# ProMOL User Guide for Windows, Mac and Linux

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The creation of ProMOL distribution kits was originated by Nikolay Darakev, who created the PyMOL MINGW windows build process in 2008 (see http://sourceforge.net/apps/mediawiki/sbevsl/index.php?title=PyMOL_MINGW_Build_Instructions).

## Introduction:

ProMOL is a plugin for the PyMOL molecular graphics environment that can be used to create active site motifs for enzymes. The program is written in Python and developed for operating systems such as Windows (XP, 7, 8), Mac OS X (including Lion) and Linux. There are no significant difference while working with ProMOL on any of the three operating systems. The dissimilarity comes from the style of the window and the 3 buttons located at the top of it (Close, Minimize and Maximize).

### ProMOL includes the abilities:

- to make and store motif templates in a growing library of hundreds of existing motif templates,
- to request alignment with subsets of the motifs by template source,
- to view the optimal alignment between a motif template and a query structure, and
- to characterize a structure from the PDB or a structure provided by the user.

## Installation:

1. **Download and Install Python:** The first step is to install Python. The best available versions which will work quite well on your computer are 2.5, 2.6 and 2.7.
Python 3.0 (or higher) is not recommended because it requires some changes in the code of PyMOL and ProMOL**.** Both (PyMOL and ProMOL) need to be upgraded in order to work with the newest versions of Python.

   http://www.python.org/download/

2. **Download PyMOL:** Since ProMOL is a plugin for PyMOL the first program which needs to be installed is PyMOL. PyMOL is available as an open source program available as a source kit from :
   - http://sourceforge.net/projects/pymol/

   and as source and binary kits by following the instructions at one of following PyMOL wiki pages:

   - http://pymolwiki.org/index.php/Linux_Install
   - http://pymolwiki.org/index.php/MAC_Install
   - http://pymolwiki.org/index.php/Windows_Install

   A proprietary version of PyMOL is also available from:

   - http://www.pymol.org

   **If you are using Windows 8 and planning to install PyMOL from sourceforge.net you may experience some difficulties. After you run the program, a small window will pop up warning you that the program is "Unknown". You have to choose "more information" and then "Run anyway".**

3. **Install ProMOL:** ProMOL is available as a compressed format from :
   - http://sourceforge.net/projects/sbevsl/files/ProMOL/
   - www.promol.com

   You can choose between downloading a .zip or .tar.gz compressed file, depending on your preferences and operating system. Furthermore, you should download the latest ProMOL version available on the site.

   a. **Windows:**

- Expand the compressed file and run the .exe file
- Install ProMOL 5 setup
- The destination folder should be located here:

C:\Python27\Lib\site-packages\pmg_tk\startup

## b. Unix or Linux

- Expand the compressed file. In unix or linux systems, or using MINGW under Windows you may unpack the tarball with

  gunzip < sbevsl-ProMol-4-1.tar.gz | tar xvf

- Install ProMOL. Plugins that consist of a single python file (e.g. plugin.py) can be installed simply by using the Plugin->Manage Plugins->Install... menu. However, this does not work with ProMOL because you need to install the ProMOL folder as well as the promol.py file. So you will need to take the following steps:
  o Find the startup folder in your PyMOL installation. For the default installation of PyMOL 1.2 under Ubuntu linux, you can find the startup folder in /usr/lib/pymodules/python2.6/pmg_tk/startup.
  o Simply place the promol.py and ProMOL folders inside the startup folder. The next time you launch PyMOL, ProMOL should appear in your Plug-ins menu.
  o If you have installed PyMOL to another location on your system, you will need to copy promol.py and the ProMOL folder to the location of the pymol installation tree that contains:

    pmg_tk/startup

    Once you have completed the installation, launch PyMOL and look for ProMOL in the Plugin menu. When all files are in place, the ProMOL gui can be opened by selecting ProMOL from the plugin menu.

**c. Macintosh**:
- Rename your MacPyMOL application (for MacPyMOL ONLY, not pymol). Under Macintosh OSX, if you have MacPyMOL (as opposed to pymol installed using fink or macports) you will need use a copy of the MacPyMOL application (MacPyMOL.app) renamed PyMOLX11Hybrid (PyMOLX11Hybrid.app), in order to get access to plugins. This is not necessary for the versions of pymol (as opposed to MacPyMOL) installed using fink or macports.
- Expand the compressed file. Macintosh systems may have a native application that will expand your .tar.gz or .zip files; if not you may wish to consider using Stuffit Expander.

- Plugins that consist of a single python file (e.g. plugin.py) can be installed simply by using the Plugin->Manage Plugins->Install... menu. However, this does not work with ProMOL because you need to install the ProMOL folder as well as the promol.py file. This can be a bit tricky on the Mac, so follow these instructions closely if you have MacPyMol renamed as PyMOLX11Hybrid:
    o Find the startup folder in PyMOL.
        ▪ Open Finder -> Applications
        ▪ If you have a three button mouse, right click on MacPyMOLX11Hybrid and select Show Package Contents. This will take you to the directory tree for PyMOL. If you don't have a three button mouse, Ctrl-click should bring up the option to Show Package Contents.
        ▪ Traverse the tree to pymol/modules/pmg_tk/startup.
    o Copy promol.py and the ProMOL folder to the startup folder.

        If you installed PyMOL to some other location (e.g. using fink or macports), you will need to find the portion of the pymol installation tree that contains

        modules/pmg_tk/startup

and place promol.py and the ProMOL folder in the startup folder.  For example in a fink PyMOL installation for python 2.4, 2.5 or 2.6 under Macintosh OSX, the promol.py file and the ProMOL folder belong under
/sw/lib/pymol-py24/modules/pmg_tk/startup or
/sw/lib/pymol-py25/modules/pmg_tk/startup or
/sw/lib/pymol-py26/modules/pmg_tk/startup

- Once you have completed the installation, launch PyMOL and look for ProMOL in the Plugin menu. When all files are in place, the ProMOL GUI can be opened by selecting ProMOL from the plugin menu.


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**Special Notes for Installing ProMOL Under Mac OS X**

There are several alternate versions of PyMOL for use under Mac OS X. In order to install ProMOL, you need to use a version of PyMOL that accepts plugins.  In the example above, a "fink" installation was assumed.  Alternatively you may wish to use a MacPorts install, or to install MacPyMOL.  You will find instructions for all three at

http://pymolwiki.org/index.php/MAC_Install

However, it is important to note that, in order to have access to plugins and be able to install ProMOL, you need to use an X11 version, rather than an Aqua version. MacPyMOL works both ways. In order to tell MacPyMOL to work with X11 and make plugins available, you need to rename MacPYMOL.app to

PyMOLX11Hybrid.app first.


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**Components:**

The ProMOL interface has 5 tabs (Welcome, EZ-Viz, Motif Finder, Motif Maker, and View Options) as well as 4 buttons at the base of the GUI (Open PDB, Fetch PDB, Random PDB and Clear) that are always available.
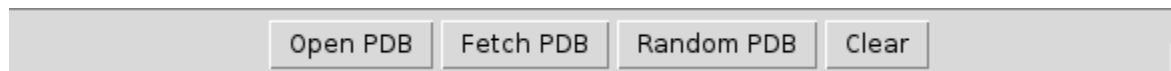
**Buttons on the ProMOL GUI:**

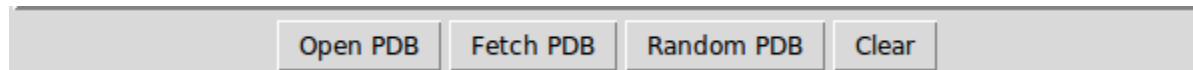The buttons on the bottom of the screen are always available, whenever ProMOL is open.

**Windows 8:**
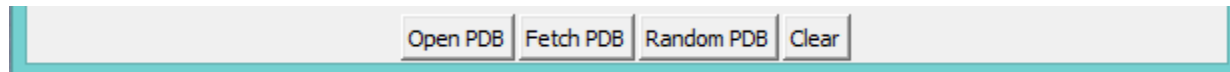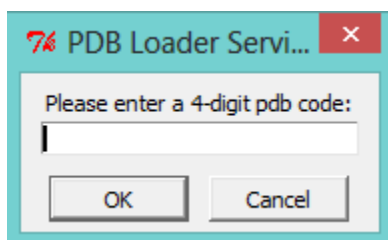


**Mac OS:**



**Linux:**



- **Open PDB** opens a dialog box that will let you search any storage devices connected to your computer for PDB files.
- **Fetch PDB** opens a dialog box that allows you to open a PDB file over the Internet, using the PDB Loader Service, a plug-in that is available on all PyMOL builds.



If you enter an invalid PDB code, you will receive an error message "You entered an invalid pdb code:  [pdb code] ".

The sample image was generated by entering "zzzz" as a PDB code:
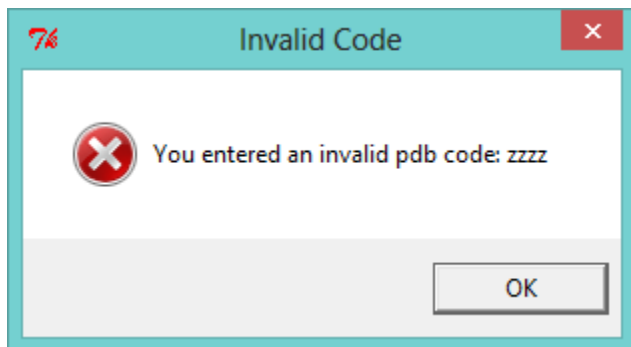


If you enter a valid PDB file, you will be able to see the result in the PyMOL Viewer window. (Example is provided in the "Tabs on the ProMOL GUI" – EZ Viz section)

- **Random PDB** loads a PDB file selected at random. This is a handy tool if you wish to test for true negatives and false positives when designing and testing motifs.
- **Clear** removes all structures that are visible in the molecular viewing screen

**Tabs on the ProMOL GUI:** The tabs are always available at the top of the screen:

**Windows 8:**



**Mac OS:**

**Linux:**



> ➢ **Welcome tab:** This is the opening screen for ProMOL.

Figure 1. ProMOL Welcome screen for Windows

Figure 2. ProMOL Welcome screen for Mac OS



**ProMOL 5.0-r219**

| Welcome | EZ-Viz | Motif Finder | Motif Maker | View Options |

## ProMOL
### Version 5.0-r219

```
Welcome to ProMOL.
All motifs loaded successfully.

Developed by the SBEVSL Project

Partial funding provided by:
NSF DUE 0402408
NIGMS 1R15GM078077
NIGMS 1R15GM078077-01
NIGMS 3R15GM078077-01S
NIGMS 2R15GM078077-02
NIGMS 3R15GM078077-02S1
RIT
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Place, Suite 330, Boston, MA 02111-1307 USA
```

| Open PDB | Fetch PDB | Random PDB | Clear |

Figure 3. ProMOL Welcome screen for Linux



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ProMOL 5.0-r209                                                    _ □ ×

 Welcome │ EZ-Viz │ Motif Finder │ Motif Maker │ View Options │

                          ProMOL
                     Version 5.0-r209

 Welcome to ProMOL.
 All motifs loaded successfully.

 Developed by the SBEVSL Project

 Partial funding provided by:
 NSF DUE 0402408
 NIGMS 1R15GM078077
 NIGMS 1R15GM078077-01
 NIGMS 3R15GM078077-01S
 NIGMS 2R15GM078077-02
 NIGMS 3R15GM078077-02S1
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 this program; if not, write to the Free Software Foundation, Inc., 59 Temple
 Place, Suite 330, Boston, MA 02111-1307 USA


            Open PDB    Fetch PDB    Random PDB    Clear
```

**ProMOL** is released under a Gnu Public License
(http://www.gnu.org/licenses/gpl.html).
The screen credits refer to funding from the National Institute of General
Medical Science, a division of the National Institute of Health, and to the
National Science Foundation Division for Undergraduate Education. Partial
funding is also provided by RIT and Dowling College.

➢ **EZ-Viz tab:** Once a protein is loaded, the EZ-Viz tab enables users to create interesting views and movies of their macromolecular structures using the drop down menus. Users do not need to learn and use PyMOL (or Python) commands to manipulate their structures with EZ-Viz. Screenshots for the EZ-Viz tab for the three operating systems are shown here.

Figure 4. ProMOL EZ-Viz tab for Windows
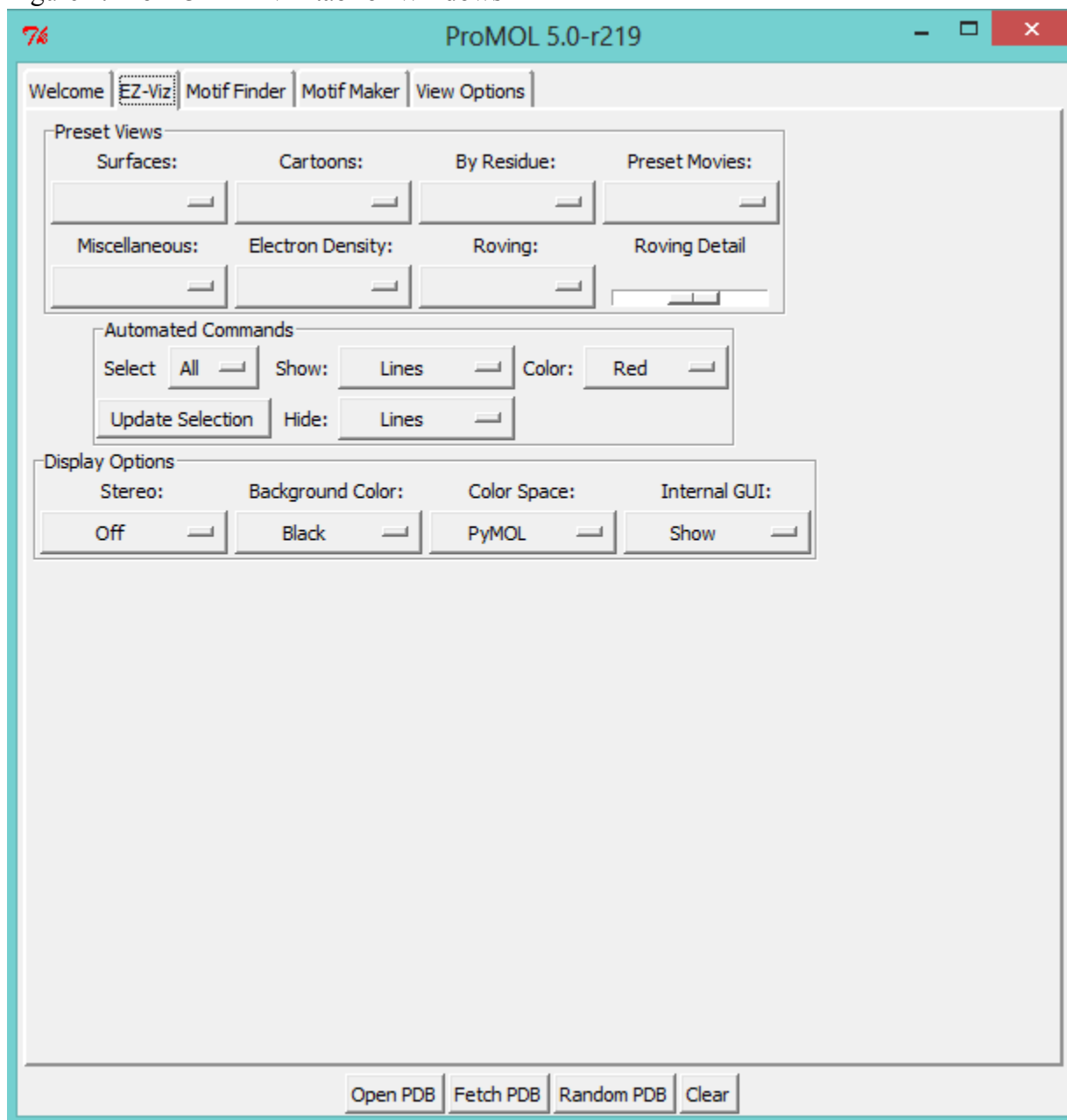
Figure 5. ProMOL EZ-Viz tab for Mac OS

Figure 6. ProMOL EZ-Viz tab for Linux
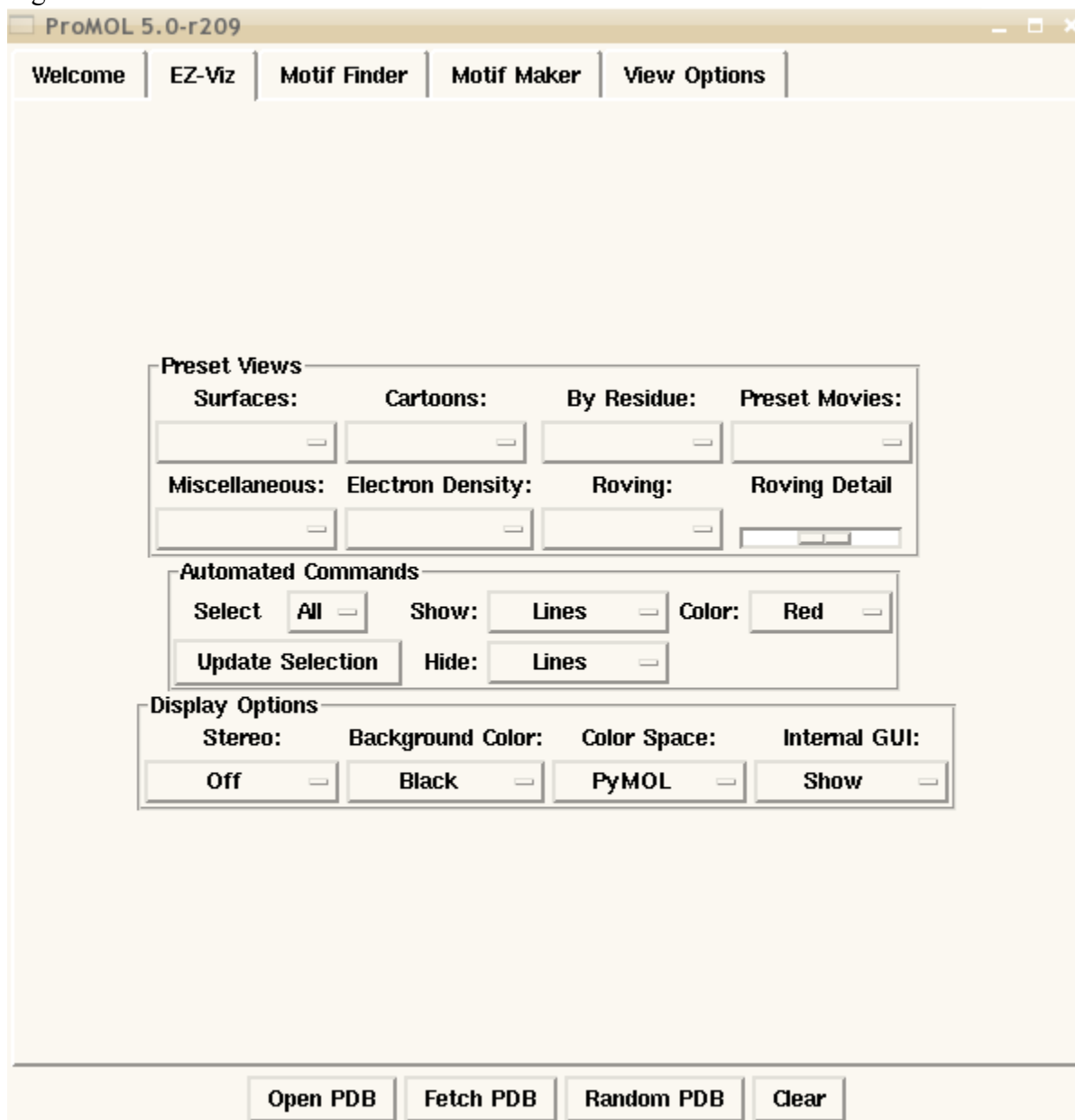


**Using EZ-Viz:**

1. Open a PDB file in PyMOL. (You can simply do this using the Fetch
   PDB button on the bottom of the ProMOL GUI). The next thing you will
   see is the popup window
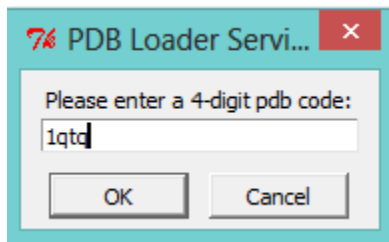
Enter the PDB ID for a structure of interest and click the OK button. For this example we will use 1qtq (glutaminyl tRNA synthetase complexed with tRNA and an amino acid analog). When you do this, the structure will appear in the PyMOL viewer window as a simple stick figure, where each stick represent a bond between two atoms in the structure.
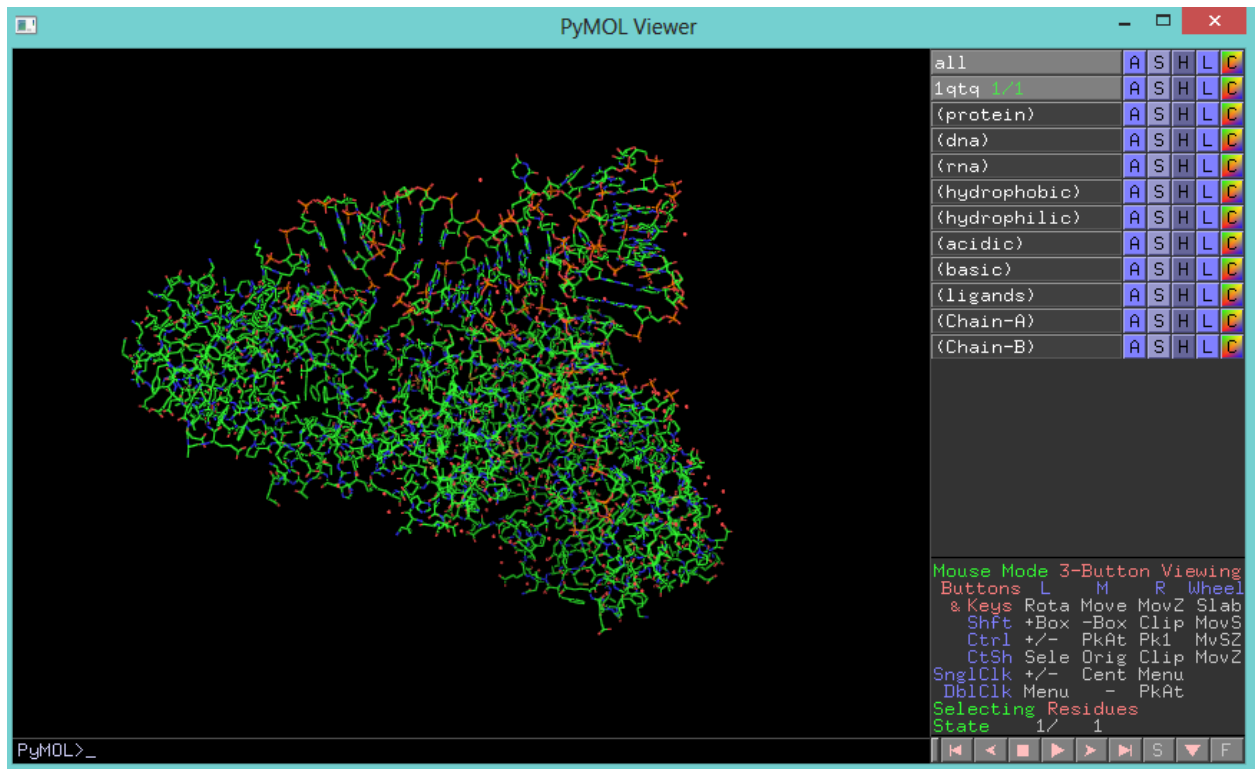


After you see this image you can change the appearance of the structure to generate a number of different views using the options in **the Preset View** area on the EZ-Viz tab. For example, you can select the **Cartoons** from the **Cartoon menu** and this will generate a view which will show

the protein as a cartoon, the DNA as a stick structure and the waters as spheres. You can also choose to remove the water from the image by selecting **Water** from the **Hide menu** in the **Automated Commands** area of EZ-Viz. You can easily manipulate and change the appearance of the structure by selecting some of the command in the **Automated Commands** area (**Select**, **Show**, **Color** and **Hide**)

**The Display Options** menu supports changing the status of the stereo mode, background color, color palette and the internal GUI for PyMOL, which appears on the right hand side of the viewer window. The internal GUI contains a list of selections within PyMOL, information about the Mouse Mode in PyMOL and the control buttons for movies within PyMOL.

This is the Cartoon version of 1qtq as implemented in EZ-Viz:
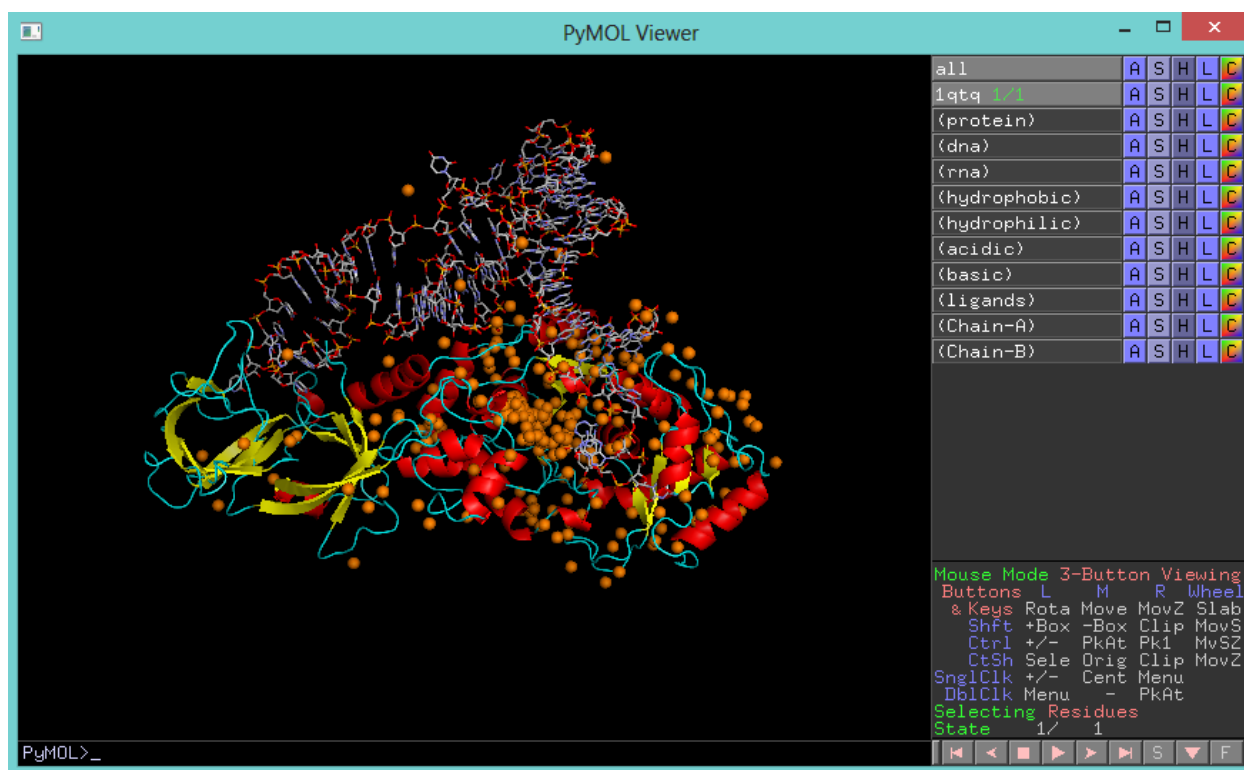


Now, let's take a look of what will happen if we hide the waters:
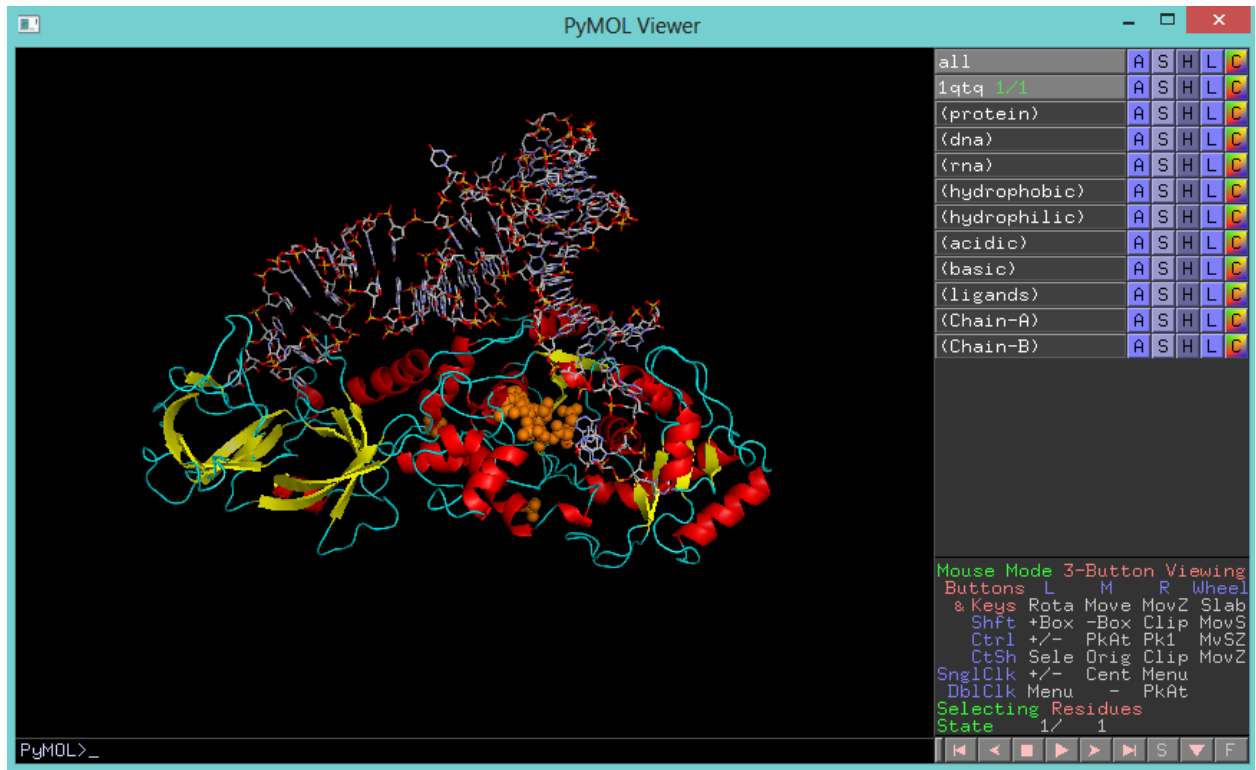
> **Motif Finder tab:**

The Motif Finder tab gives the user access to the motif search tools in ProMOL. The ProMOL code contains three sets of motifs based on three different approaches to catalytic site alignment:

- **The ProMOL motifs** were built using the ProMOL Motif Maker (Motif Maker tab), utilizing the same catalytic residues identified in the CSA.
- **The A Set** motifs were created with an automated algorithm that systematically called the motif generating routines and comparing the matching subset (the collection of residues returned by ProMOL that satisfy the residue type and distance constraints) to the residues in the motif definition.
- **The UserMotifs** are the ones that the user creates with ProMOL. They can be found in the folder:
  - Mac:

/Users/***username***/Library/Application Support/SBEVSL/ProMOL/UserMotifs
- o Windows: \Users\***username***\AppData\Roaming\SBEVSL\ProMOL\UserMotifs
- o Linux: $Home/.sbevsl/ProMol/UserMotifs

Figure 7. ProMOL Motif Finder tab for Windows
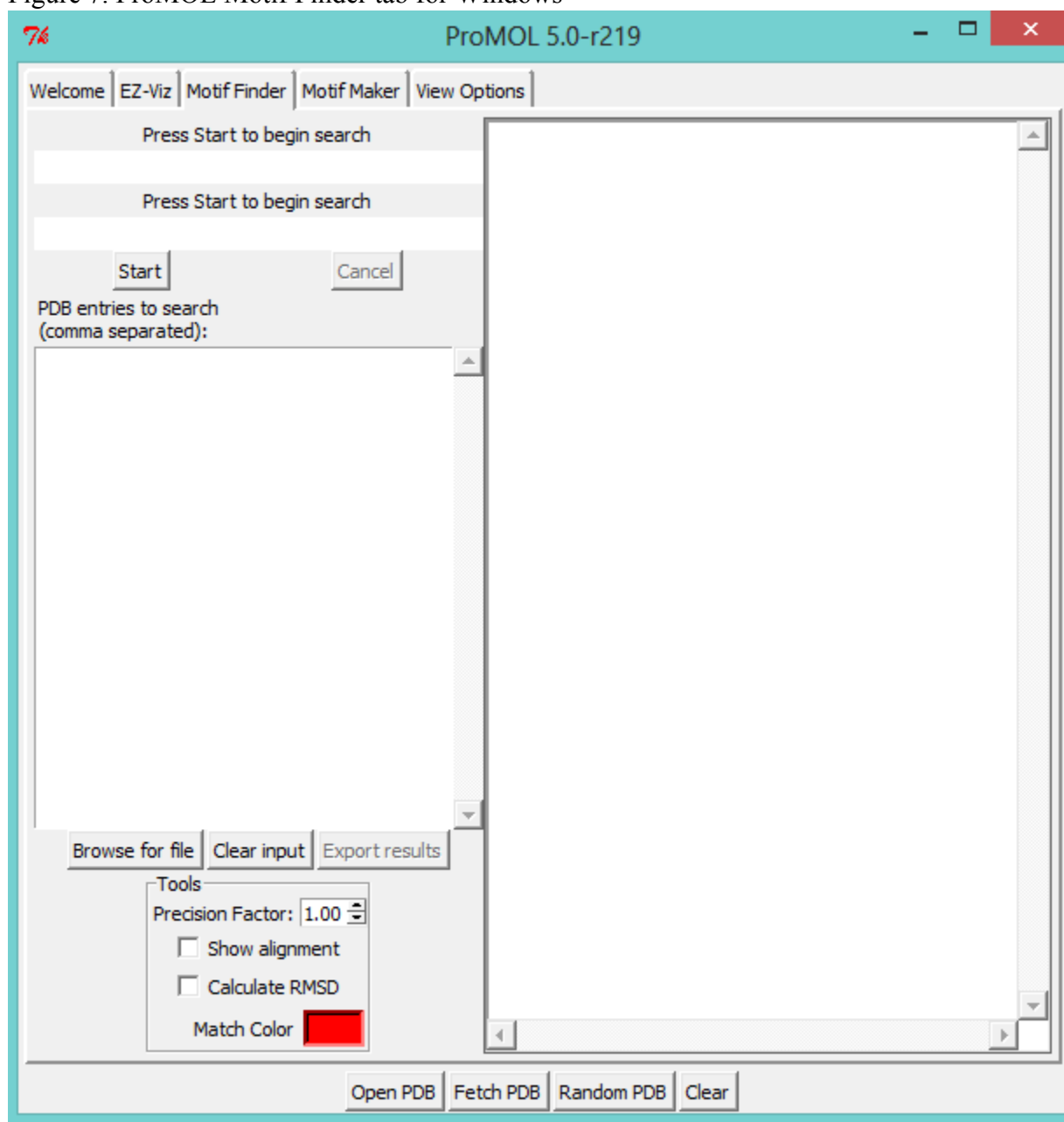
Figure 8. ProMOL Motif Finder tab for Mac OS
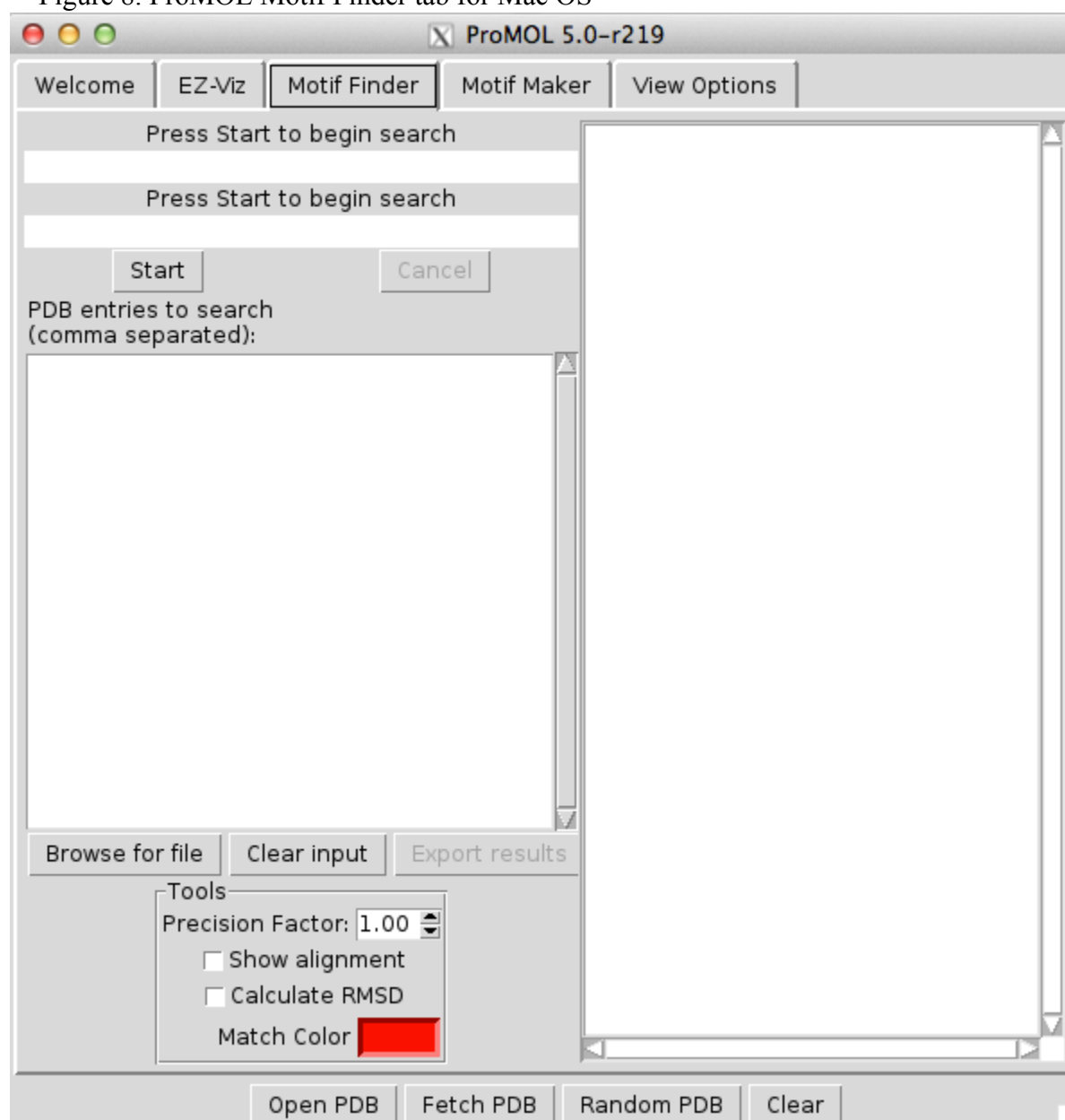
Figure 9. ProMOL Motif Finder tab for Linux
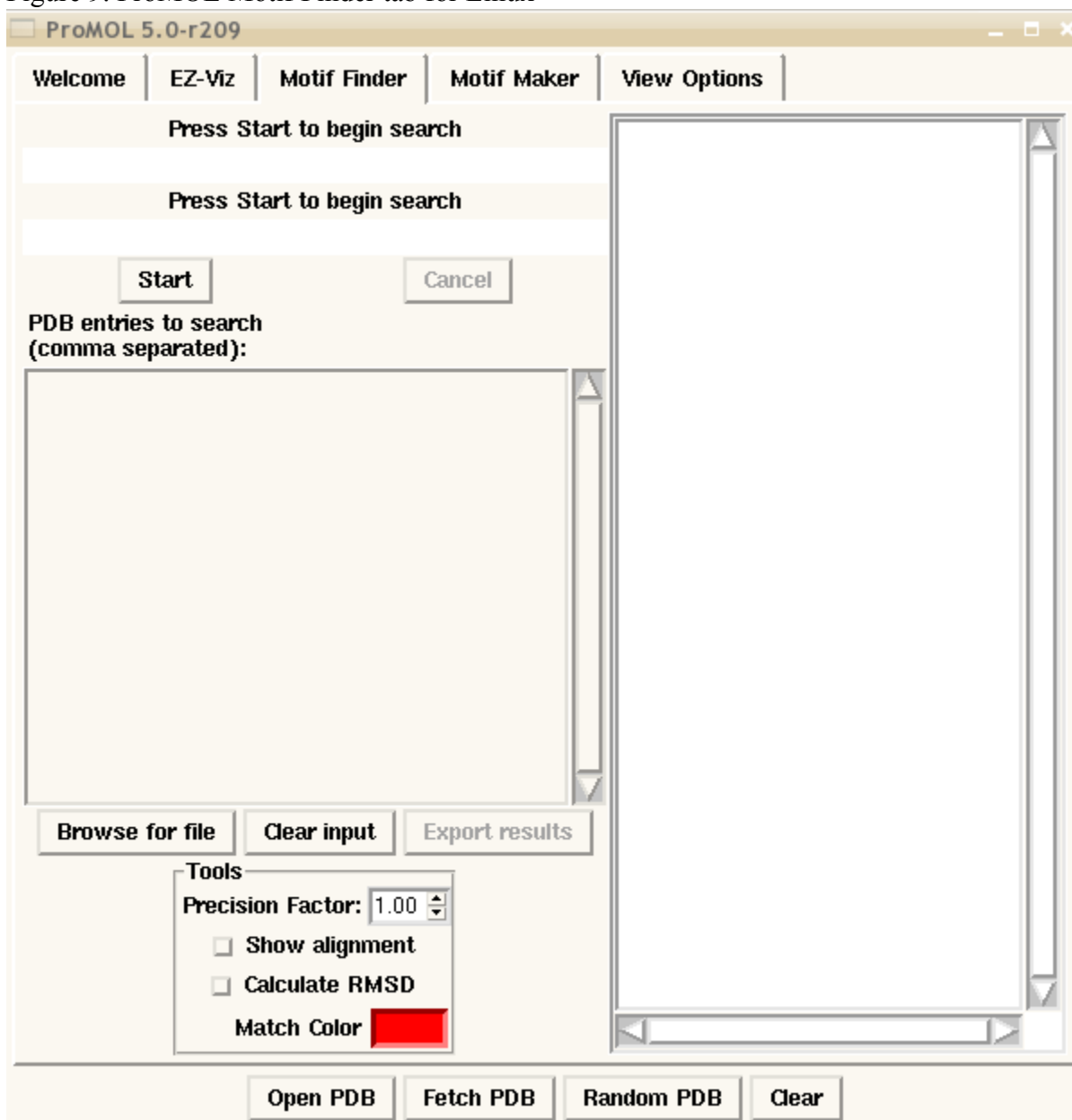


To use the Motif Finder, a protein must be loaded into PyMOL. You can do this by entering a PDB id in the box "PDB(s) to search". If you wish to search more than one structure at a time, just enter the PDB IDs separated by commas.

In case you want to clear the "PDB entrees to search" box, you just have to click on the "Clear input" button located right below the "PDB entries to search" box.
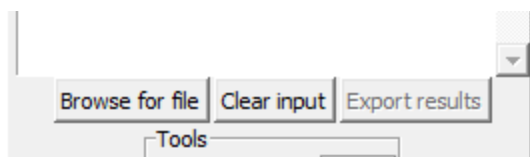
When you enter the PDB id, click the Start Button to begin searching for motifs. A popup window will appear and ask you to choose which set of motifs you would like to search against. If you choose "All Motifs" it may take a while (about 5 – 8 minutes per query structure against 200 motifs). On the other hand, if you focus on a small number of motifs, the search will be much quicker.

Once you have decided which motif set to use, you need to decide if you would like to calculate the RMSD value for each alignment. RMSD is a measure of "closeness of fit" when two structures are aligned. This additional data can be very useful, but it will add significant time to the Motif Finder search. For initial screening, we suggest that you select No for this option to increase speed.
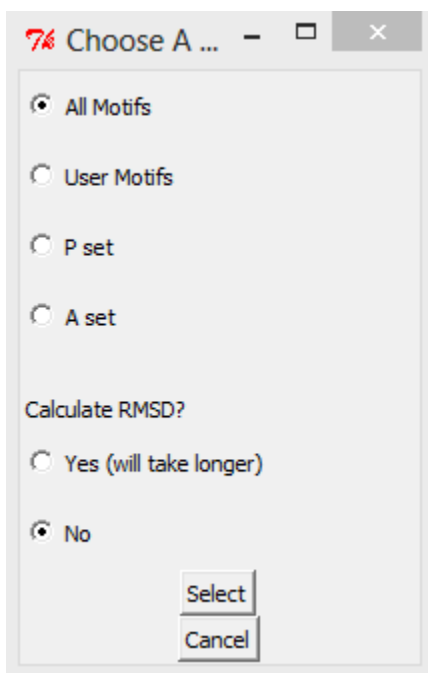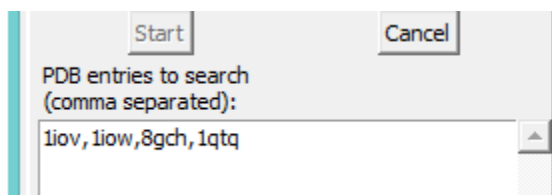
Once you have chosen your motif set, the search will begin. At the top of the windows (under the tabs) you will notice two progress bars. The top bar indicates the search progress for an individual structure, while the bottom bar indicates the overall progress for the full list of structures that are under evaluation.
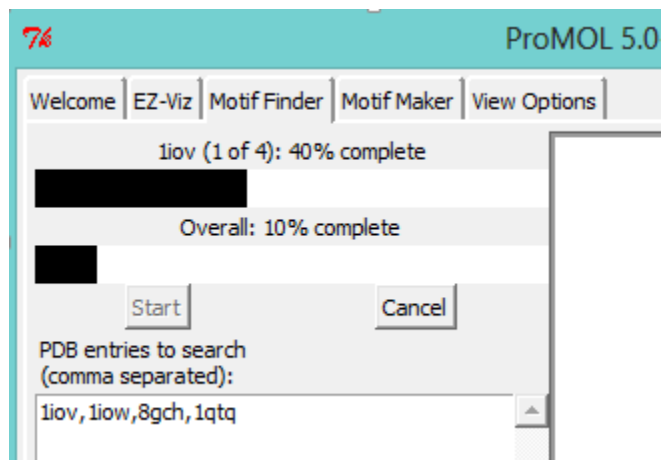


When the search is complete, the results will appear in the box on the right side of the "Motif Finder - tab "window. The results are reported by PDB id in a scrollable window.
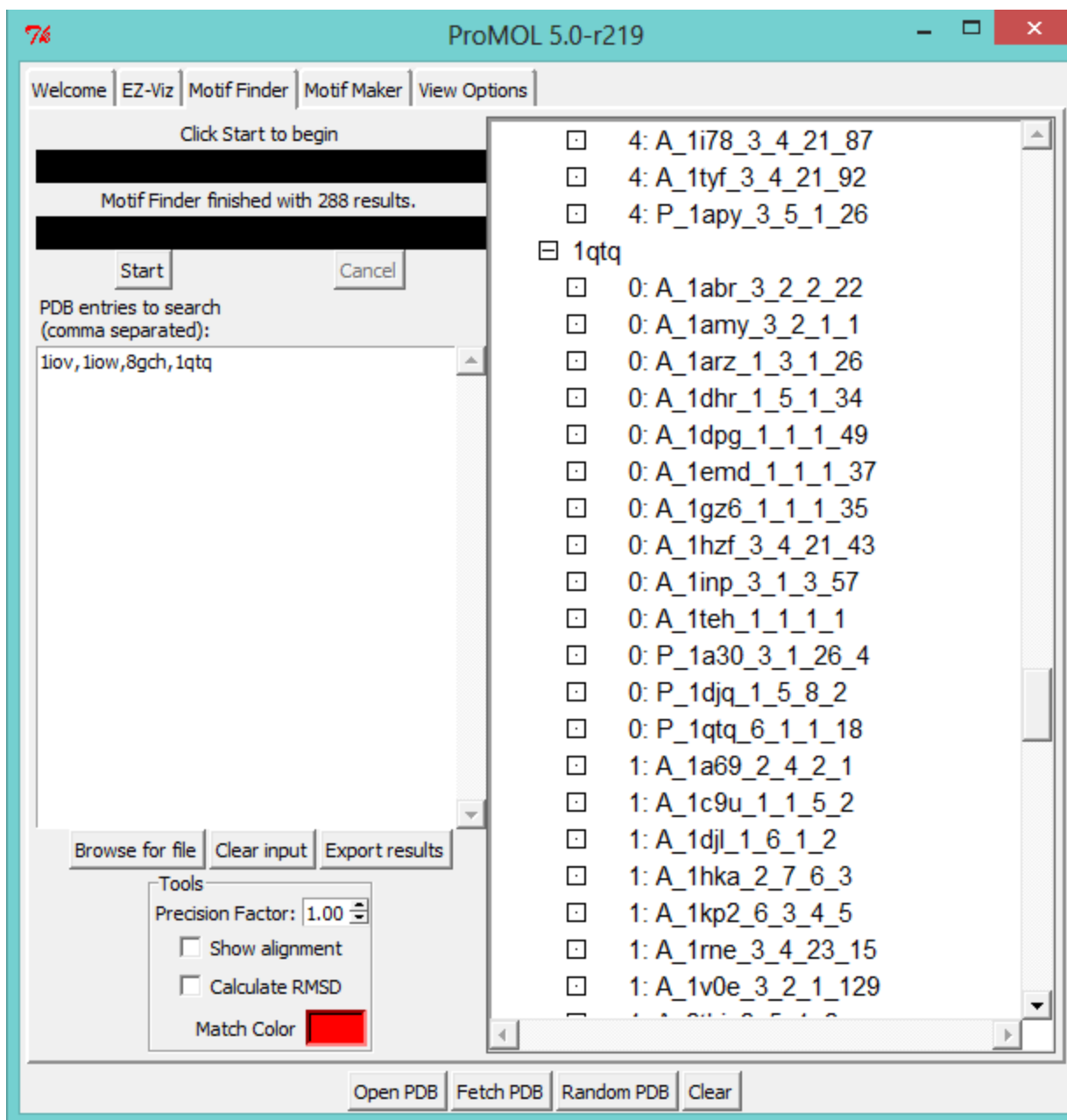
## Results

Each alignment is given a score based on a Levenshtein distance, which reflects the number of differences between the query structure and the template motifs that are listed there. In simple terms, the Levenshtein distance from the word "horse" to the word "house" is 1, since you need to change the 3<sup>rd</sup> letter from an "r" in horse to a "u" in house. If we take a look at the example from above, the 3rd result is a comparison of 1qtq to itself. You will notice that the Levenshtein distance is 0.

Levenshtein distance of 0 means that there are no changes – all of the amino acids in the active site of the template structure have been found in the active site of the query structure.
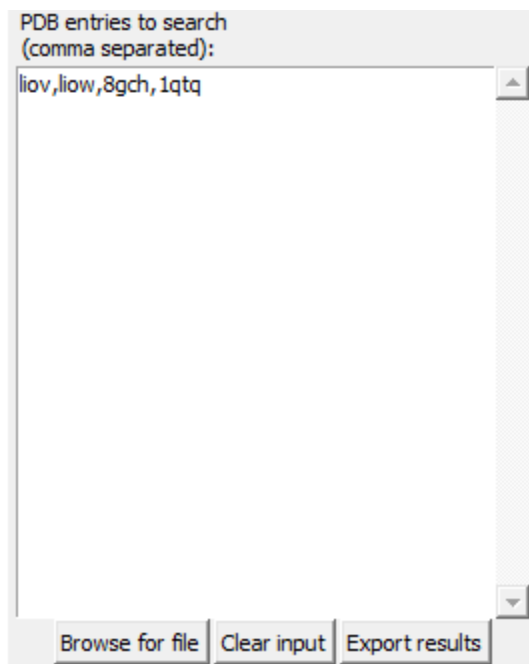
Motif-group. There are currently three motif groups in ProMOL // TODO -We need to add information about the A set!

- o Pab means the motif was created by ProMOL based on the alpha and beta carbons of the amino acids in the pdb template.
- o Pfa means the motif was created by ProMOL based on the alpha carbons, beta carbons and one side chain atom found in the pdb template.
- o U means that this is a motif the user created using Motif Maker.

**Template-file** is the pdb id for the structure that was used to build the template.

**EC#** is the Enzyme Commission number as reported by the Protein Data Bank.

If you want to export the result as a .csv file, you have to click on the "Export result" button located right after the labeled box "PDB entries to search".



**Motif Finder** window will also provide you with few other opportunities. In the "Tools" box located at the bottom of the window (right after the "PDB entries to

search" box) there are four tools – "Precision Factor", "Show alignment", "Calculate RMSD" and "Match Color".
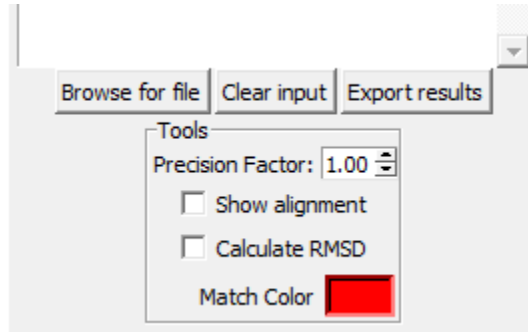


- **Precision Factor** is a multiplier of the distances in the motif, providing a way to relax or tighten the constraints for a match.
- **Show alignment -** We can compare the active sites for 1djq and 1qtq directly using the alignment tools found on the lower left hand corner of the Motif Finder tab. Simply click the Show alignment check box, then double click on the template motif that you want to superimpose on the query motif (P_1djq_1_5_8_2 in this case).

Figure 10. Motif Finder Search results for 1qtq (Windows)
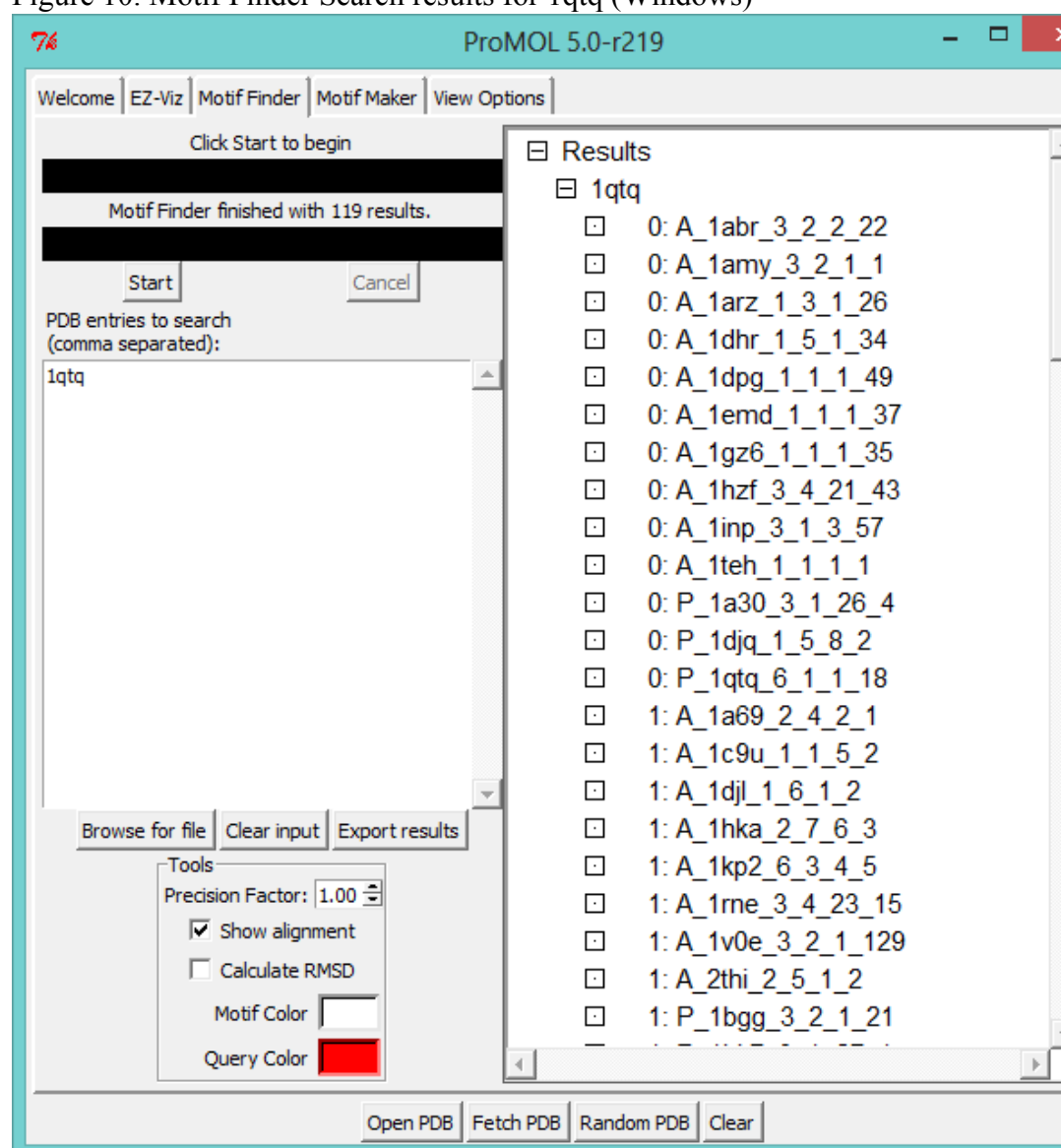
Figure 11. Motif Finder Search results for 1qtq (Mac OS)
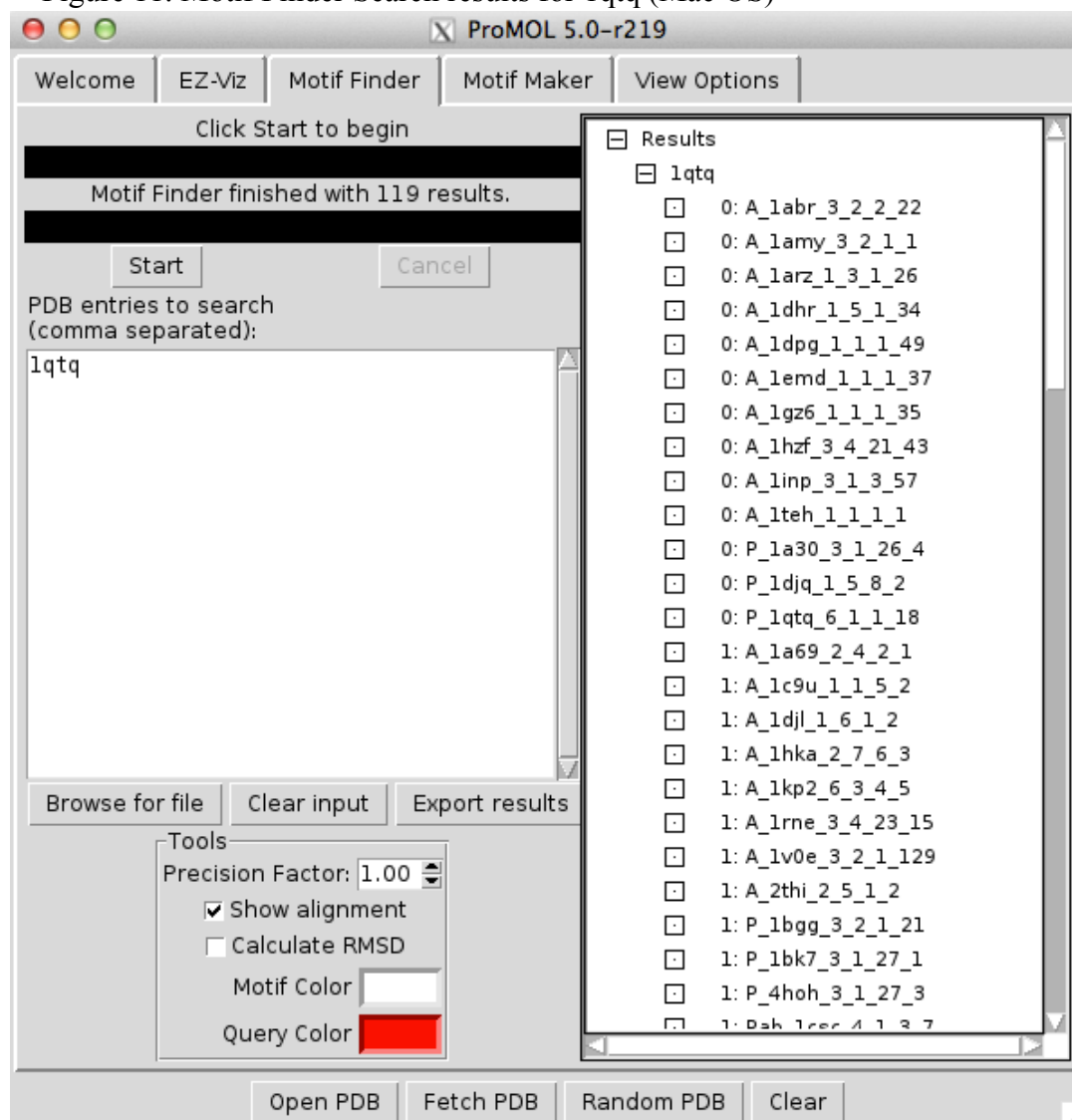
The result is shown here:
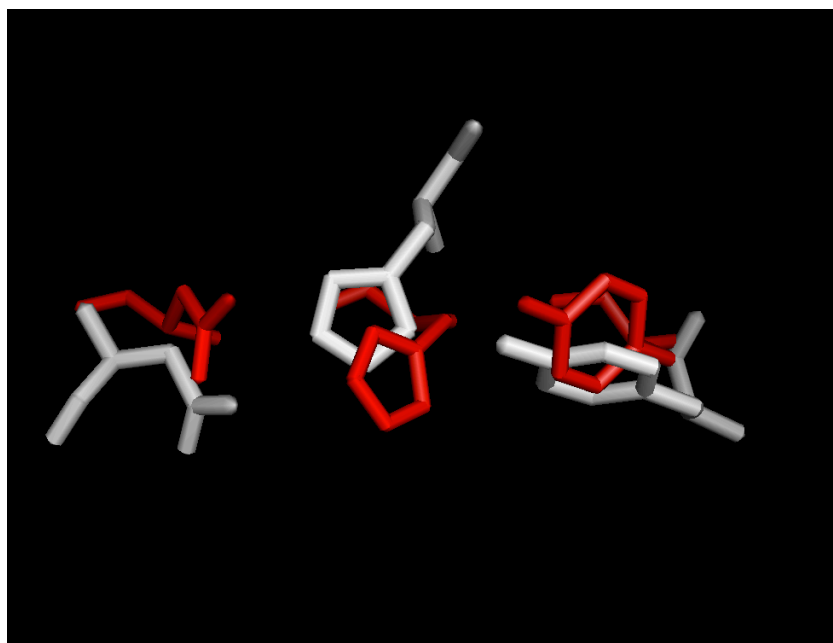


The alignment is not perfect, but the three residues (aspartate 267, histidine 172 and tyrosine 169 in 1djq; aspartate 219, histidine 215 and tyrosine 211 in 1qtq) are found in similar proximity in the two structures.

- **Calculate RMSD** is a new feature in ProMOL 5. RMSD calculations were added to ProMOL in order to allow more exact quantitative comparison of structural alignments. You can simply check the "Calculate RMSD" box for the search to find the route-mean-square distance between the query and the template active site. ProMOL performs calculations for three different comparisons between the two active sites: all atoms, alpha carbons only, and alpha/beta carbons. Lower RMSD values indicate a better match and can be used to discriminate between two alignments that have the same Levenshtein distance. For example, the RMSD all atom value for the 1qtq/1djq alignment is 2.5056 Angstroms, while the RMSD all atom value for the 1qtq alignment with itself is 0 Angstroms, indicating a much better match.

Figure 12. Motif Finder Search results for 1qtq with RMSD calculation included (Windows)
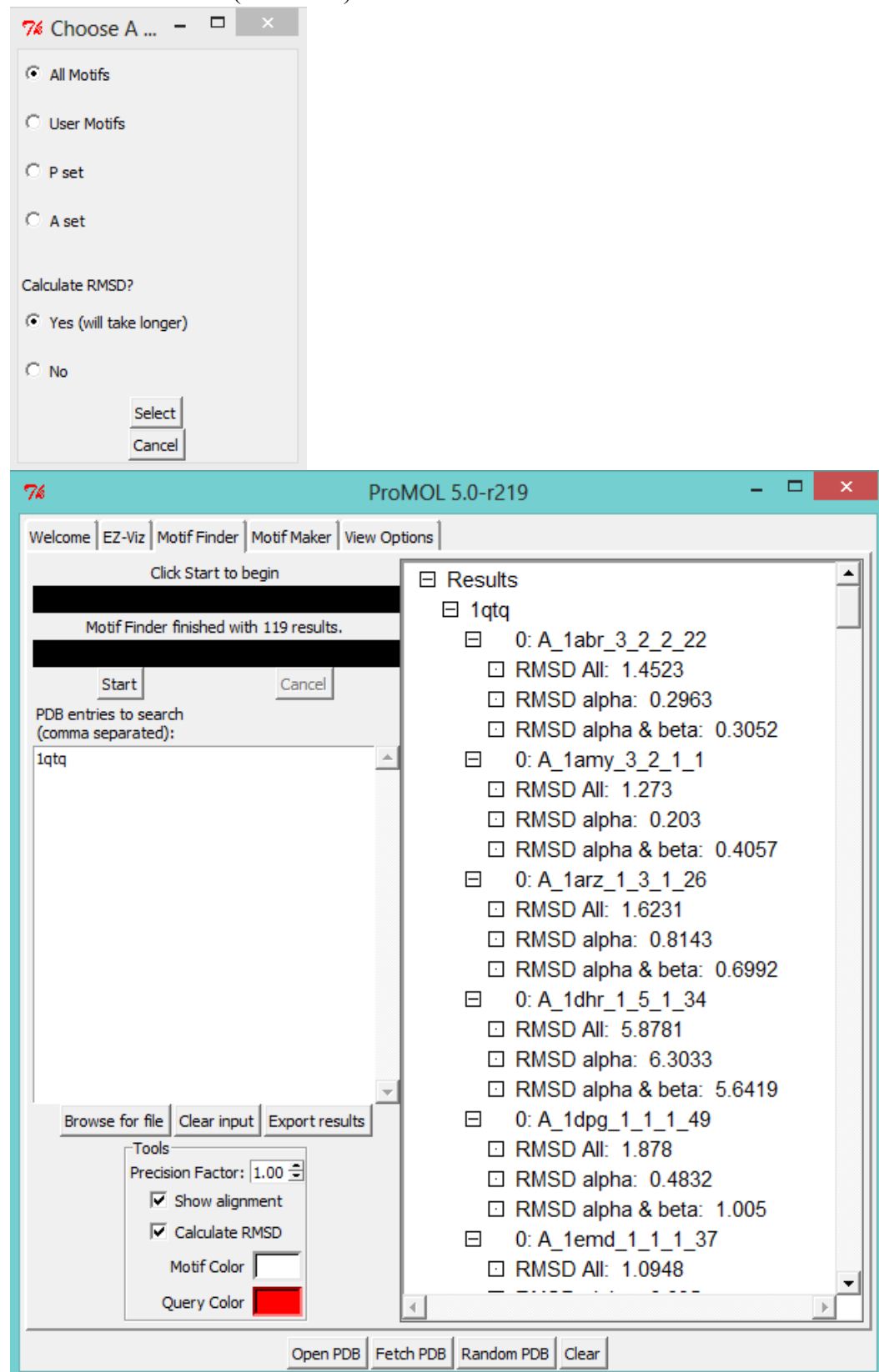
Figure 13. Motif Finder Search results for 1qtq with RMSD calculation included (Mac OS)
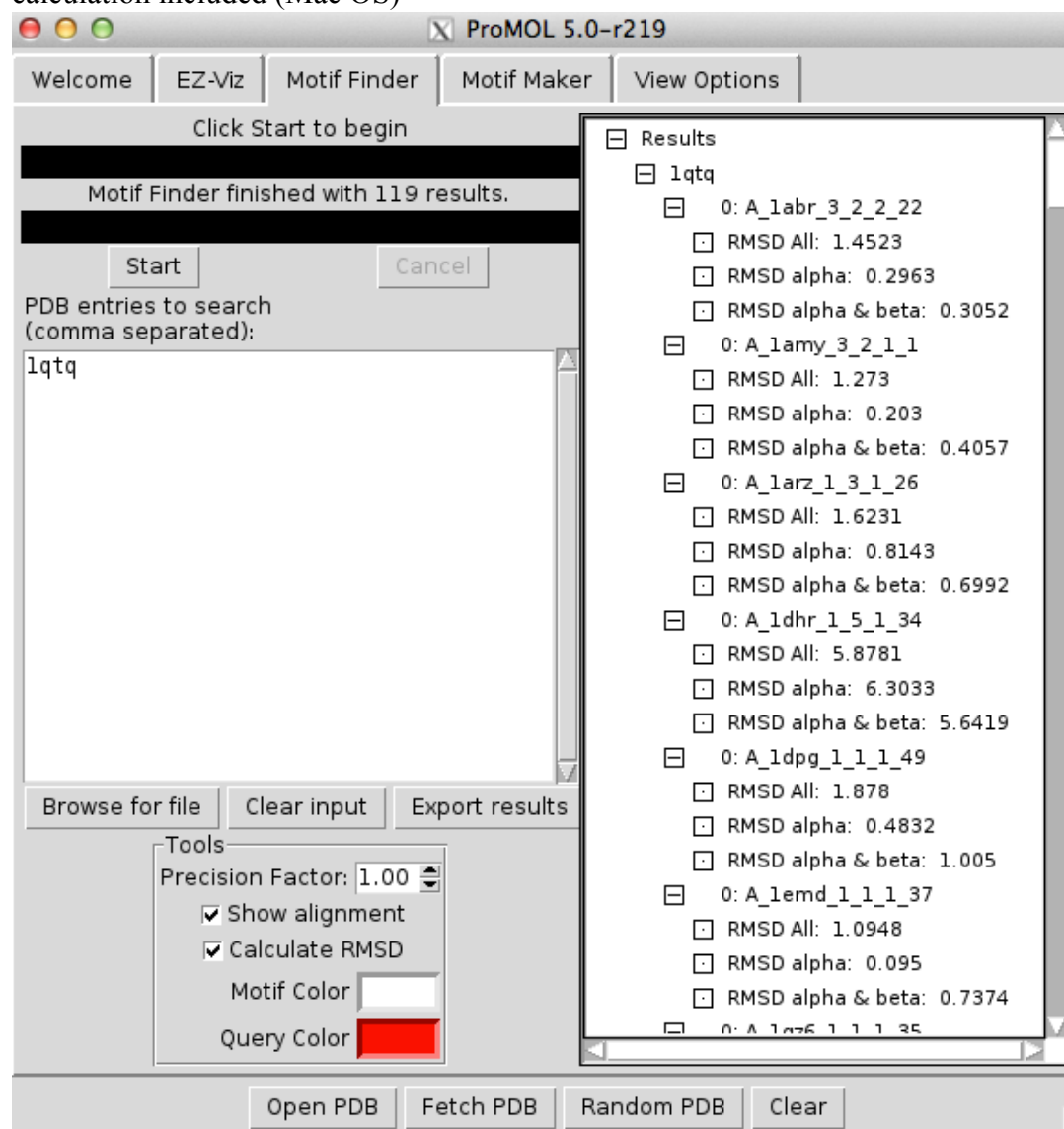
Figure 14. Motif Finder Search results for 1qtq with RMSD
calculation included (Linux)
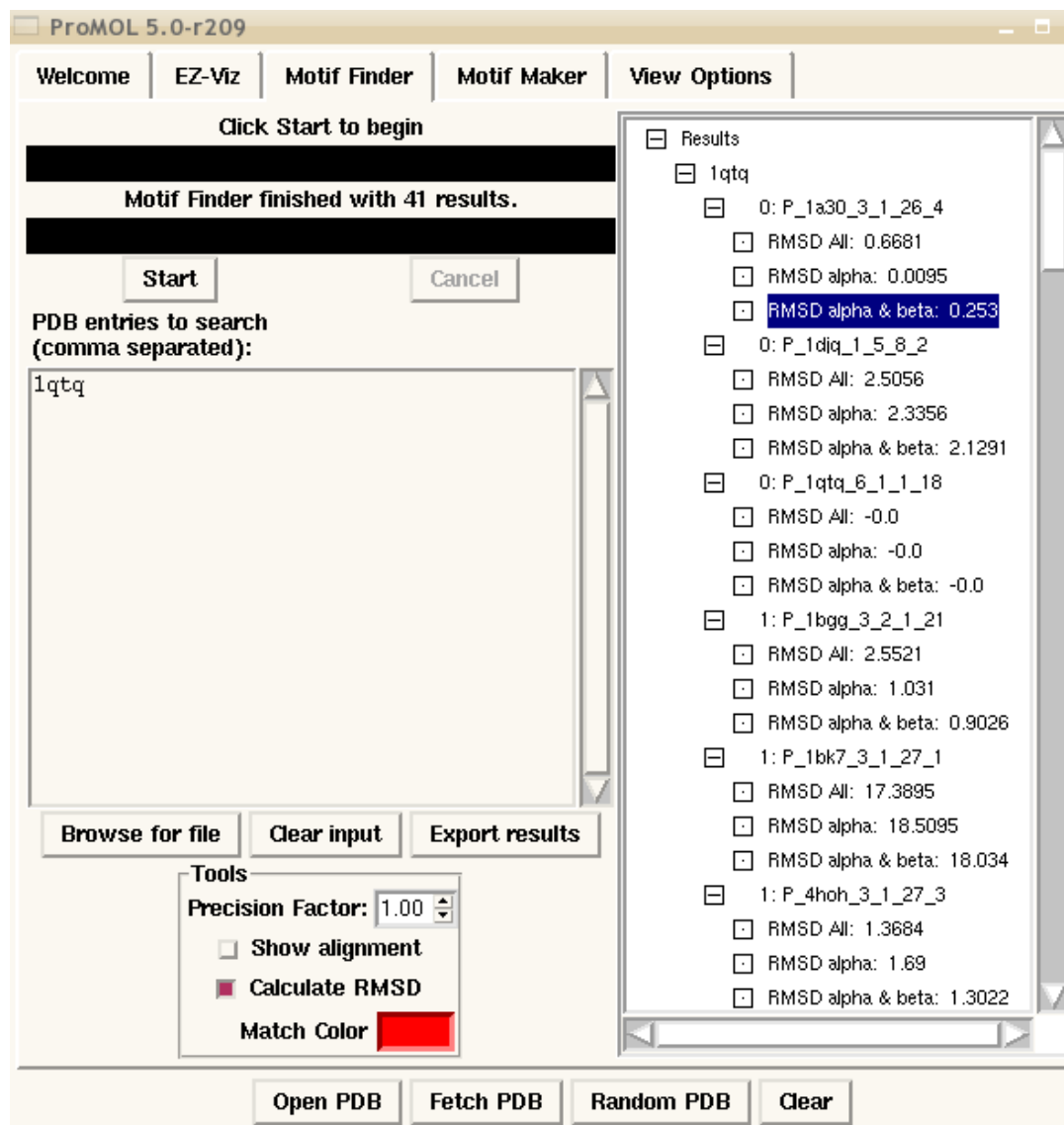


- **Match color** is another great feature which allows the users
  to change the colors used in the alignment.
  It is possible to change the colors used in the alignment by
  clicking on the colored square next to either Template Color
  of Motif Color in the Show Alignment toolbox on the Motif
  Finder tab. You can also click on individual residues in the
  PyMOL viewer window and the residue will be identified in

the PyMOL GUI. For 1qtq, you will receive this notice if you click on the beta carbon from Glutamate residue=34, "You clicked /1qtq//A/GLU'34/CB"."

➢ **Motif Maker**

The Motif Maker tab enables the user to build motifs based on definitions in the Catalytic Site Atlas. Motif definitions in ProMOL are based on enzyme family representatives selected from the PDB and information from the CSA. The distances between each atom from each of the residues in a catalytic site were measured using PyMOL's built in the measurement function. These measured distances were used to create the three-dimensional motif definition for that catalytic site. The motif definitions are then used to predict the presence of a catalytic site on the structure being tested.

Figure 15. ProMOL Motif Maker tab (Windows)

Figure 16. ProMOL Motif Maker tab (Mac OS)

Figure 17. ProMOL Motif Maker tab (Linux)



Here is a step-by-step description of how to create a motif for 3α – hydroxysteroid dehydrogenase type 3, based on pdb entry 1j96.

3α – hydroxysteroid dehydrogenase type 3(PDB id 1j96) is an annotated entry in the catalytic site atlas (CSA: http://www.ebi.ac.uk/thornton-srv/databases/cgi-

[bin/CSA/CSA_Site_Wrapper.pl](http://www.ebi.ac.uk/thornton-srv/databases/CSA_NEW/cgi-bin/CSA/CSA_Site_Wrapper.pl)) Open the CSA in your browser and then enter 1j96 (or the desired structure) in the PDB id box and then hit the Search Button.

The following page should appear:



In order to build a motif, you will need several pieces of information about a structure that you can find on the CSA page:  PDB is, EC# and the residues that constitute its active site. The information for 3α – hydroxysteroid dehydrogenase type 3, obtained from the CSA website, was entered into the Motif Maker window as shown here:

Once a motif has been entered in Motif Maker, it can be tasted on the template structure by clicking the test button found in the Motif Maker box. A test of this motif yielded an immediate match of only the desired residues. If additional residues appear (due to the distance between residues in some catalytic sites), there are ways to adjust the motif to select the desired residues. First, the precision factor can be reduced (The precision factor is a multiplier that is applied to the distances between the residues in the catalytic site.)The next adjustment is made by turning the backbone atoms on – this simply adds the backbone atoms for the residues into the motif definition. The motif definition can sometimes be improved by changing

the order of the residues as they are entered in the Motif Maker box. It is often advantageous to list the residues in the order of least common in a structure to most common in that same structure.

Once you are satisfied with a motif, click on the Save button in the Motif Maker box and the motif will be saved to your computer. The exact location of the file depends on your operating system.

- Mac OS: The motif definition file is saved as [ ] to [ ]
- Windows XP/7/8: The motif definition file is saved as U_1j96_1_3_1_20.py to C:\Users\Maria\AppData\Roaming\SBEVSL\ProMol\UserMotifs

The next step in designing a motif is to test it against homologs. A list of homologs can be found on the Catalytic Site Atlas by clicking the Homologues of 1j96 link (or the selected structure) found under Other CSA Entries. In the case of 1j96, more than 100 homologs are listed. To test a homolog, first enter the PDB code in the Homolog and Random Testing box on the Motif Maker window, then click the test button in the same box. Table 1 contains a list of structures tested and briefly summarizes the results. The first 10 homologs listed in the CSA were tested, then homologs found 10, 20 and 40 positions later in the table were tested.

| Homolog # | PDB id | Active Site Found? | Extraneous or Missing Residues |
|---|---|---|---|
| | 1j96 | Yes. Asp50, Tyr55, Lys84, His117 | None |
| 1 | 1mrq | Yes. Asp50, Tyr55, Lys84, His117 | None |
| 2 | 2alr | Yes. Asp44, Tyr49, Lys79, His112 | Asp170 |
| 3 | 2acu | No | No Tyrosine in the active site |
| 4 | 1a80 | No It was found if the Precision Factor was increased to 2.3. | Asp45, Tyr50, Lys75, His108 |
| 5 | 1abn | No | No motif found. The PDB file is alpha carbons only and won't work with ProMOL |
| 6 | 1ads | Yes. Asp43, Tyr48, Lys77, | No |

| | | | |
|---|---|---|---|
| | | His110 | |
| 7 | 1ae4 | No | No. Alpha carbons only |
| 8 | 1afs | Yes. Asp50, Tyr55, Lys84, His117 in both Chains A and B | No |
| 9 | 1ah0 | Yes. Asp43, Tyr48, Lys77, His110 | No |
| 10 | 1ah3 | Yes. Asp43, Tyr48, Lys77, His110 | No |
| 20 | 1el3 | Yes. Asp 43, Tyr48, Lys77, His110 | No |
| 30 | 1lwi | Yes. Asp50, Tyr55, Lys84, His117 in both chains A and B | No |
| 50 | 1s2a | Yes. Asp50, Tyr55, Lys84, His117 | |

When a new motif is built in Motif Maker, it should be tested with 10 or more homologs of the structure. The purpose of this testing is to look for **true positives** – structures in which ProMOL clearly identifies the existing motif correctly. Some may match perfectly; others may match poorly or not at all. In the case of a poor or non-existent match, the researcher then needs to explore the structure. Typical reasons for a poor match are substitutions in the structure (perhaps a serine was replace with a lysine by site-directed mutagenesis to give a more stable crystal), the absence of the catalytic site (homology is based on the entire sequence, not just the few residues in the catalytic site), or an overly constrained motif maker definition file.

The next stage in motif testing is a search for **false negatives** – structures that ProMOL incorrectly identifies as containing the motif. To that end, we usually test the motif against 10 randomly selected PDB files. This is done by clicking the Random radio button in the Homolog and Random Testing box, then clicking on the test button 10 times. The 1j96 motif was tested 10 times on randomly selected files (1dzk, 2l35, 1e4d, 2mgc, 1pic, 1u6j, 2eq7, 1ztz, 1q8o, 1rkc) and none returned an active site. For this limited test then, no false positives were returned.

> **View Options**

Users can visit the View Options tab (Figure 17) to adjust the way PyMOL generates images of their structures. The Preset Views box of the EZ-Viz tab enables users to generate interesting views of structures without coding in Python. The View Options tab can then be used to adjust the appearance of cartoons, spheres, sticks, and surfaces found in a structure; it is also possible to adjust the ambient light, much as a photographer would adjust the lighting in an indoor studio to provide the best view.

Figure 18. ProMOL View Options tab (Windows)
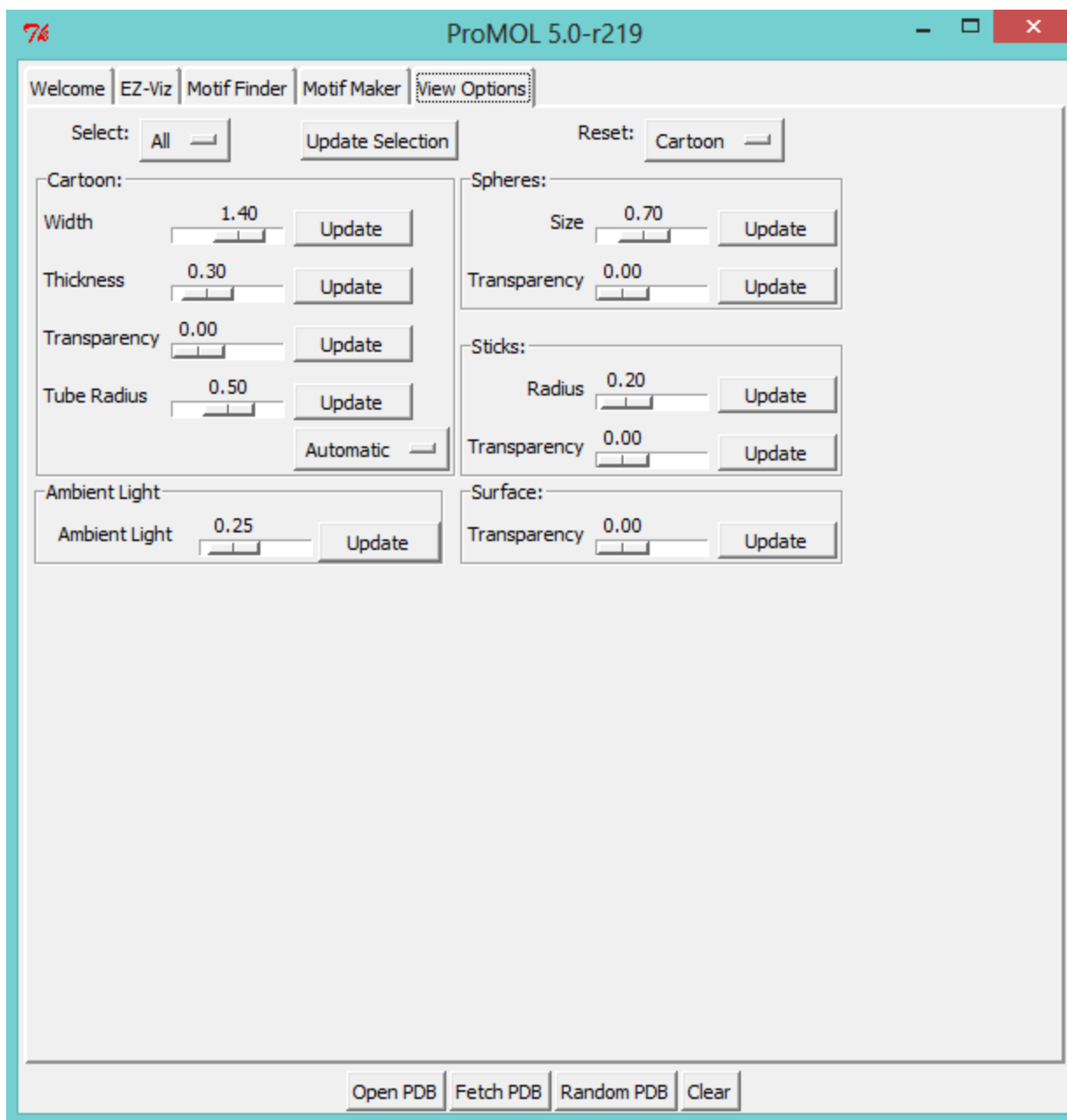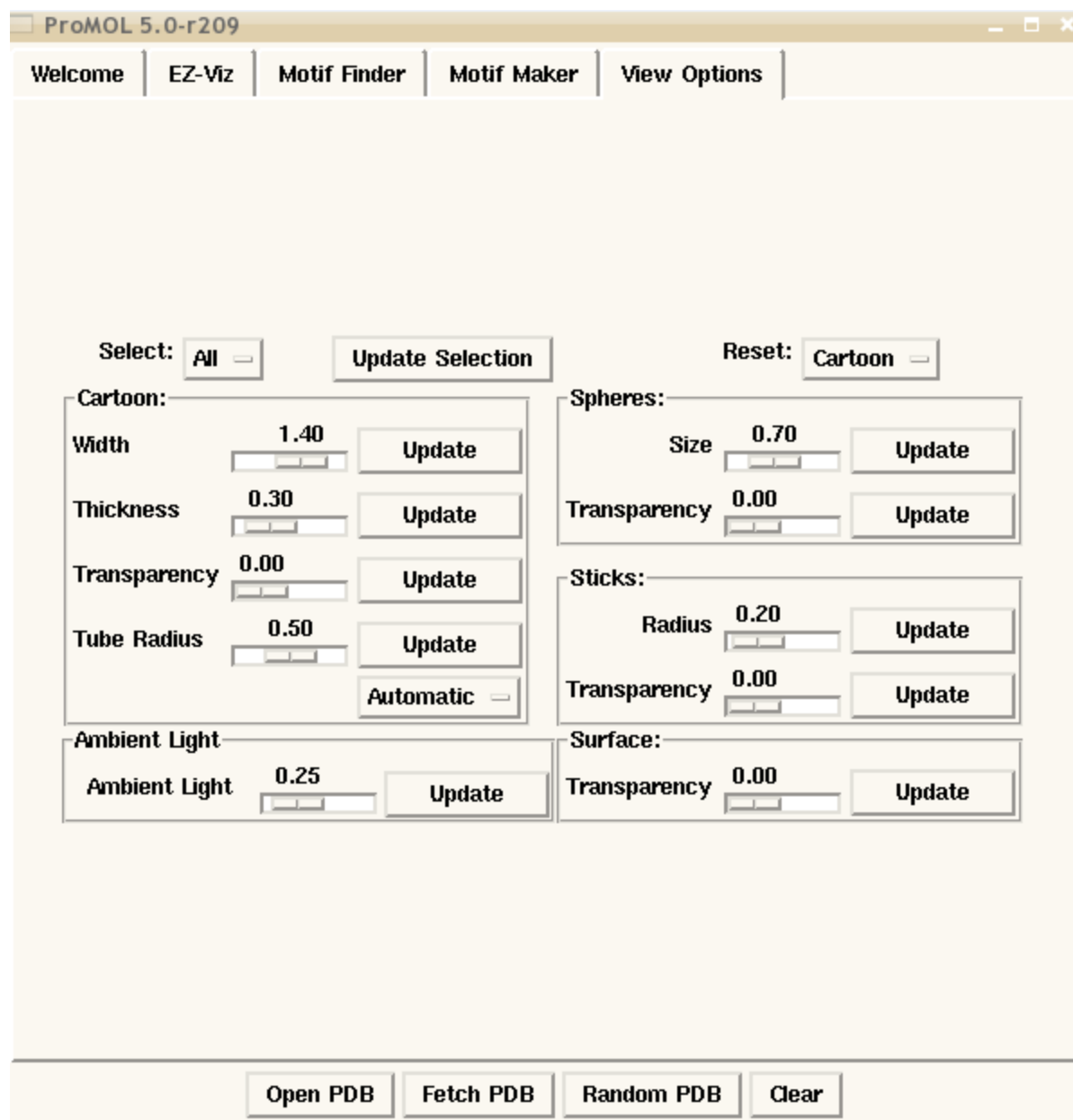
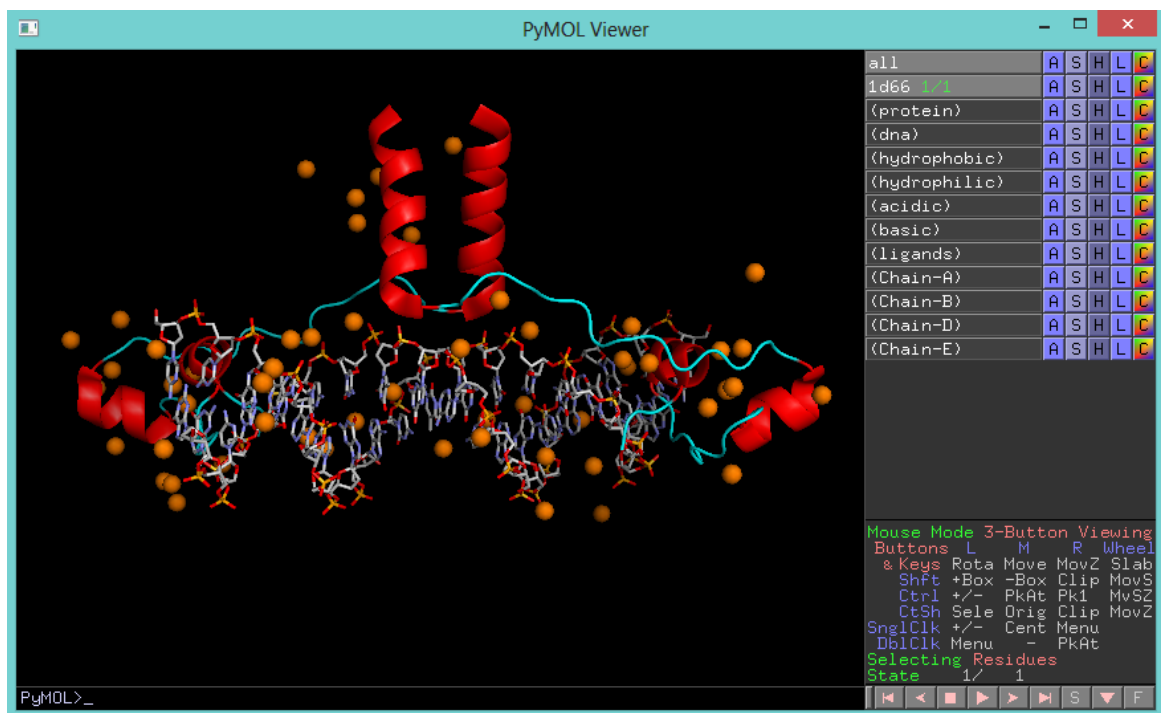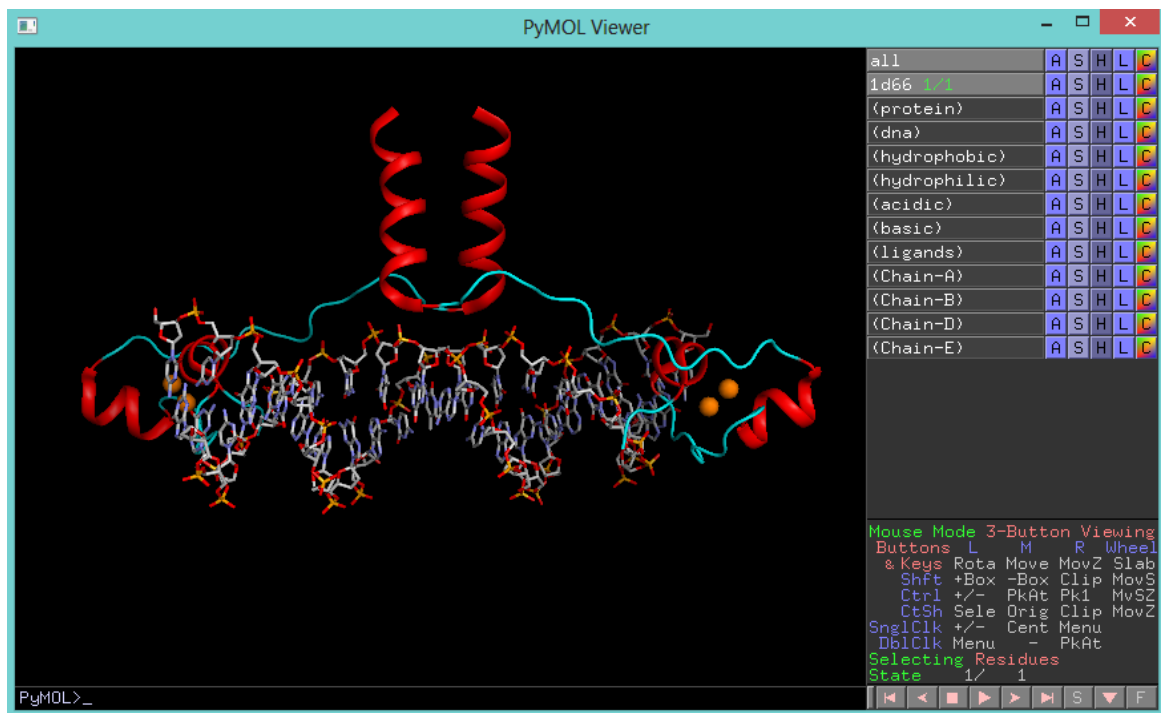Figure 19. ProMOL View Options tab (Mac OS)
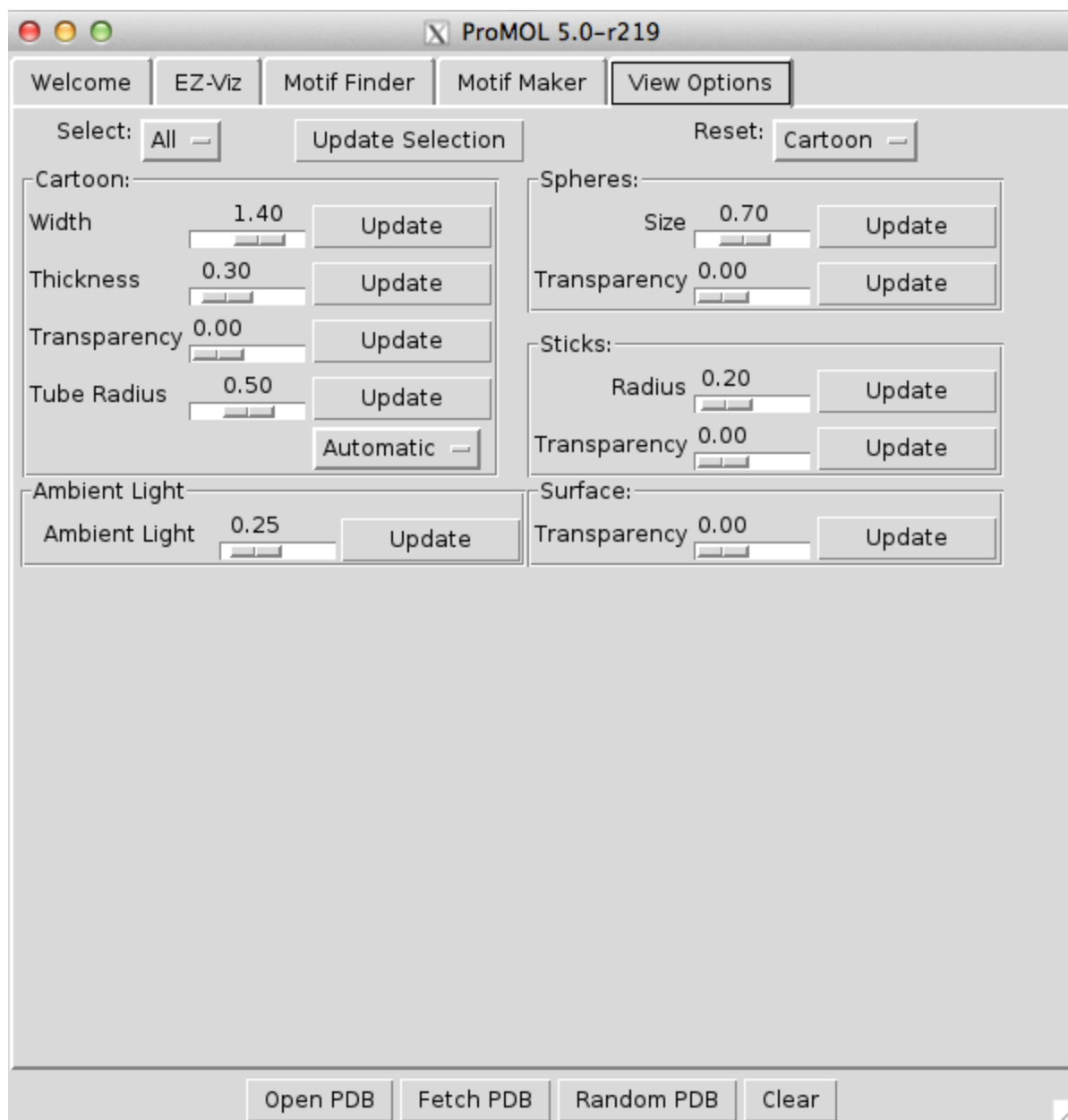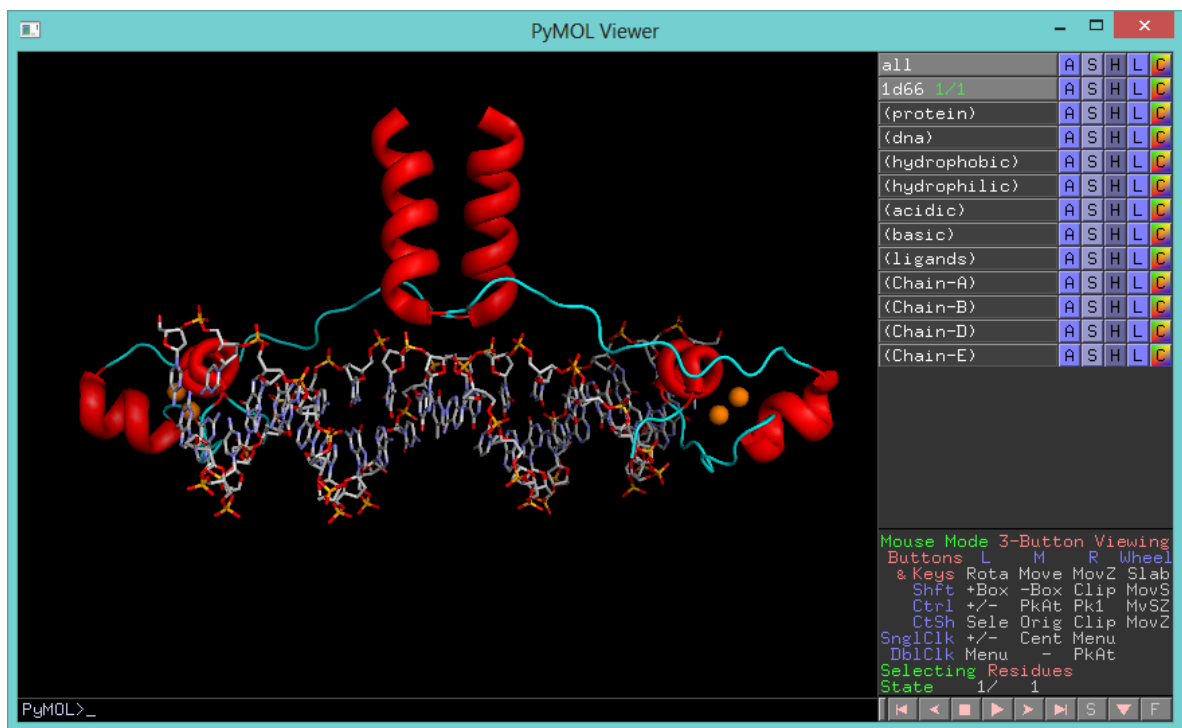
Figure20. ProMOL View Options tab (Linux)
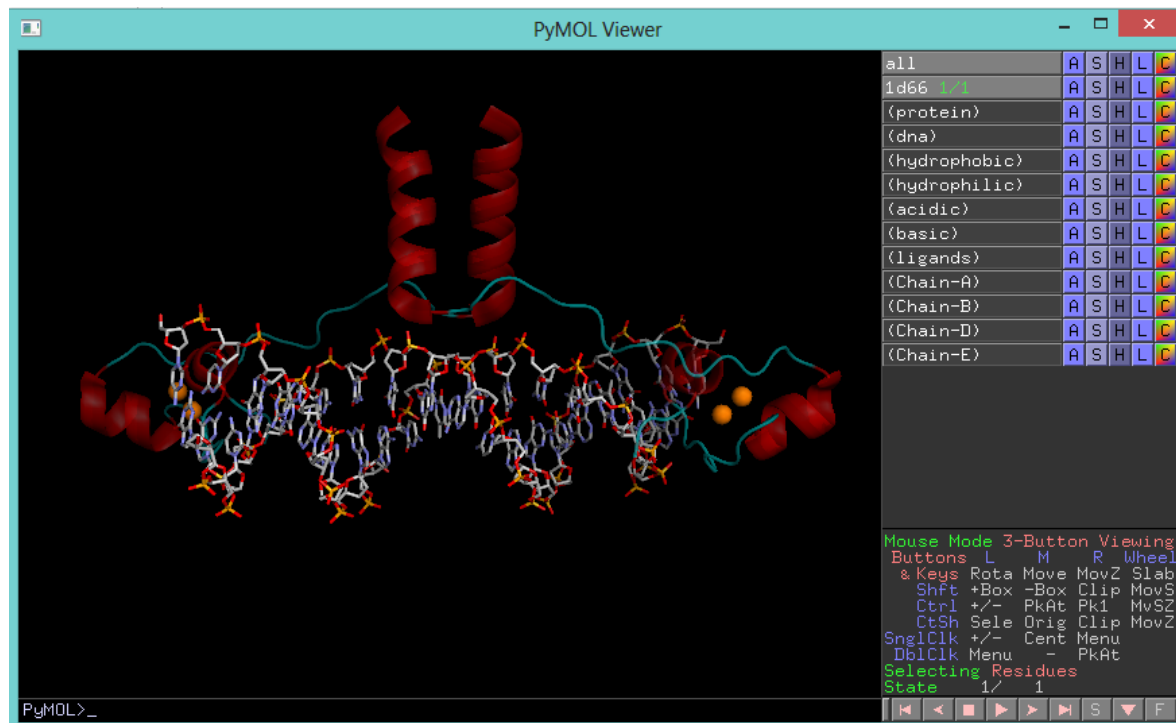
(A)

(B)



(C)

(D)

(A) The first image shows the default EZ-Viz cartoon for a DNA-protein complex (PDB is 1d66). (B) The waters have been hidden (EZ-Viz Hide Water) and on the View Options tab, Cartoon Width has been reduced from 1.40 to 0.75. (C) The Cartoon Width has been returned to 1.40, while the Cartoon Thickness has been increased from 0.30 to 0.80. (D) The transparency for the protein part of the 1d66 has been changed from 0.0 to 0.50, without affecting the appearance of the DNA.