Abstract

Recently, template-based (TB) and template-free (TF) molecule graph learning methods have shown promising results to retrosynthesis. TB methods are more accurate using pre-encoded reaction templates, and TF methods are more scalable by decomposing retrosynthesis into subproblems, i.e., center identification and synthon completion. To combine both advantages of TB and TF, we suggest breaking a full-template into several semi-templates and embedding them into the two-step TF framework. Since many semi-templates are reduplicative, the template redundancy can be reduced while the essential chemical knowledge is still preserved to facilitate synthon completion. We call our method SemiRetro, introduce a new GNN layer (DR-GAT) to enhance center identification, and propose a novel self-correcting module to improve semi-template classification. Experimental results show that SemiRetro significantly outperforms both existing TB and TF methods. In scalability, SemiRetro covers 98.9% data using 150 semi-templates, while previous template-based GLN requires 11,647 templates to cover 93.3% data. In top-1 accuracy, SemiRetro exceeds template-free G2G 4.8% (class known) and 6.0% (class unknown). Besides, SemiRetro has better training efficiency than existing methods.

1. Introduction

Retrosynthesis prediction (Corey & Wipke, 1969; Corey, 1991) plays a crucial role in synthesis planning and drug discovery, which aims to infer possible reactants for synthesizing a target molecule. This problem is quite challenging due to the vast search space, multiple theoretically correct synthetic paths, and incomplete understanding of the reaction mechanism, thus requiring considerable expertise and experience. Fortunately, with the rapid accumulation of chemical data, machine learning is promising to solve this problem (Coley et al., 2018; Segler et al., 2018). In this paper, we focus on the single-step version: predicting the reactants of a chemical reaction from the given product.

Common deep-learning-based retrosynthesis works can be divided into template-based (TB) (Coley et al., 2017b; Segler & Waller, 2017; Dai et al., 2019; Chen & Jung, 2021) and template-free (TF) (Liu et al., 2017; Karpov et al., 2019; Sacha et al., 2021) methods. Generally, TB methods achieve high accuracy by leveraging reaction templates, which encode the molecular changes during the reaction. However, the usage of templates brings some shortcomings, such as high computation cost and incomplete rule coverage, limiting the scalability. To improve the scalability, a class of chemically inspired TF methods (Shi et al., 2020; Yan et al., 2020) (see Fig. 1) have achieved dramatical success, which decompose retrosynthesis into subproblems: i) center identification and ii) synthon completion. Center identification increases the model scalability by breaking down the target molecule into virtual synthons without utilizing templates. Synthon completion simplifies reactant generation by taking synthons as potential starting molecules, i.e., predicting residual molecules and attaching them to synthons to get reactants. Although various TF methods have been proposed, the top-k retrosynthesis accuracy remains poor. Can we find a more accurate way to predict potential reactants while keeping the scalability?

To address the aforementioned problem, we suggest combining the advantages of TB and TF approaches and propose a novel framework, namely SemiRetro. Specifically, we break a full-template into several simpler semi-templates and embed them into the two-step TF framework. As many semi-templates are reduplicative, the template redundancy can be reduced while the essential chemical knowledge is still preserved to facilitate synthon completion. And we propose a novel self-correcting module to improve the semi-template classification. Moreover, we introduce a directed relational graph attention (DRGAT) layer to extract more expressive molecular features to improve center identification accuracy. Finally, we combine the center identification and synthon completion modules in a unified framework to accomplish retrosynthesis predictions.

We evaluate the effectiveness of SemiRetro on the benchmark data set USPTO-50k, and compare it with recent state-of-the-art TB and TF methods. We show that SemiRetro
significantly outperforms these methods. In scalability, SemiRetro covers 98.9% of data using 150 semi-templates, while previous template-based GLN requires 11,647 templates to cover 93.3% of data. In top-1 accuracy, SemiRetro exceeds template-free G2G 4.8% (class known) and 6.0% (class unknown). Owing to the semi-template, SemiRetro is more interpretable than template-free G2G and RetroXpert in synthon completion. Moreover, SemiRetro trains at least 6 times faster than G2G, RetroXpert, and GLN. All these results show that the proposed SemiRetro boosts the scalability and accuracy of deep retrosynthesis prediction.

2. Related work

Template-based models TB methods infer reactants from the product through shared chemical transformation patterns, namely reaction templates. These templates are either hand-crafted by human experts (Hartenfeller et al., 2011; Szymkuć et al., 2016) or automatically extracted by algorithms (Coley et al., 2017a; Law et al., 2009). For a product molecule, due to the vast search space, multiple qualified templates, and non-unique matching sites for each template, it is challenging to select and apply the proper template to generate chemically feasible reactants. To handle those challenges, (Coley et al., 2017b) suggests sharing the same templates among similar products. (Segler & Waller, 2017; Baylon et al., 2019) employ neural models for template selection with molecule fingerprint as input. GLN (Dai et al., 2019) learns the joint distribution of templates and products by decomposing templates into pre-reaction and post-reaction parts and introducing logic variables to apply structure constraints. And LocalRetro (Chen & Jung, 2021) simplifies the template by removing its background, i.e., structures that do not change during the reaction. TB methods are interpretable and accurate because they embed rich chemical knowledge into the algorithm. However, these methods do not consider the partial template based on the synthons (introduced latter), and the vast space of templates and incomplete coverage severely limit their scalability.

Template-free models Instead of explicitly using templates, TF approaches learn chemical transformations by the model. (Liu et al., 2017; Karpov et al., 2019) solve the retrosynthesis problem with seq2seq models, e.g. Transformer (Vaswani et al., 2017), LSTM (Hochreiter & Schmidhuber, 1997), based on the SMILES representation of molecules. Despite the convenience of modeling, SMILES cannot fully utilize the inherent chemical structures and may generate invalid SMILES strings. Therefore, (Zheng et al., 2019) propose a self-correct transformer to fix the syntax errors of candidate reactants. Recently, G2G (Shi et al., 2020), RetroXpert (Yan et al., 2020) and GraphRetro (Sommath et al., 2021) achieve state-of-the-art performance by decomposing the retrosynthesis into two sub-problems: i) center identification and ii) synthon completion, as shown in Fig. 1. Center identification increases the model scalability by breaking down the target molecule into virtual synthons without utilizing templates. Synthon completion simplifies the complexity of reactant generation by taking synthons as potential starting molecules. For example, RetroXpert and G2G treat it as a SMILES or graph sequence translation problem from synthon to reactant. GraphRetro completes synthons by predicting pre-defined leaving groups, but it does not provide scalable algorithm for attaching leaving groups and can not handle the case of molecule property changes, e.g., there is no residual from N to N⁻. Generally, these TF methods are more scalable but perform worse than TB approaches in top-1 accuracy.

Challenges Although the two-step TF framework significantly improves the algorithm’s scalability, the overall accuracy is relatively low. A possible solution to this issue is to enhance submodules, i.e., center identification and synthon completion. 1) The current GNN models perform well in top-1 accuracy for center identification, but top-k accuracy remains unsatisfactory. How to develop a more suitable model that provides high top-k accuracy is the first challenge. 2) In addition, synthon completion is the major bottleneck affecting the overall accuracy. Specifically, predicting and attaching residuals for each synthon are difficult because the residual structures could be complex, attaching residuals into synthons may violate chemical rules, and various residuals may agree with the same synthon (e.g., F, Cl, Br, and I have similar chemical properties). For researchers, scalability, interpretability, and training efficiency are also important. How to develop a more accurate, interpretable, and efficient synthon completion model while maintaining the scalability is the second challenge.

3. Definition and Overview

Molecule representation There are two types of dominant representations, i.e., SMILES string (Weininger, 1988) and molecular graph. SMILES is commonly used in early works (Liu et al., 2017; Schwaller et al., 2018; Zheng et al., 2019; Schwaller et al., 2019; Tetko et al., 2020) due to its simplicity. Many NLP models can be directly applied to solve related problems in an end-to-end fashion. However, these models cannot guarantee the chemical correctness of the output molecules because they ignore structure information to some extent. Similar to recent breakthroughs (Dai et al., 2019; Shi et al., 2020; Yan et al., 2020; Somnath et al., 2021), we take the molecule as a labeled graph $G(A, X, E)$, where $A$, $X$ and $E$ are adjacency matrix, atom features and bond features, seeing Table. 1. Under the graph framework, we can effectively apply chemical constraints to ensure the validity of output molecules, which is more controllable and interpretable than SMILES-based approaches.
SemiRetro: Semi-template framework boosts deep retrosynthesis prediction

Figure 1. Overview of SemiRetro. We decompose retrosynthesis into two steps: center identification and synthon completion. In step 1, we use DRGAT to extract molecule features for predicting reaction centers. By breaking product bonds in these centers, synthons can be obtained. In step 2, we use another DRGAT model to predict the semi-template for each synthon. The final reactants can be deduced from reaction centers, synthons, and semi-templates by using the residual attachment algorithm.

Table 1. Commonly used symbols

| Symbol | Description |
|--------|-------------|
| $G(A, X, E)$ | Molecular graph with adjacency matrix $A \in \{0, 1\}^{n\times n}$, atom features $X \in \mathbb{R}^{n \times d}$ and bond features $E \in \mathbb{R}^{m \times b}$. |
| $x_i$ | The feature vector of atom $i$. dim $x_i = d$. |
| $e_{i,j}$ | The feature vector of bond $(i, j)$. dim $e_{i,j} = b$. |
| $R_i, S_j, P$ | The $i$-th reactant, the $j$-th synthon and the product. |
| $c_i$ | $c_i \in \{0, 1\}$, indicating whether atom $i$ is the reaction center or not. |
| $c_{i,j}$ | $c_{i,j} \in \{0, 1\}$, indicating whether bond $(i, j)$ is the reaction center or not. |

Problem definition Retrosynthesis aims to infer the set of reactants $\{R_i\}_{i=1}^N$ that can generate the product $P$. Formally, that is to learn a mapping function $F_0$:

$$F_0 : P \rightarrow \{R_i\}_{i=1}^N.$$  (1)

Considering the unknown by-products, the law of conservation of atoms no longer holds here, which makes the problem quite challenging because the algorithm needs to generate new atoms and bonds to get potential reactants.

Overview As shown in Fig. 1, we adopt the two-step TF framework due to its scalability and effectiveness. Our method is distinguished from previous works in two folds: 1) We propose a relational graph attention (DRGAT) layer to improve the center identification performance; 2) We use semi-templates and a self-correcting module to facilitate synthon completion, which significantly reduces the problem complexity.

4. Methodology

4.1. Center identification

Center identification plays a vital role in the two-step retrosynthesis because errors caused by this step directly lead to the final failures. Previous works have limitations, e.g., RetroXpert (Yan et al., 2020) provides incomplete prediction without considering atom centers, G2G may leak the edge direction information (Shi et al., 2020), and GraphRetro (Somnath et al., 2021) provides sub-optimum top-$k$ accuracy. How to obtain comprehensive and accurate center identification results is still worth exploring.
**Reaction centers** We consider both atom centers and bond centers in the product molecule. As shown in Fig. 3, from the product to its corresponding reactants, either some atoms add residuals by dehydrogenation without breaking the product structure (case 1), or some bonds are broken to allow new residues to attach (case 2). Both these atoms and bonds are called reaction centers.

**Directed relational GAT** Commonly used graph neural networks (Defferrard et al., 2016; Kipf & Welling, 2016; Veličković et al., 2017) mainly focus on 0 and 1 edges, ignoring all layers to form the final node representation. We add shortcut connections from the input to the output in each layer and concatenate hidden representations of all layers to form the final node representation.

**Labeling and learning reaction centers** We use the same labeling algorithm as G2G to identify ground truth reaction centers, where the core idea is comparing each pair of atoms in the product \( P \) with that in a reactant \( R_i \). We denote the atom center as \( c_i \in \{0, 1\} \) and bond center as \( e_{i,j} \in \{0, 1\} \) in the product \( P \). During the learning process, atoms features \( \{h_i\}_{i=1}^{|P|} \) are learned from the product \( P \) by applying stacked DRGAT, and the input bond features are \( \{e_{i,j}\}_{i,j=1}^{|P|} \). Then, we get the representations of atom \( i \) and bond \( (i, j) \) as

\[
\begin{align*}
\hat{h}_i &= \text{Mean}(\{h_s\}_{s=1}^{|P|}), \quad \text{atom} \\
\hat{h}_{i,j} &= \text{Mean}(\{h_s\}_{s=1}^{|P|}), \quad \text{bond}
\end{align*}
\]

(2)

where Mean and \(|\cdot|\) indicate the average pooling and concatenation operations. Further, we predict the atom center probability \( p_i \) and bond center probability \( p_{i,j} \) via MLPs:

\[
p_i = \text{MLP}_0(\hat{h}_i) \quad \text{and} \quad p_{i,j} = \text{MLP}_7(\hat{h}_{i,j}).
\]

(3)

Finally, center identification can be reduced to a binary classification, whose loss function is:

\[
\begin{align*}
\mathcal{L}_1 = \sum_i c_i \log p_i + (1 - c_i) \log p_i + \quad \text{atom} \\
\sum_{i,j} c_{i,j} \log p_{i,j} + (1 - c_{i,j}) \log p_{i,j}. \quad \text{bond}
\end{align*}
\]

(4)

In summary, we propose a directed relational graph attention (DRGAT) layer to learn expressive atom and bond features for accurate center identification prediction. We consider both atom center and bond center to provide comprehensive results. In section 5.2, we show that our method can achieve state-of-the-art accuracy.
4.2. Synthon completion

Synthon completion is the main bottleneck of two-step TF retrosynthesis, which is responsible for predicting and attaching residuals for each synthon. This task is challenging because the residual structures could be complex to predict, attaching residuals into synthons may violate chemical rules, and various residuals may agree with the same synthon. Because of these complexities, previous synthon completion approaches are usually inaccurate and cumbersome. Introducing the necessary chemical knowledge to improve interpretability and accuracy can be a promising solution. However, how to provide attractive scalability and training efficiency is a new challenge.

**Semi-templates** The semi-template used in this paper is the partial reaction pattern of each synthon, seeing Fig. 4, rather than the whole reaction pattern used in GLN (Dai et al., 2019) and LocalRetro (Chen & Jung, 2021). Different from GraphRetro (Somnath et al., 2021), our semi-template encodes the chemical transformation instead of residuals. Similar to the work of forward reaction prediction (Segler & Waller, 2016), semi-template splits a binary reaction into two half reactions. Notably, we use dummy atom * to represent possible synthon atoms that match the semi-template, significantly reducing redundancy. We extract semi-template from each synthon-reactant pair by removing reactant atoms that have exact matches in the synthon. There are two interesting observations: 1) Top-150 semi-templates cover 98.9% samples; 2) Reactants can be deterministically generated from semi-templates and synthons (introduced later). Based on these observations, synthon completion can be further simplified as a classification problem. In other words, we need to predict the semi-template type for each synthon, and the total number of classes is 150+1. The first 150 classes are top-150 semi-templates, and the 151st class indicates uncovered classes.

**Learning semi-templates** For each synthon $S_j$, denote its semi-template label as $t_j, 1 \leq t_j \leq 151$, and the predicted reaction atom set as $C$. Assume that $\hat{S}_j$ is the dual synthon of $S_j$, i.e., $\bar{S}_j$ and $\hat{S}_j$ come from the same product $P$. We use stacked DRGATs to extract atom features $\{\hat{h}_i\}_i \in \hat{S}_j, \{\bar{h}_i\}_i \in \bar{S}_j$ and $\{\bar{h}_i\}_i \in \bar{S}_j$. The semi-template representation of $S_j$ is:

\[
\hat{h}_j = \text{Mean}(\{\hat{h}_i\}_i \in \hat{S}_j) || \text{Mean}(\{\bar{h}_i\}_i \in \bar{S}_j) || \text{Mean}(\{\bar{h}_i\}_i \in \bar{S}_j).
\]

Based on $\hat{h}_j$, we predict semi-template $\hat{t}_j$ as:

\[
\hat{t}_j = \arg \max_{1 \leq c \leq 151} \hat{p}_{j,c} = \text{Softmax}(\text{MLP}_8(\hat{h}_j)).
\]

Denote $\mathbb{I}_{\{c\}}(\cdot)$ as the indicator function, the cross-entropy loss used for training is:

\[
\mathcal{L}_2 = - \sum_{j \in \{1, 2, \ldots, |S_j|\}} \sum_{1 \leq c \leq 151} \mathbb{I}_{\{c\}}(t_j) \log(\hat{p}_{j,c}).
\]

**Correcting semi-templates** Considering the pairwise nature of synthons, i.e., dual synthons may contain complementary information that can correct each other’s prediction, we propose a self-correcting module to refine the joint prediction results. For $S_j$, we construct its features as:

\[
z_j = \hat{h}_j || \Phi_\theta(\hat{t}_j)
\]

where $\Phi_\theta(\hat{t}_j)$ is the learnable embedding of previous predicted class $\hat{t}_j$. Then, we use a multi-layer transformer to capture the interactions between $z_j$ and $\hat{z}_j$, and get the refined prediction $t'_j$:

\[
[z_j, \hat{z}_j] = \text{Transformer}([z_j, \hat{z}_j])
\]

\[
p_j = \text{Softmax}(\text{MLP}_8(z_j))
\]

\[
t'_j = \arg \max_{1 \leq c \leq 151} p_{j,c}
\]
The correcting loss function is:

$$L_3 = - \sum_{j \in \{1, \ldots, |S_j|\}} \sum_{1 \leq c \leq 151} \mathbb{1}_{\{c\}}(t_j) \log(p_{j,c}). \quad (11)$$

In addition, we filter the predicted pairs based on the prior distribution of the training set. If the prior probability of the predicted pair is zero, we discard the prediction.

**Applying semi-templates** Once reaction centers, synthons, and corresponding semi-templates are known, we can deduce reactants with almost 100% accuracy. This is not a theoretical claim; We provide a practical residual attachment algorithm in the appendix.

In summary, we suggest using the semi-templates to improve synthon completion performance with the help of an error mechanism. Firstly, reducing this complex task to a classification problem helps promote training efficiency and accuracy. Secondly, the high coverage of semi-templates significantly enhanced the scalability of TB methods. Thirdly, the deterministic residual attachment algorithm improves interpretability. Fourthly, the proposed self-correcting module can further improve the prediction accuracy. In section 5.3, we will show the effectiveness of the proposed method.

## 5. Experiments

As mentioned earlier, the main contributions of this paper are proposing a DRGAT layer for central identification and suggesting to use a self-correcting semi-template prediction method for synthon completion. The effectiveness of the proposed method is evaluated by systematic experiments, which focus on answering these questions:

- **Q1**: For center identification, how much performance gain can be obtained from DRGAT? Where the improvement comes from?
- **Q2**: For synthon completion, can semi-templates reduce template redundancy and improve the synthon completion performance? And how much improvement can be got from the self-correcting mechanism?
- **Q3**: For retrosynthesis, how do we integrate center identification and synthon completion models into a unified retrosynthesis framework? Can SemiRetro outperform existing template-based and template-free methods?

### 5.1. Basic setting

**Data** We evaluate SemiRetro on the widely used benchmark dataset USPTO-50k (Schneider et al., 2016) to show its effectiveness. USPTO-50k contains 50k atom-mapped reactions with 10 reaction types. Following (Dai et al., 2019; Shi et al., 2020; Yan et al., 2020), the training/validation/test splits is 8:1:1. To avoid the information leakage issue (Yan et al., 2020; Somnath et al., 2021), we use canonical SMILES as the original input for both training and testing.

**Baselines** Template-based GLN (Dai et al., 2019), template-free G2G (Shi et al., 2020) and RetroXpert (Yan et al., 2020) are primary baselines, which not only achieve state-of-the-art performance, but also provide open-source PyTorch code that allows us to verify their effectiveness. To show broad superiority, we also compare SemiRetro with other baselines, including RetroSim (Coley et al., 2017b), NeuralSym (Segler & Waller, 2017), SCROP (Zheng et al., 2019), LV-Transformer (Chen et al., 2019), GraphRetro (Somnath et al., 2021), MEGAN (Sacha et al., 2021), MHNreact (Seidl et al., 2021), and Dual model (Sun et al., 2020). As the retrosynthesis task is quite complex, subtle implementation differences or mistakes may cause critical performance fluctuations. We prefer comparing SemiRetro with open-source methods whose results are more reliable.

**Metrics** This paper uses consistent metrics derived from previous literature for both submodule and overall performance. 1. **Center identification**: We report the accuracy of breaking input product into synthons. 2. **Synthon completion**: We present the accuracy of predicting semi-templates from ground truth input synthons. When a product has multiple synthons, the final prediction is correct if and only if all synthons’ predicted semi-templates are correct. 3. **Retrosynthesis**: The metric is similar to that of synthon completion, except that the input synthons are also predicted by center identification. In other words, the retrosynthesis is correct if and only if both center identification and synthon completion are correct. Since there may be multiple valid routes for synthesizing a product, we report top-k accuracy.

**Implementation details** Thanks to the elegant implementation of G2G (Shi et al., 2020), we can develop our SemiRetro in a unified PyTorch framework (Paszke et al., 2019), namely TorchDrug. We use the open-source cheminformatics software RDKit (Landrum, 2016) to preprocess molecules and SMILES strings. The graph feature extractor consists of 6 stacked DRGAT, with the embedding size 256 for each layer. We train the proposed models for 30 and 50 epochs in center identification and synthon completion with batch size 128 on a single NVIDIA V100 GPU, using the Adam optimizer and OneCycleLR scheduler. We run all experiments three times and report the means of their performance in default. The training costs, atom features, and bond features can be found in the appendix.

### 5.2. Center identification (Q1)

**A. Objective and setting** This experiment studies how much center identification performance gain can be obtained from the proposed DRGAT. Compared to previous works, we use DRGAT to extract graph feature. We trained our model up to 30 epochs, which occupied about 4680 MB of GPU memory, where the batch size is 128, and the learning rate is 1e-3. We point out that we use canonical smiles
as inputs and consider both atom center and bond center. In contrast, RetroXpert just considers the bond center and G2G may leak the atomic order information of the non-canonical smiles. For fair and meaningful comparison, we calculate the performance improvement relative to GraphRetro.

|                | known          | unknown        |               |               |
|----------------|----------------|----------------|---------------|---------------|
|                | top-1 | top-2 | top-3 | top-5 | top-1 | top-2 | top-3 | top-5 |
| G2G            | 90.2  | 94.5  | 94.9  | 95.0  |  75.8  | 83.9  | 85.3  | 85.6  |
| RetroXpert     | 86.0  | –     | –     | –     |  64.9  | –     | –     | –     |
| GraphRetro     | 84.6  | 92.2  | 93.7  | 94.5  |  70.8  | 85.1  | 89.5  | 92.7  |
| SemiRetro      | 86.6  | 96.7  | 98.7  | 99.6  |  69.8  | 87.5  | 93.3  | 97.9  |
| **Improvement**| ++2.0 | ++4.5 | ++5.0 | ++5.1 | ++2.4 | +3.8  | +5.2  |        |

Table 2. Top-k center identification accuracy when the reaction class is known or unknown. The best and sub-optimum results are highlighted in bold and underline.

**A. Results and analysis**

1) **Highest accuracy**: As shown in Table 2, SemiRetro outperforms baselines in most cases with different k. 2) **Better potential**: Since the possible synthesis routes toward a product may be multiple, the top-k accuracy (k > 1) is important, and the performance gain of SemiRetro rises as k increases, indicating the better potential. In particular, SemiRetro achieves nearly perfect top-5 accuracy on the setting of reaction class known (acc = 99.6%) and unknown (acc = 97.9%). 3) **Attractive efficiency** The proposed model can achieve good performance after training 30 epochs, where each epoch can be finished within 1 minute, see Table 8 in the appendix.

**B. Objective and setting** This experiment studies *where the improvement comes from*. Firstly, we compare the DRGAT with well-tuned, off-the-shelf GNNs to show its superiority. Second, we do ablation studies to reveal the really important modules. All models are trained to the 100 epoches to ensure that the different models have converged, both of which have 6 layers GNN and embedding size 256. We present the results here when class is known, and more results can be found in the appendix.

|                | top-1 | top-2 | top-3 | top-5 |
|----------------|-------|-------|-------|-------|
| GCN            | 82.8  | 94.6  | 97.5  | 99.3  |
| GAT            | 75.7  | 88.7  | 92.9  | 96.6  |
| ChebNet        | 75.0  | 90.5  | 95.3  | 98.3  |
| GIN            | 77.0  | 90.8  | 95.2  | 98.3  |
| RGCN           | 85.4  | 95.9  | 98.2  | 99.5  |
| **DRGAT**      | **86.6** | **96.7** | **98.7** | **99.6** |
| w/o attention  | 86.2  | 96.0  | 98.3  | 99.4  |
| w/o directed embedding | 86.1 | 96.3 | 98.4 | 99.5 |
| w/o edge features | 85.2 | 95.6 | 98.1 | 99.4 |

Table 3. Ablation study of center identification, class known.

**B. Results and analysis**

1) **Superiority**: From Table 3, we observe that DRGAT provides better top-k accuracy than existing well-tuned GNNs. 2) **Ablation**: Both the attention mechanism, the directed embedding, and the usage of edge features bring performance gain.

5.3. Synthon completion (Q2)

**A. Objective and setting** This section reveals *the effectiveness of using semi-template* in three folds: 1) reducing the template redundancy, 2) providing good accuracy, and 3) promoting scalability and training efficiency. Firstly, we count the full-templates of GLN and semi-templates introduced in this paper. We visualize the distribution and coverage of top-k templates for analyzing the redundancy. Secondly, we present the accuracy of synthon completion with ground truth synthon inputs. The final reactants are obtained by predicting the semi-templates and applying the residual attachment algorithm. Thirdly, we compare the scalability and training efficiency of different methods in short. We trained our model up to 50 epochs, which occupied about 4108 MB of GPU memory, where the batch size is 128 and the learning rate is 1e-4.

![Figure 5. SemiRetro reduces the template redundancy.](image)

|                | top-1 | top-2 | top-3 | top-5 |
|----------------|-------|-------|-------|-------|
| G2G            | 66.8  | –     | 87.2  | 91.5  |
| GraphRetro     | **77.4** | **89.6** | **94.2** | **97.6** |
| SemiRetro      | 74.7  | 88.9  | 93.6  | 96.3  |
| G2G            | 61.1  | –     | 81.3  | 86.7  |
| GraphRetro     | **75.6** | **87.7** | **92.9** | **96.3** |
| SemiRetro      | 73.1  | 87.6  | 92.6  | 96.0  |

Table 5. Top-k synthon completion accuracy.
### Table 4. Overall performance. The best and sub-optimum results are highlighted in bold and underline. We show the performance gains relative to the important baselines, i.e., template-based GLN and template-free G2G.

| Method                  | Reaction class known | Reaction class unknown |
|-------------------------|----------------------|------------------------|
|                         | top-1    | top-2    | top-3    | top-5    | top-1    | top-2    | top-3    | top-5    |
| GLN (Dai et al., 2019)  | 64.2     | 79.1     | 85.2     | 90.0     | 52.5     | 69.0     | 75.6     | 83.7     |
| G2G (Shi et al., 2020) | 61.0     | 81.3     | 86.0     | 88.7     | 48.9     | 67.6     | 72.5     | 75.5     |
| Dual (Sun et al., 2020) | 65.7     | 81.9     | 84.7     | 85.9     | 53.6     | 70.7     | 74.6     | 77.0     |
| SemiRetro               | **65.8** | **85.7** | **89.8** | **92.8** | **54.9** | **75.3** | **80.4** | **84.1** |
| Improvement to GLN      | +1.6     | +4.6     | +4.6     | +2.8     | +2.4     | +6.3     | +4.8     | +0.4     |
| Improvement to G2G      | +4.8     | +4.4     | +3.8     | +4.1     | +6.0     | +7.7     | +7.9     | +8.6     |

### Table 6. Ablation study of synthon completion, class known.

| k= | top-1 | top-2 | top-3 | top-5 |
|----|-------|-------|-------|-------|
| SemiRetro | 75.0  | 89.4  | 93.9  | 96.7  |
| w/o filter | 74.7  | 88.9  | 93.6  | 96.3  |
| w/o self-correcting & filter | 71.5  | 87.0  | 92.6  | 96.0  |

### 5.4. Retrosynthesis (Q3)

#### A. Objective and setting

We explain how to combine center identification and synthon completion to provide end-to-end retrosynthesis predictions. We use a probability tree to search the top-k results, seeing Fig. 6, where the probability product of two-step predictions is used to rank these results.

#### B. Objective and setting

We study whether SemiRetro outperforms existing template-based and template-free methods. Baseline results are copied from their papers.

### 6. Conclusion

We propose SemiRetro for retrosynthesis prediction, which achieves SOTA accuracy and attractive scalability. Specifically, the DRGAT achieves the highest center identification accuracy. The self-correcting semi-template prediction mechanism improves both the accuracy and scalability of synthon completion. Moreover, SemiRetro has favorable training efficiency. We hope this work will promote the development of deep retrosynthesis prediction.
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References

Baylon, J. L., Cilfone, N. A., Gulcher, J. R., and Chitten-den, T. W. Enhancing retrosynthetic reaction prediction with deep learning using multiscale reaction classification. Journal of chemical information and modeling, 59 (2):673–688, 2019.

Chen, B., Shen, T., Jaakkola, T. S., and Barzilay, R. Learning to make generalizable and diverse predictions for retrosynthesis. arXiv preprint arXiv:1910.09688, 2019.

Chen, S. and Jung, Y. Deep retrosynthetic reaction prediction using local reactivity and global attention. JACS Au, 1(10):1612–1620, 2021.

Coley, C. W., Barzilay, R., Jaakkola, T. S., Green, W. H., and Jensen, K. F. Prediction of organic reaction outcomes using machine learning. ACS central science, 3(5):434–443, 2017a.

Coley, C. W., Rogers, L., Green, W. H., and Jensen, K. F. Computer-assisted retrosynthesis based on molecular similarity. ACS central science, 3(12):1237–1245, 2017b.

Coley, C. W., Green, W. H., and Jensen, K. F. Machine learning in computer-aided synthesis planning. Accounts of chemical research, 51(5):1281–1289, 2018.

Corey, E. J. The logic of chemical synthesis: multistep synthesis of complex carbogenic molecules (nobel lecture). Angewandte Chemie International Edition in English, 30 (5):455–465, 1991.

Corey, E. J. and Wipke, W. T. Computer-assisted design of complex organic syntheses. Science, 166(3902):178–192, 1969.

Dai, H., Li, C., Coley, C., Dai, B., and Song, L. Retrosynthetic prediction with conditional graph logic network. Advances in Neural Information Processing Systems, 32:8872–8882, 2019.

Defferrard, M., Bresson, X., and Vandergheynst, P. Convolutional neural networks on graphs with fast localized spectral filtering. Advances in neural information processing systems, 29:3844–3852, 2016.

Hartenfeller, M., Eberle, M., Meier, P., Nieto-Oberhuber, C., Altmann, K.-H., Schneider, G., Jacoby, E., and Renner, S. A collection of robust organic synthesis reactions for in silico molecule design. Journal of chemical information and modeling, 51(12):3093–3098, 2011.

Hochreiter, S. and Schmidhuber, J. Long short-term memory. Neural computation, 9(8):1735–1780, 1997.

Karpov, P., Godin, G., and Tetko, I. V. A transformer model for retrosynthesis. In International Conference on Artificial Neural Networks, pp. 817–830. Springer, 2019.

Kipf, T. N. and Welling, M. Semi-supervised classification with graph convolutional networks. arXiv preprint arXiv:1609.02907, 2016.

Landrum, G. RDKit: Open-source cheminformatics software. 2016. URL https://github.com/rdkit/rdkit/releases/tag/Release_2016_09_4.

Law, J., Zsoldos, Z., Simon, A., Reid, D., Liu, Y., Khew, S. Y., Johnson, A. P., Major, S., Wade, R. A., and Ando, H. Y. Route designer: a retrosynthetic analysis tool utilizing automated retrosynthetic rule generation. Journal of chemical information and modeling, 49(3):593–602, 2009.

Liu, B., Ramsundar, B., Kawthekar, P., Shi, J., Gomes, J., Luu Nguyen, Q., Ho, S., Stoane, J., Wender, P., and Pande, V. Retrosynthetic reaction prediction using neural sequence-to-sequence models. ACS central science, 3 (10):1103–1113, 2017.

Paszke, A., Gross, S., Massa, F., Lerer, A., Bradbury, J., Chanan, G., Killeen, T., Lin, Z., Gimelshein, N., Antiga, L., et al. Pytorch: An imperative style, high-performance deep learning library. Advances in neural information processing systems, 32:8026–8037, 2019.

Sacha, M., Blaz, M., Byrski, P., Dabrowski-Tumanski, P., Chrominski, M., Loska, R., Wlodarczyk-Pruszyński, P., and Iastrzebski, S. Molecule edit graph attention network: modeling chemical reactions as sequences of graph edits. Journal of Chemical Information and Modeling, 61(7):3273–3284, 2021.

Schneider, N., Stiefl, N., and Landrum, G. A. What’s what: The (nearly) definitive guide to reaction role assignment. Journal of chemical information and modeling, 56(12):2336–2346, 2016.

Schwaller, P., Gaudin, T., Lanyi, D., Bekas, C., and Laino, T. “found in translation”: predicting outcomes of complex organic chemistry reactions using neural sequence-to-sequence models. Chemical science, 9(28):6091–6098, 2018.

Schwaller, P., Laino, T., Gaudin, T., Bolgar, P., Bekas, C., et al. Molecular transformer for chemical reaction prediction and uncertainty estimation. 2019.

Segler, M. H. and Waller, M. P. Modelling chemical reasoning to predict reactions. arXiv preprint arXiv:1608.07117, 2016.

Segler, M. H. and Waller, M. P. Neural-symbolic machine learning for retrosynthesis and reaction prediction. Chemistry–A European Journal, 23(25):5966–5971, 2017.
SemiRetro: Semi-template framework boosts deep retrosynthesis prediction

Segler, M. H., Preuss, M., and Waller, M. P. Planning chemical syntheses with deep neural networks and symbolic ai. *Nature*, 555(7698):604–610, 2018.

Seidl, P., Renz, P., Dyubankova, N., Neves, P., Verhoeven, J., Segler, M., Wegner, J. K., Hochreiter, S., and Klambauer, G. Modern hopfield networks for few-and zero-shot reaction template prediction. *arXiv preprint arXiv:2104.03279*, 2021.

Shi, C., Xu, M., Guo, H., Zhang, M., and Tang, J. A graph to graphs framework for retrosynthesis prediction. In *International Conference on Machine Learning*, pp. 8818–8827. PMLR, 2020.

Somnath, V. R., Bunne, C., Coley, C. W., Krause, A., and Barzilay, R. Learning graph models for retrosynthesis prediction. In *Thirty-Fifth Conference on Neural Information Processing Systems*, 2021. URL https://openreview.net/forum?id=SnONpXZ_uQ_.

Sun, R., Dai, H., Li, L., Kearnes, S., and Dai, B. Energy-based view of retrosynthesis. *arXiv preprint arXiv:2007.13437*, 2020.

Szymkuć, S., Gajewska, E. P., Klucznik, T., Molga, K., Dittwald, P., Startek, M., Bajczyk, M., and Grzybowski, B. A. Computer-assisted synthetic planning: the end of the beginning. *Angewandte Chemie International Edition*, 55(20):5904–5937, 2016.

Tetko, I. V., Karpov, P., Van Deursen, R., and Godin, G. State-of-the-art augmented nlp transformer models for direct and single-step retrosynthesis. *Nature communications*, 11(1):1–11, 2020.

Vaswani, A., Shazeer, N., Parmar, N., Uszkoreit, J., Jones, L., Gomez, A. N., Kaiser, L., and Polosukhin, I. Attention is all you need. In *Advances in neural information processing systems*, pp. 5998–6008, 2017.

Veličković, P., Cucurull, G., Casanova, A., Romero, A., Lio, P., and Bengio, Y. Graph attention networks. *arXiv preprint arXiv:1710.10903*, 2017.

Weininger, D. Smiles, a chemical language and information system. 1. introduction to methodology and encoding rules. *Journal of chemical information and computer sciences*, 28(1):31–36, 1988.

Yan, C., Ding, Q., Zhao, P., Zheng, S., YANG, J., Yu, Y., and Huang, J. Retroxpert: Decompose retrosynthesis prediction like a chemist. In Larochelle, H., Ranzato, M., Hadsell, R., Balcan, M. F., and Lin, H. (eds.), *Advances in Neural Information Processing Systems*, volume 33, pp. 11248–11258. Curran Associates, Inc., 2020. URL https://proceedings.neurips.cc/paper/2020/file/819f46e52c25763a55cc642422644317-Paper.pdf.

Zheng, S., Rao, J., Zhang, Z., Xu, J., and Yang, Y. Predicting retrosynthetic reactions using self-corrected transformer neural networks. *Journal of Chemical Information and Modeling*, 60(1):47–55, 2019.
A. Appendix

Center identification
We show top-2 center identification predictions in Fig. 7, where synthons are obtained from breaking edge centers for downstream synthon completion. We present the probability of each prediction where the total probability of top-2 predictions exceeds 98%, indicating strong inductive confidence. Since the top-3 predictions are accurate enough, seeing Table. 2, we use them for synthon completion.

Case1: ground truth is atom center

Case2: ground truth is edge center

Figure 7. Visualize results of center identification. Case1: the ground truth is atom center, and the top-1 prediction is correct with the probability 99.3%. Case2: The ground truth is edge center, and the top-2 prediction is correct with the probability 18.4%.

Synthon completion
In Fig. 8, we present the process of predicting multiple reactants of the same product. This process provides an end-to-end view of synthon completion, containing semi-template prediction, top-k results search, and semi-template application. By default, we choose the top-4 synthon completion results for each center identification output as part of the final top-10 retrosynthesis results.

Figure 8. The overall pipeline of synthon completion. The input synthons are the outputs of the center identification module, coming from the same product molecule. We get the top-5 semi-template predictions and their probabilities of each synthon using SemiRetro (synthon completion network), then generate the joint distribution of semi-templates. We choose the top-5 predictions from this joint distribution and apply the residual attachment algorithm (introduced later) to get the final reactants.
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Table 7. Residual attachment algorithm. For easy and quick understanding, we demonstrate the core idea by visual samples. The detailed implementation can be found in the open-source code.

**Input:** Synthon, reaction center, and semi-template

**Output:** Reactant obtained by applying the semi-template on the synthon

| Step | Description |
|------|-------------|
| 1    | map atoms within the template |
| 2    | map bonds within the template |
| 3    | match the left template with the synthon |
| 4    | Attach the right template into the synthon |

Constraint: the reaction center must be within the matching area

Platform

- The platform for our experiment is ubuntu 18.04, with an Intel® Xeon® Gold 6240R Processor and 256GB memory. We use a single NVIDIA V100 to train models, where the CUDA version is 10.2.

| Method           | GLN time/epoch | GLN GPU memory/sample | G2G time/epoch | G2G GPU memory/sample | SemiRetro time/epoch | SemiRetro GPU memory/sample | total epochs | Sython completion |
|------------------|----------------|-----------------------|----------------|------------------------|----------------------|-------------------------|--------------|-----------------|
| RetroXpert       | 785s           | 274.7MB               | 440s           | 55.7MB                 | 330s                 | 147.7MB                 | 50           | 33s             |
| G2G              | 58s            | 46.1MB                | 322s           | 65.7MB                 | 30                   | 65.7MB                  | 100          | 38.2MB          |
| SemiRetro        | 56s            | 36.6MB                | 322s           | 65.7MB                 | 30                   | 65.7MB                  | 100          | 38.2MB          |

Table 8. The training costs of different methods. We run the open-source code of these methods on the same platform, reporting the training time per epoch and occupied GPU memory per sample. We also show the total training epochs mentioned in their paper (preferred) or code. If the author reports training steps, we calculate $epochs_{total} = steps_{total} / steps_{interval}$.
Important details We follow the setting of G2Gs, which provides open-source code on https://github.com/DeepGraphLearning/torchdrug/. G2Gs use different atom features in their open-source code for center identification and synthon completion. We have also tried to combine all these atom features and use the same set of features in center identification and synthon completion models. The combined atom features do not make a significant difference. In this paper, we use the same feature for both center identification and synthon completion.

| Name         | Description                                                                 |
|--------------|-----------------------------------------------------------------------------|
| Atom type    | Type of atom (ex. C, N, O), by atomic number                                |
| # Hs         | one-hot embedding for the total number of Hs (explicit and implicit) on the atom |
| Degree       | one-hot embedding for the degree of the atom in the molecule including Hs  |
| Valence      | one-hot embedding for the total valence (explicit + implicit) of the atom   |
| Aromaticity  | Whether this atom is part of an aromatic system.                            |
| Ring         | whether the atom is in a ring                                               |
| Ring 3       | whether the atom is in a ring of size 3                                     |
| Ring 4       | whether the atom is in a ring of size 4                                     |
| Ring 5       | whether the atom is in a ring of size 5                                     |
| Ring 6       | whether the atom is in a ring of size 6                                     |
| Ring 6+      | whether the atom is in a ring of size larger than 6                         |

Table 9. Atom features for center identification and synthon completion.

| Name         | Description                                                                 |
|--------------|-----------------------------------------------------------------------------|
| Bond type    | one-hot embedding for the type of the bond                                   |
| Bond direction | one-hot embedding for the direction of the bond                            |
| Stereo       | one-hot embedding for the stereo configuration of the bond                 |
| Conjugation  | whether the bond is considered to be conjugated                             |
| Bond length  | the length of the bond                                                      |

Table 10. Bond features for center identification.