Basics tutorial - VTX

A high-performance molecular visualization software

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Introduction

Molecules are groups of atoms, joined by chemical bonds, forming different types of geometry in space. This structure provides information on the function and properties of each molecule. The observation of molecules can therefore be used to understand, illustrate and educate about biological processes, and is known as molecular visualization.

Molecular visualization has always been important to chemists in structural molecular biology. Over time, modeling methods have always kept pace with technological advances. The original physical models made of paper or brass were replaced by the arrival of computers, and then enhanced by advances in video games. These advances have made it possible to analyze more molecules, of larger size and greater complexity.

This discipline presents a number of challenges, such as deciding on the representation of the molecule and its influence on the target audience. Indeed, any image depends on what you're trying to demonstrate about the molecule, and needs to be presented in such a way as to bring understanding to the chosen subject.

The aim of this tutorial is to introduce new users to VTX software and molecular visualization. It is therefore organized in such a way that a theoretical part is followed each time by a small exercise in gray backgrounds with a light bulb. The aim is to visualize the interaction zone between a ligand and a polymer.

This tutorial was written using VTX v0.4.0.

Download

VTX is freely available on Windows and Linux on : https://vtx.drugdesign.fr

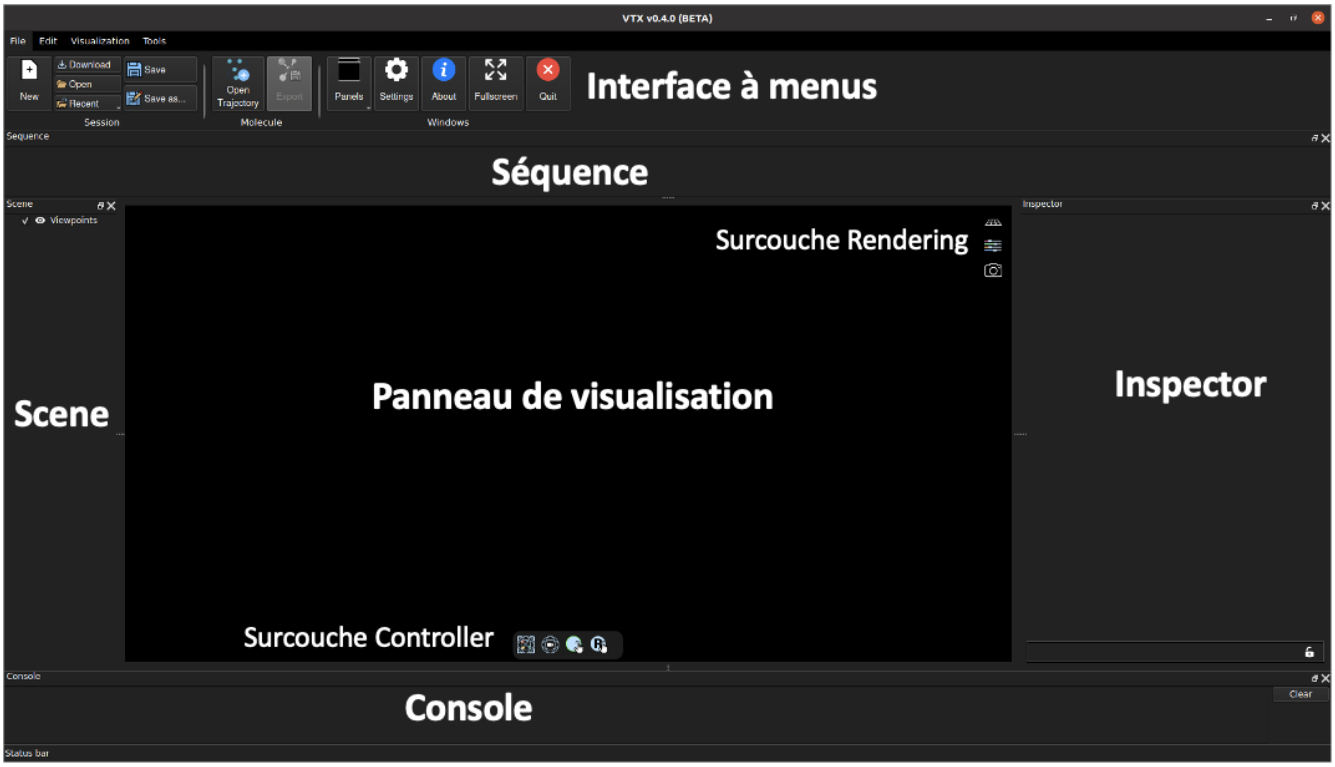
Before downloading the software, you'll find a link to a readme: (https://gitlab.com/VTX_mol/VTX/-/blob/master/README.md) with installation conditions, as well as some shortcuts and commands we'll be coming back to in this tutorial. But also commands for the interface & for future improvements.

Opening the software

On Windows, you can open the software in the “VTX_0.4.0” folder in the downloads by double-clicking on it.
On Linux, you can open the software, located in the Bin folder, using the terminal, for example, with the command “./VTX”.

UI

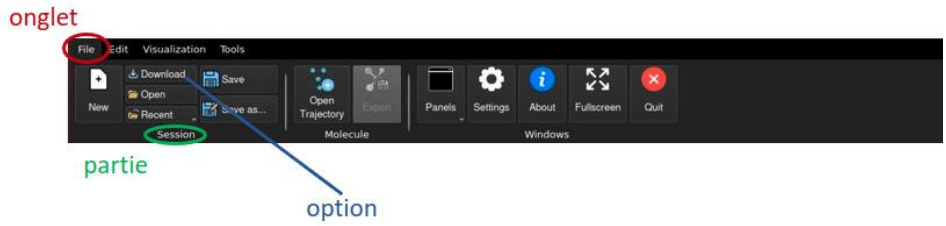
First of all, when you open the application, you're presented with various panels.



- the *scene*: lists and controls all the elements displayed in the display panel
- the *inspector*: provides additional information on what is being observed
- the *sequence*: displays the primary sequence of proteins in one-letter code
- the *console*: displays information such as what has been done.

Each of these panels can be separated to form a new window or moved to another location. To do this, click and hold on the panel while moving it to the desired location.

We also see a *menu interface* with different tabs, each linking to different tools, which we'll describe in turn. In this tutorial, we'll refer to each menu by locating it according to its tab, its part and its name, such as :



There are also overlays on the display panel with shortcuts to various options. These overlays can be removed by right-clicking, then clicking on overlays and selecting either *Show all* to show them all or *Hide all* to hide them all, then checking or unchecking *Controller & Rendering*.

Opening a molecule file

To be able to visualize molecules on a computer, we first need to determine their structures. Several techniques are available, depending on the size and crystallization capacity of the molecule under study:
- *NMR spectroscopy* is used for small molecules.
- *X-ray crystallography* for proteins that can crystallize. Indeed, some proteins are very difficult to crystallize, notably those that are highly disordered or unstable, or those that are insoluble in water. This technique is the most widely used.
- *Cryo-electron microscopy*, a rarer technique used for large molecules.

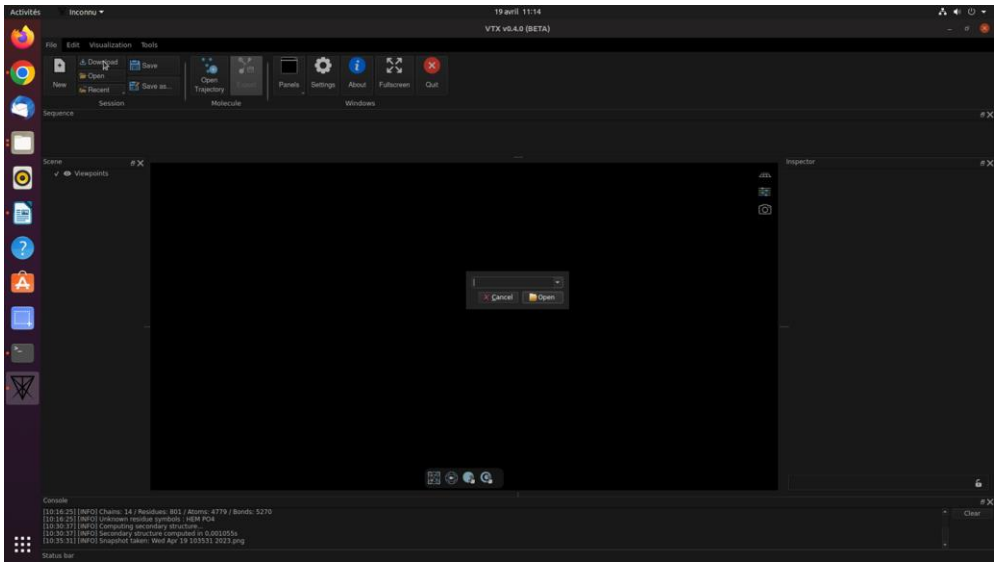
Once these structures have been obtained, they are formatted into a short text document, and submitted to the Research Collaboratory for Structural Bioinformatics (RCSB), the organization in charge of the Protein Data Bank (PDB) on which the results will be published.
The PDB is a U.S.-based, open-access digital database that serves as a global archive of data, such as the 3D structure, of proteins.

In the PDB, files are identified by a 4-character code.

For example, 4HHB corresponds to human hemoglobin. This protein transports oxygen from the lungs to the rest of the body. It is made up of 4 identical polypeptide chains, each linked to a heme. On the PDB website, you can see that it was obtained by crystallography.

Returning to VTX, we want to open a molecule in order to visualize it. There are two ways of doing this:

- You can choose to go to the Files tab, then select *download* in the session section. This will open another page where you can enter the 4-character PDB code and press *open*.



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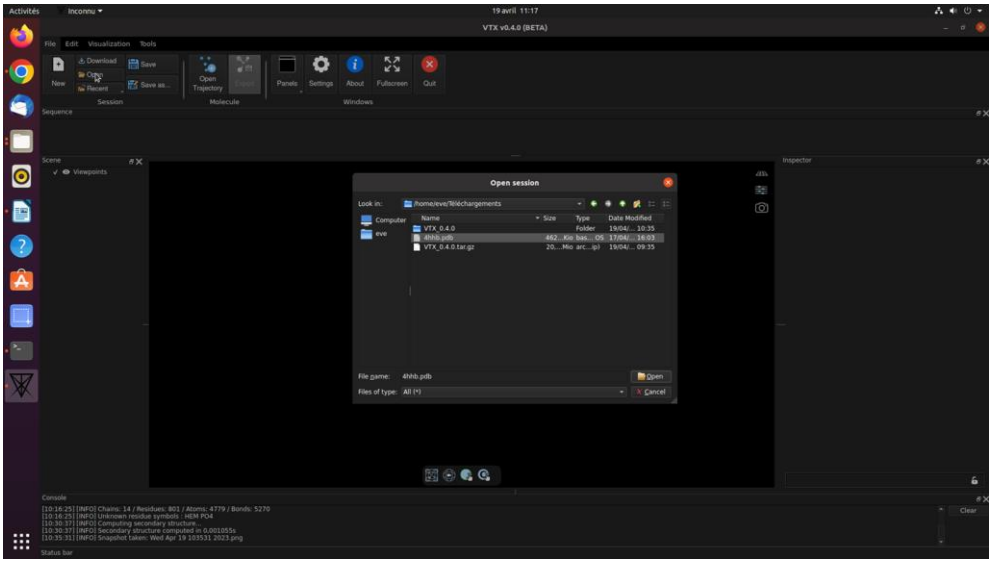
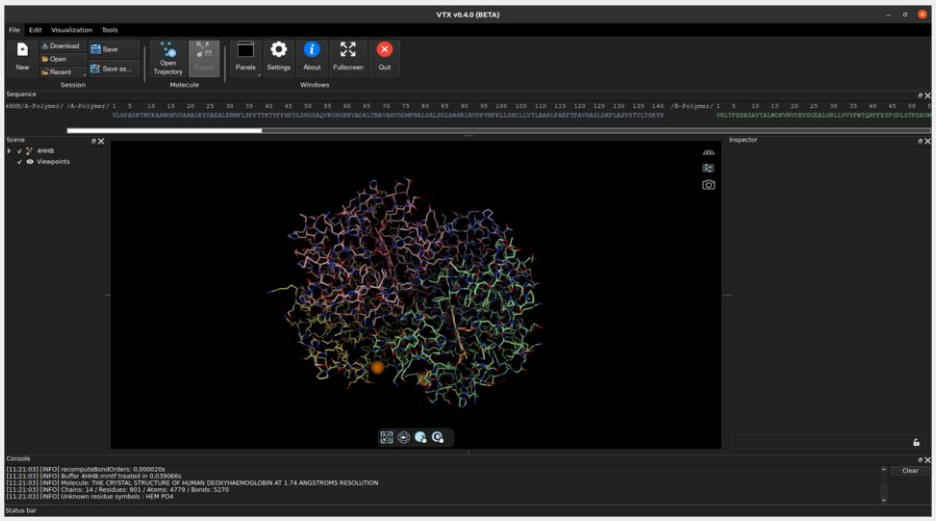
  - Alternatively, you can first download the short text corresponding to the molecule's structural data from the PDB website. To do this, search for the molecule under study, then select PDB

Format in the download files menu. The file will then appear in your computer's downloads and will be named after the PDB's 4-character code. You can then return to VTX, in the Files tab, and select *Open* in the *session* section. You will then need to select the file downloaded from PDB.



Try one of these methods with 4HHB. After that, this is what your window should look like:



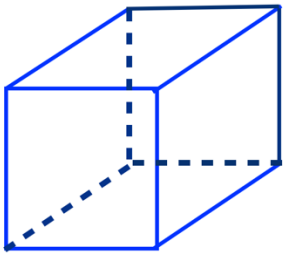
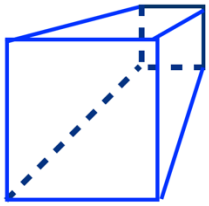
Whichever method you choose, the molecule appears on the *visualization* panel.

In the *scene*, a line appears with the code of the molecule, and by clicking on the small triangle before the name, you can see the different chains forming the molecule.

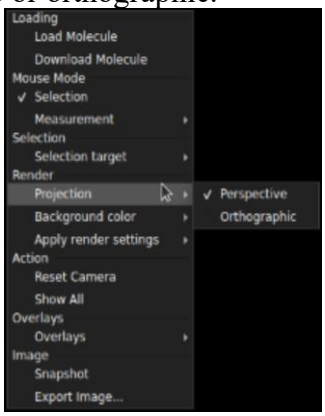
These are divided into main polymer chains, ligands, ions and waters. By clicking on the corresponding triangles, you can then see the different chains, then the amino acid residues at the origin of the protein, and finally the atoms.

The *sequence* shows the same succession of amino acids for each chain, differentiated by color.
Water molecules can be seen around each chain. These molecules may be water of crystallization, the result of experimentation to obtain the protein structure. In fact, when obtaining the structure of the molecules, it is possible to add not only water, but also solvents or ions that would still be on the PDB file.
On VTX, these can be easily removed by going to the *Edit* tab and clicking on *Waters*, or *Solvent*, or *Ions* in the *Element Visibility* section. Depending on the method used to obtain them, hydrogens may be displayed to clarify the space observed; they can also be removed in the *Edit* tab, by clicking on *Hydrogens* in the same section.

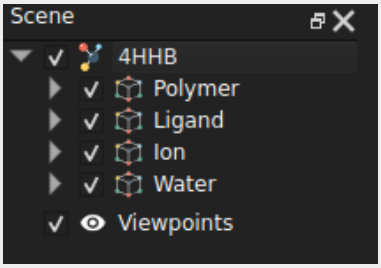
In the *Visualization* tab, in the *projection* section, you can click on either *orthographic* or *perspective*.
In the orthographic option, the molecule is represented in its true dimensions, like a drawing on a 2D plane. In the perspective option, the distances between the atoms are manipulated so that we see the molecule as we would in real life, i.e. the parts closest to us take up more space, while those farthest from us are smaller, giving us an impression of depth and therefore of 3D.

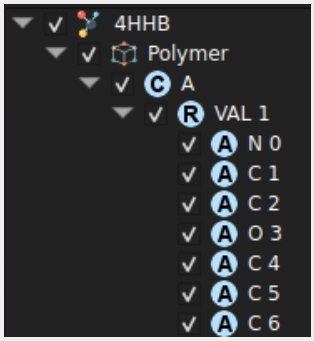
Orthographic   Perspective

This option is also available by right-clicking in the viewer panel, then clicking on projection in the render section and selecting perspective or orthographic.



For 4HHB observation, you can try unrolling the scene menus. You'll get a scene like :





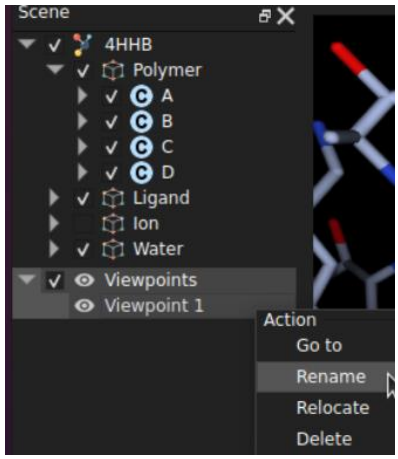
With *Element Visibility*, you can remove ions from vision. If you hide the hydrogens and the solvent, there's no difference. On the other hand, in this tutorial we'll be using waters, so leave *Waters* in green!

We're going to manipulate the molecule, so it's best to stay in perspective mode.

Mouse movements

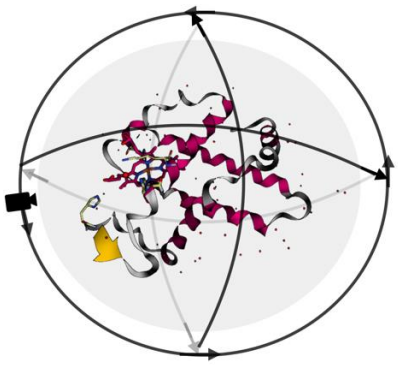
Several types of movement are possible around the molecule, each of which can be activated with the mouse or on the interface in the *Visualization* tab of the *navigation* section. However, it is recommended to use a mouse to manipulate the molecule more comfortably. At any time, you can return to the starting point by clicking on reset in the *Visualization* tab in the *navigation* section, or save your position to return to it more easily later in the same tab in the *Viewpoint* section by clicking on *create*.

This action will add a line in the *scene* called Viewpoint 1, which double-clicking on will take you back to this viewpoint. You can also rename it by right-clicking on it and then clicking Rename in the sub-menu that appears.

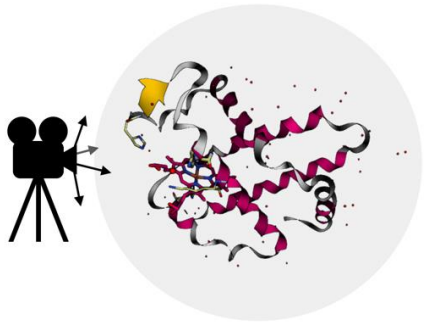


To move around the molecule (regardless of the type of movement), click and drag on one side.
On a 3-button mouse, you can use:

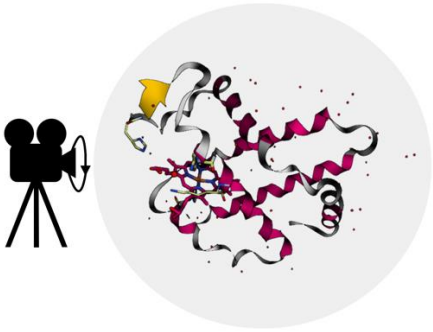
- The left button, which works as a **trackball**: This mode allows you to move the camera around the molecule as follows



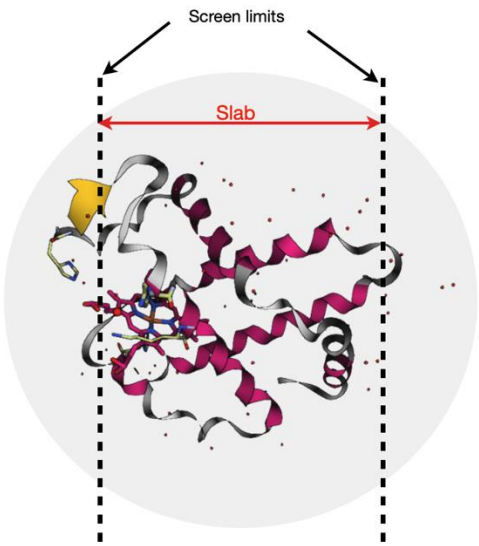
- The middle button that works in **Freecam**: This mode moves the camera angle while looking at the molecule from a fixed point. Such as:



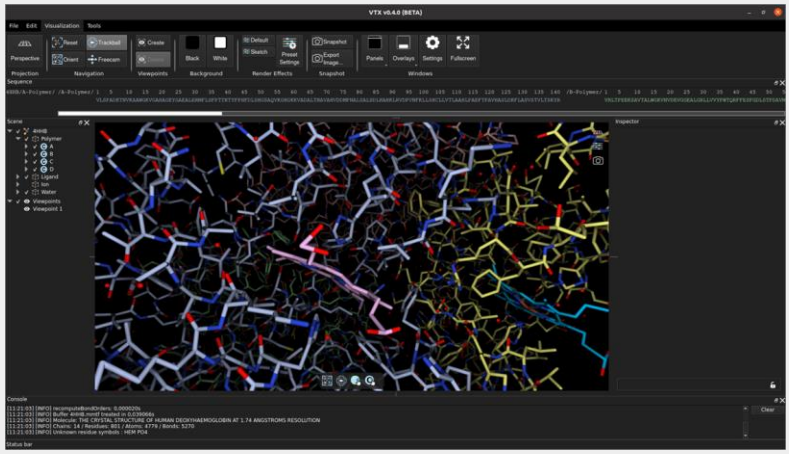
- The right button works to turn the camera on the spot, such as :



You can also reduce or increase your field of vision using the thumbwheel. By rolling it forwards, you zoom in on the area you're looking at, thus reducing the field of view. This is known as slabbing. Conversely, rolling the wheel backwards will zoom out, increasing the field of view. This process is called clipping.



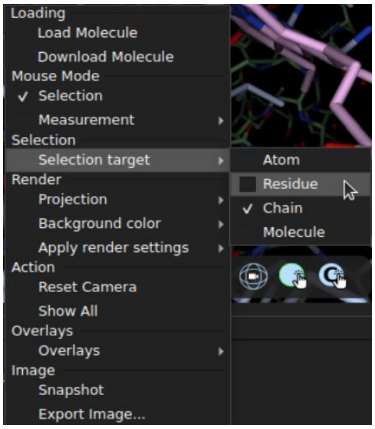
Move around the molecule to identify at least one interaction between one of the ligands and its corresponding monomer. Then record the point of view from which you are standing. For example, if you choose to observe the blue monomer, you get :



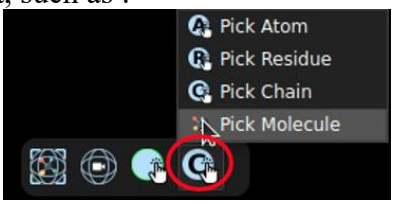
Selection Modes

By left-clicking on the molecule, we can see that it is highlighted with a green layer, which shows us that we have selected it entirely. To deselect, you can click anywhere else.

It is also possible to select part of a molecule. By right-clicking anywhere on the display page, a menu appears, allowing you to click on Target selection, then another submenu appears, offering selection at molecule, chain, residue or atom level.



You can also use the Controller overlay by clicking on the logo circled in red and then choosing from the submenu what you want to select, such as :



Once the desired selection has been made, it can be seen more clearly by moving the mouse or clicking on orient in the *Visualization* tab in the *Navigation* section. In addition, the selected part will be highlighted in the *scene* in lighter grey, making it easier to identify.

You can also select at different scales by double-clicking directly on what you want to see in the *scene*. To select a residue, you can also use the *sequence*. By double-clicking on a residue in the sequence, it will be selected in the visualization page. Conversely, if a residue is selected, it will be highlighted in the sequence.
In these two other cases, the *orient* function is performed automatically.

Following any selection, the *inspector* will display related information in different sub-sections:

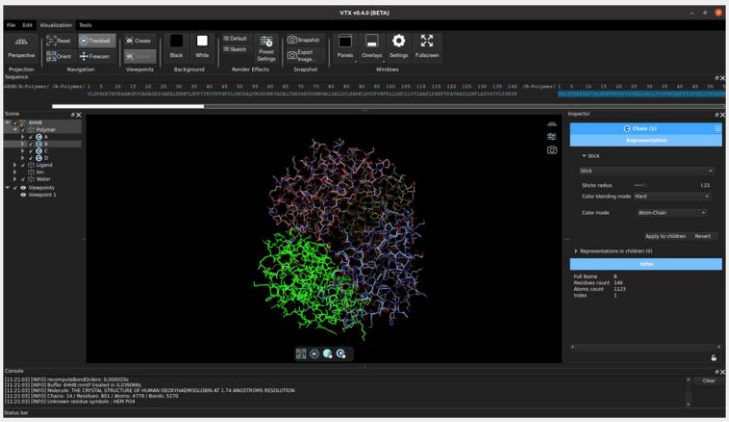
- ➢ Representation: which we will describe in detail in the section “Actions on the molecule: representations & colors”.
- ➢ Info: lists different information depending on the scale. The information available is summarized in the table below:

Scale of the selection	Informations disponibles
System	- name - chain number - atom and chain

Chain	- molecule number - atom and residue number
Residue	- residue name - atom name - covalent bond list
Atom	- name - full name - covalent bond

- ➢ Position: Only available for atoms, gives the X, Y, Z coordinates of the selection
- ➢ Transform: Only available for molecules, allows you to move the molecule or change its scale according to the X, Y, Z axes.
- ➢ Autorotation: automatically rotates the molecule according to the X, Y, Z axes.

After moving around the molecule, try selecting the polymer's B chain. You should see a screen like this:



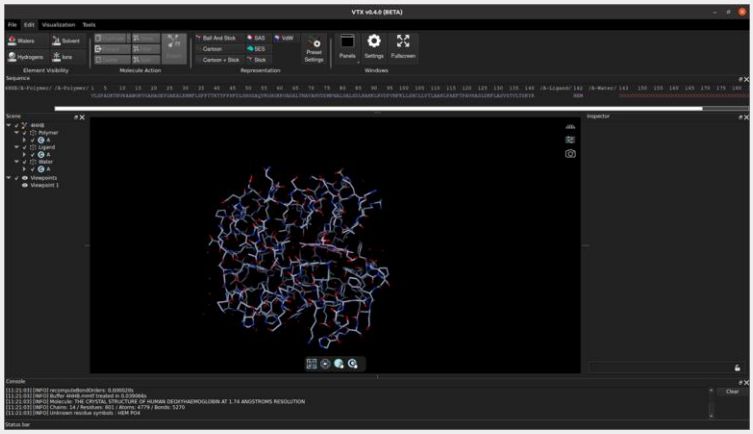
Molecule actions: show, hide, delete

It is possible to simplify the view. If the molecule is made up of parts which are not useful for what we're trying to visualize (for example, several identical chains), we can choose to delete them by selecting them and then clicking on *delete* in the *molecule action* section of the *Edit* tab, or by right-clicking on the corresponding line in the scene and then clicking on *delete* in the sub-menu.
If you don't want to see this part of the molecule without deleting it, you can hide it by clicking on Hide in the *Molecule action* section of the *Edit* tab.
If you only wish to observe a part of the molecule (at any scale), you can select it and then click on *Solo* in the *Molecule action* section, which will hide the rest of the molecule. To show what's been hidden, simply click on *Show*, and if you've lost your selection, right-click in the viewing panel and select *Show All*.

The *scene* can also be used to show or hide molecules, or parts of molecules. Each line of the scene is preceded by a checkbox which can be checked or unchecked, displaying or hiding the selection.

To manipulate a part of the molecule more simply, it is possible to select it and then click on *Extract*, which will separate it into another line of the scene where the extract will be named: "Extract of" followed by the code of the open protein. By right-clicking on this line and selecting Rename from the submenu, you can rename the extract.

The 4HHB molecule contains 4 monomers linked to their respective ligands. We will keep only the A group. Try deleting or hiding parts of the molecule so as to leave only the A monomer, the A ligand and the A water molecules. Then, if you hadn't chosen this chain and ligand, create a new viewpoint as you did when applying the "Mouse movements" section.
You should obtain a viewpoint similar to :

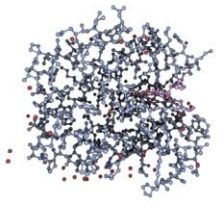
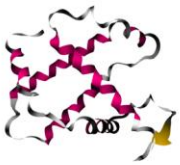
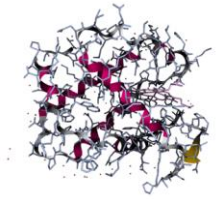
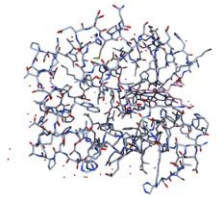
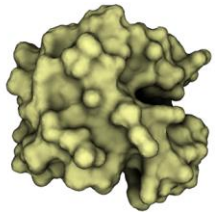
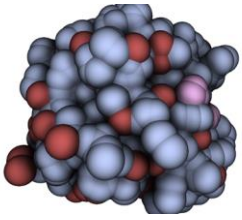


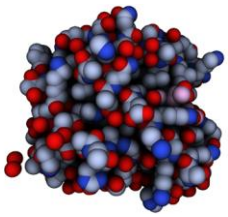
(Here we've chosen to remove unnecessary parts to simplify the view. If you have decided to hide unused parts, these parts will still appear in the scene, but just not checked).

Molecule actions: Representations and colors

There are different ways of representing molecules, each with its own specific features:

Representation	Characteristics	Example

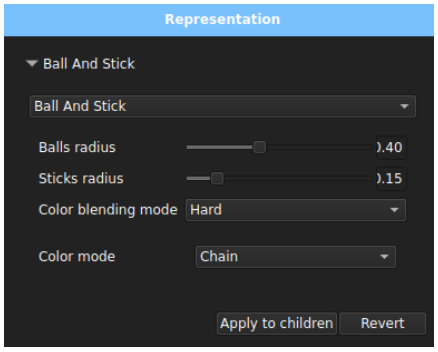
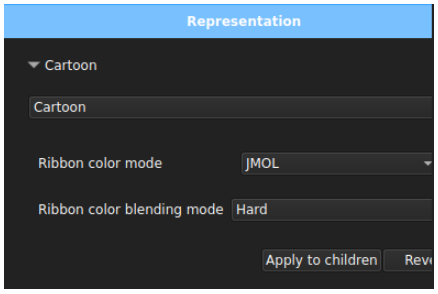
Ball & stick	Gives details of atomic resolution structures. But it's difficult to distinguish the different protein chains.	
Cartoon	Highlights aspects of secondary and tertiary structure at the protein backbone level, but makes it difficult to obtain information on the chemistry of the molecule, or to visualize its volume.	
Cartoon + stick	Highlight secondary and tertiary structures while displaying the atoms at the ends as sticks.	
Stick	Gives details of atomic resolution structures in CPK color (blue: nitrogen, red: oxygen...) but clutters the view of large molecules.	
Solvent Excluded Surface (SES)	Provides information on the molecule's overall shape, complexity and assembly. However, this representation prevents us from seeing the inside of the protein.	
Solvent Accessible Surface (SAS)	Provides information on the molecule's overall shape, complexity and assembly. However, this representation prevents us from seeing the inside of the protein.	

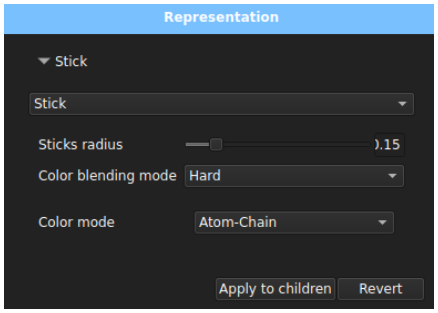
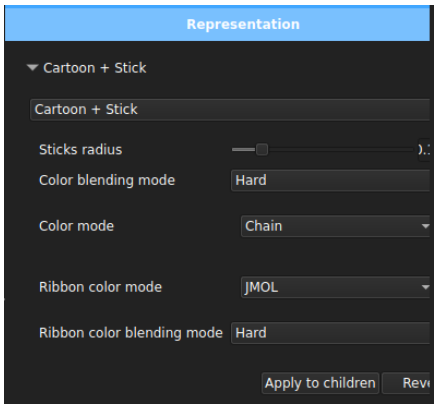
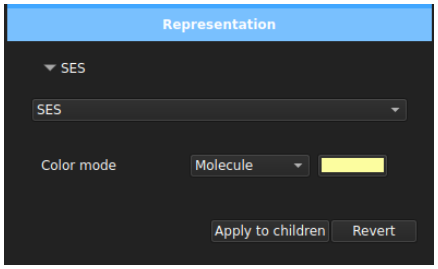
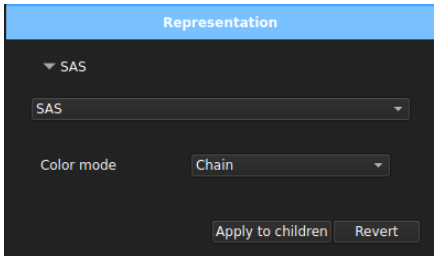
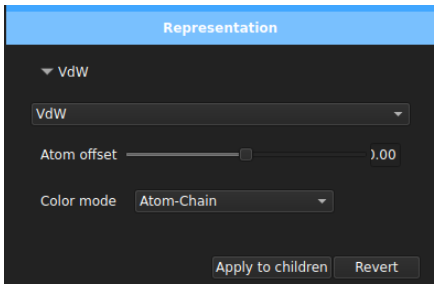
Van Der Walls (VDW)	Provides information on the molecule's overall shape and assembly, as well as its steric hindrance. In this representation, the VDW surface of each atom appears as a sphere. However, this representation prevents us from seeing the inside of the protein.	

It is possible to change the representation of the molecule or part of it. To do this, select the desired part of the molecule, then use one of 2 methods:

- The easiest way is to click on the desired representation in the *Edit* tab (Ball and Stick, Cartoon, Cartoon + Stick, SAS, SES, Stick or VDW).

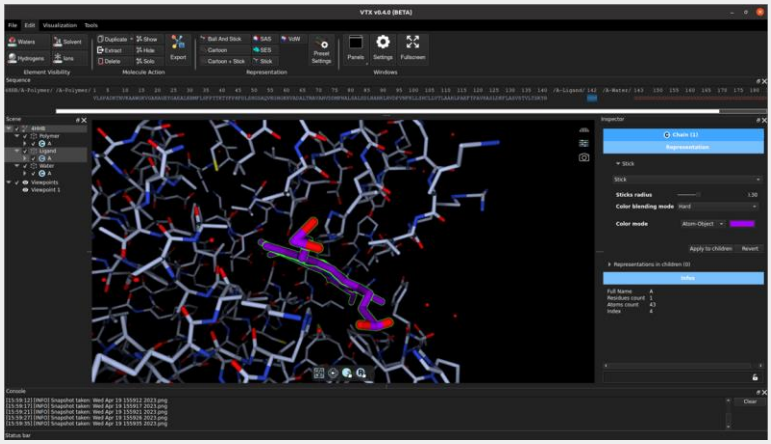
- The second method offers greater differentiation possibilities. Once the selection has been made, in the *inspector* it is possible to go to representation, then change the type of representation, then the various characteristics inherent in this representation. This method also allows you to change the color of the selection. Depending on the representation of the selection, you can :

Representation	Options	UI
Ball & stick	- change the radius of the spheres and rods of a whole chain or of certain residues to differentiate them. - change the coloring mode, i.e. color the entire molecule, chain or residue in a single color. Or color	
Cartoon	- change the coloring mode to color according to tertiary structure (Jmol), color the entire selection with the same color (Molecule, Chain, Custom), color according to residue type (Residue)	

Stick	- change stick thickness - change the staining mode to stain the entire selection while maintaining CPK staining (Atom-Chain, Atom-custom, Atom-objet), stain according to residue type (Residue), stain the entire selection with a single color (Chain, Molecule)	
Cartoon + stick	- combines the possibilities of cartoons & sticks	
Solvent Excluded Surface (SES)	- change the coloring mode to color the entire selection while retaining CPK coloring (Atom-Chain, Atom-custom, Atom-objet), color according to residue type (Residue), color the entire selection in a single color (Chain, Molecule). As for sticks.	
Solvent Accessible Surface (SAS)	- change the color mode with the same options as for sticks & SES.	
Van Der Walls (VDW)	- change the color mode with the same options.	

In the *Edit* tab, in the *representation* section, there is also a **Preset Settings** option. This allows you to create a shortcut to a representation type whose shading, SSAO intensity (for spatial orientation), blurring, border and more can be customized.
This new representation can then be selected in the same way as the first method.

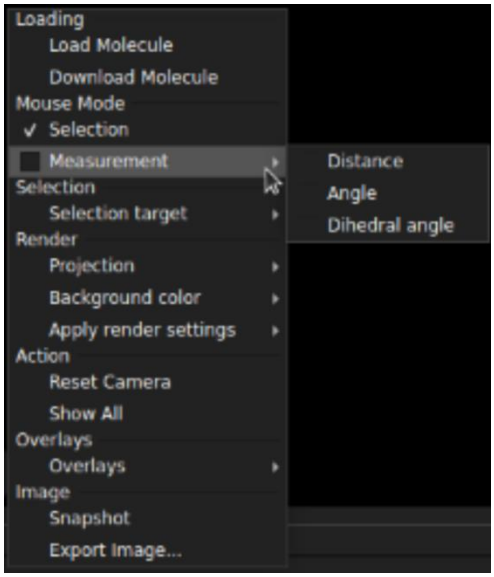
Try increasing the thickness of the sticks representing ligand A to 0.3 radius. Also change its color from the inspector with Atom-Custom to better distinguish it. Then go to Viewpoint 1 (created earlier in the mouse movement section) by double-clicking on it.



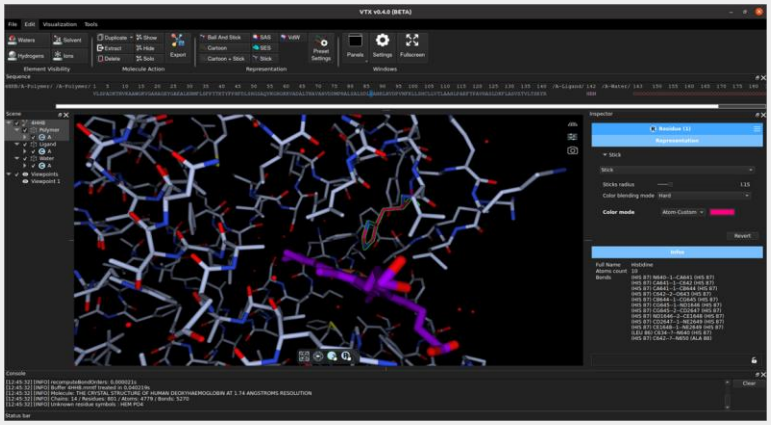
Molecule actions: Measures and Analysis

In the *Tools* tab of the interface, the **distance** button allows you to measure the distance between 2 atoms. To do this, simply click in turn on the 2 atoms that delimit the distance you wish to measure. This can be useful, for example, to determine whether a weak bond can be formed between 2 atoms. Once drawn, each distance appears in the scene, and can be shown or hidden by checking or unchecking, and renamed by right-clicking. The distance also appears in the inspector, where you can change its color.

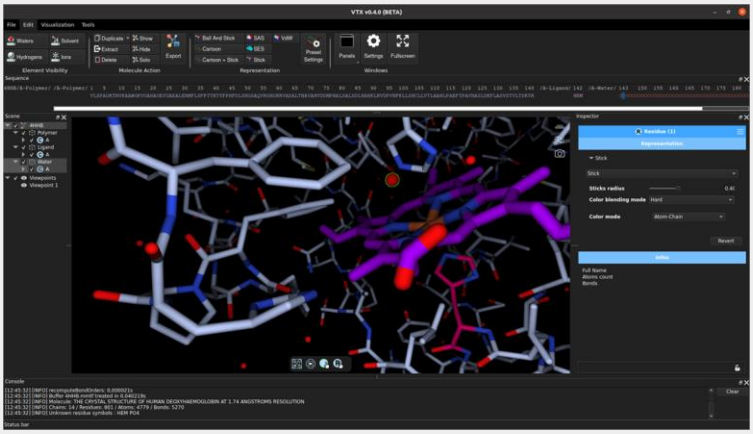
The same applies to **angles & dihedral** angles available at the same location.
All these options are available by right-clicking in the viewer panel, then clicking on measurement in mouse mode and selecting Distance, Angle or Dihedral angle.



In human hemoglobin, the heme is composed of an Fe2+ cation (shown in orange according to CPK codes) which forms a covalent bond with the F8 residue of globin located below its plane. Try selecting this residue, and changing its color with inspector atom-object. Such as:

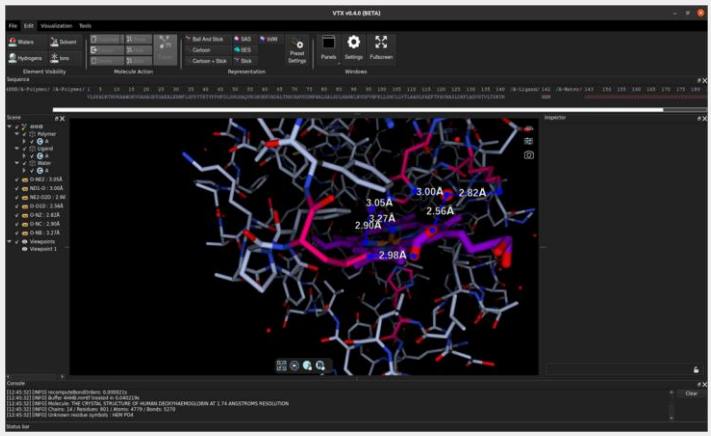


The Iron cation can also bond with a water molecule above its plane. Try thickening this molecule so that you can see it better, such as :

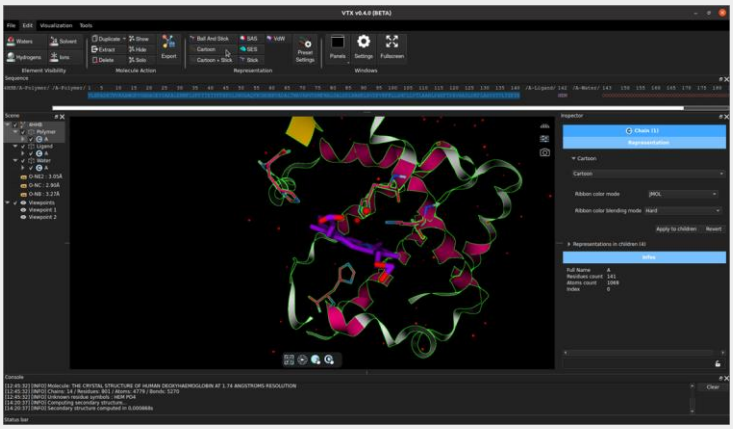


The average distance between the donor & acceptor of a hydrogen bond is around 2.7 & 3.3 Angstroms. Try using the measurement tool to find a hydrogen bond made by the water molecule you've just thickened. You should find the same as in the following screenshot (NB: to make it easier to see in this screenshot, some residues have been hidden and will be re-displayed afterwards).

You can then change the color of the residue to match that of residue F8.
Continue to look for interactions between heme and globin using the same method. All the interactions are shown below:



You can take advantage of this moment to find and create better viewpoints, so that the interaction zone is clearly visible. In addition, to better distinguish this zone, change the rest of the molecule into a cartoon (by selecting the chain and then using the interface).

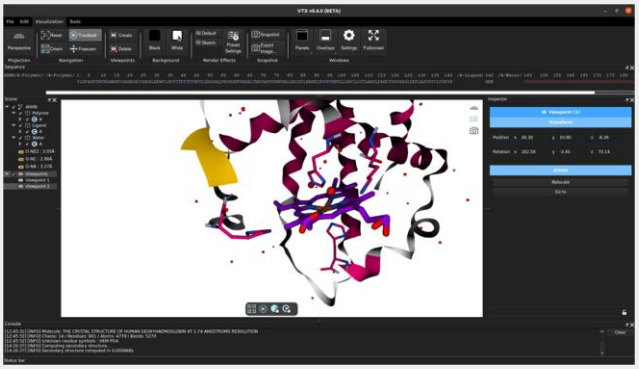


Background Color

In the *Background* section of the *Visualization* tab, you can choose between a white or black background. While a black background is often more pleasing on the screen, a white background is preferred for publications, as it is the same color as the paper and therefore provides better contrast and facilitates printing.
It is also possible to change this option by right-clicking in the visualization panel, then clicking on background color in Render and selecting black or white.

There's also a *render effects* section in the *visualization* tab, where you'll find 2 options, **Default** and **Sketch**, which allow you to modify the molecule drawing in the visualization panel. There's also the *preset settings* option, which lets you create new drawings while adjusting shading, SSAO, surround, fog, background and light color. These options are also available by right-clicking in the visualization panel, then in the render section, in Apply render settings, you can choose between Default, Sketch and Settings.

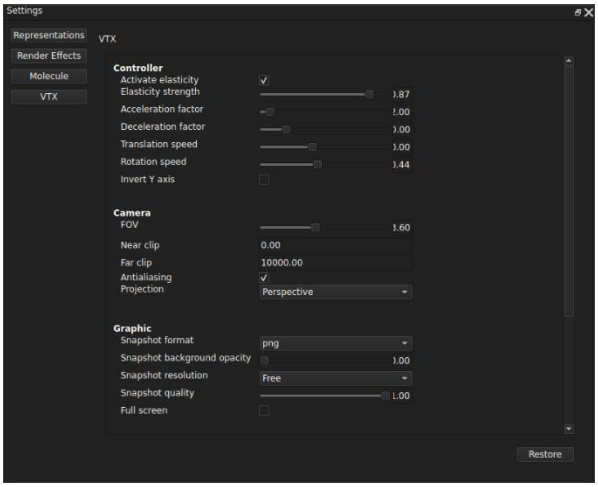
Try changing the background to white.



Snapshot

To share your work, you can take a screenshot of the visualization panel with the resulting molecule. To do this, simply click on *Snapshot* in the *Visualization* tab. Alternatively, right-click on the image and click on *Snapshot*. This capture can be found in the Snapshot folder in the VTX folder, and is automatically named with the date and time of capture.

In some cases, such as posters with colored backgrounds, you may also want a molecule on a transparent background. This is possible by going to the settings in the Windows section. In the Graphic sub-section, simply set snapshot format to pgn and snapshot background opacity to 0.



Try taking a screenshot.

Workspace saving

At any time, you can save your progress by clicking on *Save* as in the session section of the *file* tab and then simply clicking on *Save*. This saves the VTX file (.vtx) with all the modifications made. It can then be reopened at any time by opening the software and clicking on open in the *File* tab of the *session* section.
It's important to save your progress as you go along, as there's no way to go back after a mistake, so this allows you to go back without starting from scratch.

Conclusion

Congratulations on finishing this tutorial, in which we've learned the basics of VTX. We've also seen how to observe a zone of interaction between a ligand and a protein.

There are other features available that you can try out, such as trajectory alignment.

VTX is a very recent software, and as updates are made, new capabilities will be added, enabling it to compete with more implemented software such as Pymol or Chimera.