PyMOL - Exploring the 3D PDB structures of SARS-CoV-2/COVID-19
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Preface

This booklet is meant for those that are already familiar with PyMOL [Schrödinger, LLC, 2020] as a molecular graphics software for macromolecular biological structures such as proteins and nucleic acids.

If you are novice you may benefit from finding the book “Exploring Protein Structure: Principles and Practice” [Skern, 2018]. If you are at the UW-Madison the information on my blog post¹ will guide you to download this book from the library.

You can also learn how to use PyMOL from my course material now available online [Sgro, Jean-Yves, 2017].

Software information and conventions

I used the knitr package [Xie, 2015], the bookdown package [Xie, 2016] enhanced by the bookdownplus package to compile this book within the RStudio software [RStudio Team, 2015] in various formats (PDF, HTML etc.)

PyMOL figures were created on the fly by scripts run from within the RStudio framework every time the book was compiled. This was possible on a Macintosh by calling the internal PyMOL engine with /Applications/PyMOL.app/Contents/MacOS/PyMOL and providing a script.

¹http://tiny.cc/pybook
On a Linux system the command would simply be `py3on` if the software is installed and within the PATH environment. On Windows I am not sure how this would or could work.

Acknowledgments

“Summary” icon for special text boxes is from https://www.flaticon.com/free-icon/recorder_2450952
About the Author

Jean-Yves Sgro, a senior scientist with years of experience in using and teaching computer programs, creates, organizes and teaches hands on workshops.

Jean-Yves has been at UW since 1986 after a Master in Physiology and a Ph.D. in Cellular and Molecular Biology from Joseph Fourier University\(^2\), Grenoble, France, and researched at the European Molecular Biology Laboratory (EMBL\(^3\)) where he already used large computers for sequence analysis.

In Madison, at the Institute for Molecular Virology (IMV\(^4\)) he continued developing computer expertise in addition to his wet-lab research – 3D molecular visualization (virusworld\(^5\)), RNA-folding predictions, sequence and data analysis...

In 1996 he joined the UW Biotechnology Center\(^6\) to better help Campus biologists analyze and visualize their data while continuing research at IMV until 2014 when this part-time position was transferred to the

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\(^2\)https://www.univ-grenoble-alpes.fr/english/
\(^3\)https://www.embl.fr/
\(^4\)http://virology.wisc.edu/
\(^5\)http://www.virology.wisc.edu/virusworld
\(^6\)https://www.biotech.wisc.edu/
Biochemistry Department\(^7\) where he organizes and teaches hands-on tutorials on molecular graphics, data analysis as a support to the department personnel.

Tutorials are available on line from the The Biochemistry Computational Research Facility (BCRF\(^8\).)
Introduction

We are in the midst of the COVID-19 pandemic, caused by the virus named SARS-CoV-2.¹

This small booklet is an attempt to illustrate some of the SARS-CoV-2 known structures available as 3D atomic coordinates at the Protein Data Bank (PDB) with the PyMOL software.

**How to use this booklet:**

The original purpose was to provide a starting point to visualize known 3D structures from the SARS-CoV-2 virus using the PyMOL molecular visualisation software.

All figures were created by script, and all complete scripts are available in the Appendix sections C, D, E, F, G.

Script lines can be copied one-by-one and pasted within the PyMOL command line.

Alternatively, the entire script can be copied within a plain text file and saved on the computer, then activated with a command such as: @myscript.txt from within the PyMOL command line area. (See section 3.3.1.)

¹SARS: Severe Acute Respiratory Syndrome-related coronavirus
If your interest is to learn more PyMOL commands, I recommend to follow the scripts one line at a time:

Watch the result of each command (some results might not be visible immediately.)

Inquire about the command structure:
- Use PyMOL help followed by command name for immediate info.
- Find same info in https://pymol.org/pymol-command-ref.html
- Search within https://pymolwiki.org/
- Be curious with a search engine (e.g. Google)

I am creating this booklet with the principles of “Reproducible Research” in the sense that this very document can be recreated in its entirety, including the recreation of all PyMOL illustrations as they can be redrawn “on the fly” thanks to the use of the scripts that create them.

I am using PyMOL 2.3.5 Incentive Product but this version number would also be automatically adjusted should I update my PyMOL program and recompile the book.

I had started a different booklet and changed course when the pandemic started. I levied Chapter 4 from that prior (unfinished) project which explains its different style with some suggested exercises and more of the script written within the text. There were some “strange” difficulty with the ligand of the structure studied in this chapter which started the idea of these booklets.

The original format is PDF but other formats might be made available,
albeit there will be some incompleteness regarding cross-references, index, or even numbering of chapters etc.
2

SARS-CoV-2

2.1 PDB Structures

Some SARS-CoV-2 viral proteins have been solved, mostly by X-ray crystallography, as of early April 2020:

- Main protease: 83 structures with various ligands (76 of which from the PanDDA analysis group.)
- Spike protein: 5 structures
- Papain-like SARS-CoV-2 structures: 1 structure
- Other SARS-CoV-2 structures (binding domains etc.): 17 structures

Tables with the PDB accession code and structure titles are available in Appendix A with information for the data source.

PDB structure 6LU7 is the first high-resolution crystal structure of SARS-CoV-2 main protease (released February 5, 2020) and is the object of study of chapter 4.

This booklet intention is to help with the rendering of the PDB files in PyMOL and provide all scripts to create PyMOL illustrations.

However, the complete virus particle has not been solved but various artistic “renderings” are available as discussed briefly in the next section.
2.2 SARS-CoV-2 - Artistic renderings

2.2.1 Painting

Scripps Prof. David Goodsell\(^1\),\(^2\), famous for his non-photorealistic illustrations of molecules, has created a beautiful rendering of the coronavirus entering the lung as a painting displayed on the Protein Data Bank web site\(^3\).

![SARS-CoV-2 painting and key, Pr. David Goodsell.](image)

**FIGURE 2.1:** SARS-CoV-2 painting and key, Pr. David Goodsell.

*This painting depicts a coronavirus just entering the lungs, surrounded by mucus secreted by respiratory cells, secreted antibodies, and several small immune systems proteins. The virus is enclosed by a membrane that includes the S (spike) protein, which will mediate attachment and entry into cells, M (membrane) protein, which is involved in organization of the nucleoprotein inside, and E (envelope) protein, which is a membrane channel involved in budding of the virus and may be incorporated into the virion during that process. The nu-

\(^1\)https://ccsb.scripps.edu/goodsell/

\(^2\)Twitter: @dsgoodsell

\(^3\)https://pdb101.rcsb.org/sci-art/goodsell-gallery/coronavirus
2.3 3D models

Other artistic renderings have been done by computer artists. The 3D file formats used are different than the format used for PDB files and cannot readily be opened with PyMOL. Many of them are for purchase on web sites.

Author Alejandro León⁴ ⁵ created a free version that can be accessed already rendered within a web site⁶ and that can be manipulated in 3D (See figure 2.2.)

A 12 seconds video of what this looks like is available on YouTube⁷.

According to the author this 3D model of Coronavirus (SARS-CoV-2) based on the images from CDC/PHIL. The model is available to download for free (MIT License)⁸.

In addition the 3D model file can be downloaded⁹ as a compressed binary in the .fbx format that is typically used to allow transfer to and from various 3D illustration software.

A web site¹⁰ can convert this file in other 3D formats¹¹. Noteworthy is the fact that the most recent Photoshop version can open the .obj for-

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⁴Twitter: @alelepd
⁵https://alejandro.fun/
⁶https://spline.design/coronavirus3d/
⁷https://youtu.be/K00RIaAuXb4
⁸https://opensource.org/licenses/MIT
⁹https://spline.design/coronavirus3d/_assets/coronavirus3d.fbx
¹⁰https://products.aspose.app/3d/conversion/
¹¹Available formats: FBX, OBJ, 3DS, DRC, AMF, RVM, DAE, GLTF, GLB, PDF, HTML, PLY, STL, U3D
FIGURE 2.2: Details of coronavirus3d file shown on spline.design showing artistic rendering of surface trimeric spike protein.

mat into a 3D layer where the various “layers” can be assigned a color or a texture (figure 2.3.)

Here is a stereo version created with this file with Photoshop:

FIGURE 2.3: Stereo rendering of coronavirus3d file in Photoshop

The coronavirus3d (e.g., in .obj format) can also be rendered with the free 3D software MeshLab\textsuperscript{12} available for Windows/Mac/Linux. Within this software all “layers” are given the same color, but vertices can be

\footnotesize\textsuperscript{12}http://www.meshlab.net/
2.3 3D models

colored which can create “artistically nice” renderings as well (figure 2.4.)

FIGURE 2.4: MeshLab rendering of coronavirus3d file.
3

PyMOL Scripts: Short Primer

SUMMARY:
- Scripts are plain text
- PyMOL command scripts are activated with @
- PyMOL python form scripts are activated with run

3.1 Scripts are “plain text”
A plain text file will:

• only contain printable characters that can be typed from the simplest of keyboards: letters, numbers and symbols such as !, @ and $.

• is not specific to any particular word processor format and is displayed with the default font within any word processor.

• contain a “line-break” or “end-of-line” code (specific to the operating system, which can be an inconvenience sometimes.)

Software that can easily create a plain text file:

• Windows: Notepad or one of many suggested replacements1

1https://alternativeto.net/software/notepad/?platform=windows
• **MacOS**: TextEdit or one of the many suggested replacements\(^2,3\)
• **Linux**: nano, vim, emacs or some other replacement\(^4\)
• Cross-platform: Atom\(^5\)

### 3.2 Scripts formats

There are different PyMOL scripts formats:

- .pml: Scripts containing lists of **PyMOL commands**
- .py:
  - Scripts containing lists of PyMOL command in **Python form**
    (See section 3.4.)
  - Scripts containing new functions, written in Python language.

_Note:_ When activated through the command line, a file ending in .txt works as well.

### 3.3 Activating a command script

The activation of scripts may different depending on their nature if not activated by mouse menu.

With a mouse the following menu cascade can be used to activate any script form: **File > Run Script...** which then offers the choices:

- All Runnable (*.pml *.py *.pym)
- PyMOL Command Script (*.pml)

\(^2^\text{https://alternativeto.net/software/textedit/?platform=mac}\)
\(^3^\text{use menu: Format > Make plain text}\)
\(^4^\text{https://alternativeto.net/software/nano/?platform=linux}\)
\(^5^\text{https://atom.io/}\)
3.4 PyMOL command vs API

- PyMOL Command Script (*.txt)
- Python Script (*.py *.pym)
- Python Script (*.txt)
- All Files (*)

Note: in older versions of PyMOL a command file would need to end with .pml in order to be used with the mouse menu.

3.3.1 Command script

A PyMOL Command Script can be activated with the command line:

```
PyMOL>@myscript.pml
```

This assumes that the script file is located within the current directory.

3.3.2 Python script

A Python language script should use the PyMOL command run to be activated, even if @ may work in most cases when the script is only a series of commands. PyMOL will provide a warning.

```
PyMOL>@myscript.py
```

Warning: use 'run' instead of '@' with Python files?

Therefore the command should be given as:

```
PyMOL>run myscript.py
```

This is particularly true for files that provide new functions to PyMOL as we’ll see later.

3.4 PyMOL command vs API

PyMOL is a molecular graphics software based on the Python language (hence its name.) This document is using PyMOL 2.3.5 Incentive Product.
to create graphics automatically with scripts. (Scripts are located in the Appendix.)

3.4.1 PyMOL commands are API aliases

A PyMOL command has an equivalent in API\(^6\) form (written in python) and there are also less documented API commands that do not exist in PyMOL command form.

This is best understood with a simple example, let’s take the PyMOL command `color`. I can issue commands such as:

PyMOL> `color blue`

I can also specify the chain I’d like to color if there are more than one:

PyMOL> `color blue, chain A`

The command `color`\(^7\) is defined as:

```
color color [, selection ]
```

- The first word `color` is the command name
- The second `color` is the mandatory argument and should be a color name or number
- the selection is everything unless specified

But behind the scenes, PyMOL is running python language functions, and the command `color` is in fact defined with all its parameters\(^8\) as:

```
cmd.color(string color, string selection, int quiet)
```

This can also be used directly within PyMOL, for example

---

\(^6\)Application Programming Interface  
\(^7\)https://pymol.org/dokuwiki/doku.php?id=command:color  
\(^8\)https://pymol.org/dokuwiki/doku.php?id=api:cmd:color
3.5 Shell-like commands and PATH

PyMOL> cmd.color("blue")

Of course a chain name can also be specified:

PyMOL> cmd.color("blue", "chain A")

It is important that the arguments be placed within quotes or an error will occur. This is because within the definition the arguments are expected to be string which means of character type (as opposed to a number for example.)

My opinionated conclusion is that the command form appears more concise to the eyes (less need for quotes or parenthesis) and therefore more “English-like” which in turn allows a better comprehension, or understanding of the tasks that PyMOL is asked to perform, such as changing a color.

3.5 Shell-like commands and PATH

One of the trickiest things about computer is all the assumptions behind where things are and what does the computer knows about where things are.

By default PyMOL will “look” within the home user directory. On modern desktop computers it is usually within the /Users directory. For example for me it would be /Users/jsgro.

If a script is not within the current directory, a path to the script can be given, either as absolute or relative path with the appropriate preceding @ symbol or run command. For example @./pyscripts/myscript.pml. Most systems would also understand the - shortcut representing the home directory.
PyMOL also provides three commands identical to the shell commands:

- `cd`: Change the current working directory
- `ls`: List contents of the current working directory.
- `pwd`: Print current working directory.

In addition the command `bvbi2K` executes a command in a subshell under Unix or Windows (not Mac.) Therefore it is possible to change directory (`cd`), check in which directory PyMOL is looking (pwd) and list current files in that directory (`ls`).

The `cd` command works in the same way as in a Unix/Linux shell. By default PyMOL will look within the home directory as detailed above. The standard shell commands apply, including:

For example:

```bash
cd MyDirName

cd Desktop

cd ~/Desktop

cd ~/MyDirName2

cd ../
```

The `ls` command includes usage of wild card `*` and regular expressions in the search (e.g. `ls *[t] .py`, `ls c1a??29*.py`) and `tab-extension` is operational.

---

9https://pymol.org/pymol-command-ref.html
SARS-CoV-2 Protease Mpro

SUMMARY:
Unexpected problems with a seemingly simple rendering of PDB coordinates of SARS-CoV-2 main proteinase Mpro.

This is an example of PyMOL Command Scripting to create figures that can automatically be generated from a script. The final script(s) can be found in Appendix C.

At this writing the Covid-19 pandemic caused by the 2019 novel coronavirus (SARS-CoV-2) is going on. The RNA genome is 82% identical to the SARS coronavirus (SARS-CoV) and has been named SARS-CoV-2 (Gorbalenya et al. [2020]). The disease caused by SARS-CoV-2 is called COVID-19.

The structure of the virus protease has been solved by X-ray diffraction (Jin et al. [2020]). The structure was deposited 2020-01-26 and released 2020-02-05 with PDB code 6LU7 \(^1\) with title The crystal structure of COVID-19 main protease in complex with an inhibitor N3. The biological assembly is a dimer.

The peptide-inhibitor is logdged within a groove on the protease surface. Its name is PRD_002214 \(^2\), in the Biologically Interesting Molecule Reference Dictionary (BIRD).

\(^1\) http://dx.doi.org/10.2210/pdb6LU7/pdb
\(^2\) https://www.rcsb.org/bird/PRD_002214
Within the PDB file it has sequence:

```
SEQRES   1 C    6 02J ALA VAL LEU PJE 010
```

When PyMOL (2.x) opens the file, showing the structure with the new default of cartoon, the protein is fine but zooming on the PRD_002214 it appears broken in 3 parts (see figure 4.1.)

**FIGURE 4.1:** PRD_002214, cyan, appears broken into three parts.

The cause is the interpretation of the 3D coordinates for PRD_002214 in chain C. Closer inspection of the coordinates shows that its peptide-like nature causes its coordinates to be a mixture of ATOM and HETATM records (see Appendix B.)

Thanks to PyMOL command options we'll be able to modify the coordinates so that compound PRD_002214 may be represented as full in *stick* visual format.
4.1 Change record type

Even though chain C does not contain any termination TER records the result of the mixed atom records as ATOM and HETATM causes PyMOL to split the representation in 3 parts. One solution would be to change all records to HETATM which can be accomplished with PyMOL command alter.\(^3\)

The script below will accomplish this task:

```python
fetch 6lu7, async=0 as cartoon

# Change ATOM records
alter (chain C), type="HETATM"
show stick, chain C
hide cartoon, chain C
util.cbaw chain C

zoom 6lu7 and chain C
turn y, -50
turn z, -90
turn x, -30
```

This should now produce a complete stick representation of PRD_002214 compound.

Exercise:
In the script we used alter (chain C), type="HETATM". You can also try alter (seg B), type="HETATM".

\(^3\)https://pymol.org/pymol-command-ref.html#alter
FIGURE 4.2: PRD_002214, sticks, CPK colors.

Does it work for both asymmetric unit and biological assembly? Why not?

Exercise:
Try to reproduce a similar image for the biological assembly (type=pdb1.)
Does the rotation translation provided above for the asymmetric unit work as well?
Why or why not?

4.2  Surface representation: still an issue

If we now would like to use the standard surface representation that constructs a surface for the protein but not on the organic ligands, there will still be a problem of representation, this time due to the fact
that the name of the residues that were originally presented as ATOM within the compound have natural amino acid names, and therefore, in spite of now being labeled HETATM will be included in the surface.

Residue names for the compound are indeed 02J ALA VAL LEU PJE 010 (see above) and the portion ALA VAL LEU will be selected for surface construction.

One may think that a possible solution would simply to change the name of those amino acid to a generic UNK for unknown compound.

Exercise:
Test the hypothesis that changing the amino acid names within PRD_002214 to an “unknown” does (or does not) change the surface options.

Hint: alter resn ala+val+leu and chain C, resn = "UNK"
4.2.1 One solution: extract

One solution that works consists in extracting the ligand to a different PyMOL object (not a selection) so that the surface construction of the remaining structure will not include any of the ligand itself.

Assuming we already have the structure within PyMOL, this can be accomplished by the few commands below that:

1. Create a selection name for chain C as “C”
2. Extract the selection into a new object “PRD”
3. Show again surface for the rest of 6lu7

```plaintext
select C, chain C
extract PRD, C
show surface, 6lu7
```

![Figure 4.4: PRD_002214, extracted, in protein groove.](image)

4.2.2 Final solution

At this point we could think that we are done. But we are not!
4.2 Surface representation: still an issue

If we now try to create a surface for the new, independent “PRD” object we still obtain a partial surface of the molecule in the area of the (now) UNK residues.

For example with the command `show surface, PRD`.

![Figure 4.5: PRD_002214, partial surface.](image)

The likely reason is that while we changed actual amino acid names from ALA, VAL, LEU to unknown UNK, PyMOL probably remembers the properties of these residues from before they were changed. Hence the surface creation.

To erase this residual memory of properties, one solution is the write the coordinates of PRD into a file, delete the object and re-read the coordinates within PyMOL.

Let’s try if this will work with the few commands that follow.

```
save PRD.pdb, PRD
delete PRD
load PRD.pdb
hide cartoon, PRD
```
util.cbaw chain C
show surface, PRD

**FIGURE 4.6:** No surface created for PRD_002214 when reloaded.

**Exercise:**
Why is it necessary to have command `hide cartoon, PRD`?
What is the mouse menu equivalent to the `save` command?
Where is the mouse equivalent of the `delete` command?

Finally, the following settings may help when saving the coordinates into a file that will:

- Create `CONECT` records specifying which atoms are bonded
- Prevent the addition of `TER` records which could create gaps within graphics representations.

These were not necessary for the creation of the embedded illustration here but could be useful in other situations.
4.4 Biological assembly

<table>
<thead>
<tr>
<th>set pdb_use_ter_records, 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>set pdb_conect_all, on</td>
</tr>
<tr>
<td># OR</td>
</tr>
<tr>
<td>set pdb_conect_nodup, 1</td>
</tr>
<tr>
<td># no CONECT duplication is used</td>
</tr>
<tr>
<td># to store bond order</td>
</tr>
</tbody>
</table>

See [https://pymolwiki.org/](https://pymolwiki.org/) for more information on these commands.

Exercice:
Where is the file PRD.pdb saved?
Could the file be saved in a different format?
Does it contain TER records?
Are there UNK residues present?

---

4.3 Biological assembly

The biologically active assembly is a dimer as shown in figure 4.7. See script in Appendix 4.

---

4.4 Comparing structures

Beyond scripting: if you are interested in the science of the protease the following papers would be of interest: Adem et al. [2020], Zhang et al. [2020] reporting in silico search for inhibitors of the protease we have used in this chapter (Jin et al. [2020], PDB 6L7.) This structure is very similar to that of the SARS coronavirus protease reported by Tan
FIGURE 4.7: 6LU7 biological assembly. PRD_002214 shown as spheres or sticks in each monomer.

et al. [2005], (PDB 2BX4, no ligand,) and the new protease of SARS-CoV-2 has also been solved in apo form, without ligand (PDB: 6M03.)

Zhang et al. [2020] provide a good summary description of the protease function and cleavage specificity:

“[…] this enzyme is essential for processing the polyproteins that are translated from the viral RNA (Hilgenfeld [2014]). The Mpro operates at no less than 11 cleavage sites on the large polyprotein 1ab (replicase 1ab, ~790 kDa); the recognition sequence at most sites is Leu-Gln+ (Ser, Ala, Gly) (↓ marks the cleavage site). Inhibiting the activity of this enzyme would block viral replication. Since no human proteases with a similar cleavage specificity are known, inhibitors are unlikely to be toxic.”

These authors have also released the SARS-CoV-2 Mpro protease struc-
4.4 Comparing structures

The structures with and without bound ligands with the following PDB codes not cited within the paper:

- 6Y2E, no ligand

- 6Y2F and 6Y2G with complex ligand 06K

In the paper they state that the r.m.s. deviation between the two free-enzyme structures is 0.53 Å for all Ca positions (comparison between SARS-CoV-2 Mpro structure and SARS-CoV Mpro, PDB entry 2BX4.

How did they calculate this number?

My own search for calculating root-mean-square deviation (RMSD) with PyMOL pointed to many commands. However I believe that the following method was used as it provide the same answer. It is from the pymolwiki of PyMOL command super that aligns two selection with a sequence-independent structure-based dynamic programming alignment followed by a series of refinement cycles intended to improve the fit.

The following script is taken from that page with only the PDB codes modified to those of the protease without ligand.

```python
reinitialize

fetch 6Y2E, async=0
fetch 2BX4, async=0

# super 6Y2E, 2BX4

test = cmd.super("6Y2E", "2BX4")
```

```python
python
writefile=open("rmsd_file_super.txt","a")
writefile.write(\\'.join(\\'\%s' % x for x in test))
writefile.write(\\'\\n\')
writefile.close()
python_end
```

File `rmsd_file_super.txt` contains only one line:

0.530 8237075805664 1928 5 1.130696415901184 2280 1361.6253662109375 303

The first value is indeed 0.53.

One “trick” was to use the `cmd.super()` python form which allows the recoding of the data into a variable called `test`. The rest of the code is python for writing the content of the variable `test` within the `rmsd_file_super.txt` file.

Optional exercise:

Create a figure representing both structures superimposed and shown as ribbon or as cartoon.

Then create a new figure showing them side-by-side in the exact same orientation.

Hint: grid_mode
The spike (S) protein is a surface trimer glycoprotein located on the envelope of the virions. It is cleaved into S1 and S2 subunits. The S1 subunit is responsible for host-receptor binding while the S2 subunit contains the membrane-fusion machinery\(^1\).

There are 5 published structures as shown in the following table:

**TABLE 5.1: Spike protein PDB entries**

<table>
<thead>
<tr>
<th>ID</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>6LZG</td>
<td>Structure of novel coronavirus spike receptor-binding domain complexed with its receptor ACE2</td>
</tr>
<tr>
<td>6MoJ</td>
<td>Crystal structure of 2019-nCoV spike receptor-binding domain bound with ACE2</td>
</tr>
<tr>
<td>6VXX</td>
<td>Structure of the SARS-CoV-2 spike glycoprotein closed state</td>
</tr>
<tr>
<td>6VYB</td>
<td>SARS-CoV-2 spike ectodomain structure open state</td>
</tr>
<tr>
<td>6VSB</td>
<td>Prefusion 2019-nCoV spike glycoprotein with a single receptor-binding domain up</td>
</tr>
</tbody>
</table>

The first two 6MoJ and 6LZG are both showing a spike receptor region (S1) bound to the Angiotensin-converting enzyme 2 (ACE2) receptor.

\(^1\)https://www.rekombiotech.com/en/blog/detection-covid-19
Structures are almost indistinguishable with an RMDS of 0.156² are almost identical.

So choosing just one of them e.g. 6LZG is enough. We can illustrate the content of this PDB file showing how ACE2 and S1 fragment are bound. Both proteins have N-Acetylglycosamine³ labeled NAG within the PDB file and bound to ASN residues (shown in red in figure 5.1.)

![Figure 5.1: 6LZG: ACE2 and binding domain. NAG in red.](image)

The other three structures are different configuration of the trimeric structure. Figures 5.2 and 5.3 show a side by side comparison between the closed structure (6VXX) and the trimeric structure of the spike glycoprotein with a single receptor-binding domain up 6VSB.

The figures are automatically colored by chain. In 5.1 structures are shown in the original orientation when the PDB is opened, looking into the trimeric structure as from the outside.

²see previous chapter 4.4 for RMSD calculation method
³https://en.wikipedia.org/wiki/N-Acetylglycosamine
FIGURE 5.2: 6VXX (closed) and 6VSB (1 up) trimeric structure. Outside view.

To obtain figure 5.3 a simple rotation of 90 degrees around the z axis is sufficient. It then becomes clearer to spot the “1 up” fragment (green) from structure 6VSB. This is the equivalent portion labeled “receptor-binding domain” of 6LZG displayed in figure 5.1.

Note: removed in these figures are the numerous glycosylation sites that would be shown by default as “floating” sticks.)

We’ll use 6VSB trimeric structure of the spike glycoprotein with a single receptor-binding domain up. This domain corresponds to the spike receptor region (S1) of the 6M0J and 6LZG structures.

As an exercise we’ll superimpose 6LZG over 6VSB to see how the receptor would look like and be positioned in relation to the trimeric structure. Color scheme is as in figure 5.1 for 6LZG and figures 5.2 and 5.3 for 6VSB.

The scripts can be found in Appendix D.

Within the script the structures are superimposed with the PyMOL
command *super* that is not relying on sequence. However, in this case the command *align* would work equally well.

To orient the molecules the script uses the PyMOL function *set_view* for which the data can be obtained when using the graphical interface by pressing the button “Get View” at the top right or on the command-line with the PyMOL command *get_view*. This method is an alternative to PyMOL commands *turn* and *move* used in other scripts, for simplicity.

After all this work we can now compare this “modeled” structure combination with a crystal structure of PDB file 6ACK with title: “Trypsin-cleaved and low pH-treated SARS-CoV spike glycoprotein and ACE2 complex, ACE2-bound conformation 3”.

This structure contains the trimeric spike glycoprotein trimer, one of which is attached to a molecule of *angiotensin-converting enzyme 2* (ACE2) in a similar way as our model above.
**FIGURE 5.4:** 6LZG (ACE2 and binding domain) superimposed onto 6VSB receptor-binding up domain.

We can select residues that are near ACE2 and show them as stick models and zoom for a more closer look (figure 5.6.)

Let’s review some of the critical or new PyMOL commands from the scripts for this chapter (Appendix D.)

- *align* and *super* are two methods to superimpose structures. Unlike *align*, *super* does not rely on sequence information.
- *extract* is a useful command to separate a set of atoms that were previously selected. One of the effect is to allow a surface to be complete and independent of other molecules.
- *select* by *res chain C within 5 of ACE2* creates a selection based on distance with *within*.
- *util.cbc* is a simple utility meaning *color by chain*
- *util.cbaw* is also a simple utility meaning *color by atom white*
FIGURE 5.5: 6ACK: ACE2 bound to spike glycoprotein trimer.
FIGURE 5.6: 6ACK: contact amino acids from spike glycoprotein trimer (chain C) with AC2 (surface.)
The multi-domain non-structural protein 3 (Nsp3) is the largest protein encoded by the coronavirus (CoV) genome, with an average molecular mass of about 200 kD. Nsp3 is a multifunctional protein comprising up to 16 different domains and regions and is an essential component of the replication/transcription complex. It comprises various domains, the organization of which differs between CoV genera, due to duplication or absence of some domains. However, eight domains of Nsp3 exist in all known CoVs. (Review: Lei et al. [2018].)

6.1 ADP ribose phosphatase of NSP3 from SARS CoV-2

There are 3 published structures for the SARS CoV-2 ribose phosphatase portion of NSP3 as shown in the following table:

**TABLE 6.1:** PDB entries for ADP ribose phosphatase portion of NSP3

<table>
<thead>
<tr>
<th>ID</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>6Wo2</td>
<td>Crystal Structure of ADP ribose phosphatase of NSP3 from SARS CoV-2 in the complex with ADP ribose</td>
</tr>
<tr>
<td>6VXS</td>
<td>Crystal Structure of ADP ribose phosphatase of NSP3 from SARS CoV-2</td>
</tr>
</tbody>
</table>
Crystal Structure 6W02 with *ADP ribose phosphatase of NSP3 from SARS CoV-2 in the complex with ADP ribose* is very similar to that of MERS-CoV\(^1\) (5H0L) with an RMSD of 0.63 \(^2\) which is depicted in Figure 4 by Lei et al. [2018]. The two structures are easily superimposed (figure 6.1.)

**FIGURE 6.1:** 6W02 aligned with 5H0L.

Figure 6.2 illustrates a closer view of ADP within structure 6W02. Also visible is ethylene glycol (alias 1,2-ethanediol) and labeled E00 within the PDB file. Amino acid ILE 131 has been shown only as sticks to facilitate view.

\(^1\)Middle-East Respiratory Syndrome Coronavirus  
\(^2\)see 4.4 for RMSD calculation method
6.1 ADP ribose phosphatase of NSP3 from SARS CoV-2

FIGURE 6.2: Close view of ADP within 6W02.

Here are a few highlights from the scripts for this chapter (Appendix E.)

- `util.cbaw`, `util.cbab` and `util.cbay` are utilities to color by atom white, blue, and yellow respectively.
- `hide nonbonded` is a way to hide the waters and other “floating” solvent molecules.
- `organic` usually serves to select ligands, but can also select specific organic solvents.
The title for structure 6W01 is *The 1.9 Å Crystal Structure of NSP15 Endoribonuclease from SARS CoV-2 in the Complex with a Citrate.*

This structure is a good illustration for the understanding of “asymmetric unit” vs “biological assembly.”

In simple terms, crystallographers solve the mathematical problem to obtain the smallest unit that can be reproduced almost *ad infinitum* to recreate the crystal. This “asymmetric unit” is what gets deposited at the Protein Data Bank.

Fortunately these days, a set of symmetry information is built-in the PDB file so that it is possible to download the “biological assembly” which is the biologically active compound.

For this entry, the “asymmetric unit” is composed of 2 molecules while the “biological assembly” is composed of a total of 6, consisting of 2 trimers.

Note that in other cases, the “biological assembly” may consist of a smaller number than the “asymmetric unit.”

Figure 7.1 illustrates the “asymmetric unit” composed of 2 chains. Residues in the points of contact are shown as spheres. Within the PDB, information for the crystallographers would inform them that the “space group” is P 63 and would also provide relevant information about symmetry operators.
FIGURE 7.1: 6W01 asymmetric unit.

FIGURE 7.2: 6W01 biological assembly: 2 trimers.
Figure 7.2 is the first of two illustrations for the “biological assembly” that will appear as two trimers. All chains within a trimer have the same chain ID. One trimer is A and the other B. Therefore within one trimer it is not possible to uniquely address residues or atoms. This makes labeling more difficult and therefore there are no internal title within this illustration. (We’ll fix that for the next illustration.) In addition, by default PyMOL will show only one of the chain for each trimer. Each trimer contains 3 “models” or “state”, see command explanation below.

In this illustration alpha helices are shown as a helix representation. Compare with figure 7.3 using a different representation.

![Biological assembly: 2 trimers, 6 chains](image)

**FIGURE 7.3:** 6W01 biological assembly: all chains colored.

The script (Appendix F) contains a few critical PyMOL commands:

- `set all_states`, on will show all chains within each trimer
- set cartoon_cylindrical_helices, on to change the helix representation mode
- run flatten_obj.py to acquire a new function to allow the renumbering of all chains. *Please note* that file flatten_obj.py has to be downloaded within the current directory (See pymolwiki\(^1\) or download directly from Github\(^2\) - short URL\(^3\).

In addition the raytrace rendering was changed to provide a different look, with more “flat” coloring and a black line outline. This is thanks to the command set ray_trace_mode, 1. In addition cast shadows were removed with set ray_shadow, off as they would add confusion to this large structure.

\(^1\)https://pymolwiki.org/index.php/Flatten_obj
\(^2\)https://raw.githubusercontent.com/Pymol-Scripts/Pymol-script-repo/master/flatten_obj.py
\(^3\)http://tiny.cc/flatten-obj
NSP12 polymerase

(Find all image scripts for this chapter in Appendix G.)

The title for structure 6M71 is *2019-nCoV RNA-dependent RNA polymerase in complex with cofactors.* (Deposited: 2020-03-16 Released: 2020-04-01)

It is very similar to structure 6NUR with title *SARS-Coronavirus NSP12 bound to NSP7 and NSP8 co-factors* (Deposited: 2019-02-01 Released: 2019-05-29) Kirchdoerfer and Ward [2019].

Figure 8.1 shows the structure as colored and oriented as in Kirchdoerfer and Ward [2019] figure 1b, middle figure with legend: *Structure of SARS-CoV nsp12 bound to nsp7 and nsp8 co-factors.* b SARS-CoV nsp12 contains a large N-terminal extension composed of the NiRAN domain (dark red) and an interface domain (purple) adjacent to the polymerase domain (orange). nsp12 binds to a heterodimer of nsp7 (blue) and nsp8 (green) as well as to a second subunit of nsp8.

With some extra PyMOL commands the labels could be made to color-match the proteins.

Figure 8.2 compares structures 6M71 and 6NUR for which more of the nsp8 protein is visible (top right of the structure.)

Figure 1 legend continues as: *c–e Comparison of SARS-CoV nsp12 to the polymerase proteins of poliovirus24 (3OL6.pdb) [10.2210/pdb3OL6/pdb] and dengue virus55 (4V0R.pdb) [10.2210/pdb4V0R/pdb]. Viral RNA polymerases share an overall structural architecture with fingers (blue), palm (yellow), and*
**FIGURE 8.1:** 6M71 RNA-dependent RNA polymerase nsp12 in complex with cofactors nsp7 and nsp8.

thumb domains (red). Both SARS-CoV and dengue virus polymerase proteins contain N-terminal extensions colored green. The SARS-CoV nsp7 and nsp8 cofactors are colored in white and gray, respectively.

I leave the pleasure to the reader(s) to create the corresponding images for the SARS and the other viral polymerases.

The script (Appendix G) contains a few critical PyMOL commands:

- **hide everything, 6NUR.** Fetching the 6NUR1 structure early allows to color both structures at the same time. For the first image, structure 6NUR is hidden from view.
- **translate [40, 0, 0], 6M71** this command permits to separate the 2 structures for better comparison.
FIGURE 8.2: Comparison between Cov (6NUR) and Cov2 (6M71) RNA-dependent RNA polymerase nsp12 in complex with cofactors nsp7 and nsp8.
Epilogue

I hope that this booklet will help you with your PyMOL skills. I probably left a few PyMOL commands unexplained that you can easily learn from a simple web search, as I often do.

I certainly learned or relearned many aspects of using PyMOL while working on this. Perhaps even more so as I wanted the image to be able to be reproduced automatically by script with the booklet creation method itself. As detailed in the Introduction (1) I have created this booklet using the “markdown” language augmented for RStudio, bookdown and bookdownplus. I have tried to use this method to add cross-references, appendices and a book index that I hope are useful and consistent. It sure was a learning curve for me, but it was an interesting endeavor even with some late night frustrations.

To know more about bookdown, see https://bookdown.org.

The next step will be to create a (smaller) booklet for printing and coloring structures with crayons. May this help those at home with little ones and ride the difficulties we face during the pandemic.
FIGURE 9.1: SARS-CoV-2 3D model for crayon coloring.
SARS-CoV-2 PDB codes

The information in these tables is derived from the Protein Data Bank web site SARS-CoV-2 article:

- Short URL: http://tiny.cc/PDBCovid19
- Short URL: https://bit.ly/2UXfwPQ
- Archived: 03April2020
  - Short URL: http://tiny.cc/PDBCovid19ARC
  - Short URL: https://bit.ly/2X8c0ob

A.1 Main protease

Note: For clarity PanDDA analysis group deposition – Crystal Structure of has been removed for all PanDDA structures titles.
### TABLE A.1: PDB IDs of SARS-CoV-2 main protease

<table>
<thead>
<tr>
<th>ID</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>5R8T</td>
<td>PanDDA analysis group deposition of ground-state model of SARS-CoV-2 main protease screened against DSI poised (Enamine), Fraglites and Peplites (Newcastle university), Mini Frags (Astex), York 3D (York university), electrophile cysteine covalent (Weizman institute) fragment libraries</td>
</tr>
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<td>5RE4</td>
<td>SARS-CoV-2 main protease in complex with Z1129283193</td>
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<tr>
<td>5RE5</td>
<td>SARS-CoV-2 main protease in complex with Z33545544</td>
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<td>5RE6</td>
<td>SARS-CoV-2 main protease in complex with Z54571979</td>
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<td>Structure of COVID-19 main protease bound to potent broad-spectrum</td>
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<td>non-covalent inhibitor X77</td>
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A.3 Spike protein

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A.2 Papain-like protease

**TABLE A.2:** PDB IDs of SARS-CoV-2 Papain-like protease

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A.3 Spike protein
**TABLE A.3:** PDB IDs of SARS-CoV-2 spike glycoprotein

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**A.4 Other SARS-CoV-2 structures**

**TABLE A.4:** PDB IDs of other SARS-CoV-2

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### A.4 Other SARS-CoV-2 structures

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Scripts for figures in Chapter 4

C.1 Stick and surface

# Script for "Protease Mpro"

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as cartoon
color darksalmon, chain A

# Alter atom type
alter (chain C), type="HEATM"
show stick, chain C
hide cartoon, chain C
util.cbaw chain C

# Zoom and rotate
zoom 6lu7 and chain C
turn y, -50
turn z, -90
turn x, -60
turn y, 25
move z, 10

show surface
# label settings and labelling
set label_size, 20
set label_color, black
set label_position = [0.0, 1.5, 8]
label n. CG1 and resi 3 and chain C, "%s, %s" % (resn, resi)
label n. C and (i. 2 or i. 4) and chain C, "%s, %s" % (resn, resi)

bg_color white
png images/cov2-2-surf-01.png, 1000, dpi=300, ray=1

#################
# Next figure
hide surface, 6lu7
alter (chain C), type="HETATM"
alter resn ALA+VAL+LEU and chain C, resn = "UNK"
# remove labels
label
select C, chain C
extract PRD, C
show surface, 6lu7
png images/cov2-2-surf-02.png, 1000, dpi=300, ray=1

#################
# Next figure
hide surface, 6lu7
show surface, PRD
png images/cov2-2-surf-03.png, 1000, dpi=300, ray=1

#################
# Next figure
save PRD.pdb, PRD
C.2 Biological assembly

delete PRD
load PRD.pdb
hide cartoon, PRD
util.cbaw chain C
show surface, PRD
png images/cov2-2-surf-04.png, 1000, dpi=300, ray=1

C.2 Biological assembly

reinitialize
fetch 6lu7, type=pdb1, async=0
set all_states, 1
split_states 6lu7
delete 6lu7
util.cbab 6lu7_0001
util.cbak 6lu7_0002
as cartoon
bg_color white
alter (chain C), type="HETATM"
show sphere, chain C and 6lu7_0001
show sticks, chain C and 6lu7_0002
hide cartoon, chain C
util.cbaw chain C
orient
move z, 30
png images/cov2-dimer-1.png, 1400, dpi=300, ray=1
D

Scripts for figures in Chapter 5

D.1 Display content of 6LZG

# spike ACE2 + S1 fragment
reinitialize
fetch 6LZG, async=0

color wheat, chain A
color slate, chain B

remove solvent
orient
move z, 50
move x, -7

# NAG = N-Acetylglucosamine
# Show bonded AA: ASN 53 and ASN 322
show stick, (resi 53 or resi 322) and chain A
color red, organic

bg_color white

# labels:
set label_size, 20
set label_color, black
D.2 Display content of trimeric structures 6VSB and 6VXX

```bash
# spike trimerics
reinitialize
# one open
fetch 6VSB, async=0
# closed
fetch 6VXX, async=0
util.cbc
as cartoon

align 6VSB, 6VXX

# Grid mode does not work in batch
# set grid_mode, 1

# Alternate option: translate
translate [50, 0, 0], 6VSB
translate [-70, 0, 0], 6VXX

bg_color white

# Labels
```
D.3 Superimpose 6LZG and trimeric 6VSB

set label_size, 20
set label_color, black
set label_position = [2, 2, 8]
label /6VSB/A/A/ARG`246/CA, "6VSB (1 up)"
label /6VXX/A/A/HIS`245/CA, "6VXX (closed)"

gds images/cov2-trimerics-1.png, 1400, dpi=300, ray=1
# cmd.png('images/cov2-trimerics-1.png', '30cm', '10cm', dpi=300, ray=1)

###########
# Next figure
turn x, -90
label
label /6VSB/B/B/THR`500/CA, "6VSB (1 up)"
label /6VXX/A/A/LYS`444/CA, "6VXX (closed)"

gds images/cov2-trimerics-2.png, 1400, dpi=300, ray=1

D.3 Superimpose 6LZG and trimeric 6VSB

# spike trimer and ACE2 + S1 fragment
reinitialize
fetch 6VSB, async=0
fetch 6LZG, async=0
util.cbc

select S1, 6LZG and chain B
super S1, (6VSB and chain A)
as cartoon
# as ribbon
color wheat, 6LZG and chain A
color slate, S1
# show cartoon, 6LZG and chain A
# show cartoon, S1
# extract S1, S1

bg_color white
set_view ( \n    0.569421589, -0.808852911, 0.146665663, \n    0.195740119, -0.039873410, -0.979845762, \n    0.798400283, 0.586652577, 0.135621011, \n    -0.000902131, 0.000237614, -561.803344727, \n    216.354858398, 211.111328125, 255.279617310, \n    516.146301270, 607.512878418, -20.000000000 )
select none

# labels:
set label_size, 20
set label_color, black
set label_position = [0, 0, 8]
label /6LZG/A/A/ALA`614/CA, "ACE2"
label /6LZG/B/B/THR`478/CA, "receptor-binding \n domain"

png images/cov2-spike-trimer-1.png, 1400, dpi=300, ray=1

D.4 6ACK spike glycoprotein trimer with bound ACE2

# spike glycoprotein trimer with ACE2 bound reinitialize
fetch 6ACK, async=0
util.cbc
D.4 SACK spike glycoprotein trimer with bound ACE2

orient
turn z, 45
move z, 40

bg_color white

# labels:
set label_size, 20
set label_color, black
set label_position = [0, 1, 8]
label /6ACK//D/GLU`87/CA, "ACE2"
label /6ACK//B/THR`433/CA, "spike glycoprotein trimer"

png images/cov2-spike-trimer-2-ace2-1.png, 1400, dpi=300, ray=1

###############
# Next figure

extract ACE2, chain D

select byres chain C within 5 of ACE2
show stick, sele
util.cbaw sele
show surface, ACE2

set_view (\n    -0.100384109,  -0.168694198,  0.980534792,\n    -0.242882282,  0.959854066,  0.140271023,\n    -0.964840829,  -0.224080622,  -0.137331456,\n    0.004348084,  -0.002141094,  -0.107.068008423,\n    218.490600586,  243.002914429,  125.151054382,\n    52.256690979,  160.088317871,  -20.000000000 )
zoom sele
bg_color black
label

png images/cov2-spike-trimer-2-ace2-2.png, 1400, dpi=300, ray=1
E

Scripts for figures in chapter 6

E.1  Nsp3 - ribose ADP

# spike glycoprotein trimer with ACE2 bound
reinitialize
fetch 6ACK, async=0
util.cbc
orient
turn z, 45
move z, 40

bg_color white

# labels:
set label_size, 20
set label_color, black
set label_position = [0, 1, 8]
label /6ACK//D/GLU`87/CA, "ACE2"
label /6ACK//B/THR`433/CA, "spike glycoprotein trimer"

png images/cov2-spike-trimer-2-ace2-1.png, 1400, dpi=300, ray=1

########################
# Next figure
extract ACE2, chain D

select byres chain C within 5 of ACE2
show stick, sele
util.cbaw sele
show surface, ACE2

set_view (\
  -0.100384109, -0.168694198, 0.980534792,\
  -0.242882282, 0.959854066, 0.140271023,\
  -0.964840829, -0.224080622, -0.137331456,\
  0.004348084, -0.002141094, -107.068008423,\
  218.490600586, 243.002914429, 125.151054382,\
  52.256690979, 160.088317871, -20.000000000 )

zoom sele
bg_color black
label

png images/cov2-spike-trimer-2-ace2-2.png, 1400, dpi=300, ray=1
F

Scripts for figures in chapter 7

F.1 Nsp15 - asymmetric unit and biological assembly

# NSP15 asymmetric unit
fetch 6W01,async=0
as cartoon
util.cbc
orient
move z, 70
turn z, -5
# Select points of contact with 5 Å
select byres chain A within 5 of chain B
show sphere, sele
select byres chain B within 5 of chain A
show sphere, sele
bg_color white
set label_size, 20
set label_color, black
set label_position = [0, 6, 8]
label /6W01/B/B/GLN~20/CA, "Asymmetric unit: 2 chains"
set ray_trace_mode, 1
png images/cov2-nsp15-1.png, 1200, dpi=300, ray=1

####################
# Next image
# Biological assembly version 1
reinitialize
fetch 6W01, type=pdb1, async=0
set all_states, on
bg_color white
orient
move z, 30
turn y, 180
as cartoon
util.cbc
# set cartoon_cylindrical_helices, on
set label_size, 20
set label_color, black
set label_position = [2, 1, 8]
label /flat:///F/SER\'316/CA, "Biological assembly: 2 trimers"
set ray_trace_mode, 1
set ray_shadow, off
png images/cov2-nsp15-2.png, 1400, dpi=300, ray=1

########################
# Next image
# Biological assembly version 2
reinitialize
fetch 6W01, type=pdb1, async=0
# From: https://pymolwiki.org/index.php/Flatten_obj
run flatten_obj.py
flatten_obj flat, 6W01
bg_color white
orient
move z, 30
as cartoon
util.cbc
set cartoon_cylindrical_helices, on
set label_size, 20
set label_color, black
set label_position=[2, 1, 8]
label /flat//F/SER`316/CA, "Biological assembly: 2 trimers, 6 chains"
set ray_trace_mode, 1
set ray_shadow, off
png images/cov2-nsp15-3.png, 1400, dpi=300, ray=1
G

Scripts for figures in chapter 8

G.1 SARS-CoV-2 nsp12 polymerase bound to nsp7 and nsp8 co-factors

# SARS-CoV-2 NSP12
fetch 6M71, async=0
fetch 6NUR, async=0
as cartoon
color sand
color splitpea, chain B or chain D
color teal, chain C
align 6M71,6NUR
hide everything, 6NUR

set_view (\n    -0.086567082, -0.070623048, -0.993739665,\n    -0.930820167, 0.361255229, 0.055411216,\n    0.355083704, 0.929789126, -0.097008832,\n    0.000127658, -0.000919968, -318.655242920,\n    150.189804077, 138.051406860, 156.410263062,\n    264.730682373, 372.563507080, -20.000000000 )

bg_color white
set label_size, 20
set label_color, black
set label_outline_color, white
set label_position = [0.5, 6, 16]
label /6M71/C/D/ARG`111/CA, "nsp8"
label /6M71/B/C/ARG`21/CA, "nsp7"
label /6M71/D/B/ARG`96/CA, "nsp8"
label /6M71/A/A/ASP`824/CA, "polymerase"

set ray_trace_mode, 1
png images/cov2-nsp12-1.png, 1400, dpi=300, ray=1

#################
# Next image - continue
# Side by side with SARS-CoV NSP12 6NUR
# reinitialize

show cartoon, 6NUR
translate [40, 0, 0], 6M71
translate [-40, 0, 0], 6NUR
move z, -75

label /6NUR/B/B/ASP`78/CA, "6NUR"

bg_color white
set ray_trace_mode, 1
set ray_shadow, off
png images/cov2-nsp12-2.png, 1400, dpi=300, ray=1


1https://dx.doi.org/10.1038/s41564-020-0695-z
2https://www.ncbi.nlm.nih.gov/pubmed/32123347
3https://dx.doi.org/10.1111/febs.12936


\(^5\)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6538669

\(^6\)https://dx.doi.org/10.1038/s41467-019-10280-3

\(^7\)https://www.ncbi.nlm.nih.gov/pubmed/25451065

\(^8\)https://dx.doi.org/10.1016/j.antiviral.2017.11.001

\(^9\)https://www.ncbi.nlm.nih.gov/pubmed/29128390


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