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Analysis of Long Molecular Dynamics Simulations Using Interactive Focus+Context Visualization — Supplement —

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In this supplementary document, we present the reports of two additional case studies conducted individually by the protein engineering expert. For these two case studies, the same data sets are used as in the paper, comprising 100,000 and 50,000 simulation steps, respectively. The first case study reports insights about the MD simulation of the wild type of DhaA haloalkane dehalogenase (DhaAwt) with 1,2-dichloropropanol (DCP). The second case study was performed again on the MD simulation of the wild type of DhaA haloalkane dehalogenase (DhaAwt), which interacted with three molecules of 1,2,3-trichloropropane (TCP). The text below is the unmodified observation report. For a better understanding, we added figure captions.

1. Case Study I: DhaAwt + DCP

By observing the MD simulation of DhaAwt with the DCP and chloride ion (Cl-) products inside the active site, it was possible to find several interesting facts:

In the first part of the simulation, while still in the active site, DCP and Cl- are involved in an H-bond network for a long part of the time while in the active site, either with direct bonds (see Figure 1) or mediated by water molecules (Figure 2).

DCP is also involved in a H-bond network with the catalytic D106 (numbered as D103 in this simulation), mediated by waters (Figure 2). Such networks may be the main reason why DCP and Cl- remain in the active site for such a long time.

At least while DCP is still in the active site, the number of waters in the active site increases, and they come from the p2 (Figure 3: waters appearing from the left) and p3 tunnel (Figure 4). This seems a very important observation, because waters may be involved in the release or Cl- and DCP. This was never observed before.

By checking the derivative of waters (Figure 5), one could observe that a large increase resulted in the drifting of DCP from the tunnel. I observed that DCP was in the tunnel interacting with the Cl- ion, and then many waters surrounded it and disrupted the interactions, and after that DCP moved quickly to the tunnel mouth.

DCP rebinds to the main tunnel after roaming in the bulk solvent. While trying to find the factors leading to such rebinding, it seems that at that moment there were many water molecules in the tunnel and around the ligand. Then, promoted by the hydrophobic interactions of the protein residues with the hydrophobic part of the ligand, and by the H-bonds of DCP with the water molecules in the protein tunnel (Figure 6), DCP may have been "encouraged" to move into the tunnel. This is a potentially important mechanism to lead the ligand to rebinding into the protein tunnel.

In the second part of the simulation, after DCP was rebound and well inside the protein's main tunnel, the entering of water molecules was done mostly from the p1 tunnel. In this context, the water interactions with the ligand (Figure 7) may have contributed to increase the number of water coming inside the protein.

Globally, this tool helped us drawing some important conclusions regarding the unbinding and rebinding of the DCP and Cl- products from the protein DhaA, and the involvement of water molecules in that process. We suspected that the waters might have an influence on the release of those ligands, but this hypothesis we never tested in a robust way. Even more difficult would have been the visual analysis of the role of waters, since the currently used software tools (e.g., VMD) are extremely unfriendly when dealing with such large data. This tool brings a robust and user friendly way to visualize molecular dynamics simulations, and observe the potentially relevant events. From such visualization one can draw some hypotheses regarding causality or simultaneity (correlated events). Then, by iteratively using the embedded functions or their modified counterparts (inverse and derivative functions), one can quickly test those hypotheses.

2. Case Study II: DhaAwt + 3 TCP

By observing the MD simulation of DhaA with three molecules of the TCP substrate in the outside of the protein, it was possible to find several interesting facts:

At some point, the protein could accommodate more than one molecule of TCP inside (Figure 8). These ligands are hydrophobic,

and seem to be attracted towards the protein mostly due to the favorable hydrophobic interactions with some residues or with each other. This fact was already known before, and it was easily observed and confirmed with this tool.

The access of water molecules is very important in this molecular system, since it is one of the reagents involved in the catalytic hydrolysis of DCP. Initially we believed that the water molecules entered the active site mostly through the main tunnel (called p1), and this was confirmed here when no ligand was present inside the protein (Figure 9). However, when there were ligands within the enzyme, we observed that the water molecules could still access the active site through a "backside" tunnel (Figure 10). This was unexpected, since this tunnel is typically not among the one with highest throughput, and therefore is usually considered not relevant. These findings may change such view. The functions available in this tool that help tracking the water molecules inside the protein, together with the useful representations modes (with the spatial focus/context, plus the coloring schemes) highly facilitated our observations and conclusions.

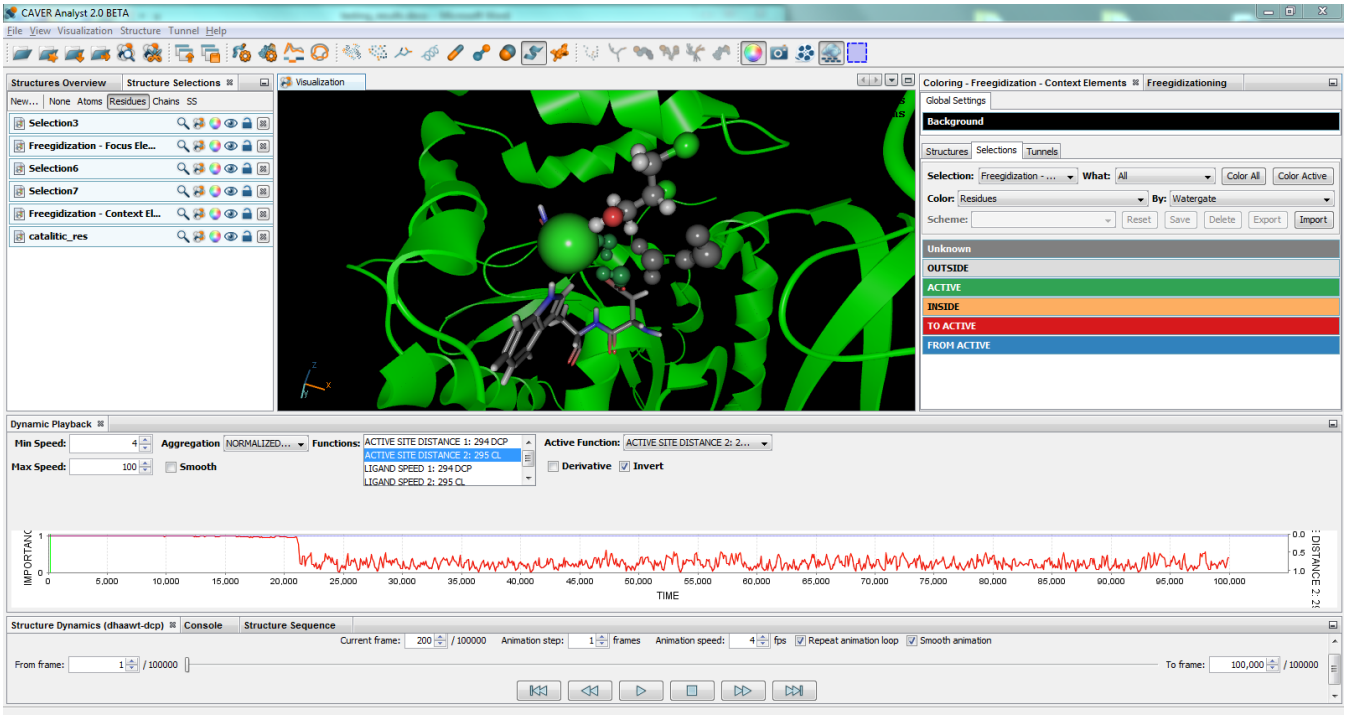

Figure 1: DCP (balls-and-sticks) and Cl- (green) forming an H-bond with direct bonds.

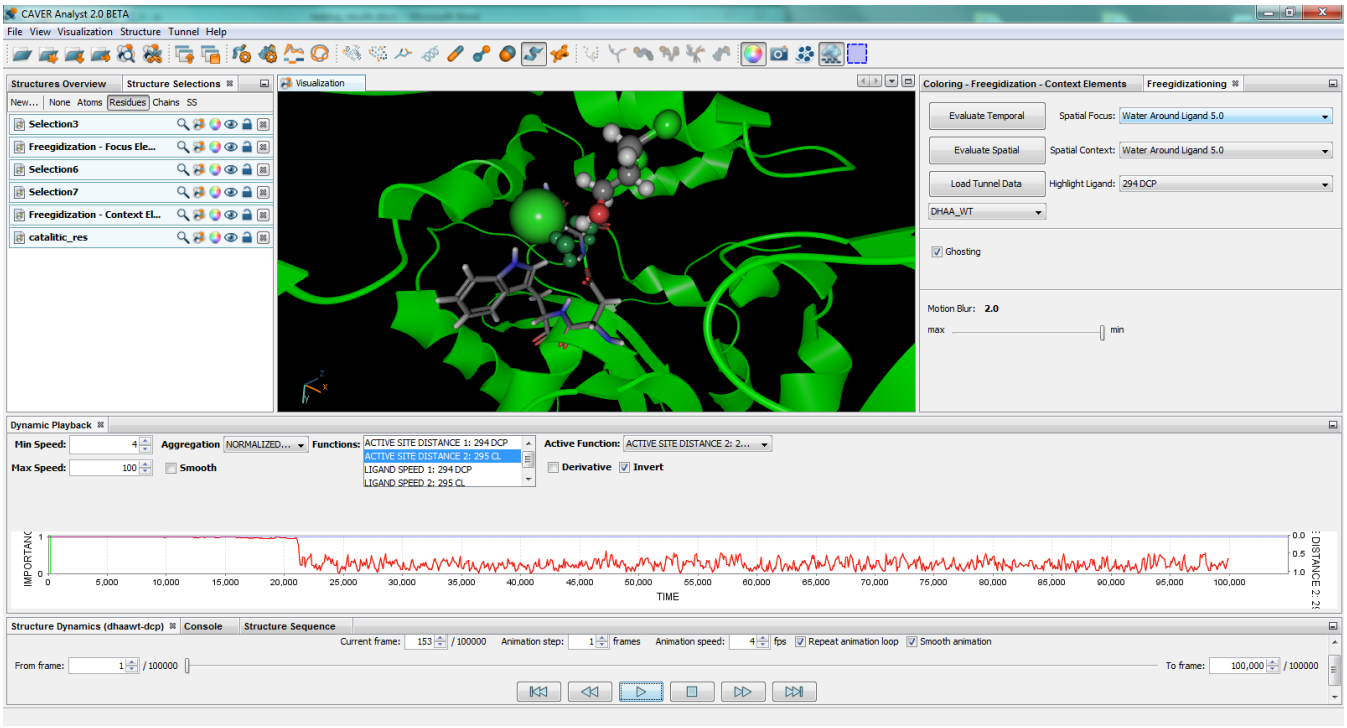

Figure 2: DCP (balls-and-sticks) and Cl- (green) forming an H-bond mediated by water molecules (dark green balls-and-sticks).

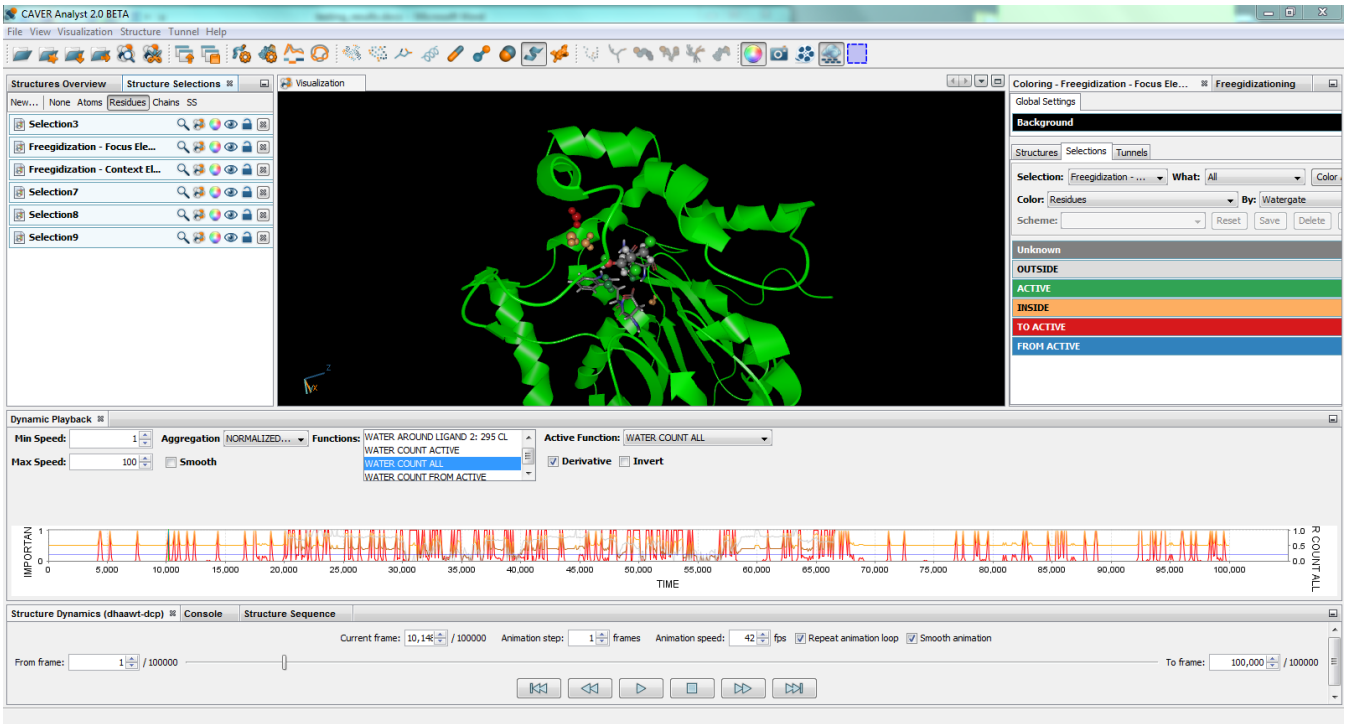

Figure 3: Water molecules (balls-and-sticks colored according to the color scheme on the right) coming from the p2 tunnel to the active site around snapshot 10,000.

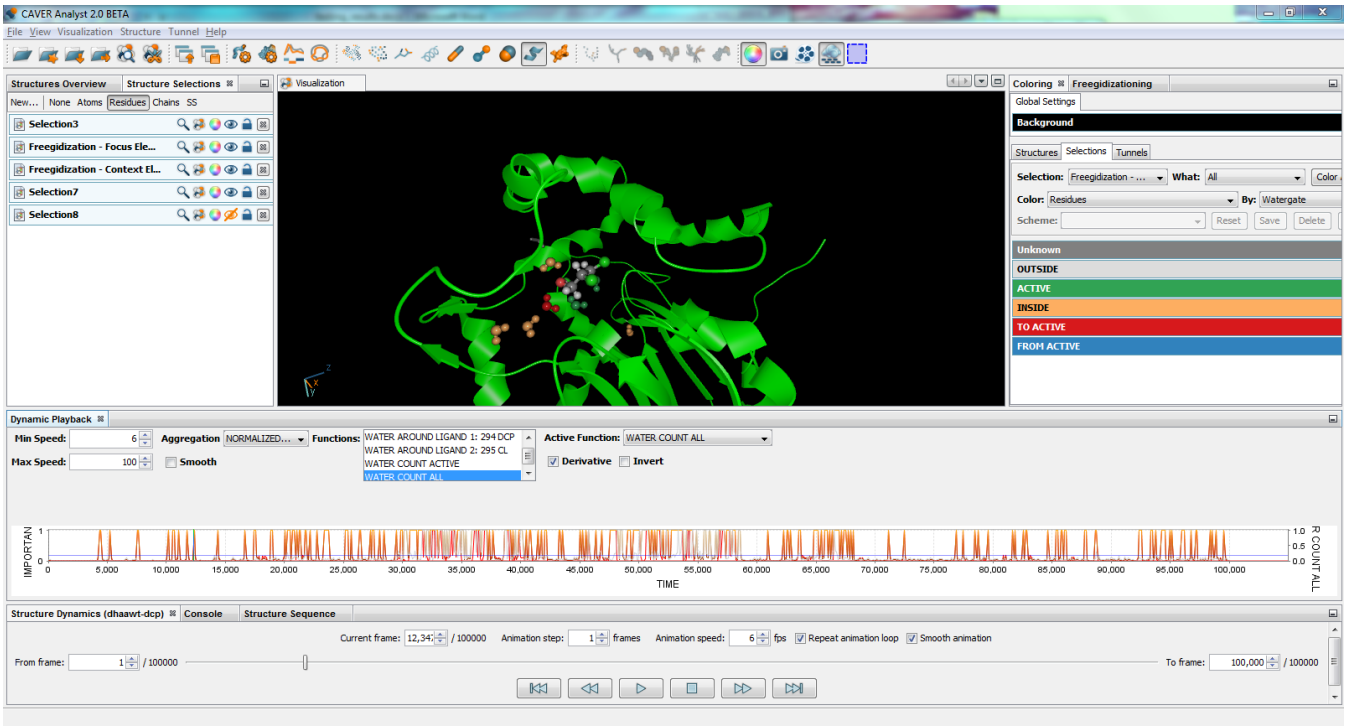

Figure 4: Water molecules coming from the p3 tunnel to the active site around snapshot 12,000.

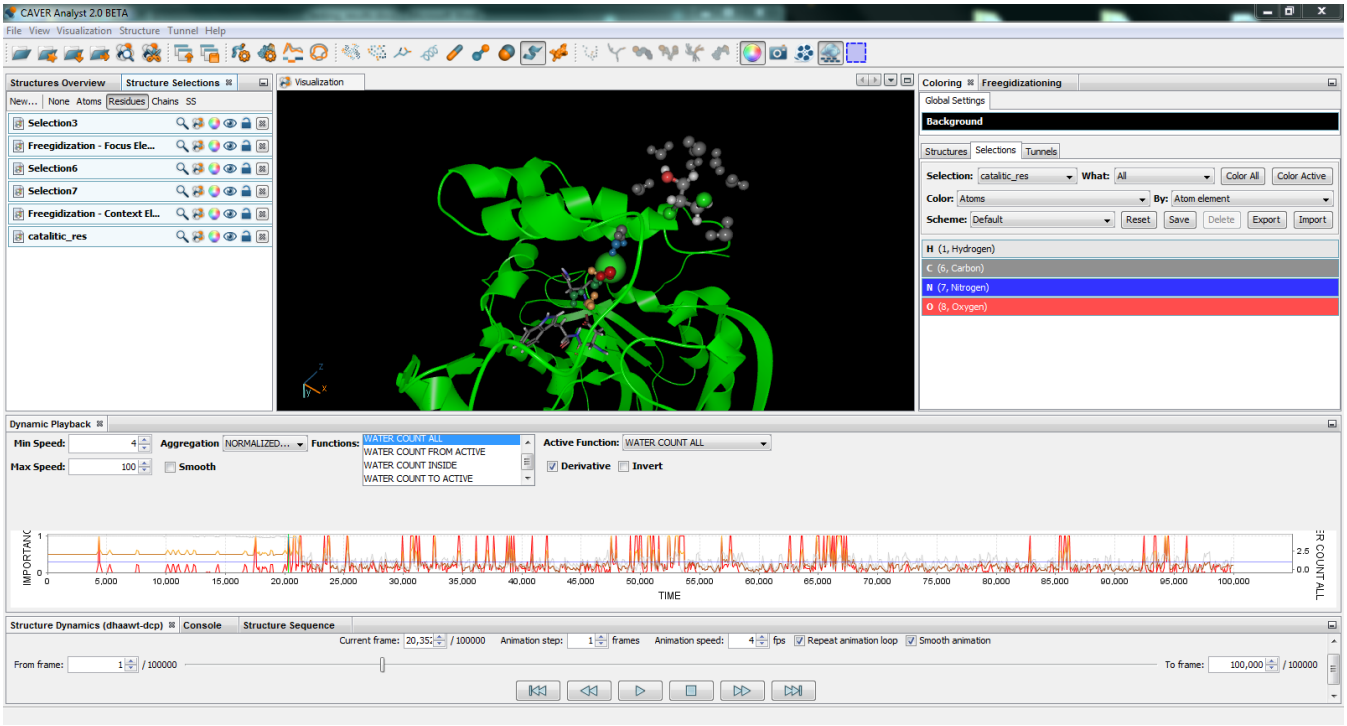

Figure 5: Increase of the number of waters causes DCP (top right) to drift from the tunnel around snapshot 20,000.

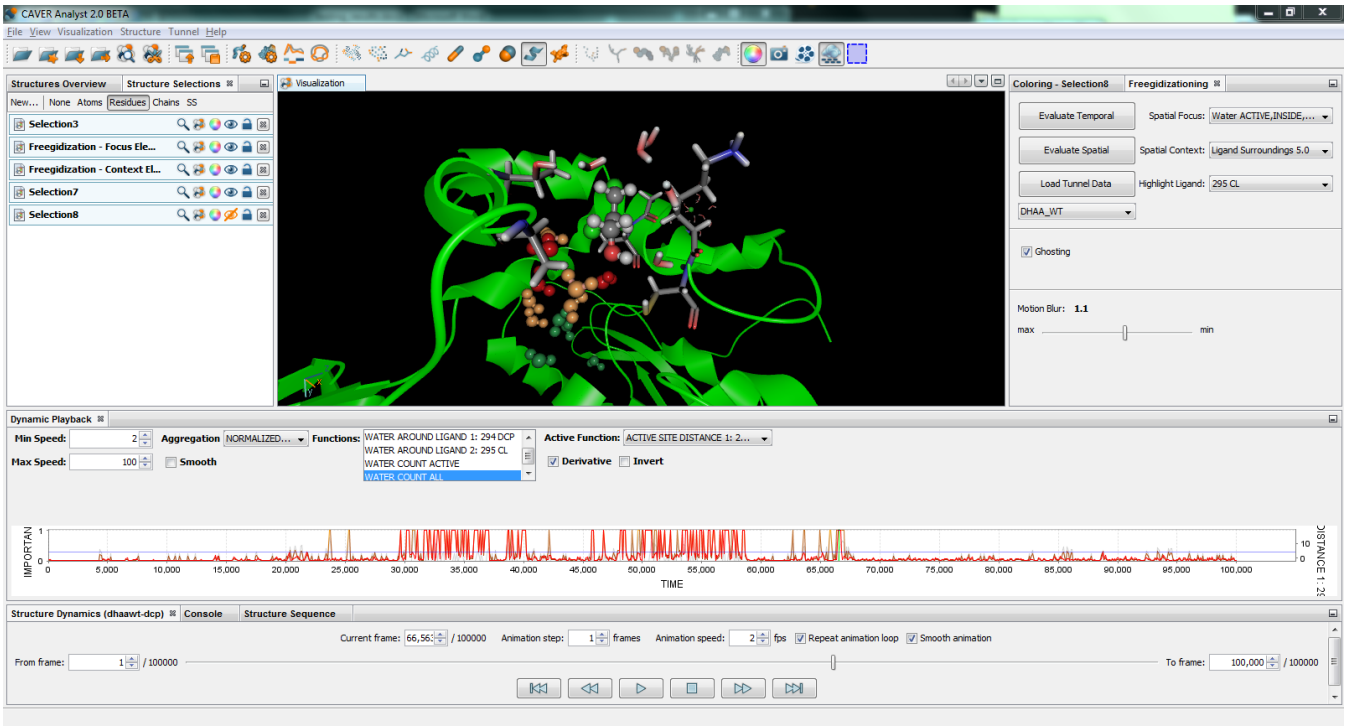

Figure 6: DCP is attracted by the residues (sticks) and waters (uniformly colored balls-and-sticks) to enter the tunnel around snapshot 66,500.

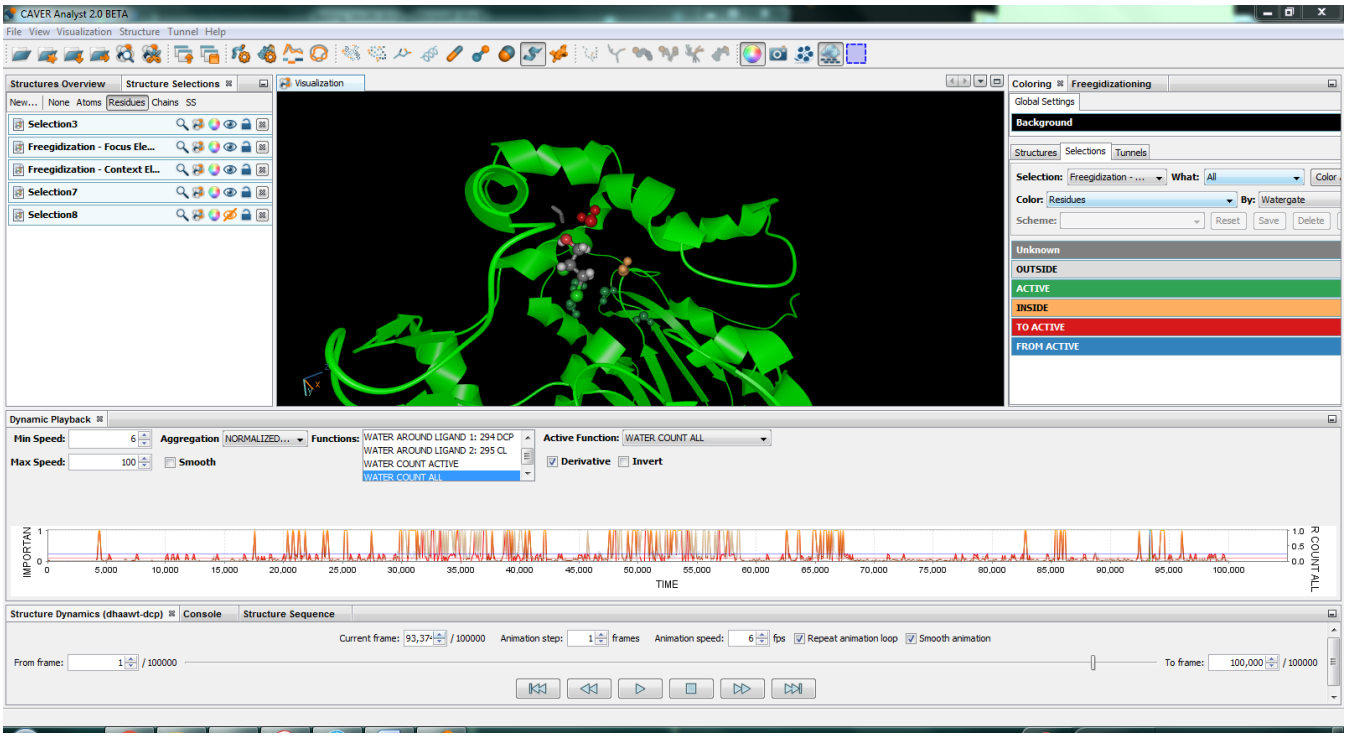

Figure 7: Ligand interacting with water molecules inside the main tunnel around snapshot 93,000.

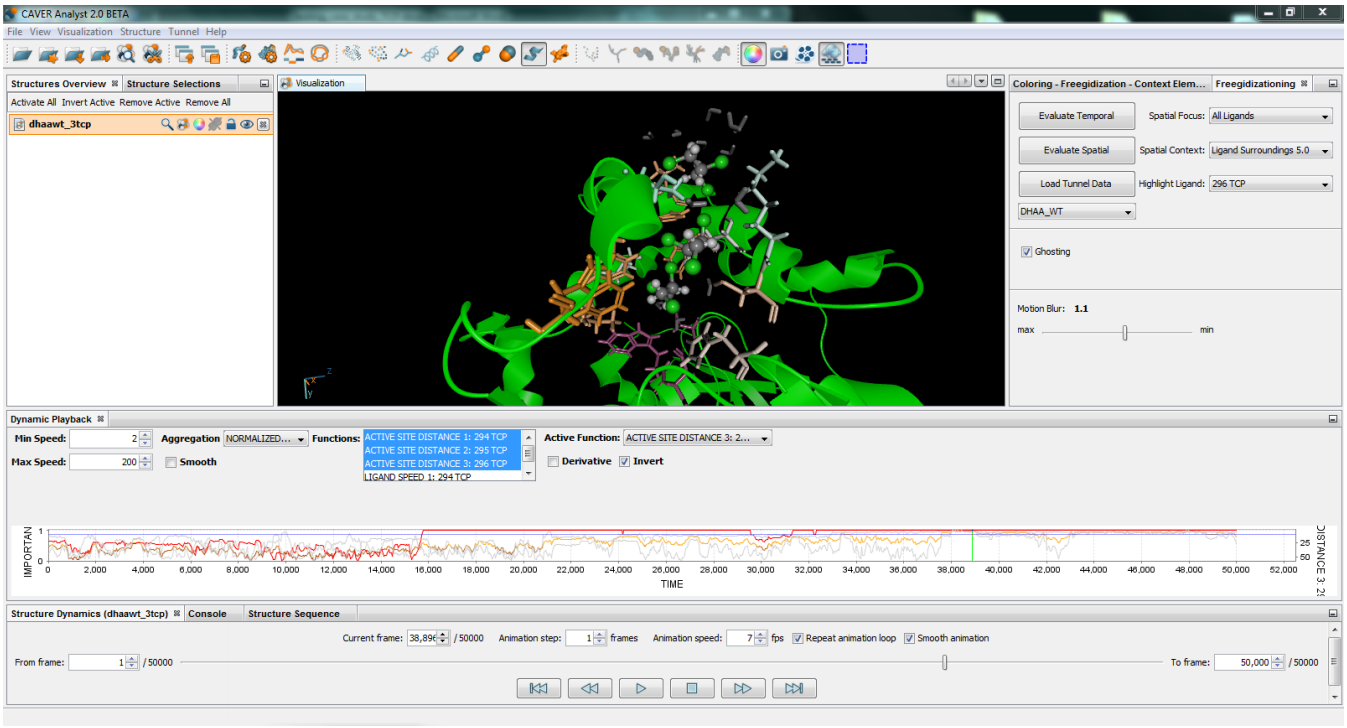

Figure 8: All three TPC molecules (balls-and-sticks) inside protein at once around snapshot 39,000.

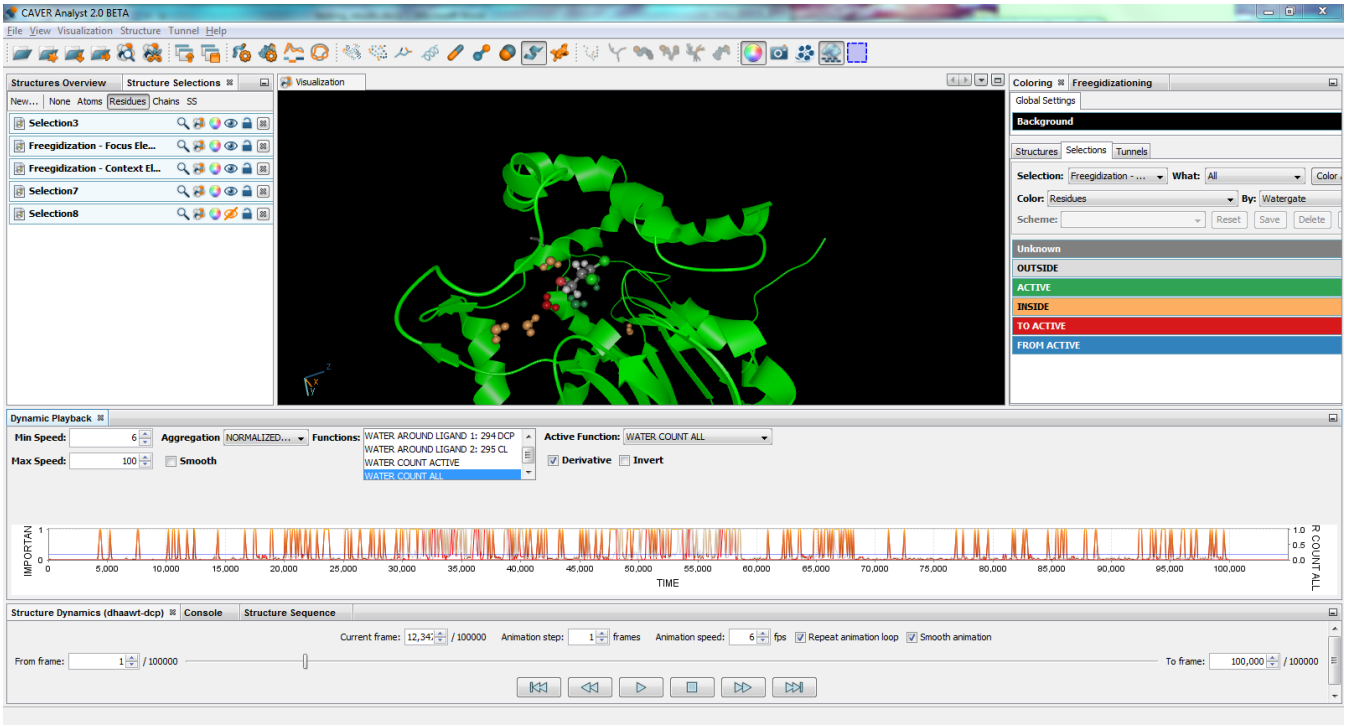

Figure 9: Water molecules are using the p1 tunnel when no ligand is inside the protein around snapshot 12,000 from the first MD simulation.

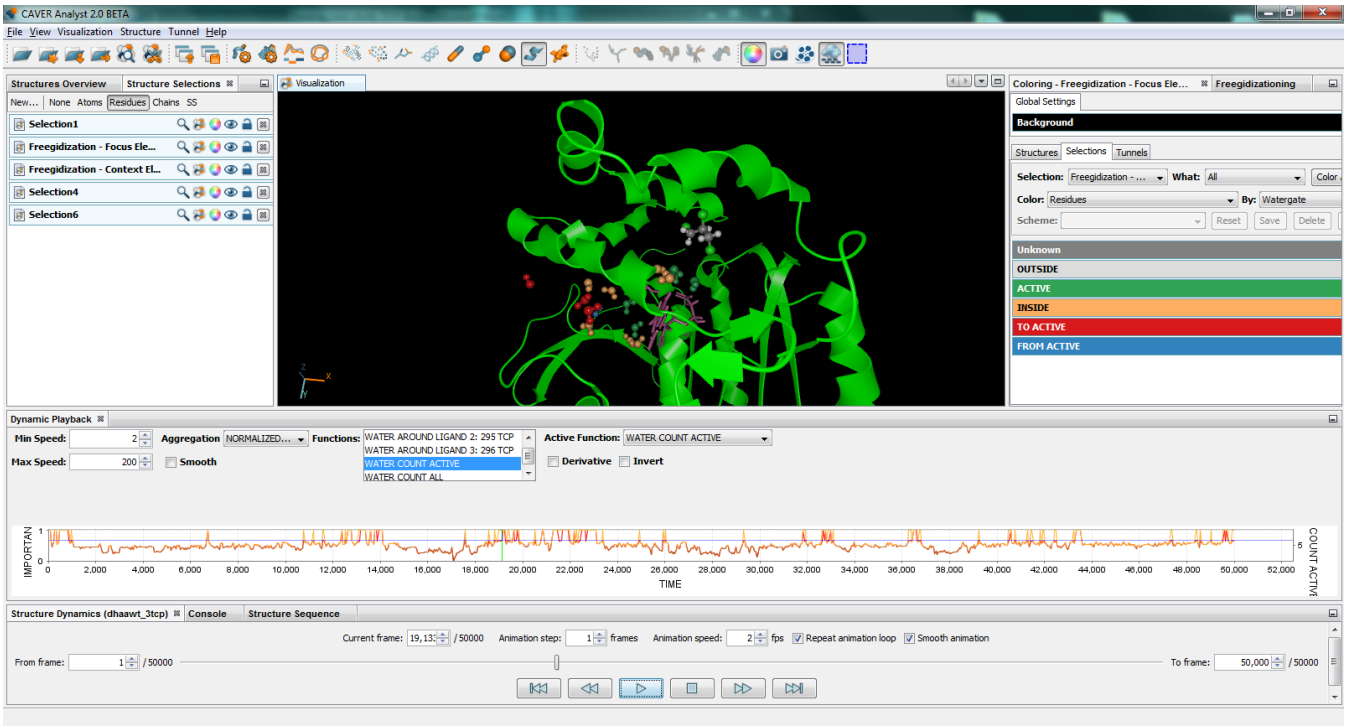

Figure 10: When a ligand is present inside the protein (balls-and-sticks, top), water molecules (balls-and-sticks using the color scheme on the right) are using another tunnel around snapshot 19,000 of the second MD simulation.