

Poster presentation

Open Access

**Multi-objective *de novo* drug design using evolutionary graphs**

Christos A Nicolaou\* and CS Pattichis

Address: Computer Science Department, University of Cyprus, 75 Kallipoleos Str., CY-1678 Nicosia, Cyprus

\* Corresponding author

from 3rd German Conference on Chemoinformatics  
Goslar, Germany. 11-13 November 2007

Published: 26 March 2008

Chemistry Central Journal 2008, 2(Suppl 1):P7 doi:10.1186/1752-153X-2-S1-P7

This abstract is available from: <http://www.journal.chemistrycentral.com/content/2/S1/P7>

© 2008 Nicolaou and Pattichis

Drug discovery and development is a complex, lengthy process and failure of a candidate molecule can occur as a result of a combination of reasons, such as poor pharmacokinetics, lack of efficacy or toxicity. Drugs compromise the numerous, sometimes competing objectives so that the benefits to patients outweigh potential drawbacks and risks [1]. *De novo* drug design, involves searching an immense space of feasible, drug-like molecules to select those with the highest chances of becoming drugs using computational technology [2]. Traditionally, *de novo* design has focused on designing molecules satisfying a single objective, such as a similarity value to a known ligand or a virtual screening score, and ignored the presence of the multiple objectives required for drug-like behavior. Recently, methods have appeared in the literature that attempt to design molecules satisfying multiple predefined objectives [3]. In this presentation we briefly review these methods and then describe a new multi-objective optimization *de novo* design algorithm that combines evolutionary techniques with graph-theory to directly manipulate molecular graphs and design structurally diverse molecules satisfying one or more objectives.

In our experimental section we present results obtained from applying the method to design molecules with a desired biological profile with the primary constraint based on a set of known ligands. The implementation of the algorithm includes an initial step where the supplied ligand dataset is analyzed to extract and characterize frequently occurring molecular subgraphs. The resulting subgraphs together with other predefined elements form the molecular building blocks used by the algorithm. In subsequent steps a set of initial molecular graphs is pre-

pared and subjected to an evolutionary process that involves fitness calculation against each objective, identification of a compromise surface (also known as Pareto-ranking), parent selection, mutation and crossover. Fitness calculation focuses on pharmacophoric similarity with the known ligands while parent selection uses a graph-based diversity method in order to preserve structural diversity of the evolved molecules. Our findings indicate that the proposed algorithm produces compromising solutions of substantial structural diversity and can thus be used for an efficient search of the pharmacologically interesting chemical space as defined by the supplied ligands and constrained by the objectives defined.

**References**

1. Nicolaou CA, Brown N, Pattichis C: **Molecular optimization using computational multi-objective methods.** *Curr Opin Drug Discov Dev* 2007, **10(3)**:316-24.
2. Schneider G, Fechner U: **Computer-based *de novo* design of druglike molecules.** *Nat Rev Drug Discov* 2005, **4(8)**:649-663.
3. Brown N, McKay B, Gilardoni F, Gasteiger J: **A graph-based genetic algorithm and its application to the multiobjective evolution of median molecules.** *J Chem Inf Comput Sci* 2004, **44(3)**:1079-1087.