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Knowledge-driven multi-objective *de novo* drug design

CA Nicolaou*[1,2], C Kannas[1] and CS Pattichis[1]

Address: [1]Computer Science Department, University of Cyprus 75 Kallipoleos Str., P.O.Box.20537, CY-1678 Nicosia, Cyprus and [2]Noesis Chemoinformatics, Metochiou 66, CY-1599 Nicosia, Cyprus

* Corresponding author

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Drug discovery is an inherently multi-objective process since drugs need to satisfy not only activity requirements but also a range of other properties such as selectivity and toxicity. However, drug discovery process practices, including both experimental and computational methods, commonly ignore this fact and focus on a single pharmaceutical objective at a time. De novo design, the branch of chemoinformatics addressing the *in silico* design of ligands from scratch, follows a similar approach typically focusing on a single objective, such as an interaction score to a target receptor or similarity to a known drug [1]. Recently, methods have appeared in the literature that attempt to design molecules satisfying multiple predefined objectives [2]. Motivated from the initial success of these algorithms [3] – as well as their widespread use in other scientific fields – we have preciously introduced MEGA, a Multi-objective Evolutionary Graph Algorithm with the aim of performing de novo design taking into account numerous pharmaceutically relevant objectives. Unlike most other evolutionary-based de novo algorithms, MEGA uses graph data structures for chromosome representation and directly manipulates the graphs to perform a global search for promising solutions. The initial version of the algorithm includes problem-domain specific knowledge in the form of weighted molecular fragments used during chemical structure evolution. Capitalizing on lessons learned we have designed an extension blending additional problem knowledge and local search capabilities to achieve faster convergence. This type of algorithm, commonly referred to as Memetic in the optimization community, has been shown to be orders of magnitude faster than traditional evolutionary algorithms [4] especially in problems searching large, complex and multimodal solution surfaces.

In our presentation we initially outline the key elements of the implementation of our algorithm. Following, we present results from the application of the memetic version of MEGA to design molecules that satisfy multiple objectives. Several test cases have been examined, including selectivity between targets and compromising similarity to a drug and drug-likeness. The results show that the inclusion of domain specific knowledge has a positive impact and should in principle be exploited since it facilitates the practical use of methods incorporating multi-objective de novo design.

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