`DiffER`: Categorical Diffusion Models for Chemical Retrosynthesis

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Abstract

Methods for automatic chemical retrosynthesis have found recent success through the application of models traditionally built for natural language processing, primarily through transformer neural networks. These models have demonstrated significant ability to translate between the SMILES encodings of chemical products and reactants, but are constrained as a result of their autoregressive nature. We propose `DiffER`, an alternative template-free method for retrosynthesis prediction in the form of categorical diffusion, which allows the entire output SMILES sequence to be predicted in unison. We construct an ensemble of diffusion models which achieves state of the art performance for top-1 accuracy and competitive performance for top-3 and top-5 accuracy. We prove that `DiffER` is a strong baseline for a new class of template-free model and is capable of learning a variety of synthetic techniques used in laboratory settings.

1 Introduction

Retrosynthesis prediction is a vital step in organic synthesis tasks, particularly those posed for drug discovery or drug engineering. In forward synthesis prediction, the products of a chemical reaction are predicted from known reactants; retrosynthesis prediction reverses this process, instead predicting possible reactants that would produce a target product. Repeated application of retrosynthesis prediction can help chemists construct synthetic pathways for drug targets [21, 20, 23], promoting the discovery and advancement of new pharmaceuticals. While numerous types of models for computer-aided retrosynthesis have been proposed, many modern approaches utilize data-driven machine learning to find suitable models for retrosynthesis prediction.

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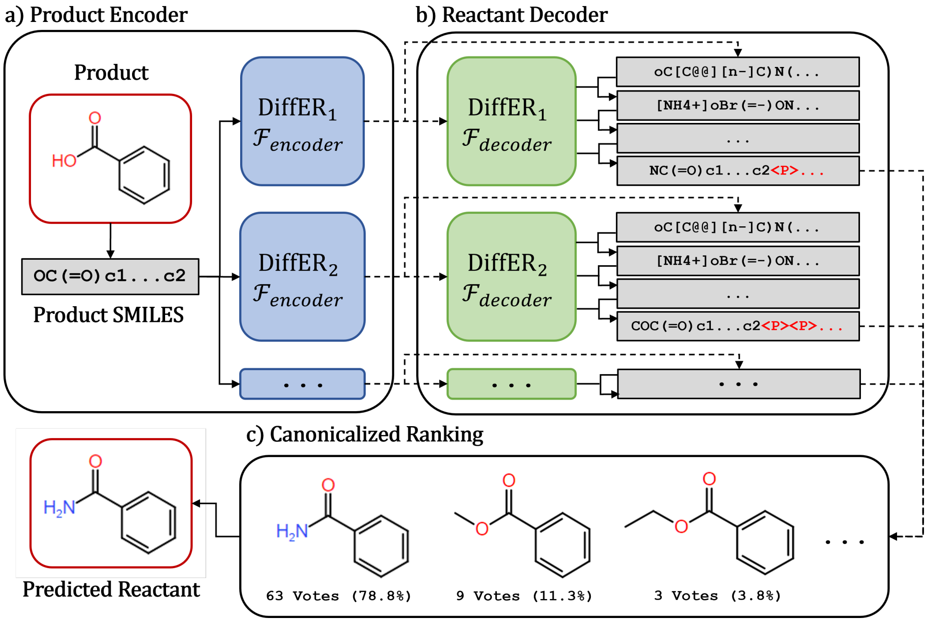

Figure 1: Schematic of `DiffER`, our diffusion process for retrosynthesis. **a)** The Product Encoder, which converts the product to a random, root-aligned SMILES form and encodes it using the encoder portion of the `DiffER` models. The encoder models also predict the size of the diffusion noise vector. **b)** The Reactant Decoder, which diffuses the reactant from randomly initialized categorical noise using the decoder portion of the `DiffER` models. Decoder models can predict pad tokens <P> to diffuse SMILES strings of varying lengths. **c)** The Canonicalized Ranking, which ranks the canonical molecules predicted by the `DiffER` models by the number of times they are generated. The top-ranked reactant is the predicted reactant.

Recent advances in machine learning models for chemical retrosynthesis have taken advantage of transformer architectures originally crafted for natural language tasks. Instead of operating on natural language, these models are set to operate on SMILES [31] encodings of chemical products and reactants, effectively translating between two molecular sets [16]. Indeed, recent work has done precisely this, going as far as using neural machine translation models originally built for language tasks for retrosynthesis prediction [34, 12]. While these models exhibit remarkable performance compared to other baseline methods for retrosynthesis, they impose autoregressive constraints during training and prediction, enforcing sequential decoding of the SMILES string. A more detailed overview of current work in single-step retrosynthesis we compare our work to is provided in Appendix B.

In this work, we offer `DiffER`, an alternative to sequential decoding of SMILES strings in the prediction process by utilizing categorical diffusion models rather than autoregressive models. This exchange allows `DiffER` to decode the entire SMILES string in unison, rather than in an autoregresssive manner. We hypothesize that by allowing the model to predict the entire SMILES string in unison, it may better learn structural relationships within the molecule. Additionally, diffusion models have experienced a recent surge of success for many generation tasks across domains. By employing categorical diffusion for the chemical retrosynthesis task, we provide a strong and competitive baseline for a new class of model. An outline of our approach is display in Figure 1, while a more detailed overview is available in Section 1.1. `DiffER` achieves state-of-the-art top-1 accuracy against a variety of baseline models and competitive performance for top-3 and top-5 accuracy.

1.1 Methods

We define the retrosynthesis task as a sequence-to-sequence modeling problem and combine the approaches of Hoogeboom et al. [11], DiffuSeq [8, 9], and MaskPredict [7] to train conditional, multinomial diffusion models for the retrosynthesis task. We utilize a traditional encoder-decoder transformer architecture to construct individual conditional diffusion models, where the encoder is responsible for learning the representation of the conditional features and the decoder acts as the diffusion approximation model. In the end, eight individual diffusion models are ensembled to produce `DiffER`, a novel ensemble model for chemical retrosynthesis.

Let $\boldsymbol{x}_t \in \{0,1\}^{K \times \ell_x}$ be a sequence of ℓ_x one-hot encoded vectors of size K representing the source and let $\boldsymbol{y}_t \in \{0,1\}^{K \times \ell_y}$ be similarly defined representing the target. Let $\mathcal{C}$ denote a categorical probability distribution with parametrized probability. Finally, let $\mathcal{F}$ represent a transformer neural network with encoder $\mathcal{F}_{\text{encoder}}$, decoder $\mathcal{F}_{\text{decoder}}$, and sequence length prediction classifier $\mathcal{F}_{\text{length}}$.

1.1.1 Forward Noising Process

Following Hoogeboom et al. [11], we define the multinomial diffusion process q as a categorical distribution $\mathcal{C}$ with probability β_t of sampling uniformly from $\{0,1\}^K$ for any step in the sequence, and apply noising to the target matrix y_t:

$$q(\boldsymbol{y}_t|\boldsymbol{y}_{t-1}) = \mathcal{C}(\boldsymbol{y}_t|(1-\beta_t)\boldsymbol{y}_{t-1} + \beta_t/K). \tag{1}$$

This forms a Markov chain allowing $\boldsymbol{y}_t$ to be directly sampled from $\boldsymbol{y}_0$:

$$q(\boldsymbol{y}_t|\boldsymbol{y}_0) = \mathcal{C}(\boldsymbol{y}_t|\bar{\alpha}_t\boldsymbol{y}_0 + (1-\bar{\alpha}_t)/K), \tag{2}$$

where $\alpha_t = 1 - \beta_t$ and $\bar{\alpha}_t = \prod_{\tau=1}^{t} \alpha_\tau$. Note that in the forward noising process, we only apply noise to the target sequence $\boldsymbol{y}_0$.

1.1.2 Conditional Denoising

We continue following the work of Hoogeboom et al. to denoise the categorical data. We construct the posterior distribution of the categorical model as

$$p_\theta(\boldsymbol{y}_{t-1}|\boldsymbol{y}_t, \boldsymbol{y}_0) = \mathcal{C}(\boldsymbol{y}_{t-1}|\boldsymbol{\theta}_{\text{post}}(\boldsymbol{y}_t, \boldsymbol{y}_0)), \tag{3}$$

where

$$\boldsymbol{\theta}_{\text{post}}(\boldsymbol{y}_t, \boldsymbol{y}_0) = \bar{\boldsymbol{\theta}} / \sum_{k=1}^{K} \hat{\theta}_k \tag{4}$$

and

$$\bar{\boldsymbol{\theta}} = [\alpha_t \boldsymbol{y}_t + (1-\alpha_t)/K] \odot [\hat{\alpha}_{t-1}\boldsymbol{y}_0 + (1-\hat{\alpha}_{t-1})/K]. \tag{5}$$

Notably, as $\boldsymbol{y}_0$ is not known during inference, it must be estimated using a neural network. Inspired by DiffuSeq [8, 9], we concatenate a representation of the source sequence to the noised representation of the target sequence to use as input to the $\boldsymbol{y}_0$ approximation model. In contrast to DiffuSeq, which uses the embedded representation of the source sequence $\boldsymbol{x}_0$, we process the source sequence with a transformer encoder model prior to concatenating, which is used as the memory component in the decoder architecture [15]. Thus, the reverse diffusion process is fully modeled as

$$p_\theta(\boldsymbol{y}_{t-1}|\boldsymbol{y}_t, \boldsymbol{x}_0) = \mathcal{C}(\boldsymbol{y}_{t-1}|\boldsymbol{\theta}_{\text{post}}(\boldsymbol{y}_t, \mathcal{F}_{\text{decoder}}(\boldsymbol{y}_t || \mathcal{F}_{\text{encoder}}(\boldsymbol{x}_0)))), \tag{6}$$

where $||$ is the concatenation operator. We denote the estimated target sequence as $\hat{\boldsymbol{y}}_0$. Additionally, we add a sinusoidal embedding of the current diffusion timestep t to the diffusion model input $\boldsymbol{y}_t$.

1.1.3 Length Prediction

One downside of the diffusion methodology compared to normal autoregressive methods is the requirement that the total length of the sequence must be known prior to inference so that the starting uniform noise distribution can be properly initialized. Prior work, such as DiffuSeq [8, 9], have primarily approached this issue by padding the sequence with observable `PAD` tokens up to a maximum length, and allowing the diffusion model to predict the location of `PAD` tokens as necessary. In contrast, MaskPredict [7] presents the idea of a length prediction token, which is learnt by the transformer encoder block and used to initialize the input to the transformer decoder. We similarly prepend a `LENGTH` token to the source sequence $\boldsymbol{x}_0$ and use the learned representation of the `LENGTH` token for the sequence to predict a target length $\hat{\ell}_y$:

$$p(\hat{\ell}_y|\boldsymbol{x}_0) = \mathcal{F}_{\text{length}}(\mathcal{F}_{\text{encoder}}(\boldsymbol{x}_0)), \tag{7}$$

where $\mathcal{F}_{\text{length}}$ is a feed-forward classifier function over integers up to the maximum sequence length dependent only on the first column of $\mathcal{F}_{\text{encoder}}(\boldsymbol{x}_0)$.

Upon initial testing, we find that the baseline implementation of MaskPredict length prediction performs poorly for this task due to its rigidity in predicting the sequence length and frequency of predicting shorter sequences than the ground truth. To remedy this, we propose a novel adjustment to the method by appending a uniform random number $n \sim \mathcal{U}(1, N)$ of observable padding tokens to the decoder sequences during training. This increases the expected length of the sequence by $\frac{(1+N)}{2}$ while allowing the diffusion model to predict pad tokens within a range of the the target length. Notably, as the probability of predicting n padding tokens is equivalent for $n \in [1, N]$, the probability of predicting sequences with lengths within $\frac{(1+N)}{2}$ of the predicted length is approximately equal. This offers benefits of both the MaskPredict and DiffuSeq approaches: The diffusion model is provided with information about the target length from the encoder while still allowing for the possibility of predicting a variety of sequence lengths rather than only the predicted target length. Intuitively, lower limits of N place more focus on the length prediction component, while higher values of N allow the model to vary more from the initial length prediction. Additionally, as the lengths of the input source sequence and output target sequence of the retrosynthesis task are highly correlated, we shift the methodology to predict the difference in length between the source and target rather than the total length of the target.

1.1.4 Ensemble Voting of Models

In order to stabilize and diversify the output of the diffusion model, we implement an ensemble of various individual diffusion models with different values of the random padding limit N. During inference, multiple samples are drawn from each model trained on different N. Outputs are then ranked according to the number of times they are sampled overall. Ties are broken using a ranked-choice voting scheme. This process encourages output diversity by combining models trained with varying degrees of reliance on the length prediction component. We refer to the constructed ensemble model as `DiffER`.

We identically construct and train the individual models that compose `DiffER`, varying only the maximum number of random padding that can be added on to the target sequence during training. We test various voting combinations of models with random padding limit $N \in \{5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90\}$. We find that models trained with $N < 20$ perform poorly, as they place too much focus on the length prediction component, which is biased toward a lower increase in length. We construct the final ensemble using eight models trained on $N \in \{20, 30, 40, 50, 60, 70, 80, 90\}$.

1.1.5 Loss Functions

We utilize a combination of mean square error (MSE) and variational lower bound (VLB) losses to train the diffusion models, the latter of which is derived using the Kullback-Leibler (KL) divergence according to Hoogeboom et al [11]. We apply MSE loss directly to the predicted target $\boldsymbol{y}_0$, while the VLB loss uses the sampled posterior of the predicted target:

$$\mathcal{L}_{\text{MSE}} = \mathbb{E}\left[||\boldsymbol{y}_0^2 - \hat{\boldsymbol{y}}_0^2||\right] \tag{8}$$

$$\mathcal{L}_{\text{VLB}} = \mathbb{E}\left[\sum_{k=0}^{K} \boldsymbol{y}_{0,k} \log \hat{\boldsymbol{y}}_{0,k} - \sum_{t=2}^{T} \text{KL}(q(\boldsymbol{y}_{t-1}|\boldsymbol{y}_t, \boldsymbol{y}_0)|q(\boldsymbol{y}_{t-1}|\boldsymbol{y}_t, \hat{\boldsymbol{y}}_0))\right]. \tag{9}$$

Finally, we include a loss term for the length prediction task using cross entropy:

$$\mathcal{L}_\ell = \mathbb{E}\left[\sum_{l=0}^{L} \ell_{y\,l} \log p(\hat{\ell_y}|\boldsymbol{x}_0)_l\right], \tag{10}$$

where ℓ_y is a one-hot encoded vector representing the length difference between $\boldsymbol{y}_0$ and $\boldsymbol{x}_0$. Additionally, when training the diffusion models, we employ the importance-based time sampling algorithm used in DiffuSeq [8, 9].

1.1.6 Reproducibility

We apply our models to the USPTO-50K [17] data set with Root-aligned SMILES augmentation [34], which greatly improves the performance of the diffusion models. We directly utilize the dataset splits provided by the authors of Root-aligned SMILES. We form `DiffER` as an ensemble of models with random padding limit $N \in \{20, 30, 40, 50, 60, 70, 80, 90\}$. Each model takes the form of a encoder-decoder transformer architecture with 6 layers and 8 attention heads with hidden dimension size 512, feed-forward size 2048, and GELU activation [10]. We utilize an Adam optimizer with learning rate 1×10^{-4} and dropout rate of 0.1. We set the number of diffusion steps to $T = 200$. We use a cosine beta schedule [3] and a Gumbel-softmax distribution for noise sampling during the diffusion process. All models are trained using a high-performance computer with Intel Xeon E5-2680 v4 CPUs (128GB memory) and NVIDIA Tesla P100 GPUs (16GB memory).

During inference, we follow the work of Zhong et al. [34] to augment the input SMILES strings. 20 random Root-aligned SMILES strings are generated for each input product and provided to `DiffER` for sampling. Thus, each model in `DiffER` outputs 20 random samples for the input string. Output samples are canonized and ranked according to rate of occurrence.

2 Results

Table 1: Top-K accuracy for tempate-based, semi-template, and template-free retrosynthesis models. The best performing model of its category for each K is in **bold** and the second best model is underlined. `DiffER` is the best performing model for $K = 1$ and the second best model for $K = 3, 5$ among template-free methods.

Category	Model	K=1	3	5	10
Template-based	Retrosim [5]	37.3	54.7	63.3	74.1
	Neuralsym [21]	44.4	65.3	72.4	78.9
	GLN [6]	52.5	69.0	75.6	83.7
	LocalRetro [2]	**53.4**	**77.5**	**85.9**	**92.4**
Semi-template	G2Gs [24]	48.9	67.6	72.5	75.5
	GraphRetro [25]	53.7	68.3	72.2	75.5
	RetroXpert [32]	50.4	61.1	62.3	63.4
	RetroPrime [30]	51.4	70.8	74.0	76.1
	G^2Retro [4]	**53.9**	**74.6**	**80.7**	**86.6**
Template-free	Seq2Seq [16]	37.4	52.4	57.0	61.7
	Levenshtein [26]	41.5	48.1	50.0	51.4
	GTA [22]	51.1	67.6	74.8	81.6
	Graph2SMILES [28]	51.2	66.3	70.4	73.9
	Dual-TF [27]	53.3	69.7	73.0	75.0
	MEGAN [19]	48.1	70.7	78.4	86.1
	Chemformer [12]	54.3	-	62.3	63.0
	Retroformer [29]	53.2	71.1	76.6	82.1
	Tied transformer [13]	47.1	67.2	73.5	78.5
	R-SMILES [34]	56.3	**79.2**	**86.2**	**91.0**
	`DiffER`	**57.6**	79.0	84.1	87.4

We compare `DiffER` to a variety of template-based, semi-template, and template-free methods for retrosynthesis prediction with unknown reaction types, detailed in Appendix B. We report top-k accuracy for $k \in \{1, 3, 5, 10\}$ following standard procedures. We construct `DiffER` as an ensemble of eight diffusion models with various hyperparameters and sample from each model twenty times with augmented input SMILES according to the work of Zhong et al. [34]. Predicted reactants sampled from the diffusion models are ranked according to the number of times they were predicted by the diffusion models. By using multiple different models with different hyperparameters to predict possible reactants for the same reaction, we encourage diversity and stability in the output reactants. Ties in reactant rankings are decided according to a ranked choice voting scheme. Further ties are broken arbitrarily. Results for the diffusion ensemble model are reported against baseline algorithms in Table 1.

Notably, `DiffER` is the best performing model for $K = 1$ (57.6%) across all model types, and is highly competitive for higher values of K, achieving the second best performance for $K = 3$ (79.0%) behind Root-Aligned SMILES [34] and third best performance for $K = 5$ and $K = 10$ (84.1% and 87.4%, respectively) behind Root-aligned SMILES and LocalRetro [2], making it the second best model among template-free approaches. The decrease in performance of ours at higher values of K can likely be attributed to a lack of outputs for higher values of K: despite generating outputs from multiple models for a diversity of input product SMILES, the output of `DiffER` tends to produce just a few candidate reactant sets for each product, producing the same output molecule numerous times in a different, non-canonical SMILES form. Indeed, Figure 2 shows a histogram of the number of sample reactions generated for the test dataset. The diffusion ensemble produces a median number of samples of 9, with 17.9% of reactions producing less than 5 samples, and 57.1% producing less than 10. Notably, we find that fewer reactants tend to be sampled when `DiffER` is correct in its output: reactions where the top-1 reactant is correctly predicted produce only 8.4 different molecules on average, compared to 12.3 for cases where the top-1 reactant does not match the ground truth. This lack of outputs is less observed in other methods such as R-SMILES which apply beam-search algorithms to sequential decoders, allowing a greater number of possible reactants to be found.

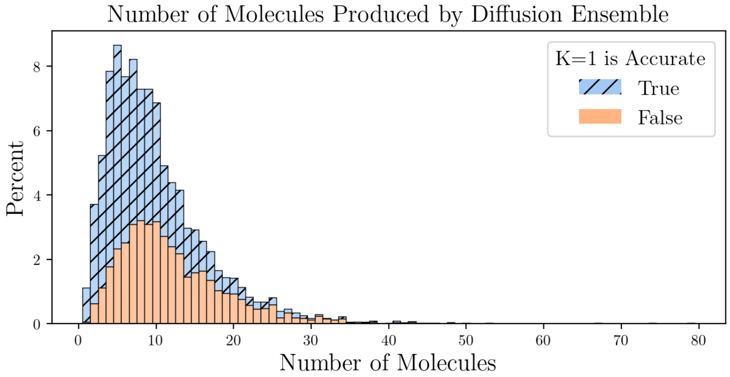

Figure 2: A histogram of the number of different molecules output by `DiffER` for each reaction during inference.The distribution has a mean of 10.0 and a median of 9. "K=1 is Accurate" indicates if the most commonly predicted molecule matched the ground-truth reaction.

2.1 Individual Model Performance

We construct `DiffER` from eight individually trained diffusion models, each of which uses a different random padding limit N (described in Section 1.1.3) during training. We report the individual performance for each of the trained models in Table 2. We compare these results to the `DiffER` ensemble as well as a baseline diffusion model trained using direct length prediction, without the length variation used in the individual `DiffER` models, also reported in Table 2.

The individual `DiffER` models greatly improve upon the baseline length prediction model, demonstrating the effectiveness of our length variation technique. The length variation technique encourages the individual models to over-predict the length of the reactant SMILES and then reduce the output SMILES to the correct size using predictable padding tokens. Meanwhile, the baseline length prediction model drastically under-performs all other models in terms of accuracy, demonstrating the sensitivity of the diffusion models for SMILES string generation to the size of the noise vector. Both the individual `DiffER` models and the baseline length prediction model exhibit low variance in the output reactants, only predicting 3.2 and 3.8 reactants on average, respectively. Notably, all models still achieves high validity from among the output molecules, indicating that the individual diffusion models are properly learning not only the SMILES grammar, but also rules of molecular validity.

When the individual models are ensembled into the complete `DiffER` model, both the accuracy and diversity of predicted reactants are significantly improved. The `DiffER` ensemble produces on average twice the number of reactants compared to the individual models, highlighting the impact of the different individual model setups on the output molecules. By combining multiple models trained on different upper limits for the length of the SMILES string, we can leverage different weightings of the length prediction mechanism. When a model is trained on a lower padding limit, more emphasis is placed on the length prediction component, as the model is less able to diverge from the predicted length. When the padding limit is larger, the diffusion model has more freedom to construct SMILES of varying lengths, but are less informed by the length prediction. By combining multiple models on various random padding limits, we improve the diversity and accuracy of the predicted reactants.

Table 2: Comparison of the `DiffER` ensemble with the individual models that make up `DiffER`. Individual models are notated as `DiffER` $_N$, where N represents the upper bound on the number of added padding tokens according to the procedure in Section 1.1.3. We additionally include single models with baseline length prediction and oracle length prediction. The individual `DiffER` models show significantly higher accuracy than baseline length prediction, but are outperformed by the `DiffER` ensemble. The oracle length model drastically outperforms all existing models.

Model	K=1	3	5	10	Sample Validity	Avg. Num. Reactants
`DiffER` Ensemble	57.6	79.0	84.1	87.4	100.0	10.0
`DiffER` $_{20}$	53.2	70.3	72.9	73.6	100.0	3.2
`DiffER` $_{30}$	55.2	71.5	74.4	75.2	99.9	3.2
`DiffER` $_{40}$	54.6	72.1	74.4	75.3	99.9	3.2
`DiffER` $_{50}$	54.9	71.3	73.7	74.4	100.0	3.2
`DiffER` $_{60}$	55.4	71.7	74.6	75.4	99.9	3.3
`DiffER` $_{70}$	54.3	71.1	73.5	74.4	99.6	3.2
`DiffER` $_{80}$	54.6	71.9	74.4	75.1	99.6	3.3
`DiffER` $_{90}$	54.5	71.6	74.2	74.9	99.8	3.3
Baseline Length	40.4	55.9	58.8	59.9	99.9	3.8
Oracle Length	77.0	88.1	89.5	90.0	99.7	2.8

Upper Limits on Performance we additionally consider a upper limit on the performance of categorical diffusion models for chemical retrosynthesis by considering an oracle model which predicts the length of the output SMILES string with 100% accuracy. This allows us to construct a diffusion model without needing to incorporate aspects of length prediction or variability in the size of the output as discussed in Section 1.1.3. Under the assumption of the length-predicting oracle, we can initialize input noise to the diffusion model of the proper size. We run this experiment for a single diffusion model and utilize the same parameters and repeated sampling during inference as discussed in the experimental setup.

Results for this experiment are presented in Table 2 in comparison to the `DiffER` models and the baseline length prediction diffusion model. The model with oracle length drastically outperforms `DiffER` as well as all existing methods for $K = 1, 3, 5$, but performs slightly worse than both Root-aligned SMILES and LocalRetro for $K = 10$. Similarly to `DiffER`, this can be attributed to a lack of variety in the predicted output, which is even more extreme for the oracle length model: on average, only 2.8 different reactants are predicted, with a median of just 2 predicted reactants. However, this lack of diversity is overcome by the oracle model's high accuracy amongst the predicted reactants.

This result highlights the importance of accurate length prediction in non-auto-regressive models, particularly in the case of molecular generation with SMILES strings. While there is some variability in the length of randomly generated SMILES string for a specific molecule, these variants generally only differ by a length of two or three, if they differ at all. If the length prediction is off from a viable value by even one or two, it may force an entirely different molecule to be generated, resulting in lower reported performance. By including the random length padding in `DiffER`, we help combat the diffusion model's sensitivity to length prediction, but remain far from the performance of a model with perfect length prediction.

3 Discussion

Our results show that categorical diffusion models offer a competitive alternative to auto-regressive models for template-free single step retrosynthesis prediction and are able to outperform state-of-the-art template-based, semi-template, and template-free methods on top-1 accuracy, and achieve similar performance to state-of-the-art models on top-3, top-5, and top-10 accuracy. The proposed `DiffER` ensemble is able to efficiently sample from the posterior distribution of possible reactant SMILES strings while maintaining the viability of output SMILES. `DiffER` is capable of reproducing existing patented reactions as well as proposing new and viable reactants (Appendix A.1).

3.1 Limitations and Directions of Future Work

Despite the strong performance of `DiffER`, there are a few notable limitations to the modeling approach. Firstly, raw diffusion models are highly sensitive to the predicted size of the output. Thus, methods such as our novel variant length padding (Section 1.1.3) must be employed to diversify target lengths and allow diffusion models to predict molecules of varying size. Secondly, `DiffER` suffers from a lack of output variety, often producing just a few possible reactants. Because diffusion models sample from an approximated posterior, reactants which the model deems more probable will be sampled at a higher rate, resulting in fewer reactants being sampled overall for a static sample size. This is particularly true in cases where the model is confident in its prediction. Finally, the model sometimes produces sub-optimal reactions, such as some of those displayed in Appendix A.1. Such reactions often undergo additional reactions alongside the target reaction, and while the desired product is a possible outcome, additional byproducts would likely be produced in many cases. These limitations highlight necessary areas of future research for not only categorical diffusion models in chemical retrosynthesis, but also categorical diffusion models for sequence generation in general:

1. Categorical diffusion models must be able to adapt to differently sized outputs. Prior work relies on predictable padding tokens to predict differently sized sequences [8, 9], but this reliance can introduce its own biases due to the prevalence of padding tokens for shorter sequences. `DiffER` overcomes reliance on predicting padding tokens by adding limited variability in the number of possible padding tokens, with some success; however, results still pale in comparison to a model with perfect sequence length prediction.
2. Additional techniques to sample categorical diffusion models must be developed in order to improve sequence diversity and coverage. Compared to the traditional applications of diffusion models in image generation, molecular SMILES generation has significantly fewer possible outputs, making the models more likely to converge to a single prediction. This effect is heightened by the the presence of multiple SMILES strings mapping to the same molecular structure: while the sequence itself may be different, the same molecule is produced. We must develop methods to encourage greater output diversity in the sampled molecules. `DiffER` attempts encourages output diversity using an ensemble approach, and while the results are significantly more diverse than single model approaches, the number of differently sampled molecules remains low.

The case studies of `DiffER` presented in Appendix A.1 additionally demonstrate directions of future research for retrosynthetic modeling as a whole, many of which are echoed in other work [4]:

3. Machine learning models for retrosynthesis are generally unaware of possible side products as a result of the generally available training data. Because these models are most commonly trained on patent reaction datasets, models are not generally exposed to explicit examples where multiple possible outcomes could occur. Indeed, the UPSTO-50K dataset has no reactant sets which map to more than one molecule, limiting the ability of the model to learn that multiple reactions may be possible for a single set of reactants. To improve the ability of ML models to understand chemical processes, incorporating additional examples into the training datasets may be beneficial, and with proper learning techniques, may lead to improved performance.
4. Evaluating the performance of ML models on chemical retrosynthesis most commonly relies on a) matching to patented reactions and b) analyzing individual case studies. Evaluating models by matching to patented reactions limits the discovery of novel techniques and pathways, as models may produce valid results that do not match patent data. In contrast, evaluating individual case studies is more adaptable to understanding the model's true performance, but is a time consuming process requiring considerable chemical knowledge. To enhance the development of ML models for chemical retrosynthesis, we must develop new methods of analysis that take into account the abundance of viable reactions as well as existing chemical knowledge.

Further research in these four tasks would greatly benefit the application of diffusion models in chemical retrosynthesis, as well as both diffusion modeling and retrosynthetic prediction models individually.

4 Conclusion

Our ensemble of categorical diffusion models provides state-of-the-art top-1 accuracy as well as competitive top-3 and top-5 accuracy. Additionally, we offer insight into the importance of length prediction and length variation methods when training diffusion models for sequence prediction tasks. We hope this work provides a suitable baseline and opens new avenues of exploration for a new class of template-free retrosynthesis model which differs from current autoregressive approaches. In future work, we plan to investigate additional methods of length prediction, as well as apply different diffusion sampling techniques to improve the diversity of sampled molecules. Finally, we plan to continue improving upon the diffusion model that comprise `DiffER`, introducing methods such as adaptive noise scheduling [33] as well as other advancements in categorical diffusion models to improve model performance.

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A Appendix / supplemental material

A.1 Case Studies

We offer additional results in the form of a case study of four different reactions, the results of which can be seen in Figures 3 and 4. We select four different reactions from the test dataset to highlight the successes and limitations of the diffusion models. For each reaction, we report the top-3 reactants sampled from the diffusion ensemble.

Reaction **a** (Fig. 3a) is a deprotection reaction in the forward direction in which the trifluoroacetamide protecting group (Fig. 3ab) is reacted with sodium borohydride in an ethanol solution to produce a primary amine at at the N1 position (Fig. 3aa). The diffusion ensemble does not predict this reactant, however, instead opting for the reduction of a nitro group, predicted 89.4% of the time, (Fig. 3ac) at the N1 position. This is a widely used and viable reaction involving metal catalyzed reduction of the nitro group using Fe, Zn, Pd or Ni. Similarly, the third ranked choice (Fig. 3ae) is also a viable option involving a debenzylation reaction which is commonly performed in the presence of a metal catalyst under a hydrogen atmosphere. The second choice reaction (Fig. 3ad), however, undergoes amide hydrolysis under harsh conditions such as a strong acid. While this is also a viable synthesis, a harsh condition such as a strong acid would likely interact with the tert-butyl ester group leading to unwanted side products. Notably, the diffusion ensemble does not predict the patented reactant, primarily predicting the reduction of a nitro group 89.4% of the time. We hypothesize that this is a result of the specific use-case of the ground-truth reaction, which is likely used in an industrial setting. Unlike the top-1 (Fig. 3ac) reactant, the ground-truth (Fig. 3ab) does not use the metal catalyzed reduction of a nitro group (top-1) or debenzylation (top-3) under a hydrogen atmosphere because it is not a safe reaction on industrial scale. While the top-1 or top-3 reactants may actually be more common in an academic lab setting, the ground-truth reactant is likely preferable on a large-scale industrial setting.

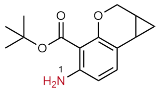
Reaction **b** (Fig. 3b) is a common reduction reaction of a ketone at C1 (Fig. 3bb) with sodium borohydride in a methanol solution to produce a secondary alcohol (Fig. 3ba). This same reaction is also predicted by the diffusion models 38.3% of the time to give the second most popular predicted reactants (Fig. 3bd). The most popular predicted reactants is an aldehyde and Grignard reagent, predicted 42.2% of the time, in which the methylmagnesium bromide reacts with the aldehyde at position C1 (Fig. 3bc) to produce the desired product in the forward reaction. However, the Grignard reagent (MeMgBr), which is a more nucleophilic reagent, is likely to react with other functional groups present in the molecule as well, such as the two amides at C2 and C4 or displace the fluorine at C5 via a nucleophilic aromatic substitution-like type reaction. In contrast, while the ground-truth/second-most predicted reaction (Fig. 3bb/3bd) could lead to unwanted products, such as the reduction the carbonyl groups at C2 and C4, these reactions are less likely to occur compared to the Grignard reaction under a proper choice of reagents such as sodium borohydride in ethanol. The top-3 reactant is predicted just 9.7% of the time, and unlike the other proposed reactants, it does not interact with the C1 carbon. Instead, it disconnects the molecule at the C1-N3 amide to reveal a C1 carboxylic acid and an N3 amine (Fig. 3be). The amide bond can be constructed in the forward reaction using a suitable amide coupling reaction condition. Yet again, this reaction is viable but would likely produce unwanted byproducts if other functional groups such as the free secondary alcohol or the primary amide in the proposed reaction were not protected first.

Reaction **c** (Fig. 4c) is an ester hydrolysis in which the C1 ester (Fig. 4cb) is reacted with sodium hydroxide and a water/ethanol mixture to produce a carboxylic acid (Fig. 4ca). This reaction is also predicted by the diffusion ensemble a vast majority of the time, forming 61.3% of the sampled reactants (Fig. 4cc). The top-2 reactant is also a viable alternative to the ground-truth reactant, just with a ethyl ester at C1 instead of a methyl ester, which is also a common reaction. Interestingly, the top-3 reactant sampled by the diffusion models is a Paal-Knorr-type pyrrole synthesis [18, 14] from an aniline (N2) and the diketone (C3-C6)(Fig. 4cd). The Paal-Knorr reactions usually involves harsh conditions such as strong acids which may not be compatible with the ether or the lactam functional groups [18, 14]. Also, the free C1 carboxylic acid may need to be protected as an ester before the pyrrole synthesis to produce the ground-truth reactant molecule (Fig. 4cb) which would need to undergo the aforementioned ester hydrolysis to produce the target molecule. Thus, 4cd could be viewed as one-step further back in the retrosynthesis chain compared to the ground-truth/top-1 reactant.

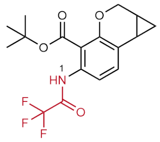
Finally, reaction **d** (Fig. 4d) is a Borch reductive amination [1] between cyclobutanone and a secondary amine in the presence of a reducing agent (Fig. 4db) to form a tertiary amine with a cyclobutyl group at N1 (Fig. 4db). The ground-truth reactants are the top-predicted reactants by `DiffER`, making up 74.3% of the predicted reactants. Both the second and third most predicted reactants are amine alkylations involving halides, in which an alkyl halide at C3 (Fig. 4dd/4de) reacts with the N1 amine to form a tertiary amine. Such N-alkylation reactions are commonly used when reduction amination does not work, and are valid alternative reactions. However, potential side reactions such as N-1 overalkylation or intramolecular N-4 alkylation would likely lead to unwanted byproducts. As such, the ground-truth/top-1 reactants are preferred.

These case studies demonstrate that the diffusion models are capable of learning a variety of viable reactions for organic synthesis, but like many other models, struggle to understand greater domain requirements or the likelihood of byproducts, as exemplified in the top-1 reactant for reaction **b** (Fig. 3bc) and top-2/3 reactants for reaction **d** (Fig. 4dd/4de). However, the models also demonstrate significant capability to properly utilize

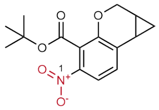
a)



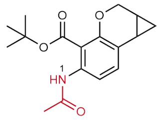
3aa, desired product



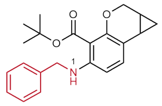
3ab, ground-truth reactants



3ac, top-1 reactants (89.4%)

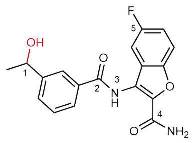


3ad, top-2 reactants (3.0%)

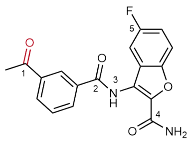


3ae, top-3 reactants (1.5%)

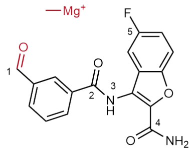
b)



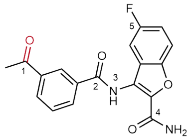
3ba, desired product



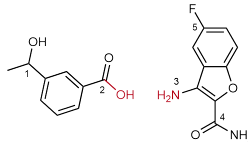
3bb, ground-truth reactants



3bc, top-1 reactants (42.2%)



3bd, top-2 reactants (38.3%)



3be, top-3 reactants (9.7%)

Figure 3: Top-3 reactants for target products **a** and **b**from the test set compared to patent reactants. Values in parentheses indicated the percentage of time that reactant was sampled from the diffusion models. Numbers next to atoms are labels used to refer to the atom. Colored regions indicate where in the molecule a reaction is expected to occur.

common and routine reactions (Fig. 3ac and Fig. 4cc) as well as more complex reactions such as ring formations (Fig. 4ce). Even in cases where the ground-truth reactants were not predicted in the top-3 reactants, the diffusion models produced suitable alternatives used in other reactions (Fig. 3ac) to accomplish the same goal. This highlights a key difficulty in assessing the accuracy and performance of models for retrosynthesis; oftentimes, multiple different reactions may be viable, and the use case for each reaction may depend on information not present in the molecular structure, such as the case of reaction **a**. Metrics of ground-truth accuracy do not capture the viability of a reaction, just that they match the patented reaction, which may lead to misrepresentation of the model's capabilities when a suitable alternative is predicted.

B Overview of Retrosynthesis Models Used for Comparison

We compare and report results against a variety of retrosynthesis models, as seen in Table 1. Models are grouped according to their model type, which includes template-based, semi-template, and template-free models.

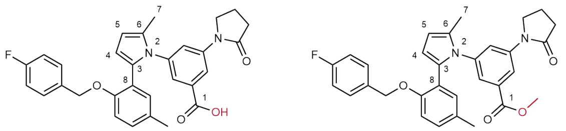
The template-based models we compare against are:

- Retrosim [5], which applies reaction templates derived from molecules similar to the target product, and ranks reactions by similarity to existing reactions;
- Neuralsym [21], which utilizes multi-layer perceptrons with molecular fingerprints of the product to predict applicable reaction templates;
- GLN [6], which uses graph neural networks to learn when and where in molecules reaction rules can be applied, while scoring the feasibility of the reaction;
- LocalRetro [2], which focuses on the local environment of atoms in the product and classifies reaction templates on an atomic level.

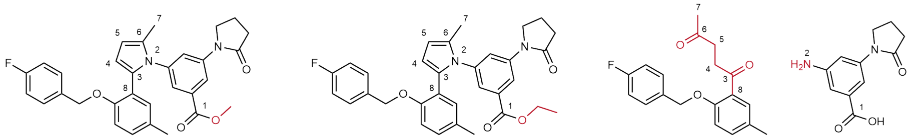
Each of these methods utilize reaction templates sourced from known reactions. The primary goals are to 1.) select where in the molecule the reaction will take place and 2.) select which reaction template is applicable.

The semi-template models we compare against are:

c)

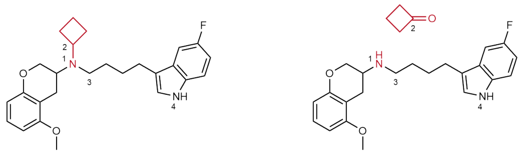


3ca, desired product **3cb**, ground-truth reactants

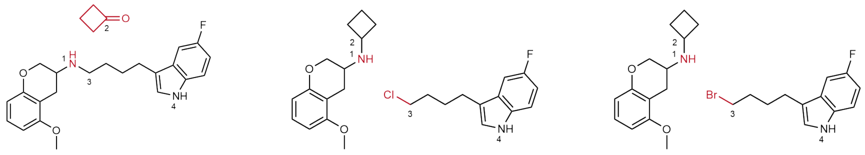


3cc, top-1 reactants (61.3%) **3cd**, top-2 reactants (18.7%) **3ce**, top-3 reactants (16.7%)

d)



3da, desired product **3db**, ground-truth reactants



3dc, top-1 reactants (74.3%) **3dd**, top-2 reactants (11.5%) **3de**, top-3 reactants (2.7%)

Figure 4: Top-3 reactants for target products **c** and **d**from the test set compared to patent reactants. Values in parentheses indicated the percentage of time that reactant was sampled from the diffusion models. Numbers next to atoms are labels used to refer to the atom. Colored regions indicate where in the molecule a reaction is expected to occur.

- G2Gs [24], which predicts reactions centers and sequentially completes synthons through the use of a variational graph autoencoder;
- GraphRetro [25], which uses message-passing neural networks to classify reaction centers and completes synthons by predicting which leaving groups to add from among a pre-selected set;
- RetroXpert [32], which uses edge-enhanced graph attention networks to predict reaction centers and completes synthons using a transformer network;
- RetroPrime [30], which uses two separate transformers, one to predict reaction centers, and the other to map synthons to reactants;
- G^2Retro [4], which uses a message passing network to predict three different types of reaction centers and sequentially adds substructures on to the synthons until complete reactants are formed.

Each of these methods first divide the product into synthons and then transform the synthons into complete reactants. The primary goals are to 1.) select where in the molecule the reaction will take place and 2.) complete synthons formed from the divided product into complete molecules which will react as needed.

The template-free models we compare against are:

- Seq2Seq [16], which applies sequence-to-sequnece encoder-decoder recurrent neural networks to predict reactant SMILES from the product SMILES;
- Levenshtein [26], which augments the training datasets of sequence-to-sequence recurrent neural networks by ensuring that the source and target SMILES strings have similar subsequences;
- GTA [22], which incorporates graphical information in a sequence-to-sequence model by limiting the self-attention layer using the adjacency matrix of the product molecular graph;
- Graph2SMILES [28], which leverages the permutation invariant nature of graph structures to remove variance that occurs when product is represented in SMILES form, and leverages transformer architectures to predict the reactant SMILES;
- Dual-TF [27], which unifies graph-based and sequence-based methods to learn an energy-based model which ranks possible reactants according to their energy score;
- MEGAN [19], which models one-step retrosynthesis as a series of graph edits, and trains a encoder-decoder graph attention model to how to adapt the product in a set of reactants;
- Chemformer [12], which pretrains a transformer architecture on SMILES strings using a masking approach and fine-tunes the model on product and reactant strings for retrosynthesis;
- Retroformer [29], which jointly processes the molecular sequence and graph and uses localized attention to relay information between the reaction center and global chemical context when constructing reactants;
- Tied transformer [13], which uses two-way transformers to encourage diversity and grammatical accuracy in predicted SMILES strings;
- R-SMILES [34], which restructures SMILES representations of products and reactants to have significant structural overlap, and then uses neural machine translation architectures to map from products to reactants.

Most of these methods utilize transformer architectures on SMILES strings, effectively translating from a product string into a reactant string. Many methods also directly incorporate information from the molecular graph, augmenting the SMILES strings with known structural information. The primary goal is to directly predict a representation of the reactant from the product, while secondary goals are to ensure the validity and viability of the predicted reactant representation.

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