AI-DRIVEN APPROACHES TO RETROSYNTHESIS: A LITERATURE REVIEW

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ABSTRACT

Novel drug discovery is a crucial and costly task, and retrosynthetic prediction plays a key role in accelerating this process by providing an efficient method for rapidly synthesizing complex molecules. Traditional rule-based or chemists-driven approaches to retrosynthesis have exhibited obvious limitations. Consequently, various deep-learning strategies have been proposed to automatically learn chemistry knowledge to address these problems in recent years. This paper reviews the recent advancements in deep learning-based retrosynthesis planning, including single-step and multi-step retrosynthesis. It also discusses the challenges associated with these methods and suggests prospective directions for the field.

Keywords retrosynthesis planning, deep learning

1 Introduction

To obtain a synthetic route to a target molecule, a common strategy is to decompose target molecules into simpler, more easily synthesized precursor structures, a process known as retrosynthetic analysis [Corey, 1991]. Retrosynthetic analysis and prediction is a significant task in organic chemistry by revealing synthetic routes for specific target molecules and identifying commercially available building blocks along the synthetic route. Traditional retrosynthesis prediction requires the expertise and experience of a human chemist, which is expensive and time-consuming, making it hard to meet the demands of practical production.

In recent years, developments in deep learning and machine learning have made computer-aided retrosynthesis prediction increasingly common. Retrosynthetic planning involves two subtasks: single-step retrosynthetic planning and multi-step retrosynthetic planning. Single-step retrosynthetic planning indicates that only one step of a chemical reaction is needed to reach the available reactant from the target product, i.e., the reactant is given directly based on the target product. Multi-step retrosynthetic planning involves analyzing products in successive multi-step predictions. This process is typically accomplished by recursively predicting the product of each step of the reaction until it reaches a level of commercially available building blocks. Therefore, the key to multi-step retrosynthetic planning is to plan the optimal reaction sequence to minimize synthesis steps, starting molecules costs, waste generation, and so forth.

2 Preliminary

Molecular Formulation. In order to apply deep learning to chemical synthesis, chemical molecules need to be represented via descriptors so that they can be processed by a computer. Descriptors typically come in two forms: the SMILES string [Weininger, 1988] and the molecular graph [Kearnes et al., 2016]. (1) For the SMILES string format, a molecular structure is represented by a sequence of ASCII characters. (2) For the molecular graph format, a molecule can be abstracted as a graph $G = \{V, E\}$, where V and E donate the set of nodes and edges of the molecule, respectively. The features of all the points and edges of a molecule form the matrices $F \in \mathbb{R}^{N\times D}$ and $E \in \mathbb{R}^{M\times K}$, which are used to represent information about atoms and chemical bonds, respectively. The adjacency matrix $A \in \mathbb{R}^{N\times N}$ describes the topological structures of the molecule.

Atom-mapping and Conservation in Reactions. Chemical reactions involve the conversion of reactants into products, and there is a one-to-one mapping between the number of each type of atom in all reactants and that in the products, which is called atom-mapping, and the reaction must follow the law of conservation of atoms. In fact, the essence of a chemical reaction is the breaking and forming of chemical bonds.

Reaction Center, Reaction Template. In retrosynthesis prediction, a reaction center refers to the specific atoms and bonds in a molecule that undergo the chemical transformation and change the bonding pattern during a reaction, which is the localized region where the reaction takes place. A reaction template is a generalized representation of a chemical reaction that describes how specific substructures in a molecule are transformed during the reaction [Dai et al., 2020]. It defines the pattern or rules that govern the conversion of reactants to products, often including the types of bonds broken and formed, as well as the functional groups involved.

Synthon and Leaving Group. Retrosynthesis prediction generates synthons by breaking bonds in the reaction centers of a target product, which are simpler precursor substructures and may not be stably present molecules. When a chemical molecule undergoes a reaction, by-products different from the target product, such as water, may be obtained, and these will not be present in the target molecule. These by-products are called leaving groups. The reactants can be formed by synthons and leaving groups.

3 Deep Learning and Retrosynthesis Prediction

In this section, we will discuss two AI-driven retrosynthesis techniques: single-step retrosynthesis methods and multi-step retrosynthesis methods.

3.1 Single-step Retrosynthesis Prediction

Existing work on single-step retrosynthesis prediction using deep learning methods falls into three main categories: template-based methods, template-free methods, and semi-template methods.

Template-based Methods. Template-based methods are similar to conventional rule-based methods in that rely primarily on predefined reaction templates or rules [Chen and Baldi, 2009] for known chemical reactions. These templates specify how certain chemical substructures are converted into others. By exploring and matching the product molecules with the templates and selecting the best based on a similarity metric [Coley et al., 2017], templates can be utilized for the prediction of reaction centers. This approach transforms retrosynthesis prediction into a classification problem, i.e., selecting a suitable reaction template for a target product.

Neuralsym [Segler and Waller, 2017] is the first attempt to apply neural networks to retrosynthesis and the first template-based method, which casts the problem as a multi-class classification problem. Template-based methods are considered reliable and interpretable because they are based on human knowledge extraction. This method is therefore poor at generalizing to out-of-domain reactions.

Template-free Methods. Template-free methods, often referred to as de novo methods, do not rely on predefined templates. Instead, they use advanced deep learning end-to-end generative models to directly learn the mapping between reactant molecules and product molecules. Related studies using this approach formulate the problem as a sequence translation or graph generation problem. Inspired by sequence-to-sequence and Transformer [Vaswani et al., 2017] models, retrosynthesis prediction is viewed as a translation problem of SMILES sequences, using autoregression to predict the next token of the SMILES of the reactant based on the SMILES of the input product and that of the reactants that have already been decoded. Recently, some approaches have used a formalization of the generation of the reactants as a series of graph generations or graph editing operations.

[Liu et al., 2017] firstly proposed the template-free retrosynthesis model designed by an Encoder-Decoder architecture based on long short-term memory (LSTM) cells. Driven by the attention mechanism and the success with transformer-based architecture, [Karpov et al., 2019] introduced the Transformer to the retrosynthesis prediction and achieved better results than LSTM-based models. With in-context learning, [Liu et al., 2023] further leverages the contextual information of the decoded reactants and the product to improve the performance of the Transformer-based model. Recently, [Igashov et al., 2023] proposed a graph-based method and introduced a Markov Bridge Model to model single-step retrosynthesis as a distribution learning problem, which suggests a better fit than the diffusion model and achieves state-of-the-art results on benchmarks.

Semi-Template Methods. The semi-template method belongs to a two-stage template-free method that first predicts the reaction center and then generates the reactant. Specifically, in the first stage, the method predicts the chemical reaction centers to get intermediate synthons based on a graph neural network. Subsequently, the synthons are transformed into actual reactants by constructing a reactant generation network, such as attaching leaving groups, sequence-to-sequence translation, graph generation, and so on.

[Shi et al., 2020] proposed the first semi-template method which is completely based on graph representation and graph convolutional network by predicting reaction centers to generate synthons first and then complete synthons to reactants. To further explore the generation of valid reactants, GraphRetro proposed by [Somnath et al., 2021] considered how the number of hydrogens attached to the atom changes from the products to the reactants.

3.2 Multi-step Retrosynthesis Prediction

The ultimate goal for retrosynthesis planning is to generate a multi-step retrosynthesis route as most molecules in the real world are not synthesized by a single reaction. Industrial drug synthesis routes usually require numerous steps, and the number of steps is also reflected in the complexity and difficulty of efficient search of multi-step retrosynthesis. Algorithms for multi-step retrosynthesis prediction typically need to construct a search tree or a directed acyclic graph, starting from the target product, based on the optional reaction routes provided by the single-step retrosynthesis methods, guided by the designed objective function, and repeated until all the building blocks are commercially available. Besides the huge search space for possible synthesis routes, the criteria for a good synthesis route is also vague, as different chemists may have distinct approaches toward a target molecule. A double-blind AB test [Segler et al., 2018] has been introduced to choose a better route while the approach is expensive and time-consuming on large-scale datasets. Moreover, after the model predicts the possible reactants, the reactant molecules may not go through the actual chemical reaction to get the target product. Even if the forward synthesis is successful, there are objective factors in industrial manufacturing such as yield, cost, and environmental pollution that need to be considered.

Toward multi-step retrosynthesis planning, the model needs to make predictions and next selections on routes given a target molecule at each step. Thus, the problem can be summarized as how to efficiently search for successful routes given a target molecule, as well as estimate the value of each route, while evaluating the synthetic routes from an economic point of view [Jiang et al., 2023]. There are many search algorithms in deep learning, ranging from uninformed algorithms such as depth-first search and breath-first search to informed algorithms such as heuristic search, proof-number search (PNS), and A* search.

Proof-Number Search. Unlike search strategies such as depth-first and breath-first search, heuristic search algorithms utilize a heuristic function to evaluate the current state to guide the search process. The heuristic function evaluates the expected cost of getting from the current node to the goal node, allowing the algorithm to identify and prioritize the expansion of those nodes that are close to the goal, thus effectively expanding the search tree. [Allis, 1994] adopted Proof-Number Search, a search algorithm applied to AND/OR trees, and they modeled the problem as a two-player zero-sum game. In this game, one player's goal is to synthesize the target molecule as efficiently as possible, while the other player works to thwart this process.

Monte Carlo Tree Search. Monte Carlo Tree Search (MCTS) [Coulom, 2007] is an algorithm that optimizes the estimation of the value from the current state to the target state through Monte Carlo simulations. It consists of four key steps: selection, expansion, simulation, and backpropagation. [Segler et al., 2018] combined three neural networks with MCTS based on the proposed Neuralsym [Segler and Waller, 2017] to perform multi-step retrosynthesis prediction. However, each node representing a combination of all precursors in a reaction significantly expands the search space and results in high computation costs.

A* Search. A* search algorithm combines the advantages of uniform cost search and best-first search to ensure the ability to find the optimal solution [Zeng and Church, 2009]. In this approach, the total cost of each state consists of two parts: one is the actual route cost from the starting state to the current state, and the other is the heuristically estimated cost from the current state to the goal state. [Chen et al., 2020] proposed Retro* algorithm based on the A* heuristic search and PNS that learns on additional value during the selection process. However, one disadvantage of the A*-like algorithm is that it results in less diverse pathways as it fails to balance exploration and exploitation [Yu et al., 2022].

Reinforcement Learning. In addition to heuristic search algorithms, deep reinforcement learning has recently been explored for solving retrosynthesis planning. Reinforcement Learning (RL) [Kaelbling et al., 1996] is an advanced machine learning paradigm in which agents learn how to maximize their cumulative reward through interaction with the environment by trial and error. In addition to not relying on large-scale annotated datasets, RL is well suited

to deal with sequential decision-making problems. [Schreck et al., 2019] formulated the retrosynthesis as a single-player game in which the model starts with a random policy and is asked to estimate the cost for each molecule. Through a series of iterative simulation games, the model continuously explores and improves the strategy in search of a better solution. [Yu et al., 2022] proposed GRASP, a goal-driven actor-critic retrosynthesis planning framework that can capture synthetic knowledge through self-generated experiences and bias the retrosynthesis planning toward the favorable goals prescribed by chemists.

4 Challenges

Datasets. Deep learning methods require large-scale annotated datasets to train the model. However, retrosynthesis datasets are still relatively incomplete and not rich enough. USPTO-50 K [Schneider et al., 2016] is a well-known dataset, which contains 50 K high-quality reactions covering ten reaction types. However, the size of USPTO-50 K is not large enough, and leaving group distribution is very imbalanced, which makes a poor generalization on out-of-distribution reactions.

Metrics. The current single-step and multi-step retrosynthesis prediction tasks lack more reasonable and universal metrics. Current top-k accuracy and success rate are insufficient to adequately judge the performance of the model. We encourage future research to construct more general and fairly comparable metrics.

Models. Most of the current research focuses on single-step retrosynthesis prediction, however, multi-step retrosynthesis planning has a wider range of applications in real industrial production and still needs more advanced methods with better performance. Meanwhile, for different single-step or multi-step retrosynthesis planning algorithms, there is still room for improving their robustness to out-of-distribution molecules, which could be an appealing research direction.

5 Conclusion

From the above discussions, we can see that the current state-of-the-art in retrosynthesis planning is still far from perfect, and there is great potential whether single-step or multi-step. In the future, we believe that the AI-driven retrosynthesis will be further improved by incorporating more advanced machine learning methods.

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