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Translational Science Solutions

Using Benchware 3D Explorer as graphical viewer for Proasis3 and ViewContacts

Benchware® 3D Explorer (BW3DE) offers effective research decision support by allowing researchers to view, understand, and share complex molecular data such as protein-ligand crystal structures, docking results, or molecular alignments. The standard VBA scripting capabilities within BW3DE provide the ability to create customized interfaces and applications based on specific organizational research needs. This application note describes the customer requested integration of BW3DE as a graphical viewer for Proasis3, a protein structure database and visualization system by Desert Scientific Software Pty Ltd (DesertSci). The integration included the visualization of protein-ligand interactions and water rank scores computed by DesertSci's ViewContacts software.

Proasis3 is a protein structure database and visualization system developed by Desert Scientific Software (DesertSci), Sydney, Australia. It has been developed for over 10 years in close collaboration with many global pharmaceutical companies. It is designed for crystallographers, modelers, and medicinal chemists to make full use of protein structure data in drug discovery programs. ViewContacts is DesertSci's new software for exploring protein-ligand binding, taking a broader view of non-covalent interactions. It was also created in collaboration with pharmaceutical industry experts [1].

Benchware 3D Explorer offers effective research decision support by allowing researchers to view, understand, and share complex molecular data such as protein-ligand crystal structures, docking results, or molecular alignments. The full power of BW3DE is available through industry-standard VBA scripting. All functionality, from manipulation of molecular structure to control of graphical objects, and creation of task-based graphical user interfaces can be achieved through the application's VBA interface. The well-designed and comprehensive object model allows fine control of the application from within VBA scripts. Chemical structure files and other data such as surfaces or fields can be loaded from remote machines using ftp or http protocols.

A major pharmaceutical company, using BW3DE as their standard modeling platform within medicinal chemistry, requested integration of BW3DE and Proasis3. This integration enables chemists to launch BW3DE from within Proasis3 on their desktop computers; to highlight ligands in binding sites, to set correct bond orders for ligands for modeling applications, and to overlay multiple protein-ligand complexes, all at the click of a button. Furthermore, additional integration with ViewContacts enables the viewing of all of the different classifications of favorable and unfavorable ligand close-contacts, and the display of water rank scores – a scheme for differentiating tightly bound from weakly bound site water molecules. With advanced visualization capabilities and well-documented VBA scripting framework BW3DE is ideally suited to be integrated with Proasis3. A further major advantage of using BW3DE as a viewer for Proasis3 is the possibility for chemists to use the ligand editing functionality in BW3DE to easily modify ligands in context of the protein's active site and explore new compounds as candidates for synthesis.

Methods

A set of VBA routines have been developed which enable BW3DE to be launched from Proasis3. VBA scripts for launching BW3DE are created on-the-fly by Proasis3. A hyperlink to server-side functionality for building a VBA script is created for each hit following a structure search in Proasis3. Clicking one of these hyperlinks initiates the building of the script on the server, which is then sent to the client browser. The script is then automatically executed on the client desktop machine by BW3DE. The structure is downloaded from the server, processed, and displayed in the modeling application.

Additional VBA macros render the structure in a style defined according to customer specifications, including: highlighting water molecules, setting bond orders correctly (according to the contents of the Proasis3 database), adding hydrogen atoms to ligands, and showing color-coded non-covalent interaction types including water ranks scores (calculated on the server by DesertSci's ViewContacts software). In addition, a custom menu entry is created in the BW3DE toolbar to enable the user to display/hide any of the different interaction types.

The Proasis3 system also enables on-the-fly alignment and overlay of any set of protein-ligand complexes. After selecting a number of structures, Proasis3 performs the overlay on the server and then fills a template VBA loader script so that all of the structures the user has requested for overlay can be downloaded and displayed. Upon clicking the link, BW3DE is launched on the client desktop machine and all pre-aligned structures are shown. Additional VBA routines color-code each protein-ligand complex separately, enabling the structures to be easily discriminated in BW3DE.

Results

Providing easy access to all protein structure data for in-house projects is a formidable informatics challenge that nearly all research organizations in the pharmaceutical industry must face. A typical project example is Influenza neuraminidase. Many companies have designed, synthesized and assayed compounds for this target as candidates for a flu drug following the initial discovery of potent inhibitors [2]. Currently, there are over 130 different publicly available structures [3,4] and Proasis3 enables all members of a research team to easily explore this data and to compare and contrast with in-house structures. Figure 1 illustrates how all structures in a neuraminidase project can be viewed in a HitList and how any individual structure can be explored in BW3DE. The launched version of BW3DE shows the new toolbar menu for DesertSci's ViewContacts software. The graphics window shows the ligand highlighted in the binding site, and two of the non-covalent interaction types have been clicked on: hbond-pi and cat-pi.

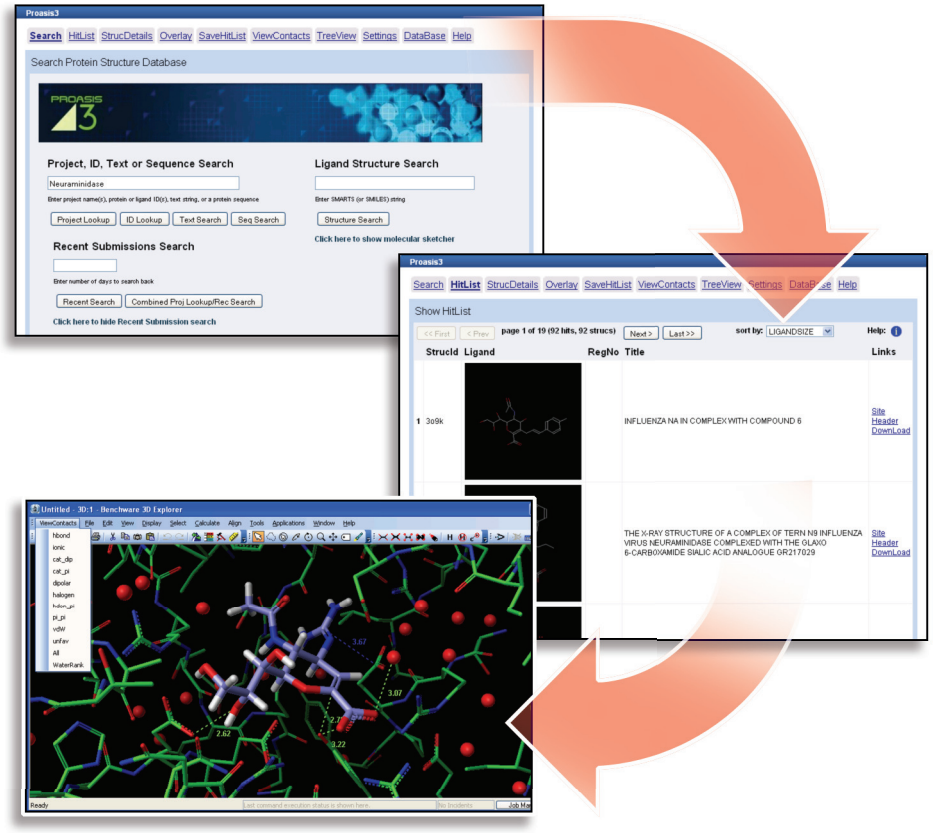

Figure 1: Fast and easy visualization of any structure in the database, from inhouse or from the public domain, at the click of a button

The Influenza neuraminidase project presents many challenges for modelers, one of which is that protein structures are often solved for different strains of the virus that typically have low sequence homology and different residue numbering schemes. These issues make structure alignment and superimposition as well as binding site overlays a complex and time consuming task. Proasis3 handles all of these issues, and overlay results can be readily shown in BW3DE, as shown in Figure 2. The overlay functionality in Proasis3 color-codes carbon atoms in a different scheme in each overlaid structure, thus enabling them to be easily discriminated.

The integration of Proasis3 and BW3DE has been a very successful enterprise. End users that were already familiar with BW3DE are very happy with the easy access to all data through Proasis3. New users of the system find it very easy to use, and crystallographers and research managers are very happy to see the internal data and software resources that they provide widely used.

Conclusions

The protein structure database and visualization system Proasis3 has been extended to allow BW3DE to be used as a graphical viewer for medicinal chemists. The extensive VBA scripting capabilities within BW3D, coupled with the data and computational chemistry resources of Proasis3, will provide many new opportunities for structure based drug design.

References

1. B. Kuhn, J.E. Fuchs, M. Reutlinger, M. Stahl, N.R. Taylor, J. Chem. Inf. Mod., 2011, in press?

2. von Itzstein, M, Wu, W-Y, Kok, G B, Pegg, M S, Dyason, J C, Jin, B, Van Phan, T, Smythe, M L, White, H F, Oliver, S W, Colman, P M, Varghese, J N, Ryan, D M, Woods, J M, Bethell, R C, Hotham, V J, Cameron, J M and Penn, C R, Nature, 1993, 363 418-423.

3. http://www.rcsb.com/

4. http://www.desertsci.com/

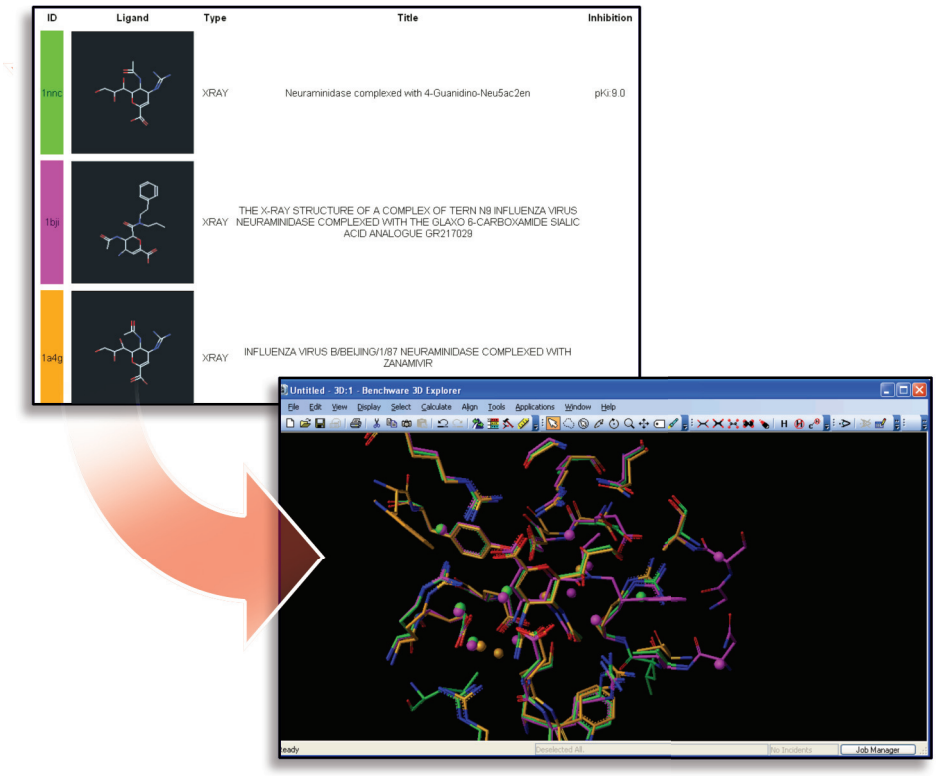

Figure 2: Automated visualization of muliplte overlayed structures, with all carbon atoms and water molecules color-coded according to structure

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