# Application of Modern Intelligent Algorithms in Retrosynthesis Prediction

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**ABSTRACT:**

In recent years, with the rapid advance of computer science, various modern intelligent algorithms have successively emerged. Transformer, based on multi-head attention mechanism, is one of the most favored AI models among in this century. The introduction of these algorithms leads to dramatic progress in retrosynthesis prediction. Unlike conventional retrosynthesis prediction models, retrosynthesis prediction based on intelligent algorithms can automatically extract chemistry knowledge from chemical reaction datasets to predict retrosynthesis routes. In this review, we provide a comprehensive overview of retrosynthesis prediction based on modern intelligent algorithms, particularly artificial intelligence algorithm. After introducing the related deep learning model, the existing chemical reaction datasets and molecular representations are presented. Subsequently, the current state-of-the art of AI-assisted retrosynthesis prediction models in recent years is discussed, including template-based models, template-free models, and semi-template-based models. Additionally, we conclude by comparing retrosynthesis prediction models across different categorizations. Finally, several challenges and limitations of these current methods are summarized, with a view to promising directions for future research.

**KEYWORDS:** artificial intelligence, retrosynthesis prediction, Machine learning, Deep learning

## 1. Introduction

Organic synthesis, an indispensable branch of chemistry, is often described as an art because it requires creativity, inspiration, and aesthetic judgment[1,2]. It is a vital technology with broad applications in drug design and synthetic biology[3–6]. Retrosynthetic analysis is a common method for the design of organic synthesis[7]. It is a process of deducing a synthetic route from the target compound by working backward. The core idea is to decompose the target compound into multiple simpler compounds or starting materials, and then synthesize these compounds or starting materials to obtain the target compound. However, with the increasing diversity and complexity of target molecules, the design of organic synthesis pathways has become exponentially difficult. To boost productivity and reproducibility of results, there is a growing expectation that organic retrosynthesis can be automated[8–10]. Thus, computer-aided synthesis planning (CASP) was born. The initial

attempts in this field can be traced back to Corey's pioneering work on rule-based synthesis prediction systems, namely the Logic and Heuristics for Automated Synthesis Analysis (LHASA) program[11]. It designs a series of reactions that recursively decompose the target compound into simpler building blocks until a commercially available starting molecular is reached. However, early rule-based models did not achieve satisfactory results due to the limitations of computational power and data availability. Recently, with the unprecedented advances in computer science[12], intelligent algorithms for a variety of tasks, such as beam search algorithms, Monte Carlo tree search algorithms, genetic algorithms, and neural network algorithms, are emerging rapidly. Furthermore, an increasing number of artificial intelligence models driven by big data have been proposed[13,14]. Due to the outstanding achievements of artificial intelligence in various tasks, the application of artificial intelligence in chemistry and drug discovery has once again attracted attention[15,16].

For chemists, CASP presents a formidable challenge, particularly in the realm of retrosynthesis prediction. This stems from the fact that, in contrast to forward reaction prediction tasks, retrosynthesis reaction prediction tasks provide limited input information while potentially yielding a multitude of output possibilities.

In recent years, many researchers have proposed various types of models for retrosynthesis prediction tasks. Single-step retrosynthesis prediction models can automatically disconnect the given product to gain candidate reactants. For candidate reactants that are not commercially available, a recursive expansion strategy is employed until all reactants along the pathway are commercially accessible or the maximum predetermined expansion steps are reached. Once accurate and recursive single-step retrosynthesis prediction is complete, multi-step retrosynthesis prediction focuses on planning the optimal reaction sequence that minimizes the number of synthesis steps, the cost of the starting molecules, the waste produced, and so forth. Hence, the performance of single-step retrosynthesis prediction models is fundamental to retrosynthesis task. These models can be roughly divided into three classes:

The first category is template-based models, which integrate domain knowledge and formal rules based on prior chemical knowledge, such as template-based algorithms. Reaction templates are a set of rules that determine how reactants are transformed to products through bond disassociation. The terms templates and rules are often used interchangeably. These models generally demonstrate high levels of both interpretability and accuracy, but they struggle to make accurate predictions outside their knowledge base in most cases.

The second category is template-free models, which typically do not incorporate chemical knowledge and are considered black-box models, such as deep neural networks. These black-box models often demonstrate lower interpretability, high computational complexity. They are susceptible to generating solutions that violate chemical knowledge. Nevertheless, they show the promising potential to discover new reaction pathways unconstrained by existing knowledge bases. With the exponential growth in computational data processing capabilities, the performance of purely data-driven models has seen a substantial improvement.

The third category is semi-template-based models, which consists of two steps: (1) they first identify the reaction centers and transform the product into synthons (intermediate molecules) using the reaction centers; and then (2) they complete the synthons into the

reactants.

In this review, we focus on contemporary retrosynthetic strategies. We provide an overview and evaluation of retrosynthesis prediction models developed primarily over the past three years. In the following sections, we first describe the related AI models in retrosynthesis prediction. Then, commonly used data sources and molecular representation in retrosynthesis prediction tasks are compared. Next, we delve into the applications of modern intelligent algorithms in template-based models, template-free models, and semi-template-based models. Finally, we provide an outlook and address potential challenges in this field.

## 2. Related deep learning algorithms

Artificial intelligence algorithms are developed to mimic human intelligence. These algorithms can extract potential rules from dataset and make predictions with these rules when provided with novel data. Deep learning (DL), as a rapidly developing branch of artificial intelligence, shows unparalleled performance in diverse tasks, thanks to the advance of computational power and modern algorithms. Generally, DL models can be divided into three categories: supervised learning, unsupervised learning, and reinforcement learning (RL).

In supervised learning method, a model is trained on a dataset of labeled samples. The model learns to map from input features to an output label. There are two main types of supervised learning models. The classification model learns to predict a discrete output label. The regression model learns to predict a continuous output value. In unsupervised learning method, a model is trained on a dataset of unlabeled samples. The model learns to identify patterns and relationships in the data without being explicitly told what to look for. In reinforcement learning methods, the agent learns to behave in an environment by trial and error. It receives rewards for taking actions that lead to desired outcomes, and punishments for taking actions that lead to undesired outcomes. The goal of the agent is to learn a rule that will maximize its expected reward over time. Most of the retrosynthesis prediction models use the supervised learning strategy, the framework of which is shown in **Fig. 1**.

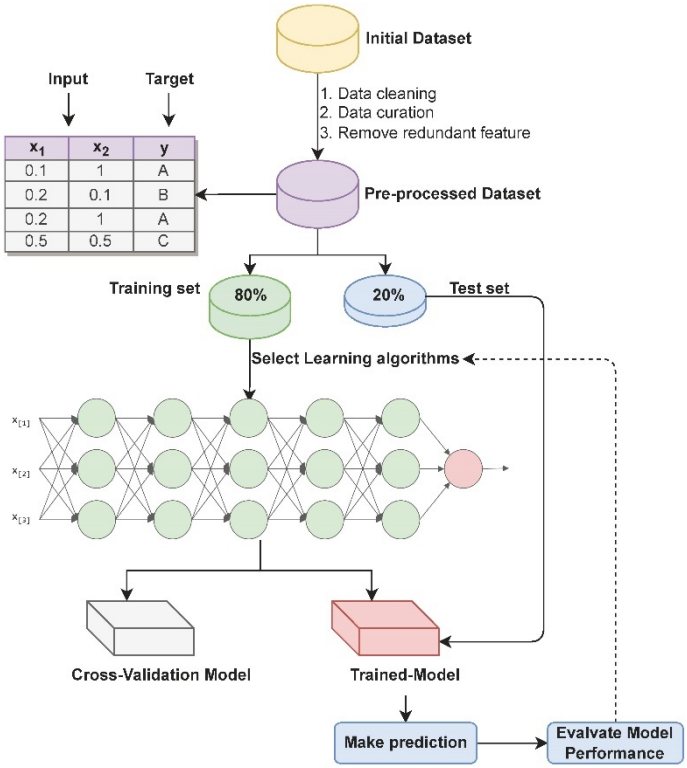


**Fig. 1 The process of supervised learning method**

Common DL algorithms in retrosynthesis prediction include Seq2Seq models, graph neural networks, reinforcement learning and search algorithms.

## 2. 1 Sequence generation model

As molecules can be represented as SMILES-based sequence, retrosynthesis prediction task can be transformed to a sequence-to-sequence task. Sequence-to-Sequence model (Seq2Seq model), which is widely used in natural language processing (NLP) field, is naturally become an effective tool for chemical sequence modeling. Seq2Seq model can generate a sequence of chemical reactants from a chemical product in the case that length of input sequence is different from length of output sequence. In this review, we focused on recurrent neural network- based Seq2Seq models and attention-based Seq2Seq models.

To solve the problem of sequence generation (such as machine translation), recurrent neural network (RNN) was first introduced for encoding and decoding[17,18]. The difference between RNN and feed-forward neural network is that it uses hidden states to record all previous information. The encoder of RNN encodes the input sentence into a fixed-length vector, and the decoder generates the target words sequentially. The framework of RNN is presented in Fig.1. However, RNN models cannot capture long-distance dependencies and are unable to parallelize calculations. The Bidirectional Long Short-Term Memory (biLSTM), a variant of RNN, is proficient at selectively retaining long-distance dependencies through gating mechanisms. Attention Mechanism is a computing resource allocation strategy, which can centralize limited computing resources for important information. When combined with attention mechanism, this biLSTM-based framework enables the hidden state to incorporate global information and addresses the problem of non-parallelizable computations [19]. To model the global attention, the multi-step attention mechanism is introduced to every decoder

layer. The Transformer model, originally introduced by Vaswani et al[21], features encoders and decoders that rely solely on Multi-Head Self-Attention mechanisms, enabling it to effectively capture long-range correlations within sequences. In recent years, Transformer-based models have emerged as a dominant force in the field of purely data-driven retrosynthesis prediction, primarily attributed to their exceptional performance.

The attention mechanism is a technique used in deep learning to assign weights to different parts of the input data, with higher weights indicating more importance. The self-attention mechanism is a specific type of attention mechanism that applies attention to different positions in the same sequence. This allows the model to capture the relationship between any two positions in a sequence, which is important for understanding the structure and meaning in the sequence. The self-attention mechanism is implemented using query, key, and value vectors, which are used to calculate the attention weights and the output. The query vector is used to calculate the similarity between the different key vectors, and the resulting weights are used to weight the corresponding value vectors to get the output.

More specifically, for set of column vectors, $H = [h_1, ..., h_T] \in R^{D_h \times T}$, the self-attention mechanisms can be conceptualized as a process that establishes interactions between different vectors $h_i$ in a linearly projected space. The encoding formulas of self-attention mechanisms is as follows:

$$\text{self-att}(Q, K, V) = \text{Vsoftmax}\left(\frac{K^{\top} Q}{\sqrt{D_k}}\right) \tag{1}$$

$$Q = W_q H, K = W_k H, V = W_v H \tag{2}$$

here, $D_k$ denotes the dimension of the column vectors in the input matrices $Q$ (queries) and $K$ (keys). $D_v$ denotes the dimension of column vectors in the matrices V (values). $W_q \in R^{D_k \times D_h}, W_k \in R^{D_k \times D_h}, W_v \in R^{D_v \times D_h}$ are three projection matrices.

The use of Multi-Head Self-Attention allows for the further capture of varied interaction information across multiple distinct projection spaces. When the self-attention model is applied within $M$ such projection spaces, it can be mathematically represented as follows:

$$\text{MultiHead}\ (H) = W_o[\text{head}_1; \cdots;\ \text{head}\ _M] \tag{3}$$

$$\text{head}\ _m = \text{self-att}\ (Q_m, K_m, V_m) \tag{4}$$

$$\forall m \in \{1, \cdots, M\}, Q_m = W_q^m H, K = W_k^m H, V = W_v^m H \tag{5}$$

here $W_o \in R^{D_h \times Md_v}$ is output projection matrix, $W_q{}^m \in R^{D_k \times D_h}$, $W_k{}^m \in R^{D_k \times D_h}$ and $W_v{}^m \in R^{D_v \times D_h}$ are projection matrices, $m \in \{1, ..., M\}$.

Fig. 2 shows the network architecture of Transformer model, which can be divided into two parts: encoder and decoder. The encoder comprises multiple layers of multi-head attention modules. The decoder generates the target sequence autoregressively, which consists of masked self-attention modules, decoder-to-encoder attention modules, and feedforward neural networks.

Besides RNN-based models and attention mechanisms-based models, Gehring et al. proposed a framework for sequence modeling[20], convolutional sequence to sequence (ConvS2S) model. Its encoders and decoders consist of multilayer convolution neural networks, which is more efficient than RNNs in some cases.

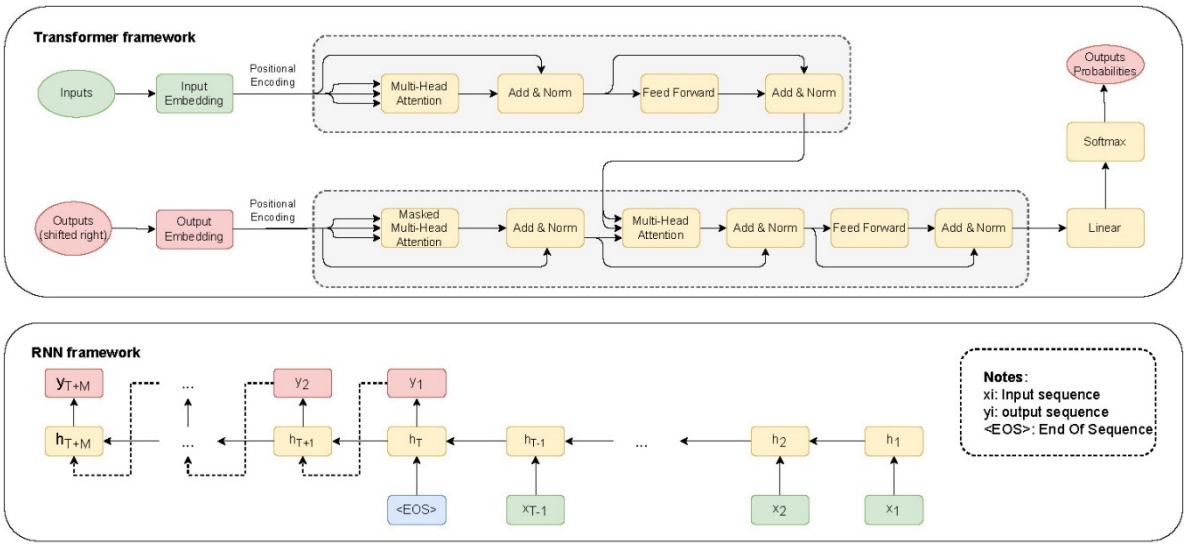


**Fig. 2 Transformer framework and RNN framework.**

## 2. 2 Graph neural networks

Molecules can be represented not only by encoding them into sequences but also by encoding them as undirected weighted graphs, a data structure from graph theory. It consists of a set of vertices, a set of edges and a set of global information, with each edge assigned a weight, and connections between vertices being directionless. For detailed discussion about graph representation for molecular, please refer to section 4.3. There are three general types of prediction tasks on graphs: graph-level, node-level, and edge-level. In general, prediction of chemical molecule belongs to graph-level type, which can be solved with Graph Neural Networks (GNNs).

GNNs are promising parameter-efficient tools for learning the structural information of graphs, enabling predictions of molecular transformations in reactions[21]. GNN is an optimizable transformation on all attributes of the graph that preserves graph symmetries (permutation invariances). Sperduti was the pioneer in applying neural networks to directed acyclic graphs[22]. This approach is also applicable to the undirected graph representation of chemical molecules. **Fig. 3** presents an example of GNN using the "message passing neural network" framework for binary classification task, which can easily be extended to the multi-class or regression task. With the numerical representation of graphs as input, this GNN learn new embeddings for all graph attributes (nodes, edges, global), without using the connectivity of the graph. This GNN uses a separate multilayer perceptron (MLP) on each component of a graph, which is called a GNN layer. For each graph attributes vector, the MLP is applied, and a learned vector is generated. Finally, it makes predictions by pooling information (such as, gathering information from edges to nodes).

Researchers have further proposed Recurrent Graph Neural Networks (RecGNNs)[23,24], where neighbor information is propagated iteratively to update the representations of target nodes. Due to the significant success of convolutional neural networks (CNNs) in computer vision, researchers introduced convolutional operations into GNNs and developed Graph Convolutional Networks (GCNs) [25]. The convolution operation in GCN is a weighted average of the features of the graph to aggregate information about features and their neighbors. However, the weights generated by aggregation operation isn't permutation invariances. To overcome this problem, researchers have introduce

attention mechanisms into GNN and proposed Graph Attention Networks (GATs)[26] and Gated Attention Networks (GAANs)[27]. Based on these works, Graph Autoencoders (GAEs)[28], Graph Generation Networks (GGNs)[29], and Spatio-Temporal Graph Convolutional Networks (STGCNs)[30] have been further developed.

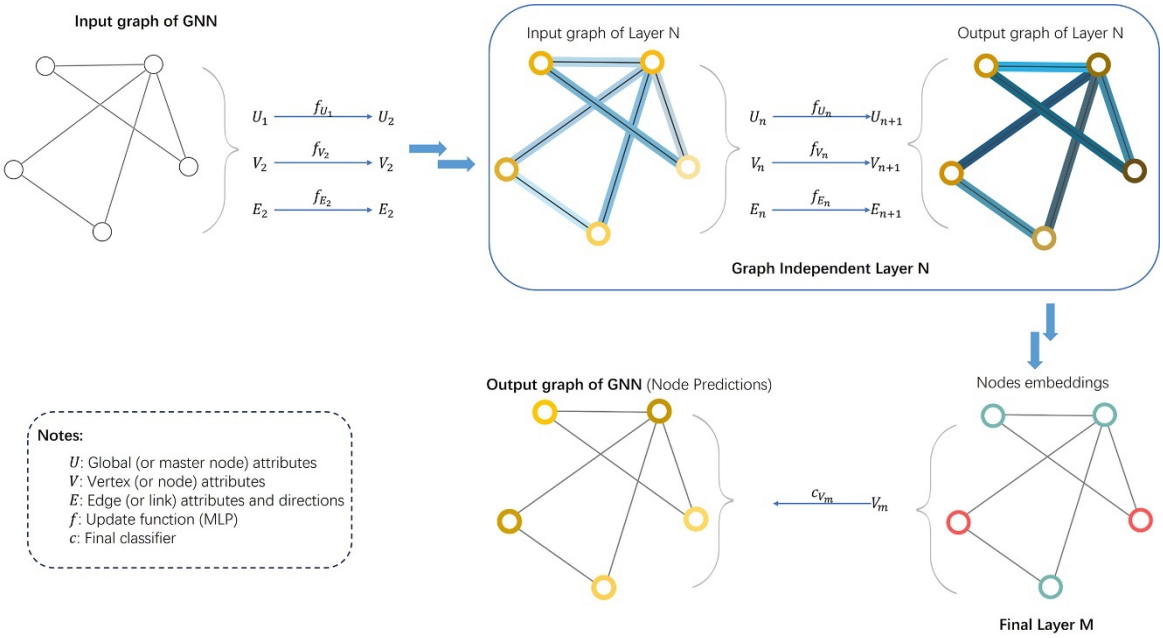


**Fig. 3 GNN framework with message passing neural network for classification tasks.**

## 2. 3 Reinforcement learning

Reinforcement Learning (RL) is a form of unsupervised learning method[31]. It addresses problems where an agent learns from interacting with the environment to achieve specific objectives, such as maximizing rewards. Similar to deep learning, a crucial challenge in RL is the allocation of contributions. Each action does not receive direct supervised information but depends on the ultimate supervised signal (reward) from the entire model, often with some delay. The key distinction between RL and supervised learning lies in RL not requiring a "correct" strategy as supervised information; instead, it focuses on delivering the delayed returns of strategies and adjusting them to maximize expected returns.

In RL, two interacting entities exist: the agent and the environment. The agent perceives the state and reward of the external environment, engaging in learning and decision-making. Decision-making involves different actions based on the external environment's state, while learning adjusts strategies based on the environment's rewards. The environment comprises all external elements to the agent, subject to changes in its state due to the agent's actions and providing corresponding rewards to the agent.

The fundamental components of RL include:

(1) The description of states $s$ as a portrayal of the environment, which can be discrete or continuous, forming the state space $S$;

(2) Actions $a$ describing the agent's behavior, also in discrete or continuous forms, forming the action space $A$;

(3) A policy $\pi(a|s)$ representing how the agent decides the next action $a$ based on the environment's state $s$;

(4) State transition probabilities $p(s'|s,a)$ indicating the likelihood of the environment

transitioning to state $s'$ after the agent's action a from the current state $s$;

(5) Immediate rewards $r(s,a,s')$ as scalar functions provided to the agent based on its action in the current state $s$, often correlated with the subsequent state $s'$.

The objective of RL is to learn a policy $\pi(a|s)$ that maximizes the expected return, with the objective function represented by: $\mathcal{J}(\theta) = \mathbb{E}_{\tau\sim p_\theta(\tau)}[G(\tau)] = \mathbb{E}_{\tau\sim p_\theta(\tau)}[\sum_{t=0}^{T-1} \gamma^t r_{t+1}]$. Here $\theta$ denotes the parameters of the policy function. Value functions are defined to evaluate the expected return of a policy $\pi$, including state value functions and state-action value functions (Q-Function). The policy can be optimized iteratively based on these value functions. Additionally, expected return can be maximized by directly searching the policy space, which includes gradient-based optimization[32,33] and gradient-free optimization.

Deep Reinforcement Learning combines RL and deep learning methodologies, employing RL to define problems and optimization goals, using deep learning to address the modeling of policy and value function, and subsequently employing error backpropagation algorithms to optimize the objective function. Mnih proposed Deep Q Networks (DQNs)[34], which serve as a pioneering cornerstone in the field of deep RL, leveraging convolutional neural networks to estimate Q values. In the Deep Q Network, two pivotal measures are employed: firstly, the freezing of target networks involves fixing the parameters within a target for a specified duration to ensure stable learning objectives; secondly, the utilization of experience replay involves constructing an experience pool aimed at eliminating data correlations. This pool consists of recent experiences gathered by the agent, forming a dataset. During training, random samples are drawn from the experience pool to substitute current samples for training. This approach breaks the similarity between adjacent training samples, preventing the model from converging to local optima. The learning process of the DQNs is illustrated as follows.

**Algorithm**: DQN with Experience Replay

**Input**: State space $S$, Action space $A$, Discount rate $\gamma$, Learning rate $\alpha$

Initialize experience pool $D$ with capacity $N$;
Randomly initialize parameters of the Q network $\phi$;
Randomly initialize parameters of the target Q network $\hat{\phi} = \phi$;
Repeat
    Initialize the starting state $s$;
    Repeat
        In state $s$, select action $a = \pi^\epsilon$;
        Execute action $a$, obtain immediate reward $r$ and the new state $s'$;
        Place $s, a, r, s'$ into $D$;
        Sample $ss, aa, rr, ss'$ from $D$;
        $$y = \begin{cases} rr, & ss' \text{ is terminal state} \\ rr + \gamma \max\limits_{a'} Q_{\hat{\phi}}(ss', a'), & \text{otherwise} \end{cases}$$
        Train the Q network with the loss function: $\left(y - Q_\phi(ss, aa)\right)^2$;
        $s \leftarrow s'$;
        Every C steps, execute action: $\hat{\phi} \longleftarrow \phi$;
    Until $s$ is the terminal state;
Until $\forall s \; and \; a, \; Q_\phi(s,a)$ converges;

**Output**: $Q_\phi(s,a)$

Since their inception, researchers have introduced numerous extensions to the value-based approach[35]. Furthermore, model-based methodologies have been proposed[36], enabling prediction of post-action states through predictive models and direct optimization of policy networks. Deep RL also works on more complex decision-making problems, such as those with goal conditions[37], hierarchical task decomposition[38], and multiple agents[39]. Deep RL has garnered significant success across diverse applications, ranging from games[40], robotics[41], and autonomous driving[42] to molecule generation[43]. This advancement is widely perceived as a crucial stride toward the development of general AI[44].

2. 4 Search algorithms

Search algorithms retrieve stored information within a data structure or computed in a search space, forming the basis for multi-step retrosynthesis prediction in planning synthesis routes. Generally, these algorithms fall into two categories: uninformed searches and informed searches. Uninformed searches do not leverage information regarding the cost of state transitions; typical examples include depth-first searches and breadth-first searches. In contrast, informed searches incorporate heuristic functions to assess the distance between the current and goal states, guiding the search progress. While not necessarily optimal, this approach ensures a favorable solution within a reasonable search time. Best-first searches represent typical heuristic searches employing a priority queue concept. The OPEN list contains currently traversable nodes, while the CLOSED list stores traversed nodes. Beam search enhances best-first search by expanding the most promising nodes within a limited set[45]. A* search amalgamates the merits of uniform cost search and best-first search, ensuring optimality in solutions[46]. In this context, the cost of each state comprises the actual cost from the starting state to the current one and the heuristic cost from the current state to the goal state. Monte Carlo Tree Search (MCTS)[47] refines value estimates from the current state to the goal state. AlphaGo[48] stands as one of the most renowned applications of MCTS, where it explores potential moves and tracks outcomes within a Go search tree. MCTS consists of four phases: Selection, Expansion, Simulation and Backpropagation. (see **Fig. 4**)

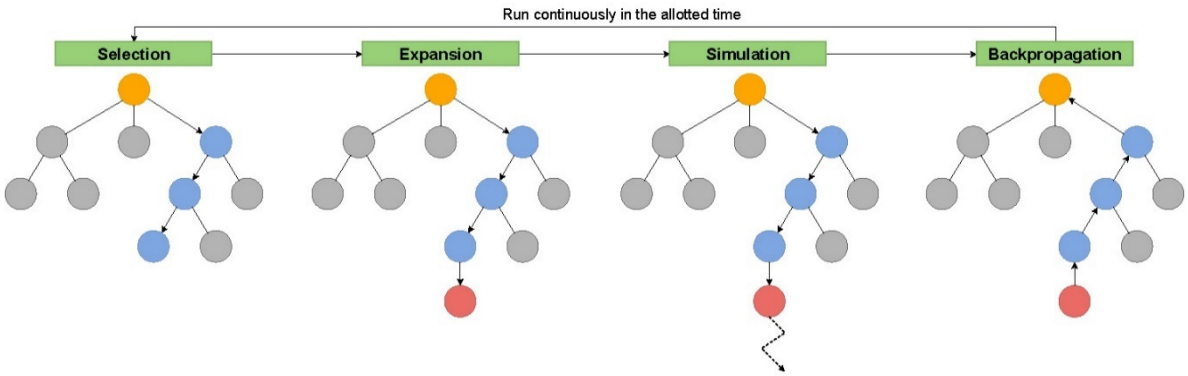


**Fig. 4 The process of MCTS: selection, expansion, simulation, and backpropagation.**

## 3. Data sources

In CASP tasks, whether through symbolic AI or purely data-driven modelling, a dataset that can be parsed by a computer is a precondition. The quality of dataset determines the model's upper limit. It is not an exaggeration to say that the quality of the dataset is more important than the model itself[49]. Therefore, computational chemist needs to pay particular attention to the characteristics of the input dataset. This section will provide a summary and comparison of common chemical reaction databases.

Journals and publishing houses have made their datasets available under licensing agreements in computer readable format, by means of automatic extraction by algorithm and expert manual coding. These include the Reaxys database, published by Elsevier, which encompasses more than 73 million reactions as of 2023. Comprehensive and up-to-date journal and patent coverage from 16,000 journals and 105 patent offices. It compiles comprehensive and up-to-date journal and patent coverage from 16,000 journals and 105 patent offices. To extract information from chemical patents, Elsevier and the University of Melbourne, Australia initiated a project based on NLP models, called ChEMU[50]. The Chemical Abstracts Service (CAS) encompasses approximately 150 million reactions spanning from 1840 to 2023, including organic, inorganic, total synthesis of natural products, and biotransformation reactions, which stands as the largest provider of reaction data. Its data sources derive from journals, patents, dissertations, and seminal reference works. Furthermore, smaller-scale datasets include SPRESI, developed by InfoChem, which encompasses 4.6 million reactions spanning the period from 1974 to 2014. Another notable dataset, Pistachio, created by NextMove Software, comprises patent data from 1976 to 2023, encompassing a vast corpus of over 13,118,970 reactions. Among researchers, the most extensively employed dataset is a subset of patent data extracted by Lowe during the period from 1976 to 2016, which encompasses 3.3 million reactions. This dataset is presently the sole publicly accessible repository of reaction data and is commonly called USPTO[51]. Moreover, USPTO 50K, a subset and preprocessed iteration of Chemical reactions from USPTO, is composed of 50,000 reactions selected randomly, covering ten distinct reaction types[52]. USPTO-MIT[53] is also a commonly used subset, which contains a wide range of reagents and possible catalysts compared with USPTO-50K. The specific detail of commonly used dataset is listed in **Table 1**.

Although the datasets mentioned above include details about molecular structures, reaction conditions (solvents, catalysts, reagents), and yields, they are not immune to errors. Moreover, the prevalence of positive data in most patents and literature contributes to an uneven distribution of product representations[54,55]. This imbalance in data distribution can have detrimental effects on model performance. Furthermore, within the CASP framework, the instances of failed reactions play an important role, especially in situations concerning regioselectivity and chemoselectivity. To overcome these challenges, THE data have been published to generate more consistent data[56]. IBM has released a method employing Natural Language Processing (NLP) to extract experimental procedures from patents and scientific literature, thereby creating structured, automation-friendly formats[57]. The Pistoia Alliance has collaborated with Elsevier to define a Unified Data Model (UDM) for the exchange of reaction information. Electronic laboratory notebooks (ELNs), a novel dataset

extracted from the electronic laboratory notebooks of a large pharmaceutical company, are not subject to the publication bias towards high-yielding reactions[58,59].

Of notable mention is that, comparing various data sources, including patents (USPTO and Pistachio), literature and patents (Reaxys), and industrial data (AstraZeneca ELN), despite similarities in their size of template sets, they differ in the coverage of reaction space. Reaxys stands out for its extensive and uniquely diverse collection of reaction templates, providing a broader reaction space[60].

**Table 1**

Overview of dataset used for retrosynthesis prediction models.

| Dataset | Source | Sample size | Reaction space coverage |
|---|---|---|---|
| Reaxys | journals and patent | 7300k | +++++ |
| ChEMU | patents | - | - |
| CAS | journals and patent | 15000k | - |
| SPRESI | literature | 4600k | - |
| Pistachio | USPTO + EPO | 9000k | ++ |
| USPTO-full | USPTO | 3300k | ++++ |
| USPTO 50K | USPTO | 50k | +++ |

## 4. Molecular representation

For CASP tasks, the quality of the dataset and the art of feature engineering play determining roles in the performance of the model. Therefore, chemists have devised numerous distinct molecular representation methods with the aid of mathematical tools. These methods aim at encapsulating the complete information of molecules using abstract mathematical symbols. 1D molecular representation methods can solely represent global molecular properties exclusive of structural patterns, such as pKa, logP, etc. 2D molecular representation methods can represent structural patterns without explicit 3D information, including SMILES (Simplified Molecular Input Line Entry System)[61,62], fingerprints, and molecular graphs, which are the mainstream methods used in retrosynthesis tasks. 3D molecular representation methods, such as image-based methods, can contain high-dimensional information, but it doesn't necessarily mean better performance in some cases. In recent years, a 3D molecular representation learning framework is proposed to capture more information in high dimension automatically[63].

### 4. 1 Molecular string representation

SMILES is the most widely adopted molecular string representation system for molecular structures. The SMILES system combines specific syntax rules and chemical principles to represent molecular structures rigorously. One of the advantages of SMILES is the ability to transform reaction prediction tasks into machine translation tasks. For sequence modeling problems, leveraging natural language processing (NLP) models in the field of artificial intelligence can solve them efficiently[64]. For example, the Transformer architecture based on the attention mechanism is one of the most favored NLP models among computational chemists. For SMILES representation of chemical reactions, reactants, reagents, and products can be linked together using symbols, which is similar with molecular fingerprint method. The ">" symbol is used to indicate the direction of the reaction. For

instance, "Reactants > Reagents > Products". However, SMILES grammar is sequence sensitive and has trouble dealing with stereochemistry. SMARTS, as an extension of the SMILES language, serves as a language for describing molecular patterns and properties. SMARTS can be used to create queries. One notable feature of SMARTS is its allowance for the use of wildcards to represent atoms and chemical bonds. As a result, it is widely employed in computerized searches for structures in compound databases, enabling efficient and flexible chemical structure searching.

Self-Referential Embedded Strings (SELFIES)[65] is a method that is both 100% robust and human-readable for representing molecular structures, which is proposed to overcome the limitation of SMILES. InChI[66], another string-based representation for chemical structures, possesses the advantage of uniqueness and reversibility in contrast to SMILES. These methods no longer involve atom-atom mapping to identify reaction centers. The SMILES of caffeine is showed in the following **Fig. 5**, including the process of ensuring its SMILES representation.

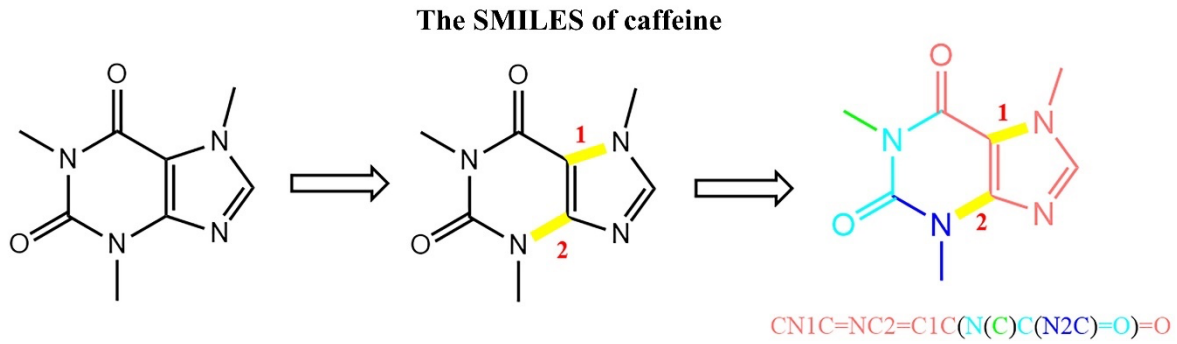


**Fig. 5 The process of getting the SMILES representation of caffeine.**

## 4. 2 Molecular fingerprints

Molecular fingerprints are another valuable tool in chemoinformatics for representing molecules. The core idea behind molecular fingerprints is to map a molecular into a bit string or a numeric array of length l, where each bit encodes whether the molecular contains a specific substructure feature. Molecular fingerprints offer several advantages, including high computational efficiency and ease of retrieval, making them an ideal choice for molecular similarity assessment. Main approaches include substructure keys-based fingerprints, path-based fingerprints, and circular fingerprints. Here, we mainly focus on commonly used molecular fingerprint methods. For an detailed introduction to complete molecular fingerprints and software please refer to Cereto-Massagué's work[67].

Substructure key-based fingerprint sets a bit string based on the presence of certain substructures or features from a given list of structural keys in a compound. The MACCS fingerprint system[68] offers two variants, one with 960 bits and the other with a more compact 166 bits, both based on SMARTS patterns of structural keys. The shorter variant, despite its reduced size, effectively captures most chemically relevant features essential for tasks such as drug discovery and virtual screening. In contrast, the PubChem fingerprint[69] comprises 881 structural keys, providing a comprehensive representation of diverse substructure features and serving as a cornerstone for similarity searches within the PubChem database. The BCI fingerprint[70], with user-customizable options and a standard substructure dictionary of 1052 keys, offers flexibility in its generation[71]. Lastly, the TGD

and TGT fingerprints[71,72], calculated from 2D molecular graphs, present two-point and three-point pharmacophore representations, consisting of 735 and 13,824 bits, respectively. These fingerprints, with their distinct characteristics, cater to a wide range of chemoinformatics applications, allowing researchers to effectively explore and analyze chemical compound data.

Path-based fingerprinting operates by scrutinizing all molecular fragments that follow predefined paths (typically linear), up to a specific number of bonds. Subsequently, each of these paths undergoes hashing to generate a unique fingerprint. These fingerprints can serve in swift substructure searches and effective filtering. Among these fingerprint types, the "Daylight Fingerprint" stands out prominently[73], comprising as many as 2048 bits meticulously encoding all possible connectivity paths within the molecule, up to a specified length.

Circular fingerprints focus on recording the environment surrounding each atom within a defined radius. They are less suitable for substructure verification queries, as identical fragments may exhibit distinct environments, but they find utility in full structure similarity searches. Molprint2D encodes the atomic environments of each atom in a molecule's connectivity table, representing these environments as strings of varying sizes[74,75]. ECFP (Extended-Connectivity Fingerprints) is an extension of the circular fingerprint based on the Morgan algorithm[76]. They represent cyclic atom neighborhoods and generate variable-length fingerprints. The commonly used ECFP variant has a diameter of 4, often referred to as ECFP4. A diameter of 6 (ECFP6) is also quite common. FCFP (Functional-Class Fingerprints) is a variant of ECFP, indexing the function of that atom. Different atoms with the similar functions are not distinguished in the fingerprint. It can represent stereochemistry information which can further be used to infer structure-activity relationships.

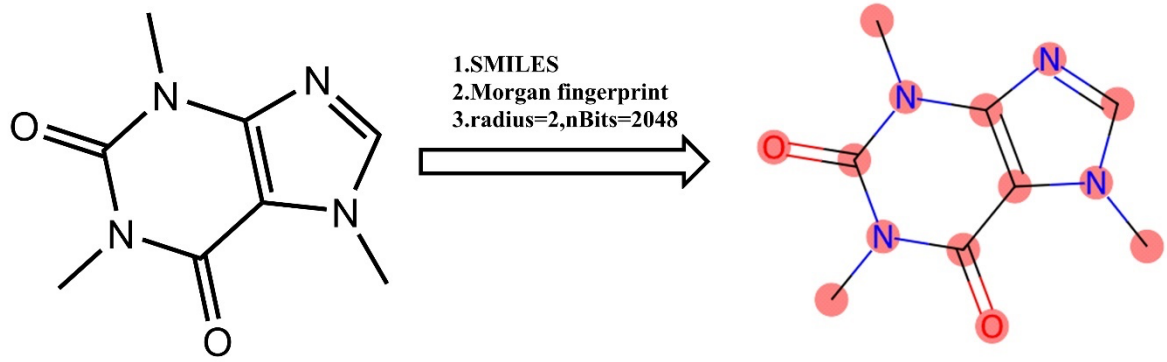


**Fig. 6 The result of the caffeine structure with highlighted atoms which are related to Morgan fingerprint.**

4. 3 Molecular graphs

With the rapid advancements in graph neural networks, molecular graphs have garnered significant attention from researchers in the CASP field. Undirected graph is a fundamental data structure in graph theory, consisting of nodes and edges with associated weights. The edges in an undirected graph have no explicit direction, allowing for bidirectional edges between node A and node B. An adjacency matrix is a square matrix used to represent a finite graph. Each of its elements represents whether the nodes are connected by edges. The size of the adjacency matrix is the number of vertices in the graph. The diagonal element of the

adjacency matrix is 0. If the element of row $i$ and column $j$ of the adjacency matrix is 1, then node $i$ and node $j$ are connected by an edge. However, the space complexity of the adjacency matrix is $O(n^2)$, where $n$ is the number of vertices in the graph. Therefore, to improve the computational efficiency, if the size of the adjacency matrix is large, adjacency matrix can be transformed to the eigenvectors of nodes, edges and global, which are generally used as inputs features.

Molecules, the fundamental constituents of matter, are composed of atoms and electrons arranged in three-dimensional space. While all particles interact, a stable separation between a pair of atoms constitutes a covalent bond. Varied atomic pairs and bonding configurations, including single and double bonds, exhibit distinct interatomic distances. This intrinsic characteristic renders the graph representation with atoms as nodes and chemical bonds as edges[77–79]. The graph representation of Caffeine is presented in **Fig. 7**, including its molecule structure, molecule graph and adjacency matrix.

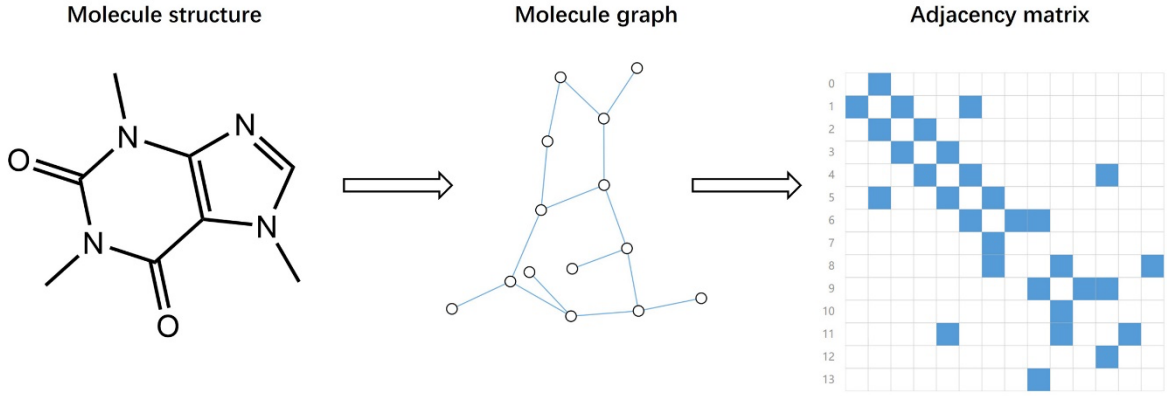


**Fig. 7 The graph representation of Caffeine.**

Compared to SMILES and molecular fingerprints, molecular graphs can represent more information about chemical structures, including atom types, bond types, topologies, etc. 3D information such as bond lengths, bond angles can also be added to the node and edge in graph representation. Moreover, graph representation is not affected by atom order. However, an efficient algorithm extracting graph representation from molecular structure is a precondition for practical application of molecular graph[78,80].

For representing reaction graphs, extracting reactions from pre-trained models stands as a promising approach. Additionally, the use of atom mapping enables a single condensed reaction graph (CGR) represent chemical reactions effectively[81], which is a superposition of reactant and product graphs.

## 5. Retrosynthesis strategy evaluation

### 5. 1 Candidate reaction evaluation

In retrosynthesis, “combinatorial explosions” is a sticky problem. Scientists strive to limit recursive unfolding to the most promising bond breaks, leading to easily synthesized structures.

Synthesizability of molecular structures is critical in candidate reaction evaluation. The Synthesis Accessibility Score (SA Score) leverages the contribution of fragments that scale linearly with commonly synthesizable structural features and penalizes the presence of rare

and intricate structural features[82,83]. Chematica develops a metric for assessing synthetic difficulty, by restricting structural complexity, reaction step length, reaction conflicts and protecting groups. The SCScore is founded on the principle that reaction products should exhibit higher synthetic complexity than their reactants[84,85]. Other evaluation encompasses support vector machine-based DRSVM[86] and current complexity metrics[87].

### 5.2 Model evolution

In a CASP modeling workflow, model evaluation plays a pivotal role. CASP tasks, owing to their specificity, differ significantly from conventional regression and pattern recognition tasks. To select models qualified to practical retrosynthesis tasks, different evaluation metrics suitable for these tasks should be adopted. Retrosynthesis tasks are generally divided into two categories: single-step retrosynthesis and multi-step retrosynthesis prediction.

For single-step retrosynthesis, Top-N accuracy calculation is a commonly used metric to evaluate the performance of single-step strategies. It examines whether the entire set of ground truth precursors, the actual reactants reported in the template library for the corresponding target molecule, are among the first N precursors suggested by the model. This metric demands an exact match in molecular structure, which can be measured using a molecular similarity. A similarity score of 1 denotes identical structures[88]. Additionally, some alternative evaluation metrics for single-step retrosynthesis have been introduced[89]. For multi-step retrosynthesis, evaluation can be achieved by using single-step retrosynthesis methodology repeatedly.

## 6. Template-based models

Template-based models often involve matching the target molecular with an entire template library. Then, the subgraph isomorphism problem is solved to obtain candidate reactants. The core of template-based systems lies in the use of retrosynthesis templates. As shown in **Fig. 8**, reaction template is represented by molecular subgraph patterns that encode changes in the connectivity of atoms during a reaction. Mathematically, a retrosynthesis template $T$ is denoted as the following rule:

$$T\colon\ p^{T} \rightarrow \{r_i^{T}\}_{i=1}^{n_r}$$

where $p^{T}$ is a subgraph of the product $P$ and can be regarded as the reaction center, while $r_i^{T}$ is the subgraph of the $i$th reactant.

Starting from a target molecule, a template is selected following predefined rules and is applied to the target molecular to determine the reactants. While template-based methods have better interpretability and accuracy than template-free methods, they are computationally demanding and have limited generalization outside the template library. The mission of modern intelligent algorithms is to lower the computational complexity of this process.

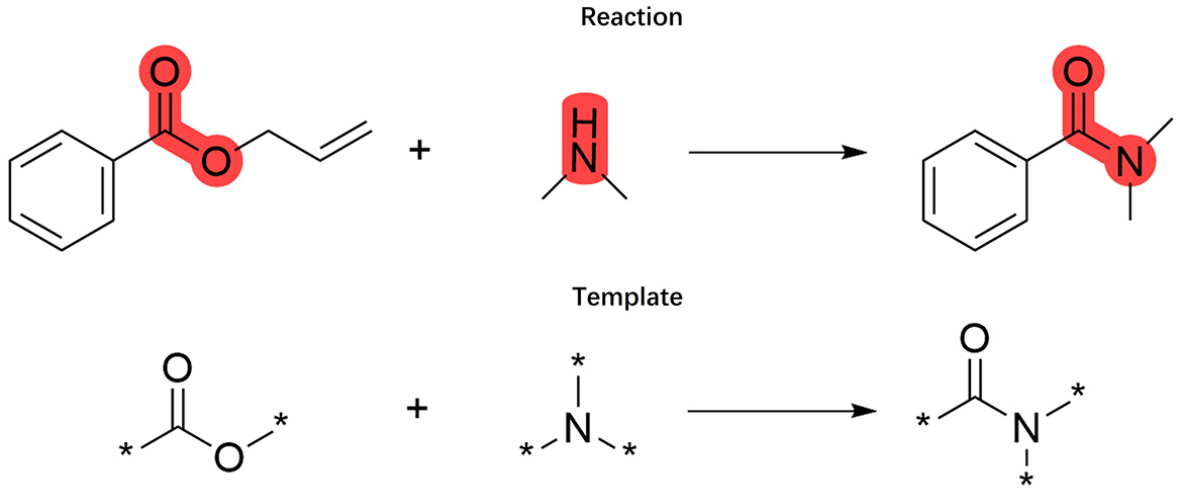


**Fig. 8 Illustration of a chemical reaction and its retrosynthesis template.**

Traditionally, reaction rules have been defined and hand-coded by experts. Szymkuc et al. provided a review on using reaction templates coded by human experts for synthetic planning[90]. With the reaction space growing exponentially at a rate of 4.4% per year[91], manually coding becomes an overwhelming task. An alternative approach to reaction coding utilizes algorithms that extract reaction centers via atom-to-atom mapping to identify correspondences between reactant and product[92–95]. For a given reaction, one can identify the set of atoms that change bond connectivity as reaction centers. Then the reaction centers and adjacent atoms are algorithmically extracted and generalized to form the corresponding retrosynthesis template.

With the reaction templates available, Coley et al. proposed a retrosynthesis method based on molecular similarity metrics[96], such as Morgan2noFeat, Dice similarity, the Tanimoto similarity and the Tversky similarity. This approach decomposes target molecular solely according to analogy to known reaction precedents, thus inherently disfavoring making creative disconnections. Segler et al. used the extended-connectivity fingerprints (ECFP) as input and constructed a deep neural network-based model that can learn to resolve reactivity conflicts and prioritize the most appropriate transformation rules, which is one of the first ML-based template models[97]. This model solves the multi-class classification problem of categorizing similar templates into subgroups. The performance of this model is often used as one of the benchmarks in template-based approaches. Watson et al. proposed an template-based approach using reverse reaction transforms(RRTs)[98]. RRTs are extracted from clusters that contain similar reaction. By searching possible synthesis routes in RRT-repository, this method decomposes a target molecular into fundamental building blocks. Genheden et al. developed the retrosynthesis software, AiZynthFinder[99]. the algorithm is based on a Monte Carlo tree search that recursively disconnects molecules into purchasable precursors. The tree search is guided by the Artificial Neural Network strategy, which suggests possible precursors by utilizing a library of reaction templates. Park et al. proposed undersampling based on the similarity (random, dissimilarity) clustering of molecular structures of products for the class imbalance problem in chemical reaction datasets[100], which significantly improved the prediction accuracy. Chen et al. proposed a local retrosynthesis framework, LocalRetro[101], which assumed that the molecular changes occur

mostly locally in the process of reaction. As a complement, a global attention mechanism is introduced to account for the nonlocal effects. Seidl et al. Proposes a template-based single-step retrosynthesis model based on modern Hopfield networks[102], which learns the encoding of molecules and reaction templates to predict the correlation of the template with a given molecule. The template representation allows generalization across different reactions. AiZynthTrain developed by Genheden et al[103], which is a robust, reproducible, and extensible end-to-end retrosynthesis model. Its process includes two pipelines that build a template-based one-step retrosynthesis model and a ringbreaker model. Additionally, they highlight the important role of heuristics. Dai et al. proposed a conditional graph logic network model based on a hierarchical sampling approach[104]. A conditional graph logic network is a conditional graph model built on graph neural networks that learns when the rules in a reaction template should be applied, implicitly considering whether the final reaction is chemically feasible and strategic. RetroComposer[105], proposed by Yan et al, which can synthesize new templates in addition to the training templates. Furthermore, they developed an effective candidate scoring model that can capture atomic level transformation.

In a broad sense, template-based models can include quantum-computation-based retrosynthesis models, as quantum computation can generate new reaction templates. Liu et al established a reaction kinetics-based retrosynthesis planning framework to design synthetic pathways[73]. The part of forward analysis consists of TST-based reaction kinetic model and DFT. The part of retrosynthesis planning includes Decision tree model and breadth-first search algorithm. To solve the problem of poor sample quality in datasets, Toniato et al. proposed to provide missing data for model retraining via first-principal computation[106].

**Table 2**

Overview of retrosynthesis prediction performance for template-based methods.

| **Methods** | **Algorithm** | **Dataset** | **Features** | **TOP-1** | **TOP-5** | **TOP-1** | **TOP-5** | **source code availability** |
|---|---|---|---|---|---|---|---|---|
| | | | | **with reaction class** | | **without reaction class** | | |
| Retrosim | Similarity | - | fingerprint | 52.9 | 81.2 | 37.3 | 63.3 | Y |
| Park | Taylor – Butina algorithm | Reaxys | SMILES+ fingerprint | - | - | 51 | 84 | Y |
| LocalRetro | Attention mechanism | USPTO-50k | graph | 63.9 | 92.4 | 53.4 | 85.9 | Y |
| Seidl et al. | Hopfield Networks | USPTO-50k | SMILES | - | - | 51.8 | 81.2 | Y |
| Neuralsym | ANN | Reaxys | ECFP | 55.3 | 81.4 | 44.4 | 72.4 | Y |
| GLN | GLN | USPTO-50k | graph | 64.2 | 85.2 | 52.5 | 75.6 | Y |
| RetroC | Multiple | USPTO- | graph | 65. | 89. | 54. | 83.2 | Y |

| | | | | | | |
|---|---|---|---|---|---|---|
| ompose r | DL models | 50k | 9 | 5 | 5 | |

## 7. Template-free models

Recently, template-free methods have attracted increasing attention because they avoid the computationally intensive problem of subgraph matching. These methods utilize textual representations of molecules (SMILES or InChI) to transform the retrosynthesis task into a translation task that can be solved by using powerful methods in Deep Learning. The process no longer involves atom-to-atom mapping to identify reaction centers. These kinds of Purely data-driven approaches usually do not need to incorporate explicit chemical knowledge. When relevant data are abundantly available, these methods can achieve satisfactory performance. The following provides an overview of these approaches, which are categorized into deep neural networks, sequence-to-sequence models, graphical neural networks, and small sample techniques.

### 7. 1 Deep neural networks

Baylonet al. present a multiscale retrosynthesis prediction framework based on Deep Highway Network (DHN)[107]. The process consists of two parts: a DHN model is built to predict the group of reaction, and the transformation rules to generate the molecular are predicted using DHNs trained on a subset of reactions within the identified reaction group. Hasic et al. train retrosynthetic models for identifying potential breakpoints on molecular substructure fingerprint representations[108]. The model uses only the individual molecular substructures of the target to identify potential disconnection sites and does not rely on additional information such as chemical reaction class. A holistic pathway evaluation mechanism is an indispensable part of retrosynthetic model. Mo et al. introduced a dynamic tree-structured long short-term memory(tree-LSTM) model[109].

### 7. 2 Sequence-to-sequence

The main idea of seq2seq is to model retrosynthesis prediction as a sequence modeling problem with target molecular as the input sequence and reactants, reagents, and catalysts as the output sequence. Transformer is the most popular seq2seq model in this century, which is purely based on multi-head attention mechanism. The introduction of Bidirectional Encoder Representations from Transformers (BERT)[110] also improved the performance of template-free strategies. Sequence-modeling-based retrosynthesis models have emerged as the most widely used AI models for retrosynthesis, with nearly all of them relying on attention mechanisms.

The idea of combining chemistry with natural language processing was first proposed by Cadeddu et al[111]. Liu et al. proposed an encoder-decoder framework consisting of two recurrent neural networks, which treats the task of retrosynthesis prediction as a sequence-to-sequence mapping problem[112]. Seq2seq model has several advantages over template-based baseline models. First, the seq-2-seq model can implicitly learn reaction rules and candidate ranking metrics, which avoids the use of independent reaction complexity ranking metrics as in the template-based approach. Second, the seq-2-seq model is easier to expand than the rule-based approach. Tetko et al. proposed a Transformer model for a retrosynthetic

reaction prediction task[113].

In recent years, Guo et al. developed a framework of Bayesian inference[114], which includes a pretrained Molecular Transformer used to forwardly predict and a model based on Bayes' law of conditional probability used to inverse the forward model into the backward one. Subsequently, a diverse set of highly probable reaction sequences are achieved via conjoint utilization of Monte Carlo search algorithm and backward model. Zheng et al. developed a template-free self-correcting retrosynthesis predictor (SCROP) to perform the retrosynthesis prediction task trained by using the Transformer model neural network framework[115]. For compounds out of training set, this method showed higher accuracy than other state-of-the-art methods. Duan et al. proposed an attention-based NMT model[116], the Tensor2Tensor (T2T) model, which has a great advantage over the machine translation task. It is more parallel and requires significantly less training time. Tetko et al. proposed the Transformer model framework based on data augmentation of input and target data[117], which removes the effect of the neural network's memorized data and improves the performance of the neural network in predicting new sequences. Seo et al. propose a new template-free model, graph truncated attention (GTA)[118], which utilizes sequence and graph representations by inserting graph information into a seq2seq model. It masks the self-attention layer using the adjacency matrix of the product numerator in the encoder and applies the new loss to the cross-attention layer in the decoder using atomic mappings obtained from an automated algorithm. Mann et al. proposed a single-step retrosynthetic prediction method using representations based on SMILES grammars[119]. An information-theoretic analysis of such grammar representations proves that they outperform SMILES and are better suited for machine learning tasks. Ucak et al. proposed a single-step retrosynthetic prediction method[120], RetroTRAE, without any SMILES-based translation problem, which also introduces a new scheme to use fragment and topological descriptors as natural inputs to the retrosynthetic prediction task. Wan et al. presents Retroformer[121], a novel structure based on Transformer. It does not rely on any chemoinformatics tools for molecular editing and jointly encodes molecular sequences and maps through localized attention. Fang et al. developed a substructure-level decoding model in which normally conserved portions of product molecules are automatically extracted using a fully data-driven approach[122]. Schwaller et al. combined molecular Transformer modeling and hyper-graph exploration strategies for predicting reactants as well as reagents[88], solvents, and catalysts for each retrosynthesis step. Schwaller et al. use an unsupervised, attention-based network of Transformer models to learn atom mappings[123]. This approach provides a link between rule-based and data-driven approaches and demonstrates enhanced chemical interpretability in the prediction results.

There are several limitations that lie in the string representation of molecular, which includes generating invalid SMILES strings and ignoring the characterization of chemical reactions. Ucak et al. introduced a new way to represent chemical reactions based on molecular fragments combining with template-free sequence-to-sequence models[124]. Zhang et al. combined molecular transformer models with data expansion and normalized preprocessing strategies[125], which improves the accuracy of forward prediction of chemical reactions, as well as single-step retrosynthesis prediction with and without reaction categories. Zhong et al. proposed Root-Aligned SMILES (R-SMILES)[126], which specifies

tightly aligned one-to-one mappings between product and reactant SMILES for more efficient prediction of synthesis.

Additionally, to improve the diversity of retrosynthesis prediction, Chen et al. proposed a model for making generalizable predictions of diverse retrosynthetic reactions[127]. Two novel pre-training methods are introduced to the Transformer framework. Additionally, a discrete latent variable model is added to the framework to encourage the model to produce diverse predictions. Toniato et al. develop a retrosynthesis model based on Transformer that increases the diversity of the predictions by prepending a classification token to the language representation of the target molecule[128]. Kim et al. developed connected two-way transformers with latent modeling using cycle consistency check[129], parameter sharing, and multinomial latent variables. The proposed model improves the accuracy, syntactic errors, and diversity of retrosynthesis. Irwin et al. proposed Chemformer[130], a Transformer-based model, and showed that self-supervised pre-training improves performance and significantly speeds up convergence for downstream tasks. At inference, the use of these prompt tokens has contribution to generate various kinds of disconnection strategies. To overcome low accuracy of predictions based on small chemical datasets, Bai et al. introduced transfer learning into retrosynthesis analysis[131], combining it with seq2seq or Transformer models for prediction and validation.

Recommendation of reaction conditions in retrosynthesis prediction is an important aspect. Andronov et al. proposed a molecular Transformer framework to tackle this issue[132].

### 7. 3 Reinforcement learning

Schreck et al. applied deep reinforcement learning to reaction path search task that identify strategies for making optimal reaction choices at each step of retrosynthesis programming based on user-defined cost metrics[133]. A neural network is trained to estimate the expected synthetic cost based on simulation experience. Wang et al. introduce a new Monte Carlo Tree Search (MCTS) variant that promotes a balance between exploration and exploitation across the synthesis space. Combining a value network trained from reinforcement learning and a solvent prediction neural network is superior in identifying shorter routes with greener solvents under the same search conditions.

### 7. 4 Graph neural networks

Graph neural networks (GNNs) are a type of deep learning model that can be used to process graph-structured data. Graphs are data structures that represent relationships between entities, such as molecules, proteins, or social networks. Undirected graphs, a kind of graph representation for molecule, with atoms as nodes and chemical bonds as edges, is inherently suitable for capturing chemical molecular structures.

Graph-enhanced Transformer model (GET), based on molecular sequence and graph information, which is significantly superior to the ordinary Transformer model in test accuracy, is proposed by Mao et al. In this framework[134], four different GET designs are developed that fuse SMILES representations with atomic embeddings learned by improved graphical neural networks (GNN). Sun et al. proposed a framework that unifies sequence-based and graph-based approaches into energy-based models (EBMs) with different energy functions[135], which establishes connections between models and reveals differences

between them. Furthermore, a new framework within the dual variables was introduced to promote consistency between forward and backward predictions. Tu et al. propose a Graph2SMILES model that combines the advantage of the Transformer model for text generation with the permutation invariance of the molecular map encoder, thereby reducing the need for input data augmentation[136]. Liu et al. propose a novel approach, RetroGNN[137], to estimate synthesizability. This process includes searching for routes using synthesis planning software for many random molecules and training a GNN with this information to predict the outcome of the synthesis planner given the target molecule. Sacha et al. proposed the Molecular Editing Diagram Attention Network (MEGAN)[138], an end-to-end encoder-decoder neural model. Representing reactions as a series of edits allows MEGAN to effectively explore the space for plausible chemical reactions. Thakkar et al. introduced a prompt describing the disconnection of molecular to overcome the training database biases in retrosynthesis recommendations[139]. The use of disconnection prompts empowers the chemist to have greater control over disconnection predictions, resulting in more diverse and creative recommendations. Wang et al. propose RetroExplainer[140], which formulates the retrosynthesis task as a molecular assembly process that contains several deep learning-guided reverse synthesis actions: multi-meaning and multi-scale graph Transformer model, structure-aware contrast learning, and dynamic adaptive multi-task learning. It outperforms state-of-the-art single-step inverse synthesis methods and has good interpretability. GNN-Retro[141], a method that combines GNN with the latest search algorithms, was proposed by Han et al. In this framework, the structure of GNN can incorporate the information of neighboring molecules, which will improve the estimation accuracy of our framework. Jiang et al. successfully improved the accuracy of the model by implementing atomic conservation rules through a molecular reconstruction pretraining task and reaction rules specifying reaction centers through a reaction type-guided comparison pretraining task[142]. Liu et al. proposed a framework for utilizing contextual information to improve retrosynthetic planning[143]. They view synthetic routes as reaction graphs and suggest integrating context through three steps: encoding molecules into embeddings, aggregating information on routes, and readout to predict reactants.

### 7. 5 Hybrid AI systems

Chemistry-informed search methods combine modern search algorithms with symbolic AI have been presented. 3N-MCTS was proposed by Segler et al. They combined MCTS with an expansion policy network that guides the search[144], and an “in-scope” filter network to pre-select the most promising retrosynthetic steps. Compared with traditional search methods based on extraction rules and hand-coded heuries, it runs 30 times faster and has good accuracy. AutoSynRoute is a template-free retrosynthetic model, proposed by Lin et al[145], which includes retrosynthesis prediction using a Transformer model and MCTS with heuristic scoring for route planning. Unlike template-based models, it can learn the global chemical environments of molecules, but inherits the shortcomings of SMILES-based models. Hong et al. proposed an experience-guided Monte Carlo tree search (EG-MCTS), in which knowledge is learned from synthesizing experiences instead of rollout[146]. SynRoute, proposed by Latendresse et al[147], uses a relatively small number of reaction templates as well as a literature-based reaction database to search practical synthetic routes to target compounds. For each reaction template, a machine learning classifier is trained to make

predictions. Chen et al. proposed an A* search with neural network-based models that represented reaction information as AND-OR trees (AND nodes for reactions, OR nodes for molecules), and the search was guided by a neural network that learned the synthesis cost of molecules from past retrosynthesis planning experiences[148]. Chematica[149,150], based on a high-quality chemical database of only 50,000 rules, utilizes penalization of nonselective reactions, strained intermediates, and unlikely structural motifs, as well as heuristic searches to guide navigation through the reaction network. Routines terminate upon identification of commercially available building blocks, saving time and cost by requiring fewer purification steps than reported methods. Introducing a bond preservation rule to circumvent reported methods enables the development of routines significantly different from patented alternatives. Additionally, Chematica has passed the Turing test.

Additionally, combining suitable ranking systems with AI methods can further improve the performance of retrosynthesis models. Lin et al. designed and trained an energy-based model to reorder product recommended[151], which can significantly improve the performance of models, such as RetroSim, a similarity-based approach, and NeuralSym, a deep learning approach. Li et al. proposed RetroRanker[152], a graphical neural network-based ranking model designed to mitigate frequency bias in the predictions of existing retrosynthesis models through reordering. RetroRanker incorporates the potential reaction changes of each set of predicted reactants when given products are obtained to reduce the rank of chemically implausible predictions. ASICS (Advanced System for Intelligent Chemical Synthesis)[153], proposed by Jeong et al. Based on pseudo-A* searches, ASICS generates optimal synthetic paths that minimize score of synthetic reaction value function, composed of the synthetic accessibility score, likelihood score, and similarity score. Additionally, it weighs the search in confirmed reaction spaces and unexplored reaction spaces.

**Table 3**

Overview of retrosynthesis prediction performance for template-free methods.

| Methods | Algorithm | Dataset | Features | TOP-1 | TOP-5 | TOP-1 | TOP-5 | source code availability |
|---|---|---|---|---|---|---|---|---|
| | | | | with reaction class | | without reaction class | | |
| Karpov Transformer | transformer | USPTO-50k | SMILES | - | - | 42.7 | 69.8 | Y |
| AutoSynRoute | transformer+MCTS | USPTO-50k | SMILES | 54.6 | 80.2 | 43.1 | 71.8 | Y |
| Bayesian-Retro(MT-predictable) | transformer+SMC | USPTO-50k | SMILES | 62.1 | 88.8 | 53.8 | 84.1 | N |
| Chemformer | transformer | USPTO-50k | SMILES | - | - | 54.3 | 62.3 | Y |
| tree-LSTM | LSTM | Pistachio +ASKC | fingerprint | - | - | 79.1 | 88.6 | N |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | OS | | | | | | |
| G2Retro | MPN | USPTO-50k | graph | 63.6 | 88.4 | 54.1 | 81.2 | Y |
| GTA | attention mechanism | USPTO-50k | SMILES | - | - | 51.1 | 74.8 | N |
| LV-transformer | transformer | USPTO-50k | SMILES | - | - | 40.5 | 72.8 | N |
| GTE | GNN+transformer | USPTO-full | graph | 76.6 | 89.6 | 44.9 | 62.4 | Y |
| MEGAN | GAN | USPTO-50k | graph | 60.7 | 87.5 | 48.1 | 78.4 | Y |
| Graph2SMILES | GNN | USPTO-full | graph | - | - | 52.9 | 70 | Y |
| SCROP | transformer | USPTO-50k | SIMLES | 59 | 78.1 | 43.7 | 65.2 | N |
| Retroformer | transformer | USPTO-50k | SMILES | 64 | 86.7 | 53.2 | 76.6 | Y |
| SMILES-grammar-based | transformer | USPTO-50k | SIMLES-like | 43.8 | 61.4 | 32.1 | 48.9 | N |
| T2T | attention mechanism | USPTO-50k | SMILES | - | - | 51 | 69 | Y |
| RetroTRAE | transformer | USPTO-full | ECFP | - | - | 58.3 | - | Y |
| Liu | seq2seq | USPTO-50k | SMILES | - | - | 37.4 | 57 | Y |
| Molecular Substructure | - | USPTO-50k | HSFP | 61.4 | 70.4 | 61.4 | 70.4 | Y |
| Fang | transformer | USPTO-full | SMILES | - | - | 50.4 | - | Y |
| AT | transformer | USPTO-50k | SMILES | - | - | 53.5 | 81 | Y |
| Substructure-based | seq2seq | USPTO-full | MACCS | - | - | 29 | - | Y |
| Dual-TF | GNN+seq2seq | USPTO-50k | graph+SMILES | 65.7 | 84.7 | 53.6 | 74.6 | N |
| seq2seq-transfer learning | transfer learning | USPTO-50k | SMILES | - | - | 60.7 | 83.5 | N |
| Two-way transformers | transformer | USPTO-50k | SMILES | - | - | 47.1 | 73.1 | Y |
| RetroExplainer | Graph Transformer | USPTO-50k | graph | 66.8 | 92.5 | 57.7 | 84.8 | Y |
| R-SMILES | transformer | USPTO-50k | SMILES | - | - | 56.3 | 86.2 | Y |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Zhang et al. | transformer | USPTO-50k | SMILES | 55 | 79 | 43 | 73 | N |
| Pre-training transformer | transformer | USPTO-50k | SMILES | 67.1 | 85.2 | 62 | 78.4 | N |

## 8. Semi-template-based models

Semi-template-based methods do not use reaction templates, or they do not directly transform a product into its reactants. Instead, semi-template-based methods follow a two-step workflow utilizing atom-mappings: (1) they first identify the reaction centers and transform the product into synthons (intermediate molecules) using the reaction centers; and then (2) they complete the synthons into the reactants.

G2Gs, was proposed by Shi et al[79], which first segment the target molecular map into a set of synthons by identifying reaction centers, and then translate the synthons into the final reactant maps through a variogram translation framework. The performance of G2Gs is better than two template-based methods, RetroSim[96] and Neuralsym[97]. Chen et al. developed a one-step retrosynthesis prediction framework, G2Retro.Its process consists of predicting the reactive centers in a target molecule, identifying the synthons to assemble the target, and then converting these synthons into reactants. G2Retro defines a comprehensive set of reactive center types and learns from the molecular maps of the products to predict potential reactive centers. Nicolaou et al. introduce a chemical context aware data-driven method based on DDRAM algorithm, to recommend synthetic routes matching a precedent-derived template[154]. Yan et al. proposed RetroXpert[155], which decomposes retrosynthesis into two steps: identification of potential reaction centers in the target molecular by graph neural networks and generation of intermediate synthetics; prediction of relevant reactants based on the obtained synthetics by a reactant generation model. Wang et al. proposed a single-step template-free and Transformer model-based approach called RetroPrime[156]. Its framework consists of decomposing a molecular into a synthon and then generating a reactant by attaching leaving groups, which was accomplished by a generalized Transformer model. Somnath et al. propose a graph-based approach that utilizes the idea that the graph topology of precursor molecules is essentially invariant during chemical reactions[157]. In the first step, the model predicts a set of graph edits that transform the target into a synthon. Then they are expanded into molecules. ReTReK, a data-driven and rule-based retrosynthesis model, is proposed by Ishida et al. They formlate four scores for synthesis route evalution. Additionally, Graph convolutional network (GCN) and MCTS are respectively used in data-driven framework of retrosynthesis prediction and path search[158]. Zhang et al. employ a chemistry-informed molecular graph (CIMG) as molecular representation[159], which defines NMR chemical shifts as vertex features, bond dissociation energies as edge features, and solvent/catalyst information as global features. For a given target, five graph neural network (GNN) models with MPNN layers are employed to choose reaction template leading to this product, infer reactant CIMG, select appropriate catalyst/solvent, and check the plausibility of the proposed reaction. Finally, MCTS is adopted to generate synthesis route pathway. Lin et al. proposed a graph-to-graph transformation model, G2GT[160], in which the graph encoder and graph decoder are built on the standard Transformer model structure

with data augmentation. Additionally, a weak ensemble approach that combine beam search, kernel, and top-k sampling methods was developed to enhance diversity. Zhong et al. propose the end-to-end framework, Graph2Edits[161], based on a graphical neural network to predict the edits of a product graph in an auto-regressive manner and generate the transformation intermediates and final reactants sequentially, which combines the two-stage process of the semi-template-based approach into one-pot learning.

**Table 4**

**Overview of retrosynthesis prediction performance for semi-template-based methods.**

| Methods | Algorithm | dataset | features | TOP-1 | TOP-5 | TOP-1 | TOP-5 | source code availability |
|---|---|---|---|---|---|---|---|---|
| | | | | with reaction class | | without reaction class | | |
| G2Gs | GCN | USPTO-50k | graph | 61 | 86 | 48.9 | 72.5 | N |
| ReTReK | GCN+MCTS | Reaxys | SMILES | - | - | 36.1 | - | Y |
| G2GT | GNN+transformer | USPTO-50k | graph | - | - | 54.1 | 74.5 | N |
| GraphRetro | MPN | USPTO-50k | graph | 63.9 | 85.2 | 53.7 | 72.2 | Y |
| RetroPrime | transformer | USPTO-50k | SMILES | 64.8 | 81.6 | 51.4 | 74 | Y |
| Graph2Edits | GNN | USPTO-50k | graph | 67.1 | 91.5 | 55.1 | 83.4 | Y |
| RetroXpert | GNN | USPTO-50k | graph | 62.1 | 75.8 | 50.4 | 62.3 | N |

## 9. Comparison of three categorizations

Top-k accuracy is a commonly used metric for evaluating single-step retrosynthesis models. However, drawing conclusions about the performance of models based solely on top-1 accuracy can be misleading because there can be multiple viable pathways in organic synthesis. Therefore, this paper jointly evaluates three different types of models using both top-1 and top-5 accuracy.

As depicted in **Fig. 9**, for cases involving reaction class, template-based models and semi-template-based models exhibit higher average accuracy. For cases where the reaction class is unknown, template-based models and semi-template-based models maintain relatively high average accuracy. Additionally, examining the data distribution reveals that template-based models and semi-template-based models have more tightly clustered distributions, indicating greater stability in these approaches. In contrast, template-free models consistently maintain high dispersion and lower stability.

In summary, template-based models consistently demonstrate high accuracy and stability. Semi-template-based models, as a relatively recent approach, also perform well and show potential to become the top-performing method. However, template-free methods

exhibit significant polarization, which highlights the critical importance of selecting appropriate AI models and optimal hyperparameters to address retrosynthesis tasks. Despite the substantial progress made in recent years, AI-assisted retrosynthesis methods still face some unresolved challenges.

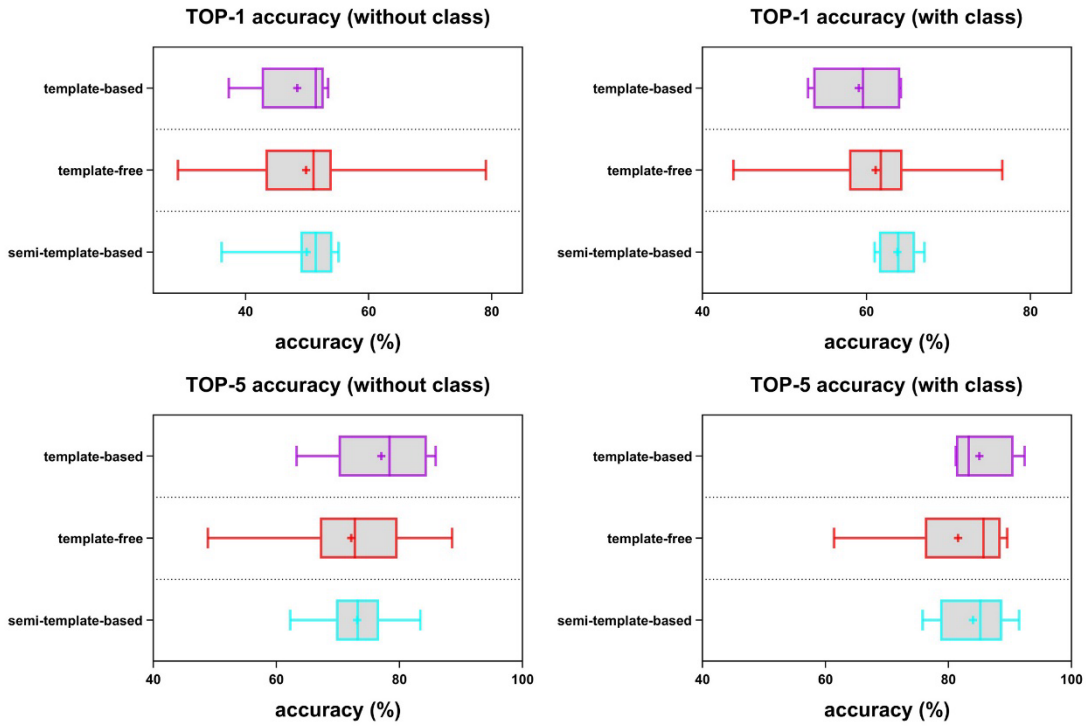


**Fig. 9 TOP-k accuracy for template-based, template-free, and semi-template-based methods.**

## 10. Challenges and future directions for retrosynthesis prediction researchers

The past several years has witnessed the rapid development of retrosynthesis models with modern intelligent algorithms However, certain challenges and limitations should be overcome.

First, insufficient high-quality data is one of the greatest challenges in utilizing AI-based methods to predict reaction route. Developing a high-performance AI model requires both quantity and quality of training data. Nevertheless, the available options for public datasets are quite limited, and their quality is inferior compared to commercial databases. Collaboration for preparing big data presents many opportunities and challenges for computational chemists. Moreover, diversity and variability of dataset can promote prediction performance. Researchers should make efforts to construct diverse dataset that covers a wide variety of data, such as stereochemistry information, solvents, and catalysts. The creation of a big and diverse chemical reaction database encompassing a wide range of data resources necessitates the development of methods to standardize, manage, and integrate various sources of reaction data.

Second, purely data-driven models often lack interpretability, posing difficulties for researchers in understanding the rationale behind predictions made by models, which is

another challenging problem. Striking a balance between mechanistic interpretability and predictivity is essential. The incorporation of model-agnostic techniques for interpretability, such as LIME[162–164], SHAP[162], and Anchors[165], can significantly contribute to the analysis of model interpretability. These methods enable both global and local explanations while pinpointing crucial features that the model relies on for predictions. Additionally, the use of explainable neural networks[166,167] should be encouraged, as they integrate interpretable layers that emphasize significant features through attention and gating mechanisms.

Third, template-free models trained on text sequences can neglect important chemical meaning behind bond disconnection, which sometimes leads to infeasible suggestions. Method to improve interpretability can be a potential solution to this challenge. Meanwhile, template-free retrosynthetic methods might be biased because rare reactions are underrepresented in dataset. In general, AI-assisted models are more likely to learn from the more frequently occurring bond disconnection rules in the dataset and neglect other bond disconnection possibilities that are rare but may lead to simpler reaction pathways. To reduce model construction bias, a potential future direction is to combine a data-driven approach with fundamental principles.

Finally, for any in silico design process, suggested synthesis routes should be validated experimentally. High-throughput and parallelized experimentation are commonly used for rapid data generation and experimental validation. However, the absence of experimental conditions in most retrosynthesis prediction models imposes further constraints on experimental planning. Latest advance in automated design of experiments (DoE) includes utilization of AI algorithms to optimize and identify feasible reaction conditions[168,169].

Based on the analysis above, there are some promising future directions for retrosynthesis prediction researchers:

1. The construction of high-quality chemical reaction datasets and developing intelligent and adaptive algorithms to deal with incomplete and inaccurate data are cornerstone of all AI-based models.
2. The analysis of model interpretability and visualization might be a hot research direction. Combining DoE with robotic experimental instruments is also an irreplaceable step.
3. It is recommended to develop more complex and comprehensive reaction rules and models to cover a wider range of chemical reaction types and conditions.
4. The combination of artificial intelligence algorithms and traditional rules should be explored.
5. More attention should be paid to acquire more efficient and environmentally friendly chemical synthesis condition in retrosynthesis prediction.

## 11. Conclusion

CASP studies have a significant impact on drug design, which can increase the speed and decrease the cost of drug synthesis. Modern intelligent algorithms have the potential to improve the efficiency and accuracy of CASP. Future research should focus on developing more robust and interpretable retrosynthesis models and extracting higher quality chemical reaction datasets from patents and literature. Interpretable analysis of AI can improve the

transparency and reliability of predictions based on AI models. The performance of data-oriented methods largely depends on the quality of reaction databases. Therefore, a high quality of dataset is indispensable. In the future, interdisciplinary collaborations between computer scientists, statisticians, organic chemists, and computational chemists will become increasingly important as they bring together different perspectives and expertise to solve organic retrosynthesis tasks. AI-assisted synthetic planning research is currently immature and further research is needed to assess its potential significance. Due to the discrepancy in training datasets, even when using identical evaluation metrics, direct comparisons of artificial intelligence model performances may not be feasible. In most cases, no model emerges as the optimal performer across all tasks.

In this review, we provide a thorough overview of the latest advancements in Computer-Assisted Structure Planning (CASP) research driven by modern intelligent algorithms. These models can be broadly categorized into three groups: template-based models, template-free models, and semi-template-based models. We present a comparative analysis of these three classes of models and concluded that semi-template-based models generally have better performances. Furthermore, we delineate the critical challenges faced in the current landscape and highlight the future direction of CASP. The recent studies in these investigations demonstrate the significant potential of artificial intelligence algorithms in retrosynthetic prediction, which can mitigate the time and cost burdens on organic chemists in synthesis planning. Finally, after reading this review, we hope that scientists working in the field of AI-assisted retrosynthesis prediction can select appropriate approaches that aligns with their research strengths. Based on the preliminary work summarized in these three classes, researchers can derive inspiration for future improvements and research directions. As retrosynthesis techniques mature, we may witness their integration into automated chemical synthesis system[170], which can improve automated chemical compounds manufacture and bring tremendous social and technological impact.

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