. After starting the PyMOL program, the user can load a PDB file, for which the molecular dynamics simulation needs to be performed. To choose some specific atoms for restraints, the user can select them on a displayed molecule model. The actual dynamics plugin can be started by clicking on the top of PyMOL: *Menu→Plugin→dynamics*.

Molecule Selection. There are three columns in the plugin's main window (Figure 2). The left one is used to choose a molecule for dynamics simulation. If molecules have been already loaded into PyMOL, the list of those should appear on the top of the column. The user can choose one for which simulation should be performed. If no molecule has been loaded into PyMOL, then the "Browse" button should appear. One can use it to select a PDB file for molecular dynamics simulation. If earlier simulations were performed using this plugin, the additional list should appear. It will allow selection of any of the previously loaded molecules. The last list in this column determines which part of a molecule should be displayed as the final result. This does not affect any calculations. The default selection is the whole protein molecule, as suggested by GROMACS.

Force Field and Water Model Choices. The middle column in plugin's GUI (Figure 2) is dedicated to the choice of force field type and water model for a given molecular dynamics

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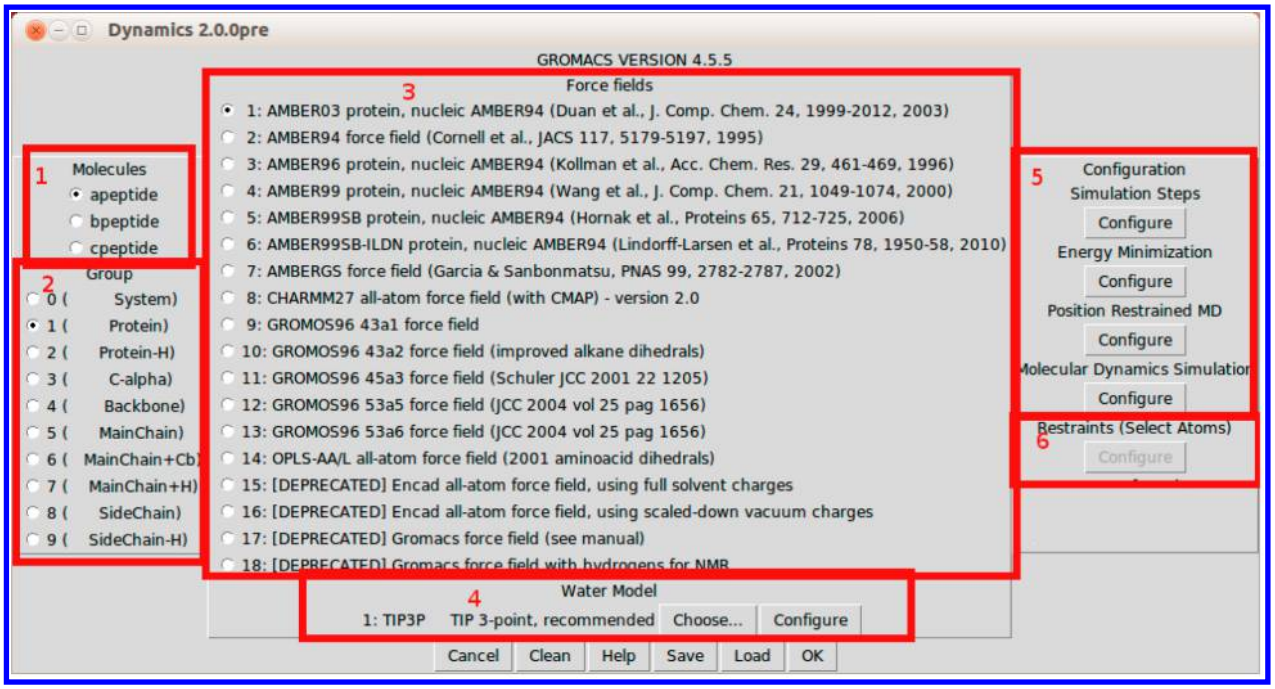

Figure 2. Graphical user interface of main window of the dynamics PyMOL plugin. (1) List of available molecules. (2) Displayed molecule group. (3) List of available force fields. (4) Water model options and configuration. (5) Molecular dynamics simulation options and advanced configuration. (6) Position restraints configuration.

simulation. The first radio button list allows one to choose one of the force field types provided by the GROMACS tool. Note that not all force fields can perform full molecular dynamics simulation for a given molecule. There is a label, below the force fields list, with a default water model suggested for a chosen force field. The user has the option to change it by clicking the "Choose..." button. Note that each force field may have different available lists of water molecule models. Next to the "Choose..." button there is a "Configure" button, which allows one to customize the water box details. Here, one can change the geometry of the box and water density, which is given in g/L units. One can also determine here the size of the water box, which is given as a multiple of molecule size. These two configuration windows are shown in Figure 3.

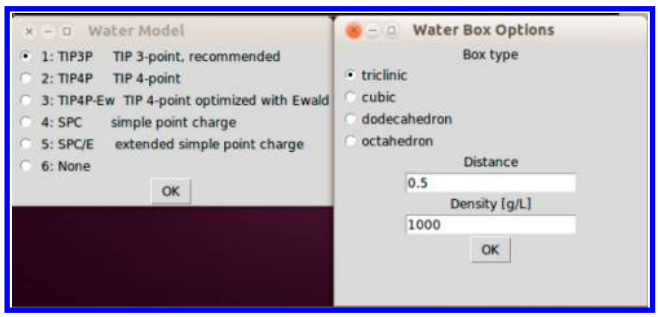

Figure 3. Water model configuration options. The left window is a list of available water models. The right window is a water box options.

Simulation Step. The right column in the plugin menu (Figure 2) is dedicated to advanced configuration. The first configuration options are for simulation steps. Not all of molecular dynamics calculations need to be done at once. By using the "Simulation Steps" button, one will get a list of available tasks to perform full molecular dynamics simulation. One can select only those that should be performed. The researcher can save partial results after finishing one phase of simulation and continue his/her project on other machine or resume work on the same computer later. One just needs to choose the checkbox "Resume Molecular Dynamics Simulation" to continue the interrupted simulation. By checking the "Restraints (optional)" checkbox, one can unlock this molecular dynamics feature. This enables further options for restraints, which will than become available in the main menu. The "Simulation Steps" window is shown in Figure 4.

Configuration. Another set of configuration options in the main menu is dedicated to "Energy Minimization". This phase of simulation is performed after immersing the given solute molecule model into the water box. Initially, some atoms in that system may collide. The purpose of the minimization phase is to move the water atoms in such a way that the molecular dynamics simulation will not start in very unfavorable energy state.

The next option is for "Position Restrained MD". After choosing that option, our plugin keeps the "main" molecule position fixed, while it allows, at the same time, the water molecules to move freely. It will provoke the water molecules to occupy the cavities that may have been created by "Energy Minimization". The next option is dedicated to the final "Molecular Dynamics Simulation", the so-called "production" run stage. To get the exact information about the available options please look at the GROMACS configuration MDP files options.[34]

If the user plans to use his/her own MDP files instead of available configuration options, then it is possible to paste them into the "~/.dynamics" directory. The file names are em.mdp, pr.mdp, and md.mdp, respectively. The "Configuration" windows are shown in Figure 5.

Restraints. If the checkbox for "Restraints (optional)" is selected, then the "Restraints (select atoms)" button become enabled in the main menu. The researcher will get the list of

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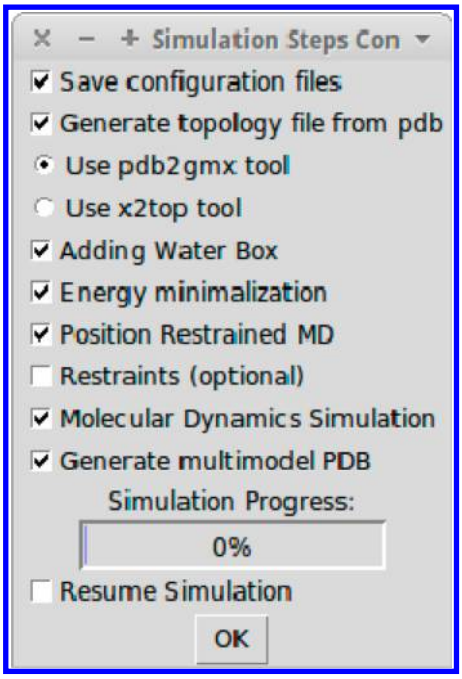

Figure 4. List of tasks to be performed during a molecular dynamics simulation run.

proposed parts of molecules to be restrainted after clicking the recently enabled button. The latest options show atoms selected in PyMOL. The user can choose one of the available lists and modify which atoms should be restrainted. Those atoms will get the big energy penalty for every move during the molecular dynamics simulation, so their positions will stay fixed. Only those atoms that are not selected will perform the proper moves according to the molecular dynamics simulation rules. The restraints window is shown in Figure 6.

Additional Buttons. There are six buttons on the bottom of the main menu window of our PyMOL plugin. They are placed in sequence from the left to the right of the main menu window. The first one is the "Cancel" button. The selection of this button will result in exiting the plugin. The "Clean" button will remove all temporary plugin files including all previous project files. The "Help" button will display brief help information. The "Save" button will allow the user to save the current molecule with all settings and any previous work in the form of a tar.bz2 archive. The "Load" button will allow the user to load a previously saved tar.bz2 archive. The "OK" button will take the user to the next window, in which the molecular dynamics simulation will be performed.

The next menu window appears after clicking "OK" button. There are four buttons here. They are placed in sequence from the left to the right of that new window. The "EXIT" button will quit plugin. The "SAVE" button will allow the user to save the current project with its progress and settings in the form of a tar.bz2 archive. The "STOP" button will suspend calculations, while the "START" button will resume or start calculations.

DISCUSSION

Our PyMOL Plugin will provide great opportunity for everyone to perform molecular dynamics simulations free of charge. It is meant to be very easy to use, but unfortunately, preparing an appropriate simulation environment might be much more complicated than it initially seems to be. The researcher might

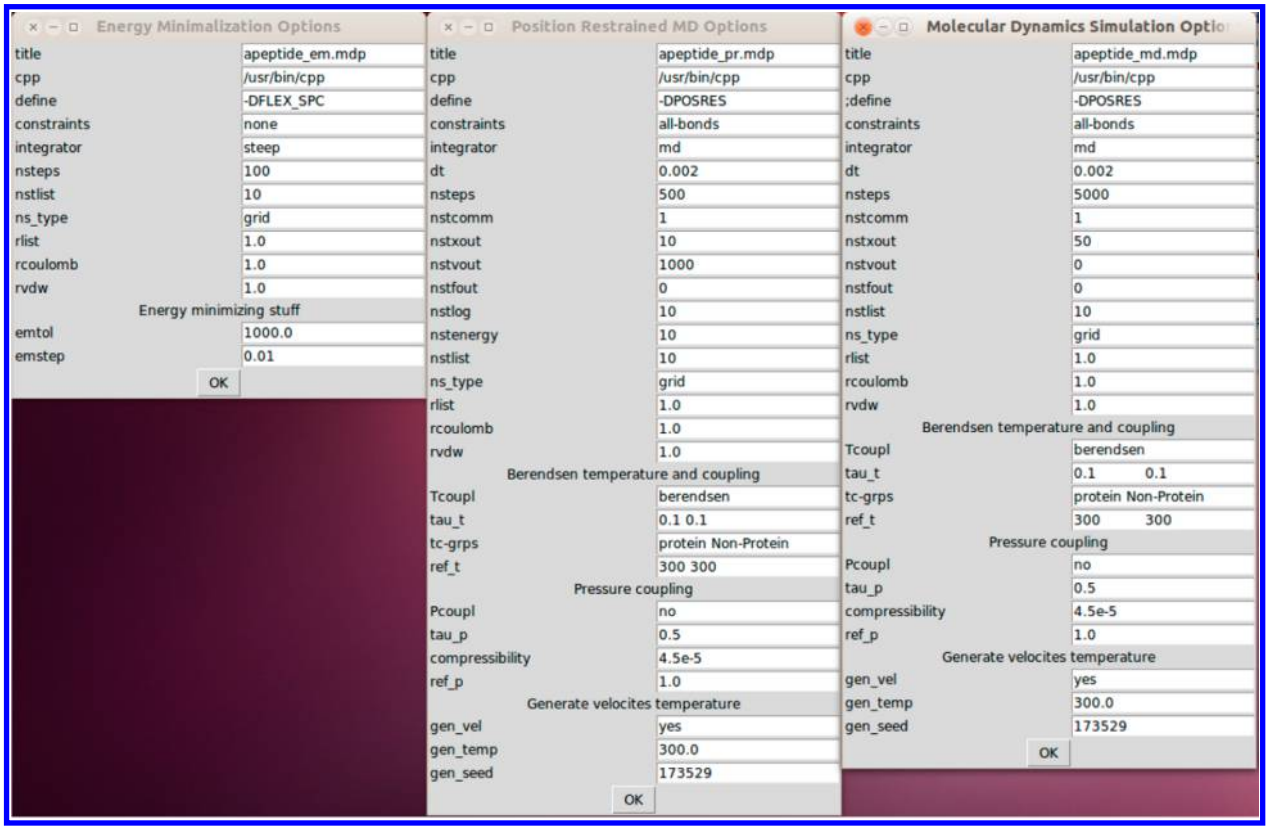

Figure 5. All available advanced options. The left column is the energy minimization. The middle column is the position restraints MD options. The right column is the final molecular dynamics simulation (production run stage MD options).

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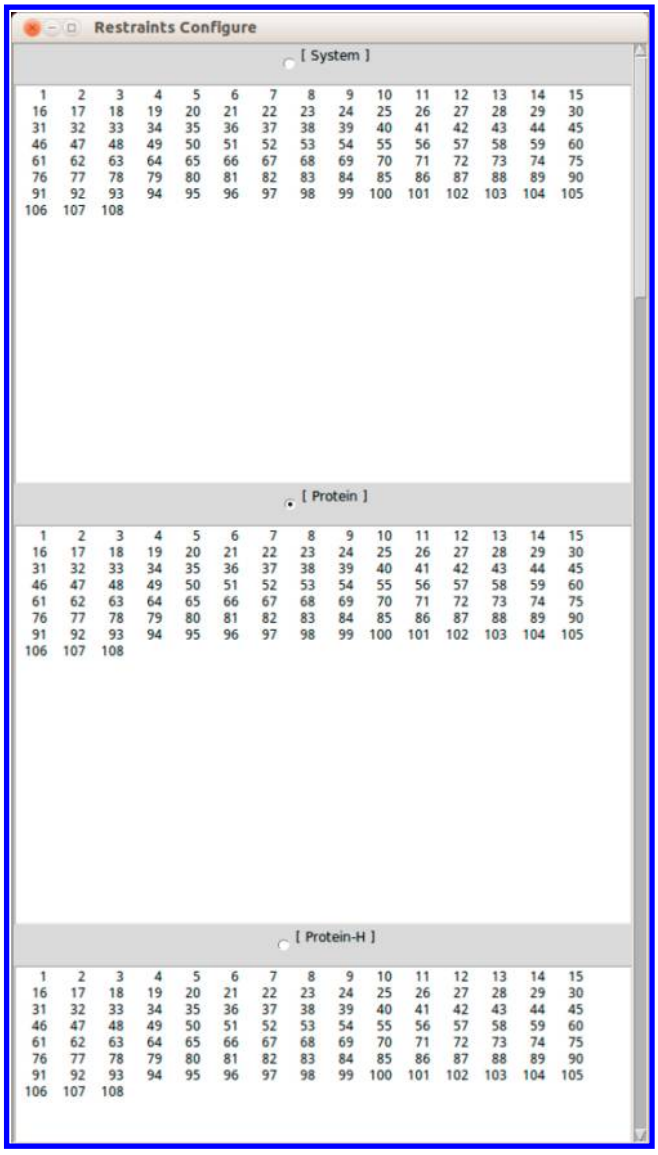

Figure 6. Selection of atoms for positional restraints.

encounter many errors that need to be addressed.[35] Our plugin is constructed that way—to work with any future versions of GROMACS—so any future enhancements will be automatically supported. Please keep in mind that the Microsoft Windows operating system is not yet supported.

There are also some features that are planned for the future releases of the plugin. Some of them are at least partially implemented already but not mentioned in this article due to stability issues. The planned features cover such areas as running plugin from a PyMOL built-in command line, or further implementation of constraints, or running independently from the PyMOL software. That ability would constitute one essential step to run our plugin via a command line with no graphic environment at all (for example, for remote work).

CONCLUSIONS

We present a novel plugin for the popular molecular graphics software PyMOL that allows one to perform molecular dynamics simulations. To our knowledge, this is the first plugin that combines the PyMOL and GROMACS functionality. It is an open source program and, together with GROMACS and PyMOL, provides the first entirely open source set of utilities to easily view, set up, and perform molecular dynamics simulations using only GUI-based tools. All programs mentioned here can be obtained by researchers free of charge and can be modified to suit the specific needs of the users. The source code of the plugin is available under the terms of a GPLv3 license from https://github.com/tomaszmakarewicz/Dynamics . Ubuntu users may use the official PPA repository: https://launchpad.net/~tomaszm/+archive/dynamics.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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