To explore drug space smarter: artificial intelligence in drug design for G protein-coupled receptors

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Appendix

Summary

Over several decades, a variety of computational methods for drug discovery have been proposed and applied in practice. Traditionally, drug design is always taken as an effort of combinational optimization in discrete chemical space. Hence, optimization methods were exploited to search for new drug molecules to meet multiple objectives. With the accumulation of data and the development of machine learning methods, computational drug design methods have gradually shifted to a new paradigm. Especially, deep learning methods have attracted particular interest in drug design. In **chapter 2**, I give a brief description of two different *de novo* methods, compare their application scopes and discuss their possible development in the future.

In drug discovery, recurrent neural networks (RNNs) have been shown to be an effective method to generate novel chemical structures in the form of SMILES. However, ligands generated by current methods have so far provided relatively low diversity. In **Chapter 3**, a new method (***DrugEx***) was proposed to design *de novo* drug-like molecules. ***DrugEx*** is also an RNN model (generator) trained through a special exploration strategy integrated into reinforcement learning. As a case study we applied our method to design ligands against the adenosine A_{2A} receptor (A_{2A}AR). Through comparing the performance with other methods, it was proven that candidate molecules designed by ***DrugEx*** had a larger chemical diversity, and better covered the chemical space of known ligands compared to the state-of-the-art.

In order to address the issue of polypharmacology, the ***DrugEx*** algorithm was updated with multi-objective optimization to generate drug molecules towards more than one specific target. The concept of evolutionary algorithms was merged into ***DrugEx***. During the training loop, scores for all objectives provided by the *environment* are used to construct Pareto ranks of the generated molecules with GPU-accelerated non-dominated sorting and Tanimoto-based crowding distance algorithms. In **Chapter 4**, the results of its application demonstrated the generation of compounds with a diverse predicted selectivity profile

toward multiple targets, offering the potential of high efficacy and lower toxicity.

As the chemical space to search for feasible drug-like molecules is immense, rational drug design tends to start from known scaffolds as the pharmaceutical core to be optimized, e.g., add or modify substituents. In order to improve its generality, ***DrugEx*** was further updated to have the capability of designing molecules based on given scaffolds consisting of multiple fragments. In **Chapter 5**, we extended the architecture of Transformer to deal with each molecule as a graph. The encoder of the graph Transformer receives the input graph of scaffolds containing multiple fragments and its decoder outputs the graph-based molecule containing the given scaffolds. We trained this generator under the reinforcement learning framework to increase the number of active ligands. As a proof, our proposed methods compared with SMILES-based methods to design $A_{2A}AR$ ligands. The results demonstrated its effectiveness in that 100% valid molecules are generated and most of them had predicted high affinity towards $A_{2A}AR$ with given scaffolds.

Up to now, widespread adoption of new *de novo* drug design techniques in the field of drug discovery is still lagging behind the most recent developments. In order to establish a close collaboration between diverse groups of experimental and theoretical scientists, ***GenUI*** was developed as a visualizion software platform that makes it possible to integrate molecular generators within a feature-rich graphical user interface. ***GenUI*** is an open-source web service and ***DrugEx*** was integrated as a proof of principle. In **Chapter 6** the details of ***GenUI*** are presented to show how it facilitates collaboration in the disparate communities interested in computer-aided drug discovery.

In Chapter 7, I draw conclusions about my contributions to the development of computational drug design and provided my perspective on how AI can be further applied in drug discovery. With these studies I made to a comprehensive investigation of the application of cutting-edge AI methods to design *de novo* drug molecules for biological targets. These studies highlight the overwhelming power of AI methods in drug discovery.