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Molecular dynamics simulation by GROMACS
using GUI plugin for PyMOL

Tomasz Makarewicz, Rajmund Kaźmierkiewicz*

Laboratory of Biomolecular Systems Simulations, Intercollegiate Faculty of Biotechnology,
University of Gdańsk and Medical University of Gdańsk, Kładki 24, 80-822 Gdańsk, Poland

PyMOL, GROMACS, plugin, molecular dynamics

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 molecular dynamics simulations using GROMACS in an easy way and through 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. That strategy gives researchers an easy access to molecular dynamics PYMOL plugin and it 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 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 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 and 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 an open source under the terms of CNRI Python License [6]. It utilizes a general-purpose and an object oriented programming language Python [7]. Thanks to its easy to use API capabilities, its functionality can be extended by the third party plugins [5]. One of PyMOL's primary use is to view the molecular models stored in PDB formatted files. Most of those files, obtained from data centers, contain single static model, but molecules in the real world are not static and they display a dynamic behavior. To convert static model into a dynamic one, one needs to perform molecular dynamics simulation. This procedure requires specific tools and a lot of science knowledge to perform. There are some others PyMOL plugins developed [8], which are able to perform molecular dynamics simulation, but they use propriety, and sometimes expensive, software such as an AMBER package.

There are quite a few advanced tools for performing molecular dynamics simulations. The most popular ones are: AMBER [9,10], CHARMM [11,12,13], GROMACS [14,15,16,17,18].
Both AMBER and CHARMM packages are closed-source and they need to be bought by the researcher. However GROMACS is developed as an open source project under the terms of GPL [19]. It can be used and modified by researcher without restrictions. Even an inexperienced user can install it easily on a given Unix-like operating system for example via repository system. GROMACS also includes wide range of AMBER and CHARMM force fields. While developers of tools for molecular dynamics simulation focus on its 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, out of 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 GUI is not desired. This approach allows to separate the preparation step from sometimes very long simulation. Also people, who are used to work 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 an easy to use and intuitive graphical PyMOL capabilities with advanced tools like GROMACS for performing the 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 the source code can easily understand
and modify it. Despite being the 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 for.

The plugin can be installed by 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 by the PPA repository [21] and can
be installed by simple, standard command “sudo apt-get install dynamics-pymol-plugin”. The
PyMOL and GROMACS programs need to be installed or compiled separately. On Ubuntu
platform those components can be installed as easy as using standard Ubuntu repositories by
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 it is also used by the 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 and therefore it needs to be
additionally installed in the system. Our software also requires an Unix-like operating system to
work properly.

The plugin's workflow

Figure 1.
The Figure 1 shows the workflow implementation of GROMACS in the PyMOL plugin needed in order to perform molecular dynamics simulations. First a protein structure file (usually a PDB file \[4,24\]) is loaded into PyMOL. When the plugin is started it will allow user to select one of the PyMOL loaded proteins, it may be any previous work, like already loaded structure or any other arbitrary PDB file. After changing default configuration (using GUI) to suit the researcher needs, the molecular dynamics simulation could be performed. First of all the plugin's logic will use GROMACS pdb2gmx \[25\] tool to convert the PDB formatted file to 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 multimodel PDB file, which will be displayed in PyMOL viewer. All the files, configuration and progress status are stored and processed in the ~/.dynamics directory. As our software development is progressing another GROMACS tools are being implemented such as x2top \[32\].

**The Graphical User Interface – configuration**

**Figure 2.**
Figure 2 displays the main GUI window of the plugin. In the left column one can select molecule which needs to be proceed and group of atoms for final display. In the middle column one can select the force field type available in GROMACS package for performing the molecular dynamics simulation. In this column one can also configure 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 could be used to transfer project files to other machine, OK will start molecular dynamics simulation.

RESULTS

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

The Molecule selection
There are three columns in the plugin's main window (see 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 a top of the column. User can choose one, for which simulation should be performed. If no molecule had been loaded into PyMOL then the Browse button should appear. One can use it to select 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 determine which part of a molecule should be displayed as a final result. It does not affect any calculations. The default selection is the whole protein molecule, as it is suggested by GROMACS.

**The Force field and the water model choices**

The middle column in plugin's GUI (see Figure 2) is dedicated to choice of a force field type and water model for a given molecular dynamics simulation. The first radio buttons 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 default water model suggested for a chosen force field. The user has an option to change it by clicking the Choose... button. Note that each force field may have different available list of water molecule models. Next to the Choose... button there is a Configure button, which allows one to customize 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. Those two configuration
windows are shown in Figure 3.

Figure 3.

**The 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 calculation need to
be done at once. By using *Simulation Steps* button one will get a list of available tasks to perform
full molecular dynamics simulation. One can select only those, which 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 on. 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. It enables the further options for restraints, which will than become available
in the main menu. The *Simulation Steps* window is shown in Figure 4.

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 minimization phase is to move the water atoms a bit, in such a way, that the molecular dynamics simulation would not start in very unfavorable energy state.

The next option is for Progression 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 take a look at the GROMACS configuration MDP files options [34].

If 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, md.mdp respectively. The Configuration windows are shown in Figure 5.

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 proposed parts of molecules to be restrained, after clicking the recently enabled button. The latest options show atoms
selected in PyMOL. User can choose one of the available lists and modify which atoms should be restrained. Those atoms will get the big energy penalty for every move during the molecular dynamics simulation, so their positions will stay fixed and 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.

*Figure 6.*

**Additional buttons**

There are six buttons on the bottom of the main menu window of our PyMOL plugin. They are placed in the sequence from the left for the right side of the main menu window. The first one is the Cancel button. The selection of that 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 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 user to load previously saved tar.bz2 archive. The OK button will take user to the next window, in which the molecular dynamics simulation will be performed.

The next menu window will appear after clicking OK button. There are 4 buttons here. They are placed in the sequence from the left for the right side of that new window. The EXIT button will quit plugin. The SAVE button will allow user to save 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.
CONCLUSIONS

We present a novel plugin for the popular molecular graphics software PyMOL which allows to perform molecular dynamics simulations. As to our knowledge it is the first plugin which combines the PyMOL and the GROMACS functionality. It is an open source program and, together with GROMACS and PyMOL, provide the first entirely open source set of utilities to easy view, set up and perform molecular dynamics simulation 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 GPLv3 license from https://github.com/tomaszmakarewicz/Dynamics . The Ubuntu users may use its official PPA repository: https://launchpad.net/~tomaszm/+archive/dynamics .

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 appropriate simulation environment might be much more complicated that it, initially, seems to be. Researcher might encounter many errors which needs to be addressed [35]. Our plugin is constructed that way, that it should 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 which are planned for the future releases of the plugin. Some of them are at least partially implemented already, but not mentioned in the article due to stability
issues. The planned features cover such areas as: running plugin from 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 command line with no graphic environment at all (for example for remote work).
Figure 1. The workflow of communication between PyMOL and GROMACS modules using authors plugin.
Figure 2. The Graphical User Interface of main window of 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 – the position restraints configuration.

Figure 3. The water model configuration options. The left window – list of available water models. The right window – water box options.
Figure 4. The list of tasks to be performed during molecular dynamics simulation run.
Figure 5. All available advanced options. The left column – energy minimization. The middle column – position restraints MD options. The right column – final molecular dynamics simulation (the production run stage MD options).
Figure 6. Selection of atoms for positional restraints.
AUTHOR INFORMATION

Corresponding Author

*Rajmund Kaźmierkiewicz, Laboratory of Biomolecular Systems Simulations, Intercollegiate Faculty of Biotechnology, University of Gdańsk and Medical University of Gdańsk, Kładki 24, 80-822 Gdańsk, Poland

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