Classification of Chemical Compound Pharmacophore Structures

Submitted by: Searle Corporation

There are a staggeringly large number of "druglike" chemical compounds which can be made, and the number of unique molecular structures may very well be in the order of 10^{100} . To date, only on the order of 10^7 compounds have been made and characterized.

The main hope in a classification is the existence of a similarity pattern in the chemical structure, called "pharmacophore". Compounds matching the same pharmacophore interact with biological molecules (enzymes, receptors, etc) in a similar fashion, and a classification of these pharmacophores would be considered an enormous breakthrough in drug discovery, providing access to a "key" to every "lock".

An immediate question is to estimate the number of these pharmacophores. Mathematically, this is a question about how an object with a small, fixed number of pharmacophoric features fills a cavity, but also an exploration of the minimum set of objects required to display all pharmacophoric elements in all possible geometric arrangements.

Participants interested in this problem should familiarize themselves with the "pharmacophore" idea. That concept as well as others are discussed in the following papers. A number of references in these papers may be of interest as well for followup:

- Pickett, S.D.; Mason, J.S.; McLay, I.M. "Diversity Profiling and Design Using 3D Pharmacophores: Pharmacophore-Derived Queries (PDQ)" J. Chem. Inf. Comput. Sci. (1996), 36, 1214-1223.

- Ashton, M.J.; Jaye, M.C.; Mason, J.S. "New Perspectives in Lead Generation II: Evaluating Molecular Diversity" Drug Discovery Today (1996), vol. 1, no. 2, 71-78.

- Greene, J.; Kahn, S.; Savoj, H.; Sprague, P.; Teig, S. "Chemical Function Queries for 3D Database Search" J. Chem. Inf. Comput. Sci. (1994), 34, 1297-1308.

- Clark, D.E.; Willett, P.; Kenny, P.W. "Pharmacophoric Pattern Matching in Files of Three-Dimensional Chemical Structures: Implementation of Flexible Searching" J. Mol. Graphics (1993), vol. 11, 146-156.

- Kuhl, F.S.; Crippen, G.M.; Friesen, D.K. "A Combinatorial Algorithm for Calculating Ligand Binding" J. Comput. Chem. (1984), vol. 5, no. 1, 24-34.

Also, there is a web page which nicely describes a commercial implementation of pharmacophore analysis:
http://www.oxmol.co.uk/prods/chem-x/phtech.html