PDBj
Protein Data Bank Japan

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Avian Flu Background

Background information on avian flu

There are many good sources for background reading. Our own eProts server has a short article on influenza neuraminidase. The journal Nature has a web page dedicated to the subject. From this page you can learn that the particular strain of influenza virus that is threatening to become pandemic (in 2007 there were 85 confirmed cases in 9 countries resulting in 58 deaths) is called "H5N1". Therefore entering the keyword "H5N1" into the xPSSS search engine is a good starting point for learning more about neuraminidase structures.

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Avian Flu xPSSS

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xPSSS search for avian flu virus neuraminidase structures.

Enter "H5N1" into the xPSSS query window, select "keywords", and then click "Go".

There are a number of matches (13 at the time of this writing), all of which correspond to one of two glycoproteins (proteins with attached carbohydrate groups): hemagglutinin and neuraminidase. Haemagglutinin mediates virus binding to cell surfaces via sialic acid receptors. Once the virus has replicated, neuraminidase removes the sialic acid from the cell surfaces, facilitating virus release. In this tutorial we are interested in the neuraminidase family. About halfway down the xPSSS results page you will find the entry 2hty.

2HTY download PDB format file

descriptor	: Neuramindase
title	: N1 neuraminidase
authors	: Russell, R.J., Haire, L.F., Stevens, D.J., Collins, P.J., Lin, Y.P., Blackburn, G.M., Hay, A.J., Gamblin, S.J., Skehel, J.J.,
exp.method	: X-RAY DIFFRACTION
deposition date	: 2006-07-26
release date	: 2006-09-05

Electron density map is available to be displayed from the Experimental Details page.

If you click on the link, you can see a summary of the 2hty entry which includes a reference to a 2006 Nature paper by R. J. Russell and co-workers. In fact a number of of the neuraminidase entries references this paper. If you have access to Nature, it is worth reading this article to see the importance that tertiary structure has on the design of antiviral drugs targeted against avian flu. The essential point is that there are

two basic influenza types(group-1 and group-2) which share approximately a 50% sequence identity. Current drugs such as Tamiflu were designed to inhibit group-2 viruses, but H5N1 belongs to group-1. The crystal structure of group 1 neuraminidases might allow the design drugs that are more effective against H5N1 influenza virus.

The pdb entry 2hty belongs to group 1. Lets first use Sequence Navigator to find some of the other subtypes.

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Avian Flu Sequence Navigator

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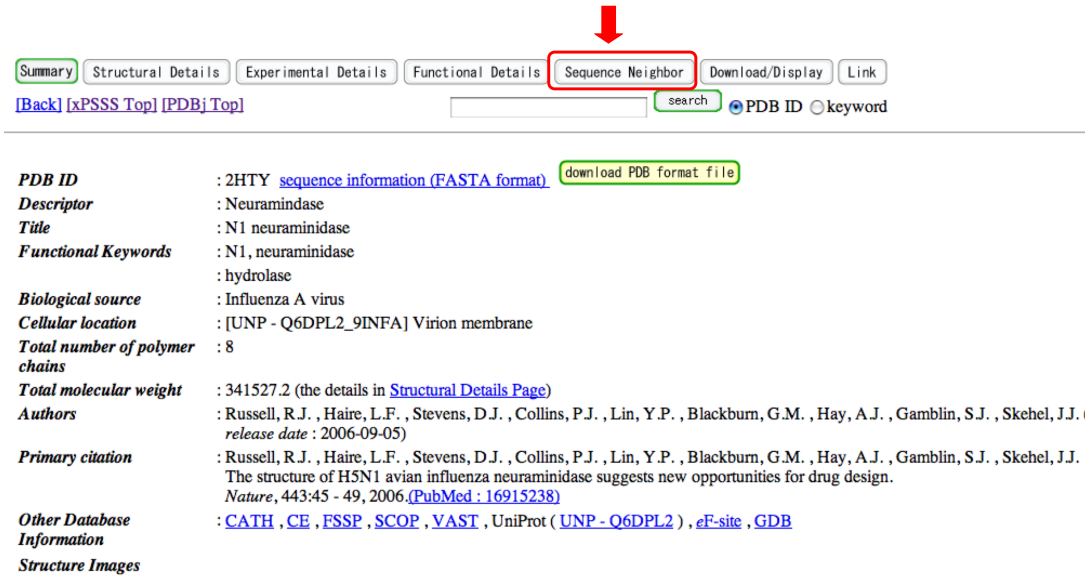
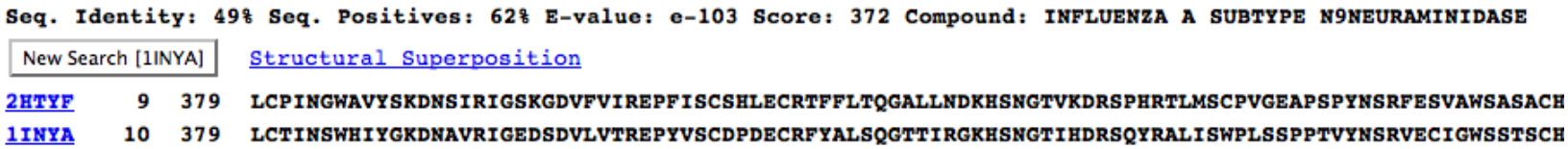
Sequence Navigator search for avian flu neuraminidase subtypes

From the 2hty summary page in xPSSS, click on the "Sequence Neighbor" button



In the Sequence Navigator results page, sequence alignments to a number of proteins (currently 30) can be found. Are all of these neuraminidases? Are all of the hits "significant"? Clicking on the "Structural Superposition" link will allow you to determine which ones are significant. If you scroll down you can find the alignment to PDB entry 1INY, which is a subtype-9 neuraminidase, from group-2, and has been a target for structure-based design of anti-influenza drugs (reference).



Note the sequence identity between 2hty and 1iny is 49%. How about the structural similarity? Check the "Structural Superposition" link. You can see only a few gaps in the alignment. By viewing the superposition in jV by clicking the "[jV version3]" link, you can get an idea of where these gaps occur. The secondary structure (c- coil, E=beta-sheet, H=helix) is indicated in the alignment. In what secondary structure do the

gaps tend to appear in? By looking for a cavity in the protein, can you guess where the active site is?

Try looking at several more neuraminidase subtypes to see if the gaps occur in similar places. In the next section we will look at the structures in more detail.

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Avian Flu Structure Navigator

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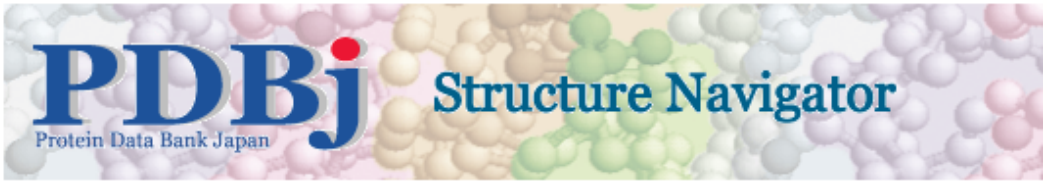
Using Structure Navigator to find human proteins related to influenza neuraminidases

Next we will examine proteins in humans that are related to the viral neuraminidases using the structure-based search engine Structure Navigator. At the Structure Navigator top page, enter the same query as before, 2hty chain A.



Protein Structure Search Engine

About Structure Navigator

Structure Navigator-RT (Opal-OP)

PDB Code: 2hty Chain A OR Upload PDB File

Return Only Sequence Representatives

Search Clear Form

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Follow the link to the results page. Are the sequence identities of the Structure Navigator hits higher or lower than the Sequence Navigator hits? The %NER (Number of Equivalent Residues) can be thought of as a structural analog to sequence identity (i.e. how similar the structures are). Is it higher or lower than the sequence identity? Can you guess why this is?

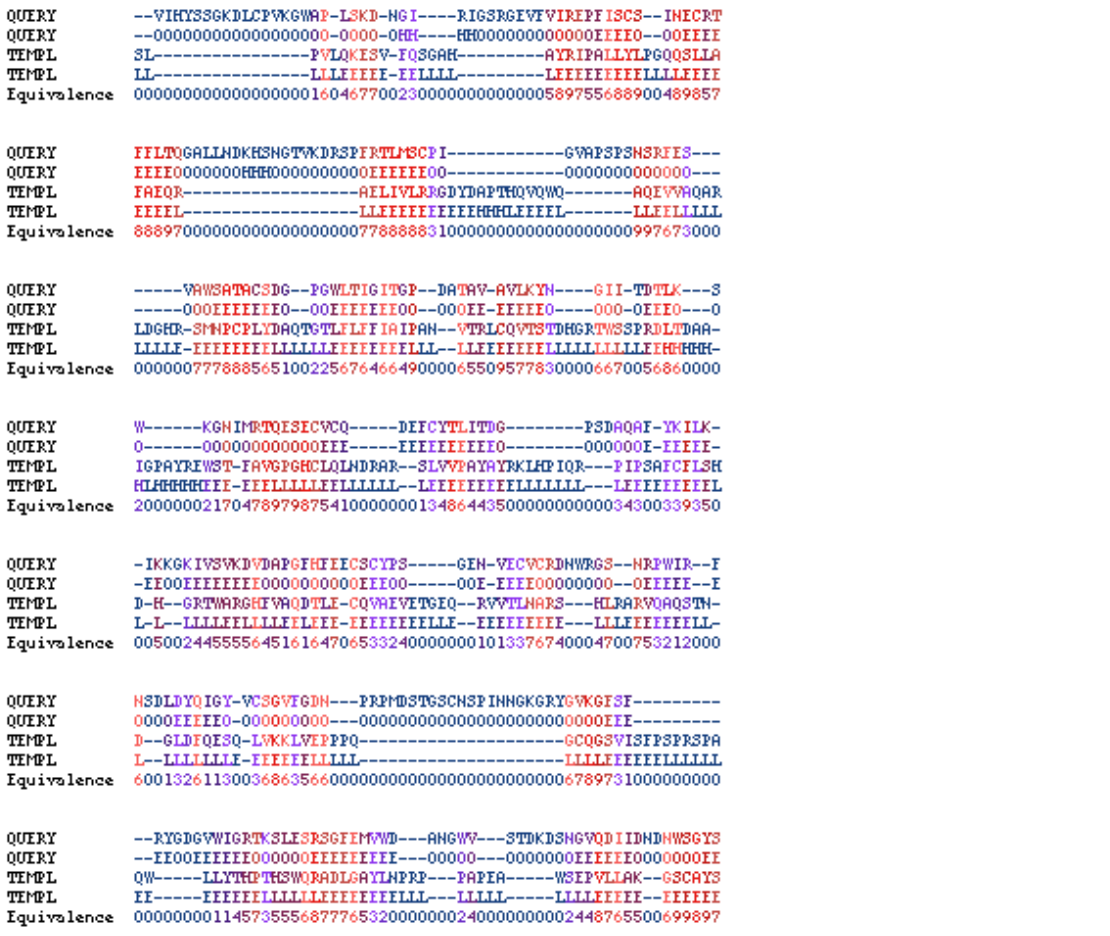
Locate the entry 1snt:

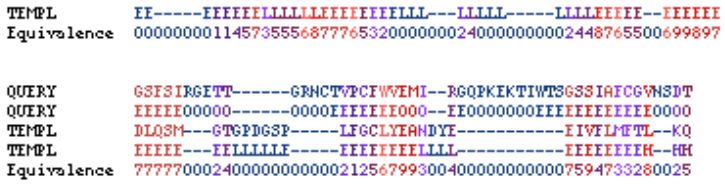
Templ	NER(4)	%NER(4)	%Seq ID	RMSD	Score	Domain	Details
1eut	155	40	7	2.701	50	2.120.10.10	alignment
1w8oA	155	40	7	2.725	50	2.120.10.10	alignment
1wcqA	155	40	7	2.720	50	2.120.10.10	alignment
1wcqC	155	40	7	2.715	50	2.120.10.10	alignment
1eur	155	40	7	2.714	50	2.120.10.10	alignment
2bq9A	154	39	7	2.742	50	2.120.10.10	alignment
2bzdC	155	40	7	2.720	50	2.120.10.10	alignment
1eus	155	40	7	2.710	50	2.120.10.10	alignment
2berA	156	40	9	3.173	49	2.120.10.10	alignment
2f0zA	146	37	7	2.839	42	2.120.10.10	alignment
2f29A	141	36	7	2.824	42	2.120.10.10	alignment
2f10A	145	37	7	2.874	41	2.120.10.10	alignment
1v0eA	140	36	7	3.355	41	4.10.1090.10	alignment
2f27A	140	36	7	2.866	41	2.120.10.10	alignment
1so7A	138	35	7	2.957	40	2.120.10.10	alignment
1vcuA	141	36	7	2.886	40	2.120.10.10	alignment
1sntA	138	35	7	2.952	40	2.120.10.10	alignment

What is its sequence identity and %NER? By clicking on the link "1sntA", you can read more about this protein in xPSSS. What is its function? Is this function related to that of the neuraminidases? Why might humans have such an enzyme?

The structural alignment can be viewed by clicking the "alignment" link.

Templ	NER(4)	%NER(4)	%Seq ID	CA-RMSD	Superposition	
1sntA	138	35	7	2.952	download	[jV version3]





How does this alignment compare with the Sequence Navigator sequence alignments above? What about the probable location of the active site?

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Avian Flu ASH

Structural alignment of neuraminidase subtypes

In this section we will use the program ASH, the eF-site database and jV to look closely at the active sites of neuraminidases and related proteins. Some of the steps involving ASH can not currently be done over the web, so we provide command-line scripts with instructions for those who are interested as well as links to the output files for those who would like to skip ahead.

Option 1: Download the superimposed files, and skip to the next step

There are six output files that can be downloaded in the following links:

The following are PDB files for types 9 and 1 influenza neuraminidase, as well as the related human protein sialidase, respectively:

flu type 9 pdb flu type 1 pdb human pdb

The following are efvet XML files containing electrostatic surface information for types 9 and 1 influenza neuraminidase, as well as the related human protein sialidase, respectively:

flu type 9 efvet-xml flu type 1 efvet-xml human efvet-xml

Option 2: Prepare the files yourself

In this section we will superimpose 2hty, chain A and 1snt, chain A onto 1iny chain A. We will superimpose both the PDB files and the efvet XML files. Here are the steps needed to do this:

1. Prepare pdb files for 2hty, chain A and 1snt, chain A, and 1iny chain A.

Usually, when we want just a part of a PDB file we must download the whole file, then edit the file using a text editor or a script. To simplify this task, we have prepared a web-based utility called Clean PDB where you can specify the PDB ID and chain(s) that you want. You can also specify the hetero-groups (ligands) that you want to be kept or removed.

In the Clean PDB form, enter the PDB ID 2hyt. The rest of the options can be left unchanged.

This simple utility can remove multiple models, select a particular chain or chains, select or remove heterogroups, and renumber your PDB file starting from 1.

PDB ID 2hty

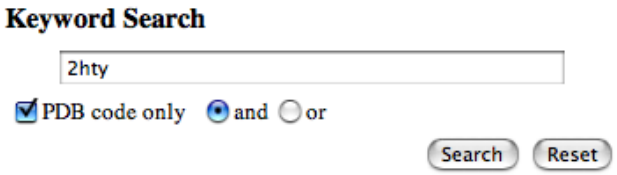
Chain ID(s) A **(Use comma to specify multiple chains)**

Heterogroups (ligands)

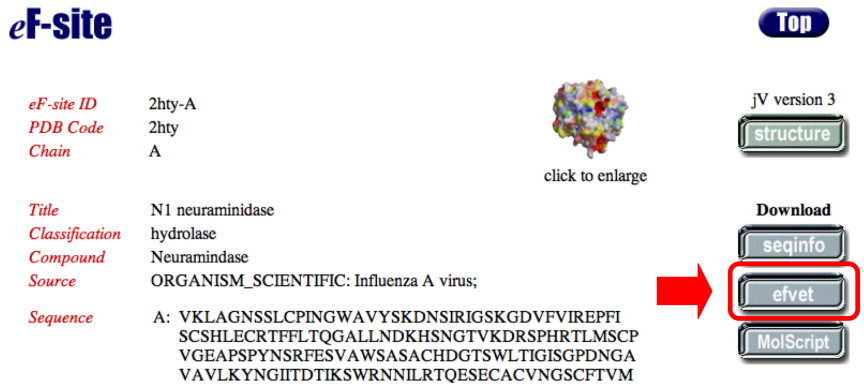
Download the resulting file, and repeat for 1iny, and 1snt.

2. Download electrostatic molecular surfaces (efvet XML) files for 2hty, chain A and 1snt, chain A, and 1iny chain A.

The electrostatic molecular surfaces can be downloaded from the eF-Site database. Enter the pdb ID 2hty and select "PDB Code only".



Click on the 2hty-A link, then click the efvet button:



Now repeat for 1iny and 1snt.

3. Superimpose 2hty, chain A and 1snt, chain A onto 1iny chain A.

Here we will use the program ASH to structurally superimpose the "cleaned-up" files above as well as

their associated surfaces onto 1iny. The web-based utility Superimpose uses ASH to superimpose a "query" PDB file onto a fixed "template" PDB file, and allows you to rotate the query surface file along with the PDB file. Here the queries are our cleaned up 2hty, chain A and 1snt, chain A files. First upload your cleaned up 2hty file as the query and upload your cleaned up 1iny file as the template. Then click "Submit".

This program will superimpose one PDB file (query) onto another (template) using the structural alignment program ASH. Also, if you have an efvet XML polygon file corresponding to the query, you can have it rotated along with your query PDB file.

Query

Chain **PDB ID** **Or PDB File** Choose File 2hty_clean_11341.pdb

Optional efvet XML File Choose File 2hty-A_efvet.xml

Template

Chain **PDB ID** **Or PDB File** Choose File 1iny_clean_11783.pdb

Submit Clear Form

A link should appear that allows you to download the rotated PDB and efvet XML files. Download them, and repeat using the cleaned-up 1snt file and associated efvet XML as the query.

You will now want to re-name your files as follows:

Clean 1iny, chain A PDB: 1inyA.pdb

Clean, rotated 2hty, chain A PDB: 2hytA_rot.pdb

Clean, rotated 1snt, chain A PDB: 1sntA_rot.pdb

1iny efvet XML: 1iny_efvet.xml (probably no change needed)

Rotated 2htyA efvet XML: 2htyA_rot-efvet.xml

Rotated 1sntA efvet XML: 1sntA_rot-efvet.xml

If you made it this far, congratulations! You are done with this section.

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Avian Flu jV

Viewing the structurally aligned neuraminidase files in jV

Please download or prepare the above files. Note that the files have been modified from their original form in two ways: First in cases where multiple chains exist in the same PDB file, only chain A and its associated ligands have been selected. Second, the flu type 1 neuraminidase and human sialidase have been superimposed on the flu type 9 neuraminidase.

Start up jV on your computer, locate and read in the six files: 1inyA.pdb, 1iny_efvet.xml, 1sntA_rot-efvet.xml, 1sntA_rot.pdb, 2hytA_rot-efvet.xml, 2hytA_rot.pdb. Note that the xml files must be read in as 'polygon' files. The result should look something like the image below.

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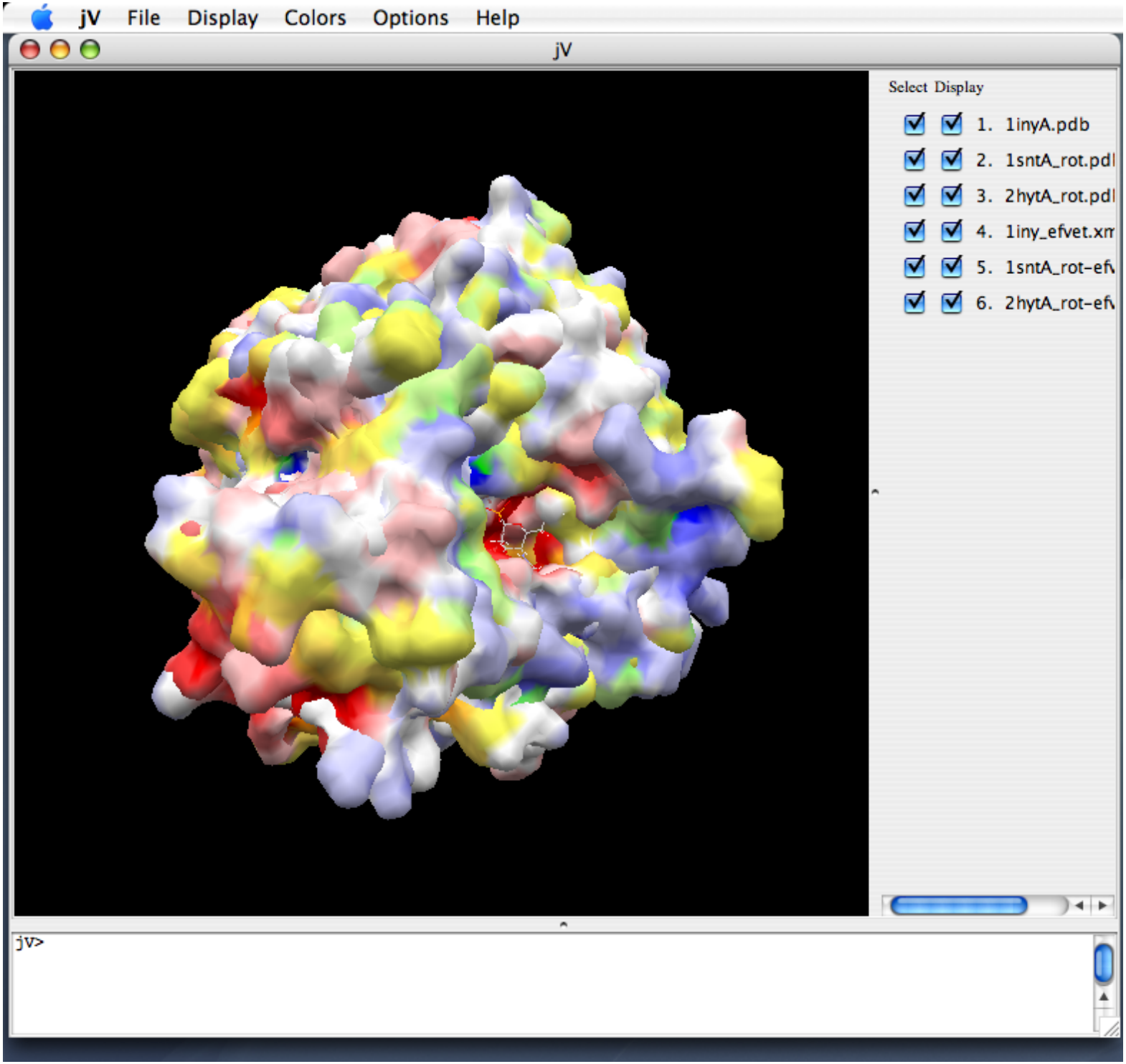
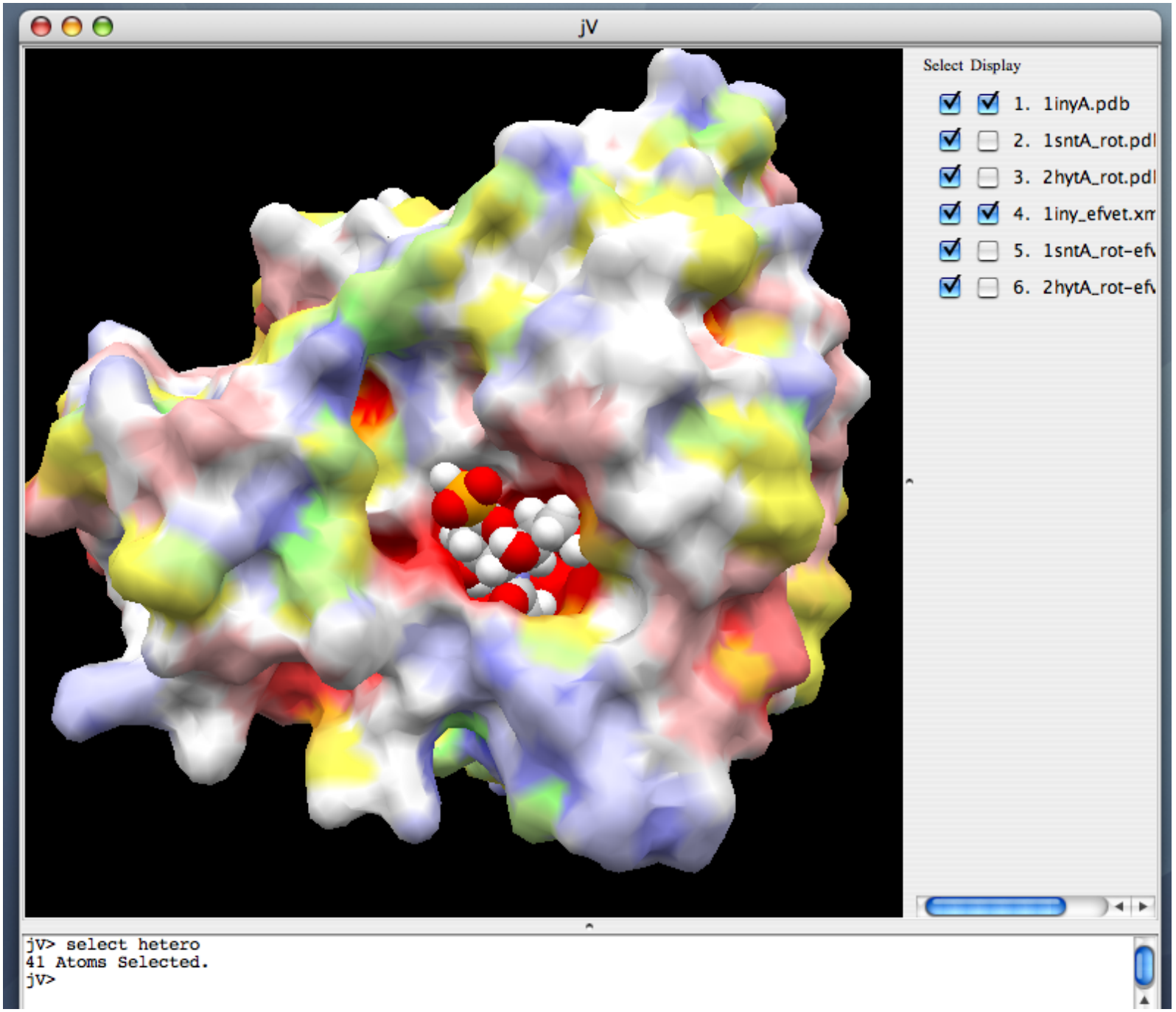


Next, make the ligands easier to see by typing "select hetero" into the command window. Then change the display of the ligand to spacefill: "Display->Spacefill". Next, un-select the display of 1sntA_rot.pdb, 2hyta_rot.pdb, 1sntA_rot-efvet.xml, and 2hytA_rot-efvet.xml, and rotate the molecule to get a better view of the ligand bound to the active site. The view should look something like that below.



Now try switching the display between the 1iny electrostatic surface and the 2hty surface. Can you see some important differences in the active sites? Lets recall what these two structures are. 1iny is subtype 9, in group-2. This is the structure from which drugs like Tamiflu were developed. 2hty is subtype 1, in group 1. It is the type that is threatening to become another influenza pandemic, and was responsible for at least 58 deaths in 2007. Do you think the drug that binds to group-2 would also bind to group-1? How about the reverse question: Would a drug that binds to group-1 necessarily bind to group-2? Can you see how it might be possible to design a drug that binds only to group-1?

Next, lets compare the viral active sites to that of the human sialidase. Where are the potential binding sites in human sialidase? Does it look like drugs that bind the viral proteins might interfere with the human proteins?

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