Chem-Path-Tracker

Automated tool to analyze chemical motifs in molecular structures

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Scope of the tutorial

This tutorial introduces the reader to the basic concepts and features of the Chem-Path-Tracker software. In this tutorial, the user is guided in the search of all the residues that surround the active site and are interconnected by hydrogen bonds. The active site has a zinc atom with a central role, and its position is maintained and stabilized by several residues from the protein structure. The result provided by Chem-Path-Tracker will show that this network of hydrogen bonds is centered on the

zinc atom and it is spread along the protein structure in a pathway that reached almost 20 angstrom of extent.

1. Files required to run the tutorial

To start this tutorial the user has to download the protein structure of guanine deaminase (pdb code 2UZ9) and install the Chem-Path-Tracker software.

- The structure of the protein can be downloaded via the PDB database that can be found at the following link: http://www.rcsb.org.

- The instructions to install the Chem-Path-Tracker plug-in can be found in the webpage: http://www2.fc.up.pt/PortoBioComp/database/doku.php?id=chem-path-tracker.

After the installation of the Chem-Path-Tracker plug-in, the program can be found in the extensions menu of the main interface of the VMD software under the PortoBioComp sub-menu.
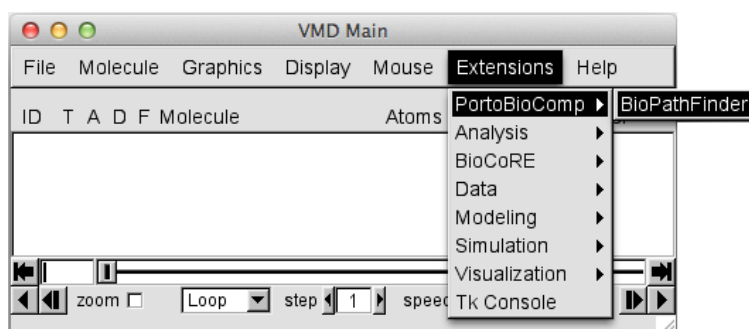

Figure 1: Location of BioPathFinder in the Extension menu of VMD.

2. Chem-Path-Tracker Interface

The Chem-Path-Tracker Gui is composed by three main tabs:

- The **input tab** allows the user to define all the variables that control the Chem-Path-Tracker algorithm. In this GUI the user can define the starting Point and the cut-off distance that are going to be used during the search process to look for the nodes that will compose the final pathway. The choice of the nodes can be done using a set of pre-existing selections that assist the user in the most common selections such: as polar residues, aromatic residues, charged residues, etc.

- The **output tab**, presents the results provided by the Chem-Path-Tracker software. In this tab, the user can find all the information regarding the residues that are involved in main path that was highlighted by the Chem-Path-Tracker software.

- The **About tab** shows general information about Chem-Path-Tracker, the authors and the contact that can be used to report errors or general doubts.
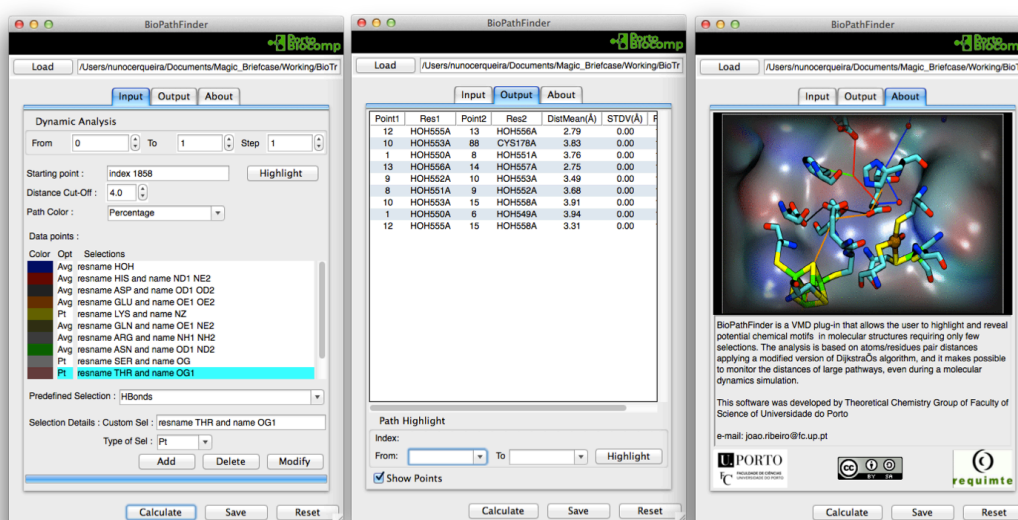

Figure 2: Different tabs present in the BioPathFinder GUI. Left: Input Tab: Middle: Output Tab. Right: the About Tab.

3. Setting up Chem-Path-Tracker .

In this tutorial we are going to search for the residues that stabilize the metal cluster that belongs to the active site of the enzyme guanine deaminase. To setup Chem-Path-Tracker to perform this type of analysis the user has to follow the next steps.

1. Start the VMD software and load the protein with pdb code 2UZ9

2. Go to the menu Extensions of VMD and select the Chem-Path-Tracker software. It can be found in the PortoBioComp submenu.

   Extensions -> PortoBioComp -> BioPathFinder

3. Select "resname ZN" as the starting point and press the "Highlight" button to visualize the selection.

4. Define a cut-off distance of 5.0 Å. This parameter defines the maximal distance between two consecutive node points that will be taken into account during the calculation.

5. Select the node points that will be taken into account in the calculation. In the "Predefined Selection" combo, select "HBonds" and press "Add" button. Then add a custom selection with the text "resname XAN". This will include the node point with the position of the substrate .

6. Press the "Save" button to save the input file and subsequently the "Calculate" button to start the calculation.

If the user followed the instructions given above, the input GUI should have a similar appearance as the one depicted in figure 3.
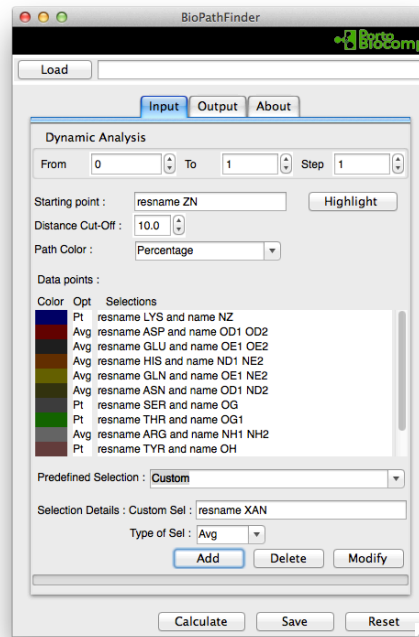
Figure 3: GUI input tab.

4. Analyzing the results

Once the calculations are finished Chem-Path-Tracker will upload the final results directly into the output GUI and can be promptly analyzed by the user in the output tab (Figure 4).

Note: As the output data is saved in a file (with extension bpf*), the user can upload the results anytime in the Chem-Path-Tracker GUI .*
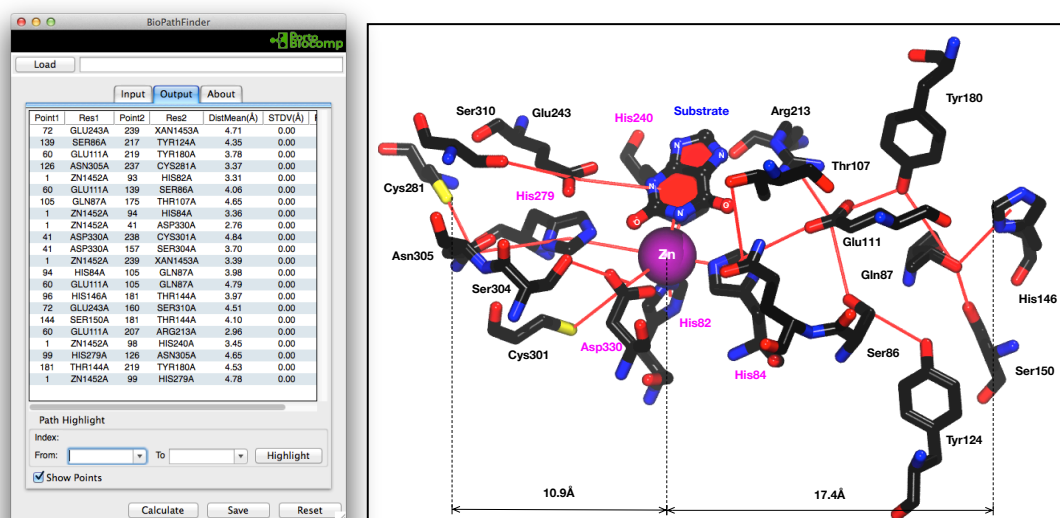

Figure 4: OutPut tab displaying the results regarding the 2UZ9 structure.

The results in the output Tab are displayed in a table and organized in atom pair distances, containing all the information regarding the residues where they belong (residue index and residue chain). The DistMean(Å) column displays the distance between the center of the two node points. As proteins structures are normally dynamic structures that interchange between different energies minima, this path analysis can also be performed against a set of frames of a Molecular Dynamics simulation (MD). In these cases the distance is given as a mean value of the distances selected by the Chem-Path-Tracker software during the MD simulation together with the respective standard deviation values.

The Perc(%) (Percentage) column reflects the number of times that a specific atom pair was selected by the algorithm during the MD simulation. This metric is useful to evaluate the conservative character of the pathways that are provided by the Chem-Path-Tracker software.

This example shows that Chem-Path-Tracker was capable of identifying several amino acid residues that are interconnected through hydrogen bonds starting from the zinc ion. These residues are not only found in the first coordination sphere of the Zinc ion but they are found in a range of more than 10 Å.

If the user wishes to highlight only a fraction of the total path, for instance, a ramification of the main path, this can be done in the output tab and following the next steps.

1. In "From" combo select index 1
2. In "To" combo select index 217
3. Press "Highlight" button

The new results will be displayed in a new window containing all the data regarding that pathway. The Path refinement connects all the nodes comprehended between the "From" and "To" index forming the shortest path between both. Here it is possible to create more than one of these refinements, allowing the user to evaluate several pathways.

In this example, the fraction of the Path has a total distance of 20.54 Å (sum of all atoms-pair distances) covering a distance between the furthest atoms of almost 11 Å. The color of the path can be changed, choosing a different color on the Path Color combo box (Figure 5).
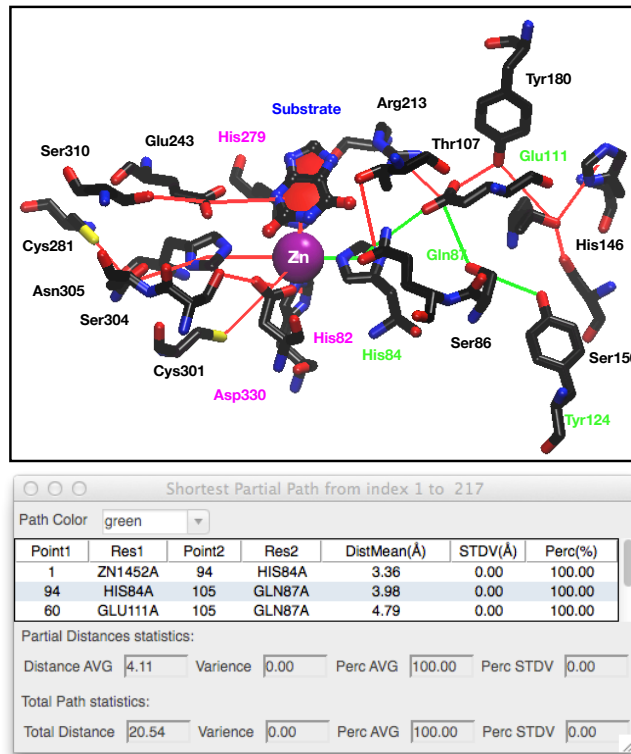
Figure 5: Refinement of the results highlighting the closest path (green) between the Zinc atom and the tyrosine residue number 124.