Diplomarbeitspräsentationen der Fakultät für Informatik

Visualization of n:m Drug Target Interactions

Masterstudium:
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Problem Domain

Recent advances in informatics introduced and enabled new computer-aided methods in many other research fields. One of these fields is drug dicovery. The goal of drug discovery is to find chemicals, which cause a particular biological activity in human body that helps human beings to cure from diseases. A computer-based approach to achieve this is **Virtual Screening** [1], where large libraries of molecules are screened virtually against a drug target by using pharmacophores (see Figure 2). But screening molecule libraries against a single target (see Figure 1) does not show side effects. Therefore, tests are applied after the screening process, where drug candidates are tested against multiple targets. In **Activity Profiling** [2], which combines these two methods, molecule libraries are screened against target sets. To analyze the huge amount of results of this process advanced visualization [3] techniques are required.

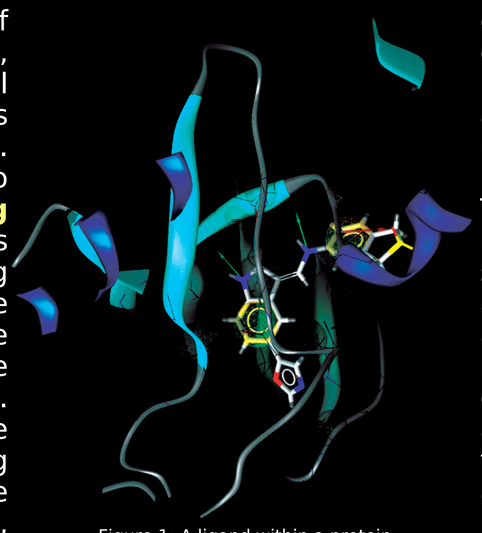

Figure 1: A ligand within a protein

Our Approach

We developed a novel visualization program (see Figure 3) that on the one hand displays activity profiles, and on the other hand allows for user-effective interactive exploration of the displayed results. The visualization is implemented in OpenGL, taking advantage of hardware-accelerated real-time rendering, and providing an interface to the screening process. This very time consuming process makes it necessary to separate the screening task from the visualization and permantly display the status of available and new incoming data. The resulting activity profiles are displayed in a 3D-map including heat- and height information, which allows the user to set filters for the target affinities in a comfortable way. The program provides **Multiple Views** [4] focusing on user interaction, which is integrated using **Linking and Brushing** techniques and allows the user to explore the connection between targets and molecules.

Results

Our solution provides a powerful tool to visualize activity profiles. The use of **advanced layout-algorithms for target-clustering** allows for an easy analysis of the huge amount of results. The highlighting and filtering mechanism enables the user to search for drug candidates and exlude those with unwanted side effects. Furthermore, detail views let the user select a molecule and explore its 2D- and 3D structure information.

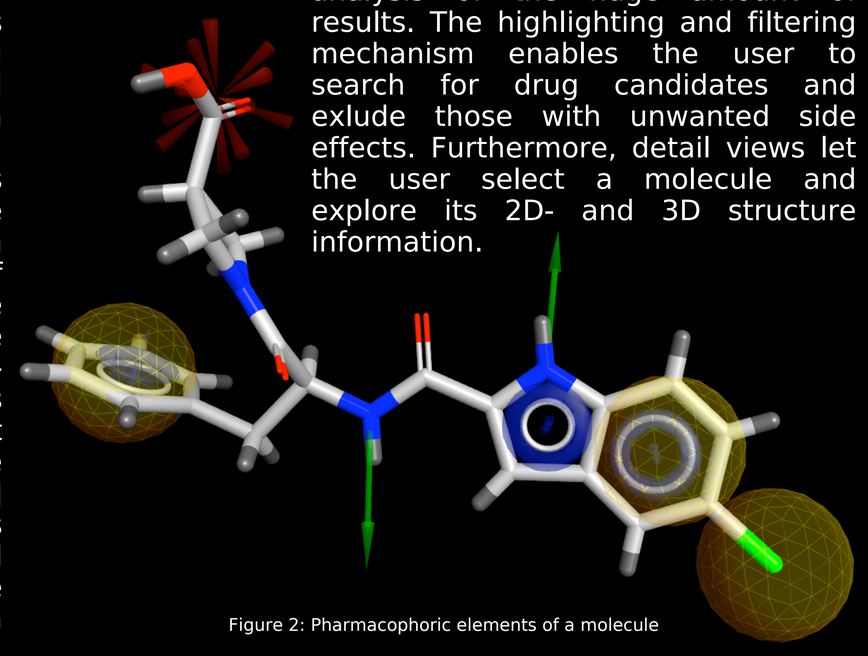

Figure 2: Pharmacophoric elements of a molecule

[1] W. Patrick Walters, Matthew T. Stahl, and Mark A. Murcko. Virtual Screening - an overview. Research Focus, 3(4):160–178, April 1998.
[2] D. Schuster, C. Laggner, and T. Langer. Why Drugs Fail - A Study on Side Effects in NewChemical Entities. Current Pharmaceutical Design, 11(27):3545–3559, October 2005.
[3] S.K. Card, J.D. Mackinlay, and B. Shneiderman, editors. Readings in Information Visualization, chapter 1, pages 1–34. Morgan Kaufman, 1999.
[4] M.Q. Baldonado, A. Woodruff, and A. Kuchinsky. Guidelines for Using Multiple Views inInformation Visualization. In Advanced Visual Interfaces (AVI2000), pages 110–119. ACM Press, 2000.

Target View

For the visualization of the activity profiles a 3D-map with heat and height information is used. The map is implemented in OpenGL to take full advantage of the hardware acceleration. Furthermore, OpenGLs 3D API allows for a perspective representation of the map, which helps the user examining the height information on the map.

Molecule View

The Molecule View is separated into two parts. One displaying all molecules and information about the amount of hits in which they are occurring and the other part which is a list of molecules remaining after the filtering (“result list“). Both parts are linked to the filtering mechanism of Apt, but only the first part allows user interaction and highlighting of hits.

Attribute View

The Attribute View shows target attributes separated into different classes. The name of the attribute and numerical information about hits from targets complying with this attribute are displayed in a tabular form. Furthermore, the Attribute View allows for highlighting and filtering hits and is bi-directionally linked with the Target- and Molecule View.

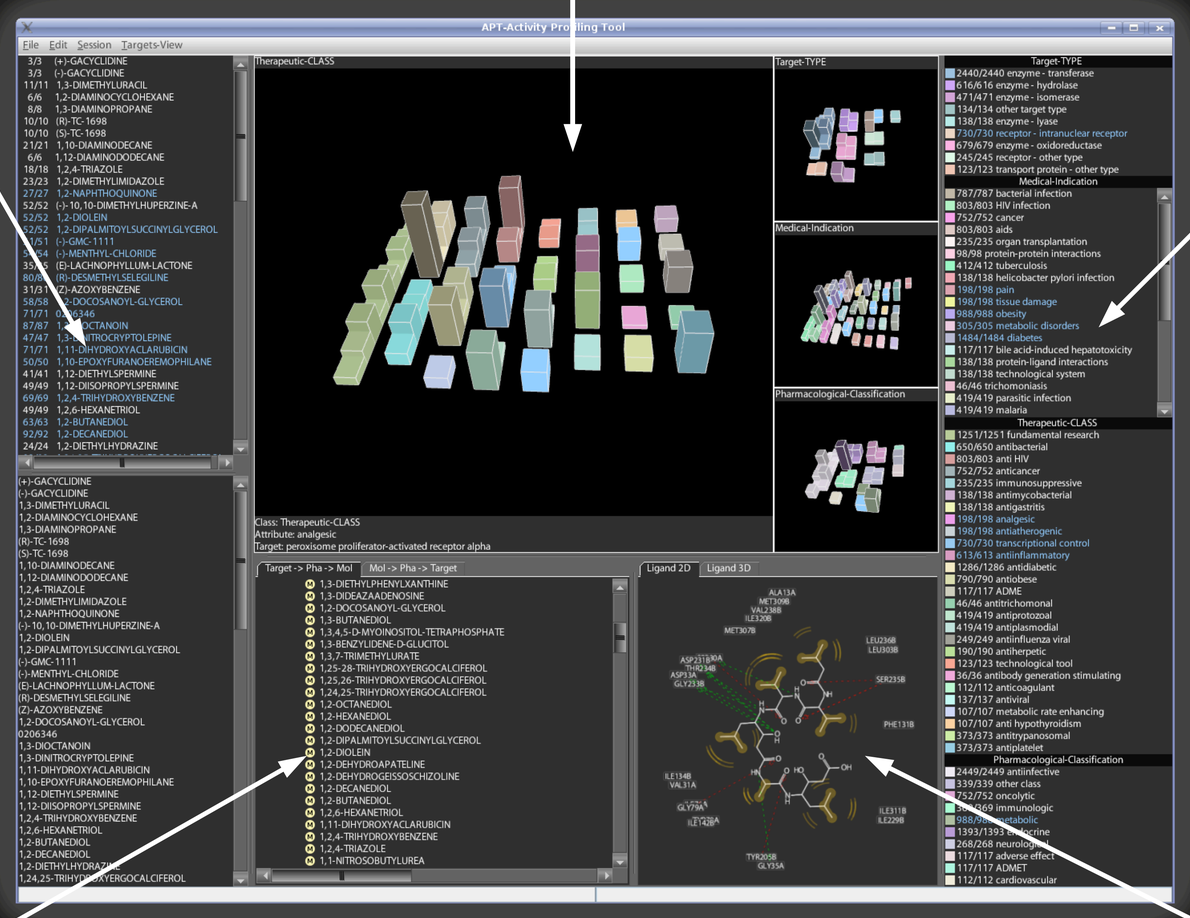

Figure 3:Apt (Activity Profiling Tool)

Tree Views

The application offers two tree views placed in a tabbed pane. Both show the relationship between molecules, pharmacophores and targets of unfiltered hits. One with molecules as top level nodes and the other one with targets as top level nodes. The trees are linked to the other views for receiving filtering information to dynamically update the trees when constraints have been added or removed. Selecting a hit in one of the trees shows the corresponding ligand in the detail views.

Detail Views

There are two detail views, which are placed on different tabs. One shows the 2D-structure and the other one the 3D-structure of the ligand and pharmacophore of the corresponding hit, that was selected in one of the tree views.

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