On our Way to the Automated Search for Ligand-Sensing Cores

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The investigation of protein-ligand interactions is one of the prerequisites for structure-based design of small molecule modulators of protein function. These interactions can be regarded based on structural similarity of secondary structure elements with impact on rational drug design [1]. The basic idea of the presented approach is the fact that a similar spatial arrangement of secondary structure elements around the binding site (‘ligand-sensing cores’) can recognize similar scaffolds independent of the overall fold [2]. The discovery of Namoline as a lysine-specific demethylase [1] (LSD1) inhibitor, which impairs the growth of prostate cancer cells, by Willmann et al. demonstrated the pharmaceutical relevance of this concept [3]. However, to date there is no automated procedure available to compare 'ligand-sensing cores' of various proteins.

We will present the results of our ongoing progress to develop an automated computational method to identify 'ligand-sensing cores' in binding pockets of otherwise unrelated proteins for all known protein structures and possibilities. Our current approach is based on detecting maximum common sub-graphs (MCS) of labeled graphs determined by variants of the Bron Kerbosch [4] maximum clique detection algorithm in appropriately defined product graphs.

In the end, the complete information of all similar ligand-sensing cores within all known protein structures will provide access to previously unused data to predict polypharmacology and to identify new lead structures. Therefore, this development leads to a valuable tool for rational drug design which will be demonstrated by the presentation of interim results achieved on test data sets based on different targets. On top of that, we are very confident to be able to determine all ligand-sensing cores of all known proteins any time soon.

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