

De Novo Drug Design Using Multi-Objective Evolutionary Graphs

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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. Successful drug candidates necessarily represent a compromise between 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 similarity ~~value~~ to a known ligand or an virtual screening interaction 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] and thereby produce candidate solutions with a higher chance of serving as viable drug leads.

In the first section of this presentation we briefly describe the Multi-objective Evolutionary Graph Algorithm (MEGA), a new multi-objective optimization de novo design algorithm that can be used to design structurally diverse molecules satisfying one or more objectives. The algorithm combines evolutionary techniques with graph-theory to directly manipulate graphs and perform an efficient global search for promising solutions. In ~~our~~ the experimental section we present results from the application of MEGA ~~for~~ designing molecules that selectively binding to a known pharmaceutical target using the ChillScore interaction score family^[4]. The primary constraints applied to the design are based on the identified structure of the protein target and a known ligand currently marketed as a drug. A detailed explanation of the key elements of the specific implementation of the algorithm is given, including the methods for obtaining molecular building blocks, evolving the chemical graphs, and scoring the designed molecules. Our findings demonstrate ~~indicate that~~ that MEGA can produce several structurally diverse candidate molecules representing a wide range of compromises of the supplied constraints and thus, can be used as an “idea generator” to support expert chemists assigned with the task of molecular design.

1. Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. Application of Complex Aldol Reactions to the Total Synthesis of Phorboxazole B. *J. Am. Chem. Soc.* **2000**, 122, 10033-10046.
2. ~~Molecular optimization using computational multi-objective methods~~. Nicolaou, C. A.; Brown, N.; Pattichis, C. Molecular optimization using computational multi-objective methods. *Curr. Opin. Drug Discov. Dev.* **2007**, 10(3), 316-24.
3. ~~Computer-based de novo design of druglike molecules~~. Schneider, G.; Fechner, U. Computer-based de novo design of druglike molecules. *Nat. Rev. Drug Discov.* **2005**, 4(8), 649-663.
4. ~~A graph-based genetic algorithm and its application to the multiobjective evolution of median molecules~~. 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.
5. Tietze, S; Apostolakis, J. GlamDock: development and validation of a new docking tool on several thousand protein-ligand complexes. *J. Chem. Inf. Model.* **2007**, 47(4), 1657-1672.